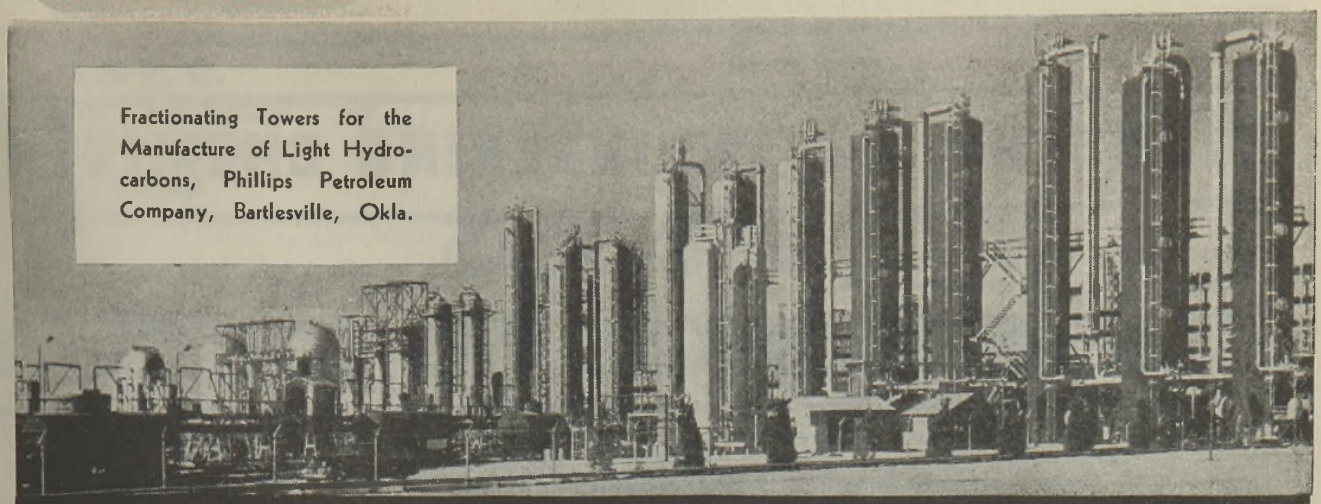
IN FEBRUARY, 1945

INDUSTRIAL AND ENGINEERING CHEMISTRY

SCIENCE IS POWER

Reprint of Editorial Matter

Advertising Omitted



Fractionating Towers for the Manufacture of Light Hydrocarbons, Phillips Petroleum Company, Bartlesville, Okla.

INDUSTRIAL AND ENGINEERING CHEMISTRY • INDUSTRIAL EDITION

ISSUED FEBRUARY 13, 1945 • VOL. 37, NO. 2 • CONSECUTIVE NO. 3

EDITORIALS 103

THE PERKIN MEDAL. Introduction 106
Du Pont Research. Medal Address . . . . . E. K. Bolton 107

SYMPATHOMIMETIC AGENTS
Introduction . . . . . John H. Speer 116
Clinical Importance and Uses . . . . . Harry Gold 117
Imidazole Derivatives with Sympathomimetic Activity . . . . . C. R. Scholz 120
Beta-Phenethylamine Derivatives . . . . . Walter H. Hartung 126
Pharmacologic Methods and Objectives in Research . . . . . M. L. Tainter 138
Relation of Structure to Deamination of Sympathomimetic Amines . . . . . Karl H. Beyer and Helen S. Morrison 143
Phenyl Propyl and Phenyl Isopropyl Amines . . . . . Boyd E. Graham, George F. Cartland, and E. H. Woodruff 149

Polyhydric Alcohol Production . . . . . C. W. Lenth and R. N. DuPuis 152
X-Ray Diffraction Examination of Gamma Alumina . . . . . M. H. Jellinek and I. Fankuchen 158
A "Reference" Precipitated Tricalcium Phosphate Hydrate . . . . . W. H. MacIntire, George Palmer, and H. L. Marshall 164
Machine Dishwashing Compounds . . . . . Ray C. Hughes and Rubin Bernstein 170
Preparation of Zein by Precipitation Method . . . . . Cyril D. Evans, R. J. Foster, and C. Bradford Croston 175
Asphaltic Products from Petroleum Extracts . . . . . P. V. McKinney, M. G. Mayberry, and H. E. Westlake, Jr. 177
Milkweed Seed Oil . . . . . Herman J. Lanson, David Habib, and P. E. Spoerri 179
Chlorinated Kerosene . . . . . Raymond M. Dean and Eugene Lieber 181
Analysis of Ternary Mixtures Containing Nonconsolute Components . Allen S. Smith 185
Effect of Synthetic Resins on Cellulose and Protein Fibers . . . . . D. H. Powers 188
Thermal Conductivity of Alcohols and Glycols . O. K. Bates and George Hazzard 193
Nature of Asphaltic Substances . . . . . Donald L. Katz and Karl E. Beu 195
Allyl Ether of Starch . P. L. Nichols, Jr., R. M. Hamilton, L. T. Smith, and E. Yanovsky 201

January's Headlines 203
Equipment and Design, by Charles Owen Brown . . . . . (Advt. Sect.) 71
Instrumentation, by Ralph H. Munch . . . . . (Advt. Sect.) 77
Plant Management, by Walter von Pechmann . . . . . (Advt. Sect.) 83
I. & E. C. Reports, 5. As We See It, 65. Last-Minute Flashes . . (Advt. Sect.) 134

Published by the American Chemical Society at Easton, Pa. Editorial Headquarters: 1155 16th Street, N. W., Washington 6, D. C., telephone, Republic 5301; cable, Jiechem (Washington). New York Editorial Branch, 60 East 42nd Street, New York 17, N. Y., telephone Murray Hill 2-4662. Chicago Editorial Branch, 310 South Michigan Avenue, Chicago 4, Ill., telephone Wabash 7376. Business Office: American Chemical Society, 1155 16th Street, N. W., Washington 6, D. C. Advertising Office: 332 West 42nd Street, New York 18, N. Y., telephone, Bryant 9-4430.

Entered as second-class matter at the Post Office at Easton, Pa., under the Act of March 3, 1879, as 24 times a year — Industrial Edition monthly on the 1st, Analytical Edition monthly on the 15th. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 13, 1918.

Remittances and orders for subscriptions and for single copies, notices of changes of address and new professional connections, and claims for missing numbers should be sent to the American Chemical Society, 1155 16th Street, N. W., Washington 6, D. C. Changes of address for the Industrial Edition must be received on or before the 18th of the preceding month and for the Analytical Edition not later than the 30th of the preceding month. Claims for missing numbers will not be allowed (1) if received more than 60 days from date of issue (owing to the hazards of wartime delivery, no claims can be honored from subscribers outside of North America), (2) if loss was due to failure of notice of change of address to be received before the dates specified in the preceding sentence, or (3) if the reason for claim is "missing from files".

Annual subscriptions — Industrial Edition and Analytical Edition sold only as a unit, members $3.00, nonmembers $4.00. Postage to countries not in the Pan-American Union $2.25; Canadian postage $0.75. Single copies — current issues, Industrial Edition $0.75, Analytical Edition $0.50; back numbers, Industrial Edition $0.80, Analytical Edition prices on request; special rates to members.

The American Chemical Society also publishes *Chemical and Engineering News*, *Chemical Abstracts*, and *Journal of the American Chemical Society*. Rates on request.

INDUSTRIAL AND ENGINEERING CHEMISTRY
REPORTS
ON THE CHEMICAL WORLD TODAY

Technology

Power Alcohol. As a fuel for the automobile engine, gasoline has always had a decided advantage over alcohol. The petroleum distillate is considerably lower in cost, and that circumstance alone has more than offset whatever disadvantages gasoline may have had in the operation of internal combustion motors. Add to this the fact that petroleum was plentiful before the war, and it is not difficult to see why supporters of an alcohol fuel program made no headway with this idea.

The war has altered this situation somewhat. Gasoline is far from plentiful as every holder of an A ration card knows, and mechanized combat is drawing upon motor fuel at a rate which has revived apprehension over the Nation's future domestic petroleum resources. These fears may not be justified, but it is easy to see that they are redirecting attention to the possibilities of basing our future motor fuel upon alcohol. If the farm chemurgists prevail, this will take the form of alcohol distilled from grain or sweet potatoes. The high raw material costs heretofore have prevented alcohol from competing with petroleum on a dollar and cents basis.

The industrial alcohol distillers, however, are trying to solve that problem. At a recent power alcohol conference held by Joseph E. Seagram & Sons, Inc., at Louisville, Ky., technologists for that company showed how a considerable reduction in costs could be achieved with a mobile distilling unit, a five-car train complete with all necessary equipment for converting corn or other grain into alcohol. The distillery on wheels may be shunted directly to the grain farmer's storage silos. The corn or wheat will enter the train at one end, and in a few hours alcohol for the operation of tractors and other farm equipment will be delivered to the farmers' storage tanks, denatured to comply with federal laws.

The first car of this mobile unit contains the boiler equipment, the second houses water treatment facilities and a maintenance shop, the third is given over to water cooling and recirculation, the fourth contains the production unit and still, and the fifth car carries the fermenter. Ingenious engineering has overcome the limitations imposed by the 9-foot height of the box cars. The alcohol is manufactured through a fast process, developed during the war by fermentation chemists, which utilizes acid hydrolysis and a mash containing efficient nutrients.

Savings are made through the reduction of transportation costs. The mobile distillery eliminates the grain haul from farm to alcohol plant, as well as the necessity of transporting alcohol back to the consumer.

Grain and alcohol hauling charges are variables, depending upon the location of the farm in relation to the distillery. In one instance it was shown that charges on grain hauled to distilleries in the Louisville area amount to around 8 cents per bushel on the finished product. The shipping costs for alcohol to points of distribution add up to another sizeable figure. It is not a complete answer to the contention of the petroleum industry that the power alcohol scheme is economically unworkable, but the industrial alcohol interests appear to have taken an important step toward reducing alcohol fuel costs as far as agricultural consumers are concerned.

Lowering costs also is but one side of the power alcohol question. An internal combustion engine has yet to be designed which will work as efficiently on straight alcohol as it does now on gasoline. The National Bureau of Standards, which has been forced by other problems to lay this work aside temporarily, has experimented extensively with alcohol fuel, and finds that the lower number of B.t.u. obtained in working with alcohol (11,760 per pound against 19,500 for gasoline) is a drawback which calls for changes in engineering, such as much higher compression ratios. On the other hand, engine wear is reduced considerably with alcohol. Other government agencies remain vitally interested in power alcohol development, and the Federal Economic Administration sees in it the means of providing nations which have no petroleum with motive power after the war. In the Philippines, Cuba, and other sugar-producing areas alcohol would be the obvious answer to a petroleum shortage, used straight or in blends with imported petroleum distillates.

In this country alcohol-gasoline blends have been proposed as a means of conserving our petroleum resources. The oil interests have opposed this European practice as a wholly unnecessary device which only adds to fuel cost and which introduces operating

(Continued on page 8)

An interpretative monthly digest for chemists, chemical engineers, and executives in the chemical producing and chemical consuming industries

problems for the car or truck owner. And they are not alone in this view. The United States Tariff Commission in its 28th Annual Report (1944) indicates that the use of such mixtures on a scale sufficient to permit petroleum conservation would necessitate an increase in alcohol production far above even wartime levels. If such a great volume of alcohol were to be derived from domestic material, in the Commission's opinion, an enormous increase would be required in agricultural production.

Important as these considerations are in the controversy, they are probably not so decisive as the question of costs. In 1940, prior to our entry into the war, the American Petroleum Institute, through its Committee on Motor Fuels, said that all attempts to market power alcohol in this country at less than 25 cents a gallon had failed, and that projects for this purpose had all failed with heavy losses to their sponsors. Even alcohol from cheap blackstrap molasses has seldom been made available commercially under 25 cents, the A.P.I. said, calling attention to the ability of the petroleum industry to manufacture gasoline at the refinery as low as 5 cents a gallon. A careful and extensive investigation, made before the war by the United States Department of Agriculture, showed that 31 cents was the average cost of alcohol f.o.b. plant, based on corn as raw material at 50 cents a bushel. It also said that corn at 75 cents a bushel would provide alcohol at 37.5 cents a gallon, f.o.b. plant.

These figures in a measure explain the effort of power alcohol interests to reduce costs through such interesting developments as the mobile distilling unit. But if advances have been scored in this direction by fermentation alcohol producers, it would be a gross mistake to conclude that technology is standing still in the petroleum industry. One example might be cited in the success of The M. W. Kellogg Company in making possible the production of gasoline from natural gas at 5 cents a gallon. With such a process, which makes gasoline synthesis from natural gas commercially practicable, a fuel is obtainable with an octane rating of 75 and demonstrates what technology has ready in the event of liquid petroleum depletion.

The Spagyric Physicians. *"I extol and adorn . . . the Spagyric physicians . . . they devote themselves diligently to their labors, sweating whole nights and days over fiery furnaces"* (*Paracelsus*). Since the ancient day when Paracelsus united chemistry and medicine, the bonds have grown more solid until it is at times impossible to distinguish between the two. This union has been blessed, the number of children and grandchildren increasing exponentially.

This war has seen the accelerated use of chemical products in medicine, for the spagyrists are with us yet, sweating in the fiery furnace of war. We want to report here on two phases of the healing art in which chemical materials are used. These two phases have not as yet come to the attention of the public generally. Though small, regarded from the viewpoint of number of patients or volume of materials used, the relief brought to the patient is immeasurably great. The first is the (*Continued on page 10*)

I. & E. C. Reports on the Chemical World Today — Technology

use of tantalum in surgery. Tantalum has several properties that are apparently not duplicated by any other metal. One of the desirable characteristics is its lack of irritation to tissue. There is no foreign-body reaction when this metal is implanted by surgery, and the surgeons have made good use of this advantage. So far tantalum's greatest use for war casualties has been in the repair of head injuries and the substitution of the metal for missing skull structure. Fifteen hundred such operations and inserts have been made. An added advantage in tantalum is that tissue grows to the metal, acting in accordance with the theory that tissue will adhere to anything that does not irritate. The tantalum is sent to the surgeon as 6-inch squares, usually about $^1/_8$ inch thick. One of the distinct advantages of tantalum is that its softness and ductility allow the surgeon to cut and fashion the metal plate quickly to fit over the cranial cavity.

The use of tantalum for surgery was first thought of by Dr. John C. Burch, of Vanderbilt University, who in 1936 persuaded the Fansteel Metallurgical Corporation to give him some tantalum for experimental work. One of the most fascinating uses for the metal is as a replacement for severed or damaged nerves. It has been estimated that 10% of war casualties are due to severed nerves, and the use of this material is helping in a vital rehabilitation job. The tantalum wire, which is 0.003 inch thick, is tied to the ends of the nerves. To prevent the tissue from growing to the wire, the tantalum wire is covered with a sheath of the metal foil. So far the amount of wire allocated to the armed forces amounts to only about half a million feet, and the number of tantalum sheets totals about six or seven thousand. Any hydrochloric acid installation includes more tantalum than the total amount used so far in surgery, but the accruing benefits are immeasurable. Tantalum sheets can be attached to the skull with tantalum screws, and the same type of fastening is utilized in reducing the fractures of bones in other parts of the body.

Part two of our report on modern iatrochemistry concerns the part acrylic resins are playing as artificial eyes. There are several advantages to be derived from the use of these light-weight plastics. An important one is that the plastic eye can be moved to some degree by the eye-socket muscles. Coloring of the replacement can be accurately matched to the natural sclera, and, according to the *Naval Medical Bulletin*, standards have been worked out for comparison. The sclera or whitish part of the eye is first made by the addition of titanium oxide and color to the acrylic material. The acrylic plastic gives to the experts for the first time a material that they can easily mold and shape to individual requirements. The art of providing a substitute for a missing eye is highly complicated. Factors must be considered which the uninitiated would never suspect. To cite a few complexities, the doctor must allow for lid projections on the replacement in order that the eye shall not have a sunken appearance. Iris color must be matched on paper as closely as possible by medical illustrators, and the diameter, flecks of color, and lines must be duplicated exactly. (*Continued on page 12*)

This paper iris is placed on the titanium colored sclera, and over it is polymerized the clear acrylic material duplicating closely the cornea. The sclera is later touched up with inks to simulate the blood vessels of the normal eye. The benefits from these methods are, as the doctors say, "cosmetic", but for an injured man the mental effect must never be overlooked. Additional benefits, say the doctors, are that facial contours are restored, light reflections are accurately reproduced, and the acrylic materials are resistant to body fluids. Incidentally; the precision and skill of the dentists has made them the ideal fabricators for these replacements.

Philippine Exports. MacArthur's triumphant return to the Philippines opens up sorely needed raw materials, but how fast these will be available and in what quantities are questions that cannot be answered at this moment. Sugar, one of the critical materials on the list of the United Nations, was the leading export item of the islands prior to Pearl Harbor. The Philippines in the years immediately preceding the outbreak of hostilities in the Pacific exported approximately one million short tons to continental United States annually, and this tonnage represented about 15% of the total U. S. sugar consumption. Three factors enter into the question of when and how much sugar the islands can be counted on to supply for world demands: (1) length of time required to chase the Japanese out of Luzon and Negros, the two largest producing areas; (2) amount of stocks left by the enemy; (3) actual condition of the fields and refineries.

It has been reported that the Japanese are using sugar cane for the production of power alcohol; if this is true, they probably have not destroyed too much of the sugar cane acreage or grinding mills.

In the list of raw materials coconut oil and copra hold high places, and soapers and manufacturers of hydrogenated shortening, oleomargarine, and other food products eagerly await authentic reports from the islands on the prospects of early exports. Soapers place coconut first on their list of high lauric-acid-content oils. To conserve the glycerol content of the meager stocks of coconut oil in the United States, soap manufacturers possessing recovery equipment have been favored at the expense of the food industries. Stringent measures were necessary since 99.98% of all coconut oil receipts and 91.64% of all copra received in the United States came from the islands.

It is probable that crushing equipment will be seriously damaged before the Japs are liquidated. Hence exports, in the main, will be in the form of copra instead of oil, but fortunately we have considerable crushing equipment on the Pacific Coast. However, gathering of the nuts on a large scale must await the final elimination of Japanese sniper and guerilla bands and the repair of shipping facilities in Manila and other ports. Quite a time will probably elapse before the return of the prewar export figure of 715,000,000 pounds. Although the U. S. fat and oil industry has increased total output well above previous production, coconut oil, while comprising only 7% of our total consumption, has been sorely missed. Indeed it was the prime fats and oils problem after Pearl Harbor.

(*Continued on page 14*)

Old Number Two. Number two is in the headlines again—cartels. In our opinion this is the No. 2 problem for the Nation, the national debt being the first.

Much of the sound and fury expended on the subject seems to be misdirected. It is highly possible that business will take a wrong slant if it concentrates attention on the people who are doing the loudest shouting and not on the problem. Unfortunately the American business man is being forced into the position of defending cartels. This probably comes from the fact that he has been accused of supporting or sponsoring cartels. This is far from the truth. At most, we think American business was forced into the agreements that were made merely because it was the preferred business policy of the nations with whom it was doing business. Now that it has become popular to attack all such agreements, it has been the practice of some to defend cartels. What should have been done was not to defend such agreements, but to insist, vocally and vociferously, that circumstances made such arrangements necessary. Even now the fight should be carried on in the spirit of "show us something better".

We think that the idea of the cartel is foreign to the American philosophy of free enterprise; in support, we quote from an article by Charles Belknap, president of Monsanto Chemical Company, in the March, 1939, issue of this journal, page 503: "Cartels are a favorite method of European countries for the regulation of manufacturing and distribution activities. Since these destroy the last semblence of competition among countries, there is a tendency among participating countries to slow down, to soldier on the job, in the knowledge that their market is simply waiting to be sold." Those are positive words, and we think they represent the true condition of things as they were and the true philosophy of American business.

The fault of cartels—the existence of cartels—may not be dumped on the doorstep of business. The fault lies with those governments that freely sponsored such agreements, and the diplomat, not the business man, is the true culprit. If our State Department is unable to convince the nations of the world that cartels are wrong, then the Department of Justice should be told about it. It is important that some manner and means of discussing the problems of world trade be devised; when a system is found that will carry on the trade of the world smoothly, the businessman of this nation should be able at least to cooperate without being indicted as a traitor.

One other argument, advanced by DeHaas of Harvard University, should appeal to the State Department: Far from the American businessman's needing the protection of agreements after the war, the protection will be wanted by the weakened enterprises of Europe which will not be able to maintain strong competition against the powerful American machine, sharpened by war and war's demand for efficiency and speed. The main point is that our new world must be ruled by free cooperation, both in politics and in business, and the best example of cooperation that we as a nation could give would be between the forces of government and business.

(*Continued on page 18*)

I. & E. C. Reports on the Chemical World Today

War and Postwar

Topsy-Turvy Alcohol. Industrial alcohol is back on the critical list again. The January holiday, the second that distillers have been granted from the production of industrial alcohol in order to make beverage alcohol, is over. Prospects for further holidays in 1945, although held out at the time the January holiday was declared, now look "very dismal", according to Chairman Krug of the War Production Board. He told a press conference that this change in plans is necessitated by the sharply increased demands for synthetic rubber and high-octane aviation gasoline. Last fall the needs of synthetic rubber manufacturers for industrial alcohol dropped, but now it has become necessary to step up output again, and maximum production of industrial alcohol will be required.

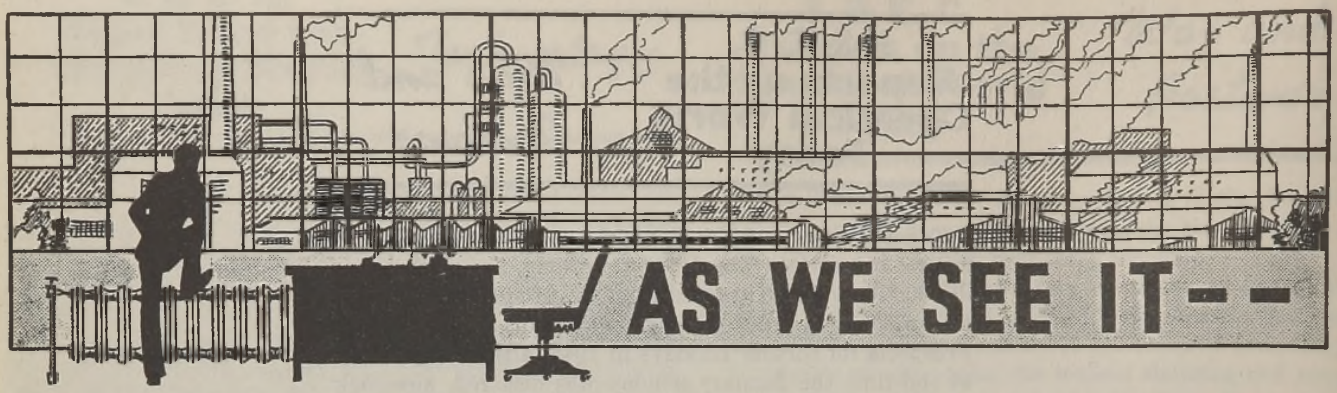
Probably one important reason for the change in the status of alcohol is the fact that new facilities for tire making will shortly become available. Last fall this was the bottleneck—not sufficient synthetic rubber. In fact, we had a surplus simply because the tire plants were not able to consume all the rubber then available.

Chairman Krug says that 900,000 tons of synthetic rubber are scheduled for production in 1945 compared with 737,000 tons in 1944. It is estimated that industrial alcohol needed for this bigger rubber program will have to be increased to 349 million gallons, as contrasted with the 228 million gallons scheduled earlier. The estimated requirements for rubber in 1945 are based on the assumption that the plants which made butadiene from alcohol will produce at maximum capacity throughout the year. This, in turn, will allow butylenes to be diverted from the rubber program to make more aviation gasoline. Total revised 1945 requirements for industrial alcohol, presented by WPB to the Industrial Alcohol Advisory Committee, reach 655 million gallons, against 609 million gallons last year and 229 million in 1942.

The rapidly expanding new war program for 1945 is creating shortages in all basic materials, and a tightening in civilian production is inevitable.

Short on Sugar. The current shortage in sugar will probably grow worse instead of better, according to those who know the industry. There are several reasons; one is the startling fact that production in major producing countries will be below normal levels. Thus Cuba, our primary source of the cane product, will turn out some 600,000 tons less than it did in 1944. Important—probably the greatest factor in the shortage—is the lack of shipping space; there are several suggestions as to how this difficulty can be overcome. One is that ships returning to Atlantic ports after depositing munitions in the Pacific stop to pick up cargoes of Cuban material.

One important technological improvement is noted in the picture—a new seeder which eliminates much of the manual labor involved in the planting of beet seed. It is expected that priorities will be given for the increased manufacture of this implement to help meet the War Food Administration's plea for 306,000 more acres of sugar beets in 1945.



This Month

DU PONT RESEARCH features the lead article this month, for we are printing the Perkin Medal Address of Elmer K. Bolton in full. Research has always been held by the Du Pont organization to be the growth factor in a chemical business, and the founder of the company, Eleuthère, started the tradition by trying to improve the earliest Du Pont product—black powder. Bolton tells part of what has happened since then; the whole story would require many volumes. We have the background of the founding of the many research and development laboratories that are traditions in the chemical industry—the Eastern Laboratory, the Experimental Station, the Haskell Laboratory, and others. Also placed in the record is the philosophy behind the development of such outstanding products as nylon, waterproof cellophane, neoprene, permissible dynamites, and lacquers.

Sympathomimetic agents are examined through six papers from the recent North Jersey meeting of the SOCIETY. The Division of Medicinal Chemistry held a symposium on the subject, and we delve into the mysteries of research objectives, structural relationships, phenethylamine derivatives, imidazole compounds, and the amines of the phenyl propyl and phenyl isopropyl family. The use of these drugs in clinical medicine is over fifty years old, but the touchstone that is modern chemistry is improving the type of compound being used. When the story can be told, we will probably learn much about how these materials are helping in the war effort as pickup pills for the fatigued soldier. At present the citizenry are using these agents in great profusion, for they are the popular cold and cough reliefs—benzedrine inhalants being a familiar type.

According to Powers, of Monsanto Chemical Company, few persons realize that, when they buy dress goods today, they are buying about 5 to 15% synthetic resin. The use of resins to improve wearing qualities has so increased over the past few years that many millions of yards are prepared annually. Material treated by the resins most frequently used—urea, melamine, and phenol formaldehydes—shows greatly increased tensile strength, elongation, and tear resistance. The best method is to apply these resins from a water solution and to polymerize inside the fiber. Shrinking of cottons is greatly reduced by melamine-type water-soluble resin, and decrease of 84% in shrinkage is reported.

Production of glycerol by methods not involving fat splitting was the starting point of a fascinating bit of research at the Miner Laboratories. Now at last the censor allows us to tell the story, after a delay of three years. The work of Lenth and Du Puis, who are the originators of the method, was begun at the request of the Association of American Soap & Glycerine Producers, Inc. Success was achieved chemically even though, in comparison with the usual manner of obtaining glycerol, the method is not economical. As finally brought to the pilot-plant stage, the technique involves the hydrogenolysis of sucrose or dextrose in a suspension of methanol, the mixture being catalyzed by a special copper-aluminum oxide.

Gamma alumina is the form preferred if drying or dehydration is the problem, and Jellinek and Fankuchen report on the diffraction examination of this unnatural substance.

Emphasis is continuing on the production of zein; Evans, Foster, and Croston tell how extraction with isopropyl alcohol can gently remove this substance from the gluten of corn.

Milking the milkweed is no trick for the chemist, and this time our art is not waiting for a waste to become a problem before finding use for it. Seeds of the milkweed, residue from making milkweed floss, contain an oil which may find an outlet as a semi-drying oil.

Another censor-held paper is that of Bates and Hazzard on the thermal conductivity of alcohols and glycols. Short and to the point, the authors have contributed important data to the literature on this subject.

Next Month

NATURE must have loved cellulose, she made so much *of* it. So too the chemist, he makes so much *from* it. Next month will turn the spotlight on this subject, as we are now filling the composing sticks with type set from several papers in a Symposium on Cellulose and Cellulose Plastics. One important phase that has never had the publicity it deserves is the making of laminates for electrical insulation. This field has several special problems which will be fully discussed. Cellulose molding compounds and cellulose esters will also come in for some searching comment.

Harvey W. Wiley is called the "father" of American food chemistry with good reason. He was a pioneer in the field, and his associates ascribe to him the major role in bringing the science of food chemistry to its present level. In recognition of his genius, the March issue will see the publication of several papers dedicated to the celebration of his hundredth birthday. As is fitting, the emphasis is on quality determinations in food. There will be articles on meat and dairy products and a discourse on volatility and flavor. Preservation of food flavors in fats, or their elimination, is a chemical problem of some magnitude. Based on this esthetic desirability are refining and deodorizing processes and the development of antioxidants.

Cashew nutshell liquid is the source of many valuable industrial materials, and from research programs sponsored by the major exploiter of this field we will have a study on the phenolic constituents of cashew oil. It will be shown that the structure of the main oil constituent is not changed by the heat treatment necessary in the industrial processes.

An important aspect of chemical engineering design is the accurate determination of vapors over boiling liquids. We have on tap for the windy month an analysis of the vapors from boiling binary mixtures with emphasis on the correlation and extrapolation of data. The systems will be water plus solvents of the acetone, methanol, and methyl ethyl ketone type. Data, it will be shown, can be taken in the subatmospheric pressures, and plotted for the entire system of pressure, temperature, and compositions, in both liquid and vapor phases.

F. S. Van Antwerpen

INDUSTRIAL AND ENGINEERING CHEMISTRY
PUBLISHED BY THE AMERICAN CHEMICAL SOCIETY

Editorials

WALTER J. MURPHY, EDITOR

A Ray of Hope

THE recent Nazi offensive in Belgium, together with MacArthur's major attack in the Philippines, have resulted in a sudden demand by our military authorities for an accelerated pace in Army inductions during the first six months of this year.

Once more we are on the horns of a dilemma—shall we dip into occupationally deferred lists to provide more soldiers at the expense of production and research, or shall we gamble on maintaining an ever increasing output of war matériel in order to supply further reserves to our military services?

Military officials and War Mobilization Director Byrnes appear to be convinced that both ends can be achieved by a further combing of the lists of those now occupationally deferred. Perhaps they are correct in such an assumption, but certainly somewhere along the line the law of diminishing returns is bound to become operative and, since we are now in the fourth year of war, that point cannot be very far off.

One ray of hope is the request from Byrnes to General Hershey to set up a priority system for the induction of industrial workers aged 26 to 30 "to minimize as much as possible the effect on essential activities".

In the past the chemical industry has fared rather badly for the reason that many draft boards and Selective Service officials have not fully understood or appreciated the relationship of the chemical industry to all other industries.

Laymen serving on draft boards can visualize the importance of a tank, a ship, a gun, or a plane to the war effort, but they see little or no connection between soda ash, methanol, sulfuric acid, or styrene and the production of essential war matériel.

The latest War Manpower Commission order is encouraging. Mr. Byrnes deserves a great deal of credit for the part which undoubtedly he has played in its formulation. For the first time real recognition has been given to the importance of chemical production and research and scientific personnel. The list of chemicals and allied products in the essential and critical categories is very comprehensive. Of greatest significance is the statement that "all technical, scientific, and research personnel, engaged in any of the activities in the list, whether or not the activity appears in bold type or regular type, are regarded as being engaged in critical activities".

Unless Germany capitulates quickly, and present indications are that despite Russian successes she will not, manpower for military purposes will continue to be a serious problem. Should we not give some thought now to widening the scope of participation of other nations in this global conflict? France, for example, and this holds true for other liberated countries, has manpower available for military service in excess of those now in uniform. Our production facilities are of such magnitude that we can furnish the necessary equipment to arm adequately all who are willing to fight a common enemy—that is, if we do not hamper the full utilization of such facilities by stripping our plants of vital personnel. With more than 12 million Americans now in uniform, we cannot be accused of failing to do our part in a military sense. Our military successes speak for themselves.

We wonder if pride on our part is getting the better of good common sense. There is a limit to what we can do in both production and furnishing military personnel. When we get away from the correct balance between the two, we are hurting rather than helping the cause of the United Nations. All nations have a stake in this struggle, and we believe many are willing, and indeed anxious, to participate in the defeat of Germany and Japan. Have we really indicated strongly enough that we welcome such participation?

Chemical Achievements of 1944

READERS' attention is called to the Symposium on Chemical Developments of 1944 featured in the January 25 issue of *Chemical and Engineering News*. Comprehensive and strictly factual, the symposium pictures the role played in America's march toward certain victory over her enemies by the chemical industry and industries closely allied to it and the chemists and chemical engineers who staff these fields.

Frequently the statement is made that the lay public is not so well informed about the activities and contributions of chemists and chemical engineers as it might be. Unquestionably this is true—there is always room for improvement.

The AMERICAN CHEMICAL SOCIETY News Service will make available to newspapers, editors, science writers, magazines, radio news commentators, and others the salient points stressed by the authors in this symposium. Members of the SOCIETY and all those interested in the proper portrayal of the work of the chemist and chemical engineer can assist by suggesting that relatives and friends read this particular issue.

The symposium can also serve to inform local draft boards concerning the vital importance of chemists and chemical engineers to the war effort and the sound reasons why such individuals should be held in the Production Army.

Reprints of the symposium are available to those who wish to participate in a practical way in spreading the gospel of enlightenment.

Postwar Military Training

THE pros and cons for universal military training of American youth in the postwar period are voluminous and might well be considered as outside the editorial spheres of a scientific journal. Certain it is that the subject will receive full attention from proponents and opponents before final action is taken. We do feel, however, that it is our duty to point out one possible and even very likely development in the writing of such an act—namely, a lack of understanding of the vital role of science in military preparedness.

If every young man, regardless of ability, aptitudes, course of study, etc., is made to spend 12 months learning the rudiments of being a soldier, we will be guilty of a serious and inexcusable waste of manpower. We will emerge from this war woefully lacking adequate numbers of workers in scientific pursuits. We are speaking not of ordinary technicians, but of those who plainly indicate that they possess the potentialities of becoming highly trained and highly skilled researchers—individuals whose training requires years of intensive study. We see no reason why such individuals should be retarded a whole year in order to teach them elementary military routine. If universal training is adopted, it should be selective in the same way that the Selective Service Act was supposed to be selective. Admittedly, it will not be easy to set up machinery to provide for such "deferments" but the difficulties are not by any manner of means insurmountable.

France is a tragic example of what misdirected universal military service can lead to in modern warfare. She had millions in uniform, but too few scientists. We should not make the same tragic mistake.

Waging the Peace

PRESIDENT ROOSEVELT'S inaugural address, one of the shortest on record, was devoted exclusively, to quote his own words, "to the achievement of His will to peace on earth".

As the President so aptly said, we are passing through a period of supreme test. It is, again quoting him, "a test of our courage—of our resolve—of our wisdom—of our essential democracy". If we leave it to others to discuss our courage, our resolve, and our essential democracy, pride in "our wisdom" becomes the danger point. It is at this point that we must begin to exercise the highest type of enlightened judgment if we are to gain the goal of lasting peace. Often what passes for wisdom is merely the prattling of fools. In building a world where wars will cease, causes of war must be eliminated. That is the task of science.

We have searched through reports on the Dumbarton Oaks and the Bretton Woods conferences for any tangible signs of full recognition of the importance of the scientists of the world. It is true that in the Dumbarton Oaks proposals the framework for international cooperation between scientists would be possible. Section C, defining the functions and powers of the Economic and Social Council, states among other things that the Council could "receive and consider reports from the economic, social, and other organizations or agencies brought into relationship with the Organization, and to coordinate their activities through consultations with, and recommendations to, such organizations or agencies".

The President publicly has acknowledged the importance of scientists in modern warfare. American scientists have been asked to cooperate with those of other nations to develop machines of destruction to be used against our enemies. How much more effective in the long run if they were asked to engage in cooperative efforts to eliminate the conditions that lead nations to war! Scientists, technologists, and engineers are potent but latent forces that could and should be incorporated into all international efforts to preserve peace. Wise leadership will seek such aid before the seeds of another world conflict are sown.

Scientists have asked for, but have failed to receive, a real opportunity to cooperate with statesmen, politicians, lawyers, and economists in framing the kind of

world in which we live. Rebuffed in the past, they are now noticeably impatient to serve, knowing full well that they have the power to bring to all mankind the higher standards of living that, together with basic Christian principles, must be the foundation stones upon which a world free from conflict is erected. The scientist must participate in the decisions made on how the fruits of his labors are utilized and distributed.

Paper Pirates and Indian Givers

EDITORS of AMERICAN CHEMICAL SOCIETY publications soon learn that editors of other journals envy them their windfall of high-class scientific material via papers presented at SOCIETY meetings which are thereby SOCIETY property according to Bylaw 3(*b*):

> All papers presented before general, divisional, regional, group, local section, or other meetings are the property of the SOCIETY, to be published in the journals of the SOCIETY or released by the appropriate editor if not retained for such publication.

At the same time they find authors of some of these papers ready to overlook this Bylaw *after* enjoying the privileges of presenting and discussing their papers on a widely publicized, widely attended, highly regarded scientific program. Such editors and authors seem to picture the SOCIETY as having cunningly acquired possession of scientific papers which are not published immediately but selfishly held by SOCIETY editors in dog-in-the-manger fashion. The result has been a brand of cooperation between some non-SOCIETY publications and some few SOCIETY authors which, deliberate or not, is detrimental to the best interests of scientific literature and the purposes of AMERICAN CHEMICAL SOCIETY meetings.

Thus, authors or their enterprising advertising departments and publicity divisions, occasionally give out copies of complete manuscripts without marking them clearly as A.C.S. property. Or, going a step further, authors sometimes simply ignore Bylaw 3(*b*) and undertake to arrange publication themselves. Editors, particularly those not above a little paper pirating, accept these "gifts" without question, and are naturally disturbed if a SOCIETY editor discovers the situation and quotes the regulation.

While there may be some excuse for the uninformed editor who publishes an AMERICAN CHEMICAL SOCIETY paper which has not been released, we see none for the author who emulates the Indian giver after enjoying the privileges of a SOCIETY meeting. He certainly cannot claim ignorance of the Bylaw, though there is some evidence that he does not understand its full implication.

Apparently it needs to be made clearer to prospective authors of A.C.S. meeting papers that the SOCIETY'S interest is not solely that of getting up a program. They need to realize that it is also interested in publication of worth-while material from these programs and in doing what it can to see that what is published is scientifically sound and well presented. This applies not only to the papers which ultimately appear in its journals, but to any meeting paper which is published, since the standards of the SOCIETY are naturally reflected by the caliber of papers it sponsors on its programs. Thus the effort is constantly toward improvement in the quality of papers presented, though it cannot be expected that all, or perhaps even a small per cent, can be ready for the printer directly following presentation. Authors impatient for early publication and editors who look hungrily at the wealth of material in the SOCIETY'S possession must realize that presenting a paper is only one step. Discussion, either via the program's open forum or the popular corridor conference, is an important second. This may lead to revision which the author wants to make before the editor sees his manuscript. The editor of course gets opinions of carefully chosen critics when the manuscript is turned over to him. Nine times out of ten he is able to send the author some constructive suggestions for further improvement in what is to be published. Naturally all this takes time, exasperating to the impatient author but relatively insignificant to the conscientious author who recognizes the dangers of hasty publication.

It is our optimistic feeling that all authors who really appreciate these facts can be counted on to help enforce the provisions of Bylaw 3(*b*) in both letter and spirit. Their wholehearted cooperation can do far more than any type of policing which the AMERICAN CHEMICAL SOCIETY might try to set up, and the procedures are simple. Each author should see that all copies of his paper are clearly marked "PROPERTY OF THE AMERICAN CHEMICAL SOCIETY. NOT FOR PUBLICATION" immediately after it is accepted for presentation at a meeting of the SOCIETY. If he intends to publish he should submit his paper promptly to the SOCIETY editor most likely concerned with the subject he is discussing. If he wants a release to publish in a non-SOCIETY journal he should include with his request a plain statement as to the reason.

These are small prices for the privileges incident to publication in the most widely circulated and read chemical journals in the world, and the protections concomittant with Bylaw 3(*b*) compliance. Those unwilling to pay should seek audiences elsewhere.

New Activities

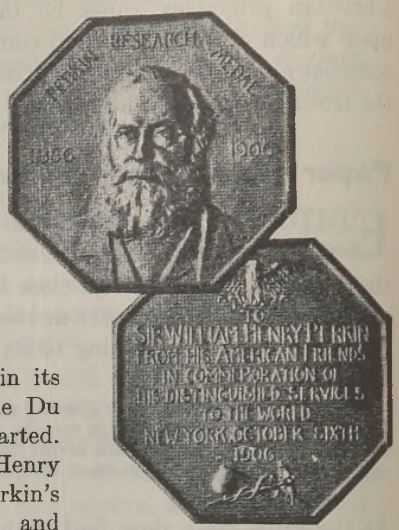
THE attention of the members of the AMERICAN CHEMICAL SOCIETY is again called to the existence of a Committee on New Activities, with C. F. Prutton as Chairman. This committee is desirous of receiving practical suggestions from the membership concerning new activities that the SOCIETY can undertake now and in the future. Suggestions should be sent to the Chairman, care of the Case School of Applied Science, Cleveland, Ohio.

THE PERKIN MEDAL

Awarded to Elmer K. Bolton

in recognition of outstanding accomplishment

in the field of industrial research



ONE of the highest honors in applied chemistry—the Perkin Medal—was presented at a dinner on January 5 at the Hotel Commodore, New York, to Elmer K. Bolton, chemical director of E. I. du Pont de Nemours & Company. In making the presentation, Marston T. Bogert of Columbia University cited the medalist particularly "for his leadership in the synthesis of neoprene, the first general-purpose synthetic rubber to be developed either in this country or abroad, and for his direction of nylon research".

Norman A. Shepard, chairman of the American Section of the Society of Chemical Industry, presided at the meeting and introduced C. M. A. Stine, vice president of the Du Pont Company, who spoke of the work and scientific accomplishments of the medalist. Lammot du Pont, chairman of the board of the company, then talked of Bolton the man; the medalist himself followed with the complete story of the role research has played in its development since the Du Pont Company was started.

In 1856 William Henry Perkin discovered Perkin's purple or mauve and thereby initiated the synthesis of dyestuffs. This, in turn, became the foundation of the vastly important synthetic organic chemical industry, beginning the utilization of coal tar. Sir William was also the first to synthesize the perfume coumarin, and he actually engaged in the manufacture of dyestuffs until 1874. He had many friends and admirers in the United States, and it is customary for those who saw the first Perkin Medal awarded to him in 1906 to wear the same or a replica of the mauve tie which made its appearance on that occasion. Jerome Alexander, Marston T. Bogert, and August Merz were those present at the dinner this year wearing their mauve ties.

The Perkin Medal was founded in commemoration of the fiftieth anniversay of the coal-tar color industry. The award may be made to any chemist residing in the United States of America for work which he has done at any time during his career, whether this work proved successful at the time of execution or publication, or whether it became valuable in subsequent development of the industry. The medalist is chosen by a committee representing the Society of Chemical Industry, the AMERICAN CHEMICAL SOCIETY, the Electrochemical Society, the American Institute of Chemical Engineers, and the Société de Chimie Industrielle.

PERKIN MEDALISTS

1906	Sir William H. Perkin	1926	R. B. Moore
1908	J. B. F. Herreshoff	1927	John E. Teeple
1909	Arno Behr	1928	Irving Langmuir
1910	E. G. Acheson	1929	E. C. Sullivan
1911	Charles M. Hall	1930	Herbert H. Dow
1912	Herman Frasch	1931	Arthur D. Little
1913	James Gayley	1932	Charles F. Burgess
1914	John W. Hyatt	1933	George Oenslager
1915	Edward Weston	1934	Colin G. Fink
1916	Leo H. Baekeland	1935	George O. Curme, Jr.
1917	Ernst Twitchell	1936	Warren K. Lewis
1918	Auguste J. Rossi	1937	Thomas Midgley, Jr.
1919	F. G. Cottrell	1938	Frank J. Tone
1920	Charles F. Chandler	1939	Walter S. Landis
1921	Willis R. Whitney	1940	Charles M. A. Stine
1922	William M. Burton	1941	John V. N. Dorr
1923	Milton C. Whitaker	1942	Martin H. Ittner
1924	Frederick M. Becket	1943	Robert E. Wilson
1925	Hugh K. Moore	1944	Gaston F. DuBois
	1945 Elmer K. Bolton		

DU PONT RESEARCH

E. K. BOLTON, *E. I. du Pont de Nemours & Company, Wilmington Del.*

IN ACCEPTING the Perkin Medal, I am deeply conscious of the fact that any credit for certain research accomplishments with which I have been connected belongs to the organizations of able research chemists with whom it has been my privilege to be associated. As their representative, I am happy to accept this award because, in honoring me, you honor them.

On occasions such as this the medalist has often discussed some phase of the research with which he has recently been associated. It is not possible for me to do this, as the greatest part of our work for the past three years has been concerned with matters covered by military secrecy. Instead, therefore, I have chosen to tell you something of the history, growth, and organization of Du Pont research. It is a story that has never been told in more than a fragmentary way, and it goes back to the beginning of the company in 1802.

The founder of our company, Eleuthère Irénée du Pont de Nemours, was a pupil of Lavoisier, father of modern chemistry. From Lavoisier Eleuthère learned the art and science of making gunpowder. But he learned more. He learned the importance of research, of continual efforts to invent the new and improve the old. He established a pattern of scientific procedure that was stamped firmly upon the Du Pont Company, and has endured and grown ever since. Early records show that from the start Eleuthère sought to improve both his process and his product, black powder. Ever mindful of the safety of his workmen, he also devoted himself to experiments that would reduce the danger of explosions. His investigations of more than 140 years ago—looking toward better quality and lower cost, with greater safety—set an example for future Du Pont research.

All Du Pont research was originally carried out in works laboratories, under the direction of the works superintendent, although over the years several members of the Du Pont family had laboratories connected with their homes, in which research work was conducted. Space does not permit a discussion of the numerous investigations carried out in the early days, but I will outline briefly one research development during the 1850's which had an important effect on the business of the company.

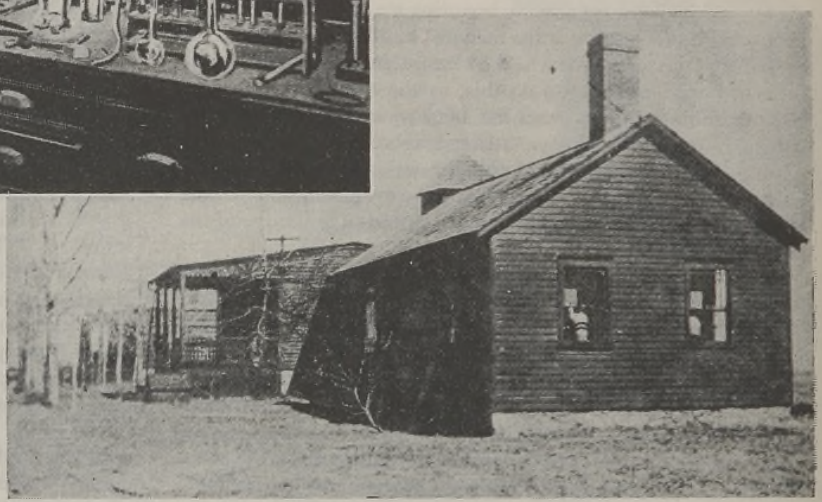
A large and new market for blasting powder was being developed at that time as an aid in mining, particularly in Pennsylvania's anthracite region. Henry du Pont, then head of the company, felt that it should be possible to develop a low-cost powder suitable for blasting. The job of developing such a powder was turned over to Lammot du Pont, grandson of Eleuthère the founder, and father of our present Chairman of the Board of Directors.

Lammot found the answer in the use of low-cost sodium nitrate instead of the relatively expensive potassium nitrate previously used as the oxidizing agent in powder. For a number of years attempts had been made to use sodium nitrate (Chile saltpeter), but the deliquescent properties of this material and its accompanying impurities had defeated every effort. The powder soon became damp and failed to fire. Lammot overcame this difficulty by glazing his powder with graphite. His B-blasting powder, or soda powder as it was commonly known, gave excellent results in the most exacting field tests, and because of its low price was adopted almost overnight throughout America's iron and coal fields. This was a contribution of major importance to the industrial development of the United States. The Civil War was yet to be fought. The industrial age had yet to be born in America. Yet here was an authentic piece of industrial research of the sort that helped to make possible our present economic and social structure.

Du Pont's first formal research laboratory was the Eastern Laboratory, erected at the Repauno dynamite plant in 1902 for research on explosives. This was one of the first industrial research laboratories in this country and, as far as I know, represented the earliest organized research effort in American chemical industry. The first director of this laboratory was the late Charles L. Reese, a leader of industrial research during the first two decades of this century. One of the men who started his career at the Eastern Laboratory and has had an important part in the development of Du Pont research is C. M. A. Stine, now a vice president, member of the Executive Committee, and adviser on research and development.

One of the early investigations in this new laboratory was undertaken to determine why certain batches of nitroglycerin required two hours or more to separate from the spent acids, while others separated in 20 minutes. Nitroglycerin is prepared by adding a mixture of sulfuric and nitric acids to glycerol under carefully controlled conditions. It was found that delay in separation resulted from the presence of colloidal silica in certain lots of glycerol. More important, it was found that the addition of a small amount of sodium fluoride to the mixture of sulfuric and nitric acids, and a small amount of sodium silicate to the

Marston Taylor Bogert, wearing the historic Perkin mauve tie, presents the medal to Elmer K. Bolton



Repauno Works Laboratory at Gibbstown, N. J., established around 1880; this is one of the early laboratories in which explosives research was carried out for what is now the Du Pont Company. The interior (*left*) was photographed in 1895; the exterior view (*below*) was taken March 27, 1897, immediately following an explosion of 7000 pounds of nitroglycerin about a half mile away.

glycerol, greatly speeded up separation. Today, this process, or some modification, is widely used in nitroglycerin manufacture.

Here also were developed the first American "permissibles"—dynamites that may be used with safety in coal mines because they do not ignite the highly flammable coal dust and methane which, before permissibles were developed, frequently led to disastrous mine explosions.

EXPANSION INTO NEW FIELDS

For about one hundred years the company manufactured only black powder, dynamite, and smokeless powder; as a result, early research activities were limited to the explosives field. Around the turn of the century, however, manufacturing activities were extended into collateral fields. First departure from explosives came in 1904 when, through the purchase of the International Smokeless Powder and Chemical Company, Du Pont began manufacture of special types of nitrocellulose for industrial applications. The next few years marked the company's entry into the field of pyroxylin solutions, belt cements, dips for the Welsbach gas mantle, and the old type of high-viscosity lacquers. Many years were to elapse before the development of Duco low-viscosity nitrocellulose lacquers.

In the meantime, research activities were extended and broadened through the establishment of the Experimental Station, near Wilmington, in 1903. This new laboratory was under the direction of the Development Department, which had just been organized for the purpose of expanding the business of the company. During the administration of Pierre S. du Pont the plan for diversifying the activities of the company in the chemical field was initiated, and this policy was continued under Irénée du Pont and Lammot du Pont, and has also been continued by Walter S. Carpenter, Jr, now president of the company.

Diversification of the company's activities was, for the most part, accomplished in two ways. First, companies well established in certain lines of manufacture were acquired. In this way Du Pont entered the manufacture of nitrocellulose-coated fabrics, nitrocellulose plastics, rubber-coated fabrics, paints, varnishes, lacquers, pigments, inorganic chemicals, electrochemical products, ammunition, and guns. The second method of expansion was to acquire patents, processes and "know-how" from established companies abroad, chiefly Great Britain and France—in many cases through the formation of subsidiary companies. By this method the company began the manufacture of intermediates and dyes, ammonia, rayon, and cellophane. Through the purchase of patents and processes from abroad, many years of research effort were saved, and the time necessary to start new activities was reduced to a minimum.

Following World War I, German patents on intermediates and dye manufacture were licensed from the Chemical Foundation. Without these patents development of the American dye industry would have been greatly retarded. In fact, it is doubtful if America could have manufactured certain important classes of dyes without these German patents. The time saved through the purchase of patents and processes from abroad was used in more advanced research. The acquisition of a company was followed inevitably and quickly by an expansion of the research activities of the new business. The acquisition of processes was followed inevitably and quickly by the establishment of research organizations to assist in reaching a production basis and to seek further advances.

This may be summarized—and it should be put this way because it describes one of the foundation stones upon which Du Pont rests—by saying that every growth in the company's manufacturing activities has been accompanied by a fully commensurate growth in research activities.

In 1911 a centralized Chemical Department was established to take care of all research activities of the company, and this plan continued in operation for about ten years. In 1921, however, a complete reorganization of the methods by which the business of the company was conducted marked the beginning of our present decentralized plan of research. Under this plan the manufacturing departments were organized with research divisions, the

personnel of which was drawn from members of the Chemical Department; these research divisions were, and still are, responsible only to the general managers of the departments. Furthermore, directors of the research divisions are on the same organization level as directors of production and sales.

The organization remaining after departmental research divisions were established constituted the nucleus of a central Chemical Department, with laboratories at the Experimental Station. This Chemical Department was wholly independent of any manufacturing department, reporting directly to the president and Executive Committee. The director of the Chemical Department has the same status as general managers of manufacturing departments and directors of auxiliary departments. He serves as adviser to all departments on research matters.

Activities of the Chemical Department are chiefly concerned with pioneering-applied and fundamental research. The results of its investigations flow into the research divisions of the manufacturing departments. Du Pont's chemical activities are so diverse as to provide a large framework of interest and experience within which a strong central research department can operate.

It should be emphasized that the Chemical Department, by virtue of its independent position, is not hampered by the daily problems arising from manufacture. The background and experience of our manufacturing departments influence the selection of their new research activities; but with a central Chemical Department, free to investigate any problem in the entire field of chemistry, there is less likelihood of attractive opportunities being neglected because they do not come within the immediate interests of the manufacturing departments.

TYPES OF RESEARCH

The research activities of the Du Pont Company in normal times fall into three broad categories: (1) improvement in existing processes and products, (2) development of new products, and (3) fundamental research.

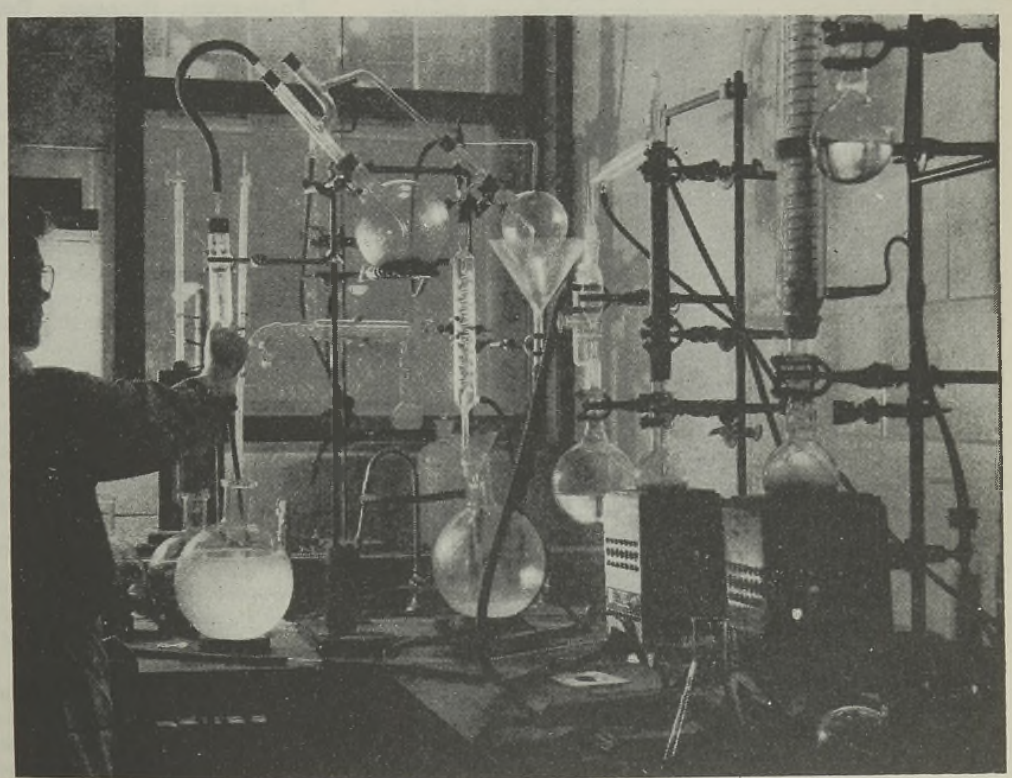
Improvement in Existing Processes and Products. Research work leading to the improvement of existing processes and products constitutes one of the main activities of the research divisions of our ten manufacturing departments. It is the "bread-and-butter" research of these departments for maintaining position in the chemical-consuming industries which we serve.

Even before the turn of the century, when the company manufactured only explosives, the policy was to sell at low prices in order to develop large volume. This policy has since been followed without deviation. As a corollary, it has had an important influence upon the research program, in that it has required continuing work on the major products of the company to reach the lowest manufacturing cost consistent with high quality.

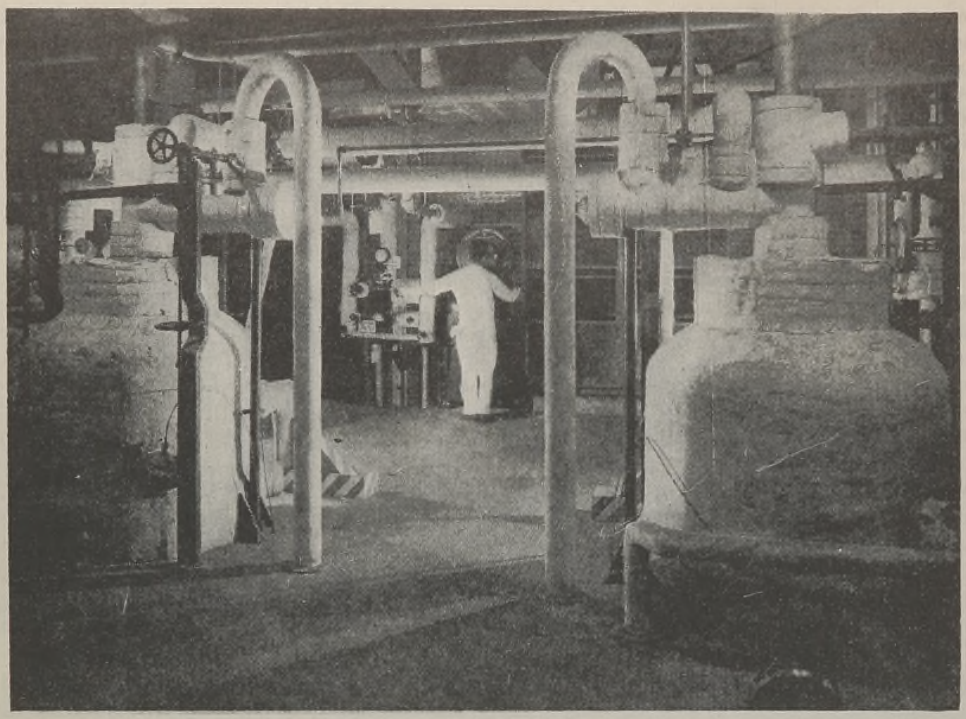
About forty years ago a technical section was organized as part of the Explosives Sales Division. The purpose was to have highly trained technical men supplement the explosives salesmen in rendering service to customers with special problems, and to teach the safest, most effective, and most economical methods of putting explosives to work. As a result of this service, large economies were effected in the use of explosives by the consuming industries.

Each of our manufacturing departments today has technical sales service to help the consumer in the most efficient use of Du Pont products. In some of the departments this service has been highly developed—for example, in the sale of dyes, textile finishes, detergents, rubber chemicals, petroleum chemicals, and a number of other products. Within the Organic Chemicals Department is a so-called Technical Laboratory where small machinery is installed for the purpose of studying different kinds of commercial dyeing, printing, and finishing of textiles, and the application of dyestuffs and finishing agents to paper and leather.

Illustrative of this type of service are the two vat-dyeing processes recently developed in the Technical Laboratory. While vat dyes have long been recognized for their extreme fastness to light and laundering, their application has been limited for the most part to cotton and viscose process rayon. This has been due to the fact that conventional processes had a deleterious effect on wool and silk, and because of other technical difficulties incident to the dyeing of such fabrics. Du Pont's new vat-dyeing processes are designed to assist in avoiding these difficulties and to



Typical setup in a modern organic research laboratory at Du Pont's Experimental Station near Wilmington. This apparatus is designed for carrying out distillations whereby various organic materials are separated and purified.



First step in making nylon at Seaford, Del., is evaporation of water from the chemicals that are shipped from Belle, W. Va. Nylon intermediates are pumped into these huge tanks to begin the processing that turns them into strong, elastic, synthetic fibers and other materials.

make possible the use of fast vat colors on a much wider variety of materials than was previously possible, including fine woolen and rayon fabrics and blends of various natural and synthetic fibers. Another illustration of the company's technical service is the process developed some time ago by the Electrochemicals Department for the continuous bleaching of cotton goods at unprecedented speeds. This new process not only hastens bleaching but also makes possible precise control of the entire operation, with resultant uniformity in color and appearance.

Hailed as outstanding contributions to the finishing of fabrics, these new dyeing and bleaching processes have been made avail able to the textile industry without cost, as part of the company's technical service, the aim of which is to develop improved processes both as regards speed and the efficient use of chemicals.

These examples are sufficient to indicate that the sales-service organizations of our manufacturing departments, comprising highly trained technical men, perform an important function in helping the consumer to obtain the best results. Moreover, these organizations constitute a valuable line of communication between the consumer and the research and production divisions. This information is of great assistance to the research chemist who studies the modification of a product to fit the needs of the consumer.

There seems to be no finality to research directed to improvement in quality and reduction of manufacturing costs, and the results of this kind of research are far-reaching. Every improvement in quality means that purchasers receive a better product. Every reduction in cost means that more purchasers can buy those products. This combination of improved quality and lowered cost, wherever it appears in American industry, is and has been a contribution of the first magnitude to raising our standard of living in peace and to the winning of ultimate victory in war.

Development of New Products. To maintain the company's contribution to an expanding economy, research directed to the development of new products is carried out by all the manufacturing departments. It is the principal means by which a department can expand into new lines of business. The chemical industry is replete with examples of products which were entrenched in public favor for a short time, only to be replaced by others of better performance and, frequently, lower cost. Chemical science is so complex that there are often many ways in the hands of the chemist to achieve the same result. For example, we have many instances of new dyes, improved in some important characteristic such as fastness to washing or fastness to light, that make serious inroads into the markets of old established products. Over a period of years we have seen how the vat dyes, characterized by excellent fastness to light and washing, have come to replace the older azo dyes. New synthetic resins have made possible the formulation of finishes vastly superior in durability to the older, conventional drying-oil types. There are many examples of this type of product obsolescence. The chemical business cannot progress without research directed to the development of new products.

The effectiveness of this kind of research is indicated by the fact that 46% of the gross sales of the Du Pont Company in 1942 consisted of products which either did not exist in 1928 or were not then manufactured in large commercial quantities.

Fundamental Research. Research of this kind was started in 1927 by C. M. A. Stine, during his tenure as chemical director, with the object of establishing or discovering new scientific facts without regard to immediate commercial use. It is thus distinguished from applied research, which uses previously established scientific facts in the solution of practical problems.

It was felt at that time that university research, while very valuable, was not sufficient to fill the existing gaps in scientific knowledge of importance to the fields of activity of the company. Research was therefore initiated in colloid chemistry, physical chemistry, organic chemistry, and physics. This was the first formal program to be carried out by a group of Du Pont scientists specifically assigned to fundamental research.

To preserve continuity of effort, the fundamental research group was organized as part of the Chemical Department. Over a period of years fundamental research has grown steadily, and although relatively small in volume compared to the research activities of our manufacturing departments, it has become one of the most valuable phases of research work in laying the foundation for new lines of applied research.

COLLATERAL RESEARCH ORGANIZATIONS

Research within the company is by no means restricted to the purely chemical field. Collateral research organizations within other departments have been and are of great value to the company.

Chemical Engineering. Studies on the design of chemical process equipment and on the selection of proper materials of construction have necessarily been carried on since the original undertaking of chemical manufacturing operations. But in 1929

a group was set up by Dr. Stine at the Experimental Station, as part of the Chemical Department's fundamental research organization, to devote its entire attention to research in chemical engineering. Its objective was the development of more knowledge concerning the important unit processes of chemical engineering. The information developed by this group on heat transfer, fluid flow, absorption, distillation, and related operations has been of great value, particularly in the design of new plants and modifications of established operations. Incidentally, the results of much of this work have been made available to the industry through numerous published papers.

Mechanical Engineering. As the Company's operations became diversified, machines were developed for the particular job, either in cooperation with equipment manufacturers, or independently. Entry into the fields of plastics, rayon, cellophane, photographic film, and nylon demanded specially designed machines. Development of special machines was undertaken in a formal way about 1935 by setting up a machine design group within the Industrial Engineering Division of the Engineering Department. The scope of this work has recently been extended by the establishment of a separate Mechanical Development Laboratory.

Engineering research has not only been instrumental in bringing chemical developments from the test-tube stage to the over-the-counter stage with a minimum of delay, but also has contributed greatly to cost reduction. In the latter connection it is of interest that research and development carried out since World War I by Du Pont engineers and chemists in connection with the manufacture of strong nitric acid, smokeless powder, TNT, and tetryl have resulted in savings to the Government of more than 600 million dollars in construction costs alone. A large part of this saving resulted from improvements in manufacturing processes which led to great increases in the capacity of the first units installed during the present war, making unnecessary the construction of plants initially regarded as essential to fulfillment of the nation's military requirements.

Haskell Laboratory of Industrial Toxicology. This important collateral research organization was established in 1935 as an integral part of the company's Medical Division. Many of the chemicals essential to industry are toxic. Exact knowledge, however, concerning degree of toxicity, how the compound enters the body, its manner of action, and how to treat possible injuries or illness arising from contact with the toxic material, makes it possible to set up protective measures that will eliminate hazards or reduce them to the minimum.

The Haskell Laboratory was established to develop information of this type concerning products made or used by the Du Pont Company. It is designed to develop information to aid in protecting the workers not only in our own plants, but also in the plants of those who use Du Pont products. Chemicals and other Du Pont materials used in various consumer products also are studied. For example, long before nylon hosiery went on the market, thousands of "patch tests" were made on volunteers among our employees to determine if nylon fabrics had any deleterious effect. Nylon was not announced until repeated practical wear tests had demonstrated this product to be wholly innocuous.

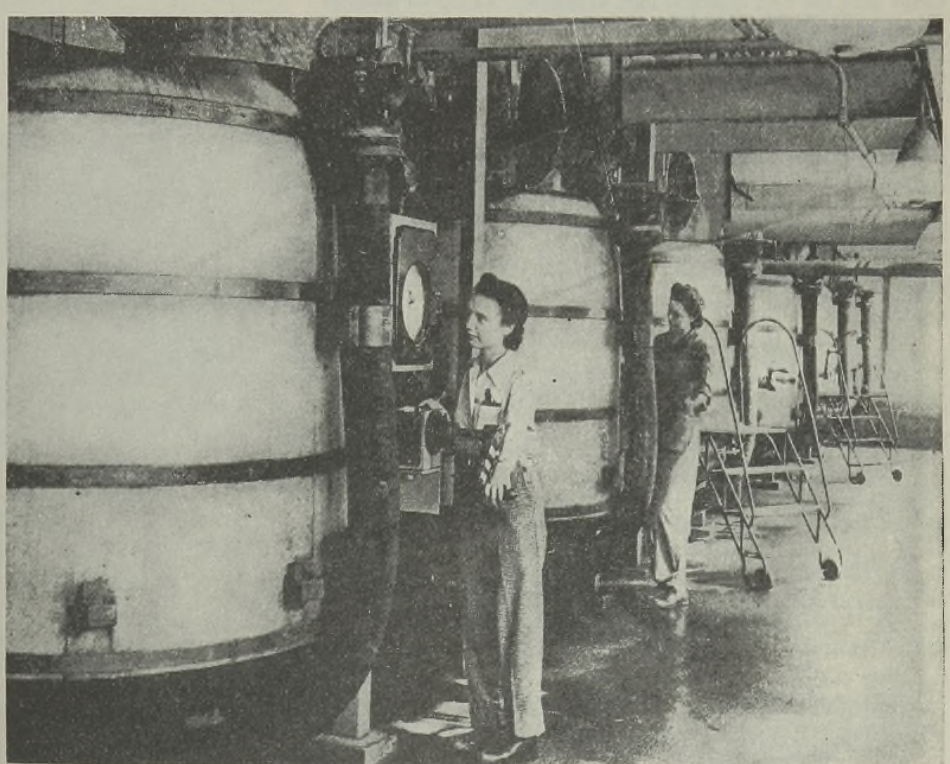
DU PONT RESEARCH POLICY

Major Activity. It is a tradition of long standing that research is a major company activity. It is looked upon as a vital function. It flourishes because of an atmosphere of appreciation, encouragement, liberality, and patience. Never was this attitude better illustrated than during the depression days of 1932, when every department of the company was economy-minded. During this period I had occasion to talk with Lammot du Pont, then president of the company, about the work of the Chemical Department. He inquired about the progress of fundamental research. I told him that transfers to other parts of the company had reduced the number of men devoted to this work. He asked if I had sought to replace these men. I replied in the negative. His comment perfectly illustrates the company's approach to research: "You know it is more important to carry out research than to pay dividends."

As president from 1926 to 1940 and in his present capacity as chairman of the board, Lammot du Pont has ever been a staunch supporter of research. In 1929 a particularly large expansion in research began, when expenditures showed a 300% increase over 1928. Since that time the company's research organization has shown continuous growth, with the exception of 1932 and 1933 when there was a slight regression from the 1929 level. Since 1940 W. S. Carpenter, Jr., has also supported the policy of a strong research program. Today, Du Pont's research organization comprises thirty-three research laboratories, with a technical and nontechnical personnel of about 3500 men and women.

Continuity. The fortunes of a research organization should not follow a profit and loss curve. It is accepted as axiomatic that

Operators in the polymerization unit of a neoprene plant control chemical reactions with the aid of recording instruments.



Film of neoprene leaving the drier. This polymer was the first general-purpose synthetic rubber to be developed.

satisfactory progress in research over a period of years cannot be maintained if research expenditures are materially reduced when business goes through a temporary slump and increased when business improves. Both neoprene and nylon were "children" of the depression.

STRONG CENTRAL RESEARCH DEPARTMENT. Part of the scheme of Du Pont research is to maintain a strong central Chemical Department devoted to long-range investigations. The primary concern of the Chemical Department is the future. Its chief purposes are to help provide new opportunities and assure future growth.

HIGH-QUALITY PERSONNEL. Since the most valuable research asset is good men, the policy of the company is to staff its laboratories with the best qualified men available. As stated recently by James B. Conant, "Ten second-rate men are no substitute for one first-class man." This has been the experience of Du Pont's research organization.

TEAMWORK. Another feature is teamwork, not only on the part of men in a particular laboratory, but also as regards interdepartmental cooperation. The Chemical Department helps to coordinate the research activities of the several manufacturing departments. To prevent unnecessary duplication, experience in one department is brought to bear on problems of other departments.

This, then, is the organization and policy of Du Pont research. What such research means to the American people in war and in peace is clear. Perhaps less evident is the basic fact that has brought this type of organization into being.

In the early days of applied research it was possible for an individual to carry in his head a large part of the technical information he was likely to need in the course of his investigations. Today the situation is different. Most of the obvious and easily attained objectives have been reached. Our body of scientific knowledge has become so large and complex as to be beyond the grasp of any individual.

Industrial research meets this situation. Through its ability to employ an adequate staff of highly trained research workers, whose various abilities can be focused on a single problem, and through its ability and willingness to venture, without hope of immediate return, sums far beyond the reach of any lone inventor, modern industry advances human knowledge in a way that was utterly impossible before its advent. Beyond that, it converts the newly gained knowledge into a higher standard of living far more quickly and on a larger scale.

The early inventor, working without aid or backing, many times met rebuffs, discouragement, and ridicule. Today, the achievements of modern industrial research have led the American people not only to accept the new, but to expect and demand it. The age-old skepticism of the average American toward the new and unheard-of has been largely eliminated by a tidal wave of invention and development.

OUTSTANDING RESEARCH ACHIEVEMENTS

DYE INDUSTRY. In 1916 the Du Pont Company decided to enter the manufacture of dyes, with the encouragement of the Government and representatives of the textile industry. The United States was almost wholly dependent upon German dyes at the outbreak of World War I. When the British blockade was imposed, employment of millions of American workmen in the dye-consuming industries was threatened. To make as rapid progress as possible, an agreement was made with the British firm Levinstein, Limited, which had manufactured a few intermediates and dyes prior to the war. After the outbreak of war, however, Levinstein operated a former German-owned indigo plant which was modern in construction. This arrangement was very helpful, particularly in enabling the company to avoid the long time that would have been necessary for the development of an indigo process.

In the manufacturing process a thin film of dried neoprene is twisted into a rope and cut into short lengths for shipping.

In starting the dye business, Du Pont was confronted by two serious difficulties which confronted other manufacturers in this field: (1) The number of chemists with graduate training in research work was very small; (2) the German patents licensed from the Chemical Foundation disclosed inadequate information and in many cases made no reference to the preferred methods of manufacture of the products covered by the patents.

Du Pont started the development of its dye business on a broad scale, realizing that to have a well-rounded business it was necessary to engage in the manufacture of all important classes of colors. Progress, however, was slow at first because no one in the research or production divisions had any previous experience in dye manufacture. It was therefore necessary in the early years of this venture to concentrate all efforts on establishing the business on a firm foundation.

From the beginning it was recognized that the manufacture of dyes could serve as the backbone of a synthetic organic chemical industry. Accordingly, in the early twenties research work was begun on rubber accelerators. This was the beginning of the period of diversification in organic chemical manufacture, and research was pursued in two directions: (1) to expand the lines of dyes, and (2) to find new products to be used by the chemical processing industries.

Today the Organic Chemicals Department, in addition to intermediates and dyes, is making rubber chemicals such as accelerators and antioxidants, petroleum chemicals such as gasoline antioxidants and extreme-pressure lubricant bases, tetraethyllead by the Kraus method for the Ethyl Corporation, synthetic camphor, textile finishes, detergents, wetting agents, seed disinfectants, perfume bases, photographic chemicals, synthetic vitamin D, neoprene, and many other organic chemicals. Over two thousand materials are now manufactured by this department. The success of this undertaking can be attributed to four important factors:

1. The expenditure of large amounts of capital during the many profitless years. At the end of the first five years the company had invested 22 million dollars in plants and working capital, and had suffered operating losses to the extent of $18,000,000.
2. Close cooperation of research, production, and sales.
3. Excellent quality of technical personnel and operators.
4. Most important of all, an abiding faith on the part of Pierre, Irénée, and Lammot du Pont that this venture was fundamentally sound, and that the organization could put this undertaking on a successful basis.

Neoprene. In view of previous unsuccessful attempts over a period of many years to make a satisfactory synthetic rubber, the development of neoprene is an interesting research accomplishment. In the fall of 1925, W. F. Harrington, now a vice president but then general manager of the Dyestuffs Department, indicated the economic position of the department was beginning to take a favorable change that would permit a start in pioneering work. He felt that we should endeavor to make a product that would have a large potential outlet. The problem of synthetic rubber was proposed, because it was considered to be one of the outstanding problems challenging organic chemists at that time.

From an economic standpoint synthetic rubber was of interest because this country was consuming more than half the world's output of natural rubber, and was wholly dependent upon foreign sources of supply. As a result of the Stevenson Export Restriction Plan, the price of rubber had risen during 1925 to more than one dollar a pound. Therefore, all factors on the economic side were favorable and encouraged work on this problem. On the technical side, however, the prospects of solution were not so favorable. Before the first World War the English and Germans had tried to make synthetic rubber without success.

When this line of research was proposed, there was a division of opinion as to the wisdom of undertaking this work, especially in view of the failure of German chemists. Dr. Harrington decided, however, to back the recommendations of the research group, and to him should be given credit for encouraging the initiation of this project.

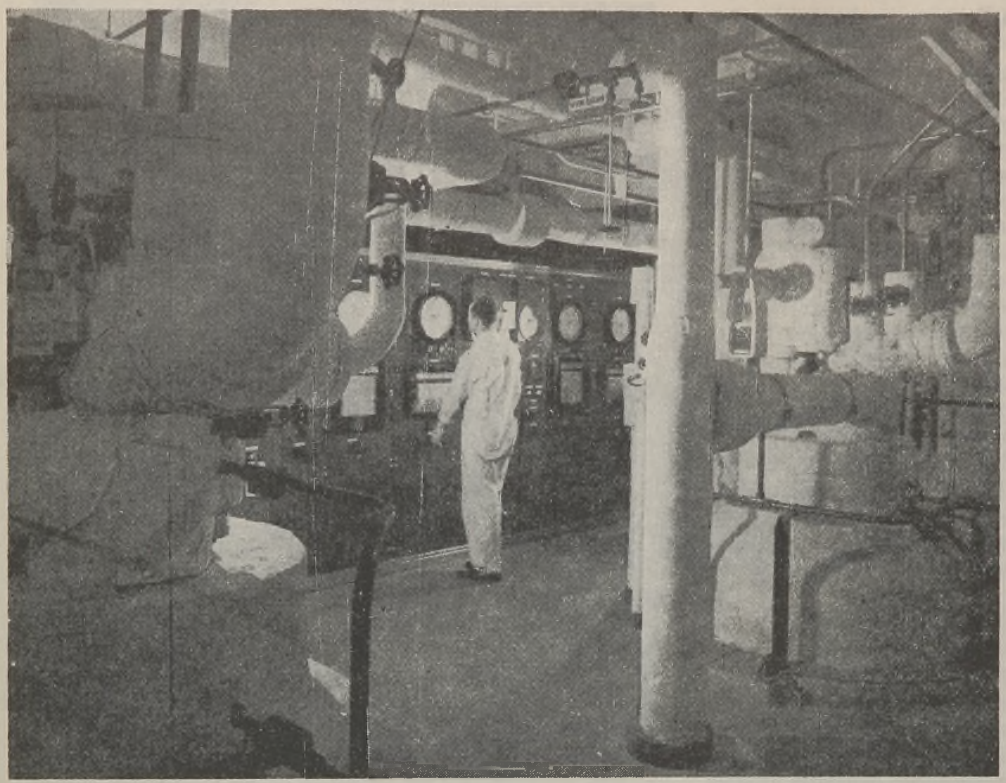
Sewing a nylon flare parachute is a joining operation in which sixteen panels, or gores, are sewn together.

The rest of the story has been told many times. Suffice it to say that, thanks to the support by management over a period of years, Du Pont research chemists in 1930 discovered that monovinylacetylene, which the late Father Nieuwland had prepared in the course of his research on acetylene, could be converted to chloroprene (2-chloro-1,3-butadiene) by treating it with hydrogen chloride in the presence of a suitable catalyst. But more important, they discovered that chloroprene polymerized readily to produce a synthetic rubber of high quality. The resulting polymer, neoprene, was the first general-purpose synthetic rubber to be developed.

While quantitatively this product occupies a secondary position in the synthetic rubber program, chiefly because of a shortage of electric power for calcium carbide manufacture, neoprene is today serving numerous important military needs that no other available material can fill.

Moistureproof Cellophane. This development is a research achievement worthy of mention because of its profound influence on the packaging of many commodities. Shortly after Du Pont acquired the cellulose film business of La Cellophane in 1923, it was realized that the transparent film as then manufactured had definite limitations. The original "plain" cellophane, so called to distinguish it from the moistureproof variety later developed in our laboratories, was decorative and had a certain utility as a wrapping material; but since it was permeable to water vapor, it was not well suited as a wrapper for cigars, cigarets, and a vast number of uses involving foods whose taste, texture, and freshness depended on maintaining the original moisture content.

Research was started, and in 1927 this defect was overcome by the development of a moistureproof lacquer which is applied to both sides of the cellophane as an extremely thin film—only about



In these autoclaves nylon polymer is created. The control panel signals the progress of each of the stages of polymerization.

0.00005 inch thick. The lacquer owes its effectiveness to the presence of an amount of suitable wax so small that, if spread out alone on the cellophane, it would give a film only a few millionths of an inch thick. For the past few years more than 75% of the total cellophane production has been the moistureproof variety.

This research achievement made cellophane a product known throughout the civilized world and having thousands of uses. Since this development resulted in a tremendous increase in production, it helped to bring the price of cellophane down to about one fourth its 1927 figure.

Ammonia and Other Products of High-Pressure Synthesis. In 1926 Du Pont undertook the fixation of atmospheric nitrogen through the synthesis of ammonia, primarily to supply the company's needs for nitric acid. At first the capacity of the plant was small, efficiency was low, and performance of equipment uncertain. Through research, however, new methods were perfected for the preparation and purification of the nitrogen-hydrogen mixture, and improved catalysts were developed. Also, equipment for use under special and severe operating conditions was designed, and the technique of handling gases under pressures up to 1000 atmospheres, over a wide temperature range, was mastered.

The business of this department was built upon a technology based on the use of water gas, for the production of which coal is the principal raw material. The availability of water gas, combined with knowledge of catalytic high-pressure techniques, led to the development of a process for methanol manufacture, and this operation is now carried out on a scale comparable with that for ammonia. In addition, many other products are made by entirely new industrial processes, with new types of catalysts, and under pressures which years ago would not have been considered practicable. Among the products of this new technology are adipic acid and hexamethylenediamine (intermediates in nylon manufacture) and ethylene glycol.

Over the past ten years there has been a rapid increase in the number of products made from water gas, including important ammonia derivatives, aliphatic acids and esters, higher alcohols, and hydrogenated products. Over a hundred items are now manufactured by our Ammonia Department, which had its beginning in the fixation of nitrogen.

There is no other group of operations within the company in which engineering plays such an important part, on account of the high pressures involved and continuity of processes. The remarkable success of this department is a tribute to the close cooperation of the chemist and the engineer.

Duco Nitrocellulose Lacquers. Few modern chemical developments have had more far-reaching implications than quick-drying, durable, low-viscosity nitrocellulose lacquers. In 1913 several weeks were required to paint the average automobile. By 1922, although the time had been substantially reduced, the paint shop still remained the bottleneck of mass production. In 1923, however, the quest for quick-drying, durable finishes culminated in the development of Duco.

Although nitrocellulose of inherently low-viscosity characteristics had previously been known, Duco represented the first practical method ever devised for making a durable pyroxylin lacquer. While these new finishes required a low-viscosity nitrocellulose, this was by no means the complete answer to the problem. Formulation of lacquers having the durability required for outdoor use involved a vast amount of experimentation with many different gums, resins, solvents, plasticizers, and pigments, with durability test panels exposed all the way from New Jersey to Florida. Before a complete range of colors was developed, this program demanded seven years of intensive research.

By reducing from days to hours the time required to finish a car, this research achievement aided materially in the mass production of automobiles, which in turn resulted in low prices.

Nylon. The latest outstanding achievement of Du Pont research is nylon. This product, which had its genesis in fundamental research under the immediate direction of the late Wallace H. Carothers, made its appearance at a most opportune time —shortly before the war in the Orient cut off further importations of silk and hog bristles. Since 1941 nylon has proved of great value in parachute fabrics, glider tow ropes, and cords for the fabric of tires used on our big bombers such as the B-29 Superfortress. It is now becoming increasingly important in the south-

west Pacific for tents, ponchos, hammocks, insect netting, and shoestrings because it is resistant to the fungi which cause mildew and rot, and also to termites which are difficult to combat in the tropics. In the form of tapered bristles, it is used also in making paint brushes for the armed services.

The story of nylon has been told many times. I should, however, like to use this development to illustrate two points which have an important bearing on Du Pont research—the value of teamwork and the importance of semiworks or pilot-plant operations. The development of manufacturing processes for nylon intermediaties, the polymer, and yarn called for a greater degree of coordinated teamwork than any other project ever undertaken by the Du Pont Company. Each and every step of the nylon process, and the equipment for it, were worked out on a semiworks scale with such thoroughness that, except for size, the first commercial plant which went into operation early in 1940 was practically a duplicate of the pilot plant.

CONCLUSION

Research becomes of service in the ordinary walks of life only when it can be translated into processes or products which contribute to raising the scale of living, to the improvement of health, to the promotion of industry and agriculture, and to the national defense The great store of scientific knowledge which has been accumulated in the past through the careful, painstaking investigations of countless scientists becomes of value to society when research points the way to harnessing it to a practical application.

It should be emphasized, however, that the research organization is only part of the team necessary to bring the fruits of scientific work to the service of mankind. It requires the wisdom and courage of management to make the investment, a capable engineering organization to design the plant, an able and experienced production organization to make material of marketable quality and suitable cost, and a sales organization to develop markets. In no small measure the success of Du Pont research depends upon the capabilities of other parts of the organization, for without them the developments which have contributed so much to the growth of the company could not have been brought to the commercial stage.

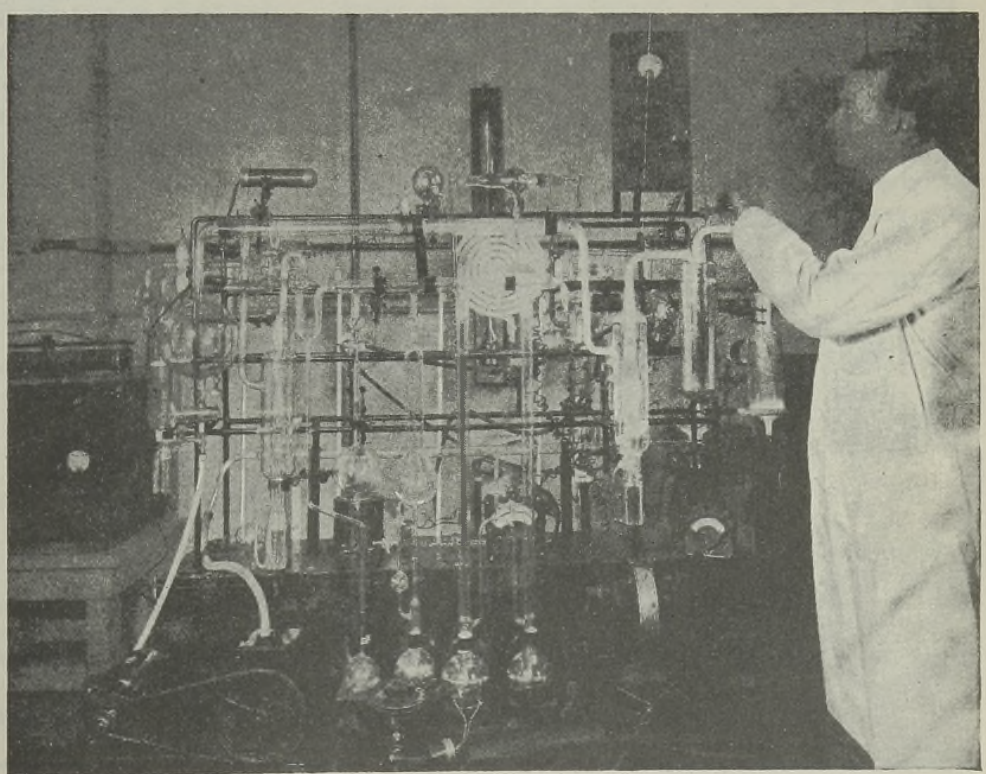
From the colonial days down to the present, our patent system has been a great stimulus to research, and an incentive to the creation of new products and processes. Large expenditures such as were involved in developing neoprene and nylon, for example, were justified because of the patent protection it was possible to establish. Were it not for this protection, the stimulus to research and invention would be greatly diminished, whether by a lone individual, by small business, or by so-called big business.

One other element should be mentioned. It is public support and favor, which must be earned. It must be earned by operating in the public interest. Without it the team effort is foredoomed. Out of the experience of many years I can say that our company's activities are uniformly motivated by a clear sense of its responsibility to the American people.

At present all research efforts are concentrated on winning the war, but as soon as peace comes all branches of the chemical industry will go forward with greatly increased research programs in an effort to make up for the lost time, although faced with a serious shortage of well-trained chemists—a shortage, I fear, that will be felt for a number of years. While war accelerates the utilization of existing scientific information, it almost eliminates fundamental research.

Since World War I, the chemical industry has made remarkable progress, due in important measure to the friendly attitude of the Government toward research. Granted a continuation of this attitude, organized research will go on creating new products, for what remains to be done is far greater than anything that has been accomplished in the past.

In the words of Pasteur: "Take interest, I implore you, in those sacred dwellings which one designates by the expressive term: Laboratories. Demand that they be multiplied, that they be adorned; these are the temples of the future—temples of well-being and of happiness. There it is that humanity grows greater, stronger, better."



Some modern research apparatus at the Experimental Station o E. I. du Pont de Nemours & Company, near Wilmington, Del.

Filling Capsules with Propadrine (a Brand of Phenylpropanolamine) Hydrochloride in the Laboratories of Sharp & Dohme, Inc.

SYMPATHOMIMETIC AGENTS

A Symposium Presented at the 108th Meeting of the American Chemical Society in New York, N. Y., before the Division of Medicinal Chemistry with John H. Speer, of G. D. Searle & Company, presiding.

Rx —more than thirty years ago, Barger and Dale published their classic paper on the relation of chemical structure to physiological activity of a large group of amines. They showed that certain of these amines with the β-phenethylamine skeleton would cause effects generally resembling those produced by stimulation of the so-called sympathetic system of nerves. Hence the name "sympathomimetic amines". Those in the field of medicinal chemistry regard Barger and Dale's paper as a classic, not because it pointed out that certain amines have certain properties, but because it gave an impetus to a systematic correlation of structure with pharmacology and set a sound pattern for such investigation.

The study of sympathomimetic amines has been fruitful ever since. Viewed from the scientific angle, many papers have been written and much brilliant work has been done. From the commercial point of view a number of valuable medicinal products have been developed, whose combined annual sales run into impressive figures. But most important, without the patient scientific progress in our knowledge of these compounds the practicing physician would lack valuable tools for treating disease.

The Division of Medicinal Chemistry is happy to have on its program for this Symposium a group of speakers who have long been identified with various phases of this problem. All are men whose work has already introduced them to our attention.

JOHN H. SPEER

CLINICAL IMPORTANCE AND USES

HARRY GOLD

Cornell University Medical College, New York, N. Y.

By—in nearly half a century since the introduction of epinephrine into clinical medicine, the importance of sympathomimetic amines in therapeutics has grown, partly as the result of greater knowledge of benefits which may be derived from increase in sympathetic activity in particular diseases, but chiefly because of the development of new synthetic compounds. The scope of their uses now extends beyond raising the blood pressure and constricting the vessels of mucous membranes. They have invaded the field of diagnosis and therapy of medical and surgical diseases involving almost every organ and system of the body: the heart, vasomotor system, respiratory system, eye, gastrointestinal system, central nervous system, skeletal musculature, endocrine system, and metabolism. This group of compounds stands in all lists of essential drugs and further in the smaller group of emergency agents. They sometimes save life. More often they relieve suffering. Their special properties are applicable more to the common diseases of everyday practice than to the rare ones.

HOW important are the sympathomimetic amines in the practice of medicine? The answer depends upon whom we ask. The professional activities of the gastroenterologist or the urologist are not materially influenced by this group of compounds. On the other hand, without these drugs the allergist would see no end of suffering and disaster. The material bearing on the importance and uses of the sympathomimetic amines is assembled here in relation to some of the major fields of medical practice; each is likely to provide a somewhat different answer to the question of how matters stand. Since the purpose is a practical one, it may not be objectionable if the groups to which I allude are somewhat loosely defined and if adherence to them is not too rigid.

Perhaps a word in defense of such a therapeutic classification is in order. In one sense it is not fundamental because it does not follow closely the basic pharmacological actions. It is well known that sharp bands drawn between therapeutic classes are often absent in the pharmacological spectrum. The property of the drug which the rhinolaryngologist utilizes for shrinking the turbinates in acute rhinitis of the common cold may well be the same as the property the anesthetist calls upon for restoring the blood pressure which has fallen abruptly in order to prevent the development of secondary shock in the course of anesthesia and operation.

On the other hand, from the discovery of a strong vasoconstrictor action in two compounds, it is not a safe prediction that they will prove equally useful to the rhinolaryngologist and anesthetist in proportion to their vasoconstrictor power. Pharmacologically, epinephrine is a much stronger vasoconstrictor than neosynephrine. Both are put to satisfactory local use for the shrinking of mucous membranes, but neosynephrine has been successfully applied by the anesthetist for raising the systemic blood pressure whereas epinephrine has failed to establish any satisfactory reputation for that purpose.

The main virtue of classification by therapeutic uses is that such classes are not arranged according to single basic actions, but according to clinical composites which involve a multitude of factors, and in which attention is focused not alone on a particular structural or physiological system but on the reactions of the patient as a whole. The result is significant information which is not obtainable in any other way. It is well known that different methods of testing compounds often yield different results. I want to suggest that therapeutic orientation, quite apart from animal experimentation, has much to offer to the synthetic chemist exploring in the field of sympathomimetic amines. Perhaps he should arrange to apply therapeutic testing more systematically and earlier in the process of screening. Without it important agents may well escape discovery.

The fields of medical practice in which the compounds of the sympathomimetic amines play an outstanding therapeutic role are rhinolaryngology, allergy, surgery and anesthesia, cardiovascular, and neuropsychiatry. There are also several areas of application in which their utility may be considered less certain or less important—namely, in disorders of the eye, the neuromuscular system, the gastrointestinal tract, the urinary bladder and its sphincters. I shall confine my remarks for the most part to those in which their uses are most extensive and important.

RHINOLARYNGOLOGY

Disorders of the upper respiratory tract (the nose, the throat, and the sinuses) make the most frequent demands on the sympathomimetic amines. It is difficult to contemplate what the therapy of the general practitioner, the pediatrician, the rhinolaryngologist, or, for that matter, the self-medication practice of the laity itself would be like if they did not have a member of this group of drugs to shrink the swollen mucosa of the nose in order to relieve breathing, or to open wider the apertures of the sinuses in order to facilitate the drainage of the hazardous stores of pus and secretions. Vasoconstriction by local application to the nasal mucosa is a property of all sympathomimetic amines in common use—namely, epinephrine, ephedrine, paredrine, propadrine, synephrine, neosynephrine, amphetamine, and others. Although special merits are often claimed for one or another member of the group, it is not possible in most cases to detect outstanding superiority in the results of their clinical application for the constriction of nasal mucous membranes. The fact that amphetamine is volatile has been put to good use with the special nasal inhaler. There is the view that epinephrine is more likely than others to produce a secondary congestion after the initial constriction, that ephedrine and other members of the group are free of the secondary congestion and produce less intense and longer acting ischemia. For the local constrictor action there is preference under most conditions for the compounds which exert the least central stimulation, such as neosynephrine, propadrine, or paredrine. It is not clear as to what objectives one would pursue in the endeavor to improve further the quality of sympathomimetic amines in relation to their local application for the shrinking of mucous membranes, except possibly greater stability and longer duration of action.

ALLERGY

The most important area of application of the sympathomimetic amines is the field of the hypersensitivity reactions. Anaphylaxis, asthma, hay fever, urticaria, angioneurotic edema, serum sickness, nitritoid reactions, and other forms of allergic responses are here included. In point of frequency these disorders constitute one of the chief sources of major physical suffering. A large part of the population has a stake in the development of suitable agents for the control of these reactions. Few people pass through life without an attack of hives at one

time or another. Asthma and hay fever affect about 3.5% of this country's population; thus about four million people in the United States seek relief among the sympathomimetic compounds from one group of disorders alone, which causes distress frequently throughout periods of several months of the year.

Human anaphylaxis is not a common encounter, but its instantaneous onset in an otherwise normal person, its streaking dash to a fatal termination by suffocation and shock, and its sudden reversal by a dose of epinephrine is one of the most dramatic experiences in medical practice.

Attacks of bronchial asthma are rarely fatal, but the suffering is often long and extreme, and the rapidity of the relief brought about by a small dose of epinephrine has few parallels in therapeutics. The same applies, although possibly in a lesser degree, to urticaria and angioneurotic edema.

The field of allergy has profited to a limited extent only from the synthetic developments among the sympathomimetic amines, and epinephrine with all its faults remains the choice of the allergist, the most dependable for the acute attack of bronchial asthma, urticaria, or angioneurotic edema. And its faults are many. Its action is so brief that the injection has sometimes to be repeated every half hour or so; as the dose is increased, the drug begins to cause palpitation, nervousness, and anxiety. Attempts have been made to overcome the difficulties with epinephrine itself in the form of the 1-100 spray and the solution in oil. Ephedrine has some value against mild attacks and is of some benefit in the prevention of attacks in patients with frequent paroxysms. It has the advantage of more prolonged action and oral administration, but its efficacy is greatly limited. It also causes unpleasant central stimulation, and large doses sometimes lead to urinary retention.

The common view is that the shock organ in bronchial asthma is the mucous membrane, and that mucosal edema is the chief feature of the attack, although bronchospasm and hypersecretion add to it. It is generally assumed that the drugs of this group combat the edema by their constrictor action in the blood vessels. This seems a reasonable explanation from the fact that the drugs are most effective early in the attack when vasodilatation may be expected to be the chief disturbance and edema negligible, and also from the fact that a nonspecific constrictor, pituitrin, is sometimes equally effective in controlling an attack. There is the possibility that differences in the antiallergic potency among the sympathomimetic amines may lie in different selective affinities for vessels of different regions. This may explain the observation that a dose of epinephrine which causes little rise of systemic pressure may cause blanching of the skin, whereas a dose of paredrine, with or without a marked rise of systemic pressure, causes no blanching of the skin. There is the fact that both cause shrinkage when applied locally to the mucosa, but when injected into the skin, epinephrine causes blanching and delays the absorption of novocaine; paredrine does neither. Such selective vasoconstrictor action is well known to pharmacologists. We recently investigated a series of compounds in which one member of the group produced an extreme constriction of the vessels of the legs without the slightest effect on the splanchnic vessels.

There still remains the fact that epinephrine seems to stand by itself. It is the most effective member of the group in the relief of clinical bronchial asthma; a compound like paredrine, which exerts a fairly strong vasoconstrictor and bronchodilator action, is almost devoid of effect against human bronchial asthma. The efficacy of epinephrine in allergy seems to be a quality of action which cannot be matched by any of the related compounds in common use, irrespective of the dose. The effect is brought on by a subcutaneous dose of 0.25 mg. or less, often too small for any detectable pharmacodynamic actions. The question has been raised by Cattell as to whether the antiallergic action of epinephrine may not be independent of its sympathetic pharmacodynamic actions. The possibility of blocking the action of a humoral substance responsible for the allergic reaction by a structurally related compound in the class which includes the sympathomimetic amines deserves some consideration. In that event, strong antiallergic derivatives possessing relatively feeble pharmacodynamic actions might not be out of the question. My attention was recently called to such a compound which gives indication of blocking certain of the actions of histamine in animal experiments.

CARDIOVASCULAR

There is a fairly large group of clinical conditions in which an urgent need exists for a sustained vasopressor action, either to overcome or to prevent vasomotor collapse. It does not include true shock for while the pressure is usually low in shock, vasoconstriction is already apt to be present and the primary difficulty is likely to be found in the capillary bed and deficient circulating blood volume. The group of conditions to which I refer are sometimes called "primary shock". It is difficult to evaluate the effect of treatment in these conditions because in many cases the blood pressure tends to return to normal without treatment. However, if the low blood pressure remains unchecked, the ensuing slowing of the circulation tends to lead to anoxic injury of the capillary bed; this may eventuate in a state of secondary shock which is frequently irreversible.

The synthetic compounds of the sympathomimetic group have given renewed impetus to the drug therapy of vasomotor depression or vascular collapse. Although epinephrine raises the systolic pressure in man, the diastolic pressure often falls; and it is virtually impossible to secure the vasopressor action without many undesirable effects—namely, rise in pulse rate, anxiety, pallor, increased metabolism, and increased work of the heart. Ephedrine provides some advantages, especially that of longer persistence of action. The newer synthetics which produce no significant central actions offer greatest promise. With compounds like paredrine, or neosynephrine it is possible to obtain a rise of blood pressure of 50 mm. or more after a subcutaneous or even oral dose, with slowing rather than acceleration of the heart, with little or no increase in the work of the heart, and without the disturbing anxiety symptoms of epinephrine or ephedrine. The need for such action is encountered throughout all phases of the practice of medicine. The surgeon and anesthetist have frequent occasion to apply it. As the result of the general anesthetic and the trauma and reflexes of the operation, the blood pressure sometimes falls gradually or abruptly from 140 to 80, and the heart rate mounts from 80 to 140. In the early period of this change a strong vasoconstrictor action may be a life-saving measure. The spinal anesthetic produces very low blood pressure, in a large proportion of cases as low as 75 mm. of mercury. A suitable dose of paredrine or any of the pharmacologically related vasopressor compounds restores the pressure or, if given shortly before the anesthetic, prevents the fall. The blood pressure often falls in the course of severe infection due to vasomotor depression. A falling pressure and rising pulse in a patient with pneumonia augurs disaster. It is often controlled by vasoconstriction. An interesting group of beneficiaries of the new sympathomimetic constrictors are the patients suffering with orthostatic hypotension. These patients are comfortable when they are recumbant. When they sit or stand their blood pressure falls so that they become weak, dizzy, and faint. In many of these cases suitable oral dosage of these drugs stabilizes the blood pressure, abolishes symptoms, and restores the victim to useful activity.

PSYCHIATRY

Mention has already been made of the fact that epinephrine causes tremor, apprehension, headache, restlessness, and anxiety. These are disagreeable central reactions which frequently arise in the course of its therapeutic application. Similar effects are produced by ephedrine, but this compound exerts additional

central stimulation which has formed the basis for its application in the treatment of depression by drugs, such as the barbiturates, and for the symptomatic relief of narcolepsy. However, the therapeutic possibilities in central actions by members of the sympathomimetic amines aroused but limited interest until the introduction of amphetamine for the treatment of narcolepsy. While ephedrine and amphetamine both cause cortical stimulation, and in large doses both may cause nervousness, unrest, and anxiety, in suitably small doses a difference in the design of their central stimulant action is detectable. Amphetamine possesses a quality of central stimulation which has wide application and is of the foremost therapeutic importance. Its uses have been successfully explored in the field of neuropsychiatry, and in this area an extensive literature now exists concerning its numerous applications.

Amphetamine exercises an influence on the intellect, the affect, and the mood. Its actions result in a change in the quality of personality which has wide appeal even though it is only temporary. It is a general psychological stimulant. It corrects such personality defects as retardation, indecision, and hesitation. The mood is lifted from mild depression to a warm glow, elation, euphoria. A feeling of anxiety and tenseness disappears. There is a sense of relaxation and pleasing calm. Confidence, initiative, and ease of decision are increased. A sense of inadequacy is replaced by feelings of the possession of energy and the desire to do things. Inertia to performance is removed. Clouding of the intellect is lifted. Thought processes are accelerated without impairment of concentration and judgment. Tests show improvement of intelligence scores. There is a tendency to increased talkativeness and speech becomes more fluent. A sense of fatigue from work and worry tends to disappear. There is evidence that the subsidence of fatigue is not only a subjective sense but is associated with an actual increase in the excitability of the central nervous system. One of its most constant effects is to promote wakefulness.

The therapeutic possibilities of such actions as these have stirred the imagination, and students of this subject have not been slow to seek out their numerous applications. One of the best established uses is in the control of the abnormal sleep pattern of the narcoleptic. In appropriate doses it overcomes in these patients the irresistible attacks of sleep which may occur several times in the course of the day's work. It also controls the sudden seizures of generalized weakness or cataplexy with which these patients are often afflicted. It has been applied with success in treating mild depression disorders, normal fatigue states, and various psychoneuroses, and in restoring wakefulness in stupor, sleep, and depression by alcohol, barbiturates, and other depressant drugs. Its application in major mental diseases is limited, although in these also some symptomatic benefits have been encountered. It sometimes brings about improvement in the dull state of self-absorbed patients with increase in speech responses, motor reactions, and affects. It has proved effective in the control of distressing symptoms of Parkinson's disease. It has improved the therapy of epilepsy by phenobarbital since it overcomes the drowsiness and ataxia caused by this drug, and thus permits the use of large enough doses of phenobarbital to control the severity and frequency of epileptic fits.

There is still another cause of ill health in the control of which amphetamine has been extensively applied, a condition which in those over 40 reduces to almost half the chance of surviving the age of 60. I refer to its use as an adjunct to other measures in the treatment of obesity. The drug impairs the appetite. The subject with an otherwise voracious appetite seems to lose interest in food. This effect is often referred to an action on the gastrointestinal tract and is explained on the basis of diminished hunger contractions. It seems more likely, however, that its psychological action is the main factor. Obesity is frequently a state of mind. People often take to eating when they are unhappy for the purpose of release from states of depression and tension. The habit of overeating acquired in this way has a firm hold on its victim and is not easily cured except with the aid of psychological measures. The actions of amphetamine on the mind are pre-eminently suited for the purpose.

There is room for much improvement in the behavior of cephalotrophic compounds of the sympathomimetic amines. In many cases the effects are distinctly unpleasant. There are some toxic reactions. The margin between the doses which produce beneficial and toxic mental effects is often critical. There is need for compounds with more selective actions. It is stated that the dextroisomer of amphetamine, dexedrine, exerts a relatively stronger central action than the racemic compound which is the one in common use.

It is well to emphasize that many people fail to perceive any beneficial psychological effects from amphetamine, that the same person may react differently at different times, and that the necessary dosage is uncertain and differs from time to time in the same person. The action of the drug is only temporary. It does not fill the place of attractive personality features of natural origin. The drug does not for long take the place of mental rest. It is not a substitute for a long-range program of psychological adjustment. Nevertheless, with due allowance for these limitations, the part the drug plays in promoting well-being is notable. Those who react favorably are better able to tide over difficult situations; they are better prepared for unusual mental and physical demands; they meet more satisfactorily some of life's more urgent experiences.

CONCLUSIONS

This review has gone far enough to indicate the wide range of applications of the sympathomimetic amines. They have invaded the field of therapy, and sometimes diagnosis, of medical and surgical disorders involving almost every system of the body. This group of compounds occupies a place of distinction among therapeutic agents. They stand in all lists of essential drugs and further in the more select group of emergency agents. They have a place in every well-equipped doctor's bag. They sometimes save life. More often they relieve great suffering, and this they do with an element of dramatic speed uncommon in drug therapy. Their special properties are applicable more to the common diseases of everyday practice than to the rare ones, and here they are so put to use that in point of frequency they hold a place among the leading therapeutic agents in the practice of medicine. Donald Clarke, the apothecary-in-chief of the New York Hospital, made a survey of the prescriptions issued in the wards and the clinics of the hospital during representative periods of the year. Approximately 950 different items were prescribed; the sympathomimetic amines accounted for about 0.6% of these. On the other hand, an actual count of several thousand prescriptions during these periods showed that these drugs are included in between 10 and 12% of all prescriptions. The experience at New York Hospital may be taken as fairly representative of the situation prevailing in the general practice of medicine and an indication that, by and large, one out of every ten prescriptions written by the physician contains a member of this group of drugs.

I should like at this point to raise a question concerning the propriety of the term "sympathomimetic" as descriptive of the group of drugs which is the subject of this symposium. It was convenient to use the term during this discussion and historically it is correct. Epinephrine, the first member of this group faithfully reproduces the effect of stimulation of the sympathetic nervous system. It was not long, however, before the therapeutic limitations of such an agent were fully in evidence, and interest began to shift from compounds of this group which mimic sympathetic activity to those in which relatively little of the original sympathomimetic pattern remained. May not the term which links these compounds in our minds to the sympathetic pattern retard progress? Perhaps some sort of chemical description as a group of agents built around the alkylamine bridge may serve the purpose better. In any case, in the intensification of special properties, such as the antiallergic action, the gastrointestinal actions, or the central actions—in short, not in the imitation but in the caricature of the sympathetic pattern—seems to lie the direction in which the therapeutic horizon of this group of agents is likely to expand.

IMIDAZOLE DERIVATIVES WITH SYMPATHOMIMETIC ACTIVITY

C. R. SCHOLZ

Ciba Pharmaceutical Products, Inc., Summit, N. J.

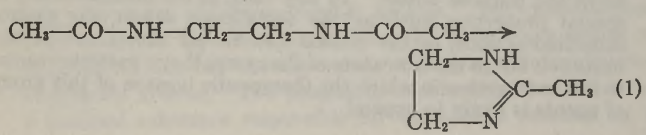
Many natural products from either plants or animals, which contain the imidazole ring—for instance, the alkaloids pilocarpine and pilosine, or histidine and histamine—show definite pharmacological activity. For this reason quite a number of synthetic imidazole and imidazoline derivatives were tested pharmacologically, and it was found that compounds containing the imidazoline ring and substituted in position 2 by either alkyl, aryl, or aralkyl, have a definite influence on the circulatory system. Within this group there are quite a number of substances which cause a marked rise in blood pressure, even in very high dilutions. These substances, upon local application, cause constriction of peripheral vessels for an unusually prolonged period of time, and this specific property offers unique advantages as vasoconstrictors. A tentative correlation of the pharmacological activity and for the chemical constitution of the imidazoline series is given.

NATURE has produced a number of compounds having the imidazole ring as part of their structure; some of them possess a strong and specific pharmacological action. A few examples follow: Histidine belongs to the group of essential amino acids. Histamine, the decarboxylation product of histidine, plays an important although not yet completely elucidated role in the animal organism. The betaine of histidine, hercynine, is found in a variety of fungi. Several alkaloids, as for instance pilocarpine, isopilocarpine, pilocarpidine, pilosine, pilosinine, etc., also contain the imidazole nucleus.

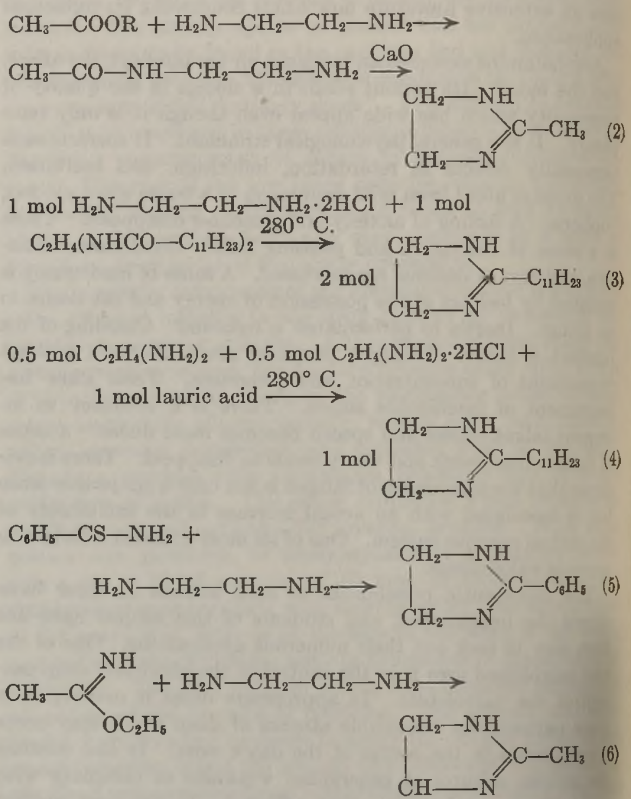
All compounds mentioned so far are imidazole derivatives having substituents or side chains on the various atoms of the imidazole ring as such. The topic of this report concerns another class of derivatives, characterized by the partially reduced imidazole nucleus, and a summary will be presented of compounds containing the 3,4-dihydroimidazole or imidazoline ring which are substituted in the 2-position.

The literature reveals that substances of this type were synthesized for the first time by Hofmann in 1888 (*5*). He prepared the 2-methylimidazoline, also called "lysidine". A few years later Forssel (*2*) synthesized the first aryl derivative of imidazoline. Since that time many 2-substituted imidazolines have been prepared and put to use for a large variety of purposes—for example, as vulcanizers and accelerators in general, as wetting, emulsifying, and cleansing agents, and also in the dye industry.

It might be of interest to mention at least some of the methods used in the synthesis of such 2-substituted imidazoline derivatives. According to Hartmann and Panizzon (*4*) partial reduction of imidazole or its derivatives is not possible. Therefore, the imidazoline ring has to be built up from ethylenediamine; for example, a diamide, such as the diacetamide, can be condensed to form the 2-methylimidazoline:



(1)



(2) (3) (4)

(5)

(6)

A similar result is obtained if the monoacetamide of ethylenediamine is heated with calcium oxide. Equation 3, where a mixture of the ethylenediamine hydrochloride and its diamide is condensed by heat, works on the same principle. With this method higher yields are obtained. Reaction 4 is also similar but has the advantage over 3 that the intermediate diamide need not be prepared specially; one can just mix the ethylenediamine with the respective acid and then carry out the condensation by heating the mixture. The condensation of ethylenediamine with thiobenzamide is illustrated in Equation 5, although it is of less general interest, whereas the reaction between imino ethers and ethylenediamine is in common use (Equation 6).

The imidazolines which have been found to have a certain pharmacological action are derivatives substituted in the 2-position by alkyl, aralkyl, and aryl groups.

2-ALKYLATED IMIDAZOLINES

Of the alkylated imidazolines, the 2-methylimidazoline has already been mentioned. Ladenburg stated in 1894 (*7*) that, when he injected 0.45 gram of 2-methylimidazoline carbonate into a rabbit, no visual effect was observed, but when it was injected into a human, diagnosed to suffer from "chronic gout", the patient is said to have been cured rapidly; no details are given on this finding.

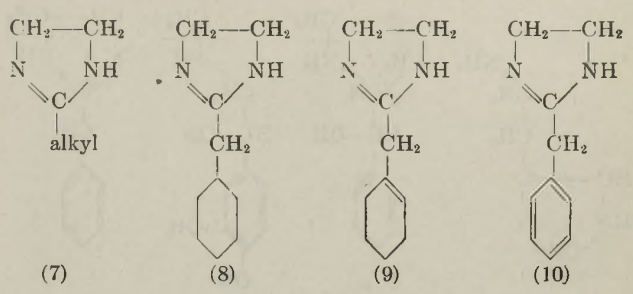
A year later Klingenstein (*6*) published the synthesis of 2-ethyl- and 2-*n*-propylimidazoline, but no data on pharmacological experiments are given.

The available literature speaks of no further work on this type of compounds until 1935, when a paper by Chitwood and Reid appeared (*1*). They prepared eleven alkylated 2-imidazolines by condensing the corresponding ethylenediamides at a higher temperature (270° C.) in the presence of magnesium or sodium metal, the alkyl radical of which contained from one to eleven carbon atoms in a straight chain. Only the first five members of this series—i.e., up to and including the amylimidazoline—were studied pharmacologically by Macht (*1*). Half a gram per kilogram of any one of these five compounds, given via the stomach, was not toxic for rabbits and did not impair their kidney functions. Only the methyl derivative increased the acidity of the urine, an observation which might have some bearing on Ladenburg's finding in human gout. The toxicity was also studied, and the author makes a special point of the finding that, contrary to the usual pharmacological experience, the toxicity decreases instead of increases with the chain length of the alkyl radical.

In contrast to this statement, however, are the experimental results obtained by the late Fritz Uhlmann in Ciba's laboratories at Basle, Switzerland, published by Hartmann and Isler in 1939 (*3*). Uhlmann studied the same compounds as Macht, and in addition the isobutyl-, isopentyl-, *n*-hexyl-, *n*-heptyl-, and *n*-octylimidazolines, and he found that the toxicity increases rather than decreases with the lengthening of the side chain. The pharmacologists have offered no explanation for these divergent findings; thus, I can present only the facts.

A similar increase in toxicity was found when these substances were tested on the isolated frog heart. Here, the longer the side chain, the smaller was the minimal dose which produced standstill in diastolic position.

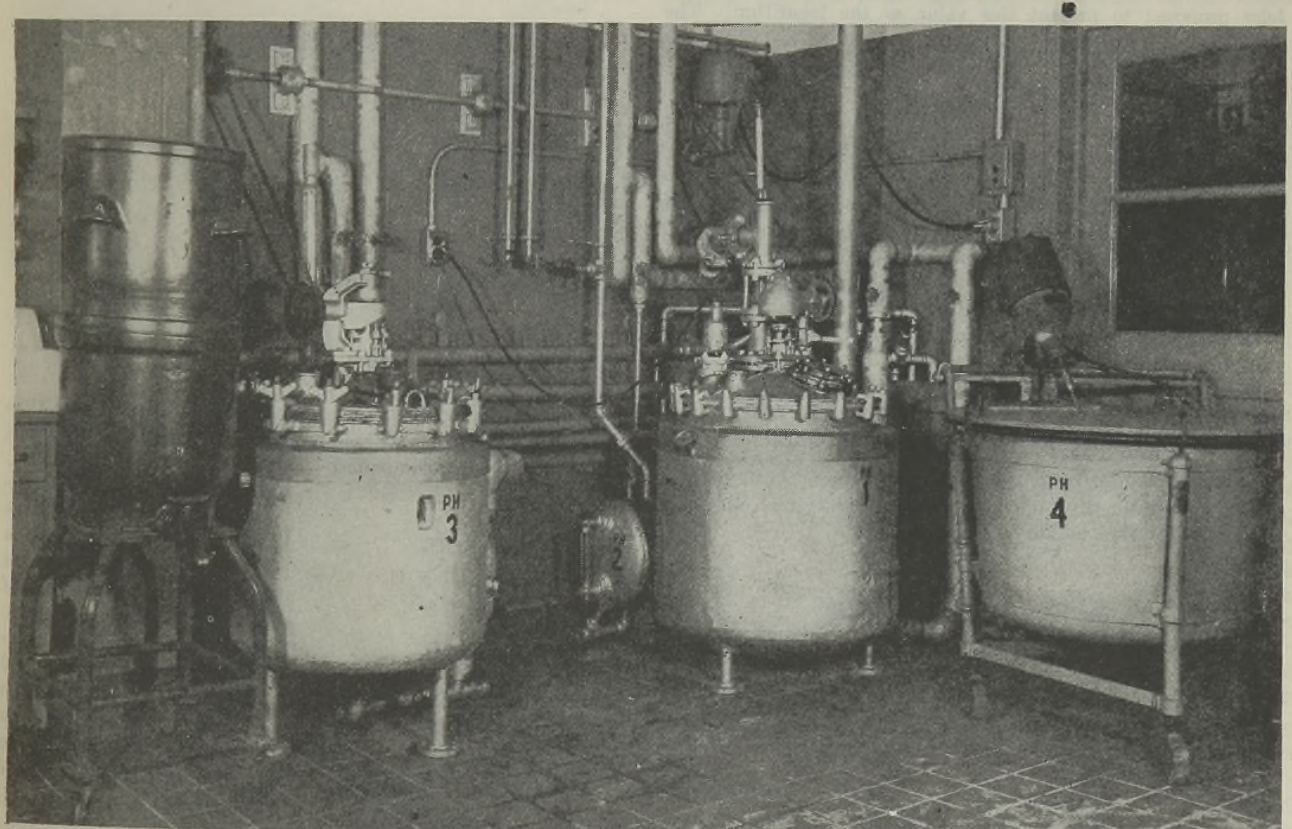
These alkylated imidazolines all dilate peripheral vessels and thereby decrease the blood pressure. Their action, however, is very weak and can be demonstrated only with a comparatively high minimal dose of 10 mg. per kg.



The two cycloalkylimidazolines studied, 2-cyclohexylmethylimidazoline (formula 8) and 2-cyclohexenylmethylimidazoline (formula 9) are somewhat less toxic than the corresponding alkyl derivative with the same number of carbon atoms. The vasodilator activity is about the same in magnitude as is that of the alkyl derivative, but the partially dehydrogenated compound is somewhat more active than the cyclohexyl derivative. The influence of unsaturation on activity is remarkable when the cyclohexenyl ring is replaced by the phenyl radical, as in 2-benzylimidazoline (formula 10); the minimal dose is 0.1 mg. per kg. or 100 times less than for the alkylated imidazolines.

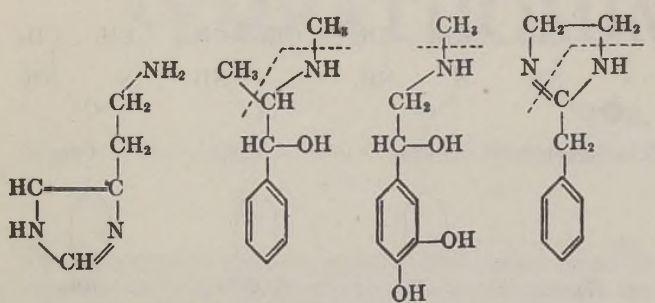
2-ARALKYLATED IMIDAZOLINES

This group of derivatives is of much greater interest pharmacologically. Before discussing the various compounds within this group, attention should be called to a structural similarity



Reaction Kettles Used in Production of Privine (α-Naphthyl-2-methylimidazoline) in Ciba Laboratories

between these compounds and the naturally occurring substances which influence the blood vessels:



(11) (12) (13) (14)

Histamine (11), ephedrine (12), and epinephrine (13) all have the ethylamine group in common, which seems to be one of the factors responsible for their action on the circulatory system. This same grouping is present in the structure of 2-benzylimidazoline (14) if we visualize the imidazoline ring split by the broken line. This, of course, is purely paper chemistry; nevertheless, it seems to warrant consideration in synthetic work because this observation has been confirmed to some extent by experimental findings on substances of this type.

To compare the vascular qualities of the compounds to be discussed, we use the reciprocal value of the minimal effective dose (gram per kilogram) as a unit of measure. If the experimental findings are presented in this way, the value for activity increases when the minimal dose decreases. Furthermore, to operate more conveniently with small figures, Hartmann and Isler proposed to present this value as the logarithm. The activity thus is expressed by the term,

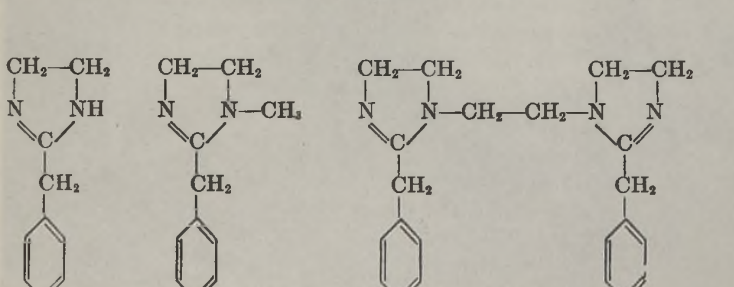
$$\log \frac{1}{\text{min. effective dose}}$$

and the figures so obtained are designated with "plus" if the substance is essentially hypertensive and with "minus" if the substance is essentially hypotensive. Calculated in this way, the activity for the 2-benzylimidazoline previously mentioned would be −5, which is comparatively high.

The 2-benzylimidazoline has the simplest structure of any aralkylated imidazoline. Substituents or radicals can be attached to three parts of this molecule: (*A*) to the imidazoline ring, (*B*) to the methylene group which forms the carbon atom bridge between the two rings, or (*C*) to the benzene ring.

CHANGES ON THE IMIDAZOLINE RING

Three representatives of subgroup *A* have been synthesized in order to study the effect of changes made on the imidazoline ring with regard to their action on blood pressure:

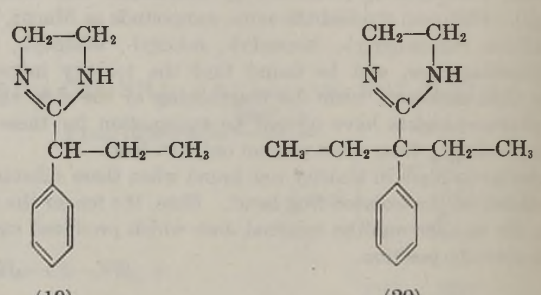


(15) (16) (17)

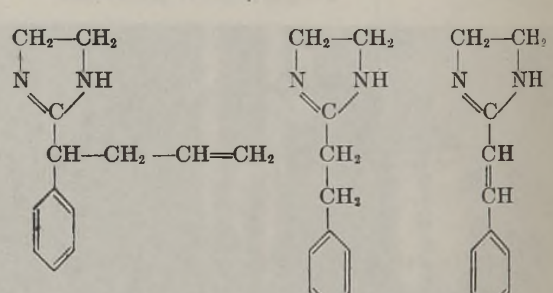
If the imidazoline ring is substituted on the nitrogen atom—for instance, in 1-methyl-2-benzylimidazoline (16) or in ethylene-1,1-bis-2-benzylimidazoline (17), the action on the circulatory system is reversed as compared to the 2-benzylimidazoline (15). Compound 17 is interesting because of its contradictory blood pressure effect; i.e., given in small doses, it raises the blood pressure considerably (+6), whereas in larger doses it causes a slight fall. The third compound studied in this group was 2-benzylhexahydrobenzimidazoline (18) which has the substitution on the 4,5-carbon atom. This compound was found to be a weak dilator, and therefore it seems that substitution on the carbon atoms in the imidazoline ring does not change the type of action but varies only the degree.

CHANGES IN CARBON BRIDGE BETWEEN RINGS

The next five compounds may be classified under subgroup *B*. One ethyl group was added in one instance, two ethyl radicals in the next, and in the third, one hydrogen atom was substituted by an allyl group, producing 2-(α-phenyl-*n*-propyl)-imidazoline (*19*), the 2-[α,α,α-(phenyldiethyl)-methyl]-imidazoline (20), and the 2-(α-phenylbutenyl)-imidazoline (21):

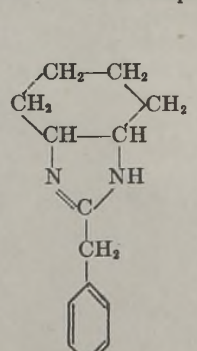


(19) (20)



(21) (22) (23)

The action on the blood pressure of compounds 19, 20, and 21 is practically the same for each one and is only slightly lower than that of the basic compound. Even lengthening of the bridge, which in itself may be saturated or unsaturated, as in 2-(β-phenylethyl)-imidazoline (22) or in 2-styrylimidazoline (23) does not alter the type of action but only the degree. The activity of these five compounds varies between −2 and −3; in other words, the addition of alkyl groups to the methylene bridge has little influence on the physiological properties of the compound, as far as blood pressure is concerned.

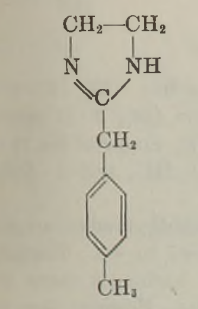


(18)

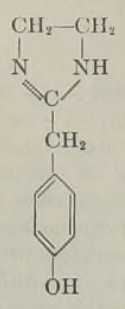
CHANGES IN THE BENZENE RING

Only one compound of subgroup *C* has been made which contains an alkyl radical in the para position—i.e., 2-(4′-methylbenzyl)-imidazoline (24). It also lowers the blood pressure, similarly to the original compound, with an activity of −4. Here again it seems that an alkyl substituent does not change the type of action, but no conclusions can be drawn from this one example.

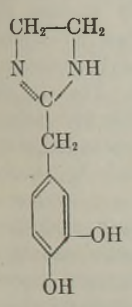
A variety of compounds has been made and studied where the aromatic ring is substituted with functional groups, such as hydroxy, methoxy, and others:



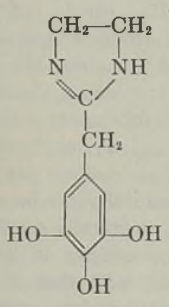
(24)



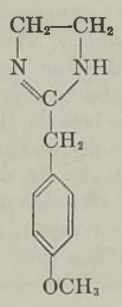
(25)



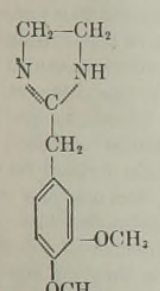
(26)



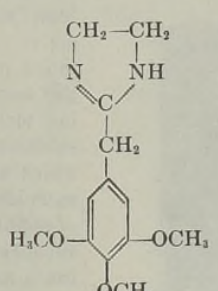
(27)



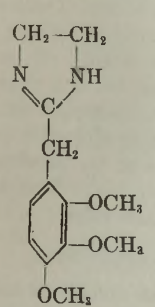
(28)



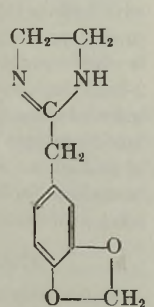
(29)



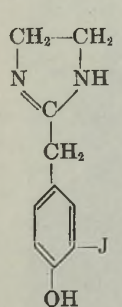
(30)



(31)



(32)



(33)

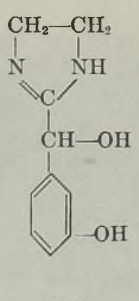
I mentioned before that the basic compound, 2-benzylimidazoline, is a strong vasodilator. If the hydrogen atom in the 4-position (i.e., para to the methylimidazoline group) is replaced by a hydroxyl, the action on the circulatory system is reversed; in other words, 2-(4′-hydroxybenzyl)-imidazoline (25) has a marked hypertensive effect (+5). The introduction of a second hydroxyl in the 3-position, as shown in compound 26, 2-(3′,4′-dihydroxybenzyl)-imidazoline, increases the activity considerably (+7); the addition of a third hydroxyl group in the 5-position, giving the 2-(3′,4′,5′-trihydroxybenzyl)-imidazoline (27), has an activity of +6, which means that the activity lies between those of substances 25 and 26.

This remarkable change in character from the compound without functional groups to the three just mentioned is made even more interesting by the fact that methylation of the compounds with one and two hydroxy groups to methoxy groups shows again a reverse of activity. The 2-(4′-methoxybenzyl)-imidazoline (28) and 2-(3′,4′-dimethoxybenzyl)-imidazoline (29) act very much like the unsubstituted parent substance, having an activity of −4. This reversing of activity holds true only for these two compounds carrying functional groups, and seems to be an exception in the relation between activity and chemical constitution as far as can be seen from the relatively small number of compounds studied.

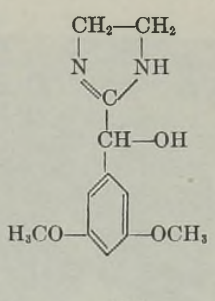
When compound 27 was methylated to 2-(3′,4′,5′-trimethoxybenzyl)-imidazoline (30), the activity was exactly the same as that of the starting material—i.e., +6. Also the last three compounds of this group—2-(2′,3′,4′-trimethoxybenzyl)-imidazolines (31), 2-(3′,4′-methylenedioxybenzyl)-imidazoline (32), and 2-(3′-iodo-4′-hydroxybenzyl)-imidazoline (33)—proved to be effective vasoconstrictors with a similar degree of activity.

A comparison between substances 30 and 31 shows that the position of the 3-methoxy groups present has some, although rather subordinate, influence on the activity. Compound 31 has an activity of +5 as compared with +6 for substance 30. Compound 33 seems to be of particular interest because it contains an iodine atom; this shows that even the substitution by a halogen does not alter the general character of action in this series of substances.

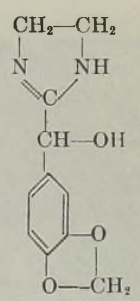
The next three compounds carry substituents on the benzene ring as well as on the methylene bridge:



(34)



(35)



(36)

These three—2-(3′,α-dihydroxybenzyl)-imidazoline (34), 2-(3′,5′-dimethoxy-α-hydroxybenzyl)-imidazoline (35), and 2-(3′,4′-methylenedioxy-α-hydroxybenzyl)-imidazoline (36)—have an alcoholic hydroxyl group at the methylene bridge, and are substituted in the benzene ring by hydroxy, methoxy, and methylenedioxy, respectively. They all come into the class of vasoconstrictors, which means that the addition of the alcoholic hydroxyl group to the bridge carbon atom does not change the type of action. In this connection, ephedrine and epinephrine have an aliphatic hydroxyl group in the same position. The degree of action seems to be influenced only slightly by the addition of the alcoholic hydroxy group, even though we have only one example of direct comparison—i.e., compound 36 with unsubstituted compound 32. If at all, the action is enhanced only slightly by the addition of the hydroxyl group at the methylene bridge.

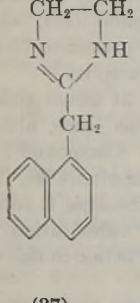
Reviewing the relation between chemical constitution and activity of the various substituted benzylimidazolines, we may conclude that in general the addition of free or methylated

phenolic hydroxy groups produce strong vasoconstrictors, reversing the activity of the parent or basic substance. The only exceptions are the methyl ethers of the mono- and dihydroxybenzylimidazolines which are, like the parent substance, vasodilators. As far as toxicity is concerned, however, we find a difference between the compounds with free hydroxyls and those with blocked hydroxyls—for instance, methoxy and methylenedioxy groups.

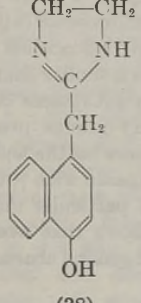
In general, all compounds which carry free hydroxyl groups are more toxic than the parent substance, whereas those which are substituted with a blocked hydroxyl group have the same or even a lesser toxicity. Furthermore, the substitution with a phenolic hydroxyl group has a strong influence on activity and toxicity. In contrast, the addition of an alcoholic hydroxyl group to the bridge carbon atom merely changes the degree of activity and toxicity slightly; i.e., both are raised somewhat.

REPLACEMENT OF PHENYL RADICAL

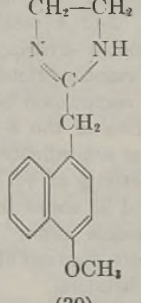
In the next group of compounds the phenyl radical has been replaced by an unsubstituted or a substituted naphthyl radical or by a quinolyl or indolyl radical:



(37)

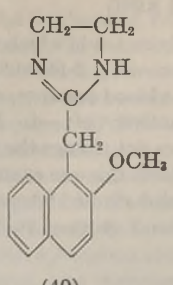


(38)

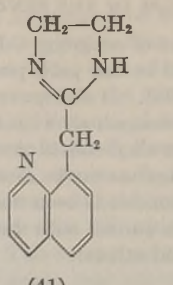


(39)

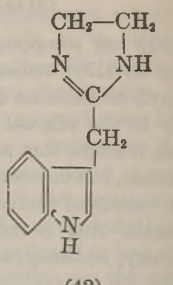
Filling and Packaging Containers for Privine Solution



(40)



(41)



(42)

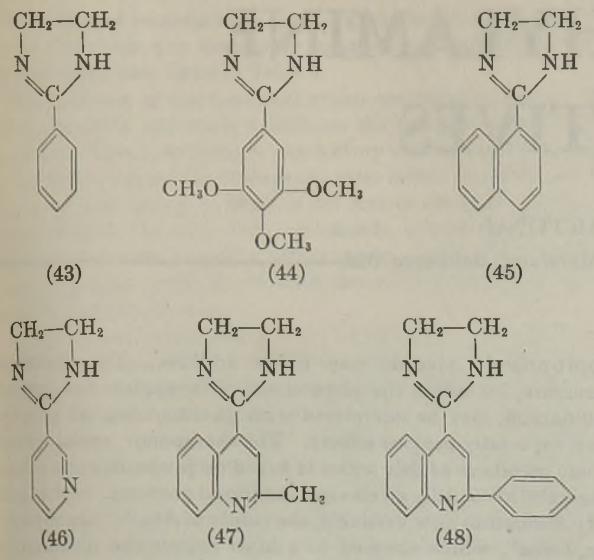
2 - (Naphthyl - 1′ - methyl) - imidazoline (37), 2 - (4′-hydroxynaphthyl - 1′ - methyl) - imidazoline (38), 2 - (4′-methoxynaphthyl-1′-methyl)-imidazoline (39), an isomer of No. 39 (40), 2 - (quinolyl - 8′ - methyl) - imidazoline (41), and 2 - (indolyl-3′-methyl)-imidazoline (42).

All four compounds containing the naphthyl radical are powerful vasoconstrictors with activities of +7 to +8. The rule regarding free or substituted phenolic hydroxyls seems to be applicable to this group of substances also. However, there is one rather astonishing fact: The unsubstituted 2-(naphthyl-1′-methyl)-imidazoline (37), which incidentally is used therapeutically, is one of the strongest vasoconstrictors in this series of imidazoline derivatives, whereas the 2-benzylimidazoline, as mentioned previously, is a strong vasodilator. The only difference between these two substances is that in the first instance a naphthyl and in the second, a phenyl radical, is attached to the 2-methylimidazoline. Both radicals are aromatic hydrocarbons, and this pharmacological difference between them is rather difficult to explain because, chemically speaking, they are similar.

When comparing the activity of 2-(4′-methoxynaphthyl-1′-methyl)-imidazoline (39) with that of the isomeric compound (40) which carries the methoxy group in the 2- instead of in the 4-position, it was found that compound 40 is somewhat less active. This same phenomenon was also found in the benzyl-substituted imidazoline series. The rule, however, concerning toxicity in relation to the free and substituted phenolic hydroxyl groups, which was brought forward for the benzylimidazolines, does not apply in the case of naphthylmethylimidazolines. All three substituted compounds of this group are much more toxic than the unsubstituted parent compound. Compounds 41 and 42 are imidazoline derivatives substituted with heterocyclic radicals. Compound 41 proved to be a strong vasodilator, which is even stronger in action (−6) than the 2-benzylimidazoline, but it is much more toxic. In contrast, compound 42 has a blood-pressure raising effect of +6, which is as high as some of the substituted 2-benzylimidazolines; but it is too toxic to have any therapeutic value.

ETHYL-AMINE RULE

So far, only those derivatives have been discussed which have a methylene bridge between the imidazoline ring and the alkyl group or the aromatic ring system. The following six synthesized compounds have the imidazoline ring directly attached to the aromatic hydrocarbon or heterocyclic radical:



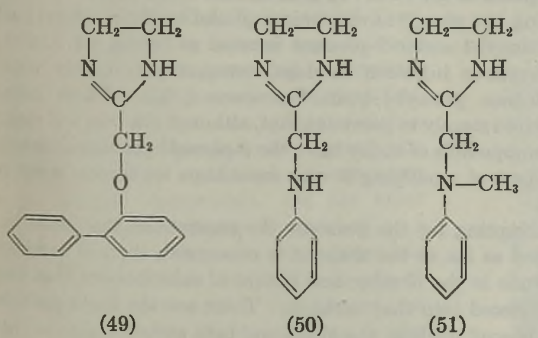
(43) (44) (45)

(46) (47) (48)

2-Phenyl-imidazoline (43), 2-(3′,4′,5′-trimethoxyphenyl)-imidazoline (44), 2-(naphthyl-1′)-imidazoline (45), 2-(pyridyl-3′)-imidazoline (46), 2-(2′-methylquinolyl-4′)-imidazoline (47), and 2-(2′-phenylquinolyl-4′)-imidazoline (48).

When these six compounds were studied pharmacologically in the laboratory animal, it was found that none of them have any activity or the activity is so small that they are of no therapeutic interest, at least as far as their effect on blood pressure is concerned. This finding may support the previously made statement that the ethyl-amine group is one of the factors responsible for the action on the circulatory system. The toxicity of these six compounds was rather low.

The last three imidazoline derivatives to be discussed also seem to follow this ethyl-amine rule, if I may call it that. All three contain this grouping but have a prolonged bridge, this time not with another carbon atom but with a nitrogen or an oxygen atom.



(49) (50) (51)

2-(*o*-Diphenyloxymethyl)-imidazoline (49), 2-(phenylaminomethyl)-imidazoline (50), and 2-(phenylmethylaminomethyl)-imidazoline (51) are all active on the circulatory system. When compounds 50 and 51 are compared with 2-(β-phenylethyl)-imidazoline (compound 22), it was found that by substituting the α-carbon atom of the bridge by a nitrogen atom, the type of action on the blood pressure was reversed. Whereas compound 22 was a vasodilator, compounds 50 and 51 are vasoconstrictors, and so is compound 49.

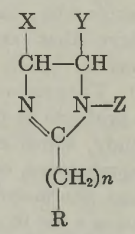
CONCLUSIONS

Before summarizing the few conclusions which can be drawn concerning the relation between the structure of these imidazoline compounds and their pharmacodynamic activities, I wish to state that I am no pharmacologist. The data reported are the result of studies made with the aim of obtaining a rough idea about the possible therapeutic value of new compounds rather than an extensive study of relations between structure and action. The pharmacologists who have gathered these data are aware of the definite shortcomings of a method which takes blood pressure as a criterion. Blood pressure is a complex phenomenon controlled and regulated by a multitude of factors, and cannot be used to analyze in detail the mechanism of pharmacological action of new chemical compounds; but it is a convenient and quick method.

Some of the compounds mentioned have been studied in greater detail. The results of these experiments have not yet been published; I have not reported them, first because I did not want to detract your attention from the main topic, and second because this unpublished work must be considered still the mental property of the investigators.

Whereas many questions are unanswered, it appears that the site of action of the imidazolines will be found rather complex and that they will not lend themselves easily to classification into sympathomimetic or parasympathomimetic drugs. I must refrain from trespassing on pharmacological territory, where chemical knowledge is of little help for orientation; therefore I restrict myself to the following conclusions, and even these should not be taken too rigidly because the number of compounds studied in this series of 2-imidazoline derivatives is rather limited.

On the basis of the general formula,



it might be said that the most active compounds are those in which:

1. The substituents X, Y, and Z on the imidazoline ring are nothing but a hydrogen atom; in other words, the imidazoline ring should not be substituted in any except the 2-position.
2. The factor *n* at the bridge between the imidazoline ring and the radical R should be 1. A simple methylene group leads to the most active compound; it might, however, be substituted by an alcoholic hydroxyl group. If *n* is 0 or 2, the activity is practically nil or at least a thousand times diminished, respectively.
3. The radical R should be an aromatic hydrocarbon or an aromatic heterocyclic. Even though the unsubstituted radicals of this series are already very active, they can still be substituted by either a hydroxyl, a methoxy, or a methylenedioxy group. However, if R is an alkyl or cycloalkyl group, the activity is reduced a thousand or even a million fold—i.e., to practically zero. Depending on what substituents are used as R, the toxicity varies over a wide range.

ACKNOWLEDGMENT

The author wishes to emphasize that the findings reported here are not his personal work but are the results of research performed by others, mostly in Ciba's laboratories in Basle, Switzerland, and published by them.

LITERATURE CITED

(1) Chitwood, H. C., and Reid, E. E., *J. Am. Chem. Soc.*, 57, 2424 (1935).
(2) Forssel, G., *Ber.*, 25, 2132 (1892).
(3) Hartmann, M., and Isler, Hans, *Arch. exptl. Path. Pharmakol.*, 192, 141 (1939).
(4) Hartmann, M., and Panizzon, L., *Helv. Chim. Acta*, 21, 1692 (1938).
(5) Hofmann, A. W., *Ber.*, 21, 2332 (1888).
(6) Klingenstein, E., *Ibid.*, 28, 1173 (1895).
(7) Ladenburg, A., *Ibid.*, 27, 2952 (1894).

Beta-PHENETHYLAMINE DERIVATIVES

WALTER H. HARTUNG

School of Pharmacy, University of Maryland, Baltimore, Md.

R—the compounds derived structurally from β-phenethylamine form an attractive series for the pharmacologist and the pharmaceutical chemist. The structure may be modified within wide limits without destroying the characteristic ability to raise the blood pressure of an experimental animal. It is now possible to ascribe, with considerable reliance, a constant qualitative or quantitative pharmacodynamic modification to the presence of certain substituents in given positions of the parent skeleton. The effect of two or more substituents, appropriately placed, may prove additive. The chemical structure, including the phenomena of isosterism and optical isomerism, may be correlated with pharmacological properties, especially pressor effects. The therapeutic usefulness of some members of this series is based on properties other than their ability to cause an elevation in blood pressure. In the light of information now available, the riddle of Abel's "benzoylepinephrine", which showed to a high degree the quantitative potency of pure epinephrine, becomes all the more enigmatic.

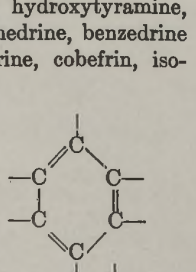
INTEREST in derivatives of β-phenethylamine was aroused at the beginning of the present century, when the nature of the epinephrine molecule was established (*88*). Interest increased when it was observed that extracts of putrified meat had pressor activity (*5*), much of which could be ascribed to the presence of tyramine (*13*). The presence also of β-phenethylamine among the putrefactive products of proteins stimulated Barger and Dale to make a study, which even by today's standards must be considered comprehensive, of the relation between the chemical constitution and pharmacological properties of compounds capable of producing a rise in the blood pressure of an experimental animal (*14*). It is to these investigators that we owe the word "sympathomimetic", and from them came conclusions which have proved quite sound.

The next advance was made in 1923 when Chen observed that ephedrine, injected into the veins of an anesthetized dog remaining alive at the close of a class exercise in pharmacology, produced a rise in blood pressure simulating that of epinephrine (*22*). This plant alkaloid, first isolated by Yamanashi and obtained in pure form by Nagai (*70*), is also a derivative of β-phenethylamine, and it was natural that Chen should have noticed its structural similarity to epinephrine.

After the first World War, chemists interested in pharmacologically active substances were greatly attracted by this field. The developments since Chen's initial experiments with ephedrine may be appreciated from an examination of the structures of specific compounds, many of them useful and well-known drugs; for example, β-phenethylamine, phenylalanine, tyramine, tyrosine, phenylethanolamine, hordenine (*66*), mescaline (*85*), *N*-methylmescaline (*86*), epinine, 1-alkyltetrahydroisoquinolines, epinephrine, sympathol or synephrine, neosynephrine, dopa or dihydroxyphenylalanine, hydroxytyramine, ephedrine, propadrine, pervitin or desoxyephedrine, benzedrine or amphetamine, veritol, paredrine, vonedrine, cobefrin, isobenzedrine, butanephrine, ephetonal, β-aminotetrahydronaphthalene, indanolamine, etc.

THE β-PHENETHYLAMINE SKELETON

All of these compounds, and many others might have been included, have in common a definite arrangement of eight carbon atoms and one nitrogen atom:



This grouping, a phenyl and an amino group on adjacent carbon atoms, was early observed to be one of the minimal essentials for pressor activity (*14*, *43*). Possible permissible deviation from this arrangement has been reported thus far from three sources. Work on aliphatic amines has resulted in the development of 2-aminoheptane or Tuamine (*77*). Perhaps after the circulatory effect of the aliphatic amines becomes more fully investigated, it may be necessary to modify this conclusion originally advanced by Barger and Dale. A second deviation has been observed in a derivative in which the phenyl nucleus is replaced by the hydroaromatic cycle. Thus, hexahydropropadrine is also capable of producing a rise in the blood pressure of an experimental animal (*41*), but since this compound has received no further pharmacological study, too much emphasis must not be placed on this exception to the observed general rule. The third is found in an analog, the phenyl having been replaced by the α-thienyl nucleus. α-Thienyl-1-amino-2-propane is rated as having 4+ activity on intravenous injection to dogs, comparing favorably with the analogous phenyl-1-amino-2-propane (*104*). These instances are cited merely to point out that, although the best and most useful compounds of today have the β-phenethylamine skeleton, the prospect of modifying it with some hope for success is not ruled out.

Accepting for the moment the restrictions that must be observed as far as the skeleton is concerned, there is considerable latitude in the number and nature of substitutions that may be introduced into that skeleton. There are the three positions in the phenyl nucleus, the alpha and beta carbon atoms in the side chain, and the amino nitrogen atom. The effects of various substituents or combinations of substituents have been studied, and the number which may be employed without destroying the sympathomimetic properties is quite large. To the chemist who is working with medicinal products this is remarkable; for in so many instances, if not in most, a physiologically active molecule does not permit much change without destroying its desirable biological properties. It is all the more gratifying, therefore, to find that so many derivatives of β-phenethylamine retain their activity, and it becomes possible within reasonable limits to analyze vectorially, as it were, the effects of a given substituent attached at a certain place in the parent skeleton. No other known group of chemically related and pharmacologically similar compounds reveals such a high degree of positive correlation between structure and activity.

The effect of introducing a methyl group in the alpha position of the side chain may be seen by comparing pairs of homologs—for example, those listed in Table I.

The presence of the α-methyl group consistently reduces the pressor activity and tends to increase the toxic properties of the molecule. These are changes which every worker wants to avoid; he wants to increase the therapeutic ratio rather than decrease it. However, this change in itself is not serious since the margin of safety, even in the more toxic compounds, is more than counterbalanced by new property conferred by the methyl group—namely, greater stability—so that the molecule becomes active after oral administration.

Unfortunately epinephrine must be given by injection to obtain the optimum therapeutic effect. Consequently, when it was observed that ephedrine would produce its characteristic effect even when given by mouth, it caught the immediate attention of the clinician. On the basis of extensive studies with the epinephrine-ephedrine series Chen and co-workers came to the conclusion that the α-methyl group confers oral activity (*23*).

β-Phenethylamine is inactive when taken by mouth, but its α-methyl derivative, $C_6H_5—CH_2—CH(NH_2)—CH_3$ (benzedrine), is active when taken orally; at the same time the duration of action is considerably extended (*74*). The same holds true for the other pairs of homologs listed in Table I. Phenylethanolamine, showing many of the properties of ephedrine, has a short period of activity and is inactive after oral administration (*24*). The higher homolog, $C_6H_5—CHOH—CH(NH_2)—CH_3$, phenylpropanolamine or propadrine, produces a rise in blood pressure that persists for longer time, and the circulatory effect is obtained when the compound is administered orally (*42*). The oral activity of cobefrin or norhomoepinephrine, m,p-$(HO)_2C_6H_3—CHOH—CH(NH_2)—CH_3$, is perhaps most interesting (*46*), especially since the nonactivity of epinephrine by mouth had been attributed to the great chemical activity of the catechol nucleus and its probable destruction on its way through the alimentary canal. But the activity of cobefrin suggests that the physiological properties of this dihydroxyphenyl derivative are modified just as are its nonphenolic analogs by the presence or absence of the methyl in the alpha position of the side chain.

The explanation for this change in properties as the length of the side chain is increased from two to three carbon atoms was recently found. Beyer (*17*) reports that compounds of this group having the amino group, substituted or not, attached to a primary carbon atom are rapidly deaminated enzymatically in the living tissues and hence are converted into nonpressor compounds. On the other hand, if the amino group is attached to a secondary carbon atom, as in the three-carbon derivatives mentioned, the enzyme is not effective and the compound is transformed biochemically at a much slower rate, and it may be transported, after absorption from the alimentary tract, with minimum change to the site of action (*48, 50*).

If the introduction of a methyl group into the alpha position has such a favorable effect, the question naturally follows about the influence of an ethyl or even higher radical. The results are unfortunate, at least as far as the circulatory activity is concerned. The higher homologs, $C_6H_5—CHOH—CH(NH_2)—R$, from phenylbutanolamine to phenyloctanolamine ($R = C_2H_5$ to C_6H_{13}) are all inactive on the blood pressure of an experimental animal, unless perhaps they lower it (*21, 45, 48*). One can but marvel at the analytical precision of living tissue in distinguishing so readily between, say, phenylpropanolamine and the homologous phenylbutanolamine.

Recently, however, interest in the longer-chain compounds is being revived, not because of their circulatory activity but because of other desirable pharmacodynamic properties; a search is underway for substances having these other properties but without the ability to influence the blood pressure. For example, Eichholtz (*29*) advances the hypothesis that Ma Huang, the chief ephedrine-containing plant, was used by the Chinese as early as 3000 B.C., not for what we use it today, but for the central stimulating properties of ephedrine, and he discusses the use and significance of such stimulants with philosophic realism.

It is probably true that at present benzedrine is prescribed less for its action on the circulation than for its other physiological properties. At any rate, with the aim of finding a better central stimulant or a stimulant without circulatory activity, Rosenmund and Karg (*79*) prepared a series of 1-phenyl-2-aminoalkanes. Perhaps after the war we shall learn about the physiological and pharmacological properties of these compounds.

Another indication of the quest for a compound with the desirable nonpressor properties is seen in the attention being given to 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol, $(HO)_2C_6H_3—CHOH—CH(NH_2)—CH_2—CH_3$ (*89*). This substance produces only the vasodilator actions of epinephrine and shows 1/71 the bronchodilator activity of epinephrine (*101*), in doses one half larger is as effective as epinephrine in relieving asthmatic attacks and is accompanied by fewer side reactions; it does not excite the nervous system; by lowering the diastolic pressure and increasing the pulse rate it improves the circulation without causing a proportionate rise in cardiac work (*89*). The name "butanephrine" is proposed for this homolog of epinephrine (*89*).

The introduction of the carboxyl group into the alpha position of β-phenethylamine leads to the structure of phenylalanine, $C_6H_5—CH_2—CH(NH_2)—COOH$, an essential aminoacid. These protein acids will not be considered at this time. One wonders, however, whether masking the carboxyl group, as in esterification, might not restore the hypertensive properties of the parent skeleton.

Before we leave the side chain, another item must be considered—namely, the cyclization, as it were, of the side chain but

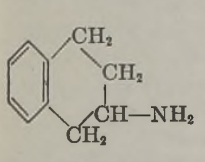
Courtesy, S. B. Penick & Company

Collecting Ephedra Herb in the Far East for the Isolation of Natural *l*-Ephedrine

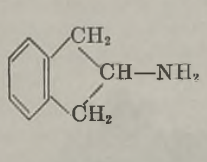
Table I. Aryl Ethylamines and Aryl Propylamines

Structure	Pressor Activity as Fraction of Epinephrine	Toxicity
$C_6H_5—CH_2—CH_2—NH_2$	1/183 (97)	60 mg./kg. intravenous to rabbits (43)
$C_6H_5—CH_2—CH(NH_2)—CH_3$	1/425 (97)	25 mg./kg. intravenous to rabbits (43)
$C_6H_5—CHOH—CH_2(NH_2)$	Same (6)	80 mg./kg. intravenous to rabbits (23)
$C_6H_5—CHOH—CH(NH_2)—CH_3$	1/60 (97)	70 mg./kg. intravenous to rabbits (23)
$(HO)_2C_6H_3—CHOH—CH_2(NH_2)$	1.2 (95)	.....
$(HO)_2C_6H_3—CHOH—CH(NH_2)—CH_3$	1/12 (95)	.....
p-$HO—C_6H_4—CH_2—CH_2—NH_2$	1/100 to 1/50 (7)	2000 mg./kg. subcutaneous to guinea pigs (7)
p-$HO—C_6H_4—CH_2—CH(NH_2)—CH_3$	1/100 to 1/50 (7)	180 mg./kg. subcutaneous to guinea pigs (7)
3,4-$(HO)_2C_6H_3—CHOH—CH_2(NHCH_3)$	(Epinephrine)	.....
$(HO)_2C_6H_3—CHOH—CH(NHCH_3)—CH_3$	1/41 (73)	.....

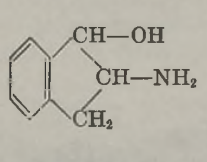
keeping the amino group in the beta position with respect to the aromatic nucleus:



β-Aminotetrahydronaphthalene



Aminoindane



Indanolamine

β-Aminotetrahydronaphthalene, administered intravenously as hydrochloride to dogs or rabbits, in doses of 10 to 70 mg. per kg., produced a strong rise in the peripheral blood pressure, accompanied by a curare effect and elevation in the temperature (*11*). It is of no use, however, as a circulatory stimulant (*97*). 2-Aminoindane and indanolamine, which may be considered as cyclized phenyl-1-amino-2-propane, possess little pressor activity, but they do show considerable promise as bronchial antispasmodics, especially the *N*-substituted derivatives (*68*).

EFFECT OF BETA SUBSTITUTION

Next let us turn to substitutions on the beta carbon atom. These have been restricted to methyl or alkyl, hydroxyl, ketone, or amine. The effect of the amino group, although under investigation (*26*), still remains unknown.

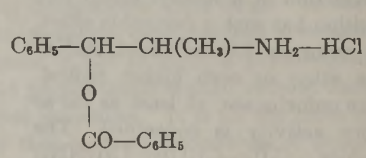
The ketones, $Ar—CO—\overset{|}{C}—N=$, have been examined for pressor activity and as a rule have been found to possess either slight activity or to be inactive. The first is the ketone corresponding to epinephrine, $(HO)_2C_6H_3—CO—CH_2—NHCH_3$; it is known as adrenalone and also as kephrine. Its pressor activity is somewhat irregular (*99*) and is reported to be 1/300 to 1/200 that of *l*-epinephrine (*58*). It is employed as a hemostat. The second ketone is a compound called "eprocaine", $(HO)_2C_6H_3—CO—CH_2—NH—C_6H_4—CO—O—CH_2—CH_2—N(C_2H_5)_2$. This compound is reported to produce a definite rise in blood pressure when injected intravenously in a pithed decerebrate cat. This compound possesses the structure of both the procaine anesthetic type and the pressor arrangement under consideration here; consequently it is described as a pressor anesthetic. It is regrettable that the pressor activity is described in such indefinite terms (*51*, *72*). Furthermore, should eprocaine prove to produce an appreciable rise in blood pressure, it will be surprising; for this will mean that the virtual substitution of a procaine residue on the amino nitrogen will be active in contrast to other molecules having large substituents attached to the nitrogen atom.

The effects produced by the presence of the alcoholic hydroxyl group on the beta carbon atom are better known. Nature has placed it there in epinephrine and in ephedrine, and the chemist has extended the series so that it becomes possible to determine accurately the contribution of this alcoholic hydroxyl group to the pharmacodynamic properties of the molecule. An indication may be found by comparing the pairs of compounds listed in Table II.

Others might be included; the pairs given will perhaps suffice to show that at least two effects may be attributed directly to the presence of the alcoholic hydroxyl group. First, there is an appreciable decrease in the acute toxicity of the molecule. Second, a decided increase appears in the pressor activity. What this means can be readily appreciated. For example, benzedrine is one seventh as active as propadrine and three times more toxic; that is, the presence of the alcoholic hydroxyl group increases (as far as pressor activity is concerned) the therapeutic ratio twenty-one fold. *m,p*-Dihydroxyphenethylamine, when the alcoholic hydroxyl group is introduced into the beta position of the parent skeleton, becomes seventy-eight times more active. A qualitative modification in pharmacological properties is also observed. The stimulating effect on the central nervous system is considerably decreased by the presence of the alcoholic hydroxyl group but is not completely abolished (*82*).

On the other hand, the presence of the alcoholic hydroxyl group has an effect on the physical properties of the molecule which leaves the desoxy analogs with a practical advantage. The vapor tension of the phenylalkylamines is sufficiently high to permit their administration by inhalation. The value of this factor is evidenced by the ubiquitous benzedrine inhaler, as well as the efforts to find other volatile vasoconstrictors.

Benzoylation of the hydroxyl introduces the anesthesiophore grouping and results in compounds of the allocaine type,



Although these ester derivatives are potent anesthetics, they possess little or no vasopressor activity (*8*). The hope of obtaining a suitable pressor anesthetic, however, should not be abandoned until the ester of the most active pressor, epinephrine or arterenol, has been examined, especially since ephedrine

cannot normally replace epinephrine in combination with procaine compounds.

The other substituents which have been introduced into the beta position of the phenethylamine skeleton are alkyl groups, and here again the methyl is of particular interest since it introduces us to the phenomenon of isosterism from both the physical and physiological points of view. The data summarized in Table III show this to best advantage. Particularly striking is the parallelism between the pharmacological properties of phenylethanolamine and β-phenylpropylamine, C_6H_5—CH(OH)—CH_2—NH_2 and C_6H_5—$CH(CH_3)$—CH_2—NH_2; their pressor activity and toxicity are amazingly similar. Referred to the parent β-phenethylamine, the introduction of either the hydroxyl or the methyl groups, of almost equal mass, seems to make little difference as far as the living organism is concerned. The difference between substitution of the methyl group in the alpha and the beta positions—that is, between C_6H_5—CH_2—$CH(CH_3)$—NH_2 and C_6H_5—$CH(CH_3)$—CH_2—NH_2, is especially noteworthy.

As already mentioned, the phenylalkylamines are also characterized by a stimulating action on the central nervous system. Phenethylamine produces stimulation in experimental animals at 80 mg. per kg. or at half the fatal dose; phenylethanolamine and β-phenylpropanolamine produce no stimulation until the lower limits of the fatal dose are reached (*82*). Thus, it appears that the presence of the β-methyl group, like the hydroxyl group, reduces the stimulant action. That this is probably no isolated instance is suggested from a comparison of the available pharmacological data of other pairs of isosteres:

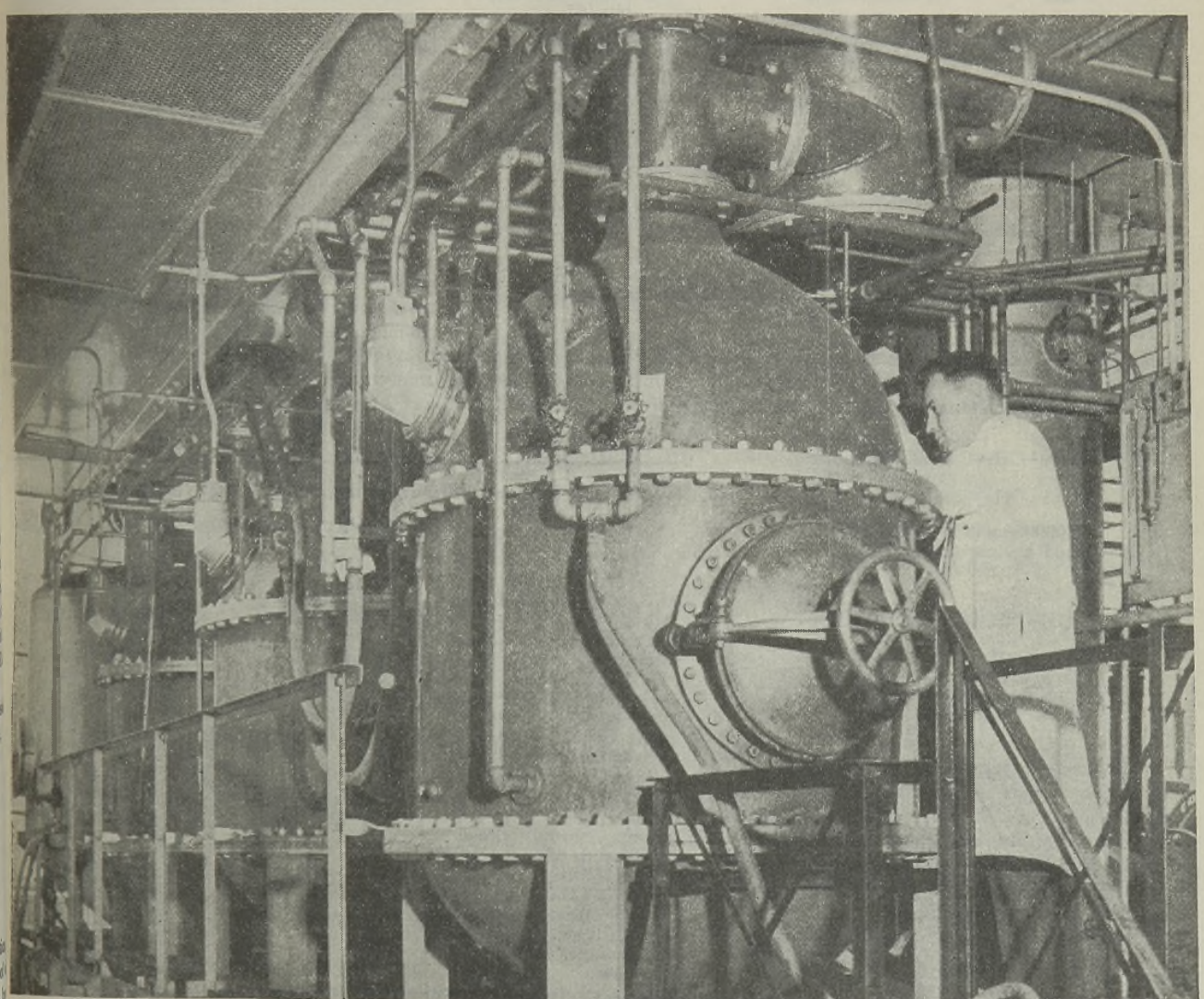
C_6H_5—CH(OH)—$CH(NH_2)$—CH_3

MLD (min. lethal dose) 80 mg./kg. of hydrochloride intravenous to rabbits (*43*)

C_6H_5—$CH(CH_3)$—$CH(NH_2)$—CH_3

LD_{50} (dose which is lethal to 50%) 290 mg./kg. to white mice (*91*)

Since the toxicity for the unsubstituted parent compound, C_6H_6—CH_2—$CH(NH_2)$—CH_3, is 25 mg. per kg. of the hydro-



Extraction Equipment Used in Isolating Adrenalin (Brand of Epinephrine) at Parke, Davis & Company Laboratories

Table II. Effect of Alcoholic Hydroxyl Group

Compound	Physiological Activity	Toxicity, Min. Lethal Dose
$C_6H_5—CH(H)—CH_2—NH_2$	1 mg./kg. to dog gives good rise that persists for 20 min. (*43*); larger doses to rabbits cause fall (*47*)	40–60, intravenous to rabbits, is fatal (*23*, *43*)
$C_6H_5—CH(OH)—CH_2—NH_2$	Pressor activity equals ephedrine (*6*); 0.5–1.2 mg. intravenous to rabbits, cats, and dogs raise blood pressure 10 to 180% (*98*)	30–90, mg./kg. intravenous to rabbits is fatal (*6*, *23*, *45*)
$C_6H_5—CH(H)—CH(NH_2)—CH_3$	1/425 epinephrine (*97*)	25 mg./kg. of hydrochloride intravenous to rabbits (*43*)
$C_6H_5—CH(OH)—CH(NH_2)—CH_3$	1/60 epinephrine (*97*)	75–90 mg./kg. of hydrochloride intravenous to rabbits (*43*)
$p\text{-}HOC_6H_4—CH(H)—CH_2—NHCH_3$	1/140 epinephrine (*11*)	.....
$p\text{-}HOC_6H_4—CH(OH)—CH_2—NHCH_3$	1/118 epinephrine (*102*)	50 mg./kg. of hydrochloride intravenous to rabbits (*65*)
$(HO)_2C_6H_3—CH(H)—CH_2—NHCH_3$	1/12 epinephrine (*98*)	.....
$(HO)_2C_6H_3—CH(OH)—CH_2—NHCH_3$	(Epinephrine)	.....
$(HO)_2C_6H_3—CH(H)—CH_2—NH_2$	1/65 epinephrine (*65*)	.....
$(HO)_2C_6H_3—CH(OH)—CH_2—NH_2$	1.2 epinephrine (*65*)	.....

chloride intravenous to rabbits (*43*), it becomes obvious that the presence of either the hydroxyl or the methyl group on the phenyl-bearing carbon atom reduces acute toxicity markedly:

$C_6H_5—CH(OH)—CH_2—NHCH_3$

0.00002 mole to pithed cat; 2.63 kg. gave 26 mm. Hg rise (*23*)

$C_6H_5—CH(CH_3)—CH_2—NHCH_3$

1 mg. equivalent to 0.00165 mg. epinephrine (*104*)

While it may be regrettable that experimental data do not permit more correlation of such isosteres, the possibilities and prospects are intriguing. However, until more information is available, the chemist should not let his imagination roam too far without the proper checks and corroboration from the laboratory.

As the size of the alkyl group on the beta carbon atom is increased, pressor activity decreases and toxicity increases. β-Phenylpropylamine is rated as a 4+ pressor and the LD_{50} intravenous to rats is 55 mg. per kg. β-Phenylbutylamine is 3+ and the correspondin LD_{50} is 38 mg. per kg. (*104*).

Since either the alcoholic hydroxyl group o the methyl group, when introduced into th beta position, seem to produce similar modifica tions in the pharmacodynamic properties, th question naturally arises: What will be the re sult if both are present simultaneously? On might expect a favorable influence from each and yet, since the two groups are isosteric, woul it not be more reasonable to expect the same resul that would be obtained, say, by the introductio of two hydroxyl groups? Two hydroxyl group on the same carbon atom are the same as th hydrated form of the carbonyl derivative, $=C(OH)_2 \rightarrow =C{:}O + H_2O$. Are tertiary alcohol

of type $Ar—C(OH)(CH_2—N)$: analogous to the ketones

of structure $Ar—C(OH)_2—CH_2—N$: ?

Tertiary alcohols of this type have been prepared. Although the data on their pharmacological behavior are unsatisfactory for our purposes, indications are that their pressor properties are reduced (as in the ketones?) and their toxicity is quite low. For example,

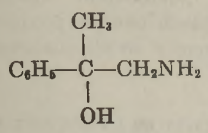
$C_6H_5—C(CH_3)(OH)—CH(NH_2)—CH_3$,

having an LD_{50} to white mice of 850 mg. per kg. is much less toxic than the same molecule with either the methyl or the hydroxyl groups missing; the toxicity is about the same order of magnitude, as might be expected from the ketone $C_6H_5—CO—CH(NH_2)—CH_3$ (*92*).

Table III. Isomerism of Phenylethanolamine and of β-Phenylpropylamine

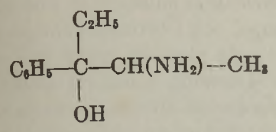
	$C_6H_5—CH(OH)—CH_2—NH_2$	$C_6H_5—CH(CH_3)—CH_2—NH$
M.P. of (±)base (±)mandelate, ° C.	129.5–130	119.5–120.5 (*60*)
M.P. of (−)base (−)mandelate, ° C.	144–145	127–127.5 (*60*)
$[\alpha]_D^{30}$ for (−)base	−20.7	−18.8 (*60*)
$[\alpha]_D$ for (−)base (−)mandelate	−58.3	−57.8 (*60*)
Solubility of (±)base (±)mandelate		
Grams/100 ml. water		
at 25° C.	11.63	11.50 (*60*)
at 37° C.	18.56	20.13 (*60*)
Grams/100 ml. normal saline soln.		
At 25° C.	11.76	11.31 (*60*)
At 37° C.	19.79	18.36 (*60*)
Mg. of (−)base (−)mandelate producing same rise in blood pressure as 0.01 mg. epinephrine	5.48	4.68 (*93*)
Min. lethal dose intravenous to rabbits, mg./kg.	30–90 (*6*, *23*, *45*)	50 (*43*)

Again, the tertiary alcohol of structure



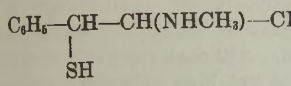
is less active than ephedrine (*69*).

Carbinols higher than methyl—e.g.,



produce a fall in blood pressure (*69*).

A thiol analog of ephedrine,



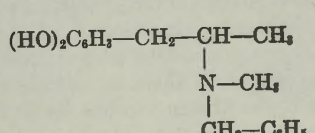
is reported, but no account of its physiological activity is given (*48*).

EFFECT OF *N*-ALKYLATION

The effect of substitution on the nitrogen atom, generally restricted to a single methyl group, cannot be accurately evaluated at present. Perhaps the effects of *N*-methylation may be better appreciated by noting its presence in two series, in the aryl alkanolamines and the corresponding aryl alkylamines (Table IV). Here also additional examples might be included but from the representative instances it appears that in the amino alcohol series the addition of the methyl group to the nitrogen atom decreases pressor activity and increases toxicity. Again, this adverse effect on the therapeutic ratio is not sufficient to cause alarm. Whether the *N*-methyl group modifies qualitatively the pharmacodynamic properties is not definite. In the case of norepinephrine it seems that the mechanism of action is less localized than it is for epinephrine, and ephedrine is more stimulant than norephedrine (*95*).

In the phenylalkylamine series (Table IV) the effects of *N*-methylation are less clear-cut. The increase in acute toxicity is not so pronounced, or it may even be decreased. The modification of hypertensive properties is unpredictable. For example, *N*-methylation of β-phenethylamine reduces the pressor activity by about half; but dihydroxyphenethylamine becomes four times more active when the *N*-methyl group is introduced. As a general rule, however, it is reported that *N*-methylation reduces the activity (*48*).

Dialkylation, or conversion into a tertiary amine, decreases the pressor activity, and the larger the alkyl group, the greater the decrease (*40*). Usually, also, this decrease in activity is accompanied by a simultaneous increase in toxicity. If the *N*-alkyl group is large enough, the molecule may even take on anesthetic properties and lose practically all its hypertensive ability (*71*). Secondary amines of structure $(HO)_2C_6H_3—CH_2—CH(CH_3)—NH—CH_2—CH_2—C_6H_4—OH—p$, as well as tertiary amines of structure



are said to possess analgesic properties (*63*).

Table IV. Arylalkylamines, Arylalkanolamines, and Their *N*-Methyl Derivatives

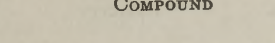
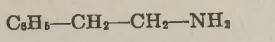
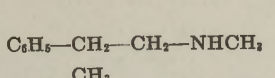
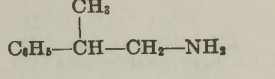
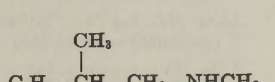
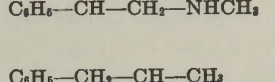
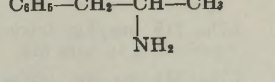
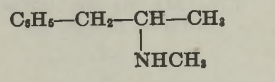
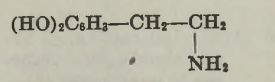
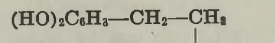
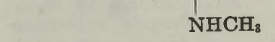
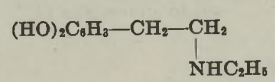
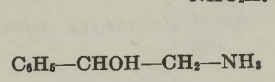
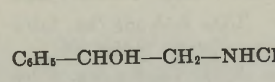
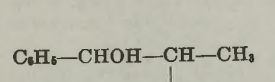
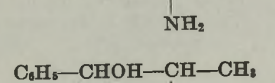
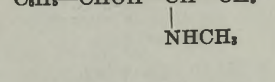
Compound	Physiological Activity	Toxicity
Arylalkylamines		
	1/133 epinephrine (*97*)	40–50 mg./kg. intravenous to rabbits (*23*)
	1/350 epinephrine (*97*)	.....
	Pressor, ++++ (*104*)	LD_{50} 55 mg./kg. intravenous to rabbits (*104*)
	Pressor, ++++ (*104*)	LD_{50} 65 mg./kg. intravenous to rabbits (*104*)
	1/425 epinephrine (*97*)	MLD 25 mg./kg. of hydrochloride subcutaneous to rats (*69*)
		MLD 17 mg./kg. intraperitoneal to rats (*49*)
	1/60 epinephrine (*7*)	.....
	1/12 epinephrine (*99*)	.....
	1/43 epinephrine (*11*)	.....
Arylalkanolamines		
	0.00002 mole to 2.63 kg. pithed cat gave rise of 58 mm. Hg (*23*)	80 mg./kg. intravenous to rabbits (*23*)
	0.00002 mole to 2.63 kg. pithed cat gave rise of 26 mm. Hg (*23*)	100 mg./kg. intravenous to rabbits (*23*)
	1 mg. of hydrochloride equivalent to 0.0125 mg. epinephrine hydrochloride (*23*)	MLD 75 mg./kg. of hydrochloride intravenous to rabbits. (*42*)
	1 mg. of *dl*-hydrochloride equivalent to 0.0105 mg. epinephrine hydrochloride (*23*)	MLD 55 mg./kg. of hydrochloride intravenous to rabbits (*42*)
	1.2 epinephrine (*95*)	LD_{50} 0.5 mg./kg. intravenous to rats (*95*)
	(Epinephrine)	LD_{50} 0.15 mg./kg. intravenous to rats (*95*)
	1/12 epinephrine (*95*)	LD_{50} 8 mg./kg. intravenous to rats (*95*)
	1/43 epinephrine (*97*)	.....

Table V. Hydroxyphenylalkylamines and -alkanolamines

Compound	Physiological Activity as Fraction of Epinephrine	Toxicity
Hydroxyphenylalkylamines		
p-HOC_6H_4—CH_2—CH_2—NH_2	1/70 (*11*)	.....
m-HOC_6H_4—CH_2—CH_2—NH_2	1/70 (*11*)	.....
3,4-$(HO)_2C_6H_3$—CH_2—CH_2—NH_2	1/50 (*7*)	.....
3,4,5-$(HO)_3C_6H_2$—CH_2—CH_2NH_2	1/35 (*11*)	.....
p-HOC_6H_4—CH_2—CH_2—$NHCH_3$	.....	LD_{50} 227 mg./kg. intraperitoneal to mice (*52*)
m-HOC_6H_4—CH_2—CH_2—$NHCH_3$	.....	LD_{50} 360 mg./kg. intraperitoneal to mice (*52*)
o-HOC_6H_4—CH_2—CH_2—$NHCH_3$	.....	LD_{50} 180 mg./kg. intraperitoneal to mice (*52*)
3,4-$(HO)_2C_6H_3$—CH_2—CH_2—$NHCH_3$ (*52*)	.....	.....
2,3,4-$(HO)_3C_6H_2$—CH_2—CH_2—$NHCH_3$ (*19*)	.....	.....
2,3-$(HO)_2C_6H_3$—CH_2—CH_2—$NHCH_3$	.....	LD_{50} 318 mg./kg. intraperitoneal to mice (*52*)
2,5-$(HO)_2C_6H_3CH_2CH_2NHCH_3$	.....	LD_{50} 234 mg./kg. intraperitoneal to mice (*52*)
3,5-$(HO)_2C_6H_3$—CH_2—CH_2—$NHCH_3$ (*19*)	.....	.....
2,6-$(HO)_2C_6H_3$—CH_2—CH_2—$NHCH_3$ (*19*)	.....	.....
p-HOC_6H_4—CH_2—$CH(NH_2)$—CH_3	1/100 to 1/50 (*8*)	MLD 150 mg./kg. of hydrochloride subcutaneous to guinea pigs (*7*)
3,4-$(HO)_2C_6H_3$—CH_2—$CH(NH_2)$—CH_3	1/50 (*8*)	MLD 388 mg./kg. of hydrochloride subcutaneous to guinea pigs (*7*)
Hydroxyphenylalkanolamines		
p-HOC_6H_4—$CHOH$—CH_2—$NHCH_3$	1/116 (*102*)	MLD 400 mg./kg. mice (*65*)
m-HOC_6H_4—$CHOH$—CH_2—$NHCH_3$	1/9 (*102*)	.....
3,4-$(HO)_2C_6H_3$—$CHOH$—CH_2—$NHCH_3$	(Epinephrine)	LD_{50} 0.15 mg./kg. intravenous to rats (*95*)
p-HOC_6H_4—$CHOH$—$CH(NH_2)$—CH_3	1/53 (*23*)	MLD 125 mg./kg. of hydrochloride intravenous to rabbits (*46*)
m-HOC_6H_4—$CHOH$—$CH(NH_2)$—CH_3	1/11.5 (*96*)	MLD 16 mg./kg. of hydrochloride intravenous to rabbits (*46*)
3,4-$(HO)_2C_6H_3$—$CHOH$—$CH(NH_2)$—CH_3	1/12 (*95*)	MLD 11 mg./kg. of hydrochloride intravenous to rabbits (*46*)
C_6H_3—(3-CH_3)-4-OH $CHOH$—$CH(NH_2)$—CH_3	1/288 (*97*)	MLD 20 mg./kg. of hydrochloride intravenous to rabbits (*46*)
C_6H_3—(4-CH_3)-3-OH $CHOH$—$CH(NH_2)$—CH_3	1/151 (*97*)	MLD 90 mg./kg. of hydrochloride intravenous to rabbits (*46*)
(−)*m*-HOC_6H_4—$CHOH$—$CH(NHCH_3)$—CH_3	1/21.7 (*101*)	.....
3,4-$(HO)_2C_6H_3$—$CHOH$—$CH(NHCH_3)$—CH_3	1/41 (*97*)	.....

Again in the realm of *N*-alkylation we find an effort to eliminate the pressor qualities of these compounds and to retain desirable nonpressor properties. One of the products is *l*-*N*-ethylephedrine (Nethacol), which may be administered orally or parenterally to patients with allergic phenomena who are unable to take ephedrine. It is reported to be about as toxic as ephedrine, and its pressor activity is one fifteenth to one tenth that of ephedrine. It dilates the bronchioles as does ephedrine, although its action is probably somewhat shorter in duration (*1*
25).

Quaternary ammonium compounds in th epinephrine-ephedrine series produce curarelike a tion, as apparently do all quaternary ammoniu compounds.

SUBSTITUTION IN PHENYL NUCLEUS

Some of the most useful hypertensive amin have an unsubstituted phenyl nucleus—for ex ample, ephedrine and benzedrine. In others th aromatic nucleus is substituted with phenolic hy droxyl groups; e.g., tyramine and neosynephrin contain a single phenolic group and epinephrin has two. Mescaline, a natural alkaloid obtaine from certain cactus species, is characterized by trimethoxyphenyl group. Accordingly, the chemis has undertaken to determine what modificatio in physiological activity may be attributed no only to these substituents but to others also. T make it possible for the pharmacologist to provid such information, many derivatives have bee synthesized. Although the study of phenyl sub stitution has not been exhausted, available dat make it possible to discern definite trends o tendencies.

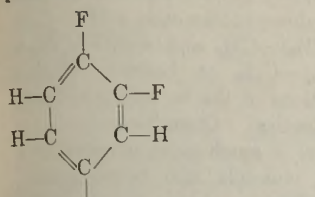
Introduction of an alkyl group into the phenyl nucleus increases the toxicity and usually lowers the pressor potency. The methyl group, in ortho, meta, or para positions, decreases the activity of β-phenethylamine, and larger alkyl groups magnify this adverse effect; if the radical is large enough, as benzyl, the compound becomes depressor (*39*). A methyl group attached to propadrine—that is, CH_3—C_6H_4—$CHOH$—$CH(NH_2)$—CH_3—in either the meta or para position decreases the therapeutic ratio to approximately a tenth. The *p*-methyl derivative is about three times more toxic and perhaps a third as active, and the *m*-methyl homolog is about four times as toxic and less than a third as active as the parent phenylpropanolamine (*42*, *44*, *97*). The attachment of ethyl and butyl radicals to the para position of ephedrine leads to strongly toxic compounds which show no circulatory effect (*28*).

Recent evidence suggests that, in the absence of the alcoholic hydroxyl group in the side chain, the results of methyl substitution, especially in in the ortho and meta positions—that is, for (*o*- or *m*-)CH_3—C_6H_4—CH_2—$CH(NH_2)$—CH_3—are not so undesirable, as described by Rohrmann and Shonle (*78*).

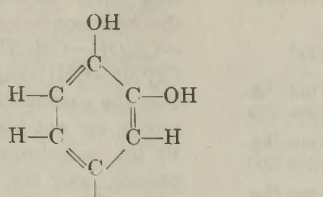
Replacing the phenyl group by *p*-xenyl, α-naphthyl, or β-naphthyl is disastrous as far as favorable pharmacological properties are concerned (*44*).

The effects of halogen substitution have been investigated. Promise for such compounds appeared when Burn reported that *p*-chlorophenethylamine, *p*-Cl—C_6H_4—CH_2—CH_2—NH_2, is several times more active than unsubstituted phenethylamine (*12*). It seemed not unreasonable to hope that the fluorine atom, atomic weight 19, might replace isosterically a phenolic hydroxyl group, molecular weight 17. Such similarity would be desirable, for it is hardly conceivable that the difluoro analog of epinephrine would be susceptible to the enzymes which inactivate

the natural hormone by attacking the molecule through its phenolic functions.



Difluoro analog



Epinephrine

This hope seems unfounded, however. At least evidence now available does not suggest that a single *m*- or *p*-hydroxyl group may be replaced by a fluorine atom without injuring the desirable properties of the active molecule.

It has been observed in a series of three *p*-fluorophenylalkylamines, *p*-F—C_6H_4—CH_2—CH_2—NH_2, *p*-F—C_6H_4—$CH_2CH(NH_2)$—CH_3, and *p*-F—C_6H_4—CH_2—CH_2—$NHCH_3$, that the fluorine atom increased the toxic properties of the parent amine by 30 to 40%. In dogs and guinea pigs all three compounds were pressor, the last being most promising, and in rabbits they lowered the blood pressure (*90*). The introduction of the fluorine atom into phenylpropanolamine (*106*) in the ortho, meta, or para positions decreases, in the order given, the pressor potency of the parent amino alcohol (*16*).

Chlorine substitution on the phenyl nucleus has been limited to the para position. As already mentioned, *p*-chlorophenethylamine, *p*-Cl—C_6H_4—CH_2—CH_2—NH_2, is more active than the unsubstituted phenethylamine. In phenylpropanolamine, on the other hand, the results are not so favorable; here the presence of the chlorine atom in the para position triples the toxicity (*44*) and reduces the pressor activity to a quarter that of the parent compound (*97*); in other words, the therapeutic ratio has been reduced to one twelfth.

Analogous bromine and iodine compounds do not appear, presumably because they are difficult, if not impossible, to prepare.

p-Nitrophenyl derivatives have been prepared, but the only indication of their physiological properties is found in nitrophenethylamine, *p*-NO_2—C_6H_4—CH_2—CH_2—NH_2, which produced a transitory depression followed by a marked rise which persisted for about 5 minutes; it is rated $^1/_{183}$ epinephrine (*11*, *100*).

Some indication of the extent to which the effects of hydroxyl substitution have been studied is given in Table V. Of the compounds listed, three occur naturally. *p*-Hydroxyphenethylamine, *p*-HOC_6H_4—CH_2—CH_2—NH_2, also known as tyramine, appears as a decarboxylation product of tyrosine, *p*-HOC_6H_4—CH_2—$CH(NH_2)$—COOH. 3,4-Dihydroxyphenethylamine, 3,4-$(HO)_2$—C_6H_3—$CH_2CH_2NH_2$, also called hydroxytyramine, may be formed by the oxidation of tyramine, or it may be formed as the decarboxylation product of DOPA, 3,4-$(HO)_2$—C_6H_3—CH_2—$CH(NH_2)$—COOH. It is undoubtedly the precursor in the biological synthesis of epinephrine (*54*). Epinephrine itself is the well-known hormone of the suprarenal medulla. A fourth natural compound of the phenolic series is believed to exist—namely, norepinephrine, 3,4-$(HO)_2$—C_6H_3—CHOH—CH_2—NH_2; it is thought to be "sympathin" or the sympathetic mediator (*9*, *20*, *38*). The other hydroxy compounds have been obtained synthetically.

Epinephrine is the most important of all these compounds. Since its basic skeleton is β-phenethylamine, efforts were early made to determine the contribution of the respective hydroxyl groups to its unusual pharmacodynamic properties; the effect of an *o*-phenolic hydroxyl were also observed.

Barger and Dale (*14*) reported that the *o*-hydroxy derivative is no more active than phenethylamine itself. According to them, the meta and para isomers are about equal in potency and about five times more active than the unsubstituted parent. Since 1909, however, additional analogs have been prepared, and with the extended series it has now become possible to evaluate better, both

Filling Ampoules and Vials of Adrenalin (Brand of Epinephrine) at the Laboratories of Parke, Davis & Company

Table VI. Methoxyphenylalkylamines and Methoxyphenylalkanolamines[a]

Compound	Physiological Activity	Toxicity[b]
p-$CH_3OC_6H_4CH_2CH_2NH_2$	1/300 epinephrine (*31*)	MLD 150 mg./kg. i.p. to mice (*31*)
m-$CH_3OC_6H_4CH_2CH_2NH_2$	1/300 epinephrine	MLD 230 mg./kg. i.p. to mice (*31*)
C_6H_3-3,4-$(OCH_3)_2$ $CH_2—CH_2—NH_2$	Slight pressor	MLD 420 mg./kg. i.p. to mice (*31*)
C_6H_2-3,4,5-$(OCH_3)_3$ $CH_2—CH_2—NH_2$	Mescaline, negligible pressor activity, induces euphoria	MLD 500 mg./kg. i.p. to mice (*36*)
C_6H_2-2,3,4-$(OCH_3)_3$ $CH_2—CH_2—NH_2$	Negligible pressor, no euphoria (*59*)	.....
p-$CH_3OC_6H_4—CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 165 mg./kg. i.p. to mice (*52*)
m-$CH_3OC_6H_4—CH_2—CH_2—NHCH_3$	.....	LD_{50} 173 mg./kg. i.p. to mice (*52*)
o-$CH_3OC_6H_4—CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 173 mg./kg. i.p. to mice (*52*)
C_6H_3-3,4-$(OCH_3)_2$ $CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 322 mg./kg. i.p. to mice (*52*)
C_6H_3-2,4-$(OCH_3)_2$ $CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 146 mg./kg. i.p. to mice (*52*)
C_6H_3-2,3-$(OCH_3)_2$ $CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 137 mg./kg. i.p. to mice (*52*)
C_6H_3-2,5-$(OCH_3)_2$ $CH_2—CH_2—NHCH_3$	Slight pressor (*52*)	LD_{50} 122 mg./kg. i.p. to mice (*52*)
C_6H_3-3,4-(O_2CH_2) $CH_2—CH_2—NHCH_3$	Initial depressor, then pressor (*52*)	LD_{50} 215 mg./kg. i.p. to mice (*52*)
p-$CH_3OC_6H_4—CHOH—CH(NHCH_3)—CH_3$	Weaker than ephedrine (*62*)	.....
p-$CH_3OC_6H_4—CH_2—CH(NH_2)—CH_3$ (*105*)	Produces 20% rise in arterial pressure (*35*)	.....
C_6H_4-p-(OCH_3) $CHOH—CH(NH_2)—CH_3$	1/2 propadrine	MLD 35 mg./kg. of hydrochloride i.v. to rabbits (*46*)
C_6H_4-o-(OCH_3) $CHOH—CH(NH_2)—CH_3$	1/225 epinephrine (*97*)	MLD 25 mg./kg. of hydrochloride i.v. to rabbits (*46*)
C_6H_3-2,4-$(OCH_3)_2$ $CHOH—CH(NH_2)—CH_3$	Predominantly depressor (*97*)	MLD 21 mg./kg. of hydrochloride i.v. to rabbits (*46*)

[a] The chemical preparation of additional members of these series is described (*10*, *19*, *56*, *57*, *61*, *76*, *105*), but pharmacological data are not included.
[b] Intraperitoneal = i.p.; intravenous = i.v.

quantitatively and qualitatively, the contribution of the different phenolic groups. It is probably true, as indicated by o-hydroxyephedrine, o-HO—C_6H_4—CHOH—$CH(NHCH_3)$—CH_3, that the o-phenolic hydroxyl group has little, if any influence, as Barger and Dale concluded. With respect to the other isomers, the opinions of these early investigators must be modified.

From comparative studies on hydroxyphenylethanolmethylamines, p-HO—C_6H_4—CHOH—CH_2—$NHCH_3$ and m-HO—C_6H_4—CHOH—CH_2—$NHCH_3$; the hydroxyephedrines, p-HO—C_6H_4—CHOH—$CH(NHCH_3)$—CH_3 and m-HO—C_6H_4—CHOH—$CH(NHCH_3)$—CH_3; and the hydroxyphenylpropanolamines, p-HO—C_6H_4—CHOH—$CH(NH_2)$—CH_3 and m-HO—C_6H_4—CHOH—$CH(NH_2)$—CH_3, it becomes obvious that the contributions of the m- and p-hydroxyl groups are not identical. Quantitatively (Table V) the m-hydroxyl is much more effective as a pressor, and the molecule also becomes more toxic. The p-hydroxyl group, on the other hand, increases the intensity of activity over that of the unsubstituted compound, but this derivative is not so potent as is its meta isomer; p-hydroxyl also reduces toxicity. There is a qualitative difference that must not be overlooked. Pharmacodynamically the p-hydroxy compounds are qualitatively little different, if any, from the unsubstituted parent; they are essentially musculotropic (*53*, *64*, *65*, *87*). The m-hydroxy derivatives, on the other hand, are more sympathicotropic—that is, show to a much greater extent the mechanism of action which is associated with the catechol nucleus (*80*, *96*, *99*). In other words, the unsubstituted phenyl compound, as in ephedrine, mimics the action of epinephrine on the sympathetic system; the introduction of a p-hydroxyl group does not change appreciably the mechanism of action; but the presence of the m-hydroxyl group causes the molecule to evoke a greater degree of sympathetic response. Thus, the m-phenolic derivative approaches nearer to epinephrine than does its para isomer. True epinephrine-like activity, however, is not obtained unless both the m- and p-hydroxy groups are present (*99*).

The 2,3- and 2,4-dihydroxy derivatives have received scant attention, but presumably their structure is unfavorable (*103*).

Since a single m-hydroxyl group produces such marked effects, the question arises as to the results if both available meta positions are occupied by phenolic groups. With a view to answering that question, 3,5-dihydroxyphenylpropanolamine, 3,5-$(HO)_2$—C_6H_3—CHOH—$CH(NH_2)$—CH_3, was recently synthesized (*57*), but it has not yet been examined for pharmacological properties.

A series of methoxyl substituted compounds is listed in Table VI. Many of the pharmacological data missing from that summary are available in another paper in this symposium (*37*). The available evidence, subject to further confirmation, suggests that the introduction of methoxyl groups, regardless of position occupied in the phenyl nucleus, increases the toxicity and decreases the circulatory effect (*48*).

Mescaline or 3,4,5-trimethoxyphenethylamine is the chief alkaloid of the mescal button, the peyotl, or the ceremonial object of a religious cult among the Indians of northern Mexico and southwestern United States. Although possessing the β-phenethylamine skeleton, mescaline is reported to be practically without effect on blood pressure (*27*, *75*), but its subjective reactions, particularly the state of induced euphoria, have been confirmed by Havelock Ellis and Weir Mitchell (*30*). Mescaline is toxic, and its continued use results in tissue damage. Perhaps structural modifications which are known to decrease the toxic properties of the derivatives of β-phenethylamine and increase their desirable qualities may lead to a molecule of value in psychotherapy.

The results of amino substitution, summarized in Table VII have been very little explored. *p*-Aminoephedrine, *p*-NH_2—C_6H_4—CHOH—CH($NHCH_3$)—CH_3, has received most attention. As a pressor it is more than twice as active as ephedrine (*97*, *101*). Its effect on the blood sugar of experimental animals resembles that of ephedrine. It is about half as toxic (*83*). Although it has received inadequate clinical trial, it is reported to be more satisfactory than ephedrine for the relief of asthma (*83*). Available evidence suggests that, at least pharmacologically, the *p*-amino group may be isosteric with the *p*-hydroxyl group.

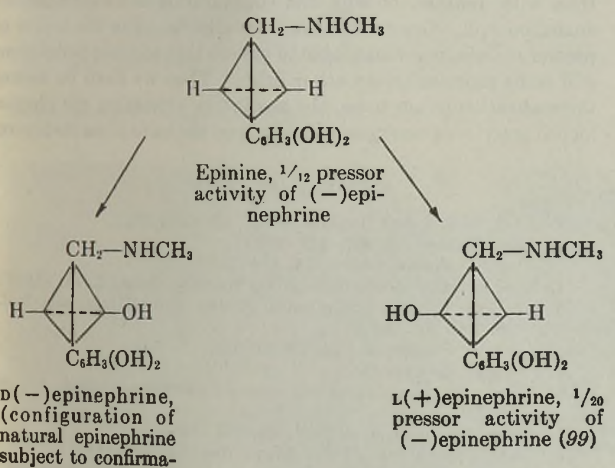
Table VII. *p*-Aminophenyl Derivatives

Compound	Physiological Activity	Toxicity
C_6H_4-*p*-NH_2 | CH_2—CH_2—$N(CH_3)_2$	Produces hypertension by nicotine-like action; activity about 10 times greater than that of C_6H_5—CH_2—CH_2—$N(CH_3)_2$ (*18*)	.....
C_6H_4-*p*-NH_2 | CH_2—CH($NHCH_3$)—CH_3	.....	300 mg./kg. orally (*50*), 85 mg./kg. intraperitoneal to rats (*50*)
C_6H_4-*p*-NH_2 | CH—CH_2—$NHCH_3$ | CH_3	.....	200 mg./kg. intraperitoneal to rats (*50*)
C_6H_4-*p*-NH_2 | CHOH—CH(NH_2)—CH_3 (*32*)	.....	.....
C_6H_4-*p*-NH_2 | CHOH—CH($NHCH_3$)—CH_3	1/15 epinephrine (*97*)	MLD 0.35 mg./kg intravenous to mice (*83*)

IMPORTANCE OF STEREOISOMERISM

Up to this point attention has been centered on major changes in the structure of the molecule—the removal or the grafting on of certain substituents in different positions of the parent skeleton. Stereoisomerism must also be considered.

The hydroxyl-bearing carbon atom of natural ephedrine rotates the plane of polarized light to the left but it belongs in the D-series (*34*). It is not unlikely, although conclusive proof is lacking, that levorotatory or natural epinephrine, with a single asymmetric carbon atom, also belongs to the D-series. If that assumption is accepted for the moment and if the conventional projection of the tetrahedral carbon atom is employed, the following correlations emerge:



The alcoholic hydroxyl on the phenyl-bearing carbon atom (Table II) was found generally to increase activity and decrease toxicity. When we compare epinine with the isomeric epinephrines, a difference is found, depending on which position the hydroxyl group takes in the phenyl-bearing carbon atom; if it forms (−)epinephrine, the activity is increased twelvefold; but if it forms (+)epinephrine, the activity is decreased by two fifths. Such a phenomenon deserves to be studied.

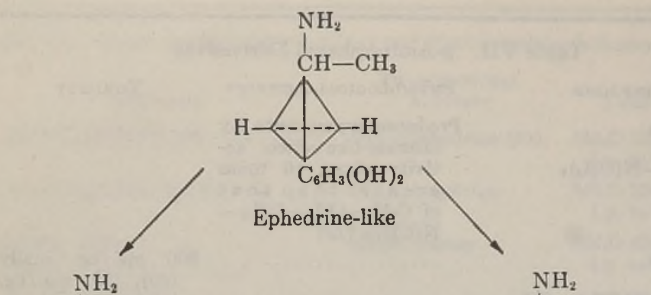
Comparable results appear in β-phenethylamine itself, even though the available data are not so striking or so positive as in the epinine-epinephrine analogs. If to the beta carbon atom is attached an alcoholic hydroxyl group or a methyl group (Table III), the levorotating isomer in each instance becomes the more active. Whether the dextrorotating amine becomes less active than the unsubstituted parent does not now appear (*60*).

The alpha carbon atom becomes asymmetric in compounds like benzedrine and ephedrine. In natural (−)ephedrine it is dextrorotatory. Efforts have been made to establish its relative configuration, but the results are not conclusive. Leithe (*67*) placed it in the D-series by correlating it with optically active α-phenethylamine. Freudenberg and Nikolai (*33*) assigned it to the L-series because of its relation to L(+)alanine; L(−)phenylalanine might prove a more appropriate reference point, and this would place it in the D-configuration (*60*).

Evidence from various sources suggests that maximum physiological activity is obtained when the alpha carbon atom, if asymmetric, is dextrorotatory (*60*). This is true for the stimulating action, for (+)benzedrine is a better stimulant than (−)benzedrine. Of the ephedrine isomers the two having the amino-bearing carbon atom rotating to the right, *l*-ephedrine and *d*-ψ-ephedrine, produce greater mydriasis than do their mirror images (*23*).

The quantitative differences between enantiomorphs and diastereoisomers have received more study and emphasis. Yet the qualitative differences must not be overlooked. It is to be hoped that they may receive more attention in the future. For example, it is suggested that (+)epinephrine shows a selective difference in "protoplasmic" reaction from its levorotatory isomer (*99*). The effect of (+)synephrine, *p*-HO—C_6H_4—CHOH—CH_2—$NHCH_3$, was antagonistic to that of (−)synephrine when studied on the perfused rabbit ear. Doses of 0.5 to 2.0 mg. (−)synephrine caused prompt vasoconstriction; (+)synephrine in doses even up to 10 mg. had no effect or caused dilatation. The racemic combination in doses up to 50 mg. never produced constriction; since this maximum amount contained 25 mg. of the (−)isomer (more than twelve times the dose of that isomer used alone), the (+)configuration is not only inactive but also capable of suppressing the strong constricting action which characterizes the levoenantiomorph (*99*).

3,4-Dihydroxyphenylpropanolamine, 3,4-$(HO)_2C_6H_3$—CHOH—CH(NH_2)—CH_3, is capable of existing in four optically active forms. Two of them have been isolated. The (−)isomer is reported to be not only 160 to 200 times more active on the blood pressure than the (+)isomer, but qualitatively more like epinephrine whereas the (+)form is more like ephedrine in its action. These qualitative differences are confirmed by tests on the isolated uterus. If the alcoholic hydroxyl group of either the (−)- or (+)isomer is replaced by a hydrogen atom and thereby destroys one center of asymmetry, the product is qualitatively like ephedrine (*81*). Schematically these results may be indicated thus:



Perhaps these differences can be explained on the basis of diastereoisomerism. A molecule with an asymmetric center reacts with the protoplasm to form a new compound or complex. Since the configuration of the protoplasm does not change, the product formed when, say, a levorotatory drug unites with the living tissue is diastereoisomeric with that formed with the dextrorotatory drug. In spite of the fact that formulas of diastereoisomers as customarily written show them to be identical, they are different compounds from practically all points of view. It is not surprising, therefore, to find pharmacodynamic differences also. If more were known about the nature of these protoplasmic reactions and of the products formed, the interpretation of observed results might be more intelligent. It is not unlikely that, just as the presence of the drug molecule modifies the nature of the tissue response, the nature of the protoplasmic reaction product also predetermines the nature of the response called forth by the drug molecule; that is, the drug and the tissue have mutually modifying effects. How else can we explain the fact that (−) benzedrine is about 47% more active as the (−) mandelate than as the (+) mandelate (*93*)? The nature of the base in both salts is identical, but the acid with which it is combined in one instance is the enantiomorph of that in the other. Is it unreasonable to assume that different tissues will do less than optically active isomeric acids?

ABEL'S BENZOYLEPINEPHRINE

Abel early became interested in the chromogenic principle of the suprarenal glands and was the first to isolate epinephrine as a polybenzoyl derivative (*4*). He subjected it to hydrolysis by hot dilute sulfuric acid and isolated a sulfate which showed a remarkably high degree of activity of the glands (*55*). From an analysis of the sulfate and other derivatives Abel assigned to the product the formula $C_{17}H_{15}NO_4$ (*3*). The correct formula for epinephrine is $C_9H_{13}NO_3$. Abel admitted his error (*1*) and agreed that his original product must have contained a benzoyl group which was not removed by hydrolysis, "an unusual circumstance in any event" (*2*).

It is practically impossible to explain or account for Abel's so-called benzoylepinephrine. We know from the structure of the hormone that at most a tetrabenzoyl derivative could have been formed—two benzoyl groups on the phenolic hydroxyls, one on the alcoholic hydroxyl group, and a fourth on the methylamino group. Abel supposed it was the *N*-benzoyl group which did not come off in the autoclave. Perhaps this would be more difficult to remove than the three *O*-benzoyl groups. However, in view of what we now know about the results of *N*-acylation of such compounds on their physiological properties, it is impossible to understand how Hunt (*55*) could have obtained experimentally a blood pressure elevation which can be expected only from the unsubstituted *l*-epinephrine molecule. Furthermore, a recent attempt by H. C. Parke to duplicate Abel's isolation of t benzoyl derivative has not proved successful (*94*).

CONCLUSION

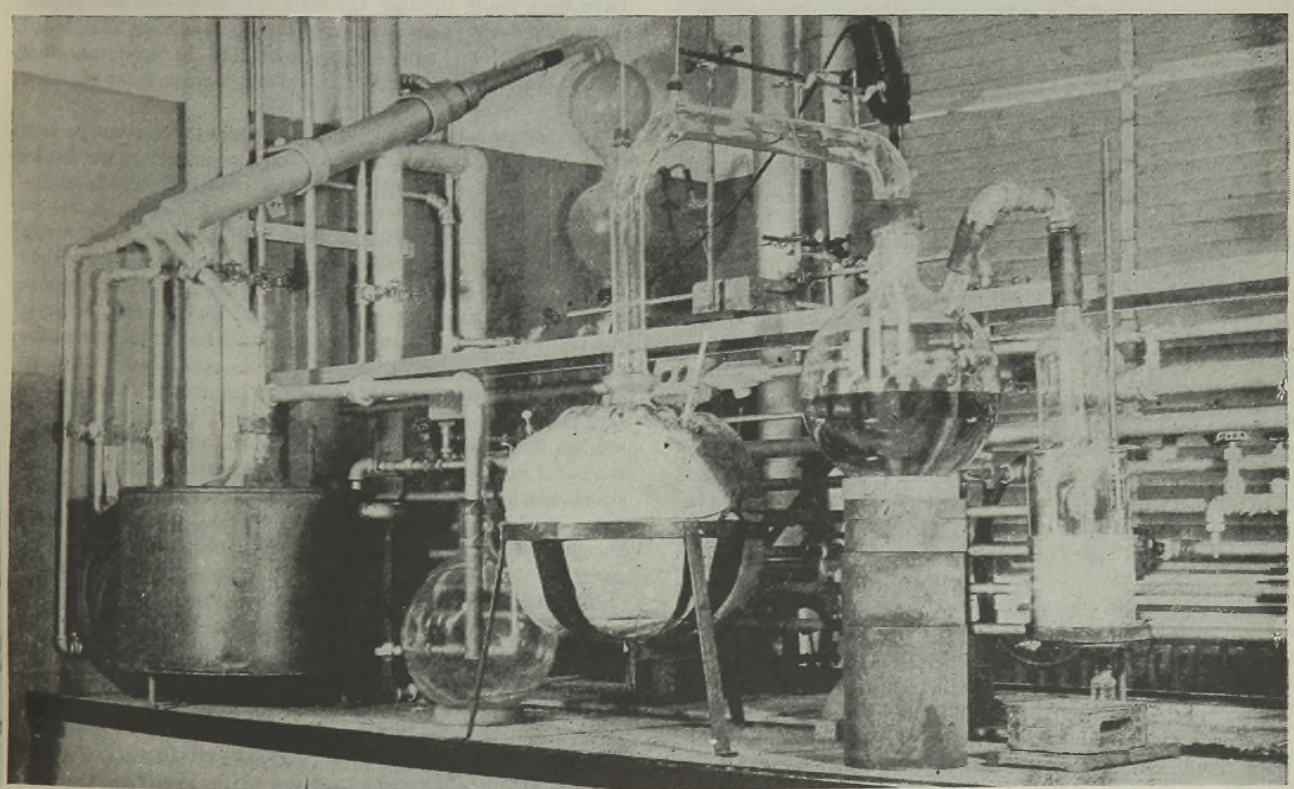
The correlation between chemical constitution of β-phenethy amine derivatives and pharmacodynamic properties is still i complete. For example, at present the relationship is based structural similarity and on pharmacological manifestatio which are similar, perhaps, only in that they show elevation blood pressure in the experimental animal. Such an elevati may be caused by one or more of several different mechanism The pharmacologists are doing an excellent piece of work assaying quantitatively and analyzing qualitatively the effec of so many compounds which the chemists are endlessly feedi into their hoppers. Let us hope that they will continue their di gence in studying the phenethylamine derivatives, whether the show promise of practical application or not. It is not incon ceivable that as more information becomes available a correl tion on some other basis may prove more advantageous. In an event, a better understanding of all the factors in one field medicinal chemistry may be expected to influence favorably th developments in others.

It becomes obvious to the chemist that conventional structur formulas are inadequate. As a student of atomic architectur working in the medicinal field, he must give greater attention t molecular plans and designs, not only to how they may be modi fied in the laboratory, but particularly to learning about an anticipating the needs and demands of the living tissue wit which the drug is to act. If possible, he must determine wh more favorable results are obtained with one kind of substitutio than with another, or why one configuration is better than it enantiomorph. Once valid clues are established in the realm o pressor amines, it is reasonable to believe that sensible deduction will come more easily in other fields. Then we shall be neare the realization of our hope, the possibility explaining the physiological activity of an organic molecule on the basis of its structure

LITERATURE CITED

(1) Abel, *Bull. Johns Hopkins Hosp.*, **12**, 337 (1901).
(2) Abel, *Science*, **66**, 307, 337 (1927).
(3) Abel, *Z. physiol. Chem.*, **28**, 318 (1899).
(4) Abel and Crawford, *Bull. Johns Hopkins Hosp.*, **8**, 151 (1897).
(5) Abelous, Ribaut, Soulie, and Toujan, *Compt. rend. soc. biol.*, 58, 462, 530 (1906).
(6) Alles, *J. Pharmacol.*, **32**. 121 (1927).
(7) *Ibid.*, **47**, 339 (1933).
(8) Alles and Knoefel, *Arch. intern. pharmacodynamie*, **47**, 96 (1934).
(9) Bacq, *Arch. intern. physiol.*, **36**, 167 (1933).
(10) Baltzly and Buck, *J. Am. Chem. Soc.*, **62**, 164 (1940).
(11) Barger, "Organic Chemistry in Biology and Medicine", New York, McGraw-Hill Book Co., 1930.
(12) *Ibid.*, p. 87.
(13) Barger and Dale, *J. Physiol.*, **38**, proc. xxii (1909).
(14) *Ibid.*, **41**, 19 (1909).
(15) Becker, Warren, Marsh, Thompson, and Shelton, *J. Pharmacol.*, **75**, 289 (1942).
(16) Beyer, personal communication.
(17) Beyer and Lee, *J. Pharmacol.*, **74**, 155 (1942).
(18) Bovet and Benoit, *Compt. rend. soc. biol.*, **136**, 328 (1942).
(19) Buck, *J. Am. Chem. Soc.*, **54**, 3661 (1932).
(20) Cannon and Rosenblueth, *Am. J. Physiol.*, **104**, 557 (1933).
(21) Chen and Schmidt, "Ephedrine and Related Substances", Baltimore, Williams and Wilkins Co., 1930.
(22) Chen and Schmidt, *Medicine*, **9**, 7 (1930).
(23) Chen, Wu, and Hendriksen, *J. Pharmacol.*, **36**, 363 (1929).
(24) Council on Pharm. and Chem., *J. Am. Med. Assoc.*, **91**, 1037 (1928).
(25) Craddock, *Cincinnati J. Med.*, **22**, 457 (1941).
(26) Cromwell and Hoeksema, *J. Am. Chem. Soc.*, **66**, 870 (1944).
(27) Dixon, *J. Physiol.*, **25**, 69 (1899).
(28) Ehrhart, *Metallbörse*, **20**, 1800 (1930).
(29) Eichholtz, *Angew. Chem.*, **53**, 517 (1940).
(30) Ellis, *Ann. Rept. Smithsonian Inst.*, **1897**, 537.
(31) Epstein, Gunn, and Virden, *J. Physiol*, **76**, 224 (1932).

(32) Foster, thesis, Univ. of Maryland, 1942.
(33) Freudenberg and Nikolai, *Ann.*, 510, 223 (1934).
(34) Freudenberg, Schoeffel, and Braun, *J. Am. Chem. Soc.*, 54, 234 (1932).
(35) Geezink and Jager, *Arch. néerland. physiol.*, 24, 79 (1939).
(36) Grace, *J. Pharmacol.*, 50, 359 (1934).
(37) Graham, Cartland, and Woodruff, IND. ENG. CHEM., 37, 149 (1945).
(38) Greer, Pinkston, Baxter, and Brannon, *J. Pharmacol.*, 62, 189 (1938).
(39) Hambourger and Jamieson, *Ibid.*, 58, 53 (1936).
(40) Hartung, *Chem. Rev.*, 9, 389 (1931).
(41) Hartung, unpublished data.
(42) Hartung and Munch, *J. Am. Chem. Soc.*, 51, 2262 (1929).
(43) *Ibid.*, 53, 1875 (1931).
(44) Hartung, Munch, and Crossley, *Ibid.*, 57, 1091 (1935).
(45) Hartung, Munch, Deckert, and Crossley, *Ibid.*, 52, 3317 (1930).
(46) Hartung, Munch, Miller, and Crossley, *Ibid.*, 53, 4149 (1931).
(47) Hasama, *Arch. exptl. Path. Pharmakol.*, 153, 165 (1930).
(48) Hauschild, *Ibid.*, 195, 647 (1940).
(49) Hauschild, *Klin. Wochschr.*, 17, 1257 (1938).
(50) *Ibid.*, 20, 363 (1941).
(51) Hill and Powell, *J. Am. Chem. Soc.*, 66, 742 (1944).
(52) Hjort, *J. Pharmacol.*, 52, 101 (1934).
(53) Hochrein and Keller, *Arch. exptl. Path. Pharmakol.*, 156, 37 (1930).
(54) Holtz and Credner, *Naturwissenschaften*, 29, 649 (1941).
(55) Hunt, *Am. J. Physiol.*, 5, proc. vii (1901).
(56) Ide and Buck, *J. Am. Chem. Soc.*, 62, 425 (1940).
(57) Iwamoto and Hartung, *J. Org. Chem.*, in press.
(58) Jaeger, *Compt. rend. soc. biol.*, 87, 1066 (1922).
(59) Jansen, *Rec. trav. chim.*, 50, 291 (1931).
(60) Jarowski and Hartung, *J. Org. Chem.*, 8, 564 (1943).
(61) Kindler and Peschke, *Arch. Pharm.*, 269, 581 (1931).
(62) Koller, *Monatsh.*, 47, 397 (1926).
(63) Külz, U. S. Patent 2,276,618 (March 17, 1942).
(64) Kuschinsky, *Arch. exptl. Path. Pharmakol.*, 156, 306 (1930).
(65) Lasch, *Ibid.*, 124, 231 (1927).
(66) Léger, *Compt. rend.*, 142, 108 (1906).
(67) Leithe, *Ber.*, 65, 660 (1933).
(68) Levin, Graham, and Kolloff, *J. Org. Chem.*, 9, 380 (1944).
(69) Lévy and Sergent-Montsaratt, *Paris Medical*, 79, 148 (1931).
(70) Nagai, *Pharm. Ztg.*, 32, 700 (1887).
(71) Novelli and Tainter, *J. Pharmacol.*, 77, 324 (1943).
(72) Osborne, *Science*, 85, 105 (1935).
(73) Pedden, Tainter, and Cameron, *J. Pharmacol.*, 55, 232 (1935).
(74) Piness, Miller, and Alles, *J. Am. Med. Assoc.*, 94, 790 (1930).
(75) Raymond-Hamet, *Bull. acad. méd.*, 105, No. 2 (1931).
(76) Reichert and Koch, *Ber.*, 68, 445 (1935).
(77) Rohrmann and Shonle, Div. of Medicinal Chem., A.C.S., Cleveland, 1944.
(78) *Ibid.*, New York, N. Y., 1944.
(79) Rosenmund and Karg, *Ber.*, 75, 1850 (1942).
(80) Schaumann, *Arch. exptl. Path. Pharmakol.*, 160, 127 (1931).
(81) Schaumann, *Med. u. Chem. Abhandl. med.-chem. Forschungsstätten I. G. Farbenind.*, 3, 383 (1936).
(82) Schulte, Reif, Bacher, Lawrence, and Tainter, *J. Pharmacol.*, 71, 62 (1941).
(83) Selinger, *Med. Klinik*, 27, 207 (1931).
(84) Slotta and Heller, *Ber.*, 63, 3029 (1930).
(85) Späth, *Monatsh.*, 40, 129 (1919).
(86) Späth and Brück, *Ber.*, 70, 2446 (1937).
(87) Stockton, Pace, and Tainter, *J. Pharmacol.*, 41, 11 (1931).
(88) Stolz, German Patent 157,300; *Ber.*, 37, 4149 (1904).
(89) Suter and Ruddy, *J. Am. Chem. Soc.*, 66, 747 (1944).
(90) Suter and Weston, *Ibid.*, 63, 602 (1941).
(91) *Ibid.*, 64, 533 (1942).
(92) *Ibid.*, 64, 2451 (1942).
(93) Swanson, Scott, Lee, and Chen, *J. Pharmacol.*, 79, 329 (1943).
(94) Sweet, personal communication.
(95) Tainter, *Arch. intern. Pharmacodynamie*, 41, 365 (1931).
(96) *Ibid.*, 42, 128 (1932).
(97) *Ibid.*, 46, 192 (1933).
(98) Tainter, *J. Pharmacol.*, 36, 29 (1929).
(99) *Ibid.*, 40, 43 (1930).
(100) Tainter, *Quart. J. Pharm. Pharmacol.*, 3, 584 (1930).
(101) Tainter, Pedden, and James, *J. Pharmacol.*, 51, 380 (1934).
(102) Tainter and Seidenfeld, *Ibid.*, 40, 23 (1930).
(103) Tiffeneau, *Ch. Richet Festschrift*, 1912, 399–412; *Chem. Zentr.*, 1914, I, 689.
(104) Warren, Marsch, Thompson, Shelton, and Becker, *J. Pharmacol.*, 79, 187 (1943).
(105) Woodruff and Conger, *J. Am. Chem. Soc.*, 60, 465 (1938).
(106) Zenitz, thesis, Univ. of Maryland, 1942.



Courtesy, Ciba Pharmaceutical Products, Inc.

High-Vacuum Distillation Apparatus Used in the Purification of Privine (α-Naphthyl-2-methylimidazoline) Base

PHARMACOLOGIC METHODS AND OBJECTIVES IN RESEARCH

M. L. TAINTER

Winthrop Chemical Company, Inc., Rensselaer, N. Y.

Rx—research on sympathomimetic amines is a field which, by comparison, is quite old and mature, since studies of these compounds have been going on for practically fifty years. However, discoveries remain to be made no matter how thoroughly this field of activity may have been cultivated. In this connection, the recent realization that the actions on the central nervous system of amphetamine might be useful was a turning to practical account of a previously undesired feature in the action of these amines. This action had been generally recognized before without realization of its possible clinical implications. There are probably other unknown or unappreciated actions of these amines which await only elucidation or application by what has been called the "informed mind". A realization of the potentialities of these compounds for producing manifold profound changes throughout the body seems to make the prospect of finding new uses for them very good.

THE role of this paper in the symposium is to discuss various biological methods of studying sympathomimetic amines and to indicate, in so far as possible, desirable objectives for future work. It is not possible to set forth in adequate detail the standard methods for investigating these amines, nor is it necessary, since the methods used are those commonly employed for pharmacodynamic studies on other drugs. However, there are methods of studying these preparations not quite so routine in their application, whose value might be worth discussion here.

The most important applications of the drugs in this family are to the circulatory system, since it is here that the most vigorous and dramatic physiological responses are elicited. Circulatory changes traditionally are thought of in terms of blood pressure and pulse rate, which are easy to observe and frequently reveal changes in which there is interest. Regarding pressure, it should be pointed out that attention is most commonly focused on the systolic; however, this taken by itself has little significance. From the standpoint of the organism as a whole, the pressure is of minor consequence except in so far as it modifies the volume flow of blood. The tissues require the passage of adequate volumes of blood through them, rather than the maintenance of some predetermined pressure. For this reason measurements of the mass movement of blood under the influence of the sympathomimetic amines are more important than readings of the systolic changes. In many instances it is possible for systolic pressure to increase while there is an actual decrease in blood flow, because peripheral vasoconstriction, in giving rise to the increased pressure, imposes so much resistance that the mass movement of blood is cut down. A general idea of the changes in blood flow may be had by comparing both the pulse pressures and pulse rates before and after the administration of the drug. This is not an invariably reliable index of blood flow, but it often gives useful information, particularly during periods of acute change.

In human beings, systolic and diastolic pressures are measured fairly readily with the ordinary recording devices. However, in animal experiments the pressure is frequently measured by a mercury manometer which, because of its inertia, can give nothing but a reduced mean pressure from which no conclusions as to systolic or diastolic pressures can be derived. It would seem to be a matter of some importance in physiological experiments to use, instead of the mercury manometer, the more modern membrane manometers, preferably with optical recording systems; if these are not available, the diaphragm types with lever writing arms are almost as satisfactory. While the latter do not give a perfect record of the form of the pulse wave, they are so much better and easier to use than the mercury manometers that they should be employed more widely.

In many cases the point of interest is not the effect of the amine on total blood flow, but rather the modifications produced in some local area of the circulation. So far, no adequate, generally applicable means is available for studying cerebral blood flow. This can be done in animal experiments by isolating the vascular supply to the head; but the attempt to localize the area being studied so as to exclude the muscular masses of the face and tongue involves so much manipulation and operative interference that it becomes difficult to interpret the data as having general significance when applied to the question of flow through the brain. In the human being, attempts to measure the flow have been made through the collection of arterial and jugular blood samples. There is no certainty that the blood so collected is representative; in any event, since it includes blood from other tissues as well as from the brain, the information it can supply is limited.

Another vascular area in which response to these amines is of immediate importance is in the nasal mucosa, where the amines are applied for vasoconstriction and reduction in turgescence. In anesthetized animals vasoconstriction of the mucosa may be measured by transforming the nasal chamber into a closed cavity and recording pressure changes therein. Although this method has some value for systemically administered drugs, it is not useful in evaluating the response to solutions applied locally, which is the point of real interest. Another procedure applicable to the patient is the measurement of the temperature of the nasal mucosa by a thermocouple applied to the tissue. The assumption is that vasoconstriction will reduce the blood flow in the mucosa and result in local cooling. The difficulty here is that the nasal mucosa may be relatively bloodless or have impaired circulation because of suffusion with fluid, with the result that the vasoconstrictor will not produce a proportionate degree of cooling. Furthermore, since only the anterior part of the nares is readily accessible for the application of the thermocouple, the area of observation is limited and may not be representative of the mucosa as a whole. A method which has been used only to a limited extent employs the von Glahn mirror, in which the subject exhales through the nostrils onto a chilled mirror surface. As the nasal mucosa shrinks, the area of fogging of the mirror increases and thereby reveals opening up of the airways. It is obvious that such an apparatus may give erratic results because the size of the area can be modified by the speed of exhalation. Probably fully as much can be gained by inspecting the nose by the usual rhinological technique, but this permits only visual esti-

mates of the degree of constriction present, which cannot be readily transformed into objective data.

Another vascular effect of the amines is constriction in connection with local anesthetics. The effects of this type of application are usually measured indirectly in terms either of prolongation of anesthesia or of diminution in the amount of bleeding. Other methods of measuring the duration of vasoconstriction in localized areas seem to be needed since the duration is of great practical importance. One method which has been used is to incorporate in the vasoconstrictor solution a highly toxic material which can be detoxified by the body fairly rapidly. As long as vasoconstriction persists, access of the toxic compound to the circulation is restrained and time is gained for neutralization. Therefore a much larger dose can be withstood than when the injection is made without the addition of the sympathomimetic amine. An experiment such as this must obviously be interpreted conservatively; nevertheless, it can give information of value as to the length of time a certain tissue area is blocked off by the amine in question.

The sympathomimetic amines generally increase pulse rate and the force of cardiac contraction. This by itself will cause an increased blood flow, particularly in cases of cardiac decompensation in which emptying of the heart is incomplete. Unfortunately, with many of the sympathomimetic amines there is produced simultaneously an arteriolar constriction in the periphery which increases the resistance to the flow of blood. Under these circumstances the potential increase in cardiac output may not be achieved or the mass movement of blood improved. Much more attention to the influence of these amines on the cardiac function and output is needed, including determinations of changes in heart size as indications of the completeness of emptying under the influence of the amine. Radiological studies of the heart should be important in this connection.

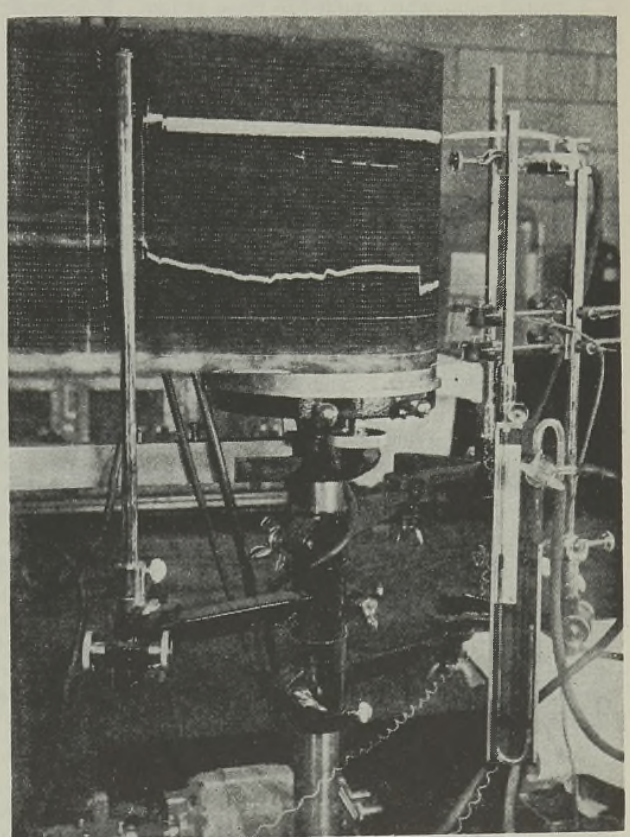
Related to the cardiac response is the effect of the amines on coronary blood flow. In many cases the factor which limits the working capacity of the myocardium is the volume of blood flowing through the coronary arteries. This is often impaired by thrombosis, arteriosclerotic plaques, or spasm. In animals the effects on coronary blood flow can be measured, but with considerable difficulty. In anesthetized animals various fairly accurate methods are available from which useful information can be obtained. However, in unoperated animals the problem is more difficult. Application of thermostromuhrs to the coronaries is required. These devices are difficult to place in a survival preparation, and are so capricious in their functioning in long-term experiments that the most meticulous care is needed if erroneous conclusions are to be avoided. Useful methods for studying human coronary blood flow are not yet available. This is a major lack, inasmuch as there is a strong possibility that species differences may render the application of animal data to the response of the human heart unduly hazardous.

Blood flow through the kidneys has assumed an entirely new importance with the demonstration in recent years that inadequate flows are associated with hypertension and have significance, therefore, beyond their effects on urine formation. Measurement of the effects of the sympathomimetic amines on renal blood flow in animals is fairly simple since in operative experiments the renal vessels can be readily approached; or if survival experiments without anesthesia are necessary, the renal vessels can be made accessible beneath the skin through transplantation experiments. In the human being it appears that the renal circulation will also become subject to direct study, at least in the hands of highly skilled and courageous investigators. The technique has been developed of inserting a long flexible catheter into a vein in the arm and, under guidance of the fluoroscope, passing it up into and through the heart, down the vena cava, and finally introducing the tip of the catheter into the renal vein. By this means venous renal blood can be collected; by comparison with arterial blood which may be obtained from any accessible artery, this renal blood will reveal significant details of renal function, blood flow, etc. The application of this procedure to the study of the sympathomimetic amines may reveal the effect of these compounds on the vascular supply to the kidneys.

BRONCHI

A rather important clinical use of the sympathomimetic amines is in combating asthmatic paroxysms, in which are involved a relaxation of spastic bronchial musculature and probably vasoconstriction of engorged bronchial mucosae. No simple method is available for studying the effects of the sympathomimetic amines on the mucosae, although much may be inferred from vasoconstrictor actions in other areas. There are, however, a number of efficient methods of observing the bronchodilator effects in experimental animals. The simplest, which is extremely useful in orientation and screening tests, is to perfuse the bronchial tree of excised guinea pig lungs with a special perfusion fluid and allow the fluid to escape from the alveoli through numerous superficial scratches on the pleural surfaces. The volume of fluid escaping reflects sharply bronchial constriction or dilation. The guinea pig is especially useful for such studies because it has a highly developed bronchial musculature from which clear-cut responses are more readily elicited than from other experimental animals. A more difficult procedure, but an extremely valuable one, is the Jackson method, which involves recording the changes in the volume of tidal air when the lungs are inflated mechanically. Bronchial constriction results in diminution in air movement in and out of the lungs, which can be antagonized readily by a bronchodilator of the sympathomimetic amine type.

In humans the methods in use are much more limited, the most efficient one being a determination of the vital capacity. If the effects of the bronchodilator are being measured in a patient from whom cooperation in the experimental procedure is possible, then a clear-cut increase in vital capacity can be demonstrated as the



Experimental Setup Employed in Determining the Effect of Sympathomimetics on Blood Pressure and on the Bronchioles

bronchi relax. Unfortunately, since a patient in the middle of an asthmatic paroxysm is not an entirely suitable subject for such a measurement, the observations are often difficult or impossible. The observation of subjective relief from the asthma is of considerable value, as is the disappearance of râles from the chest, although these are not subject to quantitative measurement like the vital capacity.

ANALEPTIC ACTIONS

The recent interest in the use of sympathomimetic amines as stimulants of the central nervous system has brought into prominence the need for measuring quantitatively this type of excitation. Considerable use has been made of measuring spontaneous activity of unanesthetized animals by various devices which record, in some manner, spontaneous movements. Compounds such as amphetamine can be shown to produce tremendous increases in movement in this type of experiment. Apparatus used can consist of cages suspended by springs, which are attached to recording systems, or of cages mounted on balloons connected to air tambours. This kind of setup records the jittery, purposeless type of muscular activity better than other special procedures. Revolving cages, in which the animal dissipates his motor drive by running, can also be used. The sympathomimetic amines apparently cause increases in running movements much more seldom than in the jittery type of activity. That is, they seem to produce a loss of neuromuscular poise rather than an urge for violent exercise. Consequently, experiments in the revolving cages show positive results only when the doses are increased far beyond those needed for the other types of stimulation. Measurements of the excitability of the brain to electrically induced convulsions have not shown a correlation with the excitant effects measured in activity cages. Therefore, it would appear that this former procedure, which is extremely useful in investigating hypnotic, anticonvulsant, or analeptic drugs, is of limited value when applied to these amines. This simply means that the site of the excitant effects of the amines is different from the origin of the electrically induced convulsions.

TISSUE IRRITATION

Improved processes are needed for studying the degree of irritation produced in tissues by the injection of these amines. It is possible, of course, to inject the compound in question and then to study the area histologically by removing a block of affected tissue and determining whether there is cellular injury, inflammation, or other evidence of adverse effects. Such a procedure is obviously not adapted to the study of human tissue reactions. Although the trypan blue test can be used for these purposes, it has special limitations in the present connection. This test consists in the injection of colloidal trypan blue intravenously. In areas where there is abnormal vascular permeability, the colloidal dye escapes through the blood vessel wall into the adjacent tissues and produces a blue stain. The amount of color is proportional to the degree of injury, unless the injury is so severe that blood flow through the area has been impaired. In that case other evidences of inflammatory changes are obvious and the test is still informative. The vasoconstrictor amines, if injected locally into tissues, reduce the blood flow through the area in question to such an extent that staining of the tissues may be prevented and interpretation of the test becomes difficult, if not impossible. However, if the injection of the dye is postponed until after the vasoconstriction has passed off, the test will reveal whether there has been injury to the vascular endothelium.

FUNDAMENTAL MECHANISM OF ACTION

From the fundamental standpoint, studies on the ultimate mechanism of action of the sympathomimetic amines are needed. It appears to be adequately demonstrated that some of the amines act as hormones, penetrating the reactive tissues to induce a physiological response. Others appear not to act by this mechanism, but rather to function as substrate competitors which, by blocking the enzyme systems inactivating epinephrine, permit it to accumulate in the tissues, with resulting physiological response. What the enzyme systems may be that are participating in these effects remains to be definitely ascertained. Many studies have been made of the effects of one enzyme system or another on these amines, but from the quantitative aspect it does not yet seem to have been proved that the systems investigated are the ones involved in the physiological inactivation of these amines. Further exploration of the mechanism of action of these amines may uncover valuable leads in the development of products with special types of activity. For the time being, such studies will probably be most fruitful if they are made on in-vitro enzyme systems, where the reacting elements can be reduced to the simplest possible terms. It is from studies such as these that the ultimately complete understanding of the mechanism of action of these compounds will be derived.

FUTURE RESEARCH

Objectives for future research in this field are manifold because these amines constitute one of the most potent groups of compounds in the therapeutic armamentarium, through their fundamental relation with the sympathetic system. In addition their newly discovered effects on the central nervous system have possibilities of producing profound changes in many functions which may have great therapeutic value.

Specificity of Action. The trend in this field appears to be toward the development of compounds with greater specificity of action. The parent substance, epinephrine, in very low levels of concentration produces many effects throughout the entire body. As a result it is not possible for it to be used to produce one single action without many simultaneous associated side actions, which are at least undesired and may be detrimental. As an example, the value of epinephrine in asthma is limited by the fact that it raises the blood pressure to such a degree that often adequate doses cannot be used without causing too great a circulatory change. In the future, therefore, attention should be directed to determining whether a new compound has some specially strong action in a certain area and may be used with a degree of specificity for that area without inducing profound changes elsewhere at the same time. As an example, desoxyephedrine is such a potent compound for stimulating the central nervous system that it can be used in doses which are fully effective on the brain with almost no side actions on the other parts of the body. Other compounds are being developed which produce the bronchial dilation of epinephrine without the profound circulatory changes and with a minimal degree of central nervous stimulation. Further investigations along these lines cannot help but result in the selection of compounds for specific actions with much greater precision and understanding than heretofore.

New Types of Compounds. The most fruitful method of development of new chemical materials probably will consist in seeking different nuclear structures, since the possibilities of permutations and combinations on the basic formula of epinephrine are fairly well exhausted. It seems unlikely that any major change can be achieved through juggling the epinephrine molecule, although it is entirely possible that improvements in the quantitative sense may arise from such studies. However, if new active nuclei could be developed with or without different types of side chains, there would seem to be a greater prospect of breaking into new ground.

Stability. One of the desiderata is to discover a compound of potency comparable to that of the catechol derivatives but without the inherent instability of this nucleus. The catechols oxidize so readily in the presence of oxygen or of traces of alkali that they suffer from certain limitations of usefulness. If a means of producing a more stable molecule without serious diminution in

potency could be found, it would represent a real advance. This might be accomplished by the development of antioxidants which would prevent the deterioration of catechol. The antioxidants now used, mainly bisulfite, are not entirely suitable because of their irritant properties and the high acidity required for effectiveness. The development of a stabilizing agent for these compounds, which could operate at a neutral pH, would be a definite contribution.

Oral Administration. Associated with the instability of the catechol nucleus is the need for a compound which can be taken orally with full effectiveness. There is a self-limiting factor involved, in that the compounds which are potent vasoconstrictors limit their own absorption by exerting this action on the mucosa of the gut. However, it is possible that members of this family, which are used for actions other than vasoconstriction, may be much more readily absorbed from the gastrointestinal tract if the molecule is adequately stable. Only the phenyl derivatives are absorbed in a reasonably effective manner when taken by mouth. Here the dose required is considerably greater than would be needed if the compound were injected, a fact which indicates incomplete absorption or fairly rapid detoxification.

It is not safe to push the dose of these highly active materials up to the point where effects are secured from oral administration, if the dose required exceeds by too much the effective injected dose. The reason is that, if an excessively large oral dose is needed to produce desired effects, and the patient, because of abnormalities in his gastrointestinal tract, absorbs the compound unusually rapidly or fails to detoxify it at the usual rate, a serious overdose may result and cause severe or even fatal effects. Therefore, to be safe in oral administration, the maximum dose must be one which would not induce serious consequences if it were administered by injection or gained access to the circulation rapidly. This criterion is adequately met in none of these amines except possibly in the phenyl derivatives, where the dose required is higher than is theoretically desirable. The great advantages of oral administration are the ease with which the drug can be taken, the avoidance of the necessity of special sterile preparations, and the prolonged effects ordinarily secured.

Prolonged Action. Lasting results from epinephrine have been sought through other means than oral administration. One of the most recent of these is the creation of a depot of epinephrine in the tissues by injecting into a muscle a suspension or solution of epinephrine in oil. The oil delays absorption of the epinephrine to such an extent that actions persisting for hours may be obtained in favorable cases, and the necessity for repeated injections is thereby avoided. Unfortunately the protective action of the oil is mechanical to a large extent. Consequently, if the injected material spreads out in a thin layer along a fascial plane, a large surface area may be exposed, absorption may take place with undesired rapidity, and severe and dangerous reactions may result in some individuals. This type of phenomenon again emphasizes the fact that the dose used in these depot preparations must be kept down to a quantity which could be tolerated by the patient if it gained access to the circulation all at one time; otherwise, there are dangerous implications in this sort of medication which would possibly make it too hazardous for general use. If, instead of using a mechanical mixture of epinephrine in oil as is done at present, methods are found for getting depot preparations of epinephrine or other amines in which the delay in absorption is achieved in some more positive manner, then the dangers of accidental overdose through too rapid absorption might be less, and this type of medication might become more popular. What are needed for this purpose are probably highly oil-soluble amines of a type not at present available.

Inhalation Solutions. A special way of administering epinephrine in cases of asthma is by inhalation of strong solutions, so that the bronchodilator material is applied almost directly to the affected area. The difficulty with this procedure is that epinephrine is such a vigorous vasoconstrictor that it clamps off the circulation to the mucosae medicated, limits absorption, and gives rise to secondary edema and inflammation. In all probability, the inhalation of strong epinephrine solutions produces irritative reactions in the respiratory tree through this vasoconstriction, particularly when the inhalation is indulged in frequently or in undue amounts. With the development of other bronchodilator compounds in which the vasoconstrictor action may not be so highly developed, there might seem to be a chance of securing a compound which could dilate the bronchial muscle without producing irritation from the vasoconstriction.

However, there is one difficulty. It is uncertain in any given patient how much of the interference in respiration is due to the spasm of the bronchial muscle and how much to secretion or to swelling and edema of the mucosae. In some patients there seems to be evidence that it is the effect of epinephrine in reducing the swelling of the mucosae rather than relaxation of spastic bronchial muscle which gives relief. Therefore, it is conceivable that a compound which is only a bronchodilator might not produce full symptomatic relief in an asthmatic paroxysm where congestion or turgescence played a prominent role. These possibilities require exploration in patients in order to determine whether the pure bronchodilators can be effective in a large enough proportion of patients to make them of clinical value.

Nasal Preparations. Another area of application of the sympathomimetic amines where studies are needed is in the vasoconstrictor solutions used in the nose. These amines can produce a deturgescence of the nasal mucosae, which opens up the nasal passages for easier breathing and may assist in the drainage of blocked sinuses. Of recent years there has been special interest in the use of volatile amines for this purpose. It is not yet clear whether part of the action of the volatile amines is due to alkalinity of the vapors or to the aromatics incorporated in them. Attempts are being made to increase the value of these preparations by incorporating in the vasoconstrictor a drug of the sulfonamide family or occasionally of other types. The sulfonamides are being used as mechanical mixtures in the vasoconstrictor solutions or possibly in molecular combination with the constrictor amine. More potent combinations may be found as research is extended in this field.

Local Anesthesia. In connection with the use of these amines with local anesthetics, there appears to be a field of exploration virtually untouched. Epinephrine, cobefrin, and neosynephrine have been widely used as vasoconstrictors in local anesthetics, but almost none of the other sympathomimetic amines have been applied in this way. Epinephrine has the great disadvantage of causing central excitation and other circulatory changes which the clinician lumps under the general heading of "local anesthetic reactions". In part, these reactions could be obviated by the use of vasoconstrictor substances which do not produce the side effects referable to the constrictor. The possibilities of the other amines, and particularly of the catechol compounds or substances which act similarly to them, have not been adequately explored. These should be restudied with the idea of determining whether adequate vasoconstrictor action might be secured without the present degrees of central stimulation.

The possibility of producing a molecular combination of these vasoconstrictor amines and local anesthetic groups, so that a single compound would have adequate anesthetic power without the necessity of adding a vasoconstrictor, has not been thoroughly investigated. It should be recalled that cocaine is a fairly effective vasoconstrictor, which probably accounts for part of its duration of action. If the vasoconstrictor amines could be used as the basis for the development of a new local anesthetic, more efficient local anesthesia might be secured. Against this is the possibility that such a product might not be so useful as it would appear at first glance, because under varied practical conditions the amount of vasoconstriction desired might differ in a manner unrelated to the degree of anesthesia needed. Therefore, until an effective compound of this type has been de-

veloped, it is impossible to be sure whether this theoretical objective would have any practical value.

With the new interest in spinal anesthesia, the question arises as to whether the vasoconstrictor amines may be used in continuous caudal or other types of prolonged spinal anesthesia. It is possible that an amine which is suitable for use in local anesthesia of subcutaneous tissue might not be the ideal preparation for injection into the spinal canal where rate of removal, protein content, and related factors are not the same as elsewhere. Experiments designed to discover the amount of irritation produced by such solutions seem necessary, so that, if there is any evidence of undue irritation, attention can be directed to the development of an amine preparation with minimum adverse effects.

Circulatory Stimulation. The fact that some of these amines may increase the blood pressure without a corresponding increase in cardiac output or blood flow has been mentioned previously. There are clinical situations in which an increase in systolic pressure imposes a strain on the cardiac muscle and thereby intensifies the collapse state instead of improving it. Therefore, it would seem to be desirable to investigate the sympathomimetic amines which do not raise systolic pressure in order to determine whether there is a compound which can increase cardiac output to a useful degree without imposing a burden of extra work on a weakened myocardium. The possibilities of a compound which reduces the main arterial pressure while it increases the stroke volume and the heart rate have already been pointed out. This compound would combine in a general way the augmentor effects of epinephrine with the vasodilator actions of the nitrites, so that the effect would be an increased movement of blood at a lower average peripheral resistance. Doubtless other compounds of this general type can be discovered, which may prove to be of greater value than epinephrine as systemic circulatory stimulants.

Gastrointestinal Tract. An almost untouched field of exploration of the amines is their use in modifying the activity of the gastrointestinal tract and particularly in the control of obesity. Spasm of the gut can be diminished with the use of these compounds. It is not so commonly realized, however, that peristalsis also is slowed down and the force of contraction diminished. There is an important group of obese patients who overeat because they have strong and vigorous hunger contractions of the stomach, resulting in appetites beyond their physiological needs. In such individuals the use of a sympathomimetic amine which will diminish the peristaltic activity of the stomach may well cut down their appetite to the point where effective reduction of body weight can be secured. These amines cannot serve as a panacea for obesity because there are many causes for this condition beside that of excessive appetite; but in that special group of patients who retain the vigorous hunger contractions of childhood in their adult years and thereby are led to eat to excess, the administration of some orally absorbable sympathomimetic amine, such as amphetamine or propadrine, may be a therapeutic measure of value.

Central Nervous System. Finally, the use of the sympathomimetic amines as stimulants for the central nervous system must be considered. Two such compounds, amphetamine and desoxyephedrine, are at present used for this purpose. The stimulation produced apparently consists in a heightening of the speed of intellectual processes and a diminution in the awareness of fatigue with no definite alteration of motor function. The main clinical applications of these reactions are in overcoming narcolepsy, in postponing the physiological need for sleep, and as a general "pick-me-up" in conditions of depression after alcoholic excesses or in the depressed states of some psychoses. For these purposes desoxyephedrine has a potency adequate for central stimulation with very little secondary effects elsewhere in the body. The fact that these amines can produce stimulation of such a specialized type in the brain tissue indicates the probability that other areas of stimulation in the brain might be uncovered from other amines of related composition. It is conceivable that stimulants for the medulla and cortex of the brain might be developed which would be of therapeutic value comparable to that of the present amines. Certainly these possibilities should be explored in all new compounds tested, since this is a field of application which has been only lightly touched up to the present time.

Production Department Where Solutions Are Prepared, Cartridge Glass Is Processed, Rubber Diaphragms and Plungers Are Made Ready, and Cartridges Are Filled and Packed for Shipment

Relation of Structure to Deamination of SYMPATHOMIMETIC AMINES

KARL H. BEYER AND HELEN S. MORRISON

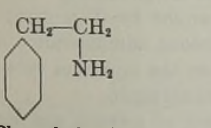
Sharp and Dohme, Inc., Glenolden, Pa.

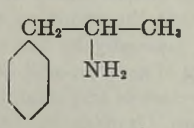
—a classification of sympathomimetic agents is outlined, together with a cursory survey of their modes of inactivation. The relation of structure to the deamination of these compounds by amine oxidase is presented in some detail. The significance of these findings from a pharmacodynamic standpoint, together with a consideration of the role of this enzyme in the etiology of hypertension, is discussed very briefly here.

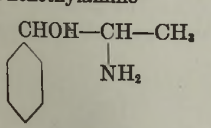
FROM both a pharmacological and clinical standpoint, it is of great importance that we have as complete a knowledge of the dynamic effect of a compound or group of compounds on bodily functions as it is possible to obtain. From a physiological standpoint, the more we know of the disposition that the body makes of a chemical, the greater is our understanding of, and ability to interpret, certain pharmacodynamic characteristics attributable to it. Health and disease may influence differently both the effect of the compound on the body and the effect of the organism on the compound.

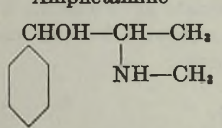
It is customary to group under the heading of sympathomimetic (pressor) amines a large number of compounds which, for our own convenience in studying their metabolization, we have classified as follows:

PHENETHYLAMINE AND DERIVATIVES. This class properly includes


Phenethylamine

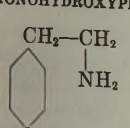

Amphetamine

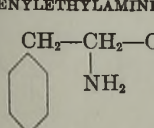

Propadrine

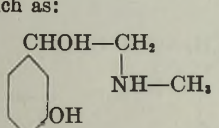

Ephedrine

and many related compounds, the deamination of which will be discussed in considerable detail.

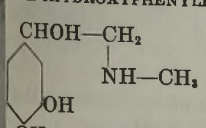
MONOHYDROXYPHENYLETHYLAMINES, such as:

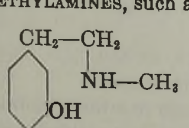

Tyramine

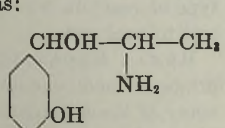

Paredrine


Neosynephrine

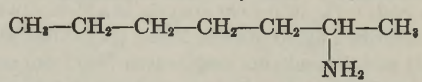
DIHYDROXYPHENYLETHYLAMINES, such as:


Epinephrine

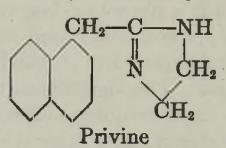

Epinine


Cobefrin

LONG-CHAIN ALIPHATIC AMINES, such as 2-aminoheptane:



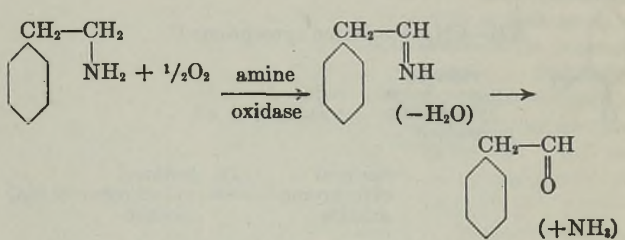
HETEROCYCLIC COMPOUNDS, particularly imidazolines:


Privine

SYSTEMS CAPABLE OF DESTROYING AMINES

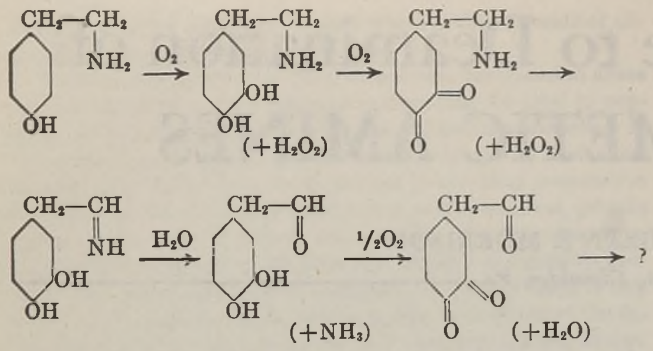
Since so many compounds of the above series have been synthesized, they lend themselves admirably to a critical evaluation of both the factors of different modes of elimination and the relation of structure to rate of inactivation by any particular system. K. H. Beyer and other investigators have described and studied several systems capable of bringing about the destruction of these compounds. They may be listed as follows, though it will not be feasible to discuss each in detail or to make the list comprehensive.

AMINE OXIDASE, or tyraminase, was first described by Hare (*25*) and partially purified by Kohn (*28*). This enzyme is capable of deaminating phenethylamine, certain of its derivatives, and a few aliphatic amines according to the following equation:



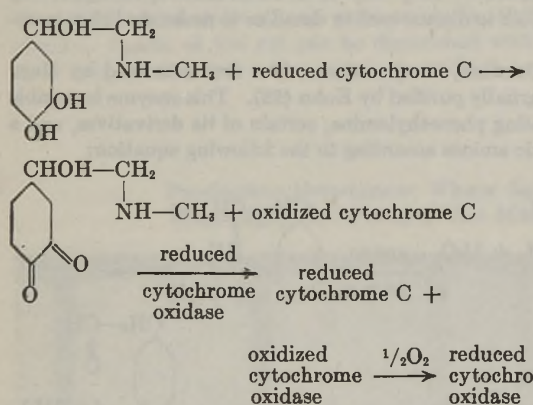
It is fairly widely distributed throughout the mammalian organism (*15*) but is probably concentrated to the greatest extent in the liver and kidneys. For the present it cannot be isolated in any great degree of purity and is most conveniently worked with by using tissue homogenates. Since the enzyme is relatively insensitive to cyanide, iron-catalyzed tissue respiration usually is abolished in the homogenates by the use of this agent.

PHENOL OXIDASE, tyrosinase, or catechol oxidase are terms used for what is undoubtedly a group of mono- and dihydroxy phenolases that are capable in varying degrees of oxidizing tyrosine, tyramine, and also compounds having a catechol nucleus. Bertrand in 1907 (*4*) was the first to describe the action of this enzyme on tyrosine. In the presence of this enzyme an atom of oxygen is introduced into the molecule on a carbon atom adjacent to the one bearing the hydroxyl group. The reaction goes on to the formation of a melanin, the first steps in the reaction probably being as follows:



Various methods for isolating the enzyme in a highly purified state have been described by Keilin and Mann (*27*), Alles, Blohm, and Saunders (*1*) and Tenenbaum and Jensen (*38*) from mushrooms, and by Kubowitz (*29*) and Dalton, Nelson, and associates (*23*) from potatoes. Despite the earlier work of Bloch (*18*) and of Pugh (*33*), claims that a phenol oxidase exists in mammalian tissues probably have not been adequately substantiated unless the recent reports by Cadden and Dill (*19*) and Hageboom and Adams (*24*) prove otherwise. The significance of such an enzyme in mammalian tissues has been questioned by Bhagvat and Richter (*16*). Perhaps the closest other approach, phylogenetically, has been the demonstration of such an enzyme in the wing feathers of birds by Charles and Rowles (*20*, *21*). This lack of an equivocal demonstration of a phenolase in mammalian tissues is a serious objection to accepting certain theories of hypertension.

Cytochrome System. Keilin and Hartree (*26*) showed that reduced cytochrome C could oxidize the ring structure of epinephrine in vitro. This we have substantiated for epinephrine, epinine, and cobefrin (*9*). The abbreviated course of the reaction is probably as follows:



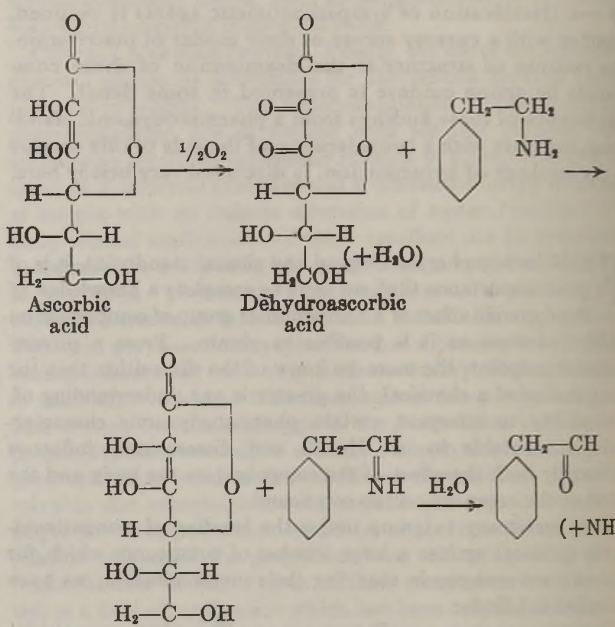
However, the in vivo significance of these results is questionable. Hydroquinone, catechol, and homogentisic acid, which are readily oxidized by cytochrome C in vitro, escape this oxidation in vivo and appear in the urine as such or in a conjugated form.

Conjugation of Catechol Nucleus of epinephrine, corbasil, and epinine, presumably with sulfuric acid, was described by Richter (*36*) and substantiated by Richter and MacIntosh (*37*). It has been reported that an enzyme, sulfosynthase, was responsible for this effect, and some evidence for the conjugation with sulfuric acid has come from the work of Torda (*39*) and of Arnolt and de Meio (*2*). Bernheim and Bernheim recently reported that the abilities to oxidize, deaminate, or conjugate tyramine, tyrosine, or phenol are variously and independently resident in different body tissues but that all these processes are aerobic, in vitro (*3*). Beyer and Shapiro (*11*) modified Richter's method to make it quantitative, and found that about 83 and 71% of an oral dose of epinine and cobefrin, respectively, appeared in conjugated form in the urine of man.

Beyer and Stutzman presented a preliminary report (*13*) to the effect that, although apparently not active, when given by mouth tyramine and paredrine appeared in the urine of man in what seemed to be the form in which they were administered. This work has been continued and will be published later.

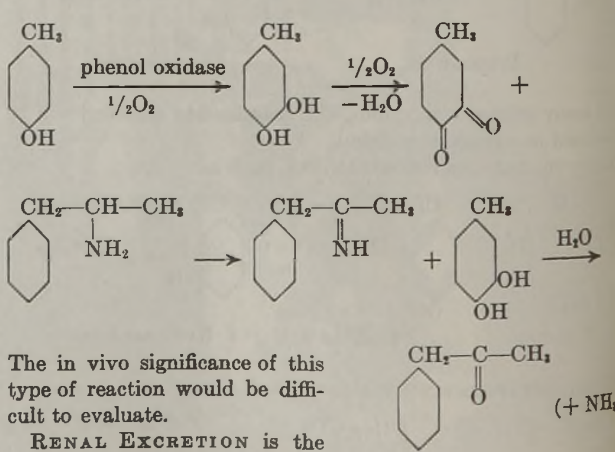
Other modes of inactivation or elimination of these compounds have been described.

Ascorbic Acid–Dehydroascorbic Acid System has been shown to deaminate a number of the sympathomimetic amines of the first group in vitro (*8*). The proposed course of this reaction is as follows:



This was substantiated in vivo for amphetamine when it was found that the excretion of the amine by dogs could be depressed markedly by the subcutaneous administration of large amounts of ascorbic acid (*7*). When the injections were ceased, the excretion of amphetamine increased again.

Phenol Oxidase in the presence of *p*-cresol was shown to deaminate amphetamine in vitro (*7*). The following equation was suggested for the reactions leading to the production of ammonia:



The in vivo significance of this type of reaction would be difficult to evaluate.

Renal Excretion is the principal mode of elimination of many of these compounds in either the free or conjugated state. Much of this work was made possible by the development of the test described by Beyer and Skinner (*5*, *12*), later used by Beyer

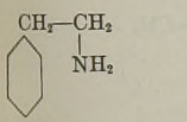
and Lee (*10*), and modified by Beyer and Stutzman (*14*). The test for the conjugated form of epinephrine, cobefrin, and epinine by Richter (*36*) and modified by Beyer and Shapiro (*11*) has permitted the study of this phase of the metabolization of these compounds.

EXPERIMENTAL METHODS

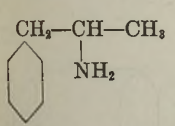
The purpose of this review is first to present an over-all summary of the modes of metabolization of this broad group of compounds and then to consider in more detail the relation of molecular configuration to their deamination. It is thus possible to limit the discussion and yet present the pertinent points in the evaluation of the other methods for inactivation as well.

The procedures for this research have been described in detail elsewhere. A liver homogenate containing amine oxidase and the conventional Warburg apparatus were used to study the rate of oxidative deamination of these agents in the presence of cyanide, which inactivates the iron- and copper-catalyzed systems and serves to fix the aldehyde formed (*17*). Where deamination of the compounds by the ascorbic-dehydroascorbic acid system or by the phenolase–*p*-cresol system was studied, the actual amount of ammonia produced was measured (*7*). The urinary recovery of the compounds was carried out by the methods considered in the paragraph on renal excretion.

It is convenient first to consider certain differences in the pharmacodynamic effect of phenethylamine and β-phenylisopropylamine (amphetamine) that may be related to their metabolization:



Phenethylamine



β-Phenylisopropylamine (amphetamine)

When phenethylamine and amphetamine are separately injected into an anesthetized or decerebrated dog, whose blood pressure is being continuously recorded manometrically on a kymograph, the order of magnitude of the pressor ratios to epinephrine is similar for the two compounds, although amphetamine has a somewhat greater pressor effect. Much more striking, however, is the fact that the duration of the pressor response to an injection of amphetamine is many times greater than for phenethylamine, an observation that indicates a fundamental difference in their metabolization. Other reports substantiate this conclusion. In 1929 Chen, Wu, and Hendriksen (*22*) reported a comprehensive study of this series of compounds, from which they concluded that the isopropylamine side chain was essential for the oral efficacy of these amines. The following year Piness, Miller, and Alles (*31*) similarly concluded that the presence of the α-methyl group in amphetamine and ephedrine was particularly responsible for the duration of action and effectiveness of these compounds when administered subcutaneously or orally, as compared with the corresponding compounds not having the α-methyl group. It was also found that amphetamine, administered orally, produced an elevation of the metabolic rate of man, dogs, and rats that persisted for several hours (*30*).

Considering the evidence presented above, it seemed likely that, whereas phenethylamine probably was deaminated in the body, phenylisopropylamine probably was excreted in large measure as such and inactivated in the body only to a slight degree, if at all. That this was so was demonstrated conclusively in this country by Beyer and Skinner (*12*) and in England by Richter (*35*) at about the same time, but by the application of different and new analytical methods. However, the former authors found that, whereas both patients and dogs normally did not excrete all of the compound, the dogs could be made to do so by the administration of a hepatotoxin, carbon tetrachloride. These experiments indicated that, while excretion was the principal mode of elimination of the compound, it was not the only one. Phenethylamine has been shown not to be excreted normally by man or dogs.

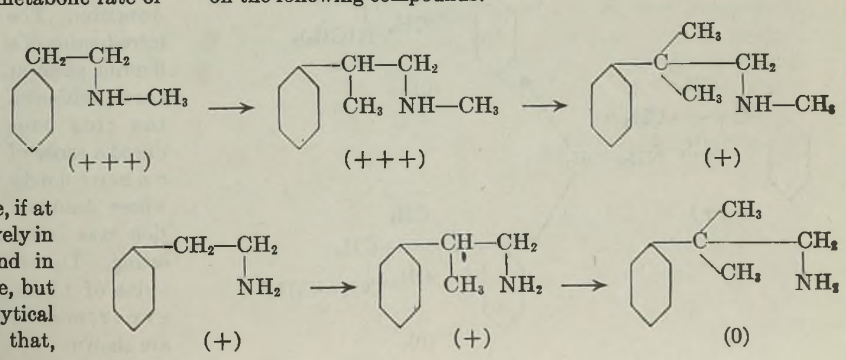
The reports of Blaschko, Richter, and Schlossman (*17*), of Pugh and Quastel (*34*), and our own experience (*12*) have demonstrated that amphetamine is not deaminated by amine oxidase, whereas phenethylamine is deaminated in vitro, although not so readily as some other compounds. There can be little doubt that the presence of the α-carbon atom in amphetamine is in some way responsible for its refractoriness to deamination by amine oxidase. This was shown by in vitro experiments using the isomers, β-phenylpropylamine, β-phenylisopropylamine, and γ-phenylpropylamine. The rate of oxygen uptake attributable to oxidative deamination of the compounds by liver homogenate and slices (*6*) was measured manometrically. Both β- and γ-phenylpropylamine were readily deaminated, whereas β-phenylisopropylamine was not deaminated. These results were later substantiated in dogs by Beyer and Lee (*10*), for neither β- nor γ-phenylpropylamine was excreted normally. However, the animals could be made to excrete the amines by use of the hepatotoxins, carbon tetrachloride and hydrazine.

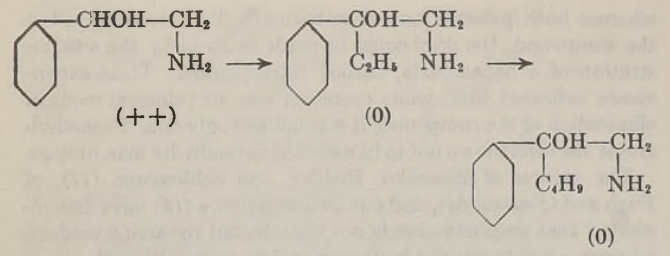
To date, the most probable explanation for the inactivation of that fraction of amphetamine that is not normally excreted lies in experiments involving ascorbic-dehydroascorbic acid systems. When air was bubbled through a solution of ascorbic acid and any of the phenylpropylamines previously discussed, buffered at pH 7.0, the compounds were deaminated (*8*). When large amounts of ascorbic acid were administered to dogs receiving daily injections of phenylisopropylamine, the excretion of the amine was markedly diminished as long as the daily injections of ascorbic acid were continued. The excretion of the amine increased again when the injection of ascorbic acid was stopped (*7*). These experiments offer evidence that the functioning of this system in deamination is significant, physiologically.

DEAMINATION EXPERIMENTS

To compare the rates of deamination of these compounds quantitatively, it was found best to group them according to the type of comparison to be noted, and to include in each group a reference compound that was deaminated readily in the presence of the enzyme, to serve as a check on the procedure. Ordinarily tyramine was used for this purpose instead of phenethylamine, because the former is a satisfactory reference compound and the deamination of the latter is not always dependable. However none of the substituted phenethylamines was deaminated so rapidly as tyramine. To simplify the correlation of structure with rate of deamination, the compounds are grouped according to individual specific types of substitution. A large part of this research has not been reported previously.

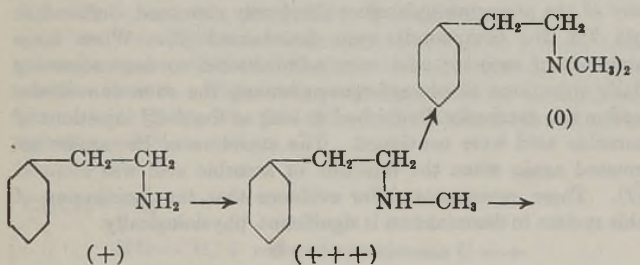
ALKYL SUBSTITUTION. The effect of single and double alkyl substitutions on the β-carbon atom of the side chain was studied on the following compounds:

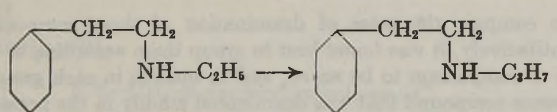


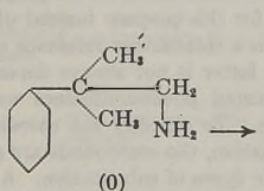


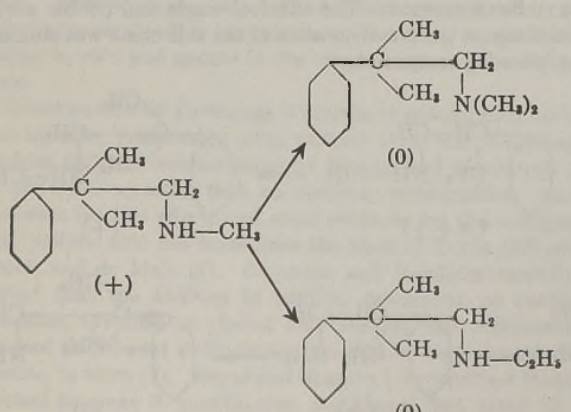
The presence and absence of deamination are indicated by + and 0. +++ indicates a rate of deamination almost as great as tyramine, to which a ++++ value should be assigned; ++ means approximately half as rapid deamination as tyramine; + slowly deaminated, and 0 not deaminated to a measurable extent in 2 hours or longer. Figure 1 serves to clarify these arbitrary values. In general, when a single methyl group was substituted for hydrogen on the β-carbon atom, there was no appreciable alteration in the rate of deamination of the parent compound, except possibly in the case of the methylamino series. Both the addition of a single longer chain or the addition of two methyl groups in this position markedly decreased the rate or abolished deamination of the compounds.

The effect of alkyl substitutions on the amino nitrogen of the side chain was studied on the following compounds:





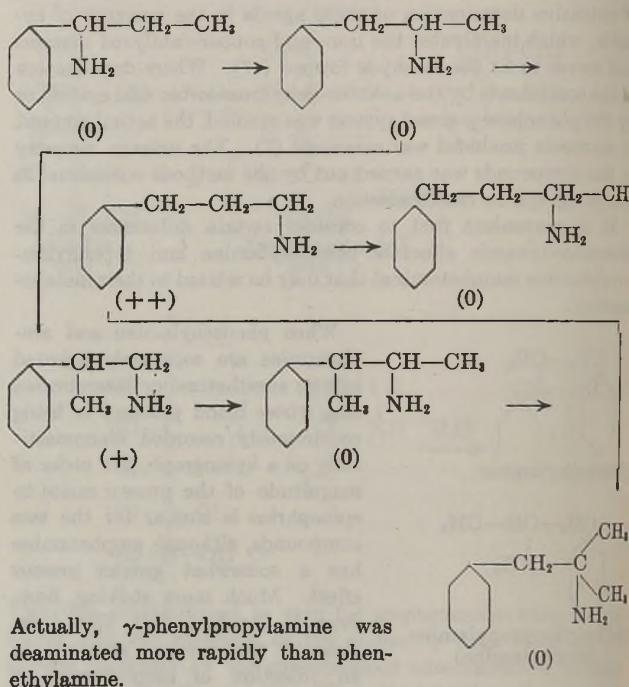




The secondary methylamino compounds were more rapidly deaminated than the primary amines in the series. However, when the length of the alkyl group on the nitrogen increased, or when both hydrogens were substituted by methyl groups deamination of the compounds did not occur.

Hydroxyl Substitution. The substitution of a hydroxyl group on the β-carbon atom increased the rate of deamination for phenylethanolamine to a greater extent than for β-methylphenethylamine.

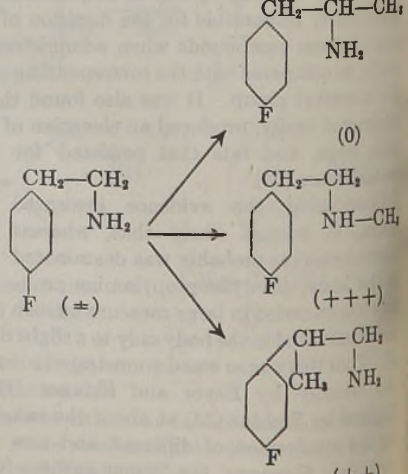
Amino Change. Shifting the position of the amino group on the side chain was always attended by complete inhibition of deamination when that group was not attached to the terminal carbon atom. This has been demonstrated for the following among numerous other compounds:



Actually, γ-phenylpropylamine was deaminated more rapidly than phenethylamine.

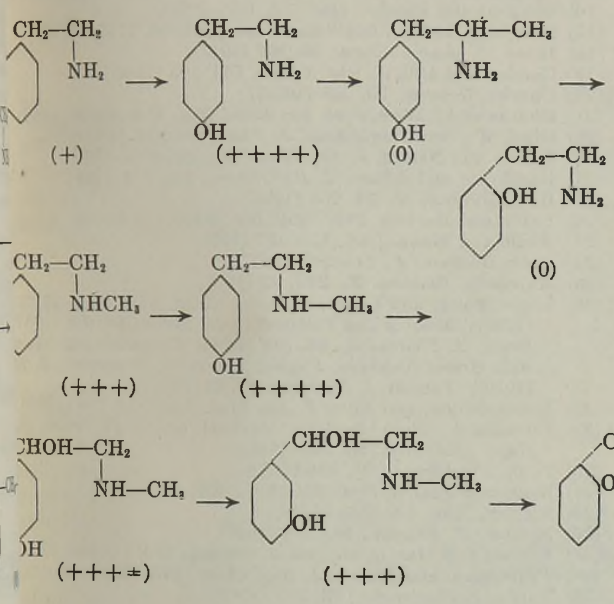
Methyl Substitution. Substitution of one or two methyl groups into the aromatic nucleus did not seem to influence the rate of deamination which might have been expected for the compounds as judged by the character of the side chain thus: β-(2,4-dimethylphenyl)-β-methylethylamine was deaminated at about the same rate as the similar compound, β-methylphenethylamine, having no aromatic substitutions. β-(2-methylphenyl)-isopropylamine was not deaminated.

Fluorine Addition. The introduction of a fluorine atom at the *p*-position on the ring produced a series of compounds whose deamination was interesting. The results of these experiments are shown:



It was rather unexpected that the fluorine atom in the *p*-position on the ring did not influence the rate of deamination materially as compared with the corresponding compounds which had no aromatic substitutions and which were deaminated except in the case of the parent compound. While no oxidative deamination of *p*-fluorophenethylamine has been observed, we have hesitated to designate its rate of deamination as 0. Both *p*-fluorophenethylamine and *p*-fluorophenylisopropylamine competed with tyramine for the amine oxidase system and so impeded the deamination of the latter compound, when both the fluoro and the hydroxy substrates were present in equimolar concentrations.

Hydroxyl Addition. The effect of adding a hydroxyl group in the *p*-position on the ring was to increase markedly the rate of deamination of the compound as compared to the corresponding compounds having no aromatic substitution. Also, as the hydroxyl group was shifted from the para to the ortho position, the rate of deamination was markedly or completely inhibited:



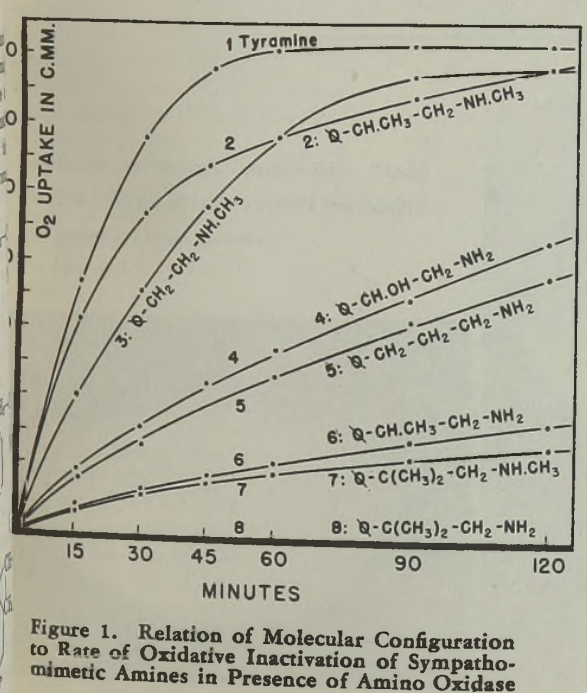
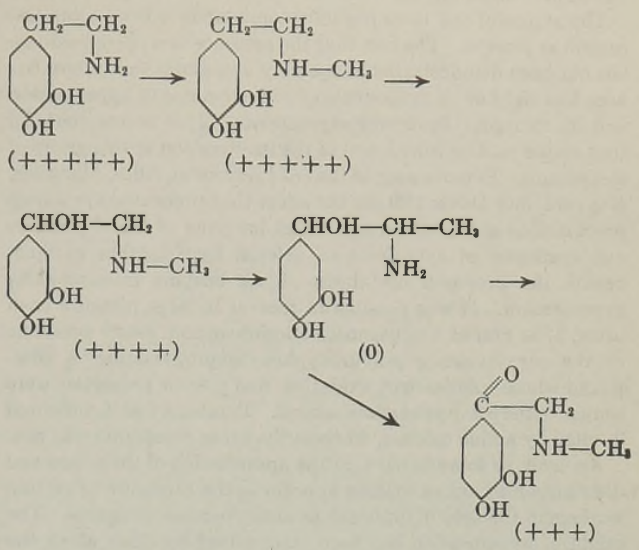


Figure 1. Relation of Molecular Configuration to Rate of Oxidative Inactivation of Sympathomimetic Amines in Presence of Amino Oxidase

Catechol Derivatives. The catechol derivatives of phenethylamines were the most rapidly deaminated of the compounds investigated:



The effect of the catechol nucleus was depressed slightly by the presence of a hydroxyl group in the side chain and, to a greater extent, by the presence of a ketone in the β-position on the side chain. Actually, autoxidation may have complicated these results, for the over-all oxygen uptake was slightly greater than theoretical for the replacement of the amino group by one atom of oxygen.

Long-Chain Aliphatic Amines. These compounds were not deaminated by the amine oxidase, whether or not the amino group was on the terminal carbon atom. 1-Aminoheptane and 2-aminoheptane were used in these studies. However, the compounds did not depress the respiration of liver homogenates to which no cyanide was added.

2-Naphthylmethylimidazoline. This imidazoline was not oxidized by the liver homogenates, judging by the absence of an increased oxygen uptake. However, this compound did decrease the respiration of liver homogenates significantly. This same phenomenon frequently has been observed under these conditions when a compound not deaminated by these preparations, such as phenylisopropylamine, was added to the homogenate. The molar concentrations and procedure for studying both this compound and the aliphatic amines were the same as those obtained in the other experiments except for the omission of cyanide in some cases.

DISCUSSION

A few salient points may be considered to warrant reiteration and elucidation. There is good correlation between deamination of phenethylamine derivatives, their pressor activity, duration of action, oral efficacy, and excretion as such. This has been worked out thoroughly for the compounds having no double or long-chain alkyl substitutions on either the β-carbon atom or the amino group. The effect of the fluoro substitution in the ring has not been studied to an extent that permits the making of such correlations at this time.

It is true that the mono- and dihydroxyphenyl compounds belonging to this group are the most actively deaminated by amine oxidase in vitro. However we are not in a position to state that this is the principal or even an important factor in the inactivation of these compounds in vivo. The fact that such a

large percentage of a given dose of the catechol derivatives appears in the urine in a conjugated form, irrespective of whether the molecule is deaminated in vitro, warrants considerable reservation in transposing these in vitro results to the intact animal.

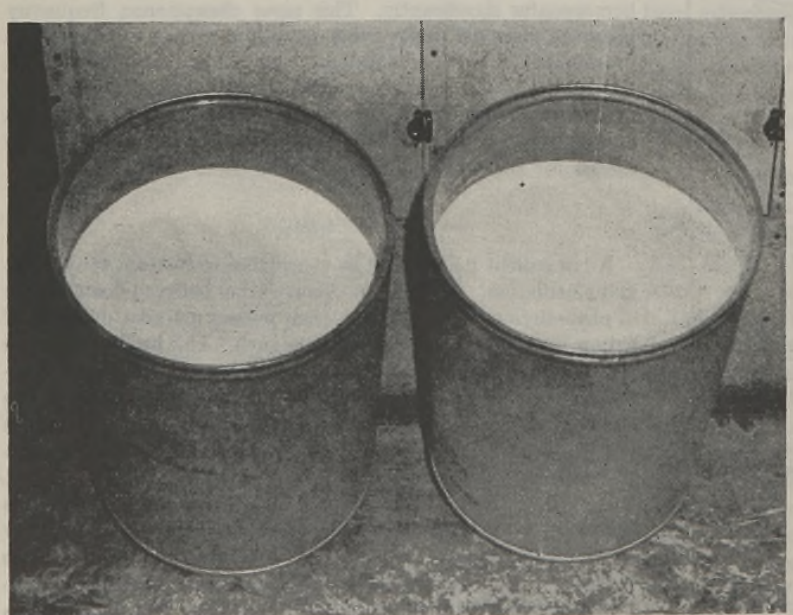
The status of the monophenolic compounds is even more uncertain at present. The fact that the presence of a phenol oxidase has not been demonstrated adequately in mammalian tissues has been lost sight of by proponents of some theories of hypertension and its therapy. From our experiments (*11*) it seems doubtful that amine oxidase functioned in the inactivation of this group of compounds. Reports such as that of Prinzmetal, Alles, Margoles, Kayland, and Davis (*32*), to the effect that preheated tyrosinase preparations can produce significant lowering of blood pressure and remission of symptoms of arterial hypertension in man, negate the proposed usefulness of the enzyme in combating hypertension. It was possible to recover in large measure from urine, after oral or subcutaneous administration, either tyramine or the corresponding *p*-hydroxyphenylisopropylamine, a compound whose colorimetric, oxidative, and pressor properties were similar to the compound administered. Tyramine was deaminated in vitro by amine oxidase, whereas the other compound was not.

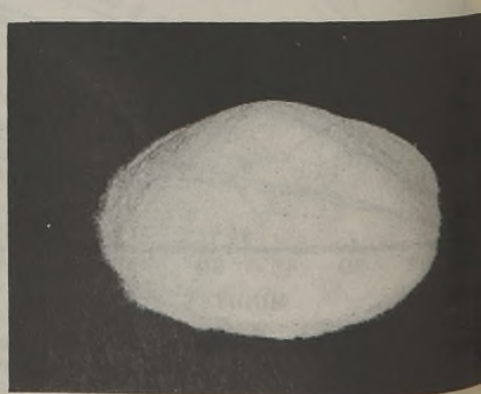
An error, or so we believe, in the appreciation of the action and distribution of amine oxidase appears in the literature of certain workers in the field of quinones as antihypertensive agents. The origin of hypertension has been rationalized by them along the lines that decarboxylation of tyrosine can occur in the ischemic kidney; but since amine oxidase is an oxidative enzyme, it cannot function properly in deaminating the resulting tyramine under conditions of reduced oxygen tension. Consequently, a pressor agent is released by the kidney that is capable of being inactivated by certain quinones. Such an hypothesis overlooks the fact that, even if such a pressor compound, susceptible to deamination by amine oxidase, were released by the kidneys, the enzyme is so widespread in mammalian tissue that it is unlikely the compound could persist long in the body. We point out again that liver is a most satisfactory source of amine oxidase for experimental purposes. There are other reasons for believing that tyramine or even epinephrine is not the agent responsible for hypertension, but these are beyond the scope of this review.

The fact that the long-chain aliphatic amines are not deaminated even in the instance where the amino group is on the terminal carbon atom is an interesting observation. The metabolism of both this type of compound and the imidazolines is the most part, unknown. We do know that neither compo was found to undergo decomposition involving the uptak oxygen in vitro in the presence of liver homogenate.

LITERATURE CITED

(1) Alles, Blohm, and Saunders, *J. Biol. Chem.*, 144, 757 (194
(2) Arnolt and de Meio, *Rev. soc. argentina biol.*, 17, 571 (1941)
(3) Bernheim and Bernheim, *J. Biol. Chem.*, 153, 369 (1944).
(4) Bertrand, *Compt. rend.*, 145, 1352 (1907).
(5) Beyer, *J. Am. Chem. Soc.*, 64, 1318 (1942).
(6) Beyer, *J. Pharmacol*, 71, 151 (1941).
(7) *Ibid.*, 71, 394 (1941).
(8) *Ibid.*, 76, 149 (1942).
(9) Beyer, unpublished data.
(10) Beyer and Lee, *J. Pharmacol*, 74, 155 (1942).
(11) Beyer and Shapiro, to be published.
(12) Beyer and Skinner, *J. Pharmacol.*, 68, 419 (1940).
(13) Beyer and Stutzman, *Proc. Fed. Am. Soc. Exptl. Biol.*, (1943).
(14) Beyer and Stutzman, to be published.
(15) Bhagvat, Blaschko, and Richter, *Biochem. J.*, 33, 1338 (193
(16) Bhagvat and Richter, *Ibid.*, 32, 1397 (1938).
(17) Blaschko, Richter, and Schlossman, *Ibid.*, 31, 2187 (1937).
(18) Bloch, *Z. physiol. Chem.*, 98, 226 (1917).
(19) Cadden and Dill, *J. Biol. Chem.*, 143, 105 (1942).
(20) Charles, *Genetics*, 23, 523 (1938).
(21) Charles and Rawles, *Proc. Soc. Exptl. Biol. Med.*, 43, 55 (194
(22) Chen, Wu, and Hendriksen, *J. Pharmacol.*, 36, 363 (1929).
(23) Dalton and Nelson, *J. Am. Chem. Soc.*, 60, 3085 (1938).
(24) Hageboom and Adams, *J. Biol. Chem.*, 145, 273 (1942).
(25) Hare, *Biochem. J.*, 22, 968 (1928).
(26) Keilin and Hartree, *Proc. Roy. Soc.*, B125, 171 (1938).
(27) Keilin and Mann, *Ibid.*, 125, 187 (1938).
(28) Kohn *Biochem. J.*, 31, 1693 (1937).
(29) Kubowitz, *Biochem. Z.*, 299, 32 (1938).
(30) Lagen, Soley, and Leake, *Proc. Soc. Exptl. Biol. Med.*, 35, (1936); Molitch and Poliakoff, *Arch. Pediat.*, 54, 683 (193 Beyer, *J. Pharmacol.*, 66, 318 (1939); Delaunois and Ma *Acta Brevia Neerland. Physiol. Pharmacol. Microbiol.*, 9, (1939); Tainter, *J. Nutrition*, 27, 89 (1944).
(31) Piness, Miller, and Alles, *J. Am. Med. Assoc.*, 94, 790 (1930)
(32) Prinzmetal, Alles, Margoles, Kayland, and Davis, *Proc. Exptl. Biol. Med.*, 50, 288 (1942).
(33) Pugh, *Biochem. J.*, 27, 476 (1933).
(34) Pugh and Quastel, *Ibid.*, 31, 2306 (1937).
(35) Richter, *Ibid.*, 32, 1763 (1938).
(36) Richter, *J. Physiol.*, 98, 361 (1940).
(37) Richter and MacIntosh, *Am. J. Physiol.*, 135, 1 (1941).
(38) Tenenbaum and Jensen, *J. Biol. Chem.*, 145, 293 (1942).
(39) Torda. *J. Pharmacol.*, 78, 331 (1943).





(*Left*) 150-Pound Drums of Synthetic Ephedrine Hydrochloride (Shown below)

Courtesy, Merck & Company, Inc.

PHENYL PROPYL AND PHENYL ISOPROPYL AMINES

Changes in Pharmacological Action on Substitution of Phenyl Nucleus and Amino Nitrogen

BOYD E. GRAHAM, GEORGE F. CARTLAND, AND E. H. WOODRUFF

The Upjohn Company, Kalamazoo, Mich.

By—the toxicity, pressor, and bronchodilator activities of a group of phenyl propyl amines and of phenyl isopropyl amines have been determined. The changes in these properties resulting from five changes in chemical structure are examined. Definite expectations as to the results of these changes are indicated for the pressor activity in four instances, and in three instances for the toxicity and bronchodilator activity. There is no correlation between any one structural change and all three of the pharmacological activities. More methoxy derivatives possess activity than previous work would indicate.

THE question of variation in pharmacological or bacteriological activity with changes in chemical structure is always of interest to the student of chemotherapy. Great differences in pharmacological activity may result from such slight changes in configuration that the chemical and physical properties differ only slightly from the original material. This makes it hazardous to predict the relation between structure and activity even when only one property is to be followed through a single series of compounds. When a substance may exhibit several types of activity, the problem becomes more complicated.

Examination of the activity of any series of compounds usually has as one object, the finding of substances that appear to have sufficient value to warrant more detailed investigation. If a large number of substances are involved, this preliminary "screening" consists of subjecting these chemical compounds to a few chosen tests. The data obtained may then be examined to see if the properties of unknown substances may be predicted, as if by a periodic table. It is the results of such a procedure that are to be examined, to see what may be "expected" in the way of changes in activity with changes in chemical structure.

Amines having the β-phenethylamine skeleton differ in pharmacological properties from those that do not. The effect of the introduction of various groups into the molecule has been studied extensively, with special emphasis on the pressor effect, but the over-all picture of the changes is still lacking. This paper summarizes the results of three pharmacological tests on a group of seventy-five methoxy and hydroxy phenyl propyl and phenyl isopropyl amines. Since all of the compounds have been synthesized and tested by this laboratory, in the interest of brevity no reference will be made to the work done by others, either in the series under discussion or in related series.

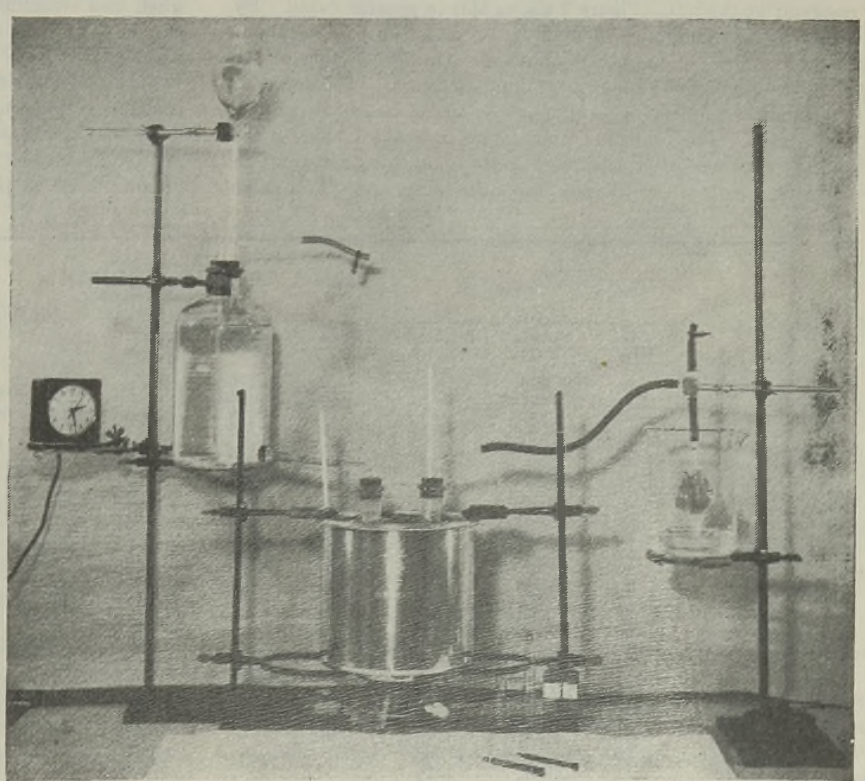
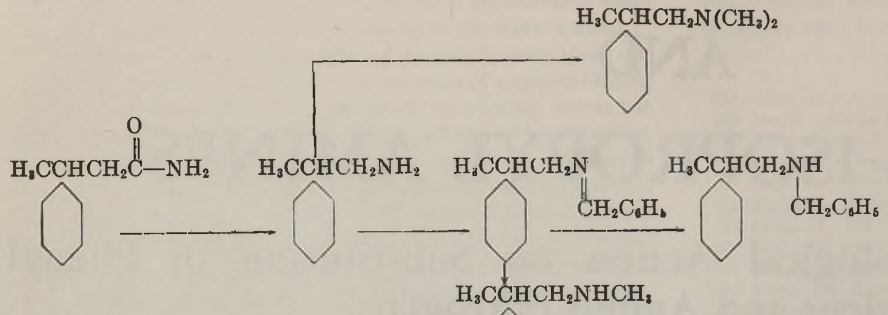


Figure 1. Equipment for Determination of Bronchodilator Rating

The preparation of the *n*-propyl amines was accomplished by the following procedure:



The preparation of the isopropyl amines differs only in the structure of the starting amide. Chemical data on the compounds under discussion appear in the literature (*2*, *3*, *5–9*).

ACTIONS TESTED

The pharmacological tests chosen were the toxicity, pressor, and bronchodilator actions. Toxicity as determined is the dose (contained in 0.5 to 1.5 cc. of solution injected intravenously at the rate of 0.25 cc. per minute into male white rats weighing between 200 and 300 grams) that will kill 50% of the animals. The pressor effect was determined by the U.S.P. procedure for epinephrine. The values reported are the fractional effectiveness of equipressor doses compared to epinephrine as unity. On account of tachyphylaxis only one determination could be made per dog. The bronchodilator effect is a measure of the relaxing effect upon the bronchial musculature of an isolated rabbit lung following constriction by a chemical agent. In this work the procedure of Sollmann and von Oettingen (*1*, *4*) was used with pilocarpine as the constricting agent. The values in Table I are proportional to the increased rate of flow through the lung. As the liquid flows through the lung shown at the right in Figure 1, air enters the reservoir at the left. Figure 2 shows this in greater detail. By adjusting the difference in fluid level, an initial rate of about thirty bubbles per minute is obtained. On constriction of the lung, the number of bubbles per minute decreases. The amine to be examined is injected; if it is active, an increased rate of flow is observed. The bronchodilator values in Table I refer to the average increase in bubbles per minute upon injection of a 0.5- and 1-cc. dose of a 1 to 100 dilution of the compound. This value is absolute, and we have refrained from giving it as a ratio compared to substances not in this series. The results can be used to compare the effectiveness among the compounds given.

COMPARISON OF CHEMICAL CHANGE WITH ACTIVITY

Many comparisons are possible with the data at hand. Many are either inconclusive, lack a sufficient number of compounds, or require excessive explanation. The comparison between five different structural changes and the three pharmacological properties are collected from Table I and listed in Table II. From these we may find some answer as to what may be expected.

The first structural difference tabulated is that of the position of a methyl group introduced in the ethylamine side chain. It can be so placed as to give either an *n*-propyl or an isopropyl amine. The data show that the isopropyl amines are of equal or greater toxicity in twenty-five of twenty-six pairs. Under pressor activity, four of the nine pairs indicated as having the same activity show zero or depressor action. The isopropyl amine has the greater pressor effect in sixteen of twenty-two active pairs. All three pairs listed as having the same bronchodilator activity are inert or constrictor. It can be stated that one would expect an isopropyl amine to be more toxic and more pressor than a similar *n*-propyl amine. There can be no expectation with respect to the bronchodilator action. It should be noted that certain of the *n*-propyl amines are more pressor than many of the isopropyl derivatives and are well within a useful range. This further complicates any sweeping statement in comparing any two types of structure. The comparisons apply only when two structures identical in all respects but one are compared. This fact should be kept in mind when considering the conclusions drawn from this and other series of compounds.

The second structural difference to be compared is that of the presence of a methoxyl or hydroxyl group in the ring. The data show that the substance with the methoxyl group is of equal or greater toxicity in twenty-seven of thirty pairs. Of those compounds listed as possessing the same pressor effect, five of the

Table I. Pharmacological Data

Name	—NH2— Toxicity	Pressor ratio	Bronchodilator	—NH.CH3— Toxicity	Pressor ratio	Bronchodilator	—N(CH3)2— Toxicity	Pressor ratio	Bronchodilator	—NH.CH2C6H5— Toxicity	Pressor ratio	Bronchodilator
Phenylisopropyl	20	1/250	−1	20	1/275	2	20	1/500	13	20	1/1000	9
2-Methoxy	60	1/1000	−2	60	Depressor	12	40	Depressor	9	20	Depressor	9
3-Methoxy	40	1/250	6	35	1/500	5	50	1/2000	10	20	1/2000	7
4-Methoxy	30	1/250	4	40	1/225	2	50	1/1600	12	40	1/2000	8
2-Hydroxy	80	1/675	1	90	1/250	3	50	Depressor	7	20	Depressor	6
3-Hydroxy	70	1/300	1	60	1/125	2	...	.....	...	35	1/2000	5
4-Hydroxy	100	1/100	0	100	1/250	3	50	1/250	5	40	1/2000	12
Phenylpropyl	50	1/700	−2	60	1/250	1	80	Depressor	4	30	1/2000	12
2-Methoxy	80	Depressor	0	70	Depressor	10	40	Depressor	8	30	Depressor	4
3-Methoxy	40	1/300	8	70	1/1000	5	70	1/2000	1	40	1/2000	16
4-Methoxy	30	1/3000	3	40	1/1000	12	60	1/2400	8	20	1/4000	16
2-Hydroxy	110	1/9600	3	140	Depressor	0	90	Depressor	9	..	.....	..
3-Hydroxy	90	1/300	−1	90	1/250	6	80	1/2000	3	45	1/2000	6
4-Hydroxy	170	1/1750	−2	170	1/750	1	140	1/2000	6	50	1/2000	12
2,3-Dimethoxy	30	0	0	...	.....	..	...	.....	...	..	.....	..
2,4-Dimethoxy	50	1/3000	8	...	.....	..	...	.....	...	..	.....	..
2,5-Dimethoxy	50	1/1200	5	40	1/650	5	40	Depressor	1	20	Depressor	12
2,6-Dimethoxy	15	Depressor	4	...	.....	..	...	.....	...	..	.....	..
3,4-Dimethoxy	140	1/675	1	130	1/4000	1	80	1/2000	1	40	1/2000	10
3,5-Dimethoxy	70	Depressor	8	...	.....	..	...	.....	...	..	.....	..
2,3-Dihydroxy	120	1/750	0	...	.....	..	...	.....	...	..	.....	..
2,4-Dihydroxy	150	1/1100	0	...	.....	..	...	.....	...	..	.....	..
2,5-Dihydroxy	100	1/4000	0	10	0	5	275	0	1	..	.....	..
2,6-Dihydroxy	90	Depressor	2	...	.....	..	...	.....	...	..	.....	..
3,4-Dihydroxy	40	1/40	−2	...	.....	..	20	Depressor	−1	..	.....	..
3,5-Dihydroxy	?	1/120	−1	...	.....	..	...	.....	...	..	.....	..

Table II. Summary of Data Taken from Table I

Structure	Pairs	Toxicity		Pressor Ratio		Bronchodilator Effect	
		Greater	Same	Greater	Same	Greater	Same
Isopropyl	26	21	4	16	9	13	3
n-Propyl		1		1		10	
OCH_3	32	24	3	5	11	21	3
OH		3		15		7	
NH_2	17	7	5	8	1	4	2
$NH.CH_3$		5		8		11	
$NH.CH_3$	16	5	3	10			1
$N(CH_3)_2$		8		1			
$NH.CH_3$	15	1	2	14	1	0	0
$NH.CH_2C_6H_5$		12		0		15	

eleven are inactive. The hydroxy group therefore appears to confer the greater pressor activity. On the contrary, with regard to the bronchodilator effect the methoxy derivative is of equal or greater activity in twenty-four of thirty-one pairs. It can therefore be expected that the methoxy derivative will be more toxic and less pressor and will have a greater bronchodilator action than the corresponding hydroxy derivative. Several of the methoxy amines have a pressor ratio sufficiently great to indicate that a further investigation of this function is in order.

The third difference in structure is the addition of a methyl group on the amino nitrogen, to give a secondary amine. Table II shows the effect on the toxicity and pressor ratio of this change to be unpredictable. The methyl group does by a ratio of about 3 to 1 increase the bronchodilator action. The effect of the addition of a methyl group to the amino nitrogen can be expected to increase the bronchodilator activity but there can be no expectation with regard to toxicity and pressor effect.

The fourth structural change is the introduction of a second methyl group on the amino nitrogen, giving a tertiary amine. The effect of this change on the toxicity and bronchodilator effect is inconclusive. In four of the five pairs where the pressor action is reported as the same, both members are inactive. This indicates that, if the methyl amine is pressor, it is more pressor than the dimethyl. With the introduction of the second methyl group therefore, it is expected that the pressor ratio will decrease but there can be no expectation with regard to the toxicity and bronchodilator action.

The last change to be discussed is the effect of introducing a large group, such as benzyl, on the amino nitrogen as compared with the introduction of a small group, such as methyl. From the data it is to be expected that a benzyl amine will be more toxic, less pressor, and a better bronchodilator than the corresponding methyl amine.

The toxicities show definite trends in three of the five cases examined, the pressor effect in four of the five, and the bronchodilator effect in three of the five comparisons. On this basis it would appear easier to predict the effect of structural changes on the pressor ratio than either of the other two properties. Upon the introduction of a methyl in the amino group it is a 50-50 chance as to whether the pressor ratio will increase or decrease. This accounts for the conflicting reports concerning the effect of this change. It is remarkable, in view of the considerable activity possessed by many of the methoxy derivatives, that they have received comparatively little attention. The lack of correlation between any one chemical change and all three pharmacological properties indicates that it is impossible to determine all types of activity with one test.

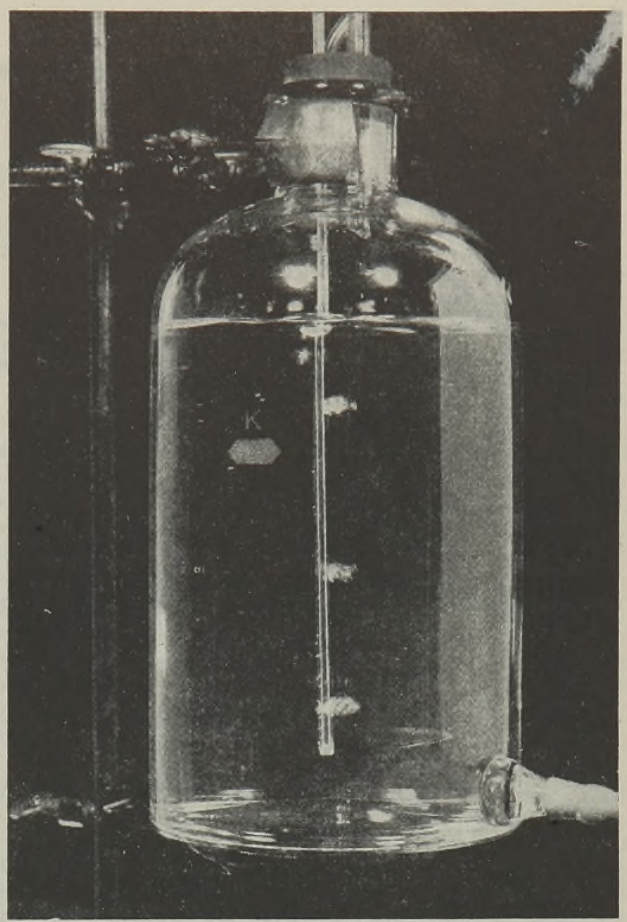


Figure 2. An Enlarged View of Reservoir, Showing the Entrance of Air Bubbles

Conclusions such as those drawn here are merely guide posts in an attempt on the part of the chemist to indicate a possible line of attack. The chemist is not interested in seats of physiological action or mechanism of action. He asks only a method that will keep him from straying too far from the road toward his goal. Results are sometimes twisted beyond their true or original meaning, but if their natural limitations are kept in mind, data of the type presented are of value.

LITERATURE CITED

(1) Graham, B. E., and Cartland, G. F., *J. Pharmacol.*, 81, 360 (1944).
(2) Howard, R. B., Jr., thesis, Kalamazoo College, June, 1941.
(3) Rayman, D. E., *Ibid.*, June, 1942.
(4) Sollmann, T., and Oettingen, W. F. von, *Proc. Soc. Exptl. Biol. Med.*, 25, 692 (1928).
(5) Woodruff, E. H., *J. Am. Chem. Soc.*, 64, 2859 (1942).
(6) Woodruff, E. H. (to Upjohn Co.), U. S. Patents 2,293,384–7 (Aug. 25, 1942); 2,309,150–1 (Jan. 26, 1943); 2,317,011–13 (April 20, 1943).
(7) Woodruff, E. H., and Conger, T. W., *J. Am. Chem. Soc.*, 60, 465 (1938).
(8) Woodruff, E. H., Lambooy, J. P., and Burt, W. E., *Ibid.*, 62, 922 (1940).
(9) Woodruff, E. H., and Pierson, Earl, *Ibid.*, 60, 1075 (1938).

Contribution 167 from the Research Laboratories of the Upjohn Company.

[A paper entitled "Medicinal Chemistry—beyond the Horizon", also presented before this symposium, was printed in *Chemical and Engineering News*, pages 37–40 (January 10, 1945). The author was Theodore G. Klumpp, Winthrop Chemical Company.]

Polyhydric Alcohol Production

BY HYDROGENOLYSIS OF SUGARS IN THE PRESENCE OF COPPER-ALUMINUM OXIDE[1]

C. W. LENTH[2] AND R. N. DU PUIS
The Miner Laboratories, Chicago 6, Ill.

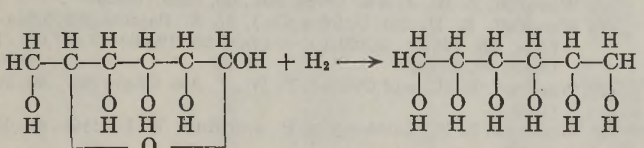
A study of the production of polyhydric alcohols by the hydrogenolysis of sugars has been carried through the pilot-plant stage. At 240° C. and 1500 pounds per square inch pressure, using a methanol suspension of either sucrose or dextrose and a special copper-aluminum oxide catalyst, an average yield of 60–65 per cent distillable polyhydric alcohols is obtained, of which about 60 per cent is propylene glycol and 40 per cent is a mixture of glycerol and other polyhydric alcohols of higher molecular weight. The latter fraction cannot be rectified by ordinary distillation methods. The hydrogenolysis products have potential use as glycerol substitutes but do not serve as an economical source of pure glycerol.

WHILE the capacity of the soap plants in the United States to produce glycerol is far greater than normal domestic requirements, the Association of American Soap & Glycerine Producers, Inc., has recognized the desirability of a supplementary source of glycerol in case of emergency when it may be called upon to produce beyond the requirements of domestic consumers. Accordingly, several years ago the Association asked this laboratory to investigate the possibilities of producing glycerol or an adequate substitute by methods not involving fat splitting.

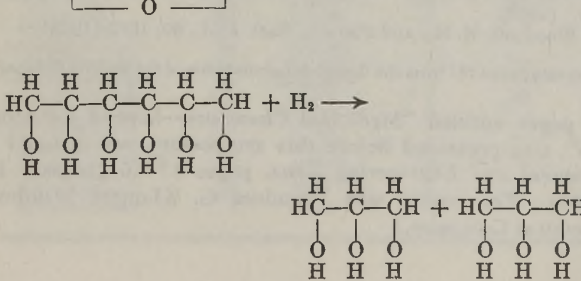
A search of the literature revealed several methods for producing glycerol—e.g., fermentation of sugars in the presence of sodium sulfite or sodium carbonate (*20*), hydrolysis of halogenated propane (*26*), and hydrogenolysis of sugars (*17*, *18*, *19*, *28*). For various reasons it was decided to study sugar hydrogenolysis, and this paper covers the results of that study.

HISTORICAL AND THEORETICAL

When dextrose is subjected to treatment with hydrogen, the formation of glycerol theoretically occurs in two stages:

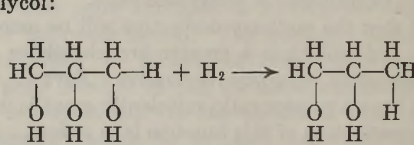


(1)



(2)

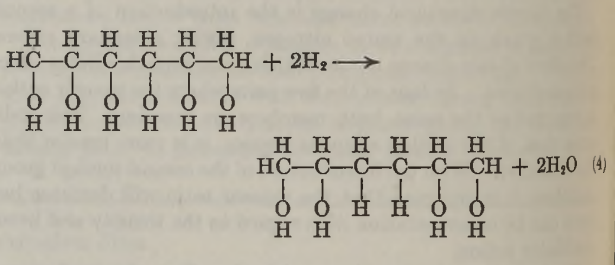
The first stage actually does occur; various sugar alcohols (sorbitol, mannitol, and dulcitol) have been prepared by this means (*16*). However, there is no proof that the second stage occurs to any large extent. The hydrogenolysis products always contain substantial quantities of propylene glycol even when the hydrogen consumption is limited to the theoretical quantity shown by Equations 1 and 2. As shown in Equation 3, which has been experimentally verified, glycerol may be reduced to propylene glycol:



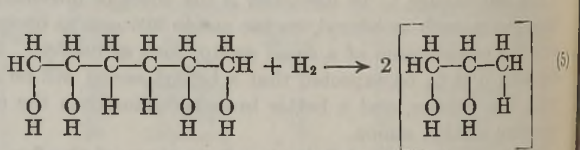
(3)

The possibility exists that the reaction rate represented by the reduction of glycerol to propylene glycol (Equation 3) substantially equals that of Equation 2, and hence most of the glycerol is reduced as fast as it is formed.

Another possible explanation for the formation of substantial quantities of propylene glycol is indicated in Equations 4 and 5:



(4)



(5)

The earliest reference to the reaction of sugars with hydrogen is made by Ipatieff (*16*), who produced the corresponding sugar alcohols from several monosaccharides by treatment with hydrogen at 84 atmospheres pressure and 100–135° C. Other investigators (*6*, *27*, *29*) followed in studying this reaction, but it was not until 1932 that Lautenschlager obtained patents (*18*, *19*) covering the hydrogenolysis of sugars. Others soon followed, and patents have been issued here and abroad covering various features of the

[1] This article was submitted for publication almost three years ago, but was withheld from publication at the request of the government censor. Restrictions have now been removed for the presentation of these data.

[2] Present address, 400 West Madison Street, Chicago 6, Ill.

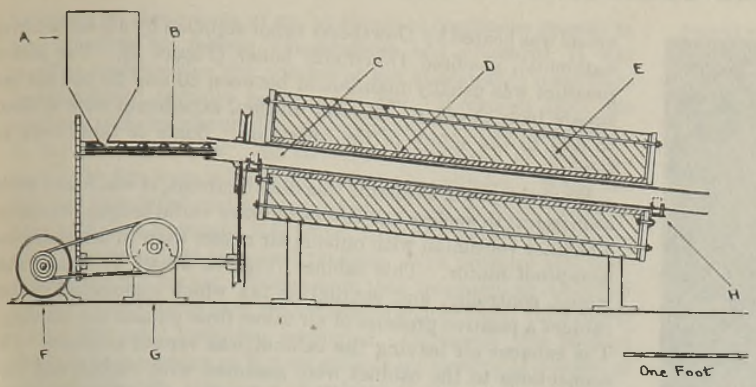


Figure 1. Diagram of Kiln

A. Hopper
B. Screw feed
C. 18–8 stainless steel tube
D. Hevi-Duty heating elements
E. Insulation
F. 1/4-horsepower motor
G. 48:1 speed reducer
H. Trunnions

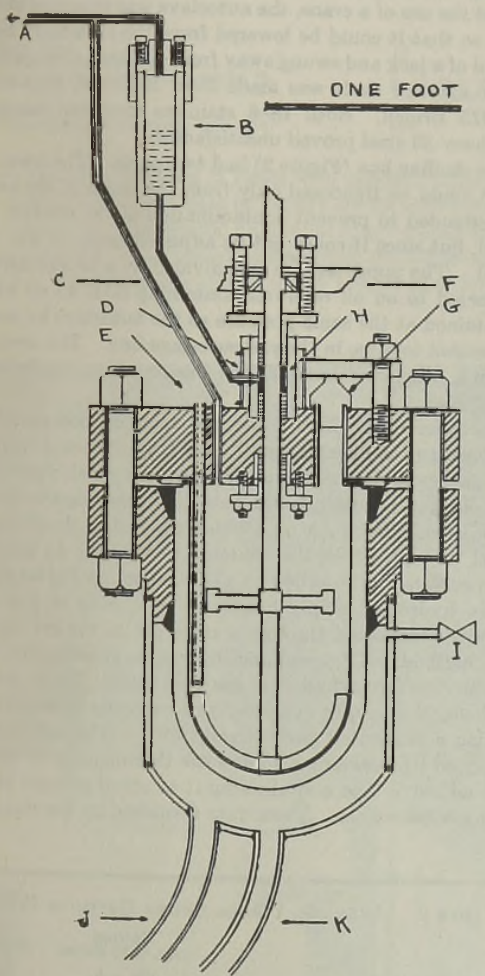


Figure 2. Diagram of Autoclave

A. To hydrogen supply and pressure gage
B. Oil reservoir
C. Hydrogen line
D. Water-cooled stuffing box
E. Thermocouple well
F. Thrust bearing
G. Handhole
H. Lantern ring
I. Air bleed-off valve
J. Dowtherm vapor line
K. Dowtherm condensate return

reaction. The outstanding point in connection with all of these patents is that the reactions were universally carried out in aqueous solution, although in the usual broad language of patents occasional mention of the possibility of using alcoholic solvents was made. However, there is no indication that such solvents were actually employed until Zartman and Adkins published their paper (*30*) on the hydrogenolysis of sugars in anhydrous ethyl alcohol solution. Their operating conditions were somewhat more severe than those of the earlier workers in that they used pressures of 300 atmospheres. Consequently, any glycerol that they might have produced was probably further reduced to propylene glycol. In any event, they were the only investigators who did not claim the production of large quantities of glycerol. While it may be argued that the use of an alcoholic reaction medium instead of an aqueous one inhibits the formation of glycerol, our work on this subject indicates little or no difference in the amount of glycerol formed between the two solvents under similar temperature and pressure conditions. It further shows that there is considerably less decomposition to tarry substances when the alcoholic vehicle is used.

As mentioned above, preliminary experiments indicated that a cleaner product results from the use of an alcoholic vehicle than from the use of water; consequently an extended study was made to establish optimum conditions for the reaction in methanol. In addition, a large number of catalysts was studied. These investigations (*1, 3, 22–25*) established that maximum conversion of sugars to polyhydric alcohols of substantially lower molecular weight occurs at pressures of less than 2000 pounds per square inch and temperatures of 225° to 250° C. in the presence of either a copper chromite–barium oxide catalyst (*7*) or the specially prepared copper-aluminum oxide catalyst described below (*2, 4, 21, 24*). It was also found that, except for slight modifications, refined cane sugar, refined beet sugar, raw cane sugar, and dextrose may be processed interchangeably. Of these, refined cane sugar was the most reactive. The other grades of sucrose required higher catalyst and promoter concentrations, and dextrose required a reduced form of the copper-aluminum oxide catalyst.

On the basis of the small-scale work briefly outlined above, it was decided to construct a small pilot plant to study the reaction products more fully.

CATALYST PREPARATION

The catalyst (*2, 4, 21, 24*) was prepared by coprecipitating copper carbonate and aluminum hydroxide in a 25-gallon stone crock. A solution of 6.25 pounds of technical copper sulfate and 16 pounds of technical aluminum sulfate in 10 gallons of hot tap water was run slowly with violent stirring into the crock which contained 13 pounds of soda ash in 7 gallons of hot tap water. The mixture was stirred for about 30 minutes after all of the salt solution had been added and was then allowed to stand about 24 hours with occasional stirring to assist in driving out the carbon dioxide.

Various forms of filtration apparatus were tested, including pressure filters, vacuum filters, and filter leaves, but the most satisfactory was a basket centrifuge. The catalyst slurry was loaded into such a centrifuge, and after a sufficiently thick cake (1 inch in a 12-inch basket) had been built up, it was washed with hot water until the washings showed only a faint cloudiness when tested with barium chloride solution. This required about one hour. The cake was then spun as dry as possible, broken into about 1-inch lumps, and dried at 100–125° C. The material shrinks considerably on drying.

The catalyst was then ignited at 1000 ± 50° C. in the kiln shown in Figure 1. This consisted of a 4-foot length of 2-inch o.d., 1/16-inch wall, 18–8 stainless steel tubing, rotated in an elec-

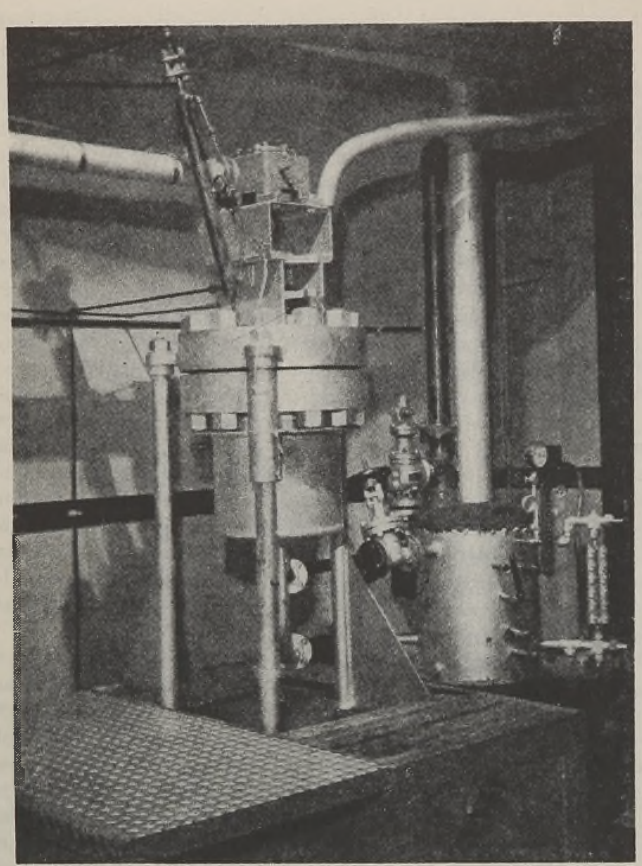


Figure 3. Autoclave and Boiler

tric furnace 3 feet long. The tube was inclined about 5° from the horizontal. A continuous feeding device to introduce the catalyst into the kiln was made from a 1-inch-diameter wood bit. The feed was adjusted so that the catalyst flowed uniformly through the kiln rotating at about 18 r.p.m. The time of travel was 4–4.5 minutes.

After heating, the catalyst is reddish brown and is almost completely insoluble in the common acids. There is reason to believe that it may consist largely of the spinel, copper aluminate, $CuAl_2O_4$ (*14*, *15*). The catalyst was ground to pass a 50-mesh screen and was then ready for use in the hydrogenolysis of sucrose.

As mentioned above, the catalyst must be reduced for use with dextrose. This may be accomplished by any of several methods. The most convenient method consisted in using the catalyst in a sucrose run and recovering it for use with dextrose. Other methods found suitable consisted in heating the catalyst in a current of hydrogen at 200–300° C. at atmospheric pressure or heating it in the autoclave with the alcohol solvent and 200–300 pounds hydrogen pressure to 200° C. The reduced catalyst produced by the last method is somewhat more resistant to poisons, of which chloride ion is an outstanding example (*8*). After reduction the catalyst has changed from brown to violet. It is stable and requires no special storage precautions to maintain its activity; in fact, a sample stored with access to air for more than four years showed no loss in activity.

HYDROGENOLYSIS OF SUGARS

The pilot-plant equipment for hydrogenolysis of sugars is shown in Figures 2 to 5. It consisted of a jacketed 5-gallon pressure vessel machined from a forged billet of 18–8 stainless steel and fitted with an anchor-type agitator. The flange for securing the head was welded to the body of the vessel. The pressure vessel was heated by Dowtherm vapor supplied by a 2-horsepower automatic, gas-fired Dowtherm boiler (Figure 3). The jacket pressure was usually maintained between 10 and 20 pounds per square inch absolute. Several unusual expedients were utilized to add to the safety of the operation. Some of these were as follows:

Since the power available was direct current, it was found more economical to enclose the 1.5-horsepower variable-speed motor in a cabinet ventilated with outside air rather than to use an explosion-proof motor. This cabinet (Figures 3 and 4) housed the motor, controller, and ventilating fan which maintained in the cabinet a positive pressure of air taken from outside the building. The exhaust air leaving the cabinet was vented outdoors. All connections to the cabinet were gasketed with rubber, and the link between the motor and reducing gear was enclosed in a tube flanged and gasketed at each end.

The Dowtherm boiler was of the enclosed flame type, and the primary and secondary air for the burners was also taken from outdoors. The flue from the boiler was connected to an exhaust blower with a by-pass connection to limit the suction.

While the pressure vessel could be filled and emptied through the small handhole in the cover, it is obvious that means for removing the head are necessary. Since the ceiling height precluded the use of a crane, the autoclave was mounted on the supports so that it could be lowered from the stationary head with the aid of a jack and swung away from the head (Figure 4).

The agitator shaft was made from K-Monel, heat-treated to 250–275 Brinell. Both 18–8 stainless steel and casehardened Allegheny 33 steel proved unsatisfactory.

The stuffing box (Figure 2) had two parts. The lower section, which could be tightened only from the inside of the autoclave, was intended to prevent contamination of the reaction mixture by oil, but since it could not be adjusted easily, it was not very useful. The upper section was divided by a bronze lantern ring connected to an oil reservoir containing SAE 40 oil which was maintained at the same pressure as the autoclave by means of a connection to a tee in the pressure-gage line. The most suitable packing was found to be Crane Packing Company's No. 101Al Super Seal.

The filler or handhole deserves comment because of its convenience and unusual design. As Figure 2 shows, it was closed by a gasketed plug held in place by a lever which was locked with only one nut. To empty the autoclave this plug was replaced by a similar one bearing a pipe which reached to the bottom of the vessel through which the contents were blown by gas pressure. The pressure was recorded on a 0–3000 pound Taylor gage.

The hydrogen supply consisted of a bank of five standard cylinders connected through a manifold to the gas supply line. The method of determining hydrogen consumption deserves comment. Two cylinders of gas were used. The pressure of one of them, the supply cylinder, was carefully measured by connecting a calibrated gage directly to it. The temperature was measured by fastening a short-scale thermometer to the cylinder with adhesive tape and allowing it to stand at least 24 hours in the room before use. From data furnished by the supplier of the

Table I. Average Yields under Optimum Conditions

	Sucrose (Av. of 35 Runs)	Dextrose (Av. of 29 Runs)
Temperature, ° C.	239 ± 5	246 ± 5
Operating pressure, lb./sq. in.	1500 ± 60	1500 ± 60
Agitator speed, r.p.m.	126	126
Yield, % by weight of sugar		
Total nonvolatile at 100° C.	75.8 ± 2.0	72.4 ± 2.0
Propylene glycol	39.5 ± 3.0	36.8 ± 3.0
Glycerol and congeners	25.1 ± 3.0	25.4 ± 3.0
Total distillable polyhydric alcohols	64.6 ± 2.0	62.1 ± 2.0
Residue	11.0 ± 2.0	9.7 ± 2.0
Hydrogen consumed		
Moles/mole sugar	5.70 ± 0.12	2.72 ± 0.12
Standard cu. ft./lb. sugar	6.45 ± 0.14	5.85 ± 0.26

hydrogen on the volume of gas at standard conditions present in the cylinders at various temperatures and pressures, it was possible to determine the volume of gas at standard conditions in the supply cylinder before each run. Hydrogen from the auxiliary cylinder was used for sweeping out the system and filling to the initial pressure. All subsequent additions of hydrogen during the run were taken from the supply cylinder. When the run was completed and the equipment cooled to room temperature, sufficient hydrogen was added from the supply cylinder to raise the pressure to its initial reading. The pressure and temperature of the supply cylinder were then measured as described above. The difference in gas volume in this cylinder then represented the total hydrogen consumed. Obviously this method depends on a number of factors such as uniformity of volume of the gas cylinders, constancy of volume of the reaction mixture, reproducibility of pressures and temperatures, and perhaps others. However, it is probable that the errors introduced by these factors, except for the change in volume of the reaction mixture, were not serious. (The volume of the reaction mixture increases about 20 per cent, and a correction factor was applied to the hydrogen consumption data to compensate for this.)

A large number of runs on both dextrose and cane sugar were conducted in the pilot plant. The usual charge consisted of the following:

Sugar, lb.	10
Methanol (anhydrous), lb.	10
Copper-aluminum oxide catalyst, lb.	0.75 (sucrose) 1.0 (dextrose)
Soda ash, lb.	0.04
Initial hydrogen pressure, lb./sq. in.	900

As there was little variation of yields with minor changes of temperature and pressure, the data in Table I are the result of averaging the figures for the indicated number of runs for both sugars.

A reproduction of a typical temperature record is shown in Figure 5. The dotted line indicates the temperature inside the reaction vessel and the dashed line shows the temperature on the outer wall of the jacket. An interesting feature is the sudden rise of temperature of reaction mixture starting at about 165° C. Over a period of 10 minutes the temperature rose to 205° and in the following 10 minutes it decreased to 195° C. This indicates that the reaction in its initial stages is markedly exothermic. Examination of the reaction mixture at this point revealed no explanation, for the only products isolated were mannitol and sorbitol.

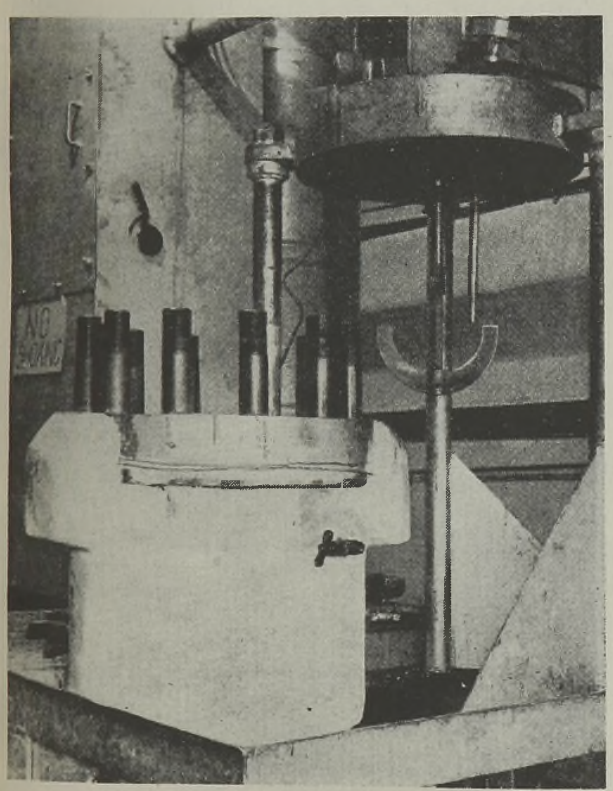


Figure 4. Autoclave Lowered from Head

A pressure chart is reproduced in Figure 6. The zigzag portion of the record represents the period during which hydrogen was added to maintain an average pressure of 1500 pounds per square inch.

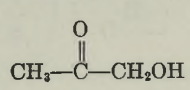
The average time required for a run starting with the equipment at room temperature was approximately 3 hours; about half of this period was required to raise the temperature to the point at which reaction started. The actual duration of the reaction was therefore about 1.5 hours. This time is almost exactly the same as that required for the reaction when carried out in small laboratory pressure vessels agitated by rocking.

The principal difference in operation between the large pressure vessel and the small laboratory ones was that in the former it was found necessary to use an amount of methanol at least equal in weight to the sugar, whereas in the small "rockers" the methanol could be reduced to 50 per cent of the weight of the sugar. Otherwise the reaction proceeded in the large vessel as smoothly and satisfactorily as in the laboratory, and there is no reason to believe that a further increase in size could not be effected without major difficulty.

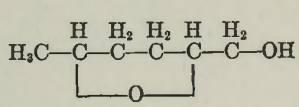
HYDROGENOLYSIS PRODUCTS

After removal from the pressure vessel, the reaction mixture was separated from the catalyst by settling overnight and decanting the supernatant liquid through a pad of filter aid on a stoneware vacuum filter box. The catalyst was centrifuged from the balance of the reaction mixture and, after being washed with several changes of methanol, was dried and stored for re-use. The washings from the catalyst were added to the main body of the filtered reaction mixture, and the whole was distilled to a still-head temperature of 100° C. to remove the methanol and most of the water formed in the reaction. The residue from this topping operation was called "nonvolatile at 100° C." (Table I). This liquid contains about 50 per cent propylene glycol which was separated by rectification in vacuo. The residue was vacuum-steam distilled to the point of decomposition to yield the product called "glycerol and congeners". The bottoms from this last treatment were semisolid and consisted principally of thermal decomposition products of some of the original sugar as well as of the hydrogenolysis products.

The propylene glycol fraction was found to contain traces of acetol (1-hydroxy-2-propanone),



and from 2 to 5 per cent of a compound demonstrated to be 5-methyltetrahydrofurfuryl alcohol,



The acetol probably is formed as a dehydration product of glycerol, as it has been shown (*24*) that acetol results from the action of the hydrogenolysis catalyst on glycerol.

The 5-methyltetrahydrofurfuryl alcohol is probably produced by the dehydration of 1,2,5-trihydroxyhexane which is discussed later.

TABLE II. COMPARISON OF NITRATED GLYCEROL-CONGENER FRACTION WITH NITRATED DYNAMITE-GRADE GLYCEROL[a]

	Glycerol-Congener Fraction	Dynamite-Grade Glycerol
Yield		
Calcd. on OH content, grams	12.3	14.8
Found, grams	10.0	12.8
% of theory	81.4	86.5
Nitrogen, %	15.8	18.2
Trauzl lead-block expansion, cc.	540	585
Abel heat stability test (180° F.), min.	8	15
40% Dynamite Prepared from Nitrated Products		
Triton value	8.28	8.55
Triton value weight strength, %	37.30	39.50
Sensitivity, inches[b]	17	12

[a] Data from R. B. Reynolds who kindly conducted the tests.
[b] Maximum height a 5-pound weight can be dropped without detonation

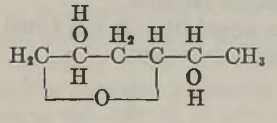
The fraction called "glycerol and congeners", representing about 25 per cent of the sugar processed, is reported in the literature (*18*, *19*, *28*) to consist largely, if not entirely, of glycerol. The following data show that this is far from true:

Specific gravity, 25/25° C.	1.198
Available hydroxyls (acetylation), %	39.7
Glycerol by acetylation, %	71.8
Glycerol (lead oxide method, *9*, *10*, *11*), %	15–16

Distillation in a Podbielniak column was ineffective in separating this mixture of polyhydric alcohols. Rehydrogenation of the mixture at 240° C. and about 1800 pounds per square inch resulted in 34 per cent propylene glycol, based on the original mixture. If this propylene glycol was formed only from glycerol present in the mixture, the concentration of glycerol must have been at least 41 per cent. However, it is possible that some of this propylene glycol was formed by hydrogenolysis of higher polyhydric alcohols present. Hass (*12*) in working on a similar mixture (although of a somewhat narrower boiling range) was able to separate over 40 per cent of the mixture as glycerol by crystallization in butanol solution, and Hass and Patterson (*13*) reported a recovery of over 60 per cent from another mixture of the same type. As these reports of Hass were published some time after the work here discussed was suspended, his method was not applied to the mixture under consideration.

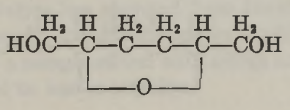
The liquid remaining after removal of propylene glycol from the rehydrogenated mixture of polyhydric alcohols was distilled into three fractions.

The first fraction, representing 25 to 40 per cent of the mixture and boiling between 120° and 125° C. (3 mm. pressure), had the same general characteristics as the material reported by Zartman and Adkins (*30*) for which they suggested the structure,



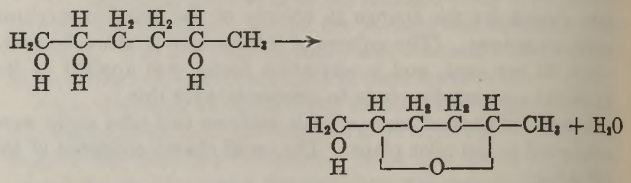
2-(4-hydroxytetrahydrofuryl) methylcarbinol

Our studies of this fraction indicated that, in addition to the above compound, an isomer,



tetrahydrofuryl-2,5-dicarbinol, may also be present. The evidence for the presence of both compounds lies principally in the fact that, after complete acetylation, this fraction of the polyhydric alcohols could be separated into two parts (boiling at 120–123° and at 123–130° C. under 6 mm. pressure) having identical acetyl numbers but differing in specific gravity (1.142 and 1.137, respectively, at 25/25° C.) and odor; the former has a pleasant esterlike aroma and the latter is odorless. Another point in favor of the presence of the dicarbinol isomer is the fact that only about 1 per cent of the amount of iodoform theoretically possible from the methylcarbinol compound could be obtained from this fraction by treatment with iodine and alkali. However, the structure of neither of these compounds was rigorously proved.

A second fraction of the mixed polyhydric alcohols boiling between 150° and 160° C. at 4 mm. corresponded to the compound believed by Zartman and Adkins to be 1,2,5-trihydroxyhexane. The properties of this fraction agreed with those described elsewhere (*5*) for the above compound. Treatment with anhydrous zinc chloride resulted in the formation of 5-methyltetrahydrofurfuryl alcohol. Of the various compounds which might be expected to undergo this reaction, only 1,2,5-trihydroxyhexane may conceivably have been produced by the hydrogenolysis of sugar:



Some of the physical properties of 5-methyltetrahydrofurfuryl alcohol were: boiling point 177–178° C. at 750 mm.; specific gravity 1.037 at 25/25° C. The acetate was prepared, and its physical properties were found to be: boiling range 95–105° C. at 25 mm.; specific gravity 1.041 at 25/25° C.

In view of the fact that 5-methyltetrahydrofurfuryl alcohol was formed by dehydration of 1,2,5-trihydroxyhexane, it is probable that the small amount of the former observed in the propylene glycol fraction had its origin in the same source as a result of the dehydrating conditions existing during the hydrogenolysis.

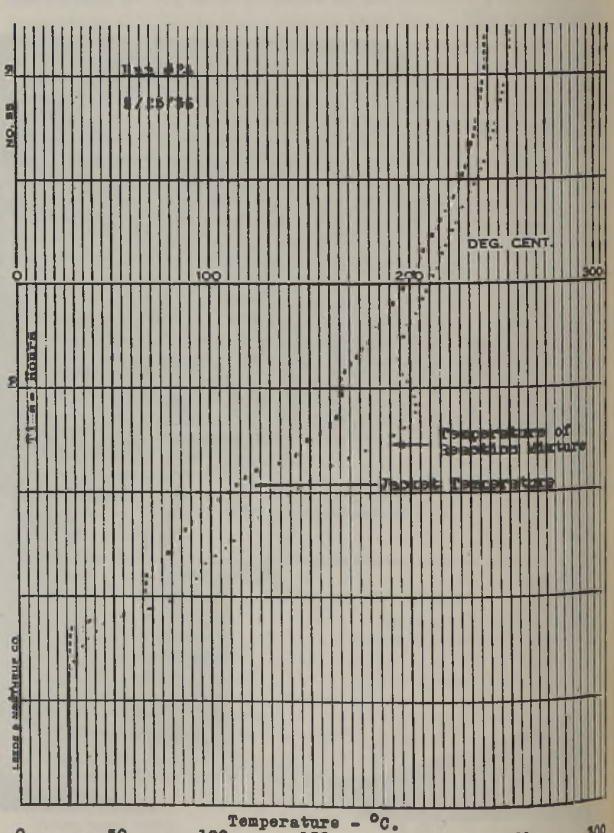


Figure 5. Typical Temperature Record

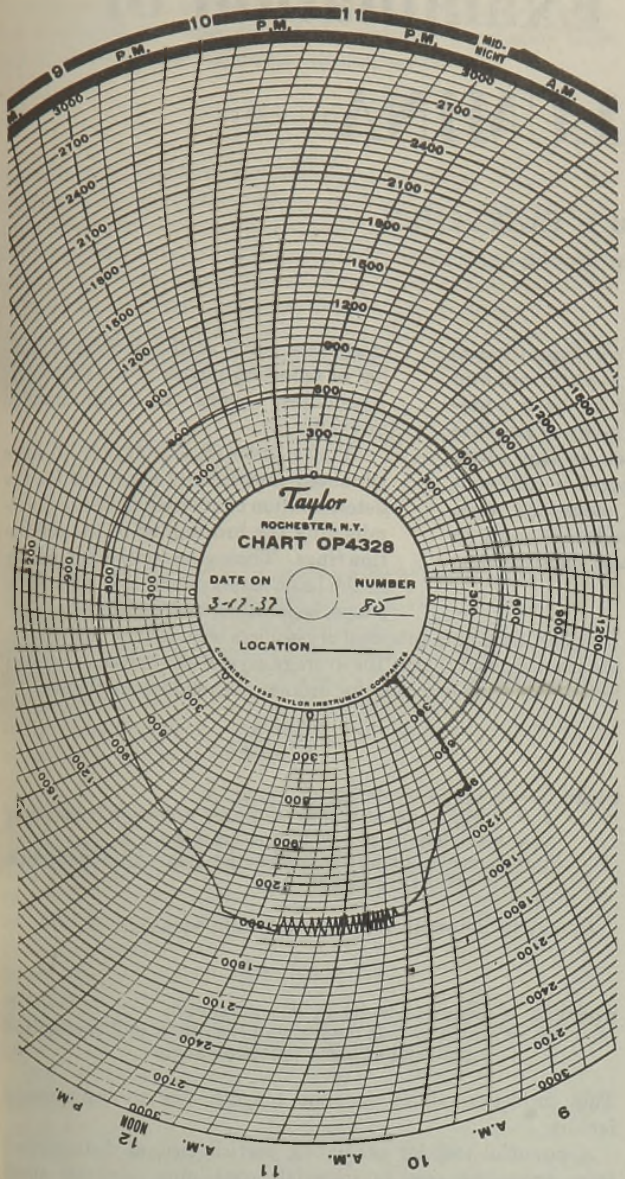


Figure 6. Typical Pressure Record

The third fraction of the polyhydric alcohols, tentatively identified by Zartman and Adkins as 1,2,5,6-hexanetetrol, was not obtained sufficiently pure to permit identification. However, it is significant that the dehydration product of this compound theoretically should be tetrahydrofuryl-2,5-dicarbinol and that evidence was found for the presence of an appreciable quantity of the latter in the first fraction of the polyhydric alcohols.

The residues from the distillation of the hydrogenolysis products were usually somewhat decomposed. However, the presence of traces of sorbitol was shown through the preparation of the chlorobenzal derivative. Other possible but unidentified components of the residue are polypropylene glycol and polyglycerol.

CONCLUSIONS

The study of the hydrogenolysis of sucrose and dextrose under the conditions employed showed that the process would not serve as a very satisfactory emergency source of glycerol because the quantity obtained is small, the glycerol is difficult to separate, and the cost of production is high. However, the entire fraction of glycerol and congeners may have application as a glycerol substitute in such fields as glue products, alkyd resins (samples of which showed interesting properties), and explosives. In the last case the data of Table II on the nitration products are of interest. They show that the nitrated polyols are not equal to nitroglycerin in many respects, but it is possible that the slightly lower strength would not be important in many applications.

The commercial utility of the hydrogenolysis products depends on many factors such as availability of cheap hydrogen and sugar. With plentiful supplies of natural glycerol available at reasonable cost, as under normal conditions, the hydrogenolysis products are not of interest as glycerol substitutes. However, in emergency, when the industry is called upon to produce in excess of domestic requirements, the hydrogenolysis products might be temporarily substituted for glycerol to a limited extent. Refined sugar is the most desirable raw material; work on cheaper grades of sugars was not encouraging although means of processing them were found (*8*). This work was based on a batch process, and while no continuous process experiments were made, it seems probable that with properly designed equipment the process should be adaptable to continuous operation.

ACKNOWLEDGMENT

The authors take this opportunity to express their gratitude for the inspiring guidance in the prosecution of this project rendered by Carl S. Miner and Otto C. Stanger, and the valuable assistance of John A. Pianfetti, J. B. Segur, and Roy H. Wittekindt.

LITERATURE CITED

(1) Assoc. of Am. Soap & Glycerine Producers. French Patent 816,952 (Aug. 21, 1937).
(2) *Ibid.*, 825,688 (March 10, 1938).
(3) Assoc. of Am. Soap & Glycerine Producers, Inc., Italian Patent 349,027 (June 5, 1937).
(4) *Ibid.*, 356,660 (Feb. 8, 1938).
(5) Beilstein's Handbuch der organischen Chemie, 4th ed., Vol. I, p. 521, Berlin, Julius Springer, 1918.
(6) Cake, W. E., *J. Am. Chem. Soc.*, 44, 839 (1922).
(7) Connor, Folkers, and Adkins, *Ibid.*, 54, 1140 (1932).
(8) Du Puis, R. N. (to Assoc. of Am. Soap & Glycerine Producers Inc.), U. S. Patent 2,282,603 (Oct. 29, 1941).
(9) Farbenfabriken vorm. F. Bayer & Co., German Patent 303,805 (July 11, 1919).
(10) *Ibid.*, 305,174 (July 11, 1919).
(11) *Ibid.*, 305,175 (July 22, 1919).
(12) Hass, H. B. (to Purdue Research Foundation), U. S. Patent 2,233,606 (March 4, 1941).
(13) Hass and Patterson, IND. ENG. CHEM., 33, 615 (1941).
(14) Hedvall and Heuberger, *Z. anorg. allgem. Chem.*, 116, 137 (1921).
(15) Holgerson, *Ibid.*, 204, 378 (1932).
(16) Ipatieff, V., *Ber.*, 45, 3224 (1912).
(17) Larcher, A. W. (to Du Pont Co.), U. S. Patent 1,963,997 (June 26, 1934).
(18) Lautenschlager *et al.*, German Patent 541,362 (Jan. 11, 1932).
(19) Lautenschlager *et al.*, U. S. Patent 1,915,431 (June 27, 1933).
(20) Lawrie, James W., "Glycerol and the Glycols", p. 116, New York, Chemical Catalog Co., 1928.
(21) Lenth, C. W., and Du Puis, R. N. (to Assoc. of Am. Soap & Glycerine Producers, Inc.), British Patent 499,417 (June 24, 1939).
(22) *Ibid.*, 490,211 (Aug. 5, 1938).
(23) Lenth, C. W., and Du Puis, R. N. (to Assoc. of Am. Soap & Glycerine Producers, Inc.), Canadian Patent 399,306 (Sept. 16, 1941).
(24) Lenth, C. W., and Du Puis, R. N. (to Assoc. of Am. Soap & Glycerine Producers, Inc.), U. S. Patent 2,201,235 (May 21, 1940).
(25) *Ibid.*, 2,290,439 (Dec. 31, 1941).
(26) McElroy, K. P. (to Carbide & Carbon Chemicals Corp.), U. S. Patent 1,466,665 (Sept. 4, 1923).
(27) Mueller, J., and Hoffmann, U. (to I. G. Farbenindustrie A.-G.), German Patent 544,666 (Feb. 20, 1932).
(28) Rothrock, H. S. (to Du Pont Co.), U. S. Patent 2,004,135 (June 11, 1935).
(29) Senderens, *Compt. rend.*, 170, 47 (1920).
(30) Zartman, W. H., and Adkins, H., *J. Am. Chem. Soc.*, 55, 4559 (1933).

PUBLISHED with permission of the Research Committee, Association of American Soap & Glycerine Producers, Inc.

X-Ray Diffraction Examination of GAMMA ALUMINA

M. H. JELLINEK[1] AND I. FANKUCHEN

Polytechnic Institute of Brooklyn, N. Y.

Controlled heating experiments have been made on γ-alumina, and the products studied by both wide-angle and low-angle x-ray scattering methods[2]. New lines in the wide-angle diagrams suggest a different unit cell from the accepted one. Both of these methods are used to evaluate crystallite and particle size.

ANHYDROUS aluminum oxide is known to exist in at least two forms, alpha and gamma alumina. The former, occurring as the mineral corundum, is the stable high-temperature modification of alumina which is the end product of all prolonged heating of other forms of alumina. Gamma alumina, on the other hand, has never been found free in nature and is metastable; ultimately it is converted to alpha alumina. Gamma alumina, whose commercial and industrial importance as a drying agent, dehydrating catalyst, and catalyst support in petroleum processes has skyrocketed in importance in the past few years, can be formed by the judicious dehydration of any of the known aluminum oxide hydrates except diaspore which dehydrates directly to alpha alumina. The temperature of dehydration is relatively unimportant, provided it is above about 600° F. and below a critical temperature, the value of which is fixed by the impurities present in the alumina and by the atmosphere of heating (steam, air, etc.). Above the critical temperature, alpha alumina will begin to be formed. Dependent upon the impurities present, however, variations of several hundred degrees Fahrenheit can be expected before the change to alpha alumina manifests itself. For highly purified aluminas, temperatures as high as 1800° F. have been reported before the alpha form makes its appearance.

This paper is concerned with the behavior of gamma alumina as it is heated at various temperatures for different lengths of time. The changes occurring in the alumina can be followed by the well known Debye-Scherrer x-ray method which indicates certain developments in the crystal structure of the alumina, along with information as to the change of crystallite size coincident with the structural development.

The crystallite size of any crystalline material can be evaluated from its Debye-Scherrer pattern by a study of the breadth of the diffraction lines at half maximum, assuming the use of essentially monochromatic radiation. Generally speaking, powder specimens containing crystallites of 0.001 cm. average diameter produce a uniform peppering of diffraction spots (*6*) in the positions of the Debye-Scherrer rings. If the average size of the crystallites is further enlarged, the diffraction spots grow larger and fewer in number, and their distribution within the rings is no longer uniform. With further decrease in crystallite size the spotty appearance of the rings disappears, and in the region 0.001 to 0.00001 cm. sharp rings of uniform intensity make their appearance. The width of these sharp rings is determined within this range by the physical characteristics of the apparatus, such as camera radius, diameter of specimen, eccentricity in centering of the specimen, characteristics of the tube, and absorption of the specimen. When the average crystallite size is reduced below approximately 1000 Å., the diffraction phenomena become less sharp as a result of the decreased number of reflecting planes in the individual crystallites; hence the rings broaden markedly (*6*).

Many authors (*2, 4, 5, 11, 12, 13*) have advanced theories and equations for the determination of crystallite size as determined by the broadening of the diffraction rings. These equations differ mainly in the basic assumptions as to crystallite shape, separation, and mode of packing. However, assuming spherical crystallites with random packing, it has been shown (*1*) that the average crystal size can be calculated by the following equation for ordinary crystalline materials:

$$L = \frac{0.89\,\lambda}{B_c \cos\theta}$$

where L = average crystallite diameter, Å.
θ = Bragg angle at which measured reflection is occurring
λ = wave length of x-radiation employed, Å.
B_c = corrected breadth of diffraction halo at half maximum intensity, radians

B_c may be determined by the following equation:

$$B_c^2 = B_o^2 - B_s^2$$

where B_o = measured width at half maximum
B_s = width at half maximum given by a well crystallized material at same reflection angle

This correction allows for line breadth due to instrumental factors.

A powerful tool for evaluating particle size, as distinguished from crystallite size, in materials containing relatively small particles is low-angle scattering of the x-rays. (The particle which is responsible for the low-angle scattering can consist of one or more crystallites in the case of crystalline materials, and consequently these particles should always be equal to or larger than the crystallites determined by line breadth computations.) This low-angle scattering phenomenon was predicted by Debye (*7*) in 1930. His predictions were based solely on the laws of optics and the refraction of radiation by molecular gases; he predicted that there should be a scattering of x-radiation at very small angles to the initial incident beam from any material whose volume, traversed by a beam of radiation, was composed of regions of different refractive indices to x-rays. Thus large objects scatter radiation at immeasurably small angles, whereas materials composed of small particles scatter radiation at larger angles that are of the order of magnitude of minutes or more. Not until Guinier (*9*) published a description of apparatus and diagrams of low-angle scattering patterns was this predicted application of x-ray diffraction brought into practice. Biscoe and Warren (*1*) applied the technique of low-angle scattering to the determination of particle sizes in carbon blacks.

Assuming that the particles or crystallites are of spherical shape and random distribution, and that the average particle

[1] Present address, The M. W. Kellogg Company, Jersey City, N. J.

[2] C. G. Shull presented a similar independent treatment of the low-angle scattering at the meeting of the American Society for X-Ray and Electron Diffraction at Gibson Island, Md., August 23, 1944.

diameter is large as compared with the wave length of the radiation employed, the intensity of the scattered x-radiation from such a system can be sufficiently approximated by

$$I = K \times \exp -\frac{R^2k^2}{5}$$

Constant K is related to the differential scattering powers of the particles and their surrounding medium, and contains such fundamental constants as the mass and charge of the electron, etc. R is the radius of the particles and k is defined as $4\pi \sin \theta/\lambda$. Fankuchen and Mark (*8*) calculated from this equation the angles at which the scattered radiation reaches half its value at $\theta = 0$, for various particles of radius R. Assuming that CuK_α radiation of $\lambda = 1.54$ Å. was used, the following calculated values were obtained:

Radius, Å.	Angle 2θ at Which I Has Fallen to Half of Initial Value, Minutes
25	63.0
50	31.5
100	15.8
200	7.8
400	3.9

This tabulation shows that the magnitude of the scattering angle 2θ is of the order of minutes, and that it depends sharply on R.

Because of the inherent difficulties encountered in measurements of scattered intensity at zero angle, the method of Biscoe and Warren (*1*) of plotting $\log I$ against k^2 is a more elegant way of interpreting the data. In a plot of this type the slopes of the lines are characteristic of the value of R with the steeper slopes representing the larger particles.

APPARATUS

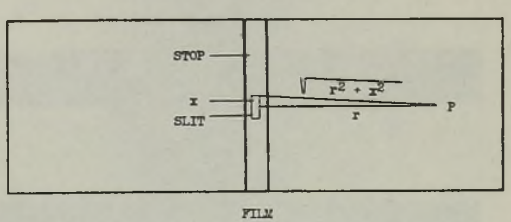
The x-ray source was a copper target line-focus tube with Lindemann glass windows operated at 35 kilovolts with a plate current of 15 milliamperes. The Debye-Scherrer diagrams were obtained with naked film in an enclosed cylindrical camera of 114.5-mm. diameter, fitted with a 1-mm. pinhole collimator and an exit tube to reduce air scattering to a minimum. The specimen was rotated during the exposures. The primary beam was filtered through nickel foil to provide essentially $CuK\alpha$ radiation before it entered the collimator. All exposures lasted 3 hours.

The low-angle diagrams were obtained by collimating the unfiltered x-ray beam through a horizontal slit system approximately 30 cm. long, passing this beam through the specimen, and receiving the scattered radiation on a flat plate at a distance of 30 cm. from the specimen. The cassette was such that $1^1/_4 \times 5$ inch film could be used. The face of the cassette was fitted with a lead stop, about 2 mm. wide and approximately 1 cm. from the film, to catch the primary undeviated x-ray beam; the cassette was made light-proof by being faced with nickel foil which also served as a filter. The cassette face had a strip about $^5/_{16}$ inch wide, running lengthwise, that was permeable to x-radiation so that the pattern obtained could easily be distinguished from the unexposed film. Satisfactory diagrams were obtained in 2-hour exposures.

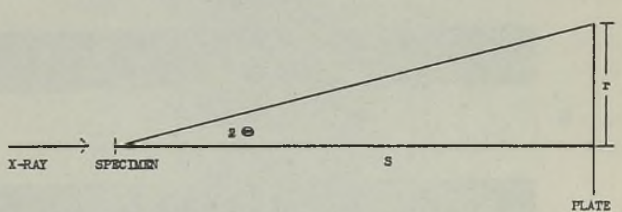
The specimens for the powder diagrams were 0.3 mm. in diameter and about 4 mm. long. They were supported in the camera on a fine wire of the same diameter and about 3 mm. long, which was mounted in molding clay on the chuck of the rotating mechanism. As the preparation of suitably sized uniform specimens is something of a problem, the method will be described, as it permits the rapid production of identical specimens. After the most desirable specimen thickness had been determined, heavy-wall Pyrex capillary tubing, with a bore equal to the optimum specimen diameter, was chosen and cut into lengths of approximately 5 cm. The ends of these sections were ground square. This is of the utmost importance since the straightness of the specimen is determined by the condition of the capillary end. If any chips are produced at the capillary opening, the end must be reground or the tube discarded. A short section (3–4 mm.) of steel wire making a mild friction fit in the bore is next introduced to serve as specimen support, and the preparation of the specimen commenced. To a small quantity of ground sample on a microscope slide is added one drop of ether and one drop of dilute collodion. The moist material is well mixed, and the paste so formed is forced into the capillary by a microspatula. When sufficient material has been forced into the tube, the end is wiped clean and placed against a clean microscope slide. At this point another piece of the steel wire longer than the capillary is introduced through the opposite end, and the specimen is tamped down. After about one minute the capillary is upended, and the specimen slowly extruded by forcing the wire through the bore. When the short wire becomes exposed, it can be seized with forceps and the specimen placed in the camera. A method substantially as described above was used by Biscoe and Warren (*1*) in the preparation of carbon black specimens.

A convenient method of mounting specimens for the low-angle studies consists in packing a paste of the specimen and collodion into a rectangular opening about 6 mm. long and 3 mm. wide, cut into a metal plate. The samples can be made of uniform thickness by placing the metal plate flat on one microscope slide, filling the orifice with the sample, and then scraping it level with the edge of another slide. The plate containing the specimen can then be mounted in front of the slit system so that the x-ray beam does not come in contact with the metal. The use of thin-wall Pyrex capillary tubes gives good results but requires great care in selecting tubes of identical bore and wall thickness, especially if comparative studies are to be made of the low-angle scattering patterns.

It is of some interest at this point to consider what effect the use of a slit system rather than a pinhole system would have upon the intensity of the scattered radiation. To a first approximation the slit may be regarded as a series of pinholes set alongside one another. Thus, the scattering at point P is the sum of the scattering from a theoretical succession of pinhole systems:



For the apparatus employed, the geometrical arrangement may be schematically represented as follows:



where S is the specimen plate distance. Thus,

$r/S = \tan 2\theta$, which can be equated to $2 \sin \theta$ at small angles (1)

It has been shown that

$$I(\theta) = K \exp -\left(\frac{4\pi \sin \theta}{\lambda}\right)^2 \frac{R^2}{5} \quad (2)$$

for a pinhole collimator; by substituting Equation 1 in 2,

$$I(r) = K \exp -\left(\frac{2\pi r}{S\lambda}\right)^2 \frac{R^2}{6}$$

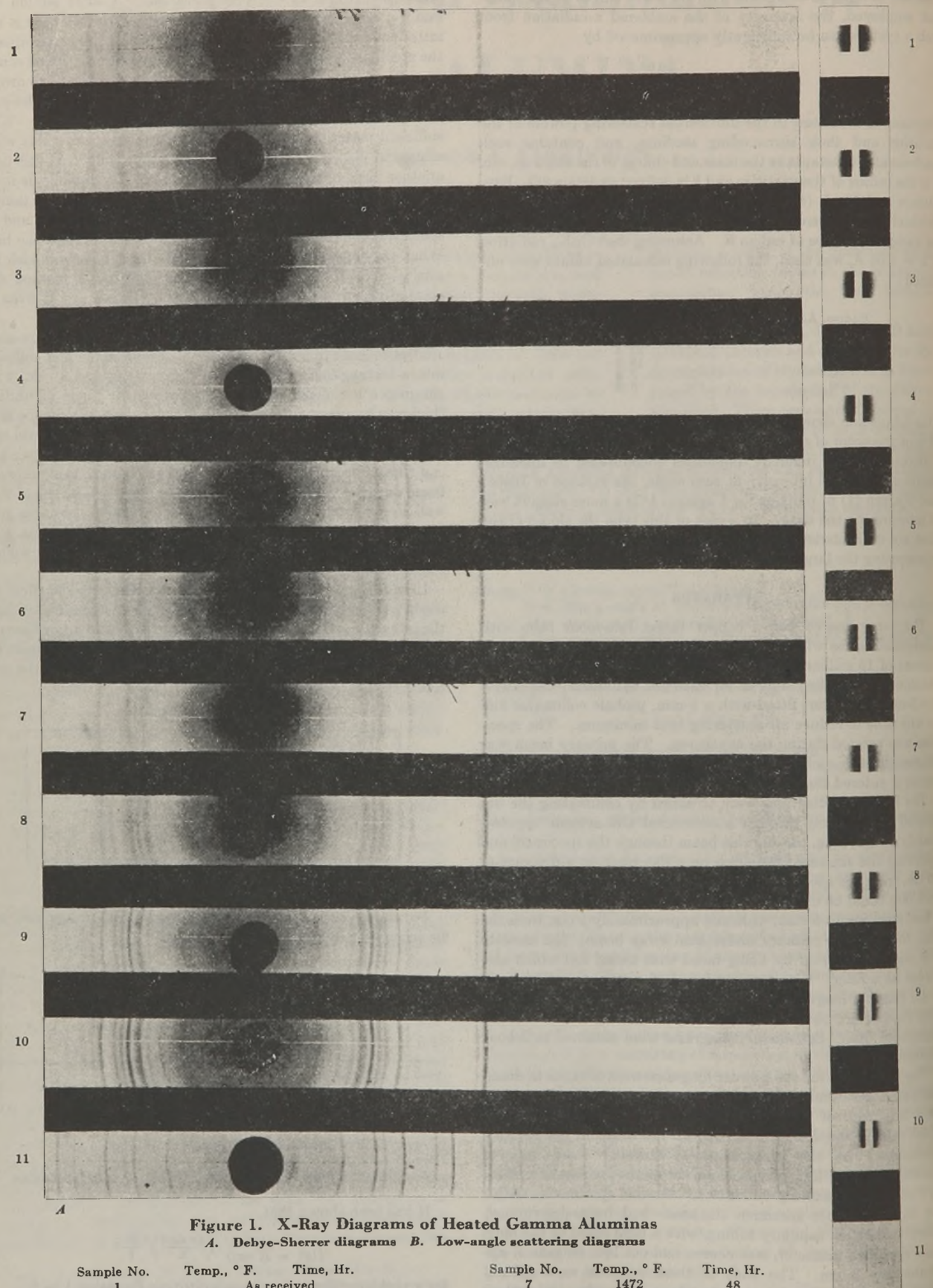


Figure 1. X-Ray Diagrams of Heated Gamma Aluminas

A. **Debye-Sherrer diagrams** ***B.*** **Low-angle scattering diagrams**

Sample No.	Temp., ° F.	Time, Hr.
1	As received	
2	1472	2
3	1600	1
4	1472	3
5	1472	6
6	1472	24
7	1472	48
8	1600	6
9	1650	16
10	1800	8
11	α-Alumina or corundum	

which can be written as

$$I(r) = K \exp^{-c^2r^2} \tag{3}$$

where $c = 2\pi R/\sqrt{5}\,\lambda S$

The intensity at a point P due to a slit collimated beam along the central line of the film is approximately given by

$$I(r) = 2K \int_0^a \exp^{-c^2(r^2+x^2)}\, dx$$

where a = half length of slit

This can be written as

$$I(r) = K' \exp^{-c^2r^2} \int_0^a \exp^{-c^2x^2}\, dx \tag{4}$$

By setting $y = cx$ and substituting in 4,

$$I(r) = \frac{K'}{c} \exp^{-c^2r^2} \int_0^{ca} \exp^{-y^2}\, dy$$

This is in the form of the probability integral and contributes only a constant factor independent of r to the scattering for any given slit system; it has the effect of raising or lowering the intensity by a constant factor.

It can similarly be shown that the cross fire through the length of the collimating slits has a similar effect and is approximately independent of the slit length. Thus the use of slits rather than pinholes results only in darker films and more x-ray intensity at any given point for equal exposure times. The particle size can still be evaluated by taking logarithms following Biscoe and Warren (*1*) and determining particle size from the slopes of the resulting curves.

PREPARATION OF ALUMINUM OXIDE SAMPLES

The aluminum oxide used in this investigation was a sample of commercially available gamma alumina that had been prepared by heating aluminum oxide trihydrate to a final top temperature of 1200° F., under such conditions that the alumina still contained 2-3% water removable by ignition at 1800° F. This alumina was ground to approximately −40 mesh, and samples were heated in an electrically heated laboratory muffle furnace whose temperature was determined by the use of either iron-constantan or chromel-alumel thermocouples reading on a calibrated millivoltmeter. The iron-constantan couple was used for some of the lower temperature work, and the chromel-alumel for heating at more elevated temperatures. After heating, the alumina samples were ground in an agate mortar until fine enough for the x-ray work.

Samples of gamma alumina were heated at 1472°, 1600°, 1650°, and 1800° F. for varying periods. Then Debye-Scherrer and low-angle diffraction diagrams were made of each specimen. Similar diagrams were also taken of a specimen of powdered alumina that had been heated strongly enough to convert it completely to alpha alumina (corundum) without fusing the sample. Table I contains the Bragg spacings and relative intensities of the diffraction rings on all the powder diagrams. The intensities are in each case relative and are obtained by assigning a value of 100 to the most intense diffraction line on each film.

INTERPRETATION OF RESULTS

The data in Table I clearly indicate that up to a certain point the effect of heating the alumina causes the appearance of more and more diffraction lines. It is also clear that all the samples, up to and including the one heated at 1472° F. for 48 hours, contain no detectable trace of alpha alumina. The increasing number of observable reflections longer than 1 Å. is testimony to the increasing perfection of the crystallites making up the specimens.

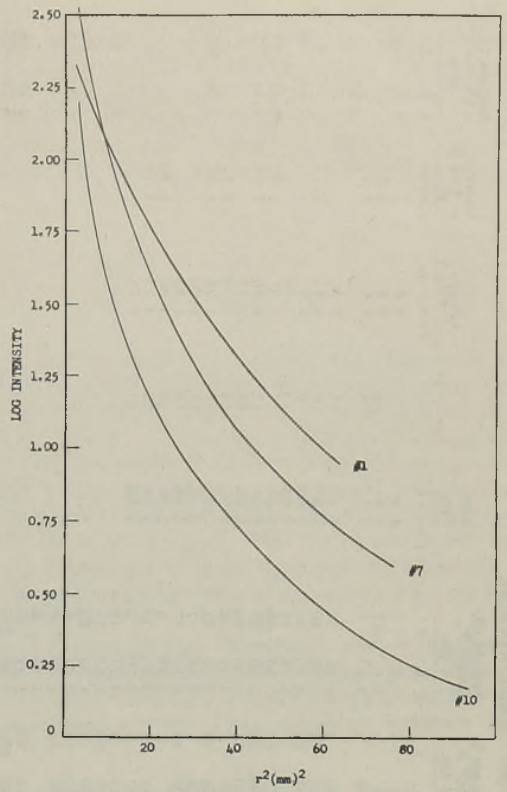


Figure 2. Low-Angle Scattering of Gamma Alumina

Figure 1*A* shows the Debye-Scherrer diagrams from which the data of Table I were obtained. It is apparent that the structural perfection and development which had occurred in the gamma alumina by heating was definitely related to an increase in the particle or crystallite size. This is indicated by the continuous sharpening of the diffraction lines in all the gamma alumina patterns. The apparent broadening of the strongest alumina line in patterns 8, 9, and 10 is not in any way related to a reversal of this general trend, but is an illusion caused by the appearance of two lines of corundum which just straddle this gamma alumina line. Thus the effect of heat on gamma alumina, produces, over a fairly large temperature range, a change that is not one of crystal form or modification but rather a perfection of structure through the growth of the alumina crystallites.

Some quantitative idea as to the changes in crystallite size with heating can be obtained from a study of the breadths of the Debye-Scherrer rings. The 1.40 Å. line of gamma alumina was used for this purpose. The measured widths at half maximum of the corundum lines at 1.41 and 1.38 Å. were used as the correction factor.

COMPUTATION OF CRYSTALLITE SIZE

A computation of crystallite size is given for specimen 1 as an example. B_c, the corrected breadth at half maximum intensity, is calculated from B_o, the observed width at half maximum, and B_s, the width at half maximum, of a well crystallized material by substituting in the equation, $B_c^2 = B_o^2 - B_s^2$:

$$B_o = 2.2°;\ B_s = 0.8°$$
$$B_c^2 = B_o^2 - B_s^2 = \overline{2.2}^2 - \overline{0.8}^2 = 2.1°$$
$$B_c = 2.1°/57.3° = 0.0366 \text{ radian}$$

This value of B_c is used in the following equation to compute L:

$$L = 0.89\lambda/B_c \cos\theta$$

TABLE I. DEBYE-SCHERRER PATTERNS OF HEATED GAMMA ALUMINA

Sample 1 Unheated		Sample 2, 1472° F., 2 Hr.		Sample 3, 1600° F., 1 Hr.		Sample 4, 1472° F., 3 Hr.		Sample 5, 1472° F., 6 Hr.		Sample 6, 1472° F., 24 Hr.		Sample 7, 1472° F., 48 Hr.		Sample 8, 1600° F., 6 Hr.		Sample 9, 1650° F., 16 Hr.		Sample 10, 1300° F., 8 Hr.		Calcd. d_{hkl} with $a = 8.4$ Å.	$h^2 + k^2 + l^2$	Assume $a = 7.84$ Å. Primitive	Assume $a = 7.84$ Å. Face Center	Sample 11, Corundum	
d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I	d, Å.	I					d, Å.	I
																6.2	6	5.9	7	5.9	2	5.6			
				4.7		4.7		4.8		4.8	10	4.7		4.7		4.5	9	4.5	13	4.5	3	4.5			
																4.23	3	4.17	1	4.2	4	3.9		3.50	38
												3.58	3			3.50	6	3.42	20	3.43	5	3.50			
												3.02	3	3.08	5	3.02	13	3.02	20	2.97	8	2.77		2.77	
				2.75	23	2.75	11	2.80	8	2.80	7	2.80	27	2.80	15	2.80	29	2.80	23	2.80	9	2.61			
																		2.70	12	2.68	10	2.48		2.85	5
								2.57	3	2.57	3	2.57	20	2.57	17	2.57	57	2.57	50	2.53	11	2.37		2.57	63
2.48	24	2.40	23	2.48	27	2.40	14	2.45	10	2.45	13	2.45	33	2.48	15	2.40	31	2.45	15	2.40	12	2.43		2.44	32
2.33	8	2.30	14	2.30	10	2.30	8	2.27	7	2.30	8	2.27	13	2.33	8	2.30	34	2.30	20	2.33	13	2.17			
																		2.30	8	2.25	14	2.10			
2.14	12	2.11	9	2.14	6	2.11	6	2.11	5	2.14	7	2.11	17	2.14	12	2.08	43	2.08	33	2.10	16	1.96		2.08	100
																2.05	1	2.05	7	2.04	17				
1.97	40	1.99	43	1.98	30	1.99	26	1.99	17	1.98	25	1.98	40	2.00	13	2.00	34	2.00	17	1.98	18	1.85			
						1.92	1	1.92	2	1.95	2	1.95	7					1.90	5	1.96	19	1.80		1.80	
								1.87	4			1.88	3	1.88	3	1.88	20	1.88	12	1.96	20	1.75		1.75	
								1.78	1	1.79	2	1.79	1			1.81	3	1.79	2	1.88	21	1.71			
										1.75	2					1.72	6	1.71	13	1.83				1.73	38
								1.65	1	1.67	1	1.64	3	1.66	7	1.62	20	1.62	15						
																1.60	9	1.59	22					1.60	100
1.54	4	1.52	11	1.52	6	1.52	6	1.52	3	1.54	5	1.54	7	1.56	5	1.52	11	1.52	8					1.56	5
												1.50	7	1.52	3	1.49	14	1.49	7					1.54	17
																		1.47	8						
																		1.44	8						
												1.44	10	1.44	8	1.43	40	1.42	33					1.41	38
1.40	100	1.40	100	1.40	100	1.44	1	1.44	5	1.44	2	1.40	100	1.40	100	1.40	100	1.39	100					1.38	63
						1.40	100	1.40	100	1.40	100	1.35		1.36		1.35		1.34							
												1.31		1.33		1.31		1.30							
														1.28		1.26		1.27							
1.23				1.23				1.23		1.24		1.26		1.25		1.24		1.25						1.24	
																1.22		1.23							
																		1.21						1.20	
																1.18									
1.15		1.15		1.14		1.15		1.14		1.14		1.13		1.15		1.15		1.14						1.15	
														1.12		1.12		1.11						1.12	
																		1.09						1.10	
1.04		1.05		1.04				1.04		1.05		1.05		1.07		1.06		1.07						1.08	

Figure 3. Plot of Slope against Particle Size

d of line used is 1.4 Å. for which $\sin\theta = 0.55$ and $\cos\theta = 0.84$, for $\lambda = 1.54$ Å.

$$L = \frac{0.89 \times 1.54}{B_c \times 0.84} = \frac{1.63}{B_c}$$

$$L = \frac{1.63}{0.0366} = 45 \text{ Å. for specimen 1}$$

By similar computations the crystallite sizes for the other specimens were obtained:

Specimen No.	Crystallite Diameter, Å.
1	45
3	55
5	59
7	67
8	62

A definite increase in average crystallite size can be seen to occur with increased severity of heat treatment. The apparent decrease in size indicated for specimen 8 is due, as previously mentioned, to the two strong corundum lines which are beginning to appear and which straddle the gamma alumina line, broadening it, and thus lead to an incorrect value for the crystallite size.

The structure of gamma alumina is generally accepted to be a cubic structure of the spinel type (*8*, *10*). The side of the unit cube is given as 7.84 Å.; to explain the observed density, a defect type structure must be assumed. Even then there appears to be a large discrepancy (8%) between the measured density and that computed from the unit cell size chosen. In Table I many lines are tabulated which are clearly not alpha alumina. Some lines

which might be confused with known corundum lines can be distinguished from them on the basis of intensity considerations. These lines are not given by earlier workers and, moreover, do not fit their unit cell choice. Nevertheless, the patterns show a steady development in character with no abrupt transitions save that which occurs when the lines of corundum begin to make an appearance. It is difficult to see how these additional lines can be due to anything but a more perfect gamma alumina structure. A primitive cubic unit cell of side 8.4 Å. fits the data rather closely, and for twelve molecules of alumina per cell the computed x-ray density is 3.4 as compared to the measured density of 3.42.

Included in Table I are the values for $h^2 + k^2 + l^2$ and the spacings expected from these indices, assuming the 8.4 Å. unit cell. The agreement with the observed spacings is within experimental error. No systematic absences are evident and the cubic cell, if correct, is primitive. Values for $h^2 + k^2 + l^2$ beyond 21 are not included, for it is felt that a check in this region is meaningless unless precision spacing measurements can be made. For comparison the spacings of both primitive and spinel type lattices of 7.84 Å. edge are included in Table I. The spacings to be expected from the primitive cell of side 7.84 Å. do not agree with the observed spacings, whereas the face-centered cell of side 7.84 Å. does not even permit enough lines to account for all the noncorundum lines. Further, more carefully controlled heating experiments should result in even more sharply defined Debye-Scherrer diagrams without the conflicting contamination of corundum.

This crystallite growth is again demonstrated in Figure 1*B* in which low-angle scattering diagrams of the eleven samples of 1*A* are shown. Although the changes in these diagrams from 1 to 7 are small and difficult to see from one to the next following, comparison of 1 and 7 indicates that the blackened area has become definitely smaller. It is also important that the grayish diffuse blackening at the outer edge of pattern 1 has been markedly reduced when a condition as represented by pattern 7 is attained. This effect was more clearly visible on the original films because of their larger size. The change occurring from patterns 7 through 11 is far greater than in the earlier patterns, and this striking change parallels the appearance of corundum and the production of large crystallites of gamma alumina. Pattern 11 shows that, by the time alumina has been heated sufficiently to convert it completely to alpha alumina, the crystallites have grown to such a size that practically no observable low-angle pattern remains.

The change that can be observed qualitatively in Figure 1*B* is shown quantitatively in Figure 2. This graph illustrates the data obtainable from photometer traces of the low-angle scattering of samples 1, 7, and 10. To obtain these curves, $\log_{10}$ of the intensity of scattering at distance r mm. from the x-ray beam center is plotted against r^2. Plotting the data in this manner yields traces whose slopes are simply related to particle radius R. The particle size may be calculated as follows: By taking logarithms of Equation 3, $I(r) = K \exp^{-c^2r^2}$, we get $\log_e I = \log_e K - c^2r^2$. Substituting $c = 2\pi R/\sqrt{5}S\lambda$,

$$\log_e I = \log_e K - \left(\frac{2\pi R}{\sqrt{5}\,S\lambda}\right)^2 r^2$$

And as $S = 300$ mm., $\lambda = 1.54$ Å.:

$$\log_e I = \log_e K - 3.72 \times 10^{-5} R^2 r^2$$

$$\log_{10} I = \log_{10} K - 1.61 \times 10^{-5} R^2 r^2$$

Thus a plot of $\log_{10} I$ against r^2 yields a curve whose slope is $-1.61 \times 10^{-5} R^2$.

Consequently, if the slopes are measured in Figure 2, particle radius R can be computed. However, we found it simpler to use a linear graph of slope against R, made on log-log paper, as $\log(-\text{slope}) = \log 1.61 \times 10^{-5} + 2 \log R$. In this manner the slope at any point along the curves in Figure 2 may be quickly determined; by referring to that slope, R may be read off directly from a plot such as that shown in Figure 3 where the logarithm of the particle radius is plotted against the logarithm of the slope.

Measurements of this type have been made at the point where $r^2 = 5$, 10, 20, and 40 for the traces shown in Figure 2. The slopes and the respective average particle sizes as read from Figure 3 follow:

Sample No.	$r^2 = 5$	$r^2 = 10$	$r^2 = 20$	$r^2 = 40$
1	50 Å.	45 Å.	41 Å.	35 Å.
7	69	59	47	34
10	88	58	43	32

From the fact that the curves of $\log I$ against r^2 are not straight lines, it is obvious that we are considering a system containing a distribution of particle sizes. We do not feel justified on the basis of present data in attempting to evaluate this distribution.

Sample 1, the starting material, is most nearly homogeneous in the range investigated. Heating does not seem to break up the starting particles to any appreciable extent but does cause a growth of some of the particles. This can be seen in two ways, first, by the appearance of larger and larger particles, and second, by the systematic lowering of the curves for values of r^2 larger than 10.

For the more severely heated specimens, most of the scattered intensity is under the central stop with our experimental arrangement. This region could be studied by using more sharply collimated x-ray beams, narrower stops, and longer specimen to film distances.

CONCLUSION

Gamma alumina has many important industrial uses. Its desiccant properties make it useful as a drying agent, and in catalytic processes it is widely used as a dehydration catalyst.

These studies have revealed that an increasing perfection in the structure of gamma alumina can be brought about by heating and that this structural development is closely connected with crystallite growth. The sharper Debye-Scherrer diagrams obtained from heated gamma alumina suggest a primitive cubic unit cell of side 8.4 Å. It has been shown that the changes in the low-angle diffraction patterns are sensitive functions of particle growth. This growth can also be followed through line-breadth studies of the Debye-Scherrer patterns. The low-angle and line-breadth results are in good agreement. Both indicate an increase in the sizes of the regions they measure, the low angle in the particle size and the line breadth in the crystallite size. The particle diameters are about twice those of the crystallites.

ACKNOWLEDGMENT

The authors are indebted to the M. W. Kellogg Company whose kindness in furnishing samples and equipment made this work possible.

LITERATURE CITED

(1) Biscoe, J., and Warren, B. E., *J. Applied Phys.*, 13, 364 (1942).
(2) Bragg, W. L., "Crystalline State", G. Bell & Sons, London, 1933.
(3) Brill, R., *Z. Krist.*, 83, 323 (1932).
(4) Brill, R., and Pelzer, H., *Ibid.*, 74, 147 (1930).
(5) Cameron, G. H., and Patterson, A. L., *Am. Soc. Testing Materials*, Symposium on Radiography and X-Ray Diffraction Methods, 1936, 324.
(6) Clark, G. L., Applied X-Rays, New York, McGraw-Hill Book Co., 1940.
(7) Debye, P., *Physik. Z.*, 31, 348 (1930).
(8) Fankuchen, I., and Mark, H., *J. Applied Phys.*, 15, 364 (1944).
(9) Guinier, A., thesis, University of Paris, 1939.
(10) Hagg, G., and Soderholm, G., *Z. physik. Chem.*, B29, 88 (1935).
(11) Meyer, K. H., "Natural and Synthetic High Polymers", New York, Interscience Pub., 1942.
(12) Murdock, C. C., *Phys. Rev.*, 35, 8 (1930).
(13) Scherrer in Zsigmondy's "Kolloidchemie", 1922.

A "Reference" Precipitated Tricalcium Phosphate Hydrate

PREPARATION AND IDENTIFICATION

Since industrial and reagent tricalcium phosphates show such variance in chemical, structural, and fertilizer properties, a process is proposed for the preparation of a tertiary precipitate of accordant composition and uniform properties as a reference material in chemical and biochemical research. The process prescribes the slow addition of concentrated H_3PO_4 to a chilled lime-saturated concentrated sucrose solution, prolonged agitation, filtration or centrifugation of the precipitate, and low-temperature drying. Chemical and x-ray examinations demonstrated that the calcium content of the aqueous solution of sucrose occurs as the sucrate rather than the hydroxide. Accordance in composition and reproducibility of product were established by chemical and x-ray determinations. Differentiation between the "reference" tricalcium phosphate hydrate and hydroxyapatite is provided through two simple chemical tests in comparisons of their 900° C. calcines.

INDUSTRIAL precipitated tricalcium phosphates are characterized by marked variance in chemical, structural, and fertilizer properties (*9*). Workers in phosphate research have been handicapped by this variance, and they should be able to obtain or prepare a reference precipitate of definite composition and uniform characteristics.

There is no accepted or sponsored procedure for making the tertiary phosphate of calcium. At least three processes had been employed in the manufacture of the several lots that were examined, and two of the purported tertiaries proved to be dicalcium phosphate. The pertinent conclusion by Hodge *et al.* (*6*) that "the composition of the precipitated phosphates is seen to depend upon the mode of precipitation rather than the amount of reactants" can be amplified by the observation that certain properties of the precipitates are affected also by temperature prevalent during periods of precipitation, protracted digestion, washing, and drying.

The primary objective of this paper is to prescribe a process by which a tricalcium phosphate of accordant composition and uniform properties can be prepared as a standard reference for chemical and biochemical researches. Although intended primarily for the preparation of small quantities, the process can be scaled to industrial batch operations to obtain a product certifiable as reagent grade (*7*).

A second objective is to fulfill the expectation "that a simple and rapid chemical test would be proposed for the identification of industrial tertiaries" (*9*). Hence, a simple technique has been evolved whereby the proposed reference tricalcium phosphate hydrate can be distinguished from hydroxyapatite without resort to x-ray identification.

PREPARATION

The present procedure is distinct from the processes that employ soluble neutral calcic salts and phosphates and from the procedure whereby an aqueous system of monocalcium phosphate and calcium sulfate is ammoniated, according to the equation (*10, 11*):

$$CaH_4(PO_4)_2 + 2CaSO_4 + 4NH_3 = Ca_3(PO_4)_2 + 2(NH_4)_2SO_4$$

A concentrated sucrose solution is saturated with calcium oxide, clarified, and neutralized by the slow addition of concentrated H_3PO_4 requisite for the formation of $Ca_3(PO_4)_2$. The system is agitated vigorously during the addition and continuously for 4 hours thereafter. The precipitate is washed free of sucrose by either centrifugation or filtration and dried at low temperature. The several factors that affect the process will be mentioned and pertinent precautions will be prescribed.

PREPARATION OF REACTANTS. *Phosphoric Acid*, 85% C.P. Determine exact P_2O_5 content and express as per cent by weight. (In titrimetric analysis, the aliquot should contain ±20 mg. of P_2O_5.)

Sucrose Solution of Lime. Dissolve 450 grams of pure sugar in 2 liters of cold, carbon-dioxide-free, distilled water. Ignite 150 grams of finely ground calcite or marble for 3 hours at 1000° C. in an electric furnace, stirring at least three times during the 1–3 hour period; cool in a desiccator and grind to pass an 80-mesh sieve. Into the 2 liters of sugar solvent in an appropriate flask introduce 75 grams of the burnt lime; stopper and shake vigorously and again hourly, six times; allow to clarify overnight or centrifuge and determine CaO content in per cent by weight.

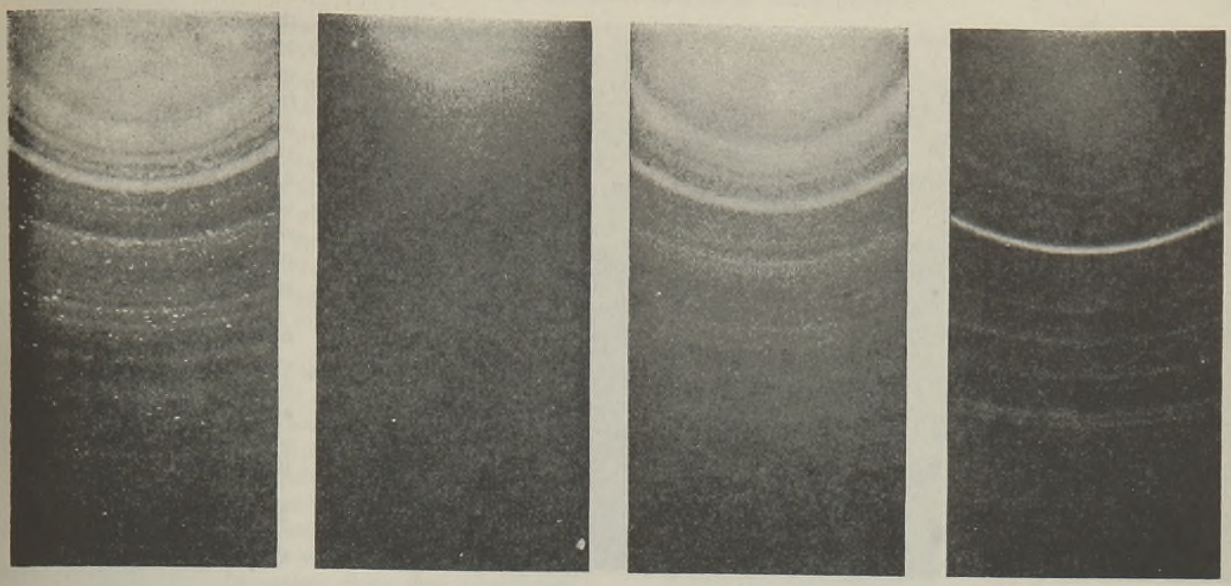
Washing Solution. Saturate 10 liters of carbon-dioxide-free distilled water with tricalcium phosphate and protect from atmosphere.

PRECIPITATION. Introduce 800 grams of the sucrose solution of lime into a 1-liter disk-covered beaker, partially immersed in a bath of iced water. A small hole in the center of the disk is provided to accommodate the shaft of a rotating blade so that the system can be agitated under cover during the addition of the acid. Add concentrated H_3PO_4 dropwise, and stir vigorously and continuously until the addition amounts to an excess of 0.25% of the stoichiometric requirement of $Ca_3(PO_4)_2$. Maintain the solution-suspension at proximately 5° C. during 4 hours of additional stirring, and either centrifuge or cover closely and allow to stand overnight. Siphon the supernatant, dilute the remaining solution with an equal quantity of "washing solution", and filter with low suction on a 12-inch Büchner funnel. Wash free of sucrose by means of successive small portions of the $Ca_3(PO_4)_2$-saturated washing solution, allowing full removal of

W. H. MACINTIRE, GEORGE PALMER, AND H. L. MARSHALL[1]

The University of Tennessee Agricultural Experiment Station and The Tennessee Valley Authority, Knoxville, Tenn.

[1] Present address, Phosphate Mining Company, Nichols, Fla.



A. Sucrose solvent, 22.5%

B. Sucrose solution of CaO [absence of sucrose and of $Ca(OH)_2$]

C. Sucrose and occluded amorphous $CaCO_3$ from *B*, after passage of CO_2

D. Calcite from $CaCO_3$ of *C*, after removal of sucrose

Figure 1. X-Ray Diffraction Patterns Showing Components of Sucrose Solution, Alone and Saturated with CaO, and after Removal of CaO by Passage of CO_2

every portion[2]. The washed precipitate should be exsiccated in a Hemphill desiccator until constant weight is attained, or dried in an electric oven overnight at 105° C., and ground to pass 100 mesh.

COMPOSITION OF THE SUCROSE SOLUTION OF LIME

The dissolubility of CaO in sugar solutions has been shown to exceed that of $Ca(OH)_2$, to increase with concentration of sucrose, and to increase with lowering of temperature (*2*). Dubrunfaut (*4*) found that at 0° C. the molecular ratio of lime to sucrose in a lime-saturated sugar solution was eight times that at 100° C. Cameron and Bell (*2*) noted that early workers ascribed the formulas $C_{12}H_{22}O_{11}.CaO$, $2C_{12}H_{22}O_{11}.3CaO$, and $C_{12}H_{22}O_{11}.3CaO$ to the compound formed in sugar solutions of variant concentration. Cameron and Patten (*3*) obtained that solid phase by warming a lime-saturated sucrose solution and found that the solid phase was amorphous and was "one of a series of solid solutions".

Because of the uncertainty as to whether the solute in lime-saturated concentrated sucrose solution is hydroxide or sucrate, it seemed advisable to establish the composition of the stipulated lime-saturated 22.5% sucrose solution. This solution had a pH of 12.4 by potentiometric determination, indicative of OH equivalence of 0.032 *N*, and contained 0.03% CO_2 by weight. Two days after an aliquot of the lime-saturated sucrose solution had been spread thinly in a Petri dish and allowed to evaporate in the laboratory atmosphere, the resultant solid showed a CO_2 content of 2.86%. Hence, upon the carbonatation of its initial $Ca(OH)_2$ content, the hydroxide content of the sucrose-lime system was replenished through hydrolysis of the sucrate.

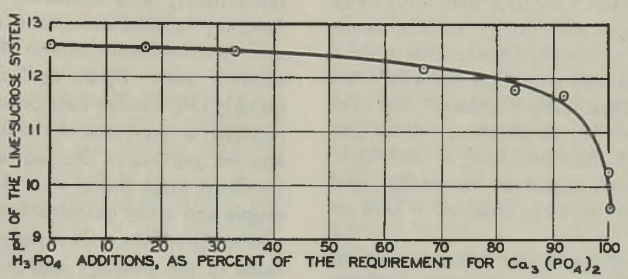


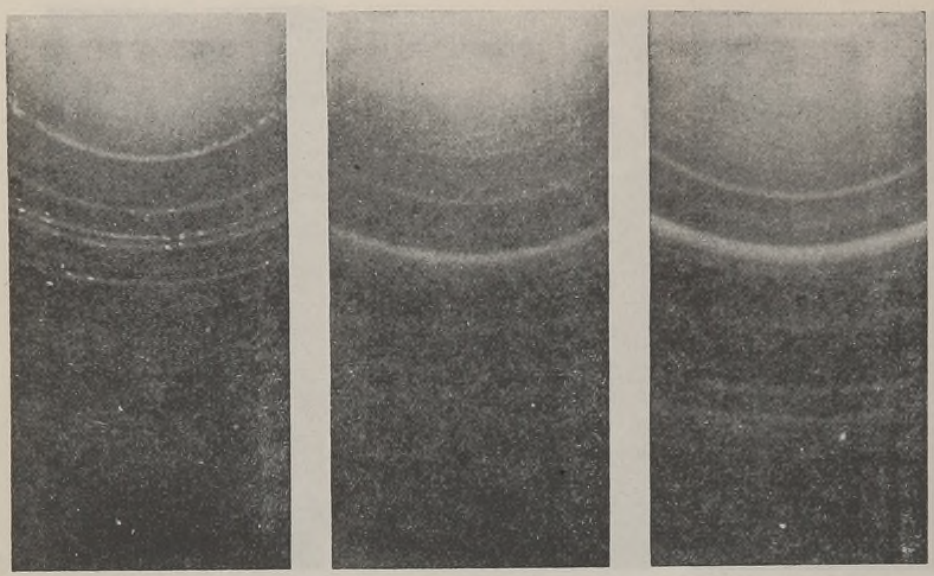
Figure 2. Changes in pH Induced by Progression in Addition of H_3PO_4 to Lime-Saturated 22.5% Sucrose Solution

The evaporated lime-free sugar solution gave the sucrose pattern *A* of Figure 1, whereas the evaporated lime-saturated sugar solution yielded no interference maxima, as in *B*. Obviously, the dissolution of the lime had effected conversion of the sucrose to noncrystalline calcium sucrate. Another portion of the lime-saturated sugar solution was subjected to a passage of gaseous CO_2 and then evaporated. Since the residue obtained by evaporation of the CO_2-treated lime-sugar solution gave sucrose pattern *C* without lines indicative of $CaCO_3$, it is apparent that the precipitation of calcium carbonate induced a reappearance of sucrose. When the residue from the evaporated mixture of sucrose and amorphous $CaCO_3$ was washed free of sucrose, the occluded carbonate clustered and registered as calcite in pattern *D*. The pattern of sucrose in *A*, its absence and the absence of the pattern of $Ca(OH)_2$ in *B*, the reappearance of the sucrose pattern in *C* without pattern indication of the observable precipitate of $CaCO_3$, and the occurrence of calcite in *D* point to the following conclusions: Calcium sucrate, rather than $Ca(OH)_2$, was the predominant solute in the sugar solution of lime; the sucrate underwent progressive hydrolysis and carbonatation during the passage of CO_2; the precipitate of $CaCO_3$ was too dispersed in the re-formed sucrose to register a pattern; and removal of the freed sucrose allowed the peptized calcium carbonate to acquire the calcite structure.

EFFECTS FROM ADDITIONS OF H_3PO_4 TO THE LIME-SATURATED SUCROSE SOLUTION

CHANGES IN pH. In planning the preparation of the "reference" tertiary phosphate, it was postulated that the calcium

[2] Filtration can be expedited by first expanding the volume of the precipitate by an equal volume of +20 −40 mesh quartz, processed by aqueous washing before and after digestion with HCl, 1 + 9. The quartz is then screened from the precipitate. Wash-drying with acetone has been found inadmissible.



A. $CaHPO_4.2H_2O$ upon $^1/_3$ neutralization of sucrose-lime solution

B. Mixture of $CaHPO_4.2H_2O$ and $Ca_3(PO_4)_2.nH_2O$ upon $^2/_3$ neutralization of sucrose-lime solution

C. $Ca_3(PO_4)_2.nH_2O$ upon complete neutralization of sucrose-lime solution

Figure 3. Composition of Precipitates Formed upon $^1/_3$, $^2/_3$, and Full Neutralization of Saturated Sucrose Solution of Lime by Concentrated H_3PO_4

sucrate solution would undergo continuous hydrolysis and thus provide a sustained reaction between $Ca(OH)_2$ and the slowly added acid. Therefore, pH changes induced by variant increments of concentrated H_3PO_4 to a constant of the lime-saturated 22.5% sucrose solution were determined potentiometrically. To 100-gram portions of the chilled lime-sucrose solution, the acid was added in fractions of 17, 34, 67, 83, 92, 100, and 100.25% of the quantity required to convert the dissolved lime to $Ca_3(PO_4)_2$. The resultant systems were closed, agitated vigorously, and brought to 20° C., and their pH values were obtained within an hour.

Figure 2 shows that the effects of the 17 and 34% additions of H_3PO_4 upon pH were not pronounced, whereas the 67% addition brought a decided decrease. Further decreases in pH were induced by the larger additions, those of 92 and 100% in particular. The sensitivity of the system in which the two solutions were brought together in stoichiometric proportion is reflected by the drop in pH from 10.27 to 9.55 that came from an excess of 0.03 ml. of 85% H_3PO_4. The distinct alkalinity of the system that received the slight excess of acid may be attributed to a temporary occlusion of the acid and/or to a measurable hydrolyzation of the mass of tertiary precipitate.

When allowed to age, however, those systems that contained 90% or more of the stoichiometric equivalence of H_3PO_4 registered decided decreases in pH values. The system that received the 92% addition went from pH 11.65 to 11.20; the system that received the 100% addition went from 10.27 to 5.72, whereas the one that received the 0.03-ml. excess showed a change in pH from 9.55 to 5.40. In the preparation of the "reference" tertiary, a similar result is attained by the prescribed 4-hour period of agitation.

Identity of Successive Precipitates Formed. Upon assumption that the sucrate would function as calcium hydroxide, the succession of primary, secondary, and tertiary phosphates would be indicated by the equations:

$$2H_3PO_4 + Ca(OH)_2 \longrightarrow CaH_4(PO_4)_2 + 2H_2O$$
$$CaH_4(PO_4)_2 + Ca(OH)_2 \longrightarrow 2CaHPO_4 + 2H_2O$$
$$2CaHPO_4 + Ca(OH)_2 \longrightarrow Ca_3(PO_4)_2 + 2H_2O$$

To elucidate this point, the H_3PO_4 was added in separates of $^1/_3$, $^2/_3$, and full stoichiometric equivalence of the CaO content of the sugar solution. The three resultant precipitates were filtered immediately and subjected to x-ray examination. The large flaky crystals, formed at the initial stage of the $^1/_3$ addition of the acid to the sucrose solution of lime, were suggestive of the monocalcium salt. Upon agitation, however, the flakes passed quickly into a milky suspension. In an attempt to establish their identity, a $^1/_{12}$ quota of the full H_3PO_4 equivalence was added to another portion of the lime-saturated sucrose solution, and the resultant large flakes were filtered immediately. Under microscopic and x-ray examination they proved to be dicalcium phosphate dihydrate. Obviously the equationed successive formations of the primary and secondary phosphates were virtually simultaneous.

Pattern *A* of Figure 3 shows $CaHPO_4.2H_2O$ as the precipitate present at the conclusion of the initial $^1/_3$ addition of H_3PO_4. The product present after the similar addition of the second $^1/_3$ portion of acid proved to be a mixture of $Ca_3(PO_4)_2.nH_2O$ and $CaHPO_4.2H_2O$, as shown by pattern *B*. The product resultant from the full addition of H_3PO_4 was the tertiary hydrate *C*. The x-ray pattern of this precipitate was identical with patterns registered by parallel precipitates that were agitated 30 minutes, 2 hours, and 4 hours before filtration. Prolonging agitation, however, induces agglomeration of crystals and affords a pattern characterized by distinction of lines, as in *C*.

Table I. Effect of Concentration of Sucrose Solution of Burnt Lime and System Temperature upon Composition and Availability of Precipitates[a] Formed by Addition of Concentrated H_3PO_4

			Precipitated Tricalcium Phosphates									
						% Citrate-Insol. P_2O_5 by:				% of Availability by:			
						Agitation at 5-min. interval	Constant agitation for 1 hour			Agitation at 5-min. interval	Constant agitation for 1 hour		
			Composition			Single[b]	Single	Double	Single	Single[b]	Single	Double	Single
Ppt.	Concn. of Sucrose Soln., %	Temp. of System, ° C.	CaO, %	P_2O_5, %	P_2O_5/CaO	1:100	1:100	1:100	1:200	1:100	1:100	1:100	1:200[c]
A-1	11.25	25	51.36	43.30	0.843	20.85	19.80	5.10	8.25	51.8	54.3	88.2	81.0
B-1	11.25	5	50.82	42.90	0.844	19.20	18.90	3.85	7.80	55.5	56.2	91.1	81.9
A-2	22.50	25	51.28	43.10	0.840	17.65	15.50	2.70	..	59.8	63.9	93.7	..
B-2	22.50	5	50.40	43.10	0.855	13.43	12.70	0.85	..	68.8	70.5	98.0	..

[a] Oven-dried at 130° C.
[b] As prescribed for commercial fertilizers by official method of A.O.A.C.
[c] Ratios of 1 gram per 100 ml. and per 200 ml. of citrate reagent.

CONCENTRATION OF THE SUCROSE SOLUTION OF LIME AND SYSTEM TEMPERATURE DURING PRECIPITATION

Since the oxide of calcium is more dissolvable than the hydrate, freshly burned lime was used in making the sucrose-lime solutions utilized in preparing the precipitates. The influence of lime concentration in the sucrose solution and the effect of system temperature upon composition and filterability of the precipitates were initial considerations. Accordingly, stoichiometric additions of H_3PO_4 were made to the lime-saturated 22.5% sucrose solution, and to one made by a 1 + 1 dilution, at 25° and at 5° C. The effect of the dilution upon calcium ionization was registered by a rise from the initial pH of 12.4 to 12.5; further dilutions gave elevations in pH up to 12.9.

The analyses of Table I indicate that the specified variance in concentration of the lime-saturated sucrose reactant exerted no appreciable effect upon composition of precipitates formed at identical temperature. The precipitates from the 22.5% sucrose solution were, however, of larger particle size and therefore more readily filterable. Although all of the products were close to theoretical in their P_2O_5/CaO ratios, the analyses indicate that the precipitates formed at 25° C. were slightly more basic and somewhat less dissolvable in ammonium citrate than those formed at 5° C. The probability of hydrolytic effects is less, however, in chilled systems, and a maintained system temperature of 5° C., therefore, is prescribed.

The patterns of Figure 4 represent the four products of Table I. Since the four tricalcium phosphate hydrates registered the same pattern, it follows that their structures were not altered measurably by the variance in the concentration of the sucrose solution of lime or by the 20° variance in system temperature.

REPRODUCIBILITY OF PRODUCT. The products and analyses of Table I were made by an experienced analyst in checking results obtained by the initial operator, who had obtained a product having a P_2O_5/CaO ratio of 0.844. To ascertain the expectancy for reproducibility of product, the process and analyses of respective products were assigned to four operators not familiar with the prescribed technique. The analyses of Table II and the x-ray patterns of Figure 5 indicate that reproducibility of product can be attained by operators not experienced in the prescribed manipulation or in the analysis of the reactants and product.

AVAILABLE P_2O_5 CONTENT OF "REFERENCE" PRECIPITATE. It has been shown that the determined P_2O_5/CaO ratio is not an infallible index to the degree of availability a precipitated tertiary will register in chemical and biochemical tests (*9*). Although there is no prescribed official procedure by which to determine the availability of precipitated tricalcium phosphates, the citrate-insoluble content by the A.O.A.C. digestion (*1*) is utilized as an inverse measure of the available content. When a 1-gram charge of a precipitated tricalcium phosphate is digested one hour in neutral ammonium citrate, with periodic agitation as prescribed for the minor water-insoluble fraction of a commercial fertilizer, the percentage availability of the tertiary phosphate is invariably less than the percentage indicated by continuous agitation of the digestate (*8*). In every comparison of Table III a higher percentage extraction (as much as 25% more) was obtained when agitation was continuous. A single digestion of a 1-gram charge in 100 ml. of neutral ammonium citrate, therefore, is not an admissible procedure for the determination of the available P_2O_5 content of a precipitated tricalcium phosphate of unidentified structure, even when the digestates are agitated continuously and regardless of the inclusion of a pulped filter.

The ammonium citrate reagent was proposed by Fresenius, Neubauer, and Luck in 1871 (*5*) as an extractant for the water-

TABLE II. "REPRODUCIBILITY" OF PRODUCT BY FOUR OPERATORS IN FOLLOWING THE PRESCRIBED PREPARATION OF PRECIPITATED TRICALCIUM PHOSPHATE[a]

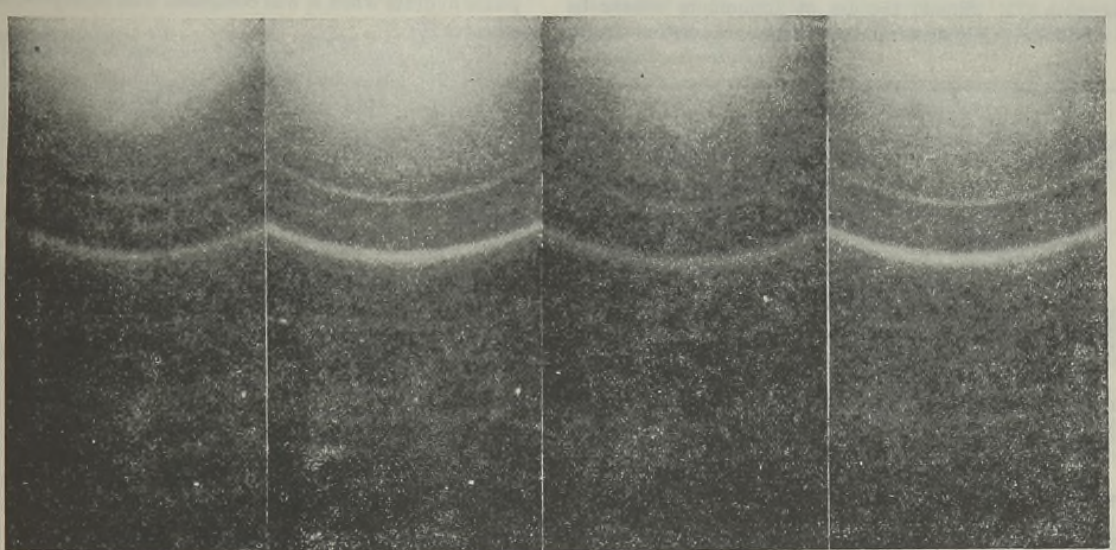
Operator	CaO, %	P_2O_5, %	P_2O_5/CaO
A	49.94	42.88	0.859
B	50.50	43.00	0.851
C	50.34	42.50	0.844
D	49.08	43.13	0.879
Theoretical[b]	51.25	43.27	0.844

[a] Products dried overnight in an electric oven. [b] $Ca_3(PO_4)_2.H_2O$.

TABLE III. AMMONIUM CITRATE AVAILABILITY VALUES FOR A SERIES OF "REFERENCE" TRICALCIUM PHOSPHATE PREPARED BY SEVERAL OPERATORS AND DRIED AT SEVERAL TEMPERATURES

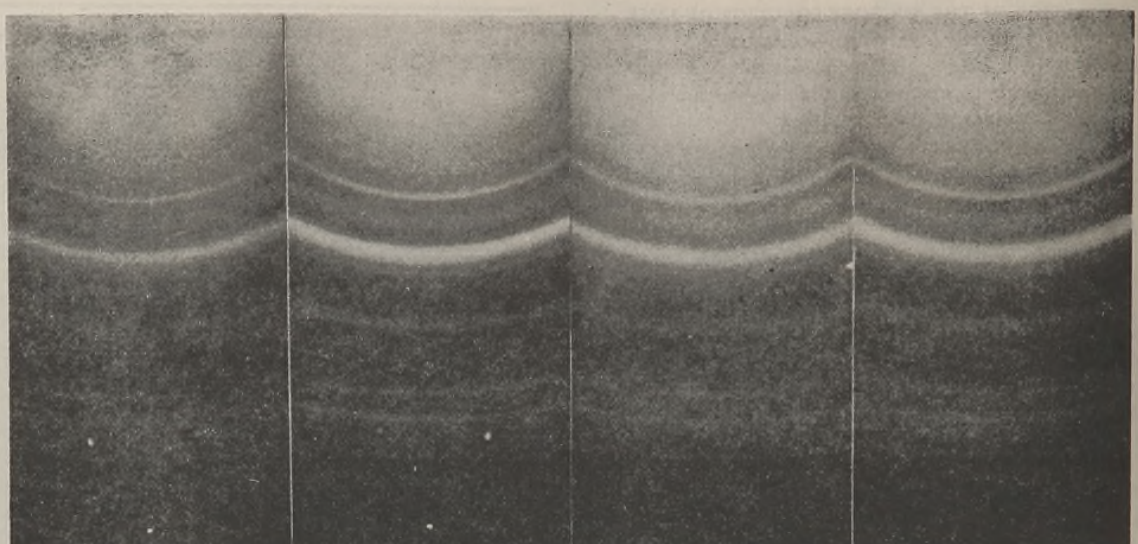
Sample No.	Drying Temp., ° C.	% Availability by Citrate Digestion with: Periodic agitation[a]	Continuous agitation[b] Single	Continuous agitation[b] Double[c]
1	130	51.85	54.27	88.22
2	130	58.86	63.87	93.76
3	130	55.22	56.15	91.07
4	130	68.84	70.53	98.02
5	120	74.70	86.59	100.00
6	130	54.65	59.07	95.35
7	120	72.59	91.18	100.00
8	105	90.95	97.10	100.00

[a] At 5-minute intervals in water bath.
[b] In electrically heated chamber.
[c] Value obtained when the result from a single digestion is augmented by the amount of P_2O_5 extracted from the residuum of the initial digestion.



A-1. 11.25% at 25° C. *B*-1. 11.25% at 5° C. *A*-2. 22.5% at 25° C. *B*-2. 22.5% at 5° C.

Figure 4. X-Ray Diffraction Patterns of Precipitates of Table I, from Sucrose Solutions of Two Concentrations at Two Temperatures



Operator A Operator B Operator C Operator D

Figure 5. X-Ray Diffraction Patterns Showing Reproducibility of Product in Preparation of Tricalcium Phosphate Hydrate by the Four Operators of Table II

insoluble phosphates, other than residues of rock, that are encountered in the analysis of acidic fertilizers. The dissolvent effectiveness of 100 ml. of the citrate solution is unduly taxed and vitiated, however, when applied to a 1-gram charge of tricalcium phosphate. This was true especially of precipitates dried at temperatures above 120° C. Decidedly higher availability values and better concordance were obtained by double digestions of 1-gram charges of the eight precipitates of Table III. Higher availability values (as much as 100%) were obtained when the charges were subjected to continuously agitated single digestions and when decreased to 0.5 gram. The pH of the neutral ammonium citrate reagent rises to 7.9 during the digestion of both 0.5-gram and 1-gram charges of the "reference" tricalcium phosphate.

A citrate digestion of a 1-gram charge of a tertiary precipitate and a successive digestion of the residue from that digestion would be consonant with the analytical removal of water-soluble phosphates from a fertilizer before its residue of relatively low citrate-soluble P_2O_5 content is subjected to the conventional citrate digestion (*1*). Should the use of ammonium citrate be deemed admissible, it appears that a successive extraction should be made if the availability of a precipitated tricalcium phosphate is to be measured by use of a 1-gram charge per 100 ml. of the reagent.

The implied recognition of the fact that the ammonium citrate digestion at 65° C. is not admissible in the evaluation of a basic slag can be extended logically to the evaluation of a precipitated tertiary calcium phosphate. In the determination of the available P_2O_5 content of basic slag by the Wagner method (*1*), continuous agitation at room temperature is prescribed for the digestion in 2% citric acid.

A freshly washed "reference" tricalcium phosphate precipitate was divided into four portions, and these were dried under four conditions: 3 days over sulfuric acid at 42 mm. pressure, and overnight at 105°, 110°, and 120° C. Subjected simultaneously to 2% citric acid digestions for 1 hour at room temperature, the four samples gave respective percentage dissolubilities of 99.8, 99.0, 99.9, and 98.3%. These analytical values are consonant with the effectiveness shown by the "reference" tricalcium phosphate hydrate when it was compared with superphosphate in pot cultures (*9*).

After 0.5-gram and 1-gram charges had been digested one hour in the 2% citric acid reagent, the solution was still definitely acidic, the initial pH of 2.50 having changed to respective values of 3.55 and 3.85. Obviously, the 2% solution of citric acid is preferable to the ammonium citrate reagent for the determination of the "availability" of precipitated tricalcium phosphates.

TABLE IV. DIFFERENTIATION OF HYDROXYAPATITE AND "REFERENCE" HYDRATED TRICALCIUM PHOSPHATE, AND THEIR CALCINES, BY AMMONIUM CITRATE AND CITRIC ACID DIGESTIONS

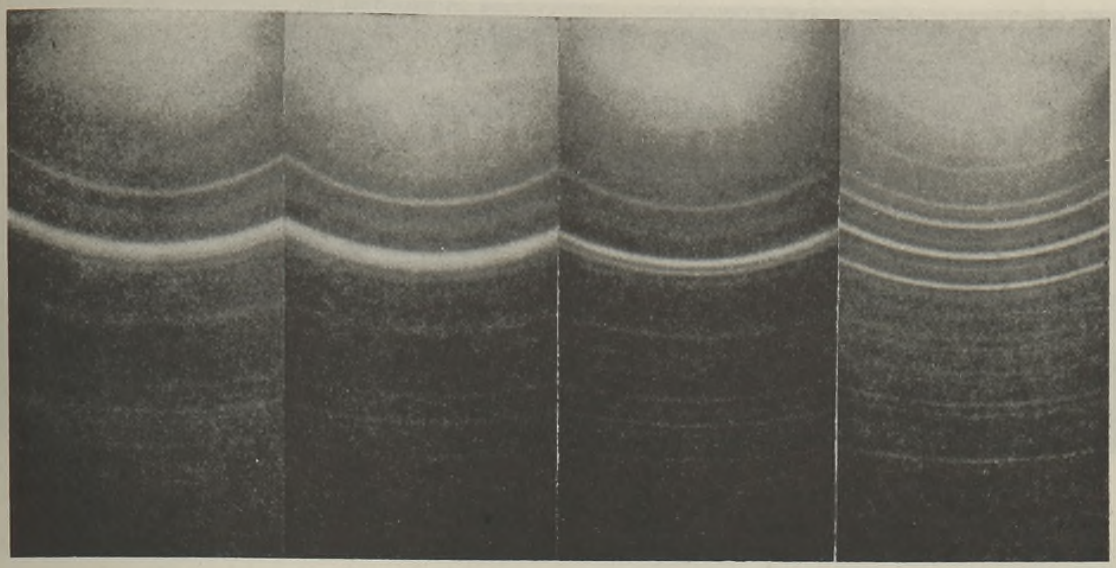
	Dissolubility of Tertiaries			
	In ammonium citrate[a]		In 2% citric acid[b]	
	Before ignition	After ignition	Before ignition	After ignition
	%	%	%	%
Hydroxyapatite				
S-903	34.6	13.2	73.6	68.6
S-982	52.8	18.0	83.9	71.6
S-986	45.9	17.7	77.4	75.8
S-989	39.0	16.0	79.2	64.5
"Reference" Precipitate[c]				
Operator 1	86.9	49.4	96.5	85.7
Operator 2	59.0	60.0	93.0	98.8
Operator 3	91.1	49.9	97.4	90.9
Operator 4	97.1	50.9	95.9	86.4
Industrial Product				
S-988	52.2	55.0	99.5	87.6

[a] Continuous agitation 1 hour at 65° C.; 1-gram charge per 100 ml. of neutral solution, 1.09 specific gravity.
[b] Continuous agitation one hour at room temperature; 1-gram charge per 100 ml.
[c] Prepared at different periods by the several operators; analyses by one analyst.

CHEMICAL IDENTIFICATION

A tricalcium phosphate hydrate and a hydroxyapatite cannot be differentiated by chemical analysis or by degree of solubility in the official ammonium citrate solution. Moreover, the x-ray diffraction pattern of the tertiary hydrate is identical with the pattern of the hydroxyapatite. Upon ignition at 900° C., however, the "reference" tricalcium phosphate hydrate precipitate from the sucrose solutions yields β-$Ca_3(PO_4)_2$, whereas the hydroxyapatite yields the oxyapatite, $Ca_{10}O(PO_4)_6$, as shown by their respective patterns in Figure 6. The relatively expensive x-ray apparatus is not common equipment, however, and it seemed desirable to evolve a simple chemical technique for the identification of a precipitated tricalcium phosphate hydrate.

Since the two precipitated tertiaries underwent no discernible change in physical condition at 900° C., it was postulated that the



A. Hydroxyapatite precipitate *B.* $Ca_3(PO_4)_2$ hydrate precipitate *C.* Oxyapatite calcine from *A* *D.* β-$Ca_3(PO_4)_2$ from calcine *B*

Figure 6. Differentiation between Hydroxyapatite and "Reference" Tricalcium Phosphate Hydrate from Sucrose-Lime Solution, Attained by Distinctive Patterns of 900° C. Calcines of the Two Materials

"reference" and the hydroxy precipitates could be differentiated through variance in the solubility of their calcines. In a test of this postulation, four tertiary industrial precipitates, established as hydroxyapatites, were compared with four "reference" precipitates obtained by four operators. The unheated precipitates and their 900° C. calcines were subjected to continuously agitated digestions in ammonium citrate at 65° C. and to continuously agitated citric acid digestions at room temperature. The comparisons in Table IV also included an industrial "precipitated tricalcium phosphate" that had been identified as such.

The results show that, by groups, the five commercial products were dissolved to a less extent than the four "reference" precipitates in the citrate reagent, although the dissolubility range was considerable within the groups. It is again evident, however, that degree of dissolubility in ammonium citrate is not an infallible criterion for differentiation of the two types of tertiary precipitates. The industrial precipitate of low citrate solubility was however, almost completely dissolved by the 2% citric acid reagent.

A maximal solubility of 18% of the charge was shown by the oxyapatite calcines from the four hydroxyapatites, whereas dissolubility values of 50 to 60% were shown by the beta calcines of the "reference" precipitates obtained from the sugar solution. The tertiaries of both groups show citric acid solubilities substantially higher than the corresponding values accorded by ammonium citrate. Unheated, the four hydroxyapatites show dissolubility of about 80% by citric acid digestion against 95% values for the four "reference" precipitates and for the industrial hydrated precipitate. Although the calcines of oxyapatite and those of β-tricalcium phosphate were both less dissoluble than their respective parent precipitates, the disparity between the degrees of dissolution shown by the citric acid digestions of the two groups of calcines continues to be substantial and serves to differentiate the parent precipitates.

It seems safe to conclude that a precipitated tricalcium phosphate can be designated as a hydroxyapatite when a 1-gram charge of 900° C. calcine registers a dissolubility of less than 20% by a continuously agitated 1-hour digestion in the ammonium citrate reagent at 65° C. In contradistinction, a tertiary precipitate is identified as a tricalcium phosphate hydrate when a like charge of its calcine shows dissolubility of as much as 50% by the stipulated citrate digestion.

As stated, however, the 2% citric acid reagent has distinct advantages. It is prepared more easily, and digestion is made at room temperature. A further advantage is that by the use of an admissible aliquot of the citric acid digestate, the analytical precipitation by molybdenum trioxide can be made directly. When an analytical charge of a precipitated tertiary is heated at 900° C. and then shows approximately 90% availability by a 1-hour continuously agitated digestion in 2% citric acid at room temperature, the product is identified as a normal tertiary hydrate. Every "reference" precipitate prepared by the presently prescribed process has met that test.

ACKNOWLEDGMENT

The foregoing studies were conducted at The University of Tennessee Agricultural Experiment Station in collaboration with The Tennessee Valley Authority, Departments of Chemical Engineering and Agricultural Relations. Acknowledgment is accorded F. D. Oldham, a former associate, by whom the tricalcium phosphate hydrate was first prepared from the lime-sugar solution of calcium oxide.

LITERATURE CITED

(1) Assoc. of Official Agr. Chem., Methods of Analysis, 5th ed., p. 39 (1940).
(2) Cameron, F. K., and Bell, J. M., U. S. Bur. of Soils, *Bull.* 49, 32 (1907).
(3) Cameron, F. K., and Patten, H. E., *J. Phys. Chem.*, 15, 67–72 (1911).
(4) Dubrunfaut, A. P., *Compt. rend.*, 32, 333 (1851).
(5) Fresenius, R., Neubauer, C., and Luck, E., *Z. anal. Chem.*, 10, 132 (1871).
(6) Hodge, H. C., Lefevre, M. L., and Bale, W. F., Ind. Eng. Chem., Anal. Ed., 10, 156 (1938).
(7) MacIntire, W. H., U. S. Patent 2,095,994 (1937).
(8) MacIntire, W. H., Marshall, H. L., and Meyer, T. A., *J. Assoc. Official Agr. Chem.*, 27, 272–83 (1944).
(9) MacIntire, W. H., Winterberg, S. H., Marshall, H. L., Palmer, George, and Hatcher, B. W., Ind. Eng. Chem., 36, 547–52 (1944).
(10) Ross, W. H., and Rader, L. F., Jr., *J. Assoc. Official Agr. Chem.*, 23, 235 (1940).
(11) Ross, W. H., Jacob, K. D., and Beeson, K. C., *Ibid.*, 15, 230 (1932).

Presented before the Division of Fertilizer Chemistry at the 108th Meeting of the American Chemical Society in New York, N. Y.

Machine Dishwashing Compounds

Figure 1. Application of Soil to Glass Squares

RAY C. HUGHES AND RUBIN BERNSTEIN

Industrial Test Laboratory, United States Navy Yard, Philadelphia, Pa.

Thirty-six dishwashing compounds, including commercially available proprietary products and experimental formulations, were tested for performance, composition, and other significant properties. As a result of these tests, those requirements which are believed to be adequate for use in specifying compounds of high effectiveness are suggested.

WHEN dishwashing is to be done on a large scale alkaline detergents are generally used. Most commercial dishwashing detergents consist of one or more of the following common alkalies: sodium hydroxide, sodium carbonate, sodium silicates, trisodium phosphate, borax, sodium bicarbonate, sodium sesquicarbonate, and modified soda. In addition, molecularly dehydrated phosphates such as tetrasodium pyrophosphate, sodium tripolyphosphate, sodium tetraphosphate and sodium hexametaphosphate are frequently present. Synthetic detergents or wetting agents are sometimes incorporated with the alkalies, but the use of too great a proportion of these materials is prohibited because of excessive foam produced in dishwashing machines.

No extensive series of tests to determine the relative value of commercially available dishwashing detergents have been reported in the literature by previous workers in this field. Baker (*2*) indicated the value of sodium metasilicate as a detergent; he based his conclusions on certain chemical and physical tests such as pH, displacement of petroleum oil from glass, emulsifying and suspending power, buffer capacity, and wetting power. Schwartz and Gilmore (*14*) showed that sodium hexametaphosphate prevents the formation of films of insoluble calcium and magnesium compounds on glassware soiled with a mixture of peanut butter, lard, and butter, and washed repeatedly. Cox (*3*) compared the detersive efficiency of trisodium phosphate, Army-issue washing soda (25% $NaHCO_3$, 65% Na_2CO_3), and Schwartz and Gilmore's hexametaphosphate mixture, and concluded that dishes washed with the latter showed no film formation and lower bacteria counts than those washed with trisodium phosphate or washing soda. Mallmann (*11*) and Hall and Schwartz (*9*), arriving at the same general conclusions as Cox, attributed the lower bacteria counts on dishes washed with a mixture containing sodium hexametaphosphate to the absence of film formation rather than to any inherent superior bactericidal action of the hexametaphosphate. Therefore, it appears from the above papers that some form of complex phosphate is desirable in dishwashing detergents to prevent or retard the formation of films which would retain bacteria.

The importance of proper washing of dishes and glassware, both from an esthetic and, especially, from a sanitary standpoint, has been well established. Cummings (*4*), in a survey of 370 public institutions, showed that eating utensils constitute an important avenue for distribution of saliva-borne disease such as pneumonia and influenza, and that the influenza case rate was three times higher for institutions using hand-washed dishes than for those using machine-washed utensils. Mallmann and Devereaux (*12*) and Krog and Dougherty (*10*) reported high bacteria counts on glassware and utensils taken from public eating and drinking establishments where washing methods were poor. Effective dishwashing compounds, when properly used, should remove food residues without deposition of hard water film and should leave the utensils physically clean and relatively free of bacteria.

The aim of this work was to determine those properties most characteristic of effective machine dishwashing compounds, and to develop specifications capable of permitting differentiation between highly effective compounds and those which are less effective. Accomplishment of this aim was considered to require the development of a reliable laboratory test of dishwashing effectiveness, measurement of the effectiveness of representative samples of available types of compounds, determination of the composition and properties of the compounds, and, finally, comparison of all data to permit the selection of significant specification requirements.

Tests of thirty-six compounds, either commercially available or proposed commercial formulations, have been made. The results of these tests have been used as a basis for the formulation of proposed specification requirements for dishwashing compounds.

SOILING TESTS

SOILING MIXTURE. The laboratory test for the measurement of dishwashing effectiveness was based on a method first described by Schwartz and Gilmore (*14*), but modified in several respects. Briefly, it consists of applying a soiling mixture having the properties of a food residue to plate-glass squares, washing the soiled squares under controlled conditions with solutions of the compound under test, and measuring the amount of soil remaining on the surfaces of the glass squares. Effectiveness of the compounds is then considered to be inversely proportional to the amount of soil left after use.

The glass squares, 5 × 5 inches, were cut from a single large sheet of 1/4-inch plate glass (Type A, second silvering quality) conforming to Federal Specifications (*5*). The uniform thickness

(within about 0.005 inch) obtained by use of a single large sheet of glass facilitated the application of the soiling mixture. Prior to use in a test these squares were washed thoroughly with soap and water, soaked in hot dichromate cleaning solution, rinsed thoroughly (finally with distilled water), and dried in an oven at 100° C. In the interval prior to use in tests, the clean squares were covered for protection from dust.

A mixture of 2 parts peanut butter, 1 part hydrogenated vegetable shortening, and 1 part butter was used for soiling the glass squares. It was prepared by weighing out the ingredients and mixing them at a temperature sufficiently elevated to melt the fats. While still hot, the mixture was passed through a 100-mesh sieve to remove coarse particles derived from the peanut butter. The prepared mixture was stored for use at room temperature in a closed container, under which conditions it appeared to be almost indefinitely stable.

The soiling mixture was applied to the previously prepared glass squares by a "soiling tube". This tube, constructed from tin plate, was 2 × 2 inches in cross section and about 5 inches long. One of the two open 2 × 2 inch ends was ground flat, and a pair of opposite sides at this end was cut back about 0.02 inch.

In soiling the glass surfaces, eight squares were lined up on a table with the edges of the squares against a metal guide. The soiling tube was placed at one end of the row of glass squares, positioned against the guide with undercut sides perpendicular to the guide, filled to a depth of 2–3 inches with the soiling mixture, grasped firmly, and drawn slowly down the row of glass squares. This operation resulted in the deposition of a film of soil 2 inches wide and about 0.02 inch thick down one side of each glass square. The two end squares were used in handling the soiling tube; the remaining six were used in the washing test. Figure 1 illustrates the application of soil to the glass squares.

Dishwashing Machine. Washing tests were made with a Sterling No. 7, U. S. Model, two-tank, conveyer-type, dishwashing machine with a capacity of 25 gallons per tank. At the conveyer speed employed in the tests, specimens being washed in this machine are first subjected for about 30 seconds to a spray of detergent solution and then to a 30-second rinse spray of water recirculated from a rinse tank; they finally pass out of the machine through a curtain spray of hot water and steam obtained directly from the lines. This final curtain spray is intermittent, being controlled by a valve tripped by passage of the dish basket, and impinges on individual specimens for about 5 seconds. Both the wash and rinse tanks are heated by injection of steam and are fitted with thermometers.

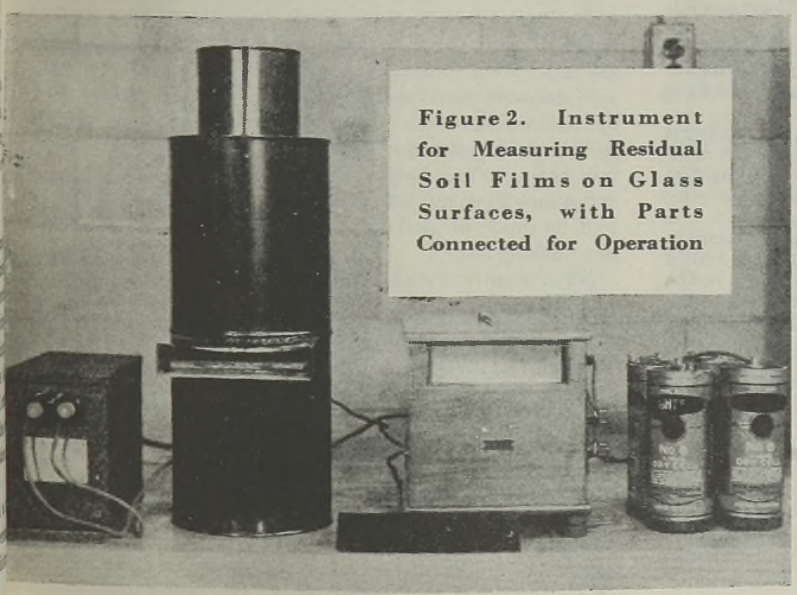


Figure 2. Instrument for Measuring Residual Soil Films on Glass Surfaces, with Parts Connected for Operation

To prepare the dishwashing machine for a test, both tanks were filled with water, steam was turned on, and temperatures were brought up to the desired points. Temperatures were initially adjusted at 140° F. for the detergent solution, 180° F. for the recirculated rinse water, and 212° F. for the curtain rinse. During a test, the rinse water temperature was kept constant by frequent adjustment of the steam valve. The temperature of the wash solution gradually rose during a test to about 160° F. because of gain of heat from the rinse tank. When temperatures had been adjusted, a small sample of water was obtained from the wash tank and reserved for a determination of hardness. A weighed sample of dishwashing compound was then added to the wash tank. This sample was dissolved, the solution was mixed by running the machine for about a minute, and a sample of the wash solution was then withdrawn for an alkalinity titration. Following preparation of the machine as described, a wash test was run immediately.

MEASUREMENT OF SOIL FILMS

Because of the apparent unsuitability of commercially available apparatus for the measurement of light soil films on glass surfaces, an instrument was designed and built especially for this purpose. It has been customary in similar studies of dishwashing compounds to employ photoelectric colorimeters for the measurement of residual soil films on washed surfaces. These instruments are designed to measure the decrease in light transmission produced by color or turbidity in liquids or solids, and have been applied to dishwashing studies to determine the decrease in transmission caused by a residual soil film on glass. The transmission of a clean glass plate is first determined, or the instrument is set to give a standard reading on a clean piece of glass. The soiled piece of glass is then substituted for the clean piece, and its transmission relative to that of the clean glass determined. Intensity of the soil film is then expressed as being proportional to the difference in transmission between the clean and soiled glass. This method suffers from the well recognized difficulty of making measurements by difference when the difference between the directly measured values is small. The maximum relative error involved in the measurement of density of films by this difference method is approximately equal to the sum of the absolute errors in the two primary measurements divided by the difference between the two primary measurements. Thus, the error becomes increasingly great with decreasing density of soil films. In practice, this method becomes unreliable for the measurement of values below approximately 1% decrease in transmission. This is the region of greatest interest in dishwashing studies, since a good compound should give nearly perfect cleaning. Previous workers have employed as many as twenty-five repeated soilings and washings prior to measurement (*14*) or have treated the washed surfaces with carbon black (*8*), to obtain larger differences in transmission of glass surfaces before and after washing, and thus make possible a more accurate measurement of effectiveness of compounds.

Tests have shown that a more satisfactory measurement of density of films on glass surfaces could be obtained by measuring the proportion of incident light scattered by the soiled surfaces. Maximum possible relative error in measurements made by this method is approximately equal to the sum of the relative errors in the measurements of incident and scattered light. Hence, if it is assumed that the two primary measurements can be made with an accuracy of 1%, measurements of density of soil films may be made by this method with an error of not over 2%.

TABLE I. COMPOSITION, PROPERTIES, AND EFFECTIVENESS OF DISHWASHING COMPOUNDS

Sample Number	Composition, % by Weight							Miscellaneous Properties				Dishwashing Effectiveness[c]				
												Soft H_2O			Hard H_2O	
	Na_2O	P_2O_5	SiO_2	CO_2	H_2O	$P_2O_5+SiO_2+CO_2$	$Na_2O+P_2O_5+SiO_2+CO_2$	Ppt. in hard H_2O, mg.	Alkalinity, % Na_2O[a]	pH	Relative degree of buffering[b]	0.10[d]	0.25	0.50	0.25[d]	0.50
1	47.6	27.3	17.8	4.9	0.5	50.0	97.6	10.4	25.2	11.9	11.1	0.2	0.1	0.1	0.2	0.3
2	35.9	24.2	11.1	..	19.6	35.3	71.2	8.4	16.0	11.6	11.8	0.3	0.1	0.0	0.5	0.2
3	35.6	30.3	8.0	0.6	20.7	38.9	74.5	9.2	14.0	11.4	3.4	0.3	0.1	0.0	0.4	0.3
4	40.5	38.0	7.5	0.4	10.9	45.9	86.4	7.4	18.5	11.1	2.2	0.2	0.1	0.1	0.3	0.4
5	46.3	19.6	4.6	18.0	12.1	42.2	88.5	11.9	18.4	11.2	5.2	0.1	0.3	0.1	0.4	0.4
6	34.7	27.4	15.1	9.7	11.3	52.2	86.9	4.6	15.6	11.3	3.0	0.6	0.1	0.2	0.3	0.2
7	41.7	22.4	8.1	15.4	8.9	45.9	87.6	2.3	16.6	10.5	6.0	0.3	0.1	0.1	0.7	0.2
8	45.2	16.6	1.3	20.1	12.5	38.0	83.2	10.2	16.4	11.0	6.2	0.7	0.1	0.1	0.4	0.3
9	42.3	25.0	9.9	9.3	13.0	44.2	86.5	9.2	15.2	10.5	5.3	0.6	0.3	0.1	0.6	0.3
10	33.5	29.3	5.6	1.5	22.9	36.4	69.9	19.6	8.8	10.9	2.5	1.4	0.4	0.2	0.5	0.3
11	37.0	21.4	13.1	6.9	19.6	41.4	78.4	12.6	20.8	11.5	5.2	1.5	0.2	0.1	1.4	0.2
12	33.2	14.6	14.3	1.5	32.4	30.4	63.6	26.5	17.4	11.6	4.6	2.6	0.1	0.1	0.6	0.2
13	31.9	14.8	14.8	3.0	34.2	32.6	64.5	24.5	18.6	11.7	5.4	2.2	0.1	0.1	0.8	0.4
14	31.4	23.3	..	2.0	35.8	25.3	56.7	32.3	9.2	11.1	3.3	2.9	0.3	0.1	0.5	0.2
15	35.7	21.7	9.1	2.8	29.7	33.6	69.3	19.1	11.6	11.5	4.4	2.4	0.2	0.1	1.2	0.2
16	34.8	10.7	10.8	8.9	28.2	30.4	65.2	20.5	17.7	11.1	4.7	2.8	0.2	0.2	1.4	0.2
17	37.8	15.8	15.4	10.7	24.1	41.9	79.7	10.5	24.3	11.6	5.7	4.7	0.6	0.1	2.2	0.2
18	55.5	10.4	0.7	26.8	2.4	37.9	93.4	4.2	25.4	11.1	7.6	2.1	0.2	0.1	7.0	1.5
19	41.8	11.1	0.5	..	9.5	11.6	53.4	23.1	3.9	10.8	1.1	5.2	0.3	[e]	...	...
20	47.1	11.3	5.1	22.3	8.4	38.7	85.8	11.7	21.4	11.4	5.8	3.2	0.5[f]	0.1	...	...
21	44.3	9.8	5.9	24.0	9.5	39.7	84.0	14.1	20.2	11.1	7.1	...	1.3	0.1	...	...
22	27.9	19.3	1.5	..	46.3	20.8	48.7	31.7	10.2	11.6	3.9	...	2.6	0.2	...	...
23	29.9	..	28.1	..	42.7	28.1	58.0	55.8	26.8	11.8	9.1	...	2.3	0.6	...	...
24	38.1	7.2	7.6	22.2	18.3	37.0	75.1	22.6	21.8	10.7	8.8	...	3.0	0.1	...	...
25	45.2	11.5	0.3	21.4	15.4	33.2	78.4	24.5	18.4	11.3	5.7	...	3.1	0.3	...	...
26	48.8	..	..	38.1	9.2	38.1	86.9	8.7	26.8	10.6	10.9	...	2.9	0.8	...	...
27	36.2	..	15.1	13.1	32.9	28.2	64.4	35.4	12.6	11.8	2.7	...	3.3	1.0	...	...
28[g]	28.0	5.5	0.6	3.2	13.4	9.3	37.3	3.7	11.2	9.5	10.4	...	1.2	3.3	...	...
29	35.7	3.9	15.2	11.4	31.8	30.5	66.2	12.8	14.2	11.7	5.8	...	4.4	0.2	...	...
30	26.9	..	24.6	..	46.0	24.6	51.5	52.3	24.4	11.9	8.8	...	3.1	1.8	...	...
31	46.2	9.1	4.1	25.5	14.8	38.7	84.9	31.2	21.5	11.4	6.0	...	4.5	0.6	...	...
32	52.8	4.9	..	36.3	4.4	41.2	94.0	10.3	23.4	11.1	8.3	...	3.8	1.5	...	...
33	55.7	3.2	..	27.6	13.2	30.8	86.5	45.4	37.8	11.5	7.4	...	4.7	0.7	...	...
34	36.9	..	12.8	18.0	29.9	30.8	67.7	48.5	25.6	11.7	6.3	...	4.9	2.4	...	...
35	54.1	5.6	0.2	28.8	9.0	34.6	88.7	25.6	28.2	11.6	6.0	...	5.0	2.8	...	...
36	56.0	4.6	1.6	31.1	1.9	37.3	93.3	24.4	31.8	11.5	7.0	...	5.8	3.9	...	...

[a] Figures are for alkalinity titratable to phenolphthalein end point.
[b] Represents ml. of 0.1 *N* HCl required to lower the pH of 50 ml. of 0.5% solution by 1 unit.
[c] Effectiveness is in inverse order to numerical values listed; e.g., low values indicate high effectiveness.
[d] Detergent concentration in per cent.
[e] Excessive foaming prevented testing of this compound at higher concentrations.
[f] It was not possible to obtain reproducible results on this compound and therefore it was not included in the tests in hard water.
[g] Contains 28.0% B_2O_3.

INSTRUMENT FOR MEASURING FILMS. Figures 2 and 3 show the instrument used to determine the density of films by measuring the proportion of incident light scattered. The instrument consisted of the following parts:

1. Light-tight housing, painted on the interior with a non-specular black lacquer.
2. Light source (32 candle-power headlamp bulb, 6–8 volts).
3. Constant-voltage transformer for operating the light source (Westinghouse induction voltage regulator, 105–127 volts primary, 25 volt-amperes, 6.5 volts, 3.8 amperes full-load secondary current).
4. Diaphragm containing a $^1/_{16}$-inch diameter hole, placed as close as possible to the light source, for the purpose of blocking off all light except that coming directly from the filament of the light source.
5. A second diaphragm, 9 inches from the first, containing a $^1/_8$-inch diameter hole. The purpose of this diaphragm, in combination with the first, is to give a nearly parallel beam of light of fairly high intensity, and to exclude scattered light from the compartment containing the photoelectric cell.
6. A photoelectric cell (Weston Model 594, Type 2) placed in a holder $7^1/_2$ inches from the second light baffle, with the center of the active surface in line with the centers of the holes in the two diaphragms. A $^1/_2$-inch diameter metal disk is glued to the center of the cover glass of the photoelectric cell. The surface of the disk is painted with nonspecular black lacquer.
7. A galvanometer (Rubicon No. 3403 H.H., sensitivity 0.0023μ amp./mm., resistance 1000 ohms, period 4.2 seconds, critical damping resistance 10,000 ohms), connected directly to the photoelectric cell.
8. An opening in the housing, just below the second diaphragm, and a rack for holding the test specimens of plate glass. The opening is fitted with a removable, light-tight cover. The rack is fastened into place so as to permit introduction of the glass squares into the light beam at an angle of about 80°. This lack of perpendicularity of the surfaces of the glass to the light beam prevents surface reflections from reaching the photoelectric cell.

The instrument operates on the following principle: When the light source is turned on and there is no diffusing medium in the light beam, the beam of light produced by the source and the two diaphragms falls entirely within the blackened disk on the photoelectric cell cover, and is absorbed without reaching the active surface of the cell. If a square of glass with surface films is then introduced into the light beam, light is scattered by the films and a part of this scattered light falls on the active surface of the cell. Assuming the use of a sufficiently sensitive galvanometer, any desired magnitude of reading may be obtained for a given film density. With the galvanometer, light source, and photoelectric cell used, it was found that any visible film would give a measurable galvanometer reading. Clean, new glass squares gave a deflection of several tenths of a millimeter, and glass which had been in use for some time gave increased deflections up to about 2 mm. as the surfaces became slightly scratched and etched. These deflections given by clean glass were always applied as corrections to deflections obtained on the same set of glass squares after use in a washing test.

No attempt was made to express measurements as the absolute proportion of incident light scattered in a test. The incident light was kept constant in intensity, and measurements were recorded as galvanometer deflections, which may be assumed to be proportional to the intensity of the scattered light.

EFFECTIVENESS OF DISHWASHING COMPOUNDS. A set of glass squares was cleaned, dried, and measured to determine the correction to be applied for surface imperfections. The squares were then soiled, washed in the dishwashing machine with the desired concentration of dishwashing compound in the manner previously described, dried for 3 minutes at 100–105° C. in a mechanical convection oven, resoiled in the same area which had been previously soiled, and washed again; this process was continued

for a total of six cycles of soiling and washing. Each cycle required a total time of 5 minutes, and the entire washing was completed in about 30 minutes.

Following the six cycles of soiling and washing, the glass squares were again measured. Three measurements were made on the soiled area of each of the six squares, and the average reading for the set was computed. From this, the average reading obtained on the thoroughly cleaned squares was subtracted. The result was considered to be proportional to the average relative film density remaining on the squares. This test was then repeated under identical conditions, and the average for the two trials was computed. In the few cases in which the duplicate trials failed to give satisfactory agreement, additional trials were made until it was considered that a reliable average had been obtained.

Washing tests were first made on all compounds under test in soft, untreated water (hardness, 1 grain per gallon) available from the taps of the laboratory, at a detergent concentration of 0.25%. Additional tests were then made in the soft water at detergent concentrations of 0.10 and 0.50%. Following completion of the tests in soft water, tests were made in hard water (10.0 grains per gallon, Ca/Mg ratio 2/1) prepared by adding calcium chloride and magnesium chloride to the tap water. Detergent concentrations for the hard water tests were 0.25 and 0.50%. Certain of the compounds, which were considered to give unsatisfactory results (galvanometer readings in excess of 1.0 cm.) in soft water at a concentration of 0.25%, were not tested at 0.10% in soft water and were eliminated from the hard water tests.

DISHWASHING COMPOUNDS

Chemical Analysis. The compounds were analyzed quantitatively for constituents usually present. These analyses were made by standard methods, with the exception of sodium oxide, which was determined by an unpublished method supplied by Charles Schwartz. The proportion of synthetic detergent and associated sulfates present in many of the compounds was not determined. This accounts for the failure in some cases of the summation of all constituents determined to approximate 100%.

Precipitate Formed in Hard Water. Because of the apparent importance of the ability of dishwashing compounds to prevent the precipitation of calcium and magnesium compounds from the water employed in the dishwashing operation, special attention was given to the measurement of this property. Various precipitation tests were tried, including that described by Federal Specification P-D-236 (*6*), and the results compared with data for washing effectiveness. One defect was generally found in the tests: The precipitates formed were frequently highly dispersed and could not be satisfactorily filtered; they either passed through or clogged the filter. Those formed by the method described by Federal Specification P-D-236 frequently could not be filtered in the course of an 8-hour day. Use of a small quantity of soap in the test solution was found effective in coagulating precipitates and thus facilitating filtration. The most satisfactory method of those tested is described as follows:

Transfer 100 ml. of a freshly prepared, filtered or decanted 1.00% stock solution of the dishwashing compound and 100 ml. of distilled water to a 250-ml. low-form beaker. Add 2 ml. of A.P.H.A. soap solution (*1*) and stir. With constant stirring, add dropwise 2 ml. of a distilled water solution containing calcium and magnesium chlorides equivalent to 9.37 mg. of calcium carbonate and 6.50 mg. of magnesium carbonate per ml. (all volumes specified should be measured accurately with pipets). Cover the beaker with a watch glass and heat in an oven at 55–65° C. for 30 minutes. Remove the solution from the oven, permit to cool to room temperature, and filter promptly through a tared, asbestos-felted Gooch crucible. Wash the beaker and precipitate with several small portions of hot water, transferring the precipitate quantitatively to the filter. The total volume of wash water employed should not exceed 25 ml. Dry the crucible and contents to constant weight at 100–105° C. and determine the weight of the precipitate.

Miscellaneous Properties. The determination of pH was made on 0.50% distilled water solutions of the compounds by a glass electrode and pH meter. No corrections were made for sodium-ion error. Results are also somewhat in error due to the unsuitability of the glass electrode for the pH range encountered; however, this effect was reduced in importance by standardizing the instrument against a buffer solution of pH 10.

Alkalinity was determined by titration to phenolphthalein end point with standardized acid. Results were calculated to per cent sodium oxide in the compound titratable to phenolphthalein end point.

Relative degree of buffering was determined by adding standardized acid to 50 ml. of an 0.50% solution of the compound until the pH of the solution was reduced by one unit. Results so obtained are approximately proportional to the buffer capacities of the solutions.

Corrosiveness of the compounds to aluminum was determined by exposing small strips of bright finished, uncoated aluminum alloy sheet (Type 1, Class 1/2H), conforming to Federal Specification (*7*), for 5 hours at 180° F. totally immersed in solutions of the compounds. The exposed strips were rinsed, dried, and examined for etching, discoloration, or other damage to the surface. Tests were made at solution concentrations of 0.25, 0.50, and 1.00%.

Practical Dishwashing Tests. Several compounds considered satisfactory, as judged from the laboratory tests, and several considered unsatisfactory were subjected to practical tests in a mess hall feeding somewhat over a thousand men. The compounds were rated for effectiveness by several observers, including some who had no previous information concerning the compounds used. Such evaluations were of necessity subjective, and the best that could be done was to rate compounds as good, bad, or indifferent.

RESULTS OF TESTS

All data that may be expressed numerically are listed in Table I. Results of tests for corrosiveness to aluminum and of practical dishwashing tests are not presented in detail. The most corrosive compounds were those containing no silicates. A minimum silicate content equivalent to 8% SiO_2 was found to inhibit corrosion adequately. This effect of silicates was noted previously (*15*).

Results of the practical dishwashing tests furnished a general confirmation of the laboratory tests. Those compounds which had been judged effective from the laboratory tests gave clean, bright dishes, glassware, and silverware, and maintained the dishwashing machine in a clean, scale-free condition. Those judged unsatisfactory from the laboratory tests were found to give films on the articles washed and to form scale in the machine.

Evaluation. The compounds in Table I are listed in order of increasing average film densities obtained in the laboratory washing test at all concentrations and hardnesses employed, with due allowance for the fact that many of the compounds were tested in soft water only and at only two concentrations. Thus, the listing is in approximate order of decreasing effectiveness. Although any given compound may be out of place in the table by several places due to error in the test results, the arrangement is useful in that it makes general tendencies and relations between performance and other properties more evident. Although an exact standard of satisfactory cleaning performance could not be established, and, consequently, no sharp division in Table I could be made between satisfactory and unsatisfactory compounds, it was found desirable to base the proposed specification requirements largely on the first nine compounds listed. The next five are considered of doubtful effectiveness and, beginning with sample 15, all others are definitely unsatisfactory.

The relation between phosphate content and effectiveness of compounds is noteworthy. Table I shows that the nine most effective compounds, with one exception, contain approximately 20% or more of P_2O_5.

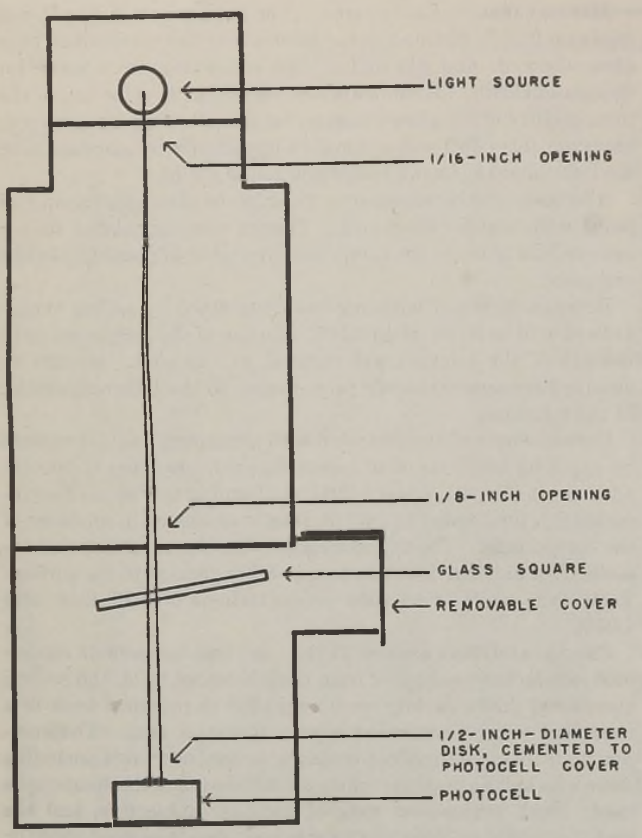


Figure 3. Cross Section of Instrument for Measuring Residual Soil Films on Glass Surfaces

There appears to be no clear relation between carbonate content and effectiveness, up to a carbonate content equivalent to about 20% CO_2. With CO_2 contents greatly above this value, performance becomes definitely unsatisfactory. These unsatisfactory compounds with high CO_2 content consist essentially of sodium carbonate.

Total sodium content (expressed as Na_2O) of the more satisfactory compounds range between approximately 30 and 45%. Values very far outside of this range indicate unsatisfactory performance and are usually associated with other undesirable composition factors—high water content, high carbonate content, or presence of ineffective constituents such as borax.

A silicate content equivalent to 8% or more of SiO_2 is desirable because of its inhibiting effect on corrosion of aluminum. Above this desirable minimum silicate content, there appears to be no undesirable effect from increasing silicate content up to the point where no further possibility exists of including the required proportion of phosphates.

As might be expected, there is some tendency toward unsatisfactory performance with increasing water content. All compounds containing over 25% of water gave doubtful or definitely unsatisfactory results.

Considered alone, there appears to be little relation between the property listed as "precipitate in hard water" and dishwashing effectiveness. However, when this property is considered in relation with other properties, its importance becomes evident. If the precipitation test is made on sodium carbonate, trisodium phosphate, and sodium metasilicate individually, a slight precipitate is obtained in the case of sodium carbonate as a result of the relatively high solubility of the carbonates and bicarbonates of calcium and magnesium. Much heavier precipitates are obtained with the phosphate and silicate. Thus, those compounds which contain small proportions of silicates and phosphates give a small weight of precipitate. Those compounds which contain satisfactory proportions of phosphates and silicates give light precipitates only if the compound contains a sufficient proportion of a complex phosphate to prevent precipitation of insoluble calcium and magnesium compounds (silicates, phosphates, and soaps). If three factors are considered—P_2O_5 content, SiO_2 content, and weight of precipitate obtained in the precipitation test—then a slight precipitate may be considered as an assurance of the presence of the desired proportion of molecularly dehydrated phosphates.

Summations of P_2O_5, SiO_2, CO_2, and of these constituents plus Na_2O are included in Table I to show the relation between content of active constituents and performance. A number of the unsatisfactory compounds have low values for these sums. Nearly all of the remaining unsatisfactory compounds, which have high values, consist largely of sodium carbonate.

Titratable alkalinity, pH, and relative degree of buffering show no marked variation with performance, within the limits of variation observed. However, values within certain limits are characteristic of the alkaline mixtures under consideration and may, therefore, form useful indications of excessive proportions of neutral, inert constituents.

PROPOSED SPECIFICATION REQUIREMENTS

It is evident that no one property can be considered a valid measure of the effectiveness of dishwashing compounds. A group of related properties, although not an exact measure of effectiveness, may be used to distinguish between highly effective compounds and those which are unsatisfactory. Suitable composition requirements are:

Constituents	% by Weight	
	Minimum	Maximum
Moisture	..	25
Alkali (as Na_2O)	30	45
Phosphates (as P_2O_5)	20	..
Silicates (as SiO_2)	8	..
Carbonates (as CO_2)	..	20
Insoluble matter	..	1
Total of P_2O_5, SiO_2, CO_2	35	..
Total of Na_2O, P_2O_5, SiO_2, CO_2	70	..

In addition, the absence of objectionable proportions of inert fillers may be assured by limits on chlorides and sulfates (a suggested reasonable requirement is a limit of 3% on chlorides and sulfates, calculated as the normal sodium salts) and a limit on insoluble matter. The weight of precipitate obtained in the precipitation test should not exceed 11 mg. Suitable limits on pH are 10.5 to 12.0. Addition of 2 ml. of 0.1 *N* hydrochloric acid to 50 ml. of a 0.5% solution of the compound should not lower its pH by more than 1 unit.

Comparison of the above requirements with the data of Table I shows that four of the nine most effective compounds conform in all respects; the extent of nonconformity of the other five compounds is not great. Changes in formulation required to make these compounds comply in all respects with the suggested requirements are so slight as to involve no possibility of significant change in performance. None of the remaining compounds conform to all of the suggested requirements; the number of properties in which there is failure to conform and the extent of departure from the suggested requirements become increasingly great as the compounds become more unsatisfactory.

Although the ideal way to assure high quality in the procurement of dishwashing compounds would be through the use of a laboratory cleaning test, much additional work would be required for the development of a simple, rapid, convenient, and valid procedure which would be suitable for use in routine inspection. Pending the development of a satisfactory laboratory test, it appears that the suggested specifications will be useful in procuring dishwashing compounds, certainly eliminating the most un-

satisfactory materials and probably assuring at least reasonably satisfactory compounds. Approximately these same requirements have been employed in a Navy Department Specification (*13*) for dishwashing detergent.

ACKNOWLEDGMENT

Suggestion of this problem by T. W. Werkenthin and N. E. Ruckman of the Bureau of Ships, Navy Department, is gratefully acknowledged. Assistance in performing various of the laboratory tests by D. E. Gallagher, Irving Stacy, and Herbert Berger (now in the armed forces) is also acknowledged. The authors are grateful for useful suggestions and information received from the following: D. F. Richardson, of this Laboratory; Charles Schwartz, Calgon, Inc.; G. J. Hucker, New York State Agricultural Experiment Station; F. W. Gilcreas and J. E. O'Brien, New York State Department of Health; J. L. Wilson and E. E. Mendenhall, Economics Laboratory, Inc.

THE views expressed in this paper are those of the authors and do not necessarily represent those of the Navy Department.

LITERATURE CITED

(1) Am. Pub. Health Assoc., Standard Methods for Examination of Water and Sewage, 8th ed., 1936.
(2) Baker, C. L., IND. ENG. CHEM., 23, 1025 (1931).
(3) Cox, W. C., *Am. J. Pub. Health*, 28, 174 (1938).
(4) Cummings, J. G., *Ibid.*, 10, 576 (1920).
(5) Federal Specification DD-G-451 of April 28, 1931, for Glass, Flat, for Glazing Purposes.
(6) Federal Specification P-D-236 of Nov. 18, 1941, for Detergents, Special (for Aluminumware, Dishwashing Machines, and Manual Cleaning).
(7) Federal Specification QQ-A-359 of June 6, 1933, for Aluminum Alloy (Aluminum-Manganese) Plates and Sheets.
(8) Gilcreas, F. W., and O'Brien, J. E., *Am. J. Pub. Health*, 31, 143 (1941).
(9) Hall, G. O., and Schwartz, C., IND. ENG. CHEM., 29, 421 (1937).
(10) Krog, A. J., and Dougherty, D. S., *Am. J. Pub. Health*, 26, 897 (1936).
(11) Mallmann, W. L., *Ibid.*, 27, 464 (1937).
(12) Mallmann, W. L., and Devereaux, E. D., *Ibid.*, 25, 1007 (1935).
(13) Navy Dept. Specification 51D8 of Jan. 3, 1944, for Detergent, Dishwashing.
(14) Schwartz, C., and Gilmore, B. H., IND. ENG. CHEM., 26, 998 (1934).
(15) Seligman, R., and Williams, P., *J. Inst. Metals*, 28, 297 (1922).

Preparation of Zein by Precipitation Method

CYRIL D. EVANS, R. J. FOSTER, AND C. BRADFORD CROSTON

Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Ill.

A laboratory procedure is described for the preparation of zein from corn gluten which consists in extracting with isopropyl alcohol, concentrating to a heavy phase solution, precipitating from the heavy phase solution into cold water, and drying the resulting protein at low temperatures. The zein from the dilute alcoholic extract is concentrated to a heavy zein phase by a nonpolar solvent which selectively removes part of the alcohol from the extract. Precipitation of the zein from its heavy phase solution is accomplished by throwing a fine stream of it into cold water with an effective rotary dispersing apparatus. This precipitate is finely divided, granular, and free from the occluded solvent which proves so troublesome in conventional laboratory methods of preparing zein. Curves showing the phase relations of mixtures of alcoholic zein solutions and petroleum ether which are important in the concentration are discussed. The method is also suitable for the recovery of modified zein preparations.

IN DEVELOPMENTAL research on nonfood uses of zein, it is desirable to have a readily dispersible raw material. Laboratory methods previously described (*3*, *4*) were designed primarily to obtain zein for nutritional studies and not for physicochemical investigations. In following these methods it is difficult to obtain a product which is completely and readily dispersible in alcohol. In connection with studies on the utilization of zein, a simple laboratory method was developed which is similar to the commercial process (*7*) and gives a friable, readily dispersible zein.

Extraction of zein from corn gluten appears to depend essentially upon the use of an alcohol as the primary solvent. Aqueous alcohol seems able to peptize preferentially this particular protein fraction, which constitutes about 70% of the protein in corn gluten. The mechanism of this peptization is still unexplained and may be through a breakdown of hydrogen bonding. Zein, after extraction by an alcohol, is readily soluble in a large number of organic solvents (*1*, *2*) and is readily soluble in dilute solutions of the strong alkalies over a narrow pH range (*5*). No satisfactory extraction technique has been developed without the use of an alcohol, although one of the early patents of Osborne (*6*) deals with an alkali extraction process. Aqueous acetone has many advantages over aqueous alcohols as a solvent for purified zein, but we have been unable to obtain satisfactory yields through its use as an extraction medium. Extraction with 70% (by weight) aqueous acetone removed about half as much protein as aqueous alcohol, and the fraction obtained showed considerable difference in solubility in comparison to normal alcohol-extracted zein.

When previously described methods are used, the most difficult part of the procedure is to obtain a redispersible, granular zein, free from residual alcohol solvent. The removal of residual solvent and drying at temperatures below 10° C. results in zein preparations which have ready solubility. The importance of keeping zein preparations cold, especially in dilute alcohol or when wetted with water, cannot be overemphasized. Zein is readily plasticized by water at temperatures above 30° C. and in this condition is easily and rapidly denatured.

The extraction is performed in the usual type of laboratory equipment. The zein dispersion is concentrated by phase separa-

tion without application of heat, through the use of isopropyl alcohol and hexane as described by Swallen (7) for the commercial preparation of zein. Commercial corn gluten is first screened to remove the fines as an aid to rapid filtration of the extracting liquor. One thousand grams of the crude gluten are extracted with 3000 ml. of 80% (by weight) isopropyl alcohol for 30 minutes

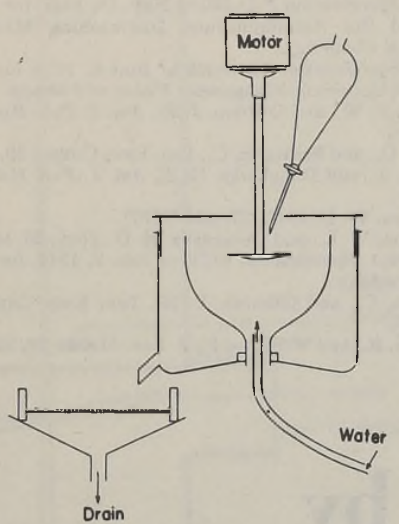


Figure 1. Zein Precipitating Apparatus

at 50–60° C. while stirring constantly. The suspension is filtered rapidly through several layers of folded cheesecloth with no attempt to obtain a clear filtrate. The solids are washed with 500 ml. of the 80% isopropyl alcohol. A second extraction is made with 1500 ml. of alcohol followed by filtration and washing with another 500 ml. The combined extracts are stored overnight at 4–10° C. to allow the fines to settle, as well as to precipitate the floc which appears upon cooling. The supernatant liquid is removed, and the remainder is separated by filtration through a rapid qualitative-type filter paper or by centrifuging. It is not necessary to employ filter aids in order to obtain a clear zein solution, provided the solids content is held below 8%. To concentrate the alcohol-extracted zein, the clear solution is shaken vigorously in a separatory funnel with about 120% of its volume of petroleum ether (Skellysolve F). Upon standing, the zein separates in a heavy-phase layer which may be drawn off from the bottom of the funnel. This separation accomplishes a rapid concentration of the zein, as well as removal of a large part of the oil and pigments.

If the concentrated heavy-phase zein solution obtained is not perfectly clear, absolute isopropyl alcohol is added until a clear dispersion is obtained. This addition is usually 10 to 15% of the total volume and serves to dilute the dispersion to a zein concentration of about 20%. This concentration has been found to be approximately the optimum for precipitation by the method used in this Laboratory. If a more highly purified product is desired, the petroleum ether phase separation may be repeated.

Table I. Nitrogen Balance of Fractions

	Total N, Grams	Total N, %
Crude gluten (1000 grams)	74.70	100
Extracted gluten residue	41.00	54.90
Spent hexane-alcohol (8.19 liters)	0.19	0.25
Heavy-phase zein solution	31.01	41.60
Coagulating water (44.48 liters)	1.44	1.93
Extracted zein (191 grams)	27.92	37.40

Analysis of Zein

Preparation No.	% N[a]	% Ash
I	15.81	0.21
II	15.69	0.34
III	15.83	0.28
Commercial zein	15.36	0.28

[a] Moisture-free and ash-free basis.

PRECIPITATION

Figure 1 shows the apparatus used to precipitate the zein from solution. The outer jacket is the draining chamber and lid ordinarily used with a basket centrifuge. A metal funnel is mounted in the jacket by a rubber stopper, and the assembly is placed on the platform of a small bench drill press. Cold water is circulated upward through the bottom of the funnel and allowed to flow out over the rim. The spinner is a 3-inch brass disk firmly fastened to the end of a $^3/_8$-inch brass shaft about 6 inches long. The disk is set within the funnel about $1^1/_2$ inches below the top and rotated at 2500 to 3000 r.p.m. Any of the larger, variable-speed, laboratory stirring motors may be used in lieu of the drill press. Modification of size and speed of rotation of the disk may be made to suit individual applications.

The zein is precipitated from solution by allowing a fine stream of zein concentrate to flow onto the surface of the rotating disk. As the solution strikes the disk, it is rapidly thrown from the circumference of the spinner into the cold water where the zein is immediately coagulated in the form of fine fibrous particles which are easily filtered off on cheesecloth. The precipitated zein is washed on the cheesecloth and soaked in ice water overnight to remove any residual solvent. After washing, the water is re-

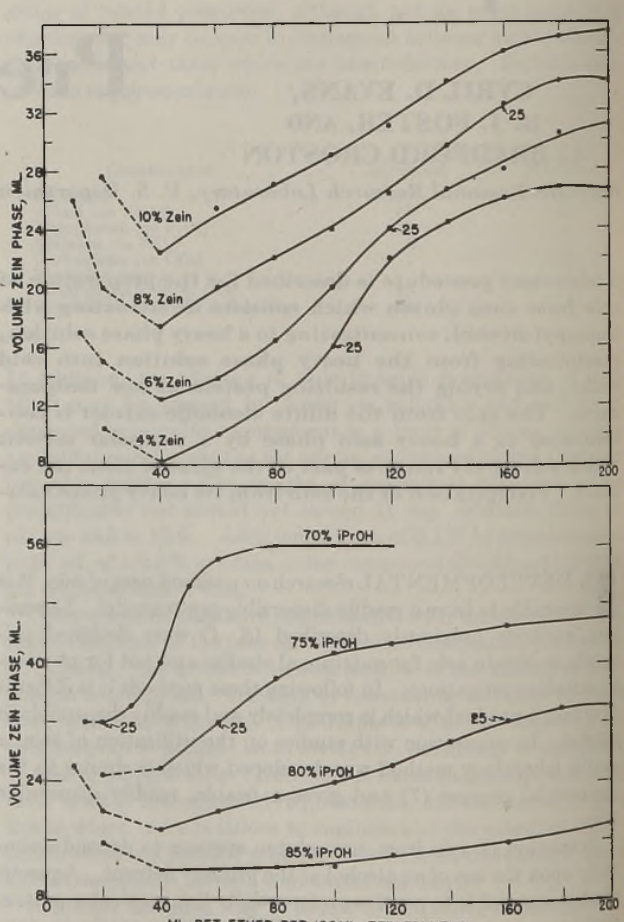


Figure 2 (*Upper*). Heavy Phase Concentration of Zein from 80% (by Weight) Aqueous Isopropyl Alcohol Containing Varying Concentrations of Zein

Figure 3 (*Lower*). Heavy Phase Concentration of Zein from Varied Concentrations of Aqueous Isopropyl Alcohol Containing 8% Zein

moved by rapid filtration, using care that the zein is always kept cold and never reaches a temperature at which it will become plastic. It is then dried at a low temperature (4–10° C.). This procedure results in a product which may be subjected to final drying in a vacuum oven at temperatures not to exceed 65° C. if a very dry product is desired. When finely ground, the resulting material will disperse rapidly in any of the zein solvents to yield a clear dispersion. Table I shows the results of a typical laboratory extraction with recovery of about 90% of the extracted protein.

PHASE RELATIONS

The exact amount of petroleum ether necessary to give optimum phase separation is predetermined by mixing 5-cc. aliquots of the zein solution with increasing amounts of petroleum ether in small, calibrated, clinical centrifuge tubes. After centrifuging for a few minutes, the zein solution collects in the bottom and its approximate viscosity may be determined by tipping the tube. It is desirable to use that amount of petroleum ether which will yield a clear supernatant liquid and a zein concentrate that is not too viscous for good flow. It is usually found that 5.5 to 6.5 ml. of the petroleum ether for each 5 ml. of zein solution gives the best separations and concentrates the zein phase to about one fifth its former volume.

Swallen (*7*) states that these phase relations are quite sensitive to the water and hexane contents, but gives no data concerning them. The concentration of protein and, to a lesser degree, the operating temperature are also important in these phase separations. Figure 2 shows the effect of adding increasing amounts of petroleum ether to different concentrations of zein in 80% (by weight) isopropyl alcohol. The degree of concentration decreases as the amount of petroleum ether added is increased above a definite minimum concentration. Concentrations of zein below 25% are desired for easy manipulation, and these points are indicated in Figure 2 by the number 25. It is apparent that concentrations of 4 to 8% zein in the original alcoholic extract are the most advantageous inasmuch as they allow considerable latitude in the final concentration. Figure 3 shows the heavy-phase separation obtained with petroleum ether when the concentration of alcohol is varied and the zein content maintained at a constant level. These curves indicate that a decreasing alcohol concentration is desired as the zein content is increased.

Similar phase relations may be determined for a number of solvent systems where a third substance, preferably nonpolar, will preferentially remove one of the components of the binary system acting as the zein solvent. A patent recently granted to Swallen (*8*) specifies the operating limits for phase separation to be between 92 and 93% ethyl alcohol. Phase separations may also be obtained by lowering the temperature of a zein dispersion. This involves utilization of the critical peptization temperature of any given zein solvent system (*1*).

Precipitation by the above-described method has also proved highly satisfactory as a means of recovering modified zein preparations. Aldehyde-treated zein, brominated zein, and acetylated zein have been recovered in this manner to yield dry friable products which retained their original solubility.

LITERATURE CITED

(1) Evans, C. D., and Manley, R. H., Ind. Eng. Chem., 33, 1416–17 (1941).
(2) Manley, R. H., and Evans, C. D., *Ibid.*, 35, 661–5 (1943).
(3) Mason, D., and Palmer, L. S., *J. Biol. Chem.*, 107, 131–2 (1934).
(4) Nolan, L. S., and Vickery, H. B., *Proc. Soc. Exptl. Biol. Med.*, 35, 449–51 (1936).
(5) Ofelt, C. W., and Evans, C. D., in preparation.
(6) Osborne, T. B., and Cornelison, R. W., U. S. Patent 691,966 (Jan. 28, 1902).
(7) Swallen, L. C., Ind. Eng. Chem., 33, 394–8 (1941).
(8) Swallen, L. C., U. S. Patent 2,272,488 (Feb. 10, 1942).

ASPHALTIC PRODUCTS FROM PETROLEUM EXTRACTS

P. V. McKINNEY[1], M. G. MAYBERRY, AND H. E. WESTLAKE, JR.
Mellon Institute, Pittsburgh, Pa.
[1] Present address, 52 East 41st Street, New York, N. Y.

The reaction of sulfur with solvent extracts from petroleum stocks leads to an asphaltlike solid whose hardness is much less dependent on temperature than is usual for such materials. It is of promise in filling joints and in caulking.

ASPHALTS, which occur in nature as such and in petroleum, are also formed from the latter during cracking processes. Asphaltic materials for commercial use are derived from these sources. Formerly asphalts were made from heavy petroleum residues by the Dubbs process, which employed sulfur at high temperatures. In more recent times the advent of blown asphalts has led to the general abandonment of the high-temperature sulfurization process because the product weathered poorly, especially where exposed to heat. Bencowitz and Boe (*2*) proposed low-temperature sulfurization, in which the sulfur appeared to be dissolved or otherwise uniformly dispersed in the asphalt. By this procedure they were able to make asphalts whose weathering characteristics compared favorably with those of blown asphalts. A section of a test brick road in Hocking County, Ohio, was laid using this Sulmor, as the material became known, as a joint filler (*5*, *6*). It was found that Sulmor was extremely satisfactory for this purpose, for it did not exude from the joints, possessed no odor, and could be handled with the equipment ordinarily used for asphalt (*3*).

The process of extracting lubricating stocks with solvents, such as phenol, Chlorex, or nitrobenzene, yields cheap raw materials which by reaction with sulfur can be converted into asphaltlike materials. This extraction process is used to remove sludging or gum-forming materials from the lubricating oil. As it is designed to give uniform lubricating oils, each process yields extracts of uniform characteristics. The properties of typical examples of these extracts are listed in Table I. They are viscous, unsaturated, naphthenic liquids, different chemically from the asphaltic residues afforded by cracking processes.

TABLE I. SOURCES AND PROPERTIES OF REPRESENTATIVE SOLVENT EXTRACTS FROM LUBRICATING STOCKS

Source of Crude Oil	Santa Fe Springs	Pennsylvania	Pennsylvania	Mid-continent	Texas
Solvent	Phenol	Chlorex	Nitrobenzene	Propane-cresol	Furfural
Sp. gr. at 10° F.	0.9984	0.9843	1.0002	0.9699	0.9791
A.P.I. gravity	10.2	12.2	10.0	14.4	13.0
Flash point, ° F.	520	560	555	540	470
Fire point, ° F.	600	630	640	605	515
Pour point (min.), ° F.	65	85	75	100	85
Viscosity, Saybolt Universal sec. at 210° F.	371	1365	>1500	>1500	>1500
Iodine No. (Wijs)	69.4	71.4	60	63.7	57.1

Sulfur has been shown to be only slightly soluble in these extracts. Above 140° C., however, a reaction occurs with the evolution of hydrogen sulfide, whose rate of formation increases with temperature (*4*). The nature of the reaction products appears to depend on the character of the petroleum extract used as well as on the conditions of reaction. Extracts having a Saybolt viscosity lower than 340 seconds at 210° F. give unsatisfactory products; those with greater values yield tough plastic solids.

REACTING SULFUR WITH PETROLEUM EXTRACTS

The extract is heated, with stirring, in an open vessel. At 120° C. the sulfur is added and the mixture stirred vigorously. As foaming decreases, the temperature is raised to 170–180° C. After 6–8 hours of stirring at this temperature, the foaming subsides and a suitable product results. The experimental details for representative examples of the reaction, together with characteristics of the products, are presented in Table II.

The products from the reaction are tough, black, asphaltlike solids. About 10% is free sulfur, which can be extracted with sodium sulfide. In a few cases around 1% of the sulfur settles if the product is held at 120–125° C. for 24 hours without stirring. The remainder of the free sulfur is lost as hydrogen sulfide evolved in large quantities during the reaction. Reheating the products to 170–180° C. causes the reaction to continue further and gives a harder material.

The similarity of this product to blown asphalt and to Sulmor is best illustrated by comparing their softening points and penetration values (Table II). Sulfurized extracts have ball and ring softening points in the same range as those of asphalt and Sulmor. The penetration curves are also similar for sulfurized extracts which have not been heated too long. Products heated for longer periods no longer soften as much as the temperature rises and, therefore, give similar penetration values at all three temperatures. Ordinary asphaltic materials show a definite and sometimes steep rise in penetration values as the temperature is raised. These values were reported by Bencowitz and Boe (*1*), for a group of representative asphalts, to have a linear relation for the same weights and time. The softening at elevated temperatures, indicated by the rise in penetration values, is one of the reasons why asphaltic materials exude from joints in hot weather. Another factor is the thermal expansion of the material and of the slabs joined by the material; but a material which does not soften appreciably at elevated temperatures will leak less from joints in hot weather.

The same effect has been obtained in a shorter reaction time by using catalysts (Table III). Red phosphorus and phosphorus pentasulfide both yield products with flat penetration curves after shorter reaction times. Among other compounds, sulfur monochloride has no action.

TABLE II. REACTION OF SULFUR WITH PETROLEUM EXTRACTS

Petroleum Extract: Crude petroleum source	Co. and identification No.	Solvent	% used	% sulfur used	Reaction Conditions: Hr.	Reaction Conditions: ° C.	Penetration: 0° C., 200 g., 60 sec.	Penetration: 25° C., 100 g., 5 sec.	Penetration: 46° C., 50 g., 5 sec.	Softening Point, ° C.	Description of Product
Mid-continent	Gulf A	Propane-phenol	60	40	6	135–172	8	31	58.6	63	.....
Mid-continent	Gulf A	Propane-phenol	60	40	8	135–186	11	24	77	58	Medium stiff
Mid-continent	Gulf A	Propane-phenol	60	40	11	135–204	4	2	1	98	.....
Mid-continent	Gulf A	Propane-phenol	50	50	10	130–191	6	6	9	75	.....
Pennsylvania	Sinclair 1	Nitrobenzene	60	40	5.8	118–177	..	..	..	..	Medium stiff
Pennsylvania	Pennzoil 2	Chlorex	60	40	6.5	136–174	..	..	..	..	Tough, like soft asphalt
Pennsylvania	Pennzoil 3	Chlorex	60	40	6.5	136–179	..	..	..	..	Hard, tough
California	Union 1757	Phenol	60	40	9.7	135–185	..	8	..	..	Hard, tough
Sulfur-asphalt mixture (Sulmor) (*2*)			..	..	..	.....	19	32	81	72.2	.....
Texas and Mexican air- and steam-blown asphalt (used in preparing Sulmor) (*2*)			..	..	..	.....	..	30	..	75.5	.....

TABLE III. EFFECT OF CATALYSTS

Reaction Mixture, %: Extract[a]	Sulfur	Catalyst	Reaction Conditions: Hr.	Reaction Conditions: ° C.	Penetration: 0° C., 200 g., 60 sec.	Penetration: 25° C., 100 g., 5 sec.	Penetration: 46° C., 50 g., 5 sec.	Softening Point, ° C.
57	38	5.0 P_2S_5	7	110–172	9	7	10	88
59.5	39.5	1.0 P	6.5	160–180	7	6	10	79
59.5	39.5	1.0 S_2Cl_2	6	128–171	15	23	81	53

[a] Gulf A, from a mid-continent crude.

Several types of aggregate have been evaluated as stiffeners for the product, among them graded sand, fine slate flour, graded anthracite, and coke. With the exception of coke, they all tend to settle and have little or no effect on the penetration values.

The presence of small proportions of drying and semidrying oils in the reaction mixture does not improve the product. The resulting reaction products are softer than those prepared by using sulfur and solvent extract alone.

Experiments have demonstrated that the industrial application of this reaction is feasible. The reaction can be carried on in an open metal kettle equipped with steam coils. An extra volume must be provided to allow for foaming, and the vessel must be well hooded because of the evolution of hydrogen sulfide. A single mixer will furnish the necessary agitation, although an egg-beater type mixer, operating above the liquid line, helps to dissipate the foam.

Estimates indicate that the new product can be manufactured at costs which permit competition with the best grades of asphalt. As shown by the flat penetration curve, the product is applicable as a joint filler or caulking compound. Experimental expansion joints on the roof of Mellon Institute have revealed no evidence of leaking or exuding after four years.

LITERATURE CITED

(1) Bencowitz and Boe, IND. ENG CHEM., ANAL. ED., 8, 157 (1936).
(2) Bencowitz and Boe, *Proc. Am. Soc. Testing Materials*, 38, 1 (1938).
(3) Duecker and Schofield, *Bull. Am. Ceram. Soc.*, 16, 435 (1937).
(4) McKinney, P. V., and Mayberry, M. G., U. S. Patent 2,354,868 (1944).
(5) Rueckel and Duecker, *Bull. Am. Ceram. Soc.*, 14, 329 (1935).
(6) Schofield, Ohio Ceramic Industries Meeting, Nov., 1935.

CONTRIBUTION from the multiple industrial fellowship maintained at Mellon Institute by Texas Gulf Sulphur Company.

MILKWEED SEED OIL

Potential Value in Protective Coatings

HERMAN J. LANSON[1], DAVID HABIB, AND P. E. SPOERRI

Polytechnic Institute of Brooklyn, N. Y.

The seeds of the common milkweed are obtained as by-products in the production of milkweed floss. These seeds contain about 22% oil which can be readily refined to a very pale color. The physical and chemical characteristics of the oil are reported. On the basis of its fatty acid composition, the oil may be classified as semidrying. In the field of protective coatings, the most promising application is in the preparation of oil-modified alkyd resins. Several long-oil and medium-oil length alkyds were prepared from milkweed seed oil, and were compared with the corresponding alkyds made with soybean oil in both pigmented and unpigmented coatings. The milkweed seed oil alkyds possess superior color retention and flexibility, although they are only slightly slower in drying than the corresponding soybean oil alkyds.

THE common milkweed plant, *Asclepias syriaca*, has been the subject of limited investigation in this country. Rheineck in 1933 (*7*) made a phytochemical study of the whole plant; several years previously Gerhardt (*2*) had briefly considered some of its commercial possibilities. Technologically this plant offers several materials of importance. The rubber and resin component has created considerable interest and recently became the subject of technological study (*3*). The stem of the plant contains a bast fiber with valuable properties, and it has been proposed for commercial use. Gerhardt suggested that the floss and oil from the seeds might be of commercial value, but before the war the over-all economic and agricultural picture was not favorable for the establishment of any significant milkweed industry in this country. However, as a result of the stoppage of kapok imports from the East Indies, the seed hairs or milkweed floss has become of great technical importance. The floss, the air-borne carrier of the seed, is used extensively today in life preservers and fliers' jackets, and recent tests have indicated its superiority over kapok. Although the plant is perennial and grows wild in many sections of the United States and Canada, a large amount is being cultivated to satisfy the great demand for the floss. The plant is hardy and requires little attention after the first year of cultivation, and its growth is valuable in preventing soil erosion. Collection of the pods is being sponsored in twenty-six states by the Federal Government, and a plant has been built by the Defense Plant Corporation to separate the floss from the seeds.

The present yield from cultivated milkweed plant is 300–400 pounds of floss per acre. Recent experiments indicate that the yield can be doubled by proper selection and cross breeding. The 1944 quota calls for 1,500,000 pounds of floss, fifteen times the 1943 production. From this quantity of floss 3,000,000 pounds each of seeds and pod shells will remain in addition to leaves. At present these materials are, in effect, waste products, and the introduction of milkweed cultivation in our permanent agricultural economy depends upon finding uses for them. Accordingly, a program of research was begun during the past year in this laboratory to study the constituents of the seeds and to indicate their commercial possibilities. This report is concerned only with the oil component and its possible utilization in protective coatings.

[1] Present address, Crown Oil Products Corporation, Long Island City, N. Y.

The seeds of the milkweed plant are rather flat and circular in shape with a diameter of about 1/8 inch. They were freed from foreign matter and ground to about 50 mesh in a Quaker mill. The oil was extracted with chloroform in a large Soxhlet apparatus having a capacity of 1 kg. of ground seeds. The oil was freed of solvent by distillation, the final traces being removed in vacuo while a fine stream of nitrogen gas was passed through the oil. A 221-gram yield of brown colored oil, representing 22.1% of the weight of the seeds, was obtained. The physical and chemical constants of the freshly extracted oil are shown in Table I. The methods of the American Oil Chemists Society (*1*) were followed in determining the acid, saponification, iodine, Reichert-Meissl, and Polenske values. The unsaponifiable matter was determined by the modified Kerr-Sorber method (*4*) and the acetyl value by a modification of the West, Hoagland, and Curtis method (*8*). A portion of the oil was saponified, and the unsaponifiable matter removed by repeated extraction of the soap solution with ethyl ether. The fatty acids were recovered in the usual manner by acidification. The iodine value (129.4) and thiocyanogen value (89.8) of the mixed acids were determined by the A.O.C.S. official methods. The following fatty acid composition was calculated by the empirical thiocyanogen values of Kass *et al.* (*5*):

Linoleic acid	46.6%
Oleic acid	50.1
Saturated acids	3.3

On standing, mucilaginous matter separated from the oil; rapid heating of a portion of the supernatant oil to 600° F. gave a separation of "break". The oil was alkali-refined by the A.O.C.S. method for hydraulic-pressed soybean oil. The resulting oil, after treatment with fuller's earth and decolorizing carbon, was limpid and very pale. Several analytical constants were determined to be as follows:

Iodine value	122.3
Saponification value	190.4
Acid value	0.38
Refractive index, n_D^{25}	1.4722

Unsaponifiable-free mixed fatty acids from this refined oil were obtained by the following procedure which eliminated the formation of troublesome emulsions usually formed in the conventional extraction of the soap solutions with ether:

To 25 grams of the oil in a 2-liter Erlenmeyer flask, 25 ml. of 95% ethyl alcohol were added. The flask was placed in a boiling water bath for several minutes, and 10 cc. of concentrated potassium hydroxide solution (100 grams KOH in 100 ml. water) was added dropwise from a pipet. After further heating in the bath for 5 minutes, the flask was removed and 125 ml. of ethyl alcohol were added. Ethyl ether (250 ml.) was added, and the contents of the flask well mixed. The resulting clear solution was transferred to a 2-liter separatory funnel, and 500 ml. of 0.2 *N* KOH solution added in a slow steady stream. The funnel was rotated gently and allowed to stand 10 minutes. The soap solution was withdrawn, 100 ml. of 0.2 *N* KOH solution was added to the ether layer, and the funnel was gently rotated as previously.

Table I. Physical and Chemical Characteristics of Unrefined Milkweed Seed Oil

Density, d_{25}^{25}	0.9221	Acetyl value	12.9
Refractive index, n_D^{25}	1.4730	Reichert-Meissl value	0.2
Viscosity (25° C.), poise	0.5	Polenske value	0.0
Iodine value	122.8	Unsaponifiable matter, %	2.53
Saponification value	191.9	Hexabromide value	0.0
Acid value	11.0		

Table II. Data on 52-R-13 Long-Oil Alkyds

	Soybean Oil	Milkweed Seed Oil	52-R-13 Specification
Acid value	7.4	7.1	5.7–10
Viscosity (70% in mineral spirits)	Z	Z_1	Y–Z_2
Color (Hellige)	3	4	4 (max.)
Phthalic anhydride, %	24.0	24.0	23.0 (min.)
Dust-free time	80 min.	120 min.	<4 hr.
Tack-free time	6 hr.	7¾ hr.	7–10 hr.

The lower layer was added to the main soap solution, and the free acids were obtained by acidification with dilute sulfuric acid (30%). The acids were taken up in petroleum ether, and after being washed free of mineral acid and dried over anhydrous sodium sulfate, the solvent was removed on a steam bath with vacuum and a stream of nitrogen gas. The mixed acids had an acid value of 204.5, corresponding to an average molecular weight of 274.0.

The content of polyunsaturated acids was obtained by spectrophotometric examination of an alcohol solution of the soaps after alkali isomerization in ethylene glycol at 180° C. for 25 minutes (*6*). A sample of unsaponifiable-free mixed fatty acids thus treated gave a specific extinction coefficient of 38.06 at 2340 Å., corresponding to 43.8% linoleic acid. There was no absorption at 2680 Å., an indication of the absence of linolenic acid[2]. The remaining constituent acids were calculated from the iodine value. The fatty acid analysis as determined by spectrophotometric means is represented thus: 43.8% linoleic acid, 51.8% oleic acid, and 4.4% saturated acids. These results are in fair agreement with the fatty acid analysis of the unrefined oil calculated from the thiocyanogen value.

Since the iodine value of the oil is about 10% lower than that of the current crop of soybean oil, it was anticipated that it would heat polymerize and dry somewhat more slowly than the latter. This was confirmed by the following procedure: Twenty grams of each of the alkali-refined oils were placed in 1 × 6 inch Pyrex test tubes. Both tubes were immersed in an oil bath kept at 585° F. for 4 hours. The viscosities were then determined by Gardner-Holdt standards to be 5.25 poises (S-T) for soybean oil and 3.40 poises (N) for milkweed seed oil. The drying times of the refined unbodied oils were checked, using 0.5% lead and 0.05% cobalt as catalysts. The drying of the milkweed seed oil was definitely slower than that of the soybean oil. The fact that soybean oil is seldom used as the sole oil component in paints and oleoresinous varnishes because of its slow bodying and insufficient drying capacity would preclude the similar application of milkweed seed oil. However, like soybean oil it could be used to advantage in blends with fast-drying oils, especially oiticica oil which displays a tendency to embrittle.

USE IN ALKYD RESINS

In view of the widespread use of oil-modified alkyd resins in specification finishes for military purposes and the probability that these resins will be utilized in protective coatings after the war to an increasing extent, the use of milkweed seed oil as the modifying oil in these glyceryl phthalate condensations was investigated. While milkweed seed oil does not possess sufficient unsaturation to be rapid drying by itself, the polymeric growth made possible in alkyd resin formation without the loss of unsaturation such as occurs in conventional oleoresinous varnish formation should greatly increase the drying capacity and film hardness. Moreover, the apparent lack of linolenic acid in the oil should make it ideally suitable in alkyds for high-temperature baking enamels, where color retention and flexibility are of paramount importance.

The widely used long-oil alkyd corresponding to Navy Specification 52-R-13 was prepared, in one case with alkali-refined soybean, and in the other with alkali-refined milkweed seed oil. Both resins were prepared similarly by glycerolysis, and were checked for drying after reduction to 50% solids and addition of 0.6% lead and 0.03% cobalt (as naphthenates) on a solids basis. The results are given in Table II.

Exterior white paints, according to Navy Specification 52-P-28, were made from both alkyds. Brush-outs were made on tin plate. With pigmentation the difference in drying was slight, both being firm and hard after 5 hours. Both paints have been exposed in a Weather-ometer to determine relative durabilities on outdoor exposure and have had 710 hours of exposure without failure. However, the paint prepared from the milkweed seed oil alkyd is somewhat whiter in color, although there appears to be no difference in degree of chalking.

White enamels were prepared from these long-oil alkyds by the following formula: 70 grams of titanium dioxide, 35 grams of titanium-calcium pigment, 155 grams of 52-R-13 alkyd (60% solids), and 27 grams of mineral spirits. The pigments and one third of the alkyd solution were mixed and given two passes through a small laboratory roller mill. The remaining vehicle and all the mineral spirits were added, together with naphthenate driers to give 0.5% lead and 0.05% cobalt based on the vehicle solids. Brush-outs were made on tin plate. Both enamels dried satisfactorily, the soybean alkyd enamel being about 45 minutes ahead in setup time. However, after 6 hours both enamels were tack-free and had excellent gloss; the milkweed seed oil alkyd enamel was somewhat superior in this respect. After overnight drying, relative hardness of films was determined with a Sward hardness rocker. The milkweed seed oil enamel gave a value of 9; that of the soybean oil enamel was 10.

It was next decided to compare milkweed seed oil with soybean oil, both in conjunction with linseed oil in a medium-oil length alkyd having 34% phthalic anhydride. Two alkyds were prepared; one contained half linseed and half soybean oil, and the other, half linseed and half milkweed seed oil. Both resins had viscosities of Z_2–Z_3 at 50% solids in mineral spirits and acid numbers below 8. They were thinned to 35% solids; after addition of driers (0.6% lead and 0.03% cobalt on solids basis), flow-outs were made on glass plate. There was no appreciable difference in drying, and, overnight, both were hard and tough. It is apparent that the presence of linseed oil has completely overcome the slower setup time of the milkweed seed oil.

To determine what value milkweed seed oil would have in an alkyd resin for baking purposes, two medium-oil length alkyds were prepared from soybean oil and milkweed seed oil, respectively; each contained 35% phthalic anhydride. Both resins had acid numbers of 3–4 and a viscosity of Y–Z at 50% solids in mineral spirits. Portions of both resins were thinned to 40% solids with Solvesso No. 2, and after addition of driers (0.1% lead and 0.01% cobalt), flow-outs were made on a white-coated steel panel. The films were baked at 250° F. for one hour and inspected for discoloration. The film from the milkweed seed oil alkyd showed remarkable resistance to discoloration and was definitely superior to that of the soybean oil alkyd. Both films were equally hard. White enamels were prepared from these alkyds, having the following composition in grams: titanium oxide, 360; zinc oxide, 65; alkyd (50% solids in mineral spirits), 850; Hi-Flash naphtha, 60; mineral spirits, 60. Driers were added (0.1% lead and 0.01% cobalt on vehicle solids); after being thinned to spraying viscosity with Solvesso No. 2, each enamel was sprayed on two steel panels. One set of panels was baked at 250° F. for 45 minutes, and the other set at 300° F. for

[2] J. P. Kass kindly provided these measurements.

30 minutes. Hardness was determined with a Sward hardness rocker as follows:

	Soybean Oil	Milkweed Seed Oil
250° F. for 45 minutes	22	16
300° F. for 30 minutes	28	26

While the hardness of the milkweed alkyd enamels is less at the lower baking temperature, this difference is minimized at the higher temperature. However, a distinct advantage is shown by milkweed alkyd enamel in resistance to discoloration, the difference being most marked at the high-temperature bake.

The results indicate that milkweed seed oil is valuable for use in the preparation of alkyd resins, since the slow drying of the oil per se is overcome, while the valuable properties of the oil (flexibility and color retention) is imparted to the film.

ACKNOWLEDGMENT

The investigations here reported were carried out under the terms of a subcontract from the Institute of Paper Chemistry. The authors desire to express sincere appreciation of the aid and counsel of Harry Lewis and the staff of that organization. They also wish to express their appreciation to Arthur Cramer and J. P. Kass for a number of the analytical determinations, and to the Crown Oil Products Corporation for the use of their laboratory facilities during part of the investigation.

LITERATURE CITED

(1) Am. Oil Chem. Soc., Official and Tentative Methods, Jan., 1941.
(2) Gerhardt, F., IND. ENG. CHEM., 22, 160–3 (1930).
(3) Grace, N. H., *et al.*, *Chem. Industries*, 54, 842–5 (1944).
(4) Jamieson, G. S., "Vegetable Fats and Oils", New York, Reinhold Pub. Corp., 1943.
(5) Kass, J. P., Loeb, H. B., Norris, F. A., and Burr, G. O., *Oil & Soap*, 17, 118–19 (1940).
(6) Mitchell, J. H., Kraybill, H. R., and Zscheile, F. P., IND. ENG. CHEM., ANAL. ED., 15, 1–3 (1943).
(7) Rheineck, A. E., *Pharm. Arch.*, 10, 69–80 (1939).
(8) West, Hoagland, and Curtis, *J. Biol. Chem.*, 104, 627–34 (1934).

PRESENTED before the Division of Paint, Varnish, and Plastics Chemistry at the 108th Meeting of the AMERICAN CHEMICAL SOCIETY, New York, N. Y. Abstracted from Part I of the Ph.D. thesis of H. J. Lanson, Polytechnic Institute of Brooklyn.

CHLORINATED KEROSENE
Preparation and Physical Properties

RAYMOND M. DEAN AND EUGENE LIEBER

Standard Oil Company of New Jersey, Bayonne, N. J.

No systematic study has been reported correlating the physical properties of chlorinated kerosene with degree of chlorination. The object of this paper is to present such a study for a kerosene fraction boiling between 348° and 525° F. and having a low aromatic content (high 'furfural miscibility temperature") and chlorinated from 5 to 60% chlorine content in steps of approximately 5%. The measurements comprise elementary analysis, refractive index, surface tension, furfural point, kinematic viscosity, solid point, specific gravity, flash and fire points, and molecular weight. These data are correlated with the degree of chlorination and the average molecular compositions obtained. A number of derived values are presented comprising molecular refraction, molecular volume, and parachlor. These are correlated against atomic chlorine contents of the chlorinated products.

THE chlorination of petroleum hydrocarbons and their utilization are becoming increasingly important and have received considerable impetus in recent times. Both the physical and chemical properties of the chlorinated products of lower-molecular-weight fractions have been extensively studied and recorded in the literature, but not much can be found for the heavier fractions of petroleum. For the latter group the industrial applications have far outstripped studies on fundamental physical and chemical properties. In fact, for certain particular fractions data are lacking entirely. This is due to the increased complexity of some of the lighter petroleum fractions extending beyond the gasoline range. Although lack of knowledge of the exact chemistry of chlorination of the higher petroleum fractions has not impeded their present industrial applications, it is generally agreed that such data would materially broaden their scope. On the other hand, lack of physical data does markedly impede progress in this field, since such data are needed for plant design and control of operation for the chlorination procedure.

Only fragmentary data have appeared in the literature on the physical properties of the chlorinated kerosene fractions of petroleum. Hartman (*1*) chlorinated kerosene from Pennsylvania petroleum by means of antimony pentachloride in the presence of iodine at 350 to 360° C. and reported the products to be principally hexachloroethane and hexachlorobenzene together with small quantities of tetrachloromethane and hexachlorobutadiene. Schrauth (*4*) chlorinated kerosene to monochloro derivatives for conversion to fatty acids. Thomas and Olin (*5*) studied the dehydrohalogenation of a chlorinated petroleum fraction to form olefins.

Table I summarizes the Engler distillation of the kerosene used in the studies reported here. Table II presents elementary analysis, molecular weight, and other pertinent data for this material. The elementary analysis and molecular weight determinations indicated the kerosene to have the average composition of $C_{12}H_{25}$. No further analysis of the composition of this material was attempted.

METHOD OF CHLORINATION

Figure 1 shows the chlorination apparatus. A 72,000-gram portion of kerosene was placed in the 12-liter Pyrex balloon flask, equipped with an alundum thimble for dispersing the chlorine, a thermometer, and a safety tube dipping into the liquid. The safety tube also served as a means of withdrawing samples from the chlorination mixture. The chlorination was conducted at 200° F., using the water bath as a heating and cooling medium. The degree of chlorination was determined approximately from time to time by weighing the flask and its contents. At the desired degrees of chlorination, samples of about one liter were with-

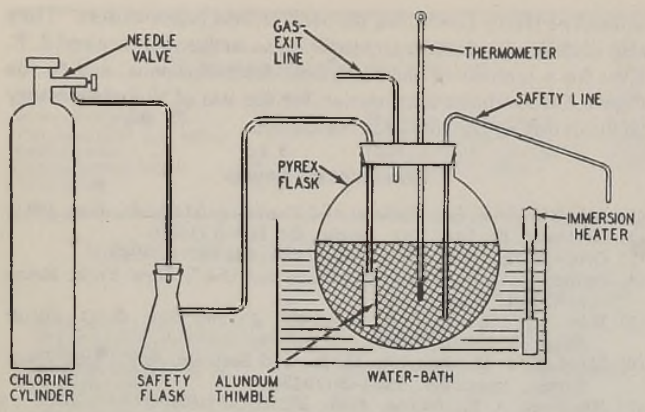


Figure 1. Apparatus Used for Chlorination

drawn. After a sample was withdrawn it was immediately cooled and blown with a gentle current of dry air, at room temperature, until the exit gases were free of gaseous hydrogen chloride.

EFFICIENCY OF CHLORINATION. The relation between efficiency of chlorination and chlorine content was determined for a sample of chlorokerosene which varied from 0 to approximately 55% chlorine by weight. The amount of chlorine lost was calculated, assuming that the only reaction was substitution of a chlorine atom for a hydrogen atom as follows:

$$R{-}H + Cl_2 \longrightarrow R{-}Cl + HCl$$

where R represents a molecule of kerosene or chlorinated kerosene. The data obtained are summarized below:

% Chlorine in Cl Kerosene	% Lost of Total Chlorine Used[a]	% Chlorine Lost Since Last Reading[b]
12.2	−8.3	−8.3
19.5	0.9	2.0
31.4	0.5	0
38.5	−0.4	−2.8
43.0	0.6	7.0
48.6	3.5	11.5
51.9	4.8	14.3
54.3	8.8	35.2

[a] Estimated error ±2%. Minus sign indicates gain.
[b] 100 minus the figures in this column gives the efficiency of chlorination.

The first column gives the calculated chlorine content of the chlorinated kerosene. The second column gives the percentage chlorine lost of the total used, and the third column gives the percentage chlorine lost for each increment of chlorine content of the chlorinated kerosene. Up to a chlorine content of approximately 12% the efficiency appears to be greater than 100%. This may be due in part to addition of chlorine to double bonds. Also, there were errors in weighing the large quantities of chlorinated kerosene and chlorine which were often of the same order of magnitude as the differences between the weights. When the chlorine content of the chlorokerosene was between 12 and 40% by weight the loss of chlorine was approximately 0%. When the chlorine content was above 40%, the loss of chlorine increased with chlorine content up to a loss of 35% for chlorinated kerosene containing approximately 55% chlorine.

TABLE I. ENGLER DISTILLATION OF ORIGINAL KEROSENE

	B.P., ° F.		B.P., ° F.		B.P., ° F.
Initial	348	40% over	430	80% over	478
10% over	390	50%	442	90%	497
15%	400	60%	456	98.5%	525
20%	406	70%	464	Final	525
30%	418	80%	478	Residue	1.5%

The chlorination for the determination of efficiency of chlorination was run in the following manner: 2.5 gallons of kerosene were placed in a 12-liter Pyrex flask fitted with an alundum thimble, a thermometer, a gas exit line, and a safety tube. A water bath fitted with an immersion heater was used for heating and cooling.

The temperature of the kerosene was raised to 175° F., and chlorine was blown in. The chlorine dissolved until the kerosene had picked up about 2% by weight of chlorine. This induction period was followed by a fairly violent reaction during which the temperature rose 10–15° F. From this point on, the reaction ran smoothly, the chlorinated kerosene gaining about 2% chlorine per hour with the temperature held at 185–205° F. From time to time the flask holding the chlorinated kerosene and the cylinder containing the chlorine were weighed and the weight changes noted. The amount of chlorine in the chlorinated kerosene was calculated on the basis of the substitution reaction only. Double this value was considered to be utilized chlorine, and this value for utilized chlorine was subtracted from the chlorine which had come out of the cylinder to give the loss figure.

ANALYTICAL PROCEDURES

Carbon and hydrogen were determined by the conventional combustion procedure. Chlorine was determined by combustion with sodium peroxide in a Parr bomb followed by a Mohr titration; the data for chlorine as presented in Table II are the mean of three independent determinations. Refractive indices were determined by an Abbe refractometer. For surface tensions at 25° C., a du Noüy precision surface tensiometer was used. Furfural miscibility temperatures were obtained by the method of Rice and Lieber (*2*). Molecular weights were determined ebullioscopically. Viscosities were found kinematically at three temperatures by the method of Ruh, Walker, and Dean (*3*). Specific gravities were determined over a range of temperatures by means of both precision hydrometers and pycnometers under thermostatically controlled conditions. The mean of three or more independent determinations were taken on all specific gravities. Solid points and open-cup flash and fire points were obtained by conventional A.S.T.M. procedures (Designations D97–39 and D92–33).

TABLE II. SUMMARY OF EXPERIMENTAL DATA

Expt. No.	Elementary Analysis, % Cl	C	H	Total	Refractive Index at 25° C.	Surface Tension (25° C.), Dynes/Cm.	Furfural Point, ° C.	Mol. Wt.	Viscosity at 100° F. Centistokes	Saybolt sec.	A.S.T.M. Solid Point, ° F.	Specific Gravity, 60/60° F.	A.S.T.M. Open-Cup Flash, ° F.	A.S.T.M. Fire Point, ° F.
107-47	0	86.06	13.99	100.05	1.4476	27.0	+98.1	176.8	1.71	..	−35	0.810	155	165
107-20	5.9	81.46	13.09	100.45	1.4530	28.0	+84.0	..	1.96	..	−45	0.841	160	175
107-14	11.1	77.12	12.36	100.58	1.4595	29.1	+66.5	..	2.33	33.8	−55	0.880	175	195
107-19	16.0	73.14	11.34	100.48	1.4657	29.7	+49.5	..	2.79	35.3	−60	0.916	195	215
107-26	20.5	68.84	10.68	100.02	1.4724	30.6	+30.9	..	3.50	37.6	−75	0.956	200	220
107-27	25.5	64.72	9.89	100.11	1.4788	31.7	+11.2	..	4.55	40.9	<−75	0.996	215	235
107-28	30.9	60.59	9.04	100.53	1.4870	33.2	−15.5	..	6.80	48.1	<−75	1.052	235	265
107-29	35.8	56.65	8.29	100.74	1.4959	35.0	..	..	11.17	62.9	−70	1.106	275	310
107-8	39.6	52.84	7.76	100.20	1.5030	36.4	..	292	18.77	92.4	−55	1.152	280	325
107-12	45.3	48.68	6.80	100.78	1.5141	38.6	..	..	48.39	224.0	−35	..	325	370
107-9	52.1	42.33	5.50	99.93	1.5289	41.9	..	..	321.9	1487.0	0	..	None	None
107-13	54.1	40.26	5.09	99.45	1.5352	43.7	..	..	941.7	4350.0	+15	..	None	None
107-15	58.4	..	..	..	1.5490	..	..	..	12,500[a]	57,750	+10	..	None	None

[a] Extrapolated value.

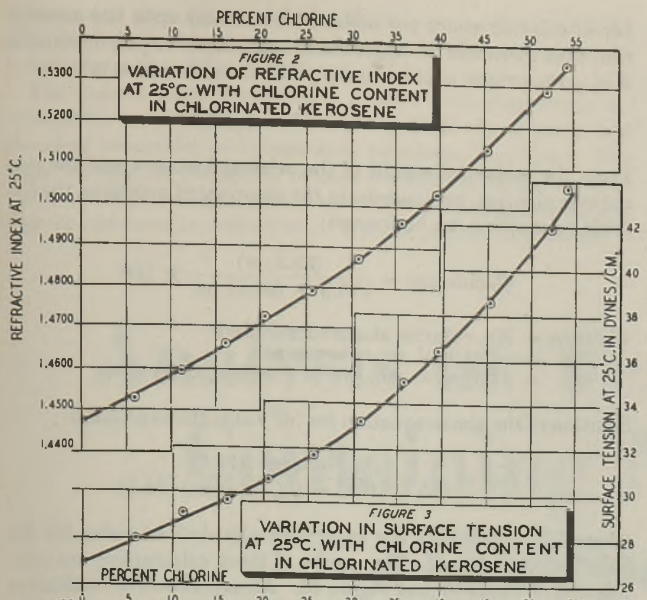


FIGURE 2
VARIATION OF REFRACTIVE INDEX AT 25°C. WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
REFRACTIVE INDEX AT 25°C.
SURFACE TENSION AT 25°C. IN DYNES/CM.
PERCENT CHLORINE
FIGURE 3
VARIATION IN SURFACE TENSION AT 25°C. WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
PERCENT CHLORINE

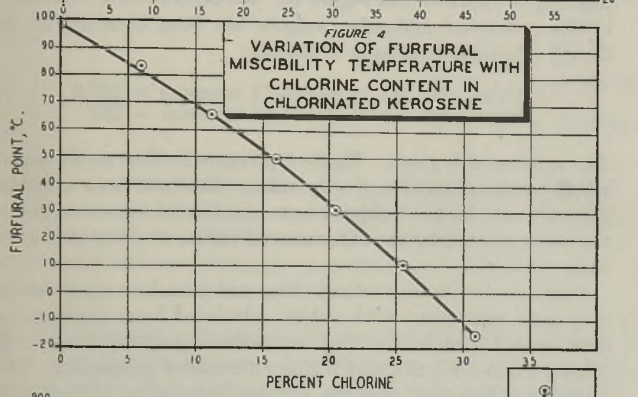


FIGURE 4
VARIATION OF FURFURAL MISCIBILITY TEMPERATURE WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
FURFURAL POINT, °C.
PERCENT CHLORINE

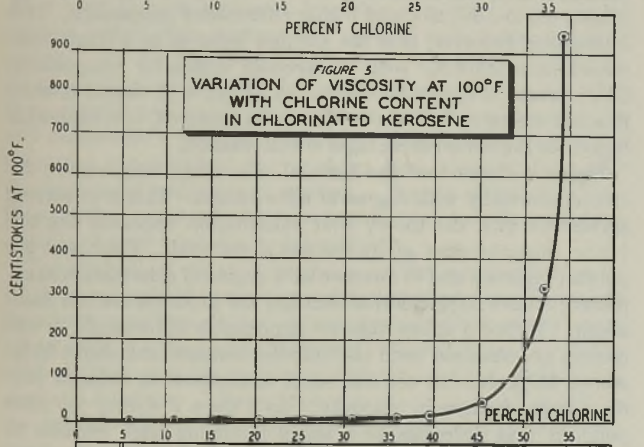


FIGURE 5
VARIATION OF VISCOSITY AT 100°F. WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
CENTISTOKES AT 100°F.
PERCENT CHLORINE

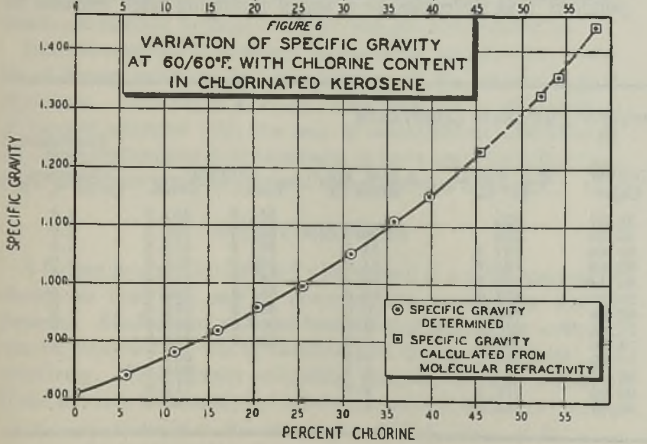


FIGURE 6
VARIATION OF SPECIFIC GRAVITY AT 60/60°F. WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
SPECIFIC GRAVITY
SPECIFIC GRAVITY DETERMINED
SPECIFIC GRAVITY CALCULATED FROM MOLECULAR REFRACTIVITY
PERCENT CHLORINE

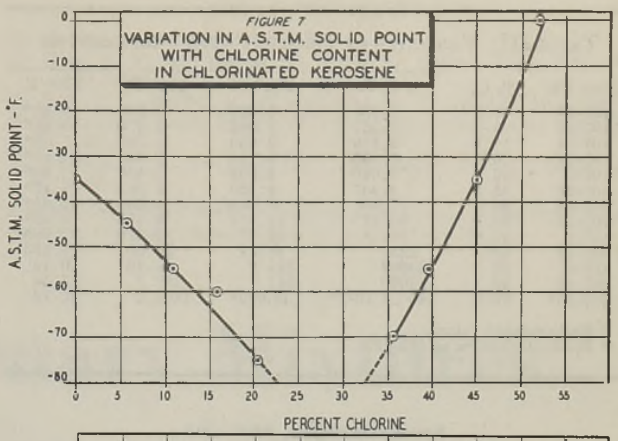


FIGURE 7
VARIATION IN A.S.T.M. SOLID POINT WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
A.S.T.M. SOLID POINT - °F.
PERCENT CHLORINE

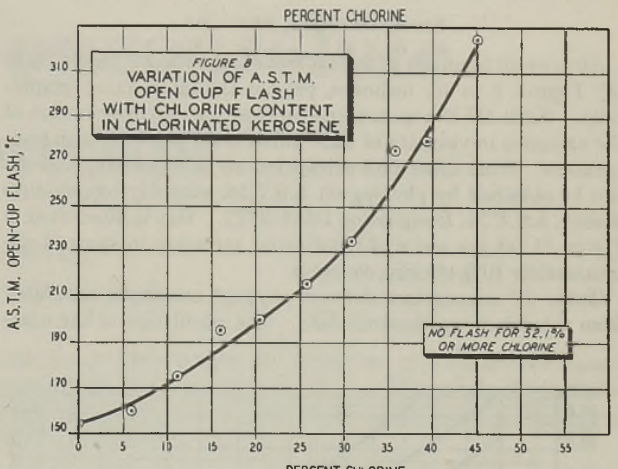


FIGURE 8
VARIATION OF A.S.T.M. OPEN CUP FLASH WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
NO FLASH FOR 52.1% OR MORE CHLORINE
A.S.T.M. OPEN-CUP FLASH, °F.
PERCENT CHLORINE

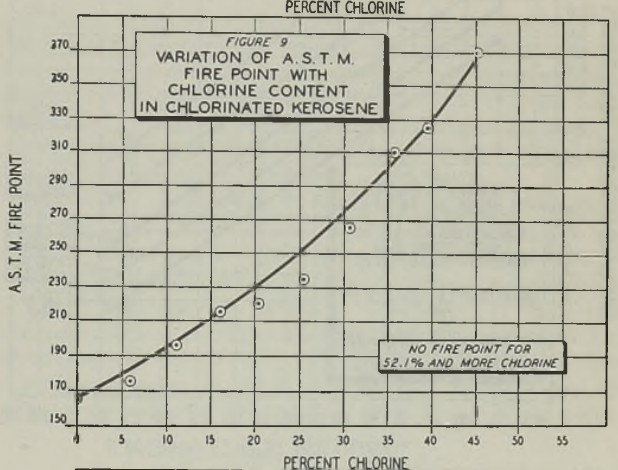


FIGURE 9
VARIATION OF A.S.T.M. FIRE POINT WITH CHLORINE CONTENT IN CHLORINATED KEROSENE
NO FIRE POINT FOR 52.1% AND MORE CHLORINE
A.S.T.M. FIRE POINT
PERCENT CHLORINE

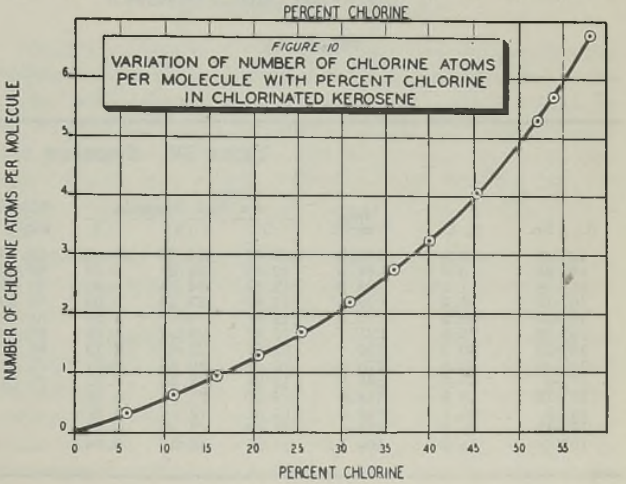


FIGURE 10
VARIATION OF NUMBER OF CHLORINE ATOMS PER MOLECULE WITH PERCENT CHLORINE IN CHLORINATED KEROSENE
NUMBER OF CHLORINE ATOMS PER MOLECULE
PERCENT CHLORINE

TABLE III. VARIATION OF VISCOSITY WITH TEMPERATURE

Run No.	% Cl	Centistokes 75° F.	100° F.	130° F.	210° F.
107-47	0.0	2.169	1.708	1.340	0.82[a]
107-20	5.9	2.551	1.963	1.470	0.88[a]
107-14	11.1	3.119	2.330	1.750	1.00[a]
107-19	16.0	3.838	2.790	2.010	1.10[a]
107-26	20.5	5.010	3.503	2.465	1.28[a]
107-27	25.5	6.847	4.550	3.063	1.47[a]
107-28	30.9	11.50	6.800	4.265	1.83[a]
107-29	35.8	20.47	11.173	6.415	2.35[a]
107-8	39.6	38.0[a]	18.77	9.520	2.995
107-12	45.3	123[a]	48.39	20.00	4.655
107-9	52.1	3000[a]	321.9	83.20	10.10
107-13	54.1	5400[a]	941.7	187.7	15.32
107-15[b]	58.4	140 (× 10³)[a]	12,500[a]	1403.0	40.74

[a] Extrapolated values.
[b] 269.3 centistokes at 160° F.

EXPERIMENTAL RESULTS

An over-all summary of the experimental data is given in Table II; Figures 2 to 10, inclusive, present the information graphically. Table III is a more extended experimental examination of the variation in viscosity of these chlorinated products with temperature. From these data extrapolations to other temperatures can be obtained by plotting on A.S.T.M. viscosity-temperature charts (A.S.T.M. Designation D341–37T). This is illustrated in Figure 11 for the series of chlorinated kerosenes in steps of approximately 10% chlorine contents.

Table IV summarizes derived physical constants calculated from the direct experimental data. The calculation of the number of chlorine atoms per molecule was based upon the assumption that there was no appreciable breakdown or polymerization during the process of chlorination; i.e., the main reaction is

$$RH + Cl_2 = RCl + HCl$$

From the molecular weight of the original kerosene and the percentage chlorine, by analysis, in the chlorinated products, the following equations can be derived:

$$\% \text{ chlorine} = \frac{(35.5)(n)}{176.8 + (34.5)(n)} \times 100$$

where n = No. chlorine atoms substituted
176.8 = exptl. mol. wt. of kerosene
176.8 + 34.5 (n) = mol. wt. of chlorinated kerosene

Solution of the above equation for (n) yields the expression:

$$(n) = \frac{(\% \text{ chlorine})(176.8)}{(35.5)(100) - (\% \text{ chlorine})(34.5)}$$

where (% chlorine) is the experimentally derived value for the chlorinated kerosene. The results of these calculations are summarized in Table IV and Figure 10. An experimental verification of the calculated molecular weights has been obtained for the 39.6% chlorinated kerosene as follows:

Calcd. mol. wt. of 39.6% Cl kerosene = 287.3
Exptl. mol. wt. of 39.6% Cl kerosene = 292

The agreement is good. Figure 6 presents further verification in which a series of specific gravity values calculated from molecular refractivities, for the highly viscous members of the series, fit into the curve plotted for the experimental values of the specific gravities.

Calculated molecular refractivities and parachors are in reasonably good agreement with values calculated from experimental data when it is considered that we are dealing with mixtures comprising mono-, di-, tri-, and higher chlorinated compounds. It is interesting, however, that the mixture behaves as a single compound in conformity with its average molecular composition. The increase of molecular volume at 25° C. with degree of chlorination seems to be quite uniform; as expected, it is somewhat higher for the lower percentages of chlorination.

Figure 4 shows that the furfural miscibility temperature decreases markedly with degree of chlorination. This is in general agreement with the theory that chlorination improves the solvency characteristics of hydrocarbon material. Flash and fire points (Figures 8 and 9) increase with degree of chlorination as expected; above 52% chlorine content, the products are not flammable. Figure 5 shows that no appreciable differentials in viscosities are obtained until the chlorine contents are above 30%. Above 50% chlorine content small increments in chlorine produce large changes in viscosity. As Figure 7 shows, the solid point at first decreases to a sharp minimum with increase in

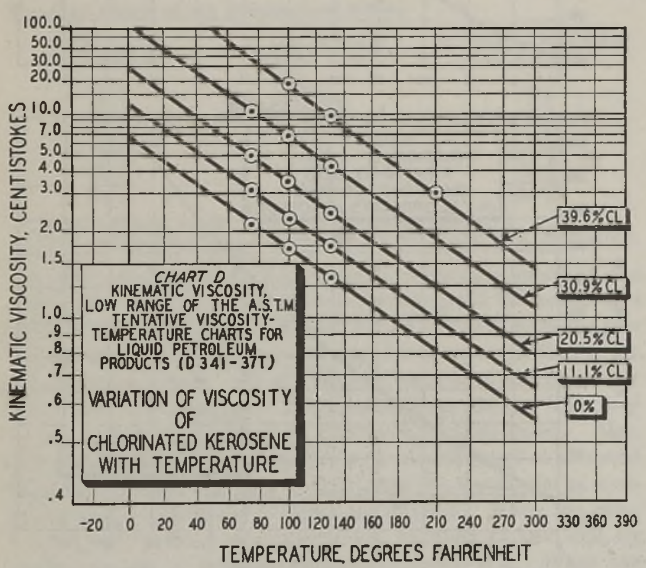


Figure 11

TABLE IV. SUMMARY OF DERIVED PHYSICAL CONSTANTS

Run No.	% Cl	Mol. Weight	Av. Mol. Formula C	H_2	Cl	Mol. Refraction Exptl.	Calcd.	Mol. Vol. at 25° C.	Δ Mol. Vol./ Atom Cl	Parachor Exptl.	Calcd.	Coefficient of Vol. Expansion (× 10⁻⁴), ° F.
107-47	0.0	176.8	12.67	24.72	None	58.85	58.55	220	..	501.6	491.7	5.0
107-20	5.9	187.5	12.67	24.41	0.31	60.68	59.34	225	16.1	517.5	503 3	5.0
107-14	11.1	198.0	12.67	24.35	0.61	62.03	61.06	227.3	11.6	527.8	518.5	5.0
107-19	16.0	208.6	12.67	23.55	0.93	63.69	62.09	230.6	11.3	538.2	522.8	5.0
107-26	20.5	220.7	12.67	23.57	1.27	65.12	64.14	232.9	10.1	547.8	541.4	5.0
107-27	25.5	235.3	12.67	23.24	1.69	67.30	66.28	237.9	10.6	564.5	558.6	4.0
107-28	30.9	252.1	12.67	22.67	2.18	69.11	68.58	242.0	10.0	580.8	575.8	4.0
107-29	35.8	270.5	12.67	22.25	2.71	71.92	71.28	246.7	9.8	600.0	597.5	3.0
107-8	39.6	288.3	12.67	22.34	3.21	74.14	74.36	251.3	9.8	616.9	625.8	4.0
107-12	45.3	314.6	12.67	21.22	3.98	..	77.73	258.1	9.5	..	649.1	..
107-9	52.1	358.9	12.67	19.74	5.27	..	83.80	271.1	9.7	..	694.5	..
107-13	54.1	375.0	12.67	19.18	5.74	..	85.98	276.1	9.9	..	710.8	..
107.15	58.4	409.3	12.67	18.01	6.74	..	90.67	285.1	9.7	..	745.6	..

chlorine and then rises rapidly for chlorine contents above 35%. This rise is undoubtedly associated with the higher viscosities obtained above 35% chlorine contents.

The present paper represents a portion of a comparative investigation on the preparation and study of the physical and chemical properties of halogenated petroleum fractions. This work has been interrupted by present conditions. However, when opportunity permits, we plan to resume our investigations and to present comparative data on other types of petroleum fractions.

LITERATURE CITED

(1) Hartman, *Ber.*, 24, 1019 (1891).
(2) Rice, H. T., and Lieber, E., IND. ENG. CHEM., ANAL. ED., 16, 107 (1944).
(3) Ruh, E. L., Walker, R. W., and Dean, E. W., *Ibid.*, 13, 346 (1941).
(4) Schrauth, German Patent 327,048 (1914); *Chem. Abs.*, 15, 2009 (1921).
(5) Thomas, C. A., and Olin, J. F., U. S. Patent 2,065,323 (Dec. 22, 1936).

PRESENTED before the Division of Petroleum Chemistry at the 108th Meeting of the AMERICAN CHEMICAL SOCIETY in New York, N. Y.

Analysis of Ternary Mixtures Containing Nonconsolute Components

ALLEN S. SMITH[1]

Blaw-Knox Company, Pittsburgh, Pa.

An indirect method of analysis for liquid mixtures of three components is described. It is applicable to ternary systems having a miscibility gap. The method requires determination of two saturation points on a solubility isotherm of the ternary by addition of two of the components to the unknown mixture. The original composition of the mixture is then obtained by graphical or algebraic calculation.

LIQUID-liquid and vapor-liquid equilibria in ternary systems have, in many instances, been studied because of the ease of analysis rather than because the systems were industrially important. In fundamental investigation it is desirable to have direct methods of analysis for homogeneous ternary mixtures, from specific analytical procedures or from adequate data for two independent physical properties. Many valuable data of industrial importance, however, have been reported for which the methods of analysis were indirect. These methods were used because they were necessary or convenient, but they are also capable of good precision and sensitivity.

The analysis of water in alcohol with the aid of dicyclohexyl (*8*) is an example of a sensitive indirect method. Aniline points have been used in a similar manner for more than twenty years (*1*) to analyze hydrocarbon mixtures. The more recent furfural method (*7*) extends the usefulness of the method to include highly aromatic solutions. The temperature of complete miscibility or the critical solution temperature is employed, and the measurements are referred to those of known compounds or mixtures.

Indirect methods at constant temperature facilitate the analysis of binary mixtures and the location of tie lines in ternary equilibria. This paper extends these methods to the analysis of ternary mixtures with one pair of nonconsolute components. In these applications it is necessary to have only solubility data at a convenient temperature and measurements of weight.

BINARY MIXTURES

A binary mixture is analyzed with the aid of a third component chosen so that one pair of nonconsolute components will be present. Alcohol and water or benzene and hexane, for example, can be analyzed by use of benzene and dipropylene glycol, respectively. The ternary solubility diagram is first obtained. If the mixture to be analyzed is homogeneous, it is titrated with a nonconsolute component to the point of immiscibility. If the mixture is heterogeneous, it is titrated with the consolute component to the point of miscibility. These points lie on the solubility curve. The original composition of the binary mixture is calculated from the weights of the sample and component, and the ternary composition is read from the curve.

If no point of immiscibility or miscibility is reached in titration, the composition of the original unknown mixture must be altered by adding one of the pure components of the mixture to bring the composition within the range of the immiscible portion of the solubility diagram. It is also necessary to do this if the end point is difficult to detect because of critical opalescence. No preliminary trials are necessary after experience is gained in use of ternary diagrams, as any one of the three components can be added to the unknown mixture at will to obtain a good end point.

TIE LINE DETERMINATION

Indirect methods are conveniently used to determine the composition of phases at equilibrium when the over-all composition of the heterogeneous ternary is known. The phases, which lie on the solubility curve, are located by use of the familiar lever arm relation in one method. The weight ratio of the two conjugate phases is in inverse relation to their distances from the ternary point, in the solubility diagram, to the solubility curve (*6*).

Bancroft and Hubard (*2*) described a graphical method for determining dineric distribution between phases at equilibrium. The phases separated at equilibrium are titrated through the region of immiscibility to saturation on the opposite side of the solubility isotherm with two of the components. The original composition of the given phases is determined by trial-and-error calculation to be that composition which required the addition of the particular amounts of the two components to depart from the isotherm and then return to it. This method serves to de-

[1] Present address, P. O. Box 48, Ann Arbor, Mich.

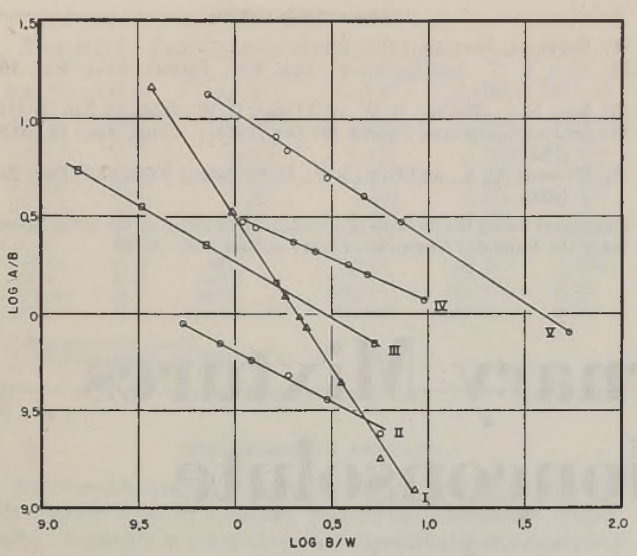


Figure 1. Solubility Data for Five Ternary Systems

System	A	B	W	Temp., °C.	Reference
I	Ethyl alcohol	Benzene	Water	25	(2)
II	2-Propanol	Nitromethane	Water	25	(9)
III	Diphenylhexane	Docosane	Furfural	45	(3)
IV	Acetone	Chloroform	Water	25	(2)
V	Methyl ethyl ketone	Carbon disulfide	Water	25	[a]

[a] Obtained by A. R. Jensen in this laboratory.

termine the composition of a ternary homogeneous mixture lying on a solubility isotherm.

TERNARY MIXTURES

The need for an indirect method of analysis arose in the course of work on ternary vapor-liquid equilibria. The vapor and liquid samples, which were obtained in the equilibrium apparatus of Colburn, Schoenborn, and Schilling (*4*) for partially miscible components, consisted of both homogeneous and heterogeneous mixtures of three components whose over-all composition was unknown. The precision of the analytical method developed is good, but the accuracy depends upon the reliability of the isothermal solubility diagram, as is true in all the indirect methods mentioned.

The method is based on the assumption that isothermal solubility in ternary heterogeneous systems follows a mass law equation of the type:

$$(a/b)^m/(a/w) = K$$

where a = consolute component
b, w = nonconsolute components
m, K = constants

Lincoln (*5*) found that his data on the system benzene-alcohol-water followed this equation. Bancroft and Hubard (*2*) confirmed this. The latter found that the system acetone-chloroform-water did not give a straight line when plotted according to the equation.

Thirty systems for which solubility data have been plotted by the mass law equation have been found to follow the equation over part of the isotherm. The deviations of the data from the logarithmic straight lines are small and, in view of the cloud point method used in most solubility determinations, could be due to experimental error. If points in some systems do represent sigmoidal curves, as in the acetone-chloroform-water system, the best straight line drawn through the points adequately represents the isotherm for the purpose. The systems also follow an equation of the type $(a/b)^m/(b/w) = K$. This form has been used although there is no theoretical justification for it. The points seem to give less dispersion from a straight line and the line is longer, which is convenient.

Solubility data for five representative systems are plotted in Figure 1 according to the equation. The same data are plotted on triangular coordinates in Figure 2. The curves in both figures extend over the same range.

The application of the method is illustrated with reference to system I. The unknown mixtures are assumed to be those represented by Arabic numerals 2 and 6 in Figure 2. Sample 2 is titrated with water to saturation at point 3, additional water is added to 4, and the mixture is titrated to miscibility at 5 with alcohol. When the unknown sample lies on the water-rich side of the diagram, as at 6, it is diluted with benzene, as to 7, titrated with alcohol to miscibility at 8, diluted with benzene to 9, and finally titrated again to miscibility at 10. The location of the unknown sample in the solubility diagram can be approximated from the proportion of the phases in a heterogeneous mixture, as the slope of the tie lines can be estimated, or by trial addition of one or more components in the case of homogeneous mixtures. The addition of nonconsolute components and titration with consolute component can then be made so that two end points are obtained, lying on the portion of the isotherm which follows the mass law equation.

The operations with the mixtures are represented in Figure 3. The numerals correspond to those in Figure 2. In each example the titration has been made with a constant amount of one of the nonconsolute components benzene or water. Each miscibility or saturation point, 3 and 5 or 8 and 10, lies on a line whose equation is:

$$\log A/B = \log K + m \log B/W \qquad (1)$$

As either B or W is the same for two pairs of points, the compositions of the two points are related in the following manner.

$$\text{At constant } B\text{:} \quad \log \frac{A_3}{A_5} = -m \log \frac{W_3}{W_5} \qquad (2)$$

$$\text{At constant } W\text{:} \quad \log \frac{A_8}{A_{10}} = (1 + m) \log \frac{B_8}{B_{10}} \qquad (3)$$

The quantities represented by A, B, and W in Equations 2 and 3 are made up of the unknown amounts of each plus the added amounts to obtain the two points on the isotherm; thus A_3 =

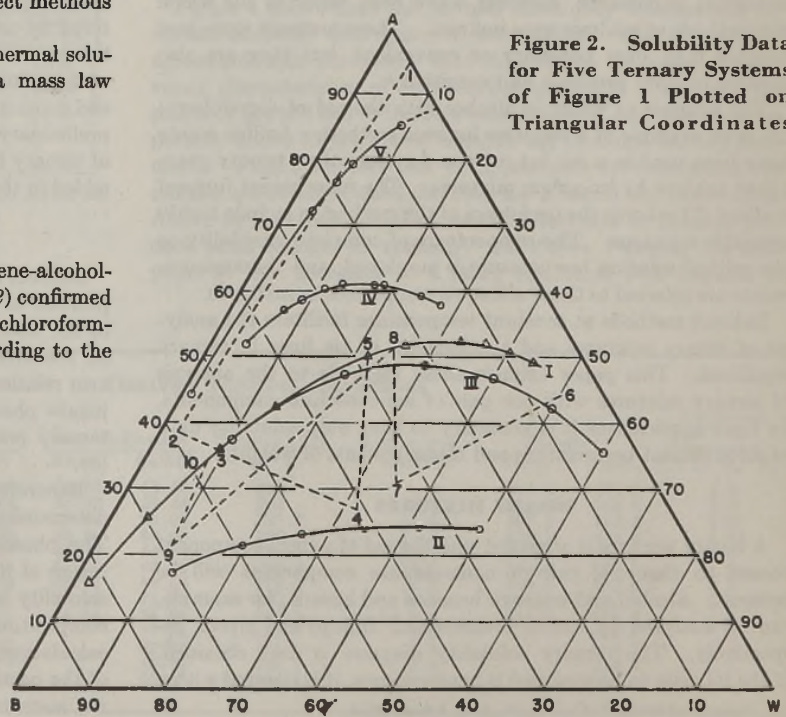


Figure 2. Solubility Data for Five Ternary Systems of Figure 1 Plotted on Triangular Coordinates

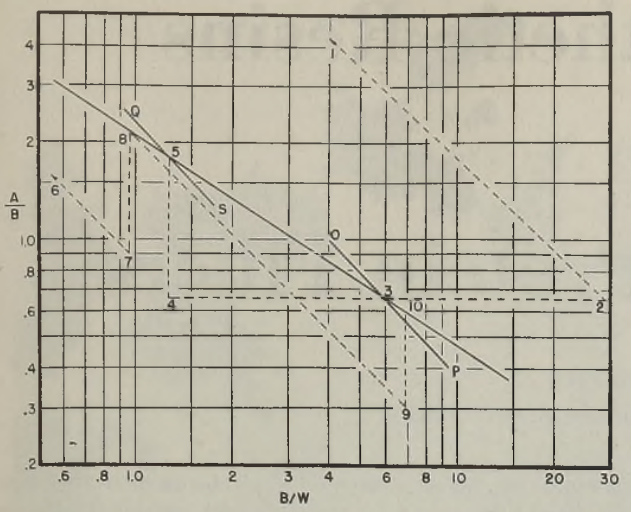


Figure 3. Operation of Mixtures Shown in Figure 2

A and $A_5 = A + x$. Trial values of one of the unknown quantities (W, for example) are substituted in Equation 2, and the value of the other quantity, A, is calculated. The value of B is obtained by difference, as the sum of A, B, and W equals the weight of sample taken for analysis. Three values are sufficient. They define a straight line represented by either OP or QS in Figure 3 and related by the following equation:

$$\log \frac{A + x}{B} = \log K' + m' \log \frac{B}{W + y} \qquad (4)$$

where A, B, W = calculated values
x, y = added quantities of A and W

If x and y are taken as the quantities necessary to obtain the first point on the isotherm, then OP represents the equation. It intersects the isotherm at point 3. The original composition of the unknown mixture is calculated from the point of intersection.

A solution can also be obtained algebraically from Equation 1 for the isotherm and from Equation 4 for the line OP or QS. The value of the abscissa at the point of intersection is:

$$\log B/W = \log \frac{K'}{K} / (m - m') \qquad (5)$$

The graphical method is more simply illustrated by an example with mixture 2 of system I:

Assume unknown mixture 2 = 244.5 g. (point 2)
Add W to saturation = 19.5 g. (point 3)
Add W to produce two phases = 88.5 g. (point 4)
Add A to miscibility = 164.5 g. (point 5)
Slope of isotherm = −0.6562 (in Equation 1 for system I)
Apply Equation 2:

$$\log \frac{A}{A + 164.5} = 0.6562 \log \frac{W + 19.5}{W + 19.5 + 88.5}$$

Assume values for W, calculate corresponding values for A and B, and obtain the values of $(A + x)/B$ and $B/(W + y)$ in Equation 4 for point 3 or for point 5:

			Point 3		Point 5	
W	A	$B = 244.5 - (A + W)$	A/B	$\frac{B}{W + 19.5}$	$\frac{A + 164.5}{B}$	$\frac{B}{W + 108}$
2	84.7	157.8	0.537	7.34	1.58	1.435
4	92.2	148.3	0.621	6.32	1.73	1.323
6	98.6	139.9	0.705	5.49	1.88	1.228

Plot the values of A/B and $B/(W + 19.5)$ for point 3, and draw straight line OP. The coordinates of the intersection are $A/B = 0.659$, $B/W = 5.9$. Therefore:

$$\left.\begin{matrix} B = 54.7\% \\ A = 36.0 \\ W = 9.3 \end{matrix}\right\} \times 264 \text{ (= total wt. of 3)} = \left\{\begin{matrix} 144.5 \text{ grams } B \\ 95.0 \text{ grams } A \\ 24.5 \text{ grams } W \end{matrix}\right.$$

Subtract quantities added to make 3 and compute composition:

$$\left.\begin{matrix} B = 144.5 - 0 = 144.5 = 59.0\% \\ A = 95.0 - 0 = 95.0 = 38.8 \\ W = 24.5 - 19.5 = 5.0 = 2.2 \\ \qquad\qquad\quad 244.5 \end{matrix}\right\} = \text{composition of unknown mixture 2}$$

The procedure would be the same if the data for point 5 were used.

If the unknown mixture had been 100 grams of 1 to which 144.5 grams of B had been added to obtain 2, the percentage composition would be obtained directly in the last step of the example. This is true whenever the sample is taken or calculated to the basis of 100. A check on the accuracy is obtained when the final composition totals 100%. This is shown by an analysis of an unknown mixture of system V for which this method was used in vapor-liquid equilibria measurements.

EXAMPLE. Heterogeneous mixture of methyl ethyl ketone, carbon disulfide, and water:

Sample	13.49 g. ≡ 100.0 g.
MEK added to saturation	15.06 g. ≡ 111.6 g.
H_2O added to immiscibility	2.9 g. ≡ 21.5 g.
MEK added to saturation	24.5 g. ≡ 181.5 g.
	Total 414.6 g.

Slope of isotherm = −0.659 (in Equation 1 for system V). Apply Equation 2:

$$\log \frac{A + 111.6}{A + 111.6 + 181.5} = 0.659 \log \frac{W}{W + 21.5}$$

Assume values for W, calculate corresponding values for A and B, and obtain values of $(A + x)/B$ and $B/(W + y)$ in Equation 4 for the second point of saturation:

W	A	$B = 100 - (W + A)$	$\frac{A + 293.1}{B}$	$\frac{B}{W + 21.5}$
9	35.39	55.7	5.89	1.825
10	48.9	41.1	8.32	1.305
11	62.5	26.5	13.41	0.814

Coordinates of intersection for the straight lines of Equations 1 and 4 for system V determined graphically are: $A/B = 10.75$, $B/W = 1.025$. Therefore:

$$\left.\begin{matrix} A = 84.46\% \\ B = 7.87 \\ W = 7.67 \end{matrix}\right\} \times 414.6 = \left\{\begin{matrix} 350.2 \text{ } A \text{ in final mixt.} \\ 32.6 \text{ g. } B \text{ in final mixt.} \\ 31.8 \text{ g. } W \text{ in final mixt.} \end{matrix}\right.$$

Subtract quantities added to obtain the second saturation point, and compute composition:

$$\begin{matrix} 350.2 - 293.1 = 57.1\% \ A \text{ in original sample} \\ 32.6 - 0 = 32.6\% \ B \text{ in original sample} \\ 31.8 - 21.5 = 10.3\% \ W \text{ in original sample} \\ \text{Total } 100.0 \end{matrix}$$

ACKNOWLEDGMENT

The criticism of Julian C. Smith and his check of the calculations are appreciated.

LITERATURE CITED

(1) Ball, J. S., U. S. Bur. Mines, *Rept. Investigations* 3721 (1943).
(2) Bancroft, W. D., and Hubard, S. S., *J. Am. Chem. Soc.*, 64, 347 (1942).
(3) Briggs, S. W., and Comings, E. W., IND. ENG. CHEM., 35, 411 (1943).
(4) Colburn, A. P., Schoenborn, E. M., and Shilling, D., *Ibid.*, 35, 1250 (1943).
(5) Lincoln, A. T., *J. Phys. Chem.*, 4, 161 (1909).
(6) Othmer, D. F., and Tobias, P. E., IND. ENG. CHEM., 34, 690 (1942).
(7) Rice, H. T., and Lieber, E., IND. ENG. CHEM., ANAL. ED., 16, 107 (1944).
(8) Robertson, G. R., *Ibid.*, 15, 451 (1943).
(9) Schumacher, J. E., and Hunt, H., IND. ENG. CHEM., 34, 701 (1942).

Effect of Synthetic Resins on Cellulose and Protein Fibers

D. H. POWERS

Monsanto Chemical Company, Everett, Mass.

When cellulose fibers are impregnated with resin-forming solutions of unpolymerized urea-formaldehyde, melamine-formaldehyde, or phenol-formaldehyde, these resin formers have little effect on the properties of the fibers until the resins are cured or polymerized within the fiber. Evidence shows that the resin is uniformly distributed through the fiber and, in certain cases, may actually react within the cellulose. Low concentrations of the resins formed within the fiber have pronounced effects on the physical properties, changing the elongation, elasticity, wet strength, moisture regain, resilience, and dyeing properties. A new method of determining the degree of resin polymerization has been developed. It is also shown that wool and protein fibers may be impregnated with resin-forming solutions; however, there is no evidence that they react with the wool protein. The medium in which the resin-forming materials are applied has a tremendous effect on the properties obtained, and it is shown that fiber swelling is necessary to ensure thorough penetration. Electron photomicrographs are shown of treated and untreated fibers.

THE commercial importance of resin-modified rayon and spun rayon fabrics is well recognized. Many millions of yards are now on the market, and the resin treatment is carried out so that no visual or apparent change occurs in the fabric. Few stores and fewer customers realize that they are buying fabrics, principally dress goods, which contain from 5 to 15% synthetic resin.

This development is quite distinct and entirely unrelated to the millions of yards of coated fabrics (principally cottons) which are covered with continuous films of elastomers for the production of raincoats, ponchos, bridge-table covers, etc. Customers and consumers of these coated fabrics always recognize that they are buying a coated material. The coating resins have little effect on the chemical and physical properties of the cotton fabrics or yarns coated. The tear resistance of the fabric is usually reduced and its tensile strength may be reduced slightly, but its resilience, elongation, and moisture pickup are unaffected. On the other hand, the resin-modified rayons have an appreciably altered tensile strength, elongation, resilience or elasticity, moisture pickup, dyeing character, and tear resistance.

The reason for the great difference in the effect of the resins in these two types of applications lies entirely in the difference in method of application. The resin-modified fabrics are produced by treating them with true solutions in water of the resin-forming chemicals, driving off the water, and polymerizing the resin formers into the actual resin. By carefully controlling the method of application, it is possible to polymerize the entire resin within the heart of the fibers with no resin polymer on the fiber surfaces or between the fibers. While most of the early work was done on viscose rayon, more recently important and striking results have been obtained on wool and protein fibers with newer resin types.

A study has been made of different resin formers, methods of application, and polymerization conditions, and the effect on the various fibers noted. It should be pointed out that resin formers may give rayon far greater resilience while keeping its original surface character, and give wool far greater washability while keeping the surface character of wool. Heretofore it was necessary to synthesize a new yarn to develop new fiber characteristics. The use of resin formers makes possible the development of new fiber characteristics in the natural fibers and yarns.

EFFECT OF RESIN TYPE

Three types of water-soluble resin formers are available—urea-formaldehyde, phenol-formaldehyde, and melamine-formaldehyde. Table I shows the effect of treating cotton sheeting with equal concentrations of each resin. Marked variations are noted with the different resins, because some surface resin polymer is probably formed on the outside of the fibers. This surface resin will affect wearing properties of the fiber in keeping with its brittleness or toughness. If no surface resin were present, the difference in wear resistance would probably not be measurable.

Plain cotton sheeting was enzyme-desized, kier-boiled, and bleached. The dry adsorbent sheeting was padded through a

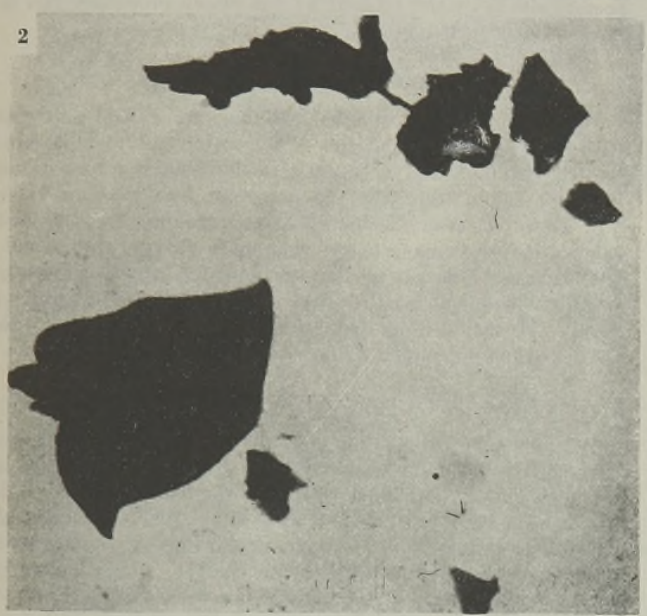
TABLE I. EFFECT OF RESINS ON COTTON SHEETING

Treatment on Sheeting	Concn. of Resin Former in Water, %	Shrinkage of Fabric on Washing, %	Tensile Strength (Scott Tester)	Abrasion (Taber Abrader)
None	0	5.2	41.5	6557
Urea-formaldehyde	5	2.8	37.5	4730
Phenol-formaldehyde	5	3.0	41.3	7780
Melamine-formaldehyde	5	1.8	40.8	6400

TABLE II. EFFECT OF RESIN CONCENTRATION ON TENSILE STRENGTH[a]

Bleached Cotton Sheeting			All Spun Rayon			All Wool Flannel	
% resin in fiber	Methylol-urea[a]	Methylol-melamine[a]	% resin in fiber	Methylol-urea[a]	Methylol-melamine[a]	% resin in fiber	Methylol-melamine[a]
0	90	90	0	85	85	0	46.6
1	88	96	1	89	89	5	63.4
3	86	95	3	96	93	10	62.7
7	70	90	5	89	97	18	59.0
10	67	88	10	88	105	24	45.1
15	65	88	15	85	106		
			20	78	104		

[a] Tensile strengths are the sum of warp and filling breaks. Figures are the average of five breaks taken on samples after conditioning for 24 hours.



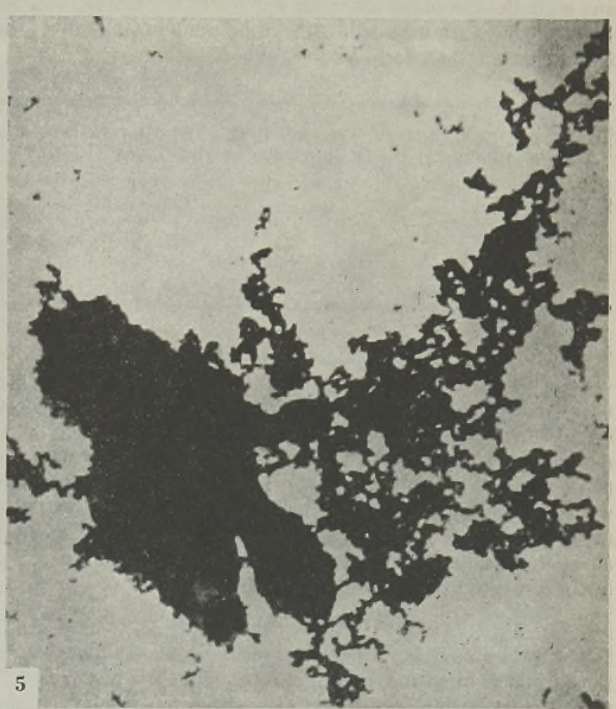


Figure 1. Scoured Wool (× 10,000)

Figure 2. Scoured Wool Impregnated with 7% Resloom M-75 (× 10,000)

Figure 3. Scoured Wool Impregnated with 1% Syton W-20 (× 10,000)

Figure 4. Scoured Wool Coated with 4% Aqueous Polystyrene Dispersion (× 10,000)

Figure 5. Dyed Wool Impregnated with 10% Resloom M-75 but Not Washed (× 10,000)

water solution of the resins. In every case an effort was made to use a completely unpolymerized reaction product of urea, phenol, or melamine with formaldehyde.

The fabric was wet out in a 5% solution of the resin former, and run through a squeeze roll so that 100 grams of cloth retained 100 grams of resin-forming solution. The water was driven off at 180–200° F. as rapidly as possible. In the case of urea and melamine 0.2% of diammonium phosphate was added as catalyst. In the case of phenol 0.2% of sodium carbonate was used.

The resins were polymerized by drying the fabrics in an electric oven for 15 minutes at 300° F. The fabrics were given a light soaping to remove any unpolymerized resin and carefully rinsed with water. The fabrics were treated, polymerized, and rinsed under controlled tension so that no shrinkage occurred during processing. To determine shrinkage, measured samples were washed in a rotary washer for one hour at 180° F. according to Federal Specification CCC-T-191a.

EFFECT OF CONCENTRATION

Cotton, rayon, and wool fabrics were treated with increasing concentrations of each resin by the procedure outlined above. Experience indicates that each fabric and fiber has a saturation point—that is, a point at which the resin former seems to spill over onto the outside of the fiber. At concentrations below this point the fabrics remain soft and flexible, but with a resin content above this point the fabric becomes stiff and begins to lose tensile strength. Concentrations from 1 to 20% of the methylol-urea and methylol-melamine resins are applied to the fabrics, and the change in strength recorded. Rayon takes up much more of the urea type resin than does cotton (Table II).

Table III. Change in Tensile Strength Resulting from Resin Impregnation (Expressed as Per Cent Change)

% Resin Concn.	Impregnated with Methylol-Melamine			Impregnated with Methylol-Urea	
	Cotton	Spun rayon	Wool	Cotton	Spun rayon
5	2	9	36	−15	4
10	0	18	34	−24	3
15	−2	36	30	−27	0

Table III expresses the change in tensile strength with increase of resin concentration on cotton, spun rayon, and wool. Impregnating with water-soluble methylol-melamine showed little effect on cotton but gave a steadily increasing effect on spun rayon. A marked increase in the strength of wool is noted even with low concentrations of resin. Even with 25% impregnated resin, the wool still shows an improved tensile strength. The methylol-urea resins do not appear to penetrate as well, as they show little effect on the adsorbent spun rayon and cause a marked reduction in the strength of cottons.

EFFECT OF SHRINKAGE

The melamine resin formers are most striking in their effect on the shrinkage of cotton, rayon, or wool, and their mixtures. In this study it is important that the fabrics treated be handled under uniform tension so that there will be no preliminary shrinkage during the resin treatment, drying, curing, or rinsing.

Table IV summarizes the actual shrinkage of a range of fabrics before and after treatment with the concentration of the methylol-melamine resin former indicated. In each case the fabrics were washed according to the standard A.A.T.C.C. procedure for shrinkage determination (*1*). The cotton procedure was used on all cotton fabrics; otherwise, the procedure for "fabrics other than cotton" was used. All shrinkages are expressed in per cent of original size, and only warp shrinkages are recorded.

The actual resin concentrations used were not necessarily the optimum, and the shrinkage wash test is a much more severe test than the fabrics might normally get. Incidentally, the volume of water used on the woolen fabrics had a tremendous effect on their shrinkage. Smaller volumes of water gave more severe mechanical action and, consequently, greater shrinkage. It should be emphasized that a cotton sheeting coated with 30% of cellulose acetate shrinks when washed by the above procedure just as much as an untreated fabric.

Table IV. Shrinkage of Fabrics Before and After Resin Treatment

Fabric	Original Shrinkage	Resin, %	Shrinkage after Resin Impregnation	Shrinkage Removed, %
Light cotton sheeting	6.74	5.2	1.09	84
Heavy cotton sheeting	5.58	4.8	1.17	79
Cotton flannel	12.6	5.5	2.1	84
Cotton lawn	3.4	4.3	0.8	77
All spun rayon	12.1	6.1	2.9	76
Filament rayon	11.4	5.9	4.3	62
Cotton-rayon-wool blanket	19.4	10.6	3.2	84
Cotton-rayon blanket	20.2	5.8	6.8	66
All wool challis	23.2	6.2	5.7	75
All wool flannel	30.1	10.8	4.1	86
All wool shirting	20.7	5.7	6.1	71
Wool-rayon shirting	24.2	12.8	4.8	80
All wool suiting	11.5	7.2	3.2	72
Cotton-rayon suiting	11.4	8.9	1.7	85
			Av.	79

EFFECT ON MOISTURE PICKUP

When cellulose is acetylated, its moisture pickup decreases with the degree of acetylation. When cotton and rayon is resin-treated with urea- and melamine-formaldehyde resin formers, its moisture pickup drops with the increase in resin content (Table V). However, even the highest concentrations of resins used calculate to less than one hydroxyl group reacted per glucose unit. On this basis it is easy to see that the reduction in moisture pickup roughly corresponds to the effect of blocking off one hydroxyl group. We do not claim that one hydroxyl group is reacted with the methylol compound but suggest such a possibility.

EFFECT ON DYEING PROPERTIES

In connection with a study of curing temperatures, it was discovered that melamine resins alter the dyeing rates of cotton or rayon so that a short quick dyeing at the boil will quickly tell whether the resin is cured and wash-fast. While a number of dyestuffs are effective, one of the most satisfactory colors proved to be Diamine Fast Blue FFB (Prototype 71). When a piece of cotton is dyed in a 3% dye bath of this color at 212° F. for 5 minutes, a dark blue shade is obtained. When a cotton fabric is treated with a 10% solution of a methylol-melamine resin and cured or baked for half an hour at 300° F., the fabric will not dye at all in 5 minutes at 212° with a 3% dye bath of Fast Blue FFB. Incidentally, when this resin-treated fabric was dyed with the same color for an hour at the boil, substantially the same deep blue shade was obtained, as shown by the untreated fabric. Consequently, it seems evident that the rate of dyeing is changed, but not the actual ability to take up this color. As a result of this discovery it has been possible to determine the shortest time necessary to fix the melamine-formaldehyde resin so that the dye will not take in 5 minutes at the boil.

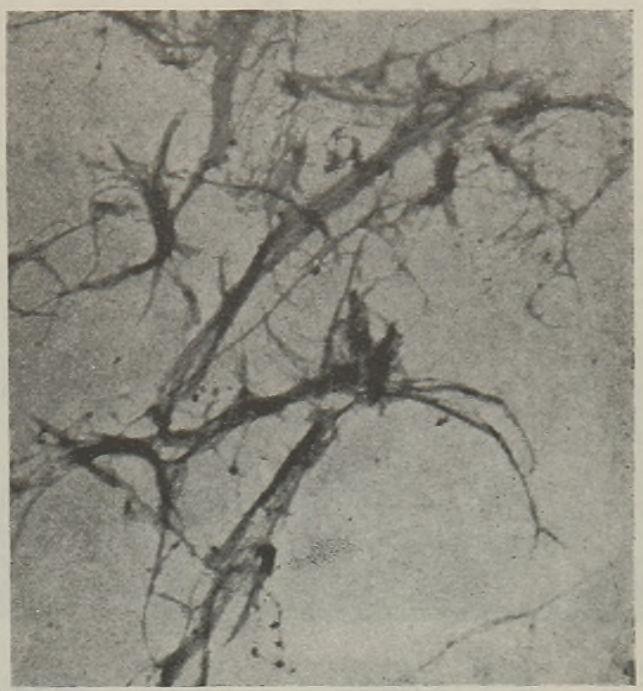
The following table summarizes the time and temperature required to get the reduced dyeing rate. These data indicate at least the curing rate of this type of resin when cured in the presence of 3% diammonium phosphate as catalyst:

Time, Min.	Temp., ° F. (° C.)
Over 30	225 (107.2)
10	250 (121.1)
4–5	275 (135)
2–3	300 (148.9)
1½–2	325 (168.8)

Unfortunately, urea-formaldehyde resins do not give the same effect as do melamine resins, and the phenol resins discolor and obscure the test. On wool no suitable colors have yet been found

Figure 6. Pure Cellulose Filter Paper (× 10,000)

Figure 7. Cotton Sheeting, Bleached and Desized (× 10,000)



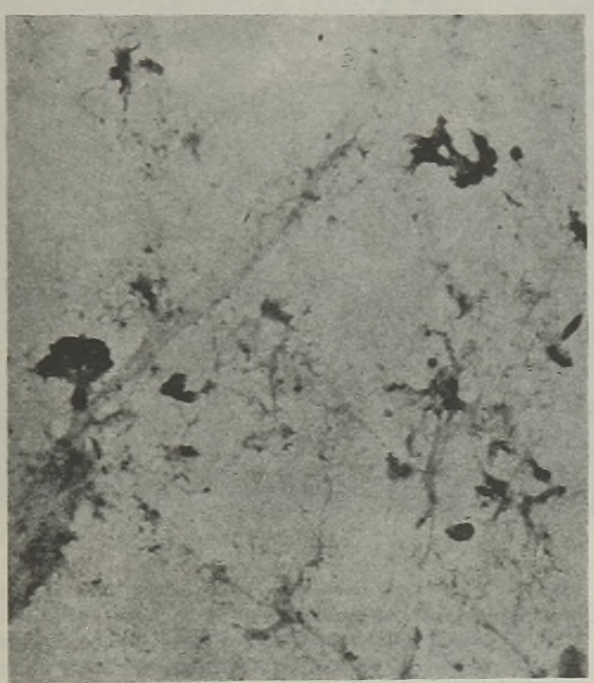


Figure 8. Cotton Sheeting Impregnated with 7% Resloom M-75 (×10,000)

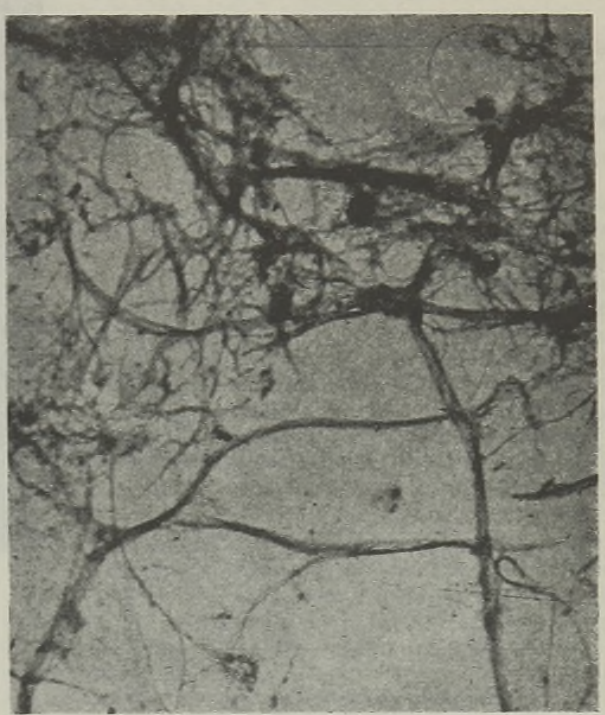
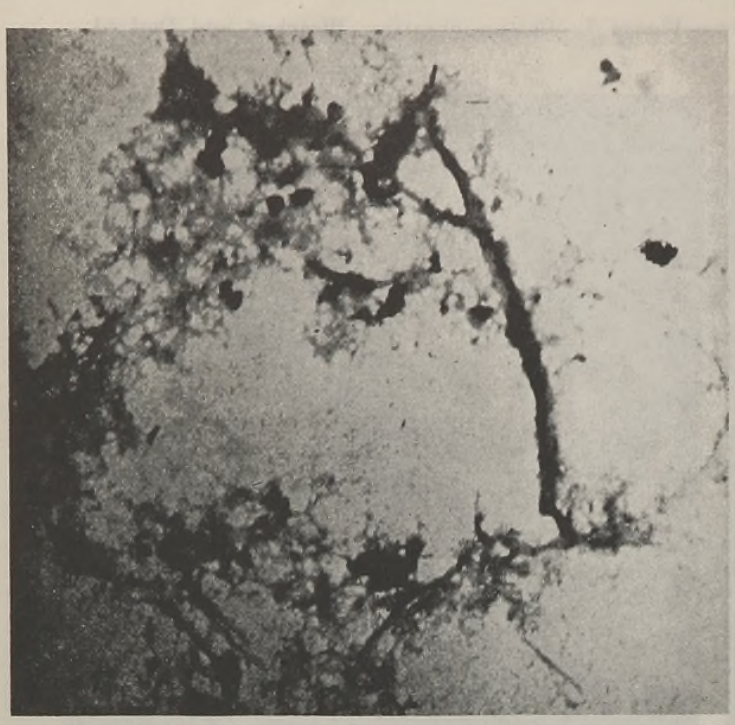


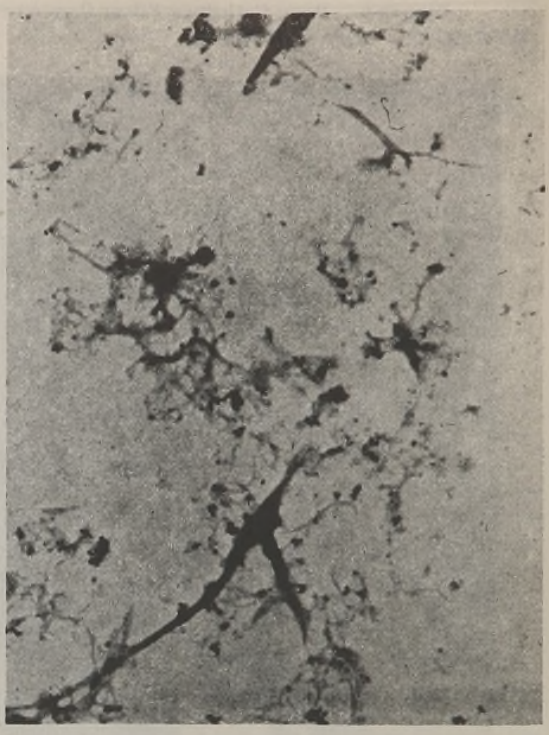
Figure 9. Cotton Sheeting Impregnated with 5% Polystyrene Dispersion (× 10,000)

to show a difference, since the melamine resins tend to make the wool pick up dye more rapidly, and no change is noted.

ELECTRON MICROSCOPE STUDIES

A number of electron photomicrographs of wool, cotton, and rayon, before and after resin treatment, are reproduced as being truly representative of the several hundred taken. The electron microscope seems to show the differences (Figure 3 and 4) between the effect of coating or surface resins and those resins or resin formers which penetrate the fiber. The use of any solvent or swelling agent was carefully avoided in the preparation of these samples, although this has been the practice of previous investigators. Hock and McMurdie (*2*) gave some interesting pictures of swollen fibers, and Husemann (*3*) published an article on the





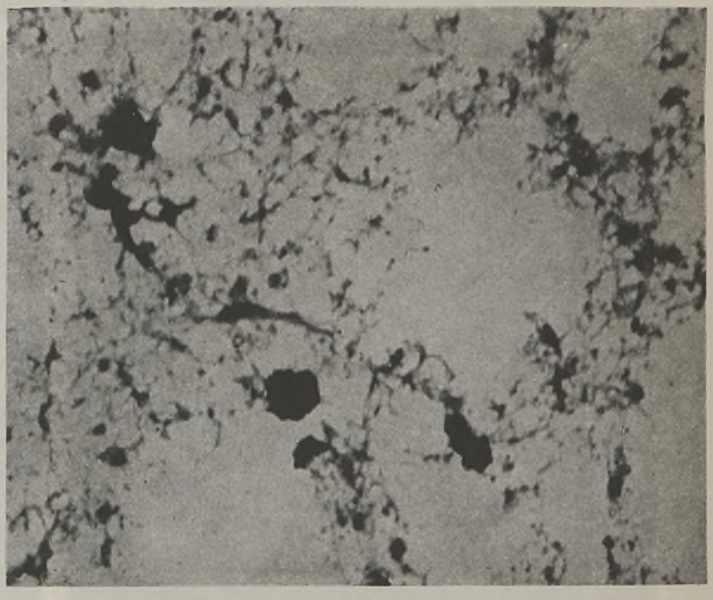


Figure 10 (*Above*). Viscose Rayon for Tire Cord (× 10,000)

Figure 11 (*Upper right*). Spun Rayon Coated with 5% Polystyrene Dispersion (× 10,000)

Figure 12 (*Right*). Filament Rayon Untreated (× 10,000)

subject. However, in this work any chemical action was avoided.

The specimens were beaten in pure water in a high-speed stirrer. About 2 grams of fabric or fiber were placed in a liter of pure water, and the suspension was subjected to severe beating in a high-speed stirrer with a knife-edge rotor turning at 9000 r.p.m. in a carefully cleaned container, with a series of baffles set to give the severest agitation possible. The sample was beaten for 1–2 hours; a drop of the beaten suspension was evaporated on the usual suspension support and examined with the electron microscope. Clearly, then, the electron photomicrographs should show any differences in the way the fibers respond to this mechanical disintegration in the absence of a swelling agent other than water.

The pictures selected are typical and indicate that Resloom and Syton seem to penetrate, and that polystyrene seems to be on the surface. As would be expected, the surface resins show a lot of "debris" or extraneous matter in the background, but the fracture of the fibers themselves is similar to that noted for the untreated or uncoated fibers. The resin formers, upon going into the fiber and being cured, produce in effect a new fiber which disintegrates in a different way. In the case of wool impregnated with the water-soluble methylol-melamine monomer, which is later cured and insolubilized, the electron micrographs indicate that the resin-modified fiber is much tougher and breaks into much larger, coarser chunks under the mechanical disintegration.

Effect of Bacteria. When a sample of wool is disintegrated in water in this high-speed mixer and allowed to stand overnight, nothing but bacteria appears in the electron micrographs. In spite of wool's well-known resistance to bacterial action, these mechanically beaten samples are completely destroyed by the bacteria. It is clear that wool, which is mechanically chopped up, is much more easily destroyed by bacteria. It also follows that the resin-forming resins which toughen the fiber and cause it to resist mechanical destruction may correspondingly increase its bacterial and moth resistance.

Wool. Figures 1 to 5 are electron photomicrographs of wool, untreated and treated with two resins that should penetrate and with one resin that coats the surface. We should again recognize that we are interpreting shadowgraphs or silhouettes of mechanically disintegrated fibers, and the method of preparation and the interpretation of the results is subject to question and discussion.

The photomicrograph of the untreated wool (Figure 1) is typical of the preparation procedure. The fragments are irregular with many fine bits and an occasional "hunk". However, the photomicrographs of the wool treated with Resloom M-75 (Figure 2)—a water-soluble melamine resin former—and with Syton W-20 (Figure 3)—a water dispersion of a submicroscopic polymer—

show that the wool breaks into coarser chunks free from the fines characteristic of the untreated material. The photomicrograph of wool treated with a surface resin such as polystyrene emulsion (Figure 4) shows the same small fragments of wool along with a great deal of debris and what may be surface resin which has come loose. A dyed woolen blanket was treated with Resloom M-75, the melamine resin was cured and insolubilized by heating, but the treated blanket was not washed. Here is found a large amount of extraneous matter (Figure 5) which may be loose dyestuff or resin. The large fragments of wool indicate the toughening action of the melamine resin which has penetrated the fiber.

TABLE V. EFFECT OF RESIN ON MOISTURE PICKUP

Resin Used	Cotton Sheeting % resin	Cotton Sheeting % moisture regain at 66% rel. humidity[a]	Spun Rayon % resin	Spun Rayon % moisture regain at 66% rel. humidity[a]	Wool Flannel % resin	Wool Flannel % moisture regain at 66% rel. humidity[a]
----	..	5.88	..	11.66	..	10.32
Methylol-melamine	1.0	5.87	1.2	11.00	9.6	10.52
	2.4	5.41	3.0	10.95	..	---
	5.0	4.69	6.1	10.42	..	---
	10.0	4.48	12.0	10.12	..	---
Methylol-urea	2.3	5.49	7.2	10.34	6.4	10.62
	5.6	5.14	..	---	..	---

[a] Moisture regain is figured on the weight of the dry fiber.

COTTON. Cellulose has a characteristic subfibril structure (Figure 6) when mechanically disintegrated in water and examined under the electron microscope. Treatment of cotton fabrics with melamine type resins gives the fabrics (Figures 7 and 8) greater resilience and less tendency to shrink on washing. Examination of melamine-treated fabrics which have been mechanically disintegrated shows certain differences under the electron microscope which are quite different from the effects noted on wool.

After melamine resin treatment the cotton fibers appear to break up into subfibrils of the same thickness and length as the untreated, but these subfibrils seem to be caught or stuck together at various points. This indicates that the resin acts as an adhesive between the subfibrils and does not penetrate them as well as in the case of wool. The samples of cotton sheeting treated with a styrene dispersion (Figure 9) show again the surface effect of this resin with no effect on the way in which the subfibrils are formed.

RAYON. The melamine and styrene resins have the same effect on rayon as they do on cotton. However, in the case of rayon the subfibrils are much shorter than those observed for cotton. This seems to confirm the reported observation that the degree of polymerization of cotton is appreciably reduced when it is converted into rayon. A sample of tire cord rayon (Figure 10) with the fine debris in the background is characteristic of all the tire cords examined. The method of spinning this yarn probably makes it extremely brittle so that it breaks up under the mechanical disintegration. There is little difference in samples of spun rayon and filament rayon, both before and after treatment with styrene type resins (Figures 11 and 12).

Care should be taken not to draw rigid conclusions from these electron photomicrographs. The method of sampling and the silhouettes obtained clearly indicate that these pictures offer interesting vistas for speculation but not for proof.

ACKNOWLEDGMENT

The author wishes to express appreciation for the great assistance of Dexter Reynolds and Elmer Rossin of the Monsanto Chemical Company in the preparation of this paper.

LITERATURE CITED

(1) Am. Assoc. of Textile Chem. and Colorists, 1943 Year Book, Vol. XX, pp. 223–6.
(2) Hock and McMurdie, *J. Research Natl. Bur. Standards*, **31** (Oct. 1943).
(3) Husemann, E., *J. makromolekulare Chem.*, **1**, 16–27 (Aug., 1943).

PRESENTED before the Division of Cellulose Chemistry at the 108th Meeting of the AMERICAN CHEMICAL SOCIETY in New York, N. Y.

Thermal Conductivity of Alcohols and Glycols

O. KENNETH BATES AND GEORGE HAZZARD

The St. Lawrence University, Canton, N. Y.

THE apparatus and experimental procedure used in these determinations were fully described in previous papers (*1*, *2*, *3*). Since problems relating to experimental procedure and precision of results were discussed in these articles, this paper will present only experimental results of the thermal conductivity and the temperature coefficient of thermal conductivity of industrial *n*-butyl and *n*-amyl alcohols, and water mixtures of industrial ethylene glycol, propylene glycol, and *n*-propyl alcohol[1]. Most of this information has been unavailable in scientific literature.

Tables I and II present the experimental data. Since *n*-amyl alcohol is completely immiscible in water and *n*-butyl alcohol is miscible only up to 8 per cent alcohol, only values for the pure liquids are given. The data in the tables cover the temperature range over which tests were made. Within this range the precision of the data is one per cent.

Figures 1 and 2 present graphically the variation of thermal conductivity with composition. Figure 1 shows the greater conductivity at 50° C. of water mixtures of ethylene glycol than of water mixtures of propylene glycol as well as the interesting point of inflection at 6 per cent propylene glycol. Figure 2 gives the variation of conductivity with composition of *n*-propyl alcohol–water mixtures at 50° C. and shows a similar point of inflection at 6 per cent *n*-propyl alcohol. These points of inflection were checked a great number of times, particularly in the range from pure water to 10 per cent *n*-propyl alcohol or propylene glycol. Such points should provide an interesting basis for theoretical work and probably exist in many other liquid mixtures.

The physical properties of the liquids tested, all of technical grade, were supplied by the manufacturer in each case and are listed in Table III. The thermal conductivity of the first five alcohols in the normal series is presented in Table IV and compared with published values of other investigators. There seems to be decreasing conductivity with increasing molecular weight.

[1] This paper was originally accepted in January, 1943, but was withheld from publication at that time at the request of the Government censor. Restrictions have now been removed for the presentation of these data.

TABLE I. THERMAL CONDUCTIVITY OF AQUEOUS GLYCOL MIXTURES

Glycol, % by Wt.	K_t, Gram-Cal., Sec.$^{-1}$, Cm.$^{-2}$, ° C.$^{-1}$, Cm.[a] 20° C.	30° C.	40° C.	50° C.	60° C.	70° C.	80° C.	90° C.	100° C.	110° C.	α_{50}[b], %, ° C.$^{-1}$
Ethylene Glycol–Water Mixtures											
100	0.000690	0.000670	0.000655	0.000635	0.000615	0.000600	0.000580	0.000565	0.000545	0.000525	−0.28
90	0.000745	0.000725	0.000710	0.000695	0.000680	0.000665	0.000645	0.000630	0.000615	0.000600	−0.23
80	0.000800	0.000785	0.000775	0.000760	0.000745	0.000735	0.000720	0.000710	0.000695	0.000685	−0.168
70	0.000860	0.000850	0.000840	0.000830	0.000820	0.000810	0.000800	0.000790	0.000780	0.000770	−0.120
60	0.000925	0.000920	0.000915	0.000910	0.000905	0.000900	0.000895	0.000890	0.000885	...	−0.058
50	0.001000	0.001000	0.001000	0.001000	0.001000	0.001000	0.001000	0.001000	0.001000	...	0.000
40	0.001075	0.001085	0.001090	0.001095	0.001100	0.001105	0.001115	0.001120	...	...	+0.052
30	0.001160	0.001175	0.001185	0.001195	0.001205	0.001220	0.001230	...	...	...	+0.098
20	0.001250	0.001270	0.001285	0.001305	0.001325	0.001340	0.001360	...	...	...	+0.135
10	0.001345	0.001370	0.001390	0.001415	0.001440	0.001460	0.001485	...	...	...	+0.168
0[c]	0.001450	0.001480	0.001510	0.001540	0.001570	0.001600	0.001630	...	...	...	+0.20
Propylene Glycol–Water Mixtures											
100	0.000520	0.000505	0.000495	0.000485	0.000475	0.000465	0.000450	0.000440	0.000430	0.000420[d]	−0.23
90	0.000585	0.000570	0.000560	0.000550	0.000540	0.000530	0.000515	0.000505	0.000495	0.000485	−0.20
80	0.000655	0.000645	0.000635	0.000625	0.000615	0.000605	0.000595	0.000585	0.000575	0.000565	−0.165
70	0.000735	0.000725	0.000715	0.000705	0.000695	0.000685	0.000675	0.000665	0.000655	...	−0.140
60	0.000815	0.000810	0.000800	0.000795	0.000790	0.000780	0.000775	0.000770	0.000765	...	−0.080
50	0.000905	0.000905	0.000900	0.000900	0.000900	0.000895	0.000895	0.000895	...	...	−0.020
40	0.001000	0.001005	0.001005	0.001010	0.001015	0.001015	0.001020	0.001020	...	...	+0.030
30	0.001095	0.001105	0.001120	0.001130	0.001140	0.001155	0.001065	...	...	...	+0.100
20	0.001210	0.001230	0.001250	0.001270	0.001290	0.001310	0.001330	...	...	...	+0.160
10	0.001320	0.001350	0.001380	0.001410	0.001440	0.001470	0.001500	...	...	...	+0.21

[a] Multiply by 2900 to convert to B.t.u., hr.$^{-1}$, ft.$^{-2}$, ° F.$^{-1}$, in.
[b] α_{50} is defined by $K_t = K_{50}[1 + \alpha_{50}(t - 50)]$ when t is measured in ° C.
[c] Pure water. [d] Pure propylene glycol at 120° C., 0.000405.

Results are presented on determinations of the thermal conductivity and the temperature coefficient of thermal conductivity for industrial *n*-butyl alcohol and *n*-amyl alcohol and for water mixtures of industrial ethylene glycol, propylene glycol, and *n*-propyl alcohol.

TABLE II. THERMAL CONDUCTIVITY OF ALCOHOLS

Alcohol, % by Wt.	K_t, Gram-Cal., Sec.$^{-1}$, Cm.$^{-2}$, ° C.$^{-1}$, Cm.[a] 20° C.	30° C.	40° C.	50° C.	60° C.	70[b] C.	80° C.	90° C.	α_{50}[b], %, ° C.$^{-1}$
***n*-Propyl Alcohol–Water Mixtures**									
100	0.000395	0.000380	0.000360	0.000345	0.000330	0.000310	0.000295	0.000280	−0.48
90	0.000420	0.000410	0.000395	0.000385	0.000375	0.000360	0.000350	...	−0.32
80	0.000470	0.000460	0.000450	0.000440	0.000430	0.000420	0.000410	...	−0.22
70	0.000535	0.000525	0.000520	0.000510	0.000500	0.000495	0.000485	...	−0.160
60	0.000610	0.000600	0.000595	0.000590	0.000585	0.000580	0.000570	...	−0.100
50	0.000710	0.000705	0.000700	0.000695	0.000690	0.000685	0.000680	...	−0.070
40	0.000830	0.000830	0.000825	0.000825	0.000825	0.000820	0.000820	...	−0.025
30	0.000965	0.000970	0.000970	0.000975	0.000980	0.000980	0.000985	...	+0.035
20	0.001105	0.001120	0.001130	0.001145	0.001160	0.001170	0.001185	...	+0.115
10	0.001285	0.001310	0.001330	0.001355	0.001380	0.001400	0.001425	...	+0.175
***n*-Butyl Alcohol**									
100	0.000375	0.000365	0.000360	0.000350	0.000340	0.000335	0.000325	0.000320	−0.23
***n*-Amyl Alcohol**									
100	0.000375	0.000365	0.000355	0.000345	0.000335	0.000325	0.000315	0.000305	−0.28

[a] Multiply by 2900 to convert to B.t.u., hr.$^{-1}$, ft.$^{-2}$, ° F.$^{-1}$, in.
[b] α_{50} is defined by $K_t = K_{50}[1 + \alpha_{50}(t - 50)]$ when t is measured in ° C.

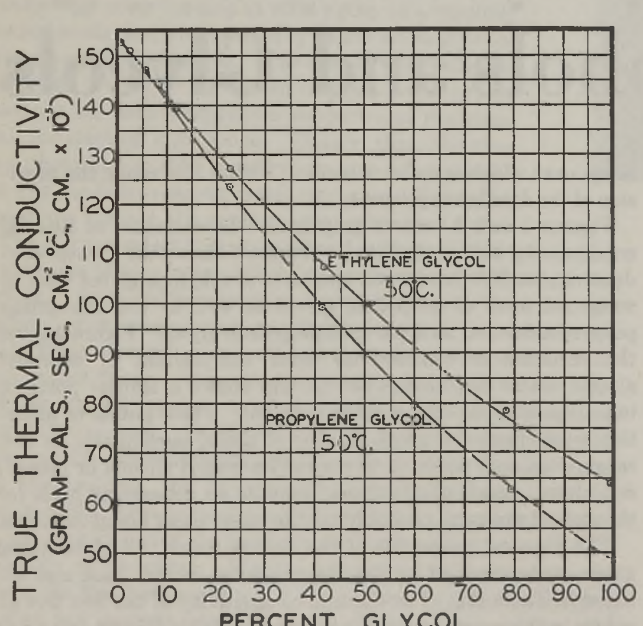


Figure 1. Variation in Thermal Conductivity with Composition of Glycol-Water Mixtures

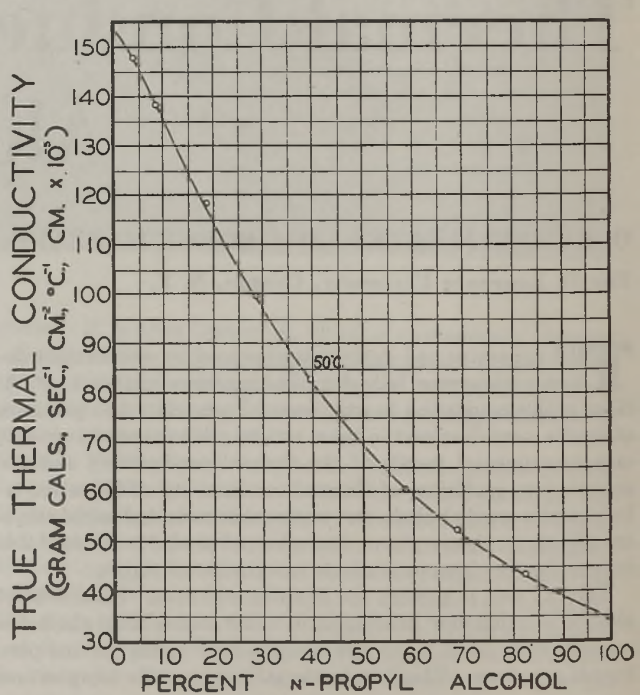


Figure 2. Variation in Thermal Conductivity with Composition of *n*-Propyl Alcohol–Water Mixtures at 50° C.

TABLE III. PHYSICAL PROPERTIES

	Ethylene Glycol	Propylene Glycol	*n*-Propyl Alcohol	*n*-Butyl Alcohol	*n*-Amyl Alcohol
Formula	CH_2OH | CH_2OH	CH_3CHOH | CH_2OH	n-C_3H_7OH	n-C_4H_9OH	n-$C_5H_{11}OH$
Mol. wt.	62.05	76.06	60.06	74.12	88.09
B.P. (1 atm.), ° C.	197.2	187.4	97.2	117.7	137.9
Sp. gr.	$1.1176d_{15}^{15}$	$1.0381d_{20}^{20}$	$0.804d_{4}^{20}$	$0.8109d_{20}^{20}$	$0.817d_{20}^{20}$

TABLE IV. THERMAL CONDUCTIVITY OF NORMAL ALCOHOL SERIES AT 30° C.

Alcohol	Bates *et al.*	Others
Methyl	0.00050 (*3*)	0.000503 (*4*)
Ethyl	0.00041 (*3*)	0.000433 (*6*)
n-Propyl	0.000380	0.000409 (*5*)
n-Butyl	0.000365	0.000400 (*4*)
n-Amyl	0.000365	0.000388 (*5*)

Table I indicates that the thermal conductivity of water is about one per cent higher at 50° C. than was previously reported (*3*). We have made several hundred determinations during the past few years on water under many different experimental conditions, and the values reported are the best we have determined up to the present time.

ACKNOWLEDGMENT

Acknowledgment is made to the Carbide and Carbon Chemicals Corporation for supplying the necessary ethylene and propylene glycol and the *n*-butyl alcohol; to E. I. du Pont de Nemours & Company, Inc., for the *n*-propyl alcohol; and to the Sharples Solvents Corporation for the *n*-amyl alcohol. We also wish to express appreciation to Gerald Palmer for his assistance with some of the liquids.

LITERATURE CITED

(1) Bates, IND. ENG. CHEM., 25, 431 (1933).
(2) *Ibid.*, 28, 494 (1936).
(3) Bates, Hazzard, and Palmer, IND. ENG. CHEM., ANAL. ED., 10, 314 (1938).
(4) Bridgman, *Proc. Am. Acad. Arts Sci.*, 59, 141 (1923).
(5) Daniloff, M., *J. Am. Chem. Soc.*, 54, 1328 (1932).
(6) Smith, J. F. D., IND. ENG. CHEM., 22, 1246 (1930).

Nature of Asphaltic Substances

DONALD L. KATZ AND KARL E. BEU[1]

University of Michigan, Ann Arbor, Mich.

Thin films of asphalt and oil have been examined in the electron microscope in a search for colloidal asphaltene particles. These films seem to be free from particles, but numerous particles appear when suspensions of asphalt in benzene and petroleum ether are examined. Micrographs at 156,000 diameters indicate asphaltene particles, if present in undiluted oils and asphalt, are less than 65 Å. in diameter.

ASPHALTIC bitumens are a product of crude oil and sometimes occur in a concentrated form as a residuum of petroleum deposits. These asphaltic bitumens may be retained in the fuel oil after refining processes, or may be concentrated for use in asphalt paving. Until they were found to precipitate from the crude oil at the time of production, mention of the term "asphaltic bitumen" would bring to mind the concentrated form used for road construction.

The peculiar nature of the precipitation of bitumen from a California well producing from 11,000 feet raised questions concerning the nature of the precipitation process and of the physical state of the asphaltic bitumen prior to precipitation. The electron microscope has been found a useful tool in making studies of the physical state of asphaltic substances (*11*). Crude oils have been examined for the presence of the asphaltic bitumen by the electron microscope. Also, a series of samples at successive stages in the manufacture from the crude oil, topped crude, reduced crude, through various grades of asphalt have been examined by the electron microscope. The formation of bitumens by the flow of oil through sand has been related to the electrical flow potential caused by the flow of the oil through the porous solid. These experiments have given a concept of the state of the asphaltic substances in crude oil and refined products, which is somewhat at variance from the views previously held.

The theoretical aspects of asphaltic bitumen have been treated by numerous authors (*1*, *7*, *8*, *9*, *10*, *13*, *14*). In general, they agree that asphalts are composed of three types of materials: the colloidal asphaltic bitumen micelles, asphaltic resins, and an oil. Nellensteyn (*8*) asserts that the asphaltic bitumen micelle, or asphaltene, contains soot and graphitic carbon. The resinous materials are believed to be protective colloids for the micelles. The addition of liquids, which have a surface tension below about 24 dynes per centimeter at 25° C., causes flocculation of the micelle, while the addition of liquids having a surface tension above 26 dynes per cm. causes peptization, according to Nellensteyn (*8*).

Swanson (*13*) separated asphalt into the three substances and presented data indicating that the resins could be used to peptize the asphaltene when in sufficient concentration; he gave photographs to show the disappearance of particles of asphaltene. Traxler and Coombs (*14*) demonstrated the thixotropic properties of asphalt, which further substantiate the colloidal nature of the materials. Benson (*2*) showed coagulation in thin films of asphalt.

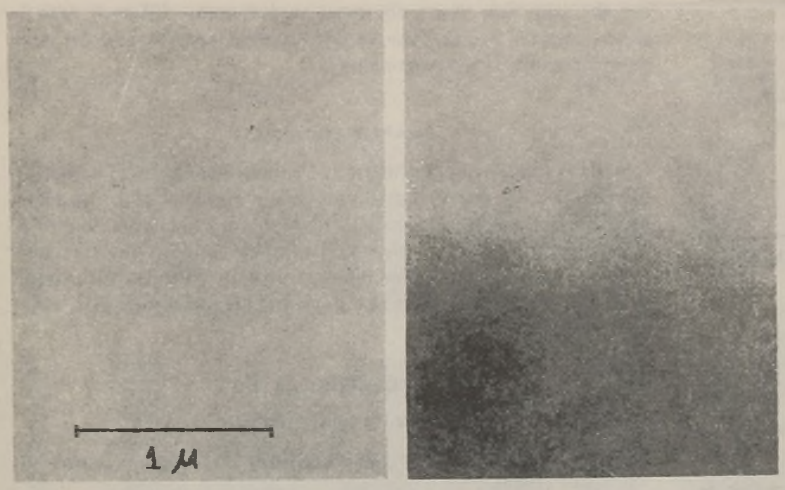
Williford (*16*) presented x-ray diffraction patterns for several asphalts and correlated these patterns with some physical properties.

PRECIPITATION DURING CRUDE OIL PRODUCTION

The occurrence of asphaltic bitumen granules in an oil and gas separator in California on a well producing from the Vedder zone of the Greeley Field raised a new problem in the behavior of asphaltic bitumen (*11*). It had been known (*5*, *6*, *15*) that the addition of volatile hydrocarbons would cause the separation of the asphaltic constituent from crude oil, but no reports indicated that the removal of dissolved hydrocarbons from a crude oil would precipitate the asphaltic bitumens.

Further investigation of the problem revealed that asphaltic bitumen was deposited in the tubing of the well, and that the pressure at the bottom of the well was in excess of the bubble-

[1] Present address, Phillips Petroleum Company, Bartlesville, Okla.



a. California crude *b.* Central East Texas crude

Figure 1. Thin Films of Crude Oil (× 25,500)

point pressure for the crude oil containing the dissolved gas; hence the asphaltic bitumen may have been precipitating prior to any phase changes taking place in the flowing oil. It appeared that the problem would be solved only after considerable light was thrown upon the nature of the asphaltic bitumen prior to its separation from the crude oil in the well.

From the description of asphaltic bitumens as composed of micelles or colloidal suspensions of asphaltenes in the oil, it appeared that the electron microscope would be a valuable tool for studying phase changes occurring as the asphaltic bitumens are precipitated from oils. Thin films of crude oil have been examined in the electron microscope to show that no particles, or at least a very low concentration of particles of asphaltic bitumens, may be observed. These films were formed by dipping a sharp tipped glass rod in the oil and coating a polyvinyl methylal film, supported by a 1/8-inch disk of 200-mesh stainless steel screen, with this oil. The volatile portion of the oil evapo-

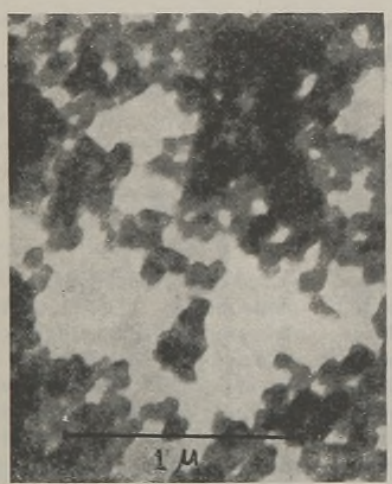


Figure 2. California Crude Oil Diluted with Benzene, Slide Washed in Petroleum Ether (× 31,400)

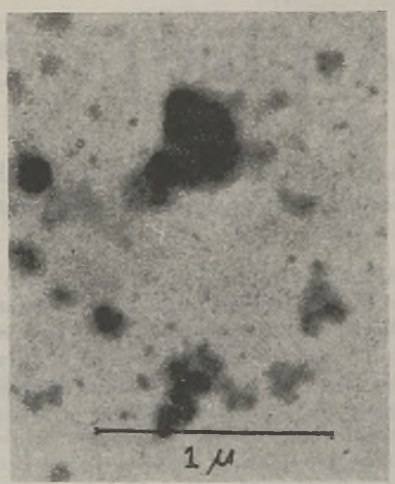


Figure 3. Bitumen Suspended in Benzene (× 31,400)

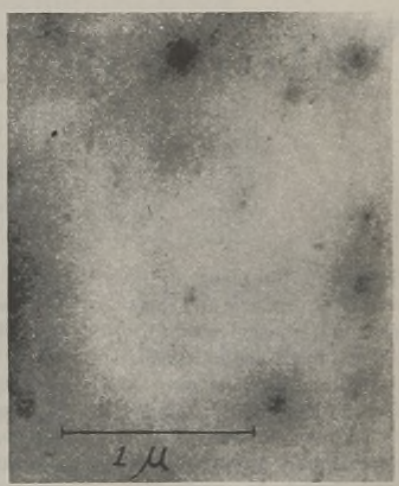
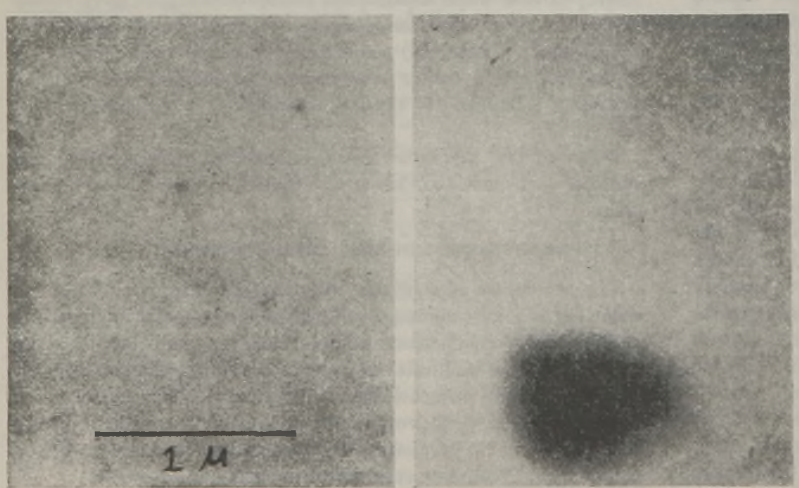


Figure 4. Thin Film of California Crude Oil after Passing through Silica (× 25,500)



a. No. 8 VSS *b.* No. 11 AB

Figure 5. Thin Films of Asphalt (× 25,500)

rates as the specimen is placed in the electron microscope under a pressure of 10^{-6} cm. of mercury. The film appears to be continuous as shown by Figure 1.

In early experiments with the electron microscope it appeared desirable to dilute the crude oils with benzene or petroleum ether, prior to the preparation of the slides. The crude oils were diluted with about 95–99% benzene and petroleum ether, and a small droplet was placed directly upon a collodion film. Particles always appeared when this process was used. Slides prepared in this manner were also dipped in petroleum ether, with the results shown in Figure 2. A suspension of the bitumen precipitated in the oil and gas separator in California was made in benzene and filtered, and a small portion of the suspension was placed upon a collodion film and observed in the microscope (Figure 3). It appears that the particles occurring in Figure 2 are similar to the asphaltic bitumen or are precipitated asphaltenes. This work verified the

TABLE I. APPEARANCE OF ASPHALT FROM VARIOUS STAGES IN MANUFACTURING OPERATIONS UNDER ELECTRON MICROSCOPE

No.	Sample	R. & B. Softening Point, ° F.	Thin Film of Material	1–5% Solution in:			Thin Film Washed in:		
				Benzene	Petroleum ether	CS_2	Benzene	Petroleum ether	CS_2
1	Crude oil[a]	...	Clear, occasional particle	Considerable medium and fine particles	Considerable No. particles, well defined	Hazy	.....	Diffuse particles	Few particles
2	Topped crude	...	Clear, few diffuse particles	Same as 1	Same as 1	.....	.....	.....	Hazy, few large particles
3	1st reduced crude	...	Clear, occasional particles	Same as 1	Same as 1	Slight haze	.....	Diffuse particles	Diffuse area
4, 5	2nd reduced crude or residuum	100	Clear	Considerable No. particles	.....	.....	.....	.....	.....
6	VSS asphalt	128	Clear	Some large particles	.....	.....	.....	.....	.....
7	VSS asphalt	140	Clear	Same as 6	.....	.....	.....	.....	.....
8	VSS asphalt	160	Clear	Same as 6	Large, sharply defined particles	Few small particles	Diffuse particles	Rings, diffuse area, particles	Webs formed
9	AB asphalt	116	Clear	Same as 6	.....	.....	.....	.....	.....
10	AB asphalt	132	Clear	Same as 6	.....	.....	.....	.....	.....
11	AB asphalt	168	Clear	Some particles	Large amount of large diffuse particles	.....	.....	.....	.....
12	AB asphalt	214	Clear	Same as 11	Same as 11	Several sharp particles	Small particles	Diffuse areas, particles	Webs and particles formed
	Gilsonite	...	Clear, occasional particle	Hazy, few particles	Some particles	.....	Sharply defined particles	.....	.....

[a] Pyridine solution shown by Figure 6*e*.

action of solvents in precipitating the asphaltic particles but showed that micelles could not be observed in the crude oils by the electron microscope.

PRECIPITATION BY ELECTRICAL EFFECTS

Two experiments involving electrical effects were conducted (*11*) to show that these effects may become responsible for the presence of asphaltic particles. Two hundred and twenty volts were placed across platinum electrodes spaced 0.5 to 1 mm. apart and suspended in the crude oil produced from the well in California which deposited bitumen in the separator. The crude oil had been filtered through No. 214 filter paper just prior to the test. After several days the electrodes were removed, the positive electrode was found to be covered with a black material, and the negative electrode was clean.

The black sludge which was filtered from the oil resembled in all respects the asphaltic bitumen found in the separator at the oil and gas well. Benzene suspensions of the material were examined with the electron microscope, which showed that the appearance of these particles and those given in Figures 2 and 3 are similar.

The flow of fluids containing polar substances through fine capillaries or porous media has been widely studied under the title of "streaming potential" (*12*). The possibility that the flow of the oil through the producing sand could be precipitating the asphaltic bitumen appeared feasible. Experiments were conducted in which the oil was examined with the electron microscope prior to flow through silica (with an appearance similar to Figure 1) and was later examined after flow through a silica plug. Figure 4 shows the bitumen particles which had appeared in the oil as the result of the flow through the silica. A streaming potential of approximately 39 millivolts was measured during this flow process (*3*).

Particles of bitumen formed by this process are believed to settle gradually from oils after several days or weeks, since particles formed by solvents settle in a matter of days. Sludges or deposits in oils in storage could be attributed to this phenomenon (*3*).

EXAMINATION OF OILS DURING ASPHALT MANUFACTURE

If asphalts are composed of micelles or colloidal particles as presented in the literature, and crude oils which contain asphaltic constituents were not found to contain particles, it should follow that the colloidal particles appear at some stage in the manufacturing process. To study the possible changes in the nature of the asphaltenes which might occur during the conversion of an asphalt-base crude oil to an asphalt for road pavements, a series of products was prepared by The Texas Company. A 23° A.P.I. central East Texas crude oil was topped and 18.2% was removed as gasoline. Removal of another 6.2% as kerosene left the first reduced crude, and further removal of 32.2% of gas oil left the second reduced crude. This 43.3% of the original crude oil had a softening point of 100° F. by the ring and ball test. Three grades of asphalt having successively higher ring and ball temperatures were prepared from the second reduced crude oil in a vacuum-shell still using steam (VSS) and four grades of asphalt were prepared by air blowing (AB) the second reduced crude for successively longer periods.

Table I lists the samples representing the stages in the manufacture of asphalt along with a summary of the findings with the electron microscope. The observations are that colloidal particles or micelles do not appear in any of the asphalt products examined by the electron microscope but can be made to appear by the use of solvents.

Crude oil, reduced crude oil, dilute solutions of the oils in benzene, carbon disulfide, petroleum ether, and pyridine, and specimens washed or dipped in solvents were observed. A new technique was necessary to prepare thin films of the asphalts which were plastic solids at room temperature. A copper wire ring about one inch in diameter was dipped into the asphalt which had been heated to 400–550° F. in a beaker and held in the air to permit the thin film inside the ring to cool. This film was placed on the 200-mesh screen either directly or with a supporting polyvinyl methylal film used for oils. Whenever the film was to be dipped in a solvent, the polyvinyl methylal film was used to prevent the complete disappearance of the asphalt film in the dipping process.

Figure 5 gives representative views of the thin films of asphalt. Occasional particles appear but not enough to indicate the presence of the asphaltenes in this form. The crude oil had occasional particles as indicated by Figure 1*b*. The presence of constituents in the asphalts capable of precipitation is indicated both by the photographs of films prepared from solutions in solvents and from dipping of the films in solvents. Figure 6 shows representative photographs of specimens prepared by placing a small quantity of a 1% solution of the asphalt in the solvent directly on the polyvinyl methylal film with evaporation of the solvent. Figure 7 gives the effect of dipping or washing the specimen in a

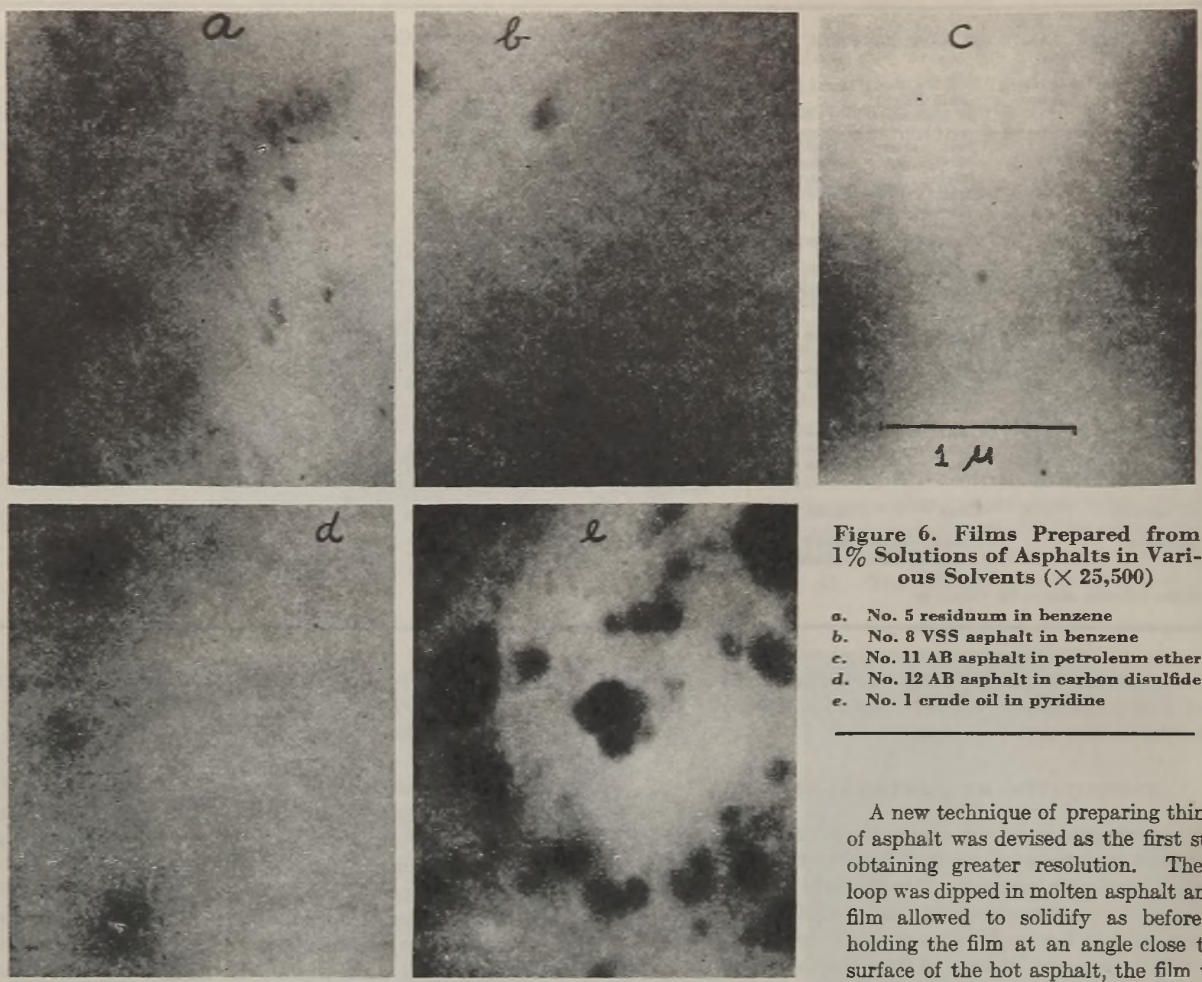


Figure 6. Films Prepared from 1% Solutions of Asphalts in Various Solvents (× 25,500)

a. No. 5 residuum in benzene
b. No. 8 VSS asphalt in benzene
c. No. 11 AB asphalt in petroleum ether
d. No. 12 AB asphalt in carbon disulfide
e. No. 1 crude oil in pyridine

solvent; Figure 7*b* is the same slide as Figure 5*a* after being dipped in petroleum ether and allowed to evaporate. Similar photographs were taken with the crude and topped crude oils. These observations indicate that the asphaltene is in a similar state in asphalt and in crude oil.

To determine whether x-rays could cause the precipitation of particles, both asphalt samples and a thin film were exposed to x-rays for times up to 4 hours using 160,000 volts. No changes in appearance of the films were observed.

EXAMINATION OF GILSONITE FILMS

Since the asphaltenes were not found as particles in petroleum asphalt films, Gilsonite (natural asphalt) films were treated in a manner similar to that used for the petroleum products. Figure 8 gives electron micrographs of the film prepared by melting the Gilsonite and dipping of the copper loop into the hot liquid, the same film washed in benzene, and films prepared from solutions. The natural asphalt behaved similarly to the petroleum products with regard to particle formation.

DETERMINATION OF PARTICLE SIZE

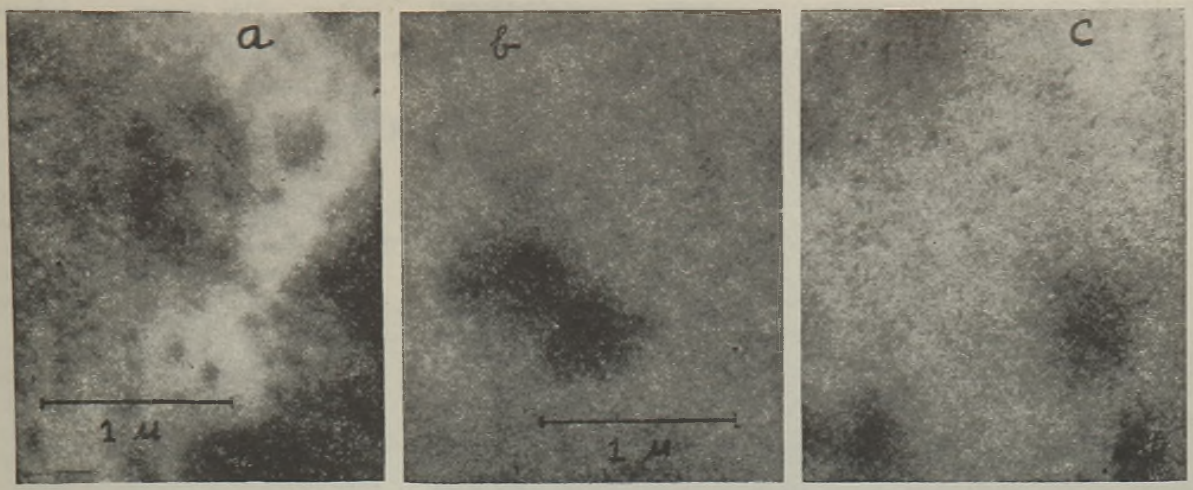
The smallest particles which appeared in the figures are 0.01 to 0.02 inch at a magnification of 25,000 diameters. This corresponds to a particle size of 100 to 200 Å. or a particle weight of 300,000 to 2,400,000, assuming spheres of unit density. An attempt to distinguish particles of this size or smaller requires consideration of the film thickness, the dispersing power of the particles relative to that of the medium, and the resolving power of the microscope.

A new technique of preparing thin films of asphalt was devised as the first step in obtaining greater resolution. The wire loop was dipped in molten asphalt and the film allowed to solidify as before. By holding the film at an angle close to the surface of the hot asphalt, the film would become fluid and thin in a small portion of the total loop. Color rings appeared around the thin portion of the film. This very thin but continuous film was placed on a Formvar film and thence on the 200-mesh specimen screen for observation. Fifteen series of photographs of asphalt films prepared in this manner at each of five magnifications from 5,100 to 15,600 diameters were made using fine slight variations from what was believed to be the best focus. The Formvar films were examined prior to placing the asphalt film on them to ensure freedom from foreign matter. Photographic enlargements of the plates gave a series of magnifications up to 156,000 diameters (Figure 9). In no cases were fine particles observed.

To ensure that the film under observation had approximately the same thickness as the particles which may be present, films of a benzene solution of asphalt were re-examined. The initial solution caused some particle formation but, upon standing for 4 days, few relatively large particles were present although the solution was black in color. It is believed that this solution contained some asphaltene which should appear as particles if they are within the range of the resolving power of the microscope. Figure 10 shows a particle, but there is no evidence of numerous small particles.

To show that the microscope was operating under conditions to give a resolving power in the range 30–60 Å., Figure 11 was taken of an indium film deposited on collodion as prepared by R. C. Williams. Individual particles as small as 0.5 mm. in diameter may be seen on the original photograph at 156,000 diameters. At this magnification, 0.5 mm. is equal to 32 Å. in the specimen.

Even with all variables controlled as carefully as possible, it is difficult to place an upper limit on the size of particles which



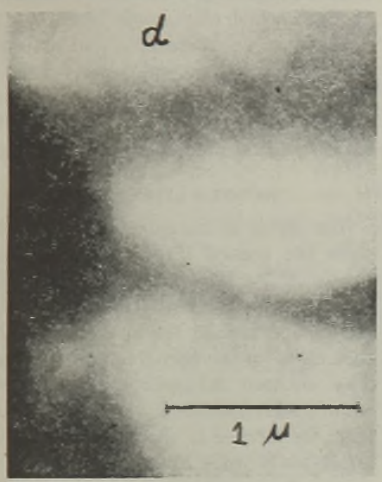


Figure 7. Effect of Dipping Films in Solvents (× 25,500)

a. No. 3 reduced crude in petroleum ether
b. No. 8 VSS asphalt in petroleum ether
c. No. 8 VSS asphalt in benzene
d. No. 8 VSS asphalt in carbon disulfide

could be present but not observed. Based on hundreds of observations such as those given in this paper, the authors believe that asphaltene does not occur as a micelle with a diameter greater than 65 Å.

STATE OF ASPHALTIC SUBSTANCES

A diameter of 65 Å. for particles corresponds to a particle weight of 90,000 for a density of 1 gram per ml. Thus the maximum number of molecules represented by an asphaltene particle, when assuming a minimum molecular weight of 1000 (*4*), would be 90. From this description of the maximum size of asphaltene particles, if they do exist, it would seem just as logical to describe asphaltene when present in crude oils as negatively charged molecules or small groups of associated molecules as to call them "colloidal particles". The asphaltene could be said to be insoluble in solvents and, hence, would precipitate in solutions of petroleum ether, benzene, carbon disulfide, and pyridine. It would follow that the colloidal effects of thixotropy, etc. (*14*), for the concentrated form of asphaltic bitumen as found in asphalts are due to particles less than 65 Å. in diameter.

The formation of particles, either when dispersing the asphalts in the solvent or when dipping the films in the solvent, has been

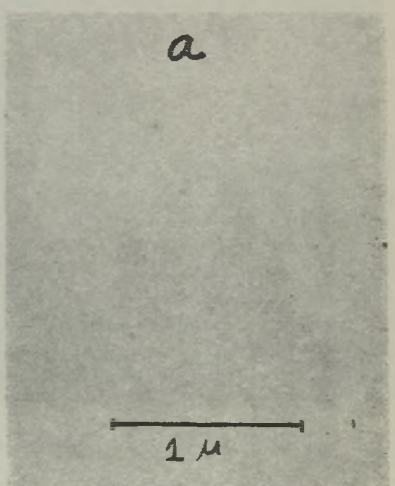


Figure 8. Gilsonite Films (× 25,500)

a. Thin film, untreated
b. Film washed in benzene
c. Film from 1% solution in benzene
d. Film from 1% solution in petroleum ether

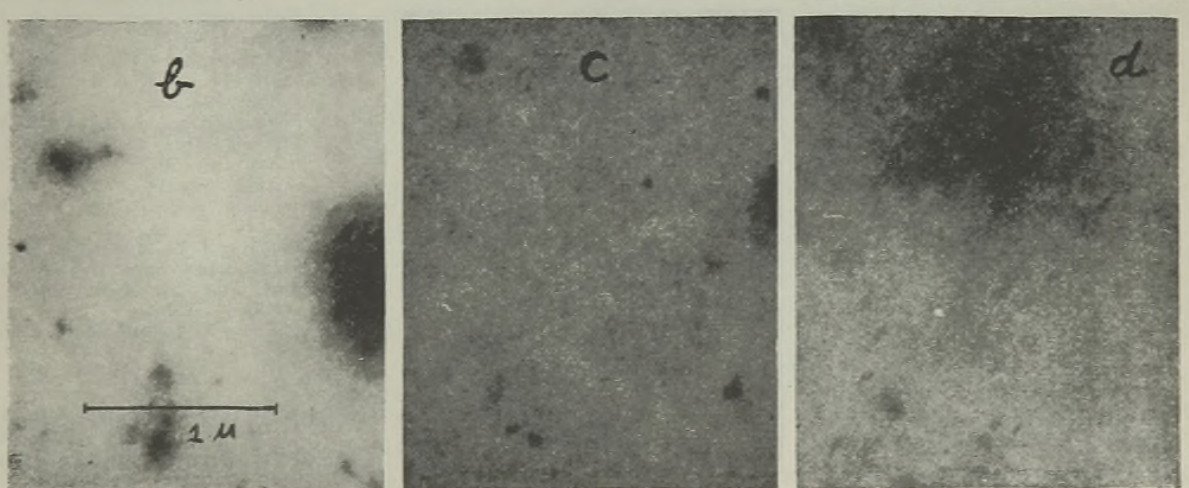
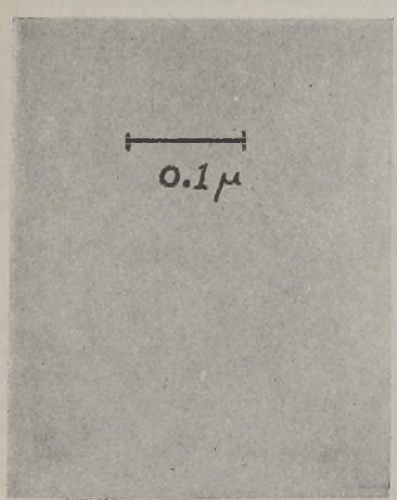


Figure 9. Thin Film of No. 8 VSS Asphalt on Formvar (× 156,000)



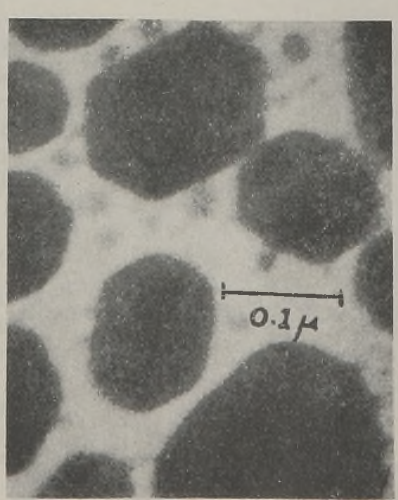


Figure 10 (*Left*). Benzene Solution of No. 8 VSS Asphalt (× 156,000)

Figure 11 (*Right*). Indium Evaporated on Collodion (× 156,000)

uniform. This phenomenon indicates that laboratory measurements and studies on asphaltic substances when diluted with solvents would be expected to yield the results from colloidal suspensions even though the asphalt or oil containing the asphaltenes did not contain the colloidal particles. One view could be that the asphaltenes are "potential colloids" and that solutions containing them easily convert into colloidal systems from changes in the composition of the solution (solvents) or from electrical effects.

The electron microscope observations of the asphalt films prepared from the successive products in the manufacturing process would indicate that no change has taken place in the state of the asphaltenes during the processing. Changes in products which exist would be due to the changes in concentration and stability of the asphaltene compounds which, in turn, result in different degrees of conversion to particles when tested with solvents or blended with other products.

ACKNOWLEDGMENT

The series of manufactured products from the central Texas crude oil was furnished by The Texas Company. L. Thomassen subjected the asphalt to the x-rays and Robert Cohen suggested the technique for the very thin asphalt films. The electron microscope observations were made possible by a Grant-in-Aid from the Horace H. Rackham School of Graduate Studies.

LITERATURE CITED

(1) Abraham, "Asphalts and Allied Substances", 4th ed., New York, D. Van Nostrand Co., 1929.
(2) Benson, *Highway Research Board Proc.*, 17, 368 (1937).
(3) Dykstra, Beu, and Katz, *Oil Gas J.*, 43 (21), 79 (1944).
(4) Eckert and Weetman, Div. of Petroleum Chem., A.C.S., New York, 1944.
(5) Godlewicz and Pilat, *Oil Gas J.*, 43 (32), 76 (1933).
(6) Kalichevsky, "Refining Lubricating Oils", New York, Reinhold Pub. Corp., 1938.
(7) Mack, *J. Phys. Chem.*, 36, 2901 (1932).
(8) Nellensteyn, *Assoc. Asphalt Paving Tech. Proc.*, 1937, 78.
(9) Nellensteyn, in "The Science of Petroleum", Vol. IV, p. 2760, London, Oxford Univ. Press, 1938.
(10) Pfeiffer and Saal, *J. Phys. Chem.*, 44, 139 (1940).
(11) Preckshot, De Lisle, Cottrell, and Katz, *Trans. Am. Inst. Mining Met. Engrs.*, 151, 188 (1943).
(12) Sahlbom, *Kolloid Chem. Beihefte*, 2, 29–140 (1910).
(13) Swanson, *J. Phys. Chem.*, 46, 141 (1942).
(14) Traxler and Coombs, *Ibid.*, 40, 1133 (1936).
(15) Vink, Ames, David, and Katz, *Oil Gas J.*, 39 (28), 34 (1940).
(16) Williford, C. L., Agr. Mech. Coll. Texas, *Bull.* 73 (1943).

ALLYL ETHER OF STARCH

Preparation and Industrial Possibilities

P. L. NICHOLS, JR., R. M. HAMILTON, LEE T. SMITH, AND E. YANOVSKY

Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pa.

Soluble allyl ether of starch has been prepared from starch acetate and also by direct allylation of starch. The compound is oxidized and polymerized to an insoluble and infusible product. Heat and paint driers accelerate the polymerization. Possible industrial uses of allyl starch as coatings, adhesives, and plastic intermediates are discussed.

THE only reference to allyl starch in the literature is that by Tomecko and Adams (*3*), who prepared what they called a "monoallyl starch" by direct substitution of starch with allyl bromide in the presence of 10% aqueous potassium hydroxide. The product had 0.5 allyl group per glucose unit. Repetition of the experiments of Tomecko and Adams gave a white amorphous powder, slightly soluble in water and practically insoluble in acetone, ethylene chlorohydrin, and other organic solvents, with 0.5 allyl group per glucose unit. This was similar to the substance obtained by Tomecko and Adams. They determined the degree of substitution by combustion analyses. We used the same method for insoluble compounds and the Wijs method for compounds soluble in organic solvents. Slight modifications in the concentrations of starch, alkali or allyl bromide or in the reaction time did not affect the composition of the final product.

A clue to the explanation of low substitution in the product obtained by Tomecko and Adams was found in the fact that no allyl bromide could be recovered in spite of the large excess used (85 to 10 grams starch or a mole ratio of 11 to 1). This was attributed to two side reactions which parallel the main reaction of etherifying the hydroxyl groups. The allyl bromide is hydrolyzed by the alkali to allyl alcohol, and this reacts with allyl bromide to form allyl ether. The hydrolysis of allyl bromide and also of allyl chloride (used in later experiments) at various temperatures and with various concentrations of alkali was therefore investigated. Equal volumes of allyl bromide or chloride and sodium hydroxide solution were mixed and stirred at various temperatures for 3 hours. At 80° C. (approximately the temperature of the reaction for the preparation of allyl starch) the results were as follows: With alkali concentrations up to 10%, about 23% of allyl bromide was hydrolyzed[1]; with 20 to 30% alkali, about 9%; and with 40 to 50%, only about 2.5%. About 21% allyl chloride was hydrolyzed with 10% sodium hydroxide, and only about 1% with 40 to 50% alkali.

These experiments pointed to the advisability of using higher concentrations of alkali in the preparation of allyl starch. As a matter of fact, when concentrated alkaline solutions were used, with the same excess of allyl bromide, compounds of a higher degree of substitution (up to 2.6 allyl groups per glucose molecule) were obtained, and a considerable amount of allyl bromide could be recovered after the reaction was complete. The powdery product thus obtained was infusible and insoluble in all organic solvents tested.

It appears that allyl ether of starch insolubilizes with greater ease than the comparatively easily oxidizable allyl ethers of simpler carbohydrates (*2*).

[1] At concentrations up to 10%, the entire amount of alkali was used up, and therefore 23% represents the minimum hydrolyzed.

METHODS OF PREPARATION

On the assumption that easily oxidizable allyl starch might be more stable in solution, we adopted a method similar to that used by Haworth, Hirst, and Webb (*1*) for methylation of starch—that is, simultaneous hydrolysis and allylation of starch acetate in acetone solution. This method, which does not require an autoclave, is carried out as follows: In a flask fitted with a mechanical stirrer and reflux condenser, 100 grams of starch acetate are dissolved in 250 cc. of acetone; 250 grams of 50% aqueous sodium hydroxide and 300 cc. of allyl bromide are added, and the mixture is heated at reflux temperature for 3.5 hours. The volatile portion of the reaction mixture is then removed rapidly (15 minutes) by distillation with steam, the gummy product remaining in the flask is washed until alkali-free, and it is then dissolved in about 150 cc. of acetone. When this acetone solution is poured into rapidly stirred water at room temperature, nearly white gummy allyl starch is obtained. The yield is about 90 grams of the gum, containing about 20% of water. An appreciable proportion of the allyl bromide used can be recovered from the steam-distilled liquid.

The same compound can be prepared with allyl chloride, which is cheaper. But for this reaction heating in an autoclave at 80° C. for about 11 hours is required.

For producing larger quantities of allyl starch, the following method is more economical: Five hundred grams of air-dry starch is stirred into 2000 grams of 50% aqueous sodium hydroxide in an autoclave at room temperature, and 2500 cc. of acetone and 3000 cc. of allyl chloride are added with constant stirring. The autoclave is heated at about 86° C. (approximately 30 pounds pressure). The liquid is then distilled with steam for about 40 minutes to remove the acetone and excess of allyl chloride. The separated gum is washed with water until free of alkali. The gum can be further purified by dissolving in acetone, filtering off the small amount of unchanged or lowly substituted starch (less than 3%), and precipitating with water. Acetone, allyl chloride, and allyl ether can be recovered from the distillate. The results of several runs are given in Table I. They were ob-

TABLE I. PREPARATION OF ALLYL STARCH

Material Used	% Moisture	Reaction Time, Hr.	Yield, Grams	Yield Cor. for Moisture of Product, %	Yield, % of Theoretical	% Allyl Content (Wijs Method)	Allyl Groups per Glucose Unit	Grams Recovered: Allyl chloride	Grams Recovered: Allyl ether
Potato starch	16	11	860	612	93	37.0	2.3	795	94
Potato starch	16	11	890	620	94	37.1	2.3	1213	79
Sweet potato starch	14	10	900	603	99	30.0	1.7	924	117
Cornstarch	12	10	986	684	98	37.4	2.4	770	72
Cornstarch	12	10	972	676	96	37.5	2.4	882	105
Tapioca starch	13	9	830	617	92	35.0	2.1	823	93
Waxy maize starch	10	20	900	617	92	33.5	2.0	460	68
Standard tapioca dextrin[a]	3	4	816	646	89	33.2	2.0	1262	89

[a] Viscosity, 8.5 centistokes in 50% solution at 130° F.

tained with the laboratory equipment available and do not represent the optimum yields and recovery of solvent.

This table shows that for most ordinary starches the reaction time is about 10 hours; for waxy maize starch, which consists entirely of amylopectin, it is 20 hours; for a starch-degradation product such as dextrin, it is 4 hours. The percentage of allyl in the product decreases somewhat with time, owing to the slow oxidation and polymerization of allyl starch, even at room temperature or below. The yields are given on a wet basis (20–25% moisture).

No attempt was made to recover the acetone from the steam distillate, which was washed with water and then fractionated to recover the allyl chloride and allyl ether. Perhaps in commercial practice the mixture of allyl chloride and acetone could be used for making the next batch.

PHYSICAL AND CHEMICAL PROPERTIES

Allyl starch prepared by these methods is a soft, gummy (but not tacky) material containing about 2 allyl groups per glucose unit. Products of lower or higher allyl content can be obtained, but they are either powdery or extremely sticky. The powdery form, due to a larger surface exposed, is much less stable. When left in the air, the gummy allyl starch becomes coated with a hard insoluble material, but this can be avoided by keeping the allyl starch under water at a comparatively low temperature. It is soluble in most organic solvents but not in aliphatic hydrocarbons. Solutions of allyl starch in acetone, alcohol, and other solvents are stable. Even a 30% solution has low viscosity. One of the methods for the purification of allyl starch is precipitation from alcohol or acetone solutions with water.

The tendency of the powdery product to become insoluble on exposure to air and the formation of an insoluble coating on the gummy product are apparently due to oxidation and the subsequent cross-linkage polymerization of the partly oxidized compounds. This process can be studied quantitatively on thin films of allyl starch deposited from solutions on surfaces of wood, glass, or metal. On exposure to air, these films gradually become insoluble. The process of insolubilization can be catalyzed by heat, chemical agents, and infrared and ultraviolet radiation.

Quantitative results on insolubilization of films (obtained by Esther M. Terry of this Laboratory) for a number of different preparations of allyl starch at different temperatures, both in the presence and in the absence of a catalyst, are given in Table II. Results obtained at room temperature are shown in Table III. The amount of drier is expressed as per cent by weight of metal (cobalt) on the basis of dry allyl starch. Table II shows that the process of insolubilization proceeds faster at higher temperatures. Addition of catalyst decreases the time required for insolubilization, although the effect is not equally marked in all cases. Infrared or ultraviolet radiation has a marked catalytic effect. The effect of cobalt naphthenate was striking in experiments at room temperature (Table III).

Preliminary experiments have shown that a large percentage of resins and plasticizers are compatible with allyl starch.

INDUSTRIAL POSSIBILITIES

Properties of allyl starch suggest that it may be used for various purposes. When dissolved in ordinary lacquer solvents, it can be utilized as a protective and decorative coating for wood, glass, metal, and other surfaces. Because of its high resistance to various solvents, solutions of acids and alkalies, and heat, it should be valuable as a lacquer and varnish for household and office furniture and numerous other articles in everyday use. Several manufacturing concerns are now testing it for these purposes.

It can be used for coating and impregnating paper and textiles, and it acts as a thermosetting adhesive suitable for preparation of laminated products.

Allyl starch can also be used for the preparation of rigid plastics. When compounded on a rubber mill with various ingredients, including sulfur and vulcanization accelerators, and "vulcanized" in a press, the gummy material forms a rigid plastic which is highly resistant to various solvents and other chemical reagents. The milled product, when placed between layers of wood, paper, or cloth, and heated under pressure, yields laminated materials of various degrees of strength and usefulness.

The compatibility of allyl starch with various resins and plasticizers indicates that it may be modified to suit certain specific requirements. Allyl starch can be copolymerized with simpler allyl carbohydrates and other monomeric substances.

Table II. Insolubilization of Allyl Starch Films, with and without Cobalt Naphthenate

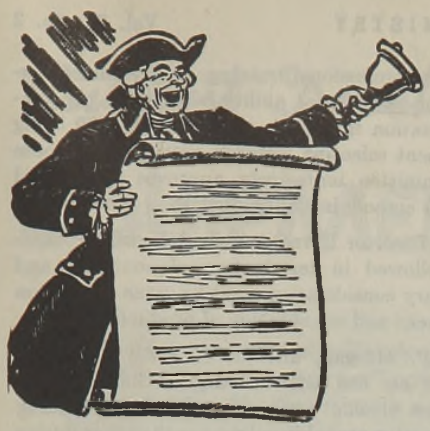
Sample No.	Drier, % Co	Temp., ° C.	Type of Heating	% Insoluble Material after: 1 hr.	2 hr.	3 hr.	4 hr.	5 hr.	6 hr.	24 hr.
1	...	120	Oven	..	100	...	...	...	...	...
2	...	120	Oven	..	100	...	...	...	...	...
3	...	100	Oven	..	86	94	99	100	...	...
	0.4		Oven	..	93	93	95	96	97	97
	0.2		Oven	..	87	93	...	100	...	...
	...		Infrared	78	97	99	100	...	...	...
	0.4		Infrared	..	91	95	100	...	...	...
	0.2		Infrared	..	91	93	97	100	...	...
4	...	100	Oven	80	89	96	98	100	...	...
	0.4		Oven	95	96	99	100	...	...	...
	0.2		Oven	95	95	100	...	...	...	...
	...		Infrared	91	96	100	...	...	...	...
	0.4		Infrared	93	96	100	...	...	...	...
	0.2		Infrared	89	97	100	...	...	...	...
5	...	100	Oven	86	95	97	98	100	...	...
	0.4		Oven	88	92	92	97	...	100	...
	0.2		Oven	91	92	94	97	99	100	...
	...		Infrared	88	95	100	...	...	...	...
	0.4		Infrared	89	92	94	97	100	...	...
	0.2		Infrared	91	...	100	...	...	...	...
6	...	100	Oven	83	95	99	99	100	...	...
	0.4		Oven	93	93	95	100	...	...	...
	0.2		Oven	91	92	92	100	...	...	...
	...		Infrared	89	97	100	...	...	...	...
	0.4		Infrared	92	96	100	...	...	...	...
	0.2		Infrared	89	93	99	100	...	...	...
7	...	80	Oven	..	...	79	81	83	88	100
	0.4		Oven	..	...	92	95	95	99	100
	0.2		Oven	..	...	94	95	96	99	100
	...		Infrared	..	...	87	94	97	98	100
	0.4		Infrared	..	...	92	97	98	99	100
	0.2		Infrared	..	...	94	94	97	99	100
	...		Ultraviolet	..	...	96	100	...	...	...
	0.4		Ultraviolet	..	...	91	99	100	...	...
	0.2		Ultraviolet	..	...	92	95	96	96	...
8	...	80	Oven	..	79	87	88	94	96	100
	0.4		Oven	89	90	93	...	94	97	100
	0.2		Oven	91	94	94	95	95	95	100
	...		Infrared	77	91	96	99	99	100	...
	0.4		Infrared	88	93	96	99	99	100	...
	0.2		Infrared	90	...	96	...	97	98	100
	...		Ultraviolet	88	92	98	98	99	...	...
	0.4		Ultraviolet	88	89	96	99	100	...	...
	0.2		Ultraviolet	89	93	94	100	...	...	...

Table III. Insolubilization of Allyl Starch Films at Room Temperature

Sample No.	Drier, % Co	% Insoluble Material after: 1 week	2 weeks	3 weeks	4 weeks
9	...	55	73	73	77
	0.4	91	99	99	100
	0.2	94	96	99	99
10	...	16	...	70	73
	0.4	99	100	..	...
	0.2	99	100	..	...
11	...	..	...	80	82
	0.4	98	100	..	...
	0.2	98	100	..	...
12	...	13	54	72	76
	0.4	98	100	..	...
	0.2	97	100	..	...
13	...	73	77	80	81
	0.4	88	100	..	...
	0.2	91	99	99	100

LITERATURE CITED

(1) Haworth, Hirst, and Webb, *J. Chem. Soc.*, 1928, 2681.
(2) Nichols and Yanovsky, *J. Am. Chem. Soc.*, 66, 1625 (1944).
(3) Tomecko and Adams, *Ibid.*, 45, 2698 (1923).



JANUARY'S HEADLINES

Events during the Month, of Interest to Chemists, Chemical Engineers, Executives

Reviewed by the Editors

¶ JANUARY 2. Agricultural and scientific leaders confer in Louisville offices of Jos. Seagram & Sons on new type of alcohol-consuming internal combustion engine, developed by Vimalert Corp. in cooperation with Indiana Farm Bur., Foreign Economic Administration, and Seagram interests.~~Hilton-Davis Chemical Co. of Cincinnati purchased by Sterling Drug of New York; Hilton-Davis Chemical Co. Division will continue manufacture of chemicals and dyes with policies and personnel unchanged.~~ Dept. of Justice pushes suit for dissolution of Aluminum Co. of America in U. S. Circuit Court of Appeals of New York; charges Alcoa, subsidiaries, and others maintained monopoly in aluminum production.

¶ JANUARY 3. McKesson & Robbins creates new Department of Animal Remedies and Agricultural Chemicals with W. C. Butler as head.~~War Production Board plans to convert airplane engine plant of Jacobs Engine Co. at Pottstown, Pa., to production of military-type tires; Firestone Tire & Rubber will operate converted plant.

¶ JANUARY 4. E. K. Bolton, chemical director of Du Pont, awarded 1945 Perkin Medal by American Section of the Society of Chemical Industry for outstanding accomplishment in field of industrial research.

¶ JANUARY 5. War Mobilization Director Byrnes requests cancellation of conventions and trade shows for more than 50 persons after Feb. 1, unless they are necessary for prosecution of war; cooperation of organizations and hotels expected, so as to make compulsion unnecessary.~~Montgomery Ward answers government suit in U. S. District Court by charging that Army threatened employees with draft unless they obeyed Army commands, after seizure of Ward properties in Chicago and six other cities.

¶ JANUARY 6. President Roosevelt asks Congress for national service act and compulsory military training of youth after war. ~~Byrnes supports President in affidavit to be used in Court, asserting that Montgomery Ward's conduct in refusing to obey orders of War Labor Board "if allowed to continue, will seriously interfere with successful prosecution of war".~~Jesse Jones, Secretary of Commerce and head of Reconstruction Finance Corp., cites need for further aid to little business by RFC loans; tells of failures of many small firms since beginning of war.~~ Secretary of Interior Ickes establishes 200,000 acres of Utah land as federal reserve, to curb monopolistic control of Nation's potash supply, and ensure government royalties and other benefits from potash production.

¶ JANUARY 7. WPB instructs Aluminum Co. of America to accept no new orders for aluminum sheet during first 4 months of 1945 to avoid crisis in that material.

¶ JANUARY 8. Air Reduction Co., manufacturer of industrial and medical gases and equipment, announces formation of Airco Export Corp. to expand, consolidate, and direct export business of Air Reduction and subsidiaries; H. R. Salisbury named president of Airco, which expects to help supply rehabilitation and development needs of devastated foreign countries, particularly for hospital supplies as well as industrial chemicals, gases, and welding equipment.~~Supreme Court sustains Government's contention that 7 major glass container companies (including Hartford-Empire, Corning, and Hazel Atlas) had violated antitrust law; supports provision for compulsory licensing of patents as preventive of future violations.~~Supreme Court declares unconstitutional Texas legislation requiring paid labor union organizers to register with Texas Secretary of State before soliciting for members.

¶ JANUARY 10. WPB prediction of further cuts in paper quotas for magazines may mean rationing of space to advertisers.~~ New chlorinated synthetic rubber is claimed by Goodyear to be suitable for use in corrosion-resistant paints, to ease demand on dwindling supply of natural product needed by Navy.~~President Roosevelt withdraws Anglo–U. S. Oil Treaty from Senate[1] in order to make revisions that will "remove grounds for misunderstanding".~~Airplane rocket launcher made of plastic by General Electric Co., aided by Baldwin Locomotive works; advantages are fire resistance, light weight, and saving of metals.~~ WM Director Byrnes calls for drastic reduction in coal use to meet shortage and hopes public cooperation will avoid need for rationing; asks WPB to prohibit outdoor display lighting, Director of Defense Transportation to eliminate special trains to resorts, and public generally to maintain maximum temperature of 68° F. in buildings and homes which burn coal.~~Senator Lister Hill of Alabama introduces bill in Senate to establish a "national fertilizer policy" and "provide for government acquisition of phosphate reserves". Bill would direct TVA to formulate program designed to "increase amount of fertilizer available to farmers, improve its quality, and lower its cost in interest of national defense, agricultural development, and watershed protection".~~Drug industry export committee announced by R. M. Dunning, chairman, with objectives of discussing problems and presenting opinions of the industry to Government; committee made up of representatives of Am. Drug Mfrs. Assoc., Proprietary Assoc. of Am., and Am. Pharmaceutical Mfrs. Assoc.

¶ JANUARY 11. National Patent Planning Commission recommends to Congress that Government grant exclusive licenses to private enterprise to exploit Government-owned inventions when "necessary and in the public interest".

¶ JANUARY 12. Foreign copper shipped to war plants in December exceeded that from domestic sources for the first time.~~ ~~Pennsylvania puts in effect a drastic work-or-fight policy.

¶ JANUARY 14. A synthetic chemical which absorbs more than 99.9% of sun's ultraviolet radiations has been used in manufacture of plastic goggle lenses, Polaroid Corp. discloses.~~Richmond Exploration Co., subsidiary of Standard Oil of Calif., has

[1] *Chem. Eng. News*, 23, 172 (Jan. 25, 1945).

been granted oil concessions covering approximately 1,000,000 acres by Government of Venezuela, H. D. Collier, president of Standard of Calif., announces.

¶ JANUARY 15. Byrnes calls on Director of Selective Service Hershey to apply a priority system to control induction of more than 200,000 men of 26 through 29 age group from essential industry to meet manpower requirements of armed services; asks Hershey to set up five categories, with most essential men last[2].

¶ JANUARY 16. Arthur E. Corbin, district chief of general salvage branch, WPB, addressing Associated Printing Salesmen, says because of supply problem in Pacific, paper and pulp needs of Government will not diminish to any extent, even after Germany is defeated.~~Secretary of Commerce Jones says U. S. plants are capable of producing a million tons of synthetic rubber a year and some government-owned factories are producing synthetic at less than cost of natural rubber before war.~~War Manpower Commission, in new classification guide for induction boards, excepts as a critical activity all technical, scientific, and research personnel engaged in scientific activities listed as either essential or critical.~~New petroleum refinery with 50,000-barrel daily capacity, near completion on Persian Gulf, is being built by U. S. engineers for Arabian American Oil Co.~~Aluminum Co. of America announces program for re-employment of 26,000 workers now in armed forces.~~War Food Administration 1945 naval stores conservation program will be essentially same as last year, except for changes in participation requirements to lift rosin output.

¶ JANUARY 17. J. P. Seiberling, president, Seiberling Rubber Co., announces $1,000,000 expansion of its Barberton plant.~~President Roosevelt asks Congress to speed passage of work-or-fight legislation for men between 18 and 45.

¶ JANUARY 18. Surplus Property Board authorizes Metals Reserve Co. to sell aluminum scrap now in storage to stretch supply of metal needed for production of war equipment.~~January holiday from industrial alcohol making for whisky distillers will probably be last this year, WPB Chairman Krug indicates.~~Production of key chemicals is interrupted, particularly in Cleveland, Buffalo, and Niagara Falls areas, because of disrupted rail traffic.~~Former Senator Guy M. Gillette unanimously confirmed by Senate as member of Surplus Property Board.

¶ JANUARY 19. Eighteen steel manufacturers, including Carnegie-Illinois, Republic, and Bethlehem, charged by Federal Government with conspiracy to restrain trade and fix prices in stainless steel industry.~~Industrial workers in the 26 to 29 age group who can be replaced should be classified for induction regardless of their status on the new WMC list of critical occupations, Lewis B. Hershey tells local draft boards in letter of instructions.~~WPB's Metals and Minerals Division says production of primary aluminum in first quarter of 1945 will reach estimated 275 million pounds, or about 100 million less than indicated requirements.

¶ JANUARY 20. Copper industry's stepchild selenium may make it possible to drive automobiles additional miles between oil changes, research results at Battelle Memorial Institute indicate; selenium will keep crankcases free from sludge and piston rings and cylinder walls bright and free from "varnish".

¶ JANUARY 22. Houdry Process Corp. announces a royalty financial arrangement for licenses of Houdry catalytic cracking processes.~~All-plastic artificial eyes, said to duplicate fit and appearance of the real eye more closely than glass eyes, are announced by American Optical Co. and will be available this year.~~Department of Justice announces opening a sealed indictment returned by federal grand jury at Newark, charging Ferris Instrument Corp. and two of its officers with conspiracy to defraud Government in connection with the renegotiation of contracts.~~Harvard President James B. Conant urges revision of GI Bill of Rights to assure professional training, at government expense, for veterans of exceptional ability.~~Senate subcommittee on war mobilization says more than $600,000,000 being spent by 40 government scientific research agencies.~~House Military Affairs Committee tentatively approves jail-backed manpower control bill embodying anticlosed shop amendment.

¶ JANUARY 23. WM Director Byrnes issues major order governing policies to be followed in termination of contracts and emphasizes that primary consideration must be given promotion of maximum employment and equalization of production load.

¶ JANUARY 24. D. P. Morgan, director of WPB Chemicals Bureau, says bad weather has interrupted grain deliveries for production of beverage alcohol during January liquor-making holiday, and that production probably will be less than that during August holiday.~~Attorney General Biddle declares America must beware of attempt by trusts and cartels, largely of British origin, to control business in postwar period.~~Lawrence Ottinger, president U. S. Plywood Corp., says company has contracted to buy 44,000 acres of timberland in Ontario.~~B. F. Goodrich and Firestone Tire & Rubber announce purchase of basic patents covering electronic vulcanization of rubber and other materials.~~FEA invites importers to enter into contract with U. S. Commercial Co. to import oils from France, essential to manufacture of perfumes, soaps, and toilet waters of prewar quality.~~Studies by Governments of United Kingdom, Netherlands, and U. S. in past 5 months indicate that heavy reliance must be placed on synthetic rubber for remainder of war.

¶ JANUARY 25. Secretary of Commerce appoints committee of 8 industrial executives, with C. E. Wilson, president of General Electric, as chairman to advise Department of Commerce and American Standards Association on future standards, including consumer goods.~~New synthetic latex, a modified butadiene-styrene type, is being produced at Government's synthetic plant at Naugatuck, Conn., according to J. P. Coe, general manager of U. S. Rubber Co.'s Naugatuck division.

¶ JANUARY 26. Vannevar Bush, director, Office of Scientific Research and Development, J. O. Hunsaker, chairman, National Advisory Committee for Aeronautics, and Karl T. Compton, president, MIT, appearing before House Committee on Postwar Military Policy, agree on imperative necessity for establishing a research board for national security in peacetime.

¶ JANUARY 27. Judge Philip L. Sullivan rules President Roosevelt's seizure of Montgomery Ward properties in Chicago and six other cities, because of CIO labor dispute, is unlawful.~~Wilbur F. Burt, vice president in charge of manufacturing, Socony Vacuum Oil, announces inexpensive method developed for producing thiophene from petroleum.

¶ JANUARY 28. WPB cancels outstanding authorizations for use of tin that existed prior to September 1, 1944.

¶ JANUARY 29. British, American, and Dutch rubber experts, who have just finished a week's meeting in Washington, foresee a possible world surplus of about 1.3 tons of rubber a year, 3 or 4 years after liberation of East Indies and Malaya.~~F. B. Davis, chairman of U. S. Rubber, estimates it will take 5 years to restore natural rubber plantations to capacity production.~~WPB bans filling stainless steel orders subject to deferred allotments.~~Antitrust Division, Department of Justice, acts to end illegal patent licensing restrictions in reconversion.

¶ JANUARY 30. WPB announces extension of three additional tire plants as part of Government's $70,000,000 program to boost military tire output by 25%.

¶ JANUARY 31. U. S. Rubber announces immediate construction of a factory in Havana, Cuba, for production of tire recapping materials and synthetic rubber soles.~~Government carries its appeal in Montgomery Ward case from U. S. District Court to Circuit Court of Appeals.

[2] *Chem. Eng. News*, 23, 172 (Jan. 25, 1945).

Current Developments in EQUIPMENT AND DESIGN

Will the trend in scientific development for the next decade be "improving the old" rather than "inventing the new"?

Discussed by Charles Owen Brown

RECENTLY Roland P. Soule, a consulting engineer, presented a stimulating analysis of the trend in technology. His review of scientific developments for the past century was provocative, but his prediction for the next decade or two should receive some comment here. He concluded that the next twenty years will not be characterized by the ascendency of any single branch of technology or the development of any fundamentally new industries in the scientific and engineering world; rather we will go back over the road we have traveled to make improvements. Although, a half century later, we do not agree with the prediction of the Commissioner of Patents in the 1880's that all invention had been made, Soule's prediction is a very probable one.

Members of the scientific professions had the privilege recently of visiting the National Chemical Exposition in Chicago. A review of exhibits revealed that the majority were improved and better models of older devices already on the market. It is no criticism to say that little new equipment was displayed. The exhibition reflected the trend of scientific progress toward making equipment and instruments more accurate, more convenient to use, or more widely useful at a lower price. This policy is basically sound and will result in making the next twenty years as profitable as any twenty-year period in the past, which witnessed the advent of new lines of progress such as automobiles, Diesel engines, streamlined trains, and airplanes. It is a sage policy to devote the next two decades to improving or to making more widely available the useful tools we now possess.

All can remember when a relatively simple plastic material was used to seal bottles of liquid by dipping the stoppered neck into a pot of melted plastic material. We imagine the first use of this process consisted in dunking each bottle by hand into an open pot of plastic which contained a glass thermometer and rested on an electric hot plate, perhaps located under an open hood. This layout may be practical for sealing a few hundred bottle tops per day, but not when several hundred thousand articles, ranging from steel machined parts to K rations, must be wrapped and sealed with a moistureproof film. Improvements are incorporated into two machines built by Castaloy Corporation, of Detroit, for the hot dipping and wrapping of small packages. Figure 1 shows one type.

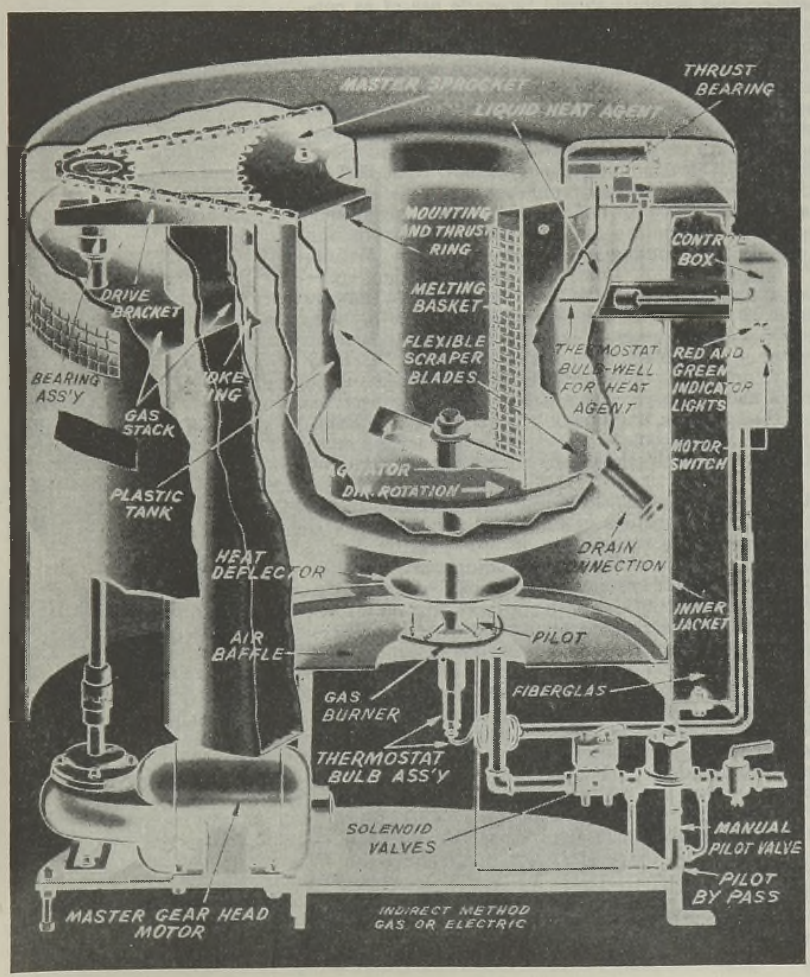


Figure 1. Indirect Heated Model for Hot Dipping and Wrapping Small Packages

The machines are made in two sizes, with direct heating applied by contact electric heaters; for indirect heating, Dowtherm is the heat transfer medium with gas or electricity as the source of heat. Unusually even and well-regulated heat flow to the melting plastic is obtained at any desired temperature level by complete instrumentation. All controls are harmonized to maintain the melt within a few degrees of the desired temperature automatically; in addition a red and green light visibly indicates the condition of the bath. After the controls are set, the cabinet containing the adjustments may be locked to prevent tampering. Should the bath temperature become irregular, the heat and power are cut off.

The imagination is stirred by the use proposed for a new product of Kano Laboratories of Chicago. This new organic liquid has an extremely low surface tension, and creeps and spreads rapidly. The application suggested is to use this material to test the porosity in welded seams in steel tanks and other welded plate work. According to the Laboratories, this material will penetrate cracks or openings less than 0.000001 inch wide. The method is simple. The material is sprayed on one side of the welded seam, and evidence of penetration of the organic fluid to the other side of the seam or weld indicates defective construction (Figure 2). The claim of the originator that it "literally goes everywhere quickly" causes one to wonder if transportation charges can be avoided. If the liquid is efficient in the use suggested, the container in which it goes to market must be perfectly welded.

Special applications for the newer plastics are numerous; one of the most interesting is known as Faxfilm, developed by Rex D. McGill. The plastic is used instead of the conventional photomicrograph to record the structure of a (*Continued on page 72*)

Figure 2. Testing the Porosity of a Welded Seam with an Organic Liquid

prepared surface. It has advantages over the photomicrograph in such applications as comparing the quality of machined surfaces. Faxfilm is used by cutting off about 1 inch of the plastic ribbon, wetting the prepared specimen surface with one or two drops of solvent, applying the film with enough pressure to give complete contact, and allowing it to dry in place. Meanwhile a cardboard frame is moistened with adhesive and placed on the film, or the film may be peeled from the specimen and mounted. The frame can be placed in a projection apparatus, and the image, enlarged to 10,000 times the area, will appear with three-dimensional properties. Details above 0.0001 inch are distinct. The entire operation has taken less than one minute, a much shorter time than is required to make a photomicrograph, and the cost is less than 6 cents. The Faxfilm kit is so small it is easily taken into the shop for use on large pieces of work in place; nothing is gained by taking the work to the laboratory.

The companies now producing carbon and graphite have entered the chemical field with heat exchangers, valves, pipes, and fittings. It is therefore logical that the great chemical resistance of carbon and graphite should be made use of as construction materials for laboratory drains and flues. In the new laboratory building of St. Lawrence Alloys & Metals, Ltd., at Beauharnois, Quebec, the flues were lined with carbon blocks from the basement to the top. The gases passing up the flue to the atmosphere may contain almost any acid and chlorine fumes, while corrosive condensate which drains down to the basement level is taken care of in carbon pipes to a proper disposal place. The total height of the carbon lining is over 30 feet. The bottom drip connections are closed with acidproof cocks.

The new alloy steels have proved to be extremely useful materials but are more difficult to machine than ordinary carbon steel. The practice is becoming general of using large amounts of "cutting" oil throughout the machining operation. The finished pieces are dripping with the oil which must not only be removed completely but be recovered for use. In one process, after the pieces have been drained, they are washed with organic solvents in automatic, mechanically driven washers. Not only are the operating machines more numerous, but the size of the individual units has increased many times. The complete removal of oil, grease, lapping, and drawing compounds, the drying, and, when desired, the automatic coating of parts with a rust-proof finish have proved to be the means of speeding up assembly lines.

Improvements in one direction often present problems in another. The increased quantities of flammable liquids used by these machines represent a serious fire hazard. Walter Kidde and Company, Inc., makers of fire-fighting equipment, have devised a built-in extinguishing system using carbon dioxide. Varying in design with the type and size of the degreaser-washer, these high-pressure systems operate on the same underlying principle—the instant discharge of large amounts of carbon dioxide within the machine at the first appearance of a flame. Mounted on the side of the washer are two or more standard steel cylinders of carbon dioxide under 850 pounds per square inch pressure. Thermostatic controls within the hood actuate relays which control the release of the high-pressure gas blanketing the combustion with inert carbon dioxide. The same relays simultaneously close all openings, louvers, and exhaust ducts and stop the motors; the cold gas is thereby enclosed within the machine. This comprehensive development merits careful study by safety committees.

These few examples are cited to reflect the policy advocated by Soule. Judged by the value of the modifications described, jobs and profits will be plentiful in view of the tens of thousands of improvements yet to be made.

Current Developments in

INSTRUMENTATION

Spectrophotometric methods are extending beyond control-laboratory uses to recording and controlling concentrations of important compounds in industrial processes.

Discussed by Ralph H. Munch

THE development of modern spectrophotometric methods has played an important part in the war effort. It is interesting to trace these developments and to note the advances in other branches of science which have made them possible. The visible spectrum has been known since before the time of Isaac Newton. In 1800 William Herschel demonstrated the existence of infrared radiation by its ability to raise the temperature of a sensitive thermometer. Somewhat later Ritter and Wollaston proved, through its blackening of silver chloride, that ultraviolet radiation existed. Progress was more rapid in the ultraviolet region for a time because light of this wave length region could be detected and its intensity determined photographically. By 1860 serious investigations of ultraviolet absorption spectra had been carried out, and absorption curves for such important compounds as benzene had been measured.

The first important work on the infrared absorption spectra of organic compounds was that of Coblentz in 1905. His research showed the immense possibilities of infrared absorption spectra as a means of identifying organic substances. It was thirty years before industrial chemists made use of the method he developed. During this time theoretical physicists who desired infrared data to use in calculating molecular structures improved the apparatus used in measuring infrared absorption to the point where such measurements could be made by automatic recording instruments; this development increased the speed and reduced the labor involved.

This same period saw greatly improved methods of measuring ultraviolet absorption. At first they were all photographic. Such methods were slow and not so precise as might have been desired. Nevertheless, ultraviolet methods proved to be a valuable aid to the organic chemist in fields of research such as vitamins and hormones. The development of the modern photoelectric cell about 1930 made possible more rapid and accurate measurements of ultraviolet intensity than could be made photographically. The high-intensity low-voltage hydrogen arc, developed about this same time, furnished a source of continuous ultraviolet radiation which could be maintained constant in intensity. These two electronic developments made possible the photoelectric ultraviolet spectrophotometer.

One of the most used, commercially available instruments of this type is the Beckman photoelectric quartz spectrophotometer made by National Technical Laboratories, South Pasadena, Calif. This instrument permits absorption measurements to be taken manually over the wave length range from 2,200 to 10,000 Å. by means of interchangeable photoelectric cells and light sources. Instruments of this type are used for many purposes, running the gamut from vitamin A analysis to the determination of benzene and toluene in special petroleum distillates or of butadiene in mixtures containing saturated hydrocarbons. For control of plant operation, National Technical Laboratories can supply this instrument in the form of a recording spectrophotometer. This form of the instrument, shown in Figure 1, will continuously record the percentage transmission of flowing samples of gases or liquids at any one wave length. This modification was developed for continuous analysis of butadiene streams but is equally applicable to many other materials having ultraviolet absorption.

For some purposes an abridged ultraviolet spectrophotometer can be used. A number of the larger chemical companies have constructed instruments of this type to meet their particular needs. Some of them are recording instruments used to control process streams; others are portable instruments for measuring the concentration of toxic solvent vapors in connection with safety programs.

Absorption measurements in the visible range are less important for analytical purposes than in either the ultraviolet or infrared. Along with spectral reflection measurements, they are used chiefly to control the color of products which have close color specifications. The General Electric recording spectrophotometer is widely used to match colors of plastics, paints, dyes, ceramics, and other such products.

Infrared absorption methods are useful in the analysis of organic mixtures. The two instruments most used for routine control work are the Perkin-Elmer Model 12-A (Figure 2) and the New Beckman Model IR-2, which is similar in appearance to the Beckman ultraviolet instrument shown in Figure 1. Both of them can be obtained with thermionic amplifiers in place of the high-sensitivity galvanometers formerly used. This feature is almost a necessity, as anyone who has tried to use galvanometers in an industrial plant can testify. The Gaertner Instrument Company manufactures a larger instrument than these two, which is usually classed as a research instrument. Many examples of complex analyses which can be accomplished by infrared methods have been given in the recent literature. Here we are not too interested in these spectacular achievements; they are overshadowed by the fact that instruments of this type are suitable for recording the absorption of continuously flowing samples (*Continued on page 78*)

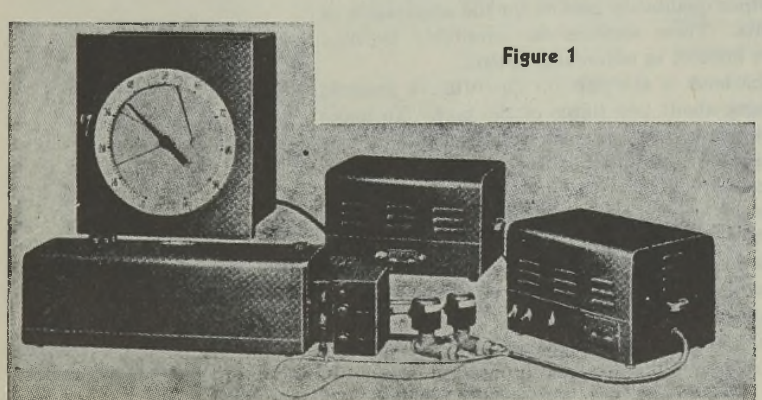


Figure 1

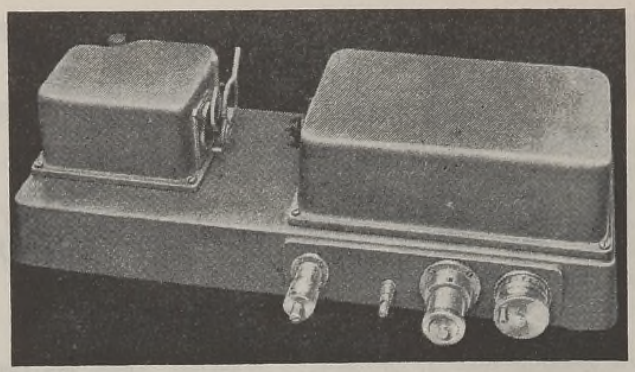


Figure 2

in an industrial plant. Only a few years ago it was thought necessary to locate equipment such as this in a subbasement to achieve constant temperature and freedom from vibration. Perhaps it should be added that applications of this kind must be carefully chosen if satisfactory results are to be obtained.

In the infrared, too, it is possible to construct an abridged spectrophotometer which is less expensive than the complete spectrophotometer. A device of this type may be as satisfactory as a more expensive full spectrophotometer in certain instances. A. H. Pfund, of Johns Hopkins University, has described such an instrument in *Science*, Volume 90, page 326 (1939).

The foregoing indicates that, while most of us think of spectrophotometers as laboratory devices, the trend is to make more use of them in control laboratories and even to utilize them for recording and controlling concentrations of important compounds in industrial processes. This type of use is so new that it is impossible to predict how successful it will become. In any event, such methods should furnish a valuable addition to the measuring and control means already available.

A book was recently published that is a "must" for those active in automatic control work. Ed Sinclair Smith, a research engineer with Bendix Aviation Corporation, is the author of "Automatic Control Engineering" (McGraw-Hill Book Company, Inc., New York, price, $4.00). To quote from the foreword: "Control engineering is not an easy subject, and it has not been made easier by the fact that its literature has been widely scattered in an occasional text, in periodicals, handbooks, society transactions, and in the foreign press." Smith's book will help make it easier to acquire a knowledge of control engineering, if not by the clearness and lucidity of its exposition of the subject, at least by furnishing a complete text on the subject.

After a brief introduction to the art of control and a short section on terminology, the author begins a descriptive treatment of control. This section gives an idea of the properties of meters and controllers and of plants to which they may be applied. It is followed by another qualitative section on the application of regulators to plants. These sections can profitably be read by anyone with an interest in automatic control.

The kernel of the book is the part on quantitative analysis of control, comprising about two thirds of the text. To make use of it, the reader must have a good command of different equations. Because the author realizes that many of those interested in automatic control have allowed the mathematics they once knew to become rusty, two appendixes review the mathematics of transients as well as methods for solving differential equations. In addition, there are appendixes containing mathematical tables, a review of basic physics, and a bibliography on control and notes on selected references. The amount of material included in the appendixes is unique; this feature will greatly help those seriously interested in the book.

Current Developments in PLANT MANAGEMENT

The foreman nowadays looks to management for help and advice. To have knowledge of how he regards management is essential if he is to receive the assistance needed.

Discussed by Walter von Pechmann

WE SPEND considerable time in learning what goes on in the mind of the average employee, but we are inclined to neglect the lower supervisory personnel in this respect. This applies especially to the foreman, with a long and satisfactory record of service, who is known to cooperate with and support management. It would be unwise to take for granted that this man is not subject to changes. If we lose intimate contact with him, his interest in the work will suffer and he will become less efficient. It is a question as to whether all the foremen who are considered unable to keep up with present-day conditions are really old-fashioned; the fact that they cannot manage well can easily be the result of dissatisfaction caused by management's apparent lack of interest in their problems.

The following discussion is presented in an endeavor to benefit the nonacademically trained, supervisory personnel in our industry by presenting problems that confront the shop foreman and suggesting possible remedial measures.

The foreman in the chemical plant holds a unique position in industry. Because of the specialized training he has received, he cannot change from one job to another without difficulty. He is usually, therefore, a steady employee and expects to be given an opportunity to reach the highest position for which he considers himself qualified. Consequently we find him, in most cases, a man who prefers growth in his field of work to an increase in pay. This knowledge is important because the hesitation of a foreman in accepting a promotion should not necessarily be interpreted as unwillingness to take on additional responsibilities; he may not be able to see where the job offered him will finally lead.

Another circumstance which applies especially to the foremen in the chemical industry is the gap between him and his superior. Although it is important to recognize this, it should not cause undue alarm. The gap is there because the foreman has difficulty in acquiring the basic knowledge requisite for a technical discussion of shop problems. Conscious of this handicap, he is inclined to be sensitive; we may, therefore, find him taking a well-meant explanation in the form of a chemical formula as a display of superior knowledge. He may also think that such an answer is an attempt on the part of the chemist to find an easy way out of an argument. It is advisable to keep the above in mind because friction—although it may be insignificant and unintentional—is inclined to break down a good relationship with his employer.

Foreman Status

Present-day conditions have changed the status of the foreman in the chemical industry more than is generally realized. In addition to increase in work, labor shortage, and, possibly, the need for supervising manufacturing processes with which he is not quite familiar, he is confronted with the fact that his authority has been restricted by government regulations and labor agreements. His job has become more vulnerable because the consequences arising from passing wrong judgments have become more serious and may even cause labor difficulties throughout the organization; he also knows that management may be held liable by government and organized labor for wrong decisions he may make. It is therefore not surprising that he has a tendency to lean more heavily on management. One of the foreman's greatest problems today is to determine to what extent he can do this without jeopardizing his position. In the absence of a clear understanding with management as to his authority, he may make decisions which should be left to management or he may refuse to pass judgment on matters which are considered to be within the scope of his duties.

We may also find him vacillating from one extreme to the other in order to feel his way out. Everyone familiar with production will agree that no strict line can be drawn between where the foreman's right to make decisions ends and where management should take matters into its own hands. Management, however, can guide the foreman by setting certain limits when new instructions are issued and can supply him with information stating the phases of business over which the foreman definitely has no control. It can also hold foremen's meetings or issue written company policies. Whatever the case may be, the foreman considers it management's duty to let him know how far he can go and feels that he should not have to feel his way to determine the extent of authority management wishes him to assume.

Foreman Complaints

The importance of accurately evaluating the foreman's knowledge of company affairs cannot be stressed too much. The fact that the foreman is considered part of management and has to execute management's wishes does not necessarily imply that he knows the reasons why management issues instructions. He expects to be supplied with enough facts to be able to explain intelligently to the workers why he has to put a new instruction into effect. (If executives would realize how much foremen resent being given explanations which are meaningless, we would not so often see instructions which start with phrases such as "It has become necessary".) Some examples follow of foreman grievances which can arise if we overestimate the foreman's knowledge in company affairs:

1. Foreman complains that a procedure which worked satisfactorily for years in his department has been replaced by another procedure, and no improvement can be noticed. Management assumed the foreman knew that the standardization of certain procedures throughout the plant has made it necessary to change the procedures in some departments.
2. Foreman believes that management is not interested in savings because a suggestion he has made and had approved, has not been put into effect. Management assumed the foreman knew that, to put the suggestion into effect, it would be necessary to obtain material which requires a priority application. The material would, in all likelihood, not be obtainable for three months.

(*Continued on page 84*)

Plant Management

These and similar situations cannot be entirely avoided, especially under present conditions of greatly increased demands on production executives. Nevertheless, the foreman's desire to be kept informed of company affairs should not be treated lightly.

Foreman Problems

The most difficult problems for the foreman to solve deal with employee discipline, promotions, and privileges. These problems are difficult to solve because they require judgment based on something rather intangible, such as knowledge of human nature, tradition, and the application of common sense. It would be wrong, however, to conclude that the foreman who hesitates to solve these problems by himself lacks self-confidence; before coming to such a conclusion, it seems advisable to make sure that the foreman's hesitation is not caused by fear that management will make a concession at his expense if trouble arises. In fairness to the foreman, we must admit that grievances can be settled, with little embarrassment to management, by admitting that the foreman's judgment was not entirely sound or that he may have misunderstood the instructions which were issued. Concerns which make use of this convenient way to maintain good relations with their workers, regardless of circumstances, should not blame the foreman if he leaves to management all decisions which cannot be backed up by facts.

One of the problems not often mentioned is how the foreman can prepare himself for a better job. Because the facilities in the chemical industry for the foreman to improve himself in his line of work are limited, he looks to management for advice. The writer has been asked frequently if a course in chemistry is desirable. It is believed that the average foreman lacks the education to finish a course in chemistry which allows the application of the knowledge gained to his work. In fact, it has been found that the application of a little knowledge in chemistry to the job will do more harm than good. Magazines of the chemical industry cannot be recommended for study because they are designed to satisfy academically educated personnel. It is believed that the desire of the foreman to improve himself could be served most successfully by a magazine written exclusively for him. This magazine would also serve thousands of young workers who want to prepare themselves to be supervisors or foremen.

It would give our foremen a more official recognition of their job and an opportunity to exchange viewpoints with associates in other plants. Management, without doubt, would benefit by such a publication because it would gain more knowledge of the foreman's way of thinking. The writer would appreciate the reaction of production chemists to such a plan.

Foreman Knowledge

One further thought may be of benefit to the chemist or chemical engineer who enters production. It is often surprising to see how years of experience in the field of chemical manufacture can compensate for a lack of education in chemistry. The writer has seen foremen who have detected conditions in need of correction a long time before a chemical analysis or a physical test revealed this fact; he also has seen foremen take corrective measures which ordinarily would require a thorough knowledge of chemistry. It is a good policy for the chemist to listen to the experienced foreman and to realize that his inability to express himself clearly, in chemical terms, does not mean that he cannot contribute to the solution of manufacturing problems caused by chemical changes.

Last-Minute Flashes
FROM THE EDITOR'S DESK

BACK on the short list are fats and oils, and latest reports indicate that the 1944–45 output will show a decline of at least a billion pounds from the all-time record of last season. Such a drop would not be serious under normal conditions, but Lend-Lease is taking huge quantities and will require further increases as the United Nations move deeper into Hitler's fast-disappearing *Festung Europa*. Lard, shortening, and salad and cooking oils moved back on the rationing list on January 22.

★ With little difficulty this month's column could be filled with tales concerning present and impending shortages. Rayon yarn quotas for military use are being raised substantially, and the civilian outlook is far from bright. Well-informed sources have reported that the military and civilians split 50-50 in 1944, but for 1945 military requirements will requisition at least 60% of the over-all total. Greatest emphasis will be on viscose employed in making high-tenacity yarns for tires, parachutes, and cargo and flare chutes. Military demands will also cut into spun rayon and acetate yarn, heretofore little affected.

★ Seizures of drug shipments in violation of the Food, Drug and Cosmetic Act increased from 408 in 1943 to 586 last year. The report of Commissioner Paul B. Dunbar of the Food and Drug Administration attributes breakdowns of control, such as excesses and shortages in active ingredients, substitutions, and other failures to meet standards, in part at least, to the loss of highly trained employees essential to drug manufacture and packaging.

★ The petroleum industry is now on record that the stepped-up demand for rockets and shells threatens war-necessary expansion of drilling, the bottleneck being lack of steel. Industry spokesman William R. Boyd, Jr., estimates that there will be only enough steel available to drill 3400 wells in the second quarter of this year instead of an anticipated 6900. He paints a black picture of petroleum shortages if relief is not given promptly.

★ Do you know that the technical facilities of the Bureau of Mines are available to all industrial and commercial consumers of fuels through a volunteer organization of about 10,000 combustion engineers, coordinators, and "waste chasers" throughout the country? This organization was started in an effort to eliminate waste, in the generation, transmission, and utilization of heat energy during the critical shortage of solid and liquid fuels. Bureau scientists are assisting in combating destructive corrosion in thousands of boiler plants operated by the War Department.

★ Latest effort to extend the supply of feed for livestock are experiments in the utilization of vegetable leaves found as waste materials in great abundance of food processing plants. It has been estimated that 4 million tons of these materials are available for use should the need for feed become critical. Experiments are said to show remarkably high food values, and chickens raised on a diet containing processed broccoli leaves had a better weight record than chicks raised on standard diets.

★ The oil industry, whose objections stymied the Anglo–U. S. agreement, is reported, as we go to press, to have reached an agreement with the State Department on a revised pact. Now the new treaty will be discussed with the British.