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PROGRESS OF CHEMISTRY

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CONTENTS

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RADIOACTIVITY AND SUB-ATOMIC PHENOMENA.

THE study of subatomic phenomena has been made possible through the development of a number of special research tools. Some of them have been known for several years, but others have been invented quite recently. On the whole, the methods of nuclear physics have been fairly stationary for some time, and it is felt that a survey might be welcome to chemists.

Only few subatomic phenomena occur spontaneously in Nature, *viz.*, those connected with natural radioactivity and with cosmic radiation. All others have to be produced by artificial means, and because of the great stability of all nuclear structures it is necessary to concentrate large energy on a single particle. The only known way of doing this is to place an electrically charged particle in a strong electrical field in which it gets accelerated. The ultimate kinetic energy achieved is equal to the potential difference through which the particle moved in the process of acceleration, multiplied by its charge. Since the charge is, in general, equal to the charge of the electron (or a small multiple of it) it is usual to give its energy in electron volts (eV. or e.v.). The energies concerned in nuclear reactions are mostly of the order of a million electron volts (MeV), *i.e.*, the energy of an electron which has fallen through a potential difference of 10^6 volts. Hence, these energies are vastly greater than those involved in chemical reactions : 1 e.v. corresponds to about 23,000 cals. per mole, and the mean kinetic energy of a molecule at room temperature, $\frac{3}{2}kT$, is only about 0·04 ev.

High-tension Apparatus.—Ions are produced in a special discharge tube and are then accelerated in a high vacuum by the application of a high potential. The acceleration tube generally consists of a number of short glass (or porcelain) sections separated by metal plates. Each insulating section thus carries only a part of the total voltage, and the danger of electrical breakdown is reduced. Each metal plate has a short length of metal tube in its centre, which nearly touches the metal tube belonging to the next plate. Thus the beam runs down the axis of one long metal tube with a number of short gaps in it, and deflection of the beam caused by fluctuating charges on the insulators is minimised. The unevenness of the field (strong at the gaps, weak in the tubes) has a desirable focusing action on the beam. The ion source has to contain a certain pressure (of the order of 0·01 mm.) of the gas in question (hydrogen, deuterium, or helium) and powerful pumps (mostly oil diffusion pumps) are required to keep a sufficiently high vacuum in the accelerating tube.

For the production of the necessary high potential there are mainly two ways. The one consists in the use of a transformer, with subsequent rectification of the alternating potential (the use of "raw," that is unrectified, A.C. has considerable drawbacks and has been abandoned). By using several rectifier tubes in cascade arrangement, it is possible to get a D.C. potential several times (say 10 times or more) the peak voltage of the transformer.

The other system is essentially the same as in the old electrostatic machines. Sometimes rotating discs are used, but in the most common form—developed by Van der Graaff—an endless insulating belt (of paper or rubberised silk) is stretched over two pulleys which are rotated as fast as possible. One of the pulleys—say, the lower one—is at ground potential, while the other is inside the H.T. electrode, a large metal box, mostly spherical. Electric charge is "sprayed" on to that side of the belt which moves upwards by means of a small rectifier and a number of sharp points which almost touch the belt. On arrival at the H.T. electrode the charge is taken off the belt by means of a similar "comb." The H.T. electrode thus gets gradually charged up and its potential goes on increasing either until there is a breakdown (spark) to ground, or until the insulation losses just balance the flow of charge carried by the belt.

Both systems have their advantages and drawbacks. The transformer-rectifier arrangement gives large currents (several milliamps.) and is stable and easy to control. On the other hand it is expensive, and there is always a "ripple" (a remnant of A.C.). A Van der Graaff generator can be built at fairly small cost and the potential is quite "smooth"; but it gives no more than a few tenths of a milliamp. at most, and as the potential depends on the insulation losses, it takes some skill to get a constant potential. It seems to be the general tendency to prefer rectifiers for less than, say, 1 MV and electrostatic machines for higher potentials.

The limiting potential for each machine depends on the amount of sparking from the H.T. electrode to ground. Sparking along the insulator can be inhibited by appropriate design, and the sparking potential may be raised by about 50% by adding a small amount of dichlorodifluoromethane ("Freon") to the air. For considerably higher potentials it is usual to place the whole system, generator and discharge tube, in a tank filled with compressed air. The largest plant of this kind has been built in Pittsburgh[1] and consists of a pear-shaped container 47 ft. long, placed with its thin end downwards. The H.T. electrode is at the centre of the thick portion of the pear, and the discharge tube, some 30 ft. long, extends from there to the bottom end. This generator can produce up to about 4 MV. In Wisconsin another high-pressure electrostatic generator has been in use for some years.[2]

The Cyclotron.[3]—In this apparatus (invented and developed by E. O. Lawrence and originally called the magnetic resonance accelerator) the use of excessively high potentials is avoided by the ingenious expedient of

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[1] W. H. Wells, R. O. Haxby, W. E. Stephens, and W. E. Shoupp, *Physical Rev.*, 1940, **58**, 162.

[2] R. G. Herb, D. B. Parkinson, and D. W. Kerst, *ibid.*, 1937, **51**, 75.

[3] See W. B. Mann, "The Cyclotron," Methuen & Co., 1940; E. O. Lawrence and D. Cooksey, *Physical Rev.*, 1936, **50**, 1131.

accelerating the ions many times by the same potential. The acceleration takes place between two "Dees," hollow semicircular electrodes, like a pill box cut in two along a diameter. The "Dees" are placed in a strong magnetic field which bends the path of the ions and thus forces them to pass repeatedly from one electrode to the other. A high-frequency potential is applied to the "Dees" and synchronised with the motion of the ions so that they get accelerated every time they pass from one "Dee" to the other. As the ions get faster the curvature of their path in the magnetic field decreases, and they spiral outwards until they (or rather, some of them) escape through a slit in one "Dee" and are directed on to the target by means of a deflecting electrode.* All this happens inside an air-tight container (called the tank) which is continually exhausted by powerful pumps.

The limiting speed of the ions is given by the strength and diameter of the magnetic field. In most cyclotrons the region over which the field is sufficiently homogeneous has a diameter of about 2—2½ ft.; with a field of 16000 gauss the limiting energy then becomes about 8 MeV for deuterons and 16 MeV for doubly-charged helium ions (α-particles, sometimes called helions). It would appear that by increasing the size of the magnet one could produce ions of any desired energy, but as the speed of the ions ceases to be very small compared to the velocity of light their mass increases according to relativity theory and it becomes increasingly difficult to maintain the necessary synchronism between their motion and the high-frequency voltage which accelerates them. The Berkeley 60″ cyclotron (60″ pole piece diameter) produces deuterons of 16 MeV (and α-particles of 32 MeV), and yet bigger cyclotrons are under construction. With protons the relativistic difficulty is felt already in cyclotrons of the usual size, and proton energies are on the whole limited to about 10 MeV or less.

A recently developed instrument, called the induction accelerator or betatron,[4] produces electrons ("artificial β-particles") of energies up to 20 MeV. Electrons circulate inside a dough-nut shaped evacuated container, which encloses the iron core of a transformer. On each revolution the electrons gain a few ev. energy, corresponding to the voltage which would be generated in a secondary winding of one turn; but during one half-cycle of the A.C. (about 1000 cycles per sec.) which is fed to the transformer, the electrons make a large number of revolutions and thus accumulate very large energy. The instrument is still being improved and its future use in nuclear physics is difficult to predict.

Neutron Sources.—Radioactive bodies as sources of particles for nuclear experiments have on the whole been superseded by artificial sources, because of the enormously greater intensity of the latter (an ion current of 100μ amp., as is customary with artificial sources, means 6×10^{14} particles a second, whereas 1 g. of radium emits only 2×10^{11} α-particles per second). The

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[4] D. W. Kerst, *Rev. Sci. Instr.*, 1942, 13, 387.

* Or else the substance to be bombarded may be placed at the end of a "probe" which is inserted between the "Dees" so as to intercept the ions before they reach the edge of the "Dees." This gives greater intensity but has certain drawbacks.

main use of radioactive sources nowadays is for the production of moderate neutron intensities, their smallness, constancy, and easy manipulation then being of great advantage. The commonest type of neutron source is a tube packed with beryllium powder and filled with some hundred millicuries of radon. Such a source emits about 20,000 neutrons per sec. per millicurie, some of which have energies up to 10 MeV. The source decays, of course, with the half-life (3·82 days) of radon. A practically constant source (half-life 1700 years) with practically identical neutron spectrum is obtained by mixing a radium salt with the beryllium, both finely powdered. The neutron yield is in general about 12,000 neutrons per sec. per mg. of radium, depending on the thoroughness of mixing. In both cases the neutrons come mainly from the disintegration of beryllium by the α-particles of radium-C'. If a γ-ray source (radium, radon, or radio-thorium) is placed inside a beryllium block, so-called photo-neutrons are obtained, with a line spectrum extending up to about 1 MeV. The intensity is somewhat smaller than from a " mixed " source.

With a H.T. tube or a cyclotron one can get much stronger sources, and a considerable selection of different neutron spectra. Bombardment of deuterium with deuterons of a few hundred KeV (1 KeV. = 1000 eV.) gives almost homogeneous neutrons of about 2·5 MeV. Carbon gives slower neutrons, and lithium a very intense emission of fast ones (up to 14 MeV). If bombarded with energetic deuterons (8 MeV or more) from a cyclotron, lithium emits neutrons of more than 20 MeV. Intense sources of slower neutrons are obtained by bombarding lithium or beryllium with protons from a cyclotron. The reactions Li(p,n) and Be(p,n) are endothermic by about 2 MeV; therefore protons of more than 2 MeV are necessary and the maximum energy of the neutrons is about 2 MeV lower than the proton energy. The systematic investigation of different neutron sources and of their relative merits is only at the beginning.

Detection Methods.—For the detection of the particles emitted in nuclear transformations, the time-honoured electroscope has come into its own again, since the development of powerful cyclotrons and H.T. tubes made possible the production of artificial radioactive elements with a radiation equivalent to many milligrams of radium. It is unsurpassed for simplicity and accuracy, in particular in its more recent forms, among which the one due to C. C. Lauritsen and T. Lauritsen[5] is particularly popular. Increased sensitivity is achieved—though with considerable complication—by the use of an electrometer valve.

All these devices, where the bulk current in an ionisation chamber is measured, do not allow one to analyse the radiation producing the ionisation into its different components, except by the slow and laborious process of inserting absorbing screens between the source and the instrument. It is therefore very fortunate that the development of radio valves has made it comparatively easy to study the ionisation pulses produced by individual disintegration particles.[6]

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[5] *Rev. Sci. Instr.*, 1937, **8**, 438.

[6] See W. B. Lewis, " Electrical Counting," Cambridge Univ. Press, 1942.

A fast electron or positron (of 1 MeV or more) produces about 20 ion pairs per cm. of path in air at N.T.P. At lower energies this so-called specific ionisation is greater, but not very much. On the other hand, a moving light nucleus (proton, deuteron, α-particle) of a few MeV energy produces several thousand ion pairs per cm., and the heavy, fast moving nuclear fragments resulting from nuclear fission make about a million ion pairs per cm. It is therefore possible to count light nuclei in the presence of large numbers of electrons, by counting only those ionisation pulses which are greater than the greatest pulses caused by an electron. Similarly, in counting fission fragments, α-particles can be " out-biased."

The amplifier used consists of several radio valves, usually with resistance-capacity coupling. At least one of the coupling links has to have a short time constant (a millisecond or less) so that the output potential of the amplifier recovers quickly after each pulse. This is particularly important if there are large numbers of electrons (or of α-particles in fission counting), in order to prevent their individual pulses from piling up and thus being counted.

The counting is mostly done by mechanical meters such as are made commercially for use in telephone exchanges. The meter may be driven by a power valve or a thyratron, biased so that only pulses above a certain size are counted. By varying the bias, the size distribution of the pulses may be obtained. At high counting rates (above a few hundred pulses per minute) the meter begins to miss pulses because some of them follow too closely for the meter to count them both. Meters with a resolving time as low as one millisecond have been constructed, but the more usual procedure is to pass the pulses through a scaling circuit, a " scale of *n*," which lets only every *n*th pulse get through to the meter. Most frequently used are scales of 2, 4, 8, 16, 32 . . . (a scale of 8 being really a cascade of 3 scales of 2), but scales of 10 have also been made.

An ionisation chamber may be constructed and used in such a way that the primary ions produce additional ions by collisions with gas molecules. The pulse may thus be enhanced by a factor of 1000 or more. The most common form is the tube counter, where a moderate potential (1000—2000 volts) between a tube and an axial wire produces a sufficiently intense electric field near the wire (which is positive). The amount of multiplication obtained depends critically on the potential. Up to a certain potential the pulse is proportional to the number of primary ions, and the counter is said to work as a proportional counter. At higher potential the size of the pulse is determined only by the operating conditions and a single primary ion is sufficient to produce a pulse. The counter then operates as a Geiger–Müller counter and records every particle which makes at least one pair of ions inside it. The pulse produced by a Geiger–Müller counter is fairly large (one volt or more) so only little further amplification is required for the operation of a mechanical recorder.

The Geiger–Müller counter has perhaps done more than any other single research tool towards the progress of nuclear physics. By increasing the sensitivity of the detection of β-particles it was largely responsible for the discovery of artificial radioactivity. Its comparative simplicity and cheapness made it possible for many laboratories to take up research based on radioactive elements, for instance on their use as tracers in chemistry and biology. Moreover, our present knowledge of the cosmic radiation is based almost entirely on results obtained with these counters. It is then surprising that there should be, to the best of the Reporter's knowledge, no monograph on this important instrument (see, however, ref. 6). Perhaps one reason is that there is as yet no agreement about the best way of making and using Geiger–Müller counters, and each laboratory has its own devices and methods. In some places, counters are made with considerable care and of an elaborate design [7] and are expected to give years of reliable service, whereas others prefer to make counters by some simple method so that they can be easily replaced (or refilled) when they fail after a few weeks or months. For the filling gas, a mixture of argon (say under 8—9 cm. of mercury pressure) and alcohol vapour (2—1 cm.) has become very popular in this country and in Europe, because it gives constant counting rate over a considerable range of voltage (say 1400—1600 volts) and produces sharp pulses of uniform size. If very large numbers are counted, the alcohol is gradually decomposed and the counter deteriorates. Greater constancy is achieved by filling the counter with hydrogen, possibly with the addition of a noble gas to lower the required voltage. Such counters are not "self-quenching" like the alcohol counters; the discharge, once started, would continue if it were not quenched by the circuit attached to the counter. The simplest (and oldest) way of quenching a counter is to include a high resistance (10^9 ohms or more) in the path of the discharge current; this makes the voltage across the counter drop, as soon as the discharge develops, and thereby extinguishes the discharge. After that it takes some time for the voltage to rise again to its full value, and therefore this arrangement is unsuitable at high counting rates. Methods have been developed * by which the voltage on the counter is lowered for a short time by an amplifier system, and a long "plateau" † together with high counting rates can be obtained with almost any filling gas. These methods are being used mainly in America.

*The Coincidence Method.**—It is possible to make an arrangement whereby only those events are recorded when two counters are "triggered" simultaneously, or, more correctly, within a time interval Δt; this is called the resolving time of the system and can be made as short as 10^{-6} sec. Such coincidences occur if one particle goes through both counters, or if the two particles which trigger the two counters are emitted within the resolving time from the same nucleus. In addition there are always some chance coincidences; their number is $2N_1N_2\Delta t$ (where N_1 and N_2 are the numbers

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[7] See, *e.g.*, O. S. Duffendack, H. Lifschutz, and M. M. Slawsky, *Physical Rev.*, 1937, **52,** 1231.

* See ref. (6).

† The "plateau" is the voltage range over which the counting rate is more or less constant, extending from the "threshold" up to the point where spurious discharges become numerous. A long plateau (of 100 v. or more) is desirable, since it means that the adjustment and constancy of the voltage supply are not critical.

of pulses per unit time, in the two counters). This formula shows that it is important to make Δt small in order to minimise the chance coincidences.

Applications of the coincidence method are too numerous for more than a small selection to be given. In the study of the cosmic radiation, two or more counters in a row are used to select particles moving in some particular direction; this arrangement, called "counter telescope," is used for measuring the angular distribution of cosmic rays under various conditions. If the counters are spread out so that one particle cannot go through all of them, they permit the study of the so-called showers of cosmic ray particles. In studying radiation from radioactive substances by interposing screens between two counters, the absorption of those particles which cause coincidences can be observed. For instance, if a source of γ-rays is placed near the counters, electrons are knocked out of the counter walls; by observing their absorption in screens placed between the counters, one can determine their maximum energy and thereby the energy of the γ-rays. If a radioactive substance emits both β- and γ-rays, it is possible to obtain coincidences between two counters, one of which has a thin window (of mica or aluminium foil) to admit the β-particles. The usefulness of the coincidence method in combination with the β-ray spectrograph was pointed out in the Report for 1940.

Compared with the prodigious spread and development of electrical counting methods, the cloud chamber, once the most powerful tool of nuclear physicists, has been rather relegated to the background. Its most common application now is the study of neutron-energy spectra, from observations of the lengths and directions of the tracks formed by protons or other nuclei in the chamber which have been set in motion on being hit by a neutron. However, the main importance of the cloud chamber lies in its power to give qualitative information on new processes rather than quantitative results concerning known ones. For instance, the slowing down of fission fragments was shown, by a number of beautiful cloud-chamber photographs,[8] to be largely due to collision with nuclei; these knock-on nuclei show up as numerous branch tracks, making the track of the fission fragment look almost like a Christmas tree.

For the study of the tracks of heavy particles such as protons, special fine-grained photographic emulsions are being more and more widely used.[9] The particles penetrate only a fraction of a millimetre in the emulsion, but in doing so, each particle causes a chain of silver grains to be formed in the developing process, and under a high-power microscope the length and direction of these tracks can be determined with considerable accuracy. A photographic plate of this sort is therefore in some way equivalent to a cloud chamber which is permanently sensitive and can be made to accumulate tracks for hours or days. This advantage is only partly offset by the considerable labour and eye strain involved in the microscopic survey of even a few square millimetres of emulsion.

O. R. Frisch.

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[8] J. K. Bøggild, *Physical Rev.*, 1941, **60**, 627.

[9] See C. F. Powell, *Endeavour*, 1942, **1**, 151.

GENERAL AND PHYSICAL CHEMISTRY.

1. THE ABSORPTION SPECTRA OF ORGANIC SUBSTANCES, AND WAVE-MECHANICS.

MODERN physics deals with the problem of spectra somewhat as follows. The completeness of the information obtainable by measurement on small objects appears to be limited by the Uncertainty Principle.[1] For instance, if a *distance* is measured with a high degree of accuracy the *momentum* of the objects measured is correspondingly vague, being disturbed by the act of measurement. A similar relationship exists between measurements of *time* and *energy*. Time and length (period and wave-length) are the attributes of *wave motion*, whereas *momentum* and *energy* characterise a *particle*. When we make measurements on an electron forming part of an atom we are necessarily dealing with very small distances; the momentum of the electron cannot therefore be fixed with any precision, and it ceases to be practicable to treat the electron within the atom as a particle. The electron is more appropriately regarded as a stationary wave, and as certain waves only are possible, just as a fundamental and its harmonics are the only modes of vibration of a string, we arrive at a kind of an explanation of the existence of electrons in atoms only in *quantised states* of certain fixed energy values. Transitions of an electron from one quantised state to others give rise to the limited number of *monochromatic lines* which characterise the spectra of atoms. The equations of wave motion which must be used to reproduce the behaviour of an electron in an atom have been developed by de Broglie, Schrödinger, Dirac, and others; they are differential equations of wave motion in the three dimensions of space involving Planck's constant, the charge and mass of the electron, and the potential-energy field in which it moves. In any example other than the simple case of the hydrogen atom, the equations are excessively difficult or impossible to solve rigorously. However, approximate solutions of varying accuracy can be obtained, and the symmetry properties of the wave motion in space can be utilised with profit in attempting to understand the absorption of light.

It is natural to try to form some physical concept of the " wave " which expresses the electron's motion in an atom. An examination of this matter shows that the square of the amplitude of the hypothetical wave motion at any region in the atom represents the probability of the electron occupying that region. The " waves " may be regarded as a " probability calculus " giving the most likely regions for the electron round the atomic nucleus, any closer specification of its position being unattainable by measurement. From this standpoint we can proceed to a qualitative geometrical consideration of the three-dimensional wave motion representing the electron in a hydrogen atom. The mathematical problem consists in specifying the

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[1] See, *e.g.*, Physics Staff, Pittsburg University, "Atomic Physics," Wiley & Sons, N.Y., 1937, Chap. 8.

positions of the nodes of stationary waves about a point in space. The "fundamental," or wave motion of lowest energy, has the highest amplitude at the centre of the atom, a spherical node at infinity, and the amplitude falling off rapidly almost to zero in all directions outwards from the centre. This means that the most probable position of the electron is somewhere within a small spherical region round the atomic nucleus. We can never ascertain where it is at any instant within that region by any physical measurement. The wave function representing this is called the *electron orbital,* since it corresponds to the Bohr concept of electron orbits in the original theory of atomic structure. Excited hydrogen atoms, having their electrons in higher energy states, are represented by harmonics of the fundamental. These harmonics have an increasing number of nodes the higher their energy, and they fall geometrically into a number of types. Those of the first type have spherical nodes separating regions of opposite phase (" onion " type) and are called *s* orbitals. The fundamental is 1*s*, the first harmonic 2*s*, the next 3*s*, etc. (Fig. 1). The second type, called *p* orbitals, is characterised by a node at the centre of the atom, and assumes three forms, (*a*) point node at centre (" spherical shell " form), (*b*) linear node through centre (" smoke-ring " form), and (*c*) planar node through centre (" hour-glass " form). The last form is of chief importance in molecule formation, and in it the electron is " most probably " situated in

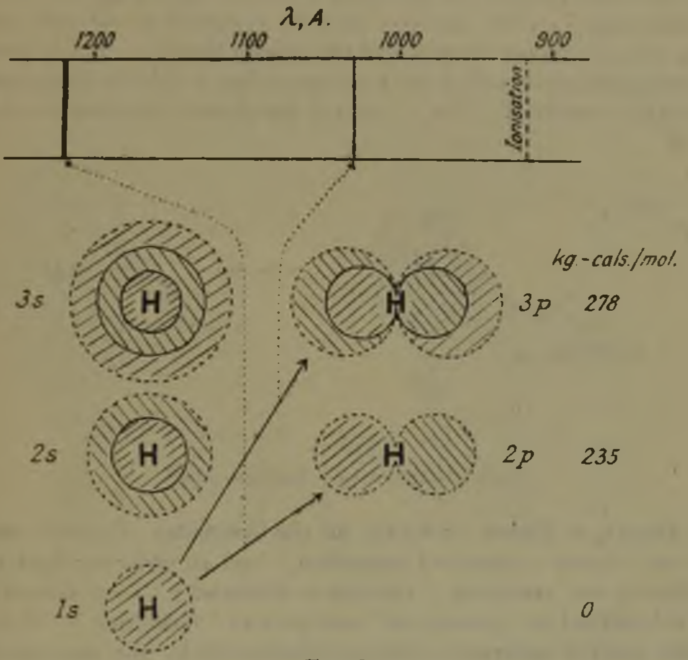

FIG. 1.

Energy states and absorption spectrum of the hydrogen atom.

two regions on the opposite sides of the nodal plane (*ABCD*, Fig. 2; opposite phases indicated by shading). We cannot discover " how " the electron can be in two places at once, but a useful hypothesis is to regard an electron in such an orbital as rapidly oscillating from side to side across the nodal plane. We can then form a kind of picture of the absorption of light. When a light ray (electromagnetic radiation) interacts with a hydrogen atom (electron in 1*s* orbital) the electron is set into " vibration." In Fig. 2 such a light ray is shown, polarised with its electric vector in the plane of the paper. If its frequency is appropriate, and it is absorbed, its energy being taken up by the atom, an excited atom with electron in a *p* orbital results, the nodal plane of the *p* orbital being at right angles to the electric vector direction, *i.e.*, the electron may be regarded as set into vibration along the electric vector direction of the absorbed light. Fig. 1 shows part of the absorption spectrum of the hydrogen atom in the far ultra-violet, and the transitions involved. The 1*s* orbital can pass as described to *p* orbitals but not directly to higher *s* orbitals, for the symmetry of these is such that there is no " dipole moment of transition," and an ordinary light ray cannot stimulate the necessary " electronic vibration; " *s*→*p* transitions are therefore described as " permitted " and *s*→*s* as " forbidden." If *s* orbitals have their perfect spherical symmetry destroyed by the near presence of other atoms, etc., *s*→*s* transitions become partially permitted, *i.e.*, would correspond to a weak absorption of light.

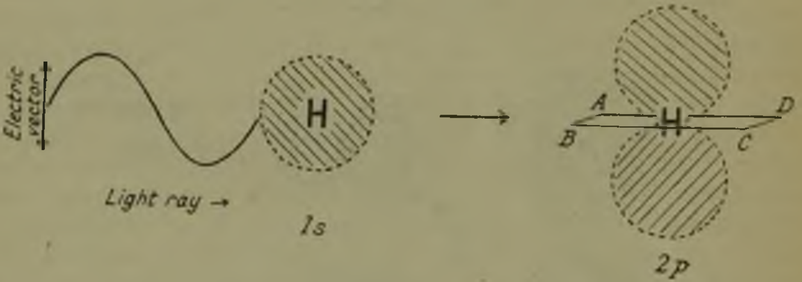

FIG. 2.
Light absorption by a hydrogen atom.

Electrons in atoms can occupy higher orbitals of more complex types, *d*, *f*, etc., distinguished by nodal surfaces of differing patterns, and the complexities of atomic spectra can be interpreted in terms of transitions between such orbitals. For an understanding of simple molecular spectra, however, it is not necessary to pursue these complexities. Reference must nevertheless be made to " electron spin." The wave-mechanical representation of spin is difficult to visualise; it can be shown mathematically to depend on the theory of relativity. On the " particle " concept it means that the electron is a body extending in space and rotating on an axis which can assume one of two orientations in the atom. According to the Pauli principle, every electron in an atom containing several must be distinguish-able from the others; this means that they must occupy (*i.e.*, be represented by) different orbitals. The orbitals described above take no account of "spin," and each can take two forms with opposite "spin." Each of the orbitals above therefore can "contain" one electron, or can "contain" two if the "spins" are opposite. This limitation of numbers of electrons in orbitals interprets the arrangement of electrons in "shells" in the Periodic Table of the elements. Every atom has one 1*s* orbital, one 2*s* orbital, three 2*p* orbitals with nodal planes mutually at right-angles, together with fixed numbers of higher orbitals 3*s*, 3*p*, 3*d*, etc., determined by the geometry of three-dimensional wave motion. Along the first row of the Table, each atom has two electrons paired in the 1*s* orbital; lithium has one in the 2*s* orbital, and hence is univalent, having one unpaired electron. Beryllium may be non-valent with two electrons paired in the 2*s* orbital, or bivalent with one electron each in the 2*s* and one 2*p* orbital. Carbon may be non-valent with two electrons paired in the 2*s* orbital and two paired in a 2*p* orbital, bivalent with the last two placed in two of the three available 2*p* orbitals, and quadrivalent with one electron each in the 2*s* and the three 2*p* orbitals. These different atomic states represent different energy levels of the atom; the one of lowest energy being called the "ground state."

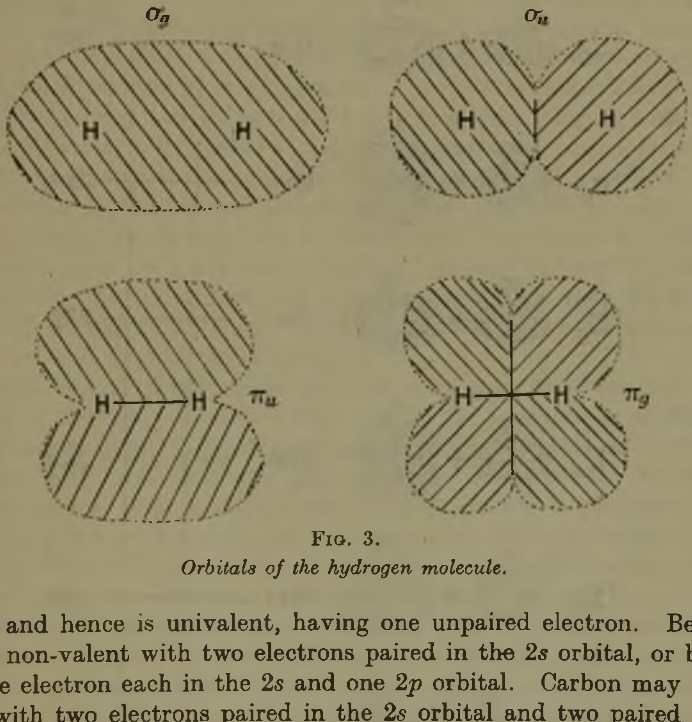

FIG. 3.
Orbitals of the hydrogen molecule.

The shapes of the orbitals of electrons in molecules differ from those of atoms because of the presence of more than one atomic nucleus. Fig. 3 shows some of the simpler types of orbital of the hydrogen molecule. The fundamental, corresponding to unexcited H_2, can be visualised as formed by the coalescence of two 1*s* hydrogen atom orbitals in phase, forming an ellipsoidal orbital with an axis of rotational symmetry along the H–H direction. Because of its derivation from atomic s orbitals, this type is designated σ_g, the subscript g standing for the fact that the wave has the same phase on both sides of its centre of symmetry. An orbital of

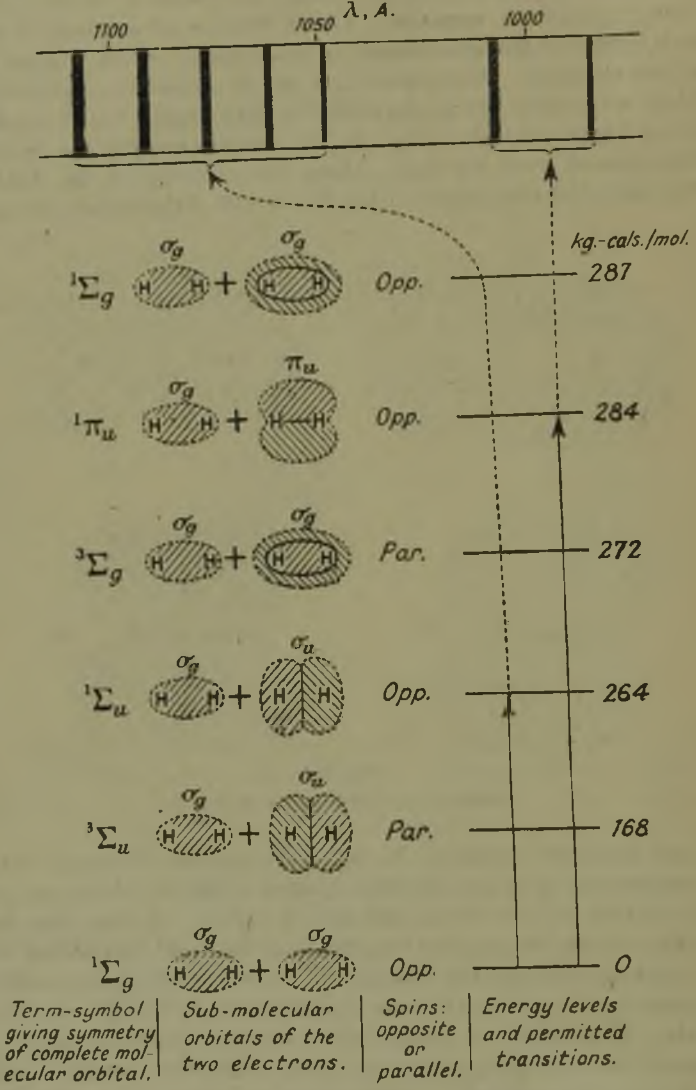

FIG. 4.

Energy states and absorption spectrum of the hydrogen molecule.

higher energy with opposite phases across the centre of symmetry is designated σ_u; this type has a nodal plane at right angles to the molecular axis. Two other orbitals are derived from atomic p orbitals by coalescence in and out of phase respectively on the two nuclei, called π_u and π_g. The former has a nodal plane containing the molecular axis, and the latter an additional nodal plane at right angles to the axis.

Fig. 4 shows some states of the hydrogen molecule, with their transitions and the absorption spectrum. The ground state of H_2 has the two electrons in σ_g orbitals with opposite spins, a state whose total resultant symmetry is designated $^1\Sigma_g$. By the absorption of light of about 1100 A., one electron passes to a σ_u orbital, giving a state represented in symmetry notation by $^1\Sigma_u$. Owing to the alteration of equilibrium inter-nuclear distance in the transition the higher state may have one or more vibrational quanta excited simultaneously (Franck–Condon principle[2]); hence the absorption is not confined to one wave-length, but consists of a series of *partial bands* differing in frequency by that of a vibrational quantum of the higher state. The partial bands are themselves built up of a series of lines of still finer frequency differences owing to the simultaneous changes of rotational energy during the transition. As shown in Fig. 4, another band system appears at about 1000 A. due to the transition of the ground state to one of symmetry $^1\Pi_u$, where one electron passes to a π_u orbital. Three other excited H_2 states are also shown; an upper state $^1\Sigma_g$, to which transition from the ground state is "forbidden" because of the absence of "transition moment," and two "triplet" states, $^3\Sigma_g$ and $^3\Sigma_u$, to which transitions are forbidden from the ground state because they would involve reversal of an electron "spin." The existence of these states is therefore not apparent in the *absorption* spectrum.

To understand recent work on molecular polarisabilities and orientations, it is necessary to form a clear idea of the processes of absorption of plane-polarised light. Let us imagine an oriented assembly of $^1\Sigma_g$ hydrogen molecules, with their molecular axes all along one direction. When plane-polarised light at 1100 A. falls on the molecules it will be strongly absorbed if its electric vector lies along the molecular axis, and one electron will pass to a σ_u orbital. If the electric vector is at right angles to the molecular axis the light is not absorbed (dichroism). Plane-polarised light at 1000 A. behaves in just the reverse way. Here the light is strongly absorbed only when its electric vector is at right angles to the axis, since at this wave-length the excited electron passes to a π_u orbital with a planar node *containing* the molecular axis (cf. remarks on atomic $s \rightarrow p$ transitions above). The development of new nodal planes on excitation is always at right angles to the electric vector direction. If the wave-lengths of the light do not coincide with positions of absorption bands, the occupied electronic orbitals are merely set into forced vibrations by the light waves with a phase lag which gives rise to the *refraction* and *dispersion* of the transparent substance.

We are now in a position to understand qualitatively the absorption processes of organic compounds. The carbon atom in its quadrivalent state

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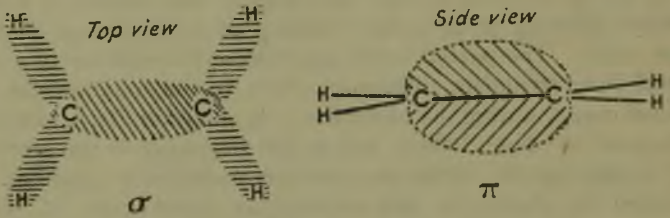
[2] See, *e.g.*, E. J. Bowen, "Chemical Aspects of Light," Clarendon Press, Oxford. 1942, p. 75; "Molecular Spectra (Diatomic Molecules)," Herzberg, Prentice-Hall, 1939, p. 413.

has its four valency electrons arranged one in the 2*s* orbital and in each of the three 2*p* orbitals which the geometry of wave motion permits having axes along three mutually perpendicular directions in space. When the atom combines with other atoms of carbon or hydrogen, the shapes of the atomic orbitals are necessarily considerably altered in becoming molecular orbitals. In methane, for example, four identical molecular orbitals are formed at the tetrahedral angle and of essentially σ_g character, a trace of *p* character remaining as an attenuated region of opposite phase on the other sides of the carbon atoms away from the C–H links. The ground state of all *single-bonded* organic compounds contains such σ_g type orbitals; *i.e.*, ellipsoidal or plum-shaped orbitals having an axis of rotational symmetry along the chemical link and containing two electrons of opposed spin. Their absorption is like that of the hydrogen molecule; diamond, methane, and ethane absorb in the far ultra-violet region only, and in the excited state one electron in a C–H or C–C link passes to a σ_u or π_u orbital without change of spin.



Orbitals of the ethylene molecule.

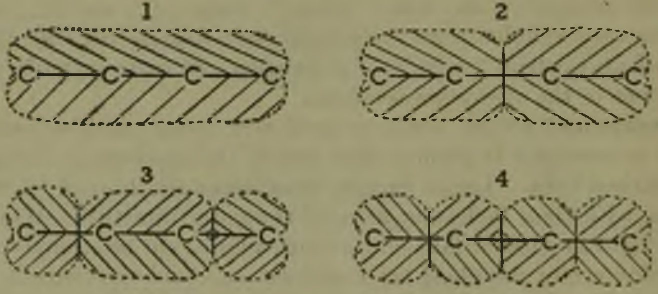


FIG. 5.

π Orbitals of the butadiene molecule.

The *double bond* of organic chemistry is supposedly modelled on the graphite modification of carbon.[3] Fig. 5 shows the orbitals in ethylene. There is a single-bond skeleton of C–H and C–C links at 120° to each other and in a plane, all of σ_g type orbitals. The remaining pair of electrons may be regarded as occupying hour-glass shaped *p* orbitals on the carbon atoms and having coplanar nodes, which coalesce to give a π_u orbital whose nodal plane is the plane of the single links. The binding of the electrons in this

[3] J. E. Lennard-Jones and C. A. Coulson, *Trans. Faraday Soc.*, 1939, **35**, 811; E. Hückel, *Z. Elektrochem.*, 1937, **43**, 752, 827; T. Forster, *ibid.*, 1939, **45**, 548.

orbital is less than that of the σ_g orbitals, and the two types do not overlap much. Ethylene absorbs at longer wave-lengths than ethane because of orbital changes of its more weakly bound π electrons. Its longest-wave absorption corresponds to one electron passing from the π_u to a π_g orbital, *i.e.*, developing a new nodal plane *across* the C–C link, the light absorbed being that polarised with electric vector *along* the link. By excitation, the energy necessary to cause rotation about the link is reduced; hence the facilitation of *cis-trans*-changes by ultra-violet light.[4] In the molecule butadiene (Fig. 5) we have the simplest *conjugated* system of double bonds with four electrons to dispose in π orbitals. We may start by imagining each carbon atom in the chain to have one electron in an atomic p orbital of hour-glass shape. By coalescence of these in phase all along the molecule a π_u orbital as shown marked 1 is produced. This by the Pauli principle can contain only two electrons. The second pair must be accommodated in an orbital of partial π_g character with one additional nodal plane across the molecular axis, *i.e.*, the left and the right half of the molecule are of opposite phase. This approximately represents the structure of the normal molecule. Absorption of ultra-violet light causes an electron from either of the orbitals 1 or 2 to pass to either of the orbitals 3 and 4 which have still more nodal planes across the axis. Four band systems will result, of which the longest wave (lowest energy) will correspond to an orbital change 2→3. Electrons in orbitals with nodal planes of this kind are called *anti-bonding*, since they weaken the strength of the link. This process of regarding the structure of conjugated molecules as built up of *non-localised* π orbitals superimposed on the σ orbital skeleton is easily extended to the polyenes. For example, β-carotene, with 22 carbon atoms alternately singly and doubly linked, has in its ground state 11 π orbitals, having 0—10 nodal planes across the molecular axis; and by absorbing light one electron passes to a still higher π orbital. It is easy to see that with increasing degree of conjugation the more bands will a molecule show and the longer will be the wave-length of the transition of least energy change, since the energy differences between higher orbitals grow less and less. Fig. 6 illustrates the arrangement of nodes and approximate energy levels of orbitals in conjugated polyenes. Fig. 7 shows how the longest wave-length of absorption varies with increasing conjugation. The reciprocal of the frequency squared is nearly a linear function of the number of double bonds. Similar relationships are obtainable for dyes of cyanine type, etc.[5]

The molecule of benzene is one of peculiar interest on these views. Fig. 8 shows six π orbitals of the "aromatic sextet." All these have a nodal plane in the plane of the ring. Orbitals 2 and 3 have in addition a nodal plane across the ring so that the two halves are out of phase; two orbitals of equal energy but of opposite character are possible. The normal molecule has a pair of electrons in each of these three orbitals. On the absorption

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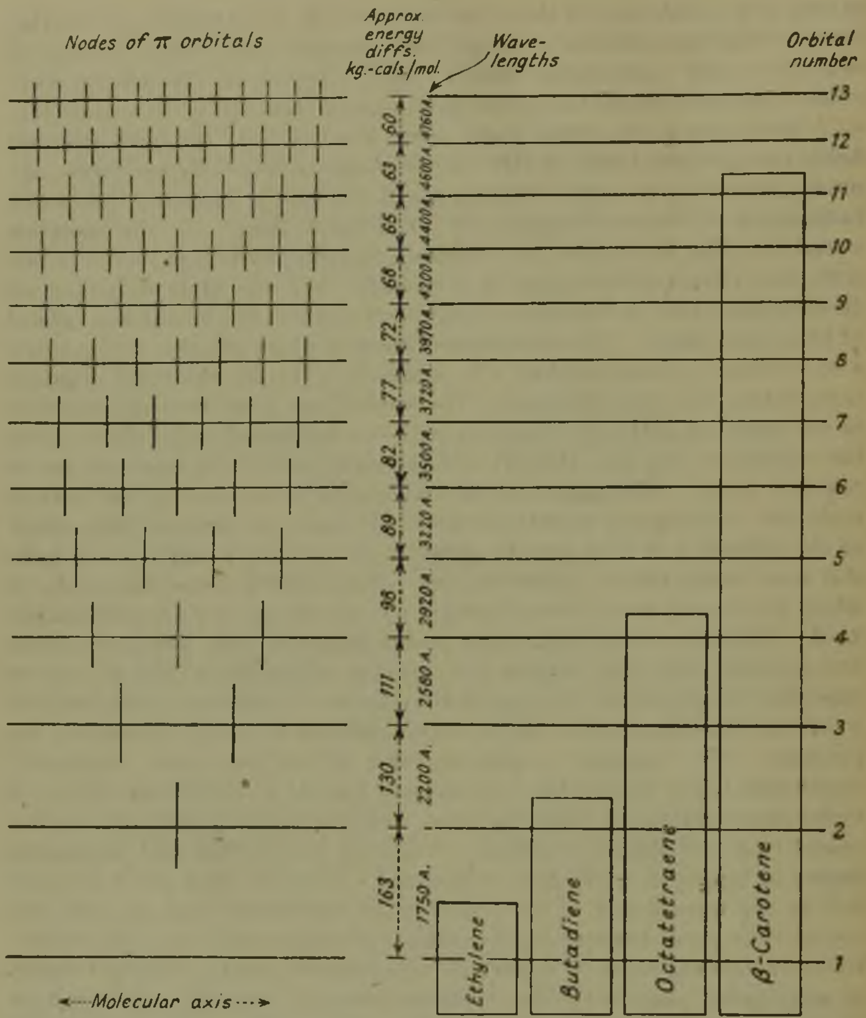
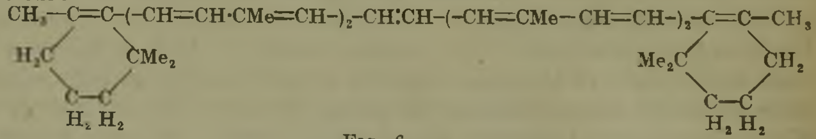
[4] See, *e.g.*, G. K. Rollefson and M. Burton, "Photochemistry," Prentice-Hall, N.Y., 1939, p. 248.

[5] *Rev. Mod. Physics*, 1942, **14**, 294.



Ethylene : $CH_2{=}CH_2$.
Butadiene : $CH_2{=}CH{-}CH{=}CH_2$.
Octatetraene : $CH_2{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH{\cdot}CH{=}CH_2$.
β-Carotene :



$$CH_3{-}C{=}C{-}({-}CH{=}CH{\cdot}CMe{=}CH{-})_2{-}CH{:}CH{-}({-}CH{=}CMe{-}CH{=}CH{-})_2{-}C{=}C{-}CH_3$$

FIG. 6.

π Molecular orbitals of conjugated polyenes.

Orbitals filled (*i.e.*, containing two electrons) in ground state enclosed in rectangles.

Passage of one electron from highest filled orbital to next higher orbital corresponds to longest-wave electronic absorption band of molecule (*e.g.*, ethylene absorption = 1750 A.; carotene absorption = 4600 A.).

of ultra-violet light, one electron passes to a higher orbital, 4, 5, or 6, which have extra nodal planes. It is clear that for light to be absorbed its plane

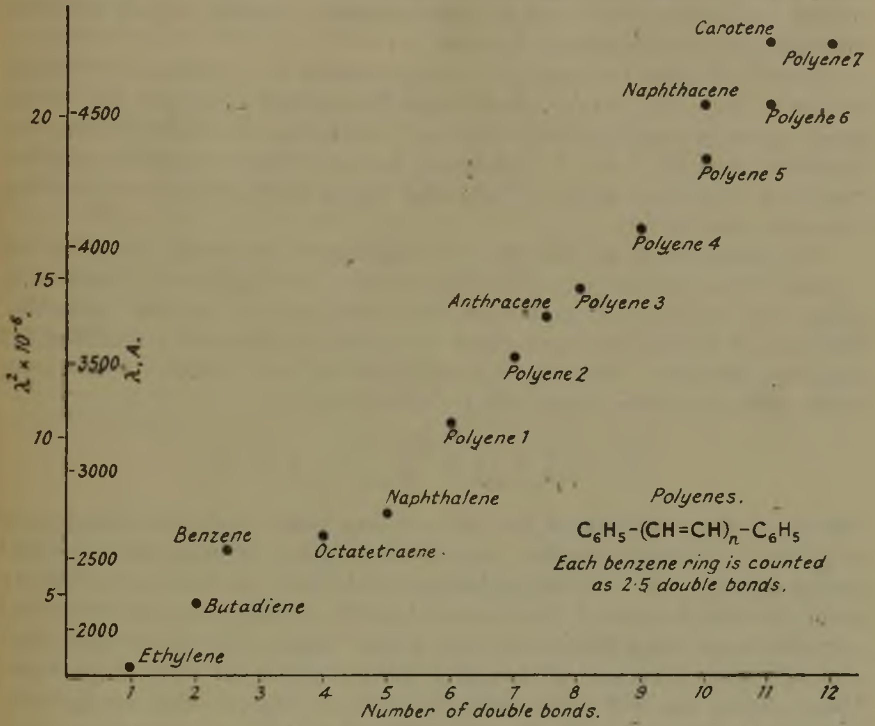


FIG. 7.

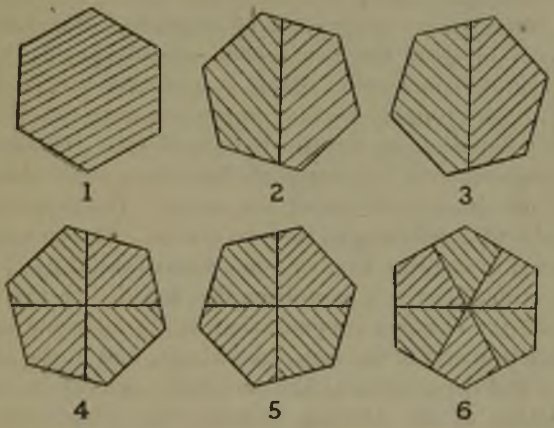


FIG. 8.

π Orbitals of benzene.

of polarisation must lie *in the plane of the ring*, since the new nodal planes developed on absorption are at right angles to this plane (cf. above). This effect is clearly shown in light-absorption (dichroism) and fluorescence-emission phenomena in crystalline anthracene and its solid solutions with naphthacene (tetracene), and in other aromatic crystals whose molecules are orientated approximately in layers.[6]

Orbitals 2—6 in benzene may be represented in a different but mathematically equivalent way; 2 and 3 may be regarded as formed by " wrapping one wave-length round the ring," clockwise or anti-clockwise, and similarly, orbitals 4 and 5 correspond to two waves wrapped round the ring, and 6 to three waves. The nodal planes at right angles to the ring rotate on this model.

The discussion so far has been of a qualitative geometric character. If " colour " is to be put on a quantitative basis, it is important to attempt to apply the algebraic equations of wave-mechanics to organic molecules. This cannot be done directly because of the intractable nature of differential equations of waves. The fundamental equation for a " wave " representing an electron in an atom is that due to Schrödinger :[7]

$$\frac{\partial^2\psi}{\partial x^2} + \frac{\partial^2\psi}{\partial y^2} + \frac{\partial^2\psi}{\partial z^2} + \frac{8\pi^2 m}{h}(E - V)\psi = 0$$

where ψ is the amplitude of the wave at any point whose co-ordinates are x, y, and z, m is the electron mass, and E and V its total and potential energy respectively. For the hydrogen atom V is of the form $-e^2/r$, where e is the electron charge and r its distance from the nucleus, and the differential equation can be rigorously solved, giving the " radius " of the hydrogen atom and its energy levels which are in complete agreement with observation. Other atoms, and still more, molecules, have V terms of more complicated type, so that the equation becomes insoluble. However, we may proceed roughly and tentatively along the following lines. Suppose we wish to calculate the longest-wave absorption of ethylene. We disregard all the single bonds and imagine the two carbon atoms placed at their known distance apart in the molecule. Each is assigned one electron in a $2p$ atomic orbital. Very roughly we may approximate to this orbital by using the Schrödinger equation as for the hydrogen atom, choosing a suitable value for the apparent nuclear charge of the carbon (since this is effectively diminished by the inner electrons of the atom). We thus have equations for ψ_A and ψ_B, A and B referring to the two atoms. The two atomic orbitals are now imagined to coalesce to give a molecular orbital ψ_M. Two different modes of approximating to ψ_M have been developed. In the first (Heitler–London method) the electron configuration in the molecule is taken as the sum of the configurations of the separated atoms, and in the second (Hund–Lennard-Jones–Mulliken method) the molecular orbital is computed as a linear combination of the atomic orbitals. The chief difference in the methods is that the former neglects, and the latter over-emphasises, the

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[6] K. S. Krishnan and P. K. Seshan, *Proc. Indian Acad. Sci.*, 1938, **8**, 487; *Rev. Mod. Physics*, 1942, **14**, 336.

[7] See, *e.g.*, H. S. Taylor, " Physical Chemistry," Vol. II, Macmillan, 1931.

possibility of both electrons in a link being simultaneously on one of the two atoms. Whichever method is adopted the calculation is then similar to that of the problem of finding the resultant frequencies of a vibrator composed of two coupled vibrators. A one-dimensional mechanical analogue is that of the frequencies of a system of two pendulums suspended from a horizontal piece of elastic stretched between two points. In this way approximate energies of the molecular orbitals are calculable from the atomic orbitals, and hence the wave-lengths of absorption bands. At present the approximate nature of such calculations does not recommend their direct use.[8] The methods of approximate treatment have been extended, however, to molecules with conjugated structures. The conjugated polyenes may be treated by more than one method to try to derive the experimental relationship of the linearity of (absorption wave-length)^2 and number of double bonds (Figs. 6 and 7).[5] The orbitals resemble the vibrations (fundamental and harmonics) of a stretched string, or the oscillations set up from side to side in a glass plate. The phenylpolyenes, $C_6H_5\cdot[CH{:}CH]_n\cdot C_6H_5$, or cyanine and related dyes containing the group

$$>\dot{N}=CH-[CH=CH]_n-N<$$

are somewhat more complicated because of the influence of the end groups, the orbitals resembling the oscillations in a plate sandwiched between two other different plates. The mathematical problem is to combine a number of vibrators (atomic orbitals) into one vibrating system to determine the resulting wave motion (molecular orbitals). Calculations along these lines are valuable for finding out how legitimate the approximations made are for the estimation of molecular orbitals.

The molecule of benzene has been very thoroughly treated by approximate methods, so its spectrum is now well understood.[9] Two modes of reaching solutions have been used. Attention is fixed only on the π orbitals round the carbon ring skeleton. In the first (L.C.A.O. = linear combination of atomic orbitals) method the lowest five or six molecular orbitals are constructed by linear combinations of six equal atomic p orbitals with nodes co-planar with the ring, and their energies computed. The accuracy of this depends on the degree of approximation to which the lengthy calculations are taken. The energy of the π electrons in the ground state of the molecule is then $2(O + \beta + \beta)$, the energy of the lowest orbital being O and that of the second and third β, each containing two electrons. A higher molecular level will have an energy $2(O + \beta) + \beta + \gamma$, where γ is the energy of a higher orbital into which an electron from the second or third orbital goes. These quantities are calculable (allowance being made for the effects of electron spins). The second method (V.B. = valency bond) divides the problem of passing from atomic to molecular orbitals into two

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[8] R. S. Mulliken, *J. Chem. Physics*, 1939, **7**, six papers; *Rep. Progr. Physics*, 1939, **6**, 212; *Rev. Mod. Physics*, 1942, **14**, 265.

[9] A. L. Sklar, *J. Chem. Physics*, 1937, **5**, 669; 1938, **6**, 645; 1939, **7**, 374; *Rev. Mod. Physics*, 1942, **14**, 232.

artificial halves.[10] Instead of attempting to evaluate the vibrations of a hexagonal assemblage of coupled *p* orbitals by direct combination, it proceeds by first coupling the *p* orbitals in pairs to form " valency " structures, and then " combines " all conceivable valency forms. All modes of writing the benzene molecule by " valency " symbols are set down, *viz.*, two Kekulé structures, three Dewar structures, and some " ionic " forms. The " energies " of these hypothetical molecules are calculated by simple combination of atomic *p* orbitals in pairs along the " double bonds." The energy levels of the " real " molecule are then approximated to as linear combinations of the valency structures, the coefficients of the linear combinations being derived by the use of a determinant just as if the problem were one of finding the resultant vibrations of a complex vibrator having several different frequencies operating together. This method, of " resonance between valency structures," enables the energy levels to be estimated if a parameter is known; and this can be derived by comparing the heats of hydrogenation of benzene and of *cyclo*hexadiene.

Calculations along these lines show that the first three higher energy levels of benzene are 35—70 kg.-cals./mole above the ground state, and therefore potentially capable of giving absorption bands in the visible region. Transitions to them, however, are " forbidden " because they are " triplet " levels, involving change of electron spin on excitation. The lowest " permitted " transition has a calculated energy change of 184 kg.-cals./mole, and is identified with the strong absorption band at 1800 A. in the far ultra-violet (= 153 kg.-cals./mole). Benzene also shows a feebler but long-known absorption band at 2600 A. This is now identified with the transition (expressed in symmetry notation) as $^1A_{1g}$ (ground state)$\rightarrow$ $^1B_{2u}$ (calc., 115 kg.-cals./mole). This transition is permitted only when simultaneous changes in vibrations of the atomic nuclei of symmetry type E_g^+ occur. The " partial band " structure of the 2600 A. benzene band due to changes of nuclear vibrations shows a series of equally-spaced partial bands due to the accompaniment of the electronic activation by the excitation of nuclear vibrations of the upper state, one quantum of E_g^+ type (lengthening and contraction of hexagon) and 0, 1, . . . quanta of A_{1g} type (symmetrical expansion and contraction; " breathing frequency "). A fainter series arises from molecules of the ground level already with one quantum of E_g^+ nuclear vibration passing to the upper state with 0, 1, quanta of A_{1g} type; the intensity of this series increases with rising temperature owing to the increasing population of vibrationally excited ground states. The frequency differences of the partial bands amount to 923 cm.$^{-1}$, the value of the nuclear " breathing frequency " A_{1g} of the upper state. The corresponding frequency of the ground state, obtained from the Raman spectrum, is 992 cm.$^{-1}$. No absorption occurs at the point corresponding to the electronic transition unaccompanied by the E_g^+ nuclear vibrational change except in solid benzene at low temperatures, where a feeble band can be recognised due to the partial removal of the quantum restrictions

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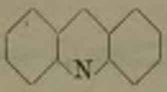
[10] See L. Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1940.

owing to the distortion of the molecule from perfect hexagonal symmetry by crystal forces. The allied hydrocarbons naphthalene, anthracene, naphthacene, and pentacene show similar equally-spaced vibration band structure in their near ultra-violet absorption. These doubtless also correspond to symmetrical expansion and contraction frequencies, which increase progressively with the molecular weight in this series of molecules. The electronic excitation here is polarised in the plane of the ring and in the direction of the greatest length of the molecule; other absorption bands at shorter wave-lengths probably arise from excitation polarised in other directions in the molecular plane. Studies of dichroism and of the polarisation of fluorescence are needed to throw light on these matters.

The replacement of carbon by oxygen or nitrogen in an organic compound does not greatly alter the energy values of orbitals of the type mentioned; hence little change occurs in the light absorption. Anthracene (I) and acridine (II), for example, have almost identical absorption bands, and only minor differences exist between those of such dyes as uranin, rhodamine, resorufin, (*iso*)quinoline red, safranine, and acriflavine, which ring the changes between C, O, and N in the 9, 10 positions of the anthracene structure. Aldehydes and ketones have a strong absorption region at 1900 A., corresponding to the absorption of ethylene, and due to a $\pi_u \rightarrow \pi_g$ orbital change in the C=O link. These substances also have a characteristic absorption band in the longer ultra-violet, about 3000 A., of low extinction coefficients, but having no counterpart in ethylenic molecules. The origin of this band must be sought in the oxygen atom. This has a shell of eight electrons; one pair in a σ_g orbital and one pair in a π_u orbital are shared with the carbon in the C=O link. The other four must be in the two remaining $2p$ orbitals of the oxygen, being in almost undisturbed atomic orbitals and taking little part in the chemical binding (two "lone pairs"). One of the orbitals of these "non-bonding" electrons will have its nodal plane normal to the link, and the other's nodal plane will be along the link and at right angles to the nodal plane of the π_u bonding orbital. It has recently been shown [11] that the weak absorption characteristic of carbonyl compounds at 3000 A. arises from an orbital change of one of these "non-bonding" electrons, an electron passing from the p orbital whose nodal plane is at right-angles to that of the π_u orbital to the excited π_g molecular orbital.

(I.)



(II.)

These orbitals are depicted in Fig. 9. The absorption at 3000 A. is accompanied by the passage of one electron from the hour-glass shaped orbital *d,d* to the unoccupied anti-bonding molecular orbital *b*. The absorption in the blue region by diazomethane and azomethane must be ascribed to similar orbital changes among the electrons in "non-bonding" atomic *p*

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[11] H. L. McMurry, *J. Chem. Physics*, 1941, **9**, 231.

orbitals of the nitrogen atom. The exact nature of the changes may be ascertainable if precise determinations of the polarisation directions of the absorbed light in oriented systems (crystals) prove possible. The light absorption of azobenzene in the blue appears to be of too long a wave-length to be analogous to the absorption of 1 : 2-diphenylethylene; here again, therefore, essentially non-binding *p* electrons on the nitrogen atoms probably play the chief rôle.

The organic dyes, by reason of their intense colour, variety of absorption in the visible region, and commercial importance, have long been in the forefront of older theories of colour and constitution. Before discussing them here a few general remarks may be made. For a substance to be notable for its " colour," it must show two features, absorption in the visible region of the spectrum, *i.e.*, at long wave-lengths, and high values of its extinction coefficients. In addition, the " width " of its absorption band or bands determines the selectivity of its colour. Absorption at long wave-lengths becomes possible when energy differences between molecular states are small enough; high conjugation brings this about, as already described for the polyenes, while changes in the orbitals of " non-bonding " electrons of nitrogen, oxygen, or sulphur may also be important (Figs. 6 and 9). High intensity of absorption, as measured by the integrated area

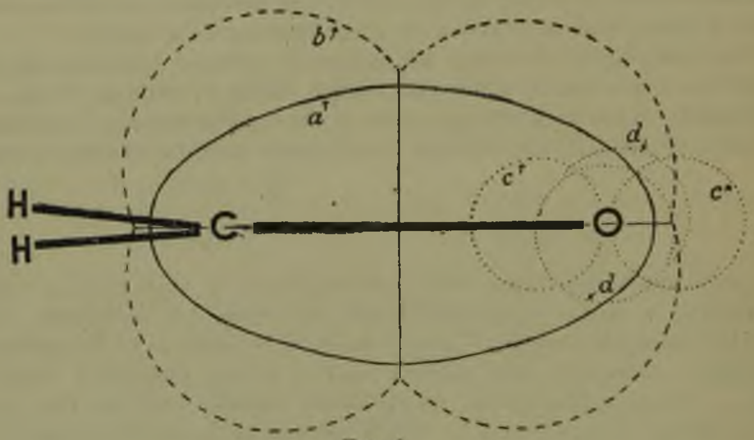


FIG. 9.

Orbitals of the carbonyl group C=O.

Thick lines = σ_g type orbitals (" single links ").

$a = \pi_u$ orbital characterised by a nodal plane in the H·CHO molecular plane. It contains two electrons in the ground state of the molecule.

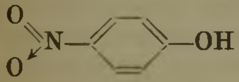
$b = \pi_g$ orbital characterised by one nodal plane in the molecular plane and another at right angles to the C–O link. No electrons occupy this orbital in the ground state.

c, c and *d, d* = non-bonding *p*-type orbitals of the oxygen atom, each containing two electrons in the ground state (" lone pairs "); *c, c* has a nodal plane at right angles to the C–O link and *d, d* one in the plane of the paper.

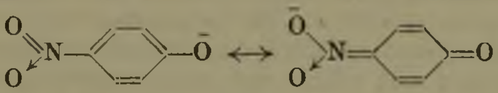
Excitation of one electron from orbital *a* to *b* occurs on light absorption near 1900 A., corresponding to the absorption of ethylene at 1750 A. The characteristic absorption of carbonyl compounds near 3000 A. causes one electron to pass from orbital *d* to *b*.

under the absorption curve (extinction coefficient–frequency) is determined by the "dipole transition moment," which is roughly the charge shift on absorption. Transitions are "forbidden" if this is zero, as is sometimes the case with molecules of high symmetry. Lowering of symmetry by molecular vibrations, and still more by the introduction of substituents, then allows of absorption increasing in strength with the loss of the symmetry. An example is found in the 2600 A. band of benzene, which is "allowed" by the co-operation of certain vibrations and is enhanced by the presence of $\cdot CH_3$, $\cdot OH$, $\cdot NH_2$, or $\cdot Cl$ in the molecule. Intensities of absorption in "forbidden" bands are also increased by the neighbourhood of a "permitted" transition.[12] In dyes the extinction coefficients are very large, corresponding to molecular orbital changes almost equivalent to the transfer of an electron across an interatomic distance, *i.e.*, to the development of "ionic" links in the molecule. Dyes also often have narrow absorption bands. Band width is determined by the slopes of the upper potential energy curve in the regions nearly vertically over the minimum of the lower curve (Franck–Condon principle). Owing to the flattening of the upper curve near its minimum a plot of extinction coefficient against frequency is always steeper on the red than on the blue side of the band.

Recent attempts to explain the "colour" of dyes have mostly been by the use of the "valency bond" mode of approach, on lines such as the following.[13] *p*-Nitrophenol itself is not "highly coloured"; the intense colour of its ion is attributed to the increased "resonance" between alternative electronic valency structures :

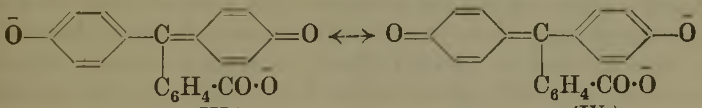


Un-ionised.

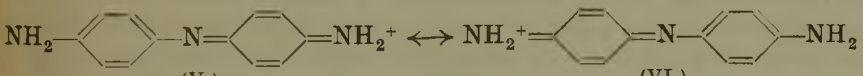


Ionised

The ions of phenolphthalein, (III) and (IV), of phenylene-blue, (V) and (VI), and of other xanthen, azine, cyanine, and triphenylmethane dyes may be



(III.) (IV.)



(V.) (VI.)

represented by approximate "mirror-image" valency structures whose "resonance" may be held to account for the colour. Perhaps this explanation by means of the artificial concepts of "valency" structures is a little too facile. The azo-dyes are not easily comprehended on this scheme. We do not yet clearly understand the details of the structure of the above

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[12] *Rep. Progr. Physics*, 1941, 8, 231.

[13] L. Pauling, *Proc. Nat. Acad. Sci.*, 1939, **25**, 577; L. C. S. Brooker, *Rev. Mod. Physics*, 1942, **14**, 275.

dye ions in terms of the orbitals occupied by the electrons in both ground and excited states. Where ionisation leads to intense absorption, as with *p*-nitrophenol, we believe it brings about a greater degree of " non-localisation " of electrons in the molecule with new orbitals of small energy differences. An important field awaits exploration by which semi-quantitative correlations may be established between such orbital changes and dye structure.

Recent work has enabled interesting deductions to be made about the geometrical nature of orbital changes when light is absorbed by dyes.[14] In crystalline anthracene and naphthacene the long-wave absorption is found to correspond to light polarised in the molecular plane and along the line of greatest width of the molecule, *i.e.*, the accompanying orbital change of the electrons involves the production of a new nodal plane normal to this line. The visible absorption band of the fluorescein (uranin) ion at 4950 A. also probably corresponds to light absorption polarised along the line of greatest width of the molecule. The emitted green fluorescence is also polarised along the same line. The same green fluorescence emitted when light is absorbed by an ultra-violet band of the uranin ion at 3125 A. is " negatively polarised," *i.e.*, its vibration direction is at right angles to that of the light absorbed. It thus appears that the 3125 A. band corresponds to light absorption polarised along the short axis of the molecule, and that a rapid internal rearrangement occurs to the excited level reached directly by absorption at 4950 A., followed by fluorescence. At high concentrations in water this dye (and many others) dimerises, and a new band appears at 4710 A. The polarisation direction of this band is unknown, but in the case of the dye ψ-*iso*cyanine, measurements on molecules oriented on mica show clearly that the corresponding dimer band is polarised along the short axis, and the monomer band along the wider molecule axis. At very high concentrations, ψ-*iso*cyanine forms a peculiar fibrillar colloid with a new very narrow absorption band. The fibrils appear to be formed by the stacking together of the flat molecules like piles of coins, and the new band is polarised along them and therefore normal to the molecular planes. We are thus enabled to identify three absorption regions with orbital changes in three mutually perpendicular directions in space in the molecule. In the fibrils the bonding forces must be of van der Waals type, possibly involving intercalated water molecules; yet the light absorption shows that the whole fibril behaves as a unit. This implies that there must be considerable overlap and intermolecular interaction between the π electron orbitals which bulge out from the molecular planes into the spaces between the molecular pile. This interaction is optically sufficient to be called an electronic linkage between the molecules, but it is certainly not strong enough to warrant representation by a " chemical " valency bond. Doubtless the coloured compounds formed in the solid state between certain flat molecules, as between 2 : 4-dinitrophenol and diphenylamine, also owe their

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[14] G. N. Lewis and M. Calvin, *Chem. Reviews*, 1939, **25**, 273; *Ann. Reports*, 1941, **38**, 23.

bands to the development of this somewhat elusive type of electronic interaction of the π orbitals.[15] The forces between the atomic planes of graphite, the peculiar behaviour of chlorophyll in plants where about 1000 molecules appear to be energetically coupled as a "photosynthetic unit,"[16] and the fluorescence of crystalline aromatic substances such as anthracene, chrysene, and diphenyl, which is so modified by minute traces of certain impurities such as naphthacene as to require the assumption of the free movement of electronic energy ("excitons") within the crystal, almost certainly owe their features to a similar loose coupling of π electrons.

E. J. B.

(*The "polarisation direction" of light referred to above means direction of electric vector, not the conventional perpendicular direction used by early physicists.*)

2. PHYSICAL CHEMISTRY OF COAL AND CARBONACEOUS MATERIALS.

The members of the coal series, together with their solid carbonisation products, appear to form a series of intermediate links between the lignins on the one hand and micro-crystalline graphite on the other. It is now becoming better understood that differences between the behaviour of one coal and another, instead of indicating specific constitutional differences, may be more concerned with the aggregational states of the coal substance. Although F. Fischer,[1] W. A. Bone,[2] R. V. Wheeler,[3] and others assumed specific constitutional differences between those portions of coal substance which could be extracted with the aid of solvents and those which resist extraction, yet the interpretation of their experimental results clearly requires revision in the light of new knowledge as to the solubility relations of high polymers.[4] M. W. Kiebler[5] has established a statistical correlation between the internal pressures of a series of solvents at a given temperature and their solvent powers for coal at that temperature.

The behaviour of coal in technical use appears to depend upon all aggregational magnitudes from the molecular to the macroscopic lump, and it will be clear from the foregoing that physical methods of examination are often more advantageously applied than chemical in its study.

Metamorphic Development of Coals.—Coals have been formed from decayed plant detrital matter which, becoming buried under other sedimentary deposits, has become indurated and passed through various stages of metamorphic development by the action of pressure and moderate heat. The

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[15] Cf. *J.*, 1943, 435.

[16] Ref. (4), p. 406.

[1] F. Fischer, H. Broche, and J. Strauch, *Brennstoff-Chem.*, 1925, **6**, 33.

[2] W. A. Bone, A. R. Pearson, and R. Quarendon, *Proc. Roy. Soc.*, 1924, **105**, *A*, 608; W. A. Bone, L. Horton, and L. J. Tei, *ibid.*, 1928, **120**, *A*, 523.

[3] C. Cockram and R. V. Wheeler, *J.*, 1927, 700; 1931, 854; J. Ashmore and R. V. Wheeler, *J.*, 1933, 1405.

[4] *Compt. rend. Trav. Lab. Carlsberg*, Sér. chim., 1938, **22**, 99; J. N. Brønsted and K. Volquartz, *Trans. Faraday Soc.*, 1939, **35**, 576.

[5] *Ind. Eng. Chem.*, 1940, **32**, 1389.

metamorphic process whereby the carbon content of the deposit is increased at the expense of the oxygen and hydrogen is usually described as increase of *rank*, or, more briefly, as " coalification."

Though the chemical changes which accompany " coalification " involve splitting off part of the carbon (as carbon dioxide, methane, or both[6]), much the same topochemical factors are likely to be operative as in the later stages of polymer-condensation reactions, and the *prima facie* resemblance of coals to solid substances of the polymer-condensation type has been remarked upon by several authors.[7, 8] It has been shown *inter alia* by W. Francis and R. V. Wheeler[9] that bright bituminous coals are readily converted by mild oxidation into alkali-soluble humic acids resembling those present in peat. It appears, therefore, that during at least some of the evolutionary stages of coalification the inner structure of the molecules has remained unaffected, the chemical change being confined to one or more of the peripheral groups.

Although in a general way the continuity of the series peat–lignite–bituminous coal–anthracite is widely recognised,[10] yet the first three members do not necessarily represent *successive* stages of development related to the age of the deposit; for instance, samples from the same seam in the South Wales coalfield showed a consistent increase of rank on traversing the seam from east to west.[11]

In the case just cited, the variation in rank appears directly related to the degree of pressure metamorphism (A. Brammall and J. G. C. Leech[12] have traced parallel metamorphic changes in the associated rocks), but other cases are known in which increase of rank has been brought about by quite other agencies. For instance, fusain, a petrological constituent of high carbon content, has been identified by E. McKenzie Taylor[13] in an Egyptian peat of geologically recent origin, and by C. A. Seyler[14] in a Greek lignite. McKenzie Taylor[15] has pointed out that during the initial rapid decay of the plant material the permeability to air and water of the overlying deposit is likely to have a determining influence on the nature of the product. He considers peat, lignite, and bituminous coals to be *alternative* end-products, formed, respectively, without a roof, under a roof which is freely permeable, and under a roof containing mainly sodium clays which cause alkaline and anaerobic conditions to be closely approached.

Coal Petrology.—It was pointed out by M. C. Stopes and by Stopes and

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[6] G. Hickling, *J. Inst. Fuel*, 1932, **5**, 326.

[7] H. E. Armstrong, *Chem. and Ind.*, 1929, **48**, 760.

[8] M. J. L. Megson and K. W. Pepper, *ibid.*, 1940, **59**, 247.

[9] *J.*, 1925, **127**, 112; see also H. H. Lowry, *J. Inst. Fuel*, 1937, **10**, 291.

[10] A. Raistrick and C. E. Marshall, "The Nature and Origin of Coal and Coal Seams," London, 1939, p. 223.

[11] Department of Scientific and Industrial Research, Physical and Chemical Survey of the National Coal Resources, No. 55.

[12] Medical Res. Council Spec. Report Series, No. 244 (1943), 125.

[13] *Fuel*, 1926, **5**, 195.

[14] *J. Inst. Fuel*, 1943, **16**, 134.

[15] *Fuel*, 1928, **7**, 230.

Wheeler [16] that coal seams generally contain visibly distinct bands of organic material conforming to types which they called respectively vitrain, clarain, durain, and fusain. Of these, the first two are " bright " coals, the third is dull and usually hard, and the fourth dull and friable (" mineral charcoal "). Although the refined methods of petrological analysis (referred to below) have thrown an entirely new light upon the inter-relation between these " banded " constituents, yet the distinction between bright and dull coals will be repeatedly referred to in what follows, and it is convenient here to emphasise some points relating to their physical and chemical structure. Durain differs somewhat in composition from the bright coal with which it it associated [17]; it has a different pore structure (rendering it more permeable to liquids, as Beeching [18] has shown) and does not swell when carbonised. According to R. Lessing,[19] its content of mineral matter is generally greater than that of bright coal. On the other hand, H. H. Lowry [20] emphasised that there was no evidence to show that the two classes contain distinct types of chemical compound, and their behaviour on the " micellar " scale of aggregational magnitudes appears not very different.[21] Fusain, which is much richer in carbon and poorer in hydrogen than the associated bright coal, is markedly more resistant to oxidation or hydrogenation.

It is now recognised that the visibly-distinct " banded " constituents of Stopes and Wheeler [16] represent *rock-types* rather than homogeneous petrological components. The pioneering work of C. A. Seyler [21a] on the optical properties of coals appears to indicate the existence of physically homogeneous components whose relation to the macroscopic lump can be compared with that of the constituent minerals in a piece of inorganic sedimentary rock. The main components derived from lignified plant tissue are limited in number (about ten), and each is characterised by its own optical reflectance coefficient. Since the reflectance coefficient is a function of the refractive index and the absorption coefficient, and it appears unlikely that a change in the one would just compensate for a change in the other, it may be presumed that each of these constituents would represent a physico-chemical entity defined as to composition and density of atomic packing, though minor variations in composition which leave the packing undisturbed are not, perhaps, precluded. Values for the refractive indices of some coals have been given by C. G. Cannon and W. H. George.[22]

" Bright " coal (the vitrain and clarain of Stopes and Wheeler) is found by Seyler to be markedly less heterogeneous than " dull " coal (durain and fusain), and generally contains one predominant constituent.[23]

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[16] *Proc. Roy. Soc.*, 1919, **90**, *B*, 470; *Fuel*, 1923, **2**, 5.

[17] F. V. Tideswell and R. V. Wheeler, *J.*, 1919, **115**, 619.

[18] R. Beeching, *J. Inst. Fuel*, 1938, **12**, 35; J. G. King and E. T. Wilkins, Conference on the Ultra-fine Structure of Coals and Cokes, London, 1943, p. 46.

[19] *Fuel*, 1922, **1**, 6.

[20] *J. Geology*, 1942, **50**, 357.

[21] C. G. Cannon, M. Griffith, and W. Hirst, Conference, etc., London, 1943, p. 131.

[21a] C. A. Seyler, *Proc. South Wales Inst. Eng.*, 1937, **53**, 254; *J. Inst. Fuel*, 1943, **16**, 134.

[22] Conference, etc., London, 1943, p. 290.

[23] C. A. Seyler, *ibid.*, p. 270.

Some Generalisations relating to Bright Coals.—Of the physical and chemical properties of coal substance, some (such as refractive index, opacity coefficient, " volatile " content, and thermal stability) increase or decrease monotonously with increase of rank, whilst others (notably calorific value, " pore " volume, and extent of inner surface) pass through maximum or minimum values. The maximum (or minimum) generally occurs at (or near) the range of *coking* coals, characterised by their ability to form macroscopic masses of maximum resistance to shattering impact when the crushed coal is carbonised in ovens.

The various empirical tests in use for the assessment of technical coking qualities have been reviewed by R. A. Mott [24] and subjected to a searching scrutiny by R. E. Brewer.[25]

Evidence of X-Ray Crystallography.—Since the original discovery by P. Debye and P. Scherrer [26] of the pseudo-graphitic nature of the " amorphous " carbons, numerous workers [27] have attempted to trace the changes in the aggregational state of carbonaceous materials by using X-ray methods. The basic assumption is made that the substances are essentially microcrystalline and that the size of the " crystallites " can be found from measurements of the degree of line broadening on the X-ray photographs. The rigorousness of this procedure has been questioned [28] on the grounds that other factors such as disorder and strain can contribute to the breadth of the diffraction lines, and the absolute values of crystallite size so obtained are therefore somewhat open to question. Moreover, as will appear later, in some cases, *e.g.*, lignin, it is by no means certain that we are dealing with " aromatic " crystallites at all.

Provided, however, that the X-ray measurements are made strictly comparative, the calculated " crystallite dimensions " can at the very worst be regarded as an index of the degree of order (in an otherwise disordered structure) and as such are of unquestionable value. There is remarkably good agreement between different workers [29] as to the size of the " crystallites," and notwithstanding the doubts expressed as to the interpretation of line-broadening data, it will be convenient to follow H. E. Blayden, J. Gibson, and H. L. Riley,[30] who have carried out the most extensive work on coals, cokes, and chars, in regarding the crystallites as structural entities.

In general, the model arrived at by the X-ray workers is that coal and its carbonised products consist largely of platelets in considerable disorder.

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[24] *Fuel*, 1942, **21**, 51.

[25] U.S. Bureau of Mines, Bulletin 445, 1942.

[26] *Physikal. Z.*, 1917, **18**, 291.

[27] U. Hofmann, *Ber.*, 1928, **61**, 435; I. D. Sedletzky and B. Brunowsky, *Kolloid-Z.*, 1935, **73**, 90; R. Jodl, *Brennstoff-Chem.*, 1941, **22**, 78, 157, 217, 256; H. L. Riley, *Trans. Inst. Min. Eng.*, 1938, **95**, 48.

[28] W. A. Wooster, Contribution to Discussion, Conference on Ultra-fine Structure of Coals and Cokes, London, 1943, p. 254.

[29] I. D. Sedletzky and B. Brunowsky, *Kolloid-Z.*, 1935, **73**, 90; G. Agde, H. Schürenberg, and R. Jodl, *Braunkohle*, Feb. 1942; H. E. Blayden, J. Gibson, and H. L. Riley, Conference, etc., London, 1943, p. 176.

[30] *Ibid.*, p. 176.

Each platelet consists of a small number of layer-planes, the carbon atoms in each layer-plane being arranged hexagonally (as in graphite) but the edge atoms being linked to peripheral groups containing the non-carbon atoms present, which limit the growth of the platelet. Of the numerous diffraction lines which characterise the prototype graphite structure, however, only two generally appear in the case of coals and their carbonisation products (carbonised below 1000°), these being related respectively to the interlayer spacing and the C–C bond distance. One reason for this (pointed out by B. E. Warren [31] for the carbon blacks) may be that the layer planes, although parallel, are arranged at random so that the carbon atoms do not satisfy the conditions either for a true hexagonal lattice, as in graphite,[32] or for a true rhombohedral lattice, as in the form of graphite described by H. Lipson and A. R. Stokes.[33] This type of " shuffle " disorder is called by Warren a " turbostratic " system.

The crystallographic changes accompanying coalification and carbonisation have been followed by Blayden, Gibson, and Riley; [30] using the line-broadening method, they find strong evidence of growth factors common to both processes. Two crystallite dimensions are quoted, the *a* (parallel to the layer planes) and the *c* (normal to the layer planes), and, in accordance with Warren's theory for turbostratic systems, a modified expression is used in the former case. The *c*/2 (interlayer) spacings found for coals, cokes, and chars by Blayden, Gibson, and Riley are all slightly greater than the value 3·35 A. for graphite. According to A. Taylor,[34] the *a* spacings derived from their data are normal (*ca.* 2·46 A.) when correction is made for the " cross-grating " effect by the method devised by B. E. Warren.[35] Both with the cokes and the coals the *a* dimension (platelet breadth) increases slowly with carbon content until *ca.* 90% of carbon is reached, whereupon it increases rapidly. The *c* dimension (platelet thickness) also increases with the carbon content up to *ca.* 92% of carbon, slowly at first and then more rapidly, but thereafter it decreases quite rapidly, indicating a more *disordered* stacking of the platelets as 100% of carbon is approached. Viewed in greater detail, the processes of coalification and carbonisation show less similarity, and it is clear that the nature of the starting material exercises an important influence which persists to very high temperatures. Thus they find that the chars prepared from pure cellulose, lignin, and glycine, whilst showing with increasing temperature of carbonisation (and therefore increasing carbon content) a growth in the *a* dimension similar to that with the carbonised products from bituminous coals, give *constant* values for the *c* dimension until 1400° is reached. At still higher temperatures, and consequently greater carbon content, growth in this direction occurs, slowly for cellulose and lignin and rapidly for glycine. Fusain, a friable charcoal-like constituent of coal seams, behaved similarly. Samples of peat and brown coal, on the

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[31] *J. Chem. Physics*, 1934, **2**, 551; J. Biscoe and B. E. Warren, *J. Appl. Physics*, 1943, **13**, 364.

[32] J. D. Bernal, *Proc. Roy. Soc.*, 1924, **106**, *A*, 749.

[33] *Nature*, 1942, **149**, 328.

[34] *Nature*, 1942, **150**, 462.

[35] *Physical Rev.*, 1942, **49**, 693.

other hand, showed marked growth in the *c* dimension at temperatures below 1000°, as well as pronounced increases in the *a* dimension.

Blayden, Gibson, and Riley [30] indicate other peculiarities in the powder photographs of bituminous coals and their carbonised products. The band indexed as 002 was found by them to be asymmetric and was therefore resolved into two symmetrical constituents. The additional band, previously reported by C. Mahadevan,[36] has been called by these workers the γ-band, and is attributed by them to large lamellar molecules held together by relatively weak intermolecular forces, the interlayer spacing being greater than 4 A. The γ-band is especially conspicuous with those constituents of bituminous coal which are soluble (or can be dispersed in) pyridine, *i.e.*, the γ-compounds of Wheeler.[3] It tends to disappear in the course of coalification or carbonisation and is absent in the high-rank anthracite.

The lamellæ responsible for the γ-band are considered to be only partly aromatic, and are therefore somewhat buckled, and the various groups attached to the periphery lead to less close packing. Carbonisation and coalification are both accompanied by aromatisation—the buckled lamellæ tend to flatten out and pack together more closely, and the γ-band to disappear. Blayden, Gibson, and Riley suggest that it is this process which causes a decided increase in the *c* dimension at temperatures up to 500°. These workers also distinguish between two types of turbostratic system, *mobile* and *rigid*, rigidity being a function of the amount of oxygen attached to the lamellæ.

In a general way these findings of the *X*-ray school of workers are in harmony with W. A. Bone's view[37] that coal substance is essentially aromatic, and that the degree of aromatisation increases as coalification or carbonisation proceeds. Not wholly satisfying in this connection, however, are the findings of I. D. Sedletzky and B. Brunowsky [38] and of R. Jodl [39] that the two characteristic *X*-ray diffraction lines (to which nearly all the above evidence refers) are also given by *lignin*, to which a cross-linked polymeric, and not a polynuclear aromatic structure is now assigned.[40] D. P. Riley [41] and also W. A. Wooster [28] have critically reviewed the crystallographic evidence which can unequivocally be derived from such diffuse *X*-ray photographs as are given by members of the coal series.

A principal characteristic of *X*-ray diffraction photographs of carbonaceous materials is the large amount of scattering at low angles, even when a well-collimated beam of monochromatic (crystal reflected) radiation is used. The effect, first observed by P. Krishnamurti [42] for carbon blacks, has been shown by A. Guinier [43] to be related to the scattering produced by gases, and originates in a random arrangement and loose packing of constituent particles. The method, which can be applied to give measurements of *true* particle

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[36] *Fuel*, 1930, **9**, 574.

[37] *J. Soc. Chem. Ind.*, 1935, **54**, 1048.

[38] *Kolloid-Z.*, 1935, **73**, 90.

[39] *Brennstoff-Chem.*, 1941, **22**, 78, 157, 217, 256.

[40] *Ann. Reports*, 1942.

[41] Contribution to Discussion, Conference, etc., London, 1943, p. 256.

[42] *Indian J. Physics*, 1930, **5**, 473.

[43] Thesis, Univ. of Paris, 1939.

size, has been used for the study of colloids of the dried-gel type. J. Biscoe and B. E. Warren[44] have used the technique to study carbon blacks, and show that the true particle or aggregate size is often many times greater than that of the crystallite itself as deduced from the usual line-broadening methods. Using a somewhat similar technique, D. P. Riley[45] has shown that, although the "gas" type scattering, indicative of large lacunæ in the packing of structural units, is present both with anthracite and with coals of low carbon content, yet the Welsh coals examined gave a diffuse *ring* indicative of the close-packing characteristic of liquids. From the mean diameter of the ring it is possible to calculate the mean particle size, and Riley thus finds evidence for the existence of structural units of 30—35 A. diameter in the coals in question. He also infers from the relative *absence* of diffuse scattering from Welsh coal samples known to contain minerals of the mica or kaolinite types (but in which the coal substance was nevertheless present in preponderant amount) that the degree of disorder of the organic matter is liable to become greatly reduced by intimate contact with inorganic layer structures. The identification by *X*-ray methods of the minerals so associated with Welsh coals has been carried out by G. Nagelschmidt and D. Hicks.[46]

"Fibre" type *X*-ray photographs, indicative of preferred orientation of structural units persisting throughout the specimen, have also been reported[47] in coals in which macrocrystalline inorganic matter was probably absent. These were in all cases anthracites, and it is perhaps significant that W. A. and N. Wooster[48], in the course of a survey of the diamagnetic properties of British coals, found unequivocal evidence on anisotropy only in anthracite. Seyler[23] has shown that the anthracites, unlike the bituminous coals of lower rank, generally show considerable optical anistropy.

Adsorption Studies.—Some of the earlier studies of coal properties are open to the objection that chemical "reactivity" was frequently confused with the accessibility of the surface to the attacking molecules. Coals are strong adsorbents, and J. I. Graham,[49] H. Briggs and R. P. Sinha,[50] and L. Coppens[51] have pointed out that the methane they contain is present (at least in greater part) in the form of adsorbed films. A systematic study of the adsorptive capacities of British coals has recently been made by M. Griffith and W. Hirst[52] with the object of correlating their behaviour on carbonisation and combustion with the extent of the inner surface. It appears that up to a point the process of "coalification" is associated with a loss of inner surface and is therefore analogous to the syneresis or ageing of a gel. In the range of coking coals, however, the inner surface passes through a minimum, and increases again as the coals become more anthracitic. These results are in harmony with the earlier findings of King and Wilkins[18] that the porosities of coals are minimal in the intermediate range, and increase

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[44] *J. Appl. Physics*, 1942, **13**, 364.
[45] Conference, etc., London, 1943, p. 232.
[46] *Ibid.*, p. 240.
[47] H. G. Turner and H. V. Anderson, *Fuel*, 1932, **11**, 262.
[48] Conference, etc., London, 1943, p. 322.
[49] *Trans. Inst. Min. Eng.*, 1937, **94**, 122.
[50] *Proc. Roy. Soc. Edinburgh*, 1935, **53**, 48.
[51] *Bull. Soc. chim. Belg.*, 1935, **44**, 215.
[52] Conference, etc., London, 1943, p. 80.

both with lower and with higher rank; also with D. P. Riley's[45] results for the low-angle scattering of X-rays which indicate that these coals of intermediate rank show the nearest approach to a close-packed liquid-type structure. In view of the "plastic" nature of coal substance (even at ordinary temperatures) it is reasonable to associate the large inner surface of the coals of high oxygen content with some form of oxygen cross-linking, and that of the anthracites with carbon–carbon cross links.

The chief interest of these adsorption studies lies in the attempts to devise techniques for the absolute evaluation of the surface area per unit weight of material, and to correlate with other methods of measurement the "micellar" sizes calculated therefrom. The term "micelle" is here used to denote regions impenetrable to the films of the adsorbed substances and without implications as to their degree of mutual detachment.

Evidence of a micellar structure for charcoal is to be found in the experiments of Bangham and his co-workers,[53] who measured the linear swelling of blocks of charcoal when exposed to gases and vapours, an effect originally discovered by F. T. Meehan.[54] It was found that the swelling is proportional, not to the quantity of gas or vapour adsorbed, but to the free energy decrement of the charcoal as calculated from Gibbs's equation :

$$m_1 \mathrm{d}G_1 + m_2 \mathrm{d}G_2 = 0$$

where m_1 is the weight of vapour adsorbed per g. of charcoal and G_1 and G_2 are the partial free energies per g. of adsorbate and adsorbent respectively.* This equation applies to any two-component system in equilibrium. Bangham, Fakhoury, and Mohamed [53] found justification, however, for identifying the free energy decrement ($-\Delta G_2$) of the adsorbent with the decrease of *surface* energy due to the formation of a film, for, in so doing, they obtained two-dimensional equations of state similar in all respects to those characteristic of adsorbed films on liquids. This point was tested further by measurements carried out with the series of lower alcohols as adsorbates. It was found that the films reproduced in detail the equations of state derived from the data of H. Cassel and F. Salditt [55] for the adsorption of the same vapours on *mercury*. Before discussing the bearing of these results on the evaluation of the surface areas of porous carbons, it will be convenient to mention their implications regarding the "micellar" structure of such carbons.

The direct proportionality between the swelling and the surface-energy lowering becomes intelligible if we regard the block of solid adsorbent as consisting of micelles adhering to each other by the action of surface forces tending to deform them by increasing the areas of contact between them. The micelles being supposed to behave elastically, it then becomes understandable that a mechanical force such as would arise from the film "pres-

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[53] D. H. Bangham and N. Fakhoury, *Proc. Roy. Soc.*, 1930, **130**, *A*, 81; *J.*, 1931, 1324; D. H. Bangham, N. Fakhoury, and A. F. Mohamed, *Proc. Roy. Soc.*, 1932, **138**, *A*, 162; 1934, **147**, *A*, 152; D. H. Bangham and R. I. Razouk, *ibid.*, 1938, **166**, *A*, 572.

[54] *Proc. Roy. Soc.*, 1927, **115**, *A*, 199.

[55] *Z. physikal. Chem.*, 1931, **155**, 321.

* It will be clear that with such material as charcoal the more usual equation in terms of partial *molar* free energies cannot be used.

sure" should cause a proportionate movement. Of interest in this connection are some measurements by J. Sandor[56] of the electrical resistivities at different temperatures of carbonised artefacts of compressed coal in a vacuum and in the presence of vapours. Sandor found that, whilst the presence of the vapour markedly increased the resistance at a given temperature, the energy barrier to the passage of electrons (shown by a linear plot of log resistance against $1/T$) remained unaffected.[57] Though capable of other interpretations, these results appear most readily explicable if we suppose that the resistance is determined by the areas of contact between the micelles, which are reduced by the presence of films.

On the basis of a model which makes no assumptions of critical importance as to the shape of the micelles (or their degree of detachment from their neighbours), but assuming that the swelling is resisted by elastic forces, D. H. Bangham and F. A. P. Maggs[58] have calculated from adsorption and swelling data, values for elastic constants of coals for comparison with directly measured values of Young's modulus. In view of the fact that these last were measured in compression, and that the elastic forces called into play are by no means identical in the two cases, the order of agreement found between the two sets of results must be considered satisfactory. Better agreement was found with monolith samples of coals than with compressed artefacts, prepared from powdered coal.

Absolute Evaluation of Surface.—The calculation of elastic constants from adsorption and swelling data involves only the free-energy changes relating to unit weight of adsorbent, so a comparison with the directly determined Young's modulus affords no independent evidence as to the adsorbing area. For the latter purpose, however, we have the comparison of the two-dimensional equations of state of the alcohol films on charcoal and on mercury. Directly comparable with the usual diagrams in which the product FA is plotted against F (F = surface-tension lowering; A = area per molecule) we have the "molecular expansion" graphs in which the expansion per g.-mol. is plotted against the expansion. By so adjusting the scale of the latter graphs as to obtain the best coincidence with Cassel and Salditt's data for the series of alcohols, Bangham[59] was able to assign values both to the area of the charcoal and to the constant λ of the equation $x = \lambda F$, where x is the percentage linear expansion of the charcoal. This method makes no assumption as to the films being unimolecular, and, in point of fact, Cassel and Salditt's data show clearly that on mercury they were not so. Both on mercury and on charcoal the orientation appears to have been of an unusual kind, and, in the case of each of the alcohols, two distinct types of film were recognisable. The graphs are reproduced in the figure. No evidence was found of thicker films being formed (for a given surface pressure) with the lengthening of the carbon chains.

Having thus established the adsorbing area of this charcoal, Bangham and his co-workers measured its heat of wetting in methyl alcohol, thus

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[56] Conference, etc., London, 1943, p. 342.

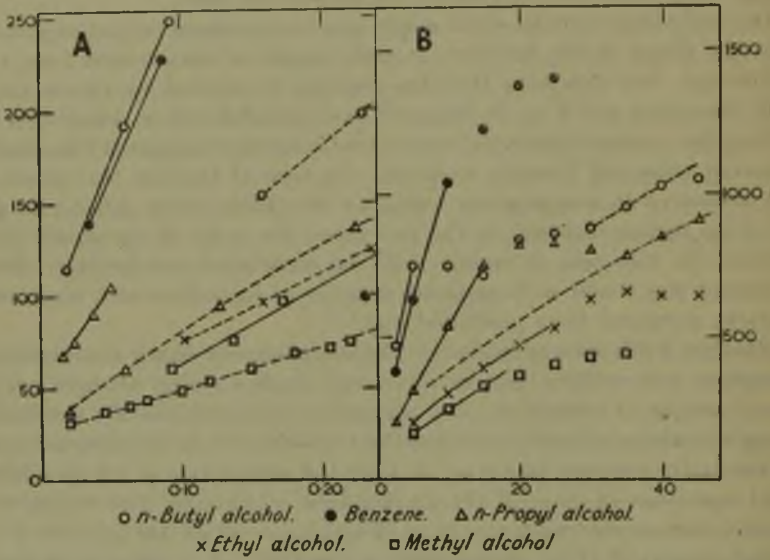
[57] J. Sandor, private communication.

[58] Conference, etc., London, 1943, p. 118.

[59] *Proc. Roy. Soc.*, 1934, **147**, *A*, 175.

enabling the heat of wetting per unit area of carbon to be calculated. This datum enables the surface area of an unknown carbon to be evaluated from its heat of wetting in this liquid. Further reference to heat of wetting methods for the evaluation of surface areas is made later.

The general similarity of behaviour as regards phase changes and equations of state of physically adsorbed films on solids and films on liquids has been emphasised by S. J. Gregg,[60] who points out that in favourable cases the monolayer capacities per g. of adsorbent can be calculated from the form of the *FA* curves even though the isotherm may not be of the Langmuir type.



A.—Molecular expansion curves for films adsorbed on charcoal (reduced to 0°).
Time-dependent observations relating to unstable films thus ————.
Time-independent observations relating to stable films thus – – – – – –.

B.—Abscissæ, values of *F*; ordinates, values of *FA* (*F* in dynes, *A* in Ångstroms) for films on mercury at 50° (Cassel and Salditt).

The further calculation of adsorbent areas, however, involves assumptions as to the molecular orientations and cross-sectional areas.

Method of Brunauer and Emmett.—A method now widely used in America for determining surface areas has been developed by S. Brunauer and P. H. Emmett.[61] In their attempts to estimate the surface area of an iron catalyst, these authors found that the adsorption of carbon monoxide at −183° was in part irreversible, and that although the reversibly adsorbed portion obeyed an isotherm very similar to that of nitrogen at this temperature, yet the total adsorption was nearly double this. They concluded that the innermost layer of carbon monoxide was irreversibly chemisorbed.

[60] *J.*, 1942, 697.

[61] *J. Amer. Chem. Soc.*, 1937, **59**, 1553; S. Brunauer, P. H. Emmett, and E. Teller, *ibid.*, 1938, **60**, 309.

Using this clue as to the monolayer capacity, they examined the isotherms of a number of other gases in order to decide how best to calculate the monolayer capacity in cases of physical adsorption where the isotherm is sigmoid, *i.e.*, concave to the pressure axis at low pressure and becoming convex as saturation is approached. The best agreement was obtained by considering the monolayer complete (and layer thickening to begin) at the point where the curve ceases to be concave to the pressure axis and the central linear portion begins.

In a later paper these authors attempted a theoretical justification of the procedure adopted, based upon the detailed balancing of the rates of condensation and evaporation in the different layers. If $s_0, s_1, s_2 \ldots s_i$ are the areas of adsorbent covered by $0, 1, 2 \ldots i$ layers, and $E_1, E_2, E_3 \ldots E_i$ the corresponding adsorption energies in these layers, then according to Brunauer and Emmett we should have

$$\begin{aligned} a_1 p s_0 &= b_1 s_1 e^{-E_1/RT} \\ a_2 p s_1 &= b_2 s_2 e^{-E_2/RT} \\ \vdots\quad &\quad\ \vdots \\ a_i p s_{i-1} &= b_i s_i e^{-E_i/RT} \end{aligned}$$

where a_1, a_2, etc., are constants relating the pressure p to the number of molecules arriving in a given area in a given time, and b_1, b_2, etc., are similar constants relating to their departure. The total area A is then given by of

$$A = \sum_{i=0}^{i=\infty} s_i$$

and the (averaged) number of layers n present at equilibrium by

$$n = \sum_{i=0}^{i=\infty} i s_i \Big/ \sum_{i=0}^{i=\infty} s_i$$

The simplifying assumption is now made that with the exception of E_1 all the adsorption energies E_2, E_3, etc., are equal to the normal energy of liquefaction of the vapour E_L; and that the terms a_2, b_2, a_3, b_3, etc., are such that their ratios a_2/b_2, a_3/b_3 . . ., etc., can be equated. The relations given can then be used to derive the equation

$$\frac{p}{n(p_0 - p)} = \frac{1}{c} + \frac{(c-1)p}{cp_0}$$

where c approximates to $e^{(E_1 - E_L)/RT}$ and p_0 is the saturation pressure. Mono-layer capacities are computed by plotting $p/y(p - p_0)$ against p/p_0, where y is the adsorption value at p.

The above equation reproduces fairly accurately the sigmoid isothermals up to pressures of *ca.* 0·35 of saturation, and the monolayer capacities calculated are in general agreement with those given by Brunauer and Emmett's earlier graphical method. The theory has been extended to cases where the width of the pores is so small as to set a limit to the layer thickening. Where there is space for only a single layer of molecules the isotherm reduces to an equation of the Langmuir form in which, however, the saturation pressure still appears.

The assumptions made by Brunauer and Emmett are clearly too crude for the equations to be of wide validity, or even of great theoretical significance. As S. J. Gregg [62] has pointed out, the appearance of the term p_0 in the case of gases above their critical temperature is wholly anomalous. No account is taken of orientational effects which give rise to phase changes in the innermost layer, or of the fact that, where supersaturated vapour can persist in contact with the solid, the adsorbed film must necessarily be of finite thickness and, as a phase, thermodynamically distinct from the bulk liquid.[63] Moreover, the assumption is made throughout that the whole of the exposed surface of an incomplete layer is available for condensation, without allowance being made for the disorder arising from the lateral mobility of the molecules. D. H. Bangham and N. Fakhoury [64] have given evidence that in a mobile monolayer the space available for the condensation of further molecules of *finite* size involves an exponential term which becomes important when the surface is only half covered. I. Langmuir, it may be recalled, derived his simple isotherm by assuming that adsorption occurred only at lattice points, these being sufficiently widely spaced for each to accommodate one adsorbed molecule.

Notwithstanding these drawbacks, Brunauer and Emmett's method undoubtedly gives consistent results which agree fairly well with independent estimates of the adsorbing surface in cases where these can be made. The assumption that the difference between the adsorption energy and the heat of liquefaction becomes small once the first monolayer is (more or less) complete appears well supported by independent experiment,[65, 66] though exceptions are known.[67] Outside the innermost layer, the difference between a thick adsorbed film (in equilibrium with vapour at a fraction of saturation) and the bulk liquid must relate to differences of entropy rather than of energy in the two states and requires a model capable of refined statistical treatment for its elucidation.

The fact that the typical sigmoid isotherms indicative of layer thickening are so much more commonly encountered with finely particulate than with porous solids has given rise to the suspicion that with the latter there is no room for their development. Although *prima facie* there is much evidence for this suggestion, yet the swelling of the solid must not be overlooked in this connection. Coal and cellulose appear to be examples of porous solids to which the generalisation does not apply. Sigmoid water isotherms for water adsorbed on charcoal are also of frequent occurrence.

Methods based on Heat-of-wetting Determination.—F. E. Bartell and Y. Fu[68] pointed out that, given the value of the wetting energy per unit surface,

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[62] Conference, etc., London, 1943, p. 110.

[63] D. H. Bangham and R. I. Razouk, *Trans. Faraday Soc.*, 1937, **33**, 1459; D. H. Bangham and Z. Saweris, *ibid.*, 1938, **34**, 554.

[64] *J.*, 1931, 1324.

[65] D. H. Bangham and S. Mosallam, *Proc. Roy. Soc.*, 1938, **166**, *A*, 558.

[66] S. J. Gregg, *J.*, 1943, 351.

[67] D. H. Bangham and R. I. Razouk, *Proc. Roy. Soc.*, 1938, **166**, *A*, 572.

[68] *Coll. Symp. Ann.*, 1930, **7**, 138.

a simple measurement of the heat of wetting of a porous solid would suffice to assess its surface. These authors failed to take into account the contribution of the adsorption energy to the wetting energy.[63] More recently, R. I. Razouk,[69] and M. Griffith and W. Hirst [52] have described routine techniques for the measurement of heats of wetting based on the method first used by H. C. Porter and O. C. Ralston.[70] Methyl alcohol was used by Bangham and his co-workers, since the energy changes per unit surface were believed to be known from the swelling experiments with charcoal, and an independent check on the adsorption data was available in A. S. Coolidge's [71] results.

There was also reason to believe that on account of its polar–non-polar character the wetting energy would be less susceptible to the presence or absence of polar oxygen-containing groups such as coals are liable to contain. F. A. P. Maggs,[72] who studied the adsorption of methyl alcohol and *n*-hexane by coal, was able to obtain values for the specific surface, both by Gregg's and by Emmett's method of calculation, in fair agreement with those calculated from the heats of wetting (in methyl alcohol) and the wetting energy per unit surface derived from Bangham's data for charcoal.

The choice of wetting liquid is, however, most important from the standpoint of the rapidity of heat liberation. With liquids of more complex molecular structure the heat liberation—even with a well-evacuated carbon—may continue for hours, and a fictitiously small value necessarily results in a calorimeter subject to heat losses. Methyl alcohol liberates the heat rapidly, and with this liquid good agreement was found by Griffith and Hirst [52] on checking their results with the aid of an ice calorimeter.

A method for measuring the areas of non-porous, finely particulate solids, which appears wholly unassailable from the theoretical standpoint, has been suggested by W. D. Harkins and G. Jura.[73] These authors first saturate the powder with the vapour of the wetting liquid, allow the heat of adsorption to become dissipated, and then measure the heat of immersional wetting. The choice of liquid is limited to those known to wet the solid completely (zero contact angle) in the presence of its saturated vapour, and the energy change per unit surface is equal to the total surface energy of the liquid. Unfortunately, the limitation is serious, for liquids of high surface tension (such as would give large energy release per unit interface) do not as a rule give complete wetting; moreover, the obligation to prove that the contact angle is really zero under these conditions may not easily be met.

Structural Changes in Coals and Carbons on Heating.—It is well known that chars heated above 800° (the actual temperature depends markedly on the starting material) lose much of their adsorptive capacity unless the heating is carried out in an atmosphere that promotes activation. With compressed artefacts the deactivation is often accompanied by pronounced shrinkage and increase of mechanical strength (elasticity) [58] and is probably

[69] *J. Physical Chem.*, 1941, **45,** 179.

[70] U.S. Bureau of Mines, Tech. Paper, No. 113.

[71] *J. Amer. Chem. Soc.*, 1924, **46**, 596.

[72] Conference, etc., London, 1943, p. 95.

[73] *J. Chem. Physics*, 1943.

due to some form of sintering. F. A. P. Maggs [74] has shown that the inner surface becomes progressively inaccessible to smaller and smaller molecules as the temperature is raised, and very long times are required for the establishment of equilibria.

G. Milner, E. Spivey, and J. W. Cobb [75] have traced the changes of density, adsorptive capacity, and reactivity (towards carbon dioxide at 900°) of a series of chars prepared from cellulose, sugar, bituminous coal, and anthracite on heating to different temperatures. These authors attribute adsorptive capacities of the products to the gasification of nuclear carbon by oxygen surviving in the char at temperatures above 500°.

Extensive studies of the structural changes accompanying the carbonisation of coals (in inert gas) have been made by C. G. Cannon, M. Griffith, and W. Hirst,[76] who used the heat of wetting in methyl alcohol as a measure of inner surface. Though some variation of the wetting energy per unit surface is not perhaps precluded, there are strong indications that such variations are not responsible for the highly characteristic curves obtained by these authors by plotting the heats of wetting against carbonisation temperature.

The curves for coals of low and intermediate rank pass through at least two maxima, high-rank coals through only one. A remarkable feature of the results is the evidence for the persistence of some of the inner surface even in coals cooled from temperatures at which they have "softened" and become nearly fluid. Moreover, the microcapillary structure characteristic of each kind of coal reappears in products heated beyond this softening stage. When the carbonisation is carried out in a pressure bomb the general features of the curves remain unchanged, though the maxima are displaced somewhat.

These results have this much in common with the *X*-ray line-broadening data of Blayden, Gibson, and Riley,[30] that in both cases there is evidence of the development, with rise of temperature, of a less open (or more ordered) structure, the process being interrupted at intermediate temperatures in the case of medium and lower-rank coals.

Elastic and Rheological Properties of Coals.—Studies of the elastic and rheological properties of coals are rendered difficult by the fact that natural monolith samples invariably contain internal cracks which greatly influence their behaviour. Exhaustive studies [77] of the size-distribution laws of broken coal (valid from the lump-sized material right down to sub-sieve sizes) have led to the conclusion that coal lumps are traversed by a random system of pre-existing cracks. These flaws are probably of a grosser order of magnitude than the micellar or micropore structure, though they may well owe their existence to unequal shrinkage consequent upon the desorption of volatile constituents.[78]

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[74] Conference, etc., London, 1943, p. 147.

[75] *J.*, 1943, 578.

[76] Conference, etc., London, 1943, p. 131.

[77] J. G. Bennett, *J. Inst. Fuel*, 1936—1937, **10**, 22, 105, 210; J. G. Bennett, R. L. Brown, and H. G. Crone, *ibid.*, 1940—1941, **14**, 111, 129, 135.

[78] D. H. Bangham, Conference, etc., London, 1943, p. 18.

In spite of these difficulties C. A. Seyler[79] was able to measure the viscosity coefficients of coals in the " softening " range of temperatures, and to show that their temperature dependence is of the usual Arrhenius-equation type. Apart from Seyler's results, there is a distinct paucity of data relating to the rheological properties of coals. In other fields, notably those relating to glasses[80] and polymerised resins,[81] such studies have yielded valuable information as to structure.

It has been demonstrated by R. G. H. B. Boddy[82] that coal substance can be made to flow at ordinary temperatures provided the deforming force be great enough. The response to small forces is almost entirely elastic. Boddy's method is to apply pressure to a field of coal particles enclosed between a microscope slide and the cover glass. The particles spread to form coherent films which can be made to flow into one another and are thin enough to be transparent. Even anthracites and fusains (with carbon contents ranging as high as 95%) can be made to show this effect. Discussing measurements (by Berkowitz) of the variation with temperature of the critical force which must be applied, Bangham[78] has pointed out that *prima facie* the deformation–force–temperature characteristics of coals are similar to those found by G. Tammann for the typical thermoplastic resin colophonium. It is inferred that very small structural units (perhaps identifiable with the " micelles ") are held together by secondary forces of the van der Waals type.

D. H. B.

3. THE APPLICATION OF ELECTROMETRIC METHODS TO THE STUDY OF SOME IONIC REACTIONS.

Electrometric methods afford a means by which chemical reactions can be followed as they actually take place in solution, and it is the purpose of the Reporter to give a résumé of the work which has been carried out along these lines. Certain branches, however, of electrometric investigations, such as those on heteropoly-acids and complex formation between metallic oxides and hydroxy-acids, are as yet incomplete, and have therefore been omitted.

Precipitation of Hydroxides.—Although metallic hydroxides are rarely precipitated in states which correspond with the formulæ usually ascribed to them, *e.g.*, $Al(OH)_3$, $Cu(OH)_2$ (the amounts of water always being higher than those indicated by the simple hydroxide formulæ), the conditions under which precipitation occurs are largely governed by the solubility products of the hydroxides when considered in terms of the ordinary hydroxide formulæ. This is all the more surprising when it is remembered that the base undergoing precipitation through the addition of alkali is generally associated with some unattacked metallic salt, in an amount which is too

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[79] D.S.I.R. Fuel Research Board, Annual Report, 1938, p. 65.

[80] E. Preston and E. Seddon, *J. Soc. Glass Tech.*, 1937, **21**, 123.

[81] R. F. Tuckett, *Trans. Faraday Soc.*, 1943, **39**, 158; R. N. Haward, *ibid.*, 1943, **39**, 267; L. R. G. Treloar, *ibid.*, 1943, **39**, 241; R. M. Barrer, *ibid.*, pp. 48, 59.

[82] *Nature*, Jan. 9, 1943; *Fuel*, 1943, **22**, 56; Conference, etc., London; 1943, p. 336.

great to be attributed to entrainment. Very often the proportion of unattacked salt associated with the base depends on the manner in which the alkali is added, and whether the mother-liquor is being agitated during the addition of the alkali. Thus, if alkali is slowly added to a copper sulphate solution with thorough stirring, a pale blue, heavy, finely divided precipitate is obtained and precipitation is complete immediately 1·5 equivs. of alkali have been added per mol. of copper sulphate.[1] This is also true of copper chloride and bromide solutions, and phase-rule work has proved that definite basic salts are produced, *viz.*, $3CuO,CuSO_4,4H_2O$; $3CuO,CuCl_2,4H_2O$.[2] If care is not taken to ensure thorough mixing and the precipitant is added rapidly, a green gelatinous precipitate is formed which is more basic than the foregoing salts, as may be seen from the fact that precipitation does not become complete until about 1·8 equivs. of alkali have been added. Provided the amount of alkali added is not more than 1·5 equivs., the gelatinous precipitate on agitation with the mother-liquor gradually becomes converted into the pale blue, less basic salt. Copper hydroxide, $Cu(OH)_2$, as such, is only precipitated under special conditions.[3]

Hence, the conditions which must be established before the precipitation of a hydroxide or basic salt can ensue are to be found in the solubility product of the hydroxide, L, and the ionic product of water, K_w; *e.g.*, for the precipitation of a basic salt containing hydrated alumina, as $L = [\mathrm{Al}^{\cdot\cdot\cdot}][\mathrm{OH}']^3$ and $K_w = [\mathrm{H}^{\cdot}][\mathrm{OH}']$, the hydrogen-ion concentration at which precipitation occurs will be given by $[\mathrm{H}^{\cdot}] = K_w \cdot \sqrt[3]{[\mathrm{Al}^{\cdot\cdot\cdot}]/L}$; or generally, for the hydroxide of a metal of valency, z,

$$[\mathrm{H}^{\cdot}] = K_w([\mathrm{M}^{\cdot\cdot\cdot z}]/L)^{1/z}$$

For ordinary analytical procedures, the concentrations of salts employed do not vary over a wide range, *i.e.*, $[\mathrm{M}^{\cdot\cdot\cdot z}]$ is confined to a narrow range of concentration, usually between 10^{-1} and 10^{-2} M. Hence, the hydrogen-ion concentration set up during precipitation will be constant within a narrow pH range, and this will be particularly the case with salts of ter- and quadrivalent metals. With bi- and uni-valent metal salts the hydroxide precipitation pH range is somewhat wider. For instance, the precipitation range of silver oxide from 0·1M-silver nitrate with 0·2N-sodium hydroxide is from pH 7·48 (at 10% precipitation) to pH 8·56 (at 90%), whereas from 0·025M-silver nitrate the corresponding range is pH 7·97 to 9·04.[4] Incidentally, silver oxide is exceptional in that it is not precipitated as a basic salt. The progressive addition of alkali to solutions of zinc sulphate causes precipitation to be complete with 1·53 equivs. of sodium hydroxide, the basic sulphate thus being approximately $ZnSO_4,3Zn(OH)_2$. When 0·1—

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[1] H. T. S. Britton, *J.*, 1925, **127**, 2152; H. T. S. Britton and F. H. Meek, *J.*, 1932, 184.

[2] H. T. S. Britton, *J.*, 1925, **127**, 2796; 1926, 2868.

[3] H. M. Dawson, *J.*, 1909, **95**, 370.

[4] H. T. S. Britton and R. A. Robinson, *Trans. Faraday Soc.*, 1932, **28**, 531; see also I. M. Kolthoff and T. Kameda, *J. Amer. Chem. Soc.*, 1931, **53**, 832; M. Prytz, *Z. anorg. Chem.*, 1931, **200**, 133; W. Feitknecht, *Helv. Chim. Acta*, 1933, **16**, 1302.

1·4 equivs. of sodium hydroxide are added to 0·025M-zinc sulphate the pH varies from 6·77 to 7·71, whereas from 0·0025M-sulphate the pH range is somewhat higher, *viz.*, 7·36—8·11. From zinc chloride solutions the precipitate is only slightly basic, but the pH ranges for 0·1—1·8 equivs. of sodium hydroxide from 0·025M- and 0·0025M-zinc chloride are respectively pH 7·13—8·15 and 7·43—8·42. Here again, the effect of the smaller zinc salt concentration is to raise the pH at which precipitation occurs.

In the case of precipitations from zinc salt solutions the anion is thus seen to have an appreciable effect on the pH range, and this is also true of cadmium and mercuric salt solutions; with other metal salts the anion has little effect on the pH range of precipitation, although anions have often a definite influence on the type of precipitate obtained, chloride in particular tending to produce colloidal solutions which coagulate when the greater part of the necessary alkali has been added.

With solutions of tervalent (*e.g.*, aluminium) and quadrivalent (*e.g.*, thorium) metal salt solutions, concentration of the salt has very little effect on the pH range in which precipitation ensues.

The following table [5] gives the pH values, determined electrometrically, at which hydroxides begin to precipitate from solutions of concentrations about 0·02M.

Kation, etc.	pH.	Kation, etc.	pH.	Kation, etc.	pH.
$Mg^{\cdot\cdot}$	10·5	$Co^{\cdot\cdot}$	6·8	$Al^{\cdot\cdot}$	4·1
$Mn^{\cdot\cdot}$	8·5—8·8	$CdSO_4$	6·7	$Th^{\cdot\cdot\cdot\cdot}$	3·5
$La^{\cdot\cdot\cdot}$	8·4	$Ni^{\cdot\cdot\cdot}$	6·7	$In^{\cdot\cdot\cdot}$	3·4
$Ag^{\cdot}$	7·5—8·0	$Yb^{\cdot\cdot\cdot}$	6·2	$Hg_2^{\cdot\cdot}$	3·0
$CdCl_2$	7·6	$Pb^{\cdot\cdot}$	6·0	$Ce^{\cdot\cdot\cdot\cdot}$	2·7
$Ce^{\cdot\cdot\cdot}$	7·4	$Be^{\cdot\cdot}$	5·7	$Hg(NO_3)_2$	2
$HgCl_2$	7·3	$Fe^{\cdot\cdot}$	5·5	$Sn^{\cdot\cdot\cdot\cdot}$	2
$Pr^{\cdot\cdot\cdot}$	7·1	$Cu^{\cdot\cdot}$	5·3	$Sn^{\cdot\cdot}$	2
$Nd^{\cdot\cdot\cdot}$	7·0	$Cr^{\cdot\cdot\cdot}$	5·3	$Zr^{\cdot\cdot\cdot\cdot}$	2
$Zn^{\cdot\cdot}$	6·8—7·1	$VO^{\cdot\cdot}$	4·3	$Fe^{\cdot\cdot\cdot}$	2
$Sa^{\cdot\cdot}$	6·8	$VO_2^{\cdot\cdot}$	4·2	$Ti^{\cdot\cdot\cdot\cdot}$	2

Soluble Basic Salts and Basic Ions.—When alkali is progressively added to solutions of most metallic salts, the first few drops cause a rapid rise in pH to the appropriate hydroxide precipitation pH, whereat the precipitate immediately begins to separate. With salts of very weak bases, however, precipitation does not usually begin until an appreciable amount of alkali has been added; for instance, *ca.* 1·5 equivs. of sodium hydroxide have to be added to a zirconium chloride solution before opalescence begins to appear, which subsequently increases in intensity until 3·8 equivs. are added, coagulation then suddenly occurring.[5] Incidentally, the change in pH is very gradual and there is no evidence of the existence of either $ZrOCl_2$ or zirconyl ions, $ZrO^{\cdot\cdot}$, in solution, such as E. Chauvenet [6] states he obtained by a parallel conductometric titration.

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[5] H. T. S. Britton, *J.*, 1925, **127**, 2110, 2120, 2142, 2148; H. T. S. Britton and A. E. Young, *J.*, 1932, 2467; H. T. S. Britton and R. A. Robinson, *loc. cit.*; J. A. C. Bowles and H. M. Partridge, *Ind. Eng. Chem.*, *Anal.*, 1937, **9**, 124; T. Moeller, *J. Amer. Chem. Soc.*, 1941, **63**, 2625.

[6] *Ann. Chim. Phys.*, 1920, **13**, 82.

Towards several reagents, zirconium sulphate solutions react quite differently from either the chloride or nitrate, so much so that R. Ruer[7] postulated the existence of a complex zirconium sulphuric acid. When sodium hydroxide is added to zirconium sulphate solution, the precipitation of a basic salt, $ZrO_2,0{\cdot}5SO_3,xH_2O$ begins immediately and the change in pH thereafter, measured with the hydrogen electrode, reveals that this basic salt must have existed in the original sulphate solution in equilibrium with 1·5 equivs. of sulphuric acid which had been set free by hydrolysis. Presumably, some kind of equilibrium must exist between the basic salt and the acid.[5]

Quinhydrone and conductometric alkali titration curves of solutions of uranyl chloride in hydrochloric acid show that very little combination of uranic hydroxide with hydrochloric acid occurs beyond the stage indicated by the salt, UO_2Cl_2, and the curves provide good reason to believe that a basic ion approximating closely to the so-called uranyl ion $UO_2^{\cdot\cdot}$ does exist in solution. Vanadium pentoxide dissolves in solutions of acids to different extents which are determined by the strengths of the acids, and glass-electrode pH measurements have shown that the salts formed are best represented by VO_2Cl, thus giving $VO_2^{\cdot}$ ions in strong acid solutions.[8] Hydrogen-electrode and conductometric titration curves of vanadium tetroxide in sulphuric and hydrochloric acid solutions show that neither of these acids combines beyond the stage $VOSO_4$ and $VOCl_2$, and the inflexions (and breaks) then produced point to the individuality of these vanadyl salts and therefore to the vanadyl ion, $VO^{\cdot\cdot}$.[9]

The violet chromium sulphate and chloride and chrome alum give solutions which are appreciably acidic, pH *ca.* 3; on treatment with alkali, they change from violet to green and undergo a linear increase in pH until the hydroxide precipitation pH (5·3) is reached. This occurs when exactly 1 equiv. of alkali has reacted. Chromium hydroxide being regarded as a triacidic base, it follows that the first hydroxyl group behaves, though anomalously, as a distinctly weaker base than the remaining two hydroxyl groups, and this disparity leads to the formation of soluble basic salts, $Cr(OH)SO_4$ and $Cr(OH)Cl_2$.[5] It should be stated that boiling of solutions of the normal violet salts produces enhanced hydrolysis and a change in colour from violet to green, and on treatment with alkali precipitation does not begin until 1·2—1·4 equivs. have been added. The pH curve corresponding to this stage suggests that the act of boiling must cause much of the first equivalent of loosely combined acid to be liberated and the soluble basic salts, $Cr(OH)SO_4$ and $Cr(OH)Cl_2$, to decompose still further.[10]

Beryllium hydroxide as a base is somewhat similar to chromium hydroxide in that one hydroxide group is much weaker than the other, and that the neutralisation of the weaker hydroxide by strong acids yields soluble basic salts of the type $BeOH(SO_4)_{0{\cdot}5}$ and $Be(OH)R$ ($R = Cl, Br, I$). This is

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[7] *Z. anorg. Chem.*, 1904, **42**, 85. [8] H. T. S. Britton and G. Welford, *J.*, 1940, 875.

[9] H. T. S. Britton, *J.*, 1934, 1842; H. T. S. Britton and G. Welford, *J.*, 1940, 758.

[10] H. T. S. Britton, "Hydrogen Ions," 3rd Edn., 1942, Vol. 2, p. 229.

reflected in the hydrogen-electrode alkali titration curves of beryllium sulphate,[5] and chloride, bromide, and iodide. During the addition of the first equivalent of sodium hydroxide the solutions remain perfectly clear, and the hydroxide does not begin to separate until just after the equivalent has been added. Moreover, the change in pH is similar to that normally given when a strong base hydrolyses the salt of a weak organic acid. From the pH values set up when 0·5 equiv. of sodium hydroxide reacts with solutions of beryllium sulphate, chloride, bromide, and iodide over an extensive range of concentrations, (Miss) M. Prytz [11] has calculated the equilibrium constants referring to the following systems :

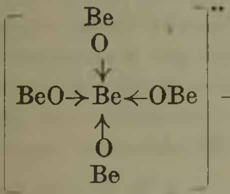
$$\text{(a)}\quad Be^{\cdot\cdot} + H_2O \rightleftharpoons BeOH^{\cdot} + H^{\cdot}$$

and

$$\text{(b)}\quad \textit{either}\ 2Be^{\cdot\cdot} + 2H_2O \rightleftharpoons Be_2(OH)_2^{\cdot\cdot} + 2H^{\cdot}$$
$$\textit{or}\quad 2Be^{\cdot\cdot} + H_2O \rightleftharpoons Be_2O^{\cdot\cdot} + 2H^{\cdot}$$

The calculations based on (b) led to exceptional constancy of the equilibrium constant : for solutions of the four beryllium salts in the order named, $K = 1{\cdot}4$, 1·7, 5·9, and $4{\cdot}4 \times 10^{-7}$.

Beryllium hydroxide is soluble in beryllium sulphate solutions. The solubility data of C. L. Parsons [12] show that, in solutions of beryllium sulphate ranging from 0·15 to 1·14M, the amounts of beryllia which dissolve correspond with the formation of soluble basic salts, which, probably through the non-attainment of true equilibria, vary irregularly from $Be(OH)_{0{\cdot}98}(SO_4)_{0{\cdot}51}$ to $Be(OH)_{0{\cdot}76}(SO_4)_{0{\cdot}62}$, with an average composition corresponding to $Be(OH)_{0{\cdot}90}(SO_4)_{0{\cdot}55}$. N. V. Sidgwick and N. B. Lewis [13] found that solutions already saturated with respect to beryllium sulphate were able to dissolve beryllium hydroxide, and as a result the solubility of beryllium sulphate itself was also increased. This is also true of beryllium selenate solutions. The solid phases in equilibrium with these basic salt solutions, however, were respectively $BeSO_4,4H_2O$ and $BeSeO_4,4H_2O$. Calculation of these workers' data reveals that their most concentrated liquid phases contained beryllium sulphate and beryllia in the proportion required by $Be(OH)_{0{\cdot}92}(SO_4)_{0{\cdot}54}$ and $Be(OH)_{0{\cdot}70}(SeO_4)_{0{\cdot}65}$, but they attributed the increased solubility of beryllium sulphate (and selenate) to the amounts of beryllia which made these increases possible and found that there were roughly 4 mols. of beryllia per mol. of sulphate (or selenate) increase in solubility. They therefore postulated that the excess of sulphate (or selenate) over that demanded by the normal solubility must have been in the form of salts :



$+ SO_4''$ (*or* $+ SeO_4''$)

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[11] *Z. anorg. Chem.*, 1929, **180**, 355; 1931, **197**, 103.

[12] *J. Amer. Chem. Soc.*, 1904, **26**, 1433.

[13] *J.*, 1926, 1287.

In other words, the liquid phases must have contained *two* solutes, the normal salt being in the greater quantity and the 4 co-ordinated "berylated" beryllium salt in the smaller. Seeing that normal beryllium salts present in solutions which are far from saturated will cause approximately an equimolecular amount of beryllium hydroxide to dissolve, this argument is obviously untenable. C. L. Parsons, W. O. Robinson, and C. T. Fuller [14] observed that when beryllium hydroxide dissolves in a solution of beryllium sulphate the equivalent conductivity is slightly decreased and the freezing point is slightly raised. According to Sidgwick and Lewis the dissolution of beryllium hydroxide in beryllium chloride solutions has a similar effect on the conductivity. This reduced conductivity might possibly be ascribed to the lower ionic mobility of the heavier kation, $Be_2O^{\cdot\cdot}$, and the smaller ionisation of the soluble basic salt, $Be_2(OH)_2SO_4$ or Be_2O,SO_4.

Amphoteric Hydroxides.—Of the metallic hydroxides which dissolve in alkali solutions only three, *viz.*, $Al(OH)_3$, Au_2O_3, and V_2O_4, of the many so far investigated function as acids which are sufficiently strong for their neutralisation with sodium hydroxide, and their consequent dissolution in alkaline solution, to be reflected in pH and conductometric titration curves.

If solutions of either aluminium sulphate or chloride are titrated with the hydroxide of sodium,[5] calcium, strontium or barium,[15] maximum precipitation is obtained when 3 equivs. (per 1 Al) of base are added, whereas during the addition of the fourth equiv. the aluminium gradually dissolves, the pH increasing from 8 to 10·5. Conductometric titration also shows that salt formation occurs with the fourth equiv. of alkali.[16] The soluble aluminates thereby formed are $NaAlO_2$ and $M(AlO_2)_2$, M being Ca, Sr, Ba.

If sodium hydroxide is added to a dilute solution of gold chloride, no precipitation of auric oxide may occur, but pH measurements, made with the glass electrode,[17] show that the auric chloride is being decomposed to form an apparently soluble basic chloride, probably existing in the form of a complex basic anion. When about two-thirds of the auric chloride have been decomposed the solution immediately becomes alkaline. After addition of more alkali the basic complex decomposes completely on standing, as shown by the fall in pH (8 to 5) and the solution does not again begin to contain free alkali until after 4 equivs. of alkali (per mol. of $AuCl_3$) have been added which is indicated by a well-defined inflexion in the pH curve, thereby showing that $NaAuO_2$ is then formed in the solution.

On adding sodium hydroxide to the blue solution of vanadyl chloride, $VOCl_2$, or sulphate, $VOSO_4$, a greyish-white precipitate is formed at pH 4·3, which turns dark brown. If the alkali is added rapidly the precipitate will dissolve readily in excess of alkali to give a clear red solution of sodium vanadite, $Na_2O,2V_2O_4$, but if it is added slowly, the combination with the excess of alkali is comparatively slow, as may be seen from the hydrogen-electrode curves. Back-titration of the alkaline vanadite solution with

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[14] *J. Physical Chem.*, 1907, **11**, 651.

[15] H. T. S. Britton, *J.*, 1927, 422.

[16] R. A. Robinson and H. T. S. Britton, *J.*, 1931, 2817.

[17] H. T. S. Britton and E. N. Dodd, *J.*, 1932, 2464.

hydrochloric acid, the hydrogen electrode being used, showed that the vanadite has the composition, $Na_2V_4O_9$, and that it is decomposed within the pH range 9—6.

The Action of Alkali on Solutions of Mercuric and Cadmium Salts in the Absence and Presence of Alkali Salts.—Solutions of mercuric nitrate, sulphate, and perchlorate have low pH values and high conductivities, and E.M.F. data show that the concentrations of mercuric ions are of the same order as the respective salt concentrations. These salts are thus typical of salts formed from a weak base and strong acids. Glass-electrode titrations [18] with alkali show that mercuric oxide begins to precipitate at very low pH values, *ca.* pH 2. This is in accord with the small solubility product of mercuric hydroxide, *viz.*, $[Hg^{\cdot\cdot}][OH']^2 = 10^{-26}$.

Mercuric chloride, bromide, cyanide, nitrite, and acetate in solution not only give rise to exceedingly small concentrations of mercuric ions and electrical conductivities but undergo very little hydrolysis; in fact, the small concentrations of hydrolysed hydrochloric acid account almost completely for the electrical conductivities of solutions of mercuric chloride.[18] In consequence, as their mercuric-ion concentrations are extremely low, much greater hydroxyl-ion concentrations have to be established before precipitation on adding sodium hydroxide begins. For instance, from approximately 0·01M-solutions of mercuric acetate, nitrite, chloride, and bromide, the respective precipitation pH ranges are 4·2—6·6, 4·0—7·2, 7·1—9·0, and 7·5—10·4. In the case of mercuric cyanide no precipitate is formed with 0·1N-sodium hydroxide even though a pH of above 12 is established.

If alkali salts of the respective acid be included in the solution of the mercuric salt, *e.g.*, potassium chloride with mercuric chloride, precipitation does not take place until considerably higher pH values are reached on adding alkali. The precise pH value is determined by (i) the equilibrium $HgCl_4'' \rightleftharpoons Hg^{\cdot\cdot} + 4Cl'$ and (ii) the solubility product, $[Hg^{\cdot\cdot}][OH']^2$. The mercuric-ion concentration is controlled by the mass-law constant of (i), *viz.*, $10^{-16\cdot8}$, and the concentration of free alkali chloride. If the latter is relatively very large, alkali may fail to precipitate mercuric oxide at all; *e.g.*, 250 mols. of potassium chloride per mol. of mercuric chloride give a solution which is not precipitated with 0·1N-sodium hydroxide. Complex anions of the type HgR_4'' are also formed with the bromide, nitrite, and acetate, which are rendered increasingly stable by the presence of increasing proportions of the appropriate alkali salt, with the result that the pH of precipitation with alkali is correspondingly raised. (The comparable complex anion, HgI_4'', in Nessler's reagent is so very stable that alkali causes no precipitation even though the excess of potassium iodide is not great—in fact, too great an excess increases the stability of the complex anion so much that the reagent loses sensitivity.)

Two points of analytical importance follow from these investigations: (i) the amount of free acid present in a solution of mercuric nitrate, sulphate,

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[18] H. T. S. Britton and (Miss) B. M. Wilson, *J.*, 1932, 2550.

or perchlorate may, after an excess of alkali iodide, bromide, or chloride has been added to convert the mercuric salt into a complex salt, be titrated with alkali and methyl-orange as indicator; (ii) pure mercuric oxide may be used to standardise solutions of acid by dissolving a weighed quantity of mercuric oxide in a concentrated solution of potassium iodide, bromide, or chloride and titrating by means of an acid and methyl-orange the alkali set free by the reaction $HgO + 4KI + H_2O \rightleftharpoons K_2HgI_4 + 2KOH$. This has been confirmed by glass-electrode titrations.[19]

Though to a lesser extent, cadmium salts exhibit characteristics similar to the foregoing, and the effect of alkali salts in raising the pH at which cadmium hydroxide precipitates on treatment with alkali has recently been demonstrated.[20]

The Reaction between Metallic Hydroxides and Weak Acids.—The problem of assessing the basic strengths of sparingly soluble metallic hydroxides is of some difficulty. Basic dissociation constants cannot be computed, as is the case with the soluble organic bases, from hydrolysis data, for the systems then involved are nearly always heterogeneous, the base (or basic salt) often being colloidally dispersed. It happens, however, that the order, in terms of pH values, in which the bases separate from solutions of their salts with strong acids, excepting certain mercuric and cadmium salts, bears a direct relationship to the extent to which their salts are hydrolysed in solution. If this pH arrangement represents the relative sequence of basic strengths, then those bases which precipitate at low pH values, *e.g.*, zirconium hydroxide, are the weakest, and those which separate from solutions at high pH values, *e.g.*, magnesium hydroxide, are the strongest.

In any case, the hydroxide precipitation pH imposes on acids with which these bases can combine *in the normal way* the necessity of being neutralised at pH values which are lower than the precipitation pH. Thus, if acetic acid be considered as a typical weak acid, $K_a = 1{\cdot}8 \times 10^{-5}$, it can be shown that for the acid to combine with a strong base, *e.g.*, sodium hydroxide, to the extent of 50%, a pH of 4·74 must be set up, for 90% a pH of 5·69, and for 99% the pH to be reached is $4{\cdot}74 + 2 = 6{\cdot}74$.[21] With weak bases, such as the hydroxides of thorium, aluminium, copper, and beryllium, which begin to precipitate at pH 3·5, 4·1, 5·3, and 5·7 respectively, it will be seen that the incidence of precipitation of the base before pH 6·74 is reached makes it impossible for these bases to form acetates completely in solution in the same way as sodium acetate, for example, can be formed. Yet copper acetate can be prepared in the crystalline form and dissolved in water without the separation of copper hydroxide. The pH of 0·01M-copper acetate is 5·84,[22] which, although higher than the hydroxide precipitation pH, 5·3, is much below pH 6·74, required by a strong base for 99% neutralisation. The pH of comparable solutions of acetates of thorium,

[19] *Idem*, *J.*, 1933, 9.

[20] T. Moeller and P. W. Rhymer, *J. Physical Chem.*, 1942, **46**, 477.

[21] H. T. S. Britton, *op. cit.*, Vol. 1, p. 179.

[22] H. T. S. Britton and F. H. Meek, *J.*, 1931, 2831.

aluminium, and beryllium are 4·31, 4·64, and 4·85 respectively. In no case therefore can the combination of acetic acid with the different weak bases be considered as normal. Because the hydroxide pH is often exceeded, it follows that the concentrations of metal ions in the acetate solutions must be much lower than in solutions of corresponding salts of strong acids. From a study of pH and conductivity data, Britton and Meek found that in solution these metal acetates undergo considerable hydrolysis, with the result that some of the metallic base exists in solution either in the uncombined state or, much more probably, as a soluble (or perhaps a very highly dispersed) basic acetate. Basic lead acetates are known which are soluble in water giving clear solutions, and conversely, solutions of lead acetate (pH of 0·01M-salt = 5·89) can dissolve appreciable amounts of lead oxide. Lead-electrode measurements of solutions of basic lead acetate, $Pb(OH)_{0{\cdot}93}(OAc)_{1{\cdot}07}$ and $Pb(OH)_{0{\cdot}96}(OAc)_{1{\cdot}04}$, indicated lead-ion concentrations which represented 0·07 and 0·12% of the total lead in the solutes. It is significant that the pH of 0·01M-beryllium acetate should be 4·85, for such a pH value is caused by the ratio $[OAc']/[HOAc]$ being 1·32/1, and, by assuming that the acetate in the basic beryllium acetate ionises, it follows that the solution contained $Be(OH)_{0{\cdot}89}(OAc)_{1{\cdot}11}$ and 0·89 mol. of free acetic acid, which shows that a little more acetic acid had reacted than that required to form $Be(OH)(OAc)$ or $Be_2O(OAc)_2$ (see above).

In a subsequent paper,[23] Britton and Meek show that the diminished metal-ion concentration of solutions of the acetates of lead, copper, beryllium, aluminium, and thorium results in the delay of precipitation of the respective hydroxide with alkali until much higher pH values are attained than is the case from the corresponding salts of strong acids. Further physicochemical evidence is advanced for the view that acetic acid is too weak to neutralise the weaker hydroxyl group of beryllium hydroxide.

Linked up with this weakness of acetic acid and its reaction, or failure to react, with weak metallic bases are the facts that (i) sodium acetate may be added to solutions of the chlorides of zirconium, thorium, aluminium, and copper without the appearance of a precipitate even though the ordinary "hydroxide pH" may be well exceeded,[24] (ii) lead sulphate dissolves in solutions of sodium acetate and ammonium acetate. The pH values corresponding to the progressive addition of sodium acetate to solutions of the acetates of thorium, aluminium, beryllium, copper, and lead show that the basic acetates existing in the original metal acetate solutions persist and, in fact, become increasingly basic as the proportion of sodium acetate is increased. Potential measurements with the lead solutions reveal that there is a parallel diminution in the concentration of lead ions.[23] The existence of soluble basic lead acetate in the presence of sodium and ammonium acetate in solution and the low lead-ion concentrations supply an explanation of the solubility of lead sulphate in solutions of alkali and ammonium acetates, the limit of the solubility being imposed by the solubility product of lead sulphate. There are no grounds for the view that complex

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[23] *J.*, 1932, 183.

[24] H. T. S. Britton, *J.*, 1926, 269.

anions, *e.g.*, $Pb(OAc)'_3$, are formed, though it is not at present certain precisely how the basic lead acetate is stabilised in solutions of sodium acetate.

To test the foregoing observations still further,[25] the reaction of malonic acid with typical metallic bases was investigated. Malonic acid is a particularly suitable dibasic acid for this purpose, as its two stages are fairly distinct from one another, the first stage being that of moderately strong acid, *viz.*, $H_2M \rightleftharpoons H^{\cdot} + HM'$, $K_1 = 2 \times 10^{-3}$, and the second stage, $HM' \rightleftharpoons H^{\cdot} + M'$, $K_2 = 4{\cdot}4 \times 10^{-6}$, that of an acid weaker than acetic.[26] Hence the neutralisation of the first stage by a base should be complete (99%) at pH 4·7, whereas the second stage is neutralisable between pH 3·36 (1%) and pH 7·36 (99%). In other words, in order for a metallic base to form the hydrogen malonate, *e.g.*, $Cu(OH)_2 + 2H_2M \longrightarrow Cu(HM)_2 + H_2O$, it must be able to set up a pH slightly higher than 4·7, and in order to react with the hydrogen ion originating from the second stage of ionisation, *e.g.*, $Cu(OH)_2 + Cu(HM)_2 \longrightarrow CuM + H_2O$, it must do so between pH 3·36 and 7·36 and set up a pH slightly higher than 7·36. H. T. S. Britton and M. E. D. Jarrett[25] selected as typical bases the hydroxides of magnesium, zinc, chromium, beryllium, copper, and aluminium and measured the specific conductivities and pH values corresponding to successive stages of the neutralisation of malonic acid. Compared with the conductivity curve corresponding to the neutralisation with sodium hydroxide, the curves for the metallic bases make it apparent that only the stronger bases, *viz.* magnesium and zinc hydroxides, react completely with the first stage, but they fail to combine completely with the second stage. Both pH and conductivity measurements show that the weaker bases, *viz.*, the other four, react partly with the first stage of ionisation of malonic acid in something akin to the normal manner, but evidently, through the pH for 99% neutralisation of the second stage—pH 7·36—being well above the respective hydroxide pH values, any reaction which occurs between the bases and the second stage is abnormal and, in any case, it is extremely small, as exemplified by the remarkable fall in conductivity as the proportion of the bases (to malonic acid) was increased and the pH values of the solutions when the amount of bases were those required to form what appeared to be the normal malonates, *viz.*, Mg, pH 5·85; Zn, pH 6·27; Cr, pH 2·68; Be, pH 3·57; Cu, pH 5·31. The pH value of the 0·04M-magnesium malonate shows that the solution must have contained hydromalonate and malonate ions in the ratio of about 1 : 3. The lower pH value of copper malonate solution indicates an even greater ratio of HM′ to M″, whereas the very low pH values of the chromium and beryllium malonate solutions show that the malonate-ion concentrations were negligibly small as the neutralisation had not proceeded beyond the first stage.

D. J. G. Ives and H. L. Riley[27] observed that the conductance ratios of the malonates and several alkylmalonates become smaller in passing through

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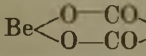
[25] *J.*, 1935, 168, 1728.

[26] H. T. S. Britton, *J.*, 1925, 1906.

[27] *J.*, 1931, 1998, H. L. Riley and (Miss) N. I. Fisher, *J.*, 1929, 2006.

the series : Mg, Zn, Ni, Cu, which incidentally is the sequence of the respective "hydroxide pH" values. They also observed that the smaller secondary dissociation constants of diethylmalonic ($5{\cdot}9 \times 10^{-8}$) and dipropylmalonic acids ($3{\cdot}42 \times 10^{-8}$) had no effect on the electrolytic dissociation of copper dialkylmalonates formed therefrom, and attempted to account for this on the basis of a complete electron grouping around the central copper atom. If copper hydroxide is unable to neutralise the second stage of malonic acid, it certainly cannot react with weaker acid stages, requiring the attainment of pH 9·23 and 9·47 respectively for 99% neutralisation, and consequently no difference could be expected on this basis.

N. V. Sidgwick and N. B. Lewis[28] state that "no doubt" the low conductivity of beryllium malonate solutions is due to the presence of a non-polar cyclic form  $Be<^{O-CO}_{O-CO}>CH_2$. A view more in accord with the combining character of beryllium hydroxide and malonic acid is that the stronger hydroxyl group of the base must have reacted with the "stronger" hydrogen ion of the malonic acid, thus $Be(OH)_2 + H_2M \longrightarrow BeOH.HM + H_2O$, so that instead of beryllium malonate being present, basic beryllium hydrogen malonate was the principal salt formed (see above). This view is supported by the fact that the pH of a 0·02M-beryllium malonate solution is approximately equal to that of a 0·02M-sodium hydrogen malonate solution. Britton and Jarrett[25] also found that such a solution can be made even more basic by saturating it with beryllium hydroxide, whereupon the pH rises to 5·59, this being very nearly the hydroxide precipitation pH, *viz.*, 5·7. The basic solute then corresponds with the formula $Be(OH)_{1{\cdot}29}(HM)_{0{\cdot}71}$. The relatively high pH value, 5·59, shows that the reaction had proceeded to the second stage to a small extent so as to set up an equilibrium between HM' and M'' ions. It seems certain, therefore, that in solution, malonates of weak bases exist largely as soluble or very highly dispersed basic malonates in equilibrium with a little hydrolysed acid. This would account for their exceptionally low conductivity, which, as Sidgwick and Lewis[28] have shown, does not change much with dilution.

Although the normal malonates of the weaker metallic bases, *e.g.*, the hydroxides of iron, aluminium, and chromium, have not been isolated in good crystalline form, yet well-defined complex malonates with the alkali metals are known; those formed from tervalent metals, R, may be represented by Na_3RM_3. H. L. Riley[29] prepared the sodium cuprimalonate, $Na_2CuM_2,2H_2O$. The constitution of the complex malonates, Na_3RM_3, is generally expressed on the basis of Werner's theory of stereoisomerism, but it is highly probable that their mode of formation is to be attributed to the ability of these weak metallic bases to react only with the first, and stronger, stage of ionisation of malonic acid, thus : $Cr(OH)_3 + 3H_2M \longrightarrow Cr(HM)_3 + 3H_2O$, leaving the second, and much weaker, stage of ionisation to be reacted upon by the strong base or alkali : $3NaOH + Cr(HM)_3 \longrightarrow Cr(NaM)_3$, *i.e.*,

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[28] *J.*, 1926, 2538.

[29] *J.*, 1930, 1642.

Na_3CrM_3.[30] This does not explain the entrance of the heavy metal into the complex anion, which may be due to some inhibiting effect imposed on the complex salt by the separation of the baser sodium ions, in the same way that the ionisation of the first stage of a dicarboxylic acid may depress the ionisation of the second stage.

The foregoing conditions refer to the formation of soluble salts as the result of the combination of weak metallic bases with weak acids. When the salt happens to be sparingly soluble in water, then the solubility product of that salt becomes a determining factor in the formation of that salt. As an example, the chromate, oxalate, and phosphate of thorium are all well-defined sparingly soluble salts, *viz*, $Th(CrO_4)_2,3H_2O$,[31] $Th(C_2O_4)_2,6H_2O$,[32] $Th_3(PO_4)_4$,[33] yet they are formed from an exceedingly weak base; the precipitation pH of thorium hydroxide is 3·5 and chromic and oxalic acids are both weak acids in their second stages of ionisation, whilst phosphoric acid is weak in its second stage and extremely weak in its third stage of ionisation. To form a *soluble* thorium chromate, thorium hydroxide would have to react with the hydrogen chromate ion, $K_2 = 4{\cdot}4 \times 10^{-7}$, $HCrO_4' \rightleftharpoons H^{\cdot} + CrO_4''$, *i.e.*, within the pH range between $pK - 2 = 6{\cdot}4 - 2 = 4{\cdot}4$ and $pK + 2 = 6{\cdot}4 + 2 = 8{\cdot}4$. As thorium hydroxide is precipitated at pH 3·5, reaction with the second stage in such a way is clearly impossible; in fact, reaction with even the first stage would be far from complete. Similar conditions apply to thorium oxalate, whereas the extreme smallness of K_3 of phosphoric acid, $2{\cdot}7 \times 10^{-12}$, requires a pH range of 9·6—13·6, the last pH only being reached in very alkaline solutions. Thorium oxalate is precipitated from fairly acid solutions, whereas the addition of trisodium phosphate to 0·01M-thorium chloride causes thorium phosphate to precipitate at pH 2·7.[33] Potassium dichromate, added to a thorium salt solution, precipitates the *normal* thorium chromate, whereas potassium chromate precipitates *basic* thorium chromate at pH 3·45,[34] this being very nearly the hydroxide precipitation pH. As will be seen from the hydrogen-electrode curve of chromic acid,[35] the pH of potassium dichromate is about 4, whereas that of potassium chromate is about 9. The pH of thorium chloride solutions is about 2·5 (pH of 0·01M-$ThCl_4$ = 2·62). Hence, when potassium dichromate is added to a thorium chloride solution the pH will rise but slightly above that of the salt solution, and if $[Th^{\cdot\cdot\cdot\cdot}]$ and $[CrO_4'']$ are large enough to exceed $L = [Th^{\cdot\cdot\cdot\cdot}][CrO_4'']^2$, a sparingly soluble crystalline thorium chromate separates, whereas the normal potassium chromate soon causes the hydroxide pH to be reached and an indefinite thorium basic chromate separates. To prepare sparingly soluble normal salts, the conditions for their precipitation must be set up in the mother-liquor at a pH *below* the hydroxide pH.

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[30] H. T. S. Britton and M. E. D. Jarrett, *J.*, 1935, 1728; cf. H. T. S. Britton, *J.*, 1926, 280.

[31] H. T. S. Britton, *J.*, 1923, **123**, 1429.

[32] H. T. S. Britton and M. E. D. Jarrett, *J.*, 1936, 1404.

[33] H. T. S. Britton, *J.*, 1927, 614. [34] *Idem*, *J.*, 1926, 125. [35] *Idem*, *J.*, 1924, **125**, 1572.

This applies particularly to the precipitation of carbonates and explains why the few carbonates which are precipitated as such, *e.g.*, $MgCO_3,3H_2O$, $ZnCO_3$, Ag_2CO_3, are precipitated by means of sodium bicarbonate and not by the alkaline sodium carbonate. In the case of carbonates of the weaker bases the reaction mixture must be saturated with carbon dioxide so as to keep the pH as low as possible below the hydroxide pH.

Basic chromates, carbonates, and borates are precipitated at the respective metal hydroxide pH values.[34] This is also true of silicates precipitated by means of an alkali silicate, *e.g.*, water glass, except of silicates of the alkali earths, which are usually precipitated between pH 10 and pH 11.[36] It is extremely doubtful, therefore, whether these heavy metal silicates are anything more than mixtures of the hydrated metallic hydroxide and silica. Thus for the precipitation of indefinite aluminium silicates the hydroxide precipitation pH, 4·1, has first to be reached, whereas if aluminium silicate were a definite salt in the true sense one would have expected it to have been precipitated at a lower pH. As H. T. S. Britton [37] has shown, silicic acid has definite acid properties between pH 7 and 12, corresponding to the formation of alkali metasilicate, Na_2SiO_3. Aluminium hydroxide obviously could not combine with silicic acid under these conditions, but it is possible that some union might take place if the resulting salt were exceedingly insoluble, and this possibly would be made manifest by precipitation at a pH below 4·1.

In addition to the formation of insoluble salts, there is the possibility that the resulting salt might be soluble but un-ionised, which makes possible the combination of a weak base with a weak acid. For instance, $K_{HCN} = 4{\cdot}5 \times 10^{-10}$, which indicates for hydrocyanic acid a reaction range of pH 7·35—11·35, and mercuric oxide is an exceedingly weak base, hydroxide pH 2, and yet hydrocyanic acid and mercuric oxide react together to form *soluble* mercuric cyanide. The explanation is that mercuric cyanide is un-ionised in solution so that mercuric and cyanide ions are removed from the reaction system. This instance is exceptional, however.

Complex Cyanides.—On the basis of the foregoing considerations, it is not easy to understand why weak bases can react with hydrocyanic acid at all; yet, in conjunction with alkali cyanides, ferric hydroxide is able to combine to form well-defined and readily soluble salts. There is no doubt that in complex compound formation, involving hydrocyanic acid, co-ördinate linkages come into play so much so that in the complex acids and salts hydrocyanic acid entirely loses its individuality.

In general, the complex acids from which the complex cyanides are derived have not been prepared, and must be regarded as hypothetical. This, however, is not the case with hydro-ferrocyanic and -ferricyanic acids. A solution of $H_4Fe(CN)_6$ has been titrated by use of the glass electrode by H. T. S. Britton and E. N. Dodd,[38] who find it to be a relatively strong acid

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[36] *J.*, 1927, 425; see also G. Hagg, *Z. anorg. Chem.*, 1926, **155**, 20.

[37] H. T. S. Britton and R. A. Robinson, *J.*, 1931, 469.

[38] *J.*, 1933, 1543.

in all its four stages, and O. E. Lanford and S. J. Kiehl[39] extrapolate a value of $6{\cdot}8 \times 10^{-5}$ as being its fourth, and therefore, smallest constant.

To ascertain how many molecules of potassium cyanide react with the various metallic salts in solution to form complex cyanides, three methods have been employed: (i) a method depending on the vapour pressure of hydrogen cyanide of solutions containing free potassium cyanide, (ii) the measurement of pH as potassium cyanide is progressively added, (iii) wherever possible, the measurement of the metal-ion concentrations during and after the formation of the complex cyanide.

The technique of the first method was based on that devised by F. P. Worley and (Miss) V. R. Browne[40] and later used to measure the hydrolysis of potassium cyanide in solution.[41] It consists in bubbling pure air very slowly through the cyanide solution and thence through 10 c.c. of 0·2% picric acid in 2% sodium carbonate for a suitable time. The hydrocyanic acid causes the picric acid solution to develop a brown colour after immersion in boiling water for 2—3 minutes, the intensity of which is directly proportional to the amount of hydrogen cyanide absorbed, which thus makes it possible, after standardisation with solutions of known hydrogen cyanide concentration, to estimate the degree of hydrolysis of potassium cyanide solutions. Solutions of the complex metal cyanides containing varying excess amounts of potassium cyanide were investigated, and the total amounts of free hydrogen cyanide determined.[42] It was found that when the solutions contained an excess of about 6 mols. of potassium cyanide to 1 mol. of the complex cyanides, *viz.*, $KAg(CN)_2$, $K_2Zn(CN)_4$, $K_2Cd(CN)_4$, $K_2Ni(CN)_4$, $K_4Fe(CN)_6$, the hydrolysis of the complex anions was completely repressed. This amount of potassium cyanide was not sufficient to repress the hydrolysis of potassium cuprocyanide, $K_2Cu(CN)_3$, or of $KAu(CN)_4$.[43] On the other hand, the hydrolysis of $K_2Hg(CN)_4$ increased as the excess of potassium cyanide was increased.[44]

The second method depends on the difference in the degrees of hydrolysis of the complex cyanides and potassium cyanide. It consists of measuring the pH as the latter salt is progressively added to solutions of metal salts. Inflexions in the curves, indicating the pH against the amount of cyanide added, appeared when this was exactly that required to form $KAg(CN)_2$, $K_2Ni(CN)_4$, $K_2Zn(CN)_4$,[44] $K_2Cu(CN)_3$, and $KAu(CN)_4$[43]. The inflexions corresponding to $K_2Cd(CN)_4$ and $K_2Hg(CN)_4$ were indefinite.

The third method consisted of measuring the metal-ion concentrations potentiometrically. Inflexions in the E.M.F.–potassium cyanide curves show that $KAg(CN)_2$, $K_2Zn(CN)_4$, and $K_2Cd(CN)_4$ are formed. By re-

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[39] *J. Physical Chem.*, 1941, **45**, 300; see also I. M. Kolthoff and O. Tomsicek, *ibid.*, 1935, **39**, 955.

[40] *J.*, 1917, **111**, 1057.

[41] R. W. Harman and F. P. Worley, *Trans. Faraday Soc.*, 1924, **20**, 502.

[42] H. T. S. Britton and E. N. Dodd, *J.*, 1931, 2332.

[43] *Idem, J.*, 1935, 100.

[44] *Idem, J.*, 1932, 1940.

versing the titration, mercuric chloride being added to potassium cyanide solution, an inflexion was obtained proving the existence of $K_2Hg(CN)_4$.

Complex Kations of Silver and Ammonia and Substituted Ammonias.—Potentiometric titrations with the glass and the silver electrode[45] have been performed to study the formation of complex silver kations in solution. When a solution of ammonia, or of an alkyl-substituted ammonia, is added to one of silver nitrate, silver oxide is partly precipitated if (i) the reactant is a sufficiently strong base to set up the hydroxide precipitation pH and (ii) the stability of the complex kation simultaneously being formed is not too great to prevent $[Ag^{\cdot}]$ from reaching the requirements demanded by the solubility product of silver hydroxide. Generally, precipitation reaches a maximum when 1 equiv. of base is added, but more base causes the silver oxide to dissolve; with ammonia, dissolution is complete with 2 mols., but greater amounts of the organic bases are required, the precise amounts depending on the stability of the complex kation being formed. Inflexions appear in both the pH and the silver-electrode potential curve. With ammonia and free bases (*e.g.*, methyl- or ethyl-amine) these inflexions extend from the addition of the first to the second equivalent, but if sufficient nitrate of the respective base is inserted in the silver nitrate solution before the addition of the base, the inflexions occur sharply when exactly 2 equivs. of base have been added (*i.e.*, 1 mol. of ethylenediamine). The pH values thereafter set up correspond to the buffer systems established by the added base and its salt already in the solution. Complex salts are therefore formed having the general formula AgR_2NO_3 (R = 1 equiv. of base).

These complex nitrates were shown to be the salts of strong bases of the formula, AgR_2OH, and it was found that the solubility of silver oxide in aqueous solutions of ammonia and the substituted ammonias could be satisfactorily calculated from the "instability constants" of the complex kations, *viz.*, $K = [Ag^{\cdot}][R]^2/[AgR_2^{\cdot}]$, and the solubility product of silver hydroxide. Glass-electrode titrations of these solutions with nitric acid revealed that such complex bases existed therein, and the pH values corresponding to their neutralisation, together with parallel conductometric titration curves, showed that these complex bases were as strong as sodium hydroxide.[45, 46] Complex silver kations are also formed with secondary and tertiary bases, including pyridine, but the stability rapidly diminishes in the order primary > secondary > tertiary. Curiously enough, however, the stability of the aniline kation is less than that of the pyridine kation.

The Action of Ammonia on Certain Mercuric Salts and on Potassium Mercuri-iodide Solutions.—The pH (glass electrode) and electrical conductivity of solutions of mercuric salts were measured during the addition of ammonia,[47] and from the data it was found that the composition of the resulting white precipitates depended on the concentrations of the reactants and on whether

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[45] H. T. S. Britton, *J.*, 1925, **127**, 2956; H. T. S. Britton and (Miss) B. M. Wilson, *J.*, 1933, 105; H. T. S. Britton and G. W. Williams, *J.*, 1936, 96.

[46] *Idem, J.*, 1935, 796.

[47] H. T. S. Britton and (Miss) B. M. Wilson, *J.*, 1933, 601, 1045.

the ammonia is added to the salt solution or *vice versa.* If sufficient ammonium salt is included in the mercuric salt solution to repress the ionisation of the added ammonia, then the 2-co-ordinated mercuric salt is precipitated, *e.g.*, $Hg(NH_3)_2Cl_2$ or fusible white precipitate. On adding 0·1N-sodium hydroxide to 0·025M-mercuric chloride, the precipitate is $3HgO,HgCl_2$, but when 0·1N-ammonia is used the precipitate is $3HgO,Hg(NH_3)_2Cl_2$. From more concentrated solutions, the precipitate approximates closely to that of "infusible" white precipitate, $HgO,Hg(NH_3)_2Cl_2$, although generally it is indefinite and may be represented as $HgO,xHg(NH_3)_2Cl_2$, in which x depends on the extent to which the ionisation of the ammonium hydroxide has been repressed and therefore on the concentration of ammonia in the solution. This also is true of the precipitates produced by adding ammonia to solutions of mercuric sulphate, nitrate, bromide, and perchlorate.

These basic ammoniated salts are precipitated at lower pH values than are the ordinary basic mercuric salts on addition of alkali. During the precipitation of mercuric oxide (and basic salts) the solubility product, $[Hg^{\cdot\cdot}][OH']^2 = 10^{-26}$, is of course obeyed, but during precipitations with ammonia the value of this ionic product is about 10^{-29}. This explains Nessler's test for ammonia. Nessler's solution is approximately 0·09M-potassium mercuri-iodide and 2·5N-potassium hydroxide. Its concentration of mercuric ions is $10^{-26·7}$ and $[OH'] = 10^0$, and therefore $[Hg^{\cdot\cdot}][OH']^2 = 10^{-26·7}$, which, being but slightly smaller than the value of the solubility product, 10^{-26}, shows that the solution is just on the verge of precipitating mercuric oxide. As a smaller value, 10^{-29}, is necessary for the separation of the oxide in the form of a basic ammoniated mercuric salt, *e.g.*, $3HgO,Hg(NH_3)_2I_2$, it follows that precipitation must ensue as soon as ammonia is allowed to react with the solution.

Ionisation of Acids.—W. Pugh [48] has followed the back-titration of sodium germanate with hydrochloric acid, using the hydrogen electrode, and finds germanic acid to dissociate as an ordinary dibasic acid, H_2GeO_4, of which $K_{a_1} = 2·6 \times 10^{-9}$ and $K_{a_2} = 1·9 \times 10^{-13}$ at 20°.

Chromic acid in solution dissociates as a normal dibasic acid, H_2CrO_4, the first stage of ionisation, $H_2CrO_4 \rightleftharpoons H^{\cdot} + HCrO_4'$ being that of a strong acid, whereas K_{a_2} (for the second stage) $= 4·4 \times 10^{-7}$.[49] The existence of di- and poly-chromic acids in solution is extremely doubtful.

Telluric acid, according to A. Rosenheim and M. Weinheber,[50] is hexabasic, *i.e.*, H_6TeO_6. In solution it behaves as a norml dibasic acid, H_2TeO_4, being weak in its first stage of ionisation, $K_{a_1} = ca.\ 10^{-7·6}$, and very weak in its second, $K_{a_2} = ca.\ 10^{-12·5}$.[51]

As far as can be ascertained from pH measurements with the glass electrode, arsenious acid is monobasic, presumably $HAsO_2$, having a dissociation constant of $10^{-9·07}$.[52]

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[48] *J.*, 1929, 1537, 1994.

[49] H. T. S. Britton, *J.*, 1925, **125**, 1572.

[50] *Z. anorg. Chem.*, 1911, **69**, 261.

[51] H. T. S. Britton and R. A. Robinson, *J.*, 1931, 458.

[52] H. T. S. Britton and (Miss) P. Jackson, *J.*, 1934, 1048.

Abnormal Acids.—Conductometric and quinhydrone electrode titrations with hydrochloric acid of solutions of sodium molybdate[53] and sodium tungstate[54] have shown that both molybdic and tungstic acids function as normal dibasic acids, H_2MoO_4 and H_2WO_4, in one respect only, *i.e.*, in regard to their maximum neutralisation with alkali. Instead of breaks (and inflexions) occurring when 1 equiv. of hydrochloric acid had reacted, these were delayed until 1·5 equivs. had been added and, thereafter, both the conductivity and the pH curve indicated that the hydrochloric acid was not reacting further. Similar conductometric titrations performed by G. Jander, K. F. Jahr, and W. Heukeshoven[55] and G. Jander and W. Heukeshoven[56] on solutions of sodium molybdate and sodium tungstate yielded data which gave continuous curves similar to those obtained by the previous authors. To interpret the curves, however, Jander *et al.* drew tangents to them in the vicinity of continuous bends and, from the points of intersection of successive tangents, arrived at invalid conclusions regarding the composition of polymolybdate and polytungstate anions. The fact that inflexions (and breaks) occur with 1·5 equivs. of hydrochloric acid led H. T. S. Britton and W. L. German to conclude that sodium poly-salts corresponding to the formula $Na_2[O(WO_3)_4]$ and $Na_2[O(MoO_3)_4]$ were then formed which were not decomposed readily on adding further amounts of the acid.

S. C. Bevan,[57] from the respective hydrated oxides, has prepared solutions of molybdic and tungstic acids, which on direct titration with alkali show that in aqueous solution these acids exist and are neutralised as $H_2[O(MoO_3)_4]$ and $H_2[O(WO_3)_4]$. Glass-electrode pH and conductivity measurements reveal that they are very strong poly-acids, which fact explains why an excess of hydrochloric acid neither precipitates tungstic oxide nor completely decomposes the poly-salts, $Na_2[O(WO_3)_4]$, in dilute solutions. The polytungstate anion, $O(WO_3)_4''$, unlike $O(MoO_3)_4''$, does not react readily with alkali except on boiling or long standing. Bevan's observations on the acid nature of phosphotungstic and phosphomolybdic acids as they behave in solution are not in accord either with L. Pauling's theory[58] or with J. F. Keggin's *X*-ray crystallographic observations.[59] The following abnormal acids have been studied potentiometrically and conductometrically : vanadic,[60] niobic,[61] tantalic.[62]

H. T. S. B.

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[53] H. T. S. Britton and W. L. German, *J.*, 1930, 2154.

[54] *Idem, J.*, 1930, 1249.

[55] *Z. anorg. Chem.*, 1930, **194**, 383.

[56] *Ibid.*, 1930, **187**, 60.

[57] Ph.D. Thesis, London, 1940.

[58] *J. Amer. Chem. Soc.*, 1929, **51**, 2868.

[59] *Proc. Roy. Soc.*, 1934, *A*, **144**, 75; J. W. Illingworth and J. F. Keggin, *J.*, 1935, 575.

[60] H. T. S. Britton and R. A. Robinson, *J.*, 1930, 1261; 1932, 1955; H. T. S. Britton and G. Welford, *J.*, 1940, 764.

[61] H. T. S. Britton and R. A. Robinson, *J.*, 1932, 2265.

[62] *Idem, J.*, 1933, 419.

INORGANIC CHEMISTRY.

THIS Report is divided into two sections, the first of which is a review of recent publications of general interest. In the second section an account is given of experimental work on the preparation of pure solid elements, based on a survey of the literature of the last 15 years or so. Some overlap with earlier *Annual Reports* has inevitably occurred, but this is not serious. The subject has not hitherto been reviewed systematically, and the classification of the various experimental methods, together with illustrative matter drawn from recent literature, will, it is hoped, be of particular value to the non-specialist.

1. GENERAL.

During the past year there has again been great interest in the applications of isotopes as indicators of reaction mechanism. Methods of preparation of the enriched non-radioactive isotope or of the radioactive isotope which serves as the indicator are now well established, but only for deuterium and its compounds are the necessary materials widely available. In this case a comprehensive series of experiments has been described on the exchange of deuterium in deuterated water with ammonia in the complex ammines of cobalt,[1] platinum, and palladium.[2] In the cobalt complexes it was shown that the hydrogen of the salts $[Co(NH_3)_6]Cl_3$ and $[Co(en)_3]Cl_3$ undergoes exchange with deuterium when dissolved in water enriched in deuterium oxide. This fact had been established by earlier observations on complex compounds of this class,[3] but in the present work kinetic measurements have been made. In buffered solutions the interchange reaction proceeds according to a pseudo-unimolecular rate law, the rate being also inversely proportional to the hydrogen-ion concentration. The stability of the complex is such that the exchange of deuterium and hydrogen cannot occur by an initial dissociation of ammonia molecules, followed by exchange of ammonia in solution. The observations are readily interpreted, however, by assuming that the metal-ammine group, $M–NH_3$, ionises as an acid, forming a metal amide group, $M–NH_2$, and a hydrogen ion. This behaviour parallels that of aquo-ammines, which form hydroxo-ammines by dissociation. There is some evidence from these experiments that the ease of acid dissociation runs parallel to the stability of the ammines.

The experiments made with the two salts $[Pt(NH_3)_4]Cl_2,2H_2O$ and $[Pd(NH_3)_4]Cl_2,H_2O$ accord in general with the results obtained with the cobalt complexes. Tetramminopalladous chloride was found to undergo interchange by the acid dissociation mechanism referred to above, and also, in acid solution, by reversible dissociation of ammonia from the complex.

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[1] J. S. Anderson, H. V. A. Briscoe, and N. L. Spoor, *J.*, 1943, 361.

[2] J. S. Anderson, H. V. A. Briscoe, L. H. Cobb, and N. L. Spoor, *ibid.*, p. 367.

[3] See, *e.g.*, J. Horiuti and G. Okamoto, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1937, **31**, 205.

A study of the homogeneous gas exchange with various halides of the chlorine of $H^{35}Cl$ in a product containing 3% of $H^{37}Cl$ and 97% of $H^{35}Cl$ has also been reported.[4] Reaction was found to be rapid with phosphorus and arsenic trichlorides, slower for phosphoryl chloride, very slow for silicon tetrachloride and sulphur monochloride, and negligible for carbon tetrachloride. A mechanism involving additive compounds such as $HPCl_4$ and H_2SiCl_6 was postulated to account for the occurrence of the exchange. Exchange between the chlorine of hydrogen chloride and solid potassium chloride was shown to be limited to the surface layers of the solid.

Comparative data on the physical properties of deuterium and hydrogen compounds have been published by A. B. Hart and J. R. Partington,[5] who have measured the dissociation pressures of the ammonia and trideuteroammonia addition complexes of a variety of metallic halides and of copper sulphate. Similar comparative data on the association of hydrogen and deuterium fluorides have also been obtained.[6] The experiments entailed the isolation of a quantity of HF or DF in a constant-volume container, and simultaneous measurements of pressure and temperature over a considerable range. The deviations from perfect-gas behaviour were then used to calculate the association factor of the gas. Degrees of association of the vapour ranging from 1·2 to 4·5 were observed, and the data as a whole conformed with a single equilibrium $6HF \rightleftharpoons (HF)_6$, though the existence of other polymers is not excluded. The heats of polymerisation were – 40,800 and – 41,100 g.-cals. for $(HF)_6$ and $(DF)_6$, respectively; further, the polymer in each case being assumed to be a single ring, the corresponding strengths of the hydrogen and deuterium bonds between fluorine atoms were 6800 and 6850 g.-cals.

The use of a radioactive bromine isotope in studying the exchange between methyl bromide and certain inorganic bromides has been described by G. B. Kistiakowsky and J. R. van Wazer.[7] Radioactive ^{80}Br with a 34-hr. half-life was prepared by irradiating bromoform containing a trace of bromine with slow neutrons. The free bromine, which contained a large part of the bromine radioactivity, was extracted with cold ammonium hydroxide solution, time being allowed for the decay of short-lived products present. Solid ammonium bromide was then isolated and converted into methyl bromide by heating with sulphuric acid and methyl alcohol. The exchange of bromine between the resulting radioactive alkyl bromide and the bromides of aluminium, barium, and potassium was followed by measuring the loss of radioactivity by the gaseous phase. The experiments, which were made in the temperature range 22—227°, showed that with aluminium bromide, which is a good catalyst for the reactions of methyl bromide, exchange of bromine between the solid bromide and the vapour occurred

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[4] K. Clusius and H. Haimerl, *Z. physikal. Chem.*, 1942, *B*, **51**, 347; *A*, 1943, I, 63.

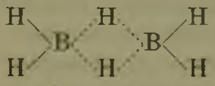
[5] *J.*, 1943, 104.

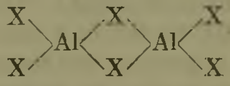
[6] R. W. Long, J. H. Hildebrand, and W. E. Morrell, *J. Amer. Chem. Soc.*, 1943, **65**, 182.

[7] *Ibid.*, p. 1829.

readily, the activation energy of the reaction being only 4·6 kg.-cals. For barium bromide, which is a poor catalyst, the activation energy was 12 kg.-cals., whilst for potassium bromide, which is devoid of catalytic activity, there was no measurable exchange. The use of the radioactive indicator has thus served to indicate a relationship between exchange and catalytic activity. A somewhat similar use of the radioactive iodine isotope ^{128}I of 25 mins. half-life is described by H. A. C. McKay,[8] who has studied the exchange of iodine and alkyl iodides in alcoholic solutions.

The structure of diborane, which for many years has been a controversial subject,[9] has been re-examined by H. C. Longuet-Higgins and R. P. Bell,[10] who have revived a formula (I) in which two hydrogen atoms form a bridge between the boron atoms. This formula, which is analogous to that of the dimeric aluminium halides (II), has much chemical and physical evidence in its favour. In particular it accounts for the ease of interconversion of the boron hydrides, in all of which similar bridges are thought to exist. The existence of products derived from the borine radical, such as BH_3,CO and BH_3,NMe_3, is also readily explained, as is the non-existence of methyl-substituted diboranes containing less than two hydrogen atoms. Trimethylboron itself is monomeric and pentamethyldiborane is unknown. The borohydrides [11] are formulated similarly, beryllium borohydride, for example, being assigned the formula (III). Physical evidence for these structures and for the nature of the bonds is fully discussed by the authors in terms of the theory of resonance. There is uncertainty in the interpretation of electron-diffraction measurements of bond length, but the vibrational and infra-red spectra of diborane are more consistent with a hydrogen-bridge structure than with one resembling ethane.


(I.)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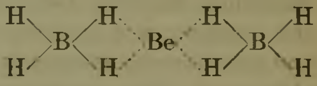
(III.)

The relative strengths of the N→B bonds in the additive compounds of trimethylamine with boron fluoride and its methyl derivatives have been studied by A. B. Burg and (Miss) A. A. Green.[12] This work, in the course of which the new compounds Me_3NBF_2Me and Me_3NBFMe_2 were prepared, has shown that the substitution of one methyl group for fluorine in Me_3NBF_3 leads to a large decrease in the N→B bond strength, whereas further substitution causes only a small further decrease.

Evidence that gallium forms an unstable borohydride under conditions similar to those yielding borohydrides of aluminium, beryllium, and lithium has now been obtained.[13] Trimethylgallium, the improved preparation of

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[8] *J. Amer. Chem. Soc.*, 1943, **65**, 702.

[9] For recent reviews, see A. B. Burg, *Chem. Reviews*, 1942, **31**, 1; S. H. Bauer, *ibid.*, p. 43.

[10] *J.*, 1943, 250.

[11] Cf. *Ann. Reports*, 1941, **38**, 65.

[12] *J. Amer. Chem. Soc.*, 1943, **65**, 1838.

[13] H. I. Schlesinger, H. C. Brown, and G. W. Schaeffer, *ibid.*, p. 1786.

which by the action of dimethylmercury on gallium has recently been described,[14] was treated with an excess of diborane at room temperature. After an induction period a rapid reaction occurred with deposition of a film of gallium; the reaction was represented by the equation

$$Ga(CH_3)_3 + 3B_2H_6 = Ga + 3CH_3{\cdot}B_2H_5 + \tfrac{3}{2}H_2$$

It was considered probable from these preliminary experiments that a borohydride of gallium was the first reaction product and that it underwent a rapid autocatalytic decomposition. When the reaction was carried out at −45° a new compound, dimethylgallium borohydride, $(CH_3)_2GaBH_4$, was obtained. This substance, which had an extrapolated boiling point of 92°, underwent slow decomposition at room temperature. Its reactions are being further studied.

A non-volatile aluminium hydride, $(AlH_3)_x$, has been prepared by O. Stecher and E. Wiberg [15] by passing trimethylaluminium with a large excess of hydrogen through a glow discharge. The volatile products were complex, but the authors succeeded in isolating and characterising two compounds, $Al_2H_2(CH_3)_4$ and $Al_2H_3(CH_3)_3$. Unlike the corresponding gallium derivative, $Al_2H_2(CH_3)_4$ did not disproportionate to aluminium hydride and trimethylaluminium.

From the non-volatile reaction products a compound having the formula $AlH_3,N(CH_3)_3$ was isolated by treatment with trimethylamine. This lost trimethylamine as it was heated, giving a series of intermediates of the type $(AlH_3)_3,N(CH_3)_3$ and $(AlH_3)_5,N(CH_3)_3$. At 100—135° a product was left which had the empirical formula AlH_3. This was a white, non-volatile solid, the chemistry of which has not yet been studied.

Evidence for the existence of an unstable volatile lower fluoride of aluminium, $(AlF)_n$, has been obtained by W. Klemm and E. Voss.[16] This work arose from the observation [17] that aluminium volatilises at a lower temperature than usual in the presence of a metallic fluoride. Klemm and Voss showed that when aluminium was heated with aluminium fluoride at temperatures between 600° and 1000° and at pressures of a few mm. a sublimate of aluminium and aluminium fluoride was formed. In this temperature range the metal is not appreciably volatile, though its fluoride volatilises to a small extent. Repeated revolatilisation of the sublimate with excess of aluminium finally gave a product in which the ratio Al : F was 1 : 1. This result was interpreted by supposing that a volatile fluoride $(AlF)_n$, which disproportionates into metal and the trifluoride on condensation, is responsible for the transport of metal through the gas phase.

The preparation of fluoro-derivatives of non-metallic elements by the Swarts reaction has been further studied by H. S. Booth and his co-workers.[18] Fluorination of thiophosphoryl tribromide by antimony trifluoride at 60—70° without a catalyst has yielded the bromofluorides PSF_2Br (b. p. 35·5°) and

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[14] E. Wiberg, T. Johannsen, and O. Stecher, *Z. anorg. Chem.*, 1943, **251**, 114.

[15] *Ber.*, 1942, **75**, 2003.

[16] *Z. anorg. Chem.*, 1943, **251**, 233.

[17] C. B. Willmore, U.S. Patent 2,184,705, 1939.

[18] Cf. *Ann. Reports*, 1941, **38**, 150.

$PSFBr_2$ (b. p. 125·3°).[19] These two compounds are noteworthy because of their high resistance to hydrolysis: PSF_2Br, which was the more resistant, was almost unattacked in 24 hours by aqueous potassium hydroxide at room temperature, though reaction was rapid at 100°. It is of interest that the partly fluorinated derivatives of phosphorus tribromide are very much less stable.

Attempts to fluorinate sulphur monochloride by the above method resulted only in decomposition. Boron trichloride has also been examined, and although reaction was carried out at reduced pressure so as to facilitate the escape from the reaction mixture of partly fluorinated products, only boron trifluoride was obtained.[20] Reaction temperatures down to $-78°$ were employed. In addition, the interaction of boron trifluoride and boron trichloride at 500°, fluorination of boron trichloride with calcium fluoride at 160°, and the use of the less reactive $SbCl_2F$ in place of SbF_3 were examined, but in each case the result was the same.

The preparation of germanium *iso*cyanate has been reported by A. W. Laubengayer and L. Reggel.[21] The method of preparation was similar to that used in preparing *iso*cyanates of silicon, boron, and phosphorus.[22] Germanium tetrachloride was dissolved in benzene, silver *iso*cyanate added, and the mixture refluxed.. The formula of the compound, which had an extrapolated boiling point of 196°, was established by analysis, and it was found to be rapidly hydrolysed by water and to undergo thermal decomposition at temperatures above 140°.

Chlorine azide, which ranks among the most unstable compounds known, has recently been reinvestigated and more fully characterised.[23] The preferred method of preparation was by the gradual addition of acetic acid to equimolecular amounts of sodium azide and sodium hypochlorite, followed by distillation in a stream of air or nitrogen at atmospheric pressure. Though there were many detonations in the course of this work, the compound was isolated and analysed, and a number of its properties were studied. Liquid chlorine azide did not conduct electricity appreciably, nor did it conduct in contact with sodium azide. (Sodium azide dissolved in liquid hydrogen azide conducts readily.[24]) The compound was soluble in ten organic solvents examined and thus behaved neither as an ionising solvent nor as a polar compound. When carried by a stream of nitrogen into an excess of liquid ammonia it reacted quantitatively according to the equation

$$3ClN_3 + 8NH_3 = N_2 + 3NH_4Cl + 3NH_4N_3$$

Chlorine azide reacted with pentane, forming hydrogen azide and monochloropentane, and with metals both a chloride and an azide were produced.

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[19] H. S. Booth and C. A. Seabright, *J. Amer. Chem. Soc.*, 1943, **65**, 1834.

[20] H. S. Booth and C. G. Frary, *ibid.*, p. 1836.

[21] *Ibid.*, p. 1783. The term *iso*cyanate is used here for a product which may be a cyanate, an *iso*cyanate, or a mixture.

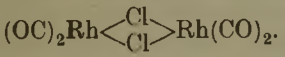
[22] G. S. Forbes and H. H. Anderson, *ibid.*, 1940, **62**, 761.

[23] W. J. Frierson, J. Kronrad, and A. W. Browne, *ibid.*, 1943, **65**, 1696.

[24] A. W. Browne and G. E. F. Lundell, *ibid.*, 1909, **31**, 435.

A further series of experiments[25] on the interaction of silver azide and chlorine azide in ethyl ether gave a deep blue solid compound of the formula N_3AgCl, which was stable below − 30° but decomposed at higher temperatures into silver chloride and nitrogen.

Cupric azide, which hitherto was believed to be a particularly unstable substance, has been re-examined in the course of the past year.[26] The substance previously described under this name was found to be a basic azide, two definite compounds of this class of the formulæ $Cu(OH)N_3$ and $Cu(N_3)_2,Cu(OH)_2$ being prepared. The pure azide was obtained by the interaction of cupric nitrate and sodium azide in aqueous solution. The flocculent precipitate was freed from basic salts by treatment with dilute hydrazoic acid. The pure salt, which when dry was only moderately sensitive to shock, was also prepared by heating the ammoniate described by L. M. Dennis.[27] Various 4-co-ordinated complex derivatives were also prepared, including the tetrammino-complex $[Cu(NH_3)_4](N_3)_2$, analogous derivatives containing amines and diamines, and also complexes of the type $[Cu^{II}(NH_3)_2(N_3)_2]$ which were shown to be non-electrolytes. The complexes containing ammonia were considerably less sensitive to detonation by shock than was the parent azide, whereas the amine complexes could not be detonated, though they burned readily when heated.

The study of metallic carbonyls by W. Hieber and his co-workers has been extended to include carbonyls of rhodium and osmium.[28] A series of rhodium carbonyl halides of the type $Rh(CO)_2X$, where $X = Cl$, Br, or I, has been prepared by the action of carbon monoxide on the trihalide at ordinary or elevated temperatures, according to the halide used.[29] These compounds were volatile and crystalline, and the molecular weight of the chloride corresponded to a dimeric formula, represented in all probability by the structure  $(OC)_2Rh{<}\begin{matrix}Cl\\Cl\end{matrix}{>}Rh(CO)_2$.

Rhodium metal, when heated in carbon monoxide at 200°/280 atm., gave a carbonyl of the formula $[Rh(CO)_4]_2$, which formed orange-yellow crystals, m. p. 76°. This compound resembles cobalt tetracarbonyl, and also illustrates a point of difference between rhodium and iridium, for iridium carbonyls are not formed directly from the metal.

Rhodium halides, when heated in carbon monoxide at 50—80°/200 atm. in the presence of cadmium, zinc, or silver to act as a halogen acceptor, gave a carbonyl of the formula $[Rh(CO)_3]_n$. If the preparation was carried out similarly but at temperatures between 80° and 230°, the product was a new carbonyl of the formula $Rh_4(CO)_{11}$, which was characterised by comparatively high stability. It was not, for example, attacked by dilute acids or alkalis, and its solubility in organic solvents was low.

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[25] W. J. Frierson and A. W. Browne, *J. Amer. Chem. Soc.*, 1943, **65**, 1698.

[26] A. Cirulis and M. Straumanis, *Z. anorg. Chem.*, 1943, **251**, 332, 335, 341.

[27] *J. Amer. Chem. Soc.*, 1907, **29**, 18.

[28] Cf. *Ann. Reports*, 1941, **38**, 71; 1942, **39**, 72.

[29] W. Hieber and H. Lagally, *Z. anorg. Chem.*, 1943, **251**, 96.

Rhodium carbonyl hydride, $Rh(CO)_4H$, was prepared by heating rhodium in a mixture of hydrogen and carbon monoxide, the former being at 50 and the latter at 200 atm. This preparation is analogous to that of cobalt carbonyl hydride.[30] The best method of preparation was by the autoclave reaction of hydrated rhodium trichloride and carbon monoxide at 200°/200 atm. The compound had a melting point of $-10°$ to $-12°$, and above its melting point lost hydrogen readily, forming the tetracarbonyl.

Osmium carbonyl halides and carbonyls have now been fully described.[31] The former have been obtained from osmium halides by the usual high-pressure reaction with carbon monoxide, and are of several types. In addition to the characteristic tetracarbonyl halides, $Os(CO)_4X_2$, corresponding with the iron compounds, compounds of the type $Os(CO)_3X_2$ and $Os(CO)_2X_2$, where $X = Cl$, Br, or I, were prepared. In addition, iodides and bromides of the type $Os(CO)_4X$ were obtained, the molecular weight of the latter corresponding with the double formula $(OC)_4Os\!<\!{X \atop X}\!>\!Os(CO)_4$.

For the preparation of pure osmium carbonyls two methods were available. The first, which gave carbonyl halides as well as carbonyls, was by the action of carbon monoxide on osmium halides in presence of a second metal to act as halogen acceptor. The second was by the action of carbon monoxide on osmium tetroxide, and was similar to the preparation of rhenium carbonyl from its heptoxide.[32] The pentacarbonyl $Os(CO)_5$ was isolated from the mixture of products formed in the reaction between osmium halides and high-pressure carbon monoxide in presence of a metallic powder. The oxyiodide, formed from the tetroxide and hydriodic acid, gave the best results. This carbonyl was remarkable for the readiness with which it lost carbon monoxide to form $Os_2(CO)_9$; indeed, the latter compound was the main product of the reaction, and was also formed in quantity by the interaction of osmium tetroxide and carbon monoxide at 150°/200 atm. Strong evidence for the existence of osmium carbonyl hydride, $Os(CO)_4H_2$, was also obtained, though this substance has not yet been fully characterised.

Copper carbonyl, the existence of which has for some time been suspected, has now been prepared by the action of carbon monoxide on heated cuprous oxide.[33] It is described as a white, readily sublimable solid, the vapour of which is dissociated at a higher temperature with deposition of copper. The empirical formula $Cu(CO)_3$ is assigned from preliminary analyses. In the same communication the formation of small yields of tellurium carbonyl by the action of carbon monoxide on tellurium is reported, though none of the properties of this substance has so far been described.

Reactions in liquid sulphur dioxide have already been described in these Reports.[34] Further work on the amphoteric behaviour of sulphites

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[30] Cf. W. Hieber *et al.*, *Z. anorg. Chem.*, 1939, **240**, 261; **243**, 145, 156.

[31] W. Hieber and H. Stallman, *Ber.*, 1942, **75**, 1472; *Z. Elektrochem.*, 1943, **49**, 288.

[32] W. Hieber and H. Fuchs, *Z. anorg. Chem.*, 1941, **248**, 256.

[33] P. L. Robinson and K. R. Stainthorpe, *Nature*, 1944, **153**, 24.

[34] *Ann. Reports*, 1939, **36**, 135.

in this solvent has now been reported.[35] Aluminium chloride has been found to react in liquid sulphur dioxide solution with tetramethylammonium sulphite according to the equations :

$$2AlCl_3 + 3[(CH_3)_4N]_2SO_3 = Al_2(SO_3)_3 + 6[(CH_3)_4N]Cl$$
$$Al_2(SO_3)_3 + 3[(CH_3)_4N]_2SO_3 = 2[(CH_3)_4N]_3\{Al(SO_3)_3\}$$

The second equation represents the redissolution of the sulphite, which is first precipitated, by an excess of the soluble tetramethylammonium sulphite, the latter behaving as a base and being analogous to hydroxides in aqueous systems or to amides in liquid ammonia. The course of the reaction in liquid sulphur dioxide is readily followed by a conductimetric titration.

The extension of this observation on amphoteric behaviour is made more difficult by the low solubility of many halides in sulphur dioxide. Conductimetric titration of stannic chloride with tetramethylammonium sulphite shows, however, that it behaves like aluminium chloride : a sulphite, or what is more probably a compound of the type SnO_2,xSO_2 analogous to an oxyhydrate in aqueous systems, is first precipitated and then redissolves in excess of the precipitant, forming $[(CH_3)_4N]_4\{Sn(SO_3)_4\}$ (tetramethylammonium orthosulphitostannate), or the corresponding meta-compound $[(CH_3)_4N]_2\{Sn(SO_3)_3\}$. Ageing of the precipitated sulphite occurs rapidly and renders it incompletely soluble. Normally, therefore, in studying these reactions excess of the sulphite is added and the excess is determined by back titration with thionyl chloride, which behaves as an acid in sulphur dioxide. The titrations are made at $-30°$.

Silicon tetrachloride and boron trichloride behaved similarly, though there is some doubt as to the composition of the precipitate. With the former, for example, formation of a true sulphite is very doubtful, and the composition is best represented as SiO_2,xSO_2. With antimony trichloride and pentachloride the reaction was again similar. It was found that, when the solid precipitated from antimony pentachloride was redissolved in excess of tetramethylammonium sulphite and was treated with excess of thionyl chloride, the compound $[(CH_3)_4N]SbCl_6$ was formed and could be isolated.

The reaction between a solution of tetramethylammonium sulphite and tin illustrates further the analogy between reactions in water, ammonia, and sulphur dioxide. In the case of the first two solvents the action of an " alkali " on zinc is represented by the equation :

$$Zn + 2KOH + 2H_2O = K_2[Zn(OH)_4] + H_2$$
$$Zn + 2KNH_2 + 2NH_3 = K_2[Zn(NH_2)_4] + H_2$$

With a solution of sulphite in sulphur dioxide evolution of hydrogen cannot occur, but in its place one would expect sulphur monoxide, since the thionyl radical is the counterpart of the hydrogen ion in water or ammonia. Actually tin was found to dissolve in a solution of tetramethylammonium

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[35] G. Jander and H. Hecht, *Z. anorg. Chem.*, 1943, **250**, 287, 304.

sulphite in sulphur dioxide, the reactions being represented by the equations

$$\mathrm{Sn} + [(\mathrm{CH_3})_4\mathrm{N}]_2\mathrm{SO_3} + 4\mathrm{SO_2} = [(\mathrm{CH_3})_4\mathrm{N}]_2\{\mathrm{Sn}(\mathrm{SO_3})_3\} + 2\mathrm{SO}$$
$$2\mathrm{SO} = \mathrm{SO_2} + \mathrm{S}$$
$$[(\mathrm{CH_3})_4\mathrm{N}]_2\mathrm{SO_3} + \mathrm{S} = [(\mathrm{CH_3})_4\mathrm{N}]_2\mathrm{S_2O_3}.$$

Analysis of the reaction products showed a ratio of tin dissolved to thiosulphate formed of 1 : 0·7—0·8, proving that this reaction scheme is substantially correct. H. J. E.

2. THE PREPARATION OF THE SOLID ELEMENTS IN A STATE OF PURITY.

The preparation of the elements in a state of high purity has engaged considerable attention during the past fifteen years, and the Reporters consider that the subject merits review at the present stage of its development. Recent advances have been concerned chiefly with the metals and with non-metallic elements which are solid under ordinary temperature and pressure conditions, and it is to these solid elements that discussion is confined in this Report. The subject has been approached from the viewpoint of experimental methods, this approach leading to a better appreciation of modern developments than a discussion of individual elements. The methods treated are designed for use on the laboratory scale, where economic considerations are not paramount, rather than for application in industrial practice.

An excellent monograph on pure metals,[1] in which their preparation and properties are authoritatively discussed, has appeared recently, and this should be consulted for details and bibliographies relating to earlier methods of preparing the metallic elements. Two reviews on the availability and use of high-purity metals [2, 3] may also be cited. In one of these [2] an account is given of efforts by the American Society for Testing Materials to obtain metal samples of consistently high and accurately known purity; the following percentage purity values for samples obtained or promised illustrate the high purity standards attained in individual cases by the use of special methods of preparation or purification: lead, zinc, and platinum, 99·9999; bismuth, 99·9984 or better; cadmium, 99·999; gold, 99·998; aluminium, 99·997—99·991; tin, about 99·995; copper, 99·994 or better; silver, 99·993 or better; nickel, 99·97 or better; magnesium, 99·97. Further improvements have no doubt been effected since these values were published.

The purity values given above and elsewhere in this Report, and in the literature generally, are in most cases based on determinations (usually by spectrographic methods) of the various *impurities* present in the samples, since chemical methods for determination of the element concerned are rarely capable of establishing its content with the necessary accuracy in an almost

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[1] A. E. van Arkel, " Reine Metalle," Berlin, 1939.

[2] T. A. Wright *et al.*, *Proc. Amer. Soc. Test. Mat.*, 1937, **37**, I, 531, 538.

[3] C. H. Desch, *Vorträge Hauptversammlung*, 1938, *Deut. Ges. Metallk.*, 1938, 1; *Met. and Alloys*, 1939, **10**, No. 4, 204.

pure sample. This " difference " method of assessing purity must clearly be used with extreme care, since it presupposes that every impurity has been detected and determined ; a number of purity estimates made in the literature are suspect because the absence of conceivable contaminants has not been fully established, and a need for caution in this respect is evident.

The preparation of pure compounds by conventional methods of fractional crystallisation, distillation, etc., is outside the scope of this Report, although attention may be directed to a recently described technique for manipulating readily oxidisable solutions and precipitates.[4] Special methods of separation applied to groups of closely similar elements are of special importance, however, in the preparation of the pure elements themselves, and the most recent work in this field is briefly discussed below. Methods of isolating or purifying the elements are then considered under appropriate sub-headings.

Separation of Closely Similar Elements by Chemical Means.—The difficulty of separating scandium from rare earths, thorium, etc., is well known, and an exhaustive experimental study and comparison of the available methods [5] is of considerable interest. Almost all the previously known methods are considered to be unsatisfactory, except fractional condensation of the chloride or sublimation of the acetylacetone complex ; the former gives satisfactory separation from all the common impurities except thorium, and possibly manganese, and the latter permits sharp separation from thorium, zirconium, hafnium, and rare earths, although iron, aluminium, and probably beryllium, accompany the scandium. Both methods suffer from the disadvantage that moderate or large quantities of material cannot be expeditiously handled, and the yields of purified material are poor. A new and useful method investigated in some detail consists in extracting with ether an acid solution of the scandium preparation containing ammonium thiocyanate ; the scandium is strongly concentrated in the ether phase. A single extraction permits recovery of 94% of the scandium present, separation from magnesium, calcium, rare earths, thorium, and manganese being almost complete ; ferrous iron, titanium, zirconium, hafnium, and uranium are largely removed, but beryllium, aluminium, indium, molybdenum, rhenium, ferric iron, and cobalt may accompany the extracted scandium. Application of the method to a large quantity of 75—80% pure scandium oxide resulted in extraction of 90% of the contained scandium in a spectroscopically pure form.

A recent method for separation of the rare-earth elements, depending on differences in the stability of their amalgams, shows considerable promise. When rare-earth acetate solutions are shaken with sodium amalgam, europium, samarium, and ytterbium are rapidly transferred to the amalgam phase ; [6] the other rare-earth metals give amalgams much less readily under the conditions proposed, their amalgam-forming power diminishing with increasing atomic number. The method has been successfully applied to separation of neodymium–samarium and samarium–gadolinium mixtures,

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[4] S. Rihl and R. Fricke, *Z. anorg. Chem.*, 1943, **251**, 405.

[5] W. Fischer and R. Bock, *ibid.*, 1942, **249**, 146.

[6] J. K. Marsh, *J.*, 1942, 398.

from which samarium amalgam is rapidly obtained with little contamination by neodymium or gadolinium.[7] Further purification is carried out by fractional decomposition of the amalgam with water or dilute acid, the samarium dissolving preferentially and leaving the other rare-earth metals in the amalgam. By one application of this two-fold reaction the neodymium content of a mixture with samarium is reduced from 70 to 0·01%—a separation which is remarkable in comparison with those achieved by the classical fractionation methods. Separation from gadolinium is considered to be equally rapid. By a very similar process, ytterbium may be isolated from mixtures with lutecium and thulium,[8] ytterbium preparations containing less than 0·01% of the accompanying rare-earth metals being readily obtained. By addition of samarium and its subsequent removal as amalgam, small quantities of ytterbium remaining in lutecium preparations may be removed, the ytterbium being co-extracted with the samarium; by this means lutecium salts containing only 0·001% of ytterbium are obtainable. Application of the same amalgam procedure to a mixture of gadolinium, samarium, and europium acetates affords a pure gadolinium acetate solution and an amalgam containing the europium and samarium; these two metals can be separated subsequently.[9] An electrolytic method of amalgam formation gives results similar to those just described in that europium, ytterbium, and samarium are concentrated in the mercury phase.[10] These new methods, judiciously combined with the older processes of fractionation, have greatly facilitated the separation of some of the individual rare-earth metals. In certain cases, however, the exclusive use of the fractionation methods appears essential, and such methods have recently been used to isolate about 12 g. of holmium oxide containing not more than 0·1% of erbium and less than 0·08% of dysprosium and yttrium.[11]

A preliminary investigation of the possibility of separating the rare earths by fractional base-exchange with zeolites has recently been described.[12] Fractionation is obtained if a concentrated solution of rare-earth salts is treated with a quantity of zeolite insufficient to exchange with all the earths; the metals most strongly held by the zeolite are those which show the smallest ionic radii in their crystalline compounds. Fractional removal from the zeolite is also possible, the ions of larger radius being removed preferentially. A chromatographic separation process has also been applied to the rare-earth elements.[13]

The separation of zirconium and hafnium still remains a process in which methods of fractionation are indispensable. A careful study has now been made of the optimum conditions for effective separation of these two metals by fractional precipitation of their ferrocyanides.[14] Four successive

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[7] J. K. Marsh, *J.*, 1942, 523. [8] *Idem, ibid.*, 1943, 8. [9] *Idem, ibid.*, p. 531.

[10] H. N. McCoy and R. P. Hammond, *J. Amer. Chem. Soc.*, 1942, **64**, 1009.

[11] W. Feit, *Z. anorg. Chem.*, 1940, **243**, 276.

[12] R. G. Russell and D. W. Pearce, *J. Amer. Chem. Soc.*, 1943, **65**, 1924.

[13] O. Erämeträ, T. G. Sahama, and V. Kanula, *Ann. Acad. Sci. Fennicæ*, Ser. A, 1943, **57**, No. 3, 5.

[14] W. C. Schumb and F. K. Pittman, *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 512.

fractionations by the procedure recommended have increased the hafnium oxide content of a mixture of the two oxides from 12 to 20, 36, 62, and 80%, respectively. The precipitation of zirconium and hafnium phosphates has also been investigated in a similar manner;[15] phosphate fractionations have hitherto been rendered difficult in this case by the gelatinous nature of the precipitates, but in the new procedure precipitation of the zirconium–hafnium phosphate in a granular form which is easily filtered off is secured by spraying the sulphate solution [2—5% of (Zr,Hf)OSO_4] and phosphoric acid (2—5%) (both in 10% sulphuric acid) at equivalent rates into a large volume of 10% sulphuric acid held at 75°. This technique, combined with a new method of reconverting the phosphates into the soluble sulphates for the next fractionation, has given new scope to a classical separation process. In a typical series of seven precipitations, in each of which about 55% of the dissolved material was converted into phosphate, hafnium oxide was enriched from 13% in the original oxide mixture to 93%, the hafnium in the concentrates representing 10% of the total quantity of hafnium in the starting material. Two successive treatments of material low in hafnium, followed by recrystallisation of the oxychloride, have yielded zirconium salts in which hafnium could not be detected by spectrographic examination.

Preparation of Elements by Thermal Decomposition of their Compounds.—Thermal decomposition of a suitable compound appears to be the simplest conceivable method of isolating an element, and although this method has relatively few applications to solid elements it has certain interesting possibilities and deserves brief mention. Pure metals of the platinum group are customarily prepared by ignition of the purified salts obtained in the course of their separation.[16] Sodium, potassium, rubidium, and cæsium have been prepared by pyrolysis of their azides in a high vacuum;[17] the reactions occur at moderate temperatures (275—395°), and after distillation (in the same apparatus) the metals are spectroscopically pure and gas-free.

Decomposition methods are particularly applicable to the less volatile elements, which cannot distil out of the heated zone and recombine with other decomposition products. This is well illustrated by C. W. von Bolton's original method of preparing tantalum,[18] in which rods of tantalum dioxide were heated to a high temperature in a vacuum by passage of an electric current. An interesting recent example of a reaction of the same general type occurs in the preparation of pure germanium by decomposition of its nitride;[19] treatment of germanium tetrachloride with ammonia affords the imide, $Ge(NH)_2$, together with ammonium chloride; the latter is washed out of the product with liquid ammonia, and the imide heated in nitrogen. At about 150° *germanam*, Ge_2N_3H, is formed, and at 350° this is converted

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[15] E. M. Larsen, W. C. Fernelius, and L. L. Quill, *Ind. Eng. Chem.* (*Anal.*), 1943, **15**, 512.

[16] E. Wichers, R. Gilchrist, and W. H. Swanger, *Trans. Amer. Inst. Min. Met. Eng.*, 1928, **76**, 602; E. Wichers, *J. Res. Nat. Bur. Stand.*, 1933, **10**, 819.

[17] R. Suhrmann and K. Clusius, *Z. anorg. Chem.*, 1926, **152**, 52.

[18] *Z. Elektrochem.*, 1905, **11**, 45.

[19] R. Schwarz, *Die Chemie*, 1942, **55**, 45.

into the nitride, Ge_3N_4; dissociation of the nitride into germanium and nitrogen takes place at 1000°.

Interesting information on the properties of carbonaceous material obtained by heating sucrose at temperatures between 300° and 1100° is given in a recent paper.[20] Material prepared by heating sucrose in hydrogen at 1000—1100° for 10 hours consists of substantially pure carbon in the form of graphite crystallites about 10 × 30 × 30 A.; specimens prepared at lower temperatures contain several % of hydrogen and oxygen.

"*Hot-wire*" *Methods*.—In "hot-wire" methods the vapour of a volatile compound of the desired element is thermally decomposed or reduced at the surface of a wire heated to a suitable high temperature by passage of an electric current, the element being deposited on the wire as a more or less coherent coating. In the preparation of a metal by this means a thin "starting wire" may be drawn from a previously prepared specimen of the metal itself, the thermal reaction then being employed to build up a homogeneous rod which may reach a diameter of several millimetres; since the deposited metal does not come into contact with any extraneous material, contamination is minimised.

The apparatus generally used in the hot-wire technique consists of a suitably designed glass or quartz bulb with heavy sealed-in leads which conduct the heating current for the wire, the latter being supported by the leads in the centre of the bulb. Suitable provision is made for introducing the reactants into the bulb, and for pumping off any volatile decomposition products. The principal experimental difficulty is the maintenance of the wire at a constant temperature; if, as in most cases, the material deposited conducts electricity, the current passing must be continuously increased as deposition proceeds, sometimes from a fraction of an ampère at the beginning of the experiment to several hundred ampères at the end.

A review of applications of the hot-wire technique, by one of its principal exponents,[21] illustrates its versatility. In the majority of the applications the reaction taking place at the wire is thermal decomposition of a halide of the element (frequently the iodide); if a supply of the element in a finely-divided form, prepared by some other method, is placed in the bulb and heated to a suitable temperature, the liberated halogen may react continuously with it, and thus replenish the halide required for decomposition at the wire. Copper, titanium, zirconium, hafnium, thorium, vanadium, chromium, molybdenum, tungsten, rhenium, iron, and nickel have all been prepared by this form of the hot-wire technique, the deposition temperatures for these elements varying from 600° to 2000°, and the temperature of the "reserve" of crude metal ranging from 20° to 800°. In other applications a mixture of hydrogen with the vapour of a halide is passed over the heated wire, and the halogen hydride liberated in the consequent reduction is pumped off; beryllium, silicon, and vanadium have been prepared by this method. Niobium, tantalum, and platinum are best

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[20] U. Hofmann and F. Sinkel, *Z. anorg. Chem.*, 1940, **245**, 85.

[21] A. E. van Arkel, *Metallw.*, 1934, **13**, 405, 511.

obtained by decomposing a halide (or carbonyl halide in the case of platinum) at the hot wire, and removing the gaseous products by direct pumping. In all these methods, essential conditions for deposition of the element are that the compound employed should be appreciably dissociated at temperatures below the melting point of the element, and that the vapour pressure of the element should be considerably less than that of the compound at the temperature chosen for the heated wire.

The most fruitful applications of hot-wire methods have been to elements of high melting point which are not readily obtained in massive form by fusion, notably to titanium, zirconium,[22] hafnium,[23] thorium,[24] niobium and tantalum,[25] rhenium,[26] and boron. In several of these examples hot-wire methods afford the only means of preparing the element in a highly ductile form, other methods giving products which are rendered brittle by traces of oxygen, nitrogen, or other impurities. In one of the more recent accounts of hot-wire methods[27] the preparation of ductile titanium is described; crude titanium, prepared by reduction of the tetrachloride (or, less satisfactorily, potassium or sodium titanifluoride) with metallic sodium, is confined with a little iodine in a bulb heated to 500° or more, the titanium being deposited on a wire heated to 1300°. As indicated above, the halogen is continuously re-used to form titanium tetraiodide, in which form the metal is conveyed from the supply of crude material and deposited by decomposition on the wire. The titanium is obtained in rods up to 7 mm. in diameter, which contain about 0·14% of iron (introduced from the vessel used in preparing the crude metal) and a little silicon, but are otherwise pure. In the original paper the effects of wire temperature and other conditions on the reaction and its products are discussed in some detail.

Commercial "pure" boron from various sources has recently been shown to contain less than 80% of the element; the balance consists of oxygen and aluminium or magnesium, the latter evidently being introduced during the reduction process.[28] Special interest therefore attaches to a new preparation of genuinely pure boron by the hot-wire method.[29] The reaction employed was the reduction of boron tribromide by hydrogen, rendered particularly suitable by the ease with which the tribromide can be purified by conventional vacuum fractionation methods in all-glass apparatus. Since boron could not be used in the "starting wire," deposition was carried out on

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[22] A. E. van Arkel and J. H. de Boer, *Z. anorg. Chem.*, 1925, **148**, 345; J. H. de Boer and J. D. Fast, *ibid.*, 1926, **153**, 1; 1930, **187**, 177; C. J. Smithells, *Metal Ind.* (*Lond.*), 1931, **38**, 336.

[23] J. H. de Boer and J. D. Fast, *Z. anorg. Chem.*, 1930, **187**, 193.

[24] Ref. (1), p. 215.

[25] W. G. Burgers and J. C. M. Basart, *Z. anorg. Chem.*, 1934, **216**, 223; K. Moers, *Metallw.*, 1934, **13**, 640.

[26] C. Agte, H. Alterthum, K. Becker, G. Heyne, and K. Moers, *Z. anorg. Chem.*, 1931, **196**, 129.

[27] J. D. Fast, *ibid.*, 1939, **241**, 42.

[28] E. H. Winslow and H. A. Liebhafsky, *J. Amer. Chem. Soc.*, 1942, **64**, 2725.

[29] A. W. Laubengayer, D. T. Hurd, A. E. Newkirk, and J. L. Hoard, *ibid.*, 1943, **65**, 1924.

0·01-in. tungsten or (preferably) "hydrided" tantalum wires, the latter consisting merely of tantalum filaments pre-treated with hydrogen at a high temperature before use. With the wire at about 1300° and a partial pressure of 18 mm. of boron tribromide in the reacting mixture (total pressure atmospheric), the boron was produced as crystals up to 1 mm. in length which were readily detachable from the wire; as much as 0·5 g. of crystalline product could be obtained in a single run. The boron was shown by spectrographic examination to be free from non-volatile impurities such as silicon, carbon, or tantalum from the wire. In this case an application of the hot-wire method has permitted a complete re-examination of the properties of boron, carried out on material of proved purity. It is noteworthy that the crystalline boron had a hardness of 9·3 on the modified Moh scale, approaching that of boron carbide. An amorphous form of boron could be prepared by using a lower wire temperature, or increasing the boron tribromide pressure in the reaction zone.

Reduction Methods.—Conventional methods of reducing oxides, halides, and other compounds by purely chemical means have in recent years been refined by the introduction of new reducing agents and a variety of new techniques. The classical method of reducing a metallic oxide with hydrogen is still applicable, however, in some cases; it is stated, for example, that pure cobalt and nickel are obtained by this simple method,[3] and the percentage purity of cobalt prepared from cobaltous oxide and hydrogen at 550—1200° has been given as 99·81—99·89%.[30] Iron of purity superior to that of electrolytic iron has recently been produced on a fairly large scale (about 500 g. of product per day) by a process involving hydrogen reduction of ferric oxide.[31] The starting material for this process was commercial electrolytic sheet iron containing 0·011% of copper and 0·018% of phosphorus. These impurities were largely removed by dissolving the metal in high-purity hydrochloric acid and allowing the solution to stand in contact with excess of the iron. The ferrous chloride was crystallised, dried, and converted into ferric oxide by treatment with steam and air at 250°; after being washed with dilute hydrochloric acid and water, the oxide contained only one-quarter to one-third of the nickel (0·0014%) present as impurity in the original iron. The ferric oxide, contained in alumina boats, was reduced by hydrogen at 750°, electrically heated tube furnaces being employed for this operation; in order to minimise spontaneous oxidation of the metal powder on removal from the furnace, the reduced material was sintered in nitrogen at 900° before the furnace tubes were opened. A preliminary melting of the iron powder was carried out in a nitrogen atmosphere; slight oxidation during this process was unavoidable, but it served to remove some of the more readily oxidisable impurities from the metal. Finally, the oxygen was removed from the main bulk of material by a process of melting in an atmosphere of hydrogen at successively reduced pressures (15, 6, and 3 cm.). The product from the last melting operation was estimated to contain at

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[30] G. F. Hüttig and R. Kassler, *Z. anorg. Chem.*, 1930, **187**, 25.

[31] F. Adcock, *J. Soc. Chem. Ind.*, 1940, **59**, 28.

most 0·006% of total impurities. Melting of the iron was in each case carried out in a high-frequency induction furnace; heating in such furnaces is produced within the mass of metal itself by alternating currents of large magnitude, induced in the metal by a suitably placed primary coil supplied from a high-frequency oscillator. The simplicity, flexibility, and all-round efficiency of induction furnaces renders them eminently suitable for melting or heat-treatment of moderate masses of metal; high temperatures are readily attained, and the complete absence of fuel combustion products and of external heating devices simplifies the problem of preserving the molten metal from contamination. The choice of a suitable inert refractory material still remains, and is a source of difficulty in many studies on pure metals; in the work on iron just described, impervious sintered alumina crucibles were selected for the melting operations.

Brief reference may be made to several other elements which are prepared in the pure state by hydrogen reduction processes. Molybdenum is obtained by reducing the dioxide in hydrogen at 900—1200°; the resulting powder is pressed into bars, which are heated electrically to just below the melting point in an atmosphere of hydrogen. This sintering process expels volatile impurities, and completes the reduction of any residual oxide. The ingots of metal can afterwards be " swaged " and drawn into wire, or rolled into sheet.[32] Pure rhenium metal is prepared by hydrogen reduction of ammonium per-rhenate, the reaction being completed at 1000°.[33] Metallic vanadium, stated to be 99·85% pure, is obtainable by reduction of specially prepared vanadium trichloride with hydrogen, but the reaction is slow.[34]

Elemental arsenic containing less than 0·002% of antimony, 0·0002% of iron, 0·005% of sulphur, and 0·01% of phosphorus is stated to be obtained by reducing recrystallised ammonium dihydrogen arsenate with ammonia at 1000°.[35]

The use of novel methods of reduction is well illustrated by two processes for the preparation of pure metallic chromium.[36] An essential condition for effective reduction of chromic oxide by hydrogen is the maintenance of the pressure of water vapour produced in the reaction at a low value.[37] In the first method this condition is secured by placing thin layers of chromic oxide (prepared by heating redistilled chromium trioxide) between plates of metallic tantalum, and " hydriding " the tantalum by heating in commercial hydrogen, from which the impurities are not absorbed; when the tantalum is saturated with hydrogen the pressure in the reaction chamber, heated at 1000°, is reduced, and the chromic oxide then undergoes reduction by the pure hydrogen evolved by dissociation of the tantalum hydride; the low pressure prevailing ensures rapid removal of water vapour from the reaction zone. In the second method calcium hydride, CaH_2, is em-

[32] C. J. Smithells, *Metal. Ind.* (*Lond.*), 1931, **38**, 336.

[33] L. C. Hurd and E. Brimm, *Inorganic Syntheses*, 1939, **1**, 175.

[34] T. Döring and J. Geiler, *Z. anorg. Chem.*, 1934, **221**, 56.

[35] A. de Passillé, *Compt. rend.*, 1934, **198**, 1781.

[36] P. P. Alexander, *Met. and Alloys*, 1934, **5**, 37.

[37] H. von Wartenberg and S. Aoyama, *Z. Elektrochem.*, 1927, **33**, 144.

ployed as the reducing agent; this liberates hydrogen on heating, and the metallic calcium set free is available to react with water vapour formed when the chromic oxide is reduced. The water is thus removed rapidly by chemical means, and the reaction responsible for its removal yields a fresh quantity of hydrogen gas for reduction purposes. The effectiveness of this ingenious process may be judged from the claim that chromic oxide can be reduced completely by calcium hydride in 30 minutes at a temperature as low as 470°. The chromium produced is 99·95% pure, the chief impurity being calcium. It is stated that a similar method of reduction has been successfully used with oxides of thorium, beryllium, vanadium, and boron.

Metallic calcium proves to be a valuable reducing agent for the preparation of certain pure metals. Granules of metallic chromium which are moderately ductile can be obtained by reducing chromic chloride or chromic oxide with calcium in a steel bomb heated (by induction) in an atmosphere of argon.[38] The successful preparation of even moderately pure chromium from the oxide and calcium is remarkable, for under low pressures calcium oxide is itself reduced by chromium; evidently the equilibrium is to a large extent dependent on pressure, the high pressure developed in a bomb favouring the formation of metallic chromium. This pressure effect may well repay further study in other similar cases. In its simple form the reduction of chromic oxide by calcium is of little practical value, for chromium is not readily melted and cast, and the granular product cannot be pressed or sintered to a coherent mass of metal. A chromium powder that can be sintered is prepared by carrying out the reduction at 1000° in a flux of molten calcium and barium chlorides, in an argon atmosphere; the use of a bomb is unnecessary in this case. The initial product, obtained by extracting soluble material from the cooled melt with water and dilute nitric acid, is given a second similar treatment with a small quantity of calcium to ensure reduction of small inclusions of oxide. Sintering of pressed bars of the pure chromium is carried out first at 1300° in a vacuum, and then at 1600—1700° in argon, the bars being placed on beryllium oxide refractory supports; the sintered metal is brittle at room temperature, but can be rolled under barium chloride at about 1250°. It is stated that thorium, uranium, and vanadium can be prepared by methods similar to that just described.

The preparation of pure titanium and zirconium by reduction of their oxides and halides has been discussed in some detail,[39] and particulars have been given of the reduction of the dioxides with calcium in a calcium chloride and barium chloride flux. Although they are ductile at moderate temperatures, the metals obtained still contain a little oxygen, the presence of which is admittedly due to the equilibria referred to above. This oxygen cannot be removed by any known deoxidiser.

A simple and elegant method for preparation of pure rubidium or cæsium from a halide by reduction with calcium has been described.[40] The halide–

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[38] W. Kroll, *Z. anorg. Chem.*, 1936, **226**, 23. [39] *Idem*, *ibid.*, 1937, **234**, 42.

[40] F. C. Schmidt, F. J. Studer, and J. Sottysiak, *J. Amer. Chem. Soc.*, 1938, **60**, 2780.

calcium mixture is placed in a nickel tube, which is practically sealed by bending over the ends and suspended in an evacuated glass enclosure. The nickel tube is heated by induction; the alkali metal then distils through the seams, and is collected in a suitably placed bulb.

The very strong affinity of elemental zirconium for oxygen, combined with the refractory nature of the oxide, renders the metal a particularly useful, if expensive, reducing agent. The alkali metals have been obtained in a very pure state by reduction of their sulphates, chromates, dichromates, molybdates, and tungstates with zirconium.[41] Excess of zirconium must be used, otherwise the reactions are explosive. For the preparation of potassium, rubidium, and cæsium, heating of mixtures of the chromates with zirconium powder (1 part to 4 parts, by weight) at 700—800° is recommended; a similar mixture with the molybdate, heated at 550°, is preferred for sodium. Lithium is obtained from the chromate (1 part to 8 of zirconium, at 450—600°), but the yield is small. These reactions are useful because the mixed starting materials are stable for indefinite periods in air, the reaction temperatures are moderate, no readily volatile products other than the alkali metals are obtained, and under optimum conditions the yields are good.

Preparation of Metals by Electrolytic Methods.—A number of metals are prepared in the pure state by electrolysis of solutions or fused salt melts containing their compounds; methods of electrolytic refining in which an anode of previously prepared crude metal is employed are discussed separately below.

Metallic gallium is successfully prepared by electrolysis of a solution of gallium hydroxide in sodium hydroxide solution, platinum electrodes being used.[42] The temperature of the solution is kept above 30°, the melting point of the metal, and the liquid gallium is collected in a shallow glass cup below the cathode, with which it remains in electrical connection. The initial product is freed from traces of lead, tin, and platinum by washing successively with hydrochloric acid (1 : 1), concentrated nitric acid, and dilute hydrochloric acid; the purified gallium is spectroscopically pure except for a faint trace of iron. Direct electrolysis of an alkaline extract of germanite ore has recently been employed to give a deposit of gallium and germanium;[43] the latter is removed by treating the deposit with chlorine and distilling off the resulting germanium tetrachloride, and the residual gallium trichloride, after removal of lead, antimony, and molybdenum by precipitation with hydrogen sulphide, is used for the electrolytic preparation of gallium metal. This new method affords a simple and rapid means of obtaining pure gallium from its principal natural source.

Tin is an interesting example of a metal the properties of which are considerably affected by traces of impurity; it has been shown that as little as 0·0035% of bismuth imparts an unusual " cored " structure to the cast

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[41] J. H. de Boer, J. Broos, and H. Emmens, *Z. anorg. Chem.*, 1930, **191**, 113.
[42] F. Sebba and W. Pugh, *J.*, 1937, 1371.
[43] D. J. Lloyd and W. Pugh, *ibid.*, 1943, 8.

metal, and inhibits the transition to grey tin at low temperatures.[44] Commercial samples of supposedly " pure " tin all showed the cored structure after casting, and a " structurally pure " product, shown to be free from bismuth, was obtained only by electrolysis of a solution of stannous chloride containing some suspended metastannic acid to adsorb impurities.

Needle-like crystals of pure thorium are stated to be obtained by electrolysis of an aqueous solution of thorium sulphamate.[45]

The technique of preparing metals by electrolysis of salt melts is illustrated by the production of pure uranium,[46] thorium,[47] tantalum,[48] and niobium [49] from melts containing complex fluorides of the metals. In the case of uranium the electrolyte consists of equal parts by weight of calcium and potassium chlorides containing the green complex fluoride KUF_5; this is fused at 775° in an electrically heated graphite crucible, which serves as the anode. The cathode is a molybdenum strip suspended in the centre of the crucible. As electrolysis (requiring 30 amp. at about 5 volts) proceeds, uranium separates as a tree-like deposit on the cathode, which is removed and replaced by a new molybdenum strip at intervals; additions of the electrolyte constituents are made when necessary. The cooled cathode material, containing solidified salts from the bath, is washed with water, dilute acetic acid, alcohol, and ether, and dried; insoluble calcium fluoride in the product is readily washed away from the very much denser uranium metal. The uranium is obtained as a coarse, grey powder, which is pressed into pellets and fused in a vacuum in an induction furnace. The metal then contains 0·06% of carbon, 0·05% of iron, and 0·01% of silicon. In this process the complex fluoride was adopted as electrolyte after tests had shown the unsuitability of a uranyl salt or uranium trioxide; these gave a deposit of uranium dioxide at the cathode during electrolysis.

A closely similar technique is used in the case of the thorium,[47] except that potassium and sodium chlorides, with $KThF_5$, are employed in the melt to obviate difficulties due to formation of calcium fluoride, which in this case is not easily washed out of the product. The pressed, sintered, and degassed metal is stated to be very soft, and to contain only 0·02% of carbon, 0·05% of silicon, and 0·005% of iron. Tantalum and niobium produced by electrolysis, under similar conditions, of the complex fluorides K_2TaF_7 [48] and K_2NbF_7 [49] are of comparable purity; in these instances, however, the " anode effect," well known in the electrolysis of melts of this type, is troublesome unless tantalum or niobium pentoxide is also added to the molten electrolyte.

Further useful details of the technique of electrolysis of fused salts are provided by a long paper on the isolation of pure rare-earth metals,[50] and a full description of the preparation of pure metallic scandium.[51] Pure

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[44] C. W. Mason and W. D. Forgeng, *Met. and Alloys*, 1935, **6,** 87.

[45] R. Piontelli and A. Giulotti, *Chim. e l'Ind.*, 1939, **21,** 478.

[46] F. H. Driggs and W. C. Lilliendahl, *Ind. Eng. Chem.*, 1930, **22,** 518.

[47] *Idem, ibid.*, p. 1302.

[48] *Idem, ibid.*, 1931, **23,** 634.

[49] C. W. Balke, *ibid.*, 1935, **27,** 1166.

[50] F. Trombe, *Ann. Chim.*, 1936, **6,** 349.

[51] W. Fischer, K. Brünger, and H. Grieneisen, *Z. anorg. Chem.*, 1937, **231,** 54.

cerium, for example, is prepared by electrolysis, at 800—850°, of a fused mixture of anhydrous cerous chloride (60%) and potassium chloride (40%), with an addition of about 5% of calcium fluoride. The apparatus found most suitable is a graphite crucible (anode), with a central rotating cathode of molybdenum or tungsten, shielded along most of its length by a concentric quartz tube; the metal collects in a sintered fluorite or quartz crucible fitted into the bottom of the graphite container, into which the lower end of the cathode projects. The cerium obtained contains potassium, which is removed by fusion in a vacuum in a tube furnace, or in a cathode-ray furnace of interesting design which permits efficient attainment of very high temperatures. Lanthanum, neodymium, and praseodymium are obtained by very similar methods, but in the preparation of samarium and gadolinium the method is modified by the use of a pool of molten cadmium as the cathode; the cadmium is afterwards distilled from the resulting alloy by heating in a vacuum at 1300°. An analogous method is applied in the preparation of scandium,[51] the cathode consisting of molten zinc of high purity; even with special precautions during electrolysis, some oxidation of the scandium–zinc alloy is difficult to prevent, and the oxide is subsequently " filtered off " from the molten metal, with inevitable loss of scandium, by passing it through a tungsten crucible with a perforation in the bottom. The zinc is finally distilled off by slow heating to 1250° in a vacuum; the scandium then remains in a highly sintered condition. Although the percentage purity of the metal obtained is given as only 94—98%, this figure must be considered in relation to the high reactivity and affinity for oxygen associated with scandium metal.

Purification of Solid Elements by Distillation.—A number of solid elements are prepared in the pure state by applying some method of purification to a crude material, rather than by direct production from a purified compound. In a number of cases, distillation at high temperatures has been investigated as a means of effecting the necessary purification. A review is available [52] covering the technique and experimental difficulties involved in some detail, and describing experiments (on the laboratory scale) on the distillation of chromium, aluminium, silicon, beryllium, iron, copper, nickel, tin, and lead. The purification of magnesium by distillation methods has also been discussed.[53]

A particularly difficult case of purification of a metal by distillation arose in work carried out at the National Physical Laboratory on the production of pure beryllium,[54] and this merits brief description. Beryllium prepared by electrolysis of fluoride melts, although 99·6—99·7% pure, obstinately retains a little oxygen, which cannot be excluded by any simple modification of the electrolysis technique; the oxygen present causes

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[52] W. Kroll, *Metallw.*, 1934, **13**, 725, 789; *Metal Ind.* (*Lond.*), 1935, **47**, 3, 29, 103, 155.

[53] W. Kaufmann and P. Siedler, *Z. Elektrochem.*, 1931, **37**, 492; J. Hérenguel and G. Chaudron, *Compt. rend.*, 1931, **193**, 771.

[54] H. A. Sloman, *J. Inst. Metals*, 1932, **49**, 365.

deposition of a beryllium–beryllium oxide eutectic in the solidified metal, and this is said to be responsible for the brittleness previously associated with metallic beryllium. A distillation apparatus was eventually constructed in which the beryllium, contained in a crucible of sintered beryllium oxide, was heated to about 1900° by induction; the vapour issued through a "baffle," designed to prevent collection of splashes of the molten metal, and was condensed on a water-cooled silica surface. The whole apparatus was kept under high vacuum. Although distillation was slow and the quantity of product small, beryllium of purity estimated at 99·95—99·97% was obtained; this metal was ductile, and contained none of the eutectic previously mentioned. Attempts to deoxidise beryllium by chemical means—including fusion in the flame of an atomic hydrogen blowpipe—were unsuccessful, and apparently distillation is the only known means of preparing an oxygen-free metal.

A simple and ingenious apparatus designed for the distillation of zinc on the laboratory scale [55] is noteworthy as a prototype; the zinc is condensed on a graphite sleeve so designed that the crystals grow downwards away from the surface, and are readily removed without metal which has been in contact with graphite. In the commercial distillation of zinc a product of 99·994% purity is stated to be obtainable; [56] the use of carborundum as a refractory material in the apparatus may be noted.

Tellurium is obtained in the pure state by vacuum distillation of a commercial electrolytic product containing selenium, copper, iron, and some oxide.[57]

Purification of Metals by Sintering or Fusion in a Vacuum.—Passing reference has already been made to sintering and vacuum fusion processes, which are of special value in dealing with metals of high melting point and high oxygen affinity, respectively. Both methods are used in the preparation of pure, ductile tantalum and niobium.[58] A crude tantalum powder is obtained by reduction of the double potassium fluoride, K_2TaF_7, with sodium; this is pressed into bars and sintered in a vacuum at a temperature just below the melting point to remove volatile impurities. Alternatively, the crude metal is converted into tantalum hydride by heating in hydrogen at 1000°, and the hydride is decomposed by sintering at 1500° or above. The sintered bars of tantalum produced in either process are brittle, and vacuum fusion is necessary to render the metal ductile; since the melting point is very high (2800—2850°), the fusion process is carried out by striking an electric arc between a block of the sintered material and an electrode of tantalum or tungsten. The final product is sufficiently ductile to be rolled without difficulty into sheets 0·1 mm. thick. Ductile niobium is produced by an exactly similar method.

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[55] E. C. Truesdale and G. Edmunds, Amer. Inst. Min. Met. Eng., Inst. Metals Divn., Tech. Publ. 1033 (1939).

[56] H. Matthies, *Metall u. Erz*, 1936, **33**, 280.

[57] F. C. Kracek, *J. Amer. Chem. Soc.*, 1941, **63**, 1989.

[58] C. J. Smithells, *Metal Ind.* (*Lond.*), 1931, **38**, 336.

Final purification of cathodic nickel has been effected by annealing the metal in hydrogen at 1050° to remove carbon and sulphur, and then fusing in a vacuum in specially bonded magnesia crucibles.[59] The product is 99·94% pure, the chief impurities being iron (0·03%) and cobalt (0·016%).

Attention may be directed to two papers dealing with the theoretical aspects of degassing of metals,[60] in which it is shown that maximum rates of degassing are reached over certain temperature ranges, which are simply related to the melting points of the metals. The results clearly have a practical bearing on the purification of metals by sintering in a vacuum.

Electrolytic Purification of Metals.—This method of refining, so well known in industrial practice, finds useful applications in the preparation of high-purity metals on the laboratory scale. Recent work in this direction is well exemplified by a method for producing 99·999% pure copper.[61] The first stage in the refining of commercial electrolytic copper to this purity is an electrolysis at low current density through a bath of sulphuric acid and copper sulphate, anodes of the crude metal and cathodes of pure copper sheet being employed in the usual manner. This electrolysis is stated to free the copper from all the important impurities except sulphur; the latter is removed by air-blowing the surface of the molten metal, a process which necessarily introduces oxygen, with clay, iron, and graphite from the melting crucible. Final purification is effected by a second electrolysis through a copper nitrate electrolyte. In each of the electrolyses " starting sheets " are first obtained by deposition on stainless steel plates, from which they can afterwards be stripped. The purified metal is cast into oxygen-free rods by melting in hydrogen in a specially designed casting apparatus.

Metallic indium estimated to contain not more than 0·001% of total impurities has been prepared by electrolytic refining of a " pure " commercial product through an indium chloride solution, two successive electrolyses being required.[62] Other metals to which electrolytic refining is particularly applicable include zinc,[63] lead,[64] manganese,[65] and silver.[66]

A particularly novel method of electrolytic purification of aluminium, in which both electrodes are composed of molten metal, has been described.[67] The lowest and densest layer in the cell is an aluminium–copper alloy containing 33% of copper; above this is the electrolyte, consisting of molten alkali-metal and aluminium fluorides and barium chloride; the upper layer is the cathode of pure, molten aluminium, which is less dense than the fused

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[59] L. Jordan, W. H. Swanger, *et al.*, *J. Res. Nat. Bur. Stand.*, 1930, **5**, 1291.

[60] G. F. Hüttig, H. Thiemer, and W. Breuer, *Z. anorg. Chem.*, 1942, **249**, 134; G. F. Hüttig and H. H. Bludau, *ibid.*, 1942, **250**, 36.

[61] J. S. Smart, jun., A. A. Smith, jun., and A. J. Phillips, Amer. Inst. Min. Met. Eng., Inst. Metals Divn., Tech. Publ. 1289 (1941).

[62] G. P. Baxter and C. M. Alter, *J. Amer. Chem. Soc.*, 1933, **55**, 1943.

[63] W. Hänig, *Metall u. Erz*, 1936, **33**, 274.

[64] R. S. Russell, *Proc. Aust. Inst. Min. Met.*, 1932, **87**, 145.

[65] H. H. Oaks and W. E. Bradt, *Trans. Amer. Electrochem. Soc.*, 1936, **69**, 567.

[66] G. P. Baxter and O. W. Lundstedt, *J. Amer. Chem. Soc.*, 1940, **62**, 1829.

[67] H. Dürr, *Giessereipraxis*, 1938, **59**, 114.

salt bath. During electrolysis the less electropositive impurities (iron, silicon, etc.) remain in the anode layer, and the more electropositive ones (magnesium and lithium) dissolve in the electrolyte as their chlorides.

Special Purification Methods applicable to Individual Elements.—In addition to the more or less general methods of preparation and purification described above, there are numerous special methods designed to remove specific impurities from particular elements. These cannot be enumerated here, but brief reference may be made to the purification of iodine by removal of other halogens and organic matter,[66] and the extraction of iron, silica, and other impurities from commercial silicon by means of acids.[68]

It has recently been pointed out [69] that the most troublesome impurity in commercial sulphur is organic material originating from the hydrocarbons always associated with non-volcanic sulphur deposits. Decomposition of organic material leads also to the presence of hydrogen persulphides. Four successive distillations of commercial sulphur do not suffice to remove the impurities, the presence of which is indicated by the development of black specks when the sulphur is boiled in a clean glass tube. The method of purification recommended is as follows: the sulphur (1 kg.) is raised slowly to the boiling point in a Pyrex flask, and boiling continued for 3—4 hours after addition of 5 g. of magnesium oxide; this serves to remove acid impurities and decompose hydrogen persulphides. The sulphur is allowed to stand for some hours at 125°, and the clear molten material is decanted from a black sludge of impurities, through a Pyrex wool filter. The sulphur is then heated at the boiling point for four successive periods of about 30 hours with 10-g. portions of magnesium oxide, the liquid being filtered after each period of boiling. The purified sulphur contains no detectable impurity. The method described is intended for use with American sulphur, in which there is no arsenic, selenium, or tellurium.

Preparation of Elements in Special Allotropic Forms.—Attention may be directed here to recent work on the synthesis of diamond,[70] in which Moissan's experiments were repeated under a variety of conditions with modern technique; molten iron containing carbon was quenched in water- or liquid-air-cooled vessels after heating at temperatures as high as 3000°. Graphite was also subjected to a momentary pressure of about 120,000 kg. per sq. cm. at 3000—3200°. Although a few very small fragments with the properties of diamond were produced in some experiments, consistent yields of diamonds were never obtained. These experiments lend added interest to the discovery, made by *X*-ray analysis, that eleven out of twelve " artificial diamonds " allegedly prepared by J. B. Hannay in 1879—1880 are indeed diamonds, at least one of them having the rare " type II " structure.[71] Hannay's attempts

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[68] N. P. Tucker, *J. Iron Steel Inst.*, 1927, **115**, 412; A. B. Kinzel and T. R. Cunningham, Amer. Inst. Min. Met. Eng., Inst. Metals Divn., Tech. Publ. 1138 (1939).

[69] R. F. Bacon and R. Fanelli, *Ind. Eng. Chem.*, 1942, **34**, 1043.

[70] P. L. Günther, P. Geselle, and W. Rebentisch, *Z. anorg. Chem.*, 1943, **250**, 357.

[71] F. A. Bannister and (Mrs.) K. Lonsdale, *Nature*, 1943, **151**, 334; (Lord) Rayleigh, *ibid.*, p. 394; F. A. Bannister and K. Lonsdale, *Min. Mag.*, 1943, **26**, 315.

at diamond synthesis were carried out by heating paraffin, bone oil, and metallic lithium to a red heat in a very strong iron tube.[72]

Black phosphorus has recently been prepared from the white form by momentary application of a pressure of about 100,000 kg. per sq. cm., at room temperature.[73] The black form is stated to be unstable under ordinary temperature and pressure conditions, and to revert to white phosphorus on keeping; the red form is the most stable allotrope. A. J. E. W.

H. J. Emeléus.
A. J. E. Welch.

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[72] *Nature*, 1880, **22**, 255; *Proc. Roy. Soc.*, 1880, *A*, **30**, 188, 450; 1882, *A*, **32**, 407.

[73] P. L. Günther, P. Geselle, and W. Rebentisch, *Z. anorg. Chem.*, 1943, **250**, 373.

CRYSTALLOGRAPHY.

1. Introduction and General.

The inorganic and the organic section in this Report review most of the new structure determinations made by *X*-ray and electron-diffraction methods during the year. A considerable volume of work is still being carried out in certain quarters, but restrictions on space and inaccessibility of many of the journals combine to make the present Report rather incomplete. It is hoped, however, that the more important structural work has been covered.

The structures of nitrous oxide, hydrogen azide, hydrazine, and ozone have now been accurately determined, and the inorganic field includes some interesting work on the structure and polymorphism of the oxides Pb_3O_4, Bi_2O_3, As_4O_6, and P_4O_{10}. The crystal structure of boron carbide B_4C is an interesting one, and electron-diffraction studies have been made on a number of boron fluoride compounds. (The boron hydrides are dealt with in another part of this volume.[1]) Finally, there is an interesting structure determination on the trimer of phosphonitrile chloride.

A fairly wide variety of organic structures have received attention, and the constitutions of pirylene (C_5H_6) and of diphenylene have been established. The first reasonably quantitative studies of aromatic molecular compounds have been published and these reveal the rather surprising absence of any kind of intimate contact between the component molecules. Distortions are reported in the dinitrodiphenyl molecule, but it is difficult to estimate the accuracy of this work. Both structural and physical investigations have been made on a number of porphin and phthalocyanine compounds. Amino-acids and peptides have received some attention, and amongst more complex substances there has been some promising work on starch derivatives. Very full analyses are reported for the rubber hydrochloride polymer, and for the simple di-isoprene derivative geranylamine hydrochloride, for which some interesting and unusual bond distances are found.

There is also an increasing volume of work on natural and synthetic fibre structures which it is not possible to cover in this Report, but mention may be made of a special article by I. MacArthur[2] on the structure of α-keratin. This is the first detailed account of the very complete fibre pattern obtained from the cortex of African porcupine quill tip. More than 100 reflections have been obtained in the range 1—150 A. The repeat unit along the fibre axis may be 198 or 658 A. It is to be expected that the detailed analysis of this pattern will ultimately add greatly to our knowledge of protein structure. In the meantime, the results obtained appear to substantiate and check in some detail the new model for α-keratin recently advanced by W. T. Astbury.[3]

X-Ray diffraction methods are being applied in a number of other directions which are beyond the scope of the present Report. These include work

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[1] P. 62. [2] *Nature*, 1943, **152**, 38. [3] *Ann. Reports*, 1941, **38**, 109.

on metal structures and transformations,[4] and on coal and carbonisation processes, some of the latter being discussed elsewhere in these Reports.[5] Another new development of interest is that of divergent-beam X-ray photography;[6] here, the crystal is placed in direct contact with the point source on the anticathode and a pattern of deficiency lines is obtained, marking the places where the primary intensity has been reduced by reflection. The method enables lattice constants to be determined easily and with great accuracy, and it has been found, for example, that individual diamonds have lattice constants varying over a range of about $3{\cdot}55970 \pm 0{\cdot}00020$ kX (1 kX = 1000 X.U.).

A number of general works which themselves constitute useful reviews may be briefly mentioned. Sir Lawrence Bragg[7] has provided a fascinating and most readable account of the history of X-ray analysis from the first experiments up to the present time. M. J. Buerger[8] has given a comprehensive account of X-ray crystallography, limiting that title to mean only the investigation of the space pattern of the crystal, and excluding the interpretation of data relating to the chemical constitution or nature of the crystal itself (a much wider subject covered by the title " X-ray analysis "). Within this limited field a very full and useful account is given, particularly of the interpretation of rotating crystal, oscillation, and moving-film photographs.

Amongst papers of a review nature, reference may be made to an X-ray study of crystal dynamics by (Mrs.) K. Lonsdale[9] in which the whole subject of diffuse, anomalous, temperature, or non-Laue reflections is very fully discussed, together with their theoretical interpretation. The Faxén–Waller theory, which explains the spread of reflecting power as due chiefly to the thermal (elastic) vibration of atoms and molecules, is found to give the best account of the results obtained from all kinds of crystals.

An early paper by A. Charlesby, G. I. Finch, and H. Wilman[10] concerned with certain new diffuse features in the electron-diffraction patterns obtained from single crystals of anthracene is of considerable interest in this connection. These authors reached the conclusion at that time that the effects were due to thermal vibrations of the molecules as complete units.

Intensity measurement presents one of the outstanding practical problems in X-ray crystal analysis. A summarising article dealing with the technique of intensity measurement by photographic methods[11] may therefore be

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[4] A. J. C. Wilson, *Proc. Roy. Soc.*, 1943, *A*, **181**, 360; (Miss) V. Daniel and H. Lipson, *ibid.*, p. 368; (Miss) O. S. Edwards and H. Lipson, *J. Inst. Metals*, 1943, **69**, 177.

[5] P. 32.

[6] (Mrs.) K. Lonsdale, *Nature*, 1943, **151**, 52; 1944, **153**, 22.

[7] " The History of X-Ray Analysis." Science in Britain series, Longmans, Green & Co., 1943.

[8] " X-Ray Crystallography," John Wiley & Sons, Inc., and Chapman & Hall, Ltd., 1942.

[9] *Proc. Physical Soc.*, 1942, **54**, 314.

[10] *Ibid.*, 1939, **51**, 479; see also *Ann. Reports*, 1939, **36**, 179.

[11] J. M. Robertson, *J. Sci. Instr.*, 1943, **20**, 175.

useful. This article does not describe photometers, but rather the various conditions and precautions necessary for the production of accurate records, and means whereby intensities of widely differing range may be correlated. Visual estimates of intensities from reliable records may be better than the most elaborate measurements made on films where some of these precautions (shape and size of specimen, development conditions, etc.) have been neglected.

2. INORGANIC STRUCTURES.

A number of elements and simple compounds have been examined in the liquid form by scattering experiments with monochromatic X-radiation, with results that give information about the structure of the liquid, and interatomic distances in general. Work carried out over a range of temperatures on liquid mercury, xenon,[1] nitrogen, nitrous oxide, nitric oxide,[2] and carbon tetrachloride[3] may be mentioned. The radial distribution curve for mercury gives a first peak at 3·00 A., but the number of atoms in the first co-ordination layer is only about 6, this being the lowest number yet found for a monatomic element. In xenon the number of nearest neighbours is 9—10 at 4·43—4·50 A. Diatomic aggregates are shown by the distribution curves for nitrogen and nitric oxide, and for nitrous oxide the data are consistent with a linear molecule. In carbon tetrachloride the peaks at 1·74 and 2·92 A. (25°) correspond very closely to L. O. Brockway's determination[4] of the interatomic distances by electron diffraction (C–Cl = 1·75 A.; Cl–Cl = 2·87 A.). These results indicate that the technique of X-ray diffraction as applied to liquids is becoming more perfect, and we may expect applications to more complicated systems in the future.

An electron-diffraction study of hydrogen peroxide and hydrazine has now been reported[5] which was made with a view to determine the length of the O–O and the N–N covalent single bond. The values found, both 1·47±0·02 A., are considerably greater than those indicated by the Pauling–Huggins radii for those atoms[6] which were 1·32 and 1·40 A., respectively. This upwards revision of the covalent single bond radii has already been discussed in these Reports.[7] The sequence of values now reported for the compounds ethane, hydrazine, hydrogen peroxide, and fluorine[8] is 1·54, 1·47, 1·47, and 1·43 A. It is a little surprising that the same values should be obtained for nitrogen and oxygen, but the distance in hydrogen peroxide may actually

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[1] J. A. Campbell and J. H. Hildebrand, *J. Chem. Physics*, 1943, **11**, 330, 334.

[2] P. C. Sharrah, *ibid.*, p. 435.

[3] E. E. Bray and N. S. Gingrich, *ibid.*, p. 351; A. Eisenstein, *Physical Rev.*, 1943, **63**, 304.

[4] *Rev. Mod. Physics*, 1936, **8**, 231.

[5] P. A. Giguère and V. Schomaker, *J. Amer. Chem. Soc.*, 1943, **65**, 2025.

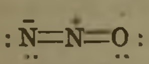
[6] L. Pauling and M. L. Huggins, *Z. Krist.*, 1934, **87**, 205.

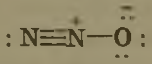
[7] *Ann. Reports*, 1941, **38**, 100; V. Schomaker and D. P. Stevenson, *J. Amer. Chem. Soc.*, 1941, **63**, 37.

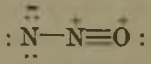
[8] L. O. Brockway, *ibid.*, 1938, **60**, 1348; M. T. Rogers, V. Schomaker, and D. P. Stevenson, *ibid.*, 1941, **63**, 2610.

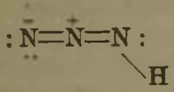
be a little less, as indeed is indicated by the very careful crystal-structure determination of hyperol[9] which gives O–O = 1·46 A.

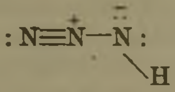
The structures of nitrous oxide and hydrogen azide have also been examined by electron-diffraction methods.[10] These two essentially linear molecules present very much the same problem, the expected resonating structures being (I)—(III) and (IV)—(VI), respectively. The diffraction

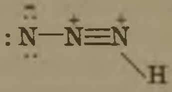

(I.)


(II.)


(III.)

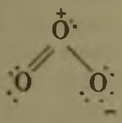

(IV.)

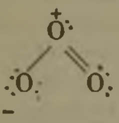

(V.)

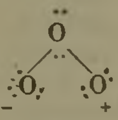

(VI.)

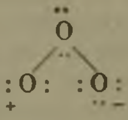
results give N–N = 1·14±0·01 A. and N–NH = 1·25±0·01 A. for the azide. For nitrous oxide the central atom cannot be precisely fixed, but the results confirm Pauling's prediction[11] of N–N = 1·12 A. and N–O = 1·19 A. Pauling's adjacent charge rule is thus confirmed, in that structures (III) and (VI) can make but little contribution to the normal state of these molecules. Any considerable contribution from these structures would drastically alter the above distances. These results are also in agreement with the results of earlier spectroscopic investigations.[12, 13]

Ozone.—The first complete structural investigation of ozone has now been made by W. Shand and R. A. Spurr,[14] using the method of electron diffraction. Precautions were taken to ensure that the ozone had a purity of 95% or better, but the calculations show that even a much larger oxygen impurity would have little effect on the results. Both radial distribution and the correlation methods were used in interpreting the results, which show that the molecule has a symmetrical angular form with the O–O bond distance 1·26±0·02 A., and the O–O–O angle 127°±3°. The non-bonded oxygen distance is only 2·24 A., which must involve considerable repulsion between the terminal oxygens. The results are in reasonable agreement with the spectroscopic work of W. G. Penney and G. B. B. M. Sutherland;[15] they correspond to a double-bond character of about 30%, and the most important resonating structures are probably (VII)—(X).


(VII.)


(VIII.)


(IX.)


(X.)

[9] See *Ann. Reports*, 1942, **39**, 103; C. S. Lu, E. W. Hughes, and P. A. Giguère, *J. Amer. Chem. Soc.*, 1941, **63**, 1507.

[10] V. Schomaker and R. Spurr, *ibid.*, 1942, **64**, 1184.

[11] "The Nature of the Covalent Bond," Cornell Univ. Press, 2nd edtn., p. 200, 1940.

[12] E. Plyler and E. F. Barker, *Physical Rev.*, 1931, **38**, 1827.

[13] E. H. Eyster, *J. Chem. Physics*, 1940, **8**, 141.

[14] *J. Amer. Chem. Soc.*, 1943, **65**, 179. [15] *Proc. Roy. Soc.*, 1936, *A*, **156**, 578, 654.

Oxides.—Single crystals of minium, Pb_3O_4, have now been obtained in the form of transparent red needles,[16] and a fairly complete analysis of the structure has been made by S. T. Gross.[17] The crystals are tetragonal, and approximate closely to the space-group *P4/mbc*. The relatively small scattering power of the oxygen atoms makes it impossible to determine their positions directly from the *X*-ray data, but these positions can be inferred from the cell dimensions and co-ordination rules. The structure can be considered roughly as compounded from PbO (red) and PbO_2 units. As in PbO_2,[18] the plumbic ions are associated with chains of oxygen octahedra with opposite edges shared. Adjacent chains approach in such a manner that three oxygen ions are further co-ordinated with each plumbous ion, giving an arrangement similar to that found in red PbO.[19] It is to be hoped that further work will reveal the structure of Pb_2O_3, of which single crystals are also available,[16] and ultimately show how the transition from one form to the other is effected.

The polymorphism of Bi_2O_3, about which some conflicting data exist, has now been re-examined by W. C. Schumb and E. S. Rittner.[20] Pure Bi_2O_3 is found to crystallise in at least 3 distinct forms : the low-temperature α-form is monoclinic with a transition point at 710° to the high-temperature β-modification, which is tetragonal. The third, or γ-form, is body-centred cubic, but is without any stable region between 25° and the melting point, and so is probably monotropic.

The polymorphism of arsenious oxide, As_4O_6, has also been re-examined by J. H. Schulman and W. C. Schumb,[21] and they find no definite evidence for the existence of any forms other than the well-known cubic and monoclinic varieties. The structure of the latter is known to be of a molecular type containing clusters of discrete As_4O_6 units,[22] but that of the monoclinic variety has not yet been fully determined. An enantiotropic relationship is now shown to exist between these two forms, the transition temperature being in the neighbourhood of −13°. Although above this temperature the cubic form is thermodynamically unstable with respect to the monoclinic form, nevertheless the cubic form may remain untransformed indefinitely in the natural state.

A very interesting but more complex problem is presented by the polymorphism of phosphoric oxide.[23] In this case there are three distinct crystalline modifications, exhibiting monotropic relationships, at least two distinct liquids, and some interesting glasses. The crystalline form familiar as a laboratory reagent is the low-temperature or volatile form. This belongs to the rhombohedral division of the hexagonal system, and the unit of structure has now been shown [24] to contain two P_4O_{10} molecules of the

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[16] G. L. Clark, N. C. Schieltz, and T. T. Quirke, *J. Amer. Chem. Soc.*, 1937, **59**, 2305.
[17] *Ibid.*, 1943, **65**, 1107.
[18] W. L. Bragg, " Atomic Structure of Minerals," Cornell Univ. Press, 1937, p. 103.
[19] R. G. Dickinson and J. B. Friauf, *J. Amer. Chem. Soc.*, 1924, **46**, 2457.
[20] *Ibid.*, 1943, **65**, 1055. [21] *Ibid.*, p. 878. [22] R. M. Bozorth, *ibid.*, 1923, **45**, 1621.
[23] W. L. Hill, G. T. Faust, and S. B. Hendricks, *ibid.*, 1943, **65**, 794.
[24] H. C. J. de Decker and C. H. MacGillavry, *Rec. Trav. chim.*, 1941, **60**, 153.

same configuration as exists in the vapour phase[25] (phosphorus atoms at the corners of a regular tetrahedron, and surrounded, again tetrahedrally, by oxygen atoms).

By heating in a sealed tube, high-temperature crystalline modifications can be obtained, which have low vapour pressures and fundamentally different structures. First, there is the orthorhombic modification whose structure has now been determined[26] and shown to consist of an infinite sheet polymer containing interlocking rings, the phosphorus atoms being surrounded by shared tetrahedra of oxygen atoms. The second high-temperature form has not so far been analysed by *X*-ray methods, but it is probably tetragonal[23] and very likely again consists of an infinite polymer, but this time of a three-dimensional type.

The different crystalline modifications of phosphoric oxide thus correspond to different states of polymerisation, and a knowledge of their structure explains their strikingly different behaviour in reactions, for example, with water. The violent reaction of the ordinary hexagonal form is replaced by a comparatively slow reaction in the case of the orthorhombic form, this probably taking place first of all along the cleavage cracks of the sheets, with slow degradation into small crystals. The three-dimensional tetragonal form also reacts slowly compared with the ordinary form, but more rapidly than the orthorhombic (sheet) form.

These structure determinations also serve to explain the phenomena of different phosphoric oxide liquid types, because, according to modern theories,[27] the liquid will inherit some of the structural features of the solid from which it is derived. On rapid heating the low-temperature hexagonal form melts to a liquid consisting mainly of P_4O_{10} molecules, but these polymerise rapidly with decrease in the vapour pressure. Transformation of the different liquid types is seen to correspond essentially to chemical reactions.

Boron Carbide.—The interesting structure of crystalline B_4C has now been determined with considerable accuracy.[28, 29] The rhombohedral unit cell (space group D^5_3d–$R3m$) with $a = 5{\cdot}19$ A., $\alpha = 66^\circ\ 18'$, contains 3 stoicheiometric B_4C molecules. The structural units, however, consist of compact groups of 12 boron atoms and linear chains of 3 carbon atoms, these groups alternating approximately as in the NaCl type of structure. The 12 boron atoms are arranged at the vertices of a nearly regular icosahedron, each boron atom having 6-fold co-ordination, being bonded to five others in the same group and to either a carbon or a boron in an adjoining group. The appreciable electrical conductivity of the crystals points to a high degree of resonance and a binding with some metallic characteristics.

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[25] G. C. Hampson and A. J. Stosick, *J. Amer. Chem. Soc.*, 1938, **60**, 1814.

[26] H. C. J. de Decker, *Rec. Trav. chim.*, 1941, **60**, 413.

[27] J. G. Kirkwood and E. Monroe, *J. Chem. Physics*, 1941, **9**, 514.

[28] G. S. Zhdanov and N. G. Sevast'yanov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **32**, 432.

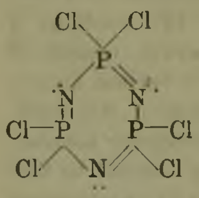
[29] H. K. Clark and J. L. Hoard, *J. Amer. Chem. Soc.*, 1943, **65**, 2115.

There appears also to be room in the structure for additional atoms, which accounts for the existence of material with a variable boron–carbon ratio.

Boron Fluorides.—An electron-diffraction investigation by S. H. Bauer and J. M. Hastings [30] on dimethylboron fluoride and methylboron difluoride has now completed the observed interatomic distance data for the series of compounds $B(CH_3)_3$, $B(CH_3)_2F$, $B(CH_3)F_2$, and BF_3. Roughly, it is found that all these compounds have the same configuration and essentially the same interatomic distances, *viz.*, planar molecules with B–C = 1·55—1·60 A., B–F = 1·29—1·30 A., and valency angles of about 120°. There are certain difficulties in interpreting these results in terms of the dependence of bond distance on bond type, and especially in comparison with the corresponding series of fluorine-substituted methanes.[31] Thus, the contribution of excited structures of the type $X_2B^{-}::F^{+}::$ and of the normal structure $X_2B:F:::$ must vary in these different compounds, but at present it is difficult to explain this in terms of the observed results.

In the molecular compound, dimethyl ether–boron trifluoride, $(CH_3)_2O:BF_3$, the boron trifluoride unit necessarily undergoes a rather drastic structural change.[32, 33] The boron valency angles become tetrahedral, with B–F = 1·41 ± 0·02 A. This is substantially the normal B–F separation for tetrahedral bonding, as in the alkali fluoborates.[34] The dimethyl ether part of the molecule remains practically unaffected, and the co-ordinate link $O \rightarrow B$ has a length of 1·52 ± 0·06 A.

Phosphonitrile Chlorides.—Although the phosphonitrile chloride series of compounds have been known for many years,[35] the structures of even the simple members have been in doubt until quite recently. An advance was made in 1939 by the full *X*-ray crystallographic determination of the structure of the tetramer,[36] which was shown to consist of a puckered 8-membered ring of alternate nitrogen and phosphorus atoms, each of the latter carrying two chlorine atoms. L. O. Brockway and W. M. Bright [37] have now made a full determination of the structure of the trimer, $P_3N_3Cl_6$, by the method of electron diffraction in the vapour. A number of earlier proposed structures involving chlorine attached to nitrogen, a three-membered nitrogen ring, open chain, etc., have been tested and eliminated, and the model which finally gives best agreement with the diffraction data is found to be (XI). The ring appears to be planar (although models with staggered rings have not been directly tested) and the P–N bond distance of 1·65 A. indicates a Kekulé type of resonance (P–N single bond = 1·80 A., and P–N double bond = 1·61 A.). The P–Cl distance



(XI.)

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[30] *J. Amer. Chem. Soc.*, 1942, **64**, 2686.

[31] L. O. Brockway, *J. Physical Chem.*, 1937, **41**, 747.

[32] A. W. Laubengayer and G. R. Finlay, *J. Amer. Chem. Soc.*, 1943, **65**, 884.

[33] S. H. Bauer, G. R. Finlay, and A. W. Laubengayer, *ibid.*, p. 889.

[34] J. L. Hoard and V. Blair, *ibid.*, 1935, **57**, 1985.

[35] H. Rose, *Annalen*, 1834, **11**, 129; J. Liebig and F. Wöhler, *ibid.*, p. 139.

[36] See *Ann. Reports*, 1940, **37**, 186.

[37] *J. Amer. Chem. Soc.*, 1943, **65**, 1551.

of 1·97 A. is in fair agreement with that reported in other compounds, *e.g.*, phosphorus trichloride, fluorodichloride, and phosphoryl chloride, etc.

Miscellaneous Structures.—A series of gallium alums have been measured by H. P. Klug and G. L. Kieffer,[38] and the structure types determined. Both the potassium–aluminium or α- and the cæsium–aluminium or β-alum type are found to occur. A number of gallium and indium trihalide bond distances obtained by W. R. Brode [39] by electron-diffraction methods have now been corrected by D. P. Stevenson and V. Schomaker.[40] The structure of silver chlorate, with atomic parameters, has been reported,[41] but details are not available. Silver bromide crystals are isomorphous.

3. ORGANIC STRUCTURES.

The very complete analysis of the infra-red spectra of ethylene and tetradeuteroethylene reported by W. S. Gallaway and E. F. Barker [1] yields new data for all the dimensions of the ethylene molecule which may have important consequences in organic structural work. They find in particular that the C–C double bond distance is $1{\cdot}353 \pm 0{\cdot}01$ A., a value somewhat higher than has previously been accepted. In most *X*-ray work it is difficult to measure this bond length accurately; *e.g.*, in stilbene [2] the resolution of the doubly linked carbon atoms is poor. In such cases it has usually been the practice to assume the spectroscopic value for this linkage in order to fix the position of such atoms definitely. Although the difference between the old value (1·33 A.) and the new one (1·35 A.) is not large, this bond length is rather fundamental and is used, for example, in the bond order–distance curves [3] for estimating the contribution of possible resonance structures to the normal state in the case of various molecules. Direct precision *X*-ray measurements of this bond length in more complex molecules would now be extremely interesting.

Amongst simple structures that of gadolinium formate has been determined by A. Pabst.[4] The dimensions of the formate group obtained by *X*-ray analysis are in good agreement with previous determinations, C–O distances of 1·27 A. and 1·33 A. with a bond angle of 121° being reported. The radius of the gadolinium ion is estimated to be 0·98 A., and it shows a nine-fold co-ordination with the surrounding oxygen ions.

An electron-diffraction study of methyl *iso*cyanide has now been carried out with the latest improved technique,[5] and the results verify that the molecule is linear, at least to within about 20°. This is in agreement with

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[38] *J. Amer. Chem. Soc.*, 1943, **65**, 2071. [39] *Ann. Physik*, 1940, **37**, 344.

[40] *J. Amer. Chem. Soc.*, 1942, **64**, 2514.

[41] S. von Náray-Szabó and J. Pócza, *Z. Krist.*, 1942, **104**, 28.

[1] *J. Chem. Physics*, 1942, **10**, 88.

[2] J. M. Robertson and (Miss) I. Woodward, *Proc. Roy. Soc.*, 1937, *A*, **162**, 568.

[3] L. Pauling, L. O. Brockway, and J. Y. Beach, *J. Amer. Chem. Soc.*, 1935, **57**, 2705; W. G. Penney, *Proc. Roy. Soc.*, 1937, *A*, **158**, 306.

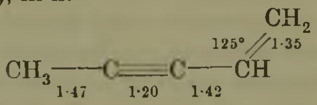
[4] *J. Chem. Physics*, 1943, **11**, 145.

[5] W. Gordy and L. Pauling, *J. Amer. Chem Soc.*, 1942, **64**, 2952.

earlier work [6] and with spectroscopic data,[7] and shows that of the structures (I) and (II) the contribution of (II) must be small. The interatomic distances are H_3C–N = 1·44±0·02 A., and N–C = 1·18±0·02 A.

$$\text{(I.)}\quad CH_3-\overset{+}{N}\equiv\overset{-}{C}\colon \qquad\qquad CH_3-\overset{\cdot\cdot}{N}=C\colon\quad\text{(II.)}$$

Constitution of Pirylene.—The hydrocarbon C_5H_6, named pirylene, was first obtained by A. Ladenburg [8] from piperidine. The structure remained obscure, although later investigators [9] favoured a doubly-unsaturated ring, possibly methylene*cyclo*butene. The subject has now been re-examined, both chemically [10] and by electron diffraction.[11] The latter work is of rather special interest, being a structure determination by vapour electron-diffraction methods in a case where only the molecular formula was known. Although this formula is comparatively simple, C_5H_6, there are actually about 30 possibilities, and the correct solution proves to be quite different from that indicated by the later chemical evidence.[9] The method employed consisted of a rather accurate radial distribution summation, followed by a study of the intensity curves for the most probable models, based on known bond distances and angles. The final result eliminates all ring structures and shows quite clearly that pirylene is actually α-methyl-β-vinylacetylene. The molecular dimensions which give the best agreement with the observations are shown in (III), in A.



$$CH_3\underset{1\cdot47}{-\!-}C\underset{1\cdot20}{\equiv}C\underset{1\cdot42}{-\!-}CH\overset{125°}{\underset{1\cdot35}{=}}CH_2$$

(III.)

Structure of Diphenylene.—W. C. Lothrop [12] recently synthesised the aromatic hydrocarbon $C_{12}H_8$ and assigned to it the structure (IV), which has since been the subject of some discussion. It represents the first definite aromatic four-membered ring, and as such the structure must be under considerable strain. *cyclo*Butadiene has never been prepared, although *cyclo*butane and other four-membered rings are well known.[13] In view of these facts, and as a result of certain catalytic reduction experiments, W. Baker [14] concluded that Lothrop's compound should be represented by (V), an arrangement where the bonds are under considerably less strain. This conclusion was supported by C. A. Coulson [15] by calculations of the strain and resonance energy.

(IV.)

(V.)

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[6] L. O. Brockway, *J. Amer. Chem. Soc.*, 1936, **58**, 2516.

[7] R. M. Badger and S. H. Bauer, *ibid.*, 1937, **59**, 303.

[8] *Ber.*, 1882, **15**, 1024; *Annalen*, 1888, **247**, 56.

[9] J. von Braun and W. Teuffert, *Ber.*, 1928, **61**, 1092.

[10] H. Sargent, E. R. Buchman, and J. P. Farquhar, *J. Amer. Chem. Soc.*, 1942, **64**, 2692.

[11] R. Spurr and V. Schomaker, *ibid.*, p. 2693.

[12] *Ibid.*, 1941, **63**, 1187; 1942, **64**, 1689.

[13] See *Ann. Reports*, 1942, **39**, 104.

[14] *Nature*, 1942, **150**, 211.

[15] *Ibid.*, p. 577.

The problem obviously demands investigation by modern physical methods, and this has now been carried out by J. Waser and V. Schomaker.[16] Their very detailed electron-diffraction investigation was made on the vapour of diphenylene, and the results are reported to confirm structure (IV) and definitely eliminate structure (V). The radial distribution curve obtained shows peaks corresponding to interatomic distances at 1·42 A. (average C–C), at 2·1 A. (diagonals of the four-ring) and at 2·44 A. and 2·78 A. (*m*- and *p*-distances in the six-ring). The curve also continues to be in satisfactory agreement with the structure (IV) out to quite large distances. Any reasonable model of structure (V) appears to be ruled out, particularly because of the absence of any distances which would correspond to the 10 diagonals of the pentagons, *i.e.*, distances of the order of 2·30 A. The higher reaches of the curve are also quite unsatisfactory for structure (V). The model which finally gives the best agreement with the experimental results is the diphenylene structure with the sides of the hexagons equal to 1·41 ± 0·02 A., the lateral connecting links of the four-ring equal to 1·46 ± 0·05 A., and the hexagon angle α equal to $121° \pm 3°$.

Only preliminary results of the crystal-structure investigation of diphenylene are available,[16] and these are peculiar in so far as they indicate 6 molecules of $C_{12}H_8$ per unit cell for space group $P2_1/a$. This would indicate that at least two of the molecules must exhibit a centre of symmetry, in conformity with structure (IV). Final judgment should perhaps be reserved until the crystal has been fully investigated, especially as with a molecule of this complexity the electron-diffraction method can at best only give average values for many of the structural parameters.

Aromatic Molecular Compounds.—The structures of these molecular compounds are of great interest, but necessarily complex from an *X*-ray point of view as they all involve rather large numbers of atoms. However, a quantitative *X*-ray determination of the structure of *p*-iodoaniline–*s*-trinitrobenzene has now been made.[17] The monoclinic unit cell (space group $P2_1/c$) contains four molecules of each of the components, and the analysis proceeds from a preliminary determination of the iodine positions by Patterson–Fourier methods to a final location of all the atoms by two- and three-dimensional Fourier synthesis. The accuracy of the determination is difficult to estimate in such a complex structure, but it is unlikely that there are any large errors, and the main features are quite clear. The most notable and rather unexpected result is that there are no short interatomic distances between the component molecules. These are arranged in such a way that the C------C distances between neighbouring benzene rings are never less than 3·5 A. The shortest intermolecular distance occurs between the nitrogen of the amino-group and a neighbouring oxygen, where the separation is 3·1 A. This may correspond to a very weak type of hydrogen bond, but such a bond cannot, of course, play any essential part in the general problem of the aromatic molecular compounds. One nitrogen–

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[16] *J. Amer. Chem. Soc.*, 1943, **65**, 1451.

[17] H. M. Powell, G. Huse, and P. W. Cooke, *J.*, 1943, 153.

carbon separation of 3·25 A. is mentioned, which seems rather less than usual, and may be of some significance.

Molecular compounds formed between the picryl halides and hexamethylbenzene have also been studied.[18] These structures are still more complex and appear to be disordered to some extent, but the significant features are again fairly clear. The structures consist essentially of alternate layers of the two components with a separation of about 3·5 A., indicating relatively weak binding. This is confirmed by a Patterson–Fourier projection, and independently by a study of certain diffuse reflections which are formed. In particular it is shown that the evidence is against the existence of ions in the structure.

Miscellaneous Complex Crystals.—An investigation of the many crystalline modifications of sodium stearate has been made,[19, 20] from room temperature to the melting point. The subject is one of extreme complexity, and no fewer than seven different phases of the γ-modification, which is dealt with in these papers, are recognised in this region. Numerous data are provided, but the subject is hardly yet suitable for a detailed report. Very finely oriented fibre photographs of sodium laurate, sodium palmitate, and sodium stearate have also been studied.[20]

A full account of the crystal structure of 4 : 4′-dinitrodiphenyl has been given by J. N. van Niekerk.[21] This crystal can be referred to orthogonal axes, but structurally it appears to belong to a monoclinic space group (*Pc*) which does not impose any molecular symmetry. The results of the analysis lead to molecular dimensions which are rather difficult to reconcile with known data for the types of bond involved. For instance, the C–C distance between the rings is given as 1·42 A., and the C–N distance as 1·56 A. There is also considerable distortion in the disposition of the nitro-groups with respect to the benzene rings. In such a complex structure it is difficult to estimate the accuracy of these figures, but they are probably subject to considerable errors. It seems possible that the initial assumption (made in order to simplify the analytical treatment) of a symmetry centre in the double ring system, which is not demanded crystallographically, may have introduced certain distortions. The structure is, however, a very interesting one and it should receive further attention.

The constitution of calycanine [22] has been further examined by *X*-ray methods, and the results appear to exclude the formula $C_{21}H_{15}N_3$ proposed by R. H. F. Manske and L. Marion [23] and support the simpler formula $C_{16}H_{10}N_2$.

A planar porphin ring is reported for tetramethylhæmatoporphyrin [24] by

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[18] H. M. Powell and G. Huse, *J.*, 1943, 435.

[19] J. W. McBain, A. de Bretteville, and S. Ross, *J. Chem. Physics*, 1943, **11**, 179.

[20] A. de Bretteville and W. McBain, *ibid.*, p. 426; J. W. McBain, O. E. A. Bolduan, and S. Ross, *J. Amer. Chem. Soc.*, 1943, **65**, 1873.

[21] *Proc. Roy. Soc.*, 1943, *A*, **181**, 314.

[22] A. Hargreaves, *Nature*, 1943, **152**, 600.

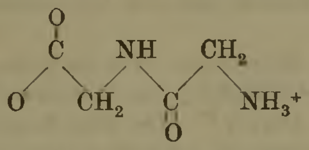
[23] See *Ann. Rev. Biochem.*, 1942, **11**, 572.

[24] H. O'Daniel and A. Damaschke, *Z. Krist.*, 1942, **104**, 114.

X-ray analysis, but further details are not available. Aetioporphyrin-I [25] has also been examined and a brief report made. In these studies comparisons are made with the ring form of phthalocyanine,[26] a closely related structure which has been fully determined.

Some very interesting measurements on the thermal expansion of certain porphin and phthalocyanine compounds have been made by A. R. Ubbelohde and (Miss) I. Woodward.[27] The work involves a new technique in dealing with single crystals over a large range of temperature which should be generally useful. Attention is particularly directed to the different behaviours of hydrogen and platinum phthalocyanine. The amplitude of the atomic vibrations (average) is calculated from the fading of the intensities, and the molecular movements in different directions are deduced from the observed expansions. The increased space requirement imposed by the platinum atom as the temperature rises, as compared with the central atoms of the other molecules, appears to be capable of explaining the observed results.

Amino-acids and Peptides.—The first quantitative *X*-ray study of a linear peptide has now been briefly reported.[28] Glycylglycine exists in at least 3 different crystalline modifications,[29] and the needle-like β-form, with a very short *b* axis (4·62 A.), has been selected for detailed study. The parameters are not yet sufficiently refined for a discussion of interatomic distances, but it is clear that the crystal is built from essentially planar molecules of the configuration (VI). The molecules are linked by hydrogen bonds of the usual type, these being disposed tetrahedrally about the terminal nitrogen atom and connecting it to one carbonyl and two carboxyl oxygen atoms of surrounding molecules. The imino-nitrogen also forms a hydrogen bond to a neighbouring carboxyl oxygen.



(VI.)

Complete structural determinations of compounds of this type are difficult owing to the many degrees of freedom, but a useful preliminary determination of unit-cell and space-group data has now been made for the following higher amino-acids [30] : *dl*-valine, *dl*-threonine, *dl*-serine, *dl*-norleucine, and *dl*-methionine.

A large air-dried crystal of β-lactoglobulin has been measured by I. Fankuchen,[31] and his results confirm the earlier measurements reported by

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[25] C. L. Christ and D. Harker, *Amer. Min.*, 1942, **27**, 219.

[26] J. M. Robertson, *J.*, 1936, 1195.

[27] *Proc. Roy. Soc.*, 1943, *A*, **181**, 415.

[28] E. W. Hughes and W. J. Moore, *J. Amer. Chem. Soc.*, 1942, **64**, 2236.

[29] J. D. Bernal, *Z. Krist.*, 1931, **78**, 363.

[30] G. Albrecht, C. W. Schnakenberg, M. S. Dunn, and J. D. McCullough, *J. Physical Chem.*, 1943, **47**, 24.

[31] *J. Amer. Chem. Soc.*, 1942, **64**, 2504.

(Miss) D. Crowfoot.[32] The cell shrinkage in different crystal directions which occurs on drying can now be estimated from the figures 111 × 60 × 62 A. (dry) and 154 × 67·5 × 67·5 A. (wet). The importance of such observations in connection with the determination of protein structures is discussed in last year's Report.[33]

Starch.—The first fibre diagram reported from a starch derivative is described briefly by R. L. Whistler and N. C. Schieltz.[34] Amylose, the component which can be extracted by water from swollen starch granules, yields strong, pliable acetate films, and these when elongated some 400—600% produce a well-defined fibre pattern with *X*-rays, indicating linear molecules with a high degree of orientation. The periodicity is 18·3 A. along the fibre axis, and the sharpness of the picture would seem to indicate considerable possibilities in the direction of detailed structure analysis.

A powder diagram showing over 20 reflections has also been obtained from the amylose–iodine complex by R. E. Rundle and D. French.[35] The data conform to a hexagonal (or pseudo-hexagonal) cell with $a = 12{\cdot}97$ A., and $c = 7{\cdot}91$ A. These figures appear to confirm a proposed helical structure for the starch–iodine complex, a representing the diameter of the helix and c the length of a turn, dimensions which are in agreement with a space-filling model of a helix with six glucose residues per turn.

Further diffraction diagrams from butanol-precipitated amylose [36] indicate a larger orthorhombic unit cell, but confirm the helical chain structure for starch.

Rubber and Isoprene Derivatives.—The long-chain polymer rubber hydrochloride $[-CH{\cdot}CH_2{\cdot}CH_2{\cdot}C(CH_3)Cl-]_n$ has been investigated in detail by C. W. Bunn and (Mrs.) E. V. Garner.[37] The fibre diagrams show that two long-chain molecules pass through the monoclinic (pseudo-orthorhombic) cell, and the positions of the atoms have been determined in conformity with the observed intensities. The chain form already predicted by Bunn [38] has been confirmed, the plane zigzag (of the paraffin-hydrocarbon type) being considerably shortened by partial folding about the >CMeCl units. The bond distances and angles appear to be approximately normal except for a distortion of the methyl group from the ideal position, similar to that found in rubber.[39]

In last year's Report [39] a paper by C. J. B. Clews dealing with polychloroprene was mentioned. It now seems likely that the unit cell dimensions recorded in that paper are erroneous, as the data given appear to be inconsistent with these dimensions.[40]

A brief report has appeared [41] of a very comprehensive investigation of an interesting di-isoprene derivative, geranylamine hydrochloride,

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[32] *Chem. Reviews*, 1941, **28**, 215.

[33] *Ann. Reports*, 1942, **39**, 111.

[34] *J. Amer. Chem. Soc.*, 1943, **65**, 1436.

[35] *Ibid.*, p. 1707.

[36] R. E. Rundle and F. C. Edwards, *ibid.*, p. 2200.

[37] *J.*, 1942, 654.

[38] *Proc. Roy. Soc.*, 1942, *A*, **180**, 67.

[39] See *Ann. Reports*, 1942, **39**, 108.

[40] C. W. Bunn, private communication.

[41] L. Bateman and G. A. Jeffrey, *Nature*, 1943, **152**, 446.

$CH_3{\cdot}C(CH_3){:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}C(CH_3){:}CH{\cdot}CH_2{\cdot}NH_2,HCl$. From an extensive survey of the intensities a complete structural determination is reported which places all the atoms to within about ±0·03 A. The value given for the C–C double bond distances seems rather low at 1·31 A., especially in view of the latest spectroscopic results.[1] The most interesting feature of the structure, however, lies in a contraction reported for the middle C–C bond in

$$-C{=}C-\underset{a}{C}-\underset{b}{C}-C{=}C- \qquad \text{(VII.)}$$

the system (VII). The bond length *ab* is given as 1·43 A., indicating a conjugation effect comparable in magnitude with that observed in butadiene and similar systems.[42] This is a surprising result and further details of the analysis will be awaited with interest.

J. M. Robertson.

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[42] See *Ann. Reports*, 1939, **36**, 175; J. M. Robertson, *J.*, 1938, 131.

ORGANIC CHEMISTRY.

1. INTRODUCTION.

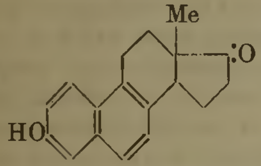
A NEW general reaction has been described by K. Ziegler and his collaborators, who show that *N*-bromosuccinimide will effect direct bromination at the allyl position. Another interesting reaction involving the allyl position has been examined by K. Alder, who finds that monoethylenic hydrocarbons will react with philodienes such as maleic anhydride to give substituted succinic anhydrides. The use of hydrogen fluoride as a condensing agent has received considerable attention; apart from the fact that its use requires special apparatus, it has many attractive features and appears particularly useful in the cyclisation of γ-arylbutyric acids and similar acids, and also in the alkylation of aromatic hydrocarbons.

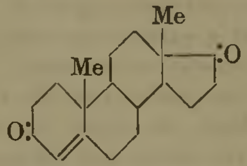
In view of the many investigations which have been made in recent years on the chemistry of acyclic sugars and related compounds, the Report on Carbohydrates is mainly concerned with a review of the more important developments in this field. Many new *aldehydo*-derivatives of the acetal type R·CHXY have been prepared, and it has been possible to isolate some of them in the two forms necessitated by the asymmetry of the *aldehydo*-carbon atom. The Arndt–Eistert synthesis has been successfully applied to the conversion of penta-acetyl gluconyl chloride into the corresponding heptonic acid; the intermediate diazo-deoxy sugar, which can be isolated as the primary product of the action of diazomethane on the acid chloride, is readily transformed into glucoheptulose, a reaction which is of considerable value for the synthesis of ketoses.

The importance of periodic acid as a reagent for the investigation of ring structures is now fully realised, and it has been used in the study of hexosans, substances which appear to be of great promise for synthetic purposes, as exemplified by the recent syntheses of cellobiose and lactose. The use of this reagent has been largely responsible for the rapid progress made in the examination of partly substituted pentitols and hexitols, though in cases where more than one chelate group is involved an outstanding problem is often the determination of the fine structure. Previous assumptions that methylene derivatives contain either five- or six-membered rings are vitiated by the isolation of 2 : 5-dimethylene mannitol; possible formulæ are therefore more numerous than were originally supposed. The partial scission of a methylene residue has been reported, in which the linkage to a primary hydroxyl is broken whilst that to a secondary is unaffected. The long controversy concerning the configurations of styracitol and polygalitol has been resolved by a synthesis of the latter substance which leaves no doubt that it is 1 : 5-anhydrosorbitol, from which it follows that styracitol is 1 : 5-anhydromannitol.

Research directed towards the synthesis of the natural secondary sex hormones and related steroids, although inevitably reduced in volume in present circumstances, has tended in the period under review towards the exploitation of the more promising of the many and varied methods previously examined. In particular, applications of the Bachmann synthesis of the oestrogenic hormone *d*-equilenin (I) have added to our knowledge of the structural and stereochemical features essential for maximal biological activity in this series, and have also resulted in the synthesis of an oestrone stereoisomer. It would seem that further development of the latter application will inevitably lead to the synthesis of the natural hormone.

(I.)



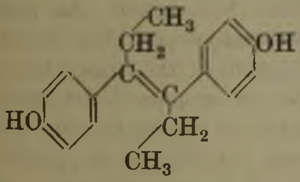


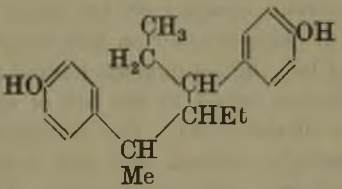
(II.)

The Robinson Mannich base method, so obviously suited to the production of the male hormones of the androstane series, has been employed in a synthesis which has yielded a product containing a maximum of eight of the sixteen possible *dl*-stereoisomerides of androstenedione (II). Notable progress can be reported in the development of methods for the introduction of the angular methyl group into preformed tetracylic systems, and applications of the Diels–Alder addition reaction and the Robinson diketone synthesis have received further attention. It has now been proved that cyclisation of di*cyclo*hexenylacetylenes, originally believed to yield perhydrophenanthrene ketones, gives compounds containing spiran systems.

There is little doubt that one of the most far-reaching developments in the sex hormone field in recent times is the discovery of highly active synthetic oestrus-producing substances such as stilboestrol, the *trans*-isomeride of structure (III). The interesting physiological properties of these hormones and their successful clinical application have provided a powerful stimulus to further research and numerous studies of the methods of preparation and of the steric configurations of the more active substances have been made. Much interest centres around investigations of the effect, known to be quite profound, of structural and spatial configuration on biological activity, since it is thought that the results of such studies may in due course help to shed light on the mode of action of these hormones. Recently it has been reported that one of the stereoisomers of (IV) is only three or four times less active than dihydrostilboestrol (hexoestrol), which suggests that configurational resemblance between synthetic and natural oestrogens may

(III.)





(IV.)

be of less importance than has hitherto been supposed, a suggestion which receives some support from recent work on the triphenylethylene oestrogens.

The systematic examination of extracts from the adrenal cortex has resulted in the identification of nearly thirty steroid constituents. Partial syntheses of several adrenal steroids which are not oxygenated in ring C have previously been reported. T. Reichstein and his collaborators have now completed a partial synthesis of dehydrocorticosterone, which is a ring-C oxygenated cortical hormone. This partial synthesis affords an unequivocal proof of the position of the ring-C oxygen atom in the adrenal steroids; the methods developed for the synthesis of dehydrocorticosterone are of a general nature and will no doubt be applicable to the partial synthesis of the other ring C-oxygenated adrenal hormones. Furthermore the successful part-synthesis of ring C-oxygenated adrenal hormones means that they can now be obtained from a bile acid, whereas hitherto they could only be obtained in very small yield by a tedious extraction process from adrenal cortex.

The isolation of 17-β-hydroxyprogesterone from adrenal cortex has been confirmed and a partial synthesis establishes its structure; the ease of isomerisation of this adrenal steroid to a perhydrochrysene derivative has been demonstrated. A new adrenal steroid-substance U has been isolated, and its structure established by conversion into an adrenal steroid of known constitution.

In the section of the Report devoted to heterocyclic compounds, a number of new or improved methods are described for the preparation of derivatives of indole, pyridine, quinoline, pyrimidine and purine. The mechanisms involved in the synthesis of indoles by two well-known methods have been studied, and the properties of the monoaminoacridines have been explained in terms of their electronic structures. A further study of the synthesis of *iso*quinolines under biologically possible conditions has been made, and the applicability of the Mannich reaction to the production of heterocyclic compounds has been considerably broadened. An investigation of the behaviour on dehydrogenation of tetrahydropyridine derivatives and of bicyclic compounds having a nitrogen atom at the bridge head is of importance owing to the use of this method for structural determination in the alkaloid field. The biological importance of the nucleotides is being increasingly realised, and has stimulated fresh attacks on the problem of synthesising such compounds. Derivatives of a new tricyclic system, flavazole, have been obtained from sugars, and their structures have been confirmed by degradative and synthetic experiments. In the field of natural products, the elucidation of the structure of biotin is the outstanding feature, and the investigations by which this result has been achieved are reviewed.

E. R. H. Jones.
H. T. Openshaw.
L. N. Owen.
F. S. Spring.

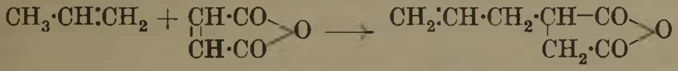
2. General Methods.

Reactions of Ethylene Derivatives involving the Allyl Position.

1. Various reactions of ethylenic derivatives involving the allyl position have been cited in these Reports. Of these may be mentioned the direct introduction of oxygen at this centre (α), oxidation at the allyl position by means of selenium dioxide, and the reaction of certain quinones with ethylenic hydrocarbons.[1] To these should be added the well-known direct oxidation at the allyl position by means of oxidising agents such as chromic acid leading to a reaction of the type [2]

$$>\mathrm{C}{:}\overset{|}{\mathrm{C}}\cdot\underset{(\alpha)}{\mathrm{CH_2}}— \longrightarrow >\mathrm{C}{:}\overset{|}{\mathrm{C}}\cdot\mathrm{CO}—$$

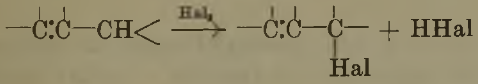
Another reaction involving the allyl position has been described by K. Alder, F. Pascher, and A. Schmitz,[2a] who show that propylene and maleic anhydride react at 220—230°/110 atm. to yield allylsuccinic anhydride:



$$\mathrm{CH_3{\cdot}CH{:}CH_2} + \begin{matrix}\mathrm{CH{\cdot}CO}\\ \|\\ \mathrm{CH{\cdot}CO}\end{matrix}\!>\!\mathrm{O} \longrightarrow \mathrm{CH_2{:}CH{\cdot}CH_2{\cdot}}\begin{matrix}\mathrm{CH{-}CO}\\ |\\ \mathrm{CH_2{\cdot}CO}\end{matrix}\!>\!\mathrm{O}$$

Similar substituted succinic anhydrides were obtained from maleic anhydride and Δ^2-butene, *iso*butene, *cyclo*pentene and *cyclo*hexene.

2. *Halogenation in the Allyl Position.*—Many cases of direct halogenation in the allyl position have been described in the literature, but an analysis of these cases shows that at normal temperatures, direct halogenation of the type



$$-\overset{|}{\mathrm{C}}{:}\overset{|}{\mathrm{C}}-\mathrm{CH}< \xrightarrow{\mathrm{Hal}_2} -\overset{|}{\mathrm{C}}{:}\overset{|}{\mathrm{C}}-\underset{\mathrm{Hal}}{\overset{|}{\mathrm{C}}}- + \mathrm{HHal}$$

is limited to hydrocarbons in which one of the unsaturated carbon atoms is fully substituted. In 1884, Sheshukov[3] demonstrated that treatment of *iso*butene with chlorine under normal conditions of temperature and pressure gives largely β-methylallyl chloride (methallyl chloride). This reaction is used for the manufacture of this allyl halide, which can be obtained in approximately 90% yield.[4] A similar substitution in the allyl position occurs when 2-methyl-Δ^2-butene[5,6] is treated with chlorine.

J. Meisenheimer[7] studied the case of triphenylmethylethylene (I) and showed that on treatment with bromine this hydrocarbon does not give a dibromo-addition product as claimed by J. Levy,[8] but a monobromo-sub-

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[1] *Ann. Reports*, 1937, **34**, 230.

[2] F. W. Semmler and W. Jakubowicz, *Ber.*, 1914, **47**, 1141; A. Windaus, *Ber.*, 1920, **53**, 491; F. S. Spring and T. Vickerstaff, *J.*, 1937, 249.

[2a] *Ber.*, 1943, **76**, 27.

[3] *J. Russ. Phys. Chem. Soc.*, 1884, **16**, 478.

[4] J. Burgin, W. Engs, H. P. A. Groll, and G. Hearne, *Ind. Eng. Chem.*, 1939, **31**, 1413; *Ann. Reports*, 1940, **37**, 205.

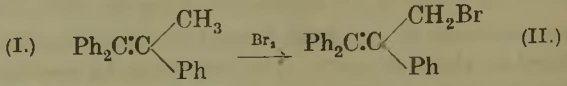
[5] N. Kondakov, *J. Russ. Phys. Chem. Soc.*, 1885, **17**, 290.

[6] D. V. Tischenko, *J. Gen. Chem. U.S.S.R.*, 1936, **6**, 116, 1549.

[7] *Annalen*, 1927, **456**, 126.

[8] *Bull. Soc. chim.*, 1921, **29**, 895.

stituted derivative (II). The structure of (II) was established by oxidation, which gives a mixture of benzophenone and phenacyl bromide :

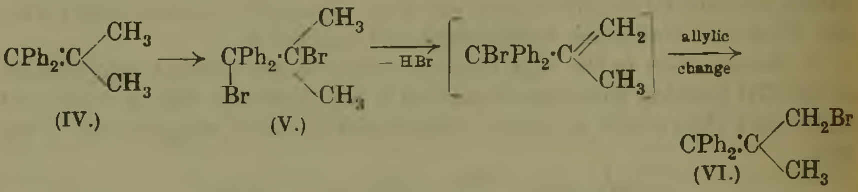


Meisenheimer concluded that the reaction proceeds by *direct* substitution. Although W. Schlenk and E. Bergmann[9] have used the observation of Meisenheimer as a proof that the original hydrocarbon has structure (III), addition of bromine, followed by loss of hydrogen bromide, giving (II), the

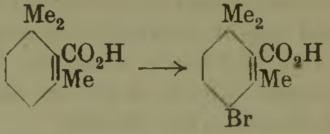
$$\underset{CH_2}{CHPh_2{\cdot}CPh} + Br_2 \longrightarrow \underset{CH_2Br}{CHPh_2{\cdot}CBrPh} \xrightarrow{-HBr} (II.)$$

(III.)

true mechanism of the reaction was established by K. Ziegler and K. Bahr.[10] Ziegler and Bahr showed that treatment of 1 : 1-diphenyl-2 : 2-dimethylethylene (IV) with bromine gives a dibromide (V) which readily loses hydrogen bromide, yielding the bromo-substituted unsaturated hydrocarbon (VI), the reaction involving an allylic rearrangement :



Although in the case of triphenylmethylethylene the intermediate dibromo-adduct is less stable and cannot be isolated, a similar mechanism operates, a remark which also applies to the direct halogenation of β-*cyclo*geranic acid to give the allyl halide (VII).[11]



(VII.)

Early attempts to apply this direct substitution reaction to a straight-chain unsaturated hydrocarbon were not successful. In 1936, however, T. D. Stewart and B. Weindenbaum[12] succeeded in preparing pentenyl chlorides by the direct chlorination of 2-pentene, but only in very small yield :

$$CH_3{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_3 \longrightarrow CH_2Cl{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_3$$

and possibly $CH_3{\cdot}CH{:}CH{\cdot}CHCl{\cdot}CH_3$

Various attempts to increase the extent of allyl substitution by the use of catalysts and by irradiation of the reaction mixtures were unsuccessful,

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[9] *Annalen*, 1928, **463**, 1.

[10] *Ber.*, 1929, **62**, 1695.

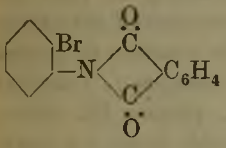
[11] G. Wendt, *Ber.*, 1941, **74**, 1242.

[12] *J. Amer. Chem. Soc.*, 1936, **58**, 98.

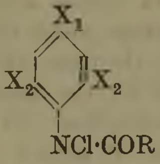
but the desired effect was obtained by using relatively high temperatures.[13] The reaction has been studied most in the case of propylene. At a temperature between 300° and 600°, chlorine and propylene react to give mainly allyl chloride. Although the commercial value of this reaction is great, as a general method the reaction is limited, since it can clearly only be applied to ethylenic derivatives which are stable at the high temperature employed.

A general approach to the problem of devising a method for direct halogenation in the allyl position under reaction conditions which are capable of general application has been made with conspicuous success by K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann.[14] A limited success had been realised previously by A. Wohl,[15] who found that *N*-bromoacetamide reacts with tetramethylethylene in ethereal solution to give a 16% yield of $CMe_2{:}CMe{\cdot}CH_2Br$. Later A. Wohl and K. Jaschinowski [16] showed that the same reagent reacts with crotonic acid to give, in very small yield, a bromocrotonic acid, the constitution of which was not established, and that propylene on treatment with *N*-bromoacetamide gives a dibromide, probably $CH_2Br{\cdot}CBr{:}CH_2$.

Ziegler and his co-workers have examined a large number of *N*-halogen compounds and a summary of the results obtained is instructive. *N*-Halogenated sulphonamides such as *N*-dichlorotoluene-*p*-sulphonamide (dichloramine-T) and *N*-halogenated sulphonimides such as $p\text{-}C_6H_4Me{\cdot}SO_2{\cdot}NCl{\cdot}COPh$, $(p\text{-}C_6H_4Me{\cdot}SO_2)_2NCl$, and *N*-chloro- and *N*-bromo-saccharin were not satisfactory. On the other hand, *N*-bromophthalimide was found to react readily with *cyclo*hexene, giving 3-bromo-Δ^1-*cyclo*hexene (50%), but a considerable quantity (21%) of a stable addition product (VIII) was produced. *N*-Chlorophthalimide is much less reactive than the corresponding bromo-derivative.



(VIII.)



(IX.)

a, $X_1 = X_2 = Cl$, $R = Me$
b, $X_1 = X_2 = Cl$, $R = Ph$
c, $X_1 = Cl$, $X_2 = Br$, $R = Me$
d, $X_1 = Cl$, $X_2 = Br$, $R = Ph$

Attention was next directed to *N*-chloroacylanilides. The members of this group, such as *N*-chloroacetanilide, which readily rearrange to nuclear substituted isomers, are obviously unsuited. A number of triply substituted members of the group (IX, *a*—*d*) were found to react with *cyclo*hexene to give 3-chloro-Δ^1-*cyclo*hexene in yields of the order 70—90%, carbon tetrachloride being used as solvent. Although this result at first sight seems very attractive, this group of compounds has the great disadvantage that the proportion of active halogen in the molecule is extremely small and this requires the use of relatively large volumes of diluent. This disadvantage was slightly mitigated by the observation that *Np*-dichloro-, *N*-chloro-

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[13] H. P. A. Groll and G. Hearne, *Ind. Eng. Chem.*, 1939, **31**, 1530.

[14] *Annalen*, 1942, **551**, 80.

[15] *Ber.*, 1919, **52**, 51.

[16] *Ber.*, 1921, **54**, 476.

p-nitro-, and *Nop*-trichloro-acetanilides are sufficiently stable (*i.e.*, do not isomerise) under the conditions employed, and react more quickly with *cyclo*hexene than the compounds (IX, *a—d*). The use of this group of compounds is the most efficient general method available for chlorination in the allyl position.

Bromination. Ziegler and his co-workers have shown that *N*-bromophthalimide is an ideal reagent for bromination in the allyl position. In contrast to *N*-bromoacetanilides it is easily prepared. It contains 45% of active halogen and the succinimide which is produced after reaction of the bromo-imide with an unsaturated compound is very sparingly soluble in carbon tetrachloride. After reaction is complete it is recovered and readily reconverted into the bromo-imide—succinimide acts as a bromine carrier. In the considerable number of reactions between unsaturated compounds and bromosuccinimide that have so far been examined, no case of addition has been observed and monosubstitution as distinct from disubstitution is the general rule.

The reactivity of *N*-bromosuccinimide is highly specific; *N*-chlorosuccinimide does not chlorinate in the allyl position, and attempts to obtain a corresponding chlorinating agent were unsuccessful. Furthermore, other *N*-bromodiacylimides, such as *N*-bromoglutarimide, *N*-bromohexahydrophthalimide and *N*-bromodibenzamide, do not resemble *N*-bromosuccinimide in this reactivity.

In view of its wide applicability several examples of the use of *N*-bromosuccinimide may be given. The reactions are usually carried out in boiling carbon tetrachloride solution.

Mono-olefins. In the case of simple olefins containing at least one methylene group in the allyl position, yields of monosubstituted derivatives of the order of 80% are obtained, the time taken for the reaction to proceed to completion being illustrated by the following examples: 1-methyl-Δ^1-*cyclo*hexene (5 mins.), Δ^1-dodecylene (25 mins.), pinene (25 mins.), *cyclo*hexene (30 mins.), Δ^4-nonene (40 mins.). In suitable cases, *e.g.*, *cyclo*hexene, the product is homogeneous, whereas in others mixtures of isomers are formed and complications arise due to the intervention of allylic rearrangements.

Concerning the orientation of the allyl halide formed, it was observed that a methylene group is much more easily substituted than a methyl group; thus a hydrocarbon $R{\cdot}CH_2{\cdot}CH{:}CHMe$ gives mainly $R{\cdot}CHBr{\cdot}CH{:}CHMe$; it is noteworthy that *N*-bromosuccinimide fails to convert propylene into allyl bromide. The exceptional slowness of the reaction between the bromo-imide and di*iso*butylene (5 hours for completion), the product of which, according to F. C. Whitmore and J. M. Church,[17] is mainly $CH_2{:}CMe{\cdot}CH_2{\cdot}CMe_3$ (X), is probably to be attributed to the heavily substituted carbon atom immediately attached to the α-methylene group.

A useful test for an allyl bromide was discovered by Ziegler and co-workers, who found that, when mixed with *cyclo*hexylamine, these bromides

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[17] *J. Amer. Chem. Soc.*, 1932, **54**, 3710.

undergo a strongly exothermic reaction, the reaction temperature increasing spontaneously to approximately 160° ; this reaction is not shown by either alkyl bromides or vinyl bromides.

Mono-olefins can be dibrominated in certain cases, but the interesting observation was made in the case of *cyclo*hexene that, when treated with two moles of the bromo-imide, the monobromide 3-bromo-Δ^1-*cyclo*hexene is the major product. If, however, 3-bromo-Δ^1-*cyclo*hexene is treated with one mole of bromo-imide, the dibromide 3 : 6-dibromo-Δ^1-*cyclo*hexene is obtained in good yield.

Dienes. Non-conjugated dienes react normally with two moles of *N*-bromosuccinimide, but conjugated dienes cannot be successfully halogenated by this reagent.

Other unsaturated compounds. In a preliminary study of various classes of unsaturated compounds it has been shown that the presence of free hydroxyl and carboxyl groups is contra-indicated, since they lead to decomposition of the reagent with formation of hypobromous acid, which adds to the ethylene linkage. Unsaturated esters, on the other hand, are readily brominated in the allyl position. *cyclo*Hexenyl acetate gives the bromo-ester (XI) and cholesteryl esters are brominated in a few minutes with quantitative formation of succinimide. Of considerable interest is the conversion of methyl crotonate and methyl β-methylcrotonate into the corresponding γ-bromo-esters, (XII) and (XIII) respectively, in high yield. The method has also been applied to β-amyrin acetate, α-amyrin acetate and methyl acetylursolate ;[18] here the intermediate bromo-substitution products are not isolated, the reaction leading to the introduction of two ethylenic linkages (with formation of a conjugated triene-ester) in the case of β-amyrin acetate, and the introduction of one ethylenic linkage in the cases of α-amyrin acetate and methyl acetylursolate to give conjugated diene-esters.

(XI.)

$CH_2Br{\cdot}CH{:}CH{\cdot}CO_2Me$ (XII.)

$CH_2Br{\cdot}CMe{:}CH{\cdot}CO_2Me$ (XIII.)

Reactions catalysed by Hydrogen Fluoride.

Hydrogen fluoride is a useful catalyst for the alkylation of aromatic hydrocarbons by means of olefins.[19] The olefin does not polymerise, the only observed reaction being alkylation. In general, hydrogen fluoride is a catalyst of fairly wide applicability and it will effect reactions which proceed in the presence of sulphuric acid, aluminium chloride or boron fluoride.[20]

In the presence of hydrogen fluoride, propylene and benzene give *iso*propylbenzene (84%), *iso*butene and benzene give *tert.*-butylbenzene (40%)

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[18] L. Ruzicka, O. Jeger, and J. Redel, *Helv. Chim. Acta*, 1943, **26**, 1235.

[19] J. H. Simons and S. Archer, *J. Amer. Chem. Soc.*, 1938, **60**, 986, 2953.

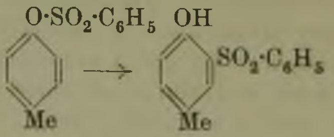
[20] J. H. Simons, S. Archer, and H. J. Passino, *ibid.*, p. 2956 ; J. H. Simons and S. Archer, *ibid.*, 1940, **62**, 451.

and di-*tert.*-butylbenzenes (40%), and *cyclo*hexene and benzene give *cyclo*hexylbenzene (60%). Benzene and *cyclo*propane react in the presence of hydrogen fluoride to give *n*-propylbenzenes only.

W. S. Calcott, J. M. Tinker, and V. Weinmayr [21] find that at the ordinary temperature benzene is alkylated by propylene in the presence of hydrogen fluoride to give either a mixture of *iso*propylbenzene (74·7%) and di*iso*propylbenzene (17%) or 1 : 2 : 4 : 5-tetra*iso*propylbenzene (77%) according to the molecular proportions employed. Other alkylations which have been realised by means of hydrogen fluoride are : naphthalene and propylene yield tetra*iso*propylnaphthalene, phenol and propylene give 2 : 4 : 6-tri*iso*propylphenol (94·5%), benzene and allyl alcohol give αβ-diphenylpropane (52%), toluene and di*iso*butylene give *p*-*tert.*-butyltoluene (77%), *m*-xylene and *tert.*-butyl alcohol give *tert.*-butyl-*m*-xylene (97%). Similarly, in the presence of hydrogen fluoride, both naphthalene and phenanthrene are *tert.*-butylated in excellent yields when treated with *tert.*-butyl alcohol. *iso*Propyl ether, *tert.*-butyl alcohol, *iso*propyl alcohol, ethylene oxide, and dibenzyl ether can also be used as alkylating agents for aromatic hydrocarbons in the presence of hydrogen fluoride.

Hydrogen fluoride catalyses the alkylation of aromatic hydrocarbons by means of alkyl halides ; [22] in this reaction it is superior to metallic halides in that self-condensation of the aromatic hydrocarbon does not occur. Direct alkylations of phenol and ethyl furoate (with *tert.*-butyl alcohol),[20] and of α-nitronaphthalene, benzoic acid, *p*-aminophenol, *p*-dimethylaminophenol, and *p*-anisidine (with *iso*propyl ether) [21] have also been reported. Although acylations of aromatic hydrocarbons by means of acid chlorides, acid anhydrides, and carboxylic acids do not proceed in high yield,[23] hydrogen fluoride is an excellent reagent for the cyclisation of a number of γ-arylbutyric acids and β-arylpropionic acids.[24]

Hydrogen fluoride can effect a number of molecular rearrangements; *e.g.*, in the presence of hydrogen fluoride, *tert.*-butylbenzene and phenol give benzene and *tert.*-butylphenol; again, in the presence of hydrogen fluoride, benzophenoneoxime undergoes a Beckmann rearrangement to yield benzanilide. Although at room temperature, hydrogen fluoride will not effect a Fries rearrangement,[24] at 100° phenyl acetate is converted in small yield into *p*-hydroxyacetophenone, and *p*-tolyl benzenesulphonate (I) gives 2-hydroxy-5-methyldiphenylsulphone (II).



(I.) (II.)

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[21] *J. Amer. Chem. Soc.*, 1939, **61**, 949, 1010 ; J. H. Simons and S. Archer, *ibid.*, 1940 **62**, 1623.

[22] J. H. Simons and S. Archer, *ibid.*, 1938, **60**, 2953, 2955 ; 1939, **61**, 1521.

[23] J. H. Simons, D. I. Randall, and S. Archer, *ibid.*, p. 1795.

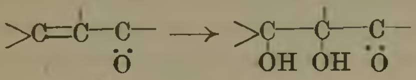
[24] L. F. Fieser and E. B. Hershberg, *ibid.*, p. 1272.

Oxidations with Hydrogen Peroxide.

E. Weitz and A. Scheffer[25] have shown that αβ-unsaturated ketones are oxidised to the corresponding oxides when treated with alkaline hydrogen peroxide, whereas under the same conditions saturated ketones such as acetone and acetophenone, unsaturated hydrocarbons such as stilbene and 2 : 3-dimethylbutadiene, and αβ-unsaturated acids such as cinnamic, fumaric and maleic acids are not attacked by the reagent. α-Diketones, on the other hand, suffer fission when treated with alkaline hydrogen peroxide, diacetyl and benzil giving acetic and benzoic acids respectively.

N. A. Milas and S. Sussman[26] have developed a particularly useful hydroxylating agent consisting of an anhydrous solution of hydrogen peroxide in *tert.*-butyl alcohol. The reagent is stable over long periods of time and is inert towards olefins; in the presence of a small amount of osmium tetroxide, likewise dissolved in *tert.*-butyl alcohol, olefins are quickly oxidised to give the corresponding glycol. Oxidation of ethylenic compounds is effected by the reagent with vanadium pentoxide[27] as catalyst, trimethylethylene and ethyl fumarate thereby giving trimethylethylene glycol and ethyl racemate respectively. On the other hand, ethylenic compounds in which the double bond is conjugated with an aromatic ring, such as anethole, *iso*eugenol, and *iso*safrole, suffer fission with formation of anisaldehyde, vanillin, and piperonal respectively. By the same reagent and vanadium pentoxide, benzene is oxidised to phenol. The oxidation of ethylenic compounds by means of hydrogen peroxide in *tert.*-butyl alcohol is also catalysed by means of chromic anhydride, but the reaction is less effective.

R. Criegee[28] has employed hydrogen peroxide in ether catalysed by osmium tetroxide for the oxidation of ethylenic compounds, and thereby obtained carbonyl compounds. This ether reagent has been used in the sterol and triterpene group. One case may be singled out for special comment; A. Butenandt and H. Wolz[29] find that αβ-unsaturated ketones are oxidised to the corresponding keto-glycols thus :



$$>C{=}\overset{|}{C}{-}\underset{\ddot{\mathrm{O}}}{C}{-} \longrightarrow >\underset{\mathrm{OH}}{C}{-}\underset{\mathrm{OH}}{\overset{|}{C}}{-}\underset{\ddot{\mathrm{O}}}{C}{-}$$

a reaction of especial interest in view of inert nature of αβ-unsaturated ketones to perbenzoic acid[30] and to osmium tetroxide in ether.[28]

Another interesting oxidation by means of hydrogen peroxide is described by N. A. Milas, P. F. Kurz, and W. P. Anslow.[31] There is considerable

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[25] *Ber.*, 1921, **54**, 2327; E. Weitz, *Annalen*, 1919, **418**, 4.

[26] *J. Amer. Chem. Soc.*, 1936, **58**, 1302; 1937, **59**, 2345.

[27] *Ibid.*, 1937, **59**, 2342; 1927, **49**, 2005.

[28] *Annalen*, 1936, **522**, 75; *Ann. Reports*, 1937, **34**, 233.

[29] *Ber.*, 1938, **71**, 1483.

[30] J. Böeseken, *Rec. Trav. chim.*, 1926, **45**, 838; K. Bodendorf, *Arch. Pharm.*, 1930, **268**, 491.

[31] *J. Amer. Chem. Soc.*, 1937, **59**, 543.

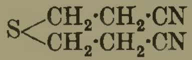
spectroscopic evidence[32] that, when exposed to light of wave-length approximating to 3000 A., hydrogen peroxide dissociates into two hydroxyl radicals. Milas and his associates exposed mixtures of hydrogen peroxide with allyl alcohol, crotonic acid, and maleic acid to the light from an ultra-violet lamp and thereby obtained glycerol (43%), dihydroxybutyric acid (30%), and *meso*tartaric acid (12—22%) respectively.

W. Treibs[33] has described the oxidation of olefins, using hydrogen peroxide with pervanadic acid [$VO_2(OH)_2$ or HVO_4] as catalyst, and acetone as solvent, the products being either glycols or oxides. Using the same oxidising agent and water and methanol as solvents, Treibs[34] found that *cyclo*hexanone is oxidised to the half aldehyde of adipic acid and *cyclo*pentanone gives the half aldehyde of glutaric acid as major products. In the case of *cyclo*hexanone this catalysed hydrogen peroxide oxidation also yields *cyclo*hexane-1 : 4-dione, a reaction which bears a resemblance to the biological oxidation of camphor[35] and of fenchone.[36] Under similar conditions aldehydes are not attacked.

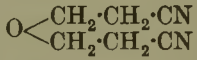
Reactions of Acrylonitrile.

Cyanoethylation.—Acrylonitrile reacts with liquid ammonia to give a mixture of $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CN$ and $NH(CH_2{\cdot}CH_2{\cdot}CN)_2$. Similar cyanoethylations of aliphatic primary and secondary amines, hydrazines, heterocyclic bases, and amino-acids have been reported.[37] Acrylonitrile also reacts with hydrogen sulphide[38] and with water[39] to give (I) and (II) respectively and cyanoethylations of alcohols and glycols[40] proceed in the same manner.

(I.)



$$S{<}\begin{matrix}CH_2{\cdot}CH_2{\cdot}CN\\CH_2{\cdot}CH_2{\cdot}CN\end{matrix}$$



$$O{<}\begin{matrix}CH_2{\cdot}CH_2{\cdot}CN\\CH_2{\cdot}CH_2{\cdot}CN\end{matrix}$$

(II.)

Phenols are readily cyanoethylated to yield β-aryloxypropionitriles,[41] and oximes react with acrylonitrile thus :[42]

$$CMe_2{:}N{\cdot}OH \longrightarrow CMe_2{:}N{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}CN$$

The cyanoethylation of compounds containing active methylene groups, such as fluorene and *cyclo*pentadiene, was mentioned in a previous Report.[43] Further examples of the addition of active methylene compounds to acrylo-

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[32] H. C. Urey, L. H. Dawsey, and F. O. Rice, *J. Amer. Chem. Soc.*, 1929, **51**, 1371; G. von Elbe, *ibid.*, 1933, **55**, 62; W. H. Rodebush and M. H. Wahl, *J. Chem. Physics*, 1933, **1**, 696; O. Oldenberg, *ibid.*, 1935, **3**, 266; A. A. Frost and O. Oldenberg, *ibid.*, 1936, **4**, 642, 781; V. Kondrat'ev and M. Ziskin, *Acta physicochim.*, *U.S.S.R.*, 1936, **5**, 301.

[33] *Ber.*, 1939, **72**, 7.

[34] *Ibid.*, p. 1194.

[35] Y. Asahina, *Ber.*, 1928, **61**, 533; 1931, **64**, 1931; 1933, **66**, 1673.

[36] E. Rimini, *Gazzetta*, 1909, **39**, 186; F. Reinartz and W. Janke, *Ber.*, 1936, **69**, 2259.

[37] E.P. 404,744; 457,621; 466,316; U.S.P. 1,992,615; 2,017,537.

[38] D.R.-P. 669,961; U.S.P. 2,163,176.

[39] H. A. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23.

[40] U.S.P. 2,280,790; 2,280,791; 2,280,792.

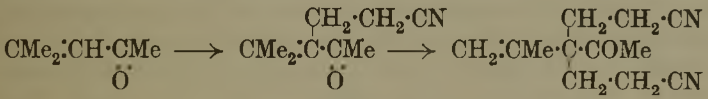
[41] D.R.-P., 670,357; F.P. 833,734.

[42] *J. Amer. Chem. Soc.*, 1943, **65**, 23.

[43] F. S. Spring, *Ann. Reports*, 1942, **39**, 140.

nitrile have since been reported.[42] Phenylacetonitrile is converted into a mono-[44] and a di-β-cyanoethyl derivative, and ethyl cyanoacetate and ethyl malonate are both converted into the corresponding di-β-cyanoethyl derivative. According to C. F. Koelsch,[45] acrylonitrile reacts with aryldiazonium chlorides to give unstable compounds of the type $\mathrm{Ar{\cdot}CH_2{\cdot}CHCl{\cdot}CN}$, which are readily converted into the corresponding cinnamonitriles. H. A. Bruson and T. W. Riener[46] have studied the reaction between acrylonitrile and ketones. They show that in the presence of benzyltrimethylammonium hydroxide, aromatic methyl ketones are converted into tri-β-cyanoethyl derivatives $\mathrm{Ar{\cdot}CO{\cdot}C(CH_2{\cdot}CH_2{\cdot}CN)_3}$. Propiophenone, α-tetralone and deoxybenzoin give the corresponding di-β-cyanoethyl derivatives. *cyclo*Hexanone and *cyclo*pentanone yield tetra-β-cyanoethyl derivatives, and corresponding cyanoethylations of aliphatic ketones are reported. Ethyl acetoacetate likewise reacts with acrylonitrile to give the ester $\mathrm{CH_3{\cdot}CO{\cdot}C(CH_2{\cdot}CH_2{\cdot}CN)_2{\cdot}CO_2Et}$. Camphor, *iso*phorone and di*iso*butyl ketone could not be cyanoethylated.

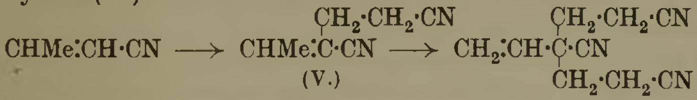
H. A. Bruson and T. W. Riener[47] have studied the reaction between αβ-unsaturated ketones and acrylonitrile. Benzyltrimethylammonium hydroxide or potassium hydroxide being used as catalyst, mesityl oxide reacts with acrylonitrile to give a mixture of (III) and (IV). Further cyanoethylation of (III) converts it into (IV). Acrylonitrile reacts with



$$\mathrm{CMe_2{:}CH{\cdot}\underset{\ddot{O}}{C}Me} \longrightarrow \mathrm{CMe_2{:}\overset{CH_2{\cdot}CH_2{\cdot}CN}{C}{\cdot}\underset{\ddot{O}}{C}Me} \longrightarrow \mathrm{CH_2{:}CMe{\cdot}\overset{CH_2{\cdot}CH_2{\cdot}CN}{\underset{CH_2{\cdot}CH_2{\cdot}CN}{C}}{\cdot}COMe}$$

(III.) (IV.)

crotononitrile in a similar way, the reaction giving (V), further cyanoethylation of which yields (VI).



$$\mathrm{CHMe{:}CH{\cdot}CN} \longrightarrow \mathrm{CHMe{:}\overset{CH_2{\cdot}CH_2{\cdot}CN}{C}{\cdot}CN} \longrightarrow \mathrm{CH_2{:}CH{\cdot}\overset{CH_2{\cdot}CH_2{\cdot}CN}{\underset{CH_2{\cdot}CH_2{\cdot}CN}{C}}{\cdot}CN}$$

(V.) (VI.)

F. S. S.

3. Carbohydrates.

Acyclic Derivatives.

It has long been realised that an aqueous solution of a reducing sugar may contain a trace of the open-chain form, but apart from a few special instances, some of which are mentioned below, the proportion is so small that detection is difficult. The absorption spectra of fructose and sorbose in aqueous solution give faint indications of the acyclic forms, but with aldoses the results are negative.[1] It has been shown, however, that aldoses, contrary to previous reports, are reducible at the dropping mercury

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[44] C. F. Koelsch, *J. Amer. Chem. Soc.*, 1943, **65**, 437.

[45] *Ibid.*, p. 57.

[46] *Ibid.*, 1942, **64**, 2850.

[47] *Ibid.*, 1943, **65**, 18.

[1] W. Bednarczyk and L. Marchlewski, *Biochem. Z.*, 1938, **300**, 42.

cathode, and that the amount of *aldehydo*-sugar present in a solution can thereby be determined.[2] The reactions of fructose 1-phosphate and, even more readily, of fructose 1 : 6-diphosphate with hydrogen cyanide, under conditions ineffective with fructose itself, indicate a tendency to react in the *keto*-form which increases as phosphate groups are introduced.[3] F. Hartley and W. H. Linnell[4] have stated that in view of the absence of mutarotation in solutions of 6-methyl fructose, 3 : 4 : 6-trimethyl fructose, 1 : 3 : 4 : 6-tetramethyl fructose, and 5-methyl glucose, the commonly accepted furanose forms should be replaced by open-chain structures, but, since these substances have not yet been obtained in crystalline condition, the absence of mutarotation is inconclusive; indeed it is evident from the considerable variations in reported specific rotations that some preparations have been of doubtful purity. The positive Schiff tests given by 5-methyl glucose[5] and 5 : 6-dimethyl glucose[6] do suggest, however, that the proportion of *aldehydo*-form in solutions of these derivatives is not inconsiderable, and it would be of interest to examine their light-absorbing properties and their behaviour under polarographic analysis.

It has been established[7] that 3 : 6-anhydro-sugars can readily be transformed into *aldehydo*-derivatives in which the anhydro-ring is still present. T. L. Cottrell and E. G. V. Percival[8] have now found that treatment of 3 : 6-anhydro-β-methyl-*d*-galactopyranoside with acetic anhydride and sulphuric acid results in scission of both rings and the production of penta-acetyl *aldehydo-dl*-galactose, a transformation reminiscent of the formation of the same product from 6-iodo-[9] and 6-tosyl-2 : 3 : 4 : 5-tetra-acetyl *d*-galactose.[10] Racemisation in the ordinary sense is of course impossible, and there is as yet no direct evidence to show how the *dl*-product is formed.

The action of lead tetra-acetate on 1 : 2-monoacetone-*d*-glucofuranose and on 2 : 3-monoacetone-*d*-mannofuranose, followed by removal of the acetone residues, has given *d*-xylo- and *d*-lyxo-trihydroxyglutardialdehydes,[11] the first members of the dialdose class to be prepared. Octa-acetyl *aldehydo*-maltose, the first crystalline *aldehydo*-disaccharide derivative, has been obtained by M. L. Wolfrom and M. Konigsberg[12] from the corresponding diethylmercaptal.

A large number of acyclic derivatives of the general formula R·CHXY are now available, where the substituents X and Y, attached to C_1, are

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[2] S. M. Cantor and Q. P. Peniston, *J. Amer. Chem. Soc.*, 1940, **62**, 2113.

[3] A. V. Stepanov and B. N. Stepanenko, *Biokhimiya*, 1940, **5**, 198, 567.

[4] *Quart. J. Pharm.*, 1940, **13**, 332.

[5] L. von Vargha, *Ber.*, 1936, **69**, 2098.

[6] M. R. Salmon and G. Powell, *J. Amer. Chem. Soc.*, 1939, **61**, 3507; K. Freudenberg and E. Plankenhorn, *Ber.*, 1940, **73**, 621.

[7] W. N. Haworth, J. Jackson, and F. Smith, *J.*, 1940, 620; W. N. Haworth, L. N. Owen, and F. Smith, *J.*, 1941, 88.

[8] *J.*, 1942, 749.

[9] F. Micheel, H. Ruhkopf, and F. Suckfüll, *Ber.*, 1935, **68**, 1523.

[10] F. Micheel and H. Ruhkopf, *Ber.*, 1937, **70**, 850.

[11] K. Iwadare, *Bull. Chem. Soc. Japan*, 1941, **16**, 40, 144.

[12] *J. Amer. Chem. Soc.*, 1940, **62**, 1153.

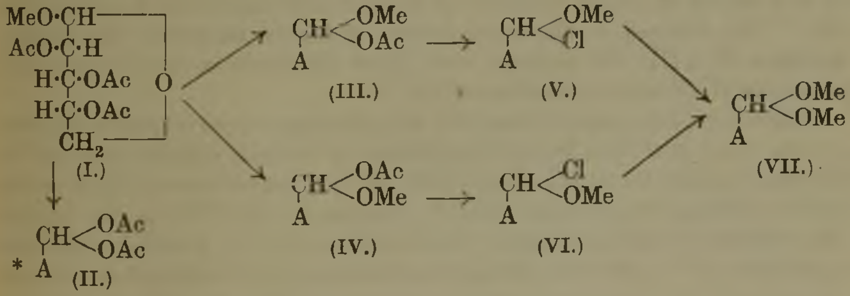
selected from the five groups SEt, OH, OAc, OMe (or OEt), Cl (Br or I). Of the possible types i—xv (see Table), thirteen have been prepared, and eight of these show asymmetry on C_1; it is therefore of great interest that types iii, viii, xi, xii, and xiv have been isolated in the two modifications demanded on stereochemical grounds.

Type	i	ii	iii	iv	v	vi	vii *	viii
X =	SEt	SEt	SEt	SEt	SEt	OH	OH	OH
Y =	SEt	OH	OAc	OMe	Cl	OH	OAc	OMe

Type	ix *	x	xi	xii	xiii	xiv	xv
X =	OH	OAc	OAc	OAc	OMe	OMe	Cl
Y =	Cl	OAc	OMe	Cl	OMe	Cl	Cl

* Not known.

Although the dimethyl acetals of glycollaldehyde, glyceraldehyde, and some partly substituted sugars have been known for many years, it is only recently that the acetals of unsubstituted pentoses and hexoses have been obtained. E. M. Montgomery, R. M. Hann, and C. S. Hudson,[13] by the use of 4% of sulphuric acid in acetic acid–acetic anhydride, found that triacetyl β-methyl-*d*-arabinoside (I) was converted into hexa-acetyl *aldehydo-d*-arabinose (II). When the sulphuric acid was replaced by 8% of zinc chloride, the methyl group was not removed and the product consisted largely of the penta-acetyl methylhemiacetal, which was isolated in the two stereoisomeric forms (III) and (IV). Each of these, with aluminium chloride or hydrogen chloride in ether, gave the corresponding tetra-acetyl *d*-arabinose 1-chloro-1-methylacetals (V) and (VI), from which was obtained tetra-acetyl *d*-arabinose dimethylacetal (VII) by treatment with silver oxide and methanol. The crystalline *d*-arabinose dimethylacetal, obtained by deacetyl-



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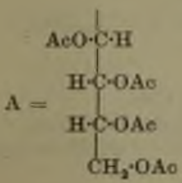
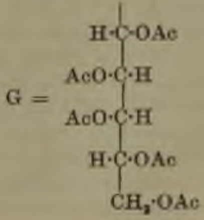
[13] *J. Amer. Chem. Soc.*, 1937, 59, 1124.

* The following abbreviations are used in this Report :—





ation, is readily hydrolysed to *d*-arabinose by aqueous acid, and in acid methanol it gives the usual equilibrium mixture of methylarabinosides. M. L. Wolfrom, L. J. Tanghe, R. W. George, and S. W. Waisbrot,[14] and H. A. Campbell and K. P. Link [15] have shown that in methanol, in the presence of mercuric chloride and cadmium carbonate or mercuric oxide, penta-acetyl galactose diethylmercaptal (VIII) is converted into the penta-acetyl dimethylacetal (IX). Similarly, the corresponding glucose [16] and mannose [17] compounds have been prepared. In each instance the crystalline hexose dimethylacetal is obtained on deacetylation. The direct formation of *d*-fructose dimethylacetal [18, 19] and *l*-rhamnose dimethylacetal [20] from the corresponding unsubstituted diethylmercaptal has also been achieved.

The first member of the hemiacetal series (type viii) to be isolated in two forms is methyl tetra-acetyl *d*-galacturonate ethylhemiacetal (X), prepared from methyl tetra-acetyl *aldehydo-d*-galacturonate.[21] Fractional crystallisation gave both an α- and a β-form. The absolute configuration on C_1 has not been determined, and the prefix α is assigned to the isomer with the higher positive rotation in the *d*-series, a convention which has also been adopted by M. L. Wolfrom.

Acetylation under mild conditions of penta-acetyl *d*-galactose methylhemiacetal (XI) yields the α- and the β-form of hexa-acetyl 1-methoxy-*aldehydo-d*-galactose,* (XII) which with hydrogen chloride in ether are converted into the same penta-acetyl 1-chloro-1-methoxy-*aldehydo-d*-galactose (XIII),[22] a result which differs from that observed [13] with the corresponding arabinose compounds (III) and (IV). (XIII) has also been obtained [23] by the action of acetyl chloride on penta-acetyl galactose dimethylacetal (IX). The halogen in these substances is highly reactive; the ethoxy-analogue of (XIII), for example, with silver carbonate in dry benzene gives penta-acetyl *aldehydo-d*-galactose (XIV).[22]

The acyclic analogues of the aceto-halogen sugars were originally obtained in only one form,[24] but by the application of the zinc chloride reagent [13] it has been possible to prepare from (XIV) the two stereoisomers of hexa-acetyl 1-chloro-*aldehydo-d*-galactose (XV).[25] Treatment of (XIV) in dry benzene with phosphorus pentachloride yields penta-acetyl 1 : 1-dichloro-*aldehydo-d*-galactose (XVI), the first substance of this type to be obtained in the sugar

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[14] *J. Amer. Chem. Soc.*, 1938, **60**, 132. [15] *J. Biol. Chem.*, 1938, **122**, 635.

[16] M. L. Wolfrom and S. W. Waisbrot, *J. Amer. Chem. Soc.*, 1938, **60**, 854; 1939, **61**, 1408.

[17] A. Scattergood and E. Pacsu, *ibid.*, 1920, **62**, 903.

[18] E. Pacsu, *ibid.*, 1938, **60**, 2277. [19] *Idem*, *ibid.*, 1939, **61**, 1671.

[20] J. W. Green and E. Pacsu, *ibid.*, 1938, **60**, 2288.

[21] R. J. Dimler and K. P. Link, *ibid.*, 1940, **62**, 1216.

[22] M. L. Wolfrom, M. Konigsberg, and F. B. Moody, *ibid.*, p. 2343.

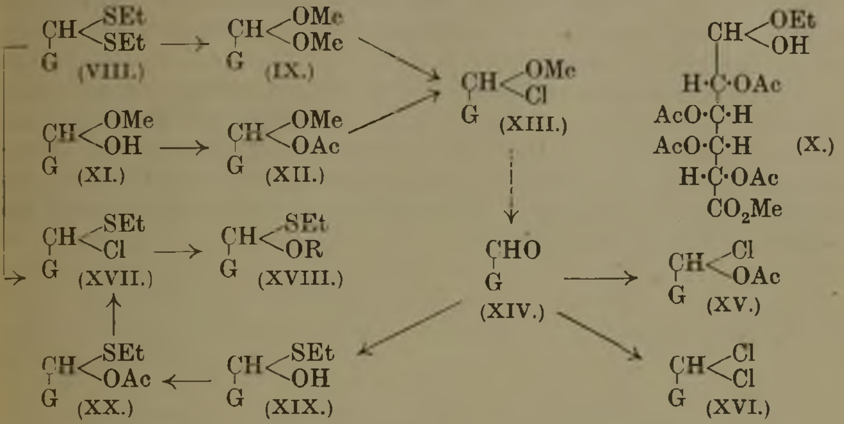
[23] M. L. Wolfrom and D. I. Weisblat, *ibid.*, p. 878.

[24] M. L. Wolfrom, *ibid.*, 1935, **57**, 2498.

[25] M. L. Wolfrom and R. L. Brown, *ibid.*, 1941, **63**, 1246.

* The nomenclature at present in use for open-chain derivatives is not altogether satisfactory; "hexa-acetyl *d*-galactose methylhemiacetal" would be preferable, and in conformity with the names adopted for (III) and (IV).

series.[26] Hexa-acetyl 1-bromo-*aldehydo-d*-galactose with ethanol and silver carbonate gives penta-acetyl *d*-galactose ethylhemiacetal; [22] this curious change is of interest inasmuch as hexa-acetyl 1-halogeno-hexoses may themselves be prepared from penta-acetyl hemiacetals.[24]



By treatment with acetyl chloride and phosphorus oxychloride, one of the thioethoxy-groups in penta-acetyl *d*-galactose diethylmercaptal (VIII) is replaced by chlorine, and the product, penta-acetyl 1-chloro-1-thioethoxy-*aldehydo-d*-galactose (XVII), reacts readily with ethanol in the presence of silver carbonate to give penta-acetyl *d*-galactose diethylmonothioacetal (XVIII, R = Et), from which *d*-galactose diethylmonothioacetal is obtained on deacetylation.[23] The use of methanol in place of ethanol results in the formation of the mixed acetal (XVIII, R = Me). Dialkyl monothioacetals have been postulated by E. Pacsu [19] as intermediates in the conversion of dialkylmercaptals into thioglycosides, alkylglycosides, and dialkylacetals, and it should now be possible to test the validity of this theory.

The thiohemiacetal (XIX) has been obtained by M. L. Wolfrom, D. I. Weisblat, and A. R. Hanze [27] by the addition of ethylthiol to penta-acetyl *aldehydo-d*-galactose (XIV). Acetylation to (XX), followed by replacement of the 1-acetyl group by chlorine, yields (XVII).

Galactose is the only sugar which has given derivatives of all the thirteen known types, but considerable progress has been made in the glucose,[16, 21, 24, 27] mannose,[17, 21, 28] and arabinose [21, 29, 30] series, in each of which stereoisomerism of type xi has been demonstrated.[13, 21] The glucose series affords the only example of the isolation of stereoisomers of type iii, this having been accomplished [27] by preparing the glucose analogues of (XIX) and (XX). The hexa-acetyl 1-thioethoxy-*aldehydo-d*-glucose [analogue of (XX)] was

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[26] M. L. Wolfrom and D. I. Weisblat, *J. Amer. Chem. Soc.*, 1940, **62,** 1149.

[27] *Ibid.*, p. 3246.

[28] M. L. Wolfrom, M. Konigsberg, and D. I. Weisblat, *ibid.*, 1939, **61,** 574.

[29] M. L. Wolfrom and M. Konigsberg, *ibid.*, 1938, **60,** 288.

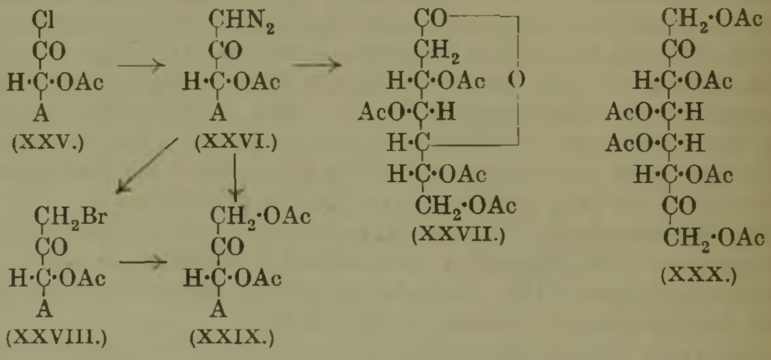
[30] M. L. Wolfrom and R. L. Brown, *ibid.*, 1943, **65,** 951.

separated into two different crystalline products, but unfortunately only the α-isomer was obtained in sufficient quantity to be carried through to *d*-glucose *O*-methyl-*S*-ethylmonothioacetal [deacetylated analogue of (XVIII)]. It is possible that the β-form, similarly treated, would give the hitherto unrecorded stereoisomers of types iv and v.

The reaction of diazomethane with the aldehyde group was shown to be applicable to *aldehydo*-sugars by P. Brigl, H. Mühlschlegel, and R. Schinle,[31] and this reaction has now been applied[32] to the *d*- (XXI) and the *l*-form of tetra-acetyl *aldehydo*-arabinose for the preparation of *d*- (XXII) and *l*-tetra-acetyl 1-deoxy-*keto*-fructose. Under similar conditions, penta-acetyl *keto*-*d*-fructose (XXIII) gives (XXIV).[33]


(XXI.) (XXII.) (XXIII.) (XXIV.)

An acid chloride reacts with diazomethane to give, as primary product, a diazomethyl ketone which can often be isolated in good yield.[34] In the sugar field, non-crystalline products were obtained from diethylidene *l*-xylonyl chloride[35] and from acetone *d*-glyceryl chloride,[36] but it has now been shown that penta-acetyl *d*-gluconyl chloride (XXV) gives crystalline penta-acetyl 1-diazo-1-deoxy-*keto*-*d*-glucoheptulose (XXVI), which undergoes the Arndt–Eistert rearrangement[37] to give tetra-acetyl 2-deoxy-δ-*d*-gluco-


(XXV.) (XXVI.) (XXVII.) (XXVIII.) (XXIX.) (XXX.)

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[31] *Ber.*, 1931, **64**, 2921.

[32] M. L. Wolfrom, D. I. Weisblat, W. H. Zophy, and S. W. Waisbrot, *J. Amer. Chem. Soc.*, 1941, **63**, 201.

[33] M. L. Wolfrom, D. I. Weisblat, and S. W. Waisbrot, *ibid.*, p. 632.

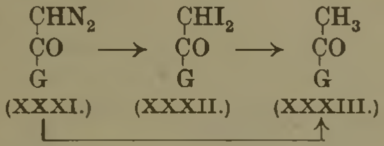
[34] F. Arndt, B. Eistert, and W. Partale, *Ber.*, 1927, **60**, 1364; F. Arndt and J. Amende, *Ber.*, 1928, **61**, 1122; W. Bradley and R. Robinson, *J.*, 1928, 1310.

[35] K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 186.

[36] K. Iwadare, *Bull. Chem. Soc. Japan*, 1939, **14**, 131.

[37] F. Arndt and B. Eistert, *Ber.*, 1935, **68**, 200; W. E. Bachmann and W. S. Struve, *Organic Reactions*, **1**, 38.

heptonolactone (XXVII).[33,38] This substance, in common with the deacetylated δ-lactone, is remarkable in that it shows no mutarotation. (XXVI) with hydrogen bromide in ether yields the 1-bromo-compound (XXVIII),[33,38] and with acetic acid it gives hexa-acetyl *keto*-*d*-glucoheptulose (XXIX), which is also obtained from (XXVIII) with acetic anhydride and potassium acetate.[39] Deacetylation yields crystalline *d*-glucoheptulose.[40] This series of reactions provides a new synthetic route for the preparation of ketoses and has been used for the conversion of penta-acetyl *d*-galactonyl chloride into *d*-galaheptulose,[40] of tetra-acetyl *d*-arabonyl chloride into penta-acetyl keto-*d*-fructose (XXIII),[38,39] and of tetra-acetyl mucyl dichloride into the interesting diketose acetate (XXX).[39] In the galactose series, the intermediate (XXXI) undergoes the Curtius reaction [41] with iodine to give the 1 : 1-di-iodo-compound (XXXII), reduced by hydriodic acid to penta-acetyl 1-deoxy-*keto*-*d*-galaheptulose (XXXIII), also obtained from (XXXI) by direct reduction.[42]



$$\begin{tikzcd}[row sep=small] CHN_2 & CHI_2 & CH_3 \\ CO \arrow[r] & CO \arrow[r] & CO \\ G & G & G \\ (XXXI.) \arrow[rr, bend right] & (XXXII.) & (XXXIII.) \end{tikzcd}$$

Oxidation of α-Glycol Groups.

Mainly as a result of the work of C. S. Hudson and his school, periodic acid has become a reagent of great importance for structural work in the carbohydrate field. The oxidation is stoicheiometric, and considerable diagnostic value may therefore be attached to the quantitative estimation of the products and of the oxidant required. α-Methyl-*d*-hexopyranosides take two moles of periodic acid and yield one mole of formic acid and one mole of *d*′-methoxy-*d*-hydroxymethyl diglycollaldehyde * (XXXIV).[43,44] The same product (XXXIV), but no formic acid, is given by α-methyl-*d*-arabofuranoside, only one mole of oxidant being required,[43] whereas α-methyl-*d*-pentopyranosides yield formic acid and *d*′-methoxy diglycollaldehyde (XXXV).[43,45] Experiments with β-methyl-*d*-hexopyranosides [43,46] and β-methyl-*d*-pentopyranosides [43,47,48] have given results similar to those

[38] M. L. Wolfrom, S. W. Waisbrot, and R. L. Brown, *J. Amer. Chem. Soc.*, 1942, **64**, 1701.

[39] *Idem, ibid.*, p. 2329.

[40] M. L. Wolfrom, R. L. Brown, and E. F. Evans, *ibid.*, 1943, **65**, 1021.

[41] T. Curtius, *Ber.*, 1885, **18**, 1283.

[42] M. L. Wolfrom and R. L. Brown, *J. Amer. Chem. Soc.*, 1943, **65**, 1516.

[43] E. L. Jackson and C. S. Hudson, *ibid.*, 1937, **59**, 994.

[44] *Idem, ibid.*, 1939, **61**, 1530.

[45] W. D. Maclay and C. S. Hudson, *ibid.*, 1938, **60**, 2059.

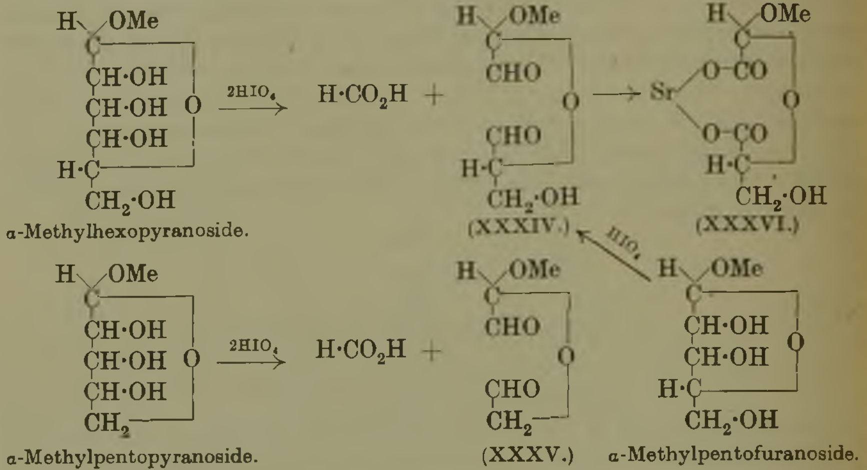
[46] E. L. Jackson and C. S. Hudson, *ibid.*, 1939, **61**, 959.

[47] *Idem, ibid.*, 1941, **63**, 1229.

[48] H. S. Isbell and H. L. Frush, *J. Res. Nat. Bur. Stand.*, 1940, **24**, 125.

* *d*′ and *l*′ distinguish the configuration of C_1, corresponding to α- and β-forms respectively of the original glycoside *in the* d-*series*. In the *l*-series the reverse holds; thus α-methyl-*l*-glucopyranoside would give *l*′-methoxy-*l*-hydroxymethyl diglycollaldehyde, the enantiomorph of (XXXIV).

obtained with the α-glycosides, except of course that the corresponding l'-aldehydes are produced. Characterisation is effected by oxidation of the aldehydes with bromine water in the presence of an alkaline-earth carbonate, leading to the isolation of crystalline salts (usually of strontium) which now serve as reference compounds. For example, in the *d*-series all α-methylhexopyranosides and α-methylpentofuranosides give strontium d'-methoxy-*d*-hydroxymethyl diglycollate (XXXVI).



α-Methylhexopyranoside.

(XXXIV.)

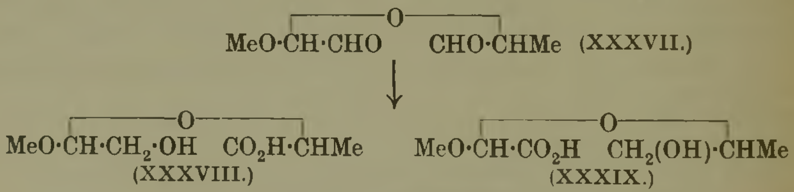
(XXXVI.)

α-Methylpentopyranoside.

(XXXV.)

α-Methylpentofuranoside.

The methylpyranosides of the methylpentoses have also been subjected to oxidation with periodic acid, and each of the four reference compounds d' (and l')-methoxy-*d* (and *l*)-methyl diglycollaldehydes (XXXVII) have been obtained in crystalline form;[43,49] hydrolysis of the corresponding dibasic acids gives either *d*- or *l*-lactic acid and thus provides a direct correlation between the latter and the sugar configurations. The dialdehydes readily undergo an intramolecular Cannizzaro reaction to give the hydroxy-acids (XXXVIII) and (XXXIX) of corresponding configuration.[50]



$$\overbrace{\text{MeO·CH·CHO} \quad \text{CHO·CHMe}}^{\text{O}} \quad \text{(XXXVII.)}$$

$$\downarrow$$

$$\overbrace{\text{MeO·CH·CH}_2\text{·OH} \quad \text{CO}_2\text{H·CHMe}}^{\text{O}} \qquad \overbrace{\text{MeO·CH·CO}_2\text{H} \quad \text{CH}_2\text{(OH)·CHMe}}^{\text{O}}$$

(XXXVIII.) (XXXIX.)

Applications of the reagent to αα-trehalose[44] and sucrose[51] have confirmed the structures previously assigned to these disaccharides. A very interesting development is reported by V. C. Barry,[52] who points out that

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[49] W. D. Maclay, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1939, **61**, 1660.

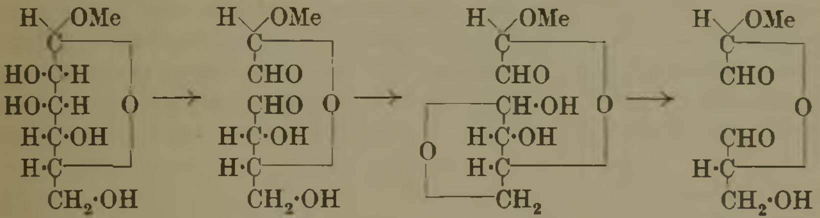
[50] E. M. Fry, E. J. Wilson, and C. S. Hudson, *ibid.*, 1942, **64**, 872.

[51] P. Fleury and J. Courtois, *Compt. rend.*, 1942, **214**, 366.

[52] *J.*, 1942, 578; *Nature*, 1943, **152**, 537.

a non-reducing polysaccharide of the laminarin type, in which consecutive pyranose units are linked through C_1 and C_3, contains an α-glycol group only on the terminal residue. This unit is therefore the only part of the chain to be attacked by periodic acid, and subsequent treatment of the oxidised polysaccharide with phenylhydrazine results in complete removal of the end-group fragments, with the result that the recovered material has a chain length one unit less than the original. A step-wise degradation is achieved by alternate treatments with periodic acid and with phenylhydrazine, a process which is obviously of great importance, since it may well provide information on the presence of cross-linkages in the macro-molecule.

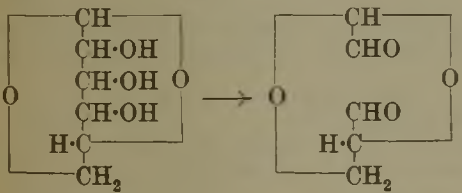
Lead tetra-acetate in certain instances behaves in the same way as periodic acid, and it will for example oxidise α-methylmannopyranoside (XL) to (XXXIV).[53] It has been suggested [54] that the usual attack on the *cis*-glycol group to yield (XLI) is followed by formation of the cyclic acetal (XLII), the glycol group of which is then attacked by the second mole of tetra-acetate. In support of this mechanism is the observation [54] that glycosides with no hydroxyl on C_6, such as 6-trityl α-methylmannoside and α-methylrhamnoside, which cannot form cyclic acetals analogous to (XLII), react with a second mole of reagent only with difficulty.*



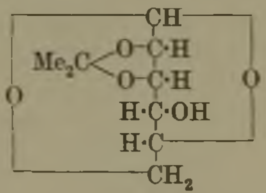
(XL.) (XLI.) (XLII.) (XXXIV.)

Glycosans.

Periodic acid has been used with striking success in the elucidation of structures of the lævoglucosan type (XLIII), in which the anhydro-ring



(XLIII.) (XLIV.)



(XLV.)

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[53] W. S. McClenahan with R. C. Hockett, *J. Amer. Chem., Soc.*, 1938, **60**, 2061.

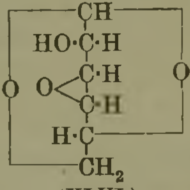
[54] R. C. Hockett and W. S. McClenahan, *ibid.*, 1939, **61**, 1667.

* A related mechanism, involving the intermediate formation of a *ψ*-glycol, has been advanced by E. Baer (*J. Amer. Chem. Soc.*, 1940, **62**, 1597) to explain the oxidation by lead tetra-acetate of simple α-keto-alcohols, which occurs in the presence of water, ethanol, etc. An aqueous or alcoholic solution of α-methylrhamnoside or 6-trityl α-methylmannoside would probably react readily with 2 mols of the reagent (compare E. Baer, J. M. Grosheintz, and H. O. L. Fischer, *ibid.*, 1939, **61**, 2607).

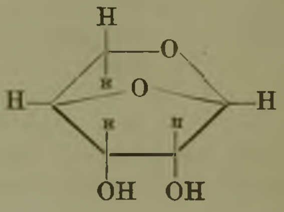
engages C_1. Lævoglucosan itself, 1 : 6-anhydro-β-*d*-glucopyranose (or *d*-glucosan ⟨1, 5⟩ β ⟨1, 6⟩), reacts with two moles of the oxidant and yields one mole of formic acid and one mole of *l′*-oxy-*d*-methylene diglycollaldehyde (XLIV), characterised as the strontium salt of the corresponding dibasic acid.[55] Identical results have been obtained with *d*-altrosan,[56] *d*-mannosan,[57] and *d*-galactosan.[58]

Hexosans are conveniently prepared by pyrolysis, and under such conditions lactose gives lævoglucosan and *d*-galactosan; [58] only the latter has a configuration amenable to the formation of an acetone compound, and separation is thereby readily accomplished. The structure of the 3 : 4-monoacetone-1 : 6-anhydro-β-*d*-galactopyranose has been established by D. McCreath and F. Smith,[59] who isolated it as a by-product in the preparation of diacetone galactose. The *d*-galactosan, obtained on mild hydrolysis, can also be prepared by pyrolysis of galactose, but it is then accompanied by a small proportion of 1 : 3-anhydro-β-*d*-galactopyranose (*d*-galactosan ⟨1, 5⟩ β ⟨1, 3⟩), the structure of which is indicated by its resistance to periodic acid and consequent absence of an α-glycol group in the molecule.[60]

Pyrolysis of ivory nut (*Phytelepas macrocarpa*) yields a crude *d*-mannosan which may be purified through the triacetate [61] or the 2 : 3-monoacetone compound (XLV).[57] The latter has been of considerable value in the synthesis of new C_4 derivatives of mannose. Methylation and hydrolysis gives crystalline 4-methyl mannose,* [57, 62] and the 4-tosyl mannosan with aqueous alkali gives a tricyclic anhydrohexosan, probably 1 : 6-3 : 4-dianhydro-β-*d*-talopyranose (XLVI).[63] The 1 : 6- and 3 : 4-rings are opened by acetolysis, and the resulting penta-acetyl hexoses on deacetylation and subsequent hydrogenation yield *d*-mannitol and *d*-iditol. The formation



(XLVI.)



(XLVII.)

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[55] E. L. Jackson and C. S. Hudson, *J. Amcr. Chem. Soc.*, 1940, **62**, 958.

[56] N. K. Richtmyer and C. S. Hudson, *ibid.*, p. 961.

[57] A. E. Knauf, R. M. Hann, and C. S. Hudson, *ibid.*, 1941, **63**, 1447.

[58] R. M. Hann and C. S. Hudson, *ibid.*, p. 1484; 1942, **64**, 2435.

[59] *J.*, 1939, 387.

[60] R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 2241.

[61] G. Zemplén, A. Gerecs, and T. Valatin, *Ber.*, 1940, **73**, 575.

[62] W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 70.

[63] R. M. Hann and C. S. Hudson, *ibid.*, 1942, **64**, 925.

* E. Pacsu and S. M. Trister (*J. Amer. Chem. Soc.*, 1941, **63**, 925), by the preparation of crystalline 2-methyl mannose, have finally confirmed that the supposed 4-methyl mannose of E. Pacsu and C. von Kary (*Ber.*, 1929, **62**, 2811) is the 2-methyl compound. 4-Methyl mannose has also been synthesised by hydrogenation of 4-methyl δ-mannonolactone (O. T. Schmidt and H. Müller, *ibid.*, 1943, **76**, 344).

of (XLVI) and its behaviour on hydrolysis are thus in conformity with the views now held concerning Walden inversion in such reactions.[64] Condensation of the acetone mannosan (XLV) with acetobromoglucose, followed by removal of the acetone residue and subsequent acetolysis, results in the formation of octa-acetyl 4-β-*d*-glucopyranosido-*d*-mannose, which on deacetylation gives crystalline epicellobiose.[65] The conversion of octa-acetyl epicellobiose, *via* hexa-acetyl cellobial, into cellobiose[66] provides a new and structurally definitive synthesis of this disaccharide. Similarly,[67] by the use of acetobromogalactose, it has been possible to synthesise epilactose and lactose.

The formation of glycosans by alkaline treatment of β-phenylglycosides[68] is likely to be of use in configurational studies, since the reaction is not given by any of the α-phenylglycosides so far investigated.

All attempts to prepare 1 : 2 : 3-triacetyl ribofuranose by detritylation of 1 : 2 : 3-triacetyl-5-trityl ribose have given 2 : 3-diacetyl 1 : 4-anhydro-α-*d*-ribopyranose (2 : 3-diacetyl 1 : 5-anhydro-β-*d*-ribofuranose), from which ribosan (XLVII) is obtained on deacetylation;[69] the simultaneous possession of a pyranose and a furanose structure makes this a substance of peculiar interest.

Polyhydric Alcohols.

Considerable attention has for a long time been directed towards the production of these substances by catalytic hydrogenation, and many recent studies have been concerned with the introduction of more efficient catalysts and with the determination of optimum conditions. The use of Raney nickel has resulted in the preparation in crystalline form of xylitol,[70] cellobiotol,[71] melibiotol,[72] and 6-β-*d*-glucosidodulcitol.[73] *l*-Gulomethylitol and *d*-rhamnitol are obtained by the condensation of diacetone-*aldehydo*-*d*-arabinose with methylmagnesium iodide, followed by removal of the acetone residues.[74] Direct condensation of glucose and phenol is claimed to yield *p*-hydroxyphenyl *d*-sorbitol.[75]

Much progress has been made in the determination of the structures of partly substituted derivatives. The dibenzylidene dulcitol prepared fifty years ago by Emil Fischer[76] gives a dibenzyl derivative, hydrolysed to a dibenzyl dulcitol which takes only one mole of periodic acid and gives no

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[64] S. Peat, *Ann. Reports*, 1939, **36**, 258.

[65] W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1941, **63**, 1724.

[66] *Idem, ibid.*, 1942, **64**, 1289.

[67] *Idem, ibid.*, pp. 1490, 1852.

[68] E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *ibid.*, 1942, **64**, 1483; 1943, **65**, 3, 1848.

[69] H. Bredereck, M. Kothnig, and E. Berger, *Ber.*, 1940, **73**, 956.

[70] M. L. Wolfrom and E. J. Kohn, *J. Amer. Chem. Soc.*, 1942, **64**, 1739; J. F. Carson, S. W. Waisbrot, and F. T. Jones, *ibid.*, 1943, **65**, 1777.

[71] P. A. Levene and M. Kuna, *J. Biol. Chem.*, 1939, **127**, 49.

[72] M. L. Wolfrom and T. S. Gardner, *J. Amer. Chem. Soc.*, 1940, **62**, 2553.

[73] P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, 1938, **125**, 355.

[74] K. Gatzi and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 914.

[75] B.P. 518,586.

[76] *Ber.*, 1894, **27**, 1524.

formaldehyde. The dibenzyl dulcitol therefore contains one α-glycol group, which cannot be of the $CH_2(OH)\cdot CH(OH)-$ type; hence the benzyl residues must be on C_2 and C_5, a conclusion which is confirmed by oxidation with lead tetra-acetate to benzyl-*dl*-glyceraldehyde. The original compound is therefore 1:3-4:6-dibenzylidene dulcitol, and this formulation is supported by its resistance to lead tetra-acetate and the non-reactivity of the ditosyl derivative towards sodium iodide.[77] The di-*o*-nitrobenzylidene dulcitol of I. Tanasescu and E. Macovski,[78] formerly thought to be 1 : 2-5 : 6-, and the dimethylene dulcitol of K. Weber and B. Tollens [79] are also said to be 1 : 3-4 : 6-derivatives,[80] but the fine structures are based on the supposed preference for six-membered rings (see p. 121). From 1 : 6-dibenzoyl dulcitol, the structure of which follows from its reaction with three moles of lead tetra-acetate to yield two moles each of formic acid and benzoylglycollaldehyde,[81] two new 2 : 3 : 4 : 5-dibenzylidene dulcitols have been prepared, which presumably represent a pair of the possible fine structures 2 : 3-4 : 5, 2 : 4-3 : 5, and 2 : 5-3 : 4, though it is conceivable that the isomerism is concerned with the presence of the asymmetric carbon atom in the benzylidene residue.[82] In this connection, it is of interest that isomerism of this type has recently been demonstrated [83] in the ortho-ester form (XLVIII) of the octa-acetyl disaccharide prepared by the condensation of 1 : 2 : 3 : 4-tetra-acetyl β-*d*-glucose with acetobromomannose; in addition to the normal biose, two distinct modifications of (XLVIII) were isolated.

It has been emphasised [81] that care must be exercised in the application of oxidative methods to acetone derivatives, owing to their sensitivity towards acids. In place of periodic acid, sodium periodate or lead tetra-acetate in acetic acid may be used, and under such conditions it has been shown that the diacetone dulcitols formerly thought [84] to be 1 : 2-3 : 4- and 3 : 4-5 : 6-compounds are in fact the 2 : 3-5 : 6- and 2 : 3-4 : 5-derivatives.[81] Furthermore, from the anomalous behaviour of tetratosyl erythritol (in which all the tosyl groups react with sodium iodide) [85] it is evident that the Oldham–Rutherford rule can no longer be extended with safety to indicate the number of free primary alcoholic groups in a polyhydric alcohol. R. M. Hann, A. T. Ness, and C. S. Hudson [86] conclude that a tosyl group in a secondary position is reactive if it is contiguous to one in a primary position.

Derivatives of other sugar alcohols for which structures have now been

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[77] W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 132.

[78] *Bull. Soc. chim.*, 1933, **53**, 1097.

[79] *Annalen*, 1898, **299**, 316.

[80] R. M. Hann, W. T. Haskins, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 986, 1614.

[81] R. M. Hann, W. D. Maclay, and C. S. Hudson, *ibid.*, 1939, **61**, 2432.

[82] W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, 1942, **64**, 136, 137.

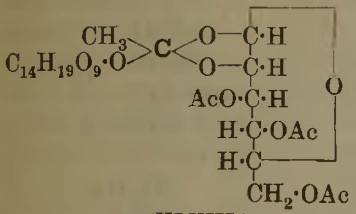
[83] E. A. Talley, D. D. Reynolds, and W. L. Evans, *ibid.*, 1943, **65**, 575.

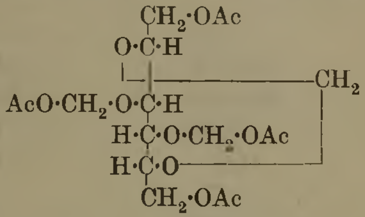
[84] R. A. Pizzarello and W. Freudenberg, *ibid.*, 1939, **61**, 611.

[85] R. S. Tipson and L. H. Cretcher, *J. Org. Chem.*, 1943, **8**, 95.

[86] *J. Amer. Chem. Soc.*, 1944, **66**, 73.

proposed include 1 : 2 : 3 : 4-dibenzylidene *d*-sorbitol,[87] 2 : 3 : 4 : 5-dimethylene [88] and 2 : 3 : 4 : 5-dibenzylidene [89] *d*-mannitol, 1 : 3- and 2 : 3-benzylidene


(XLVIII.)


(XLIX.)

d-arabitol,[90] and 2 : 3 : 4 : 5-diacetone *l*-fucitol.[91] A partial rupture of methylene-acetal residues is reported by A. T. Ness, R. M. Hann, and C. S. Hudson,[92] who have found that acetolysis of trimethylene-*d*-mannitol gives a product which is probably 1 : 6-diacetyl-3 : 4-di(acetoxymethyl)-2 : 5-methylene *d*-mannitol (XLIX), from which 2 : 5-methylene *d*-mannitol is formed on saponification. It is suggested [92] that trimethylene *d*-mannitol has a 1 : 3-2 : 5-4 : 6 structure, on the grounds that (*a*) it must contain a 2 : 5-methylene group, and (*b*) a precursor is a dimethylene *d*-mannitol which must be 2 : 3-4 : 6 or 1 : 3-5 : 6. It would appear, however, that the isolation of a methylene compound with a seven-membered ring throws doubt on all fine structures which have been based on the alleged preference for five- or six-membered rings, and the dimethylene mannitol may well be 1 : 4-3 : 6, and the trimethylene mannitol 1 : 4-2 : 5-3 : 6 (a model shows clearly that the latter structure is almost strainless). It is necessary, therefore, to provide rigid proof of fine structures by other methods, and this has been achieved by W. N. Haworth and L. F. Wiggins, [93] who have shown that in the dimethylene-1 : 6-dibenzoyl derivatives of mannitol and sorbitol the methylene residues are in the 2 : 4- and 3 : 5-positions, and that trimethylene sorbitol is the 1 : 3-2 : 4-5 : 6 compound.

The answer has now been given to the controversial problem of the structures of the naturally occurring anhydrohexitols, styracitol and polygalitol. Early observations on the epimeric character of these substances had shown that they were 1 : 5-anhydro-derivatives of mannitol and sorbitol; this ring structure has recently been confirmed by periodic acid oxidation.[94] L. Zervas [95] prepared styracitol from triacetyl hydroxyglucal and assumed it to have the sorbitol configuration (LI), but W. Freudenberg and E. F. Rogers [96] pointed out that the mannitol structure (L) was also compatible

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[87] J. K. Wolfe, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 1493.

[88] W. T. Haskins, R. M. Hann, and C. S. Hudson, *ibid.*, 1943, **65**, 67.

[89] *Idem, ibid.*, p. 1419.

[90] *Idem, ibid.*, p. 1663.

[91] A. T. Ness, R. M. Hann, and C. S. Hudson, *ibid.*, 1942, **64**, 982.

[92] *Ibid.*, 1943, **65**, 2215.

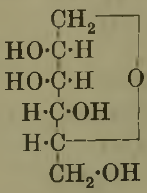
[93] *J.*, 1944, 58; and private communication from Professor W. N. Haworth.

[94] N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 64.

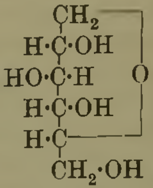
[95] *Ber.*, 1930, **63**, 1689.

[96] *J. Amer. Chem. Soc.*, 1937, **59**, 1602.

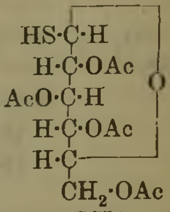
with the method of synthesis, a view which was upheld by the observation that styracitol was oxidised more readily than polygalitol with lead tetra-acetate and should therefore contain a *cis*-glycol group. This conclusion, which was supported by L. Zervas and I. Papadimitriou,[97] was reversed in a later paper [98] on the grounds that tetramethyl styracitol (a liquid) was almost identical in physical properties with the product formed by hydrogenation and dehydration of 2 : 3 : 4 : 6-tetramethyl glucose. The oxidation experiments, however, have been confirmed by R. C. Hockett, M. T. Dienes, and H. E. Ramsden,[99] who compared the reaction rates with those obtained with substances of known configuration, and the synthesis [100] of tetra-acetyl polygalitol by treatment of tetra-acetyl β-*d*-glucothiose (LII) with Raney nickel proves that polygalitol is 1 : 5-anhydrosorbitol (LI). The isolation of this substance as a by-product from the Zervas synthesis provides a final proof of the epimeric relationship and shows conclusively that styracitol is 1 : 5-anhydromannitol (L).[100] L. N. O.



(L.)



(LI.)



(LII.)

4. STEROID SYNTHESES.

Since the last review in the *Annual Reports* for 1939 interest in the synthesis of steroids has been maintained and significant progress may be said to have been made, although naturally the output of published research has diminished appreciably. No strikingly original routes have been devised and progress has been largely confined to the exploitation of methods developed earlier. Consequently in the first section of this Report the various investigations have been reviewed, as far as possible, according to the main plan of the general synthetic scheme employed. These comprise (*a*) extensions of the Bachmann equilenin synthesis, (*b*) developments of the Robinson diketone method, (*c*) syntheses based on the Robinson–Mannich base method, (*d*) applications of the Diels–Alder reaction, (*e*) introduction of angular methyl groups into preformed cyclic systems, and (*f*) studies on the cyclisation of dienynes.

It may be noted here that the discovery within the last few years of methods of converting members of the steroid sex hormone series into D-homo-derivatives (such as II) containing the perhydrochrysene skeleton

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[97] *Ber.*, 1940, **73**, 174.

[98] W. Freudenberg and J. T. Sheehan, *J. Amer. Chem. Soc.*, 1940, **62**, 558.

[99] *Ibid.*, 1943, **65**, 1474.

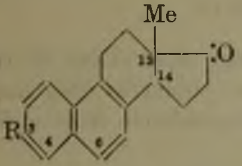
[100] N. K. Richtmyer, C. J. Carr, and C. S. Hudson, *ibid.*, p. 1477.

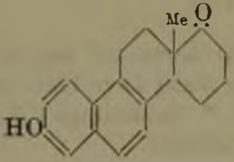
may possibly simplify the task of synthesis, in that it introduces an element of symmetry and at the same time provides a considerably increased number of objectives. Such syntheses would be of added interest in view of the highly potent hormone activity of the D-homoandrostane derivatives.

The second section contains a comprehensive survey of the literature on the chemistry of the purely synthetic œstrogens, a subject mentioned briefly in the last Report. It has been found convenient to discuss the more important of these substances in separate sections.

(*a*) Following on the notable achievement of the synthesis of *d*-equilenin (I; R = OH), detailed in the last Report on this topic,[1] Bachmann and his collaborators have synthesised a variety of related compounds, including a stereoisomer of œstrone, by employing the same basic procedure. This was evolved initially with such scrupulous attention to detail that 90% yields were attained at almost every stage, and it is worthy of mention that from 10 g. of 1-keto-7-methoxytetrahydrophenanthrene, 2·5 g. of *dl*-equilenin and an equal amount of its stereoisomeride * were obtained in spite of the fact that some twelve distinct operations were involved.[2]

(I.)





(II.)

The lack of biological activity (in 500γ doses) of the *dl*-forms of the stereoisomeric deoxyequilenin and deoxy*iso*equilenin (I; R = H) (termed *cis*- and *trans*-equilenones) emphasises the importance of the C_3-hydroxyl group in addition to the known stereochemical effect (*l*-equilenin and the diastereoisomeride *dl*-*iso*equilenin are relatively inactive), in relation to œstrus-producing properties.[3] The racemic forms of 6-hydroxyequilenone and its stereoisomer have been synthesised [4] but this transference of the 3-hydroxyl group to C_6 results in complete loss of activity.

Other extensions [5] of the synthesis have rendered possible variations in the nature of the angular group of *dl*-equilenin, and it appears that œstrogenic potency is largely preserved in the homologues up to *n*-propyl, but the *n*-butyl compound and a 16-methyl-*dl*-equilenin are inactive, as also are all the *dl*-*iso*equilenin homologues. The effect of the absence of the angular

[1] H. D. Springall, *Ann. Reports*, 1939, **36**, 307.

[2] W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 824.

[3] W. E. Bachmann and A. L. Wilds, *ibid.*, p. 2084.

[4] W. E. Bachmann and D. W. Holmes, *ibid.*, p. 2750.

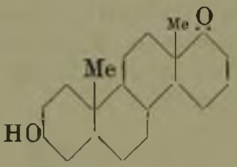
[5] *Idem*, *ibid.*, 1941, **63**, 595, 2592.

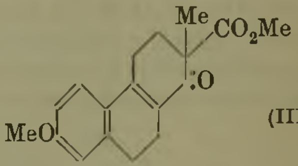
* Bachmann employs the prefix *iso*- in the equilenin series to denote the steric configuration arising from the alternative mode of linking of the two hydroaromatic rings. This is believed to be a *trans*-fusion in the naturally occurring steroids (*e.g.*, equilenin) and convincing evidence in support of this contention has been obtained by K. Dimroth and H. Jonsson (*Ber.*, 1941, **74**, 520).

methyl group on biological activity has yet to be established and a synthesis of norequilenin by some variant of this method would be of considerable interest, especially for comparison with the *x*-norequilenin prepared earlier by a different route.[6] * The acetate of the latter has now been reported[7] to be œstrogenic only in 10 mg. doses. *x*-Norequilenin might belong to the *iso*-series, but H. A. Weidlich and M. Meyer-Delius,[8] on the basis of comparative hydrogenation experiments in acid and alkaline solutions, conclude that the terminal rings in the *x*-norequilenin of Koebner and Robinson are *trans*-linked (see p. 126). A racemate which may belong to the norœstrone series has been found to be appreciably œstrogenic (see p. 132).

Syntheses of *dl*-D-homoequilenin (II) (see also p. 126) and its stereoisomer were achieved by repetition of the Arndt–Eistert homologation process, the former compound proving as potent as *dl*-equilenin. This is surprising, since D-homo-œstrone has been reported to be thirty times less active than

(IIa.)





(III.)

the natural hormone,[9] but on the contrary derivatives of the D-homoandrostane series have been found to be as potent as their natural steroid analogues;[10] for example, (IIa) is indistinguishable from androsterone in biological activity.

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[6] A. Koebner and (Sir) R. Robinson, *J.*, 1938, 1994.

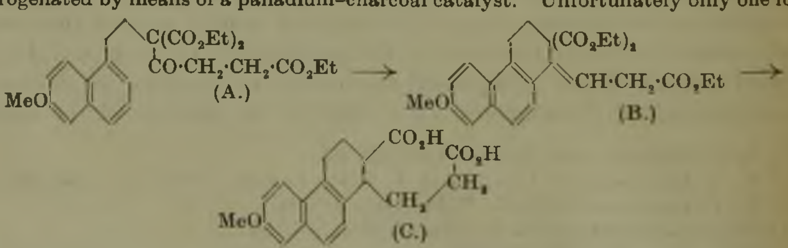
[7] *Idem, J.*, 1941, 566.

[8] *Ber.*, 1941, **74**, 1195, 1213.

[9] M. W. Goldberg and S. Studer, *Helv. Chim. Acta*, 1941, **24**, 478.

[10] M. W. Goldberg and R. Monnier, *ibid.*, 1940, **23**, 840; M. W. Goldberg and E. Wydler, *ibid.*, 1943, **26**, 1142.

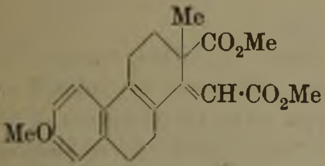
* Since this Report was written W. E. Bachmann, R. A. Gregg, and E. F. Pratt (*J. Amer. Chem. Soc.*, 1943, **65**, 2314) have described a new synthesis of a norequilenin. The keto-triester (A), prepared by condensation of the appropriate naphthylethylmalonic ester with the acid chloride of ethyl hydrogen succinate, was smoothly cyclised with phosphoric acid to (B) and the corresponding crystalline trimethyl ester was hydrogenated by means of a palladium–charcoal catalyst. Unfortunately only one form

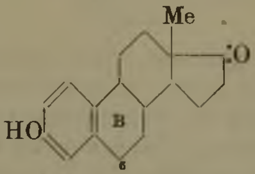


of the acid (C) was produced on decarboxylation of the dihydro-acid, and cyclisation (Dieckmann) and simultaneous demethylation gave the *x*-norequilenin of A. Koebner and (Sir) R. Robinson.[6] Hydrogenation of the ethenoid linkage after decarboxylation would appear to offer a better opportunity of obtaining the diastereoisomeric form of (C). An extension of the method yielded a D-homonorequilenin (II, without the angular Me group).

W. E. Bachmann, S. Kushner, and A. C. Stevenson[11] studied the application of the equilenin method to the synthesis of œstrone (V), where more complicated stereochemical problems are involved. The structure of the unsaturated keto-ester (III), synthesised by standard methods, was readily established by hydrogenation to the already known dihydro-compound.[12] Dehydration of the hydroxy-ester obtained by the Reformatsky reaction, with dry hydrogen chloride in benzene or with formic acid, gave the crystalline unsaturated ester (IV), and hydrogenation of the two ethenoid linkages was effected with a palladium–charcoal catalyst. The resultant mixture of stereoisomers was converted by the Arndt–Eistert chain-lengthening process into the propionic acid derivative and after Dieckmann ring closure, hydrolysis and demethylation the ultimate product [containing at most 8 *dl*-forms and obtained in 75% overall yield from (IV)] readily yielded a crystalline substance (*dl*-œstrone-*a*) which is undoubtedly an œstrone (V) stereoisomer. *dl*-Œstrone-*a*, however, is only fully active in doses of 250γ (cf. 1γ for *d*-œstrone), but the resinous mixture of the remaining stereoisomers is considerably more active and may contain *dl*-œstrone itself. Since the stereochemical configurations at the four asymmetric centres of the final product are determined during the saturation of the two ethylenic linkages of (IV) it seems safe to predict that a detailed study of this vital stage will lead to the ultimate synthesis of the racemic form of the natural hormone.

(IV.)

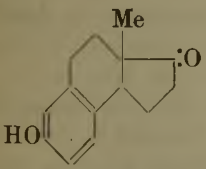


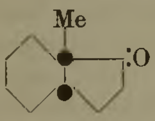


(V.)

A structural isomer of (V), containing an aromatic B ring and a 6-hydroxyl group is devoid of activity (at 1000γ).[13] A simplified œstrone model (VI) synthesised[14] by the standard route from 6-methoxy-α-tetralone exhibited negligible œstrogenic properties. The Bachmann synthesis affords a new route[15] to *cis*-8-methyl-1-hydrindanone[16] (VII) and the previously unknown

(VI.)





(VII.)

(VII*a*.)

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[11] *J. Amer. Chem. Soc.*, 1942, **64**, 974.

[12] (Sir) R. Robinson and J. Walker, *J.*, 1936, 747; 1937, 60; 1938, 183.

[13] W. E. Bachmann and A. B. Ness, *J. Amer. Chem. Soc.*, 1942, **64**, 536.

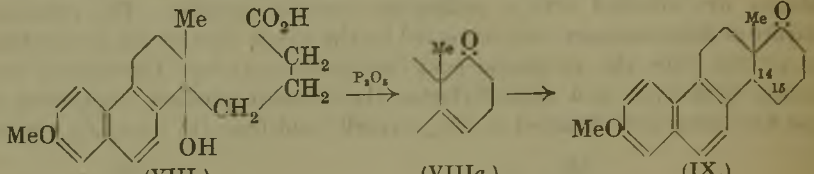
[14] W. E. Bachmann and D. G. Thomas, *ibid.*, p. 94; the corresponding deoxy-compound was synthesised earlier, *ibid.*, 1941, **63**, 598.

[15] W. E. Bachmann and S. Kushner, *ibid.*, 1943, **65**, 1963.

[16] See also V. C. E. Burnop and R. P. Linstead, *J.*, 1940, 720.

trans-form. The former ketone has been synthesised by C. D. Nenitzescu and V. Przemetzky [17] by simultaneous ring closure and reduction when the acid chloride (VII*a*) was treated with aluminium chloride in *cyclo*hexane solution.

The " pentenyl " method of G. H. Elliott and R. P. Linstead [18] has been applied [19] to 1-keto-7-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydrophenanthrene. Condensation with Δ^{δ}-*n*-pentenylmagnesium bromide gave a carbinol, which was oxidised with permanganate to the acid (VIII) and after cyclisation with phosphoric oxide, partial hydrogenation of (VIII*a*) with a platinum catalyst gave a saturated methoxy-ketone. This was formulated as (IX), although the authors expressed uncertainty as to the direction of the final cyclisation. The compound (IX) has now been found [5] to be identical with the methyl ether of *dl*-D-homoequilenin (II) and it is to be noted that hydrogenation of the C_{14-15} ethenoid linkage leads to a stereochemical configuration at C_{14} identical with that in equilenin itself, it being assumed that the more œstrogenic isomers of each pair have the same C_{14} configuration.



(VIII.) (VIII*a*.) (IX.)

(*b*) One of the most elegant routes to the steroid ring system is by (Sir) R. Robinson's diketone method [20] involving the condensation of an acetylnaphthalene with furfural, fission of the furan ring with acids to a diketone (X), which is then cyclised to a naphthyl*cyclo*pentenoneacetic acid (XI) with dilute alkali. The final cyclisation to (XII) can be effected with either sulphuric acid or acetic anhydride. Cyclisation after hydrogenation of the ethenoid linkage leads to diketones such as (XII*a*). Application of this method has already resulted in the synthesis of an *x*-norequilenin [6] and an *x*-norœstrone.[21]

H. A. Weidlich and M. Meyer-Delius [8] have considered in detail the catalytic hydrogenation of αβ-unsaturated ketones, especially in relation to steroid synthesis. For those compounds which can give rise to geometrically isomeric dihydro-ketones, they conclude that hydrogenation in alkaline media proceeds by means of 1 : 4-addition, followed by tautomerisation to the stable *trans*-form, and that in acid solutions direct *cis*-addition of hydrogen occurs to either the carbon–carbon or the carbon–oxygen double linkage, leading to *cis*-ketones, alcohols or hydrocarbons. A. Koebner and (Sir) R. Robinson [6] obtained dihydro-keto-acids by hydrogenation of

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[17] *Ber.*, 1941, **74**, 676. See also C. D. Nenitzescu, E. Cioranescu, and V. Przemetzky, *Ber.*, 1940, **73**, 313.

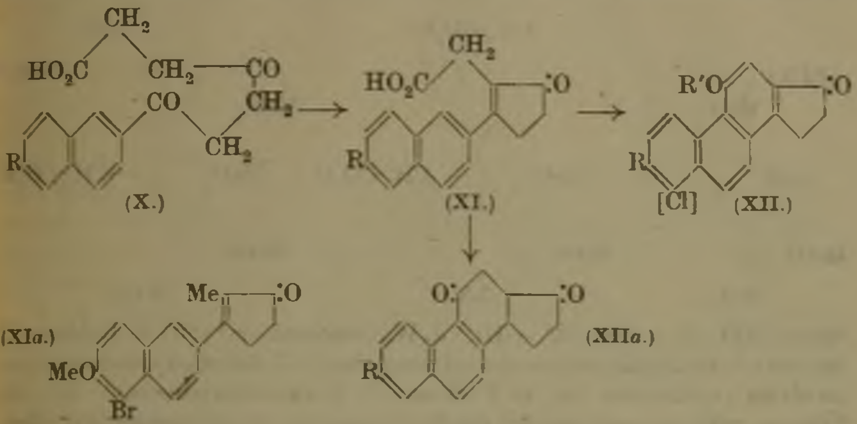
[18] *J.*, 1938, 660.

[19] V. C. E. Burnop, G. H. Elliott, and R. P. Linstead, *J.*, 1940, 727.

[20] *J.*, 1938, 1390; *Ann. Reports*, 1939, **36**, 297.

[21] (Sir) R. Robinson and H. N. Rydon, *J.*, 1939, 1395.

(XI; R = H and OMe), using palladium–strontium carbonate catalysts, but in an acidic medium (XI; R = H) was found to yield a new keto-acid,



(X.) (XI.) (XII.) (XIa.) (XIIa.)

believed to be the *cis*-form.[8] Since (XI; R = OMe) was an intermediate in the synthesis [6] of *x*-norequilenin, Weidlich and Meyer-Delius conclude that the C and D rings in the latter are *trans*-fused.

A variation of the diketone synthesis [22] starting with 5-chloro-6-methoxy-2-acetonaphthone gave a final product (XII; R = OMe, R′ = Ac, Cl as indicated), from which the chlorine atom was unexpectedly difficult to remove. H. A. Weidlich and M. Meyer-Delius [23] were successful in removing a bromine atom from a similar compound (XI*a*) by partial hydrogenation (Pd–$CaCO_3$ in KOH–EtOH) without reducing the ethylenic linkage. Subsequent hydrogenation in alkaline solution gave the *trans*-dihydro-compound. The introduction of either angular methyl or acetic acid groups into dihydro-compounds corresponding to (XI) and (XI*a*) has been attempted.[7]

The carbonyl group is usually reduced when the phenanthrene nucleus in ketones of type (XII) is hydrogenated and it is clearly desirable to have a reactive yet non-reducible group suitably sited in the five-membered ring. The method already employed [21] of opening the ring prior to hydrogenation is rather tedious and attempts have been made to protect the carbonyl group in various ways.[7] For example, a Reformatsky reaction on (XII; R = OMe, R′ = Me), followed by dehydration and hydrogenation with a Raney nickel catalyst, gave a product believed to be (XIII).[24] In some related model experiments,[25] however, hydrogenation (Raney nickel) of both the ketone (XIV) and the acid (XV) resulted in reduction of the terminal benzene ring, and from the latter two crystalline acids, probably stereoisomers of structure (XVI), were isolated. Hydrogenation of chloro-

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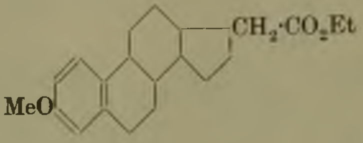
[22] (Sir) R. Robinson and J. Willenz, *J.*, 1941, 393.

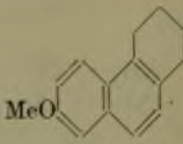
[23] *Ber.*, 1939, **72**, 1941.

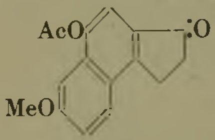
[24] (Sir) R. Robinson and S. N. Slater, *J.*, 1941, 376.

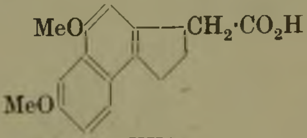
[25] L. C. Bateman and (Sir) R. Robinson, *J.*, 1941, 398; R. H. Martin and (Sir) R. Robinson, *J.*, 1943, 497.

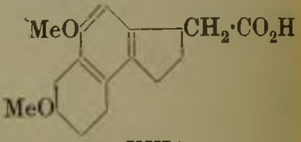
(XII; R = OMe, R′ = Ac) [22] gave complex mixtures, the only recognisable constituent being a deacetylated 9 : 10-dihydro-compound corresponding to


(XIII.)


(XVIa.)

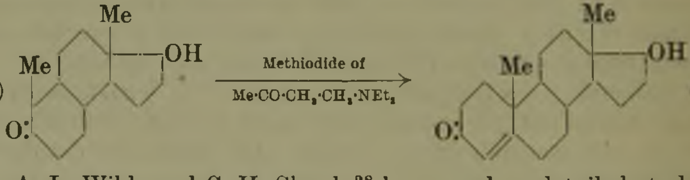

(XIV.)


(XV.)


(XVI.)

chloro-(XII; R = OMe, R′ = H). J. W. Cornforth and (Sir) R. Robinson [26] devised a very satisfactory method of preparing 2 : 7-dihydroxyphenanthrene, involving cyclisation of 6 : 6′-di-iodo-3 : 3′-dimethoxydibenzyl by the Ullmann reaction, and studied the hydrogenation of its monomethyl ether. With a " copper chromite " catalyst, reduction proceeds most readily in the phenolic ring, giving (XVI*a*) as main product, probably accompanied by some octahydrophenanthrene derivative.

(*c*) There is little doubt that application of the Robinson–Mannich base method [27] offers the most promise of success for the synthesis of non-benzenoid steroids of the testosterone (XVIII) type. Thus, application of this method to a ketone such as (XVII), assuming that it could be procured in the requisite stereochemical form, would give testosterone itself, and there are analogies indicating that this final stage would proceed in the manner indicated



(XVII.) (XVIII.)

above. A. L. Wilds and C. H. Shunk [28] have made a detailed study of the application of the method to the synthesis of the hydrochrysene derivative (XIX), isolating intermediate keto-esters and obtaining an overall yield of 83% from 2-carbomethoxy-1-ketotetrahydrophenanthrene. The purity of the dialkylaminoethyl ketone seems to be an important factor.

No conclusive evidence is as yet available to determine the orientation of the new six-membered ring in condensations of Mannich base methiodides with either 5-keto-8-methylhydrindane or *cis*-5-ketohydrindane.[29] However, although the decalone (XX) gives a hydroanthracene derivative on condens-

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[26] *J.*, 1942, 684.

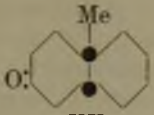
[27] E. C. du Feu, F. J. McQuillin, and (Sir) R. Robinson, *J.*, 1937, 53; *Ann. Reports*, 1939, **36**, 295.

[28] *J. Amer. Chem. Soc.*, 1943, **65**, 469.

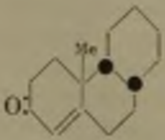
[29] F. J. McQuillin and (Sir) R. Robinson, *J.*, 1941, 586; 1938, 1097.

ation with 4-diethylaminobutan-2-one methiodide,[27] 1-methyl-*cis*-2-decalone yields the unsaturated ketone (XXI), the structure of which was proved by

(XIX.)



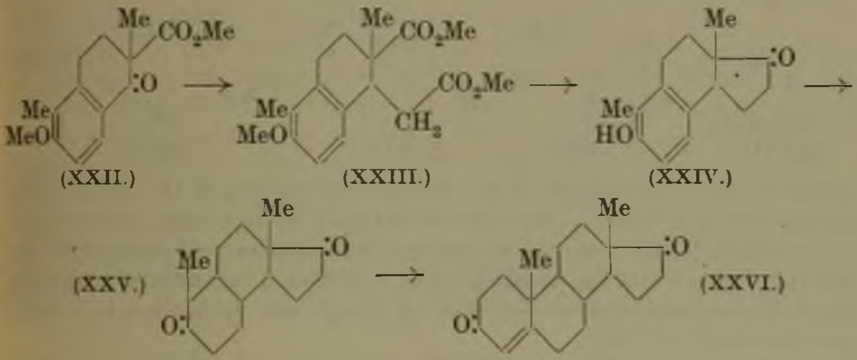
(XX.)



(XXI.)

the isolation of phenanthrene and 2-phenanthrol after selenium dehydrogenation.[30] It seems clear from the examples so far available that the Robinson–Mannich base reaction invariably involves a keto-methin ($-CO-CHMe-$) in preference to a keto-methylene ($-CO-CH_2-$) system.

R. H. Martin and (Sir) R. Robinson [31] have prepared the important diketone (XXV) as a mixture of stereoisomers in the following manner. Starting from 6-methoxy-5-methyl-1-tetralone, the keto-ester (XXII) was



(XXII.) (XXIII.) (XXIV.) (XXV.) (XXVI.)

synthesised by well-known methods and converted by a Reformatsky reaction, dehydration and subsequent reduction, into the two stereoisomeric forms of the di-ester (XXIII). These were transformed separately into the α- and β-tricyclic phenolic ketones (XXIV) by the procedure (Arndt–Eistert chain lengthening and Dieckmann cyclisation) developed in the Robinson and Bachmann schools. Advantage being taken of the valuable observation that hydrogenation with supported palladium catalysts at high temperatures and pressures effectively reduces substituted benzenoid systems, one of the two stereoisomers (α) of the phenolic ketone (XXIV) was reduced to the saturated diol, which was in turn oxidised to the saturated diketone-α (XXV). A compound of this structure can exist theoretically in sixteen *dl*-forms, eight derived from the α-series of (XXIV) and an equal number from the β-series, but, since (XXV) contains a keto-methin system, it appears likely that only eight stable racemic forms of the diketone would exist. The diketone-α, which is considered therefore to comprise at most four *dl*-forms (it actually appears to consist largely of a single stereoisomer), was condensed with the methiodide of 4-diethylaminobutan-2-one, yielding

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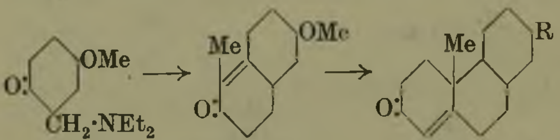
[30] (Sir) R. Robinson and F. Weygand, *J.*, 1941, 386.

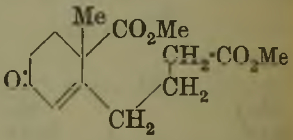
[31] *J.*, 1943, 491.

a product (XXVI) which, on the reasonable assumption that the keto-methin rather than the two keto-methylene systems are involved in this condensation, could contain half of the sixteen possible *dl*-forms of androstenedione. Biological results on this material will be of interest, although the authors consider it more likely that *dl*-androstenedione itself will be found in the second group of stereoisomerides which will result from the continuation of the synthesis with the β-isomer of the phenolic ketone (XXIV), in which the *trans*-configuration at the linkage of rings C and D is thought to be more probable.

Investigating a related route, J. G. Cook and (Sir) R. Robinson [32] converted 4-methoxy*cyclo*hexanone into the Mannich base (XXVII), which with ethyl β-ketovalerate yielded the unsaturated ketone (XXVIII). Hydrogenation, followed by a second Mannich base condensation, gave (XXIX; R = OMe) and, with ethyl *cyclo*hexanone-4-carboxylate as starting material in an analogous process, (XXIX; R = CO_2Et) was obtained. Another variant [33] involves inclusion of the *cyclo*pentanone ring in the form of the appropriate adipic acid. The keto-diester (XXX) has been prepared, so far in only 8% yield, and the complete scheme envisages reduction of the ethylenic linkage and the building up of a further six-membered ring by a Mannich base condensation, followed by Dieckmann cyclisation to a compound similar to (XXV).

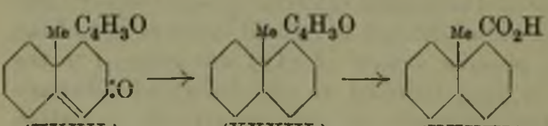


(XXVII.) (XXVIII.) (XXIX.)

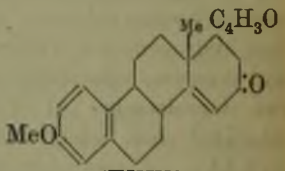


(XXX.)

Following up earlier researches [34] in which sodio-*cyclo*hexanone was condensed with styryl methyl ketone to give an octalone, the employment of furfurylideneacetone (XXXI) in such condensations has been explored by L. E. King and (Sir) R. Robinson.[35] 2-Methyl*cyclo*hexanone and (XXXI) gave an unsaturated ketone (XXXII), reduced in two stages (catalytic and Kishner–Wolff) to a furylmethyldecalin (XXXIII), which after hydrolytic fission of the furan ring, followed by permanganate oxidation, yielded the acid (XXXIV), the configuration of which has yet to be determined. The method has been utilised to synthesise (XXXV) from the known octahydro-



(XXXII.) (XXXIII.) (XXXIV.)



(XXXV.)

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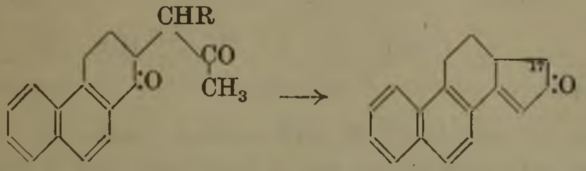
[32] *J.*, 1941, 391.

[33] (Sir) R. Robinson and E. Seijo, *J.*, 1941, 582.

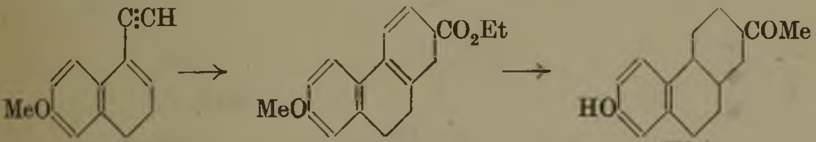
[34] W. S. Rapson and (Sir) R. Robinson, *J.*, 1935, 1285.

[35] *J.*, 1941, 465.

phenanthrene ketone, and its degradation to an x-œstrone methyl ether is being attempted. A. L. Wilds[36] has described the preparation of the diketone (XXXVI; R = H) from 2-bromo-1-ketotetrahydrophenanthrene by condensation with the sodio-derivative of acetoacetic ester. Both the diketone and the diketo-ester (XXXVI; $R = CO_2Et$) are converted in 85—90% yields into the cyclic ketone (XXXVII) with aqueous alkali. Hydrogenation of (XXXVII) with a palladium–charcoal catalyst (in neutral solution[8]) gave the expected mixture of diastereoisomers. The difficulties involved in modifying this method so as to introduce an angular methyl group and a suitable substituent in the 17-position seem formidable.


(XXXVI.) (XXXVII.)

(*d*) The most successful attempt to utilise the Diels–Alder reaction in steroid synthesis has been that of E. Dane and her collaborators[37] in which a stereoisomer, or possibly an isomer, of œstrone was synthesised dependent upon the orientation of the addition reaction, a point which still remains unclarified. The convenience of the diene synthesis has much to commend it and several applications have recently been made, mainly, however, in the form of model experiments. E. Dane and O. Hoss,[38] extending their earlier work, have employed the substituted vinylacetylene (XXXVIII) as a "diene" component in condensations with both acrylic and propiolic esters. The product (XXXIX) from the former was tetrahydrogenated and converted *via* the acid chloride and diazo-ketone into the phenolic ketone (XL). Both this and the corresponding 9 : 10-dihydrophenanthrene analogue derived from propiolic ester (the hydrogenation stage was omitted in this case) proved to be physiologically inactive. It was intended to continue the synthesis *via* the hydroxy-methylene derivative of (XL).


(XXXVIII.) (XXXIX.) (XL.)

Following model experiments which demonstrated that *trans*-1 : 2-diacetylethylene functioned as a philodiene and that the resultant γ-diketones cyclised normally, M. W. Goldberg and P. Muller[39] condensed the diene corresponding to (XXXVIII) with the diacetylethylene and obtained two

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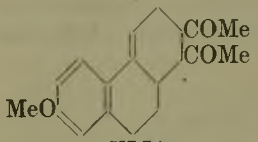
[36] *J. Amer. Chem. Soc.*, 1942, **64**, 1421.

[37] *Ann. Reports*, 1939, **36**, 291.

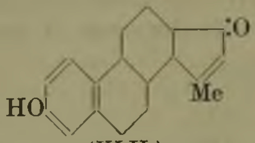
[38] *Annalen*, 1942, **552**, 113.

[39] *Helv. Chim. Acta*, 1940, **23**, 831; B.P. 536,769.

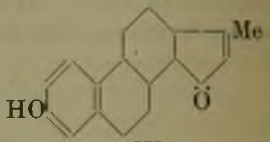
isomeric adducts (XLI), which differed only in the location of the ethenoid linkage, since they both gave the same dihydro-compound on hydrogenation.



(XLI.)



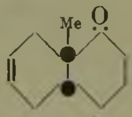
(XLII.)



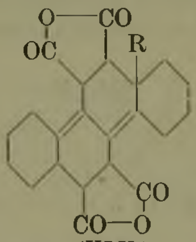
(XLIII.)

Cyclisation of dihydro-(XLI) with sodium methoxide, followed by demethylation with hydrobromic acid in acetic acid, gave a product [either (XLII) or (XLIII)] which was fully œstrogenic in 100γ doses (*d*-œstrone is active at about 0·7γ). This fact, the probable *trans*-nature of the philodiene and the known relative inactivity of the *iso*equilenins, combine to suggest that structure (XLII), including *trans*-fusion of the terminal rings, is highly probable. Further development of this synthesis would appear to be of interest.

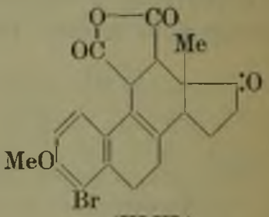
The successful addition of butadiene to 2-methyl*cyclo*hexen-3-one,[40] giving a product formulated as (XLIV), is surprising in view of earlier failures with similar philodienes.[41] The ketone has been converted into the ethynylcarbinol, and the latter partially hydrogenated and then dehydrated to a diene with which further addition reactions are contemplated. L. W. Butz and his collaborators[42] have developed a divinylacetylene addition reaction which from di*cyclo*hexenylacetylene and maleic anhydride leads to (XLV; R = H). Dehydrogenation provides evidence for the



(XLIV.)



(XLV.)



(XLVI.)

carbon skeleton of the dianhydride and the location of the ethenoid linkages is based partly on analogy and partly on light absorption evidence. The steroid analogue of (XLV; R = H) containing one *cyclo*pentane ring has also been synthesised, but introduction of a methyl group into the dienyne system gives (XLV; R = Me) in only 2% yield, the angular location of the

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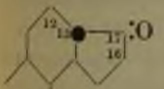
[40] W. Nudenberg and L. W. Butz, *J. Amer. Chem. Soc.*, 1943, **65**, 1436.

[41] (Sir) R. Robinson and A. R. Todd, *J.*, 1935, 1530; E. Dane, J. Schmidt, and C. Rautenstrauch, *Annalen*, 1937, **532**, 29.

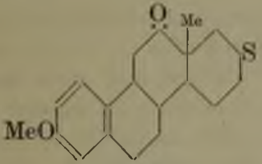
[42] L. W. Butz, A. M. Gaddis, E. W. J. Butz, and R. E. Davis, *J. Org. Chem.*, 1940, **5**, 379; L. W. Butz and L. M. Joshel, *J. Amer. Chem. Soc.*, 1941, **63**, 3344; L. M. Joshel, L. W. Butz, and J. Feldman, *ibid.*, p., 3348; L. W. Butz and J. M. Joshel, *ibid.*, 1942, **64**, 1311; W. Nudenberg and L. W. Butz, *ibid.*, 1943, **65**, 2059.

methyl group being adduced from the isolation of chrysene on dehydrogenation. Dimethyl fumarate has also been employed as the philodiene component. Extending an earlier observation,[43] A. Koebner and (Sir) R. Robinson [7] have employed a diene synthesis to prepare a ketone to which the structure (XLVI) has been provisionally assigned.

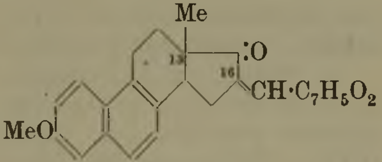
(*e*) The presence of angular methyl groups in the steroid hormones constitutes a stern challenge to the ingenuity of the synthetic organic chemist. The majority of the synthetic methods so far developed involves introduction of the requisite methyl groups prior to final cyclisation to the tetracyclic system, but undoubted advantages would accrue if methods were available for *C*-methylation of preformed tetracyclic ketones such as (XLVII) in the 13-position. Direct substitution would appear to be ruled out in view of the methylation of *trans*-α-decalone essentially in the β-position.[44] D. A. Peak and (Sir) R. Robinson [45] methylated a 12-keto-compound in the hydrochrysene series with methyl iodide in the presence of potassium *tert.*-butoxide, and although dehydrogenation gave chrysene, such observations do not furnish complete proof of the angular location of the methyl group, since G. R. Ramage and W. E. Jones [46] have reported methyl group elimination from methylhydrochrysenes on dehydrogenation. In any case the Robinson–Peak process eventually requires a suitable substituent or point of attack in ring D and (Miss) N. A. McGinnis and (Sir) R. Robinson [47] sought to furnish this by employing 3-acetyl-Δ^3-dihydrothiopyran in the Rapson–Robinson synthesis.[48] The unsaturated ketone so obtained was reduced and *C*-methylated to give a product believed to be (XLVIII).



(XLVII.)



(XLVIII.)



(XLIX.)

The 16-piperonylidene derivative of *x*-norequilenin methyl ether [6] on *C*-methylation (methyl iodide and potassium *tert.*-butoxide) [7] furnished a compound (XLIX) which is apparently not identical with the corresponding derivative of *dl*-equilenin methyl ether. Since the validity of this method has been established by experiments with the piperonylidene compound of 2-methyl*cyclo*hexanone,[49] it would appear that (XLIX) must belong to the *iso*equilenin series. W. S. Johnson [50] has contributed to the generality of the above methylation procedure by devising means for the subsequent removal of the arylidene group. The benzylidene derivative of α-decalone on *C*-methyl-

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[43] W. E. Bachman and M. C. Kloetzel, *J. Amer. Chem. Soc.*, 1938, **60**, 3204.

[44] J. W. Cook and C. A. Lawrence, *J.*, 1937, 817.

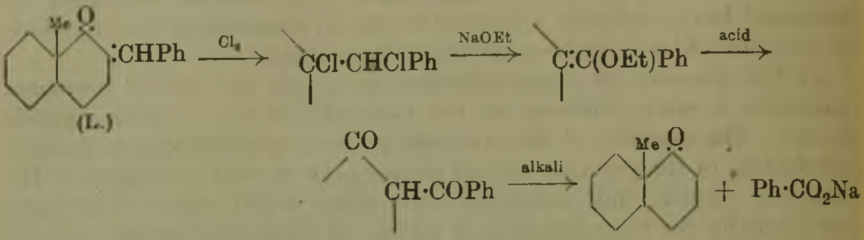
[45] *J.*, 1937, 1581. [46] *J.*, 1938, 1853. [47] *J.*, 1941, 404.

[48] *J.*, 1935, 1285; *Ann. Reports*, 1939, **36**, 295.

[49] A. J. Birch, *J.*, 1943, 661.

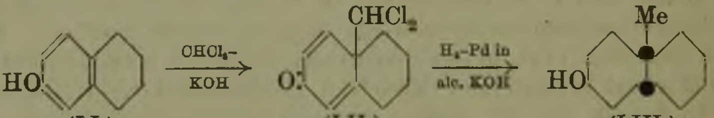
[50] *J. Amer. Chem. Soc.*, 1943, **65**, 1317.

ation gave two crystalline isomers (L), which were separately converted by the procedure indicated into *cis*- and *trans*-9-methyl-1-decalones.



(L.)

By taking advantage of an abnormal Reimer–Tiemann synthesis first observed by von Auwers, R. B. Woodward [51] has devised a method which suggests the possibility of converting compounds of the œstrane into the androstane series. In addition to the normal aldehyde, the tetralol (LI) gives a product which must be (LII), since (*inter alia*) on catalytic hydrogenation the methyldecalol (LIII) was obtained, which was oxidised to

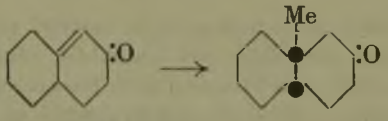


(LI.) (LII.) (LIII.)

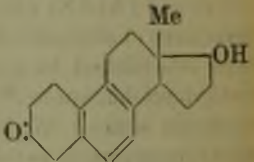
the known *cis*-10-methyl-2-decalone. Another observation of considerable significance is that 2-keto-$\Delta^{1:9}$-octalin (LIV) can be converted in 60% yield into *cis*-9-methyl-2-decalone (LV) by 1 : 4-addition of methylmagnesium iodide in the presence of cuprous bromide.[52]

J. English and G. Cavaglieri [53] carried out some model experiments in the decalin series in attempts to introduce an angular methyl group by pinacolic dehydration of a glycol such as (LVI) to the methyldecalone (LVII). The mixture of methyloctalins obtained by elimination of water

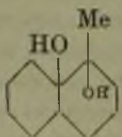
(LIV.)

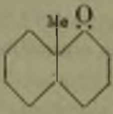


(LV.)



(LVI.)





(LVII.)

(LVIII.)

from 1-methyl-1-decalol was converted into the oxides with perbenzoic acid, which were hydrolysed to the glycols with mineral acid. One of the

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[51] *J. Amer. Chem. Soc.*, 1940, **62**, 1208.

[52] A. J. Birch and (Sir) R. Robinson, *J.*, 1943, 501.

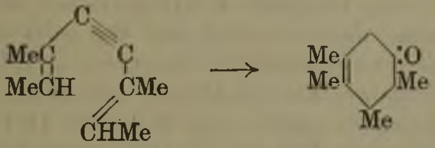
[53] *J. Amer. Chem. Soc.*, 1943, **65**, 1085; see also (Sir) R. Robinson and S. N. Slater, *J.*, 1941, 376.

crystalline glycols so produced was assigned the structure (LVI), but dehydration of this ensued predominantly without rearrangement.

J. W. Cornforth, (Mrs.) R. H. Cornforth, and (Sir) R. Robinson [54] found that reduction of 2-methoxynaphthalene with sodium and alcohol, followed by acid hydrolysis, produced β-tetralone in 56% yield. The process would appear to be applicable to all 2-methoxynaphthalenes, and should prove valuable for obtaining some hitherto difficultly accessible β-tetralones such as the 6-methoxy-compound.[55] Equilenin methyl ether, treated in this way, yields the interesting keto-alcohol (LVIII).

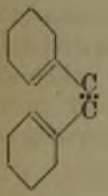
(*f*) C. S. Marvel and his collaborators [56] have made a study of the cyclisation of various dienynes with sulphuric and formic acids, exemplified in the simplest case by the conversion of the *s.*-divinylacetylene (LIX), prepared by dehydration of the acetylene glycol from methyl ethyl ketone, into the tetramethyl*cyclo*hexenone (LX). There has been much discussion as to the structures to be assigned to the cyclisation products from more complex dienynes such as (LXI), and although Marvel has carried out a considerable number of such cyclisations, and has examined thoroughly the structural features essential for this reaction to occur, it is only in the case of (LXI) that the products have been subjected to detailed investigation.

(LIX.)

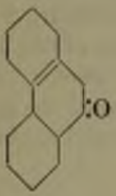


(LX.)

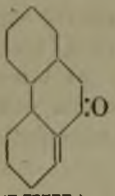
Di*cyclo*hexenylacetylene (LXI), derived from *cyclo*hexanone acetylene glycol, gave a product which was originally formulated as the βγ-unsaturated perhydrophenanthrene ketone (LXII), since a substance thought to be *as.*-octahydrophenanthrene was obtained after Clemmensen reduction



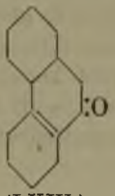
(LXI.)



(LXII.)



(LXIII.)



(LXIV.)

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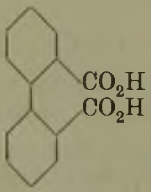
[54] *J.*, 1942, 689.

[55] G. P. Crowley and (Sir) R. Robinson, *J.*, 1938, 2001.

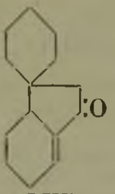
[56] A. T. Blomquist and C. S. Marvel, *J. Amer. Chem. Soc.*, 1933, **55**, 1655; D. T. Mitchell and C. S. Marvel, *ibid.*, p. 4276; P. S. Pinkney, G. A. Nesty, R. H. Wiley, and C. S. Marvel, *ibid.*, 1936, **58**, 972; G. A. Nesty and C. S. Marvel, *ibid.*, 1937, **59**, 2662; P. S. Pinkney, G. A. Nesty, D. E. Pearson, and C. S. Marvel, *ibid.*, p. 2666; P. S. Pinkney and C. S. Marvel, *ibid.*, p. 2669; C. S. Marvel, R. Mozingo, and E. C. Kirkpatrick, *ibid.*, 1939, **61**, 2003; C. S. Marvel, D. E. Pearson and L. A. Patterson, *ibid.*, 1940, **62**, 2659; C. S. Marvel and R. V. White, *ibid.*, p. 2739; C. S. Marvel, D. E. Pearson, and R. V. White, *ibid.*, p. 2741; C. S. Marvel and L. A. Patterson, *ibid.*, 1941, **63**, 2218; C. S. Marvel and L. A. Brooks, *ibid.*, p. 2630; C. S. Marvel and W. L. Walton, *J. Org. Chem.*, 1942, **7**, 88.

and selenium dehydrogenation. It seemed that the method might usefully be developed for steroid syntheses. R. P. Linstead and A. L. Walpole[57] investigated the cyclisation of (LXI) in greater detail and isolated two crystalline ketones (m. p. 39° and 94°), the latter proving to be identical with a substance separated in small yield by the previous workers from the main liquid product. Clemmensen reduction of each ketone, followed by vapour-phase dehydrogenation over palladised charcoal, gave phenanthrene (later confirmed by Marvel), and the dihydro-ketones, obtained by catalytic hydrogenation, after reaction with methylmagnesium iodide gave 9-methylphenanthrene on dehydrogenation. It merely remained to determine the positions of the ethenoid linkages and ultra-violet absorption spectra determinations readily revealed that both ketones were αβ-unsaturated. Finally, the fact that a mixture of two saturated ketones [m. p. 51° (main product) and a liquid isomer] was obtained on hydrogenation of each isomer, and that the liquid ketone was converted into the solid isomer at elevated temperatures, appeared to establish the structures as (LXIII) and (LXIV).

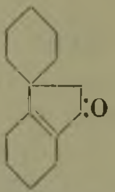
However, having shown that a substance believed to be an octahydrophenanthrene was actually a spiran type, M. Levitz, D. Perlman, and M. T. Bogert[58] suggested that the Marvel cyclisation products might be similarly constituted and they cited several cases where spirans undergo rearrangement and give benzenoid hydrocarbons on dehydrogenation. While examining this suggestion, C. S. Marvel and W. L. Walton[56] observed that *spiro*decane and methyl*spiro*decane gave naphthalene and methylnaphthalene respectively in about 30% yields on dehydrogenation over platinised charcoal at 325°. Subsequently R. P. Linstead and his associates[59] prepared and inter-related all six of the perhydro-2 : 2′-diphenic acids (LXV) demanded by classical stereochemical theory. None of these compounds, however, proved to be identical with the supposed perhydro-2 : 2′-diphenic acid which had been obtained[60] by nitric acid oxidation of the alcohol derived from the saturated ketone (m. p. 51°) mentioned above. Further, unlike all the authentic acids (LXV) which yielded ketones on pyrolysis, this acid gave only an anhydride. The formulation of the acid having thus proved incorrect, it followed that the ketone (m. p. 51°) and its precursors could not belong to the perhydrophenanthrene series at all and that phenanthrene and its



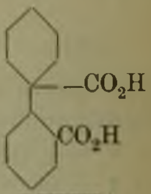
(LXV.)



(LXVI.)
(m. p. 39°.)



(LXVII.)
(m. p. 94°.)



(LXVIII.)

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[57] *J.*, 1939, 842.

[58] *J. Org. Chem.*, 1941, **6**, 105.

[59] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985, 1991, 2003, 2006, 2009, 2014, 2022.

[60] R. P. Linstead and A. L. Walpole, *J.*, 1939, 842.

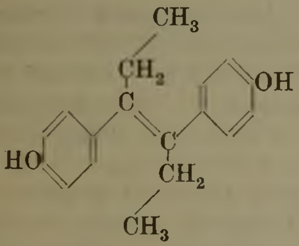
homologues had originated by means of rearrangements during dehydrogenation. R. P. Linstead and W. E. Doering [61] then formulated the original cyclisation products (formerly LXIII and LXIV) as spirans with structures represented by (LXVI) and (LXVII) and the acid degradation product as (LXVIII), which according to the Blanc rule would be expected to give an anhydride rather than a ketone on pyrolysis. The individual structures (LXVI) and (LXVII) of the isomers were readily assigned on the basis of R. B. Woodward's [62] generalisations concerning the influence of substituents and other environmental features on the ultra-violet absorption properties of αβ-unsaturated ketones. Their application in this particular case had already been noted by L. K. Evans and A. E. Gillam.[63]

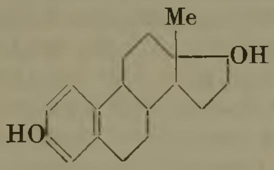
Synthetic Œstrogens of the Stilbœstrol Type.

This topic received only brief mention in the Report for 1939, but in the intervening years much attention has been paid to the development of the chemical as well as the physiological aspects of this field. It may be recalled that E. C. Dodds and his collaborators, working originally with substances containing the phenanthrene nucleus, later demonstrated the wide incidence of low potency œstrus-producing properties among organic compounds of many types,[64] studies which led to the isolation of a highly potent œstrogen from the product obtained on demethylating anethole.[65]

At the same time speculation as to possible spatial relationships between natural and synthetic œstrogens resulted in the notable discovery of highly active stilbene and diphenylethane derivatives,[66, 66a] particularly stilbœstrol *

(I.)





(IV.)

$HO{\cdot}C_6H_4{\cdot}CHEt{\cdot}CHEt{\cdot}C_6H_4{\cdot}OH$

(II.)

$HO{\cdot}C_6H_4{\cdot}C(:CHMe){\cdot}C(:CHMe){\cdot}C_6H_4{\cdot}OH$

(III.)

(4 : 4′-dihydroxy-αα′-diethylstilbene) (I), hexœstrol (3 : 4-bis-*p*-hydroxyphenylhexane) (II), and dienœstrol (3 : 4-bis-*p*-hydroxyphenylhexa-2 : 4-

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[61] *J. Amer. Chem. Soc.*, 1942, **64**, 1996.

[62] *Ibid.*, 1941, **63**, 1123; 1942, **64**, 76.

[63] *J.*, 1941, 818.

[64] For summary, see E. C. Dodds and W. Lawson, *Proc. Roy. Soc.*, 1938, *B*, **125**, 222.

[65] E. C. Dodds and W. Lawson, *Nature*, 1937, **139**, 1068; N. R. Campbell, E. C. Dodds, and W. Lawson, *Proc. Roy. Soc.*, 1940, *B*, **128**, 253.

[66] E. C. Dodds, L. Golberg, W. Lawson, and (Sir) R. Robinson, *Nature*, 1938, **141**, 247; *Proc. Roy. Soc.*, 1939, *B*, **127**, 140.

[66a] E. C. Dodds, L. Golberg, E. I. Grünfeld, W. Lawson, C. M. Saffer, and (Sir) R. Robinson, *Proc. Roy. Soc.*, 1944, *B*, **132**, 83 (added in proof).

* The name stilbœstrol, which now seems to be widely employed, is used in this report in preference to diethylstilbœstrol.

diene) (III), which are practically as potent as, and considerably more accessible than, the natural female sex hormones. They have the additional advantage of being effective when administered orally.

Stilbœstrol (I).—The designation of this substance on general grounds as the *trans*-isomer, which form is more clearly related sterically to œstradiol (IV), has been confirmed by crystallographic measurements [67] and also by hydrogenation experiments in which its behaviour was compared with that of *cis*- and *trans*-αα′-dimethylstilbenes.[68] The latter gave practically quantitative yields of *meso*- and racemic 2 : 3-diphenylbutanes respectively and hydrogenation of stilbœstrol with palladium-black in acetic acid gave an 88% yield of the racemic dihydro-compound. The latter result disagrees with an earlier report,[66] but it has been confirmed independently.[69]

In the original synthesis [66] the carbinol (V), when treated with phosphorus tribromide, gave stilbœstrol dimethyl ether and an oil, the latter yielding on demethylation a ψ-stilbœstrol, which it was suggested might be the *cis*-isomer, especially since its ether was converted into the normal stilbœstrol ether in sunlight. It has been shown, however, that the non-crystalline material formed on dehydration of (V) with potassium pyrosulphate consists essentially of the two geometrical isomers of (VI), their structures being proved by the isolation of acetaldehyde and α-ethyldeoxyanisoin on ozonolysis. They are both readily converted in the presence of iodine into

(V.) $MeO{\cdot}C_6H_4{\cdot}CHEt{\cdot}C(OH)Et{\cdot}C_6H_4{\cdot}OMe$

(VI.) $MeO{\cdot}C_6H_4{\cdot}C({:}CHMe){\cdot}CHEt{\cdot}C_6H_4{\cdot}OMe$

the dimethyl ether of *trans*-stilbœstrol (I). Alcoholic potash at temperatures above 200° and palladium in ethereal solution are also effective in isomerising ψ-stilbœstrol.[71] F. von Wessely and A. Kleedorfer [72] indicate that one of the diols (m. p. 153° and 143·5°) corresponding to (VI) is fully œstrogenic (rats) in doses of 2·5γ, whereas the isomer is inactive at 100γ. This finding does not appear to be confirmed, however, in the later paper.[70] E. Walton and G. Brownlee [73] have also examined the ψ-stilbœstrol mentioned above, isolating a substance with m. p. 151°, one fourteenth as active as stilbœstrol itself, which is presumably identical with von Wessely's higher-melting diol. These authors also describe a new stilbœstrol dipropionate, obtained in the usual manner and giving stilbœstrol on alkaline hydrolysis, yet possessing only 1/600th of the activity of the normal dipropionate. This may be a derivative of the unknown *cis*-isomer of (I).

Many attempts have been made to improve upon the original synthesis [66]

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[67] G. Giacomello and E. Bianchi, *Gazzetta*, 1941, **71**, 667; see also C. H. Carlisle and D. Crowfoot, *J.*, 1941, 6.

[68] F. von Wessely and H. Welleba, *Ber.*, 1941, **74**, 777.

[69] A. M. Docken and M. A. Spielman, *J. Amer. Chem. Soc.*, 1940, **62**, 2163.

[70] F. von Wessely, E. Kerschbaum, A. Kleedorfer, F. Prillinger, and E. Zajic, *Monatsh.*, 1940, **73**, 127.

[71] A. Serini and K. Steinruck, U.S.P. 2,311,093.

[72] *Naturwiss.*, 1939, **27**, 567, 664.

[73] *Nature*, 1943, **151**, 305.

of stilbœstrol (I) from deoxyanisoin (VII). One modification[74] involves the preparation of ethyldeoxyanisoin (IX) from the glycol (VIII), the latter being prepared by a Grignard reaction on anisoin. Another variation[75] comprises the reaction of the ketol (XI) with anisylmagnesium bromide, followed by dehydration of the carbinol to the ketone (XII), which, after

$$\underset{\text{(VII.)}}{\mathrm{R{\cdot}CO{\cdot}CH_2R}} \qquad \underset{\text{(VIII.)}}{\mathrm{R{\cdot}CH(OH){\cdot}C(OH)EtR}} \xrightarrow[\mathrm{H_2SO_4}]{50\%} \underset{\text{(IX.)}}{\mathrm{R{\cdot}CO{\cdot}CHEtR}} \xrightarrow{\mathrm{EtMgBr}}$$

$$\underset{\text{(X.)}}{\mathrm{R{\cdot}C(OH)Et{\cdot}CHEtR}} \xrightarrow{\mathrm{PBr_3}} \text{Dimethyl ether of (I)}$$

$$\underset{\text{(XI.)}}{\mathrm{Et{\cdot}CO{\cdot}CH(OH)Et}} \xrightarrow[-\mathrm{H_2O}]{\mathrm{RMgBr}} \underset{\text{(XII.)}}{\mathrm{R{\cdot}CHEt{\cdot}COEt}} \xrightarrow{\mathrm{RMgBr}} \text{(X)}$$

$$(\mathrm{R} = p\text{-}\mathrm{MeO{\cdot}C_6H_4})$$

another treatment with the Grignard reagent gives the carbinol precursor (X) of stilbœstrol dimethyl ether. The ketone (XII) has also been made by a devious route from *p*-methoxyphenylacetonitrile.[70]

E. Péteri[76] attempted to effect a rearrangement-dehydration of the carbinol (XIII), prepared from the corresponding aldehyde with ethylmagnesium bromide, by treatment with acids, a method originally employed for the synthesis of αα′-dialkylstilbenes. The yield of stilbœstrol dimethyl ether (XIV) was negligible and the parent aldehyde proved rather inaccessible. It was found, however, that (XIV) could be obtained in moderate yield by rearrangement of the carbinol (XV) on dehydration with phosphorus oxychloride in toluene, (XV) being prepared in several stages from anisaldehyde cyanohydrin. Closely related is an attempt by Z. Foldi and I. Demjén[77]

$$\begin{tikzcd}
\underset{\text{(XIII.)}}{\mathrm{CEtR_2{\cdot}CH(OH)Et}} \arrow[r] & \underset{\text{(XIV.)}}{\mathrm{R{\cdot}CEt{:}CEtR}} & \underset{\text{(XV.)}}{\mathrm{CHR_2{\cdot}CH(OH)Et_2}} \arrow[l] \\
& \text{(XVII.)}\ \mathrm{CEtR_2{\cdot}COEt} \arrow[u] & \mathrm{R{\cdot}CHCl{\cdot}COR}\ \text{(XVI.)} \arrow[u, "\mathrm{EtMgBr}"']
\end{tikzcd}$$

$$(\mathrm{R} = p\text{-}\mathrm{MeO{\cdot}C_6H_4})$$

to prepare the carbinol (X) by treating α-chlorodeoxyanisoin (XVI) with ethylmagnesium bromide, which resulted somewhat unexpectedly in the isolation of the carbinol (XV) obtained by Péteri. An analogous rearrangement is that of the oxide of stilbœstrol, which on distillation or merely on drying is converted into a ketone, the dimethyl ether (XVII) of which is reconverted into stilbœstrol dimethyl ether (XIV) by a retropinacolinic change on reduction with sodium and amyl alcohol.[70]

The method used by H. Staudinger and F. Pfenninger[78] for converting

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[74] S. Kuwada and Y. Sasagawa, *J. Pharm. Soc. Japan*, 1940, **60**, 93.

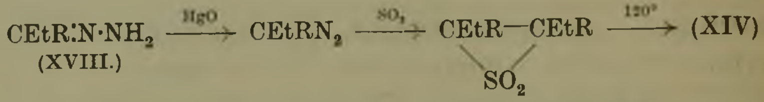
[75] S. Kuwada, Y. Sasagawa, and M. Nisikawa, *ibid.*, p. 224; see also L. F. Fieser and W. G. Christiansen, U.S.P. 2,248,019.

[76] *J.*, 1940, 833.

[77] *Ber.*, 1941, **74**, 930; see also B.P. 537,976; 537,993.

[78] *Ber.*, 1916, **49**, 1946.

benzophenone into tetraphenylethylene has been successfully employed[79] to prepare stilbœstrol dimethyl ether (XIV) in an overall yield of 25% from *p*-methoxypropiophenone. The hydrazone (XVIII) of the ketone is oxidised to the substituted diazomethane, which is converted by treatment with sulphur dioxide into the sulphone, the latter yielding (XIV) on pyrolysis.



$$\underset{\text{(XVIII.)}}{\mathrm{CEtR{:}N{\cdot}NH_2}} \xrightarrow{\mathrm{HgO}} \mathrm{CEtRN_2} \xrightarrow{\mathrm{SO_2}} \mathrm{CEtR{-}CEtR}\ (\mathrm{SO_2}) \xrightarrow{120^\circ} \text{(XIV)}$$

Possibly the most direct approach to the synthesis of stilbœstrol is that of M. S. Kharasch and M. Kleiman,[80] who, following up their earlier discovery that allyl chloride gives hexatriene on treatment with sodamide in liquid ammonia, treated anethole hydrobromide (XIX) likewise and obtained a 40% yield of a substance believed to be (XX), or the isomeric *cyclo*propane

$$\text{(XIX.)}\quad \mathrm{R{\cdot}CHBr{\cdot}CH_2{\cdot}CH_3} \xrightarrow[\text{liq. NH}_3]{\mathrm{NaNH_2}} \mathrm{R{\cdot}CH(CH{:}CH_2){\cdot}CHEtR}\quad \text{(XX.)}$$

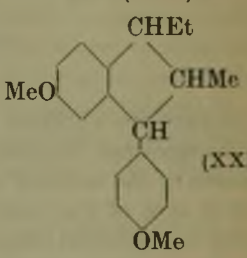
derivative, which isomerised on demethylation (alkali and glycol) and gave a 55% yield of stilbœstrol (I).

Hexœstrol (II).—During an investigation of the œstrogenic properties of a wide variety of organic compounds, E. C. Dodds and W. Lawson[81] reported that anol (p-$\mathrm{HO{\cdot}C_6H_4{\cdot}CH{:}CH{\cdot}CH_3}$) (XXI) was as active as œstrone. It was subsequently realised[82] that this activity was due to the presence of a persistent impurity produced during the preparation of anol by demethylation of anethole with alcoholic potassium hydroxide at 200°, and eventually the potent by-product was isolated as a crystalline solid, m. p. 184—185°.[83] It proved to be identical with a dihydrostilbœstrol (II) which had already been obtained by hydrogenation of dienœstrol (III)[84] and was evidently derived from an anol (XXI) dimeride which had undergone reduction.

A detailed investigation[85] of the complex mixture obtained on demethylating anethole has revealed the presence, in addition to anol (XXI) and the

$$(p)\ \mathrm{MeO{\cdot}C_6H_4{\cdot}CH{:}CMe{\cdot}CHEt{\cdot}C_6H_4{\cdot}OMe}\ (p)$$

(XXII.)



(XXIII.)

dihydrostilbœstrol (II), of the phenol corresponding to "isoanethole" (XXII), the structure of which had already been proved by G. D. Goodall

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[79] L. von Vargha and E. Kovacs, *Ber.*, 1942, **75**, 794; B.P. 526,927.

[80] *J. Amer. Chem. Soc.*, 1943, **65**, 11.

[81] *Nature*, 1937, **139**, 627. [82] *Idem, ibid.*, p. 1068.

[83] N. R. Campbell, E. C. Dodds, and W. Lawson, *ibid.*, 1938, **142**, 1121.

[84] E. C. Dodds, L. Golberg, W. Lawson, and (Sir) R. Robinson, *ibid.*, p. 34.

[85] N. R. Campbell, E. C. Dodds, and W. Lawson, *Proc. Roy. Soc.*, 1940, *B*, **128**, 253.

and R. D. Haworth.[86] In this connexion it may also be noted that W. Baker and J. Enderby [87] have shown that the crystalline anethole dimeride, "metanethole," has the structure (XXIII), and that N. R. Campbell [88] isolated 1 : 3-di-*p*-methoxyphenyl-2-methylpropane from the product obtained after prolonged heating of anethole.

Dihydrostilbœstrol (II) can exist in *meso*- and *dl*-forms. Hydrogenation of stilbœstrol itself with palladised charcoal as catalyst gave a form, m. p. 128°, whereas hydrogenation of either ψ-stilbœstrol, dienœstrol (III) or of the dimethyl ether of ψ-stilbœstrol, followed by demethylation, yielded a form, m. p. 185°.[66, 68, 69] The latter substance, now known as hexœstrol, is probably the most potent of the known œstrogens, whereas its stereoisomer (*iso*-hexœstrol, m. p. 128°) is only about 1/100th as active. C. H. Carlisle and D. Crowfoot [67] have demonstrated by *X*-ray crystallography that the higher-melting isomer is the *meso*-compound, and the racemic nature of the second form has been established by its resolution,[68] the *d*-form (active only in 100γ doses) proving to be about ten times as powerful an œstrogen as its enantiomorph. F. von Wessely and H. Welleba [68] have made a detailed study of the hydrogenation of stilbœstrol and related compounds [89] and it seems that a convenient route to hexœstrol is by hydrogenation of the residues (mainly VI) obtained after removal of stilbœstrol dimethyl ether from the dehydration product of (V), followed by demethylation by heating with ethylmagnesium iodide. The interconversion of the *dl*- and *meso*-forms can be effected by heating with either palladised charcoal [90] or hydrogen sulphide.[91]

An alternative route to compounds of the hexœstrol type, modelled on the thermal decomposition of *s*.-diphenylazomethane into diphenylethane,[92] has been developed [90, 93] and applied [94] to the synthesis of the dimethyl ethers of hexœstrol, its stereoisomer and other related compounds. Hydrogenation of the ketazine (XXIV) from *p*-methoxypropiophenone with a palladium–charcoal catalyst gave an unstable hydrazine, which was readily oxidised in air to a mixture of two compounds. These have been shown spectrographically [95] to be either *cis-trans*- or *meso-dl*-isomers of the azo-compound (XXV) and on heating they gave a 60% yield of a mixture of

$$\underset{\text{(XXIV.)}}{\mathrm{R\cdot CEt{:}N\cdot N{:}CEtR}} \longrightarrow \underset{\text{(XXV.)}}{\mathrm{R\cdot CHEt\cdot N{:}N\cdot CHEtR}} \xrightarrow{120\text{—}30^\circ} \underset{\text{(XVI.)}}{\mathrm{R\cdot CHEt\cdot CHEtR}}$$

$$(\mathrm{R} = p\text{-}\mathrm{MeO\cdot C_6H_4})$$

equal amounts of stereoisomers of (XXVI). It is interesting to note that by simultaneous decomposition of a mixture of the dihydroketazines from

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[86] *J.*, 1930, 2482. [87] *J.*, 1940, 1094. [88] *J.*, 1941, 672.

[89] See also references 66 and 69.

[90] H. Bretschneider, A. de Jonge-Bretschneider, and N. Ajtai, *Ber.*, 1941, **74**, 571.

[91] D. A. Peak and W. F. Short, *J.*, 1943, 232.

[92] J. Thiele, *Annalen*, 1910, **376**, 244. [93] B.P. 540,966.

[94] Z. Foldi and G. von Fodor, *Ber.*, 1941, **74**, 589.

[95] G. von Fodor and P. Szaruas, *Ber.*, 1943, **76**, 334.

p-hydroxy- and *p*-methoxy-propiophenones the monomethyl ether of hexœstrol was obtained, also that one of the forms of (XXV) is formed by the addition of two moles of ethylmagnesium bromide to anisaldazine.[96]

Wurtz-type reactions on anethole hydrobromide or hydrochloride employing magnesium[97] or sodium[98] gave hexœstrol dimethyl ether in yields up to 20%. Recently M. S. Kharasch and M. Kleiman[99] increased this to 40% by treating the hydrobromide with a Grignard reagent in the presence of cobaltous chloride.

Dienœstrol (XXVIII).—This other highly active œstrogen was prepared originally[66] from the pinacol (XXVII) by dehydration with acetic anhydride and acetyl chloride, followed by hydrolysis. The pinacol is obtained by

$$\text{(XXVII.)}\quad \mathrm{HO\cdot C_6H_4\cdot C(OH)Et\cdot C(OH)Et\cdot C_6H_4\cdot OH}$$

$$\downarrow$$

$$\text{(XXVIII.)}\quad \mathrm{HO\cdot C_6H_4\cdot C(\colon CHMe)\cdot C(\colon CHMe)\cdot C_6H_4\cdot OH}$$

$$\text{(XXIX.)}\quad \mathrm{(HO\cdot C_6H_4)_2CEt\cdot COEt}$$

reduction of *p*-hydroxypropiophenone with aluminium amalgam in moist ether,[66] or electrolytically,[1] and its dimethyl ether is formed by reaction of anisylmagnesium bromide with dipropionyl.[2] An *iso*pinacol, probably the *dl*-form of (XXVII), obtained by modification of the electrolytic method, is characterised by the ease with which it rearranges in the presence of acids to the ketone (XXIX), a behaviour analogous to that already noted with stilbœstrol oxide (p. 139).

The dimethyl ether synthesised[3] from (XXX), then believed to be the

$$\underset{\text{(XXX.)}}{\mathrm{MeO\cdot C_6H_4\cdot CH\colon CMeBr}} \longrightarrow \underset{\text{(XXXI.)}}{\mathrm{MeO\cdot C_6H_4\cdot CH\colon CMe\cdot CMe\colon CH\cdot C_6H_4\cdot OMe}}$$

1-bromo-isomer, by treatment with magnesium has been shown[2] to be (XXXI) by isolation of anisaldehyde and diacetyl on ozonolysis. The authentic 1-bromo-isomer of (XXX), obtained by addition of hydrogen bromide to 1-*p*-anisylprop-1-yne ($\mathrm{MeO\cdot C_6H_4\cdot C\vdots CMe}$), can be converted with magnesium and cupric chloride into the dimethyl ether of dienœstrol (XXVIII). This ether undergoes normal demethylation on heating with methylmagnesium iodide, but with alcoholic potash it gives a substance (*iso*dienœstrol) believed to be a stereoisomer of (XXVIII).

Miscellaneous Studies.—The search for new purely synthetic œstrogens and studies of the relationship between structure and physiological activity continue. Various stilbœstrol isomers and analogues containing *m*- instead of *p*-hydroxyl groups, prepared by the original method,[66] are much less

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[96] See also N. R. Campbell, E. C. Dodds, and W. Lawson, *Proc. Roy. Soc.*, 1940, *B*, **128**, 253.

[97] W. F. Short, *Chem. and Ind.*, 1940, 703; B.P. 523,320.

[98] S. Bernstein and E. S. Wallis, *J. Amer. Chem. Soc.*, 1940, **62**, 2871.

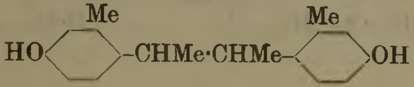
[99] *Ibid.*, 1943, **65**, 491.

[1] Glaxo Laboratories Ltd., F. A. Robinson, and J. C. L. Resuggan, B.P. 523,515.

[2] G. I. Hobday and W. F. Short, *J.*, 1943, 609.

[3] British Colloids Ltd., I. E. Balaban, and J. I. M. Jones, B.P. 547,027.

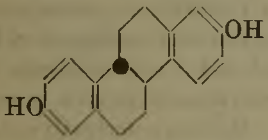
active than stilbœstrol.[4, 66a] 4 : 4′-Dihydroxy-2 : 2′-diethylstilbene, made from *o*-ethylanisaldehyde through the thio-aldehyde, followed by treatment with copper powder and finally demethylation, possesses only 1/1000th of the activity of the isomeric stilbœstrol.[5] On the other hand, the hexœstrol isomer (XXXII) is practically as potent as hexœstrol itself.[90] J. B. Niederl and A. Ziering[6] have made a number of α-cyano- and αβ-dicyano-stilbenes [*e.g.*, R·C(CN):CHR] which show but feeble œstrogenic activities. L. von Vargha and E. Kovacs[79] report that the *pp*′-diamino-analogue of stilbœstrol and various related compounds are relatively biologically inert, as also is the corresponding hexœstrol analogue in both its *meso*- and its *dl*-form.[7] In the latter case replacement of the *p*-hydroxyphenyl groups by either 3 : 4-dihydroxyphenyl or *p*-hydroxybenzyl groups has been found largely to destroy the activity. The examination of many variants of the stilbœstrol and hexœstrol types has recently been reported,[66a] but none is as potent as the parent compounds.

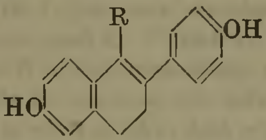


(XXXII.)

The *trans*-hexahydrochrysene diol (XXXIII) has been found to be weakly œstrogenic.[66] A. A. Plentl and M. T. Bogert[8] suggested that partially cyclised stilbœstrol and hexœstrol types such as (XXXIV; R = Et) and the related indene derivative might be of interest, in view of their close steric similarity to œstradiol (IV). The corresponding hydrocarbons were synthesised as a preliminary. The dimethyl ether of (XXXIV; R = Et) had already been synthesised, but on demethylation, disproportionation occurred and the dihydro-compound which was isolated was found to be comparatively inactive.[66] Undeterred by this failure, W. Salzer[9] effected a comparatively simple synthesis of the methyl analogue of (XXXIV), the ether (XXXV) being smoothly demethylated to (XXXIV; R = Me) by heating with methylmagnesium iodide, whereas disproportionation occurred with hot alcoholic alkali. Both (XXXIV; R = Me) and the corresponding indene derivative (XXXVI), the latter being synthesised from *m*-methoxybenzyl chloride, proved to be highly œstrogenic (in 0·3 and 0·5γ doses), thus providing further striking evidence of the profound influence of molecular architecture on physiological behaviour. Hydrogenation

(XXXIII.)





(XXXIV.)

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[4] W. H. Linnell and V. R. Sharma, *Quart. J. Pharm.*, 1941, **14**, 259.

[5] W. H. Linnell and H. S. Shaikmahamud, *ibid.*, 1942, **15**, 384.

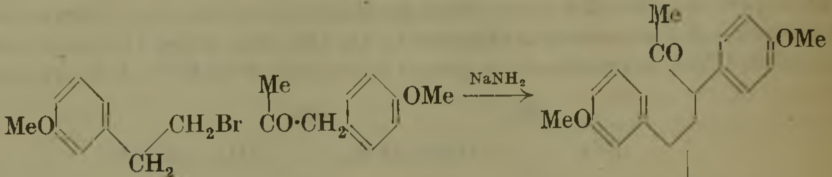
[6] *J. Amer. Chem. Soc.*, 1942, **64**, 885, 2486.

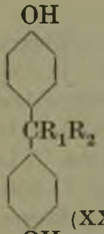
[7] B. R. Baker, *ibid.*, 1943, **65**, 1572.

[8] *Ibid.*, 1941, **63**, 989.

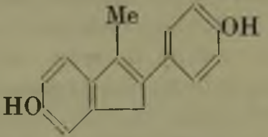
[9] *Z. physiol. Chem.*, 1942, **274**, 39.

of (XXXVI) to the dihydro-compound largely destroyed the activity,* but the symmetrical tetrahydrochrysene diol (dehydro-XXXIII), closely

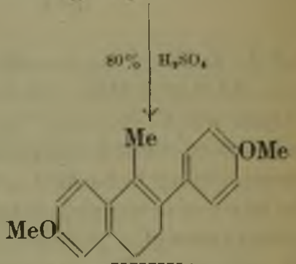




(XXXVII.)



(XXXVI.)



(XXXV.)

related to dienœstrol and synthesised by Salzer from the methoxy-β-tetralone, was moderately (10γ) active.

In a series of homologous bis-*p*-hydroxyphenylmethane derivatives (XXXVII), prepared by condensing phenol with various aldehydes and ketones, the highest activities were observed with the hexœstrol isomers (XXXVII; $R_1 = H$, $R_2 = CHEt_2$ and $R_1 = Et$, $R_2 = n\text{-}Pr$), but even these compounds were only 1/50,000th and 1/5000th as potent respectively as hexœstrol itself.[10] A large number of polynuclear analogues of hexœstrol have been synthesised by the Wurtz method and it is abundantly clear that in this series the presence of the *p*-hydroxyphenyl groups is essential if activity of a high order is to be attained.[11] Hydroxy-derivatives of fluorene have been found to possess only weak œstrogenic activity.[12] B. R. Baker [7] synthesised hexœstrol isomers such as 1 : 3- and 1 : 6-bis-*p*-hydroxyphenylhexane by the dihydro-azine method,[94] but they proved to be relatively inactive.

The first of a series of papers on alkylated bis-*p*-hydroxyphenylpropanes (XXXVIII) describes the preparation of the monoalkyl compounds (XXXVIII; $R_1 = R_2 = H$ or $R_1 = R_3 = H$) from the corresponding chalkones by 1 : 4-Grignard addition, or by condensation of anisaldehyde with *p*-acylanisoles, followed in both cases by either Clemmensen reduction or hydrogenation with " copper chromite " catalysts and demethylation.[13] These phenols show only low-order œstrogenic potency. However, E. W.

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[10] N. R. Campbell, *Proc. Roy. Soc.*, 1940, *B*, **129**, 528.

[11] N. R. Campbell and F. W. Chattaway, *ibid.*, 1942, *B*, **130**, 435.

[12] A. Novelli and M. H. Giunti, *Ciencia*, 1940, I, 19; *Chem. Abstracts*, 1940, **34**, 3330.

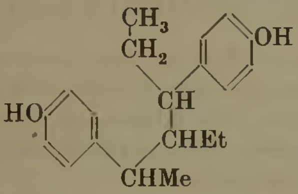
[13] A. H. Stuart and R. C. Tallman, *J. Amer. Chem. Soc.*, 1943, **65**, 1579.

* U. V. Solmssen (*J. Amer. Chem. Soc.*, 1943, **65**, 2370) reports that the ethyl analogue of a dihydro-(XXXVI), prepared by a method different from those of Salzer and of Plentl and Bogert, is about 1/20th as active as stilbœstrol.

Blanchard, A. H. Stuart, and R. C. Tallman[14] have made a preliminary report on the testing of some 134 synthetic compounds of type (XXXVIII). The trialkyl derivatives are the most potent and one of the stereoisomers of (XXXVIII; $R_1 = Me$, $R_2 = R_3 = Et$) is apparently only three or four times less active than hexœstrol. This rather surprising finding seems to cast some doubt on the validity of the fairly well-established stereo-relationship between the natural and the synthetic œstrogens, although it is still possible to write the formula of the compound in a manner (XXXIX) which

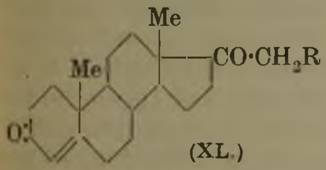
$$HO{\cdot}C_6H_4{\cdot}CHR_1{\cdot}CHR_2{\cdot}CHR_3{\cdot}C_6H_4{\cdot}OH \qquad \text{(XXXVIII.)}$$

(XXXIX.)



preserves a superficial resemblance. Further information about the activities of the many stereoisomers in this series will be awaited with interest.

It has long been considered desirable to synthesise and examine partially or fully hydrogenated compounds of the stilbœstrol type, and those derivatives resembling other sex hormones such as progesterone (XL; R = H), testosterone and corticosterone in the constitution of their terminal functional groups. (Mrs.) R. Jaeger and (Sir) R. Robinson[15] have prepared two ketones of structure (XLI; $R_1 = R_2 = Me$ and $R_1 = Et$, $R_2 = Me$) by Grignard reactions on the corresponding nitriles, the latter being synthesised by the general method devised earlier.[66] Unfortunately the œstrogenic



(XL.)

$$(p)\ HO{\cdot}C_6H_4{\cdot}CR_1{:}CR_2{\cdot}C_6H_4{\cdot}COMe\ (p)$$

(XLI.)

$$(p)\ MeO{\cdot}C_6H_4{\cdot}CHEt{\cdot}CHEt{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2R\ (p)$$

(XLII.)

properties of these substances are sufficiently powerful effectively to inhibit any progesterone-like activity they might possess. The preparation of various ketones of the stilbœstrol and hexœstrol series by means of Fries and Friedel–Crafts reactions has been claimed[16] and these substances are said to be active hormones. For example, (XLII; R = H) and (XLII; R = OH) are mentioned as possessing progestational and corticosterone-like activity respectively.

The restricted availability of the steroid hormones of the adrenal cortex encourages particularly the search for purely synthetic materials possessing this type of activity. Some preliminary experiments along these lines are

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[14] *Endocrinology*, 1943, **32**, 307.

[15] *J.*, 1941, 744.

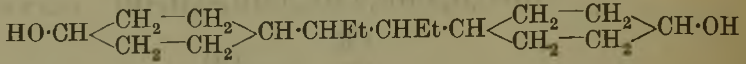
[16] Wellcome Foundation Ltd., G. Brownlee, and W. M. Duffin, B.P. 550,262.

reported[17] and it has been found[18] that both benzoylcarbinol and the stilbœstrol-like α-ketol (XLIII) (containing one meta-substituent however) are qualitatively similar to deoxycorticosterone (XL; R = OH) in their

$$(p)\ HO\cdot C_6H_4\cdot CEt{:}CEt\cdot C_6H_4\cdot CO\cdot CH_2\cdot OH\ (m) \qquad \text{(XLIII.)}$$

physiological action. A number of derivatives of hydroxydiphenyl ether containing the α-ketol side chain have also been synthesised.[19]

In a preliminary note J. F. Lane and E. S. Wallis[20] describe experiments with one of the isomeric perhydrohexœstrols (XLIV) obtained by complete

(XLIV.) 

$$HO\cdot CH{<}\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}{>}CH\cdot CHEt\cdot CHEt\cdot CH{<}\begin{matrix}CH_2-CH_2\\ CH_2-CH_2\end{matrix}{>}CH\cdot OH$$

hydrogenation of hexœstrol. This has been converted into the diketone, and the keto-ol has been prepared by partial acetylation of (XLIV), followed by oxidation and hydrolysis. No information concerning biological tests is as yet available. A number of unsuccessful attempts to prepare a hexahydrostilbœstrol have been reported.[21]

Many of the synthetic œstrogens have been shown to possess growth-inhibitory properties, and G. M. Badger[22] has synthesised a number of hydrocarbons of the stilbœstrol type, by the original method,[66] for testing as tumour inhibitors.

Triphenylethylene Œstrogens.—E. C. Dodds and W. Lawson[23] investigated the œstrus-producing properties of a number of substituted ethylenes and found that stilbene, αδ-diphenylbutadiene and triphenylethylene were fully active in rats in doses of 10—25 mg. J. M. Robson and A. Schönberg[24] independently reported the activity of triphenylethylene. Triphenylchloroethylene ($CPh_2{:}CClPh$) is more potent[25] and further investigations[26] with more highly substituted derivatives have revealed substances [*e.g.*, $(p\text{-}EtO\cdot C_6H_4)_2C{:}CBrPh$] of greater activity which, although requiring considerably greater threshold doses than stilbœstrol, produce much more prolonged effects. Tri-*p*-anisylbromoethylene ($Ar_2C{:}CBrAr$; $Ar = p\text{-}MeO\cdot C_6H_4$), which also possesses the latter property and appears to be approximately one-twentieth as active as stilbœstrol, has been prepared[27] from deoxyanisoin by reaction with anisylmagnesium bromide, followed by dehydration of the resulting carbinol and treatment of the trianisylethylene with bromine, hydrogen bromide being readily eliminated. The trianisyl-

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[17] L. Long and A. Burger, *J. Org. Chem.*, 1941, **6**, 852.

[18] W. H. Linnell and I. M. Roushdi, *Quart. J. Pharm.*, 1941, **14**, 270.

[19] J. Walker, *J.*, 1942, 347.

[20] *J. Amer. Chem. Soc.*, 1943, **65**, 994.

[21] P. Ruggli and A. Businger, *Helv. Chim. Acta*, 1941, **24**, 112.

[22] *J.*, 1941, 535.

[23] *Nature*, 1937, **139**, 627; *Proc. Roy. Soc.*, 1938, *B*, **125**, 222.

[24] *Nature*, 1937, **140**, 197.

[25] J. M. Robson, A. Schonberg, and H. A. Fahim, *Nature*, 1938, **142**, 292.

[26] A. Schonberg, J. M. Robson, W. Tadros, and H. A. Fahim, *J.*, 1940, 1327; J. M. Robson and A. Schonberg, *Nature*, 1942, **150**, 22; W. Tadros and A. Schonberg, *J.* 1943, 394.

[27] J. S. H. Davies and Imperial Chemical Industries Ltd., B.P. 549,200.

propenes and -butenes ($Ar_2C{:}CRAr$; R = Me and Et) have also been prepared by Grignard reactions and are equally active.[28]

Vitamin D Synthesis.

The section of the Report written on this topic has been deleted in view of the announcement [29] that six published papers,[30] in which considerable progress in this field was described, must be disregarded. E. R. H. J.

5. HORMONES OF ADRENAL CORTEX.

Since the last Report [1] dealing with the steroids isolated from the adrenal cortex, many outstanding advances have been made mainly as a result of the researches of T. Reichstein and his collaborators. The most spectacular accomplishment is the elaboration of a general method for the introduction of a carbonyl (or hydroxyl) group at C_{11} in the cholane nucleus and the application of this method to effect a partial synthesis of 11-dehydrocorticosterone.

To assess the value of this achievement in proper perspective it may be recalled that, of the large number of steroids isolated from the adrenal cortex, six [(I)—(VI)] are " cortical hormones." That is, when a solution of any one of the six compounds is injected daily into young adrenalectomised rats, the animals continue to live. The six hormones comprise those which are oxygenated in ring C [(I), (II), (III) and (IV)] and those which are not [(V) and (VI)]. The complete structures of the simpler group [(V) and (VI)] have been verified by partial synthesis; the partial synthesis of deoxycorticosterone (V) from cholesterol has been described in a previous report and a partial synthesis of substance S (VI) from cholesterol is described below. In the earlier stages of this work the fact that the hormone most readily available by partial synthesis from cholesterol [deoxycorticosterone (V)] was the most physiologically potent member of the group appeared as a fortunate circumstance. Subsequently,[2] however, it became clear that, in contrast to (V), the ring C-oxygenated hormones [(I)—(IV)] exhibit a remarkable effect on carbohydrate metabolism; in the anti-insulin test [3] and the Ingle test [4] the compounds (I)—(IV) show a strong diabetogenic action, whereas deoxycorticosterone (V) and substance S (VI) (in so far as this has been available for test) show little if any activity. Consequently the availability of compounds (I)—(IV) became a matter of some importance for the clinical treatment of such conditions as Addison's disease and surgical

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[28] J. S. H. Davies, L. A. Elson, and Imperial Chemical Industries Ltd., B.P. 549,353.

[29] K. Dimroth, *Ber.*, 1943, **76**, 634.

[30] K. Dimroth and E. Stockstrom, *Ber.*, 1942, **75**, 180, 326, 510, 582, 1263; *Annalen*, 1941, **549**, 256.

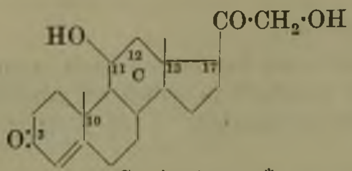
[1] F. S. Spring, *Ann. Reports*, 1940, **37**, 332.

[2] C. N. H. Long, B. Katzin, and E. G. Fry, *Endocrinology*, 1940, **26**, 309; B. B. Wells and E. C. Kendall, *Proc. Staff Meetings, Mayo Clinic*, 1940, **15**, 297.

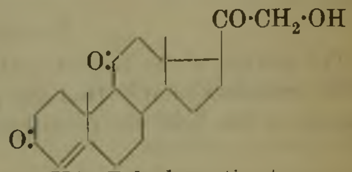
[3] J. F. Gratton and H. Jensen, *J. Biol. Chem.*, 1940, **135**, 511.

[4] D. J. Ingle, *Endocrinology*, 1940, **26**, 472; **27**, 297; E. C. Kendall, *Proc. Staff Meetings, Mayo Clinic*, 1940, **15**, 297.

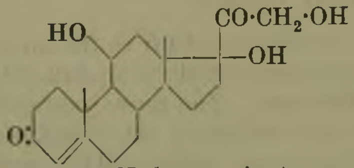
shock. Hitherto the sole method for obtaining compounds (I)—(IV) was by a laborious isolation process from adrenal cortex; the part-synthesis of dehydrocorticosterone (II) from a bile acid derivative constitutes a very valuable achievement and will no doubt be followed by the synthesis of (I), (III) and (IV) by suitable variation of the methods now developed. The partial synthesis of (II) also provides complete confirmation of the location of the ring C-oxygen atom in the adrenal steroids.



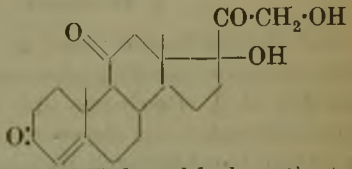
(I.) Corticosterone *



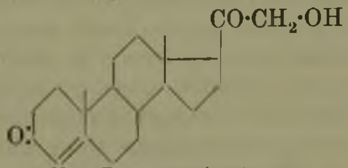
(II.) Dehydrocorticosterone



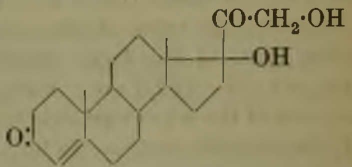
(III.) 17β-Hydroxycorticosterone



(IV.) 17β-Hydroxydehydrocorticosterone

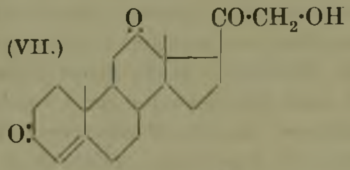


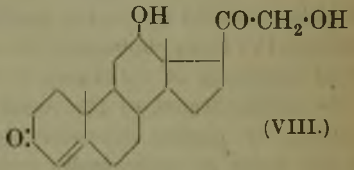
(V.) Deoxycorticosterone



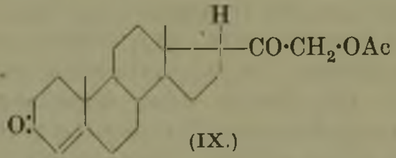
(VI.) 17β-Hydroxydeoxycorticosterone (Substance S)

(VII.)





(VIII.)



(IX.)

* In the steroid formulæ used throughout this Report, the angular methyl groups attached to C_{10} and C_{13} will be represented by strokes.

More information is available concerning the specificity of physiological action of members of the group. H. G. Fuchs and T. Reichstein [5] have prepared the compounds (VII) and (VIII) from 3α : 12β-diacetoxyätiocholanic acid.[6] These compounds differ from dehydrocorticosterone (II) and corti-

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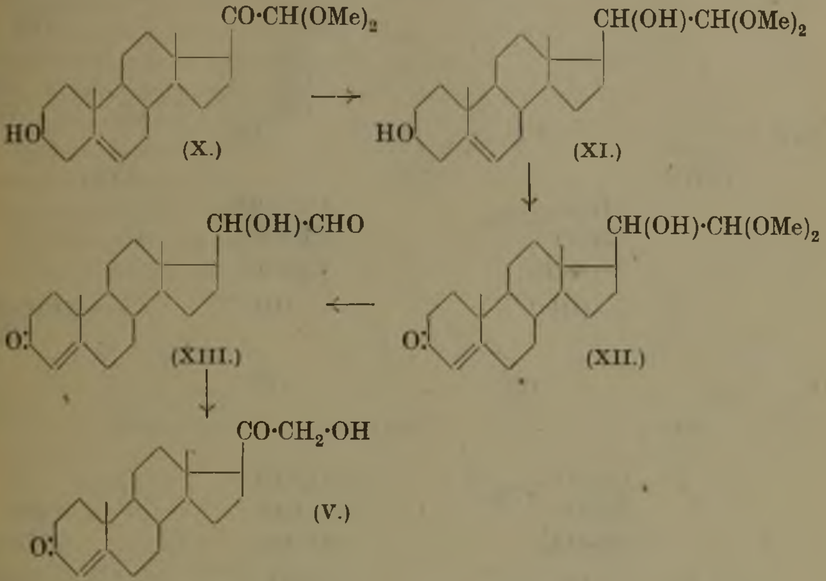
[5] *Helv. Chim. Acta*, 1943, **26**, 511.

[6] T. Reichstein and E. von Arx, *ibid.*, 1940, **23**, 747.

costerone (I) solely in the location of the ring C-oxygen atom. A preliminary biological test shows that the acetates of (VII) and (VIII) are at least considerably less active than either corticosterone or deoxycorticosterone acetate in the Everse–de Fremery test; anti-insulin tests have not yet been reported. 17-*iso*Deoxycorticosterone acetate[7] (IX), which differs from deoxycorticosterone acetate solely in the orientation around C_{17}, is inactive in the Everse–de Fremery test, in doses of 1 mg. per day.



Deoxycorticosterone.—A new partial synthesis of deoxycorticosterone (V) has been described by W. Schindler, H. Frey, and T. Reichstein,[8] starting from the unsaturated hydroxy-keto-acetal (X), the preparation of which was described in the last report.[1] Reduction of (X) by the Meerwein–Ponndorf method gave (XI), only one of the two theoretically possible isomers being isolated. Partial oxidation of this diol-acetal by the Oppenauer method gave (XII), hydrolysis yielding the hydroxy-aldehyde (XIII), which when treated with pyridine gave deoxycorticosterone.

Partial Synthesis of Substance S.—Treatment of dehydroandrosterone (XIV) (obtained from cholesterol) with allyl bromide in the presence of magnesium gave 17-allylandrostendiol (XV), which on oxidation with aluminium *tert.*-butoxide and acetone yielded the corresponding αβ-unsaturated ketone (XVI), dehydration of which gave the trienone (XVII). Oxidation of (XVII) with osmium tetroxide gave a tetrahydroxy-ketone (XVIII), which formed a monoacetone derivative (XIX). The acetate of the last compound (XX) was treated with aqueous acetic acid, which hydrolysed the acetone group to give the tetrol mono-acetate (XXI), oxidation of which with periodic acid gave the aldehyde (XXII).[9] The

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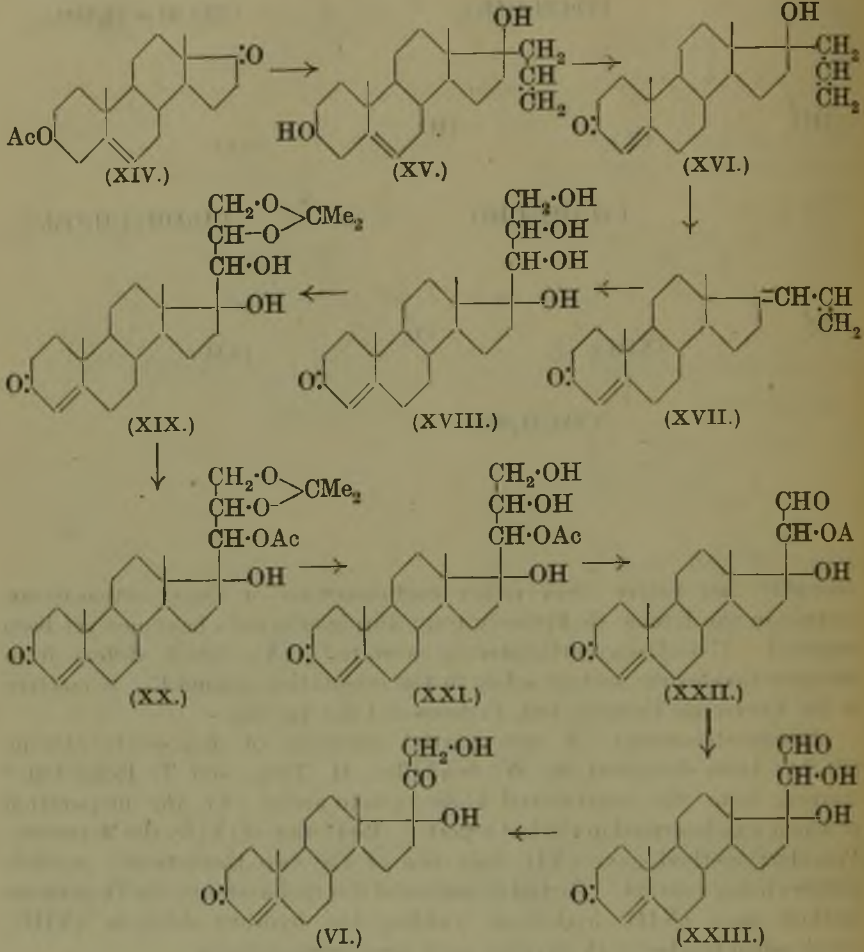
[7] *Helv. Chim. Acta*, 1940, **23**, 925. [8] *Ibid.*, 1941, **24**, 360. [9] *Ibid.*, 1940, **23**, 1114.

partial synthesis of substance S was completed by J. v. Euw and T. Reichstein,[10] who showed that hydrolysis of (XXII) with potassium bicarbonate gave (XXIII), which when treated with pyridine isomerised to a product which proved to be identical with the natural cortical hormone substance S (VI). This part-synthesis is particularly important, since the amount of substance S which has been available from adrenal cortex has hitherto been too small to allow of a full biological examination.



The method described has been very considerably simplified by the same authors [11] in a later paper. They show that controlled oxidation of the tetrol (XVIII) with periodic acid gives a mixture which must contain the aldehyde (XXIII), since treatment of this mixture with pyridine, followed by acetylation, gives an overall yield of 30% of substance S acetate.

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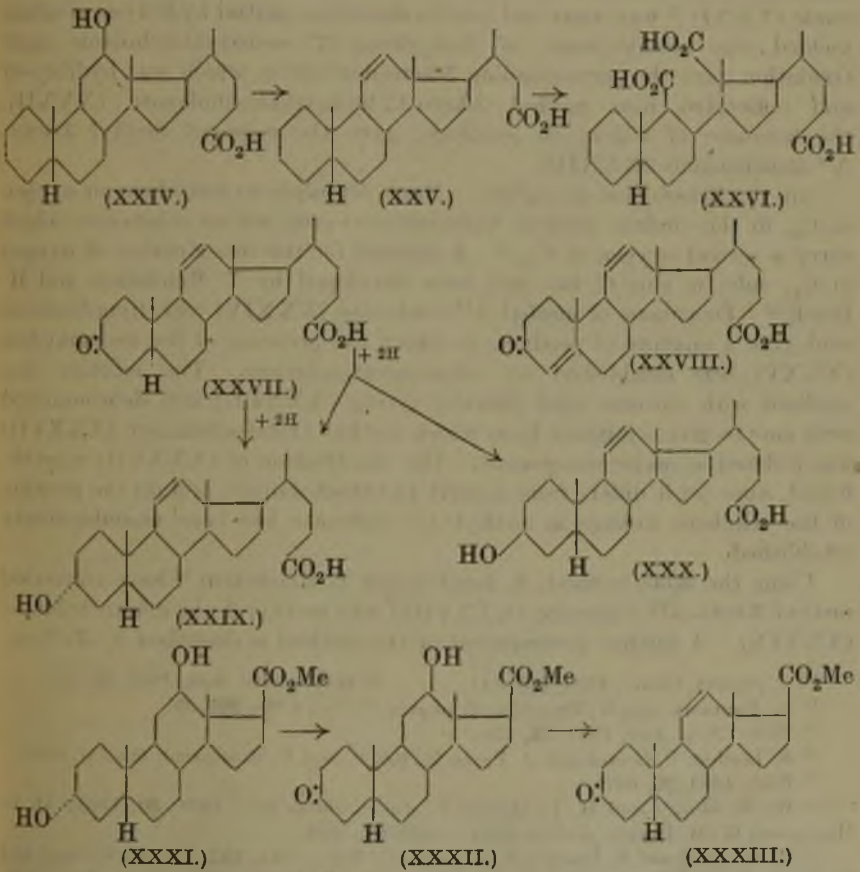
[10] *Helv. Chim. Acta*, 1940, **23**, 1258.

[11] *Ibid.*, 1941, **24**, 1140.

Partial Synthesis of Dehydrocorticosterone.—The most readily available starting material for the synthesis of an 11-oxygenated steroid is clearly a 12-oxygenated bile acid or a degradation product thereof. Reichstein and his collaborators, after many unsuccessful attempts to prepare 11-oxygenated cholane derivatives from bile acids, developed a method for the conversion of a 12-hydroxycholane derivative into a Δ^{11}-cholene derivative. The next stage consisted in the elaboration of a method for the conversion of the Δ^{11}-cholene derivative into an 11-ketocholane derivative and finally the two methods were combined with an established method for the attachment of the requisite side chain.

(i) *Preparation of* Δ^{11}*-cholene derivatives.* H. B. Alther and T. Reichstein,[12] applying a method used by H. Wieland,[13] showed that 12β-hydroxy-



cholanic acid[14] (XXIV), on being heated in a vacuum, gave Δ^{11}-cholenic acid (XXV), the constitution of which was established by its conversion into

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[12] *Helv. Chim. Acta.*, 1941, **24**, 1258.

[13] *Z. physiol. Chem.*, 1912, **80**, 287; 1916, **98**, 62; 1920, **110**, 143; 1920, **111**, 123.

[14] J. Barnett and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 926.

the tricarboxylic acid (XXVI) previously obtained by H. Wieland and P. Weygand [15] by oxidation of 12-ketocholanic acid. In a similar manner V. Burchhardt and T. Reichstein [16] showed that thermal degradation of 3-keto-12β-hydroxycholanic acid [17] gives 3-keto-Δ^{11}-cholenic acid (XXVII), and that 3-keto-12β-hydroxy-Δ^{4}-cholenic acid gives 3-keto-$\Delta^{4:11}$-choladienic acid (XXVIII). J. Press and T. Reichstein [18] showed that (XXVII) can be partially reduced to give a mixture of 3α- (XXIX) and 3β-(XXX) hydroxy-Δ^{11}-cholenic acids, which are separable by means of digitonin. The method was improved by subjecting the 12β-benzoyloxycholanic esters (instead of the 12-hydroxy-acids) to thermal degradation.[19] A. Lardon and T. Reichstein [20] applied the method to the preparation of methyl 3-keto-Δ^{11}-ätiocholenate (XXXIII). Methyl 3α : 12β-dihydroxyätiocholanate (XXXI) [21] was converted into its diacetate, partial hydrolysis of which yielded the methyl ester of 3α-hydroxy-12β-acetoxyätiocholanic acid. Oxidation gave the corresponding 3-keto-derivative, which was hydrolysed and converted into methyl 3-keto-12-hydroxyätiocholanate (XXXII), the benzoate of which, on pyrolysis, gave the required methyl 3-keto-Δ^{11}-ätiocholenate (XXXIII).

(ii) C_{11}-*Ketocholane derivatives.* Many attempts to introduce an oxygen at C_{11} in the cholane nucleus have hitherto only led to substances which carry a second oxygen at C_{12}.[22] A method for the introduction of oxygen at C_{11} only, in ring C, has now been developed by T. Reichstein and H. Reich.[23] Treatment of methyl Δ^{11}-cholenate (XXXIV) with hypobromous acid gave a mixture of products in which the presence of the bromohydrin (XXXV) was established by subsequent reactions. The mixture was oxidised with chromic acid [thereby giving (XXXVI)] and debrominated with zinc to give a mixture from which methyl 11-ketocholanate (XXXVII) was isolated as major component. The constitution of (XXXVII) is established, since (*a*) it differs from methyl 12-ketocholanate, and (*b*) the position of the ethylenic linkage in methyl Δ^{11}-cholenate has been unambiguously established.

Using the same method, A. Lardon and T. Reichstein [24] have converted methyl 3-keto-Δ^{11}-cholenate (XXXVIII) into methyl 3 : 11-diketocholanate (XXXIX). A further development of the method is described by J. Press,

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[15] *Z. physiol. Chem.*, 1920, **110**, 141.

[16] *Helv. Chim. Acta*, 1942, **25**, 821.

[17] K. Yamasaki and K. Kyoguka, *Z. physiol. Chem.*, 1935, **233**, 29.

[18] *Helv. Chim. Acta*, 1942, **25**, 878.

[19] A. Lardon, P. Grandjean, J. Press, H. Reich, and T. Reichstein, *ibid.*, p. 1144.

[20] *Ibid.*, 1943, **26**, 607.

[21] W. M. Hoehn and H. L. Mason, *J. Amer. Chem. Soc.*, 1938, **60**, 1493; H. L. Mason and W. M. Hoehn, *ibid.*, p. 2824; 1939, **61**, 1614.

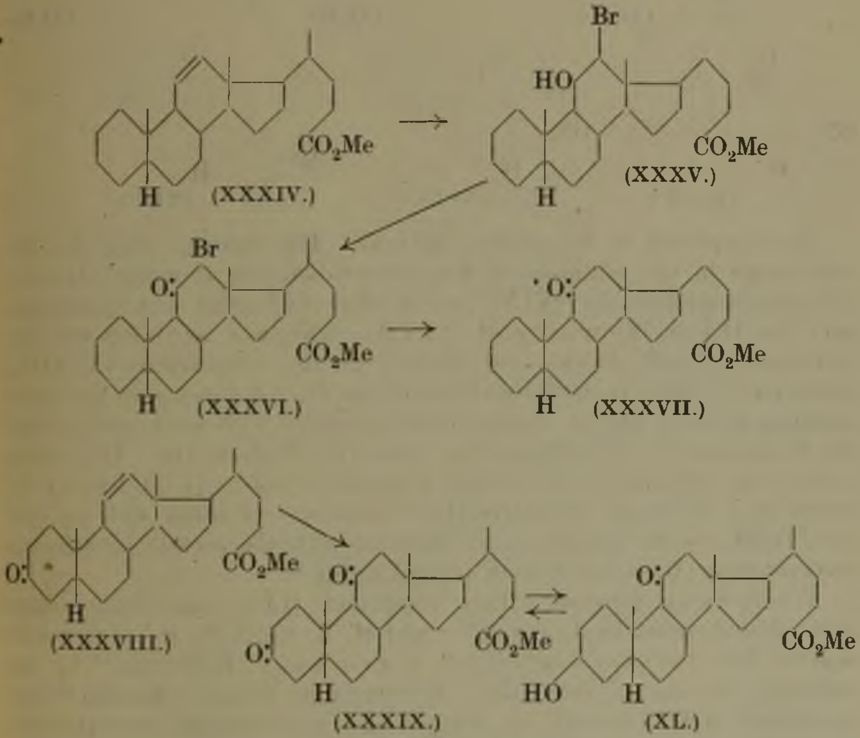
[22] H. Wieland and T. Posternak, *Z. physiol. Chem.*, 1931, **197**, 17; H. Wieland and E. Dane, *ibid.*, 1933, **216**, 99; J. Barnett and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 926; 1939, **22**, 75; R. E. Marker and E. J. Lawson, *J. Amer. Chem. Soc.*, 1938, **60**, 1334; B. B. Longwell and O. Wintersteiner, *ibid.*, 1940, **62**, 200; P. N. Chakravorty and E. S. Wallis, *ibid.*, p. 318; H. B. Alther and T. Reichstein, *Helv. Chim. Acta*, 1942, **25**, 805; S. Bergström and G. A. D. Haslewood, *J.*, 1939, 540.

[23] *Helv. Chim. Acta*, 1943, **26**, 562.

[24] *Ibid.*, 1943, **26**, 586.

P. Grandjean, and T. Reichstein,[25] who also show that on partial catalytic hydrogenation, the diketone (XXXIX) gives mainly methyl 3β-hydroxy-11-ketocholanate (XL), characterised by the fact that it gives an insoluble digitonide and is reconverted into (XXXIX) on mild oxidation with chromic acid.

Finally, A. Lardon and T. Reichstein [26] have applied the method to methyl Δ^{11}-ätiocholenate (XLI) and thereby obtained methyl 3 : 11-diketo-ätiocholanate (XLIV). In this case, the pure bromohydrin (XLII) was isolated (it seems that only one of the four theoretically possible isomers is formed), oxidation of which gave the pure bromo-ketone (XLIII). Partial catalytic reduction of (XLIV) yields as major product methyl 11-keto-3β-hydroxyätiocholanate (XLV), the structure of which follows from its re-oxidation to (XLIV), from the fact that it gives an insoluble digitonide (in contrast to the 3α-isomer), and from its facile conversion into a mono-acetate, a behaviour not shown by 11-hydroxysteroids. Of great interest is the conversion of the diketone (XLIV) into a 4-bromo-derivative, treatment of which with pyridine yields methyl 3 : 11-diketo-Δ^4-ätiocholenate (XLVI) identical with the characteristic degradation product previously obtained



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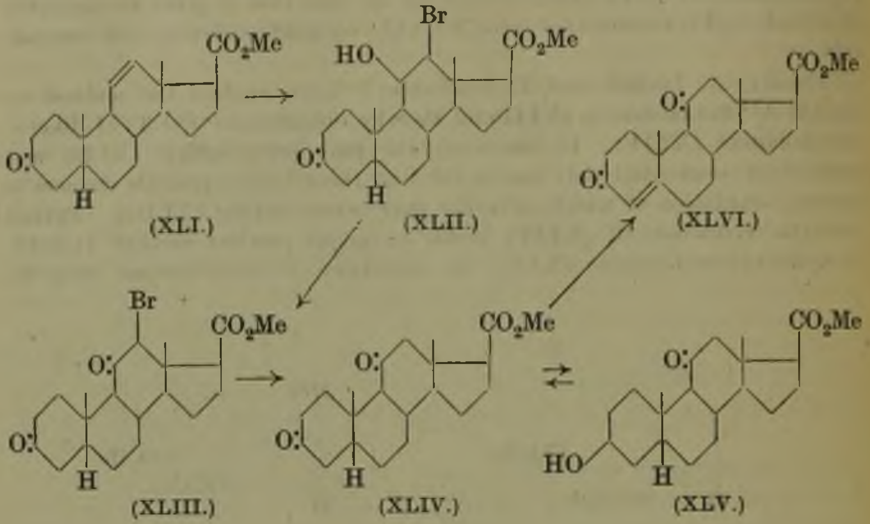
[25] *Helv. Chim. Acta*, 1943, **26**, 598.

[26] *Ibid.*, p. 705.

from corticosterone and dehydrocorticosterone;[27] this result constitutes the first confirmation by synthesis of the structures of these hormones.[28]



(iii) *Completion of the partial synthesis.* The starting point for the final stages in the synthesis of dehydrocorticosterone is methyl 11-keto-3β-hydroxyätiocholanate (XLV), which after hydrolysis and acetylation gave the 11-keto-3β-acetoxy-acid (XLVII). This was converted into the corresponding acid chloride and thence into the diazo-ketone (XLVIII), hydrolysis of which (note the stability of the diazo-ketone) gave the corresponding alcohol (XLIX), which on decomposition with acetic acid yielded the 21-monoacetate of pregnane-3β : 21-diol-11 : 20-dione (L). This monoacetate was oxidised to the acetate of pregnan-21-ol-3 : 11 : 20-trione (LI), which gave a 4-bromo-derivative (LII), treatment of which with pyridine gave (LIII), which proved to be identical with the acetate of dehydrocorticosterone (II) obtained from adrenal cortex.[29]

17β-*Hydroxyprogesterone.*—This compound (LIV) was first isolated from adrenal cortex by J. J. Pfiffner and H. B. North.[30] It has now been isolated from the same source by J. v. Euw and T. Reichstein[31] by two methods. In one of these the "hydroxy-free ketone" fraction[32] was acetylated and separated by chromatographic methods into (1) *allo*-pregnanolone acetate, (2) progesterone, (3) androstenedione, (4) 3-monoacetate of *allo*pregnane-3 : 11-diol-17-one, (5) adrenosterone, (6) 17β-hydroxy-

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[27] T. Reichstein, *Helv. Chim. Acta*, 1937, **20**, 953; H. L. Mason, W. M. Hoehn, B. F. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, 1937, **120**, 719.

[28] M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 161; T. Reichstein and H. G. Fuchs, *ibid.*, 1940, **23**, 676; C. W. Shoppee, *ibid.*, p. 740.

[29] A. Lardon and T. Reichstein, *ibid.*, 1943, **26**, 747.

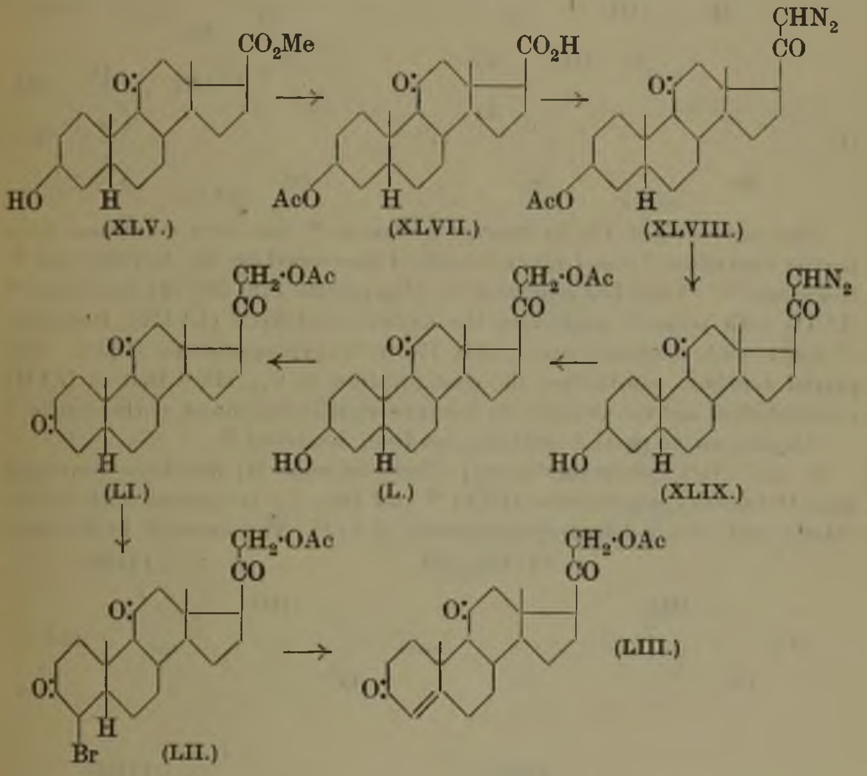
[30] *J. Biol. Chem.*, 1940, **132**, 459.

[31] *Helv. Chim. Acta*, 1941, **24**, 880.

[32] *Ibid.*, 1938, **21**, 1197, 1201.

progesterone (LIV) (50 mg. from 500 kg. of adrenal cortex), (7) 17α-methyl-D-homo-Δ^4-androsten-17α-ol-3 : 17-dione (LV), together with several other unidentified products. Of these, (1),[33] (2),[33] (4)[34] and (5)[35] have previously been isolated from adrenal cortex, but this is the first time that the presence therein of androstenedione has been reported. The amount isolated is small, and it is probably an artefact produced by aerial oxidation of substance-S (or of a similarly constituted compound).

17β-Hydroxyprogesterone shows an anomalous melting point which is due to its rearrangement to a mixture of (LV)[36] and an isomer, m. p.



162—164°. On prolonged heating with alkali, 17β-hydroxyprogesterone is isomerised to a mixture of (LV) and an isomer, m. p. 182°. It is very probable that (LV) and the compounds, m. p. 162—164° and m. p. 182°, are three of the four theoretically possible isomers of structure (LV*a* and *b*) and (LVI*a* and *b*).[37] The isolation of (LV) from adrenal cortex has probably

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[33] D. Beall and T. Reichstein, *Nature*, 1938, **142**, 479; D. Beall, *Biochem. J.*, 1938, **32**, 1957.

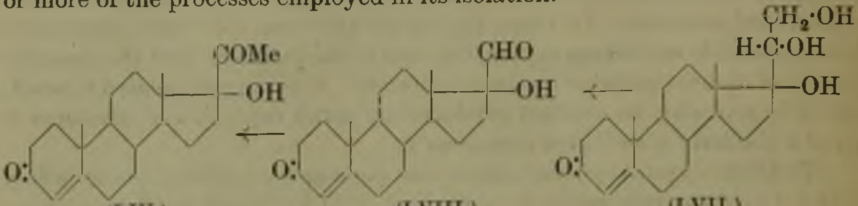
[34] T. Reichstein and J. v. Euw, *Helv. Chim. Acta*, 1938, **21**, 1197.

[35] T. Reichstein, *ibid.*, 1936, **19**, 29, 223.

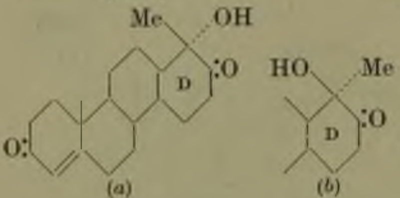
[36] *Ibid.*, 1939, **22**, 626; L. Ruzicka and H. F. Meldahl, *ibid.*, 1940, **23**, 364.

[37] C. W. Shoppee and D. A. Prins, *ibid.*, 1943, **26**, 185.

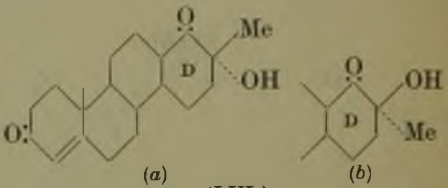
to be attributed to a rearrangement of 17β-hydroxyprogesterone during one or more of the processes employed in its isolation.



(LIV.) (LVIII.) (LVII.)



(LV.)



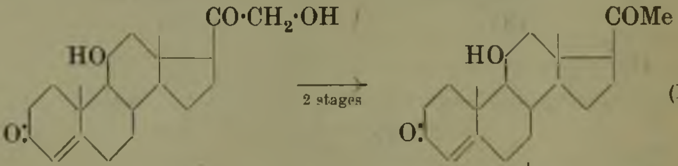
(LVI.)

The structure of 17β-hydroxyprogesterone [30] has been confirmed by a partial synthesis [38] based upon a method developed by D. A. Prins and T. Reichstein.[39] Controlled oxidation of Δ^4-pregnene-17β : 20β : 21-triol-3-one [40] (LVII) with periodic acid gives the hydroxy-aldehyde (LVIII), treatment of which with diazomethane yields 17β-hydroxyprogesterone (LIV). This partial synthesis establishes the configuration at C_{17}, since that in (LVII) is established and the changes do not involve rearrangement at this centre.

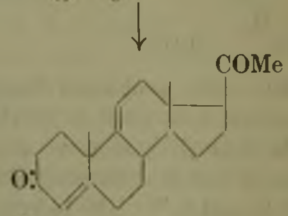
An alternative partial synthesis has been described.[41]

9- *and* 11-*Dehydroprogesterones.*—Corticosterone (I) has been converted into 11-hydroxyprogesterone (LIX) [42] and this, by treatment with hydrochloric acid, into 9-dehydroprogesterone (LX).[43] The isomeric 11-dehydro-

(I.)

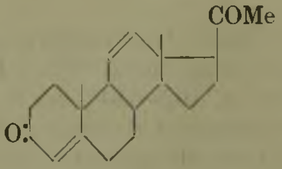


(LIX.)



(LX.)

(LXI.)



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[38] *Helv. Chim. Acta*, 1941, **24**, 945. [39] *Ibid.*, p. 396.

[40] W. Logemann, *Naturwiss.*, 1939, **27**, 196; L. Ruzicka and P. Müller, *Helv. Chim. Acta*, 1939, **22**, 755.

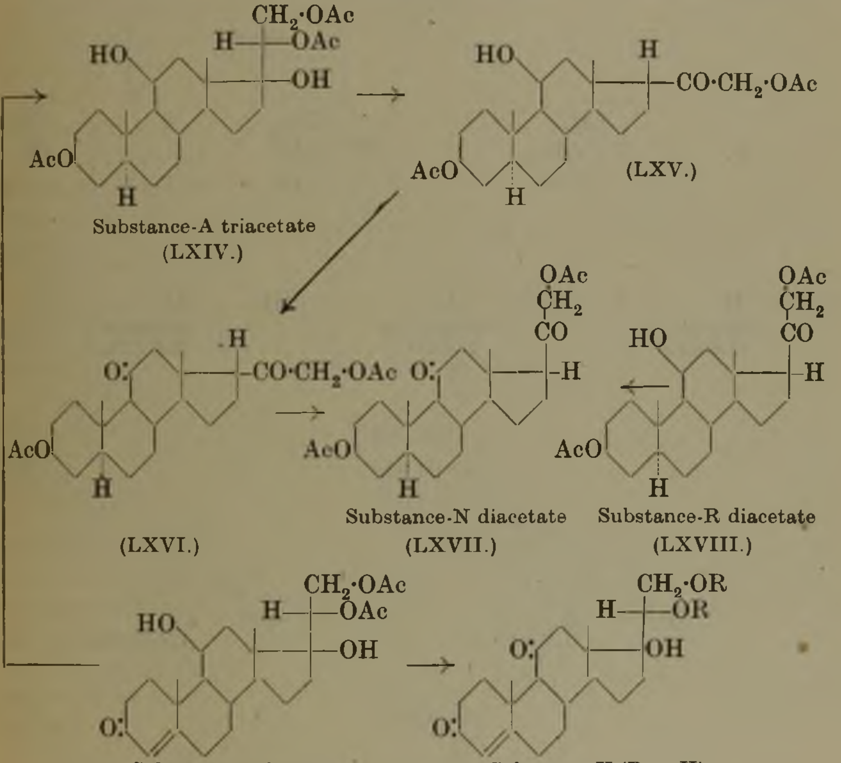
[41] P. Hegner and T. Reichstein, *Helv. Chim. Acta*, 1941, **24**, 828.

[42] T. Reichstein and H. G. Fuchs, *ibid.*, 1940, **23**, 684.

[43] C. W. Shoppee and T. Reichstein, *ibid.*, 1941, **24**, 351; P. Hegner and T. Reichstein, *ibid.*, 1943, **26**, 715.

progesterone (LXI) has been obtained by P. Hegner and T. Reichstein[43] by thermal degradation of the benzoate of 12-hydroxyprogesterone.[44] 9- and 11-Dehydroprogesterone, like 6-dehydroprogesterone,[45] show strong progesterone-activity, whereas the isomeric 16-dehydroprogesterone[46] is inactive in this respect.

Other Steroids from Adrenal Cortex.—A new member of the $C_{21}O_5$-group of adrenal steroids has been isolated and characterised.[47] It is substance U, $C_{21}H_{32}O_5$; it is an αβ-unsaturated ketone. Its structure (LXIII, R = H) has been established by a partial synthesis from substance E,[48] the diacetate of which (LXII) is converted into the diacetate of substance U (LXIII, R = COMe) by oxidation with chromic acid. Furthermore, substances A, E and U have the same configuration at C_{17} and C_{20} (and substances A and E have the same configuration at C_{11}), since hydrogenation of E-diacetate, followed by acetylation, gives the triacetate of substance A (LXIV).



Substance-A triacetate (LXIV.)

(LXV.)

(LXVI.)

Substance-N diacetate (LXVII.)

Substance-R diacetate (LXVIII.)

Substance-E diacetate (LXII.)

Substance U (R = H) (LXIII.)

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[44] M. Bockmühl, G. Ehrhart, W. Ruschig, and W. Aumuller, A.P. 2,142,170.

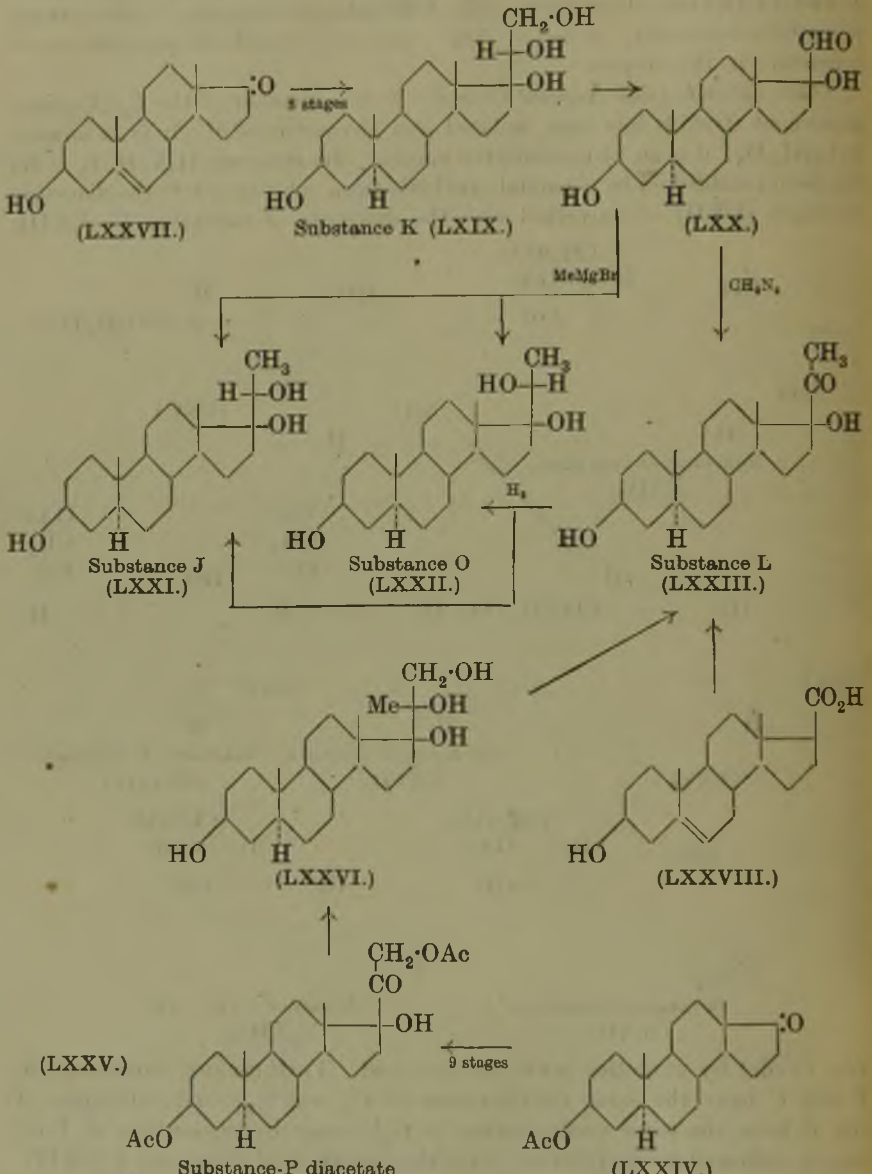
[45] A. Wettstein, *Helv. Chim. Acta*, 1940, **23**, 388.

[46] A. Butenandt and J. Schmidt-Thomé, *Ber.*, 1939, **72**, 182.

[47] *Helv. Chim. Acta*, 1941, **24**, 247E.

[48] T. Reichstein, *ibid.*, 1937, **20**, 953.

Using a method developed by K. H. Slotta and K. Neisser,[49] C. W. Shoppee and T. Reichstein [50] have converted the triacetate of substance A



into substance-N diacetate. Distillation of A-triacetate with zinc dust gives *iso*-R diacetate (LXV), which differs from substance-R diacetate in

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[49] *Ber.*, 1938, **71**, 2342; A. Serini, W. Logemann, and W. Hildebrand, *Ber.*, 1939, **72**, 391.
[50] *Helv. Chim. Acta*, 1940, **23**, 729.

the orientation around C_{17}. Although in the case of the similarly constituted 17-*iso*pregnenolone acetate,[51] isomerisation to the normal pregnenolone acetate is caused by either acid or alkali, *iso*-R diacetate (LXV) cannot be isomerised to substance-R diacetate (LXVIII), since alkali attacks the ketol group and the C_{11}-hydroxyl group is unstable in the presence of mineral acid, which effects dehydration. However, oxidation of *iso*-R diacetate gives *iso*-N diacetate (LXVI), which is readily isomerised by mineral acid to give (LXVII), identical with the diacetate of substance N isolated from adrenal cortex. (Substance-N diacetate has previously been obtained by oxidation of R diacetate.[52])

Substances J (LXXI) and O (LXXII) [and consequently substance L (LXXIII), which gives a mixture of substances J and O on hydrogenation [53]] have been shown to possess a 17β-hydroxy-configuration by an indirect method.[54] (The C_{20}-configurations assigned to substances J and O are only comparative and not absolute.) This has been confirmed by a direct conversion of substance K (LXIX) into a mixture of substances J and O. Oxidation of substance K (LXIX) with one equivalent of periodic acid gives the hydroxy-aldehyde (LXX), treatment of which with methylmagnesium bromide yields a mixture of substances J (LXXI) and O (LXXII).[55]

The hydroxy-aldehyde (LXX) has also served for a partial synthesis of substance L (LXXIII), which is obtained by treatment of (LXX) with diazomethane.[56]

A partial synthesis of substance K (LXIX) (as its triacetate) has been accomplished [58] starting from dehydroandrosterone (LXXVII) (*i.e.*, from cholesterol) and a similar method starting from *t*-androsterone acetate (LXXIV) has led to the partial synthesis of the diacetate of substance P [57] (LXXV). In its turn, P-diacetate (LXXV) has been converted into substance L (LXXIII); treatment of the former with methylmagnesium bromide gives a tetrol (LXXVI), which on controlled oxidation with periodic acid gives substance L (LXXIII).[59] The methods mentioned above for the part-syntheses of substances P and K are extremely laborious, but they have the advantage that they lead to established configurations at C_{17}; they are, of course, the " master " syntheses in the series of inter-relationships depicted.

F. S. S.

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[51] A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Ber.*, 1939, **72**, 1112.

[52] T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 1490.

[53] T. Reichstein, C. Meystre, and J. v. Euw, *ibid.*, 1939, **22**, 1107.

[54] D. A. Prins and T. Reichstein, *ibid.*, 1940, **23**, 1490.

[55] *Idem, ibid.*, 1941, **24**, 396.

[56] *Idem, ibid.*, p. 945.

[57] J. v. Euw and T. Reichstein, *ibid.*, p. 401.

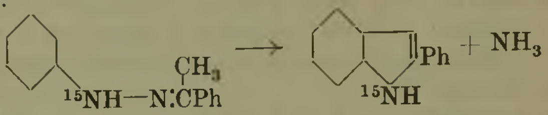
[58] H. G. Fuchs and T. Reichstein, *ibid.*, p. 804.

[59] J. v. Euw and T. Reichstein, *ibid.*, p. 418.

6. HETEROCYCLIC COMPOUNDS.

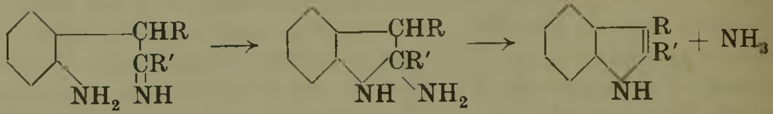
Nitrogen Ring Compounds.

Indole Derivatives.—By the use of ^{15}N as a tracer element, C. F. H. Allen and C. V. Wilson[1] have shown that the nitrogen atom which is eliminated as ammonia in Fischer's synthesis is not that originally attached to the aromatic ring :

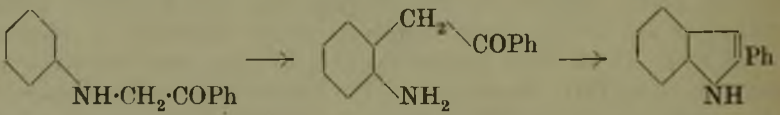


They modify the mechanism of (Mrs.) G. M. and R. Robinson[2] by assuming that the tautomeric imine form (I) of the intermediately formed diamine undergoes an addition-elimination process :

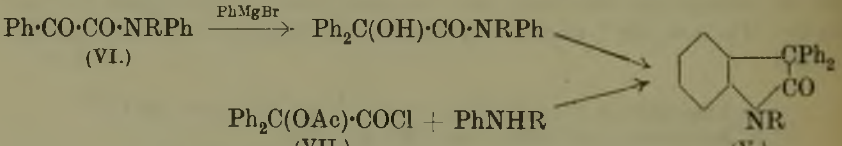
(I.)



alternatively, the imine may first suffer hydrolysis to the ketone, which then undergoes a similar addition, followed by elimination of water. The mechanism of this synthesis has been reviewed by R. B. van Order and H. G. Lindwall.[3] The conversion of phenacylarylamines (II) into 2-arylindoles (IV)[4] has been critically studied.[5] The two reaction mechanisms previously proposed[6] have been shown to be incorrect, and the reaction, which requires the presence of catalytic impurities such as amine hydrobromides, probably proceeds by a Hofmann-Martius rearrangement. Migration of the phenacyl group into the *o*-position is followed by the known[7] cyclisation of the resulting phenyl *o*-aminobenzyl ketone (III).



(II.) (III.) (IV.)



(VI.) (VII.) (V.)

3 : 3-Diphenyloxindoles (V, R = H or alkyl) have been prepared by the action of phenylmagnesium bromide on phenylglyoxylic anilides (VI,

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[1] *J. Amer. Chem. Soc.*, 1943, **65**, 611.

[2] *J.*, 1918, **113**, 639; 1924, **125**, 827.

[3] *Chem. Reviews*, 1942, **30**, 80.

[4] R. Möhlau, *Ber.*, 1881, **14**, 173; 1882, **15**, 2480; 1885, **18**, 165.

[5] A. F. Crowther, F. G. Mann and D. Purdie, *J.*, 1943, 58.

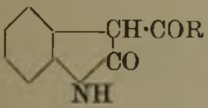
[6] E. Fischer and T. Schmitt, *Ber.*, 1888, **21**, 1071, 1811; A. Bischler, *ibid.*, 1892, **25**, 2860.

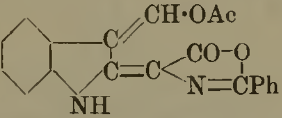
[7] E. B. Womack, N. Campbell, and G. B. Dodds, *J.*, 1938, 1402.

R = H or alkyl), and by the interaction of acetylbenzilyl chloride (VII) with alkylanilines.[8]

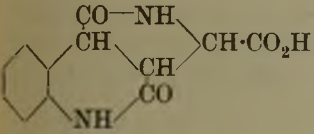
The synthetic reactions of oxindole, important for its relationship to hydroxytryptophan and indole alkaloids, have been studied by L. Horner.[9] Condensation with esters by Claisen's method [10] affords 3-acyloxindoles (VIII); except in the case of ethyl oxindole-3-glyoxylate (VIII, R = CO_2Et), the ketonic carbonyl of these products cannot be reduced. 3-Alkyloxindoles can be obtained by the condensation of aldehydes with oxindole in the presence of trimethylamine, followed by hydrogenation of the resulting alkylideneoxindoles. The abnormal, red condensation product of oxindole-3-aldehyde with hippuric acid [11] is probably the isatin derivative (IX); in contrast, (VIII, R = CO_2Et) condenses normally in the Erlenmeyer synthesis, but reduction and hydrolysis of the resulting azlactone lead to the dilactam (X) and not to the expected carboxy-derivative of 2-hydroxytryptophan. A similar rearrangement to a quinoline derivative (XI)

(VIII.)

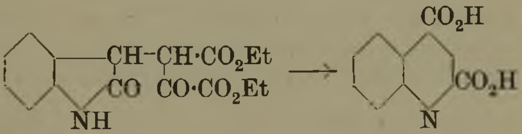




(IX.)



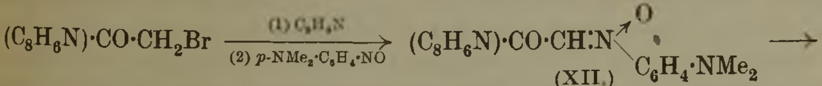
(X.)



(XI.)

occurs when the condensation product of ethyl oxindole-3-acetate and ethyl oxalate is hydrolysed, and these reactions show a marked analogy to the transformation of tryptophan, through kynurenine, into kynurenic acid.[12] 5-Hydroxyindole, also important for its relationship to physiologically active substances, has been synthesised.[13]

Indolyl and pyrryl bromomethyl ketones form quaternary salts with pyridine, which yield indole- and pyrrole-carboxylic acids quantitatively on treatment with alkali, and which react with *p*-nitrosodimethylaniline to form nitrones (XII), hydrolysed by acid to indolylglyoxal hydrates (XIII).[14]



$$(C_8H_6N)\cdot CO\cdot CH_2Br \xrightarrow[(2)\ p\text{-}NMe_2\cdot C_6H_4\cdot NO]{(1)\ C_5H_5N} (C_8H_6N)\cdot CO\cdot CH{:}N(\rightarrow O)\cdot C_6H_4\cdot NMe_2 \longrightarrow$$

(XII.)

(XIII.) $(C_8H_6N)\cdot CO\cdot CH(OH)_2$

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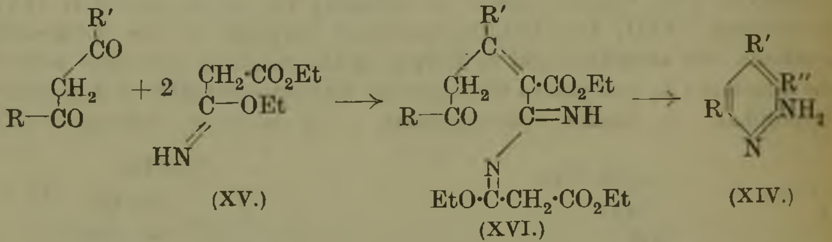
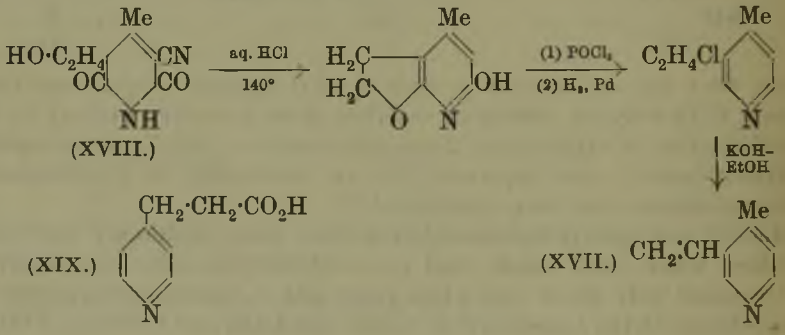
[8] R. F. Reeves and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1942, **64**, 1086.
[9] *Annalen*, 1941, **548**, 117.
[10] Cf. P. L. Julian, J. Pikl, and F. E. Wantz, *J. Amer. Chem. Soc.*, 1935, **57**, 2026.
[11] H. Fischer and K. Smeykal, *Ber.*, 1923, **56**, 2370.
[12] *Ann. Reports*, 1942, **39**, 198.
[13] F. Bergel and A. L. Morrison, *J.*, 1943, 49.
[14] G. Sanna, *Gazzetta*, 1942, **72**, 357.

Pyridine Group.—W. W. Crouch and H. L. Lochte[15] have described a new synthesis of pyridine; treatment of glutarimide with phosphorus pentachloride[16] affords 2 : 3 : 6-trichloropyridine, which can be reduced catalytically to pyridine. Chloropicolines are similarly obtained from α- and β-methylglutarimides. A. Dornow and P. Karlson[17] have extended their pyridine synthesis to include 2-aminopyridines (XIV); carbethoxyacetiminoether (XV) condenses with 1 : 3-dicarbonyl compounds (or their enol ether acetals) to yield the intermediate (XVI), which cyclises, by fission of ethyl malonate, to the 2-aminonicotinic ester (XIV, R″ = CO_2Et), convertible into (XIV, R″ = H) by hydrolysis and decarboxylation.



(XV.) (XVI.) (XIV.)

As a model for the synthesis of quinine types, 4-methyl-3-vinylpyridine (XVII) has been synthesised[18] by an adaptation of Guareschi's method.[19] α-Acetobutyrolactone condensed with cyanoacetamide to the imide (XVIII), converted into (XVII) by the route shown. Although pyridine-4-β-propionic acid (XIX) was obtained from ethyl β-ketoadipate by a similar series of reactions, the method could not be extended to the preparation of the 3-vinyl derivative of (XIX), owing to the failure of ethyl β-keto-α-(2-ethoxyethyl)adipate to condense with cyanoacetamide.[20] 2 : 5-Dialkylpyridines are prepared by the condensation of ethyl alkylmalonates with ethyl β-alkyl-



(XVIII.) (XIX.) (XVII.)

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[15] *J. Amer. Chem. Soc.*, 1943, **65**, 270.

[16] Cf. O. Bernheimer, *Gazzetta*, 1882, **12**, 283.

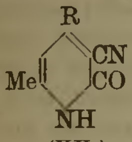
[17] *Ber.*, 1940, **73**, 542; cf. *Ann. Reports*, 1941, **38**, 224.

[18] J. R. Stevens, R. H. Beutel, and E. Chamberlin, *J. Amer. Chem. Soc.*, 1942, **64**, 1093.

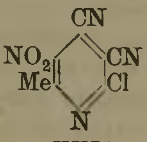
[19] J. C. Bardhan, J., 1929, 2223.

[20] J. R. Stevens and R. H. Beutel, *J. Amer. Chem. Soc.*, 1943, **65**, 449.

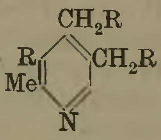
β-aminoacrylates.[21] A new route to vitamin B_6 involves the conversion of 4-carbethoxy-5-cyano-2-methyl-6-pyridone (XX, $R = CO_2Et$) [19] through the amide into the dinitrile (XX, R = CN). Nitration, followed by the action of phosphorus pentachloride, yielded (XXI), two-stage catalytic hydrogenation of which gave the triamine (XXII, $R = NH_2$), converted into the vitamin (XXII, R = OH) by the action of nitrous acid: [22]



(XX.)



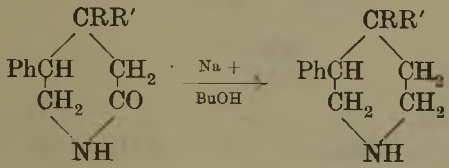
(XXI.)



(XXII.)

3-Phenylpiperidine (XXIII, R = R′ = H) and some of its 4-substituted derivatives have been prepared by the following series of reactions: [23]

$$CH_2Ph{\cdot}CN + CRR'{:}CH{\cdot}CO_2Et \longrightarrow CHPh(CN){\cdot}CRR'{\cdot}CH_2{\cdot}CO_2Et \xrightarrow[-\ EtOH]{H_2-Ni}$$



(XXIII.)

G. H. Coleman and J. J. Carnes [24] have synthesised tropane by heating *N*-chloro-*N*-methyl*cyclo*heptylamine with sulphuric acid.

3-Bromopyridine is readily prepared by heating pyridine hydrochloride perbromide at 160—170°; some 3:5-dibromopyridine is also formed. Optimum conditions for the sulphonation of pyridine and the picolines have been described.[25] Pyridine can be mercurated in the 3-position.[26] J. F. Arens and J. P. Wibaut [27] have shown that the reaction between pyridine, aliphatic anhydrides and zinc dust [28] is general, and have prepared several 4-alkylpyridines by this means. Pyridine-2-[29] and -3-aldehydes,[29, 30] but not the 4-isomer,[29] can be prepared by alkaline fission of the benzenesulphonhydrazides [31] of the corresponding carboxylic acids; this method is also useful in the thiazole,[32] pyrimidine [33] and glyoxaline [34] series. Pyridine-

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[21] V. Prelog, S. Szpilfogel, and E. Stahlberger, *Helv. Chim. Acta*, 1942, **25**, 1306.

[22] J. H. Mowat, F. J. Pilgrim, and G. H. Carlson, *J. Amer. Chem. Soc.*, 1943, **65**, 954.

[23] C. F. Koelsch, *ibid.*, pp. 438, 2093.

[24] *Proc. Iowa Acad. Sci.*, 1942, **49**, 288; cf. *Ann. Reports*, 1942, **39**, 195.

[25] S. M. McElvain and M. A. Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2227, 2233.

[26] C. K. Kanvinde, R. S. Borkar, A. N. Kothare, and V. V. Nadkarny, *J. Univ. Bombay*, 1942, **11** *A*, Pt. 3, 101.

[27] *Rec. Trav. chim.*, 1942, **61**, 59.

[28] *Ibid.*, 1941, **60**, 119; *Ann. Reports*, 1941, **38**, 223.

[29] C. Niemann, R. N. Lewis, and J. T. Hays, *J. Amer. Chem. Soc.*, 1942, **64**, 1678; 1943, **65**, 482.

[30] L. Panizzon, *Helv. Chim. Acta*, 1941, **24**, 24E.

[31] J. S. McFadyen and T. S. Stevens, *J.*, 1936, 584.

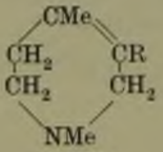
[32] E. R. Buchman and E. M. Richardson, *J. Amer. Chem. Soc.*, 1939, **61**, 891.

[33] D. Price, (Miss) E. L. May, and F. D. Pickel, *ibid.*, 1940, **62**, 2818.

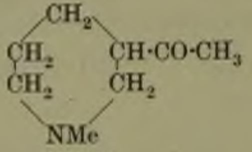
[34] Y. Tamamushi, *J. Pharm. Soc. Japan*, 1940, **60**, 184.

3-aldehyde can be converted into the -3-carbinol and -3-β-acrylic acid;[30] pyridine-3-acetic acid has been prepared[35] from 3-acetylpyridine by the Willgerodt[36] method. The amination of heterocyclic bases by alkali amides has been reviewed by M. T. Leffler.[37]

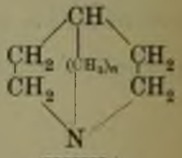
V. Prelog and co-workers[38] have shown that the dehydrogenation of hydropyridyl ketones is accompanied by rearrangement; the compound (XXIV, $R = CO{\cdot}CH_3$) is converted into 2 : 3 : 4-trimethylpyridine by palladised charcoal or by selenium at 300°, whereas the related substances [XXIV, $R = CH(OH){\cdot}CH_3$ or $R = Et$] yield the expected β-collidine. The piperidyl ketone (XXV) similarly suffers rearrangement to 2 : 3-dimethylpyridine. The dehydrogenation of *bicyclo*aza-alkanes has also been studied;[39] quinuclidine (XXVI, $n = 2$) was smoothly converted into 4-ethylpyridine, and (XXVI, $n = 1$) less readily afforded γ-picoline, on treatment with palladised charcoal or selenium at 300°. Octahydropyridocoline (XXVII, $x = y = 4$) gave a trace of quinoline, but the bases (XXVII, $x = 3$ or 4, $y = 3$) and (XXVIII, $x = 2$ or 3, $y = 3$) gave no definite products.



(XXIV.)

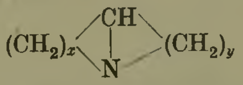


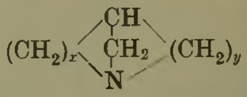
(XXV.)



(XXVI.)

(XXVII.)





(XXVIII.)

Quinolines and iso*Quinolines.*—The Friedländer synthesis is often improved[40] by using *o*-aminobenzylidene arylamines[41] in place of the sensitive *o*-aminobenzaldehydes. 3-Nitrocinchoninic acid is obtained by the alkaline condensation of isatin with nitromethane; it can be reduced to the amino-acid or decarboxylated to 3-nitroquinoline.[42] Quinoline-2- and -4-aldehydes are best obtained by oxidation of the corresponding methylquinolines with freshly prepared selenium dioxide,[43] and the 3-, 5-, 6- and 8-isomerides[44]

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[35] M. Hartmann and W. Bosshard, *Helv. Chim. Acta*, 1941, **24**, 28E.

[36] *Ber.*, 1887, **20**, 2467.

[37] "Organic Reactions," Vol. 1, p. 91. Wiley and Sons, New York, 1942.

[38] V. Prelog and A. Komzak, *Ber.*, 1941, **74**, 1705; V. Prelog, A. Komzak, and E. Moor, *Helv. Chim. Acta*, 1942, **25**, 1654; V. Prelog, E. Moor, and J. Führer, *ibid.*, 1943, **26**, 846.

[39] V. Prelog and K. Balenović, *Ber.*, 1941, **74**, 1508.

[40] W. Borsche *et al.*, *Annalen*, 1941, **548**, 50; 1942, **550**, 160; 1943, **554**, 269.

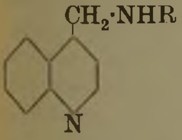
[41] A. Rilliet and L. Kreitmann, *Helv. Chim. Acta*, 1921, **4**, 596; 1922, **5**, 547.

[42] M. Colonna, *Boll. sci. facoltà chim. ind. Bologna*, 1941, 89; *Amer. Chem. Abstr.*, 1943, **37**, 3096.

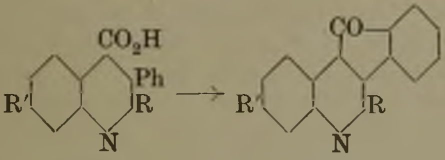
[43] H. Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654.

[44] A. H. Cook, I. M. Heilbron, and L. Steger, *J.*, 1943, 413.

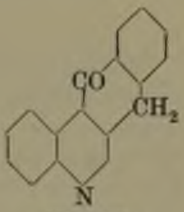
from the appropriate carboxylic acids by the method of McFadyen and Stevens.[31] *iso*Quinoline-1-aldehyde is prepared by the former method, and undergoes the normal condensation reactions.[45] Reduction of the anilides of cinchoninic acids by the method of A. Sonn and E. Müller[46] affords phenyl-lepidylamines (XXIX, R = Ph) and not the expected cinchoninaldehydes; cinchoninic alkylamides similarly give rise to alkyl-lepidylamines (XXIX, R = Me or $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$).[47] The conversion of 2-phenylcinchoninamide into 4-amino-2-phenylquinoline by the action of potassamide in liquid ammonia, under the catalytic influence of potassium nitrate or mercury, is considered to involve a Hofmann-type rearrangement.[48]



(XXIX.)



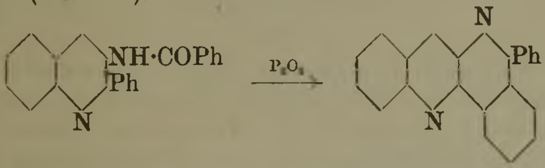
(XXX.) (XXXI.)



(XXXII.)

Many phenylquinolinecarboxylic acids in which the phenyl and the carboxyl group occupy adjacent positions on the nitrogenous ring can be cyclised to benzazafluorenones by sulphuric acid or by the Friedel–Crafts method; for example, (XXX, R = H, alkyl or Ph; R′ = H or OMe) afford the corresponding derivatives of (XXXI), but in certain cases ring closure cannot be achieved. Cyclisation of the corresponding benzyl compounds (XXX, CH_2Ph for Ph) to benzaza-anthrones (XXXII) is a less general reaction.[49] Naphthyridine derivatives could not be obtained by the cyclisation of 2-anilinonicotinic acid, *N*-(3′- or 4′-pyridyl)anthranilic acids[50] or *o*-benzamidophenyl-pyridines or -quinolines,[51] but cyclo-dehydration of 3-benzamido-2-phenylquinoline (XXXIII) gave the dibenz-1 : 5-naphthyridine derivative (XXXIV).[51]

(XXXIII.)



(XXXIV.)

The synthesis of 1-benzyltetrahydro*iso*quinolines from arylacetaldehydes and β-arylethylamines occurs under "physiological conditions," provided that the aryl group in the latter carries a substituent, such as hydroxyl, which activates the position *ortho* to the basic side-chain. The rate of re-

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[45] R. S. Barrows and H. G. Lindwall, *J. Amer. Chem. Soc.*, 1942, **64**, 2430.

[46] *Ber.*, 1919, **52**, 1927.

[47] T. S. Work, *J.*, 1942, 426, 430.

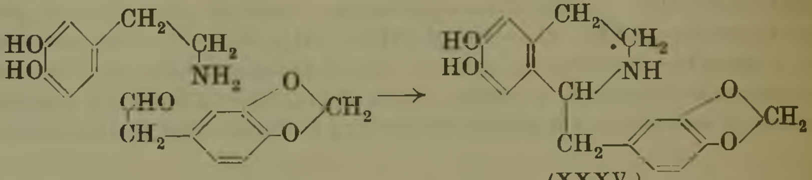
[48] H. C. White and F. W. Bergstrom, *J. Org. Chem.*, 1942, **7**, 497.

[49] W. Borsche *et al.*, *Annalen*, 1937, **532**, 127, 146; 1938, **537**, 22; 1939, **538**, 283, 292; 1940, **544**, 272, 280, 287; 1941, **548**, 64, 74; 1943, **554**, 269.

[50] W. O. Kermack and (Miss) A. P. Weatherhead, *J.*, 1942, 726.

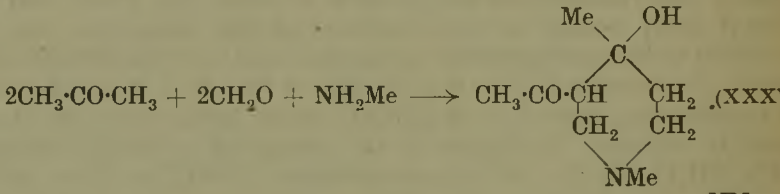
[51] V. A. Petrow, M. V. Stack, and W. R. Wragg, *J.*, 1943, 316.

action between β-(3 : 4-dihydroxyphenyl)ethylamine and homopiperonal at 25° and over the pH range 3—7 has been studied; the tetrahydro*iso*quinoline (XXXV) was produced in 77—85% yield. Piperonylglyoxylic acid reacts more slowly than homopiperonal, suggesting that the biological synthesis proceeds by way of the aldehydes rather than the pyruvic acids.[52]

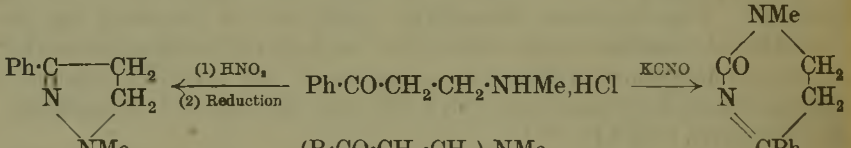


(XXXV.)

Mannich Reaction.[53]—Isolated examples of the formation of heterocyclic compounds from the products of interaction of simple ketones with formaldehyde and methylamine have been known for some time; acetone affords the piperidine (XXXVI),[54] and β-methylaminopropiophenone can be converted into the tetrahydropyrimidine (XXXVII) or the pyrazoline (XXXVIII) by means of the appropriate reagents.[55] The application of such methods was strictly limited, since with most ketones the initial condensation either produced a complex mixture of products,[56] or afforded only tertiary amines of the type (XXXIX), frequently in poor yield.



$$2CH_3{\cdot}CO{\cdot}CH_3 + 2CH_2O + NH_2Me \longrightarrow$$ (XXXVI.)



$$Ph{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}NHMe,HCl$$

$$(R{\cdot}CO{\cdot}CH_2{\cdot}CH_2)_2NMe$$

(XXXVIII.) (XXXIX.) (XXXVII.)

C. Mannich and O. Hieronimus[57] have recently shown that the use of benzylamine (or piperonylamine) in place of methylamine gives a much smoother reaction, and moderate yields of β-benzylaminoketones are obtainable; under these conditions, *cyclo*hexanone gives mainly (XL), with a smaller amount of the spiran (XLI). Condensation of (XL) with formaldehyde and a ketone (R·CO·CH$_3$) affords the decahydro*iso*quinoline (XLII; R = Me or Ph, R′ = OH) converted by dehydration and subsequent

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[52] C. Schöpf and W. Salzer, *Annalen*, 1940, **544**, 1.

[53] Review: F. F. Blicke, "Organic Reactions," Vol. 1, p. 303. Wiley and Sons, New York, 1942.

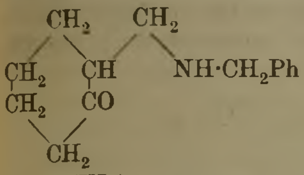
[54] C. Mannich and G. Ball, *Arch. Pharm.*, 1926, **264**, 65.

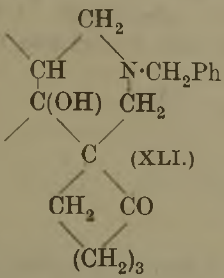
[55] C. Mannich and G. Heilner, *Ber.*, 1922, **55**, 365.

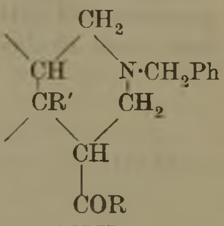
[56] C. Mannich, *Arch. Pharm.*, 1917, **255**, 261.

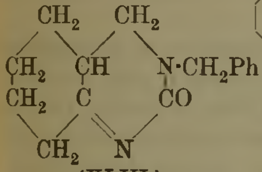
[57] *Ber.*, 1942, **75**, 49.

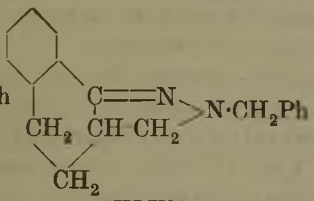
hydrogenation into (XLII, R′ = H). With potassium cyanate, the hydrobromide of (XL) yields the 2-keto-octahydroquinazoline (XLIII), disproportionated by hot acid to the decahydro- and the hexahydro-compound. The condensation product obtained from α-tetralone (analogous to XL) reacts similarly with potassium cyanate, and reduction of its *N*-nitroso-derivative yields the benzindazole (XLIV), but the keto-amines derived from acetone, acetophenone and *cyclo*pentanone give only ureas with potassium cyanate. As a model for the synthesis of alkaloidal types, *cyclo*hexanone was condensed with phenylacetaldehyde and benzylamine, the substance (XLV) being obtained in very small yield.

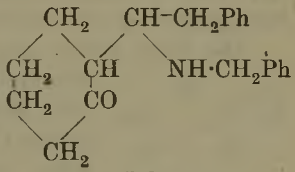

(XL.)


(XLI.)

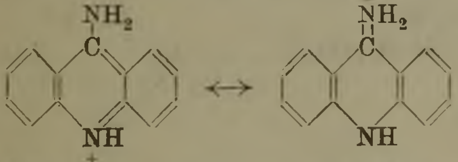

(XLII.)

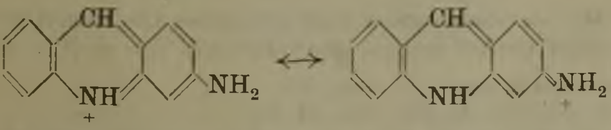

(XLIII.)


(XLIV.)


(XLV.)

Acridines.—A. Albert and R. Goldacre[58] have measured the basic dissociation constants of the five monoaminoacridines. Only the 2- and the 5-isomer have appreciably stronger basicity than acridine, and their higher degree of ionisation parallels their high antiseptic activity.[59] The ring nitrogen is the proton-binding centre in each case, and the enhanced basicity of the 2- and the 5-amino-compound is attributed to the heightened resonance effect in the ion (XLVI or XLVII) as compared with the free base.


(XLVI.)


(XLVII.)

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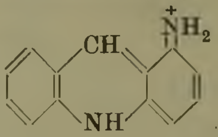
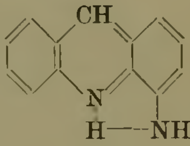
[58] *J.*, 1943, 454.

[59] S. D. Rubbo, A. Albert, and M. Maxwell, *Brit. J. Exp. Path.*, 1942, 23, 69.

The low basicity of 4-aminoacridine indicates that there is no increase in resonance energy in passing from the base to an ion of which the *o*-quinonoid structure (XLVIII) is a component. 1-Aminoacridine is more weakly basic than acridine, and this is ascribed to an "ortho-effect"; possibly the nitrogen atoms are linked by a hydrogen bond (XLIX). The varying chemical reactivity of the aminoacridines is in accord with the above considerations.[60]

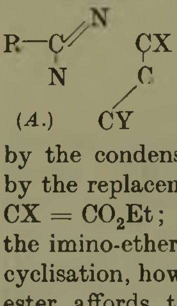
(XLVIII.)





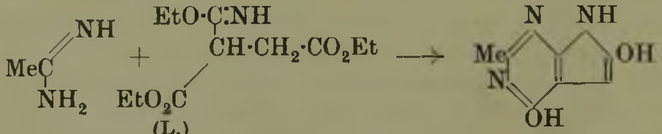
(XLIX.)

Pyrimidines and Purines.—In recent years much fresh stimulus has been given to the study of the pyrimidine group by the demonstration of the presence of this ring system in riboflavin and aneurin,[61] by the discovery of the co-enzyme functions of the dinucleotides derived from adenine and nicotinamide or riboflavin,[62] and by the investigation of the therapeutic properties of sulphanilamidopyrimidines. Numerous new synthetic methods have been developed in studies related to these topics, and further insight has been gained into the chemistry of pyrimidines.



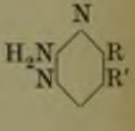
(*A*.)

The most widely applicable method for the synthesis of pyrimidines is represented by scheme (*A*); the group R may be alkyl, aryl, hydroxyl, alkoxyl, thiol, alkylthio, or amino, and the groups CX and CY in the second reactant may be carboxylic ester, cyano or carbonyl groups, or various derivatives of these. Traube's synthesis of 4-amino-6-hydroxypyrimidines by the condensation of amidines with α-cyano-esters is often improved[63] by the replacement of the latter reactant by its imino-ether [*A*, R = alkyl; CX = CO_2Et; CY = C(:NH)·OEt]; the condensation of acetamidine with the imino-ether (L) derived from ethyl α-cyanosuccinate results in a double cyclisation, however, the pyrimazole (LI) being obtained, whereas the cyano-ester affords the expected pyrimidine. Although the formyl (hydroxymethylene) derivative of methyl ethyl ketone affords the pyrimidine (LII, R = R′ = Me) on condensation with guanidine, the formyl derivatives of the higher alkyl methyl ketones (R·COMe) give rise to (LII, R = *n*-C_3H_7,



(L.)

(LI.)



(LII.)

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[60] A. Albert and B. Ritchie, *J.*, 1943, 458.

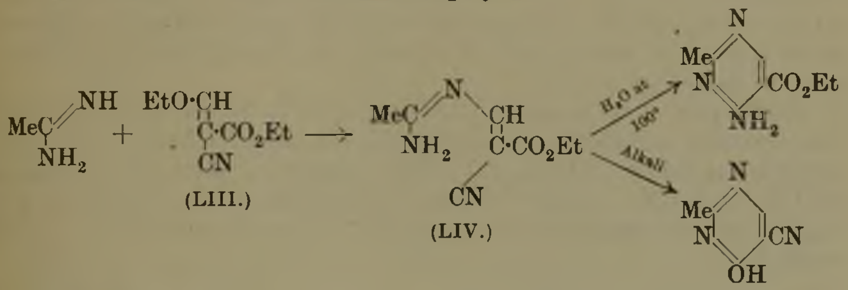
[61] *Ann. Reports*, 1935, **32**, 354; 1937, **34**, 352.

[62] *Ibid.*, 1939, **36**, 343, 353; F. Lipmann, *Ann. Rev. Biochem.*, 1937, **6**, 19.

[63] Z. Földi, G. von Fodor, I. Demjén, H. Szekeres, and I. Halmos, *Ber.*, 1942, **75**, 755.

iso-C_4H_9, *n*-C_5H_{11}, or *n*-C_6H_{13}; R′ = H), showing that in these cases the formyl ketone is R·CO·CH:CH·OH.[64]

The majority of combinations of reactants represented in scheme (*A*) yield pyrimidines when brought together in the presence of basic, or less commonly acidic, catalysts, but a number of failures have been reported. Neither urea nor thiourea affords pyrimidines when treated with αα-dialkylacetoacetic esters [65] or ethyl dicyanoacetate,[66] and urea also fails to condense with ethyl propionylacetate [67] or ethyl cyanomalonate.[66] Condensation of urea with ethyl ethoxymethyleneacetoacetate [68] and of acetamidine with ethyl ethoxymethylenecyanoacetate (LIII) [69] proceeds in two stages, and the cyclisation of the intermediate (*e.g.*, LIV) may proceed in different directions according to the conditions employed.


(LIII.) (LIV.)

Pyrimidines having a free 2-position have previously been prepared only by indirect methods involving the removal of a 2-substituent; the possible use of formamidine for the synthesis of such compounds has now been studied.[70, 71] With ethyl malonate [71] or with benzeneazomalononitrile,[70] condensation proceeds normally to yield the expected pyrimidines, but nitromalondialdehyde [72] does not yield 5-nitropyrimidine. With substances containing a more reactive methylene group, such as ethyl cyanoacetate or acetoacetate, the methylene group is attacked and the products are not pyrimidines; in the former case ethyl aminomethylenecyanoacetate (LV; R = H, R′ = CO_2Et) is obtained, and analogous products (LV; R = Me or Ph, R′ = CO_2Et) are produced with acetamidine or benzamidine in the absence of alkali. Malononitrile reacts with formamidine, acetamidine or benzamidine to give the pyrimidines (LVI, R = H, Me or Ph); that this

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[64] J. M. Sprague, L. W. Kissinger, and R. M. Lincoln, *J. Amer. Chem. Soc.*, 1941, **63**, 3028; G. W. Raiziss and M. Freifelder, *ibid.*, 1942, **64**, 2340; cf. W. T. Caldwell, E. C. Kornfeld, and C. K. Donnell, *ibid.*, 1941, **63**, 2188.

[65] T. S. Ma, Dissertation, Chicago University, 1940.

[66] J. C. Ambelang and T. B. Johnson, *J. Amer. Chem. Soc.*, 1941, **63**, 1289.

[67] A. R. Todd, F. Bergel, and Karimullah, *J.*, 1936, 1557.

[68] W. Bergmann and T. B. Johnson, *Ber.*, 1933, **66**, 1494.

[69] F. Bergel and A. R. Todd, *J.*, 1937, 364; Z. Földi and A. Saloman, *Ber.*, 1941, **74**, 1126.

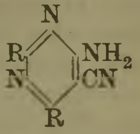
[70] J. Baddiley, B. Lythgoe, and A. R. Todd, *J.*, 1943, 386.

[71] G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *ibid.*, p. 388.

[72] R. O. Roblin, P. S. Winnek, and J. P. English, *J. Amer. Chem. Soc.*, 1942, **64**, 567.

reaction proceeds by the intermediate formation of compounds (LV, R = H, Me or Ph; R′ = CN), followed by condensation with a second molecule of

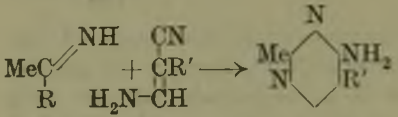
(LV.)



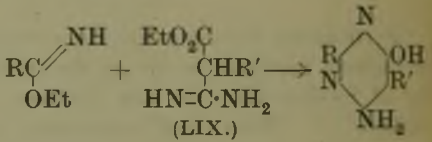
(LVI.)

the amidine, is shown by the behaviour of α-furylamidine, which with malononitrile affords (LV; R = C_4H_3O, R′ = CN) in the absence, and (LVI, R = C_4H_3O) in the presence of sodium ethoxide, and also by the successful preparation of (LVI, R = H) by the reaction of aminomethylenemalononitrile (LV; R = H, R′ = CN) with formamidine. Thus the successful use of formamidine, and, to a lesser extent, of other amidines in syntheses of the type (*A*) is dependent on the absence of a highly reactive methylene group in the second reactant.[71]

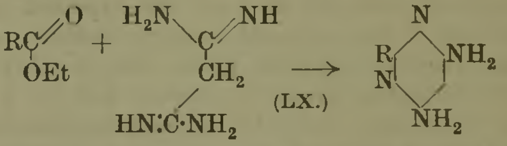
Other types of synthesis of pyrimidine derivatives which have recently been described include the reaction of thioacetamide [71, 73] (LVII, R = SH) or of acetiminoether [74] (LVII, R = OEt) with aminomethylenemalononitrile (LVIII, R′ = CN) or ethyl aminomethylenecyanoacetate (LVIII, R′ = CO_2Et) and of iminoethers with α-carbethoxyamidines [75] (LIX, R′ = H or alkyl).



(LVII.) (LVIII.)



(LIX.)



(LX.) (LXI.)

The hitherto[76] difficultly accessible 4:6-diaminopyrimidine (LXI, R = H) is readily obtained by the condensation of ethyl formate with malondiamidine (LX), and ethyl acetate gives the corresponding 2-methyl derivative (LXI, R = Me).[77]

Xanthine (LXII) has been synthesised from methyl 5-aminoglyoxaline-4-carboxylate by treatment with potassium cyanate, followed by hydrolysis and cyclisation of the resulting ureido-ester. An attempt to extend this method to the synthesis of xanthine-9-glucoside failed owing to the inaccessibility of the required glucosidoglyoxaline.[78] A new synthesis of adenine (LXIII, R = R′ = H) has been achieved;[70] 5-benzeneazo-4:6-diaminopyrimidine (from formamidine and benzeneazomalonitrile) is reduced to

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[73] B.P. 546,624.

[74] O. Hromatka, D.R.-P. 667,990.

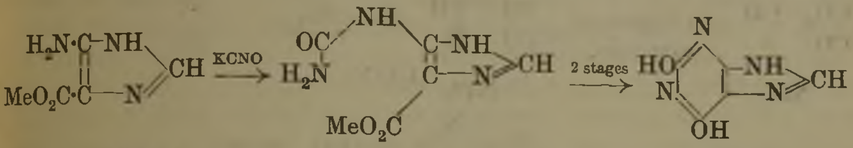
[75] Hung. Patent 126,792.

[76] E. Büttner, *Ber.*, 1903, **36**, 2227.

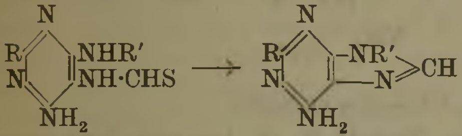
[77] G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J.*, 1943, 574.

[78] W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J.*, 1942, 232.

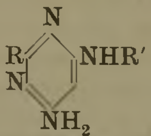
4 : 5 : 6-triaminopyrimidine, which is converted by sodium dithioformate [67] into the 5-thioformamido-compound (LXIV, R = R′ = H), and this readily cyclises on heating in water, pyridine or quinoline. This method of purine synthesis, which appears to be general, involves the use of mild conditions only, and should be suitable for the synthesis of nucleosides, since a model experiment with the pyrimidine (LXIV; R = SMe, R′ = Me) showed that cyclisation proceeds in the desired direction, producing a 9-alkylpurine (LXIII; R = SMe, R′ = Me).[79] Attention has therefore been turned [80] to the preparation of suitable 4-glycosidaminopyrimidines, and the 4 : 6-diamino-compounds (LXV; R = Me or SMe, R′ = H) have been converted into the 4-*d*-xylosidamino-derivatives (LXV, R′ = $C_5H_9O_4$) by applying the method developed by R. Kuhn and R. Ströbele [81] for the preparation of *N*-glycosides in the benzene series.



(LXII.)



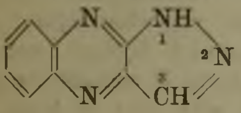
(LXIV.) (LXIII.)

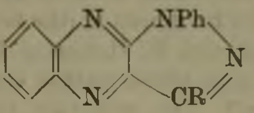


(LXV.)

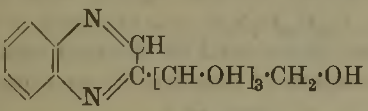
Flavazole.—H. Ohle and G. A. Melkonian [82] have described a number of derivatives of a new ring system derived from sugars, which they call flavazole (LXVI). The tetrahydroxybutylquinoxaline (LXVII) obtained by interaction of glucose and *o*-phenylenediamine [83] reacts with phenylhydrazine acetate to yield 1-phenyl-3-(*d*-*erythro*-trihydroxypropyl)flavazole (LXVIII, R = $[CH{\cdot}OH]_2{\cdot}CH_2{\cdot}OH$). The nature of the side chain was confirmed by the usual reactions, and on treatment with lead tetra-acetate the aldehyde (LXVIII, R = CHO) was obtained. Oxidation with chromic acid afforded the 3-carboxylic acid, which could be decarboxylated to 1-phenylflavazole

(LXVI.)





(LXVIII.)



(LXVII.)

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[79] J. Baddiley, B. Lythgoe, D. McNeil, and A. R. Todd, *J.*, 1943, 383.

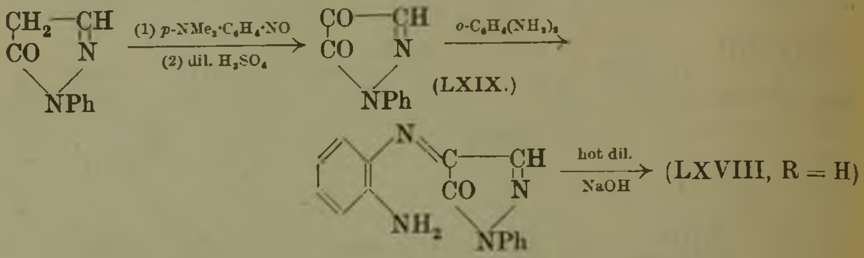
[80] J. Baddiley, B. Lythgoe, and A. R. Todd, *ibid.*, p. 571.

[81] *Ber.*, 1937, **70**, 773.

[82] *Ber.*, 1941, **74**, 279.

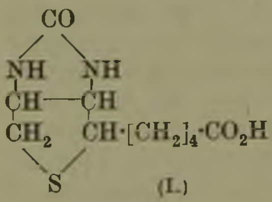
[83] K. Maurer and B. Schiedt, *Ber.*, 1934, **67**, 1980; *Ann. Reports*, 1938, **35**, 318.

(LXVIII, R = H), the structure of which was confirmed by its synthesis from 4 : 5-diketo-1-phenylpyrazoline (LXIX) and *o*-phenylenediamine. Flavazole itself (LXVI) has been prepared from (LXVII) and hydrazine by a similar series of reactions.[84]



The Chemistry of Biotin.

The constitution of biotin (bios II B) (I) has now been completely elucidated by V. du Vigneaud and his collaborators in the Cornell laboratories. The results of the earlier parts of this investigation have already been reported,[1] but will be summarised here in order to present a complete survey.


(I.)

F. Kögl and B. Tönnis [2] first isolated crystalline biotin methyl ester in relatively pure condition from egg yolk. The yield was extremely small, and the high cost of the raw material and the long and tedious nature of the concentration processes rendered the accumulation of sufficient material for structural determination very difficult. The molecular formula of the methyl ester was found to be $C_{11}H_{18}O_3N_2S$; it had only very weakly basic properties, was dextrorotatory and showed no specific ultra-violet absorption; the free acid titrated as a monocarboxylic acid.[3, 4] Having proved the identity of biotin with vitamin H (the factor preventing " egg-white injury " in rats), V. du Vigneaud, K. Hofmann, D. B. Melville, and P. György [5] succeeded in isolating pure biotin methyl ester from a vitamin H concentrate prepared from liver.[6] The molecular formula agreed with that of Kögl, and on hydrolysis free biotin, $C_{10}H_{16}O_3N_2S$, was obtained in crystalline condition.[7] The discovery that pure biotin could be obtained relatively easily from milk concentrates,[8] and the supply of considerable quantities of such concentrates

[84] H. Ohle and A. Iltgen, *Ber.*, 1943, **76**, 1.

[1] *Ann. Reports*, 1941, **38**, 235, 249; 1942, **39**, 230.

[2] *Z. physiol. Chem.*, 1936, **242**, 43.

[3] F. Kögl, *Naturwiss.*, 1937, **25**, 465; *Chem. and Ind.*, 1938, **57**, 49.

[4] F. Kögl and L. Pons, *Z. physiol. Chem.*, 1941, **269**, 61.

[5] *J. Biol. Chem.*, 1941, **140**, 643; (with C. S. Rose), *Science*, 1940, **92**, 62, 609.

[6] P. György, R. Kuhn, and E. Lederer, *J. Biol. Chem.*, 1939, **131**, 745.

[7] V. du Vigneaud, K. Hofmann, D. B. Melville, and J. R. Rachele, *ibid.*, 1941, **140**, 763.

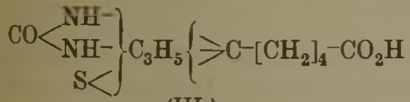
[8] D. B. Melville, K. Hofmann, E. Hague, and V. du Vigneaud, *ibid.*, 1942, **142**, 615.

by the S. M. A. Corporation, rendered available much larger amounts of biotin for degradative studies, although it was still necessary to work on the semi-micro scale.

Biotin is not inactivated by ninhydrin, and is therefore not an α-amino-acid; it contains no primary amino-group, yields no methyl iodide on treatment with hydriodic acid, and is unaffected by hydrogenation.[9] Vigorous hydrolysis with baryta[4, 10] or concentrated hydrochloric acid[11] yielded a diamino-acid (II), $C_9H_{18}O_2N_2S$, containing two primary amino-groups and forming an alkali-soluble dibenzoyl derivative. The presence of a cyclic urea grouping, suggested by this degradation, was confirmed by the re-synthesis of biotin by the interaction of the diamino-acid with carbonyl chloride.[10] The sulphur atom could not be eliminated from the molecule by the action of alkali, hydriodic acid, zinc and hydrochloric acid, or bromine water. The suspected presence of a thio-ether linkage was confirmed by the smooth oxidation of biotin to a sulphone,[10, 11] and by the interaction of biotin methyl ester and methyl iodide to yield a sulphonium salt;[11] its resistance to complete fission suggested that the sulphur atom forms part of a ring.

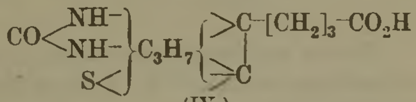
F. Kögl and T. J. de Man,[11] seeking to prove the cyclic nature of the thio-ether linkage, obtained by oxidation of biotin methyl ester and subsequent vigorous hydrolysis a product which they described as a C_9-diamino-sulphocarboxylic acid, the sulphonic acid group of which must have arisen by the hydrolysis of a *cyclic* sulphone; the Cornell group, however, showed that this substance was not a sulphonic acid, but was identical with the sulphone of the diamino-acid (II), which they also prepared by an independent method, and which was converted by carbonyl chloride into biotin sulphone.[12]

Oxidation of the diamino-carboxylic acid (II) with permanganate or nitric acid afforded adipic acid.[13] Biotin methyl ester was converted by the Curtius method into a urethane, alkaline hydrolysis of which afforded a triamine, $C_8H_{19}N_3S$, in which the carboxyl group of (II) is replaced by an amino-group. Oxidation of the triamine yielded no adipic acid, indicating that this oxidation product was derived from a side chain terminated by a carboxyl group.[14] From the foregoing evidence the partial structures (III) and (IV) may be formulated. In the case of (IV), the adipic acid would arise from the decomposition of an intermediately-formed malonic or β-keto-acid.



$$\mathrm{CO}{<}\begin{matrix}\mathrm{NH}-\\ \mathrm{NH}-\\ \mathrm{S}{<}\end{matrix}\Bigg\}\mathrm{C_3H_5}\Bigg\{{\gtrdot}\mathrm{C{-}[CH_2]_4{-}CO_2H}$$

(III.)



$$\mathrm{CO}{<}\begin{matrix}\mathrm{NH}-\\ \mathrm{NH}-\\ \mathrm{S}{<}\end{matrix}\Bigg\}\mathrm{C_3H_7}\Bigg\{\begin{matrix}{>}\mathrm{C{-}[CH_2]_3{-}CO_2H}\\ |\\ {\gtrdot}\mathrm{C}\end{matrix}$$

(IV.)

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[9] G. B. Brown and V. du Vigneaud, *J. Biol. Chem.*, 1941, **141**, 85.

[10] K. Hofmann, D. B. Melville, and V. du Vigneaud, *ibid.*, p. 207; *Science*, 1941, **94**, 308.

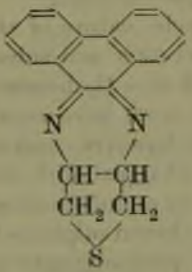
[11] F. Kögl and T. J. de Man, *Z. physiol. Chem.*, 1941, **269**, 82.

[12] *J. Biol. Chem.*, 1942, **145**, 101.

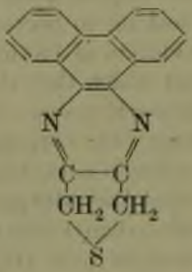
[13] K. Hofmann, D. B. Melville, and V. du Vigneaud, *J. Amer. Chem. Soc.*, 1941, **63**, 3237.

[14] *Idem, ibid.*, 1942, **64**, 188; *J. Biol. Chem.*, 1942, **144**, 513.

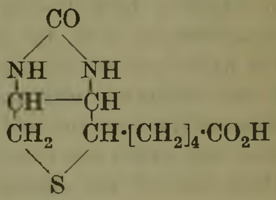
The diamino-acid (II) reacts with phenanthraquinone to form a quinoxaline derivative (V), showing that the amino-groups are attached to adjacent carbon atoms. Synthetic 3 : 4-diaminotetrahydrothiophen formed with phenanthraquinone the dihydroquinoxaline (VI), converted by heat into the quinoxaline (VII).[15] The absorption spectra of (V) and (VII) were almost identical, whereas that of (VI) was different; thus (V) is a true quinoxaline, and both the carbon atoms carrying the amino-groups in (II) must also bear hydrogen atoms.[16] The possible structures for biotin are thus limited to (VIII) and (IX), derived from (III) and (IV) respectively, since structures in which a sulphur and a nitrogen atom are attached to the same carbon atom are excluded by the stability of the diamino-acid (II) to hydrolytic reagents. 3 : 4-Diaminotetrahydrothiophen, like (II), was extremely resistant to hydrolytic fission;[15] in contrast, the 2 : 5-diamino-compound could not be obtained by hydrolysis of the urethane (X), decomposition occurring with the formation of hydrogen sulphide, ammonia and succindialdehyde.[17]



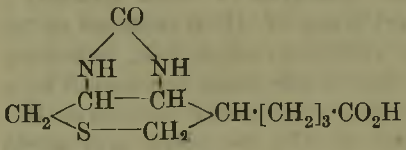
(VI.)



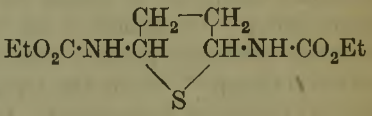
(VII.)



(VIII.)



(IX.)



(X.)

Biotin was finally shown to possess the structure (VIII) by two independent methods.[18, 19] The application of a modified Hofmann exhaustive methylation procedure to the diamino-acid (II) afforded a small yield of

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[15] G. W. Kilmer, M. D. Armstrong, G. B. Brown, and V. du Vigneaud, *ibid.*, 1942, **145**, 495.

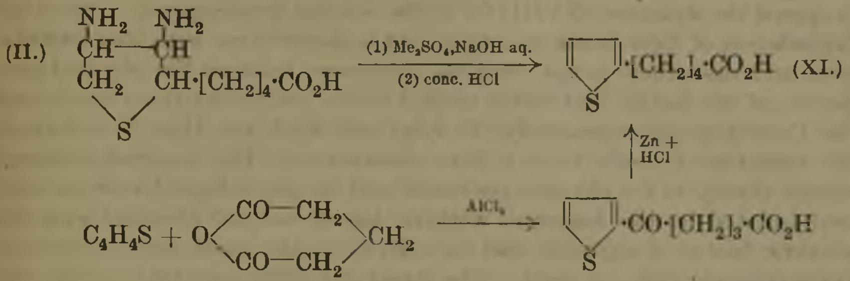
[16] K. Hofmann, G. W. Kilmer, D. B. Melville, V. du Vigneaud, and H. H. Darby, *ibid.*, p. 503.

[17] G. B. Brown and G. W. Kilmer, *J. Amer. Chem. Soc.*, 1943, **65**, 1674.

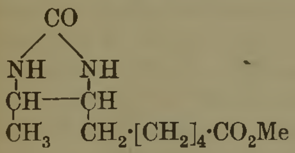
[18] D. B. Melville, A. W. Moyer, K. Hofmann, and V. du Vigneaud, *J. Biol. Chem.*, 1942, **146**, 487.

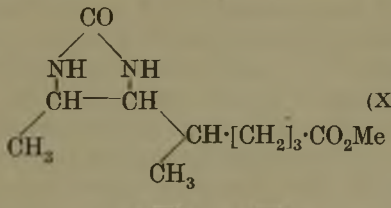
[19] V. du Vigneaud, D. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy, and S. A. Harris, *ibid.*, p. 475.

a crystalline nitrogen-free acid, which was shown to be identical with δ-(2-thienyl)valeric acid (XI), synthesised by the route shown.[18]



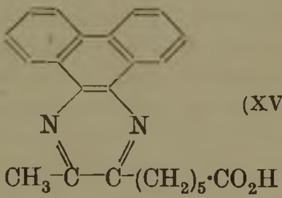
The removal of sulphur from organic sulphides by means of Raney nickel was studied,[19, 20] and the method, having been found satisfactory in model experiments on the semi-micro scale, was applied to biotin methyl ester. The sulphur atom was replaced by two hydrogen atoms, dethiobiotin methyl ester (XII or XIII) being obtained in good yield; on hydrolysis, a diamino-carboxylic acid (XIV or XV) was produced, which contained one *C*-methyl group (Kuhn–Roth), and which on oxidation with periodic acid afforded pimelic acid; both these facts support the structure (XIV). With phenanthraquinone it yielded a quinoxaline (XVI) which was optically inactive [the corresponding derivative from (XV) should be optically active], and which was identical with the quinoxaline derived from ζη-diaminopelargonic acid (XIV) synthesised by the route shown. The use of the quinoxalines facilitated comparison between the degradative and synthetic products, owing to the destruction of the molecular asymmetry.


(XII).)


(XIII)

$$\mathrm{CH_3{\cdot}CH(NH_2){\cdot}CH(NH_2){\cdot}[CH_2]_5{\cdot}CO_2H}$$
(XIV.)

$$\mathrm{CH_3{\cdot}CH(NH_2){\cdot}CH(NH_2){\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2H}$$
(XV.)


(XVI.)

$$\mathrm{Br{\cdot}[CH_2]_5{\cdot}CO_2Et + CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et \xrightarrow{\text{3 stages}} CH_3{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO_2Et}$$

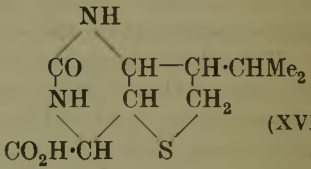
$$\xrightarrow[\text{(2) NH}_2\text{OH}]{\text{(1) EtONO,HCl}} \mathrm{CH_3{\cdot}C(:NOH){\cdot}C(:NOH){\cdot}[CH_2]_5{\cdot}CO_2Et} \xrightarrow[\text{NH}_3\text{, EtOH}]{\text{H}_2\text{, Ni, liq.}} \text{(XIV)}$$

[20] R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, 1943, 65, 1013.

Note added in proof.—On the basis of a stepwise degradation to β-carboxy-γ-methylbutanesulphonic acid (XVII), F. Kögl and his collaborators[21] have proposed the structure (XVIII) for biotin isolated from egg-yolk. Since the degradation of liver biotin to adipic acid is inconsistent with this formulation, and since there is not complete agreement between the physical properties of the biotins and biotin methyl esters isolated by the Utrecht and the Cornell group respectively, F. Kögl and E. J. ten Ham[22] undertook the isolation of biotin from a liver concentrate. The material obtained agreed closely in its physical constants and its physiological activity with that isolated by the American workers, but it was not identical with the isomeric biotin of egg-yolk, and its activity in the yeast growth test was approximately twice as great. The structural differences between the two biotins are remarkable in view of their similar biological properties.

$CHMe_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}SO_3H$

(XVII.)



(XVIII.)

H. T. O.

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[21] F. Kögl, J. H. Verbeek, H. Erxleben, and W. A. J. Borg, *Z. physiol. Chem.*, 1943, 279, 121.

[22] *Ibid.*, p. 140.

BIOCHEMISTRY.

1. Nutrition.

Vitamin C and the Healing of Wounds.

Some interesting observations have accumulated during the past few years on the influence of ascorbic acid on the repair of wounds. The implications are of both theoretical and practical importance, and a brief review of the more significant findings seems to be due.

Experimental Studies on Guinea Pigs.—One of the first to record the fact that a deficiency of vitamin C in guinea pigs causes delay in the healing of experimentally induced wounds was B. Ishido.[1] Observations of this kind began on this purely descriptive or qualitative plane; but later experimentation has introduced the quantitative element by measuring the *tensile strength* of the healing wound under varying conditions. This development has not only greatly increased the scientific value of the findings but has also shown that the implications are more immediately applicable to medical and surgical science than was at first realised. Perhaps the simplest way of summing up the results, in a single sentence, would be to say that it has been clearly demonstrated that the tensile strength of the healing wound diminishes in proportion with the extent of the deficiency of the vitamin. From this point of view, varying degrees of " partial deficiencies " of vitamin C are seen to be of consequence, the effect on the tensile strength not being limited to the last stages of scurvy or indeed to animals suffering from a complete lack of vitamin C. Valuable studies of this kind have been carried out by T. H. Lanman and T. H. Ingalls,[2] by M. K. Bartlett, C. M. Jones, and A. E. Ryan [3] and by G. Bourne.[4]

Vitamin C, Gastric Disease, and Wound Healing in Man.—L. J. Harris, M. A. Abbasy, J. Yudkin, and S. Kelly [5] observed that low reserves of vitamin C were commonly found in patients suffering from gastric or duodenal ulceration and similar ailments. The explanation was that the diets which were prescribed by medical advice in such cases, while they were designed to be low in any irritating residue or roughage, happened also to be frequently deficient in vitamin C as well. In consequence cases of scurvy have not been unknown in patients kept on such special diets. But, moreover, as H. E. Archer and G. Graham [6] observed, these patients often exhibited an unsatisfactory healing of surgical wounds, as after an operation for duodenal or gastric ulcer. It has since become customary to add synthetic ascorbic acid (or alternatively strained citrus fruit juice) to " gastric diets," with

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[1] *Virchow's Arch.*, 1923, **240**, 241.

[2] *Amer. J. Surg.*, 1937, **105**, 616.

[3] *Ann. Surg.*, 1940, **111**, 1; *New England J. Med.*, 1942, **226**, 469, 474.

[4] *Lancet*, 1942, ii, 661 and literature there cited; also *Proc. Soc. Exp. Biol.*, Cambridge, September 1943. The first-mentioned reference gives a very full review of the whole question of vitamin C and wound healing, which may be consulted for further details.

[5] *Lancet*, 1936, i, 1488.

[6] *Ibid.*, 1936, ii, 364.

the results not only that any danger of scurvy is obviated, but also that when surgical treatment is necessitated the danger of unsatisfactory post-operative healing of the wound is said to be minimised.

Vitamin C Requirements and the Tensile Strength of Wounds in Man.—We have a fairly accurate knowledge of the relative requirements of guinea pigs and man for vitamin C. The minimum dose needed to protect each species from scurvy can therefore be defined reasonably closely. Now, it is found that for optimal healing and tensile strength of wounds in guinea pigs several times more vitamin C are needed than the minimum dose required for mere protection against the gross symptoms of scurvy. It is thus possible to assess by calculation the amount of vitamin C which should be needed by a man for adequate repair of wounds. On this basis G. Bourne[7] calculates that 40 mg. of the vitamin may be required each day to secure adequate healing of wounds and that less than 20 mg. may produce a scar of low tensile strength. These conclusions seem in keeping with the observations of M. K. Bartlett, C. M. Jones, and A. E. Ryan,[8] who have given evidence that when the plasma vitamin-C level in man falls below 0·2 mg. per 100 ml. there is likely to be a reduced tensile strength in healing wounds.

Wound Healing in Experimental Scurvy in Man.—J. H. Crandon, C. C. Lund, and D. S. Dill[9] described an experiment in which a human volunteer was kept for many weeks on a diet deficient in vitamin C. A wound made after three months appeared to heal well, but one made after six months completely failed to heal. It has been argued by some writers that, since there was apparently good healing after three months without any vitamin C, a shortage of this factor in the diet can have but little practical significance, at any rate until an advanced stage of depletion is reached. As against this, however, the evidence cited in the previous paragraph, and further facts to be mentioned later, must be considered. The conclusion seems to follow that even with apparently satisfactory *superficial* healing (as after the three months in Crandon's experiments; and also in some similar observations by F. W. Fox[10]) the tensile strength of wounds would presumably be impaired in such circumstances as these, when the intake of the vitamin is low. As Bourne[4] has remarked, it is the holding power which is the really relevant point as far as normal surgery is concerned. We may add also that, apart from the special considerations of surgery, the state of normal healthy nutrition to aim at, for the population as a whole—and more particularly for the fighting services—should surely be that in which, if an injury should be sustained, there is no danger of its inadequate repair because of the past intake of vitamin C having been low. The desirable intake for this purpose, according to the conclusions already given, comes out at about the same as the "requirement" proposed some years ago by the League of Nations Commission, *viz.*, 30 mg. per day; and is therefore

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[7] *J. Physiol.*, 1942, quoted by *Lancet*, 1942, ii, 661.

[8] *New England J. Med.*, 1942, **226**, 474.

[9] *Ibid.*, 1940, **223**, 353.

[10] *Brit. med. J.*, 1941, i, 311.

definitely higher than the minimum dose of about 7—10 mg. which suffices to protect from scurvy, and which some biochemists have been inclined to consider a safe and adequate allowance for the average adult.

Surgical Applications.—We know that many individuals habitually take less than the 30 mg. of ascorbic acid daily, recommended as the standard requirement by the League of Nations Commission, or than the 20—40 mg. calculated by Bourne to be needed to secure optimal tensile strength of wounds. Correspondingly, the amount of ascorbic acid in the blood plasma is often below the value of 0·2 mg.% found by Bartlett to be desirable if risk of a diminished tensile strength is to be precluded. What evidence is there, then, that vitamin C has the fairly obvious use in surgery that these considerations would seem to imply? Various papers published of late maintain that vitamin C has indeed an important practical application of this kind. For instance, C. C. Lund and J. H. Crandon [11] found that post-operative re-opening of wounds occurred most commonly in subjects having a low level of vitamin C in the plasma. In explanation of such a finding, A. H. Hunt [12] records that an examination of surgical wounds *post mortem* brought to light the fact that there had been a poor formation of collagen in those patients whose vitamin-C intake was known to have been low. This picture, an unsatisfactory laying-down of collagen fibres, is the same as that seen in guinea pigs suffering from sub-scurvy and helps us to understand the underlying nature of the mechanical defect in question. Various clinical trials have been undertaken to test the effect of pre-medication with vitamin C before surgical operation, and some encouraging results are claimed. A. H. Hunt [12] states that the administration of vitamin C brought about a reduction by 75% in the incidence of eventration and disruption of surgical wounds. Among others, Bartlett and his colleagues [3] also speak of the good results of premedication as a routine measure for preventing post-operative herniæ. A professor of surgery in the University of London records that early in the war, unexpected trouble was experienced with wounds failing to heal. It was not realised at first that a drop in intake of vitamin C had occurred as a result of war-time conditions. When vitamin C was administered as a routine, however, the position was restored.[13]

Vitamin C and Bone Injuries.—Since it is recognised that vitamin C is needed for normal osteogenesis, it is not surprising that an animal suffering from a deficiency of the vitamin experiences difficulty in effecting adequate repair of a fracture or other bony injury. J. Hertz [14] and Bourne [4] and others have described the delayed healing of fractures observed when guinea pigs are kept on diets low in vitamin C. The underlying abnormalities are a scarcity of collagen and an impaired function of fibroblasts and osteoblasts. In parallel with his work on the healing of wounds in the soft tissues, Bourne [4] has shown that the degree of healing in an injured bone is proportional to

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[11] *Ann. Surg.*, 1941, **114**, 776.

[12] *Brit. J. Surg.*, 1941, **28**, 436.

[13] J. Paterson Ross, *Proc. Soc. Exp. Biol.*, Cambridge, September, 1943.

[14] "Studies on the Healing of Fractures, with Special Reference to the Significance of the Vitamin Content of the Diet," Copenhagen, 1936.

the adequacy of the vitamin supply, "partial deficiencies" being again of consequence and not only deficiencies so severe as to produce scurvy. By comparing the requirements of humans and guinea pigs (cf. *supra*) he calculates that 40 mg. per day are needed by an adult man for the optimum formation of bony trabeculæ, and that an intake of less than 20 mg. may seriously retard their formation.

A remarkable condition of the bones in guinea pigs, kept for long periods on diets partially deficient in vitamin C, and characterised by hyperostosis, ankylosis, and arthrosis, has been described by E. Kodicek and P. D. F. Murray.[15] The possible analogy with similar conditions seen in man should be worth exploring.

Theoretical Explanation.—The observed influence of vitamin C in promoting the healing of wounds and fractures can probably be explained on the basis of the currently accepted theories of vitamin-C action, namely, (*a*) that the vitamin is needed for maintaining the functional activity and integrity of formative cells,[16] [17] and (*b*) that in its absence there is a faulty formation of intercellular jellying substance.[18] These two theories can be regarded as complementary and are not contradictory. It may be remembered that from their study of the effects of deficiency on dental and periodontal structure, E. W. Fish and L. J. Harris [17] concluded that with increasing degrees of deficiency there was increasing failure in the functional activities of the odontoblasts, ameloblasts, osteoblasts (cells laying down dentine, enamel, bone), and other similar formative cells. With a partial chronic deficiency of vitamin C there occurred a remarkable, irregular overgrowth of amorphously formed dentine, whereas in acute total deficiency no new tissue was laid down. Probably the irregular hyperostosis now described by Kodicek and Murray [15] may be given the same explanation as that offered by Fish and Harris [17] for the rather analogous overgrowth of irregular dentine in hypovitaminosis. Whereas in avitaminosis there is a complete loss of the specialised cell activity and hence failure to lay down the new tissues, in hypovitaminosis there is only partial loss of formative function and the new tissues laid down are irregularly organised. It seems probable that the influence of vitamin C in osteogenesis and in the repair of wounds can be explained along the same lines.

L. J. H.

2. ANTIBACTERIAL SUBSTANCES PRODUCED BY BACTERIA AND FUNGI.

Introduction.

The present considerable interest in the chemotherapeutic possibilities of antibacterial substances produced by bacteria and fungi is of recent origin, but the idea of using such substances for the treatment of bacterial infections

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[15] *Nature*, 1943, **151**, 395.

[16] L. J. Harris, *Brit. med. J.*, 1933, **2**, 367.

[17] E. W. Fish and L. J. Harris, *Phil. Trans.*, 1934, *B*, **223**, 489.

[18] S. B. Wolbach and P. R. Howe, *Arch. Path.*, 1926, **1**, 1.

is quite old. S. A. Waksman[1] and R. J. Dubos and R. D. Hotchkiss[2] have pointed out that bacterial antagonism was noticed by Pasteur, who thought of the possibilities of using this phenomenon for curative purposes. Reference should be made to Waksman's article for the numerous attempts dating from 1885 to employ bacterial products for therapeutic purposes. Of these attempts, that of R. Emmerich and O. Low[3] has attracted the most notice. They tried to use the antibacterial substances produced by *Ps. pyocyanea* against, in particular, *B. anthracis* infections. Their preparation was known as "pyocyanase" and appears to have been sold in Germany till at least as late as 1936.[4] Its efficacy is, however, very doubtful. A. Gratia and S. Dath[5] noticed that culture filtrates of certain actinomycetes had the power of dissolving some pathogenic organisms. Though they did not use their preparation directly for the treatment of infections, Gratia[6] prepared "mycolysates" of organisms such as staphylococci and maintained that vaccination with these solutions was beneficial in human diseases. A. Fleming[7] noted the existence of a bacterial inhibitor produced by the mould *Penicillium notatum*, which he termed "penicillin." He investigated the antibacterial properties of his penicillin-containing broth medium in some detail and suggested that it might form a useful "antiseptic" dressing for wounds,[8] but this was not followed up. Weiland[4] suggested that the antibacterial substance produced by certain types of *B. mesentericus* should be as effective as "pyocyanase," though he does not appear to have attempted to isolate or use it. R. J. Dubos[9] isolated from *B. brevis* an antibacterial material which was found later to contain two antibacterial substances, gramicidin and tyrocidine. The crude mixture of gramicidin and tyrocidine, called tyrothricin, has been tried fairly extensively as an application to superficial wounds infected with susceptible organisms, but its toxicity precludes its use parenterally.[10] Some success attended its use, but difficulties were encountered owing to its insoluble nature. Chain *et al.*[11] reported the results of a fresh investigation into the possibilities of the isolation of penicillin and the study of its properties. They obtained from culture filtrates of *Penicillium notatum* a preparation containing penicillin in a stable form and showed that it not only possessed a high antibacterial activity and inhibited the growth of many pathogenic bacteria but was remarkably non-

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[1] *Bact. Rev.*, 1941, **5**, 231.

[2] *Trans. Coll. Phys. Philadelphia*, 1942, **10**, 11.

[3] *Z. Hyg.*, 1899, **31**, 1; R. Emmerich, O. Low, and A. Korschun, *Zentr. Bakt. Par.*, 1902, 1 Abt. Orig., **31**, 1.

[4] P. Weiland, *Zentr. Bakt. Par.*, 1936, 1 Abt. Orig., **136**, 451.

[5] *Compt. rend. Soc. Biol.*, 1924, **91**, 1442; 1925, **92**, 461, 1125; **93**, 451; 1926, **94**, 1267.

[6] *Ibid.*, 1930, **104**, 1058; *Bull. Acad. roy. Méd. Belg.*, 1934, **14**, 285.

[7] *Brit. J. Exp. Path.*, 1929, **10**, 226.

[8] *J. Path. Bact.*, 1932, **35**, 831.

[9] *J. Exp. Med.*, 1939, **70**, 1, 11.

[10] C. H. Rammelkamp, *War Medicine*, 1942, **2**, 830; *J. Clin. Invest.*, 1941, **20**, 433; W. E. Herrell and D. Heilman, *ibid.*, p. 583; E. B. Schoenbach, J. F. Enders, and J. H. Mueller, *Science*, 1941, **94**, 217.

[11] E. Chain, H. W. Florey, A. D. Gardner, N. G. Heatley, M. A. Jennings, J. Orr-Ewing, and A. G. Sanders, *Lancet*, 1940, ii, 226.

toxic. They demonstrated on mice the potentialities of penicillin as a chemotherapeutic agent against systemic bacterial infections. Later,[12] penicillin was employed successfully on man.

Following these investigations it is fair to say that chemical interest in these substances is now largely conditioned by the thought that they may be of importance in medicine. It is certain that many organisms, both bacterial and fungal, produce substances active against pathogenic bacteria.[1,13] Waksman has suggested that the antibacterial substances produced by moulds and bacteria should be called antibiotics.[14, footnote, p. 290] The term has been used in this sense in the present review.

The natural antibiotics can be divided into two classes: (1) *Antibiotics which react with protoplasmic constituents and kill both bacterial and animal cells.* It would be convenient to restrict the term "antiseptic" to this type of substance. The antibiotics of the "antiseptic" type can be subdivided into those which are active against all types of pathogenic organisms, both gram-positive and gram-negative, and those which exert a selective action, usually against gram-positive organisms (*e.g.*, gramicidin, actinomycin A, citrinin). The cause of this selectivity is not yet fully understood. The selectivity may not be absolute; it has been shown that gramicidin acquires strong bactericidal activity against gram-negative bacteria in the presence of protamines.[15] The explanation offered for this "sensitisation" of gram-negative bacteria is that protamines remove phospholipids, which are known to inhibit the antibacterial action of gramicidin. This class of "antiseptic" antibiotics is useless as a source of new chemotherapeutic substances for general administration. It may, however, provide substances of use in local application, though even for this purpose antibiotics belonging to the following class are clearly preferable.

(2) *Antibiotics which react with substances having a specific significance in the bacterial cell only.* Some of these substances do not kill bacteria even in very considerable concentrations, merely arresting their division. The term "bacteriostatic" has been suggested for this class of antibiotic.[16] For the distinction between "antiseptics" and "bacteriostatics" the concentration at which only the bacteriostatic effect is observed is of primary importance, since many antiseptics have a merely bacteriostatic and not a killing action, when used in low concentrations.

The bacteriostatics so far found are predominantly active against gram-positive bacteria. They may be expected to be relatively non-toxic to animal cells. It is in this class of antibiotics that one can hope to find new chemotherapeutic agents for general administration and therefore of value

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[12] E. P. Abraham, E. Chain, C. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley, and M. A. Jennings, *Lancet*, 1941, ii, 177.

[13] W. H. Wilkins and G. C. M. Harris, *Brit. J. Exp. Path.*, 1942, **23**, 166; 1943, **24**, 141.

[14] S. A. Waksman, E. S. Horning, M. Welsch, and H. B. Woodruff, *Soil Science*, 1942, **54**, 281.

[15] B. F. Miller, R. Abrams, A. Dorfman, and M. Klein, *Science*, 1942, **96**, 428.

[16] A. D. Gardner and E. Chain, *Brit. J. Exp. Path.*, 1942, **23**, 123.

in the treatment of systemic infections. It should be clearly understood that any substance to be used chemotherapeutically must be so little toxic that a concentration sufficient to inhibit the growth of susceptible organisms can be maintained without harm in the blood and tissue fluids for days and even weeks. The fact that an antibacterial substance can be used locally does not furnish evidence that it can be used for general administration.

Relatively early in an investigation it is possible to know whether an antibacterial substance has any chemotherapeutic prospects. The simplest test so far devised depends on the observation of bacterial respiration (of staphylococci or *B. coli*) in the Barcroft–Warburg apparatus in the presence of the antibiotic. If respiration is rapidly abolished by the addition of the antibiotic to a final concentration of about 1 : 1000, one can say with certainty that, since the organisms have been killed at this concentration, the substance is an antiseptic which will be toxic to animal tissues. If, however, a preparation known to be strongly antibacterial produces little or no effect on the respiration, there is a good chance of the substance being important from a chemotherapeutic point of view.

Further observations should be made on: (1) The toxicity of the antibacterial substance to leucocytes.[12] When there is a wide gap between the concentration toxic to leucocytes and the dilution at which the substance is completely bacteriostatic, there is a good chance of the substance being useful, at least for local application.

(2) The effect of blood, pus and tissue extracts on the bacteriostatic activity. It is a serious disadvantage if these fluids depress the activity. The inhibition of antibacterial activity may be due to the chemical combination of the active substance with a tissue constituent or to an inhibitory mechanism similar to that of *p*-aminobenzoic acid for the sulphonamides.

(3) The toxicity to mice when injected intravenously. The mice should tolerate the injection of at least several milligrams of the antibacterial substance.

It is likely that any therapeutically active substance will be to a large extent excreted unchanged or little changed in the urine, since it may be expected not to combine with the tissue cells.

Only antibiotics which pass these biological tests can be expected to be effective as general chemotherapeutic agents and to be worth further investigation with mouse protection tests. Clearly it is impossible to forecast the value of any antibiotic for chemotherapeutic purposes until it has been purified at least sufficiently for the above-mentioned biological tests to be carried out.

In addition to the chemical investigation of the antibiotics themselves, a biochemical problem is involved in the elaboration of media for the growth of the responsible bacteria or fungi. It is known that the medium plays an essential part, for on some media good growth of a fungus can be obtained but no antibiotic, while on others there is a poor growth but active substances are produced. In addition, changes in the composition of the medium may induce a fungus to produce a different antibacterial substance. The elaboration of these media has at present much in common with cookery, and there is a wide field here for biochemical enquiry.

Another field of biochemical enquiry which has as yet received little attention is the study of the mode of action of the bacteriostatics, including the interesting phenomenon of the ability of susceptible bacteria to acquire resistance to increasing concentrations of many of these substances. Attention at the present time is being directed almost exclusively to the antibacterial effects of antibiotics. Several antibiotics are fungicides [1] and may be of use in the treatment of plant diseases. It is possible that the unusual biochemical mechanisms of the moulds and bacteria may produce substances active against protozoal and other infections of man. Only a negative result has so far been reported.[16a]

Antibiotics produced by Bacteria.

"*Pyocyanase.*"—Among the first antibacterial substances produced by bacteria to be studied chemically were those produced by *Ps. pyocyanea.* Concentrates of old culture-filtrates were found to contain substances bactericidal to a number of gram-positive and gram-negative bacteria and capable of lysing thick suspensions of *V. choleræ* and *B. anthracis*; these properties were attributed to the action of a bacteriolytic enzyme termed pyocyanase.[3] Recent investigations into the nature of pyocyanase have made it clear that the antibacterial activity of old culture-filtrates of *Ps. pyocyanea* is due to the presence of several substances, none of which is of enzymatic nature.[17] The blue dye pyocyanine and a yellow degradation product of this substance, α-hydroxyphenazine, are bactericidal and an as yet chemically undefined oil of acidic nature, soluble in chloroform and alcohol, is bacteriolytic. It brings about lysis, accompanied by gel formation, of thick suspensions of *V. choleræ* in dilutions as high as 1 : 10,000. Pyocyanine, like many basic dyes, is strongly bactericidal and also very toxic.[17, 18] The α-hydroxyphenazine, though less toxic, has a much lower antibacterial activity; it is chemically unstable and of low solubility. Too little is as yet known about the physiological, biological and chemical properties of the lytic substance to assess its value as a disinfectant; it is certainly too toxic for the treatment of systemic infections.

Gramicidin and Tyrocidine.—Dubos [9, 19, 20, 21] and his collaborators have shown that filtrates of a peptone culture of *B. brevis*, an ærobic spore-bearing organism originally isolated from the soil, contain antibacterial substances. The antibacterial material can be obtained either in a protein fraction, in which it is non-dialysable, soluble in water but insoluble in organic solvents,[2, 9]

[16a] H. J. Robinson, *J. Pharm. Exp. Therap.*, 1943, **77**, 70.

[17] (*a*) H. O. Hettche, *Klin. Woch.*, 1933, **12**, 1804; (*b*) *idem*, *Z. Immun.*, 1934, **83**, 499; (*c*) R. Schoental, *Brit. J. Exp. Path.*, 1941, **22**, 137.

[18] J. F. Fazekas, H. Colyer, S. Nesin, and H. E. Himwich, *Proc. Soc. Exp. Biol. Med.*, 1939, **42**, 446.

[19] R. J. Dubos and C. Cattaneo, *J. Exp. Med.*, 1939, **70**, 249.

[20] R. J. Dubos and R. D. Hotchkiss, *ibid.*, 1941, **73**, 629.

[21] R. D. Hotchkiss and R. J. Dubos, *J. Biol. Chem.*, 1941, **141**, 155.

or in a protein-free form in which it is dialysable, insoluble in water but soluble in organic solvents.[19, 20] The water-soluble form is obtained by acidification of the culture medium and extraction of the precipitate with neutral buffer. The form soluble in organic solvents but insoluble in water is obtained by extraction of the acid precipitate with alcohol. The alcohol-soluble fraction has been termed tyrothricin;[23] apparently it is present in the original culture filtrates in some combination with proteins, from which it can be liberated by means of proteolytic enzymes.[19, 20] Tyrothricin contains two antibacterial substances, gramicidin and tyrocidine, both of which have been obtained in the crystalline state.[22] Both substances are polypeptides resistant to the action of the ordinary proteolytic enzymes. Though of similar chemical constitution, gramicidin and tyrocidine have different chemical and biological properties. Gramicidin,[21] recrystallised from acetone, melts sharply at 230°, has a low $[\alpha]_D^{25°}$ of $+ 5°$ in 95% alcohol, is soluble in the lower alcohols, acetic acid and pyridine, moderately soluble in dry acetone and dioxan, almost insoluble in water, ether and hydrocarbons. It contains no free amino- or carboxylic groups but gives a crystalline flavianate and rufianate.[24, 25, 26] On acid hydrolysis, *l*-tryptophan, *d*-leucine, alanine and a 1 : 2-hydroxyamino-compound which is not an α-amino-acid have been obtained.[24, 25] Quantitative chromatographic analysis on silica gel columns of the acetyl derivatives of the amino-acid mixture obtained after acid hydrolysis of gramicidin [28] (partition chromatography technique of A. J. P. Martin and R. L. M. Synge [27]) shows that the gramicidin molecule contains 6 residues of leucine (mainly the *d*-isomer) and *l*-tryptophan, 5 of valine (optical configuration uncertain), 3 of *l*-alanine, 2 of glycine and 2 of the hydroxyamino-compound (*iso*serine ?). The minimum molecular weight calculated from the analytical data is 2790, *i.e.*, gramicidine is considered to be a cyclo-peptide with 24 amino-acid residues.[28] Molecular weight estimations by various methods give figures from 600—3000.[24, 25, 26] The presence of amino-acids of the *d*-configuration in hydrolysates both of gramicidin and of tyrocidine was demonstrated by the fact that oxygen uptake and ammonia liberation took place in the presence of the kidney enzyme *d*-amino-oxidase, which oxidises specifically amino-acids of the *d*-configuration.[29] Tyrocidine is a basic polypeptide which was crystallised as the hydrochloride. It melts unsharply at 240° (decomp.), has $[\alpha]_D^{25°} - 101°$ in 95% alcohol, is moderately soluble in methyl and ethyl alcohols, acetic acid and pyridine, sparingly soluble in water and acetone and insoluble in ether and hydrocarbons. On acid hydrolysis, *l*-tryptophan, tyrosine, phenylalanine, alanine, a dicarboxylic

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[22] R. D. Hotchkiss and R. J. Dubos, *J. Biol. Chem.*, 1940, **132**, 791, 793.

[23] *Idem, ibid.*, 1940, **136**, 803.

[24] R. D. Hotchkiss, *ibid.*, 1941, **141**, 171.

[25] H. N. Christensen, R. R. Edwards, and H. D. Piersma, *ibid.*, p. 187.

[26] M. Tishler, J. L. Stokes, N. R. Trenner, and J. B. Conn, *ibid.*, p. 197.

[27] (*a*) A. J. P. Martin and R. L. M. Synge, *Biochem. J.*, 1941, **35**, 1358. (*b*) A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *ibid.*, 1943, **37**, 79.

[28] A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *Biochem. J.*, 1943, **37**, 86.

[29] F. Lipmann, R. D. Hotchkiss, and R. J. Dubos, *J. Biol. Chem.*, 1941, **141**, 163.

amino-acid, ammonia and nitrogenous substances of undefined nature precipitable by phosphotungstic acid were obtained.[24, 25] Gordon, Martin, and Synge, using their partition chromatography technique, have isolated and identified (in the form of their acetyl derivatives) the following amino-acids from acid hydrolysis of tyrocidine: phenylalanine (predominantly the *d*-isomer), *l*-leucine, *l*-valine, *l*-proline, *l*-tyrosine, *l*-glutamic acid, *l*-ornithine, *l*-aspartic acid, tryptophan (optical configuration not determined).[29a] No alanine was found. Gramicidin is very active against practically all gram-positive bacteria with the exception of the acid-fast organisms, inhibiting their growth in concentrations of fractions of 1γ per c.c. It has no effect on most gram-negative bacteria, with the exception of gonococci and meningococci.[23, 30] Tyrocidine possesses $\frac{1}{25}$th—$\frac{1}{50}$th of the activity of gramicidin but inhibits both gram-positive and gram-negative bacteria. Gramicidin is stated to have a predominantly bacteriostatic action, tyrocidine a bactericidal action. Tyrocidine inhibits immediately, completely and irreversibly the respiration of streptococcal and staphylococcal suspensions. The effect of gramicidin on the respiration of staphylococcal suspensions is more complex.[30a] In the presence of ammonium ions, it depresses the respiration of staphylococci; in the presence of phosphate ions, it causes an increase of their oxygen uptake which may last for more than 2 hours; this stimulation is then followed by a considerable inhibition of the respiration. Almost complete inhibition of ærobic glycolysis of suspensions of lactobacillus by gramicidin has been reported.[31] Both gramicidin and tyrocidine are hæmolytic; hæmolysis by gramicidin is slow and does not occur in the presence of 1% glucose solution; that of tyrocidine is immediate and is not affected by glucose.[20, 32, 33] Serum inhibits the hæmolysis.[33a] Tyrocidine has a lytic effect on many bacteria; gramicidin causes no bacteriolysis.[2, 20] Gramicidin has little effect on the respiration of white blood cells,[2] whereas tyrocidine causes complete inhibition of respiration and disintegration of the cells. Gramicidin is toxic to spermatozoa, whose motility is destroyed in a dilution of 1 : 10,000,000[34] and to cells in tissue culture.[34a] Both gramicidin and tyrocidine are surface-active substances, their biological activity probably being at least to some extent due to this property. Tyrocidine precipitates proteins and its antibacterial activity is therefore greatly diminished in the presence of tissue fluids. Gramicidin has no marked effect on proteins, but its antibacterial activity is neutralised by phospholipids of the cephalin type,[2, 20, 31] so that it too suffers some reduction of activity in the presence of tissue fluids. Both

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[29a] A. H. Gordon, A. J. P. Martin, and R. L. M. Synge, *Biochem. J.*, 1943, **37**, 313.

[30] E. B. Schoenbach and L. R. Seidman, *Proc. Soc. Exp. Biol. Med.*, 1942, **49**, 108.

[30a] R. J. Dubos, R. D. Hotchkiss, and A. F. Coburn, *J. Biol. Chem.*, 1943, **146**, 421.

[31] Z. Baker, R. W. Harrison, and B. F. Miller, *J. Exp. Med.*, 1941, **74**, 621.

[32] D. Heilman and W. E. Herrell, *Proc. Soc. Exp. Biol. Med.*, 1941, **46**, 182.

[33] C. H. Rammelkamp and L. Weinstein, *ibid.*, 1941, **48**, 211.

[33a] F. C. Mann, D. H. Heilman, and W. E. Herrell, *ibid.*, 1943, **52**, 31.

[34] G. Henle and C. A. Zittle, *ibid.*, 1941, **47**, 193.

[34a] W. E. Herrell and D. Heilman, *Amer. J. Med. Sci.*, 1943, **205**, 157.

gramicidin and tyrocidine are very toxic when injected intravenously into mice and dogs,[2, 35, 35a] which is not surprising in view of the fact that they both combine with vital cell constituents. Neither gramicidin nor tyrocidine protects mice against systemic infections with even the most sensitive bacteria.[20, 35a, 36] Injected at the site of the infection, gramicidin protects mice against pneumococci;[20, 35a] these are, however, essentially *in vitro* conditions. Successful results are reported from the application of tyrothricin solutions to infected surfaces or cavities in man [10] and in the treatment of bovine mastitis.[37] In many of their physicochemical and biological properties gramicidin and tyrocidine resemble closely the anionic and cationic detergents.[2, 31, 38, 38a] The basic tyrocidine has the properties of a cationic detergent, being active against both gram-positive and gram-negative bacteria; gramicidin resembles the anionic type which acts predominantly against gram-positive bacteria. The mode of action of the detergents on bacteria is not fully understood,[15, 31, 38, 39] but there seems little doubt that the antibacterial activity of gramicidin and tyrocidine has its cause in similar factors. probably acting in combination, among which may be denaturation of proteins [39] and lipoproteins and reactions with phospholipids. The view has been stated that tyrocidine is a general protoplasmic poison, whereas gramicidin has a more specific effect on certain reactions in the bacterial cell metabolism.[2, 20] It seems to the reviewers, however, that both gramicidin and tyrocidine fall into the class of antiseptics and should be regarded as general protoplasmic poisons, since both substances have been shown to combine with vital cell constituents occurring in all types of cells.

H 1.—An antibacterial substance active against gram-positive bacteria has been isolated by Hoogerheide from an ærobic spore-forming organism and has been termed H 1.[40a, b, c] Its chemical and biological properties leave little doubt that it is identical with or very closely related to gramicidin.[21]

Other Antibacterial Substances produced by Spore-bearing Aerobic Organisms.—Many strains of the common spore-forming bacteria produce substances active against *C. diphtheriæ*, staphylococci and. in some cases, against gram-negative bacteria such as *B. coli*.[4, 41, 42, 43, 44] Relatively little

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[35] C. M. MacLeod, G. S. Mirick, and E. C. Curnen, *Proc. Soc. Exp. Biol. Med.*, 1940, **43**, 461.

[35a] H. J. Robinson and O. E. Graessle, *J. Pharm. Exp. Therap.*, 1942, **76**, 316.

[36] R. J. Dubos, *Ann. intern. Med.*, 1940, **13**, 2025.

[37] R. B. Little, R. J. Dubos, and R. D. Hotchkiss, *J. Amer. Vet. Med. Assoc.*, 1941, **98**, 189.

[38] Z. Baker, R. W. Harrison, and B. F. Miller, *J. Exp. Med.*, 1941, **73**, 249; 1941, **74**, 611, 621.

[38a] D. Heilman and W. E. Herrell, *Proc. Soc. Exp. Biol. Med.*, 1941, **47**, 480.

[39] R. Kuhn and H. J. Bielig, *Ber.*, 1940, **73**, 1080.

[40] (*a*) J. C. Hoogerheide, *J. Franklin Inst.*, 1940, **229**, 677; (*b*) *idem*, *J. Bact.*, 1940, **40**, 325; (*c*) E. McDonald, *J. Franklin Inst.*, 1940, **229**, 805.

[41] E. G. Pringsheim, *Zentr. Bakt. Par.*, 1920, 2. Abt. Orig.. **51**, 72.

[42] H. Much, *Med. Klinik*, 1924, **20**, 347.

[43] H. Franke and A. Ismet, *Zentr. Bakt. Par.*, 1. Abt. Orig., 1926, **99**, 570.

[44] H. Auerswald, *ibid.*, 1938, **142**, 32.

chemical work has as yet been done on their isolation. H. O. Hettche and B. Weber[45] claim that one species produces *iso*valeric and oleic acids, to which they attribute the antibacterial effect.

Dubos and Hotchkiss[20] have studied a number of organisms of this type and have isolated substances which appear to be identical with gramicidin and tyrocidine.

Antibiotics produced by Fungi.

1. *Antibiotics produced by* Penicillia.—*Penicillin.* In 1929 Fleming[7] noticed the presence of a substance with a powerful antibacterial action, particularly against gram-positive cocci, in culture filtrates of *Penicillium notatum* and termed it penicillin. He did not isolate the substance but employed culture filtrates containing penicillin for the preparation of selective media.[7, 8] He suggested that the crude penicillin-containing broth might be used for the local treatment of indolent septic wounds.[8] P. W. Clutterbuck, R. Lovell, and H. Raistrick[46] showed that penicillin could be obtained on a synthetic medium and that it was a labile substance which could be removed from the acidified culture medium by ether. Apart from a paper by R. D. Reid[47] in which the instability of penicillin was emphasised, little further interest seems to have been taken in penicillin until, in 1940, Chain *et al.*[11] obtained from the culture medium of *Penicillium notatum* a preparation which contained penicillin in a stable form suitable for study of its pharmacological, antibacterial and chemical properties, and ultimately for chemotherapeutic experiments. The antibacterial activity of penicillin—like that of other physiologically very active substances—is measured biologically and is expressed in "Oxford units."[12, 48] The "ring" method[12] (see [48a] for a more detailed description) or the serial dilution technique[48b] is used. Penicillin with an activity of 450—500 units per mg. was found to inhibit the growth of *staphylococcus aureus* in a dilution of 1 : 25,000,000.[48] The sensitivity of a number of different bacterial species to a penicillin preparation with an activity of 250 units per mg. has been investigated.[48, 49] The antibacterial activity of penicillin is independent of the number of bacteria within wide limits.[12] Penicillin is a nitrogenous acid; considerable progress has been made in the elucidation of its structure, but for security reasons the results cannot be published at present. Previously suggested molecular formulæ for

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[45] *Arch. Hyg.*, 1939, **123**, 69.

[46] *Biochem. J.*, 1932, **26**, 1907.

[47] *J. Bact.*, 1935, **29**, 215.

[48] H. W. Florey and M. A. Jennings, *Brit. J. Exp. Path.*, 1942, **23**, 120.

[48a] J. W. Foster and H. B. Woodruff, *J. Bact.*, 1943, **46**, 187; N. G. Heatley, *Biochem. J.*, 1944, **38**, 61.

[48b] J. W. Foster, *J. Biol. Chem.*, 1942, **144**, 285; J. W. Foster and B. L. Wilker, *J. Bact.*, 1943, **46**, 377; U. Wilson, *Nature*, 1943, **152**, 475; C. H. Rammelkamp, *Proc. Soc. Exp. Biol. Med.*, 1942, **51**, 95.

[49] G. L. Hobby, K. Meyer, and E. Chaffee, *Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 277.

penicillin [50, 51, 52] are incorrect. Penicillin is a strong acid which is easily soluble in ether, chloroform, esters, alcohols and ketones, sparingly soluble in water, benzene and halogenated paraffins, and insoluble in petrol. Its alkali and alkaline earth salts are extremely soluble in water; the barium salt is also easily soluble in methyl alcohol, dioxan and pyridine, but insoluble in ether, esters, etc.[50] The barium salt in water is dextrorotatory.[53] Penicillin is stable in water only in the form of its salts between pH 5 and 7; it is quickly inactivated by H^+ ions and OH^- ions with the formation of new titratable groups.[50] Both free acid and salts are inactivated by primary alcohols, in particular methyl alcohol. Penicillin is inactivated by various metal ions, in particular copper, zinc, cadmium, and lead. It is also inactivated by oxidising agents but is fairly stable towards reducing agents. Ketonic reagents also cause inactivation.[50] The great sensitivity of penicillin to most chemical reagents has limited considerably the choice of purification methods. Distribution between solvents, treatment with aluminium and chromatography on Brockmann alumina have led to preparations of 1000 units per mg.[53] Partition chromatography on silica gel containing an inorganic base such as barium carbonate has also led to far-reaching purification.[51] A potency of 250 units per mg. has been obtained by distribution between water and solvents alone.[54] The preparations of Abraham and Chain have no characteristic absorption,[55] either in the visible or in the ultra-violet region; the preparations of Catch *et al.*[51] show an absorption band at 2650 A. ($E^{1\%}_{1\,\mathrm{cm.}}$ *ca.* 390) which is unaffected by aluminium-amalgam treatment. On inactivation of penicillin with dilute acid at room temperature and subsequent extraction with butyl alcohol a crystalline dextrorotatory derivative, termed penillic acid, has been obtained.[55a] On hydrolysis at 100° in acid solution penicillin quickly loses 2 mols. of carbon dioxide per barium atom; [50] in alkaline solution carbon dioxide is also liberated. The acid hydrolysate of penicillin gives a blue coloration with the ninhydrin reagent,[51] [53] and amino-nitrogen is liberated under the conditions of the van Slyke method. With mercuric chloride a characteristic amino-acid, termed penicillamine, is precipitated from acid hydrolysates of penicillin.[53] It has strong reducing power, reducing iodine reversibly in acid solution, gives a transient blue coloration with ferric chloride, a blue-violet coloration with the ninhydrin reagent, and contains all its nitrogen in the form of amino-nitrogen. The formula suggested for penicillamine [53] is incorrect.

Penicillin is predominantly a bacteriostatic agent, for even in high concentrations it has no inhibiting effect on the respiration of staphylococcal

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[50] E. P. Abraham and E. Chain, *Brit. J. Exp. Path.*, 1942, **23**, 103.

[51] J. R. Catch, A. H. Cook, and I. M. Heilbron, *Nature*, 1942, **150**, 633.

[52] E. P. Abraham, W. Baker, E. Chain, H. W. Florey, E. R. Holiday, and (Sir) R. Robinson, *ibid.*, 1942, **149**, 356.

[53] E. P. Abraham, W. Baker, E. Chain, and R. Robinson, *ibid.*, 1943, **151**, 107.

[54] K. Meyer, E. Chaffee, G. L. Hobby, M. H. Dawson. E. Schwenk, and G. Fleischer, *Science*, 1942, **96**, 20.

[55] E. R. Holiday, *Brit. J. Exp. Path.*, 1942, **23**, 115.

[55a] W. M. Duffin and S. Smith, *Nature*, 1943, **151**, 251.

suspensions.[12] Hobby *et al.*[56] maintain that, under certain conditions, it may exert a slow bactericidal action on *streptococcus hæmolyticus*. It appears to have the specific effect of arresting the division of bacteria; certain organisms such as *S. typhi* produce elongated forms when grown in its presence.[57] Though penicillin is chemically a highly reactive substance, it does not react with tissue constituents; organ-extracts and autolysates, protein hydrolysates, blood and pus do not significantly reduce its antibacterial activity.[12, 49] The antibacterial activity can, however, be destroyed by enzymes present in certain bacteria, both penicillin-sensitive and non-sensitive.[58] As it does not react with tissue constituents, its toxicity is low. The intravenous injection of doses as large as 20 mg. of sodium penicillin containing 325 units per mg. is tolerated without symptoms by mice.[48] Hobby *et al.*[59] found that the dose lethal to an 18 g. mouse, injected intravenously, was 30 mg. of sodium penicillin or 18 mg. of ammonium penicillin, of 250 units per mg. Leucocytes are not killed quickly by a dilution of even 1 : 100 of material containing 250 units per mg.[48] It has been a fortunate circumstance that even crude penicillin preparations containing not more than 10% of penicillin can be safely used on man in large doses.[12, 60a, b] The chemotherapeutic properties of penicillin were first demonstrated on mice infected with *Staph. aureus*, *Strept. hæmolyticus* and *Cl. septicum*. Almost complete protection was afforded to these animals when infected intraperitoneally or intramuscularly by subcutaneous injections of penicillin at frequent intervals.[12] This was later confirmed by Hobby *et al.*[59] The observations on mice were followed by the investigation of its action on natural infections in man. The first clinical results reported [12] have been amply substantiated [60a, b, c, d, e] and little doubt can now remain that penicillin is both the most effective and the least toxic chemotherapeutic agent against bacteria at present known. Perhaps in the future chemical modification of the penicillin molecule may be able to overcome its undesirable property of rapid excretion by the kidneys, and means may be found of making it more stable towards agents which at present destroy its activity. Chemical modifications may also be active against a greater range of bacteria.

Gliotoxin. An antibacterial substance with the possible composition $C_{14}H_{16}O_6N_2S_2$ was isolated from culture filtrates of *P.* (*Gliocladium*) *fimbriatum* by R. Weindling and O. H. Emerson.[61] It has a decomposition point of 219—222° and $[\alpha]_D^{19°}$ −239° in chloroform; is moderately soluble in acetone

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[56] G. L. Hobby, K. Meyer, E. Chaffee, *Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 281.

[57] A. D. Gardner, *Nature*, 1940, **146**, 837.

[58] E. P. Abraham and E. Chain, *ibid.*, p. 837.

[59] G. L. Hobby, K. Meyer, and E. Chaffee, *Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 285.

[60] (*a*) M. E. Florey and H. W. Florey, *Lancet*, 1943, i, 387; (*b*) C. S. Keefer, F. G. Blake, E. K. Marshall, J. S. Lockwood, and W. B. Wood, *J. Amer. Med. Assoc.*, 1943, **122**, 1217; (*c*) A. M. Clark, L. Colebrook, T. Gibson, M. L. Thomson, and A. Foster, *Lancet*, 1943, i, 605; (*d*) D. C. Bodenham, *ibid.*, 1943, ii, 725; (*e*) M. E. Florey and R. Williams, *ibid.*, 1944, i, 73.

[61] *Phytopath.*, 1936, **26**, 1068; **27**, 1175.

and chloroform, less soluble in hot benzene and hot alcohol, sparingly in cold alcohol and ether, and very sparingly in water. The chemical nature of the active substance has not yet been elucidated. It is active against gram-positive and gram-negative bacteria in concentrations of 1 : 1,000,000 to 1 : 100,000, but is toxic to animals in doses of 50—75 mg. per kg. body weight.[62]

Penicillic acid. This substance was first isolated by C. L. Alsberg and O. F. Black from culture filtrates of *Penicillium puberulum.*[63] Oxford and Raistrick found later that it was produced in considerable amounts by *Penicillium cyclopium.* J. H. Birkinshaw, A. E. Oxford, and H. Raistrick established its constitution as γ-keto-β-methoxy-δ-methylene-Δ^{α}-hexenoic acid.[64] Its inhibitory effect on the growth of yeast and *B. coli* was noticed by Alsberg and Black, who appear to be the first investigators to have isolated from fungi an antibiotic active against a pathogenic bacterium; they also made some pharmacological observations. A. E. Oxford, H. Raistrick, and G. Smith [65] and Oxford [66] showed that penicillic acid possessed antibacterial action against both gram-negative and gram-positive bacteria, inhibiting their growth in concentrations of 1 : 100,000 to 1 : 50,000. It reacts with ammonia and substances containing amino-groups such as amino-acids, peptone, *p*-aminobenzoic acid, with a considerable diminution of its antibacterial power.[67] Subcutaneous injection of 7 mg. kills mice, and 5 mg. causes toxic symptoms.[63] The substance appears to be a protoplasmic poison, its reactivity with amino-groups probably being the cause of its antibacterial and toxic action.

Claviformin (see also patulin and clavacin; below). The antibacterial properties of culture filtrates of *Penicillium claviforme* were established by Wilkins and Harris.[13] A substance with antibacterial properties against both gram-negative and gram-positive bacteria, acting in dilutions of 1 : 160,000 to 1 : 40,000, was obtained from these filtrates in the crystalline state by E. Chain, H. W. Florey, and M. A. Jennings and was termed claviformin.[68] The formula for this substance calculated from its elementary composition was given as $C_9H_8O_5$, but molecular weight determinations based on crystallographic *X*-ray data (D. Crowfoot and B. Low) [69] have shown that the formula $C_7H_6O_4$ is more probable. It has a melting point of 110°, is fairly soluble in water, very soluble in alcohol and acetone, moderately soluble in ether and chloroform and insoluble in petrol. Though its chemical constitution was not investigated, it was shown to be a neutral substance with strongly reducing properties. Its antibacterial activity is quickly destroyed at pH 10 at 37°, but at pH 2 it withstands boiling for 30 minutes. With ammonia and substances containing amino-groups, such as amino-acids and peptone, it reacts with the formation of yellow solutions. Serum inactivates it. It is bactericidal, causing complete

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[62] J. D. Dutcher, *J. Bact.*, 1941, **42**, 815.

[63] *U.S. Dep. Agric. Bur. Plant Ind. Bull.*, 1913, No. 270.

[64] *Biochem. J.*, 1936, **30**, 394.

[65] *Chem. and Ind.*, 1942, **61**, 22.

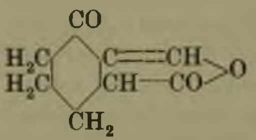
[66] *Ibid.*, p. 48.

[67] A. E. Oxford, *Biochem. J.*, 1942, **36**, 438.

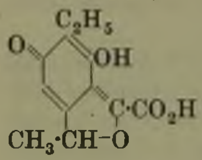
[68] *Brit. J. Exp. Path.*, 1942, **23**, 203.

[69] *Lancet*, 1944, i, 113.

inhibition of the respiration of *B. coli* suspensions. Toxicity to leucocytes is shown by the fact that it kills them in a dilution of 1 : 800,000, and it is also very toxic to mice, doses of 0·2 mg. being lethal. It is obviously a general protoplasmic poison, reactivity with amino-groups being a possible cause of its antibacterial and toxic action.



Patulin. Recently Raistrick *et al.*[70] have isolated an antibiotic from culture filtrates of *Penicillium patulum* which they name patulin. This substance was subsequently shown to be identical with claviformin.[71] The constitution of claviformin (patulin) was established by Raistrick *et al.* through degradation. It was shown to be a pyrone derivative to which the annexed formula or a tautomeric structure was assigned. Raistrick *et al.* state that the antibiotic has a beneficial effect in the treatment of the common cold, but another group of workers [72] has failed to obtain favourable results.



Citrinin and spinulosin. The antibacterial effect of quinones is a well-established fact.[73a, b, c, d, e] Raistrick and his colleagues have shown that the lower fungi produce several quinones and quinonoid substances. Two of these, citrinin and spinulosin, are produced by penicillia, *Penicillium citrinum* and *Penicillium spinulosum* respectively, and were shown to exert antibacterial activity predominantly against gram-positive organisms.[74, 75] The annexed formula is given for citrinin,[76c] whilst spinulosin has been shown to be 3 : 6-dihydroxy-4-methoxy-2 : 5-toluquinone.[76a, b] On testing a number of derivatives of benzoquinone and toluquinone with hydroxy-, methoxy- and hydroxy-methoxy-substituents, A. E. Oxford [77] found that the introduction of a hydroxy-group into the quinone nucleus often decreases, and that of a methoxy-group often considerably increases, its antibacterial activity. Quinones which react with proteins and amino-acids [67, 73c] are powerful protoplasmic poisons, and their practical value in medicine is therefore necessarily limited.

Notatin. A glucose dehydrogenase, which converts glucose into gluconic acid with the formation of hydrogen peroxide, has been found in culture

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[70] J. H. Birkinshaw, A. Bracken, M. Greenwood, W. E. Gye, W. A. Hopkins, S. E. Michael, and H. Raistrick, *ibid.*, 1943, ii, 625.

[71] E. Chain, H. W. Florey, and M. A. Jennings, *ibid.*, 1944, i, 112.

[72] C. H. Stuart-Harris, A. E. Francis, and J. M. Stansfield, *ibid.*, 1943, ii, 684.

[73] (*a*) G. T. Morgan and E. A. Cooper, *Biochem. J.*, 1921, **15**, 587; (*b*) E. A. Cooper and G. E. Forstner, *ibid.*, 1924, **18**, 941; (*c*) E. A. Cooper and R. B. Haines, *ibid.*, 1928, **22**, 317; (*d*) G. T. Morgan and E. A. Cooper, *J. Soc. Chem. Ind.*, 1924, **43**, 352T; (*e*) E. A. Cooper and S. D. Nicholas, *ibid.*, 1927, **46**, 59T.

[74] H. Raistrick and G. Smith, *Chem. and Ind.*, 1941, **60**, 828.

[75] A. E. Oxford, *ibid.*, 1942, **61**, 128.

[76] (*a*) W. K. Anslow and H. Raistrick, *Biochem. J.*, 1938, **32**, 687; (*b*) *idem*, *ibid.*, p. 803; (*c*) F. P. Coyne, H. Raistrick, and R. Robinson, *Phil. Trans.*, 1931, *B*, 297.

[77] *Chem. and Ind.*, 1942, **61**, 189.

filtrates of a strain of *Penicillium notatum* and has been termed notatin.[78] This enzyme inhibits the growth of many bacteria through hydrogen peroxide formation. Since it is inactive in the presence of catalase, it is unlikely to have therapeutic uses. Substances very similar to and probably identical with notatin have been described under the names of penatin [79] and penicillin B.[80, 81]

2. *Antibiotics produced by Aspergilli.—Penicillin-like antibiotics.* Antibiotics closely resembling penicillin in their chemical and biological properties have been isolated from culture filtrates of two aspergilli, *Aspergillus flavus* [82] and *Aspergillus giganteus*.[83] It is of interest to note that the production of penicillin is not limited to the species *Penicillium notatum* or even to the genus *Penicillium*.

Aspergillic acid. Culture filtrates of a strain of *Aspergillus flavus* have been shown to exhibit antibacterial activity.[84a, b, c, 85] A crystalline antibiotic, termed aspergillic acid, has been isolated from them.[84a] It has a melting point of 93°, is optically active ($[\alpha]_D = +14°$), and analysis and molecular weight determination agree with the formula $C_{12}H_{20}O_2N_2$. It possesses one hydroxy-group, and its absorption spectrum shows a characteristic band at 3250 A. It can be distilled with steam or in a vacuum without loss of biological activity and is stable towards acid and alkali.[86] It shows antibacterial activity against both gram-positive and gram-negative organisms,[84c, 87] but appears to be too toxic to be of use in systemic bacterial infections.

Fumigacin and clavacin. The isolation of two new antibacterial substances from *Aspergillus fumigatus* and *Aspergillus clavatus*, designated *fumigacin* and *clavacin*, has been reported by Waksman *et al.*[88a, b] Fumigacin has been obtained crystalline, melts at 185—187°, and is sparingly soluble in water but soluble in ether and chloroform; it is recrystallised from alcohol. It contains 62·7% of C and 3·7% of N; no further details about its chemical properties are as yet available.[88b] It is toxic to mice, 1 mg. killing a 20 g. mouse when injected intraperitoneally. (See note on p. 203.) Clavacin is identical with an antibiotic previously extracted by B. P. Wiesner from

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[78] C. E. Coulthard, R. Michaelis, W. F. Short, G. Sykes, G. E. H. Skrimshire, A. F. B. Standfast, J. H. Birkinshaw, and H. Raistrick, *Nature*, 1942, **150**, 634.

[79] W. Kocholaty, *J. Bact.*, 1942, **44**, 143; 1943, **46**, 313; *Science*, 1943, **97**, 186.

[80] E. C. Roberts, C. K. Cain, R. D. Muir, F. J. Reithel, W. L. Gaby, J. T. van Bruggen, D. M. Homan, P. A. Katzman, L. R. Jones, and E. A. Doisy, *J. Biol. Chem.*, 1943, **147**, 47.

[81] *Idem, ibid.*, 1943, **148**, 365.

[82] M. T. Bush and A. Goth, *J. Pharm. Exp. Therap.*, 1943, **78**, 164.

[83] F. J. Philpot, *Nature*, 1943, **152**, 725.

[84] (*a*) E. C. White, *Science*, 1940, **92**, 127; (*b*) E. C. White and J. H. Hill, *J. Bact.*, 1942, **43**, 12; (*c*) *idem, ibid.*, 1943, **45**, 433.

[85] G. A. Glister, *Nature*, 1941, **148**, 470.

[86] A. E. O. Menzel, O. Wintersteiner, and G. Rake, *J. Bact.*, 1943, **46**, 109.

[87] H. Jones, G. Rake, and D. M. Hamre, *ibid.*, 1943, **45**, 461.

[88] (*a*) S. A. Waksman, E. S. Horning, and E. L. Spencer, *Science*, 1942, **96**, 202; (*b*) *idem, J. Bact.*, 1943, **45**, 233.

A. clavatus[89] and has recently been shown to be identical with claviformin (patulin).[89a, b] Claviformin is also produced by *A. giganteus.*[89c]

Fumigatin. This substance is a quinone produced by *Aspergillus fumigatus.* It is 3-hydroxy-4-methoxy-2 : 5-toluquinone.[76a, b] Its antibacterial activity has been investigated by A. E. Oxford.[75]

Helvolic acid. Wilkins and Harris[13] found that culture filtrates of *Aspergillus fumigatus, mut. helvola*, possessed antibacterial activity. Following up this observation, E. Chain, H. W. Florey, M. A. Jennings, and T. I. Williams[90] isolated in the crystalline state an antibiotic which they termed helvolic acid. Elementary analysis shows that this substance contains C, H and O only. Crystallographic *X*-ray data (Crowfoot and Low, unpublished results) and molecular weight determinations in camphor give molecular weight values from 510 to 560. From these figures and those of the elementary analysis the most probable empirical formula for helvolic acid is $C_{32}H_{44}O_8$. Helvolic acid is a colourless monobasic acid, m. p. about 212° after crystallisation from glacial acetic acid. It is lævorotatory. The free acid is soluble in ether, chloroform, esters, glacial acetic acid, pyridine, slightly soluble in benzene, very sparingly soluble in water. With diazomethane, helvolic acid gives a crystalline methyl ester, m. p. about 261°. Helvolic acid can be heated at 100° for 10 minutes at pH 2, 7 or 10 without diminution of its antibacterial activity. N-Alkali causes slow inactivation. Helvolic acid acts mainly against gram-positive bacteria, but its action is affected by the size of the inoculum, being less in the presence of a large number of bacteria. Thus the titre for complete inhibition of *Staph. aureus* may be changed from 1 : 80,000 to 1 : 1,280,000 by a thousandfold dilution of the culture. Its action is not diminished by blood, serum, peptone or *p*-aminobenzoic acid, but yeast extracts and to a lesser degree pus contain substances which reduce its activity. Helvolic acid does not affect the oxygen uptake of staphylococcal suspensions at a dilution of 1 : 1000; its antibacterial action is therefore predominantly bacteriostatic. Intravenous injection of 10 mg. into a 20 g. mouse is lethal, but 4 mg. are tolerated without any apparent effect. Doses as large as 20 mg. administered by mouth produce no symptoms, though it is absorbed from the alimentary tract. However, repeated injections into mice during several days produce severe liver damage. It is excreted in the urine and bile. Leucocytes are not affected by helvolic acid in a concentration of 1 : 1600.

In spite of its low toxicity to leucocytes and its high bacteriostatic power helvolic acid does not give complete protection to mice against infections with staphylococci and streptococci, though it causes a considerable prolongation of life. Possibly the specific toxic effect of helvolic acid on the liver is one of the factors responsible for its failure to act as an effective

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[89] *Nature*, 1942, **149**, 356.

[89] (*a*) F. Bergel, A. L. Morrison, A. R. Moss, R. Klein, H. Rinderknecht, and J. L. Ward, *Nature*, 1943, **152**, 750; (*b*) I. R. Hooper, H. W. Anderson, P. Skell, and H. E. Carter, *Science*, 1944, **89**, 16; (*c*) H. W. Florey, M. A. Jennings, and F. J. Philpot, *Nature*, 1944, **153**, 139.

[90] *Brit. J. Exp. Path.*, 1943, **24**, 108.

chemotherapeutic agent. Unless the molecule of helvolic acid can be modified chemically in such a manner that it becomes less toxic to liver tissue, it will have no significance as a general chemotherapeutic agent, though it may be useful for local application in wounds.

3. *Antibiotics produced by Actinomycetes.—Actinomycetin.* Many actinomycetes are known to produce antibacterial substances.[1, 14, 92b] In culture filtrates of various actinomycetes bacteriolytic substances, termed actinomycetin, have been the subject of numerous studies by Gratia[6] and Welsch.[91, 92a, b] Welsch[92a, b] has shown that culture filtrates of an unspecified strain of actinomyces contain a protein with enzymatic properties capable of lysing suspensions of dead (but not living) pneumococci and streptococci. In addition ether-extractable bactericidal substances have been found. The bacteriolytic effect of actinomycetes on gram-positive bacteria appears to be due to the combined action of both types of substances.

Actinomycin A and B. S. A. Waksman and H. B. Woodruff isolated two antibacterial factors from *Actinomyces antibioticus.* These are termed actinomycin A and B.[93a, b, c] Actinomycin A, which has been obtained crystalline, is a red pigment, m. p. 250°, soluble in chloroform, benzene and alcohol, and slightly soluble in water and ether.[94] It is stated to be a polycyclic nitrogenous compound with a molecular weight of 768—1000. It exhibits a characteristic absorption spectrum in visible and ultra-violet light, and a quinonoid group which is reduced by hydrosulphite and reoxidised by air forms part of its structure. This quinonoid group may be responsible for its antibacterial action (see above, antibacterial action of quinones). In alcohol–water solution it is stable to boiling for 30 mins. but is destroyed by alkali in the cold and by acid on boiling. It has a high antibacterial power, particularly against gram-positive organisms, inhibiting the growth of *S. lutea* and *B. subtilis* in dilutions of 1 : 100,000,000 and 1 : 10,000,000 respectively. Its action is stated to be predominantly bacteriostatic, but this may only hold for low concentrations, for in higher concentrations it has been shown to have a pronounced bactericidal effect.[95] It has the properties of a general protoplasmic poison and is lethal to mice in a dose of 10γ when injected intraperitoneally.[96] The properties of actinomycin B, which is a colourless bactericidal substance active against both gram-positive and gram-negative organisms, have not yet been studied in detail.

Proactinomycin. From culture filtrates of an organism closely related to

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[91] *Compt. rend. Soc. Biol.*, 1936, **123**, 1013; 1937, **124**, 573, 1240; **125**, 1053; **126**, 244, 247, 1254; 1938, **127**, 347; **128**, 795, 1172, 1175; 1939, **130**, 104, 797, 800; **131**, 1296.

[92] (*a*) M. Welsch, *J. Bact.*, 1941, **42**, 801; (*b*) *idem, ibid.*, 1942, **44**, 571.

[93] (*a*) *J. Bact.*, 1940, **40**, 581; (*b*) *ibid.*, 1941, **42**, 231; (*c*) *Proc. Soc. Exp. Biol. Med.*, 1940, **45**, 609.

[94] S. A. Waksman and M. Tishler, *J. Biol. Chem.*, 1942, **142**, 519.

[95] S. A. Waksman and H. B. Woodruff, *J. Bact.*, 1942, **44**, 373.

[96] S. A. Waksman, H. Robinson, H. J. Metzger, and H. B. Woodruff, *Proc. Soc. Exp. Biol. Med.*, 1941, **47**, 261.

the actinomycetes and designated as proactinomycin, Gardner and Chain[16] have isolated an organic base with a powerful antibacterial effect, predominantly against gram-positive bacteria and the Neisseriæ. The substance, proactinomycin, which is stable in acid and alkali at room temperature, loses a small part of its antibacterial activity at pH 2 and 7 when kept at 100° for 10 minutes and the greater part of its activity at pH 10. It has not yet been obtained pure and its chemical properties have not been studied in detail. The substance is fairly toxic to mice, which is not surprising in view of its basic nature. The intravenous injection of 5 mg. was immediately fatal; 2 mg. caused toxic symptoms and, in a minority, death; 1 mg. had no effect.

Streptothricin. An antibacterial substance termed streptothricin, active in a concentration of 1 : 100,000 against both gram-positive and gram-negative bacteria, has been obtained by S. A. Waksman and H. B. Woodruff[97] from a soil actinomyces closely resembling *Actinomyces lavendulæ.* Waksman[98] has studied the conditions of its biological production; it is formed on protein digest media and good aeration is essential for its production. Streptothricin is a N-containing base, soluble in water and alcohol but insoluble in ether, chloroform and light petroleum. It is precipitated by protein precipitants, but protein-free preparations with a nitrogen content of 2—3% have been obtained. It has not yet been obtained in the crystalline state and few data are given on its chemical and biological properties. It is stated[98] to possess a low toxicity to animals (no figures are given) and to prevent the growth of *Brucella abortus in vivo.*[99]

The systematic study of antibiotics produced by bacteria and fungi, though still in its early stages, has already led to the discovery of a number of new types of antibacterial substances which have considerable chemical, biochemical and medical interest. Apart from their significance as local antiseptics, the crystalline polypeptides gramicidin and tyrocidine may be useful tools in the study of protein structure. The studies on penicillin have shown that it has great antibacterial power combined with low toxicity to animals and so is of considerable interest to medicine. Many of the other antibiotics so far isolated have interesting chemical features. For instance, proactinomycin is an antibiotic with alkaloid-like properties, gliotoxin is a sulphur-containing substance, actinomycin A is a quinone with much more powerful antibacterial activity than the normal quinones, helvolic acid is a relatively non-toxic bacteriostatic containing only C, H and O, but of complex nature. Obviously it will be of immediate importance to elucidate the chemical constitution of these antibiotics. In view of the results achieved so far the hope seems justified that further studies of antibiotics produced from bacteria, fungi and other natural sources will reveal the existence of

[97] *Proc. Soc. Exp. Biol. Med.*, 1942, **49**, 207.

[98] *J. Bact.*, 1943, **46**, 299.

[99] H. J. Metzger, S. A. Waksman, and L. H. Pugh, *Proc. Soc. Exp. Biol. Med.*, 1942, **51**, 251.

more new types of antibacterial substances with interesting chemical and biological properties.

E. C.
H. W. F.

3. VIRUSES.

Viruses have not been reviewed in this Report in any detail since 1937. At that time the subject was beginning to attract much attention, and at the moment the publications cover many fields of research. In consequence it is only possible to indicate the scope of the subject. A selection of the reviews on the various aspects of virus research is listed below.[1, 2, 3, 4]

The Isolation of Viruses.

Properly speaking, the virus of vaccinia was the first virus to be isolated in a form approximating to purity,[5] but, as it is a very large particle and easily visible under ordinary microscopes, this feat did not attract such attention as did the isolation of the tobacco mosaic virus by W. M. Stanley in 1935.[6] Stanley's success followed a detailed investigation of the properties of the infectious agent and would probably have proved impossible had it not been for the discovery of the local lesion technique for the estimation of virus activity by F. O. Holmes [7] and improvements by G. Samuel and J. G. Bald.[8] Prior to Stanley many attempts had been made to isolate this virus, but the various claims to have isolated the greater part of the virus from infectious sap were refuted by the discovery that the latter contained the altogether unexpected quantity of 0·1—0·2% by weight of virus protein. Stanley's isolation of a protein possessing the properties of the tobacco mosaic virus was soon confirmed,[9] and, in fact, was nearly anticipated by R. J. Best,[10] and F. C. Bawden and N. W. Pirie showed that the virus was in fact a nucleoprotein.[11] Subsequently several plant viruses were isolated by similar methods involving precipitations with ammonium sulphate and treatment with acid, alcohol, etc.[12, 13, 14, 15] Two of these, namely, the viruses of tomato bushy stunt [14] and tobacco necrosis,[15] proved to be crystallisable.

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[1] C. L. Hoagland, *Ann. Rev. Biochem.*, 1943, **12**, 615; W. M. Stanley and H. S. Loring, *Symposia Quant. Biol.*, 1938, **6**, 341; W. M. Stanley, *Physiol. Rev.*, 1939, **19**, 524; *Ann. Rev. Biochem.*, 1940, **9**, 545.

[2] *Idem, J. Physical Chem.*, 1938, **42**, 55.

[3] A. S. McFarlane, *Biol. Rev.*, 1939, **14**, 223; R. W. G. Wyckoff, *Ergeb. Enzymforsch.*, 1939, **8**, 1; E. H. Lenette, *Science*, 1943, **98**, 415.

[4] J. E. Smadel and C. L. Hoagland, *Bact. Rev.*, 1942, **6**, 79.

[5] W. G. MacCallum and E. H. Oppenheimer, *J. Amer. Med. Assoc.*, 1922, **78**, 410; J. C. G. Ledingham, *Lancet*, 1931, ii, 525; J. Craigie, *Brit. J. Exp. Path.*, 1932, **13**, 259.

[6] *Science*, 1935, **81**, 644; *Phytopath.*, 1936, **26**, 305.

[7] *Bot. Gaz.*, 1929, **87**, 39.

[8] *Ann. Appl. Biol.*, 1933, **20**, 70.

[9] F. C. Bawden, N. W. Pirie, J. D. Bernal, and I. Fankuchen, *Nature*, 1936, **138**, 1051.

[10] *Australian J. Exp. Biol. Med. Sci.*, 1936, **14**, 1.

[11] *Proc. Roy. Soc.*, 1937, *B*, **123**, 274.

[12] *Idem, Brit. J. Exp. Path.*, 1937, **18**, 275.

[13] *Idem, ibid.*, 1938, **19**, 66.

[14] *Idem, ibid.*, p. 251.

[15] N. W. Pirie, K. M. Smith, E. T. C. Spooner, and W. D. MacClement, *Parasitology*, 1938, **30**, 543.

About the same time high-speed air-turbine-driven centrifuges were developed in America for the study of viruses,[16] and it was soon realised that the activity of preparations isolated by centrifugation was greater than that of those obtained by salt precipitation, the latter procedure being shown to produce irreversible changes in the case of several viruses,[17, 18] tobacco ringspot virus being almost completely inactivated by precipitation with ammonium sulphate. In consequence centrifugation is now employed as a general routine method of isolation.

The Isolation of Viruses by "Differential" Centrifugation.—Normally viruses are isolated from tissues which contain much protein and other large molecules, such as glycogen, many of which have sedimentation rates comparable with those of viruses.[19] Consequently an attempt is usually made to obtain a starting material as free from extraneous contaminants as possible. In the case of plant viruses young plants are generally used, as they contain appreciably less dark pigment, etc. Special techniques are sometimes used for individual animal viruses; influenza A virus,[20] for instance, may be isolated from chick extra-embryonic fluid, and vaccinia virus is collected from the skin of inoculated rabbits in such a way as to damage the tissues as little as possible.[21] The solution may then be subjected to a preliminary treatment with a view to removing non-virus material. Thus plant sap is often frozen or treated with phosphate or alcohol, and animal viruses may be adsorbed specifically,[22] but in many cases the infective juices are centrifuged alternately at high and low speeds without preliminary treatment. The final product generally consists of a substance which, when examined on the ultracentrifuge or electrophoretically, is apparently reasonably homogeneous. It is relatively simple to show qualitatively that by this method a complete separation of particles having similar sedimentation constants is impossible, and, in fact, only a minor modification of the relative proportions of substance differing twofold in sedimentation constant may be achieved. It is therefore evident that, in spite of the criticisms generally levelled against this method of isolation,[4, 23] a sharp sedimentation boundary may be taken to indicate that the sub-

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[16] J. H. Bauer and E. G. Pickels, *J. Exp. Med.*, 1936, **64**, 503; R. W. G. Wyckoff and J. B. Langsdin, *Rev. Sci. Instr.*, 1937, **8**, 427.

[17] H. S. Loring, *J. Biol. Chem.*, 1938, **126**, 455; W. M. Stanley, *ibid.*, 1939, **129**, 405; H. S. Loring, M. A. Lauffer, and W. M. Stanley, *Nature*, 1938, **142**, 841.

[18] F. C. Bawden and N. W. Pirie, *Brit. J. Exp. Path.*, 1942, **23**, 314.

[19] A. R. Taylor, D. G. Sharp, D. Beard, and J. W. Beard, *Science*, 1941, **94**, 615; W. C. Price and R. W. G. Wyckoff, *Phytopath.*, 1939, **29**, 83; H. S. Loring, H. T. Osborn, and R. W. G. Wyckoff, *Proc. Soc. Exp. Biol. Med.*, 1938, **38**, 239; E. Chargaff, D. H. Moore, and A. Bendich, *J. Biol. Chem.*, 1942, **145**, 593; H. S. Loring and J. G. Pierce, *ibid.*, 1943, **148**, 35.

[20] L. A. Chambers and W. Henle, *J. Exp. Med.*, 1943, **77**, 251.

[21] R. F. Parker and T. M. Rivers, *ibid.*, 1935, **62**, 65.

[22] D. G. Sharp, A. R. Taylor, I. W. McLean, D. Beard, J. W. Beard, A. E. Feller, and J. H. Dingle, *Science*, 1943, **98**, 307.

[23] J. E. Smadel, E. G. Pickels, T. Shedlovsky, and T. M. Rivers, *J. Exp. Med.*, 1940, **72**, 523.

stance isolated is fairly homogeneous. Whether this substance is the virus is quite another matter, and is largely dependent upon the concentration of virus in the original fluid, and on the fact that many contaminants seem to be less resistant to repeated sedimentation than are viruses.

The Identity of the Isolated Substance with the Infective Agent.—In view of the preceding it is evident that claims to have isolated pure viruses must be accepted with some reserve and it may be noted that several authors have claimed only to have isolated large molecules apparently having the properties of the virus under investigation.[6, 11] In an ideal case it might be expected that a single virus particle would be able to cause an infection, but few purified virus preparations fulfil this requirement. In the case of the plant viruses many particles are required for one infection, as the method of inoculation used does not give an individual particle an appreciable chance of entering a viable cell. The conditions necessary for establishing an infection are, in addition, subject to complications other than those arising from chance. F. C. Bawden and N. W. Pirie[24] have drawn attention to the well-known fact that, though the sensitivity of *Nicotiana glutinosa* to tobacco mosaic is less on the top leaves than on the lower leaves, the latter are less sensitive to bushy stunt than the former. It is not surprising that plant viruses rarely infect in quantities less than 10^{-7} or 10^{-8} g., although this corresponds to some 10^8 particles. There is, however, no evidence that all the particles in the purified preparations are infective. Bawden and Pirie think it not unlikely that the greater part of their purified bushy stunt virus is inactive.[24] In spite of the fact that the activity of a virus may be reduced by the isolation procedure employed, and that an isolated virus may by appropriate treatments be wholly or completely inactivated, there is in many cases good reason to identify the isolated protein with the virus. Tobacco mosaic virus, for instance, has been isolated from such widely diverse plants as spinach, tobacco and *Phlox*,[2] and in no instance has activity been demonstrated in the absence of the characteristic protein.

In the case of the vaccinia virus[25] and some bacteriophage preparations[26] it is possible to show that one or a small number of particles is sufficient to cause infection, while in the case of the Shope papilloma virus[27] it is necessary to use as many as 57 million particles of the molecular weight of the characteristic substance associated with this disease in the cottontail rabbit (no virus can be isolated from the papillomata produced artificially on domestic rabbits).[28] While there would seem to be no reason to doubt the homogeneity of preparations of this virus, there appears to be insufficient evidence for the certain identification of the large particles with the virus.

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[24] *Biochem. J.*, 1943, **37**, 70.

[25] J. E. Smadel, T. M. Rivers, and E. G. Pickels, *J. Exp. Med.*, 1939, **70**, 379.

[26] G. Kalmanson and L. J. Bronfenbrenner, *J. Gen. Physiol.*, 1939, **23**, 203.

[27] H. Neurath, G. R. Copper, D. G. Sharp, A. R. Taylor, D. Beard, and J. W. Beard, *J. Biol. Chem.*, 1941, **140**, 293.

[28] J. W. Beard, W. R. Bryan, and R. W. G. Wyckoff, *J. Infect. Dis.*, 1939, **65**, 43.

In view of the availability of methods, such as that of A. Tiselius, K. O. Pedersen, and T. Svedberg,[29] which are capable of demonstrating identity of physical properties of the infective agent and the substance isolated, it is surprising that so little evidence of this type is available. While centrifugation is the obvious method and has been used with success by S. Gard and K. O. Pedersen [30] in their work on mouse encephalomyelitis, it is equally easy to use a Tiselius apparatus in a similar way. If such methods were used more frequently, it would be a simple matter to avoid the confusion caused by the reports of various authors to have isolated " pure " viruses having entirely different physical properties, as in the case of the influenza A virus.[31, 32]

General Properties of Viruses.

As a group viruses are extremely diverse in properties. Sedimentation constants vary from 50 S.[33] or less to over 5000 S.[34] Some viruses are spherical or nearly so, such as the bushy stunt, tobacco necrosis,[35] Shope papilloma,[36] and equine encephalomyelitis viruses,[37] others, such as tobacco mosaic,[9] potato X,[12] and the cucumber viruses 3 and 4, are long rods,[13] and several bacteriophages are tadpole-shaped.[38] Although there is little doubt that several plant viruses are only of molecular complexity, this is by no means the rule and vaccinia virus, for instance, has a well-defined internal structure [39] and besides containing copper,[40] fats,[41] and several enzymes,[42] which are probably merely adsorbed by the particles, has a complex antigenic structure.[4]

Of all the viruses, that of tobacco mosaic has been studied most intensively by physical methods. Sedimentation,[43] diffusion,[44] viscosity,[45] flow

[29] *Nature*, 1937, **140**, 848.

[30] *Science*, 1941, **94**, 493.

[31] L. A. Chambers, W. Henle, M. A. Lauffer, and T. F. Anderson, *J. Exp. Med.*, 1943, **77**, 265.

[32] A. R. Taylor, D. G. Sharp, D. Beard, J. W. Beard, J. H. Dingle, and A. E. Feller, *J. Immunol.*, 1943, **47**, 261.

[33] A. G. Ogston, *Brit. J. Exp. Path.*, 1942, **23**, 328.

[34] J. W. Beard, H. Finkelstein, and R. W. G. Wyckoff, *J. Immunol.*, 1938, **35**, 415.

[35] W. M. Stanley and T. F. Anderson, *J. Biol. Chem.*, 1941, **139**, 325.

[36] D. G. Sharp, A. R. Taylor, D. Beard, and J. W. Beard, *Proc. Soc. Exp. Biol. Med.*, 1942, **50**, 205.

[37] *Idem, ibid.*, 1942, **51**, 206, 332.

[38] S. E. Luria and T. F. Anderson, *Proc. Nat. Acad. Sci.*, 1942, **28**, 127.

[39] R. H. Green, T. F. Anderson, and J. E. Smadel, *J. Exp. Med.*, 1942, **75**, 651.

[40] C. L. Hoagland, S. M. Ward, J. E. Smadel, and T. M. Rivers, *J. Exp. Med.*, 1941, **74**, 69.

[41] C. L. Hoagland, J. E. Smadel, and T. M. Rivers, *J. Exp. Med.*, 1940, **71**, 737.

[42] C. L. Hoagland, S. M. Ward, J. E. Smadel, and T. M. Rivers, *ibid.*, 1942, **76**, 163.

[43] M. A. Lauffer, *J. Physical Chem.*, 1940, **44**, 1137.

[44] H. Neurath and A. M. Saum, *J. Biol. Chem.*, 1938, **126**, 435; V. L. Frampton and A. M. Saum, *Science*, 1939, **89**, 84.

[45] M. A. Lauffer, *J. Biol. Chem.*, 1938, **126**, 443; J. R. Robinson, *Proc. Roy. Soc.*, 1939, *A*, **170**, 519.

birefringence,[46] X-ray crystallography,[47] and the electron microscope [48] all confirm the elongated shape of the particles. Nevertheless the data are not mutually consistent, probably because of the polydispersity of the preparations investigated, and of the difficulty of applying theory to the case of such asymmetrical particles.

Very complete data are available on the bushy stunt virus [43, 49] and it would appear to have as much claim to homogeneity as any other protein.[50] It has a molecular weight of 10·6 million and is of interest as the first protein in which all reliable data point to the conclusion that it is considerably solvated, the amount of water bound being about 0·7 g./g.[51]

Another spherical virus which is solvated is the Shope papilloma virus, which was deduced by Neurath *et al.*[27] to be a rod with an axial ratio of some 9 : 1 from their measurements. Sedimentation, diffusion and viscosity measurements can be shown to give a very poor estimate of the *shape* of a particle, but, if combined with an estimate of the shape, may be used to deduce reliable values of wet and especially dry molecular weights. Thus the data on the Shope papilloma are consistent with a molecular weight of 48 million, which is increased by solvation to 135 million.

It is now generally accepted that all the plant viruses isolated so far are nucleoproteins, and almost without exception viruses are reported to contain nucleic acid. Vaccinia and the rabbit papilloma virus contain ribodesose nucleic acid,[52] and other viruses appear to have a pentose nucleic acid.[9, 11, 12, 13, 14] H. S. Loring [53] has studied the hydrolysis products of tobacco mosaic nucleic acid, and S. S. Cohen and W. M. Stanley [54] have investigated the physical properties of this substance, confirming the observation of Bawden and Pirie [11] that it is larger than yeast nucleic acid as usually prepared. The size of the nucleic acid particles depends to a great extent upon the treatment to which the acid is subjected, the size being greater when mild methods of isolation are used. This is similar to the observations of G. Schmidt, E. G. Pickels, and P. A. Levene [55] on thymus nucleic acid. When isolated in a mild way, the virus nucleic acid forms a birefringent gel and has a molecular weight of about 3×10^5. It depolymerises spontaneously and is apparently very asymmetrical, the axial ratio being assessed at about 30 : 1.

The amino-acids of the tobacco mosaic virus and the related rib-grass (*Plantago*) virus and cucumber viruses 3 and 4 have been examined and

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[46] J. W. Mehl, *Symposia Quant. Biol.*, 1938, **6**, 218.

[47] J. D. Bernal and I. Fankuchen, *J. Gen. Physiol.*, 1941, **25**, 111, 147.

[48] G. A. Kausche, E. Pfankuch, and H. Ruska, *Naturwiss.*, 1939, **27**, 292.

[49] H. Neurath and G. R. Cooper, *J. Biol. Chem.*, 1940, **135**, 455.

[50] M. A. Lauffer, *ibid.*, 1942, **143**, 99.

[51] R. Markham, K. M. Smith, and D. Lea, *Parasitology*, 1942, **34**, 315.

[52] C. L. Hoagland, G. I. Lavin, J. E. Smadel, and T. M. Rivers, *J. Exp. Med.*, 1940, **72**, 139; A. R. Taylor, D. Beard, D. G. Sharp, and J. W. Beard, *J. Infect. Dis.*, 1942, **71**, 110.

[53] *J. Biol. Chem.*, 1939, **130**, 251.

[54] *Ibid.*, 1942, **142**, 863.

[55] *Ibid.*, 1939, **127**, 251.

some 68% of the weight of the virus has been accounted for in hydrolysis products.[56] This group of viruses is of interest in that, although the members are morphologically similar and have a similar elementary composition, their amino-acid compositions differ. All four are to some extent antigenically related, and the host range of the four is different, the cucumber viruses being confined to the *Cucurbitaceæ*, whereas the wide host ranges of the others do not include this plant family. The serological differences observed are paralleled by marked differences in the proportions of the various aromatic amino-acids present.[57]

The Inactivation of Viruses.

Just as they differ in other properties, viruses react very differently to various treatments. As would be expected, elevated temperatures destroy all viruses, but some are surprisingly resistant. Purified tobacco mosaic virus will readily withstand temperatures up to 70°.[11] On the other hand, bushy stunt virus is rapidly inactivated at temperatures of 60° or less,[58] but apparently without appreciable change in physical or chemical properties, and many viruses are inactivated at room temperature in a few hours. The phenomenon of loss of activity without gross physical change is observed in many viruses, and means presumably that the major part of the structure of the particle must be intact for it to be infectious. Treatments destroying infectivity without causing gross change and loss of serological specificity include the effect of various radiations,[11] hydrogen peroxide,[59] formaldehyde,[60] nitrous acid,[11] keten,[61] and similar reagents. Up to 70% of the free amino-groups and a smaller percentage of the phenolic hydroxyl groups may be substituted without loss of virus activity. An important observation is recorded by Miller and Stanley,[62] who find that carbobenzyloxy-, benzenesulphonyl-, and *p*-chlorobenzoyl-tobacco mosaic virus are as much as seven times as active when tested on *Nicotiana glutinosa* as on *Phaseolus vulgaris*. This may prove to be due to a toxic effect on the *P. vulgaris* plants, but if this possibility is excluded and the observations confirmed, some revision of our views on virus activity will be necessitated.

In general, enzymes have little effect on viruses and trypsin is often used in the purification procedures,[11, 12, 13, 63] although it is known to digest at least two viruses, potato virus X [13] and alfalfa mosaic virus.[64] Pepsin also is known to digest some viruses, but as they are usually inactivated by pH values at which pepsin is active, this is not unexpected. Reported effects of enzymes on plant viruses are usually found to be due to a non-specific inhibition of the plant, and some of the effects of crude trypsin

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[56] A. F. Ross, *J. Biol. Chem.*, 1942, **143**, 685.

[57] C. A. Knight and W. M. Stanley, *ibid.*, 1941, **141**, 39.

[58] W. M. Stanley, *ibid.*, 1940, **135**, 437. [59] *Idem, Science*, 1936, **83**, 626.

[60] A. F. Ross and W. M. Stanley, *J. Gen. Physiol.*, 1938—9, **22**, 165.

[61] G. L. Miller and W. M. Stanley, *J. Biol. Chem.*, 1941, **141**, 905.

[62] *Ibid.*, 1942, **146**, 331.

[63] J. E. Smadel and M. J. Wall, *J. Exp. Med.*, 1937, **66**, 325.

[64] A. F. Ross, *Phytopath.*, 1941, **31**, 394.

on other viruses have been shown to be due to lipoidal contaminants in the enzyme.[65] Some enzymes and other large molecules form reversible complexes with viruses [11, 66, 67] and their use for purification has been suggested.

The inactivation of viruses with simultaneous loss of characteristic physical properties is caused by many treatments, including heat, high pressures,[68] exposure to extremes of acidity and alkalinity, and the effect of artificial detergents,[69] urea and allied substances,[70] and various protein denaturants.

R. M.

E. Chain.
H. W. Florey.
L. J. Harris.
R. Markham.

Note added in proof.—In a recent paper by A. E. D. Menzel, O. Wintersteiner, and J. C. Hoogerheide (*J. Biol. Chem.*, 1944, **152**, 419), which has just come to the notice of the authors, it has been shown that fumigacin, as described by Waksman *et al.*, is not a chemical entity but a mixture of helvolic acid (see p. 194) and gliotoxin (see p. p. 190).—E. C., H. W. F.

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[65] A. Pirie, *Brit. J. Exp. Path.*, 1935, **16**, 497.
[66] H. S. Loring, *J. Gen. Physiol.*, 1942, **25**, 497.
[67] S. S. Cohen, *J. Biol. Chem.*, 1942, **144**, 353.
[68] M. A. Lauffer and R. B. Dow, *ibid.*, 1941, **140**, 509.
[69] M. Sreenivasaya and N. W. Pirie, *Biochem. J.*, 1938, **32**, 1707.
[70] F. C. Bawden and N. W. Pirie, *ibid.*, 1940, **34**, 1258.

ANALYTICAL CHEMISTRY.

1. ANALYSIS OF STEELS.

IN recent years the steel analyst has had to devise methods for the determination of the elements found in steel which are not only quick and accurate but can be easily adapted to the routine examination of a large number of samples. When it is remembered that nearly one third of all the elements are to be found in steels, many of them in a single sample, details of the methods used in steel analysis will be of value to many besides the steel chemist. To a large extent the necessary speed and accuracy have been achieved by the employment of physicochemical methods, either as individual methods or in combination with chemical separations.

In the following review the basis of accepted knowledge is the methods which are to be found in text books such as " Chemical Analysis of Iron and Steel," by Lundell, Hoffman, and Bright, and " Sampling and Analysis of Carbon and Alloy Steels," being the methods of the United States Steel Corporation. Reports on the determination of each element are preceded by three headings dealing with the general application of the spectrograph to steel analysis, the use of the photoelectric absorptiometer, and polarographic and potentiometric methods. To avoid repetition of matter dealt with under these and other headings appropriate reference numbers are repeated at the head of the report on each element.

Application of the Spectrograph.—It has been found possible to determine with fair accuracy elements present in steel in small amount by using an arc and an internal-standard method. Greater reliability, however, is obtained by the use of a spark,[1] particularly where the upper electrode is made of graphite—a method which, when standardised, is applicable to higher percentages of the alloying elements giving results varying only by 0·02—0·1% from the chemical figures. The graphite electrode may be replaced by silver, and a counter electrode made of high-purity aluminium has given good results.[2] Disturbance of the lines of one element due to the presence of other elements may be a source of error. Such disturbances have been recorded by W. Holzmüller,[3] who gives a list of suitable lines for some twenty elements present in steel. Characteristic lines in the ultraviolet have also been measured.[4] The grating spectrograph, using a spark gap irradiated with ultra-violet light, has been adapted to routine use with some success in the U.S.A.[5] Modifications of the old spectroscope (" steeloscope ") [6] and of the modern spectrograph for use in the visible part of the

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[1] F. G. Barker, Iron and Steel Inst., May 1939, No. 1.

[2] T. Torok, *Spectrochim. Acta*, 1941, **2**, 26.

[3] *Z. anal. Chem.*, 1938, **115**, 81.

[4] L. A. Ignatieva and N. N. Sobolev, *Zavod. Lab.*, 1938, **7**, 949.

[5] S. Vigo, A.S.T.M. Bull., 1940, No. 107, 7.

[6] V. K. Prokofiev, *Zavod Lab.*, 1940, **9**, 1267.

spectrum ("steelometer")[7] are in everyday use. Results obtained with the latter instrument have an average deviation from the chemical figures varying from 0·03 to 0·08%.

Use of the Photoelectric Absorptiometer.—It has been remarked that the laboratory is regarded as the bottle neck of production in metallurgical work.[8] The removal of this bottle neck has been achieved by the application of the spectrograph and the photoelectric absorptiometer, and the author quoted above has shown how satisfactorily this has been achieved by using the absorptiometer.[8, 9] Experienced users are able to obtain accuracy in the determination of steel constituents as high as that obtainable with chemical methods in only a fraction of the time required by the latter methods. Moreover, with only a slight loss of accuracy the absorptiometer can be easily used for routine work by relatively inexperienced assistants with proper direction.

Polarographic and Potentiometric Methods.—Although some success has been achieved with the polarograph the method cannot be said to be suitable for routine testing,[10] and clearly it is more likely to be of use in the determination of micro-additions of alloying elements. The removal of all the iron is difficult, and traces left in solution adversely affect subsequent polarograms.[11] Greater success is possible when elements are determined by amperometric titration.

Potentiometric methods are not uncommon and they will be found under later headings. A. M. Zanko[12] has described suitable procedures for some eight alloying elements.

Aluminium.[3, 5]—The separation of small quantities of aluminium from large amounts of iron is the chief problem of this determination. P. Klinger[13] has compared four methods, *viz.*, ether extraction, electrolysis, oxidation with sodium peroxide, and precipitation with cupferron. Of these, the first gives the best results, the electrolysis giving low figures in the presence of copper and erratic results in that of titanium and vanadium. Cupferron is unsatisfactory. Sodium hydroxide precipitation of the iron gives a suitable filtrate for precipitation of the aluminium with ammonia[14] or for its detection by a colorimetric method using ammonium aurintricarboxylate,[15] which will

[7] S. S. Rimlyand, *Bull. Acad. Sci. U.R.S.S.*, 1940, **4**, 225.

[8] E. J. Vaughan, "The Use of the Spekker Photo-electric Absorptiometer in Metallurgical Analysis." Monograph published by the Institute of Chemistry, 1941.

[9] *Idem*, "Further Advances in the Use of the Spekker Photo-electric Absorptiometer in Metallurgical Analysis." Monograph published by the Institute of Chemistry, 1942.

[10] M. Von Stackelburg, P. Klinger, W. Koch, and E. Krath, *Tech. Mitt. Krupp: Forschungsber.*, 1939, **2**, 59.

[11] G. Thanheiser and J. Willems, *Mitt. Kaiser-Wilhelm Inst. Eisenforsch.*, 1939, **21**, 65; *Arch. Eisenhüttenw.*, 1939—40, **13**, 73.

[12] *Trudy Vsesoyuz Konferentsii Anal. Khim. Akad. Nauk S.S.S.R.*, 1939, **1**, 303; *Khim. Referat. Zhur.*, 1940, No. 2, 64.

[13] *Arch. Eisenhüttenw.*, 1939—40, **13**, 21.

[14] S. Shinkai and T. Nagata, *J. Soc. Chem. Ind., Japan*, 1939, **42**, 3970.

[15] L. P. Adamovich and A. J. Zagorulko, *Zavod. Lab.*, 1939, **8**, 1315; *Khim. Referat. Zhur.*, 1940, **5**, 70.

detect 0·01% of aluminium. Determination of aluminium photometrically is possible by using eriochrome-cyanine.[16] Percentages of aluminium from 0·1 to 0·001 present in the hydrochloric acid-soluble part of a steel can be determined spectrographically by using a strong spark and a long pre-sparking period.[17] The aluminium line 3961·53 is compared with iron lines at 3973·66 and 3951·16. G. Hartlief,[18] using Al 3961·5 and Fe 3963, describes a method employing the Feusner spark.

Antimony[3] *and Arsenic.*[3]—No new methods other than those indicated have recently been described.

Beryllium.—Percentages of this element between 0·1 and 1·0 have been determined without serious interference from nickel and chromium by a spectrographic method.[19] Beryllium lines 2494·6, 3321·1, and 2650·6 were compared with iron lines 2522·9, 3440·6 and 3286·8, and 2644·7 and it was later found possible to extend the range of beryllium percentages to 0·01—2·0.

Boron.[3]—No satisfactory chemical methods for boron present to the extent of 0·003% have been described, but a spectrographic method[20] using graphite electrodes impregnated with hydrochloric acid has given results for boron percentages between 0·03 and 2·01. Unequal volatility of the steel components causes changes in the intensities of the lines measured, the best pair being B 2497·72, Fe 2533·8.

Calcium.[3]—Determination of this element in cast iron as oxalate after an iron separation has been described.[21]

Carbon.[3]—Chemical methods for the determination of carbon depend almost exclusively upon combustion in oxygen, and variations in method are mainly concerned with the treatment of the carbon dioxide and improvements in the apparatus. In both macro- and micro-chemical methods the gas is absorbed in baryta. In the former case the carbonate formed is converted into barium sulphate,[22] contamination by atmospheric carbon dioxide being avoided; in the latter case the excess baryta is titrated.[23] For this purpose A. Lassieur[24] recommends potassium hydrogen phthalate. G. Zaffuto[25] has described a rapid method in which oxides of sulphur are absorbed in aqueous sodium chloride and the carbon dioxide in standard sodium hydroxide, followed by titration with oxalic acid. Factors affecting the accuracy of the combustion method have been discussed,[26] and for rapid work drying of the oxygen with magnesium perchlorate is recommended.[27]

[16] W. Koch, *Arch. Eisenhüttenw.*, 1939, **12**, 69.

[17] O. Schliessmann, *ibid.*, 1940, **14**, 211.

[18] *Ibid.*, 1939—40, **13**, 295.

[19] O. Masi, *Spectrochim. Acta*, 1941, **1**, 501.

[20] *Idem, ibid.*, p. 462.

[21] A. T. Sveshnikov and T. V. Boretskaya, *Zavod. Lab.*, 1938, **7**, 1428.

[22] H. Kempf and K. Abresch, *Arch. Eisenhüttenw.*, 1939—40, **13**, 135.

[23] M. H. Kalina and T. L. Joseph, *Heat Treat. Forg.*, 1939, **25**, 169.

[24] *Compt. rend.*, 1938, **207**, 731.

[25] *Atti X Cong. intern. Chim.*, 1938, III, 487.

[26] E. T. Saxer, R. E. Minto, and R. A. Clark, *Blast Furnace Steel Plant*, 1941, **29**, 718.

[27] *Idem, ibid.*, p. 519.

In the physical field, carbon contents of 0·5—1·1% have been correlated with magnetic saturation,[28] and a similar rapid method compares the magnetic permeability of a sample with a known steel.[29]

Chromium.[1, 3, 4, 5, 7, 8, 9, 11, 12, 16]—Little change is to be noted in the chemical method for the determination of chromium. The steel is dissolved in sulphuric and phosphoric[30] or perchloric acid,[31] followed by persulphate oxidation in the presence of silver nitrate and subsequent titration of the dichromate with ferrous sulphate and permanganate. Volatilisation of the chromium as chromyl chloride enabled W. Dietz[32] to determine this metal iodometrically in the condensate. Methods dependent upon the absorptiometer have shown great increases in speed combined with accuracy. Originally the coloured compound used was the dichromate.[8] This requires control of the acid concentration and the addition of urea to reduce silver complexes to colourless compounds and perchromate acid to dichromate. For small amounts of chromium the violet-red compound formed when diphenylcarbazide is oxidised by chromate in acid solution gives a greater photo-cell response.[9] For this method the chromate solution is obtained after precipitation of the iron, etc., by sodium hydroxide and peroxide, with subsequent addition of sulphuric acid to the alkaline chromate solution. Interference from 2% of vanadium was successfully eliminated by the use of spectrum-green filters. Both W. Koch[16] and B. Bagshawe[33] have used the diphenylcarbazide colour, the latter employing the Lovibond tintometer for comparison of his colours. V. F. Maltaev and T. P. Temirenko[34] used this same colour in the presence of the iron, comparing it with standard steel solutions to which chromium had been added.

Potentiometric methods allow of the determination in one solution of chromium, manganese, and vanadium. In one of these[35] three titrations with ferrous sulphate with appropriate treatment of the solution in between gives figures for all three elements. In another,[36] the permanganate is titrated with sodium arsenite, the chromium and vanadium with ferrous sulphate, and the quadrivalent vanadium with potassium permanganate.

Some of the spectrographic methods have already been mentioned. Recently, P. Habitz[37] has discussed the choice of homologous pairs of lines and selects Cr 3128, Fe 3167, and Cr 3147, Fe 3167. In the visible spectrum, steeloscope methods[38] for 0·02—0·13% of chromium use Cr 5208, Fe 5227

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[28] B. A. Rogers, K. Wentzel, and J. P. Riott, *Trans. Amer. Soc. Metals*, 1941, **29**, 969.

[29] H. H. Blosjo, *Trans. Amer. Found. Assoc.*, 1939, **47**, 469.

[30] E. C. Pigott, *Ind. Chem.*, 1940, **16**, 283.

[31] L. Silverman and O. Gates, *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 518.

[32] *Angew. Chem.*, 1940, **53**, 409.

[33] *J. Soc. Chem. Ind.*, 1938, **57**, 260.

[34] *Zavod. Lab.*, 1941, **10**, 357.

[35] J. Nummedal, *Arch. Math. Naturvidenskab*, 1941, **44**, 1; *Chem. Zentr.*, 1941, II, 641.

[36] A. S. Goralnik, *Zavod. Lab.*, 1941, **10**, 257.

[37] *Spectrochim. Acta*, 1941, **2**, 158.

[38] L. V. Volkova, *Bull. Acad. Sci. U.R.S.S.*, 1940, **4**, 216.

for 0·1% or more and Cr 4254, 4274, 4289 respectively with Fe 4247, 4282, 4271 for 0·1% or less.

Cobalt.[3, 10, 12]—Although α-nitroso-β-naphthol remains a satisfactory reagent for the determination of cobalt, greater speed with similar accuracy is claimed for an electrometric method[39] in which the cobalt and any manganese are titrated with potassium ferricyanide in the presence of ammonium citrate. Photometric methods depend upon the cobalt colour in hydrochloric acid solution. K. Dietrich[40] describes a variation of H. Pinsl's[41] method using a Leifo polarisation photometer with an incandescent lamp and a 668 filter. Pinsl treated the filtrate from a zinc oxide precipitation with stannous chloride and used a Nitra lamp with an S 66 filter. E. Bischof and G. Geuer,[42] using a Pulfrich photometer, measure the absorption due to a cobalt ammino-complex. Interference due to manganese can be avoided by the addition of ammonium chloride, and nickel in excess of 1% requires the preparation of an extinction calibration curve.

Copper.[3, 5, 12, 75]—Copper can be determined electrolytically in the presence of the iron by a number of methods. Working with a cell designed for low temperatures, H. A. Frediani and C. H. Hale[43] obtained satisfactory figures over a range of copper content of 0·03—6·44%. Alternatively, the electrolysis may be carried out at 60—70° from a sulphate solution with the addition of hydrazine, a pure aluminium rod being used as anode,[44] or from a sulphuric-phosphoric acid solution at 0·6 amp. without stirring.[45] A colorimetric method[46] depending upon the photometric evaluation of colloidal copper sulphide is satisfactory in the presence of 20% of tungsten, 2% of aluminium, 6% of molybdenum and 20% of chromium. In this method and in another due to K. Quandel[47] vanadium interferes. Quandel, using a Zeiss Pulfrich photometer with an HG 578 filter, measures the copper colour with rubeanic acid. After removal of the iron with ammonia, this author also measures the copper colour with thiocyanate, using an HG 436 filter with a mercury vapour lamp and correcting for the copper retained by the iron precipitate. Two organic reagents are recommended, *viz.*, salicylaldoxime[48] and dibromohydroxyquinoline oxalate.[49] In the latter case copper is completely precipitated as a complex, the iron remaining in the acid solution. Titration of copper with potassium cyanide, solution of the iron being avoided, is proposed.[50]

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[39] G. J. Steele and J. J. Phelan, *Gen. Elect. Rev.*, 1939, **42**, 218.

[40] *Metallwirts.*, 1941, **20**, 600.

[41] *Arch. Eisenhüttenw.*, 1940, **13**, 333.

[42] *Angew. Chem.*, 1941, **54**, 238.

[43] *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 736.

[44] E. V. Smekh and A. M. Naigovzen, *Zavod. Lab.*, 1940, **9**, 1218.

[45] L. Silverman, W. Goodman, and D. Walter, *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 236.

[46] G. Bogatzki, *Arch. Eisenhüttenw.*, 1941, **14**, 551.

[47] *Ibid.*, p. 601.

[48] E. Stengel, *Tech. Mitt. Krupp: Forschungsber.*, 1939, **2**, 87.

[49] A. M. Zanko and A. J. Bursuk, *Ber. Inst. physikal. Chem. Akad. Wiss. Ukr.*, 1938, 89; *Khim. Referat. Zhur.*, No. 10, 92.

[50] P. I. Schportenko and V. F. Garen, *Zavod. Lab.*, 1938, **7**, 1199.

Lead.—Separation of the lead as sulphide and subsequent determination as sulphate [51] or electrolytically as dioxide [52] are suitable procedures. Reviewing available methods, E. Gregory and others [53] note that lead segregates in steel and recommend its separation as sulphate.

Manganese.[1, 3, 4, 5, 7, 8, 9, 10, 12, 35, 36]—Both volumetric and colorimetric methods depend upon the formation of permanganate. Persulphate oxidation in the presence of silver nitrate as catalyst, followed by reduction with standard arsenite solution, appears to have superseded the bismuthate method. Osmic acid is also suitable as a catalyst.[54] G. I. Rodin [55] suggests the use of thiosulphate for the final titration. Corrosion and heat-resisting steels and carbide-bearing steels are best examined for manganese by persulphate oxidation after a zinc oxide separation of the iron and aluminium from perchloric acid solutions.[56] C. M. Johnson [57] has reviewed the use of perchloric acid in the manganese determination and has discussed the effect of molybdenum, vanadium and cobalt. E. J. Vaughan [8] uses the permanganate colour for the absorptiometer, eliminating interference due to nickel and chromium by a difference method. A potentiometric titration with potassium permanganate [58] can give accuracy equivalent to the volumetric bismuthate method. In addition to the spectrographic methods already noted, O. Masi [59] suggests adapting for steel a method due to A. Rivas [60] used for determining manganese in pure salts.

Molybdenum.[1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 37]—Despite the considerable simplification of the molybdenum method obtained by the use of the α-benzoinoxime precipitation,[61] considerable attention is still devoted to the determination of this element. To avoid the ignition of the α-benzoinoxime precipitate, W. W. Clarke [62] and C. Sterling and W. P. Spuhr [63] convert this into lead molybdate. Pure precipitates of lead molybdate can be obtained by treating the neutral filtrate from a sodium hydroxide precipitation of the iron with formic acid, ammonium chloride and paper pulp and then precipitating with lead acetate.[64] W. W. Clarke [65] dissolves ignited molybdenum trisulphide in sodium hydroxide, removes sodium tungstate, and then precipitates the lead molybdate. Butyl acetate can be used to extract the coloured compound formed by the action of stannous chloride and potassium

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[51] A. E. Pavlish, J. D. Sullivan, and J. Shea, *Met. and Alloys*, 1939, **10**, 150.

[52] G. E. F. Lundell, *Met. Progr.*, 1939, **35**, 383.

[53] E. Gregory *et al.*, *J. Iron Steel Inst.*, Advance Copy, Mid-April 1942.

[54] R. P. Forsyth and W. F. Barfoot, *Ind. Chem. Eng.* (*Anal.*), 1939, **11**, 625.

[55] *Zavod. Lab.*, 1904, **9**, 111.

[56] B. Bagshawe, *J. Soc. Chem. Ind.*, 1939, **58**, 106.

[57] *Iron Age*, 1938, No. 26, **142**, 16.

[58] M. J. Eenis, E. I. Grenberg, A. M. Zanko, and L. N. Novikova, *Zavod. Lab.*, 1940, **9**, 1082.

[59] *Met. Ital.*, 1938, **30**, 111; *Chim. et Ind.*, **40**, 681.

[60] Berheft : *Z. Ver. deut. Chem.*, No. 29; *Angew. Chem.*, 1937, **50**, 903.

[61] H. E. Knowles, *J. Res. Nat. Bur. Stand.*, 1932, **9**, Paper No. 453.

[62] *Chemist-Analyst*, 1940, **29**, 83.

[63] *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 33

[64] E. Gregory, R. B. Foulston, and F. W. Gray, *Analyst*, 1941, **66**, 444.

[65] *Chemist-Analyst*, 1941, **30**, 81.

thiocyanate on molybdenum solutions, and this coloured extract can be used for the colorimetric determination of the element.[66] G. M. Poole[67] has adapted this method for as much as 6% of molybdenum, and D. H. Heppell[68] finds it satisfactory for rapid work. R. Sperl[69] has used an ether extraction,[70] but E. J. Vaughan,[8] using controlled conditions, measures the thiocyanate colour in the presence of the iron.

P. Klinger[71] has reviewed all the methods available for molybdenum other than the benzoinoxime separation as follows. Greater reliability is obtained by hydrogen sulphide separation under pressure, but this is not absolutely necessary. Molybdenum may be weighed as trioxide or as lead molybdate after separation as trisulphide, and the latter method is unaffected by the presence of copper. Of colorimetric methods, those using thiocyanate and stannous chloride, and phenylhydrazine are satisfactory, but the xanthate colour is not reliable. Photometric methods are useful for rapid work. Potentiometric methods give good agreement with the gravimetric figures, but the stannous chloride titration requires great care.

Spectrographic methods have been mentioned. The steeloscope can be used for rapid determinations of 0·05—0·3% of molybdenum.[72] P. Habitz[37] selects as suitable homologous pairs Mo 2807, Fe 2783 and Mo 2775, Fe 2779.

Nickel.[1, 3, 4, 9, 10, 12, 31, 45]—Recent work has dealt almost exclusively with the titration of nickel with cyanide either chemically[31, 45] or potentiometrically,[73, 74] the latter method being preferred for rapid work. Separation of the nickel is not necessary provided that all the iron be oxidised. A modification of an earlier method for copper[75] makes it possible to determine nickel polarographically[76] in the presence of excess ammonia and precipitated ferric hydroxide. The polarogram is started at −0·75 v., which is beyond the copper steps at −0·09 v. and −0·34 v. Satisfactory results have been obtained in the presence of chromium, tungsten, titanium, and vanadium.

Niobium.—See Tantalum.

Phosphorus.[8, 9, 16, 53, 82]—Few gravimetric methods have been studied recently, but a satisfactory referee method eliminates arsenic with hydrobromic acid and converts the precipitate of phosphomolybdate into lead molybdate. The modern tendency has been to adopt a colorimetric method in which the ammonium phosphomolybdate is reduced to molybdenum-blue by stannous chloride.[8] This method requires that interference from arsenic, silicon, and vanadium should be eliminated, and that allowance should be made for the reduction of excess ammonium molybdate, a reaction which is

[66] L. H. James, *Ind. Eng. Chem.* (*Anal.*), 1932, **4,** 89.

[67] *Iron Age*, 1941, **148,** No. 15, 62, 145.

[68] *Ind. Chem.*, 1940, **16,** 173.

[69] *Chem.-Ztg.*, 1940, **64,** 363.

[70] C. D. Braun, *Z. anal. Chem.*, 1863, **2,** 36.

[71] *Arch. Eisenhüttenw.*, 1940, **14,** 557.

[72] J. P. Belkevitch, L. E. Bruk, and N. S. Sventitskii, *Zavod. Lab.*, 1940, **9,** 1279.

[73] R. Weihrich, *Arch. Eisenhüttenw.*, 1940, **14,** 55.

[74] O. Niezoldi, *Chem. App.*, 1938, **25,** 389.

[75] G. Thanheiser and G. Maassen, *Naturwiss.*, 1937, **25,** 426.

[76] J. S. Lialikov and J. I. Usatenko, *Zavod. Lab.*, 1938, **7,** 1100.

largely inhibited by the presence of iron. Interference from silicon can be avoided by fuming, complex vanadium molybdates do not reduce to molybdenum-blue, and arsenic can be removed by boiling with hydrobromic acid. J. L. Hague and H. A. Bright [77] remove arsenic in this manner in a method based on measuring the transmittance of a phosphate solution to which ammonium molybdate and hydrazine sulphate have been added. A. J. Bursuk,[78] measuring the molybdenum-blue colour, states that 0·03% of arsenic causes no interference. T. P. Hoar,[79] who uses an aliquot part of a sodium hydroxide solution of a phosphomolybdate precipitate for treatment with ammonium molybdate and stannous chloride, finds that as much as 0·1% of arsenic does not affect the results.

The yellow colour due to phospho-vanado-molybdate is used by G. Bogatzki [80] in a method where the iron colour is masked with sodium fluoride. H. H. Willard and E. J. Center [81] use a Coleman spectrophotometer for measurements with the same coloured compound. Diluted nitric acid solution containing small amounts of phosphoric acid gives a delicate turbidity with strychnine molybdate, a reaction which can be used for a rapid determination of phosphorus.[16]

Silicon.[1, 3, 4, 5, 7, 9]—Separation of silica from a hydrochloric acid solution is the basis of the chemical method, and to increase the speed of the separation S. N. Shkotova [82] adds a 0·1% solution of gelatin. This addition does not affect a subsequent determination of phosphorus in the filtrate. If this method is used in the presence of phosphoric acid, zirconium and titanium are co-precipitated.[83] The volume of silicic acid which separates when a hydrochloric acid solution of steel is centrifuged is proportional to the amount of silica present.[84] This method is satisfactory down to a lower limit of 0·1% of silicon, but tungsten interferes. A modified procedure can be used for silica as low as 0·04%.[85] An unusual method for the separation of the silica depends upon an electrolysis with the sample as the anode in a bath containing sodium chloride, potassium bromide, and sodium citrate.[86] A high current is used and the silica remains in the insoluble residue. A photometric method which can be used in the presence of tungsten depends on the formation of soluble yellow silicomolybdates in weakly acid solution.[87] Spectrographically, some difficulties arise with silicon owing to a variation in intensity of the silicon line for the same concentration of silicon in different alloys.[88] In using the steeloscope and the line 3905,

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[77] *J. Res. Nat. Bur. Stand.*, 1941, **26**, 405; Research paper 1386.

[78] *Zavod. Lab.*, 1939, **8**, 12.

[79] *Analyst*, 1938, **63**, 712.

[80] *Arch. Eisenhüttenw.*, 1938—39, **12**, 195.

[81] *Ind. Eng. Chem.* (*Anal.*), 1941, **13**, 81.

[82] *Zavod. Lab.*, 1939, **8**, 213.

[83] K. L. Weiss, *Arch. Eisenhuttenw.*, 1941, **15**, 13.

[84] R. Ishii, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1939, **36**, 491.

[85] *Idem, ibid.*, 1940, **37**, 143.

[86] A. Skrapski, A. Bielanski, and M. Sobieski, *Hutnuik*, 1938, **10**, 469; *Met. Abstr.*, 1939, **10**, No. 4, 225.

[87] R. Weihrich and W. Schwartz, *Arch. Eisenhüttenw.*, 1941, **14**, 501.

[88] V. K. Prokofiev, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **29**, 443.

and with a carbon steel as a standard electrode, a decrease of current produces a greater decrease of intensity of the silicon line than of the iron where the proportion of silicon exceeds 1%.[89]

Sulphur.[53]—Sulphur is still determined by one of the three methods, combustion of the steel in oxygen and absorbing the sulphur gases produced, absorbing the hydrogen sulphide resulting from a hydrochloric acid attack on the steel, or by dissolving the steel in an oxidising acid liquor with subsequent weighing of barium sulphate. The last method is the basis of a modern referee method,[53] which gives an accuracy within 0·0015% of the weight of the sample. Earlier, P. Schong [90] had claimed high accuracy with this method in which analytical procedure is specified. By using the evolution method and absorbing the gases in ammoniacal zinc sulphate it is possible to titrate this mixture directly with iodine after acidification.[91] T. P. Hoar and G. E. S. Eyles [92] treat the steel with hydrochloric acid in an atmosphere of carbon dioxide, and after absorption of the hydrogen sulphide in ammoniacal cadmium chloride add an ice-cold mixture of sulphuric acid and potassium iodate and iodide and titrate with thiosulphate. An accuracy of 0·002% is claimed. The nature of the absorbent of the sulphur trioxide in the combustion method is not critical, hydrogen peroxide, iodine, and silver nitrate being equally satisfactory.[93] A combustion method [94] which involved trapping the gases in potassium iodide and iodate has been criticised by G. Isimaru,[95] who states that carbon dioxide affects the result. A variant of this [96] is to absorb the oxides of sulphur in a little water to which a little iodine and starch have been added, further additions of iodine being made as decolorisation occurs, a method which has recently been recommended by S. M. Gutman and R. V. Gochfeld.[97] Y. Kanamori [98] obtains an accuracy of ±0·001% by absorbing the gas in hydrogen peroxide and expelling carbon dioxide from the absorbent with chlorine-free air. The use of tin as a catalyst during the combustion has been suggested.[99]

Tantalum and Niobium.[3]—The problem of the separation of these two elements owing to the absence of selective reagents has not yet been entirely solved. Spectrographically, O. Schliessmann [100] has described a procedure suitable for niobium contents greater than 0·1% and for tantalum greater than 1·0%. The steeloscope has been used for niobium in the presence of titanium and zirconium.[101] Separation even of the mixed oxides is not an

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[89] I. S. Kirin and N. S. Sventitskii, *Zavod. Lab.*, 1940, **9**, 1270.

[90] *Chem.-Ztg.*, 1939, **63**, 364.

[91] J. Zeutzius, *Z. anal. Chem.*, 1939, **116**, 102.

[92] *Analyst*, 1939, **64**, 666.

[93] M. K. Chukavin and M. N. Markelova, *Zavod. Lab.*, 1938, **7**, 1455.

[94] A. Vita, *Stahl und Eisen*, 1920, **40**, 933.

[95] *Nippon Kinzonkii Sakkai-Si*, 1939, **3**, 60.

[96] I. Kassler, *Chem.-Ztg.*, 1933, **57**, 573.

[97] *Zavod. Lab.*, 1938, **7**, 399.

[98] *Tetsu-to-Hagane*, 1940, **20**, 630.

[99] G. I. Stukanovskaja, *Zavod. Lab.*, 1938, **7**, 1455.

[100] *Tech. Mitt. Krupp : Forschungsber.*, 1939, **2**, 185.

[101] A. Fedorov, *Bull. Acad. Sci. U.R.S.S.*, 1940, **4**, 212.

easy matter, and T. R. Cunningham[102] has given details of the use of cupferron for this purpose. Photometric methods based on hydrogen peroxide colours in specified conditions of acidity appear the most hopeful methods for individual determinations of these elements, care being taken to allow for interference due to titanium. In 100% sulphuric acid niobium gives a colour with hydrogen peroxide, titanium gives a colour which is only 30% of its colour in 20% sulphuric acid and tantalum shows no colour. Consequently photometric measurements in 20% and 100% sulphuric acid allow of a determination of niobium and titanium, tantalum being determined by difference from the original weight of the mixed oxides.[103] G. Thanheiser[104] determines niobium by its colour with hydrogen peroxide in sulphuric acid and 40% phosphoric acid (a strength which eliminates the titanium colour when the titanium is less than 1%) and tantalum by the yellow colour formed with pyrogallol in 3% ammonium oxalate. A correction has to be made for titanium, determined with chromotropic acid in the same solution.

Tellurium.[3]—Te 2385·76 is compared with Fe 2378·98, an A.C. arc being used and log ratios of intensities being plotted.[105]

Tin.[3]—Existing methods have been re-examined,[106] and E. T. Saxer and R. E. Minto[107] propose titration of the reduced tin with potassium iodate after separation of the iron with ammonia from a hydrochloric acid solution.

Titanium.[3, 5, 33, 37, 101, 103]—As has been indicated under tantalum, the peroxide colour is suitable for determinations of titanium in steel. Separation of the titanium is not essential, although cupferron has been used for this purpose.[33] The Zavodskaya laboratory[108] has developed a rapid method by adding phosphoric acid and hydrogen peroxide to a perchlorate solution, a method which is unaffected by 1% of chromium. In addition to the steeloscope method,[101] L. E. Bruk and N. N. Sorokina[109] use the lines Ti 3088·032 and Fe 3083·747 for quick results with a 5% accuracy. Other homologous pairs of lines suitable for titanium determinations are Ti 3078, Fe 3097 and Ti 3168, Fe 3167.[37]

Tungsten.[3, 4, 10, 12, 68]—Tungstic oxide can be separated from a variety of solutions. This oxide and silica are precipitated quantitatively from a perchloric acid solution, and this precipitate can be ignited and weighed, the silica being removed with hydrogen fluoride.[110] This method has recently

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[102] *Ind. Eng. Chem.* (*Anal.*), 1938, **10**, 233.

[103] P. Klinger and W. Koch, *Arch. Eisenhüttenw.*, 1939—40, **13**, 127.

[104] *Mitt. Kaiser-Wilhelm Inst. Eisenforsch.*, 1940, **22**, 255.

[105] R. E. Nusbaum and J. W. Hackett, *J. Opt. Soc. Amer.*, 1941, **31**, 620.

[106] S. Mischonsniky, *Congr. Chim. Ind. Compt. rend.* 18*éme Congr.*, Nancy, Sept.–Oct. 1938, 438.

[107] *Steel*, 109, No. 3, 1941, **66**, 91.

[108] S. M. Gutman, E. N. Zarogatskaya, and Z. A. Vyvapaeva, *Zavod. Lab.*, 1940, **9**, 101.

[109] *Bull. Acad. Sci. U.R.S.S.*, 1940, **4**, 23.

[110] A. Clauberg and P. Behmenberg, *Z. anal. Chem.*, 1936, **104**, 245.

been advocated by S. M. Gutman and R. V. Gochfeld.[111] 8-Hydroxyquinoline can be used to separate tungsten in an acetic acid solution, and this precipitate can be ignited to tungstic oxide after treatment with oxalic acid.[112] Vanadium and molybdenum interfere in this method. Both D. H. Heppell [68] and D. P. Chatterjee [113] recommend dissolving precipitated tungstic oxide in standard sodium hydroxide, the latter mixing the precipitate with warm water and neutral glycerol or mannitol to avoid hydrolysis. The time taken in using the hydrochloric acid solution method and subsequent oxidation with nitric acid can be reduced if the steel is first heated to 1150—1200° for 15 minutes and quenched in water.[114] A photometric method, which requires some correction for chromium, depends upon the red colour formed by tungsten with quinol in a solution containing sulphuric and phosphoric acids.[115] It is necessary to reduce both iron and molybdenum with stannous chloride.

Uranium.—8-Hydroxyquinoline is a suitable reagent for separating uranium after removal of the iron by electrolysis and manganese with sodium carbonate.[116] Any aluminium in the uranium can be determined by fusion and precipitation of the hydroxide.

Vanadium.[1, 3, 4, 5, 8, 9, 10, 11, 12, 35, 36, 68]—The vanadium determination is possibly the most difficult having regard to the amount of manipulation required by the ordinary chemical method. Much work has been done to develop colorimetric methods. Of the colours available, that with hydrogen peroxide is suitable.[68] H. Pinsl [114] makes the determination in the presence of the iron, and adds sodium fluoride to eliminate the colour due to titanium —a method which is satisfactory for 0—2·23% of vanadium. E. J. Vaughan [8] finds it necessary for titanium-free steels to apply a correction for the coloured complex due to molybdenum. The orange colour of the phospho-vanado-molybdate complex can be measured accurately for a percentage range of vanadium 0·01—5·0,[118] as much as 10% of molybdenum, titanium, and cobalt and 20% of tungsten causing no interference. A. L. Davydov and Z. M. Vaisberg [119] have studied the formation of molybdenum-blue during the reduction of the phospho-vanado-molybdate complex. This reduction can be used to give an accuracy of 4% for 0·1—2% of vanadium. E. J. Vaughan [9] uses the same complex to separate small amounts of vanadium, and after treatment with sulphuric acid and oxidation, measures the vanadium colour with strychnine. A potentiometric titration of vanadium with ferrous sulphate, similar to that already mentioned,[35] has been made by F. Eisermann.[120]

Although some latitude can be allowed in the conditions for the spectro-

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[111] *Zavod. Lab.*, 1938, **7**, 598.

[112] Z. S. Muchina, *ibid.*, p. 407.

[113] *J. Indian Chem. Soc.*, 1940, **17**, 359.

[114] A. A. Fedorov, *Zavod. Lab.*, 1940, **9**, 1319.

[115] G. Bogatzki, *Z. anal. Chem.*, 1938, **114**, 170.

[116] A. M. Dimov and R. S. Moltschanova, *Zavod. Lab.*, 1938, **7**, 653.

[117] *Giesserei*, 1940, **27**, 441.

[118] G. Bogatzki, *Arch. Eisenhüttenw.*, 1938—9, **12**, 539.

[119] *Zavod. Lab.*, 1940, **9**, 715.

[120] *Arch. Eisenhüttenw.*, 1938—9, **12**, 245.

graphic determination of vanadium, high resolution is necessary, and with this an accuracy of ±5% can be obtained by using V 3271·3, Fe 3212.[121] For similar work, K. A. Suchenko [122] uses V 4379·24 and Fe 4376·0.

Zirconium.—The use of propylarsonic acid as a specific reagent for zirconium, by which means 0·1% of this metal can be determined in the presence of many other elements, has been proposed.[123]

Oxygen, Nitrogen, and Hydrogen.—The discussion of the methods for the determination of these elements given in "Sampling and Analysis of Carbon and Alloy Steel" is pertinent. Work has been done on the vacuum fusion method, tin being used as a flux for all three elements.[124, 125, 126] All the hydrogen can be obtained by heating to 600° in a high vacuum, higher temperatures producing more nitrogen and carbon monoxide.[127] This method of vacuum heating rather than vacuum fusion is preferred by K. Tawara [128] who heats 50—100 g. of steel at 800° for 1—2 hours.

The residue from a hydrochloric acid solution of a steel contains some of the nitrogen, particularly in titanium steels, and treatment of this residue with sulphuric acid and potassium and copper sulphates is necessary.[129] In this method the ammonia is distilled into standard hydrochloric acid, the excess of which is titrated with sodium hydroxide, sodium alizarinsulphonate being the indicator. Errors may arise in the titration of excess sulphuric acid when this is used to absorb the ammonia, owing to the presence of carbonate in the alkali and the indicator used. Bromocresol-blue is recommended.[130] Increased speed in the nitrogen determination may be obtained by dissolution in sulphuric acid, addition of tartaric acid and sodium hydroxide, and distillation of the ammonia.[131] Colorimetric determination of the nitrogen can be made by using the colour with Nessler's reagent and measuring it photoelectrically.[132] Alternatively, G. J. Veinberg [133] adds a 25% solution of thymol in alcohol to a hydrochloric acid solution of the steel, followed by sodium hypobromite. The coloured compound is extracted with ether, and the colour matched against standard ammonium chloride. Substitution of *iso*propyl for ethyl ether produces colours which are intense and unchanging.[134]

Reduction of oxides in nitrogen at 1250°, with tin as a flux, followed by conversion of the resulting carbon monoxide into dioxide by passage over

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[121] J. Wilken, *Arch. Eisenhüttenw.*, 1938—9, **12**, 133.

[122] *Zavod. Lab.*, 1938, **7**, 693.

[123] H. H. Geist and G. C. Chandlee, *Ind. Eng. Chem.* (*Anal.*), 1937, **9**, 169.

[124] P. S. Lebedev, *Zavod. Lab.*, 1938, **7**, 1378.

[125] Eight Report, Heterogeneity of Steel Ingots, *J. Iron Steel Inst.*, May 1939; Third Report of the Oxygen Sub-committee, *ibid.*, Advance Copy, May 1941.

[126] T. Yazima, *Tetsu-to-Hagane*, 1938, **24**, 947.

[127] W. C. Newell, *J. Iron Steel Inst.*, 1940, Advance Copy.

[128] *Tetsu-to-Hagane*, 1939, **25**, 413.

[129] T. R. Cunningham and H. L. Hamner, *Ind. Eng. Chem.* (*Anal.*), 1939, **11**, 303.

[130] I. Wada and R. Ishii, *Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1940, **37**, 65.

[131] H. Kempf and K. Abresch, *Arch. Eisenhüttenw.*, 1940, **14**, 250.

[132] H. F. Beeghly, *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 137.

[133] *Zavod. Lab.*, 1938, **7**, 1251.

[134] G. J. Veinberg, *ibid.*, 1940, **9**, 1073.

heated copper oxide affords a rapid method for the determination of oxygen.[135] Results obtained by this method compare favourably with those obtained by vacuum fusion methods and, apart from aluminium-killed steels, can be obtained in less than 20 minutes. Solid absorbents are satisfactory for the gases produced by reduction in hydrogen at 1250°.[136]

J. G. N. G.

2. Fractional Distillation.

The subject of fractional distillation has of recent years developed greatly and become of such wide and rapidly increasing application and importance in Analytical Chemistry that no excuse is offered for considering it again so soon after the *Annual Reports* of 1940.

It is obviously impossible, in the space available, to deal with every aspect of the subject, and for that reason careful selection has been made of the Sections which appear in this Report. Hence, no mention is made of such matters as the practical design, lay-out, and operation of columns, the theoretical design of columns and the calculations involved, the solution of problems in binary and multicomponent rectification, discussions of batch and continuous distillation, and the importance of reflux ratio. Instead, it was felt that, following the 1940 review, a rather wider consideration of certain branches of the subject might now be of use to indicate the many types of problem in which it is employed and to give some idea of the efficient apparatus which has recently become available. To that end, a fairly comprehensive bibliography is provided.

The sections on the determination of the number of theoretical plates in a column and on the choice of a column are included because such a mass of unco-ordinated and apparently contradictory data has been published on these matters that some confusion is likely to arise in the mind of the non-specialist. It is therefore hoped that these notes may assist in clarifying the position.

(i) *Normal Distillation.*

Laboratory Columns and Accessories.—A review, containing many references up to that date, of the literature on the construction, testing, and operation of laboratory fractionating columns is given by C. C. Ward.[1] He elaborates six essentials for consideration in the design of fractionating equipment: (i) the still-pot should be of adequate size and of shape suitable for maintaining a satisfactory evaporating area throughout the distillation and should be efficiently insulated; (ii) the column should have a height at least 15 times the internal diameter, should be well insulated and provided with a closely controllable heater jacket to compensate for heat losses; (iii) an effective packing or other means of bringing vapour and liquid into close contact is essential; (iv) the packing should have a large surface area, a small hold-up and pressure-drop and be capable of handling a large through-

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[135] L. Singer, *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 127.

[136] G. J. Veinberg, *Zavod. Lab.*, 1940, **9**, No. 1, 23.

[1] *U.S. Bur. Mines*, 1939, Tech. Paper 600.

put; (v) bubble-plates should have similar properties to packings; and (vi) the still-head should be capable of close regulation.

Efficient laboratory columns, then, may be divided into two broad classes, (*a*) those employing plates, which may be perforated or of the bubble-cap type, or a combination of both, and (*b*) those containing packings, which may consist of " dumped " or of uniformly arranged material. Examples of the various types were given in 1940, but mention may be made here of some which have been described recently.

A perforated plate column for analytical batch distillations has been developed by C. F. Oldershaw.[2] The plates are of 25 mm. diameter and have 42, 44, or 81 perforations. Variation of the diameter of the holes showed that with a reflux rate of 2·4 l. per hour the plate efficiency varied from 68% with diameter 1·35 mm. up to 90% with diameter 0·65 mm. For various reasons the author favours the use of 0·85 mm. perforations and a plate spacing of 25—30 mm. The paper includes the results of efficiency tests and comparisons with other columns, including the Stedman and the helix-packed type.

" Dumped " glass helices are the packing material used in an efficient column, designed by A. J. Bailey,[3] with a hold-up of less than 0·1 ml. per plate and H.E.T.P. of 5 cm. A still-head suitable for use at reduced pressures is also described. The same packing is used in an all-glass unit for the distillation of corrosive liquids, such as chlorosulphonic acid, in the absence of air and grease.[4] A continuous apparatus described by R. W. Hufferd and H. A. Krantz [5] employs nickel helices as packing material and has over 50 theoretical plates and a throughput of 3 quarts per hour. Data on distillation of toluene–methy*cyclo*hexane mixtures are given. An expanded shale aggregate packing has been investigated by H. G. Thode and F. O. Walkling,[6] who find that with hydrocarbons the efficiency and throughput compare favourably with those of other packings, whereas with aqueous systems it is even more effective. The authors suggest that this material should not only be applicable industrially but should also be of use in the separation of isotopes. H. R. Snyder and R. L. Shriner [7] have designed a column, intended in particular for the use of students, packed with crystalline carborundum, and other simple columns suitable for routine analysis have been described by L. Smith [8] and by R. W. Harkness and R. E. Bland.[9]

An extremely efficient, uniformly packed column has been designed by H. S. Lecky and R. H. Ewell.[10] A cupped, stainless-steel gauze spiral is fabricated around a central, grooved metal rod, the whole being fitted closely into a glass tube. The efficiency is as high as 18 plates per foot with

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[2] *Ind. Eng. Chem.* (*Anal.*), 1941, **13**, 265. [3] *Ibid.*, p. 487.

[4] A. W. Hixson and A. H. Tenney, *ibid.*, 1942, **14**, 345.

[5] *Ind. Eng. Chem.*, 1941, **33**, 1455.

[6] *Canadian J. Res.*, 1942, **20**, *B*, 61. [7] *J. Chem. Educ.*, 1940, **17**, 588.

[8] *Kgl. Fysiograf. Sällskap. Lund, Handl.*, **47**, No. 5, 1.

[9] *Oil Gas J.*, 1941, **39**, No. 46, 149.

[10] *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 544.

hold-up and pressure-drop only 0·4 ml. per plate and 0·1 mm. of mercury per foot respectively.

R. H. Baker, C. Barkenbus, and C. A. Roswell [11] have developed the spinning-band type of column, which has a low hold-up: their design, 545 cm. high, showed 70 theoretical plates, when tested with the heptane-methyl*cyclo*hexane mixture, with a throughput of 2·7 ml. per minute and hold-up 0·1 ml. per plate. A description of a new fractionating column for the temperature range −190° to 300° has been published by W. J. Podbielniak.[12] The packing may be of two designs, both of the precision-wound, fine-wire type, so arranged that capillary films between the closely spaced turns provide a large liquid surface. Extreme care is taken to ensure adiabatic conditions of operation, for, in addition to highly efficient vacuum jacketing around the flask, column, head, and all connections, a method of compensating for residual leakage of heat is provided. The special vacuum-jacketed ground glass joints may be used for temperature ranges from −190° to 300° while still remaining vacuum-tight. Complete interchangeability of columns and flasks allows the use of the apparatus for a wide variety of purposes. A low hold-up and good throughput are claimed, and tests showed 75 plates in 14 in. length, the performance being maintained when the diameter was increased to 1 inch. Details of efficiency data for various sizes are given. Two arrangements of apparatus, one for preparative work and the other for analytical use, suitable for fractional distillation at low temperatures are also described by H. Koch and F. Hilberath,[13] and the Simons column has been modified for liquids of b. p. −30° to −5° by E. O. Ramler and J. H. Simons.[14]

Several types of laboratory column for the separation of close-boiling hydrocarbons have been compared by G. R. Schultze and H. Stage,[15] and the same authors, with K. Klein,[16] discuss recent types and give details of a glass column, employing 4-chamber tubes, which contains 10 theoretical plates in 62 cm. length. Fractional distillation in spirals with an oscillating and eccentric movement has been accomplished by J. Piazza,[17] and F. Rosendahl [18] has described a column consisting of chambers through which the vapours pass and into which the reflux liquid is sprayed.

The design of still-heads is reviewed by R. E. Gurovich [19] and by A. R. Richards,[20] who emphasise the advantage of vapour take-off systems, in which no liquid hold-up is involved. The latter gives constructional details of a head of this type and discusses a modification in which an automatic device is incorporated for increasing the reflux ratio as the cut-point is

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[11] *Ind. Eng. Chem.* (*Anal.*), 1940, **12**, 468. [12] *Ibid.*, 1941, **13**, 639.

[13] *Brennstoff-Chem.*, 1940, **21**, 197.

[14] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 430. [15] *Z. Elektrochem.*, 1941, **47**, 848.

[16] *Z. physikal. Chem.*, 1941, *A*, **189**, 163.

[17] *Ind. y Quím.*, 1940, **3**, 22; *Anal. Inst. Invest. cient. tecn.*, 1938—9, **8—9**, 56, 78; *Anal. Soc. cient. Argentina*, 1941, **131**, 239.

[18] *Chem. App.*, 1941, **28**, 70.

[19] *Khim. Mashinostroenie*, 1940, **9**, No. 2, 17.

[20] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 649.

approached. A reflux regulator and head for laboratory columns, designed by F. D. Rossini,[21] employs a non-lubricated glass valve and provides a means of measuring throughput and of controlling and estimating the rate of take-off. A magnetically operated valve, which permits take-off of a definite amount of distillate at regular time intervals, is incorporated in a design by B. Ferguson, junr.,[22] and with the addition of a timing device and a recording thermometer a distillation curve can be automatically obtained. A vapour partition head, described by P. Arthur and C. L. Nickolls,[23] is claimed to remove impurities more efficiently than the normal type. An easily cleaned head is described by A. Turk and A. Matuszak [24] and a new type of dephlegmator by A. A. Gaushin.[25]

Among other subjects of interest to constructors of laboratory columns, mention may be made of an automatic device, employing a photoelectric relay system, to control the heat input to a still,[26] a glass needle valve, with grooved stems, suitable for controlling vapour or liquid flow in distillation heads,[27] a double spiral condenser for use in downward distillation or refluxing,[28] a device for overcoming frothing by superimposing a tube containing glass beads,[29] and details of the construction of glass bellows for vacuum jackets,[30] and of glass helices for column packings.[31]

The Determination of the Number of Theoretical Plates in a Column.—The number of theoretical plates contained in a fractionating column is commonly determined by an application of M. R. Fenske's equation [32] for a binary mixture under total reflux.

If n = the number of theoretical plates in the column, x' = the mol. concentration of the more volatile component, x'' = that of the less volatile component, and α = the relative volatility of the two components, then

$$n = \left[\log\left(\frac{x'}{x''}\right)_T\left(\frac{x''}{x'}\right)_B\right] \Big/ \log\alpha$$

where the subscripts T and B refer to the top and the bottom of the packing respectively.

The procedure is to charge the still with a suitable binary mixture, distil under total reflux until the column is in equilibrium, and then take simultaneous samples of reflux from above and below the packing for analysis. In practice, the samples are usually withdrawn from the condenser and the still-pot, allowance being made for the fractionation taking place in these zones.

Two considerations emerge. The first, a practical point, is that for

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[21] *J. Res. Nat. Bur. Stand.*, 1939, **23**, 509.

[22] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 493.

[23] *Ibid.*, 1941, **13**, 356.

[24] *Ibid.*, 1942, **14**, 72.

[25] *Khim. Mashinostroenie*, 1939, **8**, No. 8, 9.

[26] S. A. Hall and S. Palkin, *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 652.

[27] G. P. Gibson, *J. Soc. Chem. Ind.*, 1939, **58**, 317.

[28] M. T. Bush, *Ind. Eng. Chem.* (*Anal.*), 1941, **13**, 592.

[29] G. W. Harmsen, *Chem. Weekblad*, 1941, **38**, 330.

[30] D. J. Pompeo and E. Meyer, *Rev. Sci. Instr.*, 1941, **12**, 368.

[31] *E.g.*, R. W. Price and W. C. McDermott, *Ind. Eng. Chem.* (*Anal.*), 1939, **11**, 289.

[32] *Ind. Eng. Chem.*, 1932, **24**, 482.

accurate determinations of n, care should be taken so to choose the mixture that very small concentrations of one component do not occur at either end of the column. The second is that the value chosen for α will affect the determined number of plates. In many cases the arithmetic or geometric mean value of α proves satisfactory over a reasonably wide concentration range, but a common method of overcoming possible inaccuracies is illustrated by L. B. Bragg.[33] The concentrations of the components in the benzene–ethylene dichloride system are measured by the refractive index, and a graph is constructed of this property against the number of theoretical plates, use being made, not of an average value of α, but of the value corresponding to the particular conditions under consideration. Such a plot has, of course, no particular zero point, the theoretical plate scale merely representing differences, but by its use the number of plates in the column can be obtained immediately from the difference between the values corresponding to the samples from the top of the column and from the still.

Even so, the appropriate values of α are not absolutely fixed. Bragg has used " ideal " values, calculated from the vapour-pressure data of the pure components. Lecky and Ewell [10] have concluded that the system is not an ideal one, and use " apparent " volatility ratios. They show that the values obtained are in fair agreement with those obtained by Bragg's method, but for the purpose of determining the plates in a column they have constructed the corresponding plot for the " ideal " *n*-heptane–methyl*cyclo*hexane system.

In short, it may be concluded that it is essential to compare columns under absolutely identical conditions. This is very strongly emphasised by a recent publication of Bragg and A. R. Richards.[34] They have studied binary mixtures for the purpose of testing Stedman columns at reduced pressures, and have determined values of α for benzene–ethylene dichloride and *o*-dichlorobenzene–diethylbenzene mixtures at various subatmospheric pressures. Included in the data, however, is a plot for the former system at atmospheric pressure, and the values of n, for a 20—30 plate column, obtained from the middle portion of this new graph are of the order of 50% higher than those obtained from the previous plot.

A recent summary by J. Griswold [34a] provides a correlation between relative volatility data for the benzene–ethylene dichloride and heptane–methyl*cyclo*hexane test mixtures. It follows that by using the data favoured by this author for the latter system the agreement between tests made with the two mixtures is good, and the differences found by Lecky and Ewell (see above) are explained.

The Choice of a Column.—Although great importance has been attached in the literature to the H.E.T.P. of laboratory columns, it is not the only, or indeed the most important, factor to be considered in the selection of a suitable packing for a particular purpose. The larger the H.E.T.P. value, of course, the greater will be the length of column to contain a given number of plates,

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[33] *Ind. Eng. Chem.* (*Anal.*), 1939, **11**, 283.
[34] *Ind. Eng. Chem.*, 1942, **34**, 1088.
[34a] *Ibid.*, 1943, **35**, 247.

but this factor will normally enter only in the limiting case where there is insufficient height available to accommodate the required column. The short length of column obtained by using a packing with a low H.E.T.P. gives the advantages of ease of manipulation and ease of obtaining adiabatic operating conditions, but these facilities should not be allowed to over-rule the question of the time taken to carry out the distillation. In many cases it is fairly simple to overcome the difficulties associated with the H.E.T.P. at some initial expense and trouble, but if the apparatus selected is such as to require a long time in order to carry out a satisfactory separation, the user will always be faced with a considerable operating expense or loss of time.

This question of the time required to carry out a given distillation is bound up with that of the hold-up of liquid in the column while it is operating. The factors which affect the efficiency of the separation obtained from the fractionating column are: the number of theoretical plates, the reflux ratio, the total hold-up in the packing under operating conditions, and the ratio of charge to the hold-up. The effect of the first two of these factors has been much studied, but considerably less attention has been paid to the remaining two. The loss of fractionating efficiency due to increase in hold-up has been investigated theoretically by A. Rose, L. M. Welshans, and H. H. Long.[35]

The point may be brought out by the following simple consideration. Suppose we have a column with a large number of theoretical plates and running at a high reflux ratio, separating a mixture of two components, A and B, and the efficiency of the column is such that substantially pure A will be taken overhead when the concentration of A in the still is 1%. We will suppose that the column hold-up is 50 ml. and that the mixture charged to the still contains 100 ml. of component A and 900 ml. of component B. By the time distillation has proceeded to the point at which there is 1% of A remaining in the still, the contents of the latter will be approximately 875 ml. of B, and 9 ml. of A. Inside the column itself the average composition of the hold-up will be 50% of each component, and there will be, therefore, 25 ml. of A held up. The result is that, up to this point, 66 ml. of A will have been produced as distillate in a pure condition, and from now on the degree of purity will gradually fall. Now consider a similar case in which the same column and mixture are used but the volume of material charged is increased ten times. At the critical point the still will contain approximately 9,000 ml. of B and 90 ml. of A, and the hold-up in the column will contain 25 ml. of A as before. Consequently, 885 ml. out of the initial 1,000 ml. of A will have been produced in a pure state. The result of increasing the ratio of charge to hold-up has thus been to increase the recovery of pure A from 66 to 88·5%, and furthermore the rate at which the purity will fall off will be lower in the second case.

From these considerations it will be seen that two columns containing the same number of theoretical plates, operated at the same reflux ratio and with the same ratio of charge to hold-up, will give comparable fractionating efficiencies. Thus, the construction of a still and column can be so

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[35] *Ind. Eng. Chem.*, 1940, **32**, 668, 673, 675.

arranged that any type of packing will give an identical degree of separation with that of any other column, since the plates and ratio of charge to hold-up may both be varied independently and therefore appropriate values may be selected; but once these values have been fixed, the time taken to carry out a distillation has also been automatically fixed.

The question of the satisfactory ratio of charge to hold-up is one to which it is difficult to give a specific answer, but experience has shown that for efficient fractionation, particularly of complex mixtures, the still charge should be at least 20 times the hold-up.

Having by these considerations chosen a column, a certain size of charge, and a reflux ratio, the time taken to carry out the distillation will have been fixed, and it is desirable therefore, when considering column packings, to have some factor which will allow one to see whether this time is going to be long or short. The factor chosen, called the " hold-up factor," is conveniently expressed as ml. of hold-up per theoretical plate divided by the operating boil-up rate in ml. per second.[36] The value of this factor is a direct measure of the time taken to carry out any given distillation. In other words, if two columns are arranged with identical numbers of plates, charge, etc., one of them being packed with material having a hold-up factor of 4 and the other with material having a hold-up factor 8, any given distillation will take twice as long in the second column as it will in the former. Factors of similar form have also been introduced by L. B. Bragg[37] and W. J. Podbielniak.[12]

The determination of hold-up, particularly under actual operation conditions, is not easy, and only a few values are available in the literature. Moreover, their usefulness is somewhat impaired by the fact that when making comparisons between columns it is advisable to ensure that the tests have been carried out by exactly the same methods. In Tables I and II results of tests on a wide variety of column packings are given. In the first table the tests have all been made in exactly the same way under conditions similar to those which will occur in practice. In the second table some further results are given for the sake of interest, although the test data have not been determined under strict operating conditions, but in separate experiments in which cold light petroleum has been run down the column countercurrent to a stream of air (presaturated with petroleum vapour). It is known that this method of determining hold-up gives high values, and therefore it should be realised that the hold-up factors given in Table II are probably on the high side.

There is one further point to be noted when considering the data. The efficiency of a packing is often greatly increased by flooding the column before starting distillation. Several of the packings in Table I have been tested with and without this initial flooding, and the effect on the number of theoretical plates and the hold-up factor will be apparent.

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[36] Research Department, Anglo-Iranian Oil Co., Ltd. The author is indebted to this Company for permission to use data included in this Section and would particularly like to express his appreciation to Messrs. P. Docksey and J. W. Hyde for so kindly placing their experience and advice at his disposal.

[37] *Trans. Amer. Inst. Chem. Eng.*, 1941, **37**, 19.

Test Data on Column Packings.

TABLE I.

Data obtained under operating conditions.

No.	Type of packing.	Conditions of operation.	Dimensions of column.		Boil-up rate,* ml./hr.		Efficiency data at operating rate.						
			Diam., mm.	Length, cm.	At flood point.	At normal operating rate.	Theoretical plates (C_6H_6–$C_2H_4Cl_2$).	H.E.T.P., cm.	Hold-up, ml.* Static.	Dynamic.	Total.	Per theoretical plate.	Hold-up factor, ml./plate per ml./sec.
1	Glass helices, ⅛ in.	Preflooded	20	157	2,000	1,800	41·5	3·8	1·0	55	56	1·35	2·7
		Unflooded	20	157	2,000	1,800	32	4·9	1·0	55	56	1·75	3·5
2	" " ¼ in.	Unflooded	35	205	10,000	8,500	22	10·5	5·0	280	285	13·0	5·8
3	Steel " 5/32 in.	Preflooded	20	86·5	2,700	2,200	13·5	6·4	1·8	18·5	20·3	1·50	2·5
		Unflooded	20	86·5	2,700	2,200	13	6·6	1·8	18·5	20·3	1·56	2·6
4	Stedman, type 114	Preflooded	25·4	61	1,800	1,400	23	2·65	1·1	22·4	23·5	1·02	2·6
		Unflooded	25·4	61	1,800	1,400	19	3·2	1·1	22·4	23·5	1·24	3·2
5	Spiral screen (cupped spiral, 4 mm. core)	Preflooded	17	46	660	400	25	1·83	1·1	6·3	7·4	0·30	2·6
		Unflooded	17	46	660	400	11	4·2	1·1	6·3	7·4	0·67	6·1
6	Podbielniak (wire spiral)	Unflooded	3·7	128	—	150	7	18·3	—	—	1·2	0·17	4·1
7	Empty tube	Unflooded	4·15	128	—	250	8	16	—	—	0·6	0·075	1·08
8	Eyelets (No. 2) **	Preflooded	36	137	7,000	6,000	13·5	10·1	7·8	97	105	7·75	4·7
		Unflooded	36	137	7,000	6,000	13·5	10·1	7·8	97	105	7·75	4·7
9	" "	Unflooded	49	517	13,500	12,400	42	12·3	57	710	767	18·3	6·5
10	Glass tube, I.D. 6 mm., O.D. 7·5 mm., length 8 mm.	Preflooded	37·5	119	7,000	6,000	7·0	17	6	36	42	6·0	4·1
		Unflooded	37·5	119	7,000	6,000	7·0	17	6	36	42	6·0	4·1

* Light petroleum (b. p. 60°). ** Tinned brass hollow cylinders, I.D. 4·14 mm., O.D. 4·57 mm., length 3·68 mm.

TABLE II.

Data obtained by countercurrent method with cold light petroleum.

No.	Type of packing.	Dimensions of column.		Boil-up rate, ml./hr.		Efficiency data at operating rate.						
		Diam., mm.	Length, cm.	At flood point.	At normal operating rate.	Theoretical plates.	H.E.T.P., cm.	Hold-up, ml. Static.	Dynamic.	Total.	Per theoretical plate.	Hold-up factor, ml./plate per ml./sec.
11	Glass helices, ⅛ in.	20	157	2,000	1,800	32	4·9	20	62	82	2·56	5·1
12	Steel Lessing rings, $\frac{1}{16}$ in.	14	100	—	960	4·5	22	—	—	9	2·0	7·5
13	" " " ⅛ in.	14	100	—	960	3·5	28	—	—	8	2·3	8·6
14	" " " "	36	29	10,000	8,000	1·6	18·1	—	—	33·5	21	9·5
15	" " " $\frac{3}{16}$ in.	102	945	80,000	50,000	42	22·5	—	—	—	—	—
16	Porcelain Lessing rings, ¼ in.	64 102	214 415	13,000 33,000	11,000 28,000	12·9 25	16·5 16·6	— —	— —	— —	— —	— —
17	" " " ⅜ in.	102	885	47,700	43,300	41	21·6	—	—	—	—	—
18	" " " ½ in.	204	244	—	—	7·4	33	—	—	—	—	—
19	Steel helices, $\frac{3}{32}$ in.	49	873	11,000	10,000	85	10·3	—	—	—	—	—

Applications.—The requirements for columns for the separation of hydrocarbon mixtures are enumerated by C. Koeppel,[38] who describes suitable apparatus, expressing a preference for the long-vapour-path type of column. Various applications are discussed. A comparison of Podbielniak and other type columns for this purpose is made by J. J. Savelli, W. D. Seyfried, and B. M. Filbert,[39] and H. Macura and H. Grosse-Oetringhaus [40] have made experiments on the fractionation of aromatic and paraffin mixtures in columns containing various types of packings. A column is described, packed with metal spirals, by means of which as little as 1% of toluene can be detected, in mixtures with benzene and xylene, at distillation rates of the order of 30 ml. per hour. Hexane can similarly be determined in mixtures with pentane and heptane, and a modification of the column increases the sensitivity of the aromatic analysis to the extent of detecting 0·5% of toluene at a slightly higher distillation rate.

This problem of the routine analysis of coal-tar spirits has assumed considerable importance during recent years. The matter is complicated by the fact that the increasing popularity of the vertical retort has resulted in the production of what is known as " low gravity " benzole, *i.e.*, material in which the aromatic constitutents are associated with considerable quantities of other hydrocarbons. The use of empirical methods, such as the classical Colman–Yeoman procedure, is not applicable with accuracy in such cases, and a distillation test has been developed at the Government Laboratory.[41] A small, metal-spiral packed column, known as G.L. 1 design, containing 7 theoretical plates, with a low hold-up and a fixed reflux head to simplify routine operation, is used. A charge of 25 ml. is adequate and a distillation rate of 10—20 ml. per hour may be employed. The accuracy is such that under these conditions small quantities of toluene may be estimated within 0·4% or less. By increasing the charge to 100 ml. the accuracy is increased to 0·1%. To allow for associated non-aromatic hydrocarbons, the percentage of toluene present in the toluene fraction is estimated by refractive index, specific gravity, or critical solution temperature with acetic acid, and graphs have been constructed for this purpose.

Applications of the G.L. 1 column have also been extended to include the estimation of benzole in wash oil. In this test a " bridge " of *cyclo*hexanol is added to prevent the column from flooding owing to distillation of wash oil after the benzole has distilled over. The ordinary fractionation method of determining the benzene content of wash oils has been criticised by W. Brösse,[42] who describes a new method involving the use of fine fractionating columns. Several times as much benzene is claimed to be recovered with an error normally within 2%. The same system has also been studied by L. Koeppel.[43] He concludes that phenol is an undesirable constituent of wash

[38] *Oel u. Kohle ver. Petroleum*, 1940, **36**, 194.

[39] *Ind. Eng. Chem.* (*Anal.*), 1941, **13**, 868.

[40] *Oel Kohle Erdoel Teer*, 1939, **15**, 591.

[41] J. W. J. Fay, unpublished.

[42] *Tech. Mitt. Krupp : Forschungsber.*, 1940, **3**, 2.

[43] *Gas- u. Wasserfach*, 1940, **83**, 73; *Glückauf*, 1939, **75**, 465; *Chem. Zentr.*, 1940, I, 487.

oil for gas stripping, and that cracking of wash oil samples occurred during laboratory experiments in which they were heated above 190°. A development of the G.L. 1 column, known as the G.L. 2 design, is now being used for the estimation of phenols and other tar acids in mixtures which could not previously be analysed accurately and conveniently.

The reported separation and identification, by Goldwasser and Taylor, of six isomeric hexenes with an overall b. p. spread of 2·5° has been criticised by F. C. Whitmore and others[44] and by A. Rose.[45] The former, using a Podbielniak–Simons–Taylor column containing approximately 15 theoretical plates, failed to effect separation of similar mixtures having up to 2·7° spread. Rose calculates that more than 400 theoretical plates would be required for such sharp batch fractionations and that a column with only a few plates, even with a very small hold-up and with the use of a very high reflux ratio, can give no appreciable separation.

Stedman columns, the advantages of which have been reviewed by Bragg,[37] have been used for the fractionation of Turner Valley (Canada) crude oils by R. M. Donald[46] and by L. M. Watson and J. W. T. Spinks,[47] and the physical constants of many aliphatic hydrocarbons have been determined, after purification by fractionation, by D. B. Brooks, F. L. Howard, and H. C. Crafton, junr.[48] F. C. Whitmore, L. H. Sutherland, and J. N. Cosby[49] have used 20—25 plate columns to prepare pure intermediates for the synthesis and study of substituted docosanes. Among other applications, mention may be made of the use of the Piazza column for the determination of alcohol in foaming liquors[50] and wines;[51] a discussion of the general laboratory applications of this still by R. Rouzaut;[52] studies of the removal of entrained impurities from distilled water by a glass ring-packed column[53] and of the packed tower collection of phosphoric acid;[54] the dehydration of methyl benzenesulphonate;[55] and a description of a simultaneous chemical reaction and fractional distillation apparatus, applicable to any isomerisation process, in which the reaction vessel is used as the still-pot of a continuous fractionating column.[56]

A full account, with photographs, of the apparatus and methods used at the National Bureau of Standards for the analytical separation and purification of gases by fractional distillation and rectification at low temperature is given by M. Shepherd.[57] R. L. Geddes[58] has published an interesting

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[44] *J. Amer. Chem. Soc.*, 1940, **62**, 795.
[45] *Ibid.*, p. 793.
[46] *Canadian J. Res.*, 1940, **18**, *B*, 12.
[47] *Ibid.*, p. 388.
[48] *J. Res. Nat. Bur. Stand.*, 1940, **24**, 33.
[49] *J. Amer. Chem. Soc.*, 1942, **64**, 1360.
[50] *Ind. y Quím.*, 1940, **3**, 29.
[51] J. Piazza and R. Rouzaut, *Anal. Inst. Invest. cient. tecn.*, 1938—9, **8—9**, 82.
[52] *Anal. Soc. cient. Argentina*, 1941, **131**, 251.
[53] Chi-Chuan Shen, *J. Chinese Pharm. Assoc.*, 1940, **2**, 293.
[54] W. H. Baskervil, *Trans. Amer. Inst. Chem. Eng.*, 1941, **37**, 79.
[55] A. M. Shuer, *Khim. Mashinostroenie*, 1939, **8**, No. 8, 19.
[56] B. Longtin and M. Randall, *Ind. Eng. Chem.*, 1942, **34**, 292.
[57] *J. Res. Nat. Bur. Stand.*, 1941, **26**, 227.
[58] *Ind. Eng. Chem.*, 1941, **33**, 795.

correlation between true b. p. and the standard A.S.T.M. distillation curves of petroleum fractions : on the basis of a large number of collected routine results it is possible to estimate either of these curves if the other has been determined.

The microfractionation of a single drop of liquid into 30—70 fractions is described by A. A. Morton and J. F. Mahoney.[59] A vertical tubular capillary, packed with glass wool and jacketed to prevent heat loss, is employed. A graph of the b. p. of each fraction shows the existence of one or more compounds and the percentage composition can be estimated from it. Details are given of the apparatus and procedure, together with results obtained with benzene–toluene, benzene–xylene, ethyl alcohol–butyl alcohol, ethyl alcohol–methyl ether, and ethyl acetate–butyl acetate mixtures.

A small selection of patents which have been taken out provides interesting evidence of the application of fractionation processes in this sphere. J. R. Bailey [60] facilitates the separation of such materials as *n*- and *iso*-pentane by adding to the complex narrow boiling-range paraffin mixture a chemically dissimilar and easily separable carrier having a wider boiling range than the original mixture. By cutting into fractions and separating off the carrier, a series of sharply defined cuts of the initial mixture is obtained. R. R. Dreisbach and J. E. Pierce [61] retard the polymerisation of vinyl aromatic compounds during distillation by packing the column with a substantially insoluble agent effective in inhibiting polymerisation, and the same principle is applied by C. E. Barnes,[62] who uses a metal packing to inhibit polymerisation during the purification of methacrylic acid. The addition of a volatile hydrocarbon having an initial b. p. not more than 15° F. above that of the required pure material is advocated by F. M. Archibald and C. A. Cohen [63] to assist in the purification by distillation of aliphatic polyoxygenated compounds such as glycerol.

(ii) *Azeotropic Distillation.*

Reviews.—A comprehensive study of the subject has been made by B. J. Mair, A. R. Glasgow, junr., and F. D. Rossini.[64] They present the general theory and, in the particular application to hydrocarbons, find that almost all polar organic compounds produce azeotropes with these compounds. The b. p. depression, and hence the ease of separation, decreases in the order paraffins, naphthenes, mono-olefins, diolefins, aromatics. They recommend choice of an azeotrope-forming compound with b. p. 0—30° below that of the close-cut hydrocarbon fraction to be treated and emphasise the desirability of choosing a material easily separated from the hydrocarbon, as, *e.g.*, by extraction with water. The review includes a list of hydrocarbons separable by this means from petroleum.

The theory of azeotropic mixtures is dealt with by V. A. Kireev,[65] who

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[59] *Ind. Eng. Chem.* (*Anal.*), 1941, **13**, 494.

[60] U.S.P. 2,231,241.

[61] U.S.P. 2,240,764.

[62] U.S.P. 2,241,175.

[63] U.S.P. 2,228,431.

[64] *J. Res. Nat. Bur. Stand.*, 1941, **27**, 39; *Refiner*, 1940, **19**, 438.

[65] *Acta Physicochim. U.R.S.S.*, 1941, **14**, 371.

develops equations correlating composition and vapour pressure. Deduced values are found to agree well with published data for many different mixtures of organic liquids. G. Schouls [66] has derived thermodynamical distillation relationships with particular reference to rates of vaporisation and explains the constancy of temperature and pressure in azeotropic distillation by the hypothesis, which is in agreement with experimental data, of distillation at constant rates.

The behaviour of ternary mixtures on distillation has been fully discussed by W. Reinders and C. H. de Minjer,[67] who pay particular attention to the effect upon the ternary systems of azeotropic points among the binary systems. A general discussion of the theory and practice of distillation with steam and other vapours is given by G. A. Fester,[68] and, among further publications reviewing general or particular aspects of azeotropy, mention may be made of a comprehensive discussion of the subject and its uses by T. Hannotte; [69] its applications in the dehydration of acetic acid and in many industrial processes by D. F. Othmer; [70] a general discussion of third-component, or "entrainer," distillation by D. B. Keyes,[71] who gives examples in hydrocarbon and aqueous systems; a review of the maximum boiling mixtures of chloroparaffins with donor liquids by R. H. Ewell and L. M. Welch; [72] and a mathematical consideration of entropy changes during azeotrope formation by A. K. Zhdanov.[73]

Experimental Work.—Many investigators have devoted their attention during recent years to the study of relevant data. E. M. Baker, R. O. H. Hubbard, J. H. Huguet, and S. S. Michalowski [74] have constructed composition curves from refractive index and density determinations for the systems ethanol–water, ethanol–cellosolve, and cellosolve–water, and Baker, with R. E. Chaddock, R. A. Lindsay, and R. C. Werner,[75] publishes results for the corresponding ternary system. W. M. Langdon and D. B. Keyes [76] have obtained vapour–liquid equilibrium data for the ethanol–water system and also for the *iso*propyl alcohol–water mixture, in which they find that the azeotrope contains 68·35 mol.% of the alcohol. The latter system has also been studied by J. E. Schumacher and H. Hunt,[77] who have investigated the minimum-boiling azeotropes in the mixture nitromethane–*iso*propyl alcohol–water. Data are given for the ternary system and for the three corresponding binary combinations. W. D. Bonner and M. B. Williams [78] have worked at pressures down to 160 mm. of mercury on the separation of water and alcohol in presence of benzene. Using refractive index as a

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[66] *Bull. Soc. chim. Belg.*, 1940, **49**, 214.

[67] *Rec. Trav. chim.*, 1940, **59**, 207.

[68] *Rev. Centro Estud. Ing. Quim.*, Univ. Nacl. Litoral (Santa Fé, Argentina), 1940, No. 15, 97.

[69] *Chem. Zentr.*, 1940, **1**, 3578.

[70] *Chem. Met. Eng.*, 1941, **48**, No. 6, 91; *Ind. Eng. Chem.*, 1941, **33**, 1106.

[71] *Ibid.*, p. 1019.

[72] *J. Amer. Chem. Soc.*, 1941, **63**, 2475.

[73] *J. Gen. Chem. Russia*, 1941, **11**, 483.

[74] *Ind. Eng. Chem.*, 1939, **31**, 1260.

[75] *Ibid.*, p. 1263.

[76] *Ibid.*, 1942, **34**, 938.

[77] *Ibid.*, p. 701.

[78] *J. Physical Chem.*, 1940, **44**, 404.

method of analysis, they find that the water is most efficiently removed at lower pressures.

Among other binary systems investigated, interesting data have been compiled by S. Takagi[79] on the b. p.'s of formic acid–water mixtures. Starting from samples of higher and lower concentrations than those of the azeotropic mixtures, and carrying out experiments to coincidence of constant b. p.'s, he obtains results of accuracy within ±1° in temperature and ±0·1% in composition. K. Tuda, A. Oguri, and S. Hukusima[80] find 43·6% by weight (0·65 mol.) of acetic acid in the azeotrope with α-diethylamino-butan-γ-ol, and P. I. Lebed[81] reports 85% by weight of ethyl alcohol in its azeotrope with *m*-xylene. The vapour–liquid equilibria in the three binary systems formed by acetone, chloroform, and benzene have been studied by W. Reinders and C. H. de Minjer,[82] who find that only the acetone–chloroform mixture possesses an azeotropic point, the composition being 78·5% of chloroform and the maximum b. p. 64·5°. The same authors[83] have determined the course of the distillation line in the corresponding ternary mixture. H. J. McDonald[84] states that ethyl alcohol separates from the boiling ternary mixture with glycerol and benzene in such a manner that its mol.-fraction is the same in the vapour as in the liquid phase.

Applications.—The fundamental work of Mair and others, to which reference is made above, has been applied to the isolation of a number of pure substances from petroleum. The normal procedure is to subject a close-cut (approximately 2°) fraction to azeotropic distillation with a suitable polar organic liquid in a very efficient column containing between 50 and 100 theoretical plates. Using entrainer liquids such as diethylene glycol monomethyl ether, Mair and A. J. Streiff[85] have separated the aromatic hydrocarbons and isolated in a pure state naphthalene and various other compounds from petroleum, and A. R. Glasgow[86] has separated high-boiling paraffins from the same source.

An interesting application has been described by D. F. Othmer, J. J. Jacobs, junr., and J. F. Levy.[87] The continuous nitration of benzene is accomplished by using nitric acid without any dehydrating agent, the water of reaction being removed as it is produced by azeotrope formation with the benzene.

C. R. Smith[88] has made a study of the system nicotine–water and applies the results to the separation of nicotine from related alkaloids. R. Negisi and T. Isobe[89] have investigated mixtures of water with *n*- and *iso*-butyl alcohols. They find that the azeotropes contain 57·6 and 67% of the alcohols respectively, the b. p.'s being 92·6° and 90°, and claim practically quantitative separation of the alcohols from associated hydrocarbons.

[79] *Bull. Chem. Soc. Japan*, 1939, **14**, 508.

[80] *J. Pharm. Soc. Japan*, 1941, **61**, 74.

[81] *J. Physical Chem.* (*U.S.S.R.*), 1940, **14**, 277.

[82] *Rec. Trav. chim.*, 1940, **59**, 369.

[83] *Ibid.*, p. 392.

[84] *J. Physical Chem.*, 1941, **45**, 706.

[85] *J. Res. Nat. Bur. Stand.*, 1940, **24**, 395; 1941, **27**, 343.

[86] *Ibid.*, 1940, **24**, 509.

[87] *Ind. Eng. Chem.*, 1942, **34**, 286.

[88] *Ibid.*, p. 251.

[89] *Bull. Chem. Soc. Japan*, 1941, **16**, 278.

The advantages of an anhydrous entrainer liquid over steam for certain classes of material are reviewed by G. A. Fester and A. Collados,[90] who propose the use of a kerosene cut instead of water for the distillation of pyrogallol and phenols in general.

An idea of the wide application of azeotropism can be obtained by a brief survey of some patents recently taken out which involve the use of this process. For example, the drying of acetic and other aliphatic acids is accomplished by entraining the water impurity with propyl acetate and propyl alcohol,[91] di*iso*butyl ketone,[92] a mixture of di*iso*propyl ketone with ethyl *iso*propyl ketone,[93] or butyl acetate.[94] Procedures for the separation of aromatic, unsaturated, and paraffin hydrocarbons from mixtures with each other and other substances include the purification of low-boiling aromatics by azeotropically distilling associated hydrocarbons with methyl alcohol,[95] methyl acetate,[96] acetone,[97] or crotonaldehyde,[98] the separation of paraffins from olefins,[99] and the purification of indene by distillation of the oil with phenol,[1] glycols,[2] and many other organic compounds containing a carboxyl, hydroxyl, amino- or pyridinic nitrogen radical.[3] A small quantity of maleic anhydride is found to facilitate the purification of anthracene by distillation in presence of a polyhydric alcohol, such as ethylene glycol, having a b. p. in the neighbourhood of 200°.[4] A similar azeotrope-forming substance is utilised in the removal of cyclic ethers from acetone,[5] from which water may be removed by distillation with an aliphatic hydrocarbon of b. p. 28—100°.[6]

Methods for the separation and purification of phenol and its derivatives include its removal from *cyclo*hexanone by distillation with a compound containing at least two alcoholic hydroxyl groups, such as diethylene glycol.[7] Coloured impurities are removed from phenothiazine by distillation with chlorinated diphenyl ether.[8] Other interesting applications include the simultaneous production and purification of aliphatic hydroxy-substances such as glycerol by treating a corresponding halogen compound with water and removing the halogen acid from the reacting zone as the aqueous azeotrope,[9] the dehydration of unsaturated aliphatic cyanides with methylene

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[90] *Anal. Asoc. Quim. Argentina*, 1942, **30**, 36.

[91] A. W. Bright and J. H. Zeigler, U.S.P. 2,199, 982.

[92] D. F. Othmer, U.S.P. 2,275,862.

[93] *Idem*, U.S.P. 2,269,163.

[94] D. F. Othmer and R. E. White. U.S.P. 2,275,802.

[95] H. M. Spiers and H. K. Suttle, B.P. 536,172.

[96] E. Field, U.S.P. 2,279,194.

[97] *Idem*, U.S.P. 2,212,810.

[98] F. W. Sullivan, jun., U.S.P. 2,265,220.

[99] Phillips Petroleum Co., B.P. 521,092.

[1] K. H. Engel, U.S.P. 2,279,778.

[2] *Idem*, U.S.P. 2,279,779.

[3] *Idem*, U.S.P. 2,279,780.

[4] J. A. C. Yule, U.S.P. 2,213,755.

[5] British Celanese Ltd., B.P. 539,487; J. E. Bludworth, U.S.P. 2,273,923.

[6] J. F. Eversole and A. C. Plewes, U.S.P. 2,259,951.

[7] E. Field, U.S.P. 2,265,939.

[8] E. C. Britton, F. B. Smith, and R. L. Brown, U.S.P. 2,284,124.

[9] H. Dreyfus, B.P. 536,428.

chloride,[10] the concentration of aqueous halohydrin solutions,[11] and the separation of hexamethyleneimine from the diamine by distilling it as an azeotrope with water.[12]

(iii) *Vacuum and Molecular Distillation.*

Reviews.—Many publications on this increasingly important subject have been made in the last year or two. The principles involved in ordinary, vacuum and molecular distillations are discussed by M. Furter,[13] and molecular, or short-path, distillation has been reviewed by several workers, including D. D. Howat,[14] who discusses thermal efficiency and the degree of fractionation, W. F. Withers,[15] and H. I. Waterman and C. van Vlodrop.[16] S. B. Detwiler, junr.,[17] has issued a supplement to his bibliography on this subject.

Apparatus.—The performance of laboratory columns packed with Raschig rings, Berl saddles, and spiral screen gauze at reduced pressure (20 mm. of mercury) for the fractionation of terpenes has been studied by W. D. Stallcup, R. E. Fuguitt, and J. E. Hawkins,[18] who conclude that the last is the most efficient packing yet described for this type of work. E. Kirschbaum [19] has used ethanol–water mixtures to investigate the efficiency of bubble-plate columns at pressures down to 50 mm. Much information, including pressure-drop data, is presented, together with a graph indicating permissible vapour velocity as a function of other variables. The concentric-tube type of column, which has been critically examined, among other open tube types, by J. H. Westhaver,[20] has been used in an apparatus described by S. A. Hall and S. Palkin [21] for the efficient fractionation of α- and β-pinene at 20 mm. pressure. Two other vacuum stills which may be mentioned are an apparatus for the fractional vacuum distillation of small quantites of high-boiling mixtures [22] and a 2·5-l. capacity still, described by the Histology Laboratory of the University of Amsterdam,[23] suitable for fractionation, at about 10 mm. pressure, of alcohol, urine, etc. Another development is the modification, by C. E. Watts, J. A. Riddick, and F. Shea,[24] of the A.S.T.M. standard distillation apparatus to enable boiling ranges to be determined at reduced pressures.

Various devices have been designed to overcome the tendency to frothing during vacuum distillations. M. Burger, who has also designed a neat

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[10] E. C. Britton and A. R. Sexton, U.S.P. 2,263,436.

[11] W. C. B. Smithuysen, U.S.P. 2,188,254; W. Coltof, Can.P. 394,847.

[12] E. I. du Pont de Nemours and Co., B.P. 535,024.

[13] *Mitt. Lebensm. Hyg.*, 1939, **30**, 200.

[14] *Chem. Age*, 1941, **45**, 309, 323; 1942, **46**, 3.

[15] *J. Proc. Austral. Chem. Inst.*, 1942, **9**, 103.

[16] *Rev. Chim. ind.*, 1939, **48**, 314.

[17] *Oil and Soap*, 1940, **17**, 241.

[18] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 503.

[19] *Z. Ver. deut. Ing.*, 1940, No. 3, 69.

[20] *Ind. Eng. Chem.*, 1942, **34**, 126.

[21] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 807.

[22] E. Klenk and K. Shuwirth, *Z. physiol. Chem.*, 1941, **267**, 260.

[23] *Chem. Weekblad*, 1941, **38**, 546.

[24] *Ind. Eng. Chem.* (*Anal.*), 1942, **14**, 506.

continuous vacuum distillation apparatus.[25] describes a valve accessory which permits the introduction of a little air through an extra tube.[26] I. Levin [27] uses the foam level to actuate a relay to achieve the same object, and D. R. Rexford [28] has designed a device in which an air-leak, provided through a stop-cock, is operated by a counterpoised mercury bulb. The frequency of this de-foaming cycle may be adjusted between 8 and 20 phases per minute.

Pressure regulating and measuring devices have been described by many writers. An ingenious method is employed by A. Rollett.[29] An inverted glass filter cell, lacquered so that only a wedge-shaped porous surface is exposed, is immersed in mercury to the required depth and connected to a level-regulating manometer, so that the amount of gas admitted to the apparatus can be adjusted and controlled. An extremely simple but effective device, constructed from a gas-washing bottle, is described by M. S. Newman,[30] and others who have designed regulators include J. H. Thelin,[31] who obtains pressure control within 0·1 mm. of mercury up to 200 mm., B. Ferguson, junr.,[32] who employs a magnetically operated capillary leak, C. B. de Witt,[33] whose apparatus includes a trap and manometer system, and M. J. Caldwell and H. N. Barham,[34] who use a glass valve pressure regulator capable of controlling pressures above or below atmospheric to about 1 mm. of mercury. E. R. Kline [35] describes a modified McLeod gauge for the measurement of moderate vacuum (0·05—2 mm. of mercury).

A simple receiver, utilising two standard 3-way stop-cocks, which allows any required number of fractions to be collected without disturbing the pressure in the still, has been designed by R. S. Towne, E. E. Young, and L. T. Eby.[36] J. B. Cloke [37] has described a vacuum-jacketed receiver, J. W. Patterson and R. W. Van Dolah [38] adaptors for the collection of fractions, and A. J. Bailey [39] a still-head, mounted within the flask, for the low-pressure distillation of organic mixtures. Miscellaneous publications include the description of a method of economising in water during prolonged use of a filter pump,[40] a trap to prevent blackflow from suction pumps,[41] and the preparation, from shellac and pine-tar oil, of a laboratory cement, suitable for vacuum work.[42]

F. Wittka [43] has dealt in considerable detail with the equipment, described up to that time, for laboratory and large-scale molecular distillation. A

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[25] *J. Lab. Clin. Med.*, 1940, **25**, 1221.
[26] *Chemist-Analyst*, 1940, **29**, 20.
[27] *Ibid.*, p. 89.
[28] *Ind. Eng. Chem. (Anal.)*, 1941, **13**, 95.
[29] *Ber.*, 1940, **73**, 1023.
[30] *Ind. Eng. Chem. (Anal.)*, 1940, **12**, 274.
[31] *Ibid.*, 1941, **13**, 908.
[32] *Ibid.*, 1942, **14**, 164.
[33] *Chemist-Analyst*, 1941, **30**, 40.
[34] *Ind. Eng. Chem. (Anal.)*, 1942, **14**, 485.
[35] *Ibid.*, p. 542.
[36] *Ibid.*, 1941, **13**, 626.
[37] *Ibid.*, 1940, **12**, 329.
[38] *Ibid.*, 1942, **14**, 511.
[39] *Ibid.*, p. 71.
[40] G. F. Shapley, *Pharm. J.*, 1942, **148**, 71.
[41] A. E. Meyer, *Ind. Eng. Chem. (Anal.)*, 1942, **14**, 505.
[42] W. C. Fernelius, "Inorganic Syntheses," McGraw-Hill Co., No. 67, p. 189.
[43] *Angew. Chem.*, 1940, **53**, 557.

large number of diagrams and an extensive bibliography are provided. Recently, A. J. Bailey[44] has described the construction of a simple molecular still from two Pyrex micro-belljars and a heated brass plate, the apparatus being suitable for the distillation of such material as lignin. An improved form of the laboratory molecular still of Main, Shicktanz, and Rose, suitable for the separation of vegetable and animal fats and oils, is given by S. B. Detwiler, junr., and K. S. Markley,[45] a means for the intermittent withdrawal of fractions being provided.

In publications dealing with accessory equipment, D. D. Howat[14] describes low-pressure gauges and compares the relative merits of mercury and oil pumps, the design, construction, and working of which are also discussed by K. D. Sinelnikov, A. K. Walter, D. N. Ulezko, and A. N. Yamnitskiĭ.[46] S. Eklund[47] has made some measurements of ultimate vacuum and the pump speed of molecular pumps and describes a very efficient design.

Applications.—Certain aspects of this subject have been considered by J. N. Ray[48] in his discussion of recent developments in the study of the constitution of natural products. Howat[49] gives an extensive review of the literature on the preparation of vitamins *A*, *D*, and *E*.

Vacuum distillation has been applied to the study of Rumanian petroleum by T. Cosciug,[50] who collects various 2° fractions at 20 mm. pressure; to the recovery of used mineral oils by K. Thomas,[51] and to the preparation of pure lactic acid by G. Genin.[52] F. A. Norris, I. I. Rusoff, E. S. Miller, and G. O. Burr[53] have investigated the effect of vacuum distillation through packed columns on the absorption spectra of the methyl esters of highly unsaturated fatty acids. They conclude that the products obtained are sufficiently representative to be used in isolation and structure work. Use of spiral screen and Stedman columns at pressures of the order of 15—20 mm. has been made[54] for the purpose of separating certain constituents of heavy coal-tar naphtha in a pure state.

A study of petroleum and tar products by distillation under a cathodic vacuum has been made by several workers. M. Richter[55] has examined aeroplane-motor fuels and uses the results obtained by distillation in a 200-ml. copper still at 0·001 mm. pressure to determine the constitution and assess the performance of lubricants. The absolute identification of lubricating oils by the application of a similar technique is described by R. Petit, Y. Crimail, and R. Duchêne.[56] Louis[57] uses the method to study

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[44] *Ind. Eng. Chem.* (*Anal.*), 1942, **14,** 177.

[45] *Ibid.*, 1940, **12,** 348.

[46] *J. Tech. Physics* (*U.S.S.R.*), 1941, **11,** 879.

[47] *Arkiv Mat. Astron. Fysik*, 1940, **27,** *A*, No. 21.

[48] *Proc. Nat. Inst. Sci., India*, 1939, **5,** 205.

[49] *Chem. Age*, 1942, **46,** 41, 53.

[50] *Ann. sci. Univ. Jassy*, 1940, Sect. 1, **26,** 406; 415.

[51] *Z. Ver. deut. Ing.*, 1941, **85,** 33.

[52] *Lait*, 1940, **20,** No. 197, 412.

[53] *J. Biol. Chem.*, 1941, **139,** 199.

[54] J. W. J. Fay, unpublished.

[55] *Luftfahrt-Forsch.*, 1939, **16,** 212.

[56] *Chemie-Industrie*, 1941, **46,** 304; *Brennstoff-Chem.*, 1941, **22,** 237.

[57] *Bull. Assoc. franç. Techn. Pétrole*, **1938,** No. 45, 31.

paraffins and petrolatums. A rather lower pressure (10^{-5} to 10^{-6} mm.) is employed by V. A. Korovkina [58] for the investigation of the origin and chemical nature of bituminous products.

An interesting application of low-pressure technique, described by C. D. Hurd and R. W. Liggett,[59] is the analytical separation of sugars, accomplished by fractionation of their propionates. Details are given of several mixtures, and it is concluded that pressures below 0·01 mm. are best. The accuracy obtained is about 1—2% for monosaccharides and 2—4% for disaccharides.

Far too many patents have been taken out for any attempt to be made here to give anything like a comprehensive summary, but a few may be mentioned as having particular points of interest. K. C. D. Hickman has developed his unobstructed-path still for the distillation under high vacuum (0·001 to 10^{-7} mm.) of such materials as hydrocarbons and animal and vegetable oils to recover unsaturated glycerides, sterols, and vitamin fractions.[60] The same author, with J. G. Baxter,[61] has described a method of minimising oxidation of a fat-soluble oxidisable oil during high-vacuum distillation by addition of a glyceride oil containing an anti-oxidant. The use of aluminium powder as a coating for the vaporising surface of the still, to lessen the deposition of interfering solid materials, is advocated by J. C. Hecker.[62] Other stills have been described by G. Burrows [63] and by Distillation Products Incorporated.[64] One of the latter designs has as an aid to fractionation rotating screens of rods, strips, or wire gauze, and the other utilises the latent heat of condensation of the distillate for the vaporisation of the fluid operating the diffusion pump. The same company [65] and other workers [66] apply the process to the preparation of hormones, vitamins, and enzymes from fish and vegetable oils and extracts. The purification of fatty acids, oils, glycerol, and similar materials is also dealt with in patents by the Eastman Kodak Company,[67] E. Morlock,[68] K. Sondermann,[69] and others.[70] Apparatus and processes for the distillation of lubricating oils are described by J. E. Schultze,[71] R. V. Becknell,[72] and others,[73] and a combined oxidation and vacuum distillation apparatus for the production of acetic anhydride from acetaldehyde is given by D. C. Hull and C. A. Marshall.[74] A neat means of collecting a number of condensed fractions at various distances

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[58] *Khim. Referat. Zhur.*, **1940**, No. 7, 125.

[59] *J. Amer. Chem. Soc.*, 1941, **63**, 2659.

[60] U.S.P. 2,218,240, 2,221,691, 2,234,166; B.P. 530,367 (with J. C. Hecker).

[61] B.P. 535,100.

[62] U.S.P. 2,269,153.

[63] B.P. 523,754.

[64] B.P. 538,565, 540,603.

[65] B.P. 532,770.

[66] E. W. Fawcett and G. Burrows. U.S.P. 2,186,669.

[67] Fr.P. 845,957; B.P. 524.390; 524,439.

[68] U.S.P. 2,261,939.

[69] U.S.P. 2,179,833, 2,224,025.

[70] *E.g.*, T. W. Evans, J. R. Scheibli, and G. H. Van de Griendt. U.S.P. 2,234,400.

[71] U.S.P. 2,217,385, 2,217,386.

[72] U.S.P. 2,217,356.

[73] *E.g.*, D.R.-P. 699,900; V. Voorhees, U.S.P. 2,224,621.

[74] U.S.P. 2,283,209.

from the vapourising surface and providing reflux of the condensed portions is the subject of a patent by C. V. Litton.[75]

The separation of *o*- and *p*-chlorotoluenes is dealt with by P. D. Hammond and R. W. Harris,[76] who describe an apparatus for the continuous distillation of a 60% *o*-mixture through an efficient column, using a high reflux ratio, under an applied pressure not exceeding 200 mm. absolute, and by M. J. P. Bogart and J. S. F. Carter,[77] who also describe a method of distilling phenols and cresols.[78] J. W. J. F.

J. W. J. Fay.
J. G. N. Gaskin.

[75] U.S.P. 2,266,053.

[76] U.S.P. 2,240,962.

[77] U.S.P. 2,240,752.

[78] U.S.P. 2,241,110.

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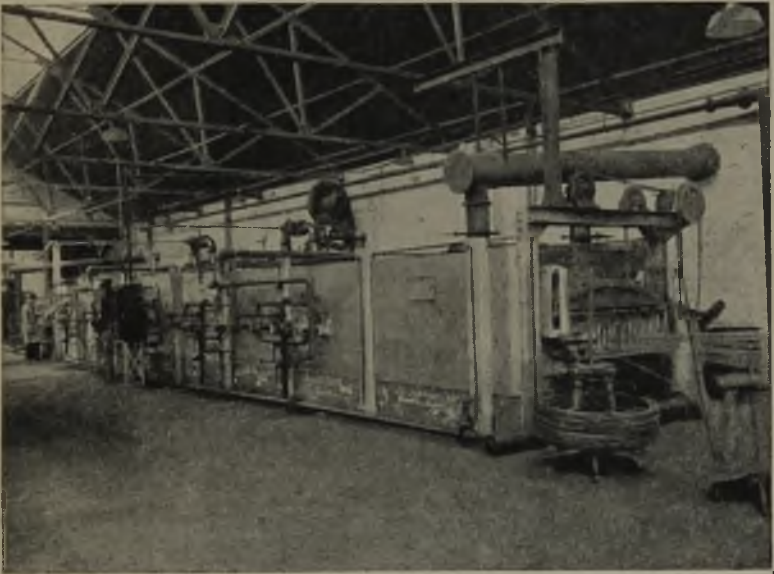

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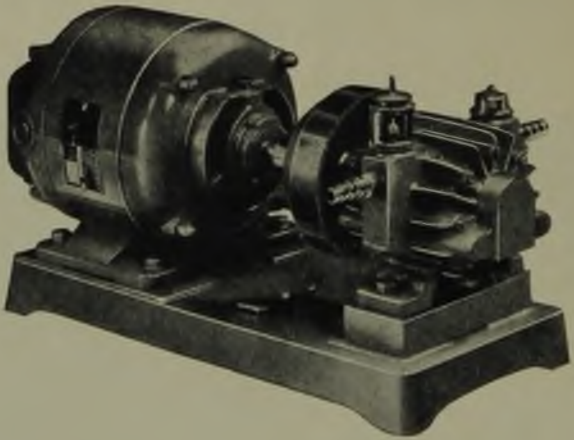

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