FIRST NATIONAL SYMPOSIUM ON ORGANIC CHEMISTRY

Held at Rochester, N.Y., December 29-31, 1925

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(obtained from Frank C.Whitmore, Evanston, Ill.)
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The Synthesis of Dihydrohydnocapric Acid, Dihydrochaulmoogric Acid and Homologues of these Acids	Roger Adams
The Causation of Certain Organic Reactions at the Surface of Solids	Homer Adkins
Sterols Occurring in Plant Fats	R.J.Anderson
Researches in the Thiazole Group	Marston Taylor Bogert et al.
Certain New Developments in the Chemistry of Free Radicals	James B. Conant
The Action of Alkalies on d-Galactose	Wm.L. Evans and G.P.Hoff
The Chemical Unsaturation of Rubber under the Action of Heat, Trichloracetic Acid, Ultraviolet Light and Mastication	H.L.Fisher and A.E.Gray
Carboxyllic Acid, Carbazyllic Acids and Carboxazyllic Acids	E.C.Franklin
The Directive Effect of the Phenol Group in the Preparation of Ketone Derivatives of Beta-Naphthol	A.J.Hill and R.N.Evans
Synthesis of Autoaldizable compounds of Biochemical Interest Containing Sulfur in Thiopolypeptide Combination	Treat B.Johnson
The Melting Curve as a Criterion of Purity of Organic Compounds	John Johnston
Dissociation in the Methylated Sugars	W.Lee Lewis and E.L.Gustus
Some Configurational Relationships	P. A. Levene
Acetylene Reactions, Mostly Catalytic	J.A.Niewland
The Opportunities for Reseach in Aliphatic Chemistry	James F.Norris
The Preparation of Arsonic Acids	C.S.Palmer
The Effect of Oxidants on Cellulose	John L.Parsons
The Oxidation of Hydrocarbons by Air at High Temperature and Pressure	E.Emmet Reid
The Dissociation of -Onium Structure	R.R.Renshaw
The Chemistry of Wood Cellulose	Louis E.Wise

THE SYNTHESIS OF DIHYDROHYDNOCARPIC ACID, DIHYDROCHAULMOOGRIC ACID AND HOMOLOGUES OF THESE ACIDS

by Roger Adams

For the past 300 years it has been known among the natives of India and China that chaulmoogra oil had a beneficial effect in the treatment of leprosy. The victims used the oil on the lesions and in addition took as much as possible orally. Unfortunately, the oil is very irritant to the intestinal tract so that in general the oral dosage could not be pushed to the curative point. It was not until 1899 that medical men made a scientific study of chaulmoogra oil. Tourtoulis attempted subcutaneous injection and, later, intramuscular injection of chaulmoogra oil in 1899. This was a painful procedure, and the oil was only very slowly absorbed.

In order to overcome this difficulty, a variety of mixtures of chaulmoogra oil with other oils or chemicals were made with the object of producing a less viscous preparation which was more readily absorbed. Perhaps the mixture most frequently used during the years, 1900-1915, was that suggested by Heiser, which consisted of 30 parts of chaulmoogra oil, 30 parts of camphorated oil, and 4 g. of resorcin.

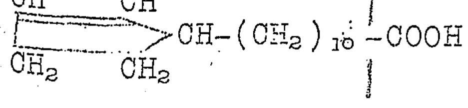
During this same period of development Dr. Rogers in India made a thorough study of the use of sodium salts of the mixed fatty acids of chaulmoogra oil first administered orally and later injected subcutaneously and finally intravenously. The last procedure proved to give excellent results and is one of the treatments now commonly employed in the far eastern countries

In 1918 Hollander and Dean used for the first time the ethyl esters of the mixed acids occurring in chaulmoogra oil, injecting them subcutaneously and later intramuscularly. This treatment was supplemented by the oral use of the free fatty acids. Good results have been obtained, and the use of these ethyl esters has proved to be one of the most satisfactory ways of treating leprosy.

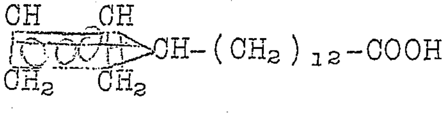
In 1920 Walker and Sweaney studied the bactericidal effect in vitro toward leprae bacilli of the sodium salts of the acids occurring in chaulmoogra oil, singly and mixed. He was able to show that both chaulmoogric and hydnocarpic acids in the form of their sodium salts were specific and that the latter was more effective than the former.

Very recently Dean has used ethyl dihydrochaulmoograte clinically with apparent success, the use of these esters having the distinct advantage of not causing such painful irritation on injection as is accompanied by the injection of ethyl chaulmoograte.

From a chemical standpoint a careful study of chaulmoogra oil was made by Power and collaborators in 1904-1907, and the chaulmoogric and hydnocarpic acids were isolated and studied. A constitution for each was proposed. Recently Shriner and Adams have modified the conclusions of Power somewhat and have shown that the hydnocarpic and chaulmoogric acids are not tautomeric.



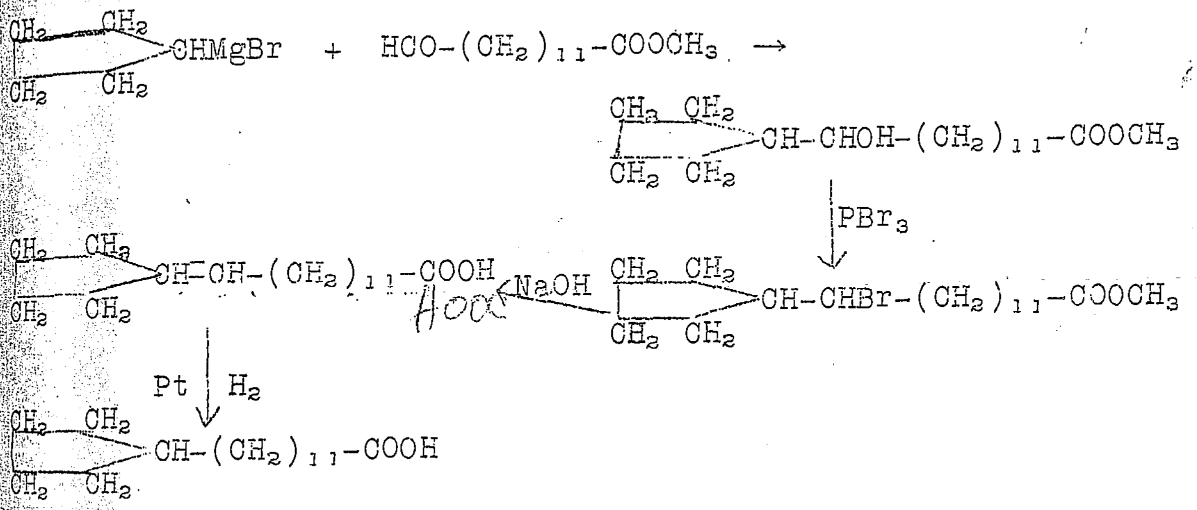
hydrocarpic acid



chaulmoogric acid

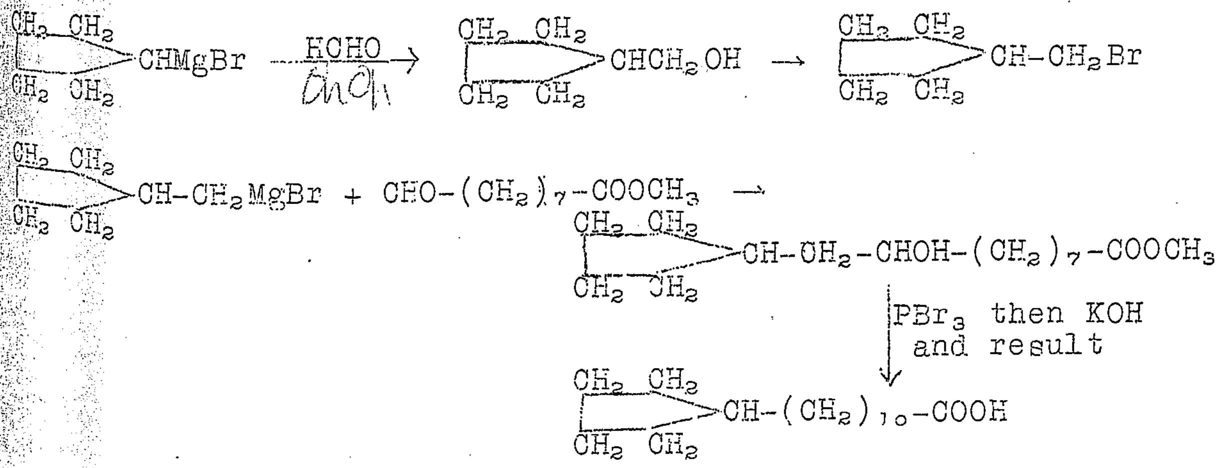
The second phase of the work has been the synthesis of dihydrochaulmoogric and dihydrohydnocarpic acids obtained by reduction of the natural products. The procedure followed for the synthesis of the dihydrochaulmoogric acid may be shown best by the following series of reactions:

$$CH_3(CH_2)_7-CH{=}CH-(CH_2)_{11}-COOCH_3 \xrightarrow{O_3} CH_3(CH_2)_7CHO + HCO-(CH_2)_{11}-COOCH_3$$



The synthesis of the dihydrohydnocarpic acid may be shown by the following series of reactions:

$$CH_3-(CH_2)_7-CH{=}CH-(CH_2)_7-COOCH_3 \xrightarrow{O_3} CH_3-(CH_2)_7-CHO + CHO-(CH_2)_7-COOCH_3$$



The Synthesis of Dihydrohydnocarpic acid, etc. (conc).

Other synthetic compounds homologous to dihydrohydnocarpic and dihydrochaulmoogric acids have been made and also acids of high molecular weight with other types of ring in the omega position. Some of these are bactericidal to leprae bacilli.

THE CAUSATION OF CERTAIN ORGANIC REACTIONS AT THE SURFACE OF SOLIDS

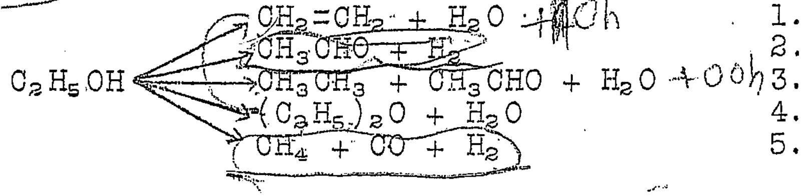
by

Homer Adkins

In explanation of the title of my paper perhaps I ought to say that I like to use the phrase, "Causation of reaction," for two reasons. One of them is that I feel it expresses the true function of the catalyst, and the other is that thereby I can usually arouse some physical chemist of the Ostwald persuasion, who believes that all reactions are going all the time, and that the function of the catalyst is to increase the rate of one or another of these going reactions.

Since most of us like to convince at least ourselves that we are working on a really fundamental problem, I should like to point out that there are only one or two reactions that are at present accepted as being unimolecular, and that, presumably, all the rest are contact reactions in which catalysis may well play a part. I have never been able to see any fundamental difference between those reactions that involve two "liquid" molecules or two "gas" molecules or two "solid" molecules or some combination of these phases. I was, of course, very much pleased to hear Dr. G. N. Lewis say at the Washington meeting that neither could he. Hence, I feel that, although the sort of reactions which we are at present considering, i.e., of a gas over a solid, are not common among organic reactions; yet a knowledge of the fundamental factors involved in these reactions will be of value in esacping from our present abysmal ignorance of organic reactions.

We were led into this line of investigation because we wanted to study the factors which determine the ratio of products resulting from simultaneous reactions. I should like to recall to your minds, by the use of a figure, five of the independent or primary reactions which ethanol may undergo at the surface of a solid catalyst.



$C_2H_5OH \rightarrow CH_2{=}CH_2 + H_2O$ 1.
$C_2H_5OH \rightarrow CH_3CHO + H_2$ 2.
$C_2H_5OH \rightarrow CH_3CH_3 + CH_3CHO + H_2O$ 3.
$C_2H_5OH \rightarrow (C_2H_5)_2O + H_2O$ 4.
$C_2H_5OH \rightarrow CH_4 + CO + H_2$ 5.

The question is:- Why does ethanol over copper give reaction 2, over alumina 1 or 4, or both, over titania 1, 2, and 3, over iron oxide 1, 2, 3, and 5, over nickel 2 ~~and 5,~~ and over zinc oxide 1 and 2? For the sake of brevity and clarity I shall confine my discussion this morning to a consideration of the reactions of the alcohols over zinc oxide, although what I have to say is borne out by studies of the reactions of aldehydes, esters, acids, and ethers, as well as of alcohols over not only zinc oxide, but over iron oxide, titania, and alumina.

There are certain points upon which most workers in this field are agreed:

1. There is a chemical compound formed between the alcohol and the catalyst. Some prefer to call it an absorption compound, but, since chemists have been willing to refer to, as chemical compounds, substances bound together in so diverse ways as are sodium chloride, sucrose, and hydrated copper sulfate, I see no reason why one should hesitate to refer to a

compound of alcohol and zinc oxide as being chemical. For in sodium chloride we have a substance that certainly does not exist in molecular form while in the solid state and perhaps does not even in solution. In the case of sucrose we have a molecule of the definite architecture and linkage so characteristic of organic compounds, while no one has yet presented a conclusive picture of the relationship between salts and their water of hydration.

2. We are agreed that only a small portion of the atoms or molecules of the catalyst are concerned or are active in this compound formation. Many otherwise intelligent and logical chemists have spoken of these as being "indefinite compounds," because no one has ever yet gotten out a compound of, say, zinc oxide and alcohol and analyzed it to a definite formula.

Since the great majority of the zinc oxide molecules are located beneath the surface of the solid, and since only a few even of those on the surface are free to combine with alcohol, it is not surprising that a gram of zinc oxide will combine with, perhaps, only a milligram of ethanol, and so analysis of the whole mass would yield anlaytical figures of small significance. We can only measure the extent of formation of these "reactant-catalyst" compounds by measuring the adsorption of gases, noting the decrease in volume during adsorption.

3. We are agreed that only a portion of the centers active for compound formation are active in catalysis. That is to say that total adsorption measurements do not tell the

whole story of catalytic activity.

Four hypotheses have been advanced to account for the fact that different catalysts produce different reactions or different proportions of reactions. In brief, these hypotheses are as follows:

1. The oldest hypothesis is that copper produces dehydrogenation and alumina dehydration because copper forms one kind of a compound and alumina another. This would necessitate that there be two zinc oxide-alcohol compounds, three titania-alcohol compounds, and four ferric oxide-alcohol compounds. It would lead one to expect that the proportion of reactions would be unvarying for a given oxide, which we know to be untrue. This hypothesis is so impossible that it is not worth serious consideration.

2. The hypothesis was advanced some eight or nine years ago that copper absorbs hydrogen; hence, it would split hydrogen out of a molecule of alcohol; and that alumina adsorbs water; so it would produce dehydration. This hypothesis fails to coincide with most of the facts ascertained since its promulgation and is disowned by its parent, Dr. Bancroft.

3. Dr. Langmuir in 1916 suggested that, when a molecule was adsorbed on a catalytic surface, the arrangement of the electrons or of their orbits was modified so that the adsorbed molecule was more susceptible to reaction. I have suggested a development of this hypothesis to cover the cases where a single molecule is broken up in different ways on the same or on different catalysts. Simply expressed, the idea is as follows: When a molecule is being adsorbed on a surface, it will be under

strain exerted by those active points on the catalyst which are within molecular distances. The precise distance between these active points will determine the direction and extent of the distortion of the electronic orbits of the adsorbed molecule. Different spacings of the active points might then result in different reaction products, just as the shape of the fragments of a piece of paper would be determined by the relationship in space of the two hands which tore the original sheet.

Based on this idea a considerable amount of work has been done in the Wisconsin Laboratory upon the selective activation of catalysts. It has been considered that, when zinc oxide was made from zinc hydroxide, the size of the pore (i.e. distance between active points) left in the catalyst would be determined in part by the size and shape of the hydroxyl group which was eliminated in the preparation of the catalyst; that a different spacing would be obtained if an isopropoxy group was eliminated as from zinc isopropoxide, and that still another spacing would result is zinc carbonate was converted into zinc oxide by the elimination of carbon dioxide.

4. Dr. H. S. Taylor during the present year has presented evidence for believing that the atoms on the surface of a nickel or copper catalyst differ in their degree of unsaturation. He has suggested that our results in obtaining selective activation may have resulted from the production of molecules differing in their degree of unsaturation and from selective poisoning of the catalysts.

Before considering these theories further I should like to briefly present a few outstanding facts that have emerged from our experimental work.

1. The relative amounts of different alcohols entering into reaction at a given temperature are independent of the catalyst whether it be alumina or zinc oxide. In the case of the primary alcohols there is a definite temperature interval for equal activity.

2. The amount of material entering into reaction is a variable factor for different preparations of the catalyst. The temperature, concentration, and reagents used in precipitation, the length of washing, the temperature of drying, all affect the activity of the catalyst.

3. The proportion of competing reactions is not characteristic of any oxide or metal (Fig. 1), i.e. with zinc oxide prepared from different solid compounds, (hydroxide, carbonate, isopropoxide, etc.), the proportions of alkene from isopropanol varies from 5 to 88%, from isobutanol from 1 to 31.5%, and from ethanol from 10 to 20%.

4. The proportion of competing reactions is relatively independent of the structure of the alcohols as compared to its dependence upon the nature of the catalyst surface. The order of the primary alcohols is the reverse in "B" zinc oxide that it is in "A" zinc oxide. Ethanol and isopropanol are interchanged in "A" zinc oxide as compared to "C" zinc oxide.

5. The proportion of competing reactions is a constant for different preparations of an oxide catalyst provided it is obtained from the same solid compound.

Causation of Reactions at Surface of Solids (con.)

It is obvious from these results that there are two independent sets of factors with respect to catalysis. The one has to do with the amount of material entering into reaction, and the other has to do with the paths followed by the reaction. This important fact has escaped the attention of chemists because they were mostly concerned with inorganic reactions which more often follow a single path of reaction. We, of course, are far more interested in the factors which determine the ratios of the products than we are in the amount of material reacting, for the former is the important thing in organic processes.

With reference to Dr. Taylor's hypothesis, it may be said that there is no reason for predicting that the methods used in this laboratory for the selective activation of oxide catalysts would result in atoms or groups of atoms differing in their degree of unsaturation, while there is a very obvious connection between our method of selective activation and our hypothesis; in fact, the method was the direct result of the hypothesis. Even if variously unsaturated atoms were produced, the temperature used with the oxide catalysts would certainly result in rearrangement to less unsaturated states, which would result in changes in the ratio of the competing reaction. On the contrary, experience has shown that the relative rates of the reactions are quite constant for different samples of catalyst, and for long periods of use, while the activity which is dependent upon the number of active centers varies greatly under the same conditions. The more unsaturated centers would certainly be poisoned first, and this would result in changes in the ratio of reactions that have not been observed to anything like the extent that has been observed with respect to the activity. Dr. Taylor further suggests that the selective activation observed in this laboratory was really due to "selective poisoning." If this were true, it is hard to explain why the ratio of reactions is so constant a value as long as the catalyst is made from a certain solid compound, whil the activity of the catalyst is so variable for different preparations of the catalyst. This is, why is it that the ratio of alkene to hydrogen is so constant over different preparations of catalyst from zinc hydroxide, while the activity of the catalyst may vary 100%, depending upon the manner of precipitation of the hydroxide, the thoroughness of washing, and the temperature at which the catalyst is dried. These latter factors unquestionably determine the number of "active centers" and the amount of "catalyst poisons," but they do not affect except in a very minor way, the characteristics of the catalyst which determine the ratio of the reaction products.

A rather conclusive answer to Dr. Taylor's suggestion is the fact that alumina obtained through the action of water upon aluminum ethoxide in xylene solutions is identical in its catalytic properties with the alumina obtained by the action of ammonium hydroxide upon an aqueous solution of aluminum nitrate. Alumina obtained by the slow hydrolysis of <u>solid</u> aluminum ethoxide is a very different sort of catalyst.

I realize that a <u>real</u> organic chemist is likely to look with disdain upon reactions which involve the formation of simple gases that may be measured by the methods of gas analysis, and that the selective activation of catalysts here described may seem of little moment because more typical organic reactions of synthesis and condensations have not been described. I hasten to point out that we have achieved equally marked cases of selective activation for condensations involving the production of liquids with zinc oxide, with titania, and with iron oxide, but that we are not in a position to treat these more important reactions from a quantitative standpoint. I fear that this phase of the subject will not be discussed in the Journal but will be concealed under patents, as I am unable to personally follow up the work.

Before closing I should like to point out a conclusion from this work that seems of general interest. Numerous attempts are now being made to measure the relative tendency of groups of compounds to enter into a given reaction. For example, the ease of ring formation for each of three compounds is desired. It has been assumed that, if A gave a yield of 75% of the cylic compound, B of 50%, and C of 25%, these figures represented the relative ease of ring formation for A, B, and C. If the relation between the conditions of reactions and the proportion of products held in that case as they have been shown to hold in the case of reactions of the alcohols over zinc oxide, and the esters over alumina, then the conclusion as to relative tendency for ring formation would be false. For, if the ease of dehydration of ispropanol as compared with ethanol had been measured over a certain zinc oxide, then the conclusion would have been that ethanol is more readily dehydrated than isopropanol, which we know to be untrue. It is not safe then to determine susceptibility for a given reaction under conditions such that the product or reaction we are interested in is only one of two or more simultaneous reactions.

If I may be permitted to recapitulate the more important points made in this paper I would say:- that organic molecules react to form chemical compounds with the relatively few atoms or molecules of the catalyst which have sufficient residual affinity. The activity of a catalyst, as measured by the amount of material induced to react, is largely determined by the number of these centers active for compound formation. The relative reactivities of the members of an homologous series is the same on different catalysts, but the proportion of the reaction products is largely a function of the catalyst. There are thus two separate and distinct phases to the problem of catalytic reactions, the one having to do with the amount of material reacting, and the other with the ratio of the reaction products. The paths followed by the reaction are, to a large extent, determined by the spacial configuration of the active points, and this is determined by the solid compound and the methods by which it is converted into the active catalyst. We have long known that the spacial configuration was an important consideration in determining the reaction of an organic compound, and I believe that it is also of primary importance in determining the effect of a catalyst.

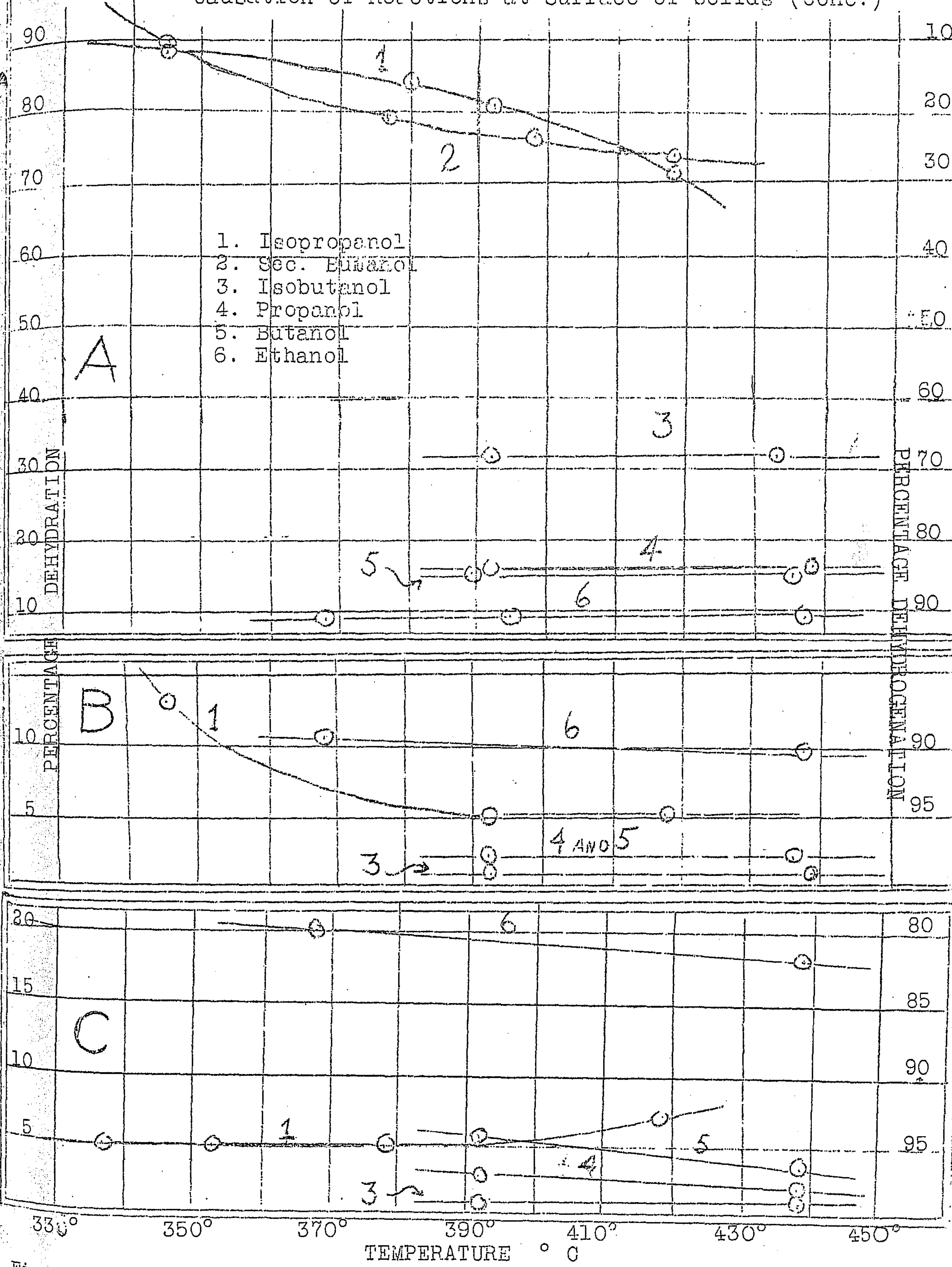


Fig. 1. The variation in the properties of alkene and hydrogen formed over three zinc oxide catalyst. All experimental work done by Dr. Wilbur A. Lazier.

STEROLS OCCURRING IN PLANT FATS

by

R. J. Anderson

In view of the physiological importance recently attributed to certain constituents of the unsaponifiable matter of plant fats, an investigation has been made of the sterols occurring in the fats extracted from some of the common grains, particularly corn, wheat, and rice. The results so far obtained indicate that the crystalline portion of the unsaponifiable matter consists of a very complex mixture. Higher aliphatic alcohols and hydrocarbons may be associated with the crystalline sterols, but, even when such compounds are absent, the sterols themselves present great complexity.

The sterols have in general similar properties, and apparently they form mixed crystals in all proportions. It is, therefore, very difficult to separate such a mixture into homogeneous compounds.

The fat extracted from rice bran contains the saturated dihydrositosterol, stigmasterol, and sitosterol, together with myricyl alcohol.

Different parts of the corn plant apparently contain several different sterols. From corn pollen we isolated a hydrocarbon, a phytosteryl palmitate, together with a high percentage of a mixture of optically inactive sterols. Corn bran contains a large proportion of dihydrositosterol, together with sitosterol, and a similar mixture occurs in corn endosperm. Corn oil derived from corn germ contains a complex mixture of sterols of which we have been able to identify only two, viz., dihydrositosterol and stigmasterol. Sitosterol is probably also present, but it is contaminated with the two compounds named above, as well as with other sterols not yet identified. The isolation of pure sitosterol from corn oil is, therefore, very difficult.

Wheat bran and wheat endosperm contain a mixture of sterols very similar to that occurring in corn and consists principally of dihydrositosterol and sitosterol. Wheat germ is stated to contain principally sitosterol. We have found, however, that a considerable proportion of dihydrositosterol also is present. Judging by the results that we have obtained, two or more sterols must be associated with sitosterol in American grown wheat germ, but these compounds have not yet been identified.

RESEARCHES IN THE THIAZOLE GROUP

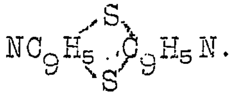
by

Marston Taylor Bogert and Co-workers

To date the thiazoles have attracted commercial attention in two directions only, namely, as dyestuffs and as accelerators for the vulcanization of rubber. A few possess agreeable odors, but as perfumes they are too weak to be of any industrial importance. Yet, if we consider their structure and properties, many interesting possibilities of usefulness in other directions also will appear.

It has been observed frequently that sulfur in cyclic union seems to be the equivalent of the -CH:CH- group in its effect upon many of the properties of the molecule. The similarity in the physical and chemical properties of the benzene and thiophene series is exhibited also by the thiazoles and pyridines, and by the benzothiazoles and quinolines. Thus, the reactivity of the methyl group in the α-, or 2-position, of pyridine or quinoline is duplicated by the methyl group in the μ-, or 2-position, of thiazole or benzothiazole; and cyanines, quinophthalones, etc. have been prepared from the latter. Other illustrations will appear in the discussion of some of our own results.

The purpose of our researches is to learn more about the chemistry of this interesting group, not alone for the development of the science itself, but with the intention of applying this knowledge to the synthesis of new products of service to humanity.

One important field of possible application is that of synthetic drugs. We are all familiar with the fact that sulfur, in various forms and combinations, has proven of therapeutic value, and Fraenkel, in a recent edition of his "Arzneimittelsynthese," states that sulfur in cyclic union, as in thiophene, ichthyol, etc., in addition to its antiseptic and antiparasitic properties, causes a marked increase in resorption, resembling iodine in this respect, although in no way similar to it pharmacologically. Cyclic sulfur compounds also show striking analgesic properties which can be ascribed only to the entry of sulfur into these molecules. Quinoline, itself a strong protoplasmic poison, when fused with sulfur gives the innocuous thioquinanthrene,  $\mathrm{NC_9H_5}\overset{S}{\underset{S}{<>}}\mathrm{C_9H_5N}$.

Further, with the exception of hot concentrated caustic, 2-phenyl-benzothiazole is remarkably stable to reagents, not being attacked readily by oxidizing or reducing agents. By concentrated or fuming acids, it can be nitrated or sulfonated, and with phosphorus pentachloride a monochloro derivative is obtained. Aluminum chloride, in carbon bisulfide solution is without action upon it. We believe that it is worth while, therefore, to attach to this stable nucleus some of the most potent of our pharmacophores and to compare the therapeutic properties of these new products with those of their benzene or quinoline analogs. The thiazoles, by the way, are much less stable than the benzothiazoles.

In addition to the synthetic drug line, our researches have had to do also with synthetic dyes and, to a limited extent, with the connection between odor and chemical constitution.

They may be classified under the following general headings:

I. Simple Thiazoles:

1. 2-Aminothiazoles
2. Thiazole dyes of Doebner Violet type

II. Benzothiazoles:

3. General methods of preparation
4. 2-Phenyl-benzothiazole and derivatives
5. 2-p-Tolyl benzothiazole and derivatives
6. 5-Methyl-2-(p-aminophenyl)-benzothiazole and derivatives
7. 6-Methyl-2-phenyl-benzothiazole and derivatives
8. 6-Methyl-2-p-aminophenyl-thiazole (Dehydrothio-p-toluidine) and derivatives
9. Thioflavines
10. Azo dyes
11. Chloramine Yellows (Colour Index No. 814)
12. Cyanines
13. Cinchophens (Atophans)
14. Arsonic acids
15. Odor and constitution

III. Polycyclic Thiazoles:

16. Benzobisthiazoles
17. Bisbenzothiazolyls
18. Phenylene bisbenzothiazoles
19. Primulines
20. Furyl benzothiazoles
21. Thienyl benzothiazoles
22. Selenazolo-benzothiazoles

1. 2-Aminothiazoles[1]

2-Aminothiazoles were prepared conveniently from the α-chloro derivatives of aldehydes or ketones, and thio-urea; a method employed first by Traumann[2] and by Popp[3]. The chloro derivatives used by us were dichloro ether (for chloro-acetaldehyde), chloro-acetone, and chloro-acetophenone, familiar lachrymatory war gases, which yielded as products 2-aminothiazole, its 4-methyl and 4-phenyl derivatives, all of which were known previously.

We can corroborate the experience of other investigators to the effect that the amino group in these compounds is not easily replaced through diazo reaction, the products being mainly tars with little or none of the compound sought. We found, however, that they could be used as couplers for diazotized aromatic amines, and prepared several new red azo dyes in this way.

2. Thiazole Dyes of Doebner Violet Type[1]

In 1888 Traumann[2] made the following statement: "In general, trithiazylmethane dyes appear not to exist, probably because the para position is lacking in the azoles. Thus, the joint oxidation of thiazylamines with methyl thiazylamine by the action of mercuric chloride, etc., likewise yields no trace of dye."

If the views expressed in the introductory portion of this paper relating to the equivalence of the sulfur and -CH:CH- groups in cylcic union are correct, the 2-aminothiazoles just mentioned carry their amino group in a position which is from this standpoint para to position 5. (Fig. I)

In support of this hypothesis we have succeeded in condensing these 2-aminothiazoles with aromatic aldehydes in the presence of hydrochloric acid (in its absence only the simple Schiff bases are formed) to monoaryl dithiazylmethanes, from which the corresponding carbinols and dyes have been obtained. Such condensations were accomplished also with 2-aminothiazoles carrying alkyls instead of aryls in position 4, thus proving that this condensation is not dependent upon an aryl group in that position, that a radical in such a position does not participate in the reaction, and that, therefore, the attachment of the aldehyde residue is in position 5, as predicted.

The aminothiazoles used in the experiments were those mentioned under 1.; the aldehydes were benzaldehyde, its p-chloro-, o-, m-, and p-nitro-, p-dimethylamino-, o- and p-hydroxy derivatives and piperonal.

That these leuco bases carried primary aromatic amine groups was evidenced by the production of azo dyes from them by diazotizing and combining with suitable couplers.

The leuco bases were generally colorless or yellowish, the carbinols (by oxidation with lead oxide in acid solution) red-black and the dyes (oxalates) green-black.

Compared with their triphenylmethane analogs, the leuco bases in both cases form crystalline addition products with benzene. Both groups of dyes form dark green crystals, the thiazoles being smaller, darker, and of less marked coppery luster. The Malachite Green dyes are easily soluble in water, the thiazole dyes less readily; addition of excess of ammonium hydroxide precipitates the carbinol in both instances as a dark solid. Both dye silk, wool, or tannined cotton a green, the thiazoles giving a bluer and duller shade and being tinctorially weaker. Both are fugitive in direct sunlight and both give red solutions in an excess of concentrated hydrochloric acid.

Although of Doebner Violet types, in the sense that the thiazole amino groups are unalkylated, the green shades produced probably represent the bathochromic influence of the sulfur present. Just as there is no very striking difference in shade between the dyeings obtained with Doebner Violet and that produced by its derivative carrying a dimethylamino group in the para position on the free phenyl nucleus, so here the shade is not greatly altered by using p-dimethylamino benzaldehyde in place of benzaldehyde in the initial condensation.

3. Preparation of Benzothiazoles

(a) Hofmann method. - For the preparation of our benzothiazoles we have used most frequently the method of Hofmann[4] with improvements suggested by Blanksma,[5] Wohlfahrt,[6] and Bogert and Snell,[7] for the production of the necessary o-aminophenyl mercaptan, or the corresponding disulfide. From these initial materials and suitable acid halides, anhydrides, esters, or aldehydes, benzothiazoles are obtained conveniently and in good yields. (Fig. 2)

Claasz[8] has claimed that the action of aldehydes upon the hydrochloric acid salt of o-aminophenyl mercaptan gave thiazolines and not thiazoles as reported by Hofmann.[9]

We[10,11] have repeated Claasz' work and checked the products against those obtained by other methods, and our results agree entirely with Hofmann's findings and are at variance with those of Claasz. If the thiazoline is formed at all in the reaction, its existence must be brief indeed, for the characteristic odor of 2-phenyl-benzothiazole is detected as soon as the mercaptan and benzaldehyde are brought into contact.

Instead of the aldehydes their chlorides ($R.CHCl_2$) may be used, but the yields are poor. On the other hand, neither the ketones nor their chlorides (R_2CCl_2) could be condensed with

The Thiazole Group

Fig. 1

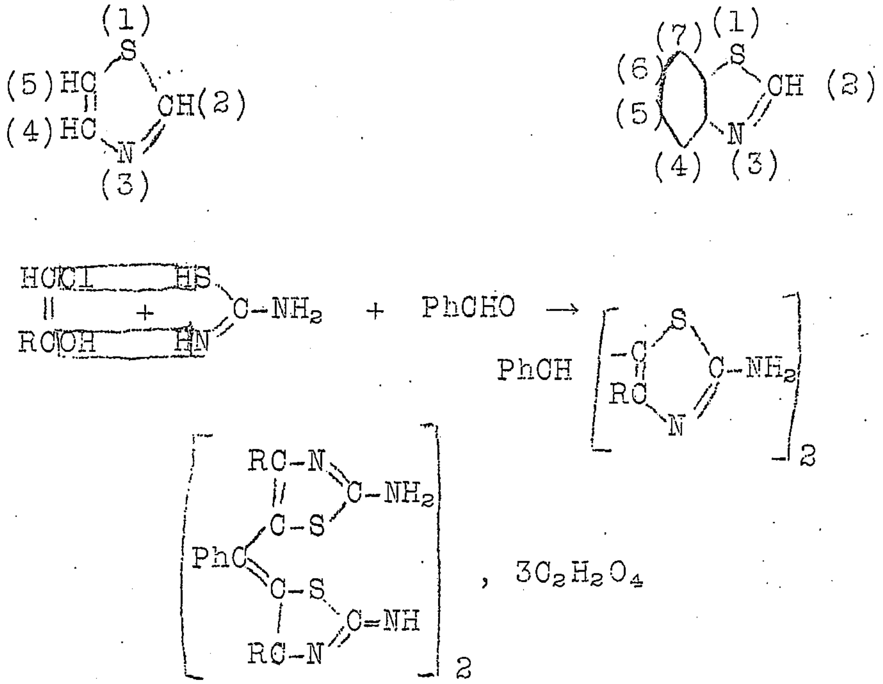


Fig. 2

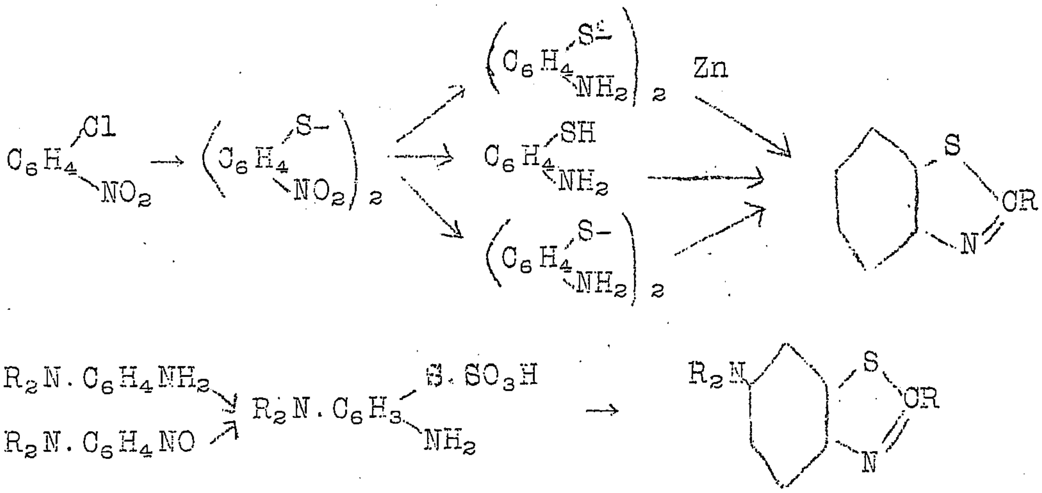
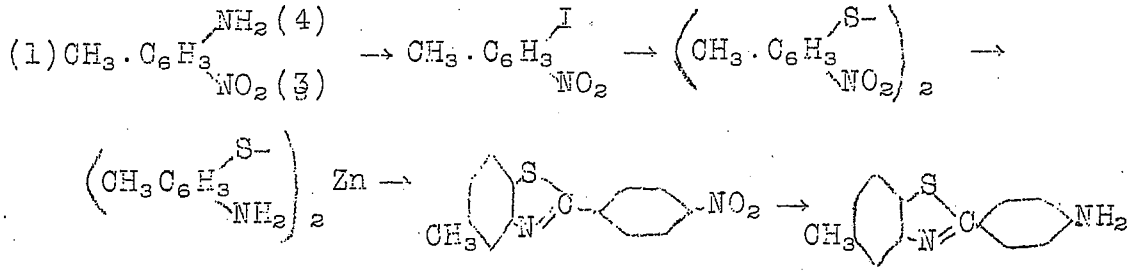


Fig. 3



the aminomercaptan.

(b) Method of Green and Perkin. - Green and Perkin[12], and more recently Heller, Quast and Blanc[13]; have shown how benzothiazoles can be obtained from aromatic amines by condensing their thiosulfuric derivatives with aldehydes, and we have taken advantage of this for the preparation of various amino benzothiazoles. It should be noted that here also the products are thiazoles and not thiazolines.

4. 2-Phenyl-benzothiazole and Derivatives

This interesting compound has been known for many years[14] and is the product of many reactions. It is generally prepared either from benzanilide[15], or benzal aniline[16], by fusion with sulfur. We prefer the latter or, still better, the action of benzoyl chloride or benzaldehyde upon the o-aminophenyl mercaptan or disulfide, as described already.

Derivatives.- We have prepared and studied many derivatives of this compound. One striking peculiarity is the relative unreactivity of the 2-phenyl group. Substituting elements or groups appear not to attack it but enter preferably in position 6 on the benzothiazole nucleus itself. Neither the Friedel Craft nor the Gattermann-Koch reaction could be carried out with it, as it was unattacked by the aluminum chloride.[17] Contrary to Hofmann's[15] statement, it is easily nitrated by fuming acid[14], the nitro group entering in position 6, whereas Naegeli[18] believed that he had shown it to be in the para position on the 2-phenyl nucleus. Not only a mononitro[17,19] but also a dinitro[19] derivative was obtained by direct nitration, while 2-nitrophenyl derivatives were secured through condensation with the corresponding nitrobenzaldehydes or nitrobenzoyl chlorides[7,19]. By reduction these nitro compounds yielded amines, from which acyl derivatives, Schiff bases, and azo dyes were prepared.

The position of the amino group in the 6-amino derivative was proven by its non-identity with the amino derivatives carrying the amino on the 2-phenyl nucleus, or with the 5-amino derivative[20], by its giving benzoic acid when fused with caustic alkali, by its coupling only once with diazotized p-nitro-aniline, and by the conversion of its benzal derivative (by fusion with sulfur) into the benzobisthiazole obtained by Green and Perkin[12] from p-phenylenediamine.

Hofmann[15] observed that phosphorus pentachloride reacted vigorously with 2-phenyl-benzothiazole with formation of a crystalline chlorinated product, which he did not investigate. Examination of this product[19] shows it to be the 6-chloro derivative, and we have obtained the same compound from the 6-amino derivative and by fusing benzal-p-chloroaniline with sulfur.

In acetic acid solution, 2-phenyl-benzothiazole takes up 4 bromine atoms with formation of an unstable addition product which loses bromine on standing, and when heated in dilute acetic acid yeidls 6-bromo-2-phenyl-benzothiazole, as proven by its synthesis from the 6-amino compound.[17]

This issimilar to the rearrangement of benzalaniline dibromide into benzal p-bromaniline.[21]

The unstable iodine addition product[17] contains but two atoms of iodine per mole of thiazole.

Like quinoline, it adds acetyl chloride readily in toluene solution, but the product is decomposed by water or by heat.[17]

The 2-o- and p-hydroxyphenyl derivatives[19] were prepared from the o-aminophenyl mercaptan and the appropriate aldehyde, the products again being thiazoles and not thiazolines. The 2-p-hydroxyphenyl and the 6-hydroxy-2-phenyl were obtained also from the corresponding amines,[19] and from the latter a nitro derivative, which was reduced to the amine.

By sulfonation of the 2-p-aminophenyl derivative[22] a sulfo acid has been obtained, but the position of the sulfo group was not determined.

5. 2-p-Tolyl-benzothiazole and Derivatives[23]

This was prepared by fusing p-tolanilide with sulfur and also by the action of potassium ferricyanide upon thio-p-tolanilide[24], the latter being a far better method.

A nitro derivative was prepared, which was reduced to the amine, and azo dyes produced from the latter.

By treatment with $KMnO_4$ the p-methyl group was oxidized to COOH, but the yield of acid was low.

6. 5-Methyl-2-(p-aminophenyl)-benzothiazole and Derivatives[25]

This synthesis is represented in Fig. 3. The product is of interest because it is an isomer of the well known dehydrothio-p-toluidine and possesses similar properties and possibilities.

7. 6-Methyl-2-phenyl-benzothiazole and Derivatives

The 2-p-nitro derivative was prepared from the zinc salt of the aminothiocresol and p-nitrobenzoyl chloride[22] and sulfo acids by elimination of the amino group (by diazotization) from dehydrothio-p-toluidine sulfo acids.[26] By the action of nitrous acid upon the latter there was obtained also a 2-p-hydroxyphenyl sulfo acid of the p-toluthiazole.[22]

8. 6-Methyl-2-(p-aminophenyl)-benzothiazole (Dehydrothio-p-toluidine) and Its Derivatives

The conditions for its production from p-toluidine and sulfur have been studied[23,26] and unsuccessful attempts made to prepare it from p-nitro[23,26] or p-amino-benzal[26] or p-amino-benzyl-p-toluidine[26] and sulfur. Although the latter method has been patented,[27] we have shown that the thiazole formed in this patented process probably originates from unremoved p-toluidine.

The best method of purifiying the crude product still remains the troublesome distillation under reduced pressure at the high temperature necessary. We have plotted its vapor pressure-temperature curve between 295 and 370° at 11-115 mm.

We have prepared it also by reduction of 2-(p-nitrophenyl)-p-toluthiazole[22] and made its benzal[23,26] and benzoyl[26] derivatives.

Since the dehydrothio-p-toluidine and primulines in the p-toluidine-sulfur melt are usually separated through their ammonium sulfonates, we have studied the sulfonation of dehydro rather carefully, obtained mono-, di-, and tri- sulfo acids, have shown that the first sulfo group probably enters the benzene portion of the benzothiazole nucleus, and the second one the 2-phenyl group, and plotted the solubilities of the ammonium monosulfonate over a considerable temperature range in dilute ammonium hydroxide solution.[26]

With carbon bisulfide the base reacts to form a symmetrical thio-urea, which when heated with aniline (or toluidines) in toluene solution undergoes an interesting rearrangement with formation of thiocarbanilide (or the toluidide) and regeneration of dehydrothio-p-toluidine[26]; but no iso-thiocyanate could be obtained from this thiourea by the action of phosphoric acid or sulfuric acid.

By the Skraup-König reaction the base yielded the corresponding quinoline, which added methyl iodide readily.[23]

9. Thioflavines

Since dehydrothio-p-toluidine is commonly manufactured in the form of a sulfo salt, the sodium sulfonate was heated under pressure with methyl alcohol and hydrochloric acid, and a dye obtained[26] resembling Thioflavine. It is doubtful whether the Cassella patent[28] covered this process, as the specifications fail to mention the use of any acid, and without it we obtained no dye.

The methylation of 6-amino-2-phenyl-benzothiazole yielded a dimethyl derivative but no thioflavine.[17]

Further work is under way in this field to learn more about the transition from a non-dyeing base like dehydrothio-p-toluidine to a valuable dye like Thioflavine merely by methylation.

10. Azo Dyes

Azo dyes have been prepared from many of the new amino thiazoles by the usual reactions, and it has been shown that thiazoles themselves may be used as couplers for diazotized bases.

Their preparation has been incidental and not a major purpose of our researches.

Perhaps the most noteworthy peculiarities observed in this connection are the resistance of certain of the diazonium salts to heat and the sensitiveness of others to light, as discovered by Green[29] in his pioneer investigations in this field. We found it necessary in the case of the diazonium chloride from dehydrothio-p-toluidine sulfo acid to boil 7 hours with 20% sulfuric acid to get the desired phenol.

11. Chloramine Yellows

(Colour Index No. 814)

A. Chloramine Yellow NN.- Uncertainty has existed as to whether this important dye was an azo color, a stilbene derivative, or a quinone type, since it is manufactured by the action of sodium hypochlorite upon dehydrothio-p-toluidine sodium sulfonate.

Its great resistance to reducing agents seemed unusual for an azo compound; its dyeings were not unlike those of certain stilbene dyes prepared from p-nitrotoluene sulfo acid; and its method of manufacture and deep color suggested the possibility of quinoid structure.

We believe that we have thrown some light upon the problem by the following experimental results:

(a) The synthesis of the dye by reduction of 6-methyl-2-(p-nitrophenyl)-benzothiazole (with zinc dust and sodium hydroxide) to the corresponding azo deriviative and sulfonation of the latter.

(b) A similar synthesis of the lower homolog, lacking the methyl groups but showing similar tinctorial properties and in which stilbene formation is excluded.

(c) The synthesis of the analogous 6-methyl-2-(p-hydroxyphenyl)-benzothiazole sodium sulfonate, alkaline oxidation of which gave no dye whatever, thus proving that the amino group was essential and that quinone formation was not involved.

The indications, therefore, are that the formula of the dye is as shown in Fig. 4.

B. <u>Isomer of Chloramine Yellow NN</u>.[25]- This was prepared from 5-methyl-2-(p-aminophenyl)-benzothiazole sodium sulfonate and sodium hypochlorite in exactly the same way as Chloramine Yellow. Physically, chemically, and tinctorially, the two are very much alike, so that it makes little difference whether the methyl group is in position 5 or 6.

12. <u>Thiocyanines</u>[23]

Some preliminary work was done on the formation of cyamines from the methyl iodides of dehydrothio-p-toluidine-quinoline and of quinaldine (+ potassium hydroxide), but this was discontinued upon the appearance of the work of Mills and his associates[30] upon the thiocyanines.

13. <u>Cinchophens (Atophans)</u>

(Fig. 5). According to Ciusa and Luzzatto[31] most of the peculiar physiological effect of Cinchophen (Atophan) is due to the 2-phenyl group, modifications of which are more apt to reduce its therapeutic value than similar changes in the benzene portion of the quinoline nucleus.

We have, therefore, prepared[17] various 2-phenyl-benzothi-

The Thiazole Group

Fig. 4

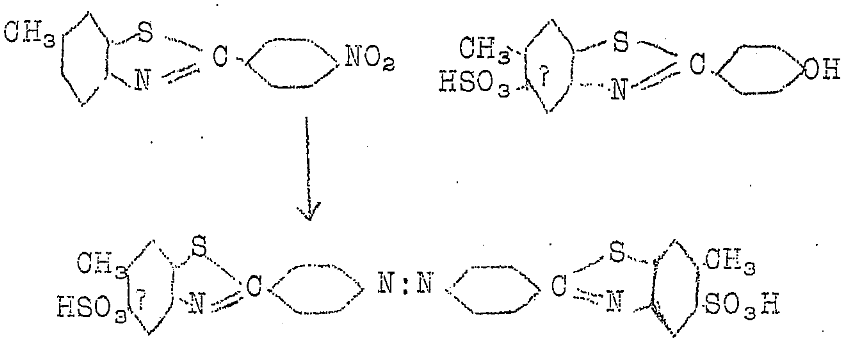


Fig. 5

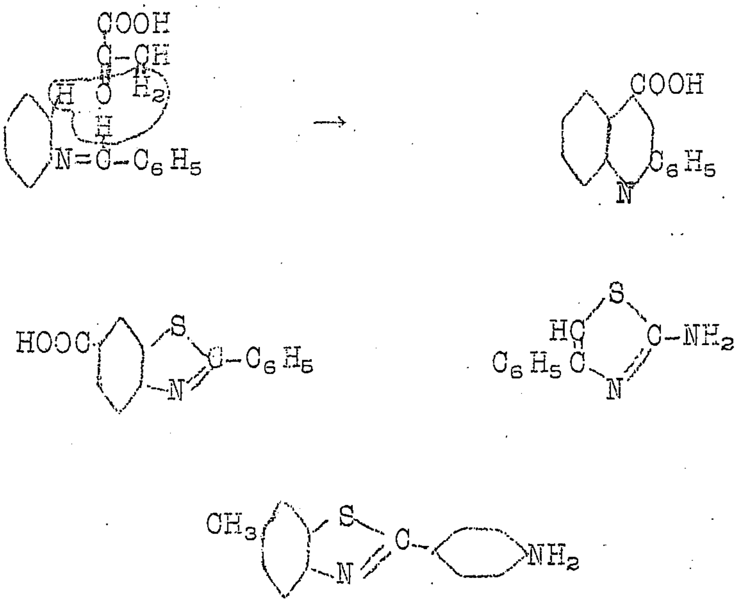
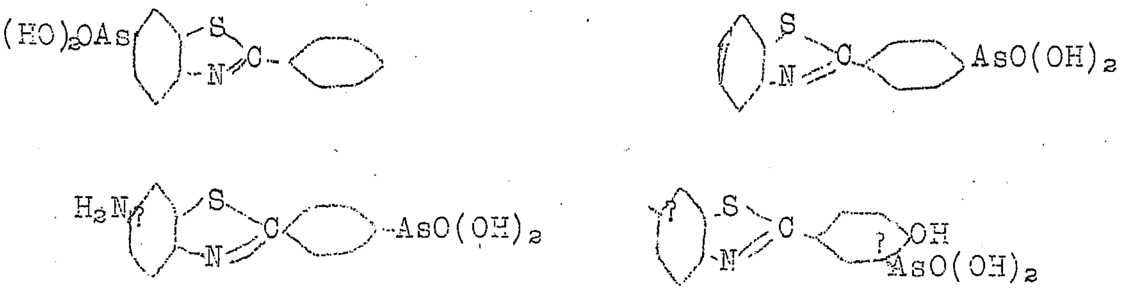


Fig. 6



azole carboxylic acids to compare their physiological properties with those of Cinchophen.

These have been prepared generally from the amino derivatives, via the cyanide, but not enough material has been accumulated yet for pharmacological examination, except in a preliminary way.

By condensation with benzaldehyde and pyruvic acid no cinchophen could be obtained from 4-phenyl-2-aminothiazole[1] or from dehydrothio-p-toluidine.[23]

14. Arsonic Acids[32]

2-Phenyl-benzothiazole arsonic acids have been prepared as follows (Fig. 6):

(a) From 6-amino-6-arsonic acid.

(b) From p-amino-arsonic acid.

(c) From p-arsonic acid → nitro derivative.

(d) From nitro-p-arsonic acid → amino p-arsonic acid.

(e) From amino-p-hydroxy → p-hydroxy arsonic acid.

Through the courtesy of Dr. A. E. Sherndal, of the H. A. Metz Laboratories, Inc., preliminary pharmacological tests have been carried out with some of these, and the results, especially in the case of (e), have been so promising as to justify the continuance and expansion of the research.

15. Odor and Constitution[33]

(Fig. 7). (a) 4-Phenyl-2-aminothiazole = faint but agreeable odor.

(b) Benzothiazole = unpleasant quinoline-like odor.

The Thiazole Group (con.)

(c) 2-Phenyl-benzothiazole = geranium or tea-rose odor.

(d) 2-p-Tolyl-benzothiazole = similar to (c), but fainter.

(e) 2-α-Furyl-benzothiazole = similar to (c), but fainter.

(f) 2-α-Thienyl-benzothiazole = similar to (c), but stronger than (e).

(g) 2-Vanillyl-benzothiazole = weak odor recalling that of vanillin.

(h) 2-Piperonyl-benzothiazole = weak odor recalling that of piperonal.

(i) p-Phenylene bisbenzothiazole = no odor (m. 263°).

(j) 2-Phenyl-benzoselenazole = similar to (c).

16. Benzobisthiazoles[17]

(Fig. 8). Prepared from the 6-benzalamino-2-phenyl-benzothiazole fused with sulfur. Identical with compound obtained by Green and Perkin[12] from p-phenylene diamine.

Mononitro and monoamino derivatives also were prepared, and these groups shown to be on the middle benzene nucleus.

17. Bisbenzothiazolyls[11]

(Fig. 8) ("Oxalamidothiophenol"). This was obtained easily and in excellent yield (60%+) by the interaction of oxalyl chloride and o-aminophenyl mercaptan. It has been obtained before by other workers, but in small amounts only and with considerable difficulty.

18. Phenylene-bisbenzothiazoles[11]

(Fig. 8). The p-compound was prepared from p-phthalyl

The Thiazole Group

Fig. 7

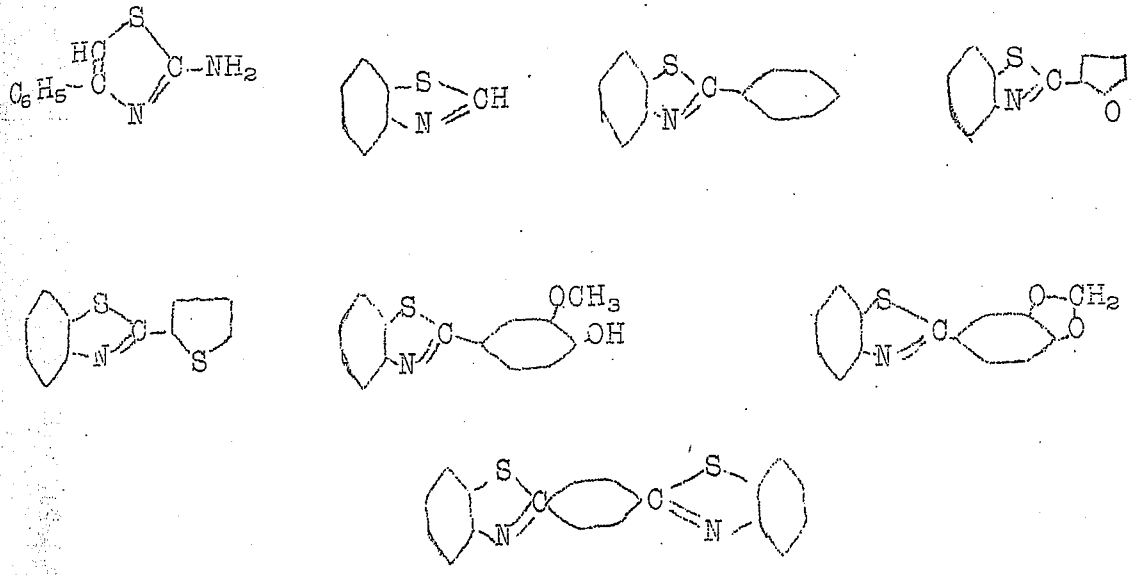


Fig. 8

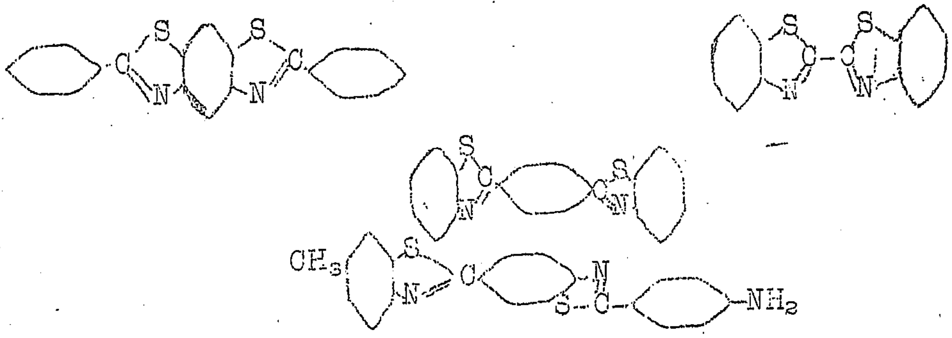
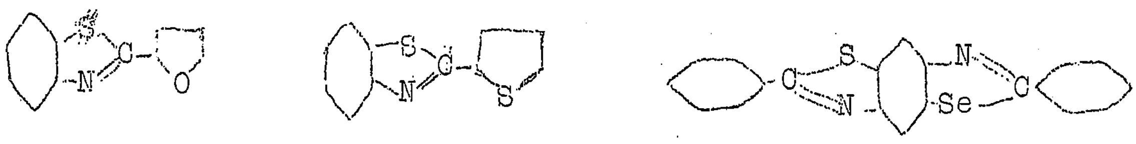


Fig. 9



chloride and o-aminophenyl mercaptan.

19. Primulines

(Fig. 8). This group of condensed p-toluidine-sulfur compounds was discovered by Green[29], but synthetic corroboration of the correctness of the formula assigned is still lacking.

Our preliminary experiments[26] to produce such structures by fusion of benzal- or benzoyl-dehydrothio-p-toluidine with sulfur were unsuccessful, but the investigation will be continued.

20. Furyl-benzothiazoles[10,11]

(Fig. 9). These were produced from o-aminophenyl mercaptan and fural, or pyromucyl chloride, or by the action of the latter upon o-aminophenyl disulfide followed by reduction.

21. Thienyl-benzothiazoles[11]

(Fig. 9). These were prepared by the action of α-thenoyl chloride upon o-aminophenyl mercaptan, or upon the disulfide and reduction of the product.

22. Selenazolo-benzothiazoles[34]

(Fig. 9). These are obtained more satisfactorily from the benzal-amino selenazoles and sulfur than from the benzal-amino thiazoles and selenium.

Bibliography

The researches summarized above are recorded in the following eleven papers, three of which are still in press:

1. Derivatives of 2-phenyl-benzothiazole. Synthesis of an analog of Cinchophen (Atophan). (With Abrahamson).

2-Para-tolyl-benzothiazole, dehydrothio-para-toluidine, and some related compounds. (With Meyer).

The Thiazole Group (con.)

The preparation of dehydrothio-para-toluidine and some of its derivatives. (With Snell).

The synthesis of benzothiazoles from ortho-nitrochloro-benzene. (With Snell).

The constitution of Columbia Yellow (Chloramine Yellow) and the synthesis of some related compounds. (With Bergeim).

A new group of dyes from poison gases through the 2-aminothiazoles as intermediates. The preparation of thiazole dyes of Doebner Violet type. (With Chertcoff).

Odor and chemical constitution in the benzothiazole group. (With Stull).

The behavior of o-aminophenyl mercaptan with aldehydes, ketones, and gem-dihalides; the synthesis of benzothiazoles. (With Stull).

The condensation of o-aminophenyl mercaptan and o-aminophenyl disulfide with acid chlorides, anhydrides, and esters. (With Stull).

Further studies on derivatives of 2-phenyl-benzothiazole. (With Corbitt).

The synthesis of some 2-phenyl-benzothiazole arsonic acids. (With Corbitt).

The synthesis of 2-(p-aminophenyl)-5-methyl-benzothiazole and incidental compounds; isomers of dehydrothio-p-toluidine and of Chloramine Yellow. (With R. W. Allen)

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CERTAIN NEW DEVELOPMENTS IN THE CHEMISTRY OF FREE RADICALS

by

James B. Conant

The preparation of pentaphenyl ethyl by Schlenk in 1922 marked the opening of a new phase in the study of compounds of trivalent carbon. The existence of this substance in the monomolecular state in solution together with the high dissociation of certain tetra-aryl-alkyl-ethanes prepared by Ziegler definitely shows that it is not necessary to have three aromatic groups attached to a trivalent carbon atom. As an outcome of certain studies on oxidation and reduction we have been fortunate in finding a new way of preparing hitherto inaccessible derivatives of dixanthyl containing saturated alkyl groups. A study of the dissociation of these compounds has enabled us to throw some light on the general problem of the relation between structure and dissociation of hydrocarbons. This paper presents the results of these studies and a brief account of the general applicability of the new method of preparing free radicals.

Vanadous and chromous salts are very powerful reducing agents; their aqueous solutions are metastable and tend to evolve hydrogen. We have found that these powerful reducing agents reduce instantaneously the salts of a great variety of organic bases, pseudo bases, and anhydro bases forming free radicals or their association products. Since the starting point is the carbinol or halochromic salt, even carbinols which readily lose water may be employed. The following diagram (Fig. 1) indicates the great variety of organic salts which can thus be very rapidly reduced. A recent study in our laboratory has shown

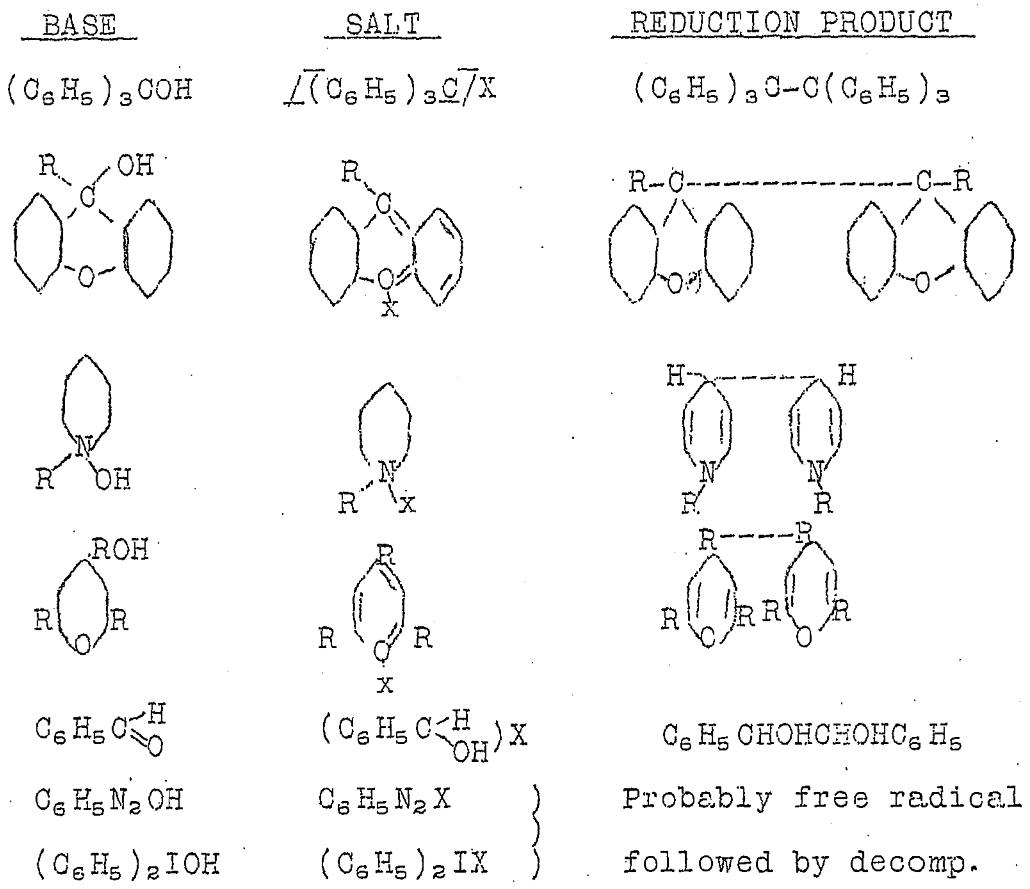
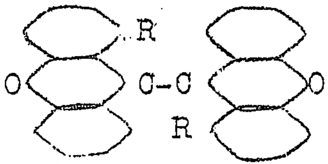


Fig. 1

that the reduction of the salts of such substances as phenylxanthenol and triphenyl carbinol is reversible and is governed by the usual electrochemical laws; indeed, a definite potential may be measured. It is thus possible to formulate quantitatively the interaction of these salts and reducing agents. In a few instances titanous chloride is sufficiently powerful to bring about the change, but in general the oxidation-reduction potential of the organic system is so low that vanadous or chromous salts must be employed. It is of interest that the process is strictly reversible only if the resulting product is appreciably dissociated into free radicals at the temperature employed. Otherwise, the reduction is irreversible and no potential can be measured. Thus, mixtures of hexaphenylethane and triphenylcarbinol in very strong acid solution (halochromic solution) develop a definite potential on a platinum electrode; mixtures of diphenylcarbinol and tetraphenylethane do not.

It should be noted in passing that the advantage of these reducing agents over a metal-acid combination or electrolytic reduction lies in the fact that it is possible very rapidly to supply a given number of equivalents of reducing power throughout a homogeneous solution. As a result, a reduction can be accomplished probably a hundred or a thousand times faster by using chromous or vanadous salts than by using the more usual methods of heterogeneous reduction. When one is dealing with such sensitive substances as free radicals, the time factor is all-important; the life of an "odd molecule" is short. Slow processes in acidic media yield only products of subsequent rearrangements and decompositions; by using homogeneous reducing agents, we generally succeed in isolating the free radical or its simple association product. In the case of the reduction of diazonium salts and iodonium salts we have not yet succeeded in isolating the first step in the process; this work is still in progress and I hope at some later time to report more definitely in this regard.

The reduction of the so-called oxonium or carbonium (halochromic) salts of the substituted xanthenols by means of vanadous or chromous salts yields the corresponding derivatives of dixanthyl in excellent yields. The process undoubtedly proceeds through the formation of an intermediate free radical. Mr. A. W. Sloan and Mr. L. F. Small have thus prepared the well-known diphenyldixanthyl and the naphthyl derivative, which are largely dissociated in solution, and a number of hitherto unknown saturated alkyl derivatives of dixanthyl. This has enabled them to investigate the dissociating influence of such saturated groups. It may be taken as already established by Ziegler's work that certain unsaturated groups are quite as potent in their influence as an aromatic group. An examination of the following table (Fig. 2) will show that in the dixanthyl series a saturated secondary alkyl group is also very powerful though perhaps less powerful than the phenyl group. Unfortunately, we have not yet been able to prepare a tertiary alkyl derivative.



R	RATE OF O_2 ABSORPTION AT 25°	ESTIMATED COLOR OF SOLUTION IN ETHYL BENZOATE (0.05M) at					OXIDATION BY $FeCl_3$ (Aq.) 25°
		-10°	25°	100°	160°	210°	
$(CH_3)_2CH-$; C_6H_{11}	Instantaneous	10	1000	10000			Very rapid
$C_6H_5CH_2-$; $C_{10}H_7CH_2-$	Very rapid	0	2(?)	20	1000	6000	Very rapid
C_4H_3-; $C_5H_{11}-$; $C_6H_{11}-$; $C_6H_5-CH_2CH_2-$; $C_6H_5-(CH_2)_3-$	50% in 5 hrs.	0	0	2	40	500	10-20 min.
CH_3-	50% in 24 hrs.	0	0	0	2	6	10-20 min.
H-	at 190° 50% in 3 hrs.	0	0	0	0	0	none

(10000 = complete dissociation)

Fig. 2

The cyclohexyl, isopropyl and secondary butyl derivatives like the phenyl and naphthyl compounds of Gomberg are so much dissociated in solution that they give highly colored solutions at 20° and practically instantaneous absorption of oxygen with the formation of peroxides. Due to the failure to obtain crystalline material in these three cases we have no molecular weight determinations. The dissociation may be perhaps estimated from the color at room temperature as of the order of 3-10% in 0.1M solution. All the other derivatives were obtained in pure crystalline condition, and their molecular weights show a degree of dissociation too small to be measured. Their behavior, however, divides them into certain classes. In the first of these we have the benxyl, chloro-benxyl, and alpha-naphthyl-methyl derivatives. Their dissociation at room temperature in 0.1M solution is probably less than .01%. The butyl, isoamyl, hexyl, phenyl-propyl, and phenyl-ethyl derivatives must be classed together, and we have no certain way of distinguishing between them. Their rate of oxygen absorption is slow but definite, and a peroxide has been isolated; their solutions on warming become colored and on cooling lose the color. The methyl derivative is distinctly different from the other simple primary alkyl compounds; the oxygen absorption is much slower, and the temperature required to produce an "appreciable dissociation" as judged by the color is much higher than in the case of the other compounds. The methyl group is, therefore, the least effective of all groups thus far studied in promoting dissociation. All the dialkyl-dixanthyls in solution undergo the intramolecular oxidation and reduction so characteristic of free radicals of all types. Fortunately, this "disproportionation" is not so rapid as in the tetraphenylethane series where it prevents a study of the dissociation of the alkyl derivatives.

The parent substance itself, - dixanthyl,- shows none of the properties of a substance which dissociates into free radicals. It is , however, distinctly more inclined to undergo cleavage between the two carbon atoms than is tetraphenylethane, for example. When treated with bromine in dilute solution at room temperature it forms xanthyl bromide with cleavage. At a temperature of 220° it absorbs oxygen at about the rate that its simple alkyl derivatives do at 20° (this may involve the hydrogen atoms and not the carbon linkage, however). Thus, there seems to be no sharp line between the highly dissociated di-naphthyl-dixanthyl and the parent substance. It is entirely a question of degree. At room temperature certain derivatives are sufficiently dissociated to give deep color and the "usual properties" of free radicals; with others these usual properties have faded almost beyond recognition, but at a slightly higher temperature reappear; with still others one must go to a considerably higher temperature to find any of these properties.

If we make the probable assumption that the temperature coefficient of the free energy of dissociation is independent of the temperature and essentially the same for all these compounds, it should be possible to sum up our results in a first approximation, involving an estimate of the free energy of dissociation of the various substances at 25°. We must judge the dissociation at several temperatures colorimetrically and extrapolate the free energy (log K) to room temperature. We hope a more careful study of the subject from this point of view will enable us to make some rough approximations and to relate the structure of hydrocarbons and their tendency to dissociate (the free energy of dissociation).

The extention of our results to other series is tempting but uncertain. We have found the cyclohexyl group of influence in this series and should be inclined, therefore, to predict that diphenyl-tetra-cyclohexyl-ethane would show some indications of dissociation at least above 150°. In an interesting recent paper Professor Marvel has prepared this substance and has shown that it can be heated to 330° in oxygen for 30 minutes without change ! This remarkable stability would certainly not be predicted from our results. Perhaps it indicates that two unsaturated or aryl groups are vital to the dissociation of a carbon-carbon linkage as Professor Marvel suggests. It still remains to be seen, however, whether it is not possible to prepare dissociable ethanes having only one aryl or unsaturated group in the alpha position (or perhaps none). Our results plainly indicate that there is no mysterious potency in an unsaturated group as far as concerns the <u>third</u> group attached to a trivalent carbon atom. Personally, I can not help but feel that this must be true in general and that we shall some day succeed in preparing a substance which has no unsaturated or aryl group attached to the critical carbon atom, but, nevertheless, has at least as much tendency to dissociate as dibutyldixanthyl.

THE ACTION OF ALKALIES ON d-GALACTOSE

by

Wm. Lloyd Evans and George Preston Hoff

It has been pointed out by Lobry de Bruyn and van Ekenstein that an equilibrium is formed when alkalies are added to aqueous solutions of certain carbohydrates, amongst which are d-glucose, d-fructose, and d-galactose. It was shown by these investigators that the addition of alkalies to the aqueous solutions of d-galactose gives rise to the equilibrium represented by equation 1.

(1) d-galactose ⇌ d-tagatose ⇌ d-talose ⇌ l-sorbose ⇌ α-d-galtose ⇌ β-d-galtose.

Nef made an exhaustive study of the behavior of certain carbohydrates towards alkalies and came to the conclusion that a series of hexose enediols are formed from the components of the above equilibrium as well as from the equilibrium which arises from the action of alkalies on d-glucose. These enediols may be thought of as the chemically active portion of these alkaline solutions, and, furthermore, they may be regarded as existing in a atate of equilibrium with those systems described by Bruyn and van Ekenstein. Each of these hexose enediols may split at the double bond and thus give rise to a series of methylenenols which may in turn react towards the alkali present in the same manner as the original hexose. This splitting in the case of the d-galactose enediols gives rise to the following series of reactions:

(a) d-Galactose 1,2 enediol → Lyxose and formaldehyde

(b) d-Galactose 2,3 enediol → Threose and Glycolic Aldehyde

(c) d-Galactose 3,4 enediol → Glyceric Aldehyde.

The products arising from the decomposition of the hexose enediols at their respective double bonds may then become a part of a much larger equilibrium system. Should these several decomposition reactions take place in the presence of oxidizing agents, it is at once clear that the general reaction will give rise to a series of oxidation products whose carbon atom content will in large measure depend on the oxidation potential of the reagent used. In the work described in this paper no oxidizing reagent was used.

It occurred to us that, should the above views with reference to the condition of the alkaline solutions of these carbohydrates be correct, then it ought to be possible to shift the point of equilibrium by choosing an appropriate set of experimental conditions, such as a change in the temperature employed. Both variables were used throughout this work.

As an index of the change taking place in an aqueous solution of d-galactose when one varies the concentration of the alkali, the aqueous solutions of this carbohydrate were examined for their formic acid content at the different alkalinities. The amount of this acid was regarded as a measure of the 1,2 enediol present in the solution. It is clear that the 1,2 enediols formed from other carbohydrates of lesser content might also be regarded as a source of this acid. As an index of the 3,4 enediol we measured the amount of lactic acid formed by a change in the variable factors referred to above. The source of the lactic acid is the glyceric aldehyde, which is formed by the splitting of the 3,4 enediol. The glyceric aldehyde thus formed passed to lactic acid through a benzilic acid rearrangement of the pyruvic aldehyde formed from glyceric aldehyde by the loss of water.

It was proven by a separate series of experiments that pyruvic aldehyde is actually formed from glyceric aldehyde.

Our results may be briefly summarized as follows:

(1) Half molecular d-galactose solutions when treated with concentrations of potassium hydroxide ranging from 0.1 N. to 9.0 N at 25° and 50° yielded formic, lactic, and acetic acids.

(2) Formic acid production is an increasing logarithmic function of the alkali concentration until the maximum effect is reached at 0.6 N KOH. Beyond that point the formic acid production is a decreasing logarithmic function of the KOH concentration. The optimum alkali concentration for 1,2-ene-diolization is considered 0.6 N. Formic acid production is an increasing function of the temperature at alkalinities up to 4.0 N. Beyond that alkali concentration less formic acid is obtained at the high temperature.

(3) Lactic acid first appears in measurable amounts at 5.0 N alkali concentration at 25° C. and at 1.5 N at 50° C. The effect of an increase in temperature is to produce greater amounts of lactic acid at any given alkali concentration and to induce its formation at lower alkali concentrations.

(4) The course of pyruvic aldehyde formation has been studied at 25° and 50° C. It is an increasing function of the alkali concentration up to the point where tar formation is noticeable. It is also an increasing function of the temperature until the tar formation interferes. Pyruvic aldehyde osazone is produced at lower alkalinities at 50° C. than it is at 25° C.

The Action of Alkalies on d-Galactose (conc.)

No osazone was formed at an alkali concentration greater than 2.63 N. This is interpreted as the hydroxyl ion concentration at which the rate of rearrangement of pyruvic aldehyde into lactic acid equals the rate of pyruvic aldehyde formation.

(5) Acetic acid production is an increasing function of the alkali concentration up to 0.6 N KOH. It is a decreasing function of alkalinities greater than that value. It is an increasing function of the temperature over the entire range of alkalinities tried.

(6) The effect of alkali concentration and temperature upon saccharinic acid formation has been studied. The presence of α-meta-galactosaccharinic acid has been established. Saccharinic acid formation from d-galactose is an increasing function of the alkali concentration. An increase in temperature causes its formation in larger amounts and at lower alkali concentrations.

THE CHEMICAL UNSATURATION OF RUBBER UNDER THE ACTION OF HEAT, TRICHLOROACETIC ACID, ULTRAVIOLET LIGHT, AND MASTICATION[a]

by

H. L. Fisher and A. E. Gray

From the work of Harries and Nagel[1] on shellac and of Pemmerer and Burkard[2], Staudinger and Fritschi[3], and Harries[4] on the hydrogenation of rubber, it would appear that there is some connection between the physical state of these substances and their chemical reactivity. Harries and Nagel[1] found that whereas the ordinary alcohol-soluble shellac yielded the maximum of 30% of aleuritic acid by cold hydrolysis with potassium hydroxide, treatment with an ethereal solution of hydrogen chloride caused the shellac to be insoluble in alcohol, and, although it was still soluble in potassium hydroxide, cold hydrolysis with this reagent then gave no more than 3% of aleuritic acid. By boiling with glacial acetic or formic acid the insoluble variety could be reconverted into the soluble variety, and now it would once again yield the maximum amount of aleuritic acid upon hydrolysis. Harries[4], with this work as a background, thought that the reason why he had never been able to hydrogenate rubber was on account of it physical condition, that is, "its degree of dispersion or aggregation." He, therefore, had rubber strongly plasticized on a mill, and was then able to hydrogenate it in the presence of platinum black.[b] Pummerer and Bufkard[2] tried "to bring into re-

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a) Part of this paper was given by the senior author under the title, "The Physical State of Colloidal Organic Substances and Their Chemical Reactivity," at the First National Symposium on Organic Chemistry, Rochester, N. Y., December 29-31, 1925.

b) It should be noted, however, that he has never published any analytical data.

action the most highly possible depolymerized and, therefore, reactive rubber" by using very dilute solutions of highly purified rubber. They were very successful. So were Staudinger and Fritschi[3), who used high temperatures (270° C) and high pressures (93 atmospheres). It is of special interest that all these experimenters did their work independently yet with the same fundamental idea of changing the rubber into a more reactive state. The hydro-rubber in all cases is apparently the same. It is like a paraffin hydrocarbon in chemical properties, has a very high indeterminate molecular weight, and gives typical colloidal solutions.

The success of these investigations was dependent, according to the different authors, upon "disaggregating" or "depolymerizing" the large rubber molecule into smaller dispersed particles or particles of lower molecular size which, in each case, are considered to be more reactive chemically. Heat and pressure are, of course, familiar agents for promoting chemical reactions, but dilution is seldom, if ever, used for the same purpose; in fact, dilution generally retards a reaction. If we take into account the fact that colloidal systems are being dealt with, the methods used all bring about a lowering of the viscosity of the rubber or of its solutions. These changes in viscosity have also been considered as due to disaggregation or to depolymerization.

Disaggregation always refers to a physical change - a diminution of the size of the particle. This diminution increases the total amount of surface exposed, and, therefore, chemical reactions will occur more rapidly, since in a heterogeneous system, according to Wenzel's law, "the amount of chemical change in the unit of time is proportional to the absolute surface."[5] Harries followed this line of reasoning. Whitby[6], ten years before, had made a plea for the use of the same explanation in connection with the formation of tackiness in rubber.

Polymerization is, of course, a chemical term with a very definite meaning. When an unsaturated hydrocarbon undergoes polymerization, it increases its molecular weight, and at the same time its unsaturation is decreased.[a] On the other hand, when a polymerized hydrocarbon undergoes depolymerization, the separate units become proportionately more highly unsaturated than the original polymerized hydrocarbon. In rubber chemistry, and also in connection with other organic substances that exist in the colloidal states, the term, depolymerization, has been used very loosely, apparently without any definite experimental data other than the change in viscosity to substantiate it. Heat, dilution, light, and mastication have all been stated to cause depolymerization. Many chemical agents also are said to depolymerize the rubber in solution. This is true, for example, of bromine, iodine, oxygen, sulfur, and sulfur monochloride.[7] Trichloroacetic acid[8] also causes this change to take place. Very recently Staudinger[9] has said "that acids decrease the viscosity of rubber solution by

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[a] Sometimes the unsaturation varies with different types of polymerization used, the chemical reactivity varying accordingly, as shown in the case of cyclopentadiene by Bruson in his dissertation from Staudinger's laboratory, Zürich, 1925.

breaking down the molecule," "that these reagents react with the end valences of the rubber so that small molecules are formed which cannot again unite," and that "the end valences undergo cyclization so that the trivalent carbon atom[a] disappears." However, even if the change is due to depolymerization and, as mentioned above, there is, therefore, a corresponding change in the chemical unsaturation, it would probably not be possible to measure this change in the unsaturation by any chemical means at our disposal.

A little over a year ago the senior author isolated from rubber that had been heated for several hours at 340-5° C a whitish powdery substance having the same elemental composition as the rubber hydrocarbon, $(C_5H_8)_x$, and giving colloidal solutions of much lower viscosity. This substance has an unsaturation of 36.48% as compared with the rubber hydrocarbon, and, since the composition is the same, it is evident that some of the double bonds must have disappeared on account of the formation of rings through intramolecular changes. Recently Staudinger[9] has published similar results and has called these substances "cylcorubbers." Staudinger has also shown that the unsaturation of rubber in solution varies with the temperature and the time.

Since heat causes a chemical change at the same time that it causes a lowering of the viscosity, it was thought that a somewhat similar chemical change might also be taking place when the other agents cause a lowering of the viscosity. Accordingly, the effect of heat was studied further, and, in addition, the effect

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[a] That is the unsaturated carbon at the end of the long chain.

of trichloroacetic acid, ultraviolet light, and mastication. Trichloroacetic acid causes a noticeable drop in the unsaturation. Ultraviolet light caused no change in unsaturation, but the solution showed a great drop in viscosity. Mastication in air causes a drop, but it was not determined whether the change was due to cyclization or to addition of oxygen or both[a)]; in an atmosphere of carbon dioxide, there was no change whatever, although the samples became very soft and sticky.

Experimental

The method used for determining the chemical unsaturation was a slightly modified Wijs method (iodine-chloride)[b)]. It is accurate to about 0.5%. All the results given are the average of at least three[c)] separate titrations on aliquot portions of the same solution, and many are from separate solutions, all agreeing to within 0.5%, often within 0.2%. Approximately 1% chloroform solutions were always used. Dilution to 0.1% showed no change in the unsaturation. With highly viscous solutions it was difficult to obtain concordant results on account of the difficulty of measuring the liquid, but by rinsing the pipette once with the solvent very good results were obtained. A second rinsing was found to be unnecessary. The unsaturation was calculated on the basis

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a) Van Rossem ("Rubber Industry," 1914, p. 149) showed that oxygen caused a rapid lowering of the viscosity of a solution of rubber during heating, although no oxygen was absorbed, the oxygen apparently acting as a catalyst, since inert gases did not do this. By analogy the change here may not be due to addition of oxygen but possibly to cyclization.

b) Kindly furnished by Mr. A. R. Kemp of New York City, who will publish the details shortly.

c) In the ultraviolet series only two separate titrations were made.

of one double bond for each C_5H_8 group.[a)]

Effect of Heat. Samples of Pale Crepe were heated between sheets of tin in a vulcanizing press for 30 minutes and for 8 hours at 141°C. The products were almost transparent and were very snappy. They formed viscous solutions which caused some difficulties in the analyses. The practice of rinsing the pipettes had not been started when they were made, but the results given below are approximately the same and show that very little, if any, change in the unsaturation has taken place. Three 30 gram samples from batches that had been masticated for one hour in the factory were heated in sealed tubes at the temperatures given and show decided decreases in the unsaturation. The products were soft and somewhat oily.

Table 1

Effect of Heat

	% Unsaturation
1. Pale Crepe, unheated	93.60
2. Pale Crepe, between tin in press, 30 min. at 141° C	92.12 (see above)
3. Pale Crepe, between tin in press, 8 hrs. at 141° C	93.21
4. Pale Crepe, heated in sealed tube, 5-1/2 hrs. at 245-265° C	90.84
5. Pale Crepe, heated in sealed tube, 7 hrs. at 285-300° C	81.40

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a) Except in the acetone-extracted sample, there are present other unsaturated substances such as the resins (unsaturated cyclic alcohols) and "resin acids" (oleic and linoleic), which are included in this calculation. There is no doubt that in the heat treatment the change is due to an intramolecular change in the rubber hydrocarbon. In the case of the trichloroacetic acid the change is small, but it is believed that this also is in the rubber hydrocarbon, as will be shown by a later publication.

The Chemical Unsaturation of Rubber (con.)

Table 1 (con.)

	% Unsaturation
6. Pale Crepe, heated in sealed tube, 2 hrs. at 285° and 5 hrs. at 345-63° C	42.60
7. Isolated product from #6 (see p. 4)	36.48

Effect of Trichloroacetic Acid. Samples of Pale Crepe were made up as outlined and the trichloroacetic acid added in the proportions given. Concordant results could not be obtained during the first few days after mixing. The results in the table were obtained after the mixture had been standing seven days. A definite lowering in the unsaturation is noted.

Table 2

Effect of Trichloroacetic Acid

	%Unsaturation	
	First series	Second Series
1. Pale Crepe, untreated	95.95	96.22
2. Pale Crepe + 10% of its weight as acid	94.65 + 10.9%	95.83
3. Pale Crepe + 54% of its weight as acid	94.24 + 53%	95.38

Effect of Ultraviolet Light. In the first two runs a 1% solution of Pale Crepe in a 100 cc. quartz flask, with carbon dioxide above the liquid and the flask tightly stoppered, was exposed at a distance of about 18 in. to the light from a quartz-mercury vapor lamp (Hanovia Chem. and Mfg. Co.) for different periods of time. Two 250 cc. quartz flasks were used in the third run and a correspondingly larger volume of solution used. The solutions became very limpid during the first periods of exposure. In each run the same solution was used throughout, samples being removed for analysis at the periods given, and carbon dioxide used each time to displace any air.

Unfortunately the unexposed solution in the first run was not analyzed. Since the figures were low, it was thought that a change had taken place, but other work showed that the original pale crepe varies considerably. In order to get rid of any dissolved air the solvent in one of the last runs was boiled, carbon dioxide passed in, the rubber added, and carbon dioxide used to displace any air above the liquid before the ground-in stopper was put in place. The high figures for the 1 hour exposure, where the solvent was boiled, are apparently freaks. During the latter part of the third run the liquids in each case turned yellow and a rather heavy insoluble film was evidently great enough to cause a change in the amount of rubber in the solution as indicated by the lower figures. The yellow color was, possibly, due to heat since the fan was not used to keep the cabinet cool in this run. A similar insoluble film had been noticed in one of the previous runs, but it was very, very thin.

The conclusion is reached that ultraviolet light causes no change in the unsaturation.

Table I

Effect of Ultraviolet Light

% Unsaturation

First Run		Second Run	
1. Unexposed	-----	1. Unexposed	94.76
2. 8 hrs. Exposure	91.21	2. 1 hr. Exposure	93.89
3. 16 hrs. Exposure	91.46	3. 2 hrs. Exposure	94.61
4. 45 hrs. Exposure	91.58	4. 8 hrs. Exposure	95.02

The Chemical Unsaturation of Rubber (con.)

Table 3 (con.)

Third Run

	CO_2 above liquid only	Solvent boiled and CO_2 in solvent and above liq.
1. Unexposed (pipette washed)	92.03	92.06
2. 1 hr. Exposure (pipette unwashed)	92.08	92.93 (?)
3. 1 hr. Exposure (pipette washed)	92.20	93.20 (?)
3. 4 hrs. Exposure	92.15	92.59
4. 28 hrs. Exposure	89.12	89.55 (see above)

Effect of Mastication. 600 grams each of Pale Crepe and of acetone-extracted Pale Crepe were masticated on a water-cooled 12-inch mill and samples taken at varying times. In the first two series the pipettes were not rinsed, hence the lower figures, but their relationships are just as striking. For mastication in the absence of air, the rolls were enclosed in tin and a constant stream of carbon dioxide was delivered upon the rubber. For the series on the 4-inch mill, only 125 grams of rubber was used. This mill works much faster and the rubber became too soft to give a "bank" after 2-1/4 hours. Physically all the long masticated samples were apparently the same,-- very soft and sticky and giving very limpid solutions. The definite conclusion can be stated, that mastication in the absence of air causes no determinable change in the chemical unsaturation.

The Chemical Unsaturation of Rubber (con.)

Table 4

Effect of Mastication

Series A, on 12-inch mill, in air.

Time	% Unsaturation Pale Crepe	Extracted Pale Crepe
30 min.	93.24	96.03
2 hrs.	92.91	95.11
4 hrs.	92.39	94.52
8 hrs.	90.84	-----(+)
Total difference	- 2.40	- 1.51

(+) After 4 hours the extracted rubber became so soft that it crept under the mill guides and was lost.

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Series B, on 4-inch mill, in air and in CO_2. Pale Crepe

Time	In Air	In CO_2
10 min.	93.60	94.15
45 min.	93.45	93.83
2 hrs.	92.80	94.29
Total difference	- 0.80	+ 0.14

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Series C, on 12-inch mill, in CO_2. Pale Crepe

Time	In CO_2
Unmasticated	95.72
15 min.	96.23
1 hr.	96.02
2 hrs.	96.08
4 hrs.	96.53
8 hrs.	96.05
Total difference	+ 0.33

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Summary

1. The changing of the chemical reactivity of rubber by various physical agents in recent work on hydrogenation is discussed.
2. The effect of various agents on the chemical unsaturation was studied, and it is shown
3. That heat, in the absence of air, at vulcanization temperatures around 141° C, even for 8 hrs., causes no appreciable drop in the chemical unsaturation, whereas at high temperatures, 245°C to 360°C, there is a lowering of the unsaturation, the amount depending on the time and temperature (verification of the work of Staudinger).
4. That trichloroacetic acid causes a definite lowering of the unsaturation.
5. That ultraviolet light causes no lowering of the unsaturation.
6. That mastication in air causes a lowering in the unsaturation possibly due to absorption of oxygen, but in an atmosphere of carbon dioxide it causes no change in unsaturation, although there is, of course, a decided change in the physical properties.

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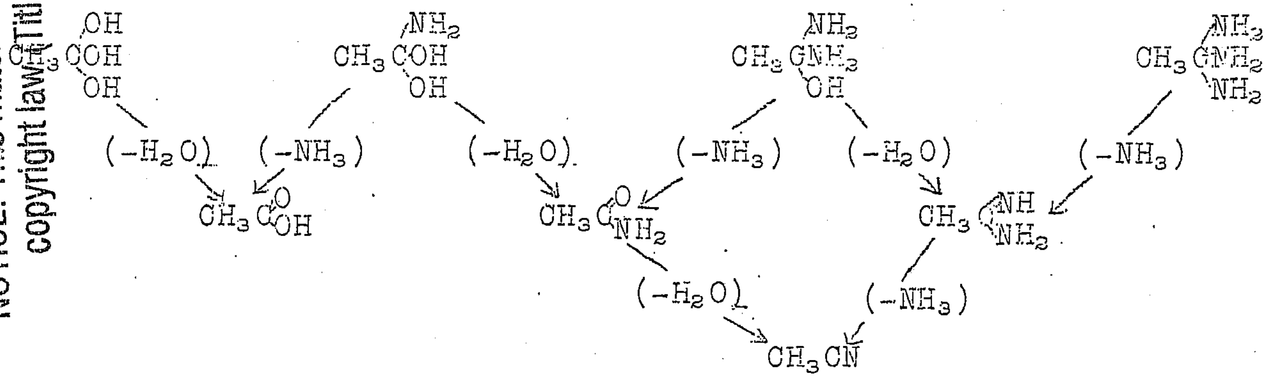
CARBOXYLLIC ACID, CARBAZYLLIC ACIDS, AND CARBOXAZYLLIC ACIDS

by

E. C. Franklin

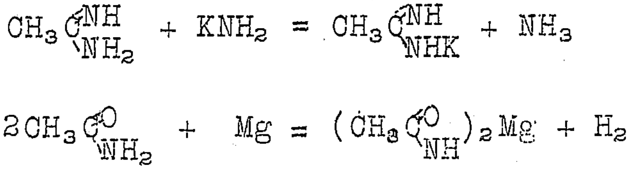
Ordinary acetic acid belongs to the oxygen or water system of compounds. It is an aquo acetic acid. Acetamidine, the nitrogen or ammonia analog of aquo acetic acid, is an acetic acid of the nitrogen or ammonia system, - it is an ammono acetic acid, - while acetamide, which is a derivative simultaneously of oxygen and nitrogen, is a mixed aquo ammono acetic acid. Methyl cyanide is acetic anammonide; that is to say, it is a compound related to ammono acetic acid as acetic anhydride is related to aquo acetic acid.

The relations between these compounds will be clear from an inspection of the scheme.



Now what of it? Well, at any rate this much.

First. Acetamidine and acetamide are acids - too weak, to be sure, to behave as acids in water solution - which show conspicuously their acid properties when in solution in liquid ammonia. Both compounds in such solutions react with ammono bases and with the more electropositive metals to form salts which in general separate from solution beautifully crystallized and of sharply definite composition. For example, acetamidine in liquid ammonia solution reacts with potassium amide - the caustic potash of the ammonia system - to form a potassium ammono acetate, and acetamide in liquid ammonia solution dissolves metallic magnesium with the evolution of hydrogen and the formation of magnesium aquo ammono acetate, the respective reactions taking place as represented by the equations:

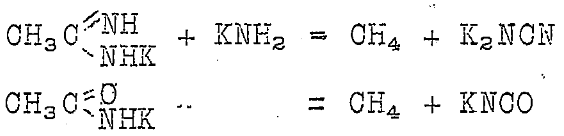


$$\mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{NH}}{\diagdown \mathrm{NH_2}} + \mathrm{KNH_2} = \mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{NH}}{\diagdown \mathrm{NHK}} + \mathrm{NH_3}$$

$$2\mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{O}}{\diagdown \mathrm{NH_2}} + \mathrm{Mg} = (\mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{O}}{\diagdown \mathrm{NH}})_2\mathrm{Mg} + \mathrm{H_2}$$

Second. Methyl cyanide in liquid ammonia solution unites with potassium amide to form potassium ammono acetate as follows: $\mathrm{CH_3CN} + \mathrm{KNH_2} = \mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{NH}}{\diagdown \mathrm{NHK}}$. This action is in accordance with the view that methyl cyanide is acetic anammonide.

Third. If the potassium derivatives of acetamidine and acetamide are, respectively, a potassium ammono acetate and a potassium aquo ammono acetate, then, just as methane and potassium aquo carbonate are formed when potassium aquoacetate is heated with potassium hydroxide, so, potassium ammono acetate when heated with potassium amide should yield methane and potassium ammono carbonate, while potassium aquo ammono carbonate when heated should give methane and a mixed aquo ammono carbonate of potassium. The reactions represented by the equations,

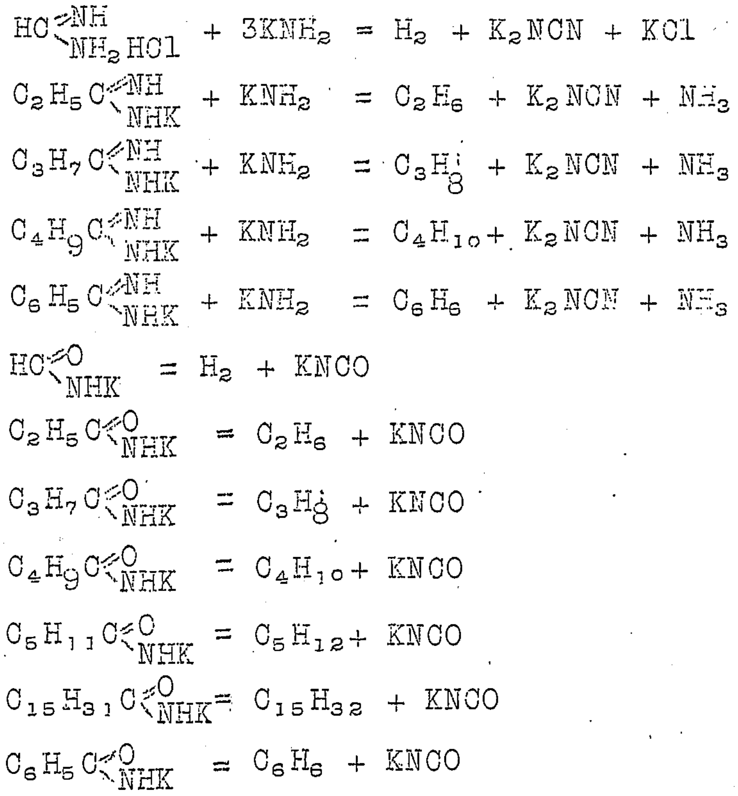


$$\mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{NH}}{\diagdown \mathrm{NHK}} + \mathrm{KNH_2} = \mathrm{CH_4} + \mathrm{K_2NCN}$$

$$\mathrm{CH_3C}\genfrac{}{}{0pt}{}{\diagup \mathrm{O}}{\diagdown \mathrm{NHK}} = \mathrm{CH_4} + \mathrm{KNCO}$$

have been experimentally realized together with similar reactions represented by the equations:

Carboxyllic Acids, etc. (con.)



$$HC\genfrac{}{}{0pt}{}{\nearrow NH}{\searrow NH_2\,HCl} + 3KNH_2 = H_2 + K_2NCN + KCl$$

$$C_2H_5C\genfrac{}{}{0pt}{}{\nearrow NH}{\searrow NHK} + KNH_2 = C_2H_6 + K_2NCN + NH_3$$

$$C_3H_7C\genfrac{}{}{0pt}{}{\nearrow NH}{\searrow NHK} + KNH_2 = C_3H_8 + K_2NCN + NH_3$$

$$C_4H_9C\genfrac{}{}{0pt}{}{\nearrow NH}{\searrow NHK} + KNH_2 = C_4H_{10} + K_2NCN + NH_3$$

$$C_6H_5C\genfrac{}{}{0pt}{}{\nearrow NH}{\searrow NHK} + KNH_2 = C_6H_6 + K_2NCN + NH_3$$

$$HC\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = H_2 + KNCO$$

$$C_2H_5C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_2H_6 + KNCO$$

$$C_3H_7C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_3H_8 + KNCO$$

$$C_4H_9C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_4H_{10} + KNCO$$

$$C_5H_{11}C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_5H_{12} + KNCO$$

$$C_{15}H_{31}C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_{15}H_{32} + KNCO$$

$$C_6H_5C\genfrac{}{}{0pt}{}{\nearrow O}{\searrow NHK} = C_6H_6 + KNCO$$

That cyanamide may be looked upon as an ammono carbonic acid, see J. A. C. S., 44, 486 (1922) and for considerations in support of the view that cyanic acid is a mixed aquo ammono carbonic acid see J. Phys. Chem., 27, 175 (1923).

THE DIRECTIVE EFFECT OF THE PHENOL GROUP IN THE PREPARATION OF KETONE DERIVATIVES OF BETA-NAPHTHOL

by

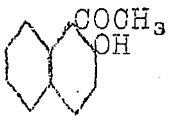
Arthur J. Hill and Raymond N. Evans

Although naphthalene is an exceedingly important intermediate for the synthesis of many dyes, it has played a rather minor role in the medicinal product and essential oil fields. Indeed, the extraordinary importance of certain naphthalene dyes has directed the channels of academic and industrial research along comparatively restricted lines. Thus, a vast amount of data has been rightly accumulated on the preparation and properties of sulfonic acids (hydroxy and amino in particular), and these investigations have brought about the solution of many intricate problems dealing with the orientating influence of groups.

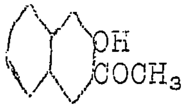
On the other hand, there are many orientation problems incompletely solved, that deal with the directive effect of substituent groups in such common reactions as that of the Friedel Craft and bromination - reactions at present finding little, if any, commercial application in this series, but of great importance in benzene chemistry.

During the course of an investigation, primarily undertaken for the purpose of synthesizing compounds having possible application in the medicinal product and essential oil industries, it became necessary to prepare the isomeric ketones I and II.

The Effect of the Phenol Group (con.)

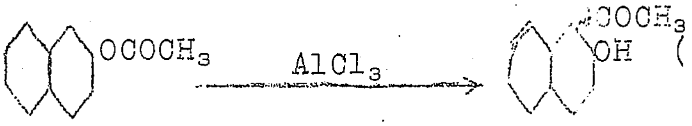


I

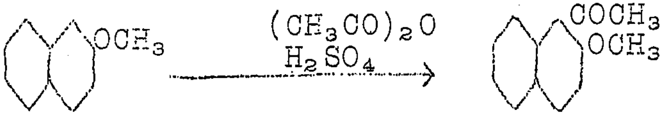


II

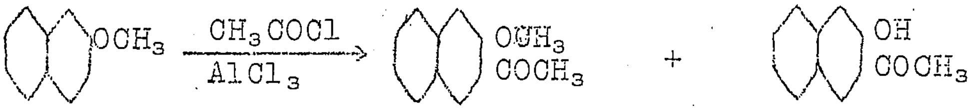
Fries[1] states that I can be prepared by the intermolecular rearrangement of beta naphthyl acetate in the presence of aluminum chloride, while the methyl ether of the same substance has been obtained by treating beta naphthol methyl ether with acetic anhydride and concd. sulfuric acid.[2]



(I)



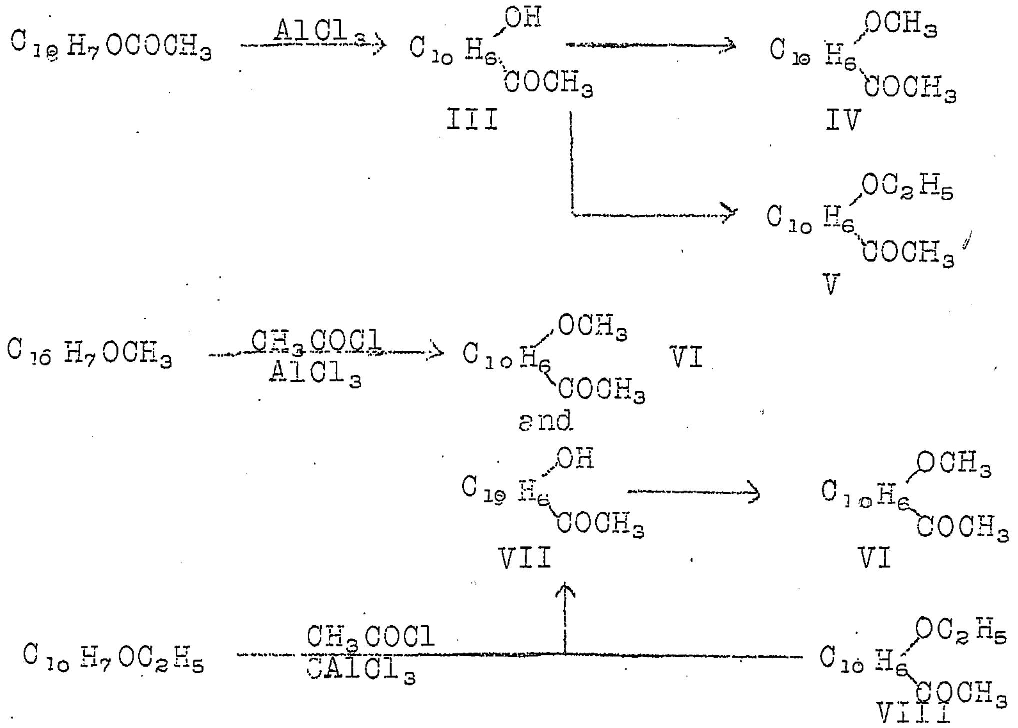
On the other hand, Witt[3] claims that II may be prepared by the action of acetyl chloride on beta naphthol methyl ether in the sense of the Friedel Craft reaction, the dimethylated product being present with the corresponding ether in the final product of reaction.



II

The writers duplicated these syntheses with the utmost care, but the results were somewhat unexpected, for the <u>same</u> ketone was obtained irrespective of the method employed. Indeed, in the fear that our conditions for the duplication of Witt's directions were faulty, a very large number of experiments were carried out, in which solvent (carbon disulfide, thiophene-free benzene, petroleum ether, and n-hexane), temperature, and time were investigated. None of these changes affected the course of reaction.

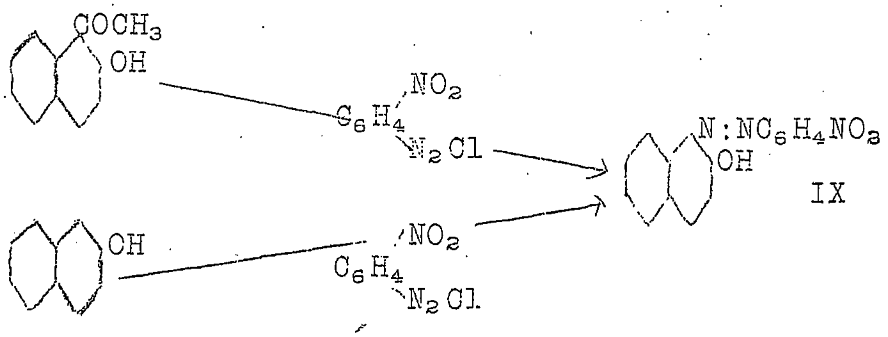
Proof of the identity of the ketones prepared by the three methods and of the fact that the writers were not dealing with mixtures is shown graphically by the following reactions:



Mixtures of III and VII, IV and VI, and V and VIII melted unchanged. The oximes and picrates of IV and VI were identical, and the same was true of IIIand VII. The crystls of IV and VI were measured on a goniometer, and the crystal measurements thoroughly confirmed the chemical proof and, therefore, the identity of the two substances.

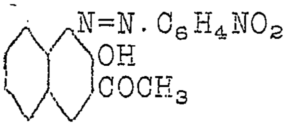
Intramolecular rearrangement of the beta naphthol ester and the Friedel Craft reaction had, therefore, produced the same substance.

The position occupied by the entering acetyl group was demonstrated by coupling with diazotized p-nitraniline. It is a well established fact that beta naphthol couples in position 1, and, if this is occupied , not at all, unless a displaceable group such as COCH or SO_3H be present. When methyl beta-hydroxy naphthyl ketone was coupled with p-nitrobenzene diazonium chloride, the CH_3CO group was displaced, and the familiar p-nitraniline red produced.



IX

Had the CH_3CO group been present in position 3, the corresponding ketone derivative (X) of this dye would have been produced, analogous to the coupling of 2-hydroxy-3-naphthoic acid with diazonium salts. Therefore, the ketone group enters position 1 in the Friedel Craft reaction and also in the rearrangement of beta naphthyl acetate.

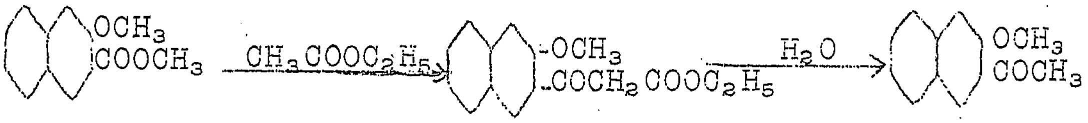


X

It should be possible to synthesize methyl 2-hydroxy-3-naphthyl ketone (II) by condensation of the methyl ether of methyl 2-hydroxy-3-naphthoate with ethyl acetate, followed by hydrolysis of the beta ketone ester thus formed. Experimental

The Effect of the Phenol Group (con.)

work on this problem is already in progress.

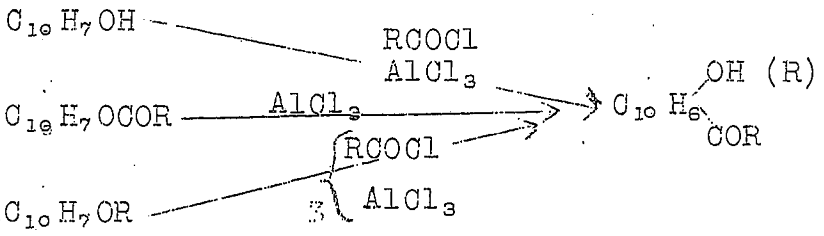


In connection with the preparation of the ketones, some interesting observations have been made with regard to the conduct of the Friedel Craft reaction and also the dealkylation of the ketome ethers. Acetyl chloride appears to have little or no effect on a carbon disulfide solution of beta naphthol in the cold. Immediately, however, on the addition of anhydrous aluminum chloride, a brisk evolution of hydrogen chloride takes place, and beta naphthyl acetate is formed. Without isolation, it may be transformed into methyl 2-hydroxy-1-naphthyl ketone by removal of the solvent and heating to 130° for 4 hours. In effec therefore, one is conducting a Freidel Craft reaction on the <u>fre</u> phenol.

When carrying out the Friedel Craft reaction on the na thol ether (methyl or ethyl), dealkylation always occurs in varying degree depending on the solvent, temperature, and the nature of the alkyl group. The use of benzene and water bath temperatures favor dealkylation, and this seems more pronounced with the ethyl than the methyl radical. Indeed, the ease with which dealkylation can be brought about by the use of aluminum chloride is noteworthy.

The beta naphthol ketones respond very slowly to the action of the usual reagents employed for the identification of this class of compounds. Thus the preparation of oximes, phenylhydrazones, or semicarbazones, using the customary procedures, was not successful. However, the free phenol, as well as the phenol ethers united quite smoothly with hydroxyl amine, provided the reaction was carried out in pyridine solution.

Since the completion of this first phase of the investigation, the writers have had occasion to prepare several of the higher ketone derivatives 4) of beta naphthol, and in no case thus far tried has there been failure to obtain the same ketone, whether by rearrangement of the appropriate ester of beta naphthol or by use of the Friedel Craft reaction.



We propose to continue this study of orientation problems, and to use these new ketones for synthetic purposes, such as the preparation of sulfonal analogues and alkyl beta naphthols. Indeed, it is the ultimate purpose of the investigation to contribute new data with regard to the relation between chemical constitution and physiological action in the naphthalene series.

1) Fries, Ber., <u>54</u>, 709 (1921)

2) Schneider, Ber., <u>54</u>, 2298 (1921)

3) Witt and Braun, Ber., <u>47</u>, 3216 (1914); Cf. Rousset, Bull. (3) <u>15</u>, 633 (1896); Gatterman, Ber., <u>23</u>, 1199 (1890)

4) The following groups are being studied: C_2H_5CO, C_3H_7CO, C_4H_9CO, and $C_5H_{11}CO$. This work will constitute the second paper of the series.

SYNTHESIS OF AUTOXIDIZABLE COMPOUNDS OF BIOCHEMICAL INTEREST CONTAINING SULFUR IN THIOPOLYPEPTIDE COMBINATION

by

Treat B. Johnson

One element that deserves more attention than it has hitherto received from biochemists is sulfur. Due to the variability of its valency it can exist in various stages of oxidation, and, thereby, undoubtedly plays a very important part in the dynamics of the living cell.

It has been known for a long time that different sulfur linkages function in the molecular structure of the sulfur proteins, but up to the present time only one definite sulfur amino acid of know constitution has been isolated in a pure condition among the products of hydrolysis, namely, <u>cystin</u>. Whether this substance actually exists as such in the original protein molecule or results by oxidation of a precursor - <u>cystein</u> - has not yet been proved.

In 1911 the writer suggested that thioamide sulfur probably exists in many sulfur proteins and proposed the name, <u>thiopolypeptide</u>, to designate that type of sulfur combinations which were related structurally to normal polypeptides. Several derivatives of this type were synthesized and their properties described. Following this research in 1911-1912 no new data has been contributed which has added further to our knowledge of thiopolypeptide sulfur until 1924 when Harris, working in Hopkins laboratory in England, suggested that denaturation of sulfur proteins was probably dependent on the presence of the thiopolypeptide grouping in such combinations. While his hypothesis deserves great merit, it is true, however, that he brought forward no positive proof of the actual existence of such linkages.

The last word in biochemical research which has renewed interest in this type of sulfur groupings is the recent announcement by Professor Abel of Johns Hopkins University that sulfur is a normal constituent of the pancreatic hormone, insulin, and that the specific activity of this remarkable substance is actually dependent on the proportion of its sulfur constituent. After an extensive research in this field and working with a very large amount of material, he has finally obtained an insulin fraction very rich in sulfur, and which shows very characteristic reactions. He concludes from observations thus far made that it behaves chemically in many respects like Johnson's thiopolypeptide combinations which were first reported in 1912. With the exception of the discovery of glutathione by Hopkins in England, this is actually the most important contribution on sulfur chemistry of biochemical interest that has been made in recent years.

In order to obtain further light on this important subject and, if possible, to obtain synthetic sulfur compounds which are susceptible to autoxidation changes, an elaborate program of organic synthesis has been inaugurated in the Sterling Chemistry Laboratory at Yale by Professor T. B. Johnson in conjunction with Dr. Elizabeth Gatewood, which has for its goal the synthesis of of new thiopolypeptide combinations of biochemical interest.

Synthesis of Autoxidizable Compounds (conc.)

Whether any of these products will undergo autoxidizable changes in the body and thereby exercise an influence on the oxidation of sugar remains to be determined. Thus far the problem has merely entered the preliminary stages of development, and no product synthesized has yet been submitted for pharmacological tests. Just as soon as material is available of required purity and syntheses have been perfected which are reliable and productive of new material, it is planned to inaugurate a cooperative research program which will promise quick results and a possible approach to the solution of a difficult but very important problem. Any chemical research which will lead to an understanding of the structure of such substances as insulin or tuberculin will be of lasting benefit to mankind.

Synthesis of Autoxidizable Compounds (con.)

Fig. 1

Mechanism of Denaturation and Coagulation without Hydrolysis of Thiopolypeptide Linkage in the Protein

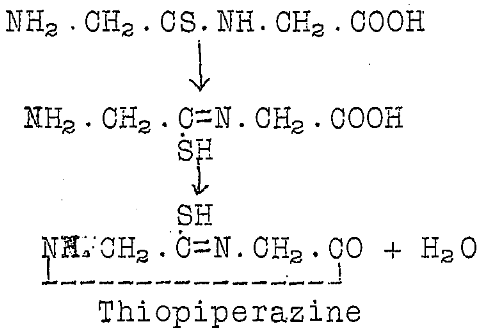


Fig. 2

Dithiopiperazines from Aminoacid Nitriles

$NH_2CH_2CN + H_2S \rightarrow NH_2CH_2.CSNH_2$

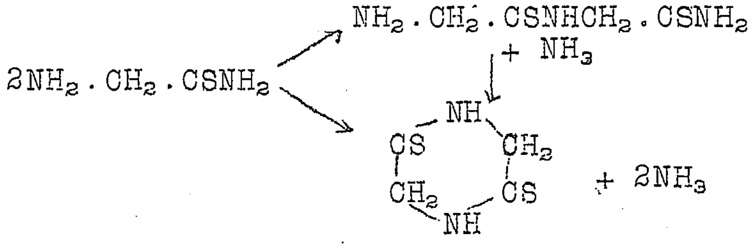


Fig. 3

Action of CS_2 on Aminoacid Nitriles

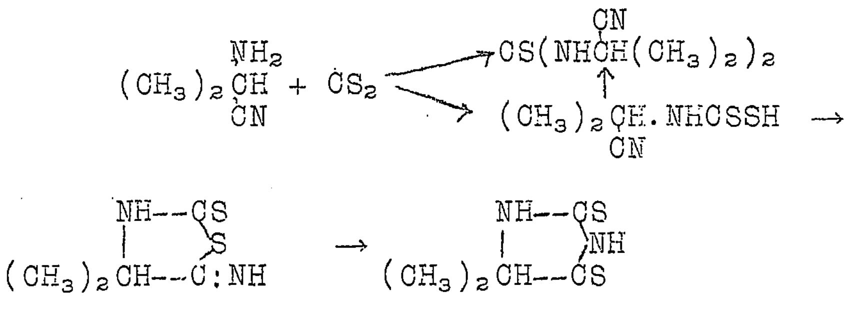
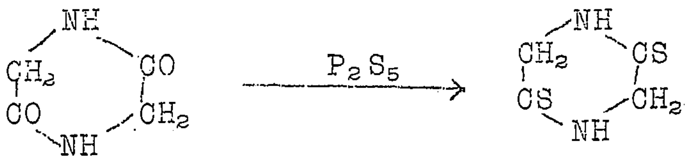


Fig. 4



Synthesis of Autoxidizable Compounds (con.)

Fig. 5

$$C_6H_5CONHCH_2COOC_2H_5 \xrightarrow{P_2S_5} C_6H_2CSNHCH_2COOC_2H_5 \xrightarrow{H_2O} C_6H_5CSNHCH_2COOH$$

Fig. 6

$$NH_2CH_2.CONHCH_2.COOH + P_2S_5 \rightarrow NH_2CH_2.CSNHCH_2.COOH$$

Thioglycyl.Glycine

Fig. 7

$$ClCH_2COOC_2H_5 + P_2S_5 \rightarrow ClCH_2CSOC_2H_5$$

$$ClCH_2CSOC_2H_5 + NH_2CH_2COOC_2H_5 \rightarrow ClCH_2CSNHCH_2COOC_2H_5 + C_2H_5OH \rightarrow$$

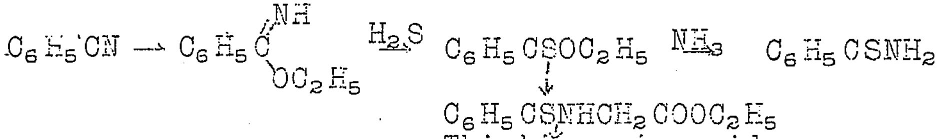
$$ClCH_2CSNHCH_2COOH \rightarrow NH_2CH_2CSNHCH_2COOH$$

Fig. 8

$$C_6H_5NCS + Mg.C_6H_5Br \rightarrow C_6H_5CSNHC_6H_5$$

$$C_6H_5.Mg.Br + SCN.CH_2COOC_2H_5 \rightarrow C_6H_5CSNHCH_2COOC_2H_5$$

Fig. 9

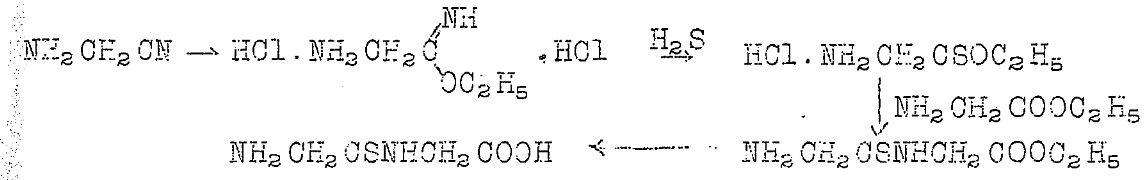


$$C_6H_5CN \rightarrow C_6H_5C\begin{matrix}NH\\OC_2H_5\end{matrix} \xrightarrow{H_2S} C_6H_5CSOC_2H_5 \xrightarrow{NH_3} C_6H_5CSNH_2$$

$$C_6H_5CSOC_2H_5 \downarrow C_6H_5CSNHCH_2COOC_2H_5$$

Thiohippuric acid

Fig. 10



$$NH_2CH_2CN \rightarrow HCl.NH_3CH_2C\begin{matrix}NH\\OC_2H_5\end{matrix}.HCl \xrightarrow{H_2S} HCl.NH_2CH_2CSOC_2H_5$$

$$HCl.NH_2CH_2CSOC_2H_5 \xrightarrow{NH_2CH_2COOC_2H_5} NH_2CH_2CSNHCH_2COOC_2H_5 \rightarrow NH_2CH_2CSNHCH_2COOH$$

THE MELTING CURVE AS A CRITERION OF PURITY OF ORGANIC COMPOUNDS

by

John Johnston

For some years we have been working towards a more systematic investigation of certain properties of closely related organic compounds - partly as an aid in the solution of certain problems of organic chemistry, partly because they form what is in effect a continuous series of substances. The main difficulty has been to secure the substances in a really pure state, for many of them as purchased carry up to several per cent of some closely related compound. Consequently, we were led to look into questions as to purification and as to criteria of purity; the conclusions and methods to which we were led are not strictly new or original, but they are not so widely known as they deserve to be.

We limited ourselves primarily to substances ordinarily crystalline because:

1) One achieves a sharper separation by crystallization than by distillation, for the melting temperature of isomers may differ by 100° as compared with a difference of 10° in boiling temperatures, the difference in melting temperature being a measure of the difference in solubility.

2) It is easier and more convenient to measure <u>accurately</u> a melting then a boiling temperature, which constitutes the most widely applicable type of test, for properties such as density or refractive index may be but little affected by the pre-

sence of isomeric substances.

The best criterion is not the melting (or freezing) point but the shape of the cooling (or heating) curve, which is the curve obtained when the temperature of the cooling crystallizing material, read at regular time intervals, is plotted. If the substance is pure, the residual liquid is of constant composition during the process of crystallization, and, therefore, the temperature remains constant; if it is not pure, the concentration of the impurity in the residual liquid increases as crystallization progresses, and, therefore, the temperature falls. In other words, in the former case the cooling curve during crystallization is a horizontal straight line; in the latter case it is a curve falling away from the horizontal, the departure being a direct measure of the molecular proportion of impurity present. We have continued processes of purification until the temperature did not change by more than 0.02° while half of the liquid froze, a criterion which corresponds to about 0.05 molar percent of impurity.

The form of apparatus used (Fig. 1) is a somewhat more generally convenient modification of that described by Washburn 1). It consists essentially of a small unsilvered Dewar tube B of pyrex (12 mm. internal diameter, 20 cm. long) into which fits fairly snugly a pyrex tube H wound externally with fine nichrome wire; by connecting this coil to a source of current through an adjustable rheostat, any desired rate of cooling or of heating may be maintained. Within this tube sits the small thin-walled test tube containing the material (0.5 - 1 cc.), in which is em-

The Melting Curve (con.)

bedded centrally the temperature measuring device - a small thermometer or, preferably, a thermoelement,-which has been calibrated in the apparatus at a series of known melting temperatures. This arrangement enables one to make with a single sample of material a series of curves with controlled rates of heating or cooling, which should yield the identical result unless there be decomposition on melting.

The values of melting temperature of organic compounds are much less certain than is desirable. As an example, take the nitroanilines, the most recent values of which, brought together in the following table, show differences up to 3°.

Melting Points - Nitroanilines

Ortho	Meta	Para	Observer
68	111	147.5	Kremann and Rodinis
71.1	112	146.8	Bogojavlensky
--	113.5	146.2	Sudborough
68.9	111.8	148	Valeton
71	114	147	Kremann
69.5	112.4	148.3	Holleman
71.5	114	147.5	Swarts
(69.3	111.8	147.5	Kohman
(			
(72	(by Cap. tube)		Collett

The divergences are least for the para, which, being the highest melting, is least soluble and more readily purified. This shows that the divergences are due more to lack of purity of the material than to the method of determination, which, however, in these instances was essentially that advocated here. To this statement there is one marked exception, namely, that by the usual capillary tube method, made on the identical sample which really melted at 69.3°. Indeed, it is well known to the chemical industry that the capillary tube method yields high and uncertain results; as is to be expected from the fact that the result depends upon (1) the rate of heating, (2) the lag of the thermometer, (3) the observer, and what he takes as visual evidence of melting. It is obvious, therefore, that the capillary tube method is a very poor criterion of purity, and should be replaced by a method of the type here advocated.

Since the impurities most likely to be present are closely related compounds which may form mix-crystals with the substance, a number of re-crystallizations may be necessary; this is most conveniently done by systematic fractional crystallization, the progress of the purification being followed by observation of the melting curve. A process of sublimation in a really good vacuum may also be useful, particularly as a means of removing residual solvent or any volatile products of decomposition (e.g. aniline from aminobenzoic acids). Incidentally, it may be observed that moisture cannot safely be removed in a vacuum over sulfuric acid because some of the latter will in time distil over into the substance, especially if it is basic. It may further be remarked that even small amounts of impurity may act as catalysts in certain reactions, and so affect the course and yield of the main reaction.

The Melting Curve (con.)

In recapitulation, the melting curve method is advocated as a reliable criterion of purity which is simpler to carry out and very generally applicable, for it can be used just as well for substances ordinarily liquid by the use of appropriate cryogenic mixtures.

Some of the points touched upon above are discussed and other references are given in papers by Johnston, Andrews, Kohman, Collett[2], and in forthcoming papers by Lazzell, Lynn, Saxton and Skau, to all of whom acknowledgement is here made.

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1) J. Ind. Eng. Chem., <u>16</u>, 275 (1924).

2) J. Physic. Chem., <u>29</u>, 882, 914, 1041, 1048, 1317 (1925); <u>30</u>, (1926).

The Melting Curve (conc.)

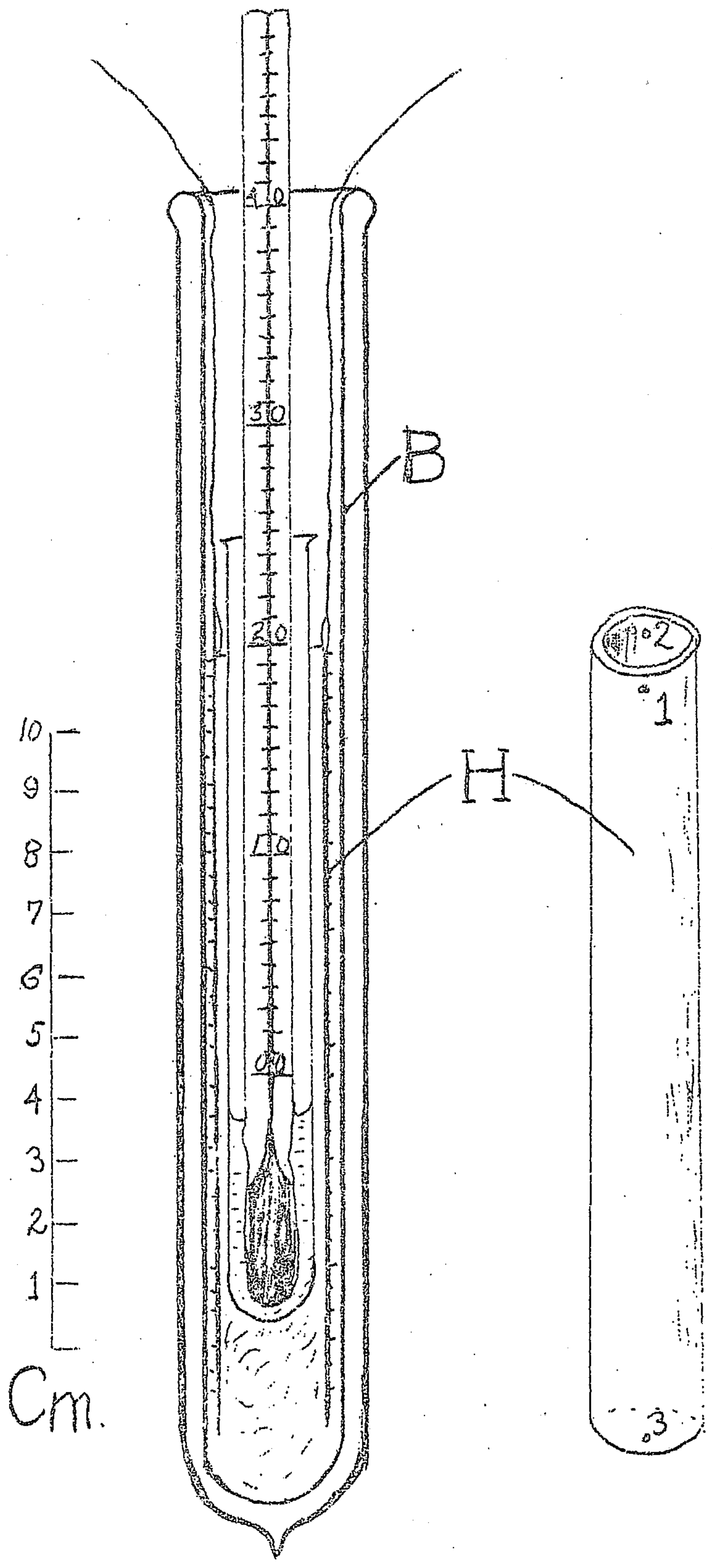


FIG. 1.

SOME CONFIGURATIONAL RELATIONSHIPS

by

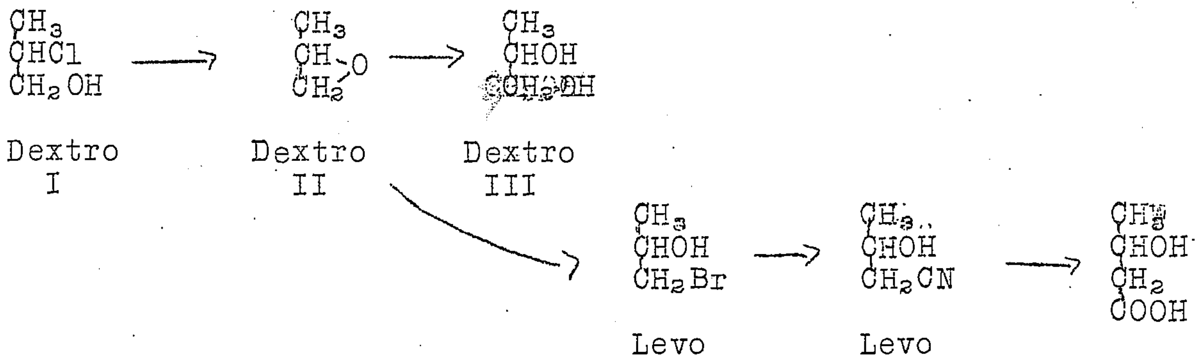
P. A. Levene

A comprehensive summary of the configurational relationships existing between the α-substituted acids was presented in Chemical Reviews. The comprehensive conclusion was then emphasized that the configuration of an α-substituted acid can be revealed by a comparison of the values of the optical rotation of the free acid and of its metal salt. A substance belongs to the d-series when the salt possesses s higher dextrorotation (or lower levorotation) than the free acid. This conclusion was reached on the basis of the data presented by Clough on the influence of external conditions on the optical behavior of a series of α-substituted acids and on the basis of the observations made by Hudson on the optical rotation of free acids and of their amides and on the basis of the data on the rotatory dispersion of α-amino and of α-hydroxy acids made by Karrer and his coworkers and by Freudenberg and his coworkers. Evidence of more direct character was presented by Levene and Mikeska, who compared the optical rotations of the α-thio acids and of the α-sulfonic acids derived from them and by Levene through his work on the configurational relationships of hexosamines and of hexosaminic acids.

Thus, the configuration of α-substituted acids can be easily correlated by several methods. The simplest of them is the comparison of the rotatory power of the free acid and of its metal salt.

Little attention was devoted to the consideration of the configuration of β-hydroxy acids. The point of reference in the series of α-substituted acids is the allocation of carbon atom (5) in glucose. The simplest member of the series is lactic acid. If β-oxybutyric acid were correlated configurationally to lactic acid, then a point of reference would be established for other β-substituted acids.

Prior to our work on this subject, an attempt to correlate the two substances was made by Abderhalden and Eichwald. These authors have synthesized β-hydroxybutyric acid from propylene oxide by the following set of reactions.



$CH_3CHClCH_2OH$ → $CH_3CH(O)CH_2$ → $CH_3CHOHCH_2OH$

Dextro I, Dextro II, Dextro III

II → $CH_3CHOHCH_2Br$ → $CH_3CHOHCH_2CN$ → $CH_3CHOHCH_2COOH$

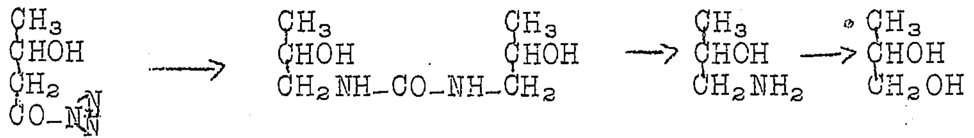
Levo IV, Levo V, Levo VI

It must be mentioned, however, that from the same oxide at times a levorotatory, at times a dextrorotatory, glycol was obtained. Hence, inasmuch as the configurational relationships of the glycol and oxide were not established, there existed no basis for correlating configurationally propylene glycol with the bromhydrin derived from it. Nevertheless, Abderhalden and Eichwald concluded that dextro propylene glycol and levo-β-hydroxybutyric acid were configurationally related.

The original plan of our work was to convert β-hydroxybutyric acid into lactic acid and thus correlate the two substances. It was planned to carry out the work in two phases. In the first β-hydroxybutyric acid was to be converted into propylene glycol.

Some Configurational Relationships (con.)

This problem was actually accomplished by the following set of reactions:



$$\begin{array}{l}CH_3\\CHOH\\CH_2\\CO\text{-}N_3\end{array} \longrightarrow \begin{array}{l}CH_3\\CHOH\\CH_2NH\text{-}CO\text{-}NH\text{-}\end{array}\begin{array}{l}CH_3\\CHOH\\CH_2\end{array} \longrightarrow \begin{array}{l}CH_3\\CHOH\\CH_2NH_2\end{array} \longrightarrow \begin{array}{l}CH_3\\CHOH\\CH_2OH\end{array}$$

Dextro VII — Levo VIII — Dextro IX — Dextro X

Simultaneously and independently the same result was obtained by P. Karrer and W. Klarer by means of the usual Hofmann reaction.

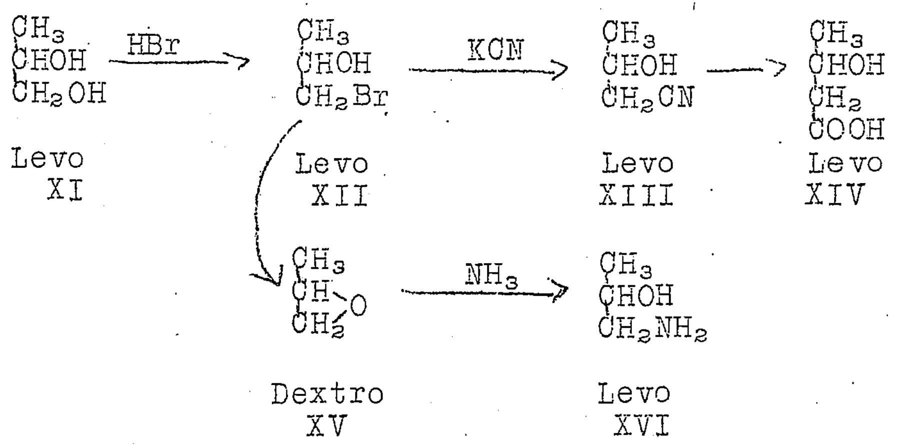
The second step of the problem, namely, the correlation of propylene glycol with lactic acid, could be accomplished either by oxidation of propylene glycol into lactic acid, or by reduction of lactic acid to the glycol. We chose the second method and reduced dextro-lactic acid to dextro-propylene glycol. From these observations we concluded that lactic acid and β-hydroxybutyric acid are configurationally related when they rotate in the same direction. This conclusion, then, was in direct contradiction to that of Abderhalden and Eichwald.

We, therefore, accomplished the synthesis of β-hydroxybutyric acid starting from active propylene glycol. The latter was converted into the bromhydrin (1-bromo-2-hydroxypropane), which through the nitrile was converted into β-hydroxybutyric acid. All these reactions were accomplished without change of the direction of rotation in any of the intermediate substances.

A change of direction of rotation did take place, however, when the bromhydrin was converted into the oxide and again when the oxide was converted into the amine (1-amino-2-hydroxypropane).

The entire set of reactions performed by us was the following:

Some Configurational Relationships (con.)



$$CH_3CHOHCH_2OH \xrightarrow{HBr} CH_3CHOHCH_2Br \xrightarrow{KCN} CH_3CHOHCH_2CN \rightarrow CH_3CHOHCH_2COOH$$

Levo XI — Levo XII — Levo XIII — Levo XIV

$$CH_3CHOHCH_2Br \rightarrow CH_3CH{>}O\,CH_2 \xrightarrow{NH_3} CH_3CHOHCH_2NH_2$$

Dextro XV — Levo XVI

In our set of reactions the bromhydrin was obtained directly from the glycol and not from the oxide; hence the probability of a Walden Inversion was smaller than in the reactions of Abderhalden and Eichwald. Also the probability is good that the substances represented by figures XI to XIV are configurationally related.

The question of the correlation of propylene glycol to the oxide is as yet difficult to answer definitely. There is reason to believe that the oxide and the glycol are configurationally related when they rotate in opposite directions. We base this assumption on two grounds. First, when the oxide is formed from 1-bromo-2-hydroxypropane, the weight of the reaction is centered on carbon atom (1). But we realize that a Walden Inversion is not entirely excluded. The second ground may be found in the fact that substitutions on the hydroxyl of carbon atom (2) lead to a change of direction of rotation. Thus, diacetyl propylene glycol, the bromoacetyl derivative, the diurethane (phenyl), all rotate in a direction opposite to that of the glycol.

But, regardless of any conclusion that will be reached concerning the configurational relationships between propylene glycol and the oxide, the synthesis of β-hydroxybutyric acid does not contradict the view formulated on the basis of the consideration of the combined results from the experiments on the degradation of β-oxybutyric acid on one hand, and from those on the reduction of lactic acid on the other. Thus, we are justified in assuming that those forms of lactic acid and of oxybutyric acids are configurationally related which rotate in the same direction.

It is well established that levo-lactic acid belongs to the d-series; hence, also levo-β-hydroxybutyric acid belongs to the d-series. In the d-series of the α-substituted acids, the metal salts have a higher dextrorotation than the free acids. The same is noted also in levo-β-hydroxybutyric acid. Thus, it seems probable that the rule which permits the classification of the α-substituted applies also to the β-substituted acids.

The experimental work was done in cooperation with Dr. H. L. Haller and Dr. A. Walti.

DISSOCIATION IN THE METHYLATED SUGARS

by

W. Lee Lewis and E. L. Gustus

Recently Mr. E. L. Gustus has studied in the laboratory at Northwestern University the products which result when 2,3,4,6-tetra-methyl glucose is oxidized with 13. moles of hydrogen peroxide in the presence of 7.7 moles of potassium hydroxide. (Alkali 0.45 N; Temp. 45°C; Time, 3 weeks). From 180.5 g. of tetramethyl glucose he obtained 31. g. of 2,5-dimethyl d-arabino-lactose, 6.5 g. of a mixture of partially demethylated acids containing four carbons, 24.22 g. of carbon dioxide, and 60.98 g. of formic acid.

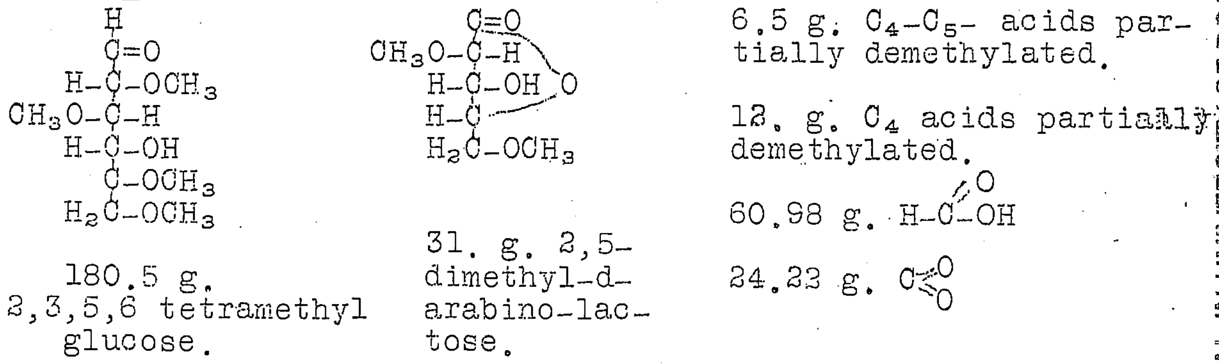


Fig. 1

Main Products on Oxidizing Tetramethyl Glucose.

It is not my purpose here to discuss the experimental aspects of this study, although they presented difficulties, but rather to point out what I believe to be an opportunity to test by this method the validity of certain reactions ascribed to the non-methylated sugars.

The relatively large amount of an acid containing five chain carbons, particularly d-arabonic, isolated in very pure form, together with the large amount of formic acid and carbon dioxide, indicates that when this substance was oxidized it broke very largely between the first and second carbon atoms. This at once raises the question of why a breaking at this point is favored over a breaking of the molecule between some other pair or pairs of carbons. The observation becomes of special interest when we recall that it was only in the later stages of the studies by Nef and his students on the products of oxidation of hexoses in the presence of alkali that he was able to demonstrate a breaking of the molecule between the first and second carbon atoms.

In order to explain what I believe to be the significance of this result and to indicate further how the reactions of the methylated sugars should clarify certain reactions of the non methylated sugars, it will be necessary to review in part Nef's theories of dissociation in the sugar molecule.

When the normal hexoses are oxidized in alkaline solutions by such agents as copper salts, air, and hydrogen peroxide, Nef and his students have shown that there are formed such acids as gluconic, mannonic, arabonic, erythryonic, threonic, glyceric, glycollic, oxalic, formic, and carbon dioxide. In other words, there are found present in the reaction mixture acids containing from six carbon atoms to one, indicating that the sugar molecule during the course of the oxidation has in effect successively broken apart between each pair of adjacent carbon atoms.

So far as the same studies have been extended to the disaccharides, they show the same acids except that these acids are mainly formed from the component hexose carrying the free

Dissociation in the Methylated Sugars (con.)

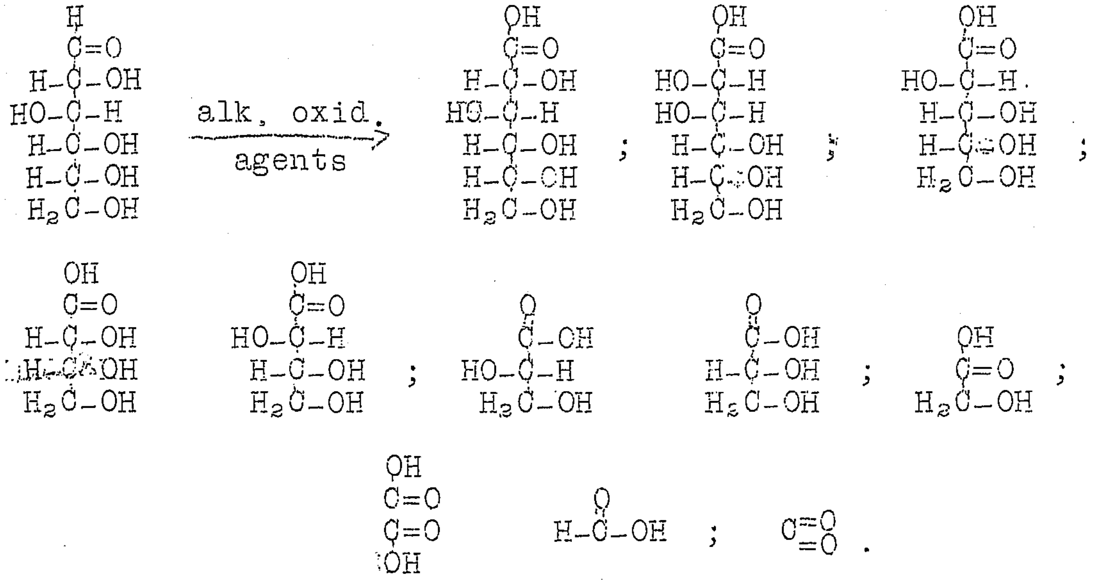


Fig. 2

Glucose and Typical Acids Obtained on Alkaline Oxidation

aldehyde, and thus appear in the reaction mixture with glucose attached as glucosido acids. Hydrolysis of these results in free glucose and the above acids.

Nef explained the presence of these acids by assuming an intermediate formation of ene-diols through the selective addition and splitting off of water.

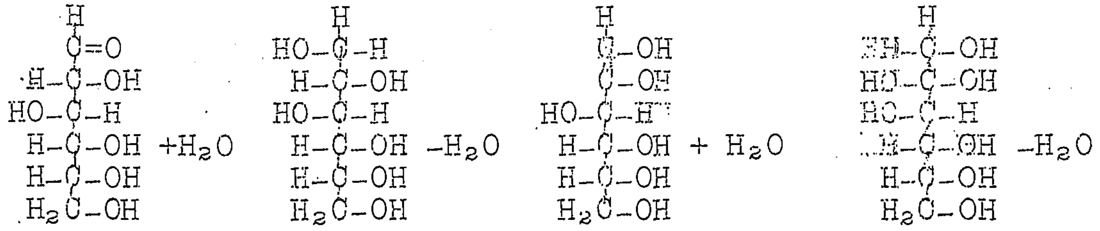


Fig. 3

The Formation of Ene-diols

by the Selective Addition and Loss of Water

Dissociation in the Methylated Sugars (con.)

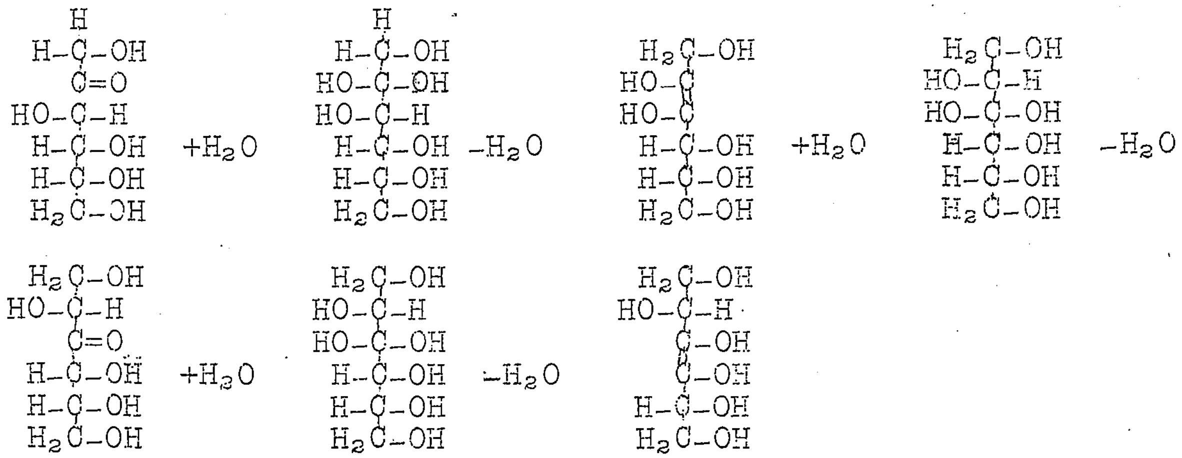


Fig. 3 (con.)

The Formation of Ene-diols

by the Selective Addition and Loss of Water

There would seem to be no theoretical reason why this process should not continue to the formation of a 4,5, and even a 5,6-ene-diol, but I know of no experimental evidence to support the assumption.

In simplest outline, Nef further postulated that those several ene-diols then dissociated in the point of the double bond, the resulting fragments being oxidized directly to the corresponding acids.

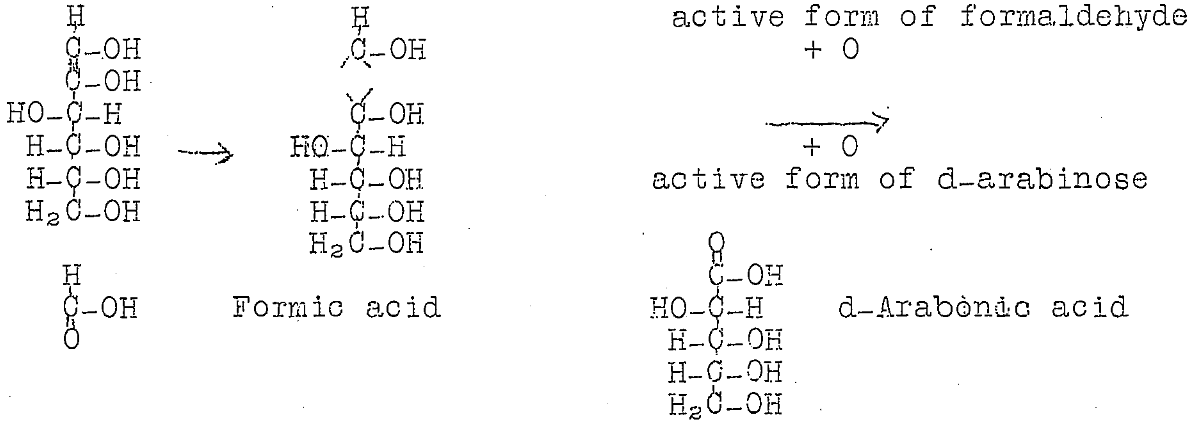


Fig. 4

Dissociation of Ene-diols

Dissociation in the Methylated Sugars (con.)

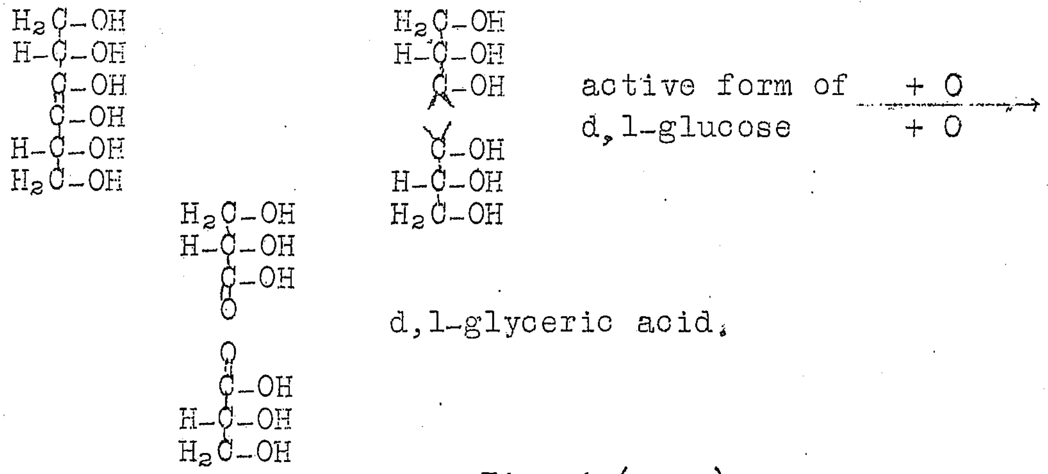


Fig. 4 (con.)

Dissociation of Ene-diols

The actual total possibilities are, however, much greater from the fact that when an ene-diol goes to a ketose the adjacent double-bond carbon becomes asymmetric and can assume either optical form.

Thus, the 3,4-ene-diol would in reality result in four sugars:

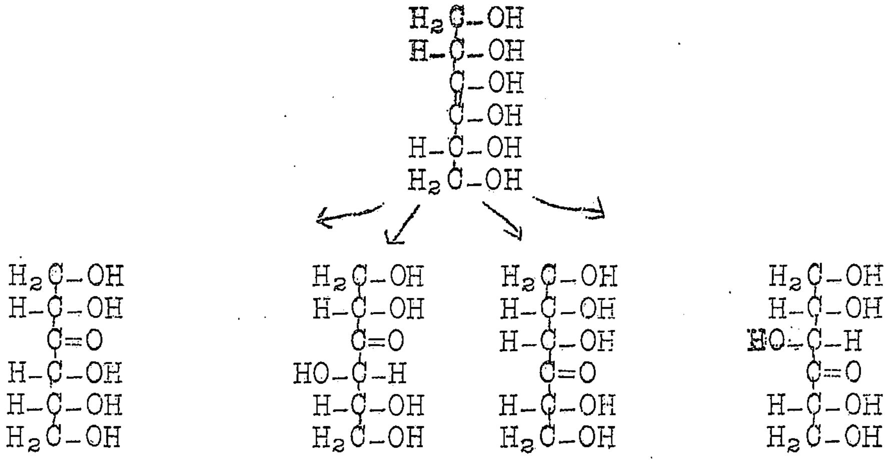


Fig. 5

Other Possible Rearrangements

Moreover, the various active aldehydic forms of the pentoses, tetroses, and trioses resulting from dissociation at

Dissociation in the Methylated Sugars (con.)

the double bond could rearrange to the ordinary aldehyde form giving corresponding isomeric ene-diols, their split products, and ketoses.

The pursuance of all of these reactions, however, through their logical sequences is not essential to our present purposes.

The above equations are intended, therefore, to be illustrative rather than comprehensive. They, however, offer adequate background for the present argument.

If this series of events, namely, selective hydration and dehydration, enolization, dissociation and oxidation, representing exactly the manner in which the final acid arises, then there seems to be no reason why a <u>methylated sugar</u> should not give the corresponding series of acids containing 1, 2, 3, 4, 5, and 6 carbons.

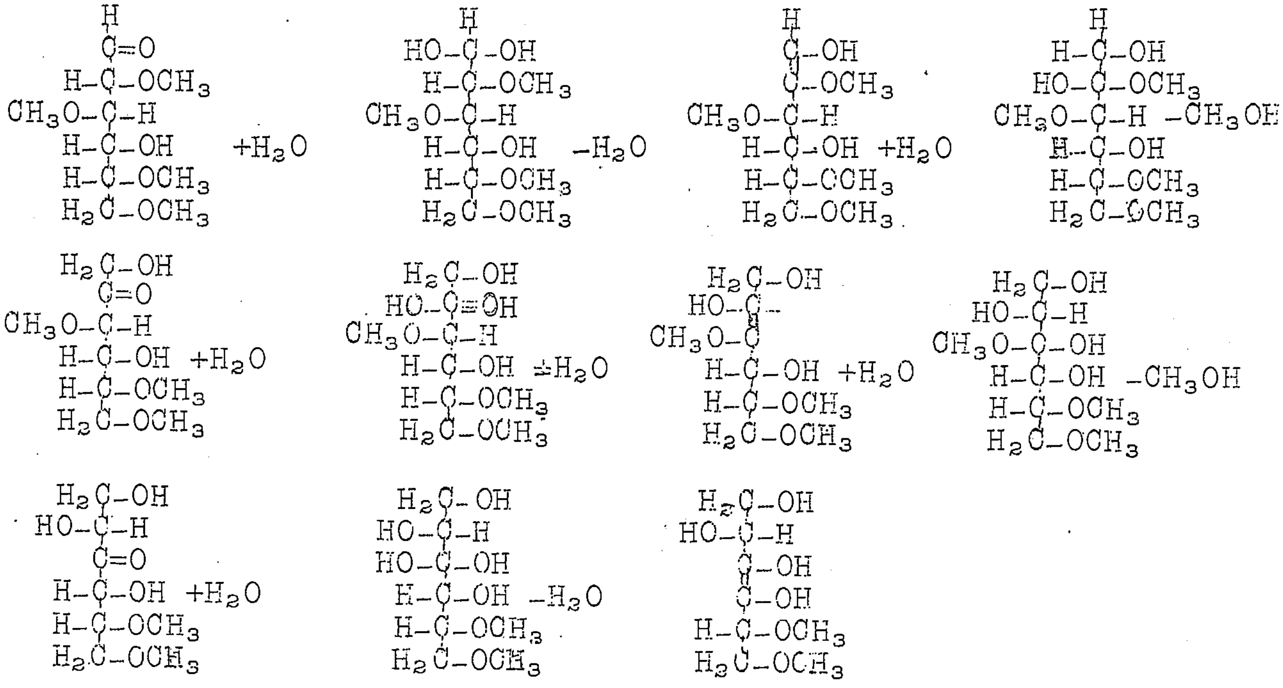


Fig. 6

Extension of the Theory of Methylated Sugars

Dissociation in the Methylated Sugars (con.)

These various ene-diols would undergo dissociation and oxidation, the active aldehyde forms would rearrange and enolize independently, all exactly in the same manner as the non-methylated homologues, for we must accept that the hemi-acetal group, $HO-C-OCH_3$, is just as unstable as the dihydroxy carbon group, $HO-C-OH$. It would lose methyl alcohol with the same readiness as the latter loses water.

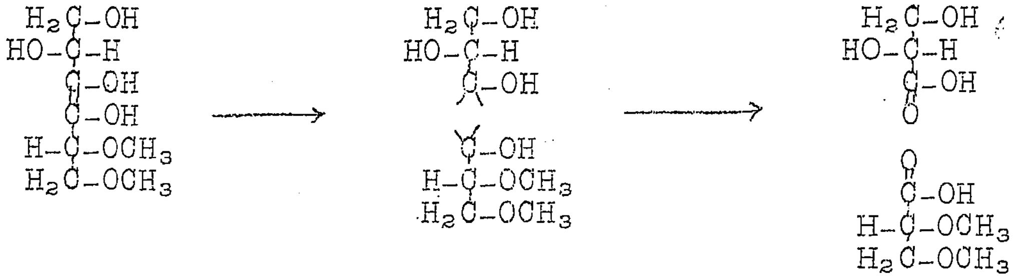


Fig. 7

Oxidation of the 5,6-Dimethyl-2,3-ene-diol of Mannose

Note also that the methylated sugars enable one to predict with exactness the character of the reacting acids, whose separation should be facilitated by the differences in optical and structural isomers accentuated by the methyl groups. Since, however, the oxidation products are experimentally different, we would be led to suspect that the mechanism of the reaction of the methylated sugars may not be exactly like that postulated by Nef for the non-methylated under the conditions, or possibly a slight modification of the latter theory would bring both sets of reactions again into harmony without delimiting any of the beautiful adequacy of Nef's theory.

We believe that such modification is found by simply assuming that ene-diols in the sugar molecule under the influence

Dissociation in the Methylated Sugars (con.)

of alkalis do not form through the selective addition and splitting off of water but through a simple enol-ketol tautomerism.

Such a modification adequately explains the formation of all ene-diols from a non-methylated sugar, accounts for the increased breaking between the first and second carbon atoms in the tetra-methylated glucose, and brings experimental results to date in harmony under one common explanation.

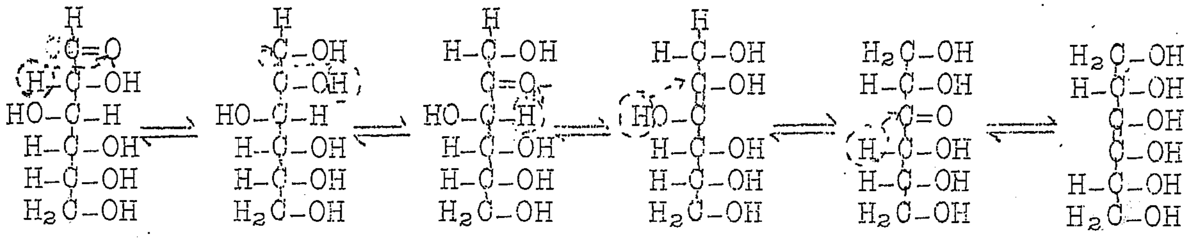


Fig. 8

Keto-enol Tautomerism in d-Glucose

If, then, the preliminary ene-diols are formed by a simple keto-enol tautomerism rather than the selective addition and splitting off of water, we should be able to predict wherein the oxidized products from the methylated sugars should differ from those derived from the methylated sugars in consequence of the replacement of active hydrogen by the comparatively non-labile, non-polar methyl group.

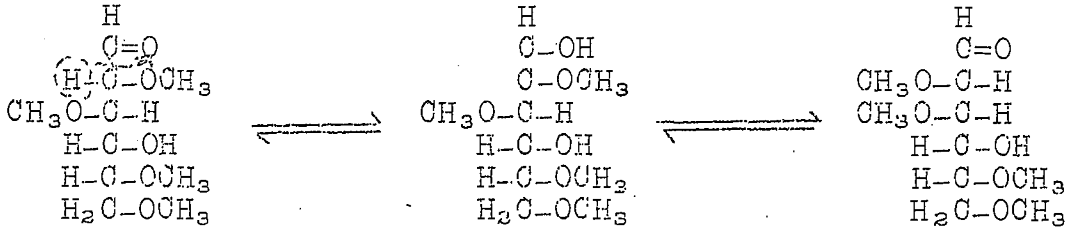


Fig. 9

Formation of Ene-diols in Methylated Sugars

by the Simple Enol-ketol Change

Dissociation in the Methylated Sugars (con.)

For the homologous ketone to form would involve the methyl attached to oxygen on the second carbon atom jumping to carbon atom no. 1. This is theoretically improbable though not absolutely without precedent. That it does not occur is evidenced by the large amount of formic and carbon dioxide, as well as 2,5,-dimethyl-d-arabino-lactose, resulting from the oxidation with alkaline hydrogen peroxide of 2,3,5,6-tetramethyl-d-glucose. Moreover, if this did happen and the 2,3,-ene-diol did form, there would result on oxidation the very characteristic d,l-lactic acids.

These considerations may profitably be extended to the Lobry de Bruyn-Van Ekenstein reaction. For simplicity, we will confine our illustrations to that part of the Lobry de Bruyn-Van Ekenstein reaction which has to do with the reciprocal interconversion of the simple hexoses, methylated and non-methylated, i.e. glucose, mannose, and laevulose. This is warranted by the fact that we have proved experimentally that the Lobry de Bruyn-Van Ekenstein equilibrium can be so regulated by temperature and strength of alkali as to limit the system to the simple interconversion of these three members. The same considerations may, however, be profitably extended to the more deep seated interconversion of the same reaction.

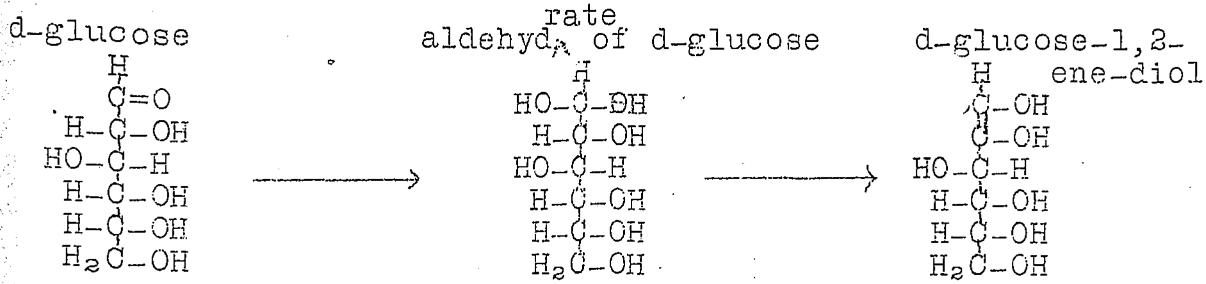


Fig. 10

The Simple Lobry de Bruyn-Van Ekenstein Equilibrium

Dissociation in the Methylated Sugars (con.)

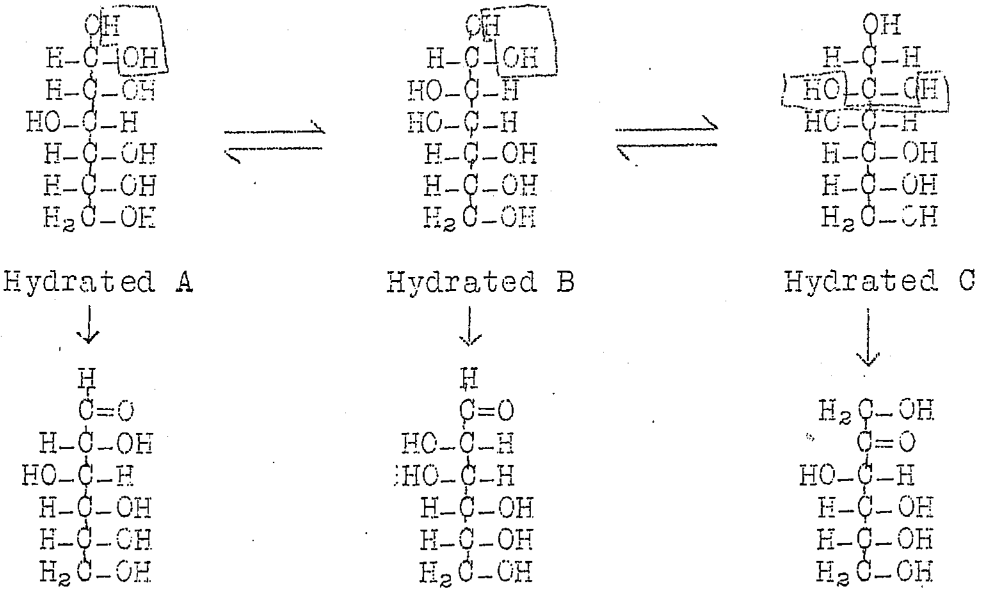


Fig. 10 (con.)

The Simple Lobry de Bruyn-Van Ekenstein Equilibrium

This finds a simple explanation by eliminating the cumbersome idea of the selective addition and splitting off of water and substituting the conception of enol-ketol isomerism.

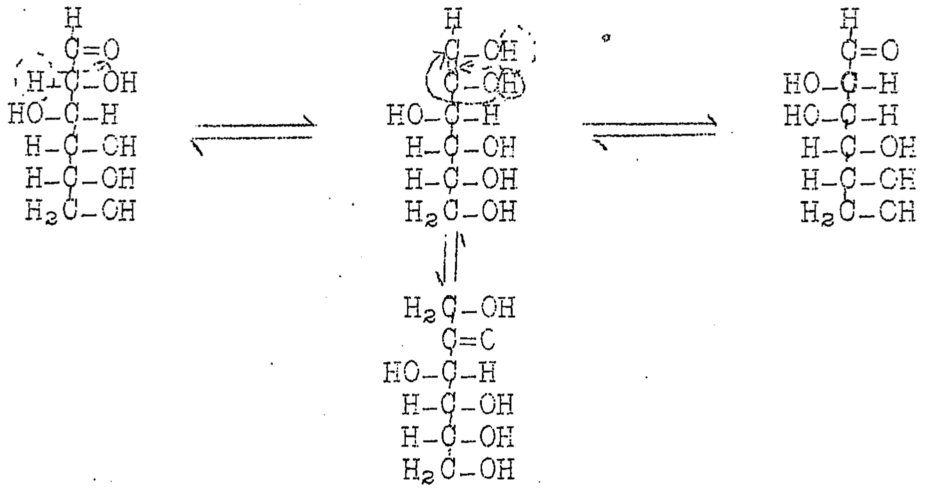


Fig. 11

Lobry de Bruyn-Van Ekenstein Interconversion

Per Enol-ketol

When, however, we apply the two methods to the corresponding methylated sugars, we get very different results.

Dissociation in the Methylated Sugars (con.)

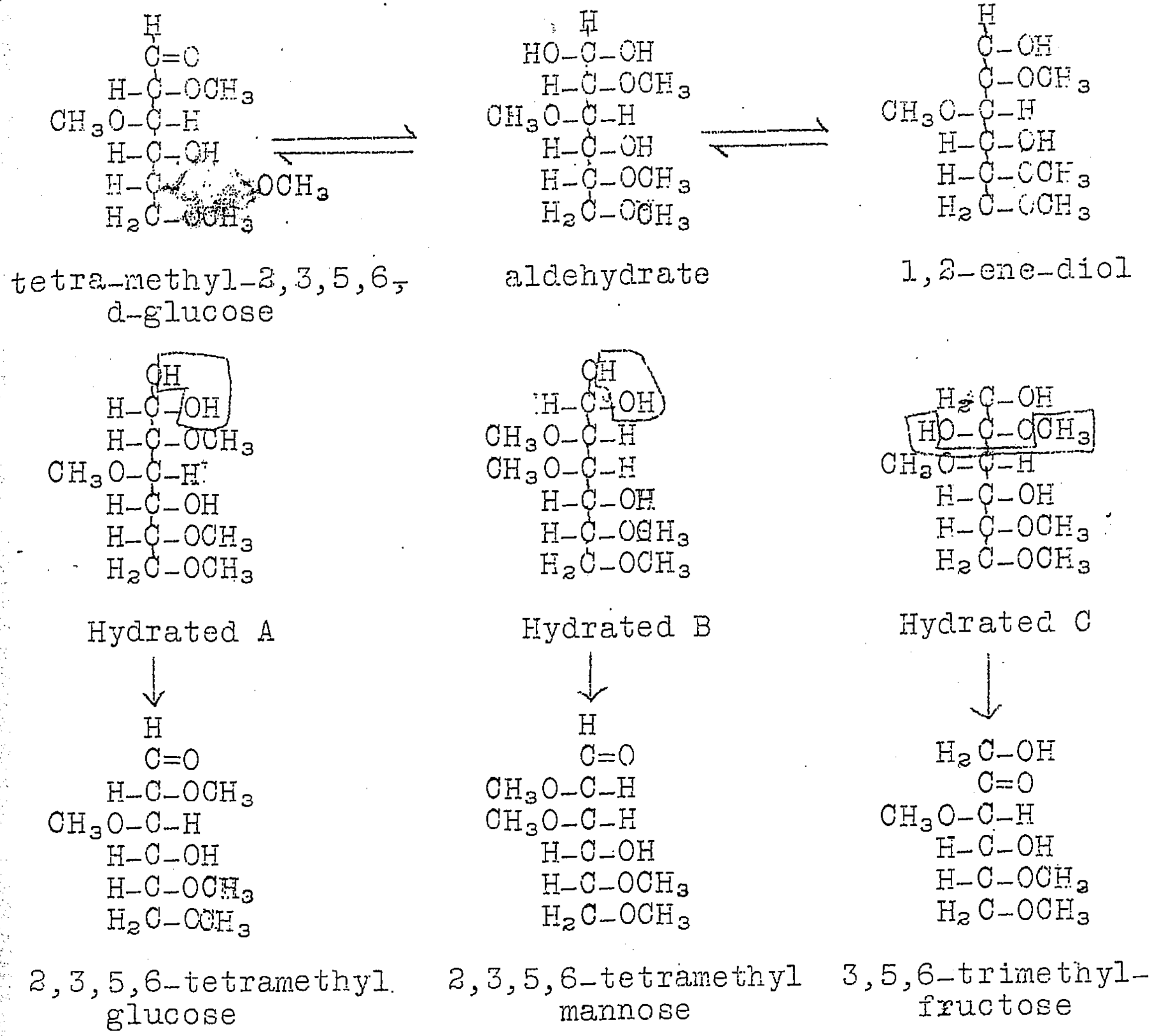


Fig. 12

Lobry de Bruyn-Van Ekenstein Interconversion

Per Hydration and Dehydration

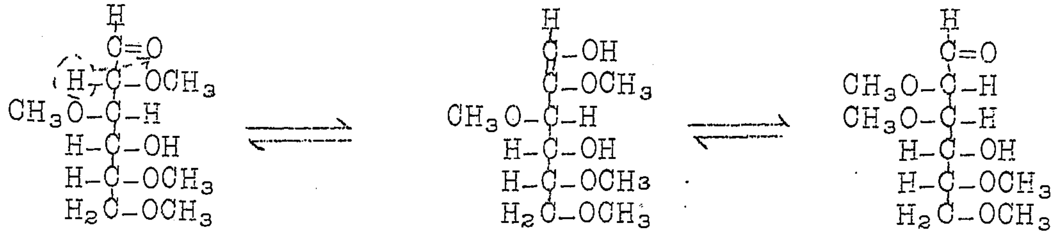


Fig. 13

Lobry de Bruyn-Van Ekenstein Interconversion

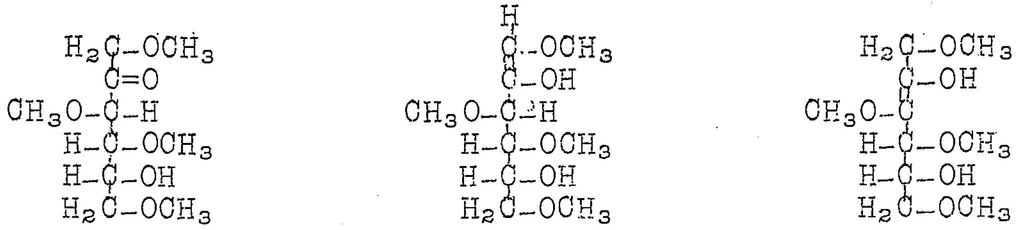
Per Enol-ketol Tautomerism

Dissociation in the Methylated Sugars (con.)

3,5,6-trimethyl fructose cannot possibly form. Assuming that the methyl in the second carbon oxygen should jump to the first carbon, we would get two methylated methyl keto hexoses.

Similarly, the same physical conditions as to alkali and temperature which induce the reciprocal interconversion of 2,3,5,6-tetramethyl glucose and mannose cannot possibly convert 1,3,4,6-tetramethyl laevulose into a homologous aldose.

The following system only can occur:



$$\begin{array}{r} H_2C-OCH_3 \\ C=O \\ CH_3O-C-H \\ H-C-OCH_3 \\ H-C-OH \\ H_2C-OCH_3 \end{array} \qquad \begin{array}{r} H \\ C-OCH_3 \\ C-OH \\ CH_3O-C-H \\ H-C-OCH_3 \\ H-C-OH \\ H_2C-OCH_3 \end{array} \qquad \begin{array}{r} H_2C-OCH_3 \\ C-OH \\ CH_3O-C \\ H-C-OCH_3 \\ H-C-OH \\ H_2C-OCH_3 \end{array}$$

Fig. 14

Lobry de Bruyn-Van Ekenstein System

With Methylated Fructose

Moreover, if these considerations be correct, the exact four acids which would result from oxidizing 1,3,4,6-tetramethyl fructose in alkaline solution can be predicted with absolute certainty.

Summary

1. Pending further confirmatory experimental evidence, it is suggested that ene-diols form in methylated and non-methylated sugars, not through the selective addition and splitting off of water as postulated by Nef, but through a simple enol and ketol tautomerism.

2. This modification is suggested as a result of finding a predominating splitting between the first and second carbon

Dissociation in the Methylated Sugars (conc.)

atoms on oxidizing 2,3,5,6-tetramethyl-d-glucose with alkaline peroxide.

3. Ketol-enol tautomerism explains all of Nef's theories of ene-diol formation, dissociation, and oxidation quite as adequately as the more cumbersome and less plausible selective hydration and dehydration.

4. Ketol-enol tautomerism quite as adequately explains all the phenomenon of the Lobry de Bruyn-Van Ekenstein effect of alkalis on non-methylated sugars.

5. However, selective addition and splitting off of water would produce the same series of ene-diols in the methylated sugars as in the non-methylated and should yield the homologous acids with one, two, three, four, five, and six carbon atoms.

6. This, however, is inconsistent with our preliminary experimental results and does not explain the greater stability of the methylated sugars. For example, 2,3,5,6-tetramethyl glucose has a reducing power of .186 to 1.00 compared to d-glucose and 2,3,5,6-tetramethyl d-galactose has a reducing power of .22 compared to non-methylated galactose as unity.

6. The application of alkalis and alkaline oxidizing agents to methylated sugars should give direct evidence in many of the reactions of non-methylated sugars for the replacement of active, mobile hydrogen by the non-labile, non-polar methyl radical, enables one to predict with great exactness the result when methylated sugars are treated with alkalis or alkaline oxidizing agents.

7. Further confirmatory experiments based on these suggestions are projected and under way.

ACETYLENE REACTIONS, MOSTLY CATALYTIC

by

J. A. Nieuwland

Very few useful or commercial products had been prepared from acetylene before the application of catalytic reagents was resorted to. In fact, very few catalysts can be used with this gas. The study of these, however, is an interesting problem inasmuch as it is possible to isolate some of the intermediate compounds, thus giving us an insight into the mechanism of catalysis itself.

It is the purpose of this discussion to outline as briefly as possible the nature of the reactions of acetylene synthesis with other organic compounds, and note the conditions under which reactions usually take place. Inasmuch as the intermediate addition products of the catalyst itself are very unstable, as they would be expected to be, a discussion of these is at present very unsatisfactory. The final products formed and the compounds with which acetylene reacts will be principally treated.

A catalyst is not always to be looked at as a substance which accelerates a reaction. The case of the preparation of tetrachlorethane with antimony pentachloride is an example where a retarding effect is desirable owing to the great reactivity of acetylene and chlorine as exemplified by the following scheme of reactions.

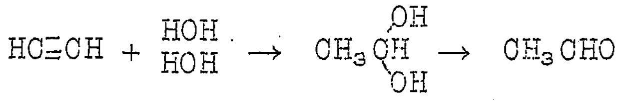
$$C_2H_2 + SbCl_5 \rightarrow C_2H_2Cl_2 . SbCl_3$$

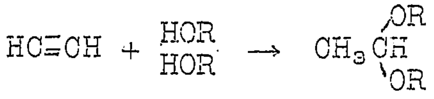
$$C_2H_2Cl_2 . SbCl_3 + 2Cl_2 \rightarrow C_2H_2Cl_4 + SbCl_5$$

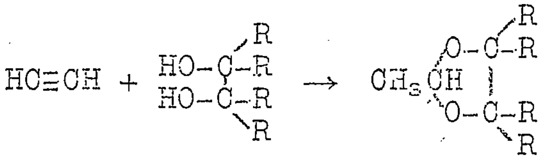
The formation of the intermediate compound takes care of the excessive energy that causes the explosions when the two gases are directly combined, so that in step the process can be performed without danger.

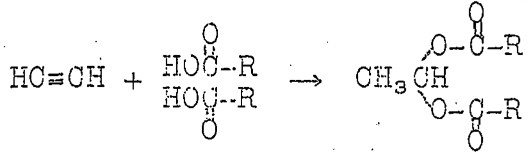
The catalysts that have been most serviceable from a commercial point of view in syntheses from acetylene of organic compounds of great variety are the salts of mercury. Halogens or cyanogen groups, however, are anticatalysts. In the presence of an oxy-acid mercuric oxide effects the addition of acetylene to any compound, aliphatic or aromatic, having labile hydrogen, with the exceptions as enumerated herewith. In all these cases the acetylene reacts usually with great rapidity and behaves as if it were anhydrous aldehyde, taking up two labile hydrogens and substituting an ethylidene group.

Hydroxyl hydrogens are usually rather easily replaced by the ethylidene group in both acids, alcohols, and neutral substances like water as shown by the following reactions.

1.

$$HC\equiv CH + \begin{matrix}HOH\\HOH\end{matrix} \rightarrow CH_3CH\begin{matrix}OH\\OH\end{matrix} \rightarrow CH_3CHO$$

2.

$$HC\equiv CH + \begin{matrix}HOR\\HOR\end{matrix} \rightarrow CH_3CH\begin{matrix}OR\\OR\end{matrix}$$
(acetals)

3.

$$HC\equiv CH + \begin{matrix}HO-C(R)_2\\HO-C(R)_2\end{matrix} \rightarrow CH_3CH\begin{matrix}O-C(R)_2\\O-C(R)_2\end{matrix}$$
(cyclic acetals)

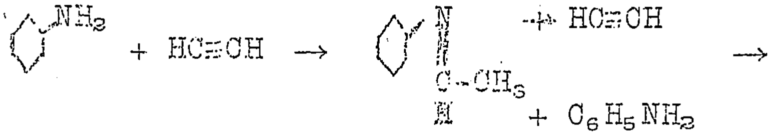
3.

$$HC\equiv CH + \begin{matrix}HOC(=O)-R\\HOC(=O)-R\end{matrix} \rightarrow CH_3CH\begin{matrix}O-C(=O)-R\\O-C(=O)-R\end{matrix}$$

The first of these reactions has been used on a large scale both here and abroad for the preparation of acetaldehyde. The latter is oxydized by air with manganese acetate as a catalyst for the preparation of glacial acetic acid. As is evident by reaction (3) this may be further combined with acetylene to form ethylidene diacetate which may be converted into acetic anhydride.

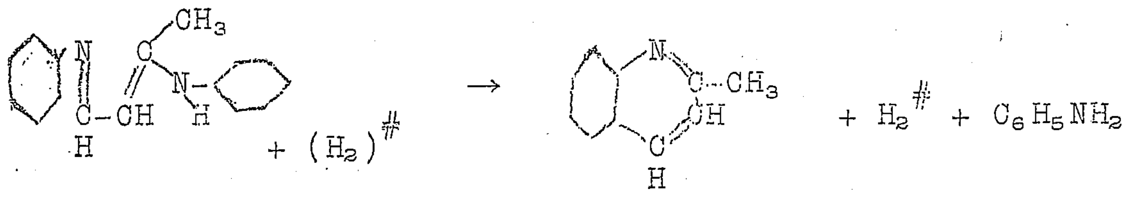
The labile hydrogen in the group, $-\overset{O}{\overset{\|}{C}}-CH_2-\overset{O}{\overset{\|}{C}}-$, may be readily substituted by the ethylidene group, provided the compound itself will not be destroyed by the acid used in the reaction. So, for example, malonic ester may be converted to ethylidene malonic ester, etc. It becomes more difficult to effect reaction in formation of acetals and acid ethylidene ethers as the molecular weight of the acid or alcohol increases.

In the aromatic series similar introduction of the ethylidene group results with greater or less ease in para or ortho position depending upon the presence of previous substituents. As a rule no substitution results when an element already substituted is doubly or trebly bonded to another. Nitro aryl compounds, aromatic aldehydes, nitriles, acids, naphthalene, etc., cannot be made to react in the nucleus. Aniline reacts with the more active amino group forming a mixture of quinaldine, o, p, and N, -ethyl anilines, hydroquinaldine, and indole in small quantity. Benzaldehyde forms cinnamic aldehyde in small quantity. Tertiary aromatic amines do not react.

4.



Acetylene Reactions, Mostly Catalytic (con.)

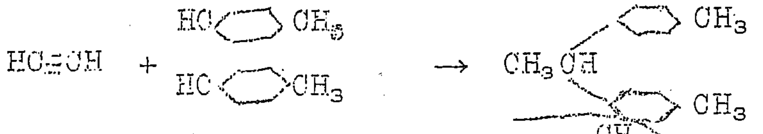


(# The hydrogen is used to change quinaldine to hydroquinaldine and ethylidene aniline to N-ethyl aniline which forms o and p ethyl aniline).

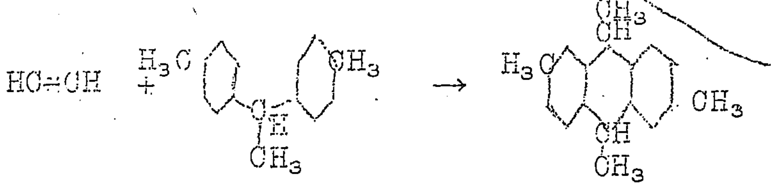
Of the aromatic compounds the phenols form compounds with the greatest ease in aqueous, alcoholic, glacial acetic acid solutions, or alone with sulphuric acid and catalyst. The first products are o, or p-ethylidene diphenylols, which further polymerize in excess of acetylene to fusible insoluble resins.

In general the heavier and higher substituted hydrocarbons of the aromatic series react more readily than benzene itself. Diphenyl ethane is obtained in small yield and with difficulty. The reaction takes place at low temperature in presence of ordinary strong sulphuric acid and mercuric oxide or sulfate or, better, both. At higher temperatures very insoluble triarylbutanes result. There is nearly always formed a small amount of dimethylanthracene hydrides. In fact, with sulfuric acid and catalyst the diarylethanes can be further converted into the anthracenehydrides mentioned by separated process.

5.



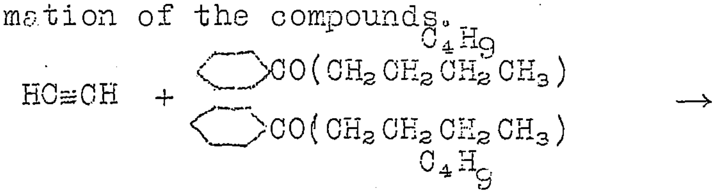
6.



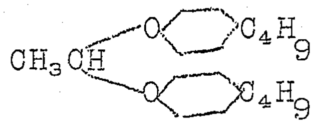
The diaryl ethanes are high boiling viscous liquids which when pure are not notably fluorescent. Besides the compounds already published in the Journal of the American Chemical Society from our laboratory, dicymyl ethane and bis-tetrahydronaphthalene ethane have been prepared. The latter boils at 396° C. and forms a dimethyldecahydronaphthanthracene by further reaction with acetylene. These hydroanthracenes are readily separated from the substituted aryl ethanes with petroleum ether in which the former are less soluble. It is a notable sidelight on the relation of substitution of the ethylidene group by acetylene that, although naphthalene does not combine with acetylene, tetrahydronaphthalene (tetraline) does so quite readily. Moreover, although α-naphthol substitutes in the ring, β-naphthol forms an ether in almost quantitative yield, indicating that the former has the hydroxyl in the aryl, the latter in the alicyclic ring. It is interesting also that no hydroanthracene derivatives can be made frommesitylene, as is evident from its structure.

The phenol ethers combine with acetylene with the same reactivity as the aryl hydrocarbons, but the more complex ethers like ethylene bis-phenyl oxide react slowly. New compounds of phenetol, ethyl and methyl ethers of the cresols, resorcinol, and hydroquinol have been made. These are mostly difficultly crystallizable, low-melting solids. The length of the aliphatic side chain does not seem to interfere with the ease of formation of the compounds.

7.

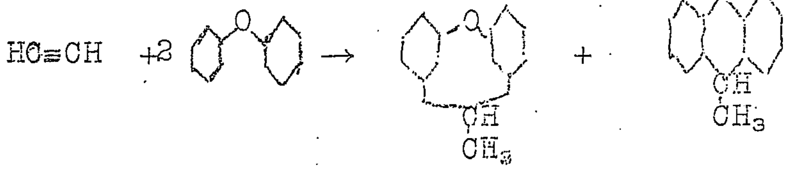


$$HC\equiv CH + \begin{matrix} C_4H_9 \\ \bigcirc CO(CH_2CH_2CH_2CH_3) \\ \bigcirc CO(CH_2CH_2CH_2CH_3) \\ C_4H_9 \end{matrix} \rightarrow$$



Diphenyl oxide forms beside the para substitution product a small amount of methylxanthene. The latter boils about 430° C.

8.



A new catalyst, cuprous chloride, in presence of a concentrated aqueous solution of primary amines, such as ammonium chloride, alkyl ammonium chlorides, urea, even pyridine chloride polymerizes acetylene in form of neutral copper salts from which the hydrocarbons can be distilled. An excess of cupric chloride with a trace of cuprous chloride forms the mixture of cis and cis-trans dichlorethylenes quite free from other halogenated acetylenes.

Divinyl acetylene forms a host of new addition products too numerous to mention. The two brom addition products with four and six bromine atoms added are very characteristic and stable compounds. A compound with hydrobromic acid is strongly irritant to the eyes.

It will be seen from the foregoing that the possibilities of reactions of acetylene catalytically affords considerable field for still further research, and only those reactions have been referred to which in any way are effected by catalysts, which, though not a new weapon in the field of acetylene chemistry, will eventually result in opening still wider possibilities of investigation.

THE OPPORTUNITIES FOR RESEARCH IN ALIPHATIC CHEMISTRY

by

James F. Norris

One of the most interesting and profitable diversions for the student and worker in any branch of science is to put aside his work now and then and review the recent progress and the trend of inquiry in his own field. I have occupied myself of late with such a study and am glad to have the opportunity to bring to the attention of the leading organic chemists of America one phase of our science which appears to me to be worthy of more intensive development. I hope to be able to make clear to you some of the great opportunities for research in aliphatic chemistry and to show that the results of such research will materially advance organic chemistry in both theory and practice.

In recent years there has been much activity in this field, and many notable advances have been made, especially on the industrial side. This development has been largely the result of two causes: the war, which made demands for large quantities of certain organic raw materials, and the desire to utilize more economically valuable by-products of the petroleum industry. The demands for acetic acid and acetone and for solvents to replace fusel oil and its esters were so successfully met, and in such a striking way, that chemists immediately visioned other triumphs in this field. The utilization of the gases obtained as a by-product in cracking petroleum is an impressive example of industrial progress.

The rapidly increasing use of motor fuel has led to a search for a substitute for gasoline with the result that a beautiful synthesis for methyl alcohol has been devised. The success in the utilization of the olefines obtained by cracking petroleum has materially led to work looking toward the more extensive use of petroleum as a raw material in chemical industry.

These noteworthy advances in the industrial applications of aliphatic chemistry have all been built on the pioneering work of investigators in the pure science. Before the world can benefit from additional applications, much fundamental research must be accomplished. I shall point out, presently, subjects for research the results of which will find immediate application in building up chemical industries based on aliphatic chemistry, and other researches which will lead, in my opinion, to improvements in the petroleum industry from the standpoint of the chemistry of the processes used. The scientific development of this industry has been marked in recent years, but most of the attention has been devoted to engineering problems; the opportunity for the chemist is still a great one.

This condition was clearly seen some time ago by Mr. Van H. Manning, who was then the director of research of the American Petroleum Institute. He sought the advice of some of the leading chemists of the country and drew up with the active cooperation of Dr. Benjamin T. Brooks a comprehensive plan for fundamental research underlying the use of petroleum. Later, a committee on petroleum was set up by the Division of Chemistry and Chemical Technology of the National Research Council, with Dr. Brooks as chairman. This committee worked in cooperation with Mr. Manning, and a revised scheme was developed, which won the active endorsement of the officials of a large petroleum company. The results of these efforts have recently been announced. Mr. John D. Rockefeller has provided a fund of $250,000, which is to be spent in encouraging and financing research in the chemistry of petroleum. Final plans for the administration of the gift have not yet been made, but it is safe to assume that the chief attention will be paid to research of a fundamental character – the kind that will appearl to the academic investigator. It is my opinion that the success of this experiment will be so great that additional sums of money will be forthcoming. The gift of Mr. Rockefaller is evidence of his appreciation of the work of chemists and is a great incentive to enter this long neglected field and show what our science can do.

I have stressed up to this point the development of aliphatic chemistry in industry, and it is now time to emphasize the fact that the more intensive study of the paraffin and olefin hydrocarbons and their derivatives will lead to a deeper understanding of the very fundamentals of organic chemistry. The time has come to devote more attention to how molecules interact rather than to what is formed by their interaction.

The nature of the bonding between atoms should be more intensively studied. The investigation of how the forces between atoms vary with changes within the molecule will lead ultimately to a conception of the organic molecule in accord with the modern views of the nature of matter. The problem of valency can be studied best with the carbon atoms because it can unite with elements of such diversified properties, and because the bonding with other atoms is so markedly modified by changes in the make-up of the molecule. Aliphatic chemistry is the most promising field in which to study the chemical properties of the carbon atom; the compounds are simpler in composition and any graded changes in the property under investigation can be readily brought about by variations in the substituents within the molecules.

What is the present status of our knowledge in this field, and why is it advisable to stress the needs and opportunities for research? To one who is working in certain divisions of aliphatic chemistry it is evident that very little is known about compounds of great interest. In recent years aromatic chemistry has attracted the attention of much the larger proportion of the investigations in organic chemistry. Compare, if you will, the number of pages in Beilstein devoted to aliphatic chemistry with the number devoted to aromatic chemistry. Look up benzene, hexane, hexylene, hexadiene, and see what you can find about these hydrocarbons. What do we know about the action of such common reagents as chlorine, sulphuric acid, and nitric acid on all these important compounds? See if anyone has studied the chemical behavior of the olefines of high molecular weight. How can you detect their presence in a mixture, and how do they behave with sulphuric acid? You will find practically nothing and yet we are preparing for the market and using quantities of these compounds that can be expressed only in numbers almost beyond comprehension. Compare, if you will, our knowledge and use of petroleum. Knowledge leads to use. The reason for the differences we find in the two cases is evident.

Why have the aliphatic hydrocarbons and their simpler derivatives been neglected? In large part, I think, because the manipulation of aromatic compounds was easier. Solids are readily handled and purified; liquids present greater difficulties. Beautiful crystals have a fascination that the chemist cannot resist. Consider our knowledge of the chlorination of benzene and of hexane. The reason I have given is a good and sufficient one. But the conditions have changed since the early work was done. We can now handle liquids conveniently. Fractionating columns of great efficiency have been designed. I have been observing recently the results of fractionation with a Widmer column which performs wonders in working on the laboratory scale. We can now distil at hundredths of a millimeter pressure and handle compounds that were outside the possibilities of study only a few years ago.

It has been supposed for years that the paraffin hydrocarbons were very inert and not, therefore, a fruitful field for study. This is not the truth in general, but in the case of inactive compounds we have the means to hasten reactions. The importance of rapid stirring as a laboratory aid and the marked influence of increased pressure on the rate of sluggish reactions have been emphasized by Reid. The knowledge of the behavior of catalytic agents has grown since the paraffin hydrocarbons were studied. We have these new laboratory tools that can be used in future work.

The recent industrial development in aliphatic chemistry has furnished for future synthetic and other work many substances which were formerly obtained only at the expense of much labor. We can now obtain acetaldehyde, certain glycols, chlorohydrins, secondary and tertiary alcohols, and from these by simple methods prepare a great variety of many types of compounds Other substances will no doubt be available. Cheap raw materials in a reasonable degree of purity for research markedly affect the growth of our science. Industries based on aliphatic chemistry and, particularly, on petroleum will furnish such compounds; and I foresee a development similar to that in aromatic chemistry where the relationship between the industry and the pure science is strikingly evident.

The Committee on the Chemistry of Petroleum of the National Research Council is now at work studying the problem of research in this field relative to the proposed fundamental investigation of the chemistry underlying the petroleum industry. This study and the report of Mr. Manning's committee will be of great service in outlining work of value. It is important to differentiate clearly research which has to do with a complex mixture like petroleum and that which starts with individual compounds of a known state of purity. It is one thing to study the cracking of petroleum and another to investigate the behavior of a single compound when decomposed by heat under definite conditions. An understanding of cracking and the intelligent use of the process can only come after the work with pure substances has been done. Research with pure substances can be classed as fundamental. Under these conditions the results obtained can be interpreted; and they can be immediately applied in the industries.

I shall now point out a few opportunities for research the results of which will be fruitful. The paraffin hydrocarbons are worthy of study. Worstall showed years ago that they could be nitrated and sluphonated, but little else has been done. The early work on halogenation left the field ~~hardly~~ touched. We are to hear tomorrow of some important work on the oxidation of these compounds. I firmly believe that research will result in making paraffin hydrocarbons the raw materials for the production of compounds of industrial significance. We must get away from our prejudice against the paraffins, which were so unfortunately named. New methods of synthesis should be sought and attention paid to methods of identification. The application of the principle of critical solubility to these compounds has given us a new tool. It is probable that other physico-chemical methods could be used with advantage. Very little is known of hydrocarbons with branched chains; and those that contain a tertiary carbon atom have not been studied at all except in a very few cases. We cannot understand the behavior of petroleum until we know how compounds of these classes react. The synthesis and study of hydrocarbons made up of condensed systems of four membered rings would no doubt be of value.

Much additional work must be done on the decomposition by heat of hydrocarbons of known structure. The behavior of compounds containing straight chains, branched chains, and points of unsaturation will lead to an understanding of the influence of structure on the linkages in the hydrocarbon molecule. The decompositions should be studied in the presence of a variety of catalytic agents, since it has been shown in the case of certain compounds that these agents are selective in their effect.

The olefines offer a fascinating opportunity for work. They are exceedingly reactive and alterations in structure produce marked changes in chemical reactivity. The determination of the free energy content of the isomeric amylenes would no doubt lead to conclusions of profound importance in the interpretation of atomic linkings and of the nature of what we call a double bond. Michael and his pupils have done pioneer work in olefine chemistry, the significance of which has hardly been recognized; but much lies ahead.

The mechanism of polymerization can be advantageously studied in this field. This involves the study of the structure of the polymers, which in all probability are higher olefines. New methods of synthesis are needed and here, as in the case of the paraffins, the compounds of high molecular weight should be investigated. We know nothing of the chemical behavior of such substances or how to identify them, although they in all probability play an important, ~~if~~ not the essential, part in lubrication.

The olefines can be made the starting point in the synthesis of many compounds. A number of them can be prepared from the secondary and tertiary alcohols that will be available before long.

A still more profitable field for research can be found in the diolefines. With these compounds interatomic forces can be studied. They and their derivatives readily undergo rearrangements and are exceedingly reactive. They furnish the best opportunity to study the behavior of atoms so bountifully supplied with chemical energy that they enter into reactions with the slightest provocation. The tendency for compounds of this class to polymerize to substances of the same general character as rubber makes their study particularly attractive. New methods of synthesis should be devised from cheap raw materials and the relation between structure and chemical behavior fully investigated. Little is known. The behavior of the simpler members of the series with such a common reagent as sulphuric acid is not recorded in the literature. It has been reported that the cracking of petroleum yields diolefines. The possibilities of developing this fact lead to almost fanciful conclusions. Shall we make rubber from petroleum some day? I believe it will be done.

Great advances have been made recently in the utilization of acetylene in synthesis. We are all familiar with the contributions of Dr. Nieuwland and the applications of acetylene in the preparation of products of industrial significance. There seems to be no end to what can be done. Improved methods for the synthesis of the homologues of acetylene would prove of value. Various catalytic reagents appear to act quite differently in condensations with acetylene. Further studies would lead to a fuller understanding of catalytic action.

The extensive use of lacquers in the automobile industry is an incentive for the study of the higher alcohols and their esters. A number of these alcohols, both secondary and tertiary, will soon be available and much interesting work can then be done. The tertiary alcohols are of particular scientific interest on account of the fact that they contain a very reactive hydroxyl group and a very inert hydroxyl-hydrogen. For this reason they should be classed by themselves. No doubt syntheses could be effected from them which are not possible in the case of other alcohols. The preparation of alcohols directly from paraffin hydrocarbons would be an advance of prime importance.

The higher fatty acids on account of their extensive use in the free condition or as esters are worthy of detailed study. New, cheap synthetic methods for these compounds from hydrocarbons would result in a revolution in many of our industries. The history of industrial organic chemistry leads us to believe that this problem will be solved. How long will it be before the chemist makes fats and soap from petroleum?

I have stressed the importance of finding new synthetic methods. The success obtained in the case of acetaldehyde, acetic acid, and methyl alcohol makes us confident of the future. I would place formaldehyde and acetic anhydride in the first rank among the compounds which should be studied from this point of view.

It is possible to take up one class of compounds after another and point out, in each case, opportunities for research. But the time available makes that impossible, and, further, I have accomplished my purpose if your attention has been centered on the desirability of going back to a branch of organic chemistry that has received but scant attention in recent years.

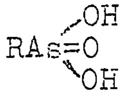
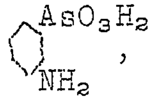
Emphasis has been put upon the kind of research which will be of value in developing potential industries. To one who has studied the relationship between pure and applied science in the industries based on organic chemistry it is clear that the advances in both branches of the science have resulted from the cooperation between the workers in the two fields. Some of us are apt to think that all the credit should be given to the investigator who shuts himself off from the world and its problems. Where would he be without the results of industrial development and without the problems that naturally spring up in the study of large scale operations and the technical use of the results of pure science? It is only necessary to study the dyestuff industry to see what an incentive it has been in the development of pure organic chemistry. Let us recognize this fact and busy ourselves with the pure science which has great possibilities ahead from the standpoint of its applications. There will be many by-paths discovered which will lead to new fields for research. The formulation of the fundamental problems springing from industrial processes furnished us with such subjects for research as catalysis in all its phases, the effect of structure on chemical reactivity, the energy relations involved in the interaction between molecules, molecular rearrangements, the nature of the bonding between atoms; in fact, the fundaments of organic chemistry. Why not investigate these problems with the very compounds which have been or can be used for the good of the world? Advance will be more rapid if this is done.

America is taking a commanding position in chemical research. Should we not turn our attention to the study of one of our great natural resources - petroleum - and build up the chemistry of the products obtainable from it? We have lagged behind. Dr. H. S. Davis has been studying recently the literature of the diolefines. Up to 1910 but three percent of the published papers were produced by American chemists; only nine percent appeared in the English language, whereas Russia furnished forty-six percent of the whole. A study of the work subsequent to 1910 would probably yield similar results. We have a fruitful field before us. Let us grasp the opportunity.

THE PREPARATION OF ARSONIC ACIDS

by

C. S. Palmer

An arsonic acid is defined as a substituted arsenic acid in which one hydroxyl group has been replaced by an organic radical and has the general formula,  $RAs\begin{matrix}\nearrow OH\\ =O\\ \searrow OH\end{matrix}$ or $RAsO_3H_2$. (Table I). The first aliphatic arsonic acid was methylarsonic acid, $CH_3AsO_3H_2$, which was prepared by Baeyer (a) in 1858 starting with cacodyl chloride. Béchamp (b) obtained the first aromatic arsonic acid, arsanilic acid, , in 1863 by heating an excess of aniline with arsenic acid at temperatures somewhat lower than used in the preparation of magenta, but the product was supposed to be an anilide of arsenic acid until Ehrlich and Bertheim proved its structure in 1907. In the meantime the first member of the aromatic series, phenylarsonic acid, and some of its homologues had been synthesized by Michaelis. Arsonic acids have found application in the treatment of certain diseases such as African sleeping sickness and paresis, but their chief importance lies in use as intermediates in the preparation of therapeutically important arseno- compounds such as the arsphenamines. The various methods for preparing the arsonic acids may be classified under three general headings.

Most of the arsonic acids in the literature have been prepared by substituting in other arsonic acids (Table Ia). Thus, numberous derivatives of arsanilic acid have been made by replacement of one or both hydrogens in the amino group or one or more hydrogens of the benzene ring. On the other hand, there seems to have been practically no successful substitutions of an aliphatic arsonic acid, such attempts resulting in the splitting off of the arsono group. All of these syntheses belong more properly to the realm of general organic chemistry than that of arsenic compounds.

The second general class of preparations are those in which some other type of organic arsenic compound is converted into an arsonic acid. (Table II). These are mainly of historical and theoretical interest. In a few special cases they still find application. Thus Lewis (c) prepared arsonated benzophenones by treating p-dichloroarsino-benzoyl chloride with $AlCl_3$ and an aromatic hydrocarbon and oxidizing the resulting arsine dichloride to an arsonic acid. In the preparation of 2-hydroxy-4-carboxyphenylarsonic acid Maschmann (d) found the product too soluble to isolate from the reaction mixture. Therefore, it was treated with H_3PO_2, throwing down the insoluble arseno compound, which was filtered off and oxidized back to the arsonic acid, which was then obtained in crystalline form.

The most interesting synthetic method is that in which the arsono group is introduced directly into the molecule. (Table III). In the aliphatic series this is done by G. Meyer's (e) reaction - action of sodium arsenite on an alkyl halide. Recently, Rosenmund (f) has attempted to extend Meyer's reaction to the aromatic series, but heating in a sealed tube is required and poor yields are obtained even when the halogen is activated by a nitro group. Béchamp's reaction, (b) which has already been mentioned, gives poor yields and is very inconvenient in the laboratory. In the plant, where the materials which fail to react can be recovered with small losses, the method has been applied very successfully both to the preparation of arsanilic acid and of p-phenolarsonic acid. In 1910 Bart(g) introduced a method of preparing arsonic acids by the action of isodiazo oxides on potassium arsenite. Later developments showed that,by use of sodium carbonate solutions of arsenic trioxide with a little copper salt as a catalyst, good yields could be obtained from normal diazonium chlorides. The method is successful, both on the laboratory scale and in the plant. It was employed in Germany during the war to make phenylarsonic acid as an intermediate for diphenylchloroarsine. The chief interest of the author has been with the arsonation in the aliphatic series, rather than in the aromatic, which has been much more extensively investigated than the former.

In the arsenic work at Northwestern, which is supported by the Public Health Institute of Chicago, it became necessary to prepare some aliphatic arsonic acids from rather expensive intermediates. It was, therefore, desirable to develop a method for small scale determination of the reactivity of our difficultly obtainable halides towards sodium arsenite. Two or three investigators(h) have followed the course of Meyer's reaction by titrating aliquots of the sodium arsenite solution with iodine at the beginning and at intervals thereafter. In this way the percentage of arsenic which changed from the trivalent state in sodium arsenite to the pentavalent in the sodium salt of the arsonic acid could be determined. The results were rough approximations, since the effect of dilution on adding the halide was usually ignored and also the reaction which took place with extremely active halides before a titration could be made.

We have found it possible to determine quickly and accurately in a small run the course of the reaction between sodium arsenite and the sodium salts of aliphatic halogenated acids (Table IV). The results are readily reproducible on the same or a much larger scale, and the yields of arsonic acids indicated by our titrations are closely paralleled by the yields of barium salts of the arsonic acids subsequently isolated. Most of the runs have been made with 0.1 equivalent of halogen acid, but a considerably smaller scale could doubtless be employed. The method consists in preparing separate solutions of sodium arsenite and of the sodium salt of the halogen acid and mixing them quickly at 20°, the total weight of water used being sufficient to give a mixture which has a readily calculated normality weight factor of sodium arsenite, then removing samples at intervals with a pipette calibrated to hold 1 cc. and immediately rinsing the pipette into a beaker containing an excess of dilute hydrochloric acid. This stops the reaction at once, and each sample can be titrated at leisure according to the common volumetric method for the determination of arsenic. When the reaction ceases in a bath at 20°, it is continued in another bath at 100° until completion. Weighings were made to one milligram, and all materials were recrystallized or redistilled before using in this work. The titration of a 1 cc. portion of the solution when the reaction starts is calculated from the specific gravity and the arsenic equivalent of the iodine. Trials on solutions of sodium arsenite alone showed the calculations to be correct to better than 0.1 per cent. The per cent of sodium arsenite which disappeared (equivalent to the yield of arsonic acid) is then calculated readily from the titrations.

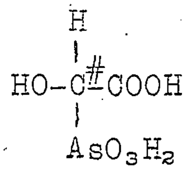
It was not possible to make runs at constant temperature on account of the exothermic nature of the reaction, but it is hoped to use these conditions with some of the more unreactive halides. Before trying out other halogen acids it seemed desirable to study the effect of various conditions on the reaction with chloroacetic acid. The results using different concentrations alkali hydroxides and halogens is presented in Tables V, VI, and VII. Potassium hydroxide gave poorer results than sodium hydroxide, in contradiction to the results of Dehn (e). However, Dehn employed dilute alcoholic solutions to obtain miscibility of arsenite and halide. With potassium arsenite less alcohol is required and there is smaller loss of halide by ether formation so that, naturally, a larger yield results. With ammonium hydroxide the ammonia reacts rather than the arsenite and only a trace of barium arsonoacetate can be isolated. The effect of halogens is not well presented on account of the too great reactivity of the bromide and iodide. This experiment is being repeated in more dilute solutions.

In Table VIII we present the effect of homology in the series, bromoacetic acid to α-bromo-n-caproic acid. The results afford hope that fairly heavy aliphatic molecules can be arsonated by Meyer's reaction.

β- Bromopropionic acid (Table IX) shows a surprising reactivity. We propose studying a γ and δ halogen acid to form a more complete comparison with the reactivity of the α- derivatives.

A beginning has been made in studying dicarboxylated arsonic acids (Table X). Bromo-malonic acid shows a good reactivity, while only one halogen of dibromo-succinic acid may be replaced and that partially.

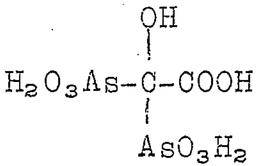
The most interesting results are obtained with dichloroacetic acid (Table XI) and trichloroacetic acid (Table XII). Using two moles of sodium arsenite to one of sodium dichloroacetate one halogen is replaced by arsonic acid and the other hydrolyzed giving arsono-glycollic acid,



$$HO-\overset{H}{\underset{AsO_3H_2}{C^{\#}}}-COOH$$

. We are attempting to resolve this compound. No optically active substance containing arsenic attached to the asymmetric carbon atom is known. It may be that one enantiomorph is more active physiologically than the other, which result would present interesting possibilities. An attempt to prepare diarsonoacetate acid, $(H_2O_3As)_2CH.COOH$, is in progress.

With three moles of sodium arsenite and one of sodium trichloroacetate, the iodine titrations indicate the formation of diarsono-glycollic acid,



$$H_2O_3As-\overset{OH}{\underset{AsO_3H_2}{C}}-COOH$$

, The barium salt of this product is readily isolated, but we cannot assign the above formula more than tentatively as yet. We are also trying to make triarsono-acetic acid, $(H_2O_3As)_3C.COOH$.

The chief object in making the aliphatic arsono-carboxylic acids is for use as intermediates in the preparation of aliphatic arseno compounds. Extensive investigation of aromatic arseno compounds led to the discovery of the valuable arsphenamines. A similar study of the practically untouched field of aliphatic arseno compounds now in progress at Northwestern might, therefore, conceivably result in a contribution to medicine.

Summary

1. A number of aliphatic halogen acids have been arsonated smoothly by Meyer's reaction.

2. A method for following the course of Meyer's reaction on a small scale has been developed and the conditions affecting the rate of reaction and the yield studied. In many cases the reaction has been found to be much more rapid than generally supposed.

3. The arsonation of dichloroacetic acid has led to the formation of arsonoglycollic acid. The resolution of this product is now being attempted.

4. A study of the arsonation of trichloroacetic acid is in progress.

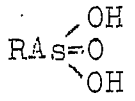
5. The derivatives of the arsono-carboxylic acids, especially arseno compounds, are being investigated.

The Preparation of Arsonic Acids (con.)

Tables

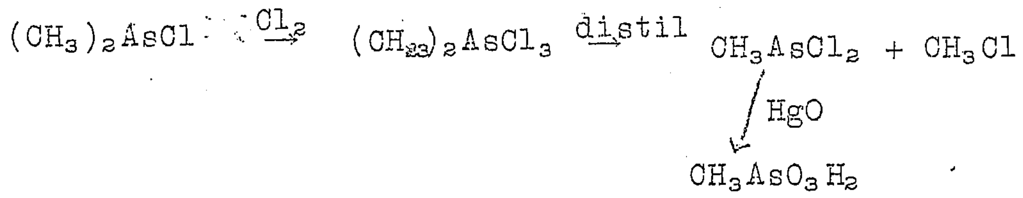
Table I

Arsonic Acids, $RAsO_3H_2$ or



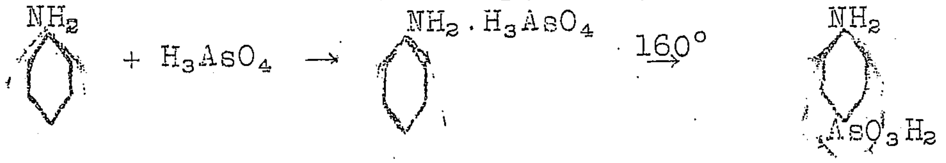
$RAs(=O)(OH)_2$

First aliphatic arsonic acid (Baeyer, 1858)



$(CH_3)_2AsCl \xrightarrow{Cl_2} (CH_3)_2AsCl_3 \xrightarrow{distil} CH_3AsCl_2 + CH_3Cl$; $CH_3AsCl_2 \xrightarrow{HgO} CH_3AsO_3H_2$

First aromatic arsonic acid (Béchamp, 1863)



Structure proved by Ehrlich and Bertheim, 1907.

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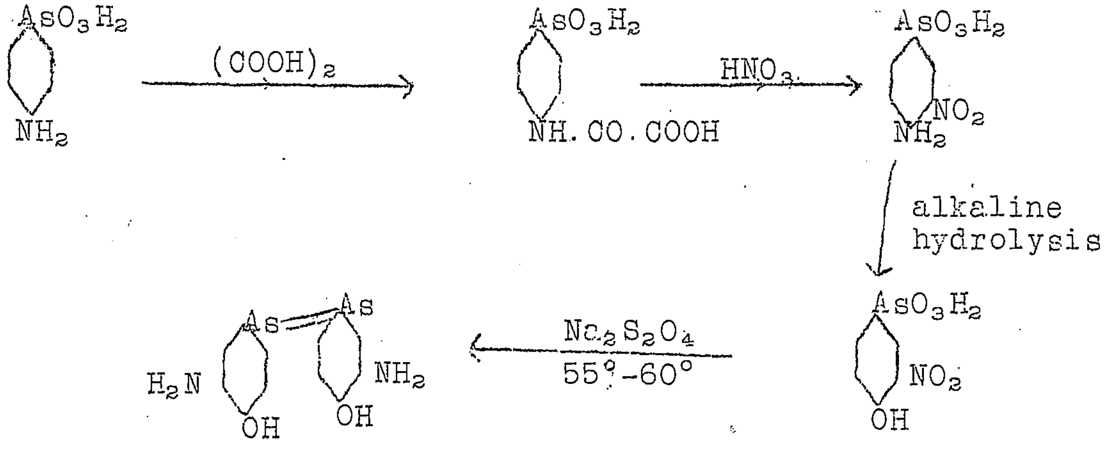
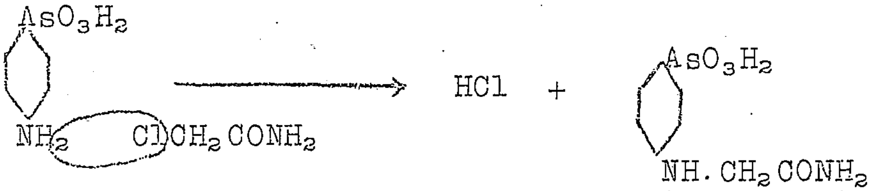
Table Ia





tryparsanide

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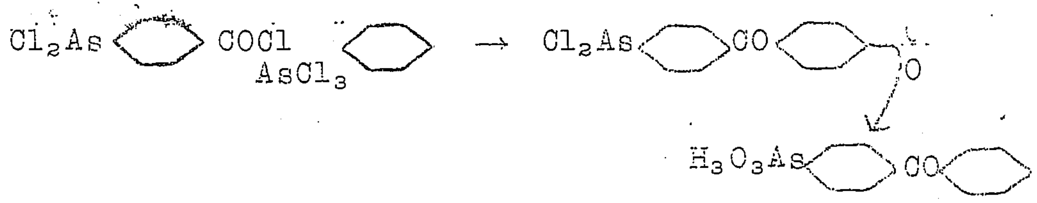
The Preparation of Arsonic Acids (con.)

Table II

Preparation of arsonic acids from other types of organic arsenic compounds.

1. $RAsH_2 + 3\ O \rightarrow RAsO_3H_2$
2. $RAsCl_2 + Cl_2 \rightarrow RAsCl_4 + 3\ H_2O \rightarrow RAsO_3H_2 + 4\ HCl$
3. $RAsCl_2 + H_2O_2 + H_2O \rightarrow RAsO_3H_2 + 2\ HCl$
4. $RAs{=}AsR + O_2 \rightarrow 2\ RAsO + O_2 + 2\ H_2O \rightarrow 2\ RAsO_3H_2$
5. $RAsOCl_2 + 2\ H_2O \rightarrow RAsO_3H_2 + 2\ HCl$

6.



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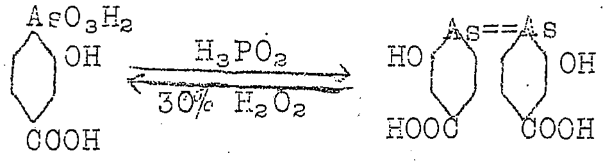

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Table III

Direct Arsonation

Aliphatic

Meyer

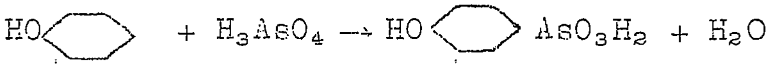
$$Na_3AsO_3 \rightleftarrows \left[\begin{matrix} Na \\ O{=}AsNa \\ Na \end{matrix}\right] + RX \rightarrow RAsO_3Na_2 + NaX$$

Aromatic

Rosenmund

$$RBr + K_3AsO_3 \rightarrow RAsO_3K_2 + KBr$$

Béchamp



Bart

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The Preparation of Arsonic Acids (con.)

Table IV

Action of 5 N sodium arsenite

on sodium chloroacetate

Time after mixing in minutes	Percent As_2O_3 gone
1.5	3.45
5	17.27
15	44.76
30	60.81
150	72.58
2550	81.87
heat 1)	83.83

1) Four hours at 100°

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Table V

Effect of concentration

N.F. of Na_3AsO_3 and of $ClCH_2COONa$	Time for 50% of As_2O_3 to react	Maximum yield obtained
10	<2 min.	82.0%
5	18	83.8
2	1750	78.8
1	∞	53.0 1)

1) By heating at 100°

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Table VI

Effect of alkali (10N)

Alkali	Min. to complete reaction	Yield
NaOH	1300	82.1
KOH	300	69.9
NH_4OH	25	1)

1) As_2O_3 precipitated and practically no arsonoacetic acid formed. Titration showed 84% of the As_2O_3 disappeared.

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The Preparation of Arsonic Acids (con.)

Table VII

Effect of halogen (8N Na_3AsO_3)

Acid	Min. to reach 50% reaction	Yield
Chloroacetic	20	82.0
Bromoacetic	<1.5	87.2
Iodoacetic	<1.5	86.7

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Table VIII

Effect of homology - series bromoacetic to α-bromo-n-caproic acid

(8N Na_3AsO_3)

Acid	Time to 50% reaction	Yield
Bromoacetic	<1.5	87.3
α-Bromopropionic	9	89.8
α-Bromo-n-butyric	130	89.4
α-Bromo-n-valeric	1200	78.7
α-Bromo-n-caproic	3400	69.5

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Table IX

Effect of position - α-bromopropionic acid and β-bromopropionic acid

Acid	Time to 50% reaction	Yield
α-Bromopropionic	9	89.8
β-Bromopropionic	10000+	62.5

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The Preparation of Arsonic Acids (con.)

Table X

Dicarboxylic acids

Bromomalonic		Dibromosuccinic 1:1		Dibromosuccinic 1:2	
Time	% reacted	Time	% reacted	Time	% reacted
6.5 1)	62.8	3950 2)	37.6	4035 3)	37.5
heat	76.2	heat	59.7	heat	46.6

1) 50 minutes at 100°
2) 1675 minutes at 100°
3) 140 minutes at 100°

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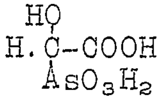
Table XI

Arsonation of dichloroacetic acid

by 10 N Na_3AsO_3

1:2 Time	% reaction	1:1 Time	% reaction
1	20	1	29
25	33	10	51
40	42.5	25	59
70	53.7	40	59
90	53.7		



$$H.\overset{HO}{\underset{AsO_3H_2}{C}}-COOH$$

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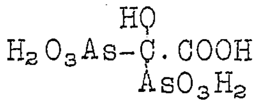
Table XII

Arsonation of trichloroacetic acid

by 10 N Na_3AsO_3

1:1 Time	% reaction	1:2 Time	% reaction	1:3 Time	% reaction
3	68	1	65	9	40
290	68	11	73	34	60
		25	76	146	65
		197	76		



$$H_2O_3As-\overset{HO}{\underset{AsO_3H_2}{C}}.COOH$$

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The Preparation of Arsonic Acids (conc.)

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THE EFFECT OF OXIDANTS ON CELLULOSE

by

John L. Parsons.

The most important physical effect of the action of oxidizing agents on cellulose, such as purified cotton fibers, is manifested in a very noticeable weakening of its strength. Depending on the amount of oxidant consumed and other experimental conditions, the fiber may even lose its structure entirely and become resolved to a powder. In a recent investigation by Knecht,1) the observation was made that, for a given amount of oxygen actually consumed by cotton yarn, there was a greater decrease in tensile strength when calcium hypochlorite solution was used than when potassium permanganate in a 7.5% sulfuric acid solution was employed. The effect of hypochlorous acid came between these two oxidants. Over-bleaching, or the prolonged action of oxidizing agents in general, leads to a degradation of fiber structure.

The chemical effect of oxidants on cellulose is to greatly decrease its resistance to the action of chemicals, such as hydrolytic agents and the solvent action of alkalies; the presence of reducing groups can be shown; and the acidic character of the material is indicated in several ways. The properties of this residual product were first investigated by Witz in 1883, but the designation of the material as "oxycellulose" was apparently made at a later date by Cross and Bevan.

Since the work of Witz, there has been a large number of contributions which have been concerned (1) with practically every kind of oxidizing agent on cotton cellulose and wood pulp of indefinite purity, (2) with various tests for oxidized cellulose, (3) with a comparison of the properties and reactions of the oxidized cellulose with the original cellulose, and (4) with the relations of these factors to industrial operations. Most of the earlier researches were not carried out in a systematic manner, nor on a quantitative basis, so that not much reliance can be placed on the conclusions drawn, which are often contradictory. No satisfactory explanation either of the course of the oxidation, or of the residual substance, termed "oxycellulose," has been given. Within the last five years, however, during which time the cellulose unit, $C_6H_{10}O_5$, has been more understood, the researches related to cellulosic degradation products have attracted greater attention. Only lately has it been recognized that the oxidizing action is influenced by the character of the fiber surface, by the concentration, impurities, and duration of action of the oxidant, and by the temperature, as well as other experimental conditions.2) Thus, acidic oxidants, such as chloric, nitric, chromic, and hypochlorous acids, may act in one or all of four ways to produce (1) hydrolysis, with tendency to hydrocellulose formation, (2) oxidation, (3) swelling, resulting in an increase of reactivity, and (4) esterification. Consequently, the reaction may become a decidedly complex one.

Before discussing the theories or explanations which have been recently advanced for the oxidation of cellulose, the significance of its various tests should be briefly considered:-

(1) The presence of a reducing group, probably aldehydic in nature, is shown by (a) the reaction with Schiff's reagent; (b) the development of a yellow color with alkalies, thus behaving

The Effect of Oxidants on Cellulose (con.)

like the simple reducing sugars; and (c) reduction of Fehling's solution. The "copper number" determination of Schwalbe, 3) or some modification of it, 4) refers to the amount of copper in grams reduced by 100 g. of degraded cellulose in Fehling's solution. Recently Hess5) has suggested that not only is the alkali-soluble portion removed by the hot solution but the latter also attacks the insoluble cellulose with the formation of reducing substances. It must be admitted that the copper number test is an empirical one and the results obtained are only comparative and not absolute.

The formation of a crystalline phenylhydrazone or osazone from the action of phenylhydrazine on oxidized cellulose has not been accomplished although the residual fibrous material assumes an orange color. Some investigators have held that a chemical combination has occurred, while others have evidence that an adsorption has taken place since the amount of reagent which is retained by the fibers varies with the experimental conditions. 6) Recently Knecht 7) had developed a technic, termed by him the "osazone" method, for following the systematic oxidation of cellulose fibers. The oxidized cellulose is transformed into the "osazone" which is determined in a volumetric manner by using titanium trichloride.

(2) Oxidized cellulose has a marked affinity for basic dyes, such as methylene blue, etc. On this basis, distinction has been recently made by Birtwell, Clibbens, and Ridge between two kinds of oxidized cellulose: The first is distinguished by a high copper number and is formed in acid solution, while the other class is characterized by a noticeable affinity for methyl-

ene blue and shows a slight reducing property.8)

(3) There is an increase both in the ease of hydrolysis and acetylation as compared with cellulose. Complete hydrolysis does not yield 100% glucose,9) and the acetate contains fewer acetylated hydroxyl groups than cellulose acetate.10)

(4) On treatment with boiling calcium hydroxide solution, oxidized cellulose, in common with hydrocellulose, maltose lactose, and cellobiose, yields among other substances isosaccharinic acid.11) The view of Hess,12) that saccharinic acids are not present in the degraded cellulose but are formed by the action of the alkali, appears logical.

(5) The evidence for the carboxyl group is found in the fact that Schwalbe and Becker13) were able to titrate oxidized cellulose with standard alkali, and also to determine the amount of barium removed from a barium hydroxide solution. Neither test seems sufficiently accurate for the purpose, however, but indicates acidity in a general way. Heuser14) had modified the Lefèvre distillation method15) for the deter[illegible]ation of glucuronic acid in the examination of oxidized cellulose. The evolution of carbon dioxide in small quantities, not exceeding 1.5%, appears to be characteristic of this material, and is a property not exhibited by cellulose, hexoses, or hydrocellulose. Recently Schwalbe and Feldtmann16) isolated a glucuronic acid salt from bleached straw and obtained a yield of 1.07% carbon dioxide from this substance when treated with hydrochloric acid. Glucuronic acid is probably present as an insoluble polymerized complex or derivative, which is firmly attached to the cellulose fiber. Derivatives of gluconic, arabonic, or

saccharic acids do not yield carbon dioxide under these conditions. The Lefèvre method is, therefore, not suitable for determining the total acidity of oxidized cellulose.

(6) Small amounts of furfural, but no hydroxymethylfurfural,14) are split off when oxidized cellulose is distilled with acid. Products have been prepared, however, which yielded less furfural than the material from which they were made.17) The formation of furfural implies the prior existence of a pentose or pentosan, existing as such, or in the form of a glucuronic acid derivative, which on hydrolysis yields a pentose. This is a point which has been frequently overlooked. Experimental data from the literature show that cellulose oxidized in neutral or slightly alkaline solutions gives the lowest furfural yields.

(7) Alkalies dissolve the reducing or aldehydic constituents of oxidized cellulose more or less completely. In view of the solvent action of alkalies on hydrocellulose,18) and on reprecipitated or regenerated cellulose,9) it seems doubtful if solubility determinations in sodium hydroxide solution can be regarded as a means of establishing the nature of oxidized cellulose. The researches of Nef and others on the action of alkalies on carbohydrates show that in such reactions a complex mixture of degradation products results, the nature of which depends in large measure on the concentration and temperature of the solution.19)

(8) Ultimate analysis points to the fact that oxidized cellulose contains more oxygen than cellulose or hydrocellulose, but there is no indication of a substance of definite composition.

(9) Oxidized cellulose is more reactive than cellulose,

that is, it is more easily acetylated, nitrated, etc.

According to Murumow, Sack and Tollens,$^{20)}$ von Faber and Tollens,$^{21)}$ Hauser and Herzfeld,$^{22)}$ Netthöffel,$^{23)}$ Schwalbe and Becker,$^{13)}$ and others, oxidized cellulose is a mixture of cellulose with its decomposition products, the latter perhaps adsorbed on the fiber. Cross and Bevan$^{24)}$ hold a similar view also. Hess$^{12)}$ is of the opinion that oxidized cellulose consists for the most part of unchanged cellulose and cellulose-A (this designation referring to a substance similar to regenerated cellulose, that is, alkali-soluble, but possessing the characteristic properties of cellulose), together with a small quantity of oxidation products.

Heuser$^{25)}$ differentiates between so-called "true" oxidized cellulose which is the portion soluble in dilute alkali, and a residue which is probably unattacked cellulose, the entire product being termed "crude xoycellulose." He then defines oxycellulose as a polyose containing a definite number of free aldehyde-carboxyl groups, which certainly implies homogeneity.

Recently Pringsheim,$^{26)}$ supported by Heuser, has sponsored the view that oxidized cellulose is a mixture of unchanged cellulose and an oxidation product of uniform composition, although the evidence offered is quite inadequate. Assuming cellulose to be a highly polymerized anhydrocellobiose, oxidized cellulose is regarded as a polymerized form of cellobionic acid and anhydrocellobiose units linked together by partial valency forces; or, in case oxidation occurs before hydrolysis, there is possibly present a dibasic aldehyde-carboxylic acid complex. These compounds or their immediate products of

The Effect of Oxidants on Cellulose(con.)

hydrolysis have not been isolated from oxidized cellulose. It is to be assumed that a dibasic aldehyde-carboxylic acid derivative of cellobiose would be hydrolyzed to yield two molecules of glucuronic acid, while cellobionic acid would hydrolyze to glucose and gluconic acid. Heuser and Stockigt[14)] obtained maximum yields of 1.5% carbon dioxide and about 4% furfural from samples of oxidized cellulose, which point to the presence of such an aldehyde-carboxylic acid in very small amounts.

Schwalbe and Becker[13)] conclude from furfural yields that a low value indicates that cellulose has been oxidized in large measure to a derivative or condensation product of gluconic acid. A high furfural value, on the other hand, indicates the formation of a glucuronic acid derivative. These investigators recognize that oxidized cellulose is a mixture of unchanged cellulose and its decomposition products, but the fact has apparently been overlooked that furfural may also result from a pentose or a pentosan in oxidized cellulose. Glucuronic acid was not determined in the more correct way, namely, by the Lefèvre method.

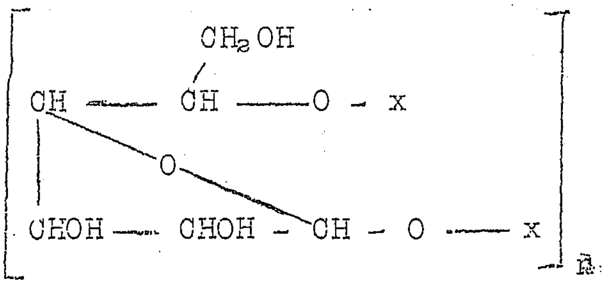
Hibbert,[27)] on the basis of his proposed cellulose nucleus, has postulated that the oxidation of the primary alcoholic group to aldehyde and then to carboxyl might occur under certain conditions, whilst under other conditions the secondary alcoholic groups might be oxidized, or it is conceivable that both types of oxidation may occur at the same time.

In a recent article comprising a study of the nitrates of cellulose and its degradation products, Atsuki[28)] considers that the oxidation of cellulose proceeds in two stages: (1) the alcoholic groups are oxidized to aldehydic and ketonic groups with partial disintegration of the cellulose molecule, and (2) the aldehydic groups are oxidized to carboxyl, which takes place with a more complete disintegration of the cellulose to compounds containing less than six atoms.

The objects of the investigation, undertaken by the writer at Yale University under Professor Hibbert,[29)] were (1) to study the course of the oxidation of cellulose by submitting a mildly bleached cotton, the purity of which was determined by analysis, to the action of potassium, magnesium, and barium permanganates in neutral solution, and chromic acid in a 90% acetic acid solution, and (2) to determine the character of the residual oxidized material by submitting it to analysis by chemical and other means. The relation between the amount of oxidising oxygen and the weight of cellulose was given by expressing the oxygen as atomic portions of O per $C_6H_{10}O_5$ unit, adopting the plan of Knecht and Thompson.[30)] Furthermore, their method of procedure was generally followed; the oxidations were carried out at room temperature, 22-26°, with 100 g. cotton, and the ratio of the weight of cotton to the volume of solution was 1:40. The mixtures were stirred intermittently. Barium permanganate was found to be more satisfactory for maintaining a neutral solution than the other permanganates, which over the higher oxidizing range yielded slightly alkaline solutions before the oxidation was complete.

For the purpose of this discussion, cellulose will be considered as a polymerized anhydroglucose complex:

The Effect of Oxidants on Cellulose (con.)



The three alcoholic groups in cellulose represent the most active parts of the structure, but their activity is very much suppressed as compared with similar groups in glucose and related compounds. Under certain conditions, as in the presence of acids, a free aldehyde group is formed, and the resulting substance behaves more like glucose and its derivatives.

As the result of nearly 50 oxidation experiments on cotton fibers, over the oxidizing range 0.01-2.00 atomic portions of active oxygen per $C_6H_{10}O_5$ unit with the previously mentioned oxidants, the evidence points to the fact that the reaction is one typical of a heterogenous system. The degree of disintegration of the fibers is more pronounced in neutral or slightly alkaline solutions than in the acetic acid solution, a fine powder being obtained in the former case when the maximum amount of oxidant was consumed. The losses are greater in neutral and slightly alkaline oxidizing media, but the reaction is more rapid in an acid solution. Furthermore, the losses always increase with increasing amounts of oxidant employed. A marked weakening of the fiber strength, from a qualitative standpoint, was not observed until over 0.10 atomic portions of oxygen were consumed. Knecht,7) in a very recent article, has stated that fiber weakening appears when 0.023 atomic portions of O are used in the form of potassium permanganate in acid solution.

The Effect of Oxidants on Cellulose -(con.)

The absorption of methylene blue by oxidized cellulose prepared with the permanganates increased from a weak blue, in the case of 0.10 atomic portion oxygen consumed, to an intense blue, when 2.00 atomic portions oxygen were used. Methylene blue absorption by the chromic acid oxidized cellulose also increased from a weak blue to an intense color over the oxidizing range 0.10-1.00 atomic portions oxygen per $C_6H_{10}O_5$, but when 2 atomic portions were consumed the color was weak. No quantitative color absoprtion measurements were made.

Carbon dioxide is one of the chief products of oxidation; the other products were not investigated. In one experiment where a loss of about 25 g. cellulose occurred as the result of the action of magnesium permanganate, the resulting filtered solution was evaporated. Less than 5 g. of an inorganic salt was obtained in the residue, which was traceable to an impurity.

Cotton cellulose oxidized in an acid solution contains a much larger amount of oxidized material than when the oxidation occurs in neutral solution, and still less in a slightly alkaline solution. The ash, copper number, alkali solubility, pentosan and glucurone constituents (calculated from the furfural and Lefèvre carbon dioxide determinations)15) have higher values in the case of cellulose oxidized in acid solution, and the percentage yields are greater over the higher oxidizing range. The data given in the following table are representative of the results obtained over the oxidizing range 0.01-2.00 atomic portions of oxygen per $C_6H_{10}O_5$ units.

The Effect of Oxidants on Cellulose (con.)

OXIDANT	ATOMIC PORTIONS O PER $C_6H_{10}O_5$	% LOSS	COPPER NUMBER	%Soly. in 10% NaOH	% PENTOSAN	AND GLUCORONE
					CONSTITUENTS	
(Cotton)	-	-	0.20-0.40	1.0	0.76	0.40
$KMnO_4$	0.33	4	4.6	24	-	-
$KMnO_4$	1.00	12	7.1	17	-	-
$KMnO_4$	2,00	26	7.8	28	-	-
$Mg(MnO_4)_2$	0.33	3	5.3	21	-	-
$Mg(MnO_4)_2$	1.00	11	7.7	35	-	-
$Mg(MnO_4)_2$	2.00	25	8.9	42	-	-
$Ba(MnO_4)_2$	0.01	0.4	0.9	1.7	-	-
$Ba(MnO_4)_2$	0.10	0.7	3.0	11	-	-
$Ba(MnO_4)_2$	33	2	5.7	29	-	-
$Ba(MnO_4)_2$	1.00	12	8.6	35	-	-
$Ba(MnO_4)_2$	2.00	30	9.9	-	1.41	1.96
CrO_3	0.01	2.6	4.0	7.1	-	-
CrO_3	0.10	3	13.6	35	-	-
CrO_3	1.00	7	18.4	49	1.95	4.92
CrO_3	2.00	14	19.3	55	2.04	4.64

Acetylation tests indicate that the number of hydroxyl or alcoholic groups decreases from three to nearly two per $C_6H_{10}O_5$ unit depending upon the amount of oxidizing agent used.

The measurements of the viscosity of cuprammonium hydroxide solutions of the various oxidized celluloses give much lower values, even when small amounts of the oxidant were consumed, compared with those of the original cotton. This fact suggests that a portion of the unattacked cellulose, probably the layer adjacent to the oxidized part, is changed in some profound manner - possibly as a result of a depolymerization or, at least, an alteration in valence forces. This is also indicated by the increase in alkali solubility. In a recent article by Neale,[31)] the statement is made that the great fall in viscosity observed after cellulose has been treated with oxidizing agents may conceivably be due to reduction in size of the anionic micelles consequent upon fission of the cellulose complex by oxidation.

The alkali solubility of oxidized cellulose depends in large measure on the concentration of the alkaline solution employed. The evidence shows that alkali solubility cannot be explained as due entirely to salt formation, or destruction of reducing constituents, but is the result, in part, of the peptizing or solvent action of a portion of the unattacked cellulose. It has been recently shown[5)] that a depolymerized cellulose, such as regenerated cellulose, may be partly or almost entirely soluble in alkali. These facts lead to the belief that alkali solubility determinations of a degraded cellulose, as criteria for purity or homogeneity, are fundamentally unsound.

The mechanism by means of which the oxidation of cellulose occurs in the initial stages would appear to involve a transformation of the primary alcoholic group to aldehyde, and this in turn to a carboxyl group. At the same time the reactivity of the attacked cellulose complex is increased. Acids tend to bring about an hydrolysis of the half-acetal linkage, -O---x. In general, however, the oxidation is accelerated to a greater extent by the presence of dilute alkalies than by the use of dilute acids. The alkali probably acts on the initially oxidized cellulose so as to give a much larger concentration of oxidizable components, this profound change being due in large measure to enolization. Rapid oxidation of the partly oxidized substances takes place to simple soluble or gaseous compounds, but the nature of the mechanism remains for the present an unsolved problem. This reaction occurs progressively while the oxidant is present, the partly oxidized cellulose being resolved at a more rapid rate than cellulose. When the oxidant is consumed, there are left on the residual fibers small amounts of substances, not unlike cellulose itself in complexity, which have undergone partial oxidation. These producfs give to oxidized cellulose its characteristic properties. The course of the reaction, however, is markedly dependent on the experimental conditions involved and on the specific properties of the oxidant used.

As a result of this investigation, together with others of recent years, oxidized cellulose is viewed as a mixture of a large amount of unattacked cellulose (which may exist in different degrees of polymerization or association) with relatively small quantities of degraded cellulose in the form of complex oxidation products, aldehydic and acidic in nature. The amounts of these substances depend on the conditions of the oxidation.

The term, <u>oxidized cellulose</u>, is suggested as a more suitable designation than <u>oxycellulose</u> for the residual product resulting from the action of oxidants on cellulose, as the latter is clearly a misnomer.

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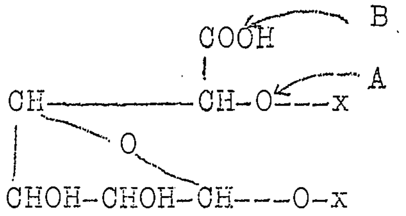
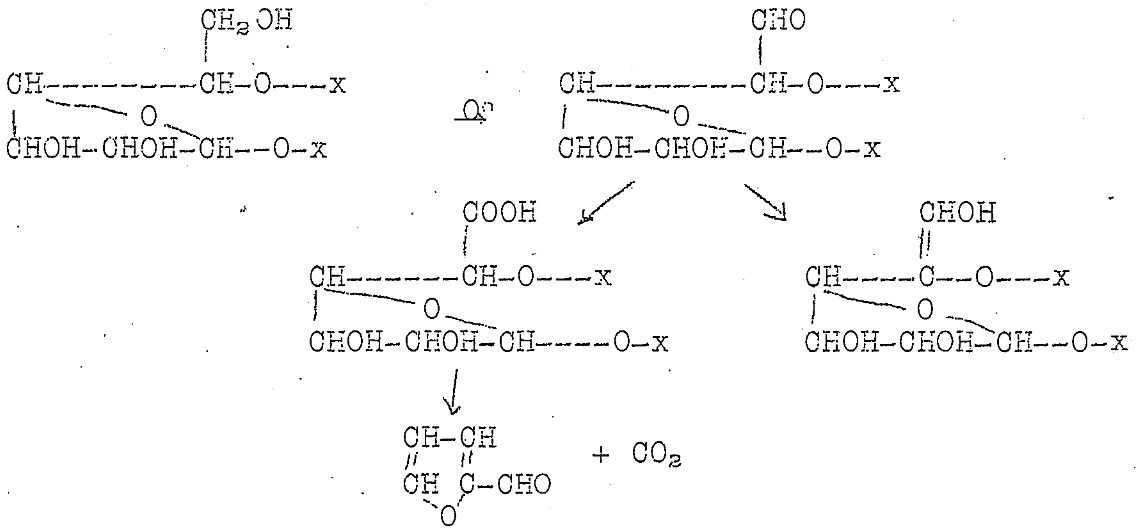
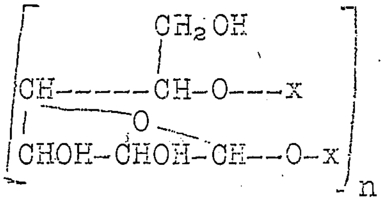
The Effect of Oxidants on Cellulose (con.)

Figures and Equations







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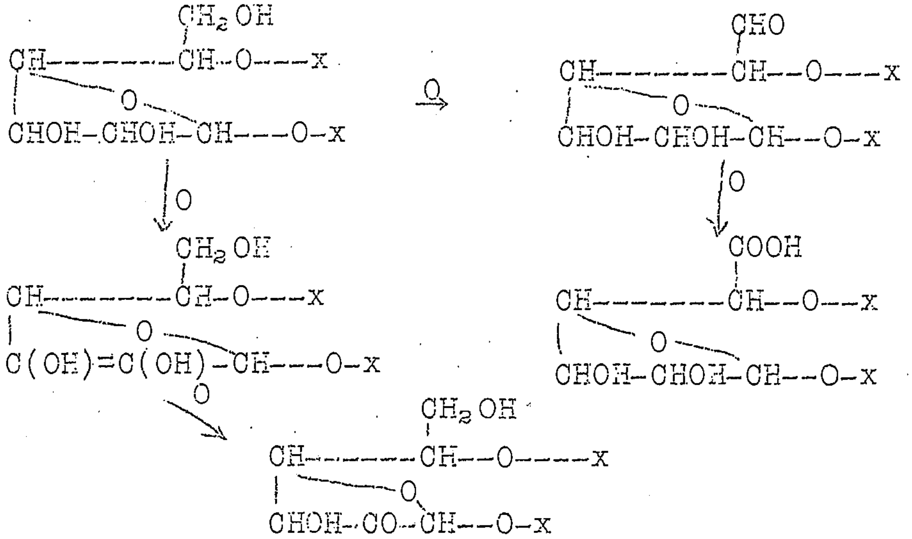
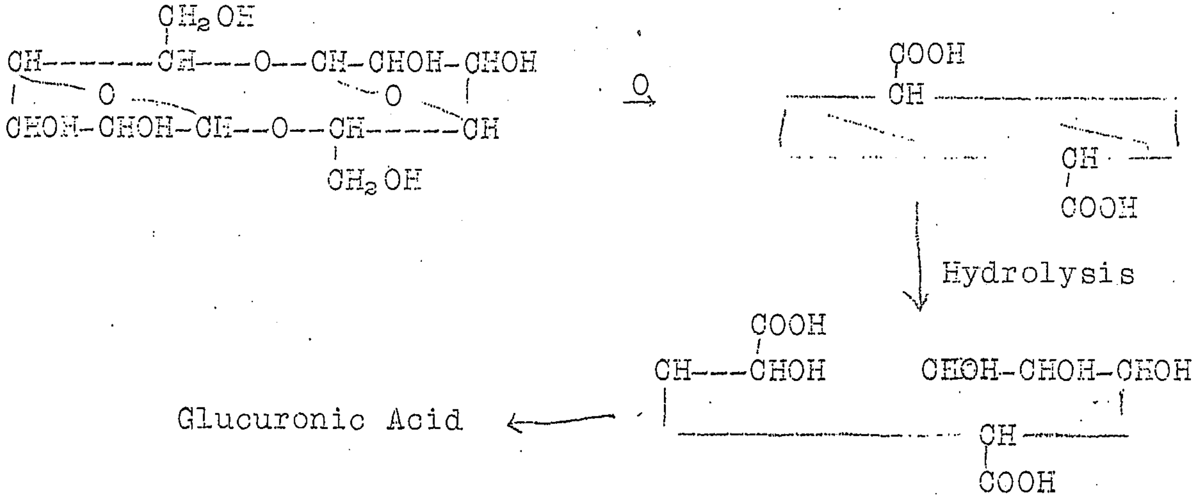


The Effect of Oxidants on Cellulose (con.)

Pringsheim



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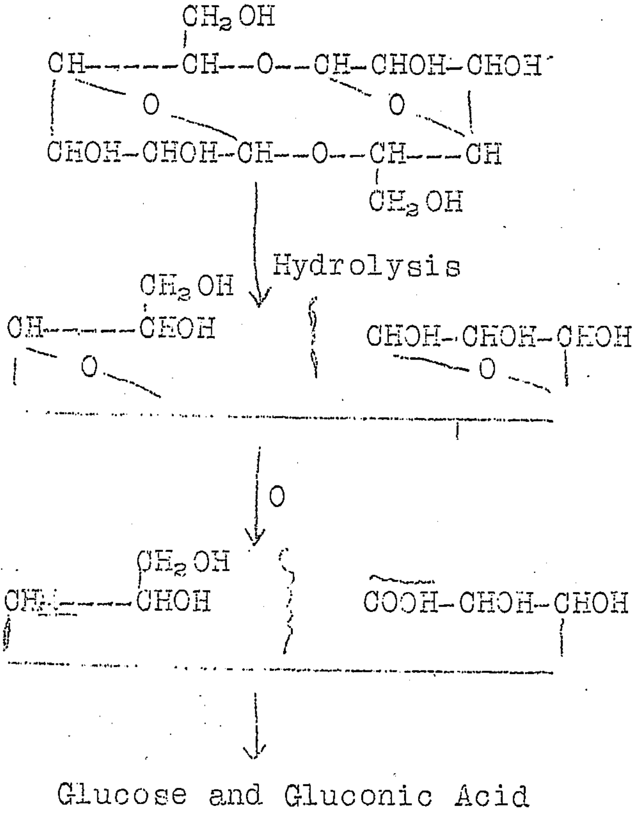

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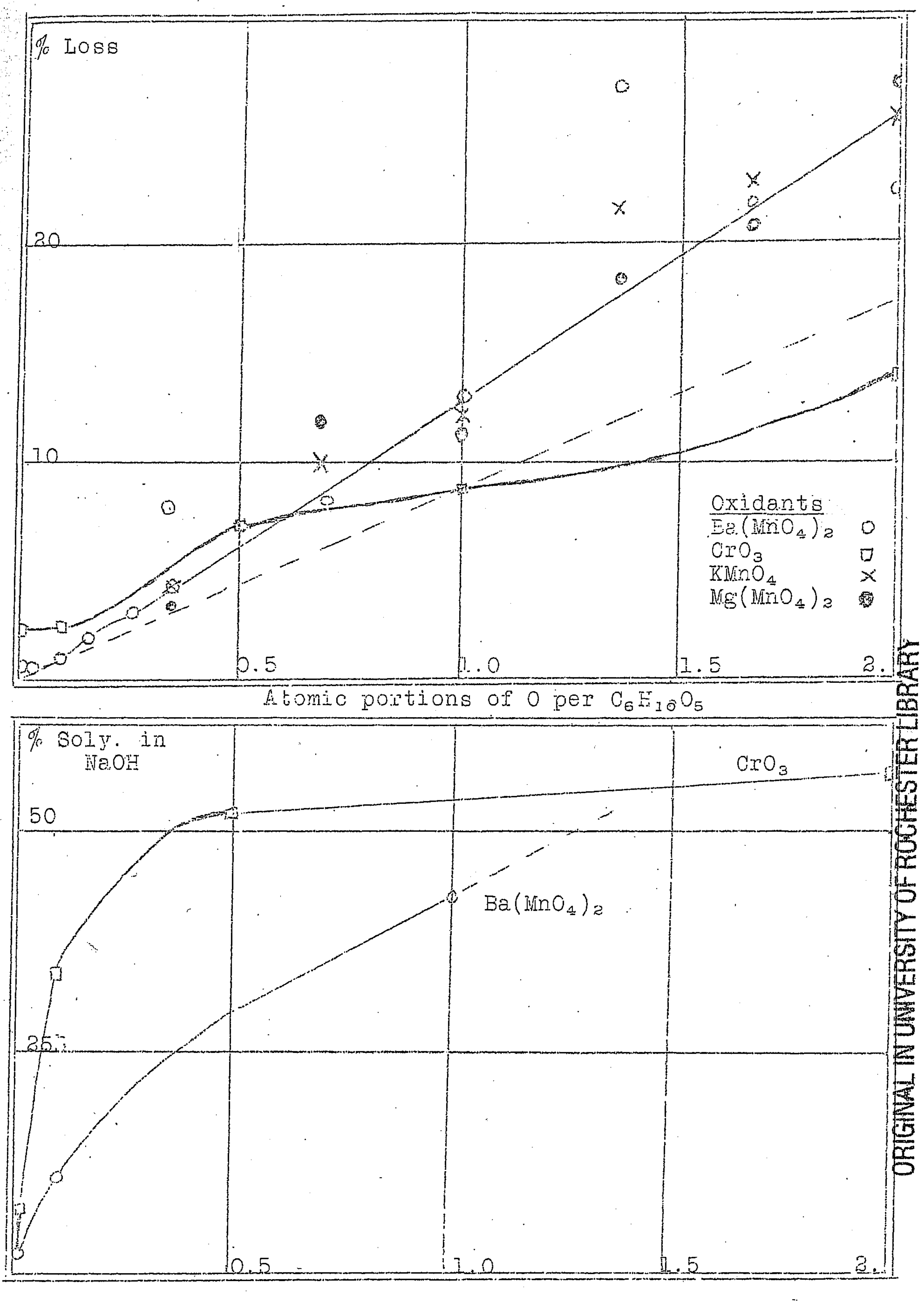

THE OXIDATION OF HYDROCARBONS BY AIR AT HIGH TEMPERATURE AND PRESSURE

by

E. Emmet Reid

As a member of the Committee on Petroleum of the National Research Council I have felt under obligation to do something to justify the appointment. An investigation of the products of the air oxidation of petroleum had already been begun at Johns Hopkins before this Committee was proposed. The appointment of this Committee is timely, as petroleum has long been one of our great American resources. It has been exploited on an enormous scale. America has led in the manufacture of petroleum products and should be the foremost in this investigation.. The recent announcement that Mr. Rockefeller has given $250,000 for the scientific study of petroleum is an additional impulse for the consideration of this problem. A number of chemists have been thinking for some years about what can be made from petroleum, and already considerable of scientific interest has been learned, and some commercial possibilities have been uncovered. It is my present purpose to take stock, in a broad way, of what has been accomplished with the hope of starting discussion and stimulating further investigation. In the past there have been two questions that have been considered: the petroleum chemists have wanted to know how many gallons of gasoline could be obtained from a barrel of oil, and the consumer how many miles he could get to a gallon. From the most wonderful source of organic compounds we have been manufacturing only B.T.U.'s.

The Oxidation of Hydrocarbons (con.)

Within the last few years this state of mind has changed radically, and researches of many kinds have been going on all over the world with a view to the transformation of hydrocarbons into useful substances. At last the organic chemist is waking up and doing his bit. The problems belong to organic chemistry, and we, as organic chemists, are failing in our duty and neglecting an opportunity if we do not concern ourselves with them.

The useful products, benzene, toluene, phenol, etc., which are obtained from coal tar, constitute only a small fraction of one percent of the coal; yet, on them has been founded a chemical industry which has been a marvel to the world and which has been an important factor in directing the course of history. Petroleum is practically 100% hydrocarbons, all of which may possibly be transformed into useful compounds.

The only aliphatic hydrocarbons that are at all well known are the paraffins, and we know almost nothing of their reactions. The name, paraffin, has prevented chemists from investigating them. There could be no prospect of results from the study of compounds that have no affinity and hence no reactions. Until recently there has been little scientific investigation of aliphatic hydrocarbons. Oil chemists have crowded the Patent Office with processes of "cracking," but have spent little time considering the nature of the hydrocarbons that are cracked or in investigating the products of the cracking. Each new cracking process is heralded as superior to all others in the yield and quality of gasoline and in not leaving carbon in the apparatus.

The amazing thing about carbon compounds is the stability of the carbon to carbon bond. When one carbon atom joins itself to another, there is a fixedness which we seldom meet anywhere else in chemistry. Sodium and chlorine unite with evolution of an enormous amount of energy, and we think of sodium chloride as a most stable compound. It is true that we can heat it to an extremely high temperature without decomposing it. It melts at 801° and boils at 1490°. We write the formula, NaCl, with great confidence, but modern research shows us that this molecule, NaCl, does not exist as a definite, permanent entity. It was first discovered that in solution it is broken up almost completely into Na^+ and Cl^- ions. Some NaCl moelcules do remain, but even these are in mobile equilibrium with the ions, decomposing and reforming all the time. The sodium and chlorine atoms are changing partners continually. If we evaporate the solvent, the ions reunite, but promiscuously. We dissolve a quintillion molecules of sodium chloride and recover a quintillion, but the chances are a billion to one that any given chlorine atom will come out in company with its original sodium partner. Recent X-ray pictures have shown us that in solid sodium chloride each sodium atom is linked impartially to 8 chlorine atoms, and conversely that each chlorine atom is joined to 8 sodiums. In the solid state the molecule NaCl does not exist. In the vapor phase above 1500° such molecules probably are found, but even these are in mobile equilibrium.

The case of an organic compound is entirely different. If we dissolve a quintillion molecules of sugar in water, with the exception of possibly one or two which are dissociated, they all retain their individuality, and, when the water is evaporated off, we recover the quintillion molecules of sugar unchanged, each with identically the same 12 carbon atoms, the same eleven oxygens, and the same 22 hydrogens. Furthermore, X-ray analysis seems to show that carbon molecules maintain themselves as entities in the solid form. In the lump of sugar which you put in your coffee, each sugar molecule contains the same atoms which came together in the stalk of cane down in Cuba.

The most convincing evidence of the stability of the structure of organic compounds is found in optical activity. Not only do the same atoms and groups remain in combination with the same carbon atom, but maintain their same relative positions around it. Not only does the sugar molecule that has gone through all the vicissitudes of refining, solution, and crystallization, and of long storage contain identically the same 12 carbon, 11 oxygen, and 22 hydrogen atoms, but each carbon atom holds its attendant groups in the same relative positions as it did in the sap of the cane.

The stability of the union of one carbon to another is but the beginning of the story; a number of carbons can unite similarly to form a chain, a ring, or a more complicated structure, and this is likewise permanent. We do not know how many carbons can be built into a single molecule, but a hydrocarbon $C_{50}H_{102}$ has been found in a coal mine, and one, $C_{60}H_{122}$, has been put together by chemical methods.

The Oxidation of Hydrocarbons (con.)

Those who are best informed as to atomic structure seem to agree that the carbon to carbon bond is non-polar and that the carbon to hydrogen bond is likewise non-polar. Hence in a molecule such as n-decane there is no one place in the molecule much more liable to attack than any other, and there is no one place in the chain at which a break is particularly likely to occur. The end carbons and their hydrocarbons are somewhat differently circumstanced from those in the middle of the chain. In the cases of branched chains, there are further differences. In toluene there is so much difference between the reactions of the aliphatic methyl and the aromatic phenyl that we have little difficulty in directing an attack so as to affect either part of the molecule that we wish; we can chlorinate to benzyl chloride or to chlortoluene. We can oxidize the methyl group completely without touching the nucleus. With unsaturated hydrocarbons the ethylene bond is, of course, a point of attack.

Considerable progress has been made in the halogenation of methane and of higher hydrocarbons to give useful products, but in the halogenation of hydrocarbons there are two difficulties: 1) getting the halogen in, and 2) getting it out. Of course, I do not mean that there is usually any lack of reactivity of the halogens, but there is trouble in directing and controlling the process so as to obtain the desired product. While chlorine is comparatively cheap, its atomic weight is high as compared with that of carbon, and usually two atoms must be used for one that is introduced. For 16 g. of methane 71 g. of chlorine is required. Halogenated hydrocarbons, e.g. methyl chloride, ethyl chloride, etc., are seldom used as such, but are intermediates. The halogenated hydrocarbons must be transformed into a halogen-free product, which involves further reactions and the use of additional chemicals, commonly lime, soda, or sodium acetate. Probably the most troublesome part is the removal of the last trace of halogen. Perfumers are especially fastidious about their materials and will not use materials which contain infinitesimal amounts of halogens. Solvents, for certain uses, must be absolutely halogen-free.

If we can obtain compounds from hydrocarbons by air oxidation, we have used the cheapest possible reagent, and we obtain directly products that are desirable. A number of chemists have been investigating this problem. In most cases the aim has been to obtain commercially valuable products with little regard to the scientific side. Classes of compounds rather than individuals have been produced.

Emphasis has been put on the permanence of the union of carbon with other atoms and, particularly, with a fellow carbon atom. All that has been said is true, and yet the half has not been told, but this sugar molecule which maintains its identity so wonderfully at low temperatures goes to pieces at higher. Aliphatic hydrocarbons are amazingly permanent at moderate temperatures, but begin to undergo changes and rearrangements at moderately elevated temperatures. These reactions are slow at 200°C., but become more and more rapid till cracking temperatures are reached around 370° to 400°C. where they become extremely rapid. Then molecules are bro-

The Oxidation of Hydrocarbons (con.)

ken up into smaller fragments, which may unite to form other molecules larger or smaller than the original and with the liberation of some carbon and hydrogen. If oxygen is present in this mele, we may expect the formation of oxygenated compounds.

The great difficulty in any scientific investigation of aliphatic hydrocarbons is that we are practically limited to petroleum fractions, since pure individual aliphatic hydrocarbons are out of the question for any except very small scale experiments. As petroleum consists not only of dozens and, possibly, hundreds or, even, thousands of hydrocarbons, but these belong to at least three distinct classes the reactions of which are very different, the situation is extremely complicated. Emphasis must be put on the fact that, though the differences between the individual hydrocarbons present are comparatively small, yet there are differences which mean that, if sufficient care is taken in the control of reactions, there is a possibility of differential treatment.

The study of the air oxidation of petroleum goes back many years. In a German patent of 1889, it was proposed to pass a current of air or oxygen, with or without pressure, at a more or less elevated temperature through hydrocarbons. Acids, aldehydes, ketones, unsaturated hydrocarbons, and polymers are said to have been obtained. In [illegible] work that has gone on since then a wide range of conditions has been used, two important variables being temperature and the partial pressure of oxygen. With most hydrocarbons oxidation by air is slight below 100°C.; so the temperatures have been usually from 100° on up to, according to one patent, 500°. Brown coal paraffin has been oxidized at 13°. As low as 1% of oxygen in nitrogen has been used; that is, a partial pressure of 7.6 mm.,which is to be contrasted with pure oxygen at 14 atmospheres, a pressure range of 1400 to 1.

It is curious that the best results have so far been obtained with paraffin wax, which has been commonly thought of as extremely inert. By prolonged contact with air at moderately elevated temperatures this inert substance is almost quantitatively oxidized, the product being chiefly a mixture of high molecular weight acids and hydroxy acids.

The higher the temperature and the more drastic the oxidation, the less is the relation of the products to the starting material; the more severe the treatment, the smaller are the fragments into which large molecules are broken and the less resemblance of these fragments to the structures from which they came. It is well known that the products of a cracking operation depend more on the process of cracking than on the nature of the stock that is cracked, and it is the same way with high temperature oxidations.

One way of estimating the progress in this field is to review the products that have been obtained by various methods of oxidation of petroleum, the starting material usually being either paraffin wax or heavy distillates. We find acids, saturated and unsaturated, mono and diabasic, aldehydes, alcohols, esters, acid anhydrides, hydroxy-acids, hydroxy aldehydes, and ketones. This list covers much of aliphatic chemistry. We cannot expect to get sugars and polypeptides. More is known about acids than about any other class. Acids are believed by some to be the primary products. They are formed under all conditions but in varying amounts from one or two percent up to practically 100%. The yield of acids decreases with elevation of the reaction temperature. A number have been identified: formic, acetic, propionic, butyric, pentoic, caproic, heptoic, caprylic, pelargonic, capric, lauric, tridecylic, myristic, pentadecylic, palmitic, margaric, stearic, nondecylic, and arachidic. While the even numbered acids, lauric to arachidic, are found in animal and vegetable substances, oxidation of hydrocarbons furnishes chiefly the odd numbered acids from C_{13} to C_{19}. In addition to acids, we find what appear to be acid anhydrides. Hydroxy-acids are formed, but just what they are is not known. Lactones are also present. Unsaturated acids have been found, but they have not been identified. There are also aldehyde acids and some dibasic acids.

On paper the simplest oxidation product of a hydrocarbon is an alcohol. It is easy to rub out a hydrogen and put a hydroxyl in its place. Alcohols have been reported by a number of experimenters, but are never found in large quantities. It is hard to imagine a process that does not go through the alcohols, but, if they are formed first, they must be rapidly oxidized to aldehydes and acids. Esters are found, but it has been claimed that they are primary products from which the alcohols are derived by saponification. We write the halogenation of a hydrocarbon, $CH_3 . CH_3 + Cl_2 \rightarrow$

$CH_3.CH_2Cl + HCl$. The analygous reaction with oxygen would be $CH_3.CH_3 + O_2 \rightarrow CH_3.CHO + H_2O$, the product being an aldehyde or, possibly, a ketone.

Aldehydes and ketones are formed in considerable quantities, but much less is known about what they are. Formaldehyde appears to be present under some conditions. Acetaldehyde and its higher homologs are formed. Acetone has been identified, and its homologs appear to be obtained. One American company is putting on the market a solvent which is said to be obtained by the vapor phase oxidation of kerosene. It is essentially a complex mixture of higher ketones with some aldehydes.

A few experiments have been carried out with known substances, particularly with stearic acid and with hexadecane. In both cases acids were obtained similar to those from petroleum. There are two mechanisms that may be imagined: Oxidation may take place and decomposition follow, or we may have cracking followed by oxidation of the fragments. In a long paraffin molecule the point of attack seems to be the end methyl group. The acid so formed might lose carbon monoxide to go to an aldehyde, or, more probably, carbon dioxide to form a hydrocarbon. We know that the hydrogen on the carbon atom next to the hydroxyl is the most readily oxidized. This suggests an alpha keto acid as the next step. This would lose carbon dioxide readily to form an aldehyde which, either during its formation or subsequently, would oxidize to an acid. We may imagine cracking as taking place first. In that case a fragment or free radical, RCH_2, will

The Oxidation of Hydrocarbons (con.)

exist for an instant. It may combine with another fragment to form a hydrocarbon or it may meet oxygen, in which case some oxidation product will result. In order to form an alcohol this free radical would have to meet a free hydroxyl group. It is not likely that such are present in the raaction mixture. Hence, the formation of alcohols would not seem to be probable. If a hydrocarbon breaks in two, the common result is two acids. We are familiar with the oxidation rupture of ring compounds. We know that cyclohexanone readily yields adipic acid. An important achievement has been the direct oxidation of benzene to fumaric and maleic acids. From the chemistry of triphenyl methyl we know that a free radical combines instantly with molecular oxygen to give a peroxide. The free radicals resulting from the rupture of a hydrocarbon would doubtless combine with oxygen with great ease. The unstable peroxides would readily pass into more stable forms.

In a mixture of hydrocarbons cracking begins not much above 200°C. In the oxidations that are carried out at low temperatures, the acids that are formed are comparable in molecular weight to the hydrocarbons which are oxidized, but at high temperatures the products are of much smaller molecular weights, showing that cracking has taken place before, during, or subsequent to the oxidation. Even when the reaction vessel is at a comparatively low temperature, the instantaneous local temperature at the part of the hydrocarbon molecule that is being oxidized may be high enough to cause cracking.

The Oxidation of Hydrocarbons(con.)

The object of this paper is to stimulate investigation by calling attention to what has been accomplished and suggesting lines of future work. It has been shown that all the common classes of organic compounds can be produced by direct oxidation of hydrocarbons. There are two problems in driving an auto, to get it started and to steer it. If it will go, there is a chance of making it go where we want to go. It is the same way with chemical reactions: if they go at all, there is a chance of influencing them to go as we want them. These reactions go; now let us find out how to regulate them so as to produce what we want. A blunderbus loaded with bird shot will hit everything in the region in front of it, but it does not deliver enough lead in any one spot to accomplish anything. In this problem we are now in the blunderbus stage: we get a little of everything, but not enough of any one thing to be worth while. The solution of the problem appears to involve two things: determining the exact conditions for the formation of each possible product and devising means for maintaining any set of conditions with the necessary accuracy.

So far, catalysts have not been found to have much effect, but the search for a "suitable catalyst" should not be abandoned. We have at our disposal a wide range of temperatures and pressures. Other conditions can be varied.

When the title for this paper was sent in, it was hoped that the results of a study that has been going on for more than a year at Johns Hopkins would be far enough along by this time for the announcement of the results, but such is not the case. The results will be published as soon as they are complete. A number of products that have been reported by others have been identified.

It has seemed to me better to use the time at my dispoal at this meeting in a general statement of the present situation and in an effort to stimulate discussion and investigation.

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THE DISSOCIATION OF -ONIUM STRUCTURE

by

R. R. Renshaw

The dissociation of a number of physiological active -onium compounds has been determined in water and in borate buffer solution at pH = 7.8 by determining the decrease in ionizable halogen and also the absence of odor of dissociation products. A number of these substances give no appreciable dissociation under these conditions, and yet they show an extreme range in physiological activity. These results along with previous work make certain that the physiological activity of these substances is not connected with any property that is ordinarily considered chemical.

Both old and new experiments show that many sulfonium compounds undergo -onium dissociation very readily. This is in marked contrast to the stability of the corresponding quarternary ammonium compounds. Adopting the Kossel-Lewis atom, this instability may be attributed to the unbalanced structure of the sulfonium radical.

The spacial configuration of the tertiary amines is strikingly similar to the sulfonium ions. Since the latter have been obtained in enantiomorphic forms, the form should also exhibit this phenomenon. The failure to isolate optical isomers of tertiary nitrogen in compounds where the valences are not fixed may be explained by a rapid intramolecular shift producing racermerisation.

Since the sulfonium compounds are more stable than the oxomium, it is possible that enantiomorphic form of tertiary phosphorus could be more readily isolated than those of tertiary nitrogen

NOTE: The remaining pages of R. R. Renshaw's paper are not present in the program book at the University of Rochester Library. – EEF

THE CHEMISTRY OF WOOD CELLULOSE

by

Louis E. Wise

Ever since Payen found that woody tissue contained a resistant, insoluble polysaccharide ($C_6H_{10}O_5$), "cellulose," this substance has been recognized as the characteristic component of the cell wall. Yet the term substance might be challenged. Cross and Bevan, the great English monographers on cellulose, thought of celluloses from different sources as chemically related but by no means identical substances. A cellulose isolated from spruce wood, admittedly different physically from cellulose obtained from the seed hair of the cotton plant, was also considered chemically different from cotton cellulose.

Schwalbe in his "Chemie der Cellulose" evidences the same point of view. He speaks of celluloses (cellulosearten) and evidently thinks of a number of different compounds. This general viewpoint has persisted during the past decade. However, in a recent work of Heuser, largely as the result of isolated pieces of experimental data furnished by the laboratories at Darmstadt and Berlin, a new working hypothesis has been formulated. Heuser points out that certain cellulose fractions isolated from straw, wood, and cotton are chemically very similar, provided sufficient means of purification are used. His hypothesis then is that only one type of cellulose exists, and that this is the same chemical individual in all plants. Heuser's hypothesis, scanty as are experimental data to support it, has, nevertheless, ap-

The Chemistry of Wood Cellulose (con.)

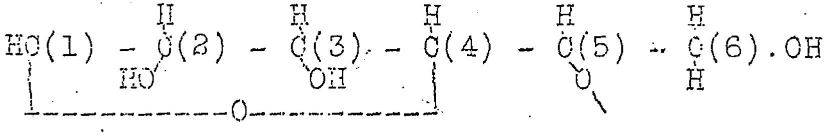
pealed to a large body of investigators. Others, notably some of the American chemists, have rejected it.

The definition of wood cellulose has not been standardized and depends on the viewpoint of the individual investigator. There are a number of polysaccharides, intimately associated with each other in the cell wall, which show similar resistance to chemical attack and which have very similar physical properties. If we term these collectively cellulose, then, undoubtedly, the celluloses obtained from different species of wood must be considered chemically different. If, however, we recognize that a certain portion of these polysaccharides in all types of woody tissue is very similar to, if not identical with, cotton cellulose, Heuser's hypothesis of the chemical identity of all celluloses of the higher plants becomes understandable.

It is all a question of a point of view then, whether a given specimen of wood contains 45% cellulose or, let us say, 60% cellulose. The adherents of Heuser might accept the lower figure, while the disciples of Cross and Bevan might easily be inclined towards the higher figure.

Any progress that is made on the constitution of wood cellulose will probably be antedated by progress on the constitution of cotton cellulose. Von Weimarn, in a recent article, claims that our efforts in attempting to determine the chemical structure of cotton cellulose are premature, and that we should direct our efforts to obtaining microcrystals of cellulose. Possibly, he is right. On the other hand, it would appear important to obtain and correlate data on the similarity or dissimilarity of celluloses from different sources. Such data should be valuable in indicating whether different types of cellulose could be used industrially in the place of cotton or spruce cellulose (where fiber length or fiber structure are not primary considerations). For example, we might determine whether purified poplar or long leaf pine cellulose could be used equally as well in the rayon industries as cotton or spruce cellulose, and whether other wood celluloses could be used as future raw materials for those industries utilizing cellulose nitrates, acetates, or ethers.

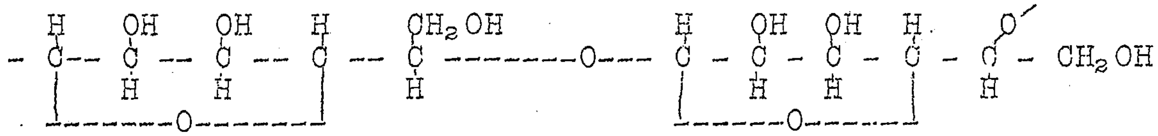
Before discussing the nature of wood cellulose further, it may be well to outline the properties of cotton cellulose, which serves as a standard with which other forms of cellulose have been compared. Cotton cellulose has the composition, $(C_6H_{10}O_5)_n$ contains three alcoholic hydroxyl groups for every six carbon atoms (as shown by its trimethyl derivative and triacetate), and on complete hydrolysis yields only d-glucose. Acetolysis yields cellobiose octaacetate and glucose pentaacetate. Methylation followed by hydrolysis gives a very high yield of a definite compound, 2,3,6-trimethyl glucose. On the basis of these reactions it has been assumed that the cotton cellulose molecule or unit is made up solely of anhydroglucose residues of the type:



$$\underbrace{HC(1) - \underset{HO}{\overset{H}{C}}(2) - \underset{OH}{\overset{H}{C}}(3) - \overset{H}{C}(4)}_{O} - \underset{O}{\overset{H}{C}}(5) - \underset{H}{\overset{H}{C}}(6).OH$$

joined through positions (1) and (5), and that the anhydrocellobiose grouping must occur in cellulose.

The Chemistry of Wood Cellulose (con.)



Various hypotheses regarding the size of the cellulose molecule have appeared in the cellulose literature. Views on this subject can be briefly summarized as follows: (a) A relatively enormous molecule made up of a number of anhydrodextrose residues, many of which go to make up the anhydrocellobiose linkages referred to above. (b) A large aggregate made up of comparatively small units, each one of which contains the anhydroglucose linkage or the anhydrocellobiose linkage a relatively small number of times. The units are held together in the larger aggregate by means of secondary valence. From the work of Herzog and his associates it appears that the cellulose units are crystalline and orientated in the cellulose fiber.

The first viewpoint outlined under (a), although still held by individual investigators, has been largely replaced by that referred to under (b). Just what the constitution of the individual cellulose unit really is or what the forces are that hold these units together still form the subject of extended debates, which are not included in the present paper.

If we accept the idea of a relatively small crystalline unit in a relatively large aggregate, a rather crude but useful picture may be obtained by likening these units to bricks in the wall - this wall being the cellulose aggregate. The individual cellulose units or bricks are believed to be in the form of rhombohedra. The mortar between these bricks would represent the secondary valence. If the units or bricks remain undisturbed, but the secondary valence (or motar) is tampered with, changes in state which are so characteristic of cellulose are noted. The individual units or blocks of these units become more or less separated from each other, and a greater surface area is exposed with the various properties that go with such increased surface. Hydration of cellulose would involve the separation of units without, however, chemically changing the individual units. For example, in the swelling caused by the beating of cellulose in the presence of water a material is formed which shows on air drying an increased hygroscopicity,and an enhanced power of adsorbing dye stuffs, and a lowered resistance to certain chemicals. These properties are accounted for in our hypothesis by the increased surface area when the units become partially separated from each other. Complete peptization of cotton in cuprammonium solutions and in other cellulose solvents involves a complete disintegration of the cellulose aggregate, with more or less complete separation of the cellulose units from one another. When cellulose is precipitated in hydrated form from its sols, the bricks or units are presumably in large measure intact. However, they no longer present the same orderly arrangement and orientation which was manifested in the original cell wall.

A different picture obtains when the little units themselves are broken down. Such degradation often follows the partial or complete disintegration of the cellulose aggregate (the wall). It is then that the primary valences within the cellulose unit are disturbed. Hydrolysis, acetolysis, and oxidation of cellulose are examples of such changes. Partial hydrolysis, usually referred to under the obscure term, "hydrocellulose," would mean the hydrolysis of a fraction of the cellulose units originally present in the aggregate. A similar picture would obtain in the case of partially oxidized cellulose (oxycellulose). In either case the partially hydrolyzed or oxidized material may be held in the aggregate consisting in part of unchanged cellulose units

In general, wood cellulose is defined as a residue remaining after some more or less drastic treatment of wood to remove lignin and some of the less resistant carbohydrates of the cell wall. Such treatment might involve the preparation of chemical pulp by any of the well-known pulping processes followed by mild bleaching; by treatment with chlorine dioxide followed by sodium sulphite; by treatment with phenol in the presence of catalysts; by bromination followed by treatment with ammonia;or by a chlorination method followed by suitable alkaline treatment. In the United States at least, the term, wood cellulose, has generally referred to the residue isolated by a chlorination method. This residue, when subjected to further purification, such as digestion with cold alkali and careful washing, has been termed alpha cellulose. The soluble portion removed from cellulose may be separated further into two fractions, the one precipitated by acids and arbitrarily termed beta cellulose and the other remaining dissolved after such treatment and termed gamma cellulose. To the best of our knowledge neither the beta nor the gamma fractions from different woods have been critically investigated. It is the alpha cellulose from wood which most closely resembles the cellulose of cotton.

We have spent some time in preparing samples of alpha cellulose from different species of wood by the chlorination method and ~~in~~ investigating these products by the acetolysis reaction. This work was done by Mr. Russell, formerly of Syracuse University, now in the New Jersey Experiment Station. He found that, on treating alpha cellulose (obtained from various commercial species of wood by repeated chlorination followed by sulphite treatment, and finally by treatment with 17.5% sodium hydroxide) with acetic anhydride in the presence of sulphuric acid, appreciable amounts of cellobiose octaacetate were obtained in every case. A series of quantitative studies carried out under identical conditions, using thermostat control, gave yields of cellobiose octaacetate which vary from 24 to 33% of the theoretical yield. Highly purified cotton cellulose under similar conditions yielded approximately 35% of the octaacetate. The results of Mr. Russell's experiments are given in the appended table. Besides this, Mr. Russell found that carefully purified cellulose obtained from long leaf pine by the sulphate process and from spruce by the sulphite process also yielded appreciable amounts of cellobiose octaacetate; 33% in the first case and over 30% in the second. It is evident, then, that, as far as the cellobiose reaction is concerned, wood cellulose from different sources and that isolated by different methods from the same source behave very similarly to cotton cellulose, and that the cellobiose grouping is characteristic of all the celluloses studied.

Alpha cellulose from wood has other properties in common with those of cotton cellulose. For example, Heuser and his co-workers have shown that both may be hydrolyzed almost quantitatively to d-glucose. The rate of hydrolysis after peptization of the cellulose by means of acid is nearly identical with that of cotton cellulose.

Hertzog and his collaborators at Berlin, using the X-ray method, have obtained interference figures from cotton cellulose which are practically identical with those of wood cellulose.

Hess and his co-workers at Berlin have shown that, when equal amounts of purified cotton cellulose and cellulose obtained from spruce wood are dissolved, each in a definite volume of a carefully standardized cuprammonium solution with exclusion of air, the specific rotations of these two solutions are practically identical. Thus, a cuprammonium solution of cotton representing four molecules of cellulose to ten molecules of copper per hundred liters of solution showed α= -3.36°. Under similar conditions a solution of wood cellulose showed α= -3.29°. The completed rotation curves of the cotton cellulose cuprammonium complex and the spruce wood cellulose cuprammonium complex were, to all intents and purposes, identical.

It has also been shown that acetylation of cotton and acetylation of wood cellulose yield what seemed to be idenitcal cellulose triacetates in very nearly the same amounts. Nitration of wood cellulose yields nitrates very similar to those obtained from cotton.

These facts taken by themselves would argue for the identity of cotton and alpha wood cellulose were it not for a few disconcerting pieces of experimental data which may be interpreted in several different ways. Sherrard and Blanco have shown that alpha cellulose from some coniferous woods yields small but appreciable quantities of mannose on hydrolysis. Furthermore, Mr. Russell and I have shown that wood cellulose isolated from the hardwoods, even when carefully purified, still contains small amounts of furfural-yielding substances or substances related to furfural. This same finding has been made by the chemists of the Forest Products Laboratory.

The question now arises, do these data vitiate Heuser's hypothesis that wood cellulose and cotton cellulose are identical, or can they be brought into harmony with it? It must be assumed at the outset that the wood cellulose <u>aggregate</u> is a very variable one. It is doubtful whether the same investigator can succeed in isolating the identical aggregate from the same sample of wood in two successive experiments. This does not mean that the great majority of the units in such an aggregate (in the case of alpha wood cellulose) may not be identical with the unit in cotton cellulose.

If this is true, those units which are chemically <u>not</u> identical with the cotton cellulose unit and which may make up a part of the wood cellulose aggregate, might reasonably be considered units of those carbohydrates which become intimately associated with the cellulose units during the growth of the cell. The fact that some of these adsorbed carbohydrates remain closely associated with the cellulose, even after drastic treatment which would normally dissolve pentosans, mannans, etc., is not out of harmony with our general knowledge regarding changes in the properties of substances following adsorption. Purification of wood cellulose always involved the attempted removal of extraneous material with a minimum change in the cellulose. On the other hand, it does not permit the solution and reprecipitation of cellulose under conditions which might favor the removal of extraneous material, and it is common knowledge that solids held by gelatinous precipitates may be exceedingly difficult to remove, and that in the past solid solutions have been mistaken for chemical compounds. Taking these facts into consideration, and realizing that cotton and wood cellulose may have many chemical properties in common, it appears to formulate an hypothesis for the structure of wood cellulose which is very similar to that advanced for cotton cellulose. In the case of the wood cellulose aggregate (the wall), most of the units (bricks) appear to be identical with those in the cotton cellulose aggregate. Varying amounts and varying types of other units, however, may also be present in the wood cellulose aggregate, such units being associated with the cellulose units during growth. The number and type of these foreign units depend on the conditions of cell growth and also on the purification to which the wood cellulose has been subjected.

The hypothesis naturally accounts for any mannose that may be found in hydrolysis mixtures obtained from the cellulose of coniferous woods. It also explains the presence of furfural-yielding substances which contaminate the alpha cellulose isolated from hardwood.

While this hypothesis is no more than a working hypothesis, and while the brick wall analysis must not be taken too literally, it appears more readily acceptable than an hypothesis which admits the possibility of a different cellulose unit or molecule for each species of wood. Furthermore, it agrees with the more modern viewpoint on cotton cellulose, its flexibility is apparant, and it accounts satisfactorily for any percentage of pentosans or foreign hexosans that may be found in the cellulose aggregate. Up to the present no experimental data appears to contradict the hypothesis, but it must be remembered that the wood cellulose aggregate has not been explored with the same degree of thoroughness that has marked the study of cotton cellulose. Until this has been done, the preceding hypothesis remains little more than a stimulus to further research.

The Chemistry of Wood Cellulose (conc.)

PENTOSAN CONTENT OF VARIOUS CELLULOSES AND YIELDS OF CELLOBIOSE OBTAINED

Cellulose from	Pentosan Content Calculated from Furfural Yield	Percentage yield of Cellobiose octaacetate (in round numbers) based on theoretical yield of 2.09 grams of the acetate from 1 gram of cellulose .
Pine	1.5	26
Balsam	1.7	27
Spruce	1.5	27
Cedar	2.0	27
Hemlock	1.8	25
COTTON	1.15	33 to 35.5
Birch	3.3	28
Maple	3.3	29
Aspen	5.6	24
Beech	3.2	33
Oak	3.0	26

The Chemistry of Wood Cellulose (con.)

Fig. 1

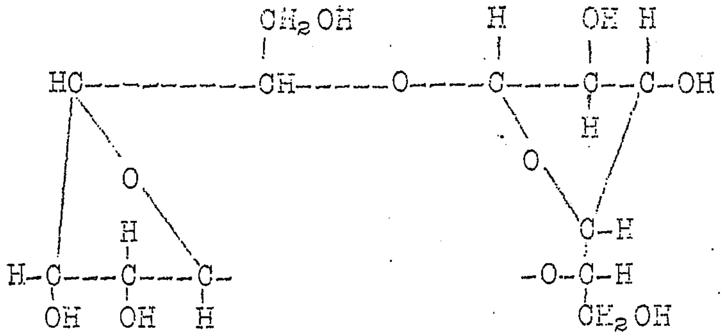
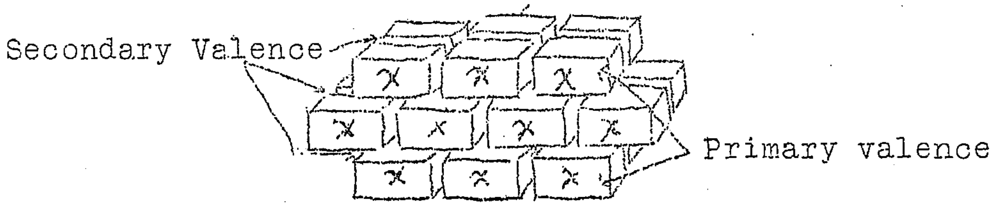
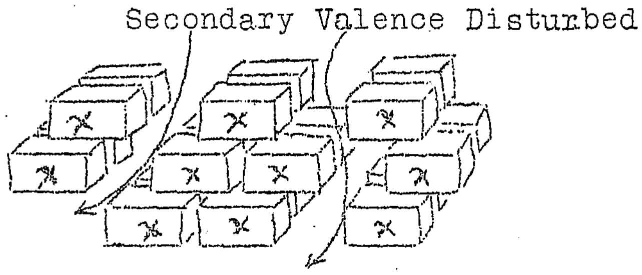


Fig. 2



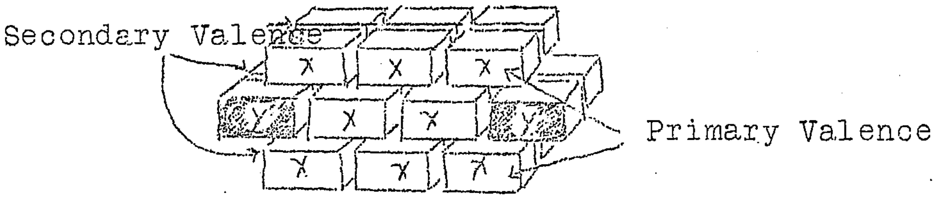
χ = Cellulose Unit

Fig. 3



χ = Cellulose Unit

Fig. 4



χ = Cellulose Unit
Y = Non-Cellulose Unit