[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

CHEMICAL HOMOLOGY

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In the first volume of Grignard's recent "Traité de Chimie Organique," there occurs (pp. 826–834) a section on homology and homologous series. M. Locquin, the author, closes his treatment of the subject with the statement, "Par tout ce que précède, on voit que si les chimistes se font une idée assex claire de ce qu'on doit entendre pars corps homologues, il est assez difficile de donner de l'homologie en général une définition nette et précise." With this opinion, the author of the present paper is in thorough agreement. And if, as is highly probable, most chemists have no such "idée assez claire," the difficulty of precise definition is thereby only increased.

The reason for this unsatisfactory state of affairs is however not hard to discover. M. Locquin's treatment of homology shows clearly that he, like his forerunners, has attempted to set up a definition such that the term homolog should be applicable only where chemists find it useful and instructive. In other words, he has tried to devise a language (or rather a part of a language) in which no one can say anything trivial. That efforts in this direction are foredoomed to failure seems almost self-evident. In such a scheme, an adequate definition of homology would be a textbook on organic chemistry.

The present paper is an attempt to avoid the difficulty just mentioned. The object in view is to give to the general idea of homology a precise meaning, and to furnish a set of terms designed to permit any particular variety of homology to be precisely identified. It will be left to each individual chemist to decide whether or not he finds any one such variety significant.

An illustration borrowed from mathematics may serve as an example of the method to be followed. Mathematicians have a clear and exact definition of the term "function," but they recognize a wide variety of functions. There are continuous and discontinuous functions, algebraic and transcendental functions, functions of a real variable, functions of a complex variable, functions where the independent variable is not a number at all; and so on at great length. On certain kinds of function there is a large literature; other kinds have been only occasionally and briefly

mentioned. To all mathematicians up to date, many sub-varieties of function have seemed so useless and uninteresting that no mention whatever has been made of them. Nevertheless, if any competent person were to consider one of these hitherto unregarded types, he would have no doubt that the mathematical expressions engaging his attention really were functions, and he would be able quite briefly and precisely to identify them. That is to say, mathematicians have very wisely defined the word function so that, if unrestricted, it expresses an idea far too general to be of much use. Certain varieties of function are now of great importance, others as yet of no importance at all. But the interests of individual mathematicians and the fortuitous momentary state of mathematics play no rôle in the definition of the fundamental concept.

In attempting to apply to chemical homology reasoning parallel to that just described, it quickly becomes evident that the notion of similarity of chemical behavior should be rigorously excluded both from the fundamental concept of homolog and from the subsidiary definitions which fix the different varieties of homology. The reasons for these exclusions are twofold. In the first place, similarity of chemical behavior is a most elusive idea, because two compounds may resemble one another closely with respect to one reaction, but differ widely with respect to another. In the second place, similar and dissimilar are not sharply distinguished concepts like odd and even, or greater and less. How closely must two compounds resemble one another with respect to some one reactive property in order to be called in this respect similar? It is hopeless to expect unanimity on such points, even if the persons consulted are experts.

On the other hand, the atomic-molecular hypothesis and the structural theory furnish chemists with a set of concepts which can be precisely defined. Given the structural formula for a particular substance, there is, for example, no doubt whether or not this formula involves a tertiary nitrogen atom. Whether the compound should or should not be called a base is a question which in certain instances may be argued indefinitely. It is therefore on formal properties of composition and structure that the definitions of homology and of its subsidiary varieties should be made to depend.

But clearly, no set of structurally distinct compounds can have all structural features in common. In forming a set of homologs, it will therefore be necessary to retain certain structural features but to abandon others as common properties for the members of the set. At first sight, it might seem convenient to say that the features to be retained should be those having an important bearing on the reactive properties of the compounds in the set, whereas those to be abandoned should be the ones having little bearing on such properties. But it is just this effort to inject

the notion of importance into the definition of homology which has wrecked all previous attempts to give a precise meaning to that term. Hence another method will here be followed. The object will be to give a definition of homology which (within specified wide limits) should permit the individual chemist to retain any structural feature he may consider important as a common property of the homologs he has in mind. His views on importance and his choice of the structural features to be retained as invariants will not affect the general idea of homology; on the other hand, an attempt will be made so to divide the general field that any chemist may easily designate the particular kind of homology he wishes to consider.

Underlying every structural formula, there is a molecular formula independent of structure. On these molecular formulas is based the fundamental concept of homology here adopted.

Definition I.—The members of a set of distinct molecular formulas are all homologous if and only if the differences between them are all multiples of some unit complex ($A_aB_b\ldots.$). If it be desired to give this definition a more technical mathematical form, the statement may be revised as follows:

Definition Ia.—The members of a set of distinct molecular formulas are all homologous if and only if they are all congruent modulo ($A_aB_b\ldots.$). A suitable name for this all-inclusive kind of homology would be "molecular" homology.

Objections may be urged against the fundamental definition here given, but, besides its purely formal character, it has one merit which, in the opinion of the author, outweighs all disadvantages. Apparently, molecular homology is a necessary condition for homology of any kind. That is to say, if the distinct molecular formulas of a set of compounds are not all molecular homologs, then the compounds cannot be said to be homologous in any sense of that term hitherto regarded as useful. Undoubtedly many instances of molecular homology are devoid of chemical interest, but, as has already been indicated, that difficulty cannot be eluded without expanding the definition of homology to the dimensions of a textbook. A more important objection to the above definition is that, if a set of distinct molecular formulas contains only two members, these two formulas must in all cases be homologous. However, if the number is greater than two, homology need not always occur, and even if the number is only two, no specified variety of homology need necessarily appear.

Definition II.—If a unit complex ($A_aB_b\ldots.$) be specified and denoted by U, then any set of distinct molecular formulas which differ from one another by multiples of U may be called U-homologous. (Mathematically speaking, molecular formulas which are congruent modulo U may be

called U-homologous.) In particular, if U = (C + 2H), the homologs would be molecular (C + 2H) homologs. The only homologs which have so far been extensively discussed as such in the chemical literature are the (C + 2H) homologs, and the rest of this paper will be devoted to that part of the subject. Consequently, for the sake of brevity the restrictive symbol (C + 2H) will hereafter be omitted. But throughout the whole development, the possibility of using other unit complexes (moduli) such as (N + H) or (Si + 2H) or (C + O) or (6C + 4H) has not been forgotten. It would therefore be easy to apply in other fields concepts and terms analogous to those here employed, should the need for so doing ever arise.

A convenient way to make the transition from molecular to structural homology is to define the fundamental process by which the structural formula of any compound may be transformed into that of a homologous compound of higher molecular weight—henceforward to be called an upper homolog of the initial compound. It has been suggested that replacement of a hydrogen atom by an alkyl radical be chosen for this basic process. But this choice is extremely unsatisfactory. If it were adopted, glutaric acid (HOOC—CH_2—CH_2—CH_2—COOH) would not be a homolog of of succinic acid (HOOC—CH_2—CH_2—COOH), and carbon tetrachloride would have no homologs at all. It seems far better to adopt interpolation rather than substitution as the fundamental process, for although any substitution of a hydrogen atom by an alkyl radical is equivalent to the interpolation of an alkylene radical, the converse proposition that every interpolation of an alkylene radical is equivalent to the substitution of a hydrogen atom by an alkyl radical is false.

Definition III.—In order to pass from the structural formula of the compound A to the structural formula of some one of its upper homologs, break one bond in the formula of A and interpolate the structural formula of a bivalent alkylene radical (> C_nH_{2n}) between the two free valences thus obtained. Repeat the process just described as often as may be necessary to arrive at the formula of the desired homolog.

It should be remarked that in the general case, where the interpolated complex is not necessarily a multiple of (C + 2H), if the unit complex contains any negative coefficient, the given definition of upper structural homology becomes meaningless. In other words, although unit complexes with negative coefficients may have some application to molecular formulas, they have no bearing on the kind of structural problems hereafter considered.

A distinct advantage of Definition III is that it at once suggests a scheme for classifying types of homology. For, in any particular instance, the defined process of homolog formation determines the values of three

variables: (1) the number of bonds ruptured during the whole process; (2) the particular bond ruptured in each single step; (3) the structural type of the bivalent alkylene radical interpolated after each successive rupture. It will be shown later that fixing the value of each of these three variables is sufficient to define the kind of homology under consideration with the requisite clarity and precision.

Before going on to this demonstration, it is, however, desirable to consider certain difficulties which arise (as it seems inevitably) when the transition is made from molecular to structural homology. Molecular homology has been shown to be nothing more than a chemical version of the modular congruence of linear forms with positive integer coefficients, and as such it is a symmetrical transitive relation. But to retain these characteristics as essential features of structural homology is difficult and probably undesirable. For example, *n*-propylbenzene and *p*-xylene are both structural homologs of benzene. It is, however, awkward to insist that each of these compounds be a structural homolog of the other. In fact, many attempts have convinced the author that it is extremely difficult to deal in any satisfactory manner with sets of structural homologs if all the compounds in such a set are put on a par with one another. A far better method is to select some one member of the set and to describe the other members with respect to the chosen reference compound. For this reason, scant attention will here be paid to what have in the past been called "homologous series." Instead of these conventional series, the sets of upper structural homologs of specified compounds will be discussed. Experience has shown, moreover, that it is convenient to speak sometimes of a set of upper structural homologs with the reference compound excluded, and sometimes of a set consisting of a reference compound together with its upper structural homologs. In the first instance, the phrase used will be "proper upper structural homologs"; in the second, it will be simply "upper structural homologs."

Proper upper structural homology is essentially an unsymmetrical relation and therefore irreflexive. Upper structural homology on the other hand is reflexive and only non-symmetric. Both relations are transitive. They may be regarded respectively as chemical representations (for finite classes) of the abstract mathematical relations frequently illustrated by "includes as a proper subclass" and "includes." Such relations are not in general sufficient to arrange in linear order the members of a finite set within their respective fields. Hence if B_1 and B_2 are distinct upper structural homologs of A, it cannot be inferred that B_2 is an upper structural homolog of B_1 or vice versa. All that can be said is that each is not an upper structural homolog of the other.

If a compound A lies in the converse domain of either of the above-

mentioned chemical relations, then the upper (or proper upper) structural homologs of A constitute a sub-domain of the relation in question. This sub-domain may be called the domain for A. If a particular kind of upper structural homology is specified, the result is (in general) to restrict the domain for A. If X and Y are two distinct members of the domain for A, and X lies in the converse domain of the relation, then it may be inquired whether or not Y is a member of the domain for X. Such questions will, however, be no further discussed in this paper; attention will be centered instead on the relations of the upper structural homologs to the reference compound. Furthermore, since only upper homology is to be dealt with henceforward, the restrictive adjective "upper" will frequently be omitted for the sake of brevity.

Whether a set of structural homologs corresponds to what has heretofore been called a homologous series depends (in part) on the choice of a reference compound and on the decision whether homology or only proper homology is to be considered. But so far as is known, every set customarily called a homologous series may be easily and exactly described in the terminology to be indicated.

Recurring to the three variables previously mentioned (p. 4), the first thing to note is that in every instance the concept involved is structural. It is vacuous as applied to molecular formulas. Therefore, if a value is given to any one of these variables, the type of homology thus specified must be a variety of structural homology, and the word "structural" becomes redundant. Hence it is omitted in the remainder of this paper.

It is convenient first to consider the last one of the variables listed—that is the structural type of bivalent alkylene radical to be interpolated between the free valences formed by the rupture of a single bond. A number of classes and subclasses of such bivalent alkylene radicals may easily be defined. One method is not to specify any restriction, and by convention, when no restriction is mentioned, alkylene radicals of all kinds are to be admitted. Another scheme is to restrict the interpolands to bivalent alkylidene radicals (α, α alkylene radicals). Both of these conditions give rise to precisely definable classes of homologs.* But the method which has so far yielded the most important and useful types of homology is to consider only alkylene radicals which contain no methyl group. If this condition is met, the radicals are of the straight-chain α, ω type. A name is needed for the particular kinds of homology thus obtained. They will here be called "linear."

* It is possible, by defining not only the structures but also the steric configurations of the interpolated alkylene radicals, to arrive at various sets of steric homologs. In fact, all of the ideas here applied only to structural differences may be developed so as to take into account the finer distinctions of stereochemistry. But these finer distinctions are no further considered in this paper.

The second variable to be considered is the number of bonds ruptured in transforming the formula of the reference compound into that of any given homolog. For example, the formula of ethylbenzene can be obtained from that of benzene by the rupture of one bond. To obtain from the formula of benzene the formula of any one of the xylenes necessitates the successive rupture of two bonds. Unfortunately, comparison of the formula of the reference compound with that of any one of its homologs does not always suffice to fix unambiguously the number of bonds ruptured during the transformation. Such a comparison does however fix a lower limit for this number. Hence the following definition:

Definition IV.—If n be the least number of bonds which must be ruptured in order to transform the formula of compound A into that of one of its upper homologs B, then B will be called an n-stage upper homolog of A. By convention, when nothing is mentioned about the value of n (that is when no stage is specified) homologs of all possible stages are to be considered. It is important to note that in the process of forming a many-stage homolog, each single interpolation is commutative with every other single interpolation. Hence it is unnecessary to specify the order in which the individual interpolations are performed.

The stage of the homologs comprised in a single set may be fixed in a great variety of ways. A set may consist entirely of homologs of one specified stage. Or again, it may consist of homologs of several different stages corresponding to a list of specified values of n. Even absurd specifications can be given. For example, the five-stage homologs of methane constitute the null class. This last possibility may be regarded as a blemish on the proposed system, but it is well-nigh impossible to devise a fool-proof notation. All that can reasonably be required is that, if the system proposed be used in an absurd fashion, the absurdity should usually be readily apparent. And this requirement the system here outlined easily fulfills.

The last variable to be considered is the type of bond ruptured during any one stage of a transformation. Experience has shown that in many cases it is sufficient to describe this bond in terms of the element or pair of elements, two atoms of which are connected by the bond in question.

Definition V.—If the formula of a homolog B is obtained from the formula of a compound A by a process involving the rupture of a bond between atoms of the elements ρ and σ, then B will be called a ρ—σ homolog of A. Inspection of the formulas of the reference compound A and of one of its homologs B does not always suffice to fix the sort of bond which must be ruptured during the transformation of A into B. For example, the formula of normal propyl alcohol may be obtained from that of ethyl alcohol by the rupture of a C—H or a C—C or a C—O bond. Consequently a further convention is here required. If the word "exclusive"

is placed before the symbol ρ—σ, the set of homologs defined will consist of those compounds whose formulas can be obtained by the rupture of a ρ—σ bond and by no other method. If the word "exclusive" is omitted, then the symbol ρ—σ will refer to all homologs whose formulas can be obtained by the rupture of a ρ—σ, bond regardless of whether any formula thus obtained might also have been obtained by the rupture of some other sort of bond.

In many instances, the reference compound is such that all or part of the definition with respect to the three variables just discussed may be omitted. An O—H or an O—C homolog of a simple monohydric alcohol cannot be anything but one-stage; any homolog of methane must be a C—H homolog; any homolog of hydrogen must be one-stage and H—H. Hereafter, when such degenerate cases are considered, the description will be abbreviated as far as possible.

It cannot be denied that the system here outlined may, if used without purpose or judgment, lead to bizarre results. By insisting on arbitrary sets of values for n, by specifying different types of bonds to be ruptured and different types of alkylene radicals to be interpolated during the various stages of the transformation, it is possible to draw together into one set of upper homologs compounds which have only remote chemical relations to one another. But it is also characteristic of the system that to produce such ridiculous results usually requires conscious effort and the use of long, intricate lists of restrictions. The useful sets of upper homologs can almost always be briefly defined. Unfortunately, some very queer sets can also be briefly designated. The set of linear O—O homologs of hydrogen peroxide consists of hydrogen peroxide itself, the hydrated form of formaldehyde (if such a compound exists) and all the α, ω straight-chain saturated glycols. But it should be remembered that no one who objects to considering such a set of homologs is in any wise required to do so, and that if anyone does elect to consider so outlandish a collection of compounds, the burden of proof that he is acting reasonably rests upon his own shoulders.

Among the various kinds of homolog so far indicated, one type is distinguished by very marked characteristics. Suppose that one particular ρ—σ bond in the formula of A is uniquely determined and labelled r—s; and suppose that the interpolated alkylene radical L contains no methyl group. Then if B_1 and B_2 are two distinct r—s, L upper homologs of A, either B_1 is an L upper homolog of B_2 or B_2 is an L upper homolog of B_1. In other words, under such circumstances the upper homology relation is not only asymmetric and transitive but also (in the sense of Russell) connected. And any relation which is connected, asymmetric, and transitive within a certain sub-field is serial within that sub-field; that is, it serves to arrange the individuals composing the sub-field in linear order.

Hence the use of the word linear to describe the L type of alkylene radical and the type of homology to which it gives rise. Some writers have shown a tendency to restrict the term "homologous series" to sets of upper homologs of this limited one-stage linear type. Indeed they have gone even farther, and have imposed restrictions on the choice of a reference compound to serve as the first member of such a series. Whatever may be the decision on these points, to the author it seems unwise to restrict the term "set of upper homologs" to the aforementioned special class of sets.

The various applications of the system here outlined may be illustrated by considering some of the different sets of upper homologs obtained when the reference compound is methyl alcohol.

(1) The structural homologs.
All saturated monohydric alcohols and all saturated mono-ethers. Not a very useful classification.

(2) The six-stage homologs.
The null class.

(3) The one-stage homologs.
All saturated monohydric alcohols and all alkyl, methyl mono-ethers. Not a very useful classification.

(4) The O—H homologs.
Methyl alcohol and all alkyl, methyl mono-ethers. Again not a very useful classification.

(5) The proper O—H homologs.
All the alkyl, methyl ethers. A useful class.

(6) The proper linear O—H homologs.
All the straight-chain alkyl, methyl ethers. A homologous series.

(7) The C—H homologs.
All the saturated monohydric alcohols.

(8) The exclusive C—H homologs.
The null class.

(9) The one-stage C—H homologs.
All the primary saturated monohydric alcohols.

(10) The proper two-stage C—H homologs.
All the secondary saturated monohydric alcohols.

(11) The proper three-stage C—H homologs.
All the tertiary saturated monohydric alcohols.

(12) The one-stage linear C—H homologs.
All the primary straight-chain saturated monohydric alcohols. A homologous series.

(13) The proper two-stage linear C—H homologs.
All the saturated secondary monohydric alcohols with straight-chain carbon skeletons. A class with interesting possibilities, although as yet not much used.

(14) The O—C homologs.
All the saturated monohydric alcohols. Identical with example (7).

(15) The O—C linear homologs.
All the primary straight-chain saturated monohydric alcohols. A homologous series. Identical with example (12).

The sets described above as homologous series are those which would come under that head according to most of the definitions of homologous series yet given. Several of the other sets would probably be considered to be homologous series by some chemists but not by others.

The terms so far employed often suffice to determine uniquely the values of the three variables mentioned, and so they frequently designate a unique set of homologs. But where very special sets are contemplated the system breaks down. Suppose for example the set to be considered consists of the one-stage linear C—C homologs of benzil, where the bond to be ruptured is the one between the two carbonyl groups. (This particular set, by the way, is regarded by M. Locquin as quite useless.) Such a set cannot be identified by using the simple terminology so far given. Under such circumstances, a good plan would be to follow a suggestion made at another point by M. Locquin—that is, to give the structural formula of the reference compound and to mark the particular bond (or bonds) to be ruptured.

Examination of M. Locquin's article has shown that every series which he regards as homologous can easily be described in the terminology here used. The cycloparaffins without side-chains, for instance, are the linear C—C homologs of ethylene. If it be desired to exclude ethylene itself from the set, the linear C—C homologs of cyclopropane may be considered instead. The straight-chain saturated aliphatic acids are the linear C—H homologs of formic acid. But as formic acid itself differs markedly in its reactions from all the other member of this set, it would, according to the views of M. Locquin, here be better to consider the proper linear C—H homologs.

Many other examples might be furnished, but enough has already been said to give an adequate idea of the scope and elasticity of the system advocated. Further applications may be left to the reader. No claim is made that this system is the only possible, or even the best possible, one. It merely represents the best that the author has been able to do, and it is published partly in the hope that others may be led to improve upon it. But at very least, it has the merit of eliminating from one part of the terminology of chemistry the value judgments which have no place in the vocabulary of an exact science.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

CONDENSATION OF 4-DIMETHYLAMINOBENZALDEHYDE WITH VANILLALACETONE AND VANILLALACETONE DERIVATIVES

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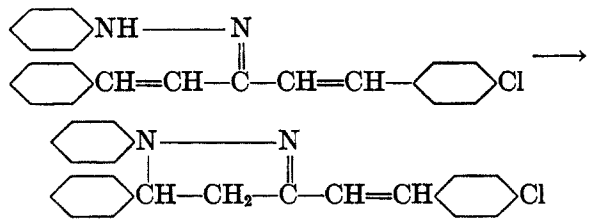
In an effort to determine the effect of constitution on the rearrangement of the phenylhydrazones of unsymmetrically substituted dibenzalacetones into the isomeric pyrazolines, it was found that the closing of the pyrazoline ring involved the unsaturation farthest away from the phenyl nucleus containing such an "acidic" radical as halogen or the nitro group.[1] When the hydrazone obtained from styryl 4-dimethylaminostyryl ketone was tested the closing of the ring involved the unsaturation nearest to the dimethylamino radical which may be regarded as representing a "non-



acidic" group.[2] Such behavior suggested further study of the question, and this requires the synthesis of a number of α,β-diunsaturated ketones containing the 4-dimethylaminobenzal radical. For the other radical of the ketone it was proposed to use vanillal or one of its substitution products which are easily obtained from the vanillin derivatives now known.[3] This report contains observations made in the preparation of such ketones.

To obtain such an unsymmetrical ketone two steps were involved. First, it was necessary to condense one of the aldehydes with acetone, after which the purified product was condensed with the aldehyde containing the other required radical. Vanillin and its substitution products were readily condensed with acetone to give a monovanillal derivative by

[1] RAIFORD AND ENTRIKIN, *J. Am. Chem. Soc.*, **55**, 1125 (1933).

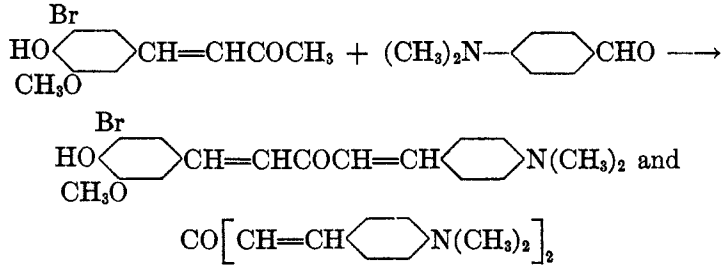
[2] RAIFORD AND HILL, *ibid.*, **56**, 174 (1934).

[3] Many of these have been made available in recent years through the studies of Raiford and co-workers [*ibid.*, **57**, 2500 (1935)] who have prepared all bromine and chlorine substitution products of vanillin demanded by theory.

following a modification of the general method of Francesconi and Cusmano,[4] who used as condensing agent a 10 per cent. aqueous solution of sodium hydroxide as previously recommended by Claisen and Claparede.[5]

In the present work it was found that best results were obtained in preparation of monobenzal derivatives when more acetone than previously suggested was used. Likewise, with these and with the dibenzal compounds the use of more solvent such as alcohol, a more concentrated solution of alkali, and treatment at room temperature rather than that of the steam bath gave more satisfactory results. The presence of much water in the reaction mixture and an elevated temperature lowered the yields through formation of resinous material, and made it difficult to purify the products. These differences were emphasized by the following example. When 5-bromovanillalacetone was condensed with 4-dimethylaminobenzaldehyde at room temperature as described below, a yield of 74 per cent. of the required mixed ketone was obtained. In a repetition of the experiment, modified to the extent that the reaction mixture was heated for two hours on the steam bath, the yield was 52 per cent. With a second reptition, conducted at room temperature with a more dilute solution of alkali, the yield was 48 per cent.

It might be supposed that the desired unsymmetrical dibenzalacetones could be obtained with equal ease by condensing vanillalacetone and its substitution products with 4-dimethylaminobenzaldehyde or by condensing the required vanillin derivative with 4-dimethylaminobenzalacetone. As a matter of experiment the first method only gave the required product. Thus, the condensation of 5-bromovanillalacetone with 4-dimethylaminobenzaldehyde at room temperature gave a good yield of the required unsymmetrical ketone along with a small portion of di(4-dimethylaminobenzal)acetone, first obtained by Sachs and Lewin.[6] Attempts to reverse



this order and condense 5-bromovanillin with 4-dimethylaminobenzalacetone were unsuccessful. In one such experiment the recovery of the

[4] FRANCESCONI AND CUSMANO, *Gazz. chim. ital.*, **38**, [II], 75 (1903).
[5] CLAISEN AND CLAPAREDE, *Ber.*, **14**, 350 (1881).
[6] SACHS AND LEWIN, *Ber.*, **35**, 3576 (1902).

unchanged vanillin derivative was almost quantitative, and that of the dimethylaminobenzalacetone was more than 90 per cent.

The formation of the tetramethyl derivative in the present work indicates that the dimethylaminobenzal radical replaces the vanillal group from a portion of the vanillalacetone (starting material) and then condenses with the remaining methyl group of the acetone. This interpretation seems probable because it was shown by specific test that the dimethylaminobenzal radical will not replace the substituted vanillal radical from the unsymmetrical ketone which already contains a dimethylaminobenzal group. Thus, when an alcoholic solution of a portion of purified 5-bromovanillal(4-dimethylaminobenzal)acetone was treated

TABLE I

SUBSTITUTED VANILLAL DERIVATIVES OF ACETONE

SUBSTITUENT IN VANILLAL RESIDUE	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
2-Chloro-	76[a]	Toluene-ligroïn	Yellow plates	133–134	$C_{11}H_{11}ClO_3$	15.67	15.35
5-Chloro-	57[a]	Dilute acetic acid	Yellow needles	143–144	$C_{11}H_{11}ClO_3$	15.67	15.68
6-Chloro-	91[b]	Benzene	Yellow plates	145.5–146.5	$C_{11}H_{11}ClO_3$	15.67	15.58
2-Bromo-	69[a]	Toluene	Yellow plates	139–140	$C_{11}H_{11}BrO_3$	29.52	29.47

[a] These values refer to purified products.

[b] Purification caused considerable loss.

with *p*-dimethylaminobenzaldehyde in the presence of caustic soda solution, as specified for these condensations, 87 per cent. of the starting material was recovered, and nothing else could be isolated from the mixture.

EXPERIMENTAL

4-Dimethylaminobenzalacetone.—This was prepared as a reference substance in accordance with the method used by Sachs and Lewin,[6] modified to the extent that much larger proportions of acetone and alkali were used. Fifty grams of the required aldehyde was mixed with 200 cc. of acetone, 75 cc. of 10% solution of sodium hydroxide was dropped in with stirring, the stirring was continued for several hours, and the mixture was allowed to stand. The solid that separated was collected and washed free from alkali. A yield of 75% was obtained. The previous workers recorded no yield. Crystallization from alcohol or ligroïn gave yellow leaflets that melted at 132°. Sachs and Lewin first reported 234–235° for this product, but Rupe and Siebel,[7] who repeated the work, found 132° and suggested that the higher value

[7] RUPE AND SIEBEL, *Z. Farbenind.*, **5**, 301 (1906).

TABLE II

VANILLAL (4-DIMETHYLAMINOBENZAL)ACETONE AND SUBSTITUTION PRODUCTS

SUBSTITUTED VANILLAL	YIELD, %	SOLVENT	CRYSTALLINE FORM	M.P., °C.	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
Vanillal (unsubstituted)	56	Alcohol	Orange leaves	199	$C_{20}H_{21}NO_3$	—	—	4.33	4.34
2-Chloro-	67[a]	Dilute alcohol	Orange leaves	186–7	$C_{20}H_{20}ClNO_3$	9.90	9.92	—	—
5-Chloro-	68[b]	Alcohol[c]	Red plates	203–204	$C_{20}H_{20}ClNO_3$	9.90	10.25	—	—
6-Chloro-	19[d]	Acetone solution treated with water	Greenish-red needles	95–110	$C_{20}H_{20}ClNO_3 \cdot \frac{1}{2}H_2O$[e]	9.66	9.66	—	—
2-Bromo-	54[f]	Alcohol	Red rods	194–195	$C_{20}H_{20}BrNO_3$	19.90	20.03	—	—
5-Bromo-	71[g]	Alcohol[c]		203–204	$C_{20}H_{20}BrNO_3$	19.90	19.79	—	—
6-Bromo-	22[h]	Alcohol	Green needles	120–128 (gas evolved)	$C_{20}H_{20}BrNO_3 \cdot \frac{1}{2}C_2H_5OH$[i]	18.80	18.90	—	—

[a] Less than 1% of di(4-dimethylaminobenzal)acetone was isolated here.

[b] Extraction of the crude reaction product with benzene gave 4% of the symmetrical tetramethyl derivative.

[c] Used to extract foreign material.

[d] Represents purified material. There was also isolated 14% of the symmetrical tetramethyl derivative.

[e] When this material was dried in partial vacuum for several days it lost its water of crystallization. *Anal.* Calc'd for $C_{20}H_{20}ClNO_3$: Cl, 9.90. Found, Cl, 10.18.

[f] Refers to purified material.

[g] Five per cent. of the symmetrical tetramethyl derivative obtained also.

[h] The symmetrical tetramethyl derivative was here the chief product. The yield was 42%.

[i] A portion of this material was heated at 130° until its weight was constant and its color was orange. This melted at 185–185.5°. *Anal.* Calc'd for $C_{20}H_{20}BrNO_3$: Br, 19.90. Found. Br, 19.81.

previously reported indicated that a polymer had been obtained by the first workers. Repetition of the experiment by them[8] showed that the discrepancy was due to a typographical error.

Monovanillal derivatives of acetone.—These products were obtained by following Claisen's general method, modified to the extent that more alcohol and much less water were employed. The details for a single case will be given. One-tenth of a molecular proportion of 5-chlorovanillin was dissolved in a mixture of 75 cc. of alcohol and 60 cc. of acetone by gentle warming on the steam bath. Then a solution of 10 g. of sodium hydroxide in 10 cc. of water was added, the mixture was stirred for several hours at room temperature and set aside for about one week. The sodium salt of the condensation product which separated was collected, washed with acetone, dissolved in water, and the liquid was rendered acid with dilute acetic acid. The product that precipitated was purified by crystallization from a suitable solvent. Analytical and other data for the new ones obtained are given in Table I.

Vanillal (4-dimethylaminobenzal)acetone.—Ten g. of vanillalacetone and 7.76 g. of 4-dimethylaminobenzaldehyde were dissolved in 100 cc. of alcohol by warming on a water bath, a solution containing 10 g. of sodium hydroxide in 10 cc. of water was added, stirring was begun, and the mixture was allowed to come quickly to the room temperature. During this period the precipitation of the red sodium salt of the ketone was so copious that it was necessary to add 100 cc. of alcohol in order to continue stirring, which was carried on for about six hours. The mixture was allowed to stand for about a week, the solid was collected, washed with ether, and the ether extract was retained. The remaining sodium salt of the unsymmetrical ketone was suspended in water, and the salt was decomposed by hydrochloric acid. Ammonium carbonate solution was next added with stirring until effervescence ceased*, and the solid was collected, and crystallized from a suitable solvent. Analytical and other data for this and related compounds are given in Table II.

The solvent was distilled from the ether† extract, and the residue was crystallized from alcohol from which it separated in orange-red leaves that melted at 191°. A second crystallization from toluene did not change this, and a mixture melting point determination with an authentic sample of di(4-dimethylaminobenzal)acetone, prepared as directed by Sachs and Lewin[6] showed no depression.

SUMMARY

1. Condensation of vanillalacetone with 4-dimethylaminobenzaldehyde gives vanillal(4-dimethylaminobenzal)acetone and a smaller amount of di(4-dimethylaminobenzal)acetone. In most cases the quantity of the latter is increased by the use of a halogen-substituted vanillal radical. The largest yield of the symmetrical product was obtained when 6-bromovanillin was one of the starting materials. Under the conditions of these experiments the 4-dimethylaminobenzal group does not displace the vanillal radical from an unsymmetrical α,β-diunsaturated ketone containing both these radicals.

2. Further work is in progress.

[8] SACHS AND LEWIN, *Ber.*, **39**, 3785, (1906).

* This method of treatment was found necessary because the dimethylamino radical makes the ketone basic enough to form with hydrochloric acid a salt of sufficient solubility to cause considerable loss at this point.

† In some cases extraction with benzene was found more suitable.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT]

GUANIDINE STRUCTURE AND HYPOGLYCEMIA: SOME SULFUR-CONTAINING DIGUANIDINES

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INTRODUCTION

In 1935 Ackermann and Heinsen[1] reported that a marked fall in the blood-sugar level of dogs followed the administration of diguanylcystamine, $H_2N—C(:NH)—NH—CH_2CH_2—S—S—CH_2CH_2—NH—C(:NH)—NH_2$, a diguanidine containing the dithio linkage. This observation was especially interesting, as the dithio linkages appear to be essential for the physiological activity of the insulin molecule. With the possibility in mind of a relationship between guanidine structure, dithio linkages and insulin-like properties, we undertook to prepare and study physiologically the following new compounds: β,β'-dithiobis (α-guanidopropionic acid) dihydrochloride (I)‡, 4,4′-diguanidodiphenyldisulfide (II) and 4,4′-diguanidodiphenylsulfide (III), and thereby to extend the work on sulfur-containing diguanidines and their physiological behavior.

Only a few diguanidines containing dithio linkages appear to have been reported in the literature to date. Kapfhammer and Müller[2] prepared β,β'-dithiobis (α-guanidopropionic acid) (IV). Greenstein[3], in 1935, synthesized and described 5,5′-(dithiodimethylene) diglyco-

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[1] ACKERMANN AND HEINSEN, *Z. physiol. Chem.*, **235**, 115 (1935).

‡ The nomenclature in this field is unfortunately complicated by lack of uniformity. For example, Kapfhammer and Müller[2] reported β,β'-dithiobis(α-guanidopropionic acid) (IV) as α-diguanido-β-dithiodilactic acid. Greenstein[3,4] designated the anhydro form of this compound as anhydro α,α'-diguanido-di-(β-thiopropionic acid) and also as cystine cyamidene, and described α,α'-dithiobis(ϵ-guanidocaproic acid) as ϵ,ϵ'-diguanido-di-(α-thio-n-caproic acid). In discussing compounds of this type we have applied the rules for nomenclature adopted by *Chemical Abstracts* as an authoritative basis of nomenclature and have used it throughout this paper.

[2] KAPFHAMMER AND MÜLLER, *ibid.*, **225**, 1 (1934).

[3] GREENSTEIN, *J. Biol. Chem.*, **112**, 35 (1935).

cyamidine (V) and its dihydrochloride (VI), and also α,α'-dithiobis (ϵ-guanidocaproic acid)[4]. Ackermann and Heinsen (1) reported the synthesis and physiological properties of diguanylcystamine and tetramethyldiguanylcystamine.

As the low solubility in water of β,β'-dithiobis (α-guanidopropionic acid) (IV) renders it unsatisfactory for physiological studies, and also, since 5,5′-(dithiodimethylene) diglycocyamidine (V) is not a diguanidine but is a meta diazine, we prepared the dihydrochloride of β,β'-dithiobis (α-guanidopropionic acid) (I) which was readily soluble in cold water and therefore suitable for animal experimentation. It is significant to note here that this dihydrochloride (I) is the uncommon reaction product of hydrochloric acid reacting with β,β'-dithiobis (α-guanidopropionic acid) (IV), and is not merely another salt of a known base. The major product is the dihydrochloride (VI)§ of 5,5′-(dithiodimethylene) diglycocyamidine (V), (the meta diazine mentioned above), which was prepared and described by Greenstein.[3]

The two aromatic sulfur-containing diguanidines were selected for investigation for several reasons. Like neosynthalin,[5] which lowers blood sugar as a result of toxic action, they both contain a skeleton of twelve carbon atoms. The arrangement of these carbon atoms into two benzene rings is especially advantageous in that it should provide data in support or refutation of the statement that, "the benzene nucleus is not productive of hypoglycemia."[6] In addition, since one of our diguanidines is a disulfide and the other a monosulfide with their substituent groups in exactly corresponding positions, a direct comparison between these two types of sulfur linkages may be obtained. This is highly desirable because of possible connection with investigations on the rôle of the disulfide groups in the physiological activity of insulin. Furthermore, the availability of these two sulfur-containing diguanidines permits direct comparative physiological studies with two similar diguanidine structures, namely, 4,4′-diguanidobiphenyl and 4,4′-diguanidodiphenylmethane. The latter compounds together with certain other guanidines will be described in a subsequent paper.

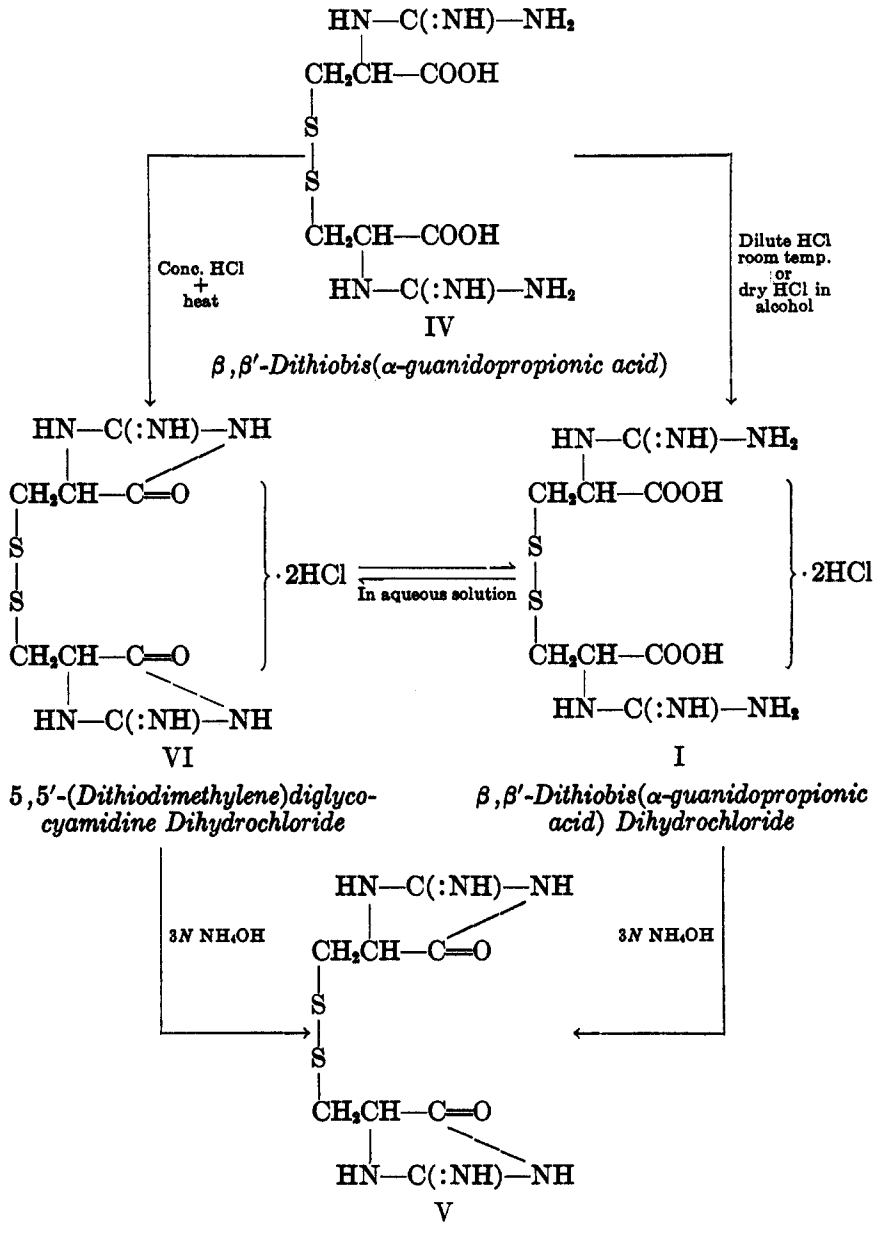
[4] GREENSTEIN, *ibid.*, **109**, 529 (1935).

§ Repetition of Greenstein's preparation of 5,5′-(dithiodimethylene)diglycocyamidine dihydrochloride (VI) gave a product, which after two recrystallizations from a methyl-ethyl alcohol mixture, melted at 154–155° (uncorr.). This is slightly higher than the melting point (150°) reported by Greenstein.

[5] FRANK, *Deutch. med. Woch.*, **53**, 1845 (1927); FRANK, NOTHMANN, AND WAGNER, *Klin. Woch.*, **7**, 1996 (1928).

[6] BISCHOFF, SAHYUN, AND LONG, *J. Biol. Chem.*, **81**, 325 (1929).

The structural relationships between the compounds involved in this work are shown in the following chart.



IV

β,β′-Dithiobis(α-guanidopropionic acid)

VI

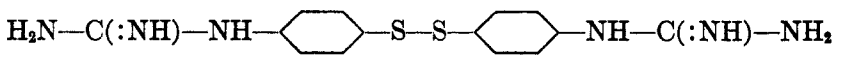
5,5′-(Dithiodimethylene)diglycocyamidine Dihydrochloride

I

β,β′-Dithiobis(α-guanidopropionic acid) Dihydrochloride

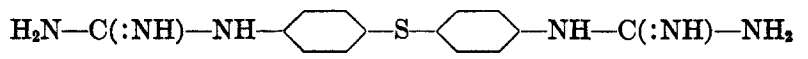
V

5,5′-(Dithiodimethylene)diglycocyamidine



II

4,4′-*Diguanidodiphenyldisulfide*



III

4,4′-*Diguanidodiphenylsulfide*

EXPERIMENTAL

Synthetic Part

Preparation of β,β′-dithiobis(α-guanidopropionic acid)dihydrochloride(I).—The starting compound for the preparation of β,β′-dithiobis(α-guanidopropionic acid) dihydrochloride (I) was β,β′-dithiobis (α-guanidopropionic acid) (IV) which was obtained in 57.4% yield (purified crystalline compound) from cystine by the method of Kapfhammer and Müller[2] excepting that *S*-methylisothiourea hydroiodide was substituted for *S*-ethylisothiourea hydrobromide.

Anal. Calc'd for $C_8H_{16}N_6O_4S_2$: N, 25.92. Found: N, 25.96 (micro-Kjeldahl).

A. β,β′-Dithiobis(α-guanidopropionic acid) (IV) with a molecular quantity of dilute hydrochloric acid.—β,β′-Dithiobis(α-guanidopropionic acid) (IV) heated on the steam bath with the stoichiometrical quantity of 0.1*N* hydrochloric acid (ratio 1:2) underwent decomposition accompanied by rupture of the dithio linkages as proved by the formation of free sulfur in appreciable quantity. Repetition of this experiment consistently gave the same result.

B. β,β′-Dithiobis(α-guanidopropionic acid) (IV) with an excess of dilute hydrochloric acid.—β,β′-Dithiobis(α-guanidopropionic acid) (IV) gave β,β′-dithiobis-(α-guanidopropionic acid) dihydrochloride (I) when treated with a large excess of dilute hydrochloric acid either at atmospheric pressure on a steam bath or at room temperature *in vacuo*. The latter procedure, which gave better yields, is described below.

Six grams (0.0185 mole) of β,β′-dithiobis(α-guanidopropionic acid) (IV) was dissolved in a solution of 120 cc. of concentrated hydrochloric acid diluted to 600 cc. with water. (This is exactly the same weight ratio as was used by Greenstein but differs in concentration of the acid.) The solution was evaporated to dryness *in vacuo* at room temperature. The residue (6.5 g.) was treated with boiling absolute ethyl alcohol, and the alcohol-insoluble fraction was separated by filtration and dried. It weighed 5 g. and melted at 144° (uncorr.), which agrees exactly with the melting point reported by Greenstein[3] for impure 5,5′-(dithiodimethylene)diglycocyamidine dihydrochloride (VI).

Anal. Calc'd for $C_8H_{14}Cl_2N_6O_2S_2$: N, 23.20. Found: N, 22.51 (micro-Kjeldahl).

Several volumes of cold dry acetone was added to the filtrate, whereupon a white amorphous precipitate formed at once. After standing over might in an ice chest, the acetone-alcohol supernatant liquid was decanted, and the precipitate was *rapidly* washed with anhydrous ether and dried at room temperature *in vacuo* over calcium chloride. The dried material was twice purified by dissolving it in a very small volume of boiling absolute ethyl alcohol, reprecipitating with dry acetone, washing with anhydrous ether and drying as described above. The purified compound did

not melt sharply but softened at about 94°, started to evolve a gas at 96°, the evolution of gas becoming very noticeable at 111° and continuing until 146° (uncorr.), when the substance finally decomposed. The final decomposition temperature is interesting in view of the melting point of impure 5,5′-(dithiodimethylene)diglycocyamidine dihydrochloride (144°). β,β′-Dithiobis(α-guanidopropionic acid) dihydrochloride (I) was a white, very hygroscopic powder whose aqueous solutions gave a positive Sakaguchi[7] reaction for guanidine residues. With alkaline lead acetate solution it gave a light-brown colored precipitate which did not turn black even after standing for one-half hour. The average yield from two experiments was 26.3%.

Anal. Calc'd for $C_8H_{18}Cl_2N_6O_4S_2$: C, 24.18. Found: C, 24.94
H, 4.57. Found: H, 4.99 (Semi-micro.)
N, 21.16. Found: N, 21.07 (Average of five analyses; micro-Kjeldahl.)

From the yields it appears that, even when a large excess of dilute acid is used, 5,5′-(dithiodimethylene)diglycocyamidine dihydrochloride (VI) predominates.

C. β,β′-Dithiobis(α-guanidopropionic acid) (IV) with dry hydrogen chloride.—Dry hydrogen chloride slowly bubbled into an ice-cold suspension of β,β′-dithiobis-(α-guanidopropionic acid) (IV) in either absolute methyl or ethyl alcohol followed by removal of the solvent *in vacuo* at 40-60° yielded β,β′-dithiobis(α-guanidopropionic acid)dihydrochloride (I). However, although this method gave higher yields and was less time consuming than the procedure described in Section B, it had the disadvantage of yielding a product which was difficult to purify and probably was always slightly impure as judged by the analytical data.

Anal. Calc'd for $C_8H_{18}Cl_2N_6O_4S_2$: N, 21.16. Found: N, 20.44 (micro-Kjeldahl).

Action of ammonia upon β,β′-dithiobis(α-guanidopropionic acid) dihydrochloride (I).—Three-gram samples of β,β′-dithiobis(α-guanidopropionic acid) dihydrochloride (I) prepared by three different procedures [*B-1*, by evaporation to dryness upon the steam bath of a solution of β,β′-dithiobis(α-guanidopropionic acid) (IV) with an excess of dilute hydrochloric acid; *B-2*, by evaporation to dryness at room temperature *in vacuo* of a solution of (IV) with an excess of dilute hydrochloric acid; *C-1*, by reaction between (IV) and dry hydrogen chloride in anhydrous alcoholic media], were dissolved in cold water, and each was treated with a slight excess of an ice cold solution of 3*N* ammonium hydroxide. In every case a white precipitate formed almost immediately. The precipitates were collected by filtration, washed with ice water, absolute ethyl alcohol, and ether, dried at room temperature *in vacuo*, and analysed.

Anal. Calc'd for $C_8H_{16}N_6O_4S_2$: N, 25.92
[β,β′-dithiobis(α-guanidopropionic acid) (IV)]
for $C_8H_{12}N_6O_2S_2$: N, 29.16*
[5,5′-(dithiodimethylene) diglycocyamidine (V)]
Found: (base from dihydrochloride *B-1*) N, 29.77
(base from dihydrochloride *B-2*) N, 29.59 (micro-Kjeldahl.)
(base from dihydrochloride *C-1*) N, 28.55

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[7] SAKAGUCHI, *J. Biochem. Tokyo*, **5**, 25, 133 (1925).

* The theoretical nitrogen content for 5,5′-(dithiodimethylene) diglycocyamidine (V) reported by Greenstein[3], page 37, should be 29.16%.

These data show that 5,5′-(dithiodimethylene) diglycocyamidine (V) was formed from β,β′-dithiobis(α-guanidopropionic acid) dihydrochloride (I) by reaction with ammonium hydroxide, and suggests that, in aqueous solution, an equilibrium exists between (I) and 5,5′-(dithiodimethylene) diglycocyamidine dihydrochloride (VI). Such an equilibriun would be similar to that which exists between glutamic acid and pyroglutamic acid in aqueous solution and which was recently discussed in detail by Wilson and Cannan[8].

If this equilibrium hypothesis is valid, then (I) in aqueous solution should give low values for primary amino nitrogen (assuming that the guanidine groups react) as determined by the method of Van Slyke[9] since the terminal amino groups are engaged in splitting out water to produce the anhydro form (VI). Conversely, if (VI), which contains no primary amino nitrogen, is partially converted into (I) in aqueous solution, then some amino nitrogen should be obtained when the method of Van Slyke is applied because the opening of the two meta diazine rings by the addition of two molecules of water must produce two primary amino groups at the terminal positions of each guanidine residue.

Amino nitrogen determinations carried out at 21° on freshly prepared sloutions of (I) and (VI) gave the following results:

For β,β′-dithiobis(α-guanidopropionic acid) dihydrochloride (I) $C_8H_{18}Cl_2N_6O_4S_2$:

Sample (mg.)	*Calcd. N, as NH_2 (mg.)*	*Found: N, as NH_2 (mg.)*	
33.4 (15 min.)	2.35	0.592	
33.4	2.35	0.542	
33.4 (20 min.)	2.35	0.671	
33.4	2.35	0.587	
		Avge. 0.598	(25.45% of the theoretical)

For 5,5′-(dithiodimethylene) diglycocyamidine dihydrochloride (VI) $C_8H_{14}Cl_2N_6O_2S_2$

71.54	0.00	2.63
71.54 (20 min.)	0.00	2.68
71.54	0.00	2.85
	Avge.	2.72

The above data supported the suggestion that (I) and (VI) in aqueous solution exist in a state of equilibrium.

The results also showed, obviously, that the guanidine residues in the two compounds investigated reacted with nitrous acid to liberate nitrogen, a fact which is interesting in view of Van Slyke's observation[9] that the guanidine groups in guanidine, creatine, and arginine did not react with nitrous acid.

Preparation of 4,4′-diguanidodiphenyldisulfide sulfate.—4,4′-Dithioaniline prepared from *p*-chloronitrobenzene by the method of Lantz[10] melted at 78° (uncorr.) after recrystallization from 50% ethyl alcohol. The average yield from several runs was 50%. The picrate, recrystallized from 95% ethyl alcohol, melted at 183° (uncorr.).

The dihydrochloride was made by bubbling dry hydrogen chloride into an absolute ethyl alcohol solution of the base. The precipitated dihydrochloride was purified by dissolving it in hot ethyl alcohol and reprecipitating with acetone. The purified

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[8] WILSON AND CANNAN, *J. Biol. Chem.*, **119**, 309 (1937).

[9] VAN SLYKE, *ibid.*, **9**, 185 (1911); **12**, 275 (1912).

[10] LANTZ, U. S. Patent No. 1,933,217 (1933).

4,4'-dithioaniline dihydrochloride was obtained in the form of colorless needles, soluble in water, m.p. 231° (uncorr.).

Anal. Calc'd for $C_{12}H_{14}Cl_2S_2N_2$: Cl, 22.08. Found: Cl, 21.84.

Twenty grams (0.062 mole) of 4,4'-dithioaniline dihydrochloride and 7 grams (0.167 mole) of cyanamide (Eastman Kodak Co.) in 150 cc. of absolute methyl alcohol were heated under reflux on the steam bath for eighteen hours. The resulting solution was then concentrated to one-third of its original volume, diluted to about 425 cc. with water, treated with Norite, cooled in an ice bath, and made alkaline with a slight excess of an ice-cold 10% solution of sodium hydroxide. (This procedure was adopted after preliminary experiments had shown that the dihydrochloride of the diguanidine could not be isolated in crystalline condition from the reaction mass.) The base, 4,4'-diguanidodiphenyldisulfide (II), separated at once as a voluminous yellow precipitate, which was collected by filtration and air-dried at 100° (yield 17 g.).

A small amount of the crude base was recrystallized from boiling dilute (35%) ethyl alcohol. The purified compound was obtained in the form of pale yellow plates, m.p. 178° (uncorr.).

Anal. Calc'd for $C_{14}H_{16}N_6S_2$: N, 25.29. Found: N, 24.53 (micro-Kjeldahl).
S, 19.29. Found: S, 19.11 (Carius).

The remainder of the crude base was converted directly into the sulfate by heating it on the steam bath with a large volume (about 500 cc.) of very dilute sulfuric acid. The hot solution was treated with Norite, and filtered, and the filtrate was allowed to cool *very slowly*. Soon a heavy viscous oil settled out. The clear, pale yellow supernatant liquid was separated from the oil by decantation and allowed to stand for several days, after which crystals of the sulfate precipitated. These were collected by filtration and washed with ice water and absolute ethyl alcohol. The oily layer was taken up in a large volume of hot, very dilute sulfuric acid and allowed to crystallize *slowly*. The conversion of the oil into a crystalline solid was tedious and required many repetitions of the dilute sulfuric acid procedure.

The sulfate was finally purified by recrystallization from dilute ethyl alcohol. When first obtained, the sulfate appeared as fine white needles which became pale yellow upon standing. Storage of the colorless material either in a non-oxidizing atmosphere or in the dark failed to prevent the transition into the yellow variety. The melting points of both varieties were identical, 257–258° (uncorr.), and a mixture melting point showed no depression. Furthermore, there appeared to be no change in the crystalline form accompanying the transition, and analyses on each variety gave identical results. The final yield (purified yellow form) was 4.0 g.

Anal. Calc'd for $C_{14}H_{16}N_6S_2 \cdot H_2SO_4$: Sulfate S, 7.45. Found: S, 7.44
N, 19.53. Found: N, 19.41.
(Semi-micro Dumas).

The picrate of 4,4'-diguanidodiphenyldisulfide (II), after recrystallization from 95% ethyl alcohol, was bright orange and melted at 199° (uncorr.).

Preparation of 4,4'-diguanidodiphenylsulfide sulfate.—*p*-Thioaniline (*p*-aminophenylsulfide) was kindly supplied by E. I. duPont de Nemours & Company. It was purified by recrystallization from 35% ethyl alcohol until the melting point was 107–108° (uncorr.). The picrate, recrystallized from 95% ethyl alcohol, melted at 194° (uncorr.).

The corresponding dihydrochloride was obtained by bubbling dry hydrogen chloride into an absolute ethyl alcohol solution of the purified base. After recrystallization from 95% ethyl alcohol with the addition of ether, the dihydrochloride melted at 241° (uncorr.).

Anal. Calc'd for $C_{12}H_{14}Cl_2N_2S$: Cl, 24.53. Found: Cl, 24.69.

Twenty grams (0.069 mole) of *p*-thioaniline dihydrochloride and 6 g. (0.143 mole) of cyanamide in 230 cc. of absolute methyl alcohol were heated under reflux on the steam bath for fifteen hours. The resulting solution was then concentrated at room temperatiure *in vacuo* to one-fifth of its original volume. The concentrate was diluted with 600 cc. of water, treated with Norite, and cooled in an ice bath. It was then made alkaline with a slight excess of an ice-cold 10% solution of sodium hydroxide. The oil which first separated crystallized upon standing in the ice chest. The crystals were collected by filtration, washed with ice water, and dried at room temperature *in vacuo* over sulfuric acid.

A small sample of the crude 4,4′-diguanidodiphenylsulfide (III) was purified by recrystallization from boiling water. The purified base, glistening colorless prisms, melted at 203–204° (uncorr.) with decomposition.

Anal. Calc'd for $C_{14}H_{16}N_6S$: S, 10.67. Found: S, 10.77. (Carius).

The remainder of the crude base was converted directly into the sulfate by dissolving it in hot dilute sulfuric acid and allowing the solution to cool slowly. The sulfate crystallized out readily in glistening white plates. It was recrystallized without difficulty from hot dilute sulfuric acid, care being taken to wash the crystals thoroughly with ice water to remove any adhering sulfuric acid. The dried sulfate (6.0 g.) did not melt up to 290°.

Anal. Calc'd for $C_{14}H_{16}N_6S \cdot H_2SO_4$: N, 21.10. Found: N, 20.98 (micro Kjeldahl)
Sulfate S, 8.05. Found: 8.01.

The picrate of 4,4′-diguanidodiphenylsulfide, after recrystallization from 95% ethyl alcohol, was bright yellow and melted at 168° (uncorr.).

As in the case of 4,4′-diguanidodiphenyldisulfide (II), it was found by preliminary experimentation that the dihydrochloride of 4,4′-diguanidodiphenylsulfide (III) could not be isolated from the reaction mass, and therefore the procedure, as described above, was adopted. It should also be noted, that, recrystallization of the sulfate of 4,4′-diguanidodiphenylsulfide (III) presented none of the difficulties encountered in recrystallization of the sulfate of the corresponding disulfide (II). There was no transition of 4,4′-diguanidodiphenylsulfide sulfate from the white to the yellow variety as was noted with 4,4′-diguanidodiphenyldisulfide sulfate. Similar transitions between white and yellow forms of the same compound have been reported in the literature on amino derivatives of aromatic sulfides.

The Sakaguchi reaction for guanidine residues could not be applied to either of these two aromatic sulfur-containing diguanidines, as the formation of a black precipitate completely masked the color of the solution.

Physiological Part

The physiological investigation of β,β'-dithiobis(α-guanidopropionic acid) dihydrochloride (I), 4,4′-diguanidodiphenyldisulfide sulfate and 4,4′-diguanidodiphenylsulfide sulfate was carried out at The Lilly Research Laboratories.* The data obtained are recorded in the accompanying table.

It is evident from these results that no hypoglycemia followed administration of these three sulfur-containing diguanidines even in doses as high as 100 mg. (calculated as free base) per kilo of body weight. Also, there was no evidence of acute toxicity with any of the three diguanidines. The failure to obtain hypoglycemia is

* For an outline of the method used for the physiological assay, the reader is referred to a previous paper: BRAUN AND LUDWIG, J. ORG. CHEM., **2**, 442 (1937).

consistent with the observations of Greenstein and Friedgood[11] who reported that α,α-dithiobis(ϵ-guanidocaproic acid) produced no hypoglycemia, but in high doses gave marked hyperglycemia accompanied by death of some of the animals. On the other hand, these negative results are not in accord with the observations of Ackermann and Heinsen[1] who reported that diguanylcystamine produced marked hypoglycemia. However, these investigators noted also that tetramethyldiguanylcystamine caused a sharp increase in the blood sugar.

Since it has been shown here that β,β'-dithiobis(α-guanidopropionic acid) dihydrochloride (I) and 5,5'-(dithiodimethylene) diglycocyamidine dihydrochloride (VI) both gave the same base, 5,5'-(dithiodimethylene) diglycocyamidine (V), when their aqueous solutions were treated with ammonium hydroxide, and since administration of (I) produced no hypoglycemia, it might reasonably be presumed that the anhydro form, (VI), is also devoid of hypoglycemic properties.

TABLE

COMPOUND	DOSE IN MG. FREE BASE PER KILO	BLOOD SUGAR IN MG. PER 100 CC. BLOOD TIME AFTER ADMINISTRATION			
		Initial	1.5 hr.	3 hr.	5 hr.
β,β'-Dithiobis(α-guanidopropionic acid) dihydrochloride (I)	17.5	88.0	107.0	93.0	102.0
	17.5	102.0	109.0	100.0	110.0
	100.0	117.2	108.8	105.9	114.4
4,4'-Diguanidodiphenyldisulfide (II) (Sulfate)	17.5	105.0	117.0	105.0	114.0
	17.5	107.0	114.0	107.0	110.0
	100.0	111.6	103.1	101.7	105.9
4,4'-Diguanidodiphenylsulfide (III) (Sulfate)	17.5	89.0	103.0	88.0	99.0
	17.5	107.0	127.0	105.0	105.0
	100.0	91.8	107.4	104.5	103.1

While entirely too few diguanidines containing the dithio linkage have been prepared and studied for hypoglycemic properties to permit the formulation of any conclusion regarding a possible relationship between structure and physiological activity in this type of compound, nevertheless, it appears evident from the data now available that the mere presence of guanidine residues and dithio linkages in a molecule will not render that compound capable of producing hypoglycemia.

The authors wish to thank Dr. H. A. Lubs of E. I. du Pont de Nemours & Company, Wilmington, Delaware, for the *p*-thioaniline used in this work, and Mr. H. A. Shonle and Dr. E. D. Campbell of The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, for the physiological assays.

SUMMARY

1. Methods for the preparation of β,β'-dithiobis (α-guanidopropionic acid) dihydrochloride (I) have been described, and some evidence for a

[11] GREENSTEIN AND FRIEDGOOD, *J. Biol. Chem.*, **114**, Proc. xliv (1936).

possible equilibrium relationship between (I) and its anhydro form, 5,5′-(dithiodimethylene) diglycocyamidine dihydrochloride (VI) in aqueous solution has been presented.

2. The methods of synthesis for 4,4′-diguanidodiphenyldisulfide (II), its picrate and sulfate, and for 4,4′-diguanidodiphenylsulfide (III), its picrate and sulfate, have been described.

3. The physiological behavior of these three diguanidines has been investigated, and the observations are recorded and briefly discussed in relation to the general problem of guanidine structure and hypoglycemic activity.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY, RIVERSIDE, ILLINOIS]

THE ADDITION OF HYDROGEN FLUORIDE TO THE DOUBLE BOND*

ARISTID V. GROSSE AND CARL B. LINN

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It is well known that the facility of addition of hydrogen halides to olefinic compounds decreases rapidly in the sequence hydrogen iodide, hydrogen bromide, and hydrogen chloride. Hydrogen fluoride has been reported as incapable of adding to olefins.[1]

Recent work in our laboratories by V. N. Ipatieff and one of the writers[2] has demonstrated the direct addition of olefin to paraffin in the presence of such catalysts as boron fluoride with hydrogen fluoride. It has been assumed by us that the alkylation of paraffins involves an initial hydrohalogenation of the olefin, followed by a condensation of the paraffin with the alkyl halide, involving elimination of hydrogen halide. For instance,

$$CH_2 = CH_2 + HF \rightarrow C_2H_5F$$
$$(CH_3)_3CH + C_2H_5F \rightarrow (CH_3)_3CC_2H_5 + HF$$

In the investigation of this proposed mechanism it was discovered that the olefins studied readily add hydogen fluoride, according to the general scheme

$$-\overset{|}{C}=\overset{|}{C}- + HF \longrightarrow -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{F}{C}}-\,.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad H$$

The addition reaction is noncatalytic. It takes place equally as readily in the presence or absence of boron fluoride, and in steel, nickel, copper, aluminum, or paraffin vessels.

The reaction is particularly suitable as a preparative method. It has been used successfully not only for hydrocarbons, but other compounds as well.

The present study is devoted to the hydrofluorination of ethylene, propylene, and cyclohexene and the respective preparations of ethyl,

* Presented before the Organic Division of the American Chemical Society at its ninety-fourth meeting, Rochester, N. Y., Sept. 6, 1937.

[1] See W. Böckenmueller, "Organische Fluorverbindungen," Ferdinand Enke, Stuttgart, **1936**, pp. 33 and 34.

[2] IPATIEFF AND GROSSE, *J. Am. Chem. Soc.*, **57**, 1616 (1935).

i-propyl and cyclohexyl fluorides. The formation of hitherto unknown tertiary alkyl fluorides, such as *tert.*-amyl and *tert*-butyl fluorides, was readily accomplished, but description is reserved for a subsequent publication.

In view of the close chemical relationship of the lower cycloparaffins to olefins and the accomplishment of their catalytic addition to paraffins[3] the reaction between cyclopropane and hydrogen fluoride, leading to *n*-propyl fluoride, was included in this investigation.

In all cases studied a competing reaction is the formation of polymers (or hydrofluorinated polymers), which under some conditions may predominate over simple addition. The polymers obtained, either directly during hydrofluorination, or by reaction of prepared fluorides, as well as the mechanism of polymerization, will be discussed in a separate publication. Suffice it to say here that all fluorides so far studied with the exception of ethyl fluoride are converted by excess of hydrogen fluoride more or less readily at room temperature into polymers of the original olefin.

In general the method employed for the gaseous olefins was to introduce the predetermined quantities of hydrogen fluoride into a bomb into which the olefin was then forced under pressure. Anhydrous hydrogen fluoride was used throughout this investigation. Fifty per cent. aqueous acid does not add to the olefins here described, but in some particular cases it may be used to advantage.

With the exceptions noted in the experimental part the pressures used were about 10 atmospheres for ethylene and 3 atmospheres for propylene. The temperatures employed ranged from − 60° to + 90° in the case of ethylene, and from − 45° to + 75° in the case of propylene. The yield of ethyl fluoride increased continuously with increase in temperature, but the opposite effect was observed in the cases of *i*-propyl and cyclohexyl fluorides.

The length of contact time has no appreciable effect on the yield in the case of ethylene (see Table II), and only such effect as may be attributed to secondary polymerization in the case of propylene (see Table III). The propyl fluoride obtained from propylene was that which would be predicted on the basis of Markownikoff's Rule and Kharasch's[4] theory, namely *i*-propyl fluoride.

The reaction of hydrogen fluoride with cyclopropane was conducted at 25° by successive additions of cyclopropane to a reaction system originally

[3] A. V. Grosse and V. N. Ipatieff, reported before the Organic Division of the American Chemical Society at its ninety-second meeting, Pittsburgh, Pa., Sept. 8, 1936; see Abstracts.

[4] Kharasch, Engelmann, and Mayo, J. Org. Chem., **2**, 298 (1937).

containing an excess of hydrogen fluoride. The product consisted of normal propyl fluoride, containing small amounts of the iso fluoride.

Under proper reaction conditions the olefins reacted to completion. The maximum yields obtained equalled 80–90 per cent. of the olefin charged.

The analyses and some physical constants of the fluorides prepared, determined with the help of Mr. R. C. Wackher, are recorded in Table I. The fluorine determinations were made by burning the substance in excess air in a platinum tube and titrating the hydrogen fluoride produced. An exception was ethyl fluoride; it was analyzed by the more intricate Meslans[5] method. A detailed description of the analytical method and more complete data on physical properties will be described in a separate publication.

TABLE I

ANALYSES AND SOME PHYSICAL CONSTANTS OF FLUORIDES

FLUORIDE	% FLUORINE		M.P.	B.P. (760 mm.)	REFRACTIVE INDEX
	Found	Calc'd			
$C_2H_5 \cdot F$	38	39.6	−143.2	−37.7	n_D^{-40} 1.3057
n-$C_3H_7 \cdot F$	30.4	30.6	−159	− 3.2	n_D^{-30} 1.3326
i-$C_3H_7 \cdot F$	30.2	30.6	−133.4	−10.1	n_D^{-20} 1.3240
$C_6H_{11} \cdot F$	18.3	18.6	+13.0	71.2 (300 mm.)	n_D^{20} 1.4147

EXPERIMENTAL

Description of apparatus—The hydrofluorinations of ethylene and propylene were carried out, unless otherwise indicated, in an Allegheny metal autoclave of 1200 cc. capacity, fitted with a mechanical stirrer and a pressure gage. The autoclave contained a close fitting nickel liner; the inlet and exit tubes, as well as the stirrer, were also of nickel.

The reaction with cyclopropane was carried out in a duraluminum bomb of 250 cc. capacity.

When superatmospheric pressures are not necessary the hydrofluorinations are best carried out in a copper flask or cylinder, fitted with copper stirrer and tubes.

Isolation of reaction products.—The reaction products were usually siphoned over under pressure into a copper receiver, cooled with dry ice-acetone mixture to from −70° to −80°. This receiver contained an excess of finely crushed ice to combine with the unchanged hydrogen fluoride; a line led from there through a soda-lime tower into a glass trap cooled to about −80°, and from there into a gas collecting bottle. The contents of the copper receiver were allowed to warm up to room temperature during which time the gaseous fluorides boiled out and were recondensed in the glass trap. The polymers were separated from the aqueous acid in the copper

[5] MESLANS, *Bull. soc. chim.*, [3], **9**, 109 (1893); *Z. anal. Chem.*, **33**, 470 (1894).

receiver. The crude fluoride usually had a purity of over 95%. One Podbielniak distillation of the crude material gave a very pure product.

Sources of reagents.—Hydrogen fluoride, obtained from the Harshaw Chemical Company, Cleveland, Ohio, was a C.P. product. It was water-white, and contained 0.1% or less of water. On evaporation it left a residue of less than 0.04%, containing some iron and copper. *Ethylene*, from the Ohio Chemical and Manufacturing Company, was over 99.5% pure. *Propylene*, from The Matheson Company, was 99% pure; n_D^{-50}. 1.3640. *Cyclohexene*, C.P., from Eastman Kodak Company, n_D^{20} 1.4457. *Cyclopropane*, from The Mallinckrodt Chemical Works, 99% pure, $n_D^{-42.5}$ 1.3799. *Boron fluoride*, was originally prepared in our own laboratory, but was later obtained, compressed in cylinders, from the Harshaw Chemical Company. The C.P. product solidified to perfectly white crystals and contained only traces, if any, of silicon fluoride.

Addition of hydrogen fluoride to ethylene.—(A) Experiments in Allegheny metal autoclave.—In all experiments 10 g.-moles (200 g.) of anhydrous hydrogen fluoride

TABLE II

PREPARATION OF ETHYL FLUORIDE

EXPT. NO.	% YIELD, BASED ON C_2H_4 REACTING	% ETHYLENE REACTING	TEMP., °C. ±5°	REACTION TIME, HOURS	MOLE RATIO, HF:C_2H_4	MOLE RATIO, BF_3:HF	n_D^{20} OF POLYMERS
1	81	100	90	5	3.32	—	1.4850
2	45	92	25	5	3.09	—	1.4310
3	49	97	25	24	1.86	—	1.4365
4	55	100	25	67	2.94	—	1.4677
5	27	95	0	6	3.00	—	1.4320
6	22	100	0	24	1.01	—	1.4309
7	0	<5	−60	4	3.05	—	—
8	49	99	25	24	1.82	0.01	1.4389
9	22	98	0	24	1.08	0.02	1.4332

was used. The results are given in Table II. The reacting ethylene unconverted into the expected fluoride was recovered in the form of oily, slightly yellow-colored, polymers.

The ethylene was forced in intermittently over a period corresponding to about three-quarters of the reaction time from a weighted bomb, under continuous stirring. Pressures up to 10 atmospheres were usually sufficient; only in experiment 1 (see Table II), at 90°, was a pressure of 20–25 atmospheres necessary to overcome the vapor pressure of the bomb contents. After the addition the stirring was continued for the last quarter of the run. A marked temperature rise was noted during the early part of the reaction, but this diminished as the rate of ethylene absorption fell off during the later stage of the experiment.

When boron fluoride was used, in the ratio of from 0.004 to 0.03 moles of boron fluoride per mole of hydrogen fluoride, practically identical results were obtained. This is illustrated by experiments 8 and 9 in comparison with experiments 3 and 6 of Table II. The results prove that boron fluoride is not necessary as a catalyst in hydrofluorinations.

(B) Experiment in duraluminum vessel.—Five gram moles of anhydrous hydrogen fluoride was placed in a bomb of 250 cc. capacity; 2 moles of ethylene was forced in over a period of 2 hours at about 25°, and the bomb was then rotated for 4 hours. The ethylene reacted to completion. A 44% yield of ethyl fluoride was obtained; the rest of the ethylene polymerized.

Addition of hydrogen fluoride to propylene.—(A) Experiments in Allegheny metal autoclave.—In all experiments 10 g.-moles (200 g.) of anhydrous hydrogen fluoride was used. In all cases propylene reacted to completion. Within the limits of error of Podbielniak distillation no normal propyl fluoride was found in our products. The results are recorded in Table III.

The liquid propylene was forced in at a constant rate from a graduated charger for three-quarters of the reaction time*, under continuous stirring. The reaction appeared to be instantaneous, and was accompanied by a marked temperature rise. Over 98% of the crude fluoride boiled from −11 to −10° at 750 mm.

The presence of boron fluoride is not necessary, as a comparison of experiments 2 and 7 shows.

TABLE III

PREPARATION OF *i*-PROPYL FLUORIDE

EXPT. NO.	% YIELD, BASED ON C_3H_6 CHARGED	TEMP., °C. ±5°	REACTION TIME, HOURS	MOLE RATIO, HF:C_3H_6	MOLE RATIO, BF_3:HF	n_D^{20} OF POLYMERS
1	62	−45	2	3.20	—	1.4616
2	61	0	5	1.08	—	1.4618
3	60	0	2	2.40	—	1.4619
4	51	0	2	5.60	—	1.4551
5	49	0	19	2.54	—	1.4588
6	2	+75	2	2.74	—	1.4534
7	42	0	3	1.12	0.075	1.4609

(B) Experiment in paraffin vessel.—A paraffin cylinder of about 200 cc. capacity (20 cm. long, 6 cm. diameter, 6 mm. wall thickness) was made out of a mixture (about 10:1) of solid white paraffin wax (so-called "Texwax") and cetane; the latter was added to prevent the development of cracks at low temperatures. A paraffin funnel and a paraffin-covered condenser of the Dewar vessel type were inserted into the top of the vessel. The paraffin cylinder was inserted into a snugly-fitting thin-walled glass cylinder, and the whole was immersed into an acetone-dry ice bath cooled to about −25 to −30°. Fifty grams (2.50 moles) of pure hydrogen fluoride, containing about 0.5% of moisture, was distilled into the vessel by means of a platinum tube sealed into the paraffin funnel. About 20–25 g. (0.50 moles) of pure propylene was added during the next half hour, while the condenser was kept cold with lumps of dry ice. The reaction was practically instantaneous—during some additions, even violent—so that some propylene was lost through the upper exit tube of the condenser. After standing for 1 hour, the reaction vessel was allowed to warm to room temperature, under dry ice reflux. After 3.5 hours the dry ice was removed

* Except in experiment 5 (Table III), where propylene was added at a constant rate for 3 hours, and was then stirred for 16 hours.

from the condenser, and the volatile reaction products were allowed to condense, first in a receiver containing 50 g. of chipped ice cooled to −78° and then in 2 dry receivers, also at −78°. After distillation from the reaction vessel practically ceased receiver I was allowed to warm; any distilled hydrogen fluoride dissolved in the ice (and water) and 16.6 g. (0.3 moles) or 19.5 cc. (d_4^{-78} 0.86) of pure water-white *i*-propyl fluoride (n_D^{-20} 1.3239) collected in receiver II. No polymers were found in the paraffin vessel.

(C) Aqueous hydrofluoric acid (48%) and propylene.—Two and three-quarters g.-moles of propylene was added rapidly to 7.25 moles of hydrogen fluoride and 8.72 moles of water in the Allegheny metal autoclave at 25°. There was no temperature rise, and after stirring for 18 hours at 25° all of the propylene was recovered. No trace of *i*-propyl fluoride or polymers was found.

TABLE IV

PREPARATION OF CYCLOHEXYL FLUORIDE

EXPT. NO.	% YIELD, BASED ON CYCLOHEXENE REACTING	% CYCLOHEXENE REACTING	TEMP., °C. ± 5°	REACTION TIME, HOURS	MOLE RATIO, HF:C_6H_{12}	n_D^{20} OF POLYMERS
1	80	100	−35	1.25	2.05	1.4822
2	54	96	10	1.25	1.11	1.5155
3	10	100	35	5.0	2.05	1.5121

TABLE V

PREPARATION OF *n*-PROPYL FLUORIDE

EXPT. NO.	% YIELD, BASED ON CYCLOPROPANE REACTING		INITIAL TEMP., °C.	REACTION TIME, HOURS	MOLE RATIO, HF:C_3H_6
	Normal fluoride	Isofluoride			
1	80	8	25	0.25	2.62
2	70	6	25	2.0	2.67
3	49	3	25	7.0	2.97

Addition of hydrogen fluoride to cyclohexene.—In all experiments 10 g.-moles (200 g) of anhydrous hydrogen fluoride was used. The results are recorded in Table IV.

The cyclohexene was added continuously, under stirring. The addition caused a marked temperature rise. At the end of the addition the reaction product was immediately poured on cracked ice. The fluoride, particularly the crude product, decomposes on heating to 90–100° with copious evolution of hydrogen fluoride, and has to be distilled in a vacuum.

Our fluoride was very pure. It boiled from 71.0 to 71.4° at 300 mm., and all fractions, except the first,* in experiment 2, had the same index of refraction and the

* The small amount of unreacted cyclohexene in the first cut could be readily evaluated by Francis' bromine number determination (cyclohexyl fluoride is not rapidly attacked), or by its index of refraction.

same melting point (see Table I). We found the density of our fluoride, d_4^{20} 0.9279, to be slightly lower than the value given by F. Swarts[6] (0.9296).

Reaction of hydrogen fluoride with cyclopropane.—In all experiments 4.0 g.-moles anhydrous hydrogen fluoride was used. In every case all the cyclopropane reacted. The results are recorded in Table V.

The cyclopropane was added in batches. Much heat was evolved after each addition, and the bomb was immediately cooled in ice.

The overheating due to the uncontrolled rate of addition and the lack of stirring are at least partly responsible for the isomerization of the normal into the iso fluoride.

Long contact time favors the polymerization of the *n*-propyl fluoride, and should be avoided.

SUMMARY

1. The direct addition of hydrogen fluoride to the double bond, termed hydrofluorination, has been accomplished.

2. Alkyl fluorides, such as ethyl, *i*-propyl, cyclohexyl and *n*-propyl fluorides respectively, have been prepared by the hydrofluorination of the olefins: ethylene, propylene, and cyclohexene, and the cycloparaffin, cyclopropane.

3. The reaction is not catalytic and takes place as readily in paraffin as in metal vessels.

4. The maximum yields of fluorides obtainable are over 80 per cent. of the calculated, based on the olefin. Generally low temperatures and short reaction times gave better yields. An exception is ethyl fluoride.

5. In all hydrofluorinations studied the competing reaction was the formation of polymers of the olefin, and higher-molecular-weight fluorides, which reduced the yields of the desired alkyl fluorides.

[6] SWARTS, *Bull. Sci. acad. Belg.*, **22**, 105, (1936).

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

CATALYTIC EFFECTS IN THE BROMINATION OF TOLUENE

M. S. KHARASCH, PHILIP C. WHITE, AND FRANK R. MAYO

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Numerous previous investigations of the bromination of toluene have dealt with the effects of light, temperature, concentrations, catalysts, and solvents. Of various interpretative hypotheses hitherto advanced, none accounts adequately for all the phenomena reported.

The observation in this laboratory that side-chain bromination of toluene is markedly facilitated by traces of organic peroxides and oxygen may be interpreted in a manner that permits the correlation of many hitherto unrelated, and some apparently discordant, data. In the light of the present and previous studies[1] the authors believe that hydrogen bromide is a source of bromine atoms in the presence of oxygen and sufficiently active oxygen-carriers. The working hypothesis proposed is that side-chain bromination of toluene is a chain reaction initiated by bromine atoms, whereas nuclear bromination is a slow bimolecular reaction in which bromine atoms do not participate. It is the purpose of the present communication to show that this hypothesis is consistent with the earlier experimental data, and to report certain supplementary studies that also tend to support it.

REVIEW OF THE LITERATURE

It was early observed that nuclear and side-chain bromination of toluene are two separate and independent reactions and that their relative rates, and consequently the ratios of their respective products, vary widely with the experimental conditions.[2] Ordinarily *o*- and *p*-bromotoluenes (hereafter referred to as "bromotoluenes") are the only products of nuclear bromination. *m*-Bromotoluene is formed only in very high bromine concentrations, and in the presence of a catalyst.[3] Even then, the yield is only a fraction of one per cent. Likewise, polybromo compounds are not formed except in the presence of large amounts of catalyst, such as thirty mole per cent. of aluminum bromide,[2] or beryllium bromide.[4]

[1] KHARASCH, MARGOLIS, WHITE, AND MAYO, *J. Am. Chem. Soc.*, **59**, 1405 (1937); KHARASCH, ENGELMANN, AND MAYO, J. ORG. CHEM., **2**, 298 (1937).

[2] VAN DER LAAN, *Rec. trav. chim.*, **26**, 1 (1907).

[3] HOLLEMAN, *ibid.*, **33**, 183 (1914).

[4] PAJEAU, *Compt. rend.*, **202**, 1795 (1936).

Catalysts exert a strong influence on the direction of bromine substitution in toluene. In general the catalytic effect may be divided into two classes. Metals, metal halides, and iodine increase the rate of nuclear substitution. Aluminum bromide seems to be the most effective of such catalysts. At 50° as little as 0.4 mole per cent of aluminum bromide (per mole of bromine) raises the yield of bromotoluenes from 46 per cent. to 99.5 per cent.[2] To produce such an effect with iodine at 25°, about 5 mole per cent. is required.[5] Photobromination, even in diffuse light yields 98 per cent. of benzyl bromide, and is complete in a few minutes, while reaction in the dark requires many days.[2] Ozone has an effect similar to light, greatly accelerating the side-chain reaction.[6] It appears to be a general rule that when benzyl bromide is the predominant product, the reaction is an extremely rapid one, while nuclear substitution is by comparison slow. Such a difference is to be expected between a bimolecular reaction and a chain reaction involving bromine atoms. The chain reaction involves unstable reactive intermediates; it must proceed rapidly or not at all.

TABLE I

EFFECT OF DILUTION UPON THE RATIO OF SUBSTITUTION PRODUCTS

MOLE RATIO TOLUENE/BROMINE	BENZYL BROMIDE IN TOTAL BROMIDES (%)
4.3	24
8.0	42
10.4	56
20.6	82
28.5	95

Temperature exerts a strong influence on the direction as well as the rate of the bromination reaction. Regardless of other factors, such as concentration and catalysts, it is uniformly true that the higher the temperature, the higher the yield of benzyl bromide.[2]

The effect of the bromine concentration upon the ratio of the two products in the absence of solvent and catalyst, was first observed by Bruner and Dluska,[5] and later studied by Holleman and Polak[7]. The more dilute the solution the higher is the relative yield of benzyl bromide. The effect appears at all temperatures studied. Table I records the results of reactions carried out by Holleman[7] at 50° in the dark, and allowed to run to com-

[5] BRUNER AND DLUSKA, *Bull. intern. acad. sci. Cracovie*, **1907**, 691; *C. A.*, **2**, 1272 (1908).

[6] BRUNER AND LAHOCINSKI, *ibid.*, **1910**, 560; *C. A.*, **5**, 3045 (1911).

[7] HOLLEMAN AND POLAK, *Rec. trav. chim.* **27**, 435 (1908).

pletion. At very high dilution (100:1 or greater) and at elevated temperature the product is 100 per cent. benzyl bromide.

The dependence of the type of substitution upon concentration indicates that diminishing bromine concentration will change the direction of substitution during the course of the reaction. Hence the ratio of the products depends upon the point at which the reaction is stopped. Failure to recognize this is doubtless the cause of considerable disagreement among the observations of the early workers. Because Holleman's reaction went to completion his results do not show, as do those of Bruner, the interesting fact that while the rate of nuclear substitution falls off normally with increasing dilution, the rate of substitution in the side-chain is actually higher in more dilute solutions.[5] This would be expected if bromine molecules in some way hinder the side-chain substitution. We believe that bromine molecules act as "chain breakers" by combining with

TABLE II

EFFECT OF SOLVENTS ON THE BROMINATION OF TOLUENE[a]

SOLVENT	TIME, DAYS	BROMINE REACTED (%)	BENZYL BROMIDE IN TOTAL BROMIDES (%)
Carbon disulfide	33	38	82
Carbon tetrachloride	30	48	50
Benzene	30	73	38
Acetic acid	5.5	61	4
Nitrobenzene	1	92	3

[a] The toluene/bromine ratio was 10:1; solvents were added to give a volume equivalent to that of a 40:1 toluene-bromine mixture.

bromine atoms. Hence the rate of substitution in the methyl group decreases with increasing concentration of molecular bromine.

Bruner and his co-workers also studied the effect of various solvents on the bromination of toluene, both in the light and in the dark. For the dark reaction the results set forth in Table II are representative.[8] These investigators call attention to the direct relation between the ionizing power of the solvent and its effect in catalyzing nuclear and inhibiting side-chain substitution. Although carbon disulfide and carbon tetrachloride act merely as inert diluents, acetic acid and nitrobenzene have pronounced effects. Similar influences prevail in the photobromination, where acetic acid and nitrobenzene retard the rate of reaction and lower the yield of benzyl bromide to about 70 per cent.

[8] BRUNER AND VORBRODT, *Bull. intern. acad. sci. Cracovie*, **1909**, 221; *C. A.*, **4**, 3067 (1910).

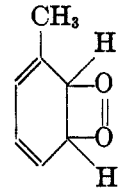
A brief outline of the various theories proposed to account for the solvent effect will serve to show the general confusion existing in this field. Holleman explains these results on the basis of the relative solubility of hydrogen bromide in the various solvents,[7] but while his data for acetic acid solution demonstrate the inhibition of the side-chain substitution by hydrogen bromide, they do not establish any positive catalytic effect on nuclear substitution. LeBlanc and Andrich[9] attempt to interpret these data on the basis of differences in the degree of bromine solvation in associating solvents, such as toluene and ethyl acetate. Increased solvation, they suggest, decreases the photosensitivity of the bromine, and hence inhibits side-chain substitution. However, this interpretation fails to explain the effect of solvents on the yield of bromo-toluenes. Lauer and Oda[10] assume that the "ionoid character" of the ring is raised (with a corresponding increase in reactivity) because of the greater association of the toluene molecule in such solvents. It is argued that since association presumably takes place through the methyl group, substitution in the side-chain is thereby blocked. It might be predicted, therefore, that the more dilute the solution or toluene in the solvent, the less would be the degree of its association, and that higher rather than lower yields of benzyl bromide would be obtained. The results of experiments 26 and 27 (Table VI) do not fulfill this prediction.

The "after-effect" observed by Bruner and Lahocinski[6] is significant in the light of the present work on catalysis by peroxides. They report that photobromination is accompanied by the production of a catalyst which, upon addition of more bromine, causes very rapid reaction in the dark with the formation of 90–95 per cent. benzyl bromide. Oxygen is absorbed during the formation of the catalyst, and the solution takes on a yellow color. Replacement of the dissolved oxygen, before illumination, by carbon dioxide, hydrogen, or nitrogen prevents the occurrence of the "after effect," as does the addition of iodine or hydrogen bromide after the photobromination. Such a catalyst is not produced by illumination of a solution of toluene, benzyl bromide, and hydrogen bromide, so bromine is apparently necessary. The more dilute the bromine solution during the "after-effect," the greater is the influence of the catalyst. It is apparently destroyed or ineffective in very concentrated bromine solutions.

Further work on this "after-effect" shows that the catalyst formed liberates iodine from potassium iodide.[9] An attempt to isolate the catalyst yielded a small amount of material with a "phenol and cresol-like" odor. LeBlanc and Andrich assume the catalyst to be peroxidic. Since catalyst-formation takes place under the influence of light in the visible region of the

[9] ANDRICH AND LEBLANC, *Z. wiss. Photochem.*, **15**, 148, 183, 197, (1916).
[10] LAUER AND ODA, *Ber.*, **69B**, 978, 1061 (1936).

spectrum, which is not absorbed by either toluene or oxygen, it must be the bromine which renders the reaction light-sensitive. This property of bromine is cited as one established in other photochemical reactions.[11] The mode of action of the catalyst is not explained. They do suggest the formation of an intermediate:



In view of the findings of the present study it seems probable that this peroxide acts as do others to produce bromine atoms, thus initiating chain reactions resulting in substitution in the methyl group.

Oxygen itself is well-known to be involved in the photochemical reaction, but the fact seems to have received little attention. LeBlanc and Andrich found that in experiments conducted in an atmosphere of oxygen their yields of benzyl bromide were slightly higher and were more nearly reproducible than when the reaction was carried out in air.[9] Bruner and Czarnecki[12] observed that removal of oxygen by evacuation or replacement by an inert gas retarded the photobromination, *but they did not analyse the products to determine what effect this might have upon the direction of the reaction.* Furthermore, in the dark and in highly dilute solution, they observed an autocatalytic effect which depended upon the presence of oxygen for its existence. Here the reaction produced 100 per cent. of benzyl bromide, while the slower reaction, in the absence of oxygen, gave only 80–90 per cent. of benzyl bromide.

In summary it may be said that substitution in the side-chain is favored by dilution, high temperature, light, and the presence of oxygen, ozone, and some peroxide-like substance formed under the influence of light in the persence of bromine. Nuclear substitution, on the other hand, is catalysed by metal halides, iodine, and certain ionizing solvents, and is favored by high bromine concentrations.

DISCUSSION OF MECHANISM

It was originally assumed that the metal halides catalyzed nuclear substitution through "active" complexes such as $MBr_3 \cdot Br_n$. However, Bancroft has pointed out that such an "active complex" might be ex-

[11] BRUNER AND KROLIKOWSKI, *Bull. intern. acad. sci. Cracovie*, **1910**, 192; *C. A.*, **5**, 2248 (1911).

[12] BRUNER AND CZARNECKI, *ibid.*, **1910**, 516; *C. A.*, **5**, 3751 (1911).

pected to stimulate the side-chain as well as ring substitution.[13] It is now the consensus of opinion that the halogen carriers activate the hydrocarbon ring rather than the bromine molecule.

In the case of the uncatalyzed bromination of toluene it has been suggested that the mechanisms of nuclear and side-chain substitution differ with respect to the active agents involved in the respective substitutions. Holleman postulated that "HBr_n" attacks the nucleus, while bromine molecules cause substitution in the chain. This hypothesis is consistent with the results of his experiments in acetic acid solution, where hydrogen bromide decreases chain substitution. According to this hypothesis the temperature effect is due to the decomposition of the complex "HBr_n" by heat, which left the side-chain substitution the predominant reaction. However, Holleman himself recognized the failure of the theory to explain the dilution effect. At the beginning of the reaction no hydrogen bromide is present in the mixture, yet in concentrated bromine solution nuclear substitution proceeds very rapidly even in the absence of "HBr_n."

Bruner and co-workers suggested the bromine atom as the reagent for nuclear substitution, but offered no evidence in confirmation of this theory.

LeBlanc and Andrich ascribe the temperature effect to the decrease in solvation of the bromine molecule, but make no attempt to apply their theory to other factors affecting the reaction.

The hypothesis proposed by the present authors implies: (1) that factors favorable or inimical to the production of bromine atoms in the reaction system accelerate or retard side-chain substitution; (2) that factors operating to reduce the length of reaction chains, by the removal of bromine atoms or otherwise, inhibit side-chain substitution. Such factors are regarded as having only incidental effects upon the rate of nuclear substitution, and as affecting the ratio of products obtained primarily by altering the rate of one of two competing reactions.

Some bromine atoms doubtless exist in dilute toluene solutions of bromine by virtue of thermal dissociation, even at room temperature; increase in temperature would increase this dissociation. On the assumpgion that the heat of dissociation of bromine is in the neighborhood of 46,000 calories, the concentration of bromine atoms should be about a hundred times greater at 80° than at room temperature. Hence, a rather large positive temperature coefficient for side-chain substitution is implied. The work of Bruner and Diuska[5] shows that the temperature coefficient for substitution in the side-chain is over four times as large as that for nuclear substitution. To some extent a change in concentration would also affect the degree of dissociation of the bromine molecules by

[13] BANCROFT, *J. Phys. Chem.*, **12**, 417 (1908).

operation of the mass law. While this effect is in qualitative agreement with the facts, it is doubtless too small to be of much significance.

If hydrogen bromide in the presence of oxygen is a source of bromine atoms as suggested,[1] then the results of Bruner *et al.* at high dilution, which revealed an autocatalytic reaction in the side-chain bromination in the presence of oxygen are explained, in part at least, by the increase in hydrogen bromide concentration as the reaction proceeds. This phenomenon would appear only at a dilution such that the formation of benzyl bromide is the principal reaction, and when the amount of available oxygen is relatively large. If interaction of oxygen and hydrogen bromide produces bromine atoms, it is obvious that peroxides and ozone should be still more effective in this respect. The very strong catalytic effect of these substances in the formation of benzyl bromide is thus explained.

It has long been recognized that visible light is effective in the direct photodissociation of bromine molecules. It now appears probable that, in the presence of bromine, visible light may be effective in the secondary production of bromine atoms, (1) by activating the interaction of oxygen and hydrogen bromide,[14] or (2) by activating the interaction of oxygen with hydrocarbons to form peroxidic catalysts,[6,9] or both.

Hence it appears that oxygen, peroxides, light, and heat all act on a reaction mixture of bromine and toluene in such a way as to increase the number of bromine atoms present; all increase the rate and extent of side-chain substitution. The effects of bromine concentration and solvents come under the category of factors influencing chain-length.

The chain presumably proceeds through one or both of the following pairs of reactions:

(1*a*) $$C_6H_5CH_3 + Br\cdot \rightarrow C_6H_5CH_2\cdot + HBr$$

(1*b*) $$C_6H_5CH_2\cdot + Br_2 \rightarrow C_6H_5CH_2Br + :\dot{\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}}\cdot$$

(2*a*) $$C_6H_5CH_3 + :\dot{\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}}\cdot \quad C_6H_5CH_2Br + H\cdot$$

(2*b*) $$H\cdot + Br_2 \rightarrow :\dot{\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}}\cdot + HBr$$

Once started, the chains continue until broken by some side-reaction. If, as seems probable, the bromine molecule acts as a chain-breaker by the formation of Br_3, it is to be expected that in concentrated bromine solutions the chain length will be relatively short, and the yields of benzyl bromide corresponding low. Likewise certain solvents (notably solvents rich in oxygen) act as inhibitors of the chain reaction.

[14] *Cf.* KHARASCH AND MAYO, *J. Am. Chem. Soc.*, **55**, 2468 (1933).

RESULTS

Dilution.—The addition of a small amount of an organic peroxide to a dilute toluene solution of bromine increases the rate of reaction greatly in the dark and raises the yield of benzyl bromide. This catalytic effect is greatest in dilute solutions of bromine, and vanishes in very concentrated solutions. Furthermore, the peroxide is more effective if added slowly during the course of the reaction, presumably because the catalyst is

TABLE III

THE EFFECT OF ASCARIDOLE ON THE BROMINATION OF TOLUENE IN DARKNESS

EXPT. NO.	MOLES TOLUENE[a]	MOLES ASCARIDOLE[a]	TIME, HOURS	YIELD OF BROMIDES ISOLATED (%)	ESTIMATED[b] YIELD, (%)		
					Total Bromides	Benzyl Bromide	Bromo Toluenes
1	2	0	23	72	89	1	88
2	2	0	0.75	38	47	0.3	47
3*	2	.03	23	64	82	4	78
4*	2	.03	0.75	37	47	4	43
5	5	0	23	48	58	2	56
6*	5	.03	23	53	65	17	48
7	10	0	96	61	75	7	68
8*	10	0	23	14	22	1	21
9*	10	.03	23	67	94	85	9
10*	10	.03	5	79	94	89	4
11	10	.03	0.06	73	90	87	3
12	20	0	91	25	33	11	22
13	20	0	48	15	22	8	14
14	20	.03	0.5	85	100	95	5
15	20	0 (*in vacuo*)	91	21	30	10	20

* Indicates average of two or more experiments.

[a] Per mole of bromine.

[b] The basis of estimation is explained in the experimental part.

gradually destroyed in the course of the reaction. Benzoyl peroxide, ascaridole, and triacetone peroxide are all catalysts, but ascaridole was used in the recorded experiments. Table III records the results of a series of experiments at 25° in the presence of air, with and without peroxide, at various dilutions and reaction times. While a comparison of the various control experiments confirms the observations of earlier workers as to the dilution effect, the latter is much more strikingly evident in the case of the peroxide experiments. Here any variation in the initial

concentration of the bromine atoms is overshadowed by the much greater atomic concentration from interaction of hydrogen bromide and peroxides. The wide variation in yield of benzyl bromide is due to the facts that the nuclear substitution is faster and the chain reaction is interrupted in concentrated solution.

Since the life of a bromine atom in such solutions must be extremely short, and the peroxide present is rapidly destroyed in forming atoms, one would expect the chain reaction to be extremely rapid. A comparison of the benzyl bromide yields in experiments 9 and 11 shows clearly that the reaction initiated by the peroxide has run its course within a few minutes. However, in the control experiments in dilute solution, where dissociation and the action of air on hydrogen bromide furnish a continuous supply of bromine atoms, the yield of benzyl bromide increases uniformly with time, as is shown by experiments 7, 8, 12, 13. The effect of oxygen in the production of bromine atoms in these control experiments

TABLE IV

EFFECT OF PEROXIDE ON THE BROMOTOLUENE ORTHO-PARA RATIO[c]

EXPERIMENT	TIME	YIELD OF BROMIDES ISOLATED, (%)	BENZYL BROMIDE, (%)	FREEZING POINT, BROMO-TOLUENES	% *o*-BROMO TOLUENE
Control	4 days	61	90	−8°C.	54
3 Mole % Ascaridole	1 day	68	10	−9°C.	55

[c] The toluene/bromine ratio was 10:1 for both experiments.

is apparently insignificant at 20:1 dilution (*cf.* 12 and 15), although the work of Bruner indicates that it is appreciable at 200:1 dilution.

The rate of nuclear substitution shows a uniform increase with increasing bromine concentration. The data do not warrant any kinetic interpretation which might throw light on the mechanism of ring bromination. It may be said only that the data are not inconsistent with the hypothesis of a bimolecular reaction for nuclear substitution, and that they do exclude the possibility that nuclear substitution takes place through a bromine-atom mechanism.

The bromotoluenes from one control and one peroxide-catalyzed experiment were analysed by the freezing-point method of van der Laan[2] (assuming the absence of *m*-bromotoluene) to determine whether the presence of peroxide during the reaction has any influence on the ortho/para ratio in the nuclear-substitution product. The data recorded in Table IV indicate that there is no such effect. The composition in each case was determined directly from the freezing-point curve given by van der Laan.

Inhibitors.—The complete inhibition of side-chain substitution by very small concentrations of certain substances supports the postulate that a chain mechanism is operative in the peroxide-catalyzed reaction. Several nitroso compounds have been found to have this effect, as, to a much lesser degree, has ethyl alcohol.[15] Table V records the results of several such experiments, with corresponding controls for comparison. Qualitative tests showed many similar substances, such as isoamyl nitrite, *p*-nitrosodimethylaniline, and even sodium nitrite, to be effective inhibitors. The inhibition is not due merely to the binding or destruction of the peroxide by an equivalent quantity of inhibitor, for it also occurs in the photobromination. In the presence of a few mole per cent. of isoamyl

TABLE V

EFFECT OF INHIBITORS ON THE PEROXIDE-CATALYZED REACTION[c]

EXPT. NO.	INHIBITOR	MOLES[a] INHIBITOR	MOLES ASCARIDOLE[a]	TIME, HOURS	YIELDS OF BROMIDES ISOLATED (%)	ESTIMATED[b] YIELDS, %		
						Total Bromides	Benzyl Bromide	Bromo Toluenes
8*		None	0	23	14	22	1	21
9*		None	.03	23	67	94	85	9
10*		None	.03	5	79	93	89	4
16	C_6H_5NO	.03	0	24	33	40	1	39
17*	C_6H_5NO	.03	.03	24	33	44	1	43
18	N_2O_4	.03	.03	23	16	24	1	23
19	C_2H_5OH	2.6	0	23	50	67	0.5	66
20*	C_2H_5OH	.03	.03	23	50	67	15	52
21	H_2O	.03	3	4	79	95	92	3
22	AcOH	.03	3	24	78	94	82	12
23	$C_6H_5NO_2$	.03	3	24	83	98	85	13

*, [a], [b] Have the same significance as in Table III.

[c] The toluene/bromine ratio was 10:1 for all experiments.

nitrite the light-activated reaction is complete only after many hours, whereas it normally requires only a few minutes. Water, acetic acid, and nitrobenzene have no appreciable inhibitory effect when present in small concentrations (a few mole per cent. on the basis of the bromine present).

Solvents.—The use of solvents in the peroxide-catalyzed reaction, as is shown in Table VI, merely confirms the observations already made.

Carbon tetrachloride is an inert diluent, and decreases the rate of side-chain and nuclear substitution. Acetic acid and nitrobenzene, however, strongly inhibit the peroxide-catalyzed chain reaction. It may be noted also that the rate of nuclear substitution is increased. This effect is con-

[15] SWENSSON, *Z. wiss. Photochem.*, **20**, 206 (1921); *C. A.*, **15**, 2838 (1921).

sistent with the relatively high dielectric constants of these solvents as well as with the suppression of side-chain bromination. Experiment 29 shows that the solubility of hydrogen bromide in acetic acid cannot account for the catalysis of nuclear substitution. Also, the association theory of Lauer and Oda previously mentioned above is refuted by experiments 26 and 27, where the yield of benzyl bromide is not affected (within experimental error) by the change in concentration of the toluene.

Light.—In photobromination experiments at 10:1 dilution the yield of benzyl bromide is lowered by exclusion of oxygen. It is interesting to note that the rate of bromination is also markedly decreased (24 hours

TABLE VI

EFFECT OF SOLVENTS ON THE PEROXIDE-CATALYZED REACTION

EXPT. NO.	SOLVENT[c]	MOLES TOLUENE[a]	MOLES ASCARIDOLE[a]	TIME, HOURS	YIELD OF BROMIDES ISOLATED (%)	ESTIMATED[b] YIELDS,%		
						Total Bromides	Benzyl Bromide	Bromo Toluenes
8*	None	10	0	23	14	22	1	21
9*	None	10	3	23	67	94	85	9
24	Carbon tetrachloride	2	0	24	11	14	0.5	13
25*	Carbon tetrachloride	2	3	23	26	33	25	8
26	Acetic acid	1	0	23	29	36	0.5	35
27	Acetic acid	2	0	23	32	42	0.4	42
28	Acetic acid	2	3	23	32	40	1	39
29	Acetic acid	2	(0.97 mole HBr)	23	15	19	0.2	19
30	Nitrobenzene	2	3	23	95	95	2	93

*, [a], [b] Have the same significance as in Table III.

[c] Sufficient solvent was added to bring the volume up to that of a 10:1 toluene-bromine solution.

in vacuo, as compared with 20 minutes in air). In experiment 35 bromine atoms were apparently produced by the action of light on molecular bromine, for the product is principally benzyl bromide, yet the slow reaction indicates that the concentration of atoms thus produced is very small compared to that arising from peroxide action. A still more marked oxygen effect is observable in the 5:1 dilution experiments. Here the nuclear substitution predominates, because the high bromine concentration inhibits the chain reaction. In the absence of oxygen the yield of benzyl bromide is only 15 per cent., and the rate of reaction is extremely slow, while in the presence of air over 70 per cent. of benzyl bromide is formed in a few hours.

These results invite reconsideration of the extent to which the direct photochemical dissociation of molecular bromine is actually involved in the so-called photobromination reaction. The materials used in these experiments were carefully degassed, and the degree of evacuation was high (10^{-5} mm.). However, no attempt was made to remove the oxygen layer adsorbed on the glass, and traces of oxygen are necessarily present even after the best evacuation. The fact that under these conditions only 15

TABLE VII

OXYGEN EFFECT IN PHOTOBROMINATION

EXPT. NO.	MOLES TOLUENE[a]	AIR	ILLUMINATION[c]	MOLES ASCARIDOLE[a]	TIME, HOURS	YIELD OF BROMIDES ISOLATED (%)	ESTIMATED YIELDS[b], %		
							Total[d] Bromides	Benzyl Bromide	Bromo Toluenes
31	5	+	+	.03	0.3	83	100	90	10
32	5	+	+	0	2.5	84	100	75	25
33	5	−	+	0	57	79	95	15	80
11	10	+	−	.03	0.06	73	90	87	3
34	10	+	+	0	0.3	94	100	90	10
35	10	−	+	0	24	95	100	68	32

[a], [b] Have the same significance as in Table III.

[c] 100-W. incandescent lamp at 30 cm. distance.

[d] Usually illuminated until bromine color disappeared.

TABLE VIII

PEROXIDE EFFECT IN THE BROMINATION OF ETHYLBENZENE

MOLES ASCARIDOLE[a]	TIME, HOURS	YIELD BROMIDES ISOLATED (%)	
		Nuclear	Side-chain[c]
0	25	14	26
2 mole %	1.5	6	91

[a] Has the same significance as in Table III.

[c] No analysis was made to determine whether this was the α or β compound; by analogy with the photobromination of toluene it is probably the α isomer.

per cent. of benzyl bromide was formed after fifty-seven hours' illumination (experiment 33), suggests the possibility that if no oxygen were present light might be without effect on the reaction. The experimental data presented certainly do not prove this to be the case; on the other hand, *they cannot be taken as indicating unquestionably that light does have a direct effect on the reaction independent of the presence of oxygen.* It may be that in solutions of these concentrations light produces no bromine atoms whatsoever except through the activation of small amounts of oxygen.

An alternative explanation of the oxygen effect is that oxygen combines with some "chain-breaker" which otherwise is free to inhibit the light-sensitized reaction.

As confirmatory evidence that the differences shown in these experiments are due to oxygen, it is noteworthy that in the reactions in which air is present, decolorization always starts at the surface and proceeds downward through the solution. On the other hand, in the vacuum experiments decolorization proceeds uniformly throughout the entire reaction mixture.

Ethylbenzene.—Several experiments were carried out with ethylbenzene. With this compound, at a 1:1 ratio of bromine to the hydrocarbon in the dark, only the nuclear substitution products are formed.[16] A strong peroxide effect was observed in this reaction at a dilution of 7:1; the results are recorded in Table VIII.

EXPERIMENTAL

Materials—Mallinckrodt's "Analytical Reagent" toluene was distilled through an eight-ball Snyder column. The fraction boiling at 109.5°–110.3° at 749 mm. was stored over sodium and used directly. Commercial grade ethylbenzene was shaken with mercury for several days to remove sulfur, then dried and distilled; b.p. 134.8°–135.2° at 747 mm. Baker's C.P., bromine was used without further purification. One test experiment using bromine which had been carefully washed with alkali and permanganate, then dried and distilled from phosphorus pentoxide, gave exactly the same results as those obtained with the commercial C.P. product. Ascaridole, obtained from the Eastman Kodak Co., was used in all the recorded experiments. The solvents were of the best reagent grade and were distilled immediately prior to use.

Apparatus—Most of the experiments were carried out in a Pyrex 200-cc. four-necked flask equipped with two 50-cc. dropping funnels, a mercury-sealed stirrer, and a reflux condenser. This flask was equipped with ground glass joints throughout, and was partially immersed in a thermostat kept at 25°. The whole apparatus was covered with several layers of glazed black cloth which permitted the manipulation of the stopcocks without admission of light. On the rare occasions when it was necessary to examine the mixture during the course of the reaction this was done with the aid of a small flashlight.

Procedure.—The bromine and the ascaridole, the latter diluted with a few cubic centimeters of toluene or solvent, were admitted to the reaction mixture through the two dropping funnels. The bromine was added at once, while the peroxide solution was admitted intermittently over a period of five or ten minutes. The mixture was stirred during this period, and the hydrogen bromide evolved passed through the condenser into a water trap. The bromine was measured volumetrically, 0.040 or 0.080 moles being used. In some of the control experiments, in which the reaction was allowed to run several days, the reagents were merely mixed in a large open test-tube in the dark and kept at room temperature.

With the exception of the photobrominations, in which the solutions were illuminated at room temperature until colorless, the reaction was interrupted while bro-

[16] SCHRAMM, *Ber.*, **18**, 606 (1885).

mine was still present. In most experiments a current of air was passed through the stirred solution for an hour at the end of the reaction to remove as much hydrogen bromide as possible and thus reduce the amount of washing necessary. The reduction of the remaining bromine was then accomplished with little or no exposure to light by pouring the reaction mixture into an excess of dilute sodium bisulfite solution in a covered separatory funnel. The organic phase was immediately washed with water until the washings no longer showed a precipitate with silver nitrate. In those experiments in which acetic acid was used as a solvent, carbon tetrachloride was employed to extract the product from the aqueous solution after the unchanged bromine had been destroyed. When the reaction was carried out in nitrobenzene, the extent of bromination was determined by titration of the residual bromine. Since the solvent and products could not be separated by fractionation in this case, the analysis for benzyl bromide was carried out on an aliquot sample according to the method described below.

The excess toluene was removed from the washed product by distillation under 20–30 mm. pressure. The products themselves were then distilled at the same pressure from a small Claisen flask with a long, indented neck. No effort was made to separate the bromotoluenes from the benzyl bromide. The boiling range of the products was from 70°–95° depending upon the composition and the exact pressure.

The yield of bromides isolated given in the various tables are those calculated from the weight of the distillate. However, there is necessarily a certain amount of loss in the washing by hydrolysis of benzyl bromide, and in the distillation. Material being carried over with the unchanged toluene would be principally the lower-boiling bromotoluenes. Conversely any hold-back in the distilling flask would be the side-chain substitution product. This last factor is negligible since the residue, except when ascaridole was used, was only 0.1–0.2 g. This fact also attests the absence of any higher bromination products.

The "estimated yields" were arrived at by a consideration of the yields obtained in the photobrominations which had gone to completion, and of the loss found in the treatment of artificial mixtures. Washing and distillation resulted in combined losses of 15–20%, as is indicated by experiments 32 and 33. In experiments in which the yield was very low the same loss by weight would be a much larger factor. However, the treatment of artificial mixtures indicated that the loss in purification of very small samples was only 25%, and was about equally divided between bromotoluene and benzyl bromide. A 1:1 mixture of benzyl bromide and bromotoluenes, weighing 2.0 g., lost 0.5 g. upon washing and distillation, and the remaining material was 53.0% benzyl bromide. Hence the net yields were estimated as actually being 10–25% too low, depending on the quantities of reagents used in the individual experiment. The precision of the "estimated yield" is ±10%.

In the analysis of benzyl bromide a small weighed sample of the product was treated with an excess of standard silver nitrate in alcohol solution. Then the excess silver nitrate was determined according to the method of Volhard. All analyses were carried out in duplicate. The yields of benzyl bromide and bromotoluene were calculated directly from the results of the analysis and the estimated yield. The precision of the *relative* yields of these products is ±1%.

Experiments which were carried out *in vacuo* were performed in the following manner. The toluene and bromine were placed in separate tubes, and these were joined by an inverted U-tube fastened to the vacuum line. To facilitate sealing there were constrictions in the tubing where the U-tube joined the line and the tube

containing the toluene. Both tubes were chilled in liquid nitrogen, and the system was evacuated to a pressure of 10^{-5} mm. The yoke and tubes were temporarily closed off by means of a stop-cock above the constriction. Both reactants were warmed to their boiling points to permit escape of dissolved gases. They were then chilled once more, and the system was re-evacuated. This degassing process was repeated twice. The system was sealed off and removed from the line, and the bromine was distilled into the toluene by allowing it to warm to room temperature. The reaction tube was then sealed off and was ready for illumination. The control reaction in a sealed or open tube of the same diameter was carried out simultaneously.

SUMMARY

1. The work of various investigators on the bromination of toluene has been summarized and few of the mechanisms they propose for the reactions involved have been discussed.

2. A strong oxygen effect, which influences the direction as well as the rate of the reaction, has been observed in the photobromination of toluene.

3. A number of inhibitors of the side-chain bromination of toluene have been discovered.

4. The side-chain bromination of ethylbenzene is influenced by oxygen and/or peroxides.

5. A chain reaction carried by bromine atoms has been proposed as a probable mechanism for side-chain bromination. It is in accord with the facts previously observed and is substantiated by the catalytic effects of oxygen and peroxides under various conditions.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS

XIX. THE ADDITION OF HYDROGEN BROMIDE TO TRICHLOROETHYLENE

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Previous investigations[1] have demonstrated that the "normal" addition of hydrogen bromide to halogenated ethylenes and propylenes (vinyl chloride, 1-chloropropene, etc.) proceeds at a very much slower rate than addition to the corresponding alkenes. However, in spite of the fact that the peroxide-catalyzed "abnormal" addition of the halogen ethylenes is rapid, it has been possible to effect a "normal" addition under strictly antioxidant conditions. Thus, in the case of vinyl chloride, 60–70 per cent. of the 1,1 isomer was obtained in 7–14 days, depending upon the antioxidant used. It appeared probable, therefore, that if the substitution of hydrogen atoms by halogen atoms decreases the rate of "normal" addition, the "normal" addition in the case of trichloroethylene would become very slow, and that the result of the reaction would be the peroxide-catalyzed addition product. Our expectations concerning the slowness of the "normal" reaction were realized. This reaction is so slow that we could find no uncatalyzed "normal" addition of hydrogen bromide to trichloroethylene. Furthermore, we were able to adduce additional evidence that the presence of two hydrogen atoms on the terminal carbon atom of the double bond is not an essential structural feature for molecules which exhibit a "peroxide effect."

PREVIOUS WORK

There appears to be no previous record of the addition of hydrogen bromide to trichloroethylene. Hydrogen chloride has been added to this compound in the presence of aluminum chloride by Prins,[2] who obtained unsymmetrical tetrachloroethane in the temperature range 30–40°. With

[1] See KHARASCH, ENGELMANN, AND MAYO, J. ORG. CHEM., **2**, 288 (1937) for references.

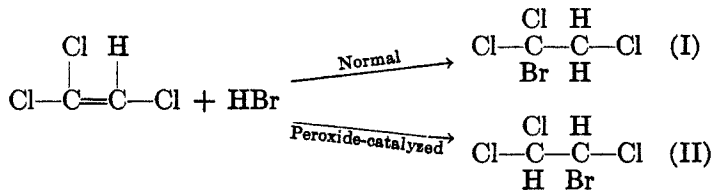
[2] PRINS, *Rec. trav. chim.*, **45**, 80 (1926).

the same catalyst, Muller and Honn[3] used somewhat higher temperatures and obtained other products as well as unsymmetrical tetrachloroethane, probably *via* halogen interchange.

1,1,2-Trichloro-1-bromoethane is not described in the literature. Van de Walle[4] describes 1,1,2-trichloro-2-bromoethane, and submits proof of structure for it and also for the third possible compound of the same empirical formula, 1,1,1-trichloro-2-bromoethane.

DISCUSSION OF RESULTS

From considerations of structure, it appears that hydrogen bromide could add to trichloroethylene to give either 1,1,2-trichloro-1-bromoethane (I) or 1,1,2-trichloro-2-bromoethane (II):



Upon the basis of the hypothesis previously advanced,[5] the unsymmetrical tetrahalide (I) should be the "normal" addition product while the symmetrical tetrahalide (II) should be the "abnormal" addition product, and the latter should be formed in the presence of oxygen and/or peroxides.

Table I shows that we were unable to detect any addition of hydrogen bromide to trichloroethylene under "antioxidant" conditions, even after 30 days in sunlight or when the reaction mixture was heated to 100° for two days. In a number of cases, the reaction mixture was kept for two months in the dark without showing any signs of addition.

The slowness of the "normal" addition is also shown by results which were obtained in the attempted addition of anhydrous hydrogen iodide to trichloroethylene. Hydrogen iodide is the halogen acid which adds most readily to ethylene bonds. An equimolecular mixture of the two showed only a faint iodine color and no volume change after four days' standing in darkness in the absence of air at room temperature. The iodine color was comparable to that given by hydrogen iodide alone in a few weeks under the same conditions. When a similar mixture was exposed to sunlight for two weeks, 25 per cent. of the trichloroethylene was reduced to

[3] MÜLLER AND HÖNN, *J. prakt. Chem.*, **133**, 289 (1932).

[4] VAN DE WALLE, *Bull. soc. chim. Belg.*, **28**, 304 (1914).

[5] KHARASCH AND DARKIS, *Chem. Rev.*, **5**, 571 (1928); KHARASCH AND REINMUTH, *J. Chem. Educ.*, **8**, 1703 (1931).

1,1,2-trichloroethane and a large quantity of iodine separated. There was no evidence of any product of higher boiling point than trichloroethane. It is concluded that no appreciable addition of hydrogen iodide took place in the dark, and that if any addition took place in the light the product was quickly reduced by hydrogen iodide.

TABLE I

ADDITION OF HYDROGEN BROMIDE AND HYDROGEN CHLORIDE TO TRICHLOROETHYLENE IN THE ABSENCE OF AIR AND PEROXIDES

MOLES[a] HBr	ADDED SUBSTANCES	MOLES[a] OF ADDENDUM	ILLUMINATION	REACTION TIME[b], DAYS	ADDITION (%)	REMARKS
1.30	Ph_2NH	.015	None	60	0	
1.30	Ph_2NH	.015	Sunlight	30	0	
2.15	EtSH	.031	None	60	0	
1.65	PhSH	.038	None	60	0	
1.37	*t*-Bu—N=C	.022	None	60	0	
1.63	PhSH *t*-Bu—N=C	.030 .079	Pyrex Hg arc	0.83	0	
1.81	AcOH EtS	2.19 .067	None	60	0	
1.46	cOH PhSH	.715 .030	None	60	0	
1.58	AcOH PhSH	.909 .054	None	2 (100°)	0	
1.55	$FeCl_3$	.005	None	1	73	Addition product exclusively 1,1,2-trichloro-1-bromoethane (I).
1.15	$FeCl_3$	.004	None	1	81	
1.85	$AlCl_3$	.005	None	1 (0°)	35	
1.50	$AlCl_3$	.006	None	1	—	Inseparable mixture
MOLES[a] HCl						
1.57	$FeCl_3$	.003	None	6	49	Addition product exclusively 1,1,1,2-tetrachloroethane
1.62	$AlCl_3$	.004	None	3 (0°)	22	

[a] Calculated on basis of trichloroethylene used.

[b] Reactions were carried out at room temperature except as noted.

Table I shows that, as might be anticipated from the results of Kharasch, Engelmann, and Mayo,[1] ferric chloride catalyzes the "normal" addition of hydrogen bromide to trichloroethylene. Yields of over 80 per cent. of the unsymmetrical tetrahalide (I) were obtained by use of a few thousandths of a mole of ferric chloride. The reaction requires several hours

at room temperature. The same result was obtained with aluminum chloride at 0°, but with yields of only 30–40 per cent. We attribute the poor yield not to inferiority of aluminum chloride as a catalyst, but rather to its slight solubility in the reaction mixture. At room temperature, in

TABLE II

ADDITION OF HYDROGEN BROMIDE TO TRICHLOROETHYLENE IN THE PRESENCE OF AIR[c] AND/OR PEROXIDES

MOLES[a] HBr	PEROXIDE	MOLES[a] PEROXIDE	ILLUMINATION	TOTAL REACTION TIME,[b] HOURS	% YIELD[a, d] ADDITION PRODUCT	REMARKS
1.50	None	—	None	60×24	0	
1.50	Bz_2O_2	.024	None	17	2	
1.74	Bz_2O_2	.099	None	120	5	Peroxide added at 4 daily intervals.
1.81	Bz_2O_2	.110	None	24	27	
2.63	Bz_2O_2	.207	None	48	1	
1.50	Bz_2O_2	.004	None	24	3	Peroxide added to HBr—C_2HCl_3 mixture just before sealing.
1.50	BzO_2	.004	None	24	1.2	Peroxide added to C_2HCl_3 just before adding HBr.
1.50	Bz_2O_2	.004	None	24	0.8	Solution of Bz_2O_2 in C_2HCl_3 allowed to stand 25 hours before adding HBr.
1.07	Bz_2O_2	.010	Sunlight, 3 hrs.	3	57	
1.10	Ascaridole	.025	Sunlight, 5 hrs.	5	1	Peroxide destroyed very rapidly.
1.50	None	—	Pyrex Hg arc, 3½ hrs.	3½	6	
1.50	Bz_2O_2	.004	Pyrex Hg arc, 3½ hrs.	3½	30	
1.50	None	—	Sunlight, 9 hrs.	27	91	
1.50	Bz_2O_2	.004	Sunlight, 9 hrs.	27	89	
1.50	Bz_2O_2	.004	Sunlight, 9 hrs.	27	90	Air excluded.

[a, b] Have same significance as in Table I.

[c] All runs in presence of air except for one experiment as indicated.

[d] Product exclusively 1,1,2-trichloro-2-bromoethane (II).

the presence of aluminum chloride, part of the excess hydrogen bromide reacts with the addition product to give hydrogen chloride and a complex mixture of boiling-range 90–200° at 20 mm. No definite fractions were isolable on the Podbielniak column.

To substantiate our belief that the compound formed in the presence of

aluminum or ferric chlorides was the unsymmetrical tetrahalide (I), addition of hydrogen chloride to trichloroethylene in the presence of ferric chloride was tried, since a "peroxide effect" has never been observed with this hydrogen halide. The addition proceeded slowly at room temperature to give unsymmetrical tetrachloroethane exclusively. Aluminum chloride at 0° gave the same product, corroborating Prins'[2] results at room temperature.

Table II records the results of experiments made in the presence of air or peroxides. Ascaridole was found to decompose rapidly in a reaction mixture, with the result that the mixture became opaque and only slight addition took place. Benzoyl peroxide was found to be soluble in the reaction mixtures and to cause development of little or no color on standing. The results show that in the presence of air and in darkness, no addition takes place unless a peroxide is added and that even then, the reaction is extremely slow. When the reaction is carried out in the light (sunlight or mercury arc), either air or added peroxide will accelerate the reaction. The product was always exclusively 1,1,2-trichloro-2-bromoethane.

Comparable experiments with mercury arc illumination indicate that the reaction is faster in the presence of both air and added peroxides than in the presence of air alone. Another experiment in sunlight shows that peroxides catalyze the addition in the absence of air. That air alone is as effective as peroxides alone in sunlight is readily explainable. Oxygen in the light can furnish small amounts of peroxides over a long period while benzoyl peroxide may be destroyed slowly under the conditions of the experiment.

The proof of structure of the two possible addition products, (I) and (II), is given in the experimental part.

EXPERIMENTAL

Trichloroethylene.—Trichloroethylene was obtained from the Eastman Kodak Company, and after suitable purification a constant-boiling fraction was collected and used. The trichloroethylene used in our work was stabilized with diphenylamine. Any desired quantity of the pure reagent was obtained by simple distillation from this stock.

Technique.—Experiments were made either in the presence or absence of air according to the procedures of Kharasch and Mayo.[9] After the bombs had stood for the desired length of time, they were cooled to −80° and opened. Excess hydrogen halide was removed by shaking and warming to room temperature. Since the progress of the addition could be estimated by noting the change in volume of the contents of the bomb, the procedure adopted when little or no change was observed was to transfer the residue in the bomb tube to a small distilling apparatus and to note the boiling range. Usually the temperature of the vapor did not rise above 90°,

[9] KHARASCH AND MAYO, *J. Am. Chem. Soc.*, **55**, 2468 (1933).

except when certain added materials were present. If the volume change during the course of the addition was significant, the bomb contents were distilled *in vacuo* (water pump) into a receiver cooled to −80°. The distillate was then fractionated on the Podbielniak[10] column at a pressure of 20–22 mm. A trap was used to recover any unchanged trichloroethylene. The fractions collected had a boiling range of 0.2° or less. After distillation, the index of refraction was determined.

Identification of addition products.—Table III summarizes the physical constants of the addition products obtained, and determinations of the molecular weights and halogen contents of the hydrogen bromide addition products. Halogen determinations were made according to the method of Vaughn and Nieuwland[11] and Fajans.

Proof of structure.—Compound I was treated with zinc in hot alcohol. The product was unsymmetrical dichloroethylene. This was confirmed by treatment

TABLE III

PHYSICAL CONSTANTS OF ADDITION COMPOUNDS OF TRICHLOROETHYLENE

PROPERTY	$Cl_2BrC-CH_2Cl$ (I)	$Cl_2CH-CHClBr$ (II)	$Cl_2BrC-CHClBr$	Cl_2C-CH_2Cl	$Cl_2CH-CHCl_2$
b.p./760 mm.	152°	171° (172°)[4]	204° (dec.)	129° (130°)[6]	144.5° (145.0°)[6]
b.p./50 mm.			116.5°		
b.p./20 mm.	54.0°	68.9°			
n_D^{20}	1.5217	1.5302	1.5710	1.4828 (1.4821)[7]	1.4947 (1.4951)[8]
$n_D^{14.5}$		1.5326 (1.5325)[4]			
Mol. wt. in benzene (cryoscopic)	206.2 (calc'd 212.3)	198.9, 201.9			
% Halogen calc'd as Cl^- for volumetric analysis	66.67 66.91 66.56 (calc'd 66.71)	66.62 66.59 66.62			

[6] *International Critical Tables*, McGraw-Hill Book Co., New York City, **1928**. Vol. III, p. 216.

[7] HENNE AND HUBBARD, *J. Am. Chem. Soc.*, **58**, 404–6 (1936).

[8] ECKART, *Chem. Abstr.*, **17**, 2356 (1923).

with chlorine and identification of the resulting unsymmetrical tetrachloroethane (yield from I, 52%) by boiling point and index of refraction.

Since 1,1,1-trichloro-2-bromoethane gives the same product with zinc in hot alcohol, hydrolysis of I with alcoholic sodium phenate was carried out. The product was trichloroethylene in 60% yield. This product was identified by boiling point and index of refraction, and also by addition of bromine. The identity of the bromine addition product was confirmed by boiling point. By similar treatment, II also gave trichloroethylene.

[10] PODBIELNIAK, *Ind. Eng. Chem., Anal. Ed.*, **5**, 119 (1933).

[11] VAUGHN AND NIEUWLAND, *Ind. Eng. Chem., Anal. Ed.*, **3**, 274 (1933).

Compound II was likewise treated with zinc in hot alcohol. The products were the *cis* and *trans* symmetrical dichloroethylenes. When these were treated with chlorine, symmetrical tetrachloroethane (yield, 69%) was obtained, identified by boiling point and index of refraction.

SUMMARY

1. In the presence of anhydrous ferric or aluminum chloride, hydrogen bromide adds to trichloroethylene to give 1,1,2-trichloro-1-bromoethane, which is not formed in the absence of such catalysts.

2. In the presence of air and benzoyl peroxide, hydrogen bromide adds very slowly to trichloroethylene to give 1,1,2-trichloro-2-bromoethane. The formation of this product is markedly accelerated by light in the presence of either air or added peroxides.

3. Physical constants and proof of structure for the above compounds are given. Boiling points and indices of refraction are also given for both tetrachloroethanes and for 1,1,2-trichloro-1,2-dibromoethane.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

PREPARATION AND REACTIONS OF 9-ANTHRYLMAGNESIUM BROMIDE

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Investigations in the field of carcinogenic compounds have stimulated renewed interest in meso-substituted anthracene derivatives and methods for their synthesis. The development of 9-anthrylmagnesium bromide as a synthetic reagent is therefore of considerable import, particularly in view of the wide applicability of the Grignard reaction and the ready availability of 9-bromoanthracene from the bromination of anthracene.[1] Miller and G. B. Bachman[2] have reported that 9-bromoanthracene does not react appreciably with magnesium and ether even in a sealed tube at 200°. Dufraisse, Velluz, and Velluz[3] however obtained a Grignard reagent from 9-phenyl-10-bromoanthracene by reaction with a large quantity of ethyl bromide and excess magnesium in anhydrous ether. We have now prepared 9-anthrylmagnesium bromide in several different solvents and have investigated its reactions with a number of reagents.

When 9-bromoanthracene was heated in a benzene-butyl ether mixture with a slight excess of pure, pulverized magnesium, and iodine was employed to activate the magnesium, a 73 per cent. yield of the Grignard reagent was obtained in twelve hours. Further heating did not materially increase the yield. When ethyl bromide was used to activate the magnesium a clear, red-brown solution of the Grignard reagent was obtained; when iodine was employed the solutions were always dark brown and the reaction products were more difficult to isolate. Ordinary magnesium turnings reacted to the extent of only 55 per cent. in twenty-four hours, and solutions prepared from impure magnesium were found to contain a large quantity of dark by-products. When 9-bromoanthracene was allowed to react with magnesium in boiling *n*-butyl ether the production of the Grignard reagent was found to be 71 per cent., complete in thirty minutes, but the resulting solutions were again very dark. The by-products in this reaction were dark tars, for the most part, although one crystalline product was obtained whose nature was not determined.

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[1] BARNETT AND COOK, *J. Chem. Soc.*, **125**, 1086 (1924).

[2] MILLER AND G. B. BACHMAN, *J. Am. Chem. Soc.*, **57**, 767 (1935).

[3] DUFRAISSE, VELLUZ, AND VELLUZ, *Bull. soc. chim.*, [5], **4**, 1260 (1937).

9-Anthrylmagnesium bromide was also prepared in anhydrous ethyl ether, the magnesium being activated with ethyl bromide. Under these conditions the mixture must be shaken frequently during the first few hours of reaction in order to prevent coating of the magnesium, and the reagent is obtained as a dense, cream-colored precipitate. This method of preparation produces the reagent in purest condition and in superior yields (86–87 per cent.). For some reactions however it is advisable to dissolve the solid Grignard reagent in benzene.

The Grignard reaction offers a convenient method for preparing 9-anthroic acid. This acid has been previously prepared by the action of aluminum chloride on a mixture of anthracene and oxalyl chloride,[4] by the hydrolysis of 9-cyanoanthracene,[5] and by the action of phosgene on anthracene at 200° in a sealed tube.[6] We have now prepared the acid in 72 per cent. yield by passing carbon dioxide into a hot suspension of 9-anthrylmagnesium bromide in ether-benzene.

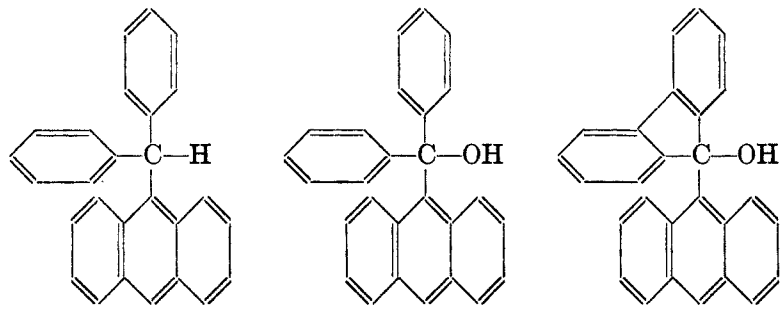
9-Benzoylanthracene can also be prepared in good yields by interaction of 9-anthrylmagnesium bromide and benzonitrile or from 9-cyanoanthracene and phenylmagnesium bromide, followed by hydrolysis of the ketimine obtained. It was found that 9-cyanoanthracene was readily produced when 9-bromoanthracene and cuprous cyanide were heated together in a small volume of dry pyridine at 220°. This method offers another convenient route to 9-anthroic acid.[5] As in the case of the β-methylnaphthylphenanthrylketimines,[7] diortho-substitution in the ring attached to the ketimino group appears to introduce considerable steric hindrance, for 9-anthrylphenylketimine hydrochloride must be heated to 145° for several days in a sealed tube with dilute hydrochloric acid in order to effect complete hydrolysis to the ketone.

The Grignard reagent reacts with alkyl halides to give 9-alkylanthracenes. Methyl iodide and diphenylbromomethane give 9-methylanthracene and 9-anthryldiphenylmethane (I) respectively. The yields of the products actually isolated in pure condition were, however, low due to the fact that the products had to be separated mechanically from accompanying anthracene.

Reaction of 9-anthrylmagnesium bromide with ketones gives the expected tertiary carbinols. Thus, 9-anthryldiphenylcarbinol (II) is obtained from reaction with benzophenone, and 9-anthrylbiphenylenecarbinol (III) from fluorenone. The ketones were always allowed to react

[4] LIEBERMANN AND ZSUFFA, *Ber.*, **44**, 208 (1911).
[5] KARRER AND ZELLER, *Helv. Chim. Acta*, **2**, 486 (1919).
[6] GRAEBE AND LIEBERMANN, *Ber.* **2**, 678 (1869).
[7] BACHMANN AND PENCE, *J. Am. Chem. Soc.*, **57**, 1131 (1935).

with the Grignard reagent in the cold, for when the mixture was refluxed after addition of benzophenone the yield of carbinol was considerably reduced, and no 9-anthrylbiphenylenecarbinol was ever isolated when the reaction mixture of 9-anthrylmagnesium bromide and fluorenone was refluxed. In these instances also, the reduced yields of pure product were caused by the necessary mechanical separation from accompanying anthracene in the hydrolysis mixture.

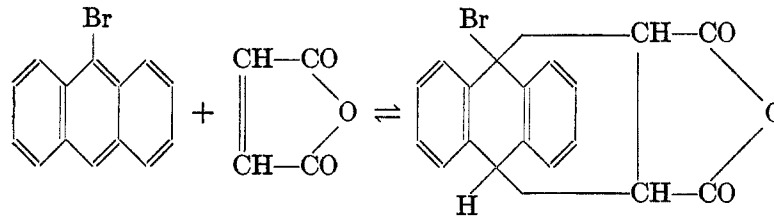


I II III

Finally, the reaction of 9-anthrylmagnesium bromide with iodine offers a convenient method for the preparation of 9-iodoanthracene. This new halide was obtained in 53 per cent. yield when an ethereal solution of excess iodine was added to the cold, solid Grignard reagent.

9-Bromoanthracene was found to react readily with maleic anhydride in boiling xylene solution to give 9-bromoanthracene-9,10-*endo*-α,β-succinic anhydride (IV). The addition reaction of anthracene derivatives with maleic anhydride has been found to be reversible, and both the rate and the extent of reaction are influenced by meso-substitution.[8] Thus, 9-methylanthracene reacts with maleic anhydride more rapidly than does anthracene, while 9-phenylanthracene reacts much slower than anthracene. In the case of both anthracene and 9-methylanthracene, however, the equilibrium in boiling xylene is 99 per cent. toward adduct formation, while with 9-phenylanthracene reaction proceeds only 75 per cent. to completion. We have now found that the addition of 9-bromoanthracene to maleic anhydride is somewhat slower than the addition of anthracene itself, but the equilibrium in boiling xylene is very favorable to adduct formation (at least 94 per cent.). Barnett[9] has recently observed the reaction of 9-bromoanthracene with maleic anhydride in *o*-dichlorobenzene but the yield of adduct was not reported.

[8] BACHMANN AND KLOETZEL, *ibid.*, **60**, 481 (1938).
[9] BARNETT, *J. Chem. Soc.*, 1225 (1934).



IV

We have found that 9-bromoanthracene also reacts readily with lithium in anhydrous ether, and this preliminary survey is being extended to include reactions of 9-anthryllithium as well as an investigation of the Grignard reaction involving meso-halides of polycyclic anthracene derivatives.

EXPERIMENTAL

9-Bromoanthracene.—Technical (80–85%) anthracene was crystallized twice from toluene and then brominated according to the method of Barnett and Cook.[1] The crude product was distilled *in vacuo*, fractionally crystallized from petroleum ether (90–100°) five times to remove anthracene and finally fractionally crystallized from a large volume of ethanol to remove dibromoanthracene. The product melted at 100–101°; yield, 55%.

9-Bromoanthracene-9-10-endo-*α,β-succinic anhydride* (IV).—When a solution of 1.0 g. of 9-bromoanthracene and 0.40 g. of sublimed maleic anhydride in 5 cc. of dry xylene was heated, a deep-yellow color was produced which gradually faded on further heating. The solution was refluxed for two hours and cooled, whereupon 1.30 g. (94% yield) of colorless crystals separated. The adduct crystallizes from acetic anhydride in nacreous plates, m.p. 253–254° (dec.), which sublime unchanged *in vacuo* (225°/0.5 mm.).

In another experiment a mixture of 100 mg. of 9-bromoanthracene, 39 mg. of maleic anhydride and 2 cc. of xylene was refluxed for thirty minutes. After evaporation of the xylene by a current of air the residue was heated for a few minutes on the steam bath with 5 cc. of 40% potassium hydroxide solution to hydrolyze the adduct to the dicarboxylic acid. The potassium salt of the acid was then dissolved in hot water, and benzene was added. The layers were separated, and evaporation of the benzene yielded 29 mg. of unreacted 9-bromoanthracene, indicating 71% reaction.

9-Cyanoanthracene.—To 2.0 cc. of dry pyridine was added 1.0 g. of dry cuprous cyanide, and after the vigorous reaction had subsided 2.57 g. of 9-bromoanthracene was added. The mixture, protected from moisture by a mercury trap, was heated in a metal bath at 220° for nine hours, cooled, and then shaken with dilute ammonium hydroxide and ether. The ethereal layer was washed with water, dilute hydrochloric acid, again with water, and dried. The residue, after evaporation of the ether, crystallized from ethanol in yellow needles; yield, 1.76 g. (87%); m.p. 174–175°. The nitrile prepared by Karrer and Zeller[5] melted at 170–172°.

9-Anthrylmagnesium bromide.—For use in the preparation of the Grignard reagents, pure (99.7%; from the Aluminum Company of America), cleaned magnesium ribbon was pulverized in a Wiley mill, washed twice with acetone and dried. The

n-butyl ether was distilled (139.5–140.5°/745 mm.) and stored over lithium wire; anhydrous ethyl ether and thiophene-free benzene were stored over sodium wire.

Method A.—9-Bromoanthracene melting below 100° is not satisfactory for the preparation of the Grignard reagent by this method. For each experiment a mixture of 2.57 g. (0.01 mole) of 9-bromoanthracene, 0.26 g. of pulverized magnesium, 5 cc. of butyl ether, 15 cc. of benzene and 0.10 g. of iodine was refluxed on the steam bath for twelve hours, and was constantly protected from air and moisture by a mercury trap. A vigorous reaction began in less than one-half hour and a deep-brown solution of the Grignard reagent was finally obtained. The reagent crystallizes readily from the butyl ether-benzene mixture in colorless needles when the solution is cooled.

To determine the extent of the reaction, the hot solution of Grignard reagent was filtered through cotton into standard normal hydrochloric acid and after complete reaction the excess acid was titrated with standard alkali. The anthracene obtained from hydrolysis checked the titration within 2%. In a number of experiments where heating was continued for varying periods of time the yields were as follows: six hours, 67%; twelve hours, 73%; twenty-four hours, 73%; forty-eight hours, 74%. The by-products in this reaction were mostly dark tars, although one product sublimed *in vacuo* (250°/0.5 mm.) and crystallized from toluene in long, yellow needles; m.p. 313–315°.

Method B.—A mixture of 2.57 g. of 9-bromoanthracene, 0.26 g. of pulverized magnesium, 5 cc. of butyl ether, 15 cc. of benzene and five drops (approximately 80 mg.) of ethyl bromide was refluxed on the steam bath for twelve hours. Reaction began immediately, and a clear, red-brown solution of the Grignard reagent was obtained.

Method C.—A mixture of 2.57 g. of 9-bromoanthracene, 0.26 g. of pulverized magnesium and 20 cc. of butyl ether was refluxed on the sand bath. After one hour reaction was found by titration to have gone 69% toward completion; after one and one-quarter hours, 70%. When 0.05 g. of iodine was used to activate the magnesium, 66% reaction took place within fifteen minutes and 71% in thirty minutes. The solution obtained was dark-brown.

Method D.—A mixture of 2.57 g. of 9-bromoanthracene, 0.50 g. of pulverized magnesium, 20 cc. of ethyl ether and five drops of ethyl bromide was refluxed on the steam bath for twenty-four hours. The solution, which becomes cloudy within fifteen minutes, must be shaken frequently during the first few hours to prevent coating of the magnesium. The Grignard reagent is finally obtained as a dense, cream-colored precipitate and may be used as such, or the ether may be boiled off and the solid dissolved in 60 cc. of anhydrous benzene by boiling for approximately ten hours. Hydrolysis of a sample of Grignard reagent prepared in this way yielded 1.53 g. (86%) of pure anthracene; m.p. 212–213°.

9-Iodoanthracene.—To the cold suspension of solid Grignard reagent prepared by method D was added a solution of 3.0 g. of iodine in 50 cc. of anhydrous ether. The iodine color quickly disappeared and a clear yellow solution was formed. This was washed with water and with aqueous sodium bisulfite, dried and evaporated. The residue crystallized from ethanol in broad, yellow needles; m.p. 82–83°; yield, 1.61 g. (53%).

Anal. Calc'd for $C_{14}H_9I$: I, 41.8. Found: I, 42.4.

9-Methylanthracene.—To a cold suspension of solid Grignard reagent in ether prepared by method D was added 7.5 g. of methyl iodide and 25 cc. of anhydrous benzene. The excess magnesium quickly disappeared and after refluxing for forty-eight hours the solution became clear yellow. The product was hydrolyzed with

dilute acetic acid, and the organic layer was washed, dried, and evaporated. When the residue was crystallized slowly from ethanol, large yellow tablets of 9-methylanthracene were obtained which could be separated mechanically from accompanying anthracene; yield, 0.80 g. (41%). The hydrocarbon crystallized from ethanol in long, yellow blades; m.p. 78–79°.

9-Anthroic Acid.—To a suspension of 9-anthrylmagnesium bromide prepared by method D was added 25 cc. of anhydrous benzene, and dry carbon dioxide was passed into the boiling mixture for one and one-half hours. The solution became clear yellow while a gummy deposit formed on the surface. After adding water the mixture was heated, the layers were separated and the organic layer was extracted with dilute ammonium hydroxide. Acidification of the combined aqueous extracts with dilute hydrochloric acid precipitated 1.6 g. (72%) of 9-anthroic acid which crystallized from dilute ethanol in yellow needles; m.p. 215–216° dec.

9-Anthrylphenylketimine.—(*a*) *From 9-anthrylmagnesium bromide and benzonitrile.*—A solution of 1.25 g. of benzonitrile in 20 cc. of anhydrous benzene was added to a suspension of solid 9-anthrylmagnesium bromide in ether prepared according to method D. The mixture was refluxed for six hours, hydrolyzed with dilute acetic acid, and the organic layer was shaken for five minutes with 10 cc. of 36% hydrochloric acid, whereupon the ketimine hydrochloride separated in crystalline form. The salt crystallizes from ethanol-ethyl acetate in orange leaflets; m.p. 272–274°.

Anal. Calc'd for $C_{21}H_{15}N \cdot HCl$: Cl, 11.2. Found: Cl, 11.2.

The ketimine hydrochloride is very soluble in hot ethanol, slightly soluble in chloroform or acetone and nearly insoluble in hot ethyl acetate or hot carbon tetrachloride.

Warming for a few minutes on the steam bath with benzene and dilute ammonium hydroxide converted the hydrochloride to 9-anthrylphenylketimine. The product obtained by evaporation of the benzene crystallized from ethanol or acetone in pale yellow, diamond-shaped plates m.p. 152–153°; yield, 2.45 g. (87%). The ketimine sublimes *in vacuo* (195°/0.5 mm.) in tablets. It gives a red-orange color with concentrated sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}N$: C, 89.6; H, 5.4. Found: C, 89.0; H, 5.3.

(*b*) *From 9-cyanoanthracene and phenylmagnesium bromide.*—To the Grignard reagent prepared from 1.5 g. of bromobenzene in 5 cc. of anhydrous ether was added 1.0 g. of 9-cyanoanthracene and 15 cc. of anhydrous benzene, and the mixture was refluxed for six hours. The ketimine was isolated as previously described; yield, 1.26 g. (92%); m.p. 152–153°. No depression of the melting point was produced when a sample was mixed with ketimine prepared from 9-anthrylmagnesium bromide and benzonitrile.

9-Benzoylanthracene.—9-Anthrylphenylketimine hydrochloride is not readily hydrolyzed to the ketone. A sample heated with dilute hydrochloric acid in a sealed tube for six hours at 180° was hydrolyzed only to the extent of 20%, and considerable decomposition appeared to have taken place. The hydrolysis was finally effected in 93% yield by heating 0.8 g. of the hydrochloride, 50 cc. of water and 1 cc. of 36% hydrochloric acid for eighty hours at 145° in a sealed tube. The ketone crystallized from ethanol in broad, yellow needles; m.p. 145–146°.

9-Anthryldiphenylmethane (*I*).—To the slightly cooled solution of the Grignard reagent prepared by method B was added 2.6 g. of diphenylbromomethane in 20 cc. of anhydrous benzene. The solution became much lighter in color and solidified. The mixture was refluxed for ten hours, hydrolyzed with dilute acetic acid, and the

organic layer was evaporated. The residue crystallized from benzene in nodules; yield, 0.34 g. (10%). 9-Anthryldiphenylmethane crystallizes from benzene in practically colorless prisms; m.p. 204–205°.

Anal. Calc'd for $C_{27}H_{20}$: C, 94.1; H, 5.9. Found: C, 93.7; H, 5.8.

9-Anthryldiphenylcarbinol (II).—To the slightly cooled solution of 9-anthrylmagnesium bromide prepared according to method A was added 1.82 g. of benzophenone. The mixture was shaken and allowed to stand at 25° for twenty hours, and then at 0° for forty-eight hours. The yellow addition product was filtered and hydrolyzed with cold aqueous ammonium chloride. By allowing an ethereal solution of the product to evaporate slowly, large transparent tablets of the carbinol were obtained which could easily be separated mechanically from anthracene; yield, 1.20 g. An additional 0.14 g. of carbinol was obtained when the filtrate from the addition compound was hydrolyzed; total yield, 37%.

A 36% yield of the same carbinol was obtained when 2.0 g. of benzophenone was added to a benzene solution of 9-anthrylmagnesium bromide prepared according to method D, and the solution was refluxed for five hours.

9-Anthryldiphenylcarbinol crystallizes from ether or benzene-petroleum ether in colorless, hexagonal prisms; m.p. 191–192°. With concentrated sulfuric acid the carbinol gives an intense yellow color.

Anal. Calc'd for $C_{27}H_{20}O$: C, 90.0; H, 5.6. Found: C, 89.7; H, 5.4.

9-Anthrylbiphenylenecarbinol (III).—To a slightly cooled solution of the Grignard reagent prepared by method A was added 1.35 g. (75% theoretical) of fluorenone. The mixture was shaken and allowed to stand at 25° for sixteen hours and at 0° for five hours. The brown-yellow addition compound was filtered and hydrolyzed with cold, aqueous ammonium chloride. When an ethereal solution of the product was allowed to evaporate slowly, the carbinol was obtained in long prisms which could be conveniently separated mechanically from anthracene; yield, 0.90 g. An additional 0.19 g. of carbinol was obtained when the filtrate from the addition compound was hydrolyzed; total yield, 1.09 g. (30%). 9-Anthrylbiphenylenecarbinol crystallizes from benzene-petroleum ether in long, colorless needles; m.p. 205–206°. It gives an intense brown-red color with concentrated sulfuric acid.

Anal. Calc'd for $C_{27}H_{18}O$: C, 90.5; H, 5.1. Found: C, 90.3; H, 5.0.

9-Anthryllithium.—A mixture of 2.57 g. of 9-bromoanthracene, 20 cc. of anhydrous ether and 0.20 g. of lithium wire was refluxed for twenty-four hours. Reaction began immediately, the lithium became coated with a yellow precipitate and a yellow-brown solution was obtained. Excess lithium was decomposed with methanol, the ether was boiled off and a large volume of water containing a little hydrochloric acid was added. The precipitated anthracene was filtered and recrystallized from benzene; yield, 0.85 g. (48%); m.p. 211–213°.

SUMMARY

9-Anthrylmagnesium bromide has been prepared and a study has been made of its reaction with a number of reagents.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

THE RAMAN SPECTRA OF SOME HYDROCARBONS CONTAINING TERTIARY C—D LINKAGES

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In the Raman spectra of compounds of the type R_3CH[1] there appears in each case one line which is to be associated with a vibration of the hydrogen atom along the line of the C—H bond at a frequency which is theoretically nearly, but not entirely, independent of the masses of the substituent groups R. Nevertheless, it is evident from an inspection of the limited available data relating to this point that the magnitude of this C—H frequency is by no means constant, that, in fact, it varies over a considerable range according to the nature of the substituent groups. It occurs in the spectrum of chloroform[2] at 3018 cm^{-1}, and in the spectrum of isobutane[3] (R = CH_3) at 2868 cm^{-1}. Tetrachloroethane[4] and pentachloroethane[4] each give rise to a Raman line at 2985 cm^{-1}. That the effect is not primarily a mass effect is clear, not only from the above data, but also from the fact the frequencies for chloroform and for bromoform[5] are identical within the limits of experimental errors. In view of the relatively simple nature of this vibration, the obvious conclusion is that these differences in frequency of vibration arise through variations in the binding force brought about by changing the character of the substituent groups. In this event the phenomenon becomes of interest in relation to the effect of substitution on the chemical reactivity of carbon-to-hydrogen linkages, an effect which, with properly chosen substituent groups, may be very striking indeed. In particular, it would be of interest to determine whether the effects of various organic groups on the binding force of tertiary hydrogen atoms can be differentiated in this way, and, if so, whether the variations thus produced are at all related to the chemical properties of the substances.

[1] For a theoretical discussion, and pictorial representations, of the modes of vibration of molecules of this type, see KOHLRAUSCH, *Z. physik. Chem.*, **B28**, 340 (1935).

[2] KOHLRAUSCH, "Der Smekal-Raman-Effekt," Julius Springer, Berlin, **1931**, p. 304.

[3] REITZ AND SABATHY, *Monatsh.*, **71**, 103 (1937).

[4] KOHLRAUSCH, "Der Smekal-Raman-Effekt," p. 306.

[5] KOHLRAUSCH, *ibid.*, p. 308.

One can readily envisage a number of different mechanisms whereby the binding force in a compound of the type under consideration might be subject to variation according to the nature of the substituent groups. The first would be a direct electrostatic effect producing a resultant force of attraction, or repulsion, which would be superimposed on the normal covalent binding force. In all probability this effect is largely responsible for the higher C—H binding force in chloroform, as compared with isobutane, which is revealed by the difference in Raman frequencies. A second mechanism, which might be operative even in the absence of any appreciable direct electrostatic interaction, involves an indirect or inductive effect operating through the bonds by which the substituent groups are attached. The magnitude of this effect would depend upon the electron affinity of the groups, and the resultant contribution to the C—H binding force would be in most cases, but not always, opposite in sign to that produced by direct interaction. Finally, it is conceivable that the shape of the potential energy surface for the normal state of the molecule, and hence the binding force, may be altered by an interaction of typically quantum-mechanical character between the normal electronic state and low-lying excited electronic states, the position of which, and hence the extent of interaction, would be greatly influenced by the substituent groups. This circumstance is probably common enough, and the phenomenon is of fundamental importance to chemistry, but, except in extreme cases, the effect on the binding force would be quite small. The chief result of such an effect would be a displacement of the potential energy surface in the neighborhood of the minimum without very much distortion in this region. Insofar as carbon-to-hydrogen bonds are concerned, the phenomenon will undoubtedly be of greater significance in molecules which are more definitely acidic than those dealt with at this time.

The whole question of the relationship between chemical reactivity, or what is loosely termed chemical bond strength, and physical bond strength rests in a highly unsettled state. This is largely because the magnitude of the latter, which refers to the energy required to dissociate the molecule at this bond into neutral unexcited components, is experimentally inaccessible in all but the simplest of cases. The most pessimistic view would be that even if such data were available their utility in the solution of chemical problems would be limited to the relatively few reactions in which the simple process of dissociation actually occurs. In the more general case it appears that the energy of formation of new bonds becomes available, in part at least, during the process of dissolution of the old bonds rather than after it so that the critical energy of activation is less than the bond energy and is not related to it in any simple

way. The mechanism of such processes has been greatly clarified by Eyring,[6] who has given the name "activated complex" to the transition state, and it is the great virtue of the activated complex theory that it enables us for the first time to see precisely how the various physical characteristics of molecules enter into the determination of the activation energy and of the rate at which the barrier may be traversed. In this theory the bond energies appear as an important set of parameters, so also, implicitly, do the binding forces, but these alone are insufficient to determine the chemical behavior of the system.

But although a knowledge of the bond energies, or of the binding forces, must leave something to be desired in this respect, there would still seem to be a reasonable expectation of finding in the values of these constants some manifestation of the various electrical influences which organic chemists have come to speak of as decisive factors in chemical reactivity. There is, perhaps, less reason to expect significant variations to occur in the binding force for bonds of a given type than in the energy of dissociation. The former refers to the force of binding at the equilibrium positions of the atomic nuclei whereas certain factors which may affect the energy of dissociation, such as interactions with higher electronic states and also structural resonance in the products of dissociation may make their appearance only at greater distances of separation. Presumably just such a situation arises in the hexaarylethanes where, according to Pauling and Wheland,[7] the C—C bond in the unexcited molecule is a normal one and its instability arises as a consequence of resonance phenomena appearing at large distances of separation. However, such a bond could only be described as normal on the basis of binding force if the underlying assumptions are correct, or with reference to a hypothetical electronic state of the dissocation products, as the term bond strength is generally used, and as we have defined it above, the C—C bond in a compound of this type is without question a weak one. The concept of binding force may then prove useful in either event, and it has the distinct advantage of relating to a quantity which is experimentally more readily ascertainable.

In the determination of C—H binding force by the method of Raman spectra, we may anticipate the experimental difficulty of recording and identifying the particular C—H line, in which we are interested, in the spectrum of a compound which may contain several C—H bonds and which may give rise to a number of C—H lines in the same spectral region. Without some means of uniquely identifying this line we should be confined at the outset to the study of very simple molecules. The

[6] EYRING, *J. Chem. Phys.*, **3**, 107 (1935).

[7] PAULING AND WHELAND, *ibid.*, **1**, 362 (1933).

Raman spectrum of isobutane, for example, contains six lines in the region from 2718 cm^{-1} to 2959 cm^{-1}, the identification of which in the absence of any other data presents a very difficult problem. With the aid of the hydrogen isotope, however, this difficulty can be easily overcome. Substitution of deuterium for hydrogen in a tertiary position shifts the corresponding Raman line to a much lower frequency without influencing appreciably the positions of other C—H lines which may be present. A particular C—H line may therefore be identified by its disappearance on making this substitution, or, if it happens to be obscured by adjacent or coincident lines, its position may be determined approximately, at least, with reference to the new C—D line.

Making use of this device, we have examined the Raman spectra of a number of hydrocarbons containing tertiary C—H bonds and the corresponding deutero compounds in which only the tertiary hydrogen is replaced by deuterium. Fortunately the C—D lines occur in a region which is quite free of other lines, and were observed in each case with no other difficulty than that of producing Raman spectra in small samples of material. We were not able in any instance to observe the disappearance of a C—H line on substituting deuterium due to the obscuring influence of very much more intense C—H lines of different origin, and our conclusions, therefore, are based on the variations in position of the C—D lines. For the purpose at hand, this makes little or no difference as the force constants for isotopic molecules are negligibly different.

The series of hydrocarbons selected provides a considerable range in the chemical behavior of the tertiary C—H linkages, and extends from triphenylmethane by successive substitution of methyl groups for phenyl groups to isopropylbenzene and finally, as a compound comparable in this respect with isobutane, which we could not handle in the apparatus at hand, isobutylbenzene. This series does not represent by any means the maximum possible range in behavior, as the choice was governed by the desirability of working with substances of low melting point which could be obtained in a high state of purity without undue difficulty, and also we wished to reserve for later investigations some of those cases where the enhanced reactivity of hydrogen is connected with the possibility of tautomerism. There is to be observed in the series we have selected a transition from the weakly acidic properties of the aliphatic C—H group in triphenylmethane, and the high susceptibility of the molecule to attack at this point by oxidizing agents, to the complete absence of acidic properties in isobutylbenzene and its lesser sensitivity toward oxidizing agents.

The observed C—D Raman lines (*cf.* Fig. 1) were as follows: triphenylmethane 2132 cm^{-1}, 1,1-diphenylethane 2122 cm^{-1}, isopropylbenzene 2152 cm^{-1}, and isobutylbenzene 2147 cm^{-1}, the experimental error being ± 5

cm^{-1} in each instance. Thus there are small variations which are definitely beyond the limits of experimental error, and there is also perhaps a slight trend in the direction to be expected but it is by no means as clear-cut as might be desired, and the overall difference is not more than one per cent. The conclusions to be drawn are that the C—H binding force remains essentially constant within this group of compounds, that in this respect the bonds are in each case of normal strength and comparable with the corresponding bond in isobutane, and that the factors which give rise to their differences in chemical behavior exert a scarcely appreciable influence on the normal state of the molecules.

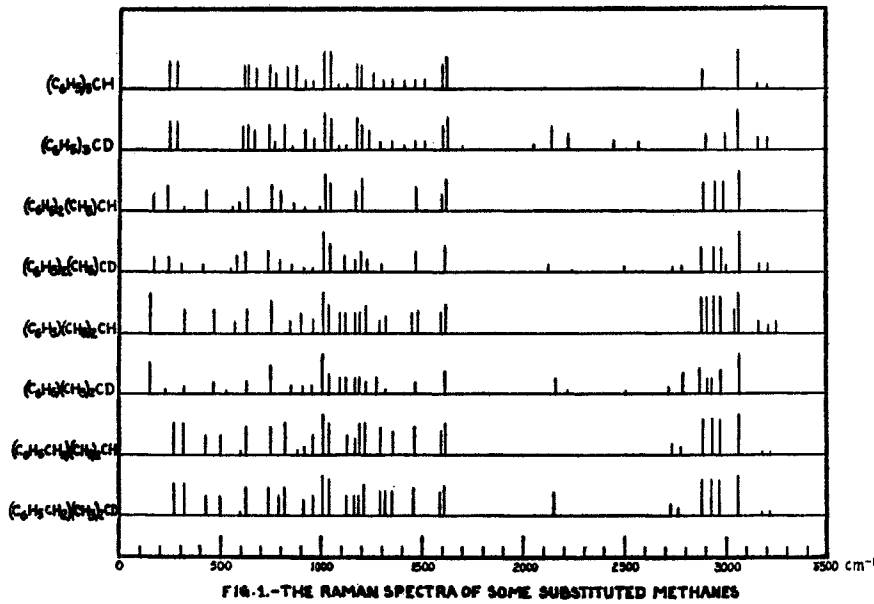

FIG. 1.—THE RAMAN SPECTRA OF SOME SUBSTITUTED METHANES

FIG. 1

This result seems especially significant in the case of triphenylmethane as we could have predicted that the aliphatic carbon to hydrogen bond in this molecule is a relatively weak bond, from the standpoint of dissociation energy, for the same reason that the carbon-to-carbon bond in hexaphenylethane is weak, that is, the occurrence of resonance in the triphenylmethyl radical, although in the case of triphenylmethane the effect could only be half as large. However, it may be noted in this connection that there is no chemical evidence, of which we are aware, of any striking differences in the thermal stability of tertiary C—H groups, and that this is not necessarily in contradiction of the supposition that this bond in

triphenylmethane is abnormally low in dissociation energy. A reduction in the bond energy of as much as 25 kcal. would still, in all probability, not enable the simple dissociation process to compete with the more complicated type of reaction mechanism pictured by the activated complex theory. The precise mode of thermal decomposition is not known. Jaeger[8] reports simply that it begins to decompose, with the appearance of a brown coloration, at 165°. The decomposition is evidently rather slow, even at the boiling point, 359°.

For the purposes of comparison, the frequencies of the C—D lines in some other types of compounds may be given. These lines occur in the spectra of deuterochloroform[9] and of deuterotetrachlorethane[10] at 2256 cm^{-1} and 2240 cm^{-1}, respectively. The increase in these frequencies over those from the hydrocarbons mentioned above, is to be attributed, in our opinion, largely to electrostatic effects. The C—D line in the spectrum of deuterodichlorethylene[10] occurs at 2325 cm^{-1}, and there is thus present in this molecule a still greater enhancement of the binding force which is to be associated with the presence of unsaturation. This effect is well known and appears not only in ethylenic compounds but also in the acetylenes and aromatic compounds.

EXPERIMENTAL

The experimental arrangement for the excitation of Raman spectra was essentially that described by Wood,[11] and by Wood and Rank.[9] Light from a mercury arc is focused on the tube containing the material to be examined by means of a cylindrical glass container filled with 33% sodium nitrite solution. This solution is effective in removing the Hg λ 4047 lines while allowing the Hg λ 4358 group to be transmitted.[12] In order to remove the Hg λ 4916 line and other lines in this region emitted by the source, a Wratten 34 filter was placed between the condensing lens and the Raman tube. This Wratten filter reduces the intensity of the Hg λ 4358 line appreciably, but without it the region in which the C—H Raman lines occur is badly obscured. The Raman tubes were of the conventional shape, that is, with one end horn-shaped, and blackened on the outside, the other end being closed by a plane window which was fused in. The straight part of the tube was silvered on the outside except for a broad slit through which the exciting radiation entered. For the work with triphenylmethane a jacketed tube was used, the material being maintained in a molten state by passing steam through the jacket. The Raman spectra were recorded on Eastman Type IJ plates, with iron arc spectra for comparison, using a Steinheil spectrograph in the three prism, short arm, arrangement.

We experimented briefly and unsuccessfully with the high-voltage spiral discharge

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[8] JAEGER, *Z. anorg. Chem.*, **101**, 111 (1917).
[9] WOOD AND RANK, *Phys. Rev.*, **48**, 63 (1935).
[10] TRUMPY, *Z. Physik*, **98**, 672 (1936).
[11] WOOD, *Phys. Rev.*, **45**, 392 (1934).
[12] PFUND, *ibid.*, **42**, 581 (1932).

tube recommended by Glockler and Davis[13] for the excitation of Raman spectra, the chief difficulty being the removal of traces of nitrogen, and finally adopted a simple form of low-voltage mercury arc which was very kindly suggested to us by Dr. Ralph Munch. This is a vertical arc of Pyrex glass, the cathode being a pool of mercury in the lower end, and the anode is a tungsten spiral sealed in the upper end. These arcs were found to be simple and inexpensive to construct and completely satisfactory in operation.

Of the four hydrocarbons included in this study, two have been previously investigated. The Raman spectrum of isopropylbenzene is described by Kahovec and Reitz,[14] and an attempt to obtain the Raman spectrum of triphenylmethane was made by Petrikaln and Hochberg.[15] The latter authors, using an ether solution of triphenylmethane, observed an intense continuous emission spectrum, *i.e.* a fluorescence spectrum, and were not able to record the Raman scattering. In our first attempts, using molten triphenylmethane, we also observed this intense fluorescence, but it was discovered that the impurities responsible for the fluorescence could be removed by distillations in very high vacua. Baker,[16] and also Orndorff and coworkers,[17] observed the presence of spurious bands in the ultraviolet absorption spectra of both diphenylmethane and triphenylmethane which they attributed to anthracene. However, Capper and Marsh[18] concluded that the fluorescent emission in the visible region up to λ 4750, which they observed in anthracene, was not due to anthracene but to traces of the compound chrysogen. Our experience with triphenylmethane would indicate that the fluorescent impurity is not anthracene, but a substance considerably less volatile. To guard against further difficulties of this kind, and also to preclude the possibility of photochemical oxidation, the final purification in all cases was effected by a series of high-vacuum distillations, the Raman tube being the receiver in the final distillation so that it could be filled and sealed without exposure of the material to air.

The preparation of the desired isotopic hydrocarbons presented, as might be expected, a problem in itself. A useful survey of previous work in this field has been published recently by Erlenmeyer.[19] In our work two factors were of paramount importance in the selection of methods, namely, the necessity of minimizing the consumption of heavy water, and the necessity of avoiding the introduction of deuterium in any position other than that desired. The first requirement weighed heavily because of the relatively large amounts of material needed, and the fact that the deuterium, once used, was for all practical purposes unrecoverable. The second requirement imposed certain limitations as to reagents and experimental conditions if exchange reactions, and consequently undesirable substitution of deuterium, were to be avoided. In fulfilling both of these specifications, methods involving the use of metalloörganic compounds as intermediates seemed to offer the greatest promise.

Normally, the preparation of a monodeutero hydrocarbon could be carried out by forming the Grignard reagent from the corresponding halide and treating the Grignard reagent with heavy water or with a deutero acid. This method was used for

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[13] GLOCKLER AND DAVIS, *J. Chem. Phys.*, **2**, 881 (1934).

[14] KAHOVEC AND REITZ, *Monatsh.*, **69**, 363 (1936).

[15] PETRIKALN AND HOCHBERG, *Z. physik. Chem.*, **B3**, 217 (1929).

[16] BAKER, *J. Chem. Soc.*, **91**, 1490 (1907).

[17] ORNDORFF, GIBBS, MCNULTY, AND SHAPIRO, *J. Am. Chem. Soc.*, **49**,

[18] CAPPER AND MARSH, *J. Chem. Soc.*, **129**, 724 (1926); *J. Am. Chem. Soc.*, **47**, 2847 (1925).

[19] ERLENMEYER, *Z. Elektrochem.*, **44**, 8 (1938).

the preparation of benzyldimethylmethane-*d*; the Grignard reagent was formed from benzyldimethylchloromethane and treated with deuteroacetic acid. However, the preparation of Grignard reagents from tertiary chlorides which are structurally able to form olefines by the loss of HCl, and which do so readily, is generally an unsatisfactory process, and we were unable to prepare isopropylbenzene and 1,1-diphenylethane by the Grignard method. The Raman spectrum of our sample of benzyldimethylmethane-*d* shows unmistakably the presence of a small amount of olefine, notwithstanding the fact that it had been carefully fractionated.

It is, however, in precisely such cases that Ziegler's ether cleavage method[20] for the preparation of alkali metal compounds is applicable, and although the experimental operations are somewhat more troublesome the process is free from side reactions. The preparation of phenyldimethylmethane-*d* by way of the potassium compound formed by the cleavage of the methyl ether of phenyldimethylcarbinol by sodium-potassium alloy was found to be completely satisfactory. The preparation of methyldiphenylmethane-*d* was accomplished by forming the potassium compound from the methyl ether of diphenylmethylcarbinol and subsequent treatment with deuteroacetic acid.

Samples of triphenylmethane-*d* were prepared in two different ways, one being the treatment of the sodium compound, formed from triphenylchloromethane and sodium amalgam by the method of Schlenk,[21] with deuteroacetic acid, the other being the reduction of triphenylchloromethane by zinc dust in deuteroacetic acid. The latter is an adaptation of Gomberg's method[22] for the preparation of triphenylmethane, and it is the most convenient method of preparing this hydrocarbon from the chloride. It requires an excess of acetic acid but since the excess acid can be recovered and used again this did not constitute an objection to its use. However it, was found that, while the Raman spectrum of the material prepared from triphenylmethyl sodium exhibited a single new C—D line, the material prepared by reduction of chloro compound with zinc showed this line and also a number of other new lines in the same region. These additional lines are almost certainly due to aromatic C—D linkages, for they check as well as could be expected with lines occurring in the Raman spectra of deuterated benzenes.[23] This indicated that some exchange of hydrogen had occurred during the preparation of the compound, a result which should not be surprising in view of the fact that zinc chloride is formed during the reaction and could exert a catalytic influence on the exchange reactions similar to that observed with aluminum chloride acting on other aromatic compounds.[24]

In order to determine the extent to which exchange of nuclear hydrogen had taken place samples prepared by the two methods were analyzed. The total deuterium content was first determined by measuring the density of water resulting from the combustion of the material. The combustions were carried out according to the usual macro-combustion procedure using samples of 1.5 to 2.0 grams, but the water was collected by freezing in traps, and the adsorbed water in the catalyst was brought into equilibrium with the heavier water resulting from these combustions by previous combustions of larger amounts of the same material. The water was purified first by heating in a sealed tube with a small amount of potassium permanganate and

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[20] ZIEGLER AND THIELMANN, *Ber.*, **56**, 1740 (1923).

[21] SCHLENK, in HOUBEN-WEYL, "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, **1923**, Vol. 4, p. 974.

[22] GOMBERG, *Ber.*, **36**, 383 (1903).

[23] WOOD, *J. Chem. Phys.*, **3**, 444 (1935).

[24] KLIT AND LANGSETH, *Z. physik. Chem.*, **A176**, 65 (1936).

sodium carbonate for 12 hours, and subsequently by a series of vacuum distillations as described by Kharasch, Brown, and McNab.[25] The density determinations* were made by the temperature-float method. Two determinations on triphenylmethane prepared by the zinc reduction method gave 5.34 and 5.38 mole % deuterium, and for triphenylmethane prepared from triphenylmethyl sodium 5.20 and 5.10 mole % deuterium; theoretical for triphenylmethane-*d* 6.25 mole % deuterium. To determine the extent of substitution in positions other than the tertiary position, samples of triphenylmethane were chlorinated with phosphorus pentachloride according to the method of Auwers,[26] the chloro compound was hydrolyzed in hot alkaline solution, and the resulting carbinol was analyzed for deuterium. The deuterium content of triphenylcarbinol obtained from triphenylmethane which had been prepared by the zinc reduction method was found to be 0.48 mole %, while the triphenylmethane prepared from sodium triphenylmethyl yielded a carbinol containing 0.16 mole % deuterium. These results, therefore, confirmed the conclusion that there had occurred a greater amount of hydrogen exchange during the preparation of triphenylmethane by Gomberg's method. The extent of such substitution is, however, in both cases quite small.

The analytical results show that in our preparations the tertiary hydrogen has been replaced by deuterium to the extent of somewhat more than eighty percent. Our failure to obtain complete substitution of deuterium is probably to be attributed to insufficient drying of reagents and solvents and possibly also to some exchange of hydrogen between acetic anhydride and acetic acid (or water) during the formation of deuteroacetic acid.

The possibility of forming 1,1-diphenylethane and isopropylbenzene by reduction of the chloro derivative with zinc and acetic acid was investigated and found to be wholly unsatisfactory. 1,1-Diphenyl-1-chloroethane, on treatment with zinc dust in acetic acid, gave a practically quantitative yield of the olefine, while phenyldimethylchloromethane yielded a small amount of isopropylbenzene and a larger amount of a mixture of two solids which were not positively identified.

DATA

Triphenylmethane (ordinary).—Sixty grams of triphenylmethane from the Eastman Kodak Company was refluxed for two hours with zinc and glacial acetic acid, filtered hot through a 200-mesh sintered glass plate, and precipitated by the addition of cold water. The white crystalline product was recrystallized from absolute alcohol and vacuum dried. The crystals melted sharply at 92.5°. The material was then distilled four times in high vacuum and finally sealed off under vacuum in a jacketed Raman tube.

Raman lines:† 240 (7), 280 (7), 612 (6), 627 (6), 667 (5), 736 (6), 763 (4), 824 (6), 867 (6), 911 (2)*b*, 952 (2)*c*, 1009 (10), 1037 (9), 1079 (1), 1117 (1), 1170 (8), 1192 (6), 1255 (4), 1300 (2), 1348 (2), 1407 (2), 1460 (2), 1506 (2), 1598 (6), 1613 (8), 2879 (5), 3059 (10), 3155 (1), 3201 (1).

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[25] KHARASCH, BROWN, AND MCNAB, J. ORG. CHEM., **2**, 36 (1937).

* We are indebted to Mr. W. R. Sprowls for carrying out the density measurements.

[26] AUWERS, *Ber.*, **40**, 2163 (1907).

† *Note:* All frequencies have been calculated assuming excitation by Hg λ 4358. Lines designated by the letters *b* and *c* are probably due to excitation by Hg λ 4339 and Hg λ 4347, respectively. Visual estimates of the intensities are given in parentheses following the numerical values of the frequencies in cm^{-1}.

Triphenylmethane-d—First method: Triphenylmethylsodium was prepared according to the method of Schlenk.[21] The entire reaction was carried out in a long-necked 1-l. flask with side-arm which served as an outlet for nitrogen gas and for the introduction of reagents. Commercial nitrogen was used after purification by passage over a copper spiral heated to 450°, through three gas bubblers containing Fieser's solution,[27] a bubbler containing sulfuric acid, and a series of towers containing potassium hydroxide, calcium chloride, and phosphorus pentoxide, in order. An ether solution containing 25 grams of recrystallized triphenylchloromethane was poured quickly into the reaction flask, and ether was added to make a total volume of 800 cc. To this was added 1200 grams of 1 % sodium amalgam. The flask was then closed, disconnected, and shaken for two hours. The theoretical amount of deuteroacetic acid, prepared by the addition of 99.6% D_2O to acetic anhydride, was then added, and the ether layer was decanted. After evaporation of the ether a yellow residue remained which, on recrystallization from alcohol, yielded 15 grams of triphenylmethane-*d*, m.p. 91–92°.

Second method—Fifteen grams of finely powdered triphenylchloromethane was stirred continuously in 60 g. of deuteroacetic acid with 15 g. of zinc dust for 30 minutes, the reaction being conducted in an atmosphere of nitrogen. Control experiments using ordinary acetic acid indicated that this time of reaction, rather than a period of several hours as Gomberg allowed, did not affect the yield adversely and resulted in a better quality of product. The excess deuteroacetic acid was removed by distillation, and the residue was extracted with ordinary hot glacial acetic acid from which the triphenylmethane-*d* was precipitated by the addition of cold water. After recrystallization from alcohol the product was colorless; m.p. 92°. This material, and also that prepared by the first method, was distilled three times in high vacuum, with discard, each time, of a small residue, before being collected in jacketed Raman tubes.

Raman lines: 239 (7), 278 (7), 605 (6)*i*, 628 (6), 664 (5), 736 (6), 760 (2), 811 (6)*i*, 851 (1)*i*, 912 (5)*b*, 953 (3)*c*, 1008 (9), 1038 (8), 1080 (1), 1118 (1), 1167 (8), 1191 (6), 1228 (5)*i*, 1283 (2)*i*, 1342 (2), 1401 (1), 1458 (2), 1506 (2), 1598 (6), 1616 (8), 2132 (6)*i*, 2894 (4), 3055 (10), 3153 (3), 3200 (3). There were present in the spectrum of the material prepared by the second method the following lines in addition to those listed above: 1694 (1)*i*, 2042 (1)*i*, 2214 (4)*i*, 2439 (2)*i*, 2565 (2)*i*.

1,1-Diphenylethane (ordinary).—Approximately 85 g. of diphenylmethylcarbinol, m.p. 80–81°, was converted to the olefin by refluxing for 5 hours, according to the method of Tiffeneau.[28] The heavy viscous oil was dried over potassium carbonate and then distilled under reduced pressure, the fraction boiling at 152–153° at 19 mm. being collected. Eighty-five cubic centimeters of the olefin was dissolved in 115 cc. of absolute alcohol, 3 g. of platinum oxide catalyst[29] was added, and the mixture was shaken under a pressure of two atmospheres of hydrogen for two hours at room temperature. After separation from the catalyst by filtration, the alcohol was removed by fractional distillation. The remaining colorless oil was dried over potassium carbonate, and then distilled under reduced pressure. All of the material distilled between 135 and 138°, and a 10-cc. fraction, b.p. 137–138° at 12.5 mm., was collected in a Raman tube and sealed off. The material did not give a positive test for unsaturation.

Raman lines: 162 (5), 234 (7), 313 (1), 424 (5), 551 (1), 586 (2), 628 (6), 742 (7), 789

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[27] FIESER, *J. Am. Chem. Soc.*, **46**, 2639 (1924).

[28] TIFFENEAU, *Ann. chim.*, [8], **10**, 359 (1907).

[29] ADAMS, *Organic Syntheses* **8**, 92.

(5), 852 (2), 918 (1), 986 (1), 1011 (9), 1039 (7), 1164 (5), 1196 (8), 1461 (6), 1590 (4), 1612 (8), 2882 (7), 2940 (7), 2981 (7), 3060 (10).

Methyldiphenylmethane-d.—Unsuccessful attempts were made to develop a procedure for the preparation of this compound from 1,1-diphenyl-1-chloroethane by way of the Grignard reagent and by reduction with zinc in ordinary acetic acid. The chloro compound was prepared by passing dry hydrogen chloride into a benzene solution of diphenylmethylcarbinol at −10°, according to the method of Schoepfle and Ryan.[30] Employing a variety of forms of activated magnesium, no reaction could be obtained at temperatures below 40°. The action of zinc dust in acetic acid resulted in the formation of 1,1-diphenylethylene. To a solution of 25 g. of the chloro compound and 60 g. acetic acid, 8 g. of zinc dust was added in small portions over a period of 30 minutes, the mixing being carried out at −10°. The mixture was then allowed to warm to room temperature, and after filtration the liquid was subjected to fractional distillation at 12 mm. pressure. The acetic acid distilled at 20°, and practically all of the remaining liquid at 126°. This fraction (18 g.) was identified as 1,1-diphenylethylene by examination of the Raman spectrum. About 0.5 g. of a colorless solid, m.p. 124° was isolated from the residue. This substance, soluble in benzene, slightly soluble in ether and in alcohol, was not definitely identified, but may be 2,2,3,3-tetraphenylbutane, m.p. 126–127°.[31]

The successful preparation of methyldiphenylmethane-*d* was accomplished by treatment of 1,1-diphenylethylpotassium with deuteroacetic acid. The potassium compound was prepared by the reaction of diphenylmethylcarbinol methyl ether with sodium-potassium alloy, according to the procedure of Ziegler and Schnell,[32] the only important modification being in the method of purifying the ether. Fifty grams of diphenylmethylcarbinol was dissolved in a solution containing 12 g. of sulfuric acid in 100 g. of methanol, and after standing overnight at room temperature, the mixture was poured onto crushed ice and then extracted with ether. The ether solution was washed with dilute sodium hydroxide solution, dried over sodium sulfate, and fractionated at 12 mm. pressure. Forty-five grams of an impure product, boiling at 135° at 12 mm., was collected, the impurity being largely 1,1-diphenylethylene. This product was dissolved in 200 cc. of anhydrous diethyl ether and shaken with 2 g. of sodium-potassium alloy (1 part sodium, 5 parts potassium) in an atmosphere of nitrogen. A blue color appeared first, which on continued shaking gave way to an intense red coloration. At this point the shaking was discontinued, and dry carbon dioxide was passed into the liquid until the color was discharged. The material was then filtered, and the liquid was distilled at 12 mm. pressure. A fraction of 32 g., boiling at 140° at 12 mm., was collected; m.p. 37° (Lit.[32] m.p. 35–36°). Thirty grams of this material was placed in a nitrogen-filled flask together with 300 cc. of anhydrous diethyl ether and 10 g. of sodium-potassium alloy. The flask was then closed and placed in a shaker for 24 hours. Deuteroacetic acid (6.85 g.), dissolved in 20 cc. of diethyl ether, was then added, whereupon the red color of the mixture was immediately discharged. The material was filtered, and the liquid was distilled under reduced pressure; yield, 22 g. methyldiphenylmethane-*d*; b.p. 136–137°, at 12 mm.

Raman lines: 164 (4), 236 (4), 298 (2)*i*, 408 (2)*i*, 548 (1), 576 (4)*i*, 620 (5)*i*, 733 (6)*i*, 790 (3), 850 (2), 907 (1)*b*, 950 (1)*c*, 1008 (10), 1034 (7), 1108 (4)*i*, 1161 (3), 1194 (5), 1219

[30] SCHOEPFLE AND RYAN, *J. Am. Chem. Soc.*, **52**, 4027 (1930).

[31] ZIEGLER AND SCHNELL, *Ann.*, **437**, 235 (1924).

[32] ZIEGLER AND SCHNELL, *ibid.*, p. 242.

(3)*i*, 1293 (2)*i*, 1461 (5), 1606 (8), 2122 (1)*i*, 2240 (0)*i*, 2494 (1)*i*, 2736 (1), 2777 (2), 2875 (6), 2935 (6), 2974 (6), 2994 (2), 3061 (10), 3162 (2), 3206 (2). Our photographs of this spectrum show a considerable number of lines not present in the spectrum of the light compound. These additional lines are not all due to isotopic effects, but in several cases to the fact that the photographs of the heavy compound were more fully exposed. There was materially less continuous background (fluorescence) from the deutero compound than from the ordinary, which indicated that the former was of higher purity.

Isopropylbenzene (ordinary).—Isopropylbenzene was prepared from isopropyl chloride and benzene by the Friedel-Crafts reaction according to the procedure recommended by Boedtker.[33] It was purified by fractional distillation at atmospheric pressure; b.p. 150.6–150.9°. A fraction, boiling at 150.7°, was collected for the Raman investigation.

Raman lines: 148 (10), 318 (6), 466 (6), 569 (3)*c*, 628 (6), 748 (8), 842 (3), 895 (5), 952 (3)*c*, 1007 (10), 1034 (7), 1087 (5), 1114 (5), 1161 (5), 1188 (5), 1219 (7), 1286 (3), 1313 (4), 1448 (5), 1471 (6), 1589 (5), 1610 (8), 2874 (9), 2905 (9), 2938 (9), 2968 (9), 3039 (6), 3059 (10), 3159 (3), 3208 (2), 3246 (3).

Phenyldimethylmethane-d.—As in the case of methyldiphenylmethane-*d*, unsuccessful attempts were made to utilize the Grignard procedure and the zinc–acetic acid reduction method before resorting finally to the use of the potassium compound. We were unable to form the Grignard reagent from 2-phenyl-2-chloropropane, and an attempt to prepare isopropylbenzene from the chloro compound by treatment with zinc dust and acetic acid, according to the procedure outlined above, resulted in a mixture containing small amounts of isopropylbenzene, 2-phenylpropene-1, and larger amounts of two solid substances which melted at 117° and 96°, respectively, after recrystallization from alcohol.

The methyl ether of phenyldimethylcarbinol, which was needed for the preparation[34] of the potassium compound, was prepared from 2-phenyl-2-chloropropane. One hundred forty grams of the halide was mixed with 400 g. of anhydrous methanol and 300 g. of potassium hydroxide, and the solution was allowed to stand at room temperature overnight. The solution was then poured onto a large quantity of crushed ice, extracted with ether, and the ether solution after drying over sodium sulfate was subjected to fractional distillation. Yield, 100 g., b.p. 78–82° at 17 mm. This material was further purified, as in the previous case, by treatment with a small quantity of sodium-potassium alloy. Yield of pure product, 2-phenyl-2-methoxypropane, 65 g., b.p. 82° at 20 mm. Ten grams of this material, dissolved in 500 cc. of anhydrous diethyl ether, was treated with 10 g. of sodium-potassium alloy by shaking in a closed flask, filled with nitrogen, for 24 hours. Four grams of deuteroacetic acid was then added, the mixture was filtered, and the liquid was combined with that obtained from two further batches. Fractional distillation yielded 20 g. isopropylbenzene-*d*, b.p. 149–151°, of which a 10-g. fraction boiling at 151.0° was used in the Raman work.

Raman lines: 144 (8), 222 (1)*i*, 313 (2), 461 (3), 528 (1)*i*, 625 (4), 745 (7), 847 (2), 902 (2)*b*, 950 (2)*c*, 1005 (10), 1034 (5), 1089 (4), 1117 (4), 1163 (4), 1185 (3), 1218 (4), 1270 (4)*i*, 1313 (1), 1461 (3)*i*, 1610 (6), 2152 (4)*i*, 2216 (1)*i*, 2500 (1)*i*, 2717 (2), 2785 (6), 2865 (7), 2906 (4), 2928 (4), 2968 (6), 3059 (10).

Isobutylbenzene (ordinary).—Benzyldimethylcarbinol was prepared from benzyl

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[33] BOEDTKER, *Bull. soc. chim.*, [3], **25**, 845 (1901).

[34] ZIEGLER AND SCHNELL, *loc. cit.*, p. 255.

magnesium chloride and acetone according to the method of Tiffeneau,[35] b.p. 100–104° at 10 mm., and dehydrated[36] by heating on a steam bath with acetic anhydride and a few drops of sulfuric acid. Sixty-five cubic centimeters of the olefin, b.p. 182°, dissolved in absolute alcohol, was treated with platinum oxide catalyst and hydrogen at two atmospheres pressure for 1.5 hours. After separation of the liquid by the catalyst by filtration, and removal of the alcohol by distillation, the material was subjected to fractional distillation, yielding isobutylbenzene, b.p. 170–173°. A fraction boiling at 170–170.3° was collected for the Raman work.

Raman lines: 262 (8), 313 (8), 422 (5), 496 (5), 594 (1), 625 (7), 742 (7), 815 (8), 879 (1), 909 (2)*b*, 953 (5)*c*, 1006 (10), 1034 (8), 1122 (5), 1160 (4), 1183 (4), 1210 (8), 1286 (6), 1344 (6), 1455 (7), 1591 (6), 1609 (8), 2729 (3), 2768 (2), 2881 (9), 2925 (9), 2968 (9), 3063 (10), 3176 (1), 3212 (1).

Benzyldimethylmethane-d.—β-Chloroisobutylbenzene was prepared by saturating the carbinol at 0° with dry hydrogen chloride, and purified by distillation under reduced pressure, b.p. 86–89° at 10 mm. The Grignard reagent was formed from 7 g. of magnesium and 50 g. of the chloro compound at 50°, using a drop of methyl iodide to start the reaction. It was found desirable to begin with a relatively concentrated solution of the halide in ether, about 1:1, and to dilute the halide further during the addition so that the final volume was about 1 l.; otherwise the mixture becomes too viscous for smooth reaction. The halide was added over a period of three hours, after which stirring was continued for an additional hour. Five and nine-tenths grams of deuteroacetic acid, dissolved in 100 cc. ether, was then added slowly with stirring. The reaction mixture was filtered, and the filtrate was shaken successively with small amounts of sodium carbonate and silver nitrate. After a preliminary distillation at low pressure, and removal of the ether, the product was fractionated at atmospheric pressure, yielding benzyldimethylmethane-*d*, b.p. 170.5–171.5°. The Raman spectrum of this material exhibited a number of lines which were recognized, with reference to the work of Savard,[37] and also of Prevost, Donzelot, and Balla,[38] as lines due to dimethylstyrolene and are indicated below by the letter *o* following the numerical value of the shift. The line at 1658 cm^{-1} is especially characteristic of olefins and is generally very intense so that its presence here does not necessarily indicate a high proportion of olefine in the product.

Raman lines: 264 (8), 312 (8), 424 (5), 497 (5), 597 (1), 624 (7), 737 (7), 788 (5)*i*, 815 (7), 841 (5)*o*, 906 (4)*b*, 952 (5)*c*, 1003 (10), 1035 (9), 1122 (5), 1161 (5), 1181 (5), 1208 (8), 1287 (6), 1318 (6)*i*, 1346 (6), 1453 (7), 1586 (6), 1606 (8), 1658 (7)*o*, 2147 (6), 2720 (3), 2760 (2), 2880 (9), 2925 (9), 2925 (9), 2965 (9), 3059 (10), 3172 (1), 3212 (1).

SUMMARY

1. It is pointed out that the position of the C—H line (longitudinal or "valence" vibration) in the Raman spectra of compounds of the type R_3CH is determined largely by the C—H binding force, and that a comparison of the influences of various types of substituents (R) may be made on this basis. The available data indicate that, when R is a halogen, the C—H binding force is considerably greater than in the case where R is a

[35] TIFFENEAU, *Compt. rend.*, **137**, 575.

[36] TIFFENEAU, *Bull. soc. chim.*, [4], **29**, 815 (1921).

[37] SAVARD, *ibid.*, [5], **2**, 633 (1935).

[38] PREVOST, DONZELOT, AND BALLA, *Compt. rend.*, **198**, 1041 (1934).

methyl group. The present work was undertaken to determine whether the influence of various organic groups could be differentiated.

2. Since it is not ordinarily possible to identify the tertiary C—H lines in the spectra of compounds which contain a large number of C—H groups of different types, use has been made of the isotope effect, and the comparisons were made on the basis of lines due to tertiary C—D linkages. The deutero compounds, in which only the tertiary hydrogen was replaced by deuterium, were prepared by treatment of sodium, potassium, or magnesium compounds with deuteroacetic acid.

3. The compounds examined were triphenylmethane-*d*, methyldiphenylmethane-*d*, phenyldimethylmethane-*d*, and benzyldimethylmethane-*d*. Variations of about 1 per cent. in the frequency of the C—D Raman shift were observed.

4. These variations are held to be of little significance, and it is concluded that the binding force is, in each case, normal. It follows that the factors which give rise to the variations in the chemical reactivity of the tertiary C—H groups in this series of compounds do not appreciably influence the character of the binding in the normal states of the molecules. It is concluded also that the enhancement of the C—H binding force in halogen-substituted methanes is due primarily to electrostatic attraction between halogen and hydrogen.

5. The Raman spectra of the analogous hydrocarbons of normal isotopic composition (triphenylmethane, 1,1-diphenylethane, isopropylbenzene, and isobutylbenzene) are also described. Of these, only the spectrum of isopropylbenzene has been previously reported. It has been shown that previous failure to obtain the Raman spectrum of triphenylmethane has been due to the presence of a fluorescent impurity which is less volatile than triphenylmethane and which may be removed by distillation in high vacuum.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE THERMAL REARRANGEMENT OF *N*-CHLORO-ACETANILIDE IN AQUEOUS SOLUTION

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During the fifty years which have elapsed since Bender[1] discovered *N*-chloroacetanilide and its rearrangement to chloroacetanilide under the catalytic influence of hydrochloric acid, many papers have been published on this subject. These articles, for the purposes of the present discussion, can be catalogued as follows: (1) investigations in aqueous solutions; (2) investigations in non-aqueous solutions; (3) investigations in the dry state. Each of these classifications can be divided into (*a*) thermal and (*b*) photochemical investigations, and still again into those concerned primarily with the theory of the reaction, and those consisting mainly of tables of rates of reaction. In still another group of papers, the authors have accepted the mechanism of the *N*-chloroacetanilide rearrangement as proved, and have used the conclusions with respect to this reaction to bolster their arguments for or against a mechanism of some other reaction, such as halogenation, or in support of some general theory of reaction. We shall concern ourselves in this paper largely with the thermal mechanism of the "rearrangement" in aqueous solution. It cannot be too strongly emphasized that any remodelling of the mechanism in aqueous solutions makes it imperative to reëxamine the superstructure based upon this foundation.

The early work in this field was strongly influenced by Armstrong's[2] views on substitution reactions. He contended that something more than a mere interchange of positions of radicals took place when *N*-chloroacetanilide rearranged. Later[3] when he found that hydrochloric acid is a specific catalyst for this rearrangement he stated: "It appears legitimate to assume that it (the isomeric change) is dependent on the combination of chloroamine with hydrogen chloride. A condition of extreme instability is thus engendered, and probably the first consequent change is one in which an atom of chlorine attached to the nitrogen atom escapes from the

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[1] BENDER, *Ber.*, **19**, 2272 (1886).

[2] ARMSTRONG, *Brit. Assoc. Reports*, **1899**, p. 685.

[3] ARMSTRONG, *J. Chem. Soc.*, **77**, 1047 (1900).

molecule together with an atom of hydrogen from the nucleus; a chlorine atom then slips into the nucleus in place of the latter, whilst the atom of hydrogen introduced in the molecule of hydrochloric acid takes the place of the chlorine atom of the chloroamine, the ortho or para derivative being formed according to the conditions prevailing at the moment of change."

Blanksma[4] found that the rate of the reaction was monomolecular, and so he concluded that the reaction was truly intramolecular. Orton[5] adopted this same viewpoint when he suggested that Armstrong's pentavalent nitrogen compounds might rearrange by way of a quinonoid path. Later Orton and Jones[6] mention a "strong *prima facie* case" for the quinquavalent nitrogen intermediate, but in another article they[7] definitely abandoned this point of view. In the meantime, Acree and Johnson[8] thought that they had found definite proof of this mechanism when they obtained the same products from *N*-bromoacetanilide and hydrochloric acid, as from *N*-chloroacetanilide and hydrobromic acid. The idea of a true intramolecular rearrangement persists in articles by Bell.[9] He however also considers another path, and concludes that the solvent composition would have a large influence on the relative amounts going by the two paths. Thus, "In aqueous hydrochloric acid the rearrangement of *N*-chloroacetanilide takes place chiefly" by the other path.

Olson, Porter, Long, and Halford[10] using radioactive hydrochloric acid as a catalyst, showed that a pentavalent nitrogen intermediate, in which the two chlorines are equivalent, is impossible. They concluded, however, that under their experimental conditions forty per cent. of the *N*-chloroacetanilide rearranged without coming into radioactive equilibrium with the chloride ion in solution *if the concentration of chloride ion remained constant during the experiment.* This result, they stated, was in agreement with the assumption that this fraction rearranged intramolecularly.

The genesis of another mechanism is found in Chattaway and Orton's[11] discovery that *N*-chloroacetanilide and hydrochloric acid produce chlorine and acetanilide. The possibility that hypochlorous acid is an intermediate in the chlorine formation is seen from their[12] experiments on substituted

[4] BLANKSMA, *Rec. trav. chim.*, **21**, 366 (1902); **22**, 290 (1903).
[5] ORTON, *Proc. Roy. Soc.*, (London), **71**, 153 (1902).
[6] ORTON AND JONES, *J. Chem. Soc.*, **95**, 1457 (1909).
[7] ORTON AND JONES, *Proc. Chem. Soc.*, **25**, 233 (1909).
[8] ACREE AND JOHNSON, *Am. Chem. J.*, **37**, 410 (1906); **38**, 258 (1907).
[9] BELL, *J. Chem. Soc.*, **1936**, 1154.
[10] OLSON, PORTER, LONG, AND HALFORD, *J. Am. Chem. Soc.*, **58**, 2467 (1936).
[11] CHATTAWAY AND ORTON, *J. Chem. Soc.*, **75**, 1045 (1899).
[12] CHATTAWAY AND ORTON, *ibid.*, **77**, 134 (1900).

nitrogen chlorides with acids on which hypochlorous acid has no action. Later Orton and Jones[6] stated that no evidence had been found which required the intermediate formation of hypochlorous acid during the reaction. In the same article, Orton and Jones stated that the equilibrium,

$$\mathrm{ArNHAc} + \mathrm{Cl_2} \rightleftharpoons \mathrm{ArNClAc} + \mathrm{HCl}$$

always was rapidly established, and then slowly displaced by the formation of chloroanilide. The solvent composition had a large influence on the equilibrium—in glacial acetic acid, hydrochloric acid was not detectable. About the same time, they[7] made very definite statements in favor of the chlorine mechanism. Again the following year, they[13] mentioned the two mechanisms and adhered to the one based upon the direct action of chlorine on the anilide or on a "dynamic isomeride" of it ("quinonoid"). They showed also that the velocity of the reaction was increased by the addition of acetanilide. Barnes and Porter[14] found that in glacial acetic acid, the maximum rate of transformation of *N*-chloroacetanilide obtained by the addition of β-acetnaphthalide was greater than that which could be obtained by the addition of acetanilide. They stated that this was in conflict with the predictions based on the theory of Orton and Jones but they offered no satisfactory substitute for that theory.

Olson, Porter, Long, and Halford[10] showed that sixty per cent. of the chlorine came into radioactive equilibrium with the chloride ion in solution before reacting to form chloroacetanilide. This was in harmony with the idea that the mechanism involved a small steady-state concentration of chlorine, but definitely excluded a real equilibrium between chlorine and the reactants. The conclusion that chlorine, if present, must be at a steady-state concentration can be got from the experiments of Orton and King,[15] who determined the relative amounts of *C*- and *N*-chlorination of acetanilide by chlorine. Orton, Soper, and Williams'[16] rate determinations of *C*- and *N*-chlorination of acetanilide by chlorine lead to the same decision. Olson, Halford, and Hornel,[17] correcting for the chloride ion which was produced during the experiment, concluded that all of the *N*-chloroacetanilide which reacted to form chloroacetanilide came into radioactive equilibrium with the catalyzing chloride ions, and it therefore had passed through the chlorine stage. The production and disappearance of chlorine as steps in the series of reactions involved in this rearrangement thus appears to be well established. The rate of the rearrangement usually

[13] ORTON AND JONES, *Brit. Assoc. Reports*, **1910**, p. 85.
[14] BARNES AND PORTER, *J. Am. Chem. Soc.*, **52**, 2973 (1930).
[15] ORTON AND KING, *J. Chem. Soc.*, **99**, 1369 (1911).
[16] ORTON, SOPER, AND WILLIAMS, *ibid.*, **1928**, 998.
[17] OLSON, HALFORD, AND HORNEL, *J. Am. Chem. Soc.*, **59**, 1613 (1937).

is followed by determining the loss in the power of solutions to oxidize iodide ion. The production of chlorine involves no such loss. The rate work on this problem therefore involves at least two assumptions—first, that the steady-state concentration of chlorine has been attained, and second that no side reactions occur unless proper allowances have been made for them. Blanksma[4] proved that the rate of the rearrangement as followed by the determination of loss of oxidizing power, involves the concentration of *N*-chloroacetanilide to the first power, and that of hydrochloric acid to the second power. Acree and Johnson[8] showed that the appearance of the second power of hydrochloric acid concentration in the rate law might be due to the fact that the reaction is catalyzed by hydrogen and chloride ions. Orton and Jones[7] found that as the concentration of acetic acid was increased, the second power of hydrochloric acid in the rate law changed gradually to the first power. The change was rapid at about sixty-five per cent. acetic acid. Harned and Seltz[18] showed that the rate of rearrangement in aqueous hydrochloric acid was proportional to the product of the activities of hydrogen and chloride ions, rather than the concentration product, but that this simple rate law was not obeyed if salts, such as sodium chloride, were added. Soper[19] determined the hydrolysis constant of *N*-chloroacetanilide. Combining this with the hydrolysis constant of chlorine, and the rates of *C*- and *N*-chlorination of acetanilide, he was unable to show that the production of chlorine was the slow step in the Orton series of reactions. He emphasized the necessity for adding enough acetanilide to obtain the maximum rate of rearrangement in order to suppress the *N*-chlorination of chloroacetanilides. The activity rate law proposed by Harned and Seltz[18] was checked by Soper and Pryde[20] after they had corrected for the activity of *N*-chloroacetanilide and for a side reaction involving hydrolysis of the *N*-chloroacetanilide. They stated that their results were not in harmony either with a concentration theory or with the Brønsted theory. Belton[21] studied the rate of rearrangement in aqueous hydrochloric acid solution to which various amounts of (1) sodium chloride, or (2) perchloric acid had been added. In the second series, he found that the results could be expressed by a concentration theory rather than by an activity theory. In the first series, no simple relationship could be obtained using the concentration, the activity, or the Brønsted theory.

Dawson and Millet[22] not only corroborated Harned and Seltz's[18] con-

[18] HARNED AND SELTZ, *ibid.*, **44**, 1475 (1922).
[19] SOPER, *J. Chem. Soc.*, **127**, 98 (1925); *J. Phys. Chem.*, **31**, 1192 (1927).
[20] SOPER AND PRYDE, *J. Chem. Soc.*, **1927**, 2761.
[21] BELTON, *ibid.*, **1930**, 116.
[22] DAWSON AND MILLET, *ibid.*, **1932**, 1920.

clusions that the addition of salts invalidated the simple activity law for catalysis by hydrogen and chloride ions, but decided that the rate could best be represented by a law which involved the concentration of nonionized hydrochloric acid. The side reactions mentioned by Soper and Pryde[20] were found by Percival and LaMer[23] to be insignificant since there was a complete absence of time drifts in their velocity constants.

The existence of a side reaction which produces chloride ions, was first noticed by Blanksma.[4] It was investigated more fully by Orton and Gray[24] who thought that it was a reversible hydrolysis of *N*-chloroacetanilide, and a subsequent reduction of the hypochlorous acid by aniline. The additions of nitric, sulfuric and perchloric acids, in the order named, were effective in producing chloride ions. Soper and Pryde[20] found a similar hydrolysis. In the experiments of Olson, Halford, and Hornel[25] a very considerable fraction of the *N*-chloroacetanilide was used up in producing chloride ion. Until the influence which this side reaction exerts on loss of oxidizing power has been established, we obviously cannot use this reaction as a basis of deciding for or against the various general theories of reaction rates.

The relative amounts of ortho and para chloroacetanilides formed under various conditions were investigated by Orton and Jones[26] who found that in the chlorination of acetanilide by chlorine in glacial acetic acid, twice as much para as ortho chloroacetanilide was formed. Dilution of the solvent by water did not affect this ratio. On the other hand, in the chlorination by bleaching powder, or in the rearrangement, the two isomers were formed in equal amounts. These statements were revised by Orton and Bradfield[27] who decided that when the acid was diluted to fifty per cent. the para-ortho ratio dropped to three halves for the chlorination of acetanilide by chlorine. Olson, Halford, and Hornel[25] recovered only fifty per cent. of the chlorine used up in the direct chlorination of acetanilide by chlorine, as *p*-chloroacetanilide. They therefore assumed that para and ortho chloroacetanilides are formed in equal amounts. Their solvent was aqueous ethyl alcohol.

Olson, Halford, and Hornel[25] concluded: (1) that the total loss in oxidizing power could be accounted for by measuring the production of chloroacetanilides and chloride ion, if it were assumed that two equivalents of oxidizing power were lost for each mole of chloride ion or chloroacetanilide formed.

[23] PERCIVAL AND LA MER, *J. Am. Chem. Soc.*, **58**, 2413 (1936).
[24] ORTON AND GRAY, *Brit. Assoc. Reports*, **1913**, p. 136.
[25] OLSON, HALFORD, AND HORNEL, *J. Am. Chem. Soc.*, **59**, 1613 (1937).
[26] ORTON AND JONES, *J. Chem. Soc.*, **95**, 1058 (1909).
[27] ORTON AND BRADFIELD, *ibid.*, **1927**, 986.

The present investigation is an extension of the preceding paper. We do not find it necessary to alter any conclusions stated there, but we have found that the unknown substance X, to which reference was made as being produced along with the chloride ion, is itself an oxidizing agent which contributes to the iodine titre. We have therefore amplified the experimental procedure so as to determine the concentration of this substance at various times. The *N*-chloroacetanilide was prepared by the method of Barnes and Porter.[28] The temperature was 40° throughout this investigation. For most runs a solvent containing twenty per cent. alcohol was used. It was prepared as follows: to two hundred cubic centimeters of absolute ethyl alcohol, measured at 20°, enough water and sulfuric acid were added, so that at 40° the solution would occupy one liter and have the required hydrogen-ion concentration. The thermostat was placed in a dark corner of the laboratory, but the reaction was not otherwise shielded from light.

In making a run, the solvent was brought to temperature, and the weighed, finely divided *N*-chloroacetanilide was added. After solution which usually required about two minutes, a weighed amount of sodium chloride was added. Zero time was taken as the time of addition of sodium chloride. The total oxidizing power was determined in the usual way by pipetting five or ten cubic centimeters of the reaction mixture into excess potassium iodide solution, and then titrating the liberated iodine with sodium thiosulfate solution. The new oxidizing agent which we will designate as X, was determined by pipetting ten cubic centimeters of the reaction mixture into an equal volume of solvent which was saturated with sodium chloride. After standing for ten minutes at 40°, excess potassium iodide solution was added and the iodine was titrated. From the experimental work to be presented, it will be evident that under these conditions the *N*-chloroacetanilide was completely destroyed, but X was reduced by only a negligible amount. The chloride ion was determined by chilling rapidly sixty-five cubic centimeters of the reacting solution to about 5°, and then extracting twice with equal volumes of cold benzene. Chlorine and acetanilide are both preferentially soluble in benzene, and so about fifteen minutes was permitted to elapse before separating from the aqueous phase the first time, thus permitting the chlorine and acetanilide to react, and the resulting hydrochloric acid to be reëxtracted by the water. After the second extraction the water layer was filtered through ordinary dry filter paper. To fifty cubic centimeters of this solution, excess silver nitrate was added, and the silver chloride was determined gravimetrically.

In Fig. I and Fig. II, we have plotted the experimental results for two runs. Other runs using intermediate initial chloride ion concentrations

[28] BARNES AND PORTER, *J. Am. Chem. Soc.*, **52**, 1721 (1930).

gave intermediate results. Fig. III is for a run where the initial *N*-chloroacetanilide concentration was halved; Fig. IV for a run where the hydrogen-ion concentration was halved, and finally Fig. V for a run using twenty-five per cent. alcohol. Various experiments also were performed on the addition of acetanilide and ortho and para chloroacetanilides. Only the acetanilide had a definite accelerating effect on the overall oxidizing rate, which was particularly marked in those solutions which were low in

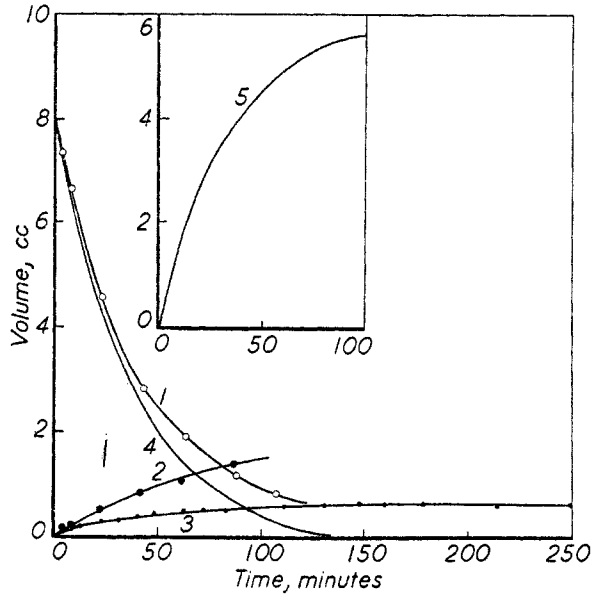


FIG. I. Initial concentration of *N*-chloroacetanilide is 0.04 moles/liter. Initial concentration of chloride ion is 0.04 moles/liter. Initial concentration of hydrogen ion is 1.43 moles/liter. 20% alcohol.

Curve No. 1 represents the total oxidizing power. Curve No. 2 represents the increase in chloride ion. Curve No. 3 represents the concentration of X. Curve No. 4 represents the *N*-chloroacetanilide plus chlorine. Curve No. 5 represents the production of ortho and parachloroacetanilides.

chloride ion. The effects on the production of X and chloride ion were small.

It will be noticed that the curve for X in Fig. II divides into two branches at $t = 200$ minutes. At this time one hundred cubic centimeters of solution was withdrawn from our reaction flask and put into an equal volume of solvent saturated with sodium chloride. At definite intervals samples were withdrawn from the mixture to determine the rate at which X disappears under those conditions. The rate was so slow that we have

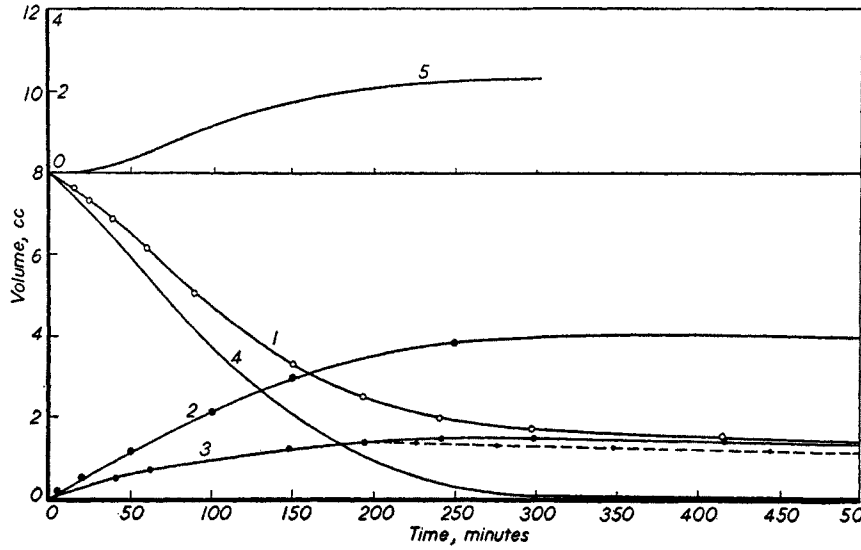


FIG. II. Initial concentration of *N*-chloroacetanilide is 0.04 moles/liter. Initial concentration of chloride ion is 0.005 moles/liter. Initial concentration of hydrogen ion is 1.43 moles/liter. 20% alcohol.

Curve No. 1 represents the total oxidizing power. Curve No. 2 represents the increase in chloride ion. Curve No. 3 represents the concentration of X. Curve No. 4 represents the *N*-chloroacetanilide plus chlorine. Curve No. 5 represents the production of ortho and parachloroacetanilides.

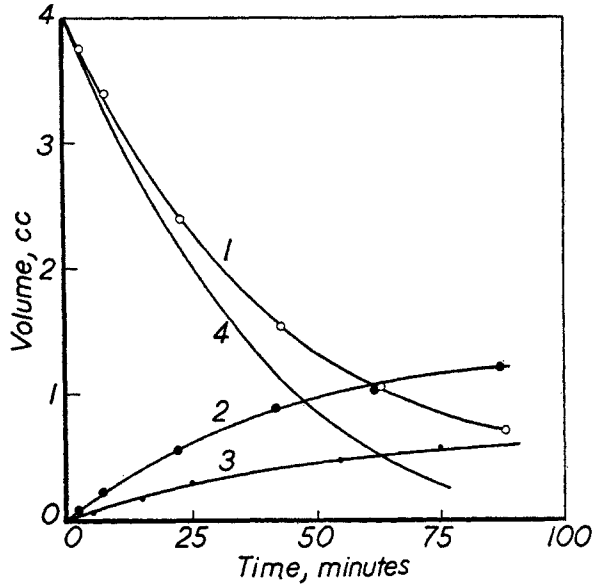


FIG. III. Initial concentration of *N*-chloroacetanilide is 0.02 moles/liter. Initial concentration of chloride ion is 0.04 moles/liter. Initial concentration of hydrogen ion is 1.43 moles/liter. 20% alcohol.

Curve No. 1 represents the total oxidizing power. Curve No. 2 represents the increase in chloride ion. Curve No. 3 represents the concentration of X. Curve No. 4 represents the *N*-chloroacetanilide plus chlorine.

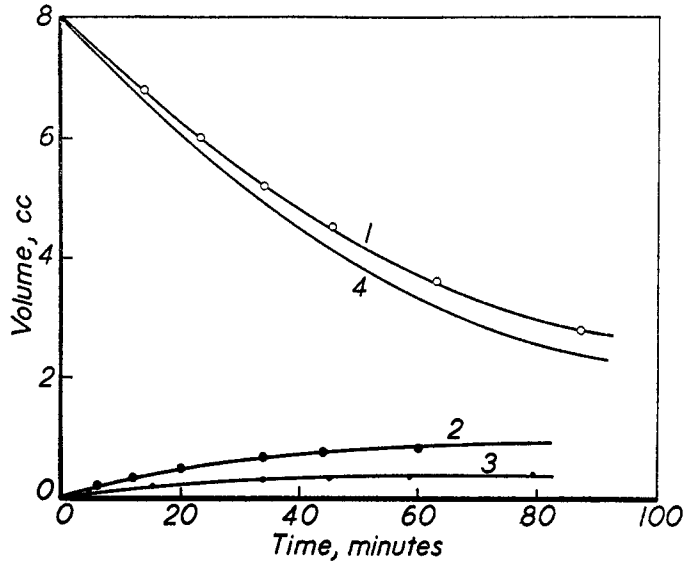


FIG. IV. Initial concentration of *N*-chloroacetanilide is 0.04 moles/liter. Initial concentration of chloride ion is 0.04 moles/liter. Initial concentration of hydrogen ion is 0.717 moles/liter. 20% alcohol.

Curve No. 1 represents the total oxidizing power. Curve No. 2 represents the increase in chloride ion. Curve No. 3 represents the concentration of X. Curve No. 4 represents the *N*-chloroacetanilide plus chlorine.

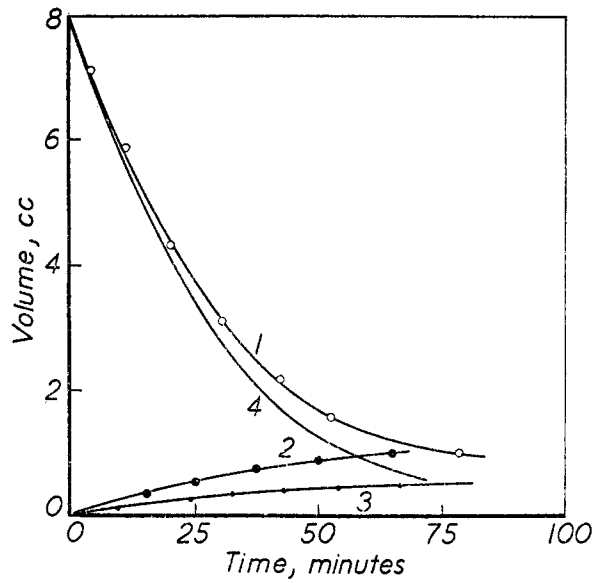


FIG. V. Initial concentration of *N*-chloroacetanilide is 0.04 moles/liter. Initial concentration of chloride ion is 0.04 moles/liter. Initial concentration of hydrogen ion is 1.43 moles/liter. 25% alcohol.

Curve No. 1 represents the total oxidizing power. Curve No. 2 represents the increase in chloride ion. Curve No. 3 represents the concentration of X. Curve No. 4 represents the *N*-chloroacetanilide plus chlorine.

neglected to make a correction for the ten minutes interval which was normally present in all our determinations.

From the curves in the above figures, we see that the initial rate of production of X as well as that of chloride ion, (*a*) is independent of the concentration of chloride ion, *i.e.* the initial slope of the X curve in Fig. I is the same as the slope of the corresponding curve in Fig. II; (*b*) is directly proportional to the initial concentration of *N*-chloroacetanilide, *cf.* Fig. I and Fig. III; (*c*) is directly proportional to the hydrogen-ion concentration, and (*d*) is somewhat lowered by an increase in the alcohol concentration. We see furthermore that the initial slope of the chloride ion curve is twice that of the X curve. We must conclude therefore that the initial production of chloride ion and of X are not independent processes. Furthermore when a sufficient time has elapsed so that the oxidizing power of the solution is due solely to X, the chloride ion concentration continues to increase. In fact at this state of the reaction, the increase in the chloride ion concentration is equal to the decrease in the concentration of X. We therefore are led to postulate that the side reaction which produces chloride ions, involves first a unimolecular activation of a molecule of *N*-chloroacetanilide, possibly to a quinonoid structure, followed by a rapid reaction with two more *N*-chloroacetanilide molecules, producing X and two chloride ions and losing four equivalents of oxidizing power; X then slowly decomposes to produce Y, which is not an oxidizing agent, and a chloride ion. Keeping the hydrogen-ion and alcohol concentrations constant, the simplest mechanism which occurs to us in which cognizance is taken of these experimental data is:

$$\begin{array}{l} \mathrm{NCl} + \mathrm{Cl^-} + \mathrm{H^+} \underset{k_4}{\overset{k_1}{\rightleftharpoons}} \mathrm{CH} + \mathrm{Cl_2} \xrightarrow{k_3} \mathrm{CCl} + \mathrm{Cl^-} + \mathrm{H^+} \\ \quad \downarrow k_2 \\ \quad \mathrm{NCl'} \\ + \mathrm{2NCl} \\ \quad \downarrow k_5 \\ \mathrm{X} + \mathrm{2Cl^-} \\ \quad \downarrow k_6 \\ \mathrm{Y} + \mathrm{Cl^-} \end{array}$$

where we have designated *N*-chloroacetanilide by NCl, acetanilide by CH, and chloroacetanilide by CCl. From what has been said, k_5 is so fast that the production of X is measured by k_2, and so we can neglect k_5; k_6 can be got from Fig. II where it is shown to be small. Likewise k_4 from the

work of Soper and his collaborators as well as from the radioactive work is known to be small compared to k_3, and therefore we can ignore it here. In addition it can be seen that the concentrations of acetanilide and chlorine are equal *unless other chlorinatable substances are present.* The rate of the reaction as usually followed gives the change in total oxidizing power, *i.e.* $-\left(\frac{d\,(\mathrm{NCl})}{dt} + \frac{d\,(\mathrm{Cl_2})}{dt} + \frac{d\,(\mathrm{X})}{dt}\right)$. When account is taken of the corresponding change of acetanilide, we see that the titration by the conservation law also is equal to $\frac{d\,(\mathrm{Cl}^-)}{dt} + \frac{d\,(\mathrm{CCl})}{dt}$. Therefore when we substract and total increase in chloride ion, whether it be present as such or temporarily combined as chlorine, from the loss in oxidizing power, we get a curve representing the production of ortho and para chloroacetanilides. We thus obtain curves No. 5 in Fig. I and Fig. II. The induction period which is so marked in Fig. II must also be present in Fig. I. Its absence means merely that we haven't accurate enough data near the beginning of the reaction. The form of this curve is in complete accord with Orton's chlorine intermediate mechanism, the concentration of chlorine building up from nothing at zero time to its maximum steady-state value, and then gradually decreasing. It is no doubt this steady state which various authors had in mind when they discussed an "equilibrium."

The influence which factors have on the steady-state concentration gives at least a partial explanation of a number of phenomena which have been observed by various investigators. Thus an increase in the concentration of *N*-chloroacetanilide, chloride ion or hydrogen ion increases the rate of formation of chlorine. These factors apparently have no effect on the rate of disappearance of chlorine, and so the steady state concentration should be increased. An increase in the concentration of substances like alcohol, increases the activity of ions, but decreases the activity of the *N*-chloroacetanilide, *i.e.*, makes it more soluble. The change in the rate of formation will depend on which effect is predominant. On the other hand the rate of disappearance is decreased because of the decreased activities of chlorine and acetanilide, probably resulting in an increased concentration of chlorine. The addition of chlorinatable substances like acetanilide has no effect on the rate of production but a marked effect on the rate of disappearance of chlorine, resulting in a decrease of its steady-state concentration.

The effect on the observed rate of disappearance of total oxidizing power is much more complex. Thus the rate will be proportional to the first power of the activity of *N*-chloroacetanilide and of hydrogen ions if the concentration of chlorine is kept essentially constant. The rate also will

be proportional to the activity of chloride ions, if the above condition is fulfilled, and if, in addition, the production of X is negligible. Where one of the above reactants is present initially to only a small amount, the effect of depletion of this constituent due to the steady-state condition of chlorine and acetanilide becomes very noticeable. Thus in the experiment shown in Fig. II, the building up of the steady-state concentration of chlorine and acetanilide decreases the concentration of chloride ion to less than one-half of its initial value in spite of the production of chloride ion by the X reaction. This effectively checks the further disappearance of *N*-chloroacetanilide by this path. The rate is increased by the regeneration of chloride ion as chloroacetanilide is formed, and as chloride ion is produced by the other path. This accounts for the induction period in the overall rate in Fig. II, for the production of chlorine involves no loss in oxidizing power. The addition of acetanilide or acetnaphthalide increases the rate by decreasing the steady state concentration of chlorine, thus increasing the concentration of chloride ion. This explains why the addition of acetanilide is especially effective when the concentration of chloride ion is small. The small decrease in the production of X on the addition of acetanilide may be due entirely to the increased amount of *N*-chloroacetanilide which disappears by the chlorine path. No doubt effects analogous to those described could be found if the concentrations of the other reactants were decreased. The extensive tables of reaction rates published by Rivett[29] and by Fontein[30] might prove to be valuable sources of information in this connection.

Throughout this article we have been interested in mapping the course of the reactions, and in the qualitative effect of various factors and not in a determination of absolute rate constants. However we frequently were aided in the approach to our conclusions by a more quantitative procedure which we now sketch.

From the curve for total oxidizing power and the curve for X we can obtain an approximate curve for *N*-chloroacetanilide as shown in Fig. I and Fig. II. It differs from the true curve by the chlorine concentration. We can fit the total chloride ion concentration by the empirical expression

$$(Cl^-) = a + be^{-ct} = F(t)$$

where a is the initial concentration of chloride ion, b is the initial slope, c is a constant characteristic of each run, and t is the time, which must not be taken too large. From this we could obtain the true concentration of chloride ion if at the various times we knew the amount of chloride ion

[29] RIVETT, *Z. physik. Chem.*, **82**, 201 (1913); **85**, 113 (1913).
[30] FONTEIN, *Rec. trav. chim.*, **47**, 635 (1928).

which is combined as chlorine. Lacking this information, we can substitute the approximate expression in

$$\frac{d(\mathrm{NCl})}{dt} = -k_1(\mathrm{NCl})[F(t)] - k_2(\mathrm{NCl}).$$

This can be integrated directly, and so first approximations to k_1 and k_2 can be obtained. From this we get $k_1 = 0.60$ moles/min. and $k_2 = 3.6 \times 10^{-3}$ moles/min.

Likewise an approximate value of k_3 can be got from the chloroanilide curve by assuming that the concentration of chlorine is stationary at some value of t. Thus in Fig. II., when $t = 30$ min., $d(\mathrm{CCl}/dt = 5.56 \times 10^{-5}$ moles/min., (NCl) = 0.0339, $(\mathrm{Cl}^-)_{total} = 0.0086$. The condition for constant chlorine concentration permits us to write

$$k_1 (0.0339 - x) (0.0086 - x) = 5.56 \times 10^{-5} = k_3 x^2,$$

where $x = (\mathrm{Cl}_2) =$ (acetanilide). Solving, we find $x = 0.0066$, $k_3/k_1 = 1.275$.

TABLE

t	$(\mathrm{Cl}^-)_t$	(NCl)	X	k_3/k_1	$(\mathrm{Cl}^-)_{actual}$
30	0.0086	0.0339	0.0066	1.275	0.0020
60	.0119	.0271	.0077	1.37	.0042
90	.0147	.0207	.008	1.32	.0067

We have tabulated the results of calculations at several times. If it were necessary, these approximate values could be used to obtain the next higher approximations, etc., until a self-consistent set of data were obtained.

SUMMARY

It has been shown that in aqueous solutions *N*-chloroacetanilide disappears by at least two paths. In one path hydrogen ion and chloride ion react with *N*-chloroacetanilide to build up a steady-state, as distinguished from an equilibrium, concentration of chlorine and acetanilide. These substances then react to form ortho and para chloroacetanilides, regenerating hydrogen and chloride ions. The addition of chlorinatable substances like acetanilide or acetnaphthalide increases the rate of this reaction by decreasing the amount of chloride ion fixed as chlorine. This path thus conforms to the mechanism proposed by Orton and Jones.

In the second path which is catalysed only by hydrogen ion three molecules of *N*-chloroacetanilide condense to form a new compound which we

have called X and two chloride ions. X, in acid solution, oxidises iodide ion instantaneously, bromide ion measureably fast and chloride ion only very slowly. X furthermore decomposes slowly, losing its oxidising power to form another chloride ion and some new compound. At 40°, using 20 per cent. aqueous alcohol as solvent, about 70 per cent. of the *N*-chloroacetanilide disappeared by the first path when the initial concentration of chloride ion was 0.04 molar. When the initial concentration of chloride ion was reduced to 0.005 molar, the amount going by that path was reduced to about 25 per cent. The second reaction apparently is prominent enough to warrant a very full investigation of it before any general conclusions based upon the quantitative study of this rearrangement can be accepted.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

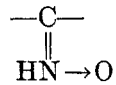
THE TAUTOMERISM OF OXIMES

A. H. BLATT

Received May 7, 1938

The oximes are tautomeric substances in that they furnish both oximino (I) and nitronic (II) derivatives. In addition, when certain special structural requirements in the remainder of the molecule are satisfied, they may furnish cyclic derivatives corresponding to structures I and II.

I



II

The examples of individual oximes which furnish both oximino and nitronic derivatives are far too numerous even for listing,[1] but, by contrast, the cases in which the tautomeric possibilities of oximes have been explored in detail and where derivatives of tautomeric modifications of pairs of stereoisomeric oximes have been obtained and studied are limited to the following four.

Semper and Lichtenstadt[2] isolated and characterized the methyl ethers and *N*-methyl derivatives of both oximes of phenyl *p*-tolyl ketone, while Plowman and Whitely[3] secured comparable derivatives from the oximes of mesoxmono-*p*-tolylamide (III). Brady and Mehta[4] described the methyl ethers and *N*-methyl derivatives of both oximes of *p*-nitrobenzophenone, and Griffiths and Ingold[5] obtained from *o*-phthalaldehyde derivatives of the open-chain oxime, and isolated cyclic oximino and nitronic modifications. This last work we shall discuss in some detail later. To this brief list we have now to add another example of oxime-nitrone tautomerism which involves also ring-chain tautomerism. The case in point is furnished by the monoximes of *cis*-phenyldibenzoylethylene (IV).

III

IV

[1] *Cf.* FREUDENBERG, "Stereochemie," Franz Deuticke, Vienna, **1933**, pp. 992-6 and 1035-6.

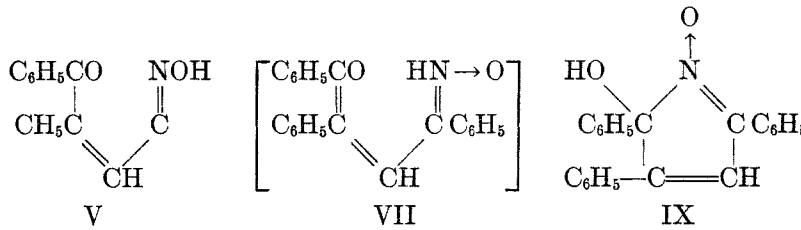
[2] SEMPER AND LICHTENSTADT, *Ber.*, **51**, 928 (1918).

[3] PLOWMAN AND WHITELY, *J. Chem. Soc.*, **125**, 587 (1924).

[4] BRADY AND MEHTA, *ibid.*, **125**, 2297 (1924).

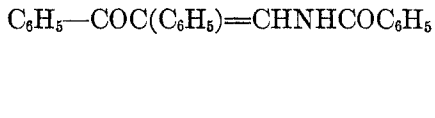
[5] GRIFFITHS AND INGOLD, *ibid.*, **1925**, 1698.

When *cis*-phenyldibenzoylethylene (IV) is treated with hydroxylamine in acidic or basic solution only the relatively unhindered carbonyl group reacts with the reagent. From the two monoximes, (V) and (VI), two nitronic tautomers, (VII) and (VIII), and two cyclic modifications, (IX) and (X), are possible. Of these six tautomers we have isolated, as such or in the form of derivatives, the four corresponding to the unbracketed formulas below. The two modifications which could not be isolated are, as will be pointed out in more detail later, precisely those from which ring closure to the cyclic tautomers would be expected to take place, and their non-existence constitutes to the best of our information the first chemical evidence as to the configuration of oxime derivatives of the nitronic type.

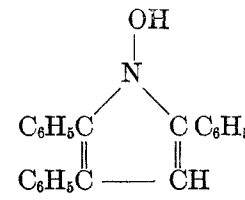


In earlier work it was shown[6] that when *cis*-phenyldibenzoylethylene and hydroxylamine hydrochloride react the product is the hydroxypyrrolenine nitrone (IX) which can be converted to and obtained from the open chain oxime (V). The cyclic nitrone is stable in acid media while the oxime is stable in alkaline media. Presumably, in the reaction between the diketone and hydroxylamine hydrochloride, the oxime is first formed and is then converted to the nitrone in the acid solution. The structure and configuration of the oxime (V) were established by a Beckmann rearrangement to the amide (XI) and by the hydrolysis of this amide to benzoic acid, formic acid, desoxybenzoin, and ammonia. The structure of the cyclic nitrone (IX) was shown by its reduction, *via* the hydroxypyrrole (XII), to triphenylpyrrole (XIII).

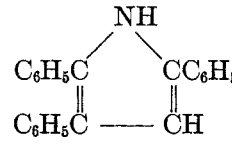
[6] BLATT, *J. Am. Chem. Soc.*, **56**, 2774 (1934); **58**, 590 (1936).



XI



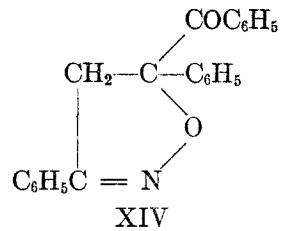
XII



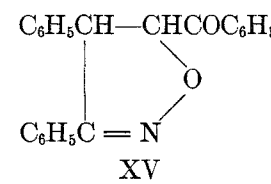
XIII

In none of the reactions of the oxime (V) or the nitrone (IX) was there obtained any evidence for the existence of the open-chain nitrone (VII).

In the experimental portion of this article are found the details of the reaction between *cis*-phenyldibenzoylethylene and hydroxylamine. This reaction was first studied by Olivera-Mandalà and Calderaro[7] who obtained a product melting at 140–141°, which had the composition of a monoxime of the diketone, was inert toward all the reagents which they tried, and which they considered to be an isoxazoline—either (XIV) or (XV). We have never succeeded in isolating this material but this failure is none too surprising, for the reaction between phenyldibenzoylethylene and hydroxylamine, like that between benzalacetophenone and the same reagent,[8] is unusually complex, and in order to secure reproducible results must be carried out under rather carefully specified conditions. Operating as we did the principal product of the reaction was found to be the hydroxyorthoxazine (X).



XIV



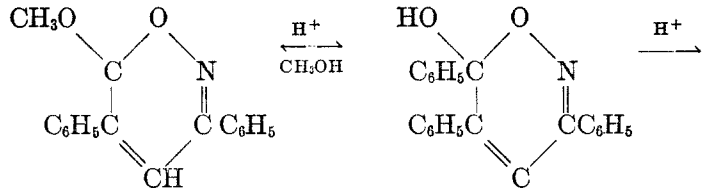
XV

The most striking feature of the chemical behavior of the orthoxazine (X) is its sensitivity to acids. With methyl alcohol and hydrochloric acid

[7] Olivera-Mandalà and Calderaro, *Gazz. chim. ital.*, **44**, II, 85 (1914).

[8] Fleck, Dissertation, Leipzig, **1903**; Auwers and Müller, *J. prakt. Chem.*, **137**, 57 (1933).

it furnishes in a rapid reaction the methyl ether (XVI). In all probability this etherification, like that of so many tertiary alcohols and glycosides, is readily reversible for if contact with the alcoholic acid is at all prolonged a characteristic cleavage to benzonitrile and the dimethyl acetal of phenylbenzoylacetaldehyde (XVII) occurs. The acetal is obviously a secondary product, for acetic acid alone brings about direct cleavage of the hydroxyorthoxazine to benzonitrile and oxymethylene desoxybenzoin, and oxymethylene desoxybenzoin, as has recently been shown,[9] furnishes with hydrochloric acid and methyl alcohol the acetal (XVII). The acid cleavage establishes the carbon chain present in the orthoxazine as well as the location of the nitrogen atom, while the ease of etherification indicates the presence of a tertiary, glycosidic hydroxyl group.



XVI X

$C_6H_5—CN + C_6H_5—COC(C_6H_5)=CHOH$

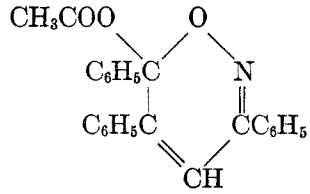
$+$

$C_6H_5—COCH(C_6H_5)CH(OCH_3)_2$

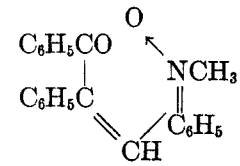
XVII

From the orthoxazine (X) it was not possible to secure either reactions of or derivatives of the open chain oxime (VI) but derivatives of the open-chain nitrone (VIII) could be secured. With acetic anhydride, the orthoxazine furnishes the acetate (XVIII) which is easily converted to the ether (XVI). With benzenesulfonyl chloride there is no reaction, and with phosphorus pentachloride the principal process is cleavage. The orthoxazine, which is insoluble in aqueous alkali, dissolves readily in alcoholates, and these solutions on treatment with methyl iodide yield, together with small amounts of the methoxyorthoxazine (XVI), principally the methyl derivative (XIX) of the open-chain nitrone. The structure of this methylation product follows from its ready hydrolysis by hydrochloric acid to *cis*-phenyldibenzoylethylene and β-methylhydroxylamine hydrochloride.

[9] BLATT, *J. Am. Chem. Soc.*, **60**, 1164 (1938).



XVIII



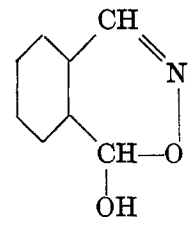
XIX

The information obtained from the study of the monoximes of *cis*-phenyldibenzoylethylene and presented in the preceding paragraphs constitutes, it is believed, the most complete description available up to this time of oxime tautomerism in all its forms. The most interesting result of the study is that it makes possible the assignment of configurations to the nitronic tautomers of oximes and to their derivatives. The basis for assigning these configurations is the following. The configuration of the oxime (V) follows from its behavior on a Beckmann rearrangement assuming a *trans* shift to have taken place. The nitronic tautomer of this oxime could be either (VII) or (VIII). But (VII) is precisely the tautomer which on structural and steric grounds would be expected to be the precursor of the cyclic nitrone (IX) and consequently the configuration (VII) is the one to be assigned to the non-existent open-chain nitronic tautomer of (V). In converse fashion the stereoisomeric oxime (VI) is, on structural and steric grounds, the precursor of the hydroxyorthoxazine (X) and the non-existence of the oxime (VI) is understandable on this basis. The open-chain nitronic tautomer of this oxime has, by exclusion, the configuration (VIII) and such a configuration is consistent with the existence of derivatives of this tautomer. The configurations thus arrived at are, it will be noticed, those which correspond to the respective oximes with which the nitrones are tautomeric and no shifts in the relative positions of the oxygen and nitrogen atoms are involved in the tautomerism. This is only reasonable and to be expected but it is nevertheless satisfying to have substantiating evidence from ring closure. Especially is this true since in the past it has been generally assumed that the alkyl derivatives of the nitronic tautomers of the oximes corresponded in configuration to the oximes from which they were prepared and this correspondence has been used as the basis of one method of assigning configurations to the oximes themselves.[10]

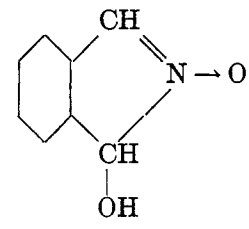
If the conclusions arrived at in the last paragraph with respect to the configurational relationship between an oxime and the tautomeric nitrone are generally valid, then it follows that Griffiths and Ingold[5] in their study of the cyclic tautomers of *o*-phthalaldehyde monoxime, mentioned at the

[10] SUTTON AND TAYLOR, *J. Chem. Soc.*, **1931**, 2190.

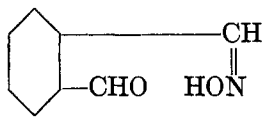
beginning of this article, were dealing with a more complex situation than was realized at the time. For they obtained from *o*-phthalaldehyde and hydroxylamine the two products (XX) and (XXI) which are the cyclic modifications corresponding to the oxime (XXII) and the nitrone (XXIII). These results indicate that both stereoisomeric oximes, (XXII) and (XXIV), are formed in the reaction between the aldehyde and hydroxylamine, and that they undergo cyclicization, the former in the oximino form and the latter in the nitronic form.



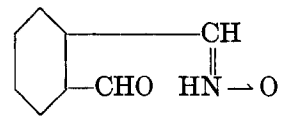
XX



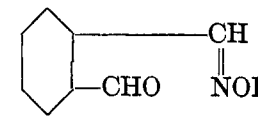
XXI



XXII



XXIII



XXIV

EXPERIMENTAL

The course of the reaction between *cis*-phenyldibenzoylethylene and hydroxylamine varies so widely with the concentrations of the reactants and the operating conditions that, in order to obtain the hydroxyorthoxazine (X), it is essential to adhere closely to the following directions. A solution of 5.6 g. (0.08 mole) of hydroxylamine hydrochloride in 10 cc. of water is chilled and added to a cold solution of 3.2 g. (0.08 mole) of sodium hydroxide in 10 cc. of water. The resulting alkaline solution is added to 12.5 g. (0.04 mole) of *cis*-phenyldibenzoylethylene dissolved in 200 cc. of boiling alcohol. The orange colored reaction mixture is kept gently boiling for an hour during which time an odor of benzonitrile develops and a small precipitate of sodium chloride forms. It is then diluted with 140 cc. of hot water, which dissolves the salt, and allowed to cool slowly.

The precipitate of hydroxyorthoxazine (X) which forms on cooling is filtered and dried.* The crude product, which is obtained in the form of glistening plates, discolored yellow, weighs between 5.3 and 5.8 g. It is crystallized by solution in 50 cc. of hot alcohol, filtration and addition of 15 cc. of hot water to the filtrate.

* The filtrate on standing turns dark and occasionally deposits a colorless solid which is sparingly soluble in alcohol and which, when purified by crystallization from that solvent, melts at 191–192°. This material furnishes on analysis the following figures: C, 80.3; H, 6.0. This composition corresponds roughly to the substance, $C_6H_5COCH(C_6H_5)CH(NH_2)COC_6H_5$ (calc'd for $C_{22}H_{19}NO_2$: C, 80.24; H, 5.8), and the material gives a positive isonitrile test. It was not examined further, however, since it was not regularly obtained.

This furnishes from 5.0 to 5.5 g. of product which melts at 159-160°. Material of this degree of purity is satisfactory for all the reactions of the orthoxazine but it retains a very slight yellow color which can only be removed by repeated crystallization. Removal of the color in this way does not change the melting point.

Anal. Calc'd for $C_{22}H_{17}NO_{12}$: C, 80.7; H, 5.2.
Found: C, 80.8; H, 5.35.

3,5,6-Triphenyl-6-hydroxyorthoxazine (*X*) is moderately soluble in hot alcohol and sufficiently soluble in the cold to make it advisable to add water to its alcoholic solutions on crystallization. It is only sparingly soluble in carbon tetrachloride, ether and petroleum ether and is moderately soluble in methyl alcohol, acetone, benzene and chloroform. It is destroyed by prolonged heating with alcoholic alkali. Benzenesulfonyl chloride in pyridine, cold, is without effect on the orthoxazine but phosphorus pentachloride in ether causes cleavage to benzonitrile. In the pentachloride reaction there is occasionally obtained a small amount of a high-melting solid; the yield is so small, however, and the reaction so erratic that the material was not examined in any detail.

Action of acids on the orthoxazine (*X*).—When 0.3 g. of the hydroxyorthoxazine was dissolved by warming in 1.9 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid, the solution became milky after two to three minutes and solidified when rubbed with a glass rod. Filtration furnished 0.25 g. of the methyl ether (XVI), which melted at 105-107°, and crystallization from methyl alcohol yielded the pure ether melting at 108°.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; OCH_3, 9.1.
Found: C, 81.4; H, 5.4; OCH_3, 9.1.

Throughout the etherification of the orthoxazine as described in the last paragraph there is a persistent odor of benzonitrile. This has its origin in the simultaneous cleavage of the orthoxazine which is brought about by acids and which can be carried out either with the orthoxazine or its methyl ether and in the presence or absence of alcohol. The following experiments are typical.

When 0.3 g. of the hydroxyorthoxazine (X) was dissolved by warming in 2.5 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid and the solution was left overnight, it deposited on chilling 0.2 g. of the dimethylacetal of phenylbenzoylacetaldehyde (XVII) which was identified by comparison with a synthetic sample of the acetal.[9] Similarly, when 3.25 g. of the methoxyorthoxazine (XVI) suspended in 25 cc. of methyl alcohol and 1 cc. of concentrated hydrochloric acid was warmed for a half hour then left overnight, the pale yellow solution on chilling deposited 1.6 g. of the acetal (XVII) which was identified by a mixture melting point determination. The filtrate, after the separation of the acetal, was shaken out with ether and water, then with 10% sodium hydroxide. The ether extract on evaporation left an oil which smelled of benzonitrile and which furnished 1.0 g. of benzamide on hydrolysis with hydrogen peroxide and alkali.[11] Cleavage in the absence of alcohol is illustrated by the following experiments. When the orthoxazine (X) was dissolved by warming in glacial acetic acid, the acid removed by evaporation over potassium hydroxide at room temperature in a desiccator and the residue distilled in vacuum, benzonitrile was identified in the distillate by hydrolysis to benzamide. In a parallel experiment starting with the methoxyorthoxazine (XVI), oxymethylene desoxybenzoin was identified in the distillate by the formation of its copper derivative with copper acetate, by the melting point of a mixture of this copper derivative with a synthetic sample, and by the characteristic wine-red coloration

[11] McMaster and Langreck, *J. Am. Chem. Soc.*, **39**, 114 (1917).

shown by the alcoholic solution of the copper derivative on the addition of ferric chloride.[12]

Acetylation of the orthoxazine (*X*).—When 0.5 g. of the hydroxyorthoxazine was dissolved by warming in 2 cc. of acetic anhydride and the solution, after cooling, was poured into water the acetoxyorthoxazine (XVIII) was formed in quantitative yield. For analysis the product was crystallized from alcohol.

Anal. Calc'd for $C_{24}H_{19}NO_3$: C, 78.0; H, 5.1.
Found: C, 77.9; H, 5.25.

3,5,6-Triphenyl-6-acetoxyorthoxazine (*XVIII*) is sparingly soluble in alcohol and crystallizes splendidly from that solvent in colorless, transparent cubes which melt at 117–118°. The close relationship of this acetate to the hydroxyorthoxazine (X) is shown by its behavior toward alcoholic acid and alkali. When 0.5 g. of the acetate was dissolved by warming for two minutes with 1.9 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid, the odor of methyl acetate was very noticeable. On scratching the warm solution with a glass rod, 0.4 g. of the methoxyorthoxazine (XVI), identified by a mixture melting point determination, precipitated. Similarly when 0.5 cc. of normal sodium hydroxide was added to a solution of 0.18 g. of the acetate in 3 cc. of hot ethyl alcohol, the reaction mixture turned yellow and the odor of ethyl acetate was apparent. After five minutes, dilution with 2.5 cc. of water and chilling furnished 0.1 g. of the hydroxyorthoxazine (X).

Methylation of the orthoxazine (*X*).—When 3.3 g. of the orthoxazine was dissolved in 20 cc. of sodium methylate solution containing 0.46 g. of sodium, a clear yellow solution resulted. Four grams of methyl iodide was added and the reaction mixture was left at room temperature for twenty hours. Cautious addition of a small volume of water precipitated 0.8 g. of the methoxyorthoxazine (XVI). The filtrate, after removal of this precipitate, was taken up in ether and shaken out with water. The ether extract furnished 2.0 g. of the nitrone (XIX)—part of which precipitated in the separatory funnel—and an additional 0.15 g. of the methoxyorthoxazine. The nitrone was crystallized from methyl alcohol and melted at 167°.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6.
Found: C, 80.97; H, 5.7.

The structure of the nitrone (XIX), which showed no methoxyl groups in a Zeisel analysis, was determined by hydrolysis. A solution of 1.1 g. of the nitrone in 5 cc. of methyl alcohol and 0.5 cc. of hydrochloric acid was heated on the steam bath for thirty minutes. Addition of 5 cc. of water precipitated 1 g. of *cis*-phenyldibenzoylethylene, identified by a mixture melting point, and evaporation of the filtrate after removal of this precipitate left a crystalline residue of *β*-methylhydroxylamine hydrochloride which melted at 82–85° and reduced Fehling's solution in the cold.[13]

SUMMARY

When *cis*-phenyldibenzoylethylene reacts with hydroxylamine in acidic or basic solution only the relatively unhindered carbonyl group is involved. From the two stereoisomeric monoximes thus formed, two nitronic tautomers and two cyclic tautomers are theoretically possible. Four of these six tautomers have been described, and it has been shown that each nitrone has the same configuration as the oxime with which it is tautomeric.

[12] WISLICENUS AND RUTHING, *Ann.*, **379**, 242 (1911).
[13] KIRPAL, *Ber.*, **25**, 1715 (1892).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE AND THE STATE UNIVERSITY OF IOWA]

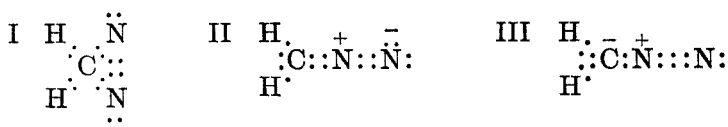
REACTIONS OF DIAZOMETHANES WITH GRIGNARD REAGENTS

GEORGE H. COLEMAN, HENRY GILMAN, C. E. ADAMS, AND P. E. PRATT

Received May 16, 1938

The first recorded preparation of a compound of the diazomethane type was that of diazocamphor. This was prepared by Schiff and Maissen[1], who apparently did not appreciate the significance of the compound. It was not until Curtius[2] prepared diazoacetic ester that the aliphatic diazo compounds were established as a new class.

Both cyclic and linear formulas have been proposed for diazomethane and supported on the basis of the chemical and physical properties of the compound. In discussing the structure of aliphatic diazo compounds Taylor and Baker[3] call special attention to the relatively recent work of Boersche. In a review of the work in this field Boersche[4] considered the following possibilities for the structure of diazomethane:



He concluded that previously there had not been sufficient physical or chemical evidence to decide between the cyclic and linear formulas. He examined the compound by means of electron diffraction analysis and on the basis of his results proposed that diazomethane be regarded as a resonance-hybrid of structures II and III. Hurd[5] in an excellent review and discussion of the structure and chemistry of aliphatic diazo compounds favors three linear formulas, one stable and two reactive. Using

[1] SCHIFF AND MAISSEN, *Gazz. chim. ital.*, **11**, 171 (1881).

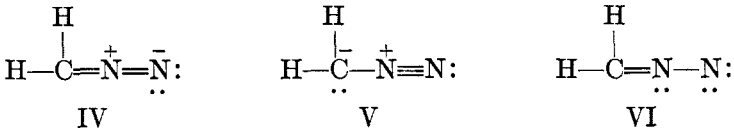
[2] CURTIUS, *Ber.*, **16**, 2230 (1883).

[3] TAYLOR AND BAKER, "Sidgwick's Organic Chemistry of Nitrogen." Oxford University Press, Oxford, **1937**, p. 362.

[4] BOERSCHE, *Monatsh.*, **65**, 331 (1935).

[5] GILMAN, "Organic Chemistry," John Wiley & Sons, Inc., New York, **1938**, Vol. I, p. 645.

the abridged electronic formulas, structure IV is the stable form and the resonance isomers V and VI the reactive forms.

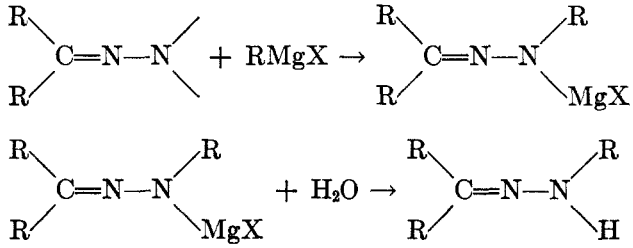


IV V VI

Reactions with acids, alcohols, aldehydes, ketones, etc. may be represented as occurring with structure V and those with Grignard reagents, phosphines and others with structure VI.

The present research was undertaken for the purpose of gaining additional evidence concerning the intermediate compounds formed in the reactions of aliphatic diazo compounds, particularly with Grignard reagents, and of studying the generality of the reactions of diazomethane and substituted diazomethanes with Grignard reagents.

Zerner[6] in his study of the reaction of diazoacetic ester and diazomethane with several Grignard reagents found evidence to indicate that hydrazones were formed. The reaction was represented by the following equations:



The similarity of Zerner's formula for the diazo compound to VI is worthy of note.

The final position of the hydrogen which upon hydrolysis replaced the —MgX group is of little value in interpreting the reaction since a hydrogen atom so easily rearranges. The —MgX group can be replaced[7] by a variety of groups which do not readily rearrange and a part of the work here reported concerns such replacements. While replacement-labeling reactions are generally quite reliable there are some exceptions. Illustrative of this is the recent work of Kohler[8] and co-workers, involving addition of bromomagnesium enolates to the carbonyl linkage. Therefore, particularly when dealing with ionized compounds as in the present case, conclu-

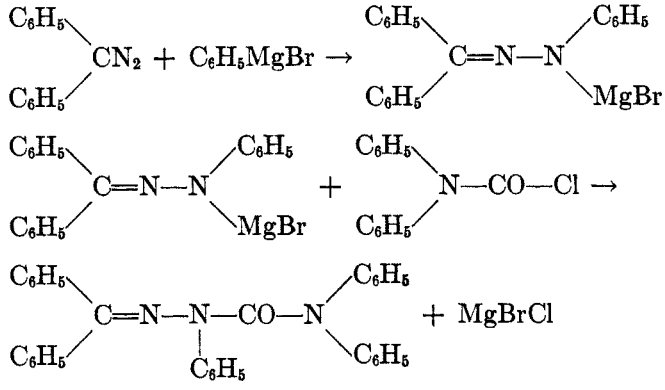
[6] ZERNER, *Monatsh.*, **34**, 1609 (1913).
[7] GILMAN AND SCHULZE, *Rec. trav. chim.*, **47**, 752 (1928).
[8] KOHLER, TISHLER, AND POTTER, *J. Am. Chem. Soc.*, **57**, 2517 (1935).

sions concerning the structures of intermediates established by such replacement-labeling reactions are subject to certain limitations.

The diazo compound selected for this part of the study was diphenyldiazomethane. It was chosen because it contains no other reactive group, no easily rearrangeable hydrogen, also because of the relative ease of preparation, and because it has been used in many studies as a typical aliphatic diazo compound.

Diphenyldiazomethane was treated with an equimolecular amount of phenylmagnesium bromide, and hydrolyzed, benzophenone phenylhydrazone being obtained as was expected from the work of Zerner[6] and Forster and Cardwell.[9]

The reaction was then repeated except that diphenylcarbamyl chloride was added to the reaction mixture of the phenylmagnesium bromide and diphenyldiazomethane before hydrolysis. On hydrolysis in the cold a yellow crystalline compound was formed. It was thought that the reaction might have taken place in the following manner:



If this mechanism is the correct one the intermediate compound, $(C_6H_5)_2C{=}N{-}N(MgBr)C_6H_5$, should be the same as that formed when benzophenone phenylhydrazone is treated with phenylmagnesium bromide. This intermediate compound should give the same final product when treated with diphenylcarbamyl chloride. This was found to be the case; the compounds were identical. The assumption that the compound obtained in both reactions was benzophenone 2,4,4-triphenylsemicarbazone was further supported by hydrolysis to benzophenone and a base corresponding in analysis and melting point to 2,4,4-triphenylsemicarbazide. The benzophenone triphenylsemicarbazone was also synthesized in a slightly different manner. Benzophenone phenylhydrazone was treated

[9] FORSTER AND CARDWELL, *J. Chem. Soc.*, **103**, 861 (1912).

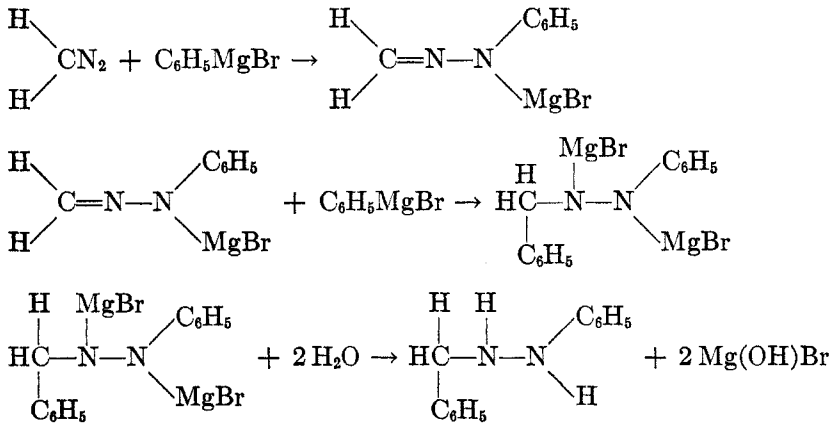
with sodium amide forming the sodium derivative and to this was added diphenylcarbamyl chloride. The product was the same as that formed by the other two methods.

Diphenyldiazomethane was next treated with benzylmagnesium chloride. Benzophenone benzylhydrazone was formed. The reaction was repeated except that diphenylcarbamyl chloride was added to the initial reaction product before hydrolysis. A well defined crystalline compound was obtained, presumably benzophenone 2-benzyl-4,4-diphenylsemicarbazone.

The compound was also synthesized from the known benzophenone 4,4-diphenylsemicarbazone[10] by replacing the active hydrogen by —MgX and treating with benzyl bromide. The melting point of a mixture of the two compounds showed them to be the same. Upon hydrolysis benzophenone and a base corresponding in analysis to 2-benzyl-4,4-diphenylsemicarbazide were formed.

In order to carry out the primary reaction with another typical aliphatic Grignard reagent, methylmagnesium iodide was used. Benzophenone methylhydrazone was the product and was identified by hydrolysis to benzophenone and methylhydrazine.

From the reaction of unsubstituted diazomethane with phenylmagnesium bromide, Zerner[6] isolated benzaldehyde phenylhydrazone which he supposed had been formed by the oxidation of 1-phenyl-2-benzylhydrazine. In the present work when diazomethane was allowed to react with a slight excess of phenylmagnesium bromide it was impossible to isolate any definite compound. However when a large excess of the Grignard reagent was used 1-phenyl-2-benzylhydrazine was formed. The reaction may be represented by the following equations:



[10] TOSCHI AND ANGLIOLANI, *Gazz. chim. ital.*, [1], **45**, 205 (1915); [*C. A.*, **9**, 2388 (1915)].

The hydrazine was identified by oxidation with hydrogen peroxide to benzaldehyde phenylhydrazone.

The reaction of ethylmagnesium bromide with benzaldehyde phenylhydrazone reported by Grammaticakis[11] is of interest in this connection. With benzaldehyde phenylhydrazone, 1-α-phenyl-*n*-propyl-2-phenylhydrazine was formed. With phenylhydrazones of ketones a similar reaction apparently did not occur.

When benzylmagnesium chloride was used with diazomethane under the same conditions as phenylmagnesium bromide, the product was 1-methyl-2-benzylhydrazine rather than the expected 1-benzyl-2-phenethylhydrazine. The 1-methyl-2-benzylhydrazine was identified by reduction to benzylamine and methylamine.

$$H_2C{=}N_2 + C_6H_5CH_2MgCl \rightarrow CH_3NHNHCH_2C_6H_5$$

$$CH_3NHNHCH_2C_6H_5 + H_2 \rightarrow CH_3NH_2 + C_6H_5CH_2NH_2$$

n-Butylmagnesium bromide with diazomethane formed a compound having the general properties and correct analysis for 1-methyl-2-*n*-butylhydrazine. It was not identified by the reduction method.

When diazomethane was treated with ethylmagnesium iodide, methylmagnesium iodide, and methylmagnesium bromide, respectively, decomposition occurred during the reaction and it was not possible to isolate definite compounds from the reaction mixtures.[12]

In the reactions of diazomethane with the benzyl and *n*-butyl Grignard reagents in which hydrazines were formed it is evident that a reaction equivalent to reduction must be involved.

Many studies have been made of the reducing action of Grignard reagents. Of these that by Kharasch and Weinhouse[13] may be mentioned, and the reduction of nitrogen compounds by Gilman[14] and coworkers, by Rheinboldt and Kirberg[15], and by Franzen and Deibel.[16] The reduction of nitrogen compounds by Grignard reagents is particularly significant with respect to the present work.

The only other known case in which a Grignard reagent apparently adds to a terminal atom is with isocyanides. The reaction does not go particu-

[11] GRAMMATICAKIS, *Compt. rend.*, **202**, 1289 (1936); **204**, 502 (1937).

[12] MERLIN J. MAURY (State University of Iowa) has shown that phenyldiazomethane reacts with phenylmagnesium bromide and benzylmagnesium chloride to form benzaldehyde phenylhydrazone and benzaldehyde benzylhydrazone, respectively, in good yields.

[13] KHARASCH AND WEINHOUSE, *J. Org. Chem.*, **1**, 209 (1936).

[14] GILMAN AND COWORKERS, *J. Am. Chem. Soc.*, **47**, 2406 (1925); **48**, 2004 (1926); *Rec. trav. chim.*, **49**, 212 (1930); **50**, 522 (1931); J. ORG. CHEM., **2**, 84 (1937).

[15] RHEINBOLDT AND KIRBERG, *J. prakt. Chem.*, **118**, 1 (1928).

[16] FRANZEN AND DEIBEL, *Ber.*, **38**, 2716 (1905).

larly well. Perhaps the most complete recent account of it was given several years ago.[17]

Attention may be called to an apparent lack of correlation between aliphatic diazo compounds and compounds like ketenes, isocyanates, and isothiocyanates. With these latter classes containing terminal cumulated unsaturated linkages Grignard reagents add to the terminal unsaturated linkage,

$$RN{=}C{=}O + RMgX \rightarrow RN{=}\underset{\displaystyle R}{\overset{\displaystyle |}{C}}{-}O{-}MgX$$

while with aliphatic diazo compounds the addition is apparently to the terminal atom. A reasonable conclusion is that the reactive form of the aliphatic diazo compounds with which Grignard reagents react does not have a terminal cumulated unsaturated linkage.

EXPERIMENTAL

Diphenyldiazomethane.—The method of preparation was a modification of that used by Staudinger.[18] Mechanical stirring instead of shaking during the oxidation of the benzophenone hydrazone was found to be more convenient. Low-boiling (30-40°) petroleum ether was used. The yields obtained were a little lower (75-85%) than those recorded by Staudinger (85-98%) but the reaction time was shorter. With shaking, the time for complete oxidation was six to nine hours. With efficient stirring three to four hours was found to be sufficient.

Grignard reagents.—A standard solution of phenylmagnesium bromide (about 2 moles per liter) was prepared,[19] and the desired amount was pipetted out for each experiment. This was found to be as accurate as individual preparations of phenylmagnesium bromide for each experiment, provided the bottle was kept tightly stoppered when not in use. The other Grignard reagents described were prepared just previous to their use.

The Grignard reagents were added slowly with stirring to ethereal solutions of diphenyldiazomethane by means of a dropping funnel. The reaction flask was kept at 0° to −5° to avoid decomposition of the diazo compound due to the heat of reaction.

Phenylmagnesium bromide with diphenyldiazomethane.—Twenty-eight grams (.14 mole) of diphenyldiazomethane was treated with 25.5 g. (.14 mole) of phenylmagnesium bromide. After addition of the Grignard reagent, the stirring was continued for one-half hour, and the reaction mixture was then hydrolyzed with ammoniacal ammonium chloride solution. A yellow crystalline solid insoluble in ether and water was formed. This was filtered off, dried, and weighed. It melted at 134-136°,* and a mixture with benzophenone phenylhydrazone showed no depression in melting point.

The ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated until nearly all of the ether was driven off. On cooling more benzo-

[17] GILMAN AND HECKERT, *Bull. soc. chim.*, **43**, 224 (1928).

[18] STAUDINGER, ANTHES, AND PFENNINGER, *Ber.*, **49**, 1928 (1916).

[19] GILMAN AND MEYERS, *Ind. Eng. Chem.*, **15**, 61 (1923); GILMAN, WILKINSON, FISHEL, AND MEYERS, *J. Am. Chem. Soc.*, **45**, 150 (1923).

* All melting points are uncorrected.

phenone phenylhydrazone separated. The mother liquor was not further investigated. The total yield of benzophenone phenylhydrazone was 27 g. (70%).

Diphenylcarbamyl chloride with the addition product of diphenyldiazomethane and phenylmagnesium bromide.—Thirteen grams (.07 mole) of diphenyldiazomethane in 50 cc. of dry ether was treated with 12 g. (.07 mole) of phenylmagnesium bromide. Stirring was continued for one-half hour after addition, and then 16 g. (.07 mole) of diphenylcarbamyl chloride in 75 cc. of ether was slowly added. The reaction mixture was allowed to stand at room temperature for two hours, and was then hydrolyzed with dilute hydrochloric acid in the cold. A yellow solid, benzophenone 2,4,4-triphenylsemicarbazone, precipitated. It was filtered, dried and weighed; weight 13 g. After two recrystallizations from alcohol the compound melted at 160–161°.

Anal. Calc'd for $C_{32}H_{25}N_3O$: N, 8.99. Found: N, 9.40.

Benzophenone 2,4,4-triphenylsemicarbazone from benzophenone phenylhydrazone.—To 5 g. (.018 mole) of benzophenone phenylhydrazone in ether was added 3.4 g. (.018 mole) of phenylmagnesium bromide to replace the hydrogen by the —MgBr group. To this was added an ether solution of 4.2 g. (.018 mole) of diphenylcarbamyl chloride. The reaction mixture was hydrolyzed with dilute hydrochloric acid, leaving a light yellow precipitate which on recrystallization from alcohol melted at 160°, and by the melting point of a mixture proved to be identical with the benzophenone 2,4,4-triphenylsemicarbazone obtained in the previous experiment. The yield was 4 g. (47%).

Benzophenone 2,4,4-triphenylsemicarbazone from the sodium derivative of benzophenone phenylhydrazone.—Fifteen grams (.055 mole) of benzophenone phenylhydrazone and 3 g. (.07 mole) of sodium amide were intimately mixed by grinding quickly in a mortar. The mixture was transferred to a distilling flask and heated gently in a stream of dry hydrogen. On cooling, the sodiumbenzophenone phenylhydrazone solidified. The flask was broken under dry ether in a mortar; the contents were ground up quickly, and transferred to a three-necked flask with about 140 cc. of ether. To this mixture under vigorous stirring, was added 15 g. (.064 mole) of diphenylcarbamyl chloride in small portions. The reaction mixture was stirred for one-half hour after the addition was completed, and then 100 cc. of water added to dissolve the sodium chloride. The yellow solid which had formed was filtered off and recrystallized from alcohol; weight 8 g. The melting point was 156–158°, and the melting point of a mixture with the benzophenone 2,4,4-triphenylsemicarbazone obtained in the two previous experiments showed it to be the same compound. Two grams more of the compound was obtained from the ether layer. The total yield was 10 g. (39%).

Hydrolysis of benzophenone 2,4,4-triphenylsemicarbazone.—Two and five-tenths grams (.005 mole) of benzophenone triphenylsemicarbazone was refluxed with stirring in 85 g. of 20% hydrochloric acid for one-half hour. The solution was cooled, extracted with ether, and the dried ether layer was evaporated to an oil on a steam bath. When seeded with a crystal of benzophenone it solidified to a crystalline mass, which was shown to be benzophenone by comparison with an authentic sample; weight 0.8 g. (88%).

The acid water layer was made alkaline with sodium hydroxide, and extracted with ether; the dried ether layer was evaporated and 10 cc. of alcohol was added. On cooling, the white crystalline 2,4,4-triphenylsemicarbazide separated. The crystals after washing three times with small portions of alcohol melted at 124–125°. Rupe[20] records 128° as the melting point of 2,4,4-triphenylsemicarbazide.

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[20] RUPE, *Ber.*, **33**, 247 (1900).

Anal. Calc'd for $C_{19}H_{17}N_3O$: N, 13.86. Found: N, 14.27.

Diphenyldiazomethane with benzylmagnesium chloride.—Sixteen grams (.082 mole) of diphenyldiazomethane was treated in the usual way with a slight excess of benzylmagnesium chloride and the reaction mixture hydrolyzed. The crude product weighed 18.2 g. After recrystallization from alcohol it melted at 80.8-81.2°.

Diphenylcarbamyl chloride on the addition product of benzylmagnesium chloride and diphenyldiazomethane.—Eight grams (.041 mole) of diphenyldiazomethane was treated with 6.4 g. (.042 mole) of benzylmagnesium chloride. To the reaction mixture was added 8.8 g. (.04 mole) of diphenylcarbamyl chloride. The reaction mixture was hydrolyzed with ammonium chloride solution, and the yellow benzophenone 2-benzyl-4,4-diphenylsemicarbazone filtered off, dried, and weighed; weight 8 g. The melting point was 118-125°. After two recrystallizations from alcohol it melted at 137-139°.

Anal. Calc'd for $C_{33}H_{27}N_3O$: N, 8.75. Found: N, 9.07.

Benzophenone 2-benzyl-4,4-diphenylsemicarbazone from benzophenone 4,4-diphenylsemicarbazone.—Four grams (.01 mole) of benzophenone 4,4-diphenylsemicarbazone, prepared according to the method given by Toschi and Angliolani[10] was treated with 3.4 g. (.018 mole) of phenylmagnesium bromide in 25 cc. of dry ether to replace the active hydrogen with $-MgBr$. To the resulting reaction mixture was added 6 g. (.047 mole) of benzyl chloride and 25 cc. of dry benzene. The ether was then distilled off. The solution was refluxed for one hour, cooled, and hydrolyzed with dilute hydrochloric acid. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to a small volume. Absolute alcohol was added, and the solution was evaporated again to remove the remaining benzene. On standing in the cold a small crop of crystals formed; m.p. 125-130°. After two recrystallizations from alcohol they melted at 136-137°. The melting point of a mixture with the benzophenone 2-benzyl-4,4-diphenylsemicarbazone obtained in the preceding experiment showed them to be identical. The yield was 0.5 g. (10%).

Hydrolysis of benzophenone 2-benzyl-4,4-diphenylsemicarbazone.—Five grams (.01 mole) of benzophenone 2-benzyl-4,4-diphenylsemicarbazone was refluxed for one hour with 80 g. of 20% hydrochloric acid. The cold solution was extracted with ether, and the washed and dried ether solution was evaporated to an oil, which on standing solidified to crystalline benzophenone. The acid water layer was made alkaline and extracted with ether. The washed and dried ether solution was evaporated until nearly all of the ether had been driven off; 10 cc. of alcohol was added and the solution cooled. The crystals which formed melted at 109-110° after being washed twice with small portions of alcohol. The yield was 1.5 g. (50%). The compound is slightly soluble in ether and cold alcohol, and more soluble in hot alcohol.

Anal. Calc'd for $C_{20}H_{19}N_3O$: N, 13.7. Found: N, 14.00.

Diphenyldiazomethane with methylmagnesium iodide.—Using 13.2 g. of diphenyldiazomethane and a slight excess of methylmagnesium iodide, the reaction was carried out and the product isolated as previously described for the reaction with benzylmagnesium chloride. The crude product weighed 12 g. After recrystallization from alcohol it melted at 42-43° in a capillary tube. On a copper bar the melting point was 46-47°. The product was hydrolyzed by refluxing for ten hours with dilute sulfuric acid (6*N*). Benzophenone and methylhydrazine sulfate were obtained. After recrystallization both were identified by melting points.

Diazomethane.—This compound was prepared by the method of Arndt.[21]

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[21] *Organic Syntheses*, John Wiley & Sons, N. Y., **1935**, Vol. 15, p. 3.

Diazomethane with phenylmagnesium bromide.—To a solution of phenylmagnesium bromide containing approximately 0.20 mole was added dropwise with stirring 0.05 mole of diazomethane dissolved in anhydrous ether. The reaction was carried out in an atmosphere of nitrogen and at room temperature or a few degrees below. The mixture was stirred for several hours and then hydrolyzed with ammonium chloride solution. The ethereal layer was dried and a solution of hydrogen chloride in anhydrous ether added until precipitation was complete. The weight of the hydrochloride was 5.6 gr. (48% yield). It was purified by preparing the free base in ether and again adding ethereal hydrochloric acid.

Anal. Calc'd for $C_{13}H_{15}ClN_2$: Cl, 15.38. Found: Cl, 15.30.

The oxalate was prepared by adding an alcoholic solution of oxalic acid to an ethereal solution of the free base. The melting point of the oxalate was 187–188°. The melting point of the oxalate of 1-phenyl-2-benzylhydrazine recorded in the literature is 190°. The compound was further identified by oxidation to benzaldehyde phenylhydrazone with hydrogen peroxide according to the method of Thiele.[22] The product was identified by comparison with an authentic sample of benzaldehyde phenylhydrazone.

Diazomethane with benzylmagnesium chloride.—Using 0.05 mole of diazomethane the reaction was carried out as described with phenylmagnesium bromide. The 1-methyl-2-benzylhydrazine hydrochloride weighed 3.5 g. (41% yield). It melted at 139–140°.

Anal. Calc'd for $C_8H_{13}ClN_2$: Cl, 20.6. Found: Cl, 20.3.

The product was reduced to benzylamine and methylamine by sodium amalgam by the method of Schlenk.[23] The amines were separated by fractional distillation of an ethereal solution and converted to the substituted benzamides which were identified by comparison with authentic samples.

Diazomethane with n-*butylmagnesium bromide.*—The usual procedure was followed except that the temperature of reaction was about 5°. From 5.1 g. of diazomethane, 9 g. of the hydrochloride of methyl-2-*n*-butylhydrazine was obtained (53% yield). The melting point was 114–115°.

Anal. Calc'd for $C_5H_{15}ClN_2$: Cl, 25.6. Found: Cl, 25.4.

Diazomethane with ethylmagnesium iodide, methylmagnesium iodide, and methylmagnesium bromide.—Reactions were carried out with the three reagents in the usual way. However, in each case as the diazomethane came in contact with the Grignard reagent there was an evolution of gas. No hydrazine hydrochloride was isolated.

SUMMARY

1. Evidence is presented concerning the apparent structure of the intermediate compounds formed in the addition of Grignard reagents to diphenyldiazomethane.

2. Diazomethane reacts with phenylmagnesium bromide to form 1-phenyl-2-benzylhydrazine, with benzylmagnesium chloride to form 1-methyl-2-benzylhydrazine, and with *n*-butylmagnesium bromide to form 1-methyl-2-*n*-butylhydrazine.

[22] THIELE, *Ann.*, **376**, 267 (1910).

[23] SCHLENK, *J. prakt. Chem.*, **78**, 52 (1908).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

DIBENZOTHIOPHENE: ORIENTATION AND DERIVATIVES

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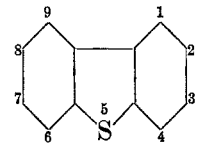
Received May 17, 1938

INTRODUCTION

The extensive studies by Courtot and by Cullinane have shown that halogenation[1], nitration,[2] and sulfonation[3] involve the 2 position in dibenzothiophene.



This corresponds with related nuclear substitution reactions in the oxygen analog, dibenzofuran. However, nitration of dibenzofuran yields the 2- and the 3-nitro compounds, the latter greatly predominating. Disubstitution in dibenzothiophene proceeds symmetrically to give 2,8 derivatives like 2,8-dibromodibenzothiophene and 2-bromo-8-nitrodibenzothiophene.

Two other important nuclear substitution reactions are the Friedel-Crafts reaction and metalation. We have shown that acylation by the Friedel-Crafts reaction also involves the 2 position, as is the case with dibenzofuran.

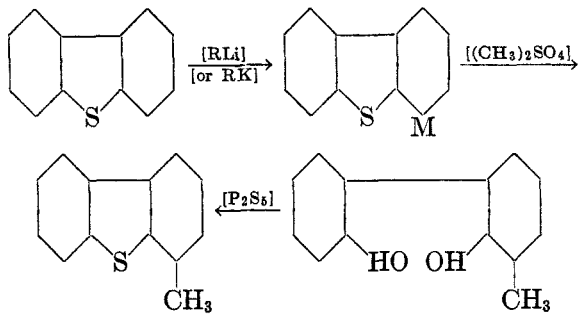
Metalation.—An examination of polynuclear heterocyclic compounds previously metalated, reveals that metalation of such types is unique in the sense that it makes possible the direct introduction of nuclear substituents into positions not otherwise available by direct substitution.[4] Metalation of dibenzothiophene by RLi or RK compounds involves the 4 position, which again finds its counterpart in the dibenzofuran series. The structure of the new organolithium and -potassium compounds was established by the following sequence of reactions.

[1] COURTOT, NICOLAS, AND LIANG, *Compt. rend.*, **186**, 1624 (1928).

[2] COURTOT AND POMONIS, *ibid.*, **182**, 931 (1926); CULLINANE, DAVIES, AND DAVIES, *J. Chem. Soc.*, **1936**, 1435.

[3] COURTOT AND KELNER, *Compt. rend.*, **198**, 2003 (1934).

[4] See some leading references in the following paper.



The yields of 4-dibenzothienyllithium, or the corresponding dibenzothiophene-4-carboxylic acid obtained by carbonation, vary in a striking manner with the nature of the R group in the RLi compounds used as metalating agents.

METALATING AGENT	% YIELD OF 4-ACID
n-Butyllithium	55
Phenyllithium	12
α-Naphthyllithium	7.6
p-Anisyllithium	0

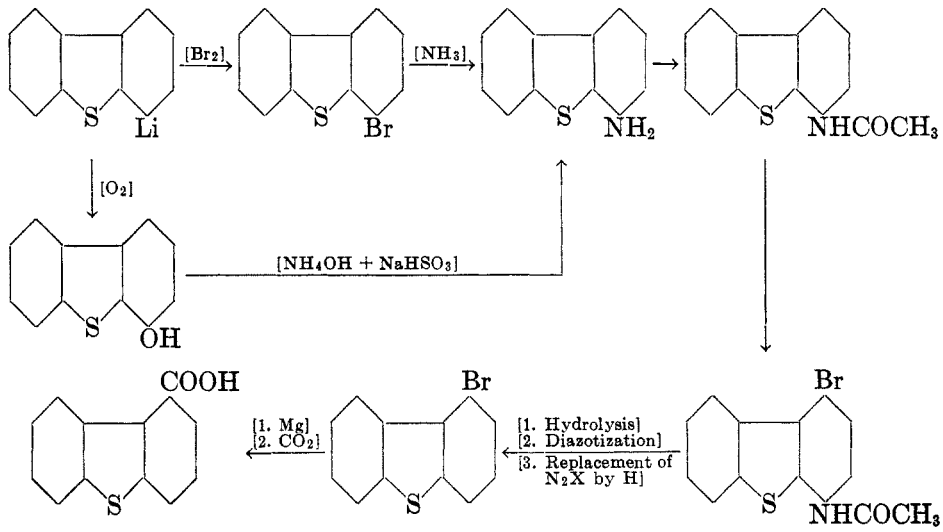
This series follows that obtained by Kharasch and co-workers[5] in the cleavage of unsymmetrical organomercurials. However, the results obtained with *p*-anisyllithium may be anomolous, for the acid obtained subsequent to carbonation was shown to be largely 2-methoxy-5-bromobenzoic acid and only a small quantity of *p*-anisic acid was isolated.[6] Apparently the *p*-anisyllithium metalates the unreacted *p*-bromoanisole used in its preparation. Metalation of dibenzothiophene by phenyl-calcium iodide involves the 3 position. This is quite unlike the case of dibenzofuran which undergoes metalation in the 4 position by all metalating agents so far examined. Details on the metalation by phenylcalcium iodide are contained in the following paper.

1-Substituted dibenzothiophenes.—There is no method for the direct introduction of substituents into the 1 position. However, 1-substituted dibenzothiophenes were made available by the sequence of reactions shown on page 110.

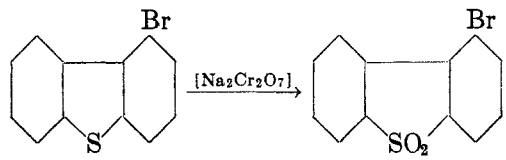
The constitution of the dibenzothiophenecarboxylic acid obtained in this manner was established by showing the acid to be unlike dibenzothiophene-3-carboxylic acid,[7] the only possible alternative acid inasmuch as the struc-

[5] KHARASCH AND FLENNER, *J. Am. Chem. Soc.*, **54**, 674 (1932).
[6] Studies by W. H. LANGHAM.
[7] See following paper.

tures of the 2- and the 4-carboxylic acids were unequivocally established. Dibenzothiophene-2-carboxylic acid was prepared previously[8] by carbonation of the Grignard reagent obtained from authentic 2-bromodibenzothiophene.



Also, the structure of the 1-bromodibenzothiophene was proved by oxidizing it to a bromodibenzothiophene-5-dioxide which was shown to be unlike the 2- and 3-bromodibenzothiophene-5-dioxides.



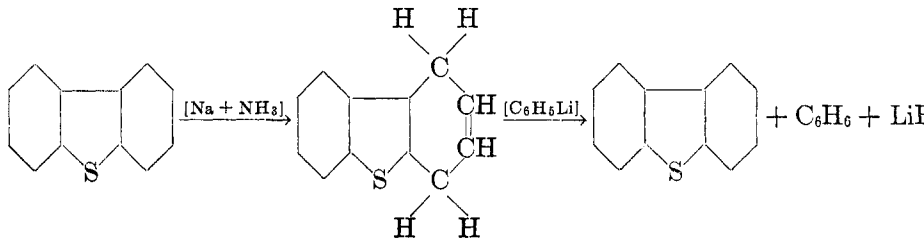
Dihydrodibenzothiophene.—Reduction of dibenzothiophene by sodium in liquid ammonia gives a dihydro compound which probably is 1,4-dihydrodibenzothiophene, by analogy to the behavior of dibenzofuran[9] and naphthalene. The dihydro compound adds one molecule of bromine to give a dihydro-dibromide which loses hydrogen bromide to yield dibenzothiophene.

Of greater interest is the conversion of the dihydro compound to dibenzothiophene by means of organometallic compounds. When the dihydro-

[8] COURTOT, NICOLAS, AND LIANG, *Compt. rend.*, **186**, 1624 (1928), and private communication from Professor Courtot.

[9] STUDIES BY C. W. BRADLEY.

dibenzothiophene is treated with phenyllithium under conditions identical with those employed in metalations, a very smooth dehydrogenation occurs to yield dibenzothiophene, benzene, and lithium hydride.



The same dehydrogenation occurs with other highly reactive organometallic compounds such as RNa and RK types.

EXPERIMENTAL

Dibenzothiophene.—Dibenzothiophene was prepared in essential accordance with a method outlined in the patent literature.[10] In a typical experiment, 500 g. of technical biphenyl and 208 g. of sulfur were melted together in a 5-l. round-bottomed flask, immersed in an oil bath. While the temperature of the bath was maintained at 115–120°, 25 g. of powdered, anhydrous aluminum chloride was added over a period of one and one-fourth hours. The temperature was kept at the 115–120° range until the end of the third hour and then gradually allowed to rise, reaching 240° at the end of the eighth or ninth hour. When cool, the mass in the reaction flask was extracted three times by boiling gently with 500 cc. of water, cooling, and decanting the water. Then eight alcohol extractions were made, boiling each time with a liter of alcohol and decanting hot. The combined extracts were digested with Norite and filtered immediately through a hot Büchner funnel. Upon cooling, almost colorless needles separated from the filtrate. Concentration of the liquors yielded additional dibenzothiophene. The crude compound usually melts as high as 98° and is suitable for many purposes. The yield is 65–70%. Distillation under reduced pressure (b.p., 152–154°/3 mm.) followed by crystallization from alcohol gives beautiful colorless needles melting at 99°. The highly purified compound prepared by distillation and recrystallization from alcohol gives maximum yields of metalation products and is strongly recommended for this type of nuclear substitution. The less pure compound was found satisfactory for other reactions.

The picrate, prepared in hot ethanol solution, crystallizes from ethanol as yellow needles melting at 125°.

Cullinane and Davies[11] reported recently the reduction of dibenzothiophene-5-dioxide to dibenzothiophene by means of sulfur. We were independently led to the same reaction by the observation of Courtot and Motamedi[12] that heating a mixture of selenium and diphenylene sulfone gave dibenzoselenophene. In a 25-cc.

[10] Tschunkur and Himmer, *D. R. P.* 579,917 (1933), [*C. A.*, **28**, 1053 (1934)].

[11] Cullinane and Davies, *Rec. trav chim*, **55**, 881 (1936).

[12] Courtot and Motamedi, *Compt. rend.*, **199**, 531 (1934). Also, private communication from Professor Courtot.

Claisen flask was placed 5 g. (0.023 mole) of dibenzothiophene-5-dioxide and 0.9 g. (0.028 g. atom) of sulfur. A thermometer was dipped into the reaction mixture, and the flask was heated in a metal bath. The molten mass was heated at 320° for two and one-half hours, during which time sulfur dioxide and hydrogen sulfide were evolved. The temperature was then raised to 340° for an additional one-half hour, causing gentle boiling, and then heating was increased until 2.3 g. of distillate was collected. This crude product (m.p., 94–95°) was recrystallized and yielded 54% of dibenzothiophene.

2-Acetyldibenzothiophene.—A Friedel-Crafts reaction was carried out with 30 g. (0.16 mole) of dibenzothiophene, 225 cc. of dry carbon disulfide, 60 g. of powdered aluminum chloride and 13 g. (0.16 mole) of acetyl chloride to give a 70% yield of ketone, which when recrystallized from alcohol, melted at 111°.

Anal. Calc'd for $C_{14}H_{10}OS$: S, 14.2. Found: S, 14.1.

The oxime was prepared in almost quantitative yield by the procedure of Bachmann and Boatner,[13] and melted at 160–161° after recrystallization from alcohol.

Anal. Calc'd for $C_{14}H_{11}NOS$: N, 5.81. Found: N, 5.55, 5.59.

2-Acetyldibenzothiophene was oxidized to dibenzothiophene-2-carboxylic acid by the method of Fuson and Tullock[14] using iodine-potassium iodide and sodium hydroxide in dioxane as a medium. The acid (m.p., 253°) was converted to the methyl ester (m.p., 75°) by means of diazomethane, and identification was completed by comparison with an authentic specimen of the ester.

Methyl dibenzothiophene-2-carboxylate.—In the purification of 2-bromodibenzothiophene there is a significant loss by recrystallization. However, the less pure material, obtainable in 70% or greater yields, is satisfactory for reactions such as amination.

An activated magnesium was found desirable, but not necessary, for obtaining satisfactory yields of the corresponding Grignard reagent in reasonable time. Carbonation of the latter yields the 2-acid.

Methyl dibenzothiophene-2-carboxylate, prepared from the acid and diazomethane, melted at 74–75° after recrystallization from methanol.

Anal. Calc'd for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.5.

Dibenzothiophene-4-carboxylic acid by metalation.—Ten grams (0.054 mole) of dibenzothiophene in 75 cc. of ether was metalated by treatment with 0.1 mole of *n*-butyllithium in 75 cc. of ether. The reaction mixture was refluxed gently for 13 hours and then carbonated by pouring upon solid carbon dioxide. After removal of the excess carbon dioxide, the mixture was extracted with water, and the water layer was acidified with hydrochloric acid. Recrystallization from methanol gave a colorless acid melting at 252–253°.

Anal. Calc'd for $C_{13}H_8O_2S$: Neutral. equiv., 228.1; C, 68.38; H, 3.54; S. 14.1.
Found: Neutral. equiv., 237; C, 68.18; H, 3.80; S, 14.0.

The yield of acid is greatly diminished if the dibenzothiophene is not purified by distillation. When phenyllithium is used as the metalating agent the yield of acid is almost insignificant if the highly purified dibenzothiophene be not used. In the α-naphthyllithium metalation the α-naphthoic acid obtained subsequent to carbonation is readily removed from the dibenzothiophene-4-carboxylic acid by extraction with hot water.

Decarboxylation of dibenzothiophene-4-carboxylic acid.—About 0.1–0.2 g. of the acid was mixed with an equal quantity of copper powder and 2–3 cc. of quinoline

[13] BACHMANN AND BOATNER, *J. Am. Chem. Soc.*, **58**, 2099 (1936).
[14] FUSON AND TULLOCK, *ibid.*, **56**, 1638 (1934).

and heated in a test-tube immersed in a metal bath, in accordance with the usual procedure of Johnson. Gas evolution was apparent at 120°, and the bath was kept at 200° for one hour. Steam distillation from a solution acidified with sulfuric acid gave dibenzothiophene.

Methyl dibenzothiophene-4-carboxylate.—The methyl ester, prepared by means of diazomethane, melted at 95° after recrystallization from methanol.

Anal. Calc'd for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.1.

4-Methyldibenzothiophene.—*A.* By metalation. The dibenzothienyl-4-lithium was prepared in the usual manner by means of *n*-butyllithium and treated with an ether solution of dimethyl sulfate at room temperature until there was a negative color test. The reaction mixture was worked up in a customary manner to give the 4-methyldibenzothiophene which melted at 65° after recrystallization from dilute methanol.

Anal. Calc'd for $C_{13}H_{12}S$: S, 16.0. Found: S, 16.1.

B. By ring closure. In a small Claisen flask was placed a mixture of 2 g. of 3-methyl-2,2′-dihydroxybiphenyl and 1 g. of phosphorus pentasulfide. The flask was heated in a metal bath, the temperature being raised gradually from 165° (at which evolution of hydrogen sulfide set in) to 400° in 45 minutes, after which the heating was increased until a small quantity of colorless liquid distilled. The liquid solidified, and the solid was recrystallized from methanol to give small needles melting at 66.5°. A mixture with the methyl compound obtained by metalation (m.p., 65°) melted at 65.5°.

4-Hydroxydibenzothiophene.—A mixture of 0.5 mole of dibenzothienyl-4-lithium and 0.5 mole of ethylmagnesium chloride in ether was treated with oxygen (Ivanoff's procedure[15]). The temperature was kept below 3° by regulating the intake of oxygen, and a negative color test after 5 hours showed the reaction to be complete. Alkaline extraction and then acidification gave a 33% yield of the phenol, melting at 157–159°. Recrystallization from dilute methanol gave fine, colorless needles melting at 167°. The phenol gives a green color with ferric chloride solution.

Anal. Calc'd for $C_{12}H_8OS$: S, 16.0. Found: S, 15.9.

Dinitro-4-hydroxydibenzothiophene.—A 77% yield of the dinitro phenol was obtained by nitrating 0.5 g. of 4-hydroxydibenzothiophene in glacial acetic acid by concentrated nitric acid. The dark-orange, crystalline powder melted with decomposition at 204°. Recrystallization from glacial acetic acid did not raise the melting point.

Anal. Calc'd for $C_{12}H_6N_2O_6S$: N, 9.65. Found: N, 9.45.

4-Methoxydibenzothiophene.—A 94% yield of the 4-methoxy compound was obtained by reaction of 4-hydroxydibenzothiophene, dimethyl sulfate and sodium hydroxide. Recrystallization from alcohol gave heavy, colorless crystals melting at 123°.

Anal. Calc'd for $C_{13}H_{10}SO$: S, 15.0. Found: S, 14.9.

4-Aminodibenzothiophene.—*A.* By the Bucherer reaction. In accordance with a procedure by Fieser and co-workers[16], 1.5 g. of 4-hydroxydibenzothiophene, 7.5 g. of sodium bisulfite, 15 cc. of water, 15 cc. of concentrated aqueous ammonia, and 7.5 cc. of dioxane were sealed in a Carius tube and heated for 11 hours at 200–210°. Upon opening the tube no pressure was noted and there was no darkening of the contents. The mixture was transferred to a separatory funnel with a little more than an equal volume of water, and the whole was extracted with ether. The ether

[15] IVANOFF, *Bull. soc. chim.*, **39**, 47 (1926).

[16] FIESER AND CO-WORKERS, *J. Am. Chem. Soc.*, **59**, 478 (1937).

extracts were dried over solid sodium hydroxide, and from the ether was then precipitated by dry hydrogen chloride, 0.4 g. (25% yield) of amine hydrochloride. After one recrystallization of the hydrochloride the free base was obtained by treatment with ammonia. The melting point, 110°, was not raised by recrystallization from methanol.

Anal. Calc'd for $C_{12}H_9NS$: N, 7.04. Found: N, 7.02.

B. By amination of 4-bromodibenzofuran. Ninety-two grams (0.5 mole) of dibenzothiophene was metalated by *n*-butyllithium. The mixture was then cooled in an icebath while nitrogen containing bromine vapor was passed slowly over the stirred surface. The nitrogen was first passed through a wash-bottle containing about 80 g. of bromine, and a slight pressure was maintained on the system by allowing the excess nitrogen to escape through the condenser against a 10 mm. head of mercury. In two and one-half hours the reaction was complete, as indicated by a negative color test. Excess bromine was removed by a bisulfite wash, and the ether solution was freed of solvent by distillation. The crude product, weighing 90 g., was directly aminated in portions as described below.

Into a steel bomb of 500 cc. capacity was introduced 25 g. of crude 4-bromodibenzothiophene, 20 g. of freshly prepared cuprous bromide, and 500 cc. of concentrated aqueous ammonia. The bomb was heated for 10-11 hours at 210-220°. When cool, the contents were transferred to a separatory funnel and extracted with ether. The washed and dried ether extract gave 8.3 g. of amine hydrochloride when saturated with dry hydrogen chloride. This crude salt represented a 37% yield on the basis that the starting material was pure 4-bromodibenzothiophene. The free base was obtained by treatment with aqueous ammonia, and purification was effected by treating a hot methanol solution with Norite and a pinch of sodium hydrosulfite (to prevent darkening by oxidation). The methanol solution was filtered hot, and diluted with hot water just to the point of turbidity. Slow cooling gave the pure amine.

4-Acetamidodibenzothiophene.—A practically quantitative yield of 4-acetamidodibenzothiophene was obtained by allowing a solution of the amino compound and acetic anhydride in benzene to stand overnight. On recrystallization from benzene the compound melted at 198°.

Anal. Calc'd for $C_{14}H_{11}NOS$: N, 5.82. Found: N, 5.93.

1-Bromo-4-acetamidodibenzothiophene.—Five grams (0.021 mole) of 4-acetamidodibenzothiophene was dissolved in 175 cc. of glacial acetic acid and treated with 22 cc. of a 0.1 molar solution of bromine in acetic acid. The addition required 30 minutes, and the solution was then stirred an additional hour before pouring into 800 cc. of water to which a little sodium bisulfite had been added. The yield was 86%, and the melting point after recrystallization from acetic acid was 254°.

Anal. Calc'd for $C_{14}H_{10}BrNOS$: N, 4.38. Found: N, 4.28.

1-Bromo-4-Aminodibenzothiophene.—Six grams of the acetamido compound was hydrolyzed by refluxing in a mixture of 450 cc. of absolute alcohol and 150 cc. of concentrated hydrochloric acid for 6.5 hours. The yield of free base, obtained from the salt by treatment with aqueous ammonia, was 5.5 g. On recrystallization from alcohol the amine melted at 156°.

Anal. Calc'd for $C_{12}H_8BrNS$: N, 5.04. Found: N, 5.01.

1-Bromodibenzothiophene.—The procedure used for deamination was essentially that of Cullinane[17]. To a solution of 2.25 g. of 1-bromo-4-aminodibenzothiophene in 63 cc. of alcohol was added cautiously a mixture of 13 cc. of oleum (20% sulfur

[17] CULLINANE, *J. Chem. Soc.*, **1932**, 2367.

trioxide) and 10 cc. of water. While the resulting solution was kept at 80°, 6 g. of sodium nitrite was added slowly. The reaction was then completed by refluxing for 30 minutes. Dilution of the reaction mixture with water, and cooling, gave a red solid which was filtered out, extracted with hot dilute sodium hydroxide and then with boiling alcohol, a small amount of Norite being added. From the hot, filtered alcoholic extract, after careful dilution with water and cooling, was isolated a 47% yield of 1-bromodibenzothiophene melting at 84° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{12}H_7BrS$: S, 12.2. Found: S, 11.7, 11.8.

1-Bromodibenzothiophene-5-dioxide.—To a cool solution of 7 cc. glacial acetic acid, 3 drops of concentrated sulfuric acid, 2 drops of water and 0.05 g. of sodium dichromate, was added 0.035 g. of 1-bromodibenzothiophene. On working up the oxidation product in the usual manner, there was isolated 0.024 g. (61% yield) of the dioxide, which melted at 170-171° after recrystallization from ethanol.

Anal. Calc'd for $C_{12}H_7BrO_2S$: S, 10.84. Found: S, 10.73.

Dibenzothiophene-1-carboxylic acid.—The Grignard reagent was prepared in the customary manner from 1-bromodibenzothiophene, using an activated magnesium, and then carbonated to give the acid which melted at 176–177° after recrystallization from methanol.

Anal. Calc'd for $C_{13}H_8OS$: Neutral. equiv., 228; S, 14.05.
Found: Neutral. equiv., 229; S, 13.9.

One-tenth gram of the acid was decarboxylated in the usual manner to give dibenzothiophene.

Methyl dibenzothiophene-1-carboxylate, prepared from the acid and diazomethane, melted at 72-72.5° after recrystallization from methanol. Because the melting point of this methyl ester is close to that of the methyl ester of the 2-acid (75°), a mixture melting point determination was made, and a marked depression was noted.

Anal. Calc'd for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.2.

Mercuration of dibenzothiophene.—Two attempts to mercurate dibenzothiophene by refluxing an alcoholic solution of dibenzothiophene and mercuric acetate gave no mercurial. Mercurous acetate was formed to some extent, and a large proportion of the original dibenzothiophene was recovered unchanged.

Mercuration was effected when the calculated quantity of mercuric acetate was slowly added to a melt of dibenzothiophene at 140-145°. Unfortunately, the product was much more difficult to purify than the products of mercuration of dibenzofuran. A milky suspension, which changed to an amber glassy resin, was obtained when the melt was poured into hot propanol. A more tractable solid was obtained when the material precipitated from propanol was digested briefly with chloroform. This product melted with decomposition at 215° and was probably the monomercurial admixed with some di-mercurial.

Anal. Calc'd for $C_{14}H_{10}HgO_2S$: Hg, 45.3. Found: Hg, 47.7, 48.5.

2-Acetamidodibenzothiophene.—A. By nitration, reduction and acetylation. This is the procedure first used by Courtot and Pomonis[2]. However, since they gave no experimental details and since the melting point of our product was different from that of theirs, an outline of the procedure is given. The 2-nitrodibenzothiophene prepared in accordance with their directions was reduced to the 2-amino compound by treatment of a suspension of the nitro compound in alcoholic ammonia with zinc dust and ammonium chloride. A solution of 1.5 g. of the amine thus obtained, in 50 cc. of benzene, was treated with 1 cc. of acetic anhydride. On standing, the acetamido derivative separated and was removed by filtration. The compound

melted at 178° after recrystallization from benzene. It is possible that their reported melting point (168°) is due to a typographical error.

Anal. Calc'd for $C_{14}H_{11}NOS$: N, 5.81. Found: N, 5.64, 5.72.

B. By amination of 2-bromodibenzothiophene followed by acetylation. A mixture of 2 g. of 2-bromodibenzothiophene, 2 g. of cuprous bromide, and 15 cc. of concentrated aqueous ammonia was heated in a sealed tube for 8 hours at 200–225°. When cool, the contents of the tube were washed out, extracted with ether, and the ether extract was saturated with gaseous hydrogen chloride. A 62% yield of the amine hydrochloride was isolated. Aqueous ammonia liberated the amine which melted at 129° after recrystallization from methanol. The amine was acetylated as described above.

C. By the Beckmann rearrangement of the oxime of 2-acetyldibenzothiophene. A quantitative yield of crude acetamido compound was obtained when 40 g. of the oxime in 500 cc. of dry benzene warmed to 40° was treated with an equal quantity of phosphorus pentachloride. Crystallization of the acetamido compound from benzene containing a few drops of acetic anhydride to reconvert any free base to the acetyl derivative, gave yields of pure acetamino compound which averaged above 70%.

Nitro-2-acetaminodibenzothiophene.—Twenty grams (0.083 mole) of 2-acetamidodibenzothiophene was dissolved in 800 cc. of acetic anhydride by warming slightly. The solution was then cooled to 25°. Some solid separated during the cooling. Then with stirring, 15 cc. (0.36 mole) of fuming nitric acid was added over a 5 minute period, keeping the temperature at 25–27°. The red solution was allowed to stand 25 minutes and then poured into about 3 l. of ice and water. Recrystallization from methanol yielded 16 g. or 67% of nitro-acetamido compound melting at 208.5–209°. In several experiments, a less soluble material (3 to 4% yield) separated first from the methanol as yellow needles, and this melted at 250° with decomposition, after recrystallization from acetic acid.

Anal. (Compound, m.p., 208.5-209°) Calc'd for $C_{14}H_{10}N_2O_3S$: N, 9.79. Found: N, 9.74 and 9.80. (Compound, m.p. 250°): Calc'd for $C_{12}H_8N_2O_2S$: N, 11.5. Found: N, 11.3, 11.6.

The nitro-2-acetamidodibenzothiophene (m.p. 208.5-209°) was hydrolyzed in an attempt to determine whether the compound melting at 250° was the nitro-amino product. Five-tenths of a gram of the nitro-acetamido compound was refluxed for one and one-half hours in a mixture of 20 cc. of absolute alcohol and 20 cc. of concentrated hydrochloric acid. At the start all of the material was in solution, but the mixture gradually became turbid. An odor resembling acetaldehyde was noticeable at the top of the condenser. The mixture was poured into cold water, made alkaline with ammonium hydroxide, and the reddish solid was separated by filtration. The product (yellow needles) melted at 85-86° when first crystallized from methanol; then recrystallization from dilute acetic acid gave a colorless compound melting at 88° and free of nitrogen.

Anal. Found: S, 22.4, 22.4; C, 65.74, 65.78; H, 3.29, 3.32.

1,4-Dihydrodibenzothiophene.—To a solution of 10 g. (about 40% excess) of sodium in 600 cc. of liquid ammonia was added, slowly and with stirring, 30 g. (0.16 mole) of dibenzothiophene. The excess sodium and reaction products were ammonolyzed by the cautious addition of 50 g. of solid ammonium nitrate. The crude product, 26 g. or an 85% yield, was collected at 160–165°/6 mm. Losses upon recrystallization are large, and the melting point after recrystallization from methanol is 76°.

Anal. Calc'd for $C_{12}H_{10}S$: C, 77.36; H, 5.42.
Found: C, 77.44; H, 5.50.

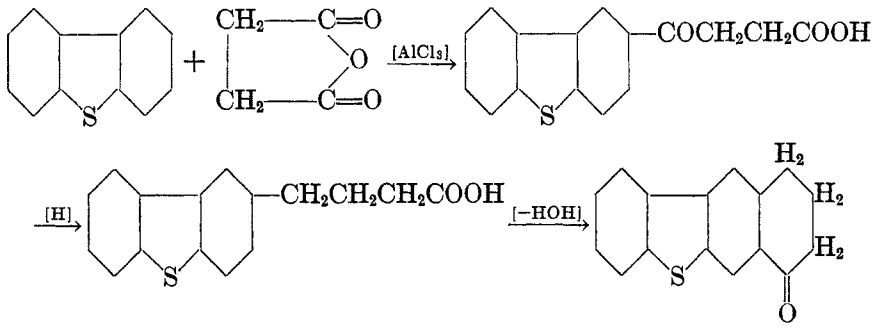
The picrate (red needles) melts at 105° after recrystallization from alcohol. Aqueous ammonia regenerates the dihydrodibenzothiophene.

One-half gram of the dihydro compound in 10 cc. of chloroform was cooled in an ice bath and treated cautiously with a solution of bromine in carbon tetrachloride until the faint color of bromine persisted. Nearly the theoretical amount of bromine was absorbed, and no hydrogen bromide was evolved. In one experiment when the solvents were removed under diminished pressure, and the residue was recrystallized from methanol, a nearly quantitative yield of dibenzothiophene was obtained. In another experiment the solvents were removed carefully and the oil remaining was kept cool for a long time without signs of crystallization. Evidently the bromine addition product is unstable and loses hydrogen bromide easily, as in the case of dihydronaphthalene.[18]

Dehydrogenation of 1,4-dihydrodibenzothiophene with RM compounds.—A. With phenyllithium. A filtered ether solution of phenyllithium (about 0.15 mole) was added to 10 g. (0.054 mole) of dihydrodibenzothiophene in 75 cc. of ether. The mixture was kept at 0° under nitrogen and immediately assumed a red color, which deepened during the first hour. After two hours a fine precipitate was visible, and after three hours the ice bath was removed, and the mixture was allowed to come to room temperature and remain there for one hour. It was then heated to reflux gently for 4 hours, cooled, and carbonated. The products isolated were 5 g. of benzoic acid, 1 g. of benzene (identified by its dinitro derivative) and 9 g. of dibenzothiophene.

B. With phenylisopropylpotassium. To 3 g. (0.016 mole) of 1,4-dihydrodibenzothiophene was added the phenylisopropylpotassium prepared from 0.035 mole of 2-phenylisopropyl methyl ether in accordance with the directions of Ziegler[19]. The mixture was refluxed for 7 hours, carbonated, and worked up in the usual manner to give 1 g. of dibenzothiophene. There was also obtained 2.8 g. of a crude acidic material which could not be crystallized to definite compounds. By analogy with dibenzofuran it appears quite probable that dehydrogenation first took place, followed by metalation of the resulting dibenzothiophene by the excess RK compound which, because of its high reactivity, may have given both mono- and polymetalation and therefore mono- and polybasic acids.

Keto-tetrahydrothiobrazan.—An interest in the biological properties of some polynuclear thienyl types, prompted the synthesis of thiobrazan derivatives. One of these was prepared by the following sequence of reactions.



[18] BAMBERGER AND LODTER, *Ber.*, **20**, 1706 (1887).

[19] ZIEGLER AND CO-WORKERS, *Ann.*, **473**, 18 (1929).

A. β-2-Dibenzothenoylpropionic acid. Reaction was carried out with 92 g. (0.5 mole) of dibenzothiophene, 55 g. (0.55 mole) of succinic anhydride, suspended in a mixture of 400 cc. of tetrachloroethane and 200 cc. of nitrobenzene, and 150 g. (1.1 mole) of aluminum chloride. The temperature throughout the preparation was 0–5°, and hydrolysis was effected by ice and concentrated hydrochloric acid. The yield of pure β-2-dibenzothenoylpropionic acid was 74 g. or 66%, and the compound melted at 160.5–161° after recrystallization from a large volume of ethyl acetate.

Anal. Calc'd for $C_{16}H_{12}O_3S$: Neutral. equiv., 284.2; S, 11.3.
Found: Neutral. equiv., 285; S, 11.1.

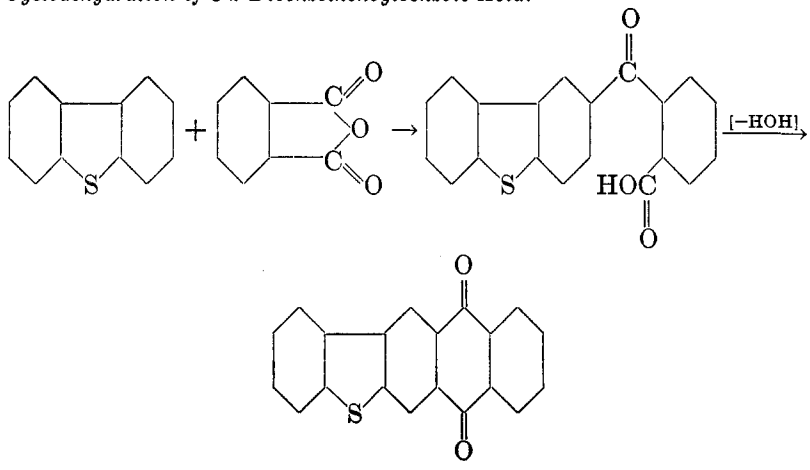
B. γ-2-Dibenzothienylbutyric acid. Reduction of the keto acid was effected by Martin's[20] modification of the Clemmensen method. A mixture of 50 g. of amalgamated mossy zinc, 25 g. of the dibenzothenoylpropionic acid, 38 cc. of water, 88 cc. of concentrated hydrochloric acid, 75 cc. of toluene and 3 cc. of glacial acetic acid was refluxed for 30 hours. At approximately 6-hour intervals, three 25-cc. portions of concentrated hydrochloric acid were added through the condenser. The solid obtained, after removing the toluene by steam distillation, was recrystallized from dilute methanol to yield 16 g. or 67% of acid melting at 131°. In addition, 3 g. of the original keto-acid was recovered.

Anal. Calc'd for $C_{16}H_{14}O_2S$: Neutral. equiv., 270.2; S, 11.9.
Found: Neutral. equiv., 270; S, 11.4.

C. Cyclization of γ-2-Dibenzothienylbutyric acid. Four grams of dibenzothienylbutyric acid was dissolved in 100 cc. of 88% sulfuric acid and stirred for 15 minutes at room temperature. The deep-red solution was then poured upon ice and, after standing, the dilute acid was decanted from the green, tarry precipitate, which was washed with dilute sodium hydroxide, filtered, and dried. The thiobrazan melted at 178° after recrystallization from alcohol. Ring closure of the acid could lead to either the β- or γ-thiobrazan, the former by cyclization in the 3 position of dibenzothiophene and the latter by cyclization in the 1 position. In the reactions pictured at the beginning of this section we have indicated the more probable cyclization: namely, that in the 3 position leading to 1-keto-1,2,3,4-tetrahydro-β-thiobrazan.

Anal. Calc'd for $C_{16}H_{12}OS$: S, 12.7. Found: S, 12.6.

Cyclodehydration of o-*2-Dibenzothenoylbenzoic Acid.*—



[20] MARTIN, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

Reaction between 92 g. (0.5 mole) of dibenzothiophene, 82 g. (0.55 mole) of phthalic anhydride and 100 g. of aluminum chloride was carried out as in the preparation of the thiobrazan. The crude *o*-2-dibenzothenoylbenzoic acid, melting with frothing at 120–125° and weighing 135 g. was probably an unstable hydrate. Part of it was converted to the ethyl ester by means of diazoethane. Recrystallization from petroleum ether (b.p., 60–68°) gave ethyl *o*-2-dibenzothenoylbenzoate melting at 105–106°.

Anal. Calc'd for $C_{22}H_{16}O_3S$: S, 8.91. Found: S, 9.04.

The *o*-2-dibenzothenoylbenzoic acid (3 g.) was cyclicized by the procedure of Fieser and Fieser,[21] by addition to a fused mixture of 4.16 g. of sodium chloride and 20.8 g. of aluminum chloride kept at 100–110°. The mixture was then heated at 150° for one-half hour. The benzothienyl-anthraquinone melted at 285–286° after recrystallization from glacial acetic acid.

Anal. Calc'd for $C_{20}H_{10}O_2S$: S, 10.2. Found: S, 10.2. As is the case with the thiobrazan, cyclodehydration might occur in either or both of two positions. The reactions illustrated at the beginning of this section indicate the linear formula.

SUMMARY

The 1,3, and 4 positions of dibenzothiophene have been made accessible, the latter two by metalation reactions. Organoalkali compounds have been used for the smooth dehydrogenation of 1,4-dihydrodibenzothiophene to dibenzothiophene.

[21] FIESER AND FIESER, *J. Am. Chem. Soc.*, **54**, 3749 (1932).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

RELATIVE REACTIVITIES OF ORGANOMETALLIC COMPOUNDS. XVIII. SELECTIVE METALATIONS OF DIBENZOTHIOPHENE

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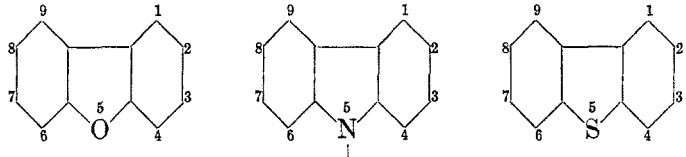
INTRODUCTION

Metalation of dibenzofuran (I) has invariably involved the 4 position, irrespective of the kind of metalating agent (metals, inorganic salts like mercuric acetate or organometallic compounds).[1]



I II III

Metalation of carbazole (II) or 5-ethylcarbazole by means of organometallic compounds also involves the 4 position, but when mercuric acetate is used metalation takes place in the 2 position.[2]

When dibenzothiophene (III) is metalated by organoalkali compounds, metalation takes place in the 4 position[3] as might have been expected from the close similarity of dibenzothiophene and dibenzofuran. However, metalation of dibenzothiophene by phenylcalcium iodide involves the 3 position. This result was quite unexpected because organocalcium compounds are uncommonly like organoalkali compounds in chemical reac-

[1] (*a*) GILMAN AND YOUNG, *J. Am. Chem. Soc.*, **56**, 1415 (1934); **57**, 1121 (1935).

(*b*) GILMAN AND CO-WORKERS, *Rec. trav. chim.*, **55**, 79 (1936), for metalation of dibenzofuran by phenylcalcium iodide.

[2] (*a*) GILMAN AND KIRBY, J. ORG. CHEM., **1**, 146 (1936).

(*b*) MILLER AND BACHMAN [*J. Am. Chem. Soc.*, **57**, 2447 (1935)] have shown that mercuration of fluorene in acetic acid takes place in the 4 position, and mercuration with no solvent involves both the 3 and the 4 positions.

[3] GILMAN AND JACOBY, J. ORG. CHEM., **3**, 108 (1938).

tivity.[4] It is significant that metalation of dibenzothiophene involves positions hitherto not accessible by direct nuclear substitutions.

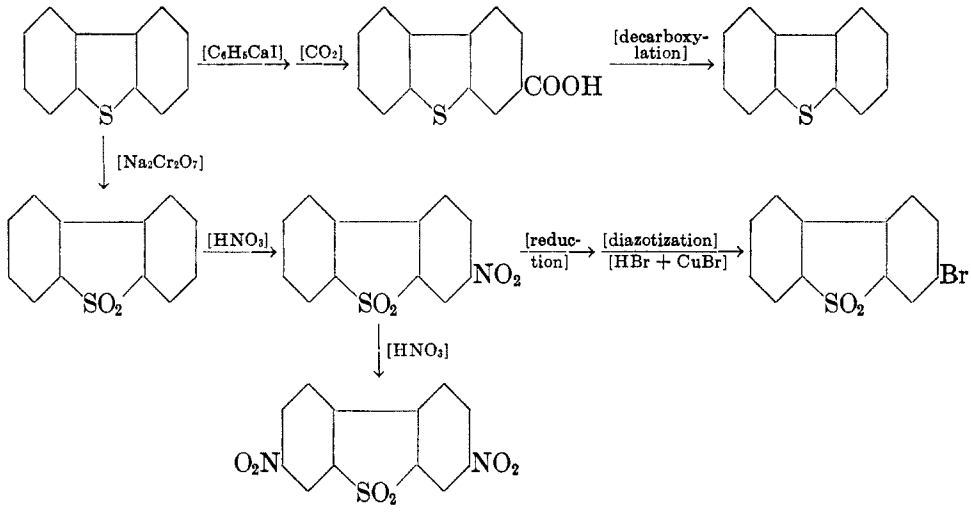
Proof of structure of substituents in the 3 position.—Two indirect procedures were used to show that metalation by phenylcalcium iodide involved the 3 position. The first of these was by analogy with the established orientation of the related dibenzofuran. Prior to these studies, but one of the four possible dibenzothiophenecarboxylic acids was known: namely, that one having the carboxyl group in the 2 position. In the preceding paper it was shown that the acid obtained by carbonation of the dibenzothienyl alkali compound (prepared from dibenzothiophene by metalation with RLi or RK) has the carboxyl group in the 4 position. The acid obtained by phenylcalcium iodide metalation must have been either the 1 or the 3 derivative. The 1-acid was then prepared (by reactions strictly analogous with the preparation of the corresponding acid of dibenzofuran) and shown to be unlike the acid prepared *via* phenylcalcium iodide.

The second method for establishing the 3 position was by means of the related dioxide or sulfone of dibenzothiophene. Cullinane, Davies, and Davies[5] recently showed that nitration and bromination of dibenzothiophene-5-dioxide gave 3,7-dinitrodibenzothiophene-5-dioxide and 3,7-dibromodibenzothiophene-5-dioxide, respectively. No mononuclear substitution was reported. After several unsuccessful experiments, conditions were found for mononitration in satisfactory yields. The nitro compound must be the 3-nitrodibenzothiophene-5-dioxide, because further nitration gave the authentic and symmetrical 3,7-dinitrodibenzothiophene-5-dioxide. As illustrated in the following chart of transformations, the 3-nitrodibenzothiophene-5-dioxide was converted through the corresponding amine and diazonium compound to the 3-bromodibenzothiophene-5-dioxide. Unfortunately, this bromo-sulfone could not be reduced to the corresponding 3-bromodibenzothiophene because of the removal of nuclear bromine during reduction. If 3-bromodibenzothiophene had become available in this way, the 3-acid could readily have been prepared by means of the corresponding Grignard reagent.

The acid obtained from phenylcalcium iodide metalation must have the carboxyl group in either the 1 or the 3 position, and it was an easy matter to rule out the 1 position. This was done by showing that the authentic 3-bromodibenzothiophene-5-dioxide was unlike the bromodibenzothiophene-5-dioxide prepared by oxidation of the bromodibenzothiophene from which the supposed, but not previously established, 1-acid was prepared.

[4] Gilman and Bailie, *ibid.*, **2**, 84 (1937).

[5] Cullinane, Davies, and Davies, *J. Chem. Soc.*, **1936**, 1437.



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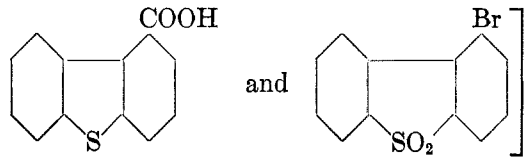

EXPERIMENTAL

Preparation of dibenzothiophene-3-carboxylic acid.—Phenylcalcium iodide was prepared in the customary manner,[1b] using 122.4 g. (0.6 mole) of iodobenzene, 48 g. (1.2 g. atom) of calcium turnings, and 300 cc. of ether. The mixture was allowed to settle overnight, and then the ether solution of phenylcalcium iodide was decanted into a 1-l. flask containing 27.6 g. (0.15 mole) of dibenzothiophene and 250 cc. of ether. The mixture was refluxed gently for 24 hours and then carbonated with solid carbon dioxide. The acid was isolated, by extracting first with dilute sodium hydroxide and then precipitating by hydrochloric acid, as a yellow heavy precipitate. Subsequent to digestion with boiling water, filtration gave 3 grams of brownish acid which when recrystallized from methanol yielded an almost colorless product. The dibenzothiophene-3-carboxylic acid appeared to decompose or decarboxylate at 300–305°, but had no sharp melting point.

Neutralization equivalent: calc'd, 228; found, 234. The low yields of acid obtained by carbonation subsequent to metalation are reminiscent of experiments on the metalation of related heterocycles by phenyl*calcium* iodide.[1b,2a]

Decarboxylation. About 0.1–0.2 g. of the 3-acid was heated in 2–3 cc. of quinoline at 200° for one hour with an equal amount of copper powder. Evolution of gas was noticed as low as 120°. The mixture was then cooled and transferred to a small

distilling flask where it was mixed with 50 cc. of water and 3 cc. of concentrated sulfuric acid. Distillation gave a yellowish, crystalline solid in the distillate. The solid, after sublimation, melted at 97–98° and was shown to be dibenzothiophene.

Methyl dibenzothiophene-3-carboxylate.—The methyl ester was prepared from the acid and diazomethane in ether solution. Recrystallization from a 1:2 mixture of methanol and ethanol gave colorless crystals melting at 129–130°.

Anal. Calc'd for $C_{14}H_{10}O_2S$: S, 13.2. Found: S, 13.1.

Preparation of dibenzothiophene-5-dioxide.[6]—To a cold mixture of 550 cc. of glacial acetic acid, 200 cc. of 50% sulfuric acid and 75 g. sodium dichromate was added 55.2 g. (0.3 mole) dibenzothiophene. The mixture was kept at 60° and shaken for one-half hour, after which the temperature started to drop. The reaction mixture was poured into cold water, and the yellowish heavy precipitate was filtered off. Crystallization from benzene gave a 90% yield of dioxide melting at 232°.

3-Nitrodibenzothiophene-5-dioxide.—To a mixture of 5.5 cc. of glacial acetic acid and 5.5 cc. of concentrated sulfuric acid in a 200-cc. three-necked flask equipped with stirrer, thermometer, and dropping funnel, was added 2.5 g. of dibenzothiophene-5-dioxide. A paste formed, and this was kept at a temperature of 4° while 8.85 g. of fuming nitric acid (sp. gr., 1.5) was added during a five-minute period. After stirring for one-half hour, the reaction mixture was poured into 100 cc. of cold water, and the precipitate filtered and washed with water. The melting point was 265–266° after two crystallizations from acetone and two from 1,4-dioxane. The yield was 82%.

Anal. Calc'd for $C_{12}H_7NO_4S$: N, 5.36. Found: N, 5.47.

3-Nitrodibenzothiophene-5-dioxide was nitrated at 80° by a mixture of equal parts of nitric acid (sp. gr., 1.5) and concentrated sulfuric acid to give 3,7-dinitrodibenzothiophene-5-dioxide which was shown to be identical with a specimen prepared in accordance with the directions of Cullinane and co-workers.[5]

3-Aminodibenzothiophene-5-dioxide.—A mixture of 18 g. of 3-nitrodibenzothiophene-5-dioxide, 45 g. of granulated tin, 225 cc. of concentrated hydrochloric acid, 600 cc. of water, and 200 cc. of ethanol was refluxed until the suspension became a clear solution. On cooling, white plate-like crystals of the hydrochloride separated. These were washed with hydrochloric acid, dried, and then treated with 10% sodium hydroxide to obtain the yellowish amine which after recrystallization from methanol melted at 259–260°. The yield was 33%.

Anal. Calc'd for $C_{12}H_9NO_2S$: N, 6.06. Found: N, 6.30.

3-Bromodibenzothiophene-5-dioxide. A solution of 7 g. of 3-aminodibenzothiophene-5-dioxide in 160 cc. of hot glacial acetic acid was cooled rapidly to room temperature and gradually stirred into a solution of nitrosyl sulfuric acid which had been prepared by adding with vigorous stirring 5 g. of finely powdered sodium nitrite to 35 cc. of concentrated sulfuric acid. The diazotization was conducted below 20°, and the diazo solution was poured gradually into a solution of 15 g. of cuprous bromide in 160 cc. of hydrobromic acid. The procedure was essentially that of Hodgson and Walker.[7]

The 3-bromo compound was isolated by customary procedures, and after recrystallization from ethanol melted at 224–225°. The yield was 95%.

Anal. Calc'd for $C_{12}H_7BrO_2S$: S, 10.8. Found: S, 10.7.

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[6] Private communication from Professor Ch. Courtot. See, also, STENHOUSE, *Ann.*, **156**, 332 (1870).

[7] HODGSON AND WALKER, *J. Chem. Soc.*, **1933**, 1620.

SUMMARY

Metalation of dibenzothiophene by organoalkali compounds takes place in the 4 position, as is the case with the related dibenzofuran. However, metalation by phenylcalcium iodide (which markedly resembles organoalkali compounds in other respects) occurs in the 3 position. Both positions are otherwise inaccessible by direct nuclear substitution reactions.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, REHOVOTH, PALESTINE]

SYNTHESES AND REACTIONS OF SUBSTITUTED α-NAPHTHOQUINONES

ERNST BERGMANN AND FELIX BERGMANN

Received May 25, 1938

Fieser and co-workers have observed a very peculiar reaction of 2,6-dimethyl-1,4-naphthoquinone[1] with diazomethane—reaction taking place in the free 3 position, coupling two quinone molecules by a methylene bridge. In order to study this reaction, which is somewhat similar to the known reactions of diazomethane with nitroso compounds and thioketones[2], we investigated the synthetic possibilities leading to 2-phenyl-6,7-dimethyl- and to 2,6,7-trimethyl-1,4-naphthoquinone and the behavior of these substances. Furthermore, the chemical reactions of 2,3-dimethylnaphthoquinone have been studied for comparative purposes.

I. The obvious method was the diene synthesis, which, however, as far as we know, has been carried as far as the stage of the true naphthoquinones only for simple cases as described in a patent of I. G. Farbenindustrie A. G.[3] Toluquinone, with 2,3-dimethylbutadiene, gives the normal addition product (I), m.p. 94°, in boiling benzene or without solvent at 100–110°[4]. At 150–170°, two products have been isolated, one, m.p. 223–224°, which is isomeric with (I), and — sometimes — a second one, m.p. 110°. The higher-melting substance, undoubtedly, is 2,6,7-trimethyl-5,8-dihydro-1,4-dihydroxynaphthalene (II), as it is produced by isomerisation of (I) with hydrobromic acid[5]. It is the first case to our knowledge, in which this type of isomerisation has been found to occur spontaneously in the course of synthesis. The lower-melting product (m.p. 110°), on the other hand, is the desired 2,6,7-trimethyl-α-naphthoquinone (III). That follows apart from the analysis, from the following

[1] FIESER AND SELIGMANN, *J. Am. Chem. Soc.*, **56**, 2690 (1934); FIESER AND HARTWELL, *ibid.*, **57**, 1479 (1935). It may be noted that the reaction product, m.p. 293°, assumed to be a diquinone is in fact a hydroquinone, as ferric chloride converts it into the real diquinone, m.p. 249°.

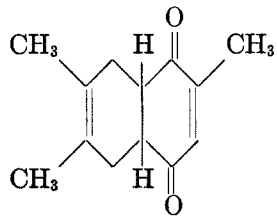
[2] See, *e.g.*, STAUDINGER AND MIESCHER, *Helv. Chim. Acta*, **2**, 534 (1919); BERGMANN, MAGAT, AND WAGENBERG, *Ber.*, **63**, 2576 (1930).

[3] *British Patent* 324 661; *cf. Chem. Zentr.*, **1930**, II, 809.

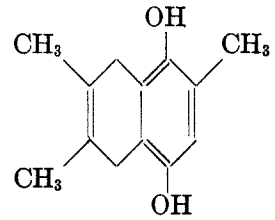
[4] In accordance with the observation of CHUANG AND CHAN, *Ber.*, **68**, 876 (1935), toluquinone reacts with 1 mole of the diene only.

[5] DIELS AND ALDER, *ibid.*, **62**, 2337 (1929).

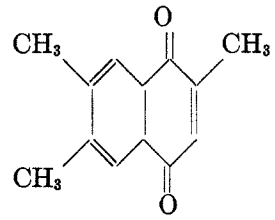
observations: II is oxidised by ferric chloride to give 2,6,7-trimethyl-5,8-dihydro-α-naphthoquinone (IV), m.p. 129°, and this, on selenium dehydrogenation, is converted into the substance, m.p. 110°, therefore III. The same end-product is produced directly by selenium dehydrogenation of I.



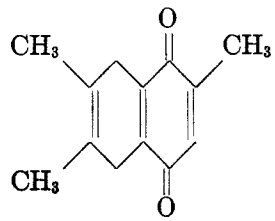
I



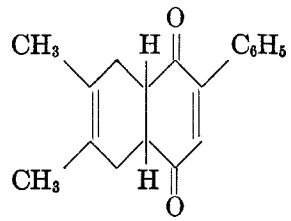
II



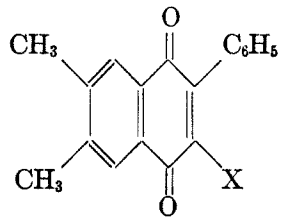
III



IV



V



VI

With phenylquinone too, which we used for the first time for diene synthesis[6], 2,3-dimethylbutadiene reacts differently according to conditions. At 100° without diluent the normal 2-phenyl-6,7-dimethyl-5,8,9,10-tetrahydro-α-naphthoquinone (V), m.p. 113–114°, is formed, while at elevated temperatures the desired 2-phenyl-6,7-dimethyl-α-naphthoquinone (VI, X=H) m.p. 127°, is formed, although in trivial yield*. Two ways are open for its preparation in larger quantities: V is converted by hydrobromic acid into the isomeric hydroquinone m.p. 137°, then by ferric chloride into 2-phenyl-6,7-dimethyl-5,8-dihydro-α-naphthoquinone, m.p. 119°, which may be dehydrogenated by selenium. Or, the primary addition product, m.p. 113–114° (V), is directly subjected to selenium dehydrogenation, and the 2-phenyl-6,7-dimethyl-1,4-dihydroxynaphthalene (m.p. 197–198°) obtained is oxidised subsequently by means of ferric chloride solution. Obviously, V, on heating, is first isomerized (see above);

[6] On some experiments with 2,5-diphenylquinone, see ALLEN AND RUDORFF, *Can. J. Research* **15B**, 321 (1937); *C. A.*, **32**, 124 (1938).

* Cyclopentadiene, also, with phenylquinone, gives the normal addition product, m.p. 79–80°, in benzene solution.

then selenium acts exclusively on the supernumerary nuclear hydrogen atoms.

When we applied to V or to 2-phenyl-6,7-dimethyl-1,4-dihydroxynaphthalene (m.p. 197–198°) the oxidation by air in presence of alkali, which has given very favorable results in the anthraquinone series[5], we obtained 3-hydroxy-2-phenyl-6,7-dimethyl-α-naphthoquinone, m.p. 157–158° (VI, X=OH) which exhibited all the characteristic features of those hydroxyquinones. Our observation parallels the formation of hydroxyjuglone from juglone[7], and the synthesis of phthiocole by Anderson and Newman[8].

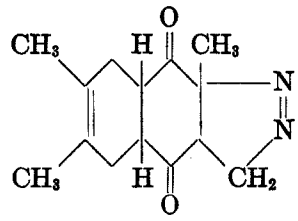
II. *With diazomethane* I gives immediately a colourless addition product (VII), m.p. 142°. This is decomposed in boiling ligroïn (130°), yielding a nitrogen-free substance, for which we would suggest the formula (VIII) of 2, 3, 6, 7-tetramethyl-5, 8, 9, 10-tetrahydro-α-naphthoquinone. The substance could not be isolated in the crystalline state, but gave a crystalline derivative (IX), m.p. 155–156°, on treatment with hydrobromic acid and subsequent dehydrogenation with ferric chloride solution. In the same way, 2,6,7-trimethyl-α-naphthoquinone (III) is converted by diazomethane into 2,3,6,7-tetramethyl-α-naphthoquinone, m.p. 167–168°, no "bimolecular" product being formed, as in the case of 2,6-dimethylnaphthoquinone, described by Fieser and co-workers. We have been able to isolate along with Fieser's substance, a low-melting by-product which according to its properties most probably is 2,3,6-trimethylnaphthoquinone. Furthermore, one of the products formed from 2-methylnaphthoquinone, on interaction with diazomethane, proved to be 2,3-dimethyl-α-naphthoquinone.

It appears that diazomethane, even when the nuclear quinone double bond is partly blocked, adds primarily—at least to a certain extent—in the normal way, forming a pyrazoline derivative. Thermally, then, nitrogen is split off, and by rearrangement of the radical nuclear methylation takes place. The non-methylated α-naphthoquinone is the only case where no such methylation has been observed[9]. The occurrence of nuclear methylation supports satisfactorily formula VII with regard to the direction of the entering diazomethane molecule. Diazomethane, apparently, parallels completely the diene additions of those quinones. A further example in this direction is supplied by our observation, that

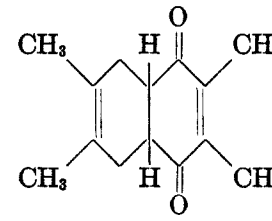
[7] MYLIUS, *Ber.*, **18**, 469 (1885).

[8] ANDERSON AND NEWMAN, *J. Biol. Chem.*, **101**, 773 (1933); **103**, 197, 405 (1933).

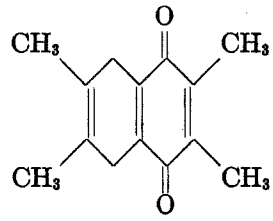
[9] PECHMANN AND SEEL, *Ber.*, **32**, 2297 (1899); FIESER AND PETERS, *J. Am. Chem. Soc.*, **53**, 4080 (1931).



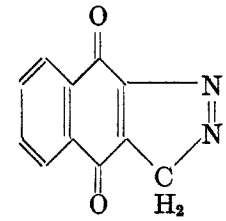
VII



VIII



IX



X

2-bromo-α-naphthoquinone adds diazomethane to give a condensation product which easily loses hydrogen bromide, yielding α-naptho[2,3]-pyrazole-4,9-dione (X). The analogous observation with regard to diene syntheses, has recently been reported by Fieser and Dunn[10].

The above-reported nuclear methylation is interesting both from a theoretical and from a preparative point of view. It is superficially reminiscent of the well-known conversion of aldehydes into methylketones by means of diazomethane; but it stands in close analogy to the formation of ethyl β-methyl- and α,β-dimethylcinnamates from ethyl cinnamate and α-methylcinnamate, respectively[11], on thermal decomposition of the primarily formed pyrazoline derivatives, and to the formation, from α-naphthoquinone and diphenyldiazomethane, of 2-benzohydryl-α-naphthoquinone[12].

While these relationships seem perfectly clear, no analogue so far has been reported for the Fieser reaction proper, the conversion by diazomethane of 2,6-dimethylnaphthoquinone into the "bimolecular" product formulated as (XI, X=CH_3). (One would assume, that its formation is due to a second stabilisation reaction of the radical remaining from the decomposition of the primary addition product.) In fact, we have observed a second case: in the reaction of 2-methylnaphthoquinone with diazomethane, besides the normal addition product, m.p. 114°, and 2,3-

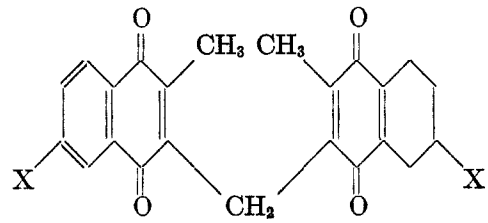
[10] FIESER AND DUNN, *J. Am. Chem. Soc.*, **59**, 1016, 1024 (1937).

[11] v. AUWERS AND KOENIG, *Ann.* **496**, 252 (1932); v. AUWERS AND UNGEMACH, *Ber.*, **66**, 1198 (1933).

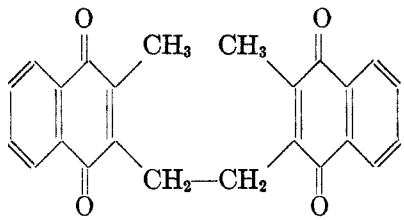
[12] FIESER AND PETERS, *J. Am. Chem. Soc.*, **53**, 4080 (1931).

dimethylnaphthoquinone (see above), a "bimolecular" nitrogen-free substance, m.p. 242°, was obtained, undoubtedly in principle analogous to Fieser's compound. A minor difference is, that our substance is a diquinone, while Fieser's, as stated above, contains a hydroquinoid system.

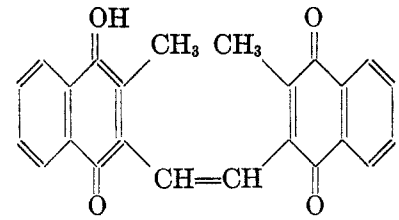
Theoretically, it is possible, that the bridge combining the two quinone molecules is built up not by one, but by two carbon atoms, in analogy with the reaction of aromatic nitroso compounds, yielding dinitrones, *e.g.*, $C_6H_5 \cdot N(:O)=CH-CH=N(:O) \cdot C_6H_5$, with diazomethane[13]. Therefore we think it interesting that we can produce an—however indirect—argument in favour of Fieser's formula. Theoretically, according to the above, the two structures XII and XIII would have to be taken into account, which would not easily be discriminated from (XI, X=H) by purely analytical methods. We were able to obtain the substances XII and XIII, which proved different from the above-mentioned diazomethane product,



XI



XII

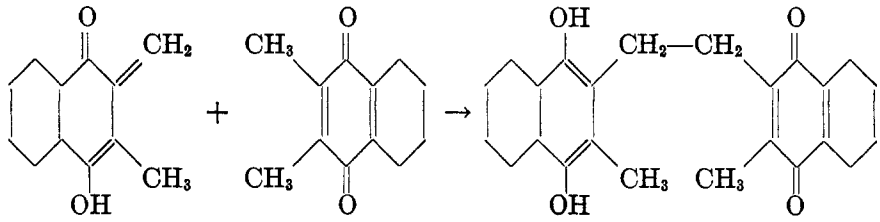


XIII

in the following, somewhat surprising way. When 2,3-dimethylnaphthoquinone is treated with benzohydrylsodium, and the product is subsequently exposed to air in the presence of alkali, two products are formed—the differences in formation conditions not being absolutely defined: a diquinone $C_{24}H_{18}O_4$, m.p. 261° or a diquinone, $C_{24}H_{16}O_4$, m.p. 228°, to which we ascribe formulas XII and XIII respectively. Benzohydrylsodium, apparently, does not actually take part in the reaction; it is

[13] v. Pechmann, *Ber.*, **30**, 2461.2875 (1897); v. Pechmann and Schmitz, *ibid.*, **31**, 293 (1898); v. Pechmann and Seel, *ibid.*, **31**, 296 (1898); v. Pechmann and Nold, *ibid.*, **31**, 557 (1898); Bamberger, *ibid.*, **33**, 945 (1900).

suggested that it merely enolizes 2,3-dimethylnaphthoquinone[14]. So XIV is formed, which adds one molecule of the non-enolized quinone according to the following scheme:



XIV

Subsequently, dehydrogenation takes place to form XII or XIII. The acting methyl in the above reaction is activated by the carbonyl group *via* the conjugated double bond[15]. The occurrence in XIII of a double bond is indicated by the observation that alcoholic ferric chloride introduces an additional oxygen atom, forming a substance $C_{24}H_{16}O_5$, m.p. 184°. We did not try to decide whether the entering oxygen atom forms an oxide ring (—CH—CH—) or a keto-group (—CO—CH_2—). The enolization

of 2,3-dimethylnaphthoquinone (→XIV) is in complete analogy to the interconversion of 2-hydroxy-α- and 4-hydroxy-β-naphthoquinones[16]. In this connection, it seems worth reporting that the substance (XIII) is obtained also by exposing 2,3-dimethylnaphthoquinone to air in presence of methyl alcoholic potash solution. This reaction and the above one recall the formation of the dye anthraflavone from 2-methylanthraquinone[17].

EXPERIMENTAL

2,6,7-Trimethyl-5,8,9,10-tetrahydro-α-naphthoquinone (*I*).—Toluquinone (5 g.) and 2,3-dimethylbutadiene (7.5 g.) are heated in a sealed tube at 110° for one hour. The excess dimethylbutadiene is evaporated; the residue crystallizes; from methanol or isopropyl alcohol, needles, m.p. 93–94°. Concentrate sulfuric acid gives a red color reaction. The same product is obtained in boiling benzene solution (4 hours), but at the same time a considerable amount of toluquinhydrone is formed.

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[14] For references on the enolizing action of organo-alkali compounds see BERGMANN, *J. Chem. Soc.*, **1936**, 412.

[15] See FUSON, *Chem. Rev.*, **16**, 1 (1935); FUSON AND CO-WORKERS, *J. Am. Chem. Soc.*, **58**, 1979, 2450 (1936). Compare, also for references, KUHN AND GRUNDMANN, *Ber.*, **70**, 1318 (1937).

[16] See MEYER-JACOBSOHN, Berlin and Leipzig, **1903**, Vol. II, Part 2, pp. 390–398.

[17] HOUBEN, "Das Anthracen und die Anthrachinone," Leipzig, **1928**, p. 269. Compare BERGMANN AND BLUM-BERGMANN, *J. Am. Chem. Soc.*, **59**, 1439 (1937).

Anal. Calc'd for $C_{13}H_{10}O_2$: C, 76.47; H, 7.84.
Found: C, 76.44; H, 7.89.

2,6,7-Trimethyl-5,8-dihydro-1,4-dihydroxynaphthalene (II).—(*a*) When to a solution of I (0.1 g.) in glacial acetic acid 1 drop of hydrobromic acid is added, the mass solidifies quickly. The product is collected and precipitated from its dioxane solution by light petroleum (b.p. 80–100°). Needles, m.p. 224°.

Anal. Calc'd for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84.
Found: C, 76.43; H, 8.20.

(*b*) Toluquinone (8 g.) and 2,3-dimethylbutadiene (12 g.) are heated as above, but at 150–170°. The crystalline mass is purified as sub (*a*); m.p. and mixture m.p. 224°; yield, 12 g. From the mother-liquors, occasionally, a yellow substance separates. It forms, after recrystallisation from isopropyl alcohol and light petroleum (b.p. 80–100°) yellow needles, m.p. 110° which give the same dark-red color reaction with concentrated sulfuric acid as I or II, and were identified as 2,6,7-trimethylnaphthoquinone (III, see below).

2,6,7-Trimethyl-5,8-dihydro-α-naphthoquinone (IV).—One gram of II is suspended in alcohol and heated with an alcoholic solution of ferric chloride (3 g.) for 5 minutes. On addition of water, yellow crystals are obtained, which are recrystallized from benzine (b.p. 80–110°). Long, silky needles, m.p. 129°, which still give the dark-red color reaction with concentrated sulfuric acid and suffer slight discoloration on heating or continued exposure to air.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93.
Found: C, 77.28; H, 7.20.

2,6,7-Trimethyl-α-naphthoquinone (III).—(*a*) The addition product (I) (1 g.) is heated with selenium (1 g.) at 200–210°, until the evolution of hydrogen selenide ceases. The residue is extracted with ethyl acetate and chloroform. From this solution crystals remain which are triturated with methyl alcohol and recrystallized from light petroleum (b.p. 80–100°). Yellow needles, m.p. 110°; yield 0.1 g.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0.
Found: C, 78.2, 77.4; H, 6.0, 6.1.

(*b*) One gram of IV was treated with selenium (0.3 g.) at 280° as sub (*a*). The product was purified by high vacuum (0.03 mm.) distillation and subsequent recrystallisation from light petroleum.

2-Phenyl-6,7-dimethyl-5,8,9,10-tetrahydronaphthoquinone (V).—Phenylquinone[18] (4 g.) and 2,3-dimethylbutadine (10 g.) were heated at 100° for one hour in a sealed tube. The product crystallises spontaneously. From light-petroleum, yellowish needles, m.p. 113–114°; yield, 4.5 g.; dark-red color-reaction with concentrated sulfuric acid.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8.
Found: C, 81.19; H, 7.42.

2-Phenyl-6,7-dimethyl-5,8-dihydro-1,4-dihydroxynaphthalene (as II).—One hundred milligrams of V is isomerized in glacial acetic acid solution by addition of a few drops of hydrobromic acid. The mixture congeals spontaneously; the product is collected and recrystallized from light petroleum (b.p. 80-100°). The crystals, m.p. 137°, oxidize spontaneously in the air and therefore undergo discoloration quickly. Analyses were very unsatisfactory.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 7.0.
Found: C, 79.3; H, 7.4.

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[18] Preparation according to KVALNES, *J. Am. Chem. Soc.*, **56**, 2478 (1934).

2-Phenyl-6,7-dimethyl-5,8-dihydro-α-naphthoquinone (*as III*).—The foregoing substance is dissolved in alcohol, and ferric chloride solution added. The solution turns first black-green, then brown, and the product separates spontaneously. From isopropyl alcohol orange-red needles, m.p. 119°. Bright colors have been found to be characteristic for α-naphthoquinone derivatives with three parallel nuclear double bonds.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.7; H, 6.7.
Found: C, 81.3; H, 6.4.

2-Phenyl-6,7-dimethyl-1,4-dihydroxynaphthalene.—The addition product (V, 2 g.) reacted with selenium (1.5 g.) at 280–300°. The greyish reaction product was recrystallized from ligroïn. Stars of prisms, m.p. 197–198°; yield, 1 g. concentrated sulfuric acid gives a violet color reaction.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1.
Found: C, 81.4, 81.7; H, 6.3, 6.4.

2-Phenyl-6,7-dimethyl-α-naphthoquinone.—(*a*) The foregoing hydroquinone (0.1 g.) was gently heated with alcoholic ferric chloride solution, and the reaction product was precipitated with water. From light petroleum (80–100°) yellow clusters of needles, m.p. 127°, which give a violet solution in concentrated sulfuric acid.

Anal. Calc'd for $C_{18}H_{14}O_2$: C, 82.4; H, 5.3.
Found: C, 82.2; H, 5.7.

(*b*) 2-Phenyl-6,7-dimethyl-5,8-dihydro-α-naphthoquinone (as III), m.p. 119°, is dehydrogenated with an equal amount of selenium.

(*c*) Phenylquinone (4 g.) and 2,3-dimethylbutadiene (10 g.) are heated in a sealed tube to 150° for one hour and to 200° for another hour. The residue remaining after evaporation of the excess dimethyl butadiene was triturated with a mixture of light petroleum (b.p. 40–60°) and isopropyl alcohol, and recrystallized from methyl alcohol. The mixture of 2-phenyl-6,7-dimethyl-α-naphthoquinone and (the prevailing) 2-phenylquinhydrone[19] had to be separated mechanically. The melting point of the former, and of its mixtures with known specimens, was 127°.

3-Hydroxy-2-phenyl-6,7-dimethyl-α-naphthoquinone (*VI*).—(*a*) The addition product (V, 1 g.) was dissolved in 15% methyl alcoholic potash solution, and a stream of air was passed through the liquid. A green precipitate is formed at first; it dissolves again subsequently, and finally a reddish solution is obtained, which is precipitated with dilute hydrochloric acid. From butyl acetate or ligroïn orange-red leaflets, m.p. 158°; yield 6.4 g. The substance dissolves in concentrated sulfuric acid with dark-brown, in methyl alcoholic potash solution with red, color, and gives a dark-red coloration with alcoholic ferric chloride solution, a violet one with boric-arctic anhydride.

Anal. Calc'd for $C_{18}H_{14}O_3$: C, 77.7; H, 5.0.
Found: C, 78.0, 78.2; H, 5.3, 5.5.

The same substance was obtained when the dark-red solution of 2-phenyl-6,7-dimethyl-1,4-dihydroxynaphthalene (m.p. 197–198°) was treated with an air-stream until the color remained reddish. *The methyl ether*, prepared with diazomethane in violent interaction,† formed greenish-yellow, shiny prisms, m.p. 186° which gave none of the above color reactions.

Anal. Calc'd for $C_{19}H_{16}O_3$: C, 78.1; H, 5.7.
Found: C, 78.5, 78.0; H, 6.3, 6.4.

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[19] For its formation, compare CRIEGER, *Ber.*, **69**, 2758 (1936).

† With dimethyl sulfate, no methylation could be forced.

Phenylquinone (1.84 g.) and *cyclopentadiene* (0.66 g.) were heated in benzene solution (10 cc.) for 2 hours on the water bath. After evaporation of the solvent, ligroïn was added, a brown syrupy by-product was removed by filtration, and the solution was cooled. Long prisms, which were recrystallized from isopropyl alcohol; m.p. 79–80°; yield, 0.45 g. concentrated sulfuric acid gives a dark-red solution.

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6.
Found: C, 81.3; H, 6.0.

2-Bromo-α-naphthoquinone and diazomethane (*X*).—2-Bromo-α-naphthoquinone[20] (2 g.) were treated with diazomethane (1 g.) in ethereal solution. The violent reaction results in a heavy, bromine-containing precipitate, which after 24 hours' standing (ice box) was collected (m.p. 272–280°, dec.), and triturated with concentrated ammonia solution at room temperature. The 3-naphtho[2,3]pyrazole-4,9-dione (X) was filtered and recrystallized from glacial acetic acid; m.p. 345°. The substance is undoubtedly identical with that described by Fieser and Peters[21]. Its analogy with anthraquinone, as stressed by the American authors, is underlined by the observation that zinc-dust and alkali give a brilliant green vat.

Anal. Calc'd for $C_{11}H_6N_2O_2$: C, 66.0; H, 3.0.
Found: C, 65.7; H, 3.6.

Diazomethane and V.—The addition product (V, 0.9 g.) in methyl alcohol reacted quickly upon ethereal diazomethane solution. A small quantity of colorless crystals appeared, which dissolved subsequently. The product, isolated after 24 hours' standing, was a reddish syrup; b.p. 170°/0.3 mm.

Anal. Calc'd for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.5.
Found: C, 74.3; H, 6.8.

Diazomethane and I.—The condensation product (I, 1.2 g.), treated with diazomethane as above, gave long white needles, which could be recrystallized from isopropyl alcohol. Stars of stout prisms; m.p. 146° (dec.). Analysis showed, that a true *addition-product* was formed.

Anal. Calc'd for $C_{14}H_{18}N_2O_2$: C, 68.3; H, 7.3; N, 11.4.
Found: C, 68.6, 68.3; H, 7.7, 7.4; N, 11.7.

When this product (0.2 g.) was boiled in ligroïn for 1 hour, and the solvent was removed, a resinous residue was obtained. This was isomerized in glacial acetic acid solution by means of hydrobromic acid, and the product (m.p. 232°) was subsequently oxidised with ferric chloride in alcoholic solution. The *2,3,6,7-tetramethyl-5,8-dihydro-α-naphthoquinone* (*IX*), so obtained, formed brown-red needles, from isopropyl alcohol; m.p. 155–156°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4.
Found: C, 77.4, 77.9; H, 7.1, 7.3.

Diazomethane and 2,6,7-trimethylnaphthoquinone (*III*).—Diazomethane reacted on standing at room temperature for 24 hours with 2,6,7-trimethyl-α-naphthoquinone (0.3 g.) in methyl alcohol solution. The solution was evaporated, and the residue was triturated with a mixture of acetone and light petroleum (b.p. 40–80°). The m.p. (175°) of the product fell on recrystallisation from a mixture of butyl acetate and ligroïn; it was constant at 167–168°. Apparently, oxidation had taken place, the final product being *2,3,6,7-tetramethyl-α-naphthoquinone*. Concentrate sulfuric acid gives a red-violet color-reaction.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.6; mol. wt., 234.
Found: C, 78.8, 78.4; H, 7.0, 6.7; mol. wt. (camphor), 234.

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[20] ZINCKE AND SCHMIDT, *Ber.*, **27**, 2753 (1894).

It may seem surprising, that a hydroquinone should have been formed in the presence of excess diazomethane. Obviously, the methylation is sterically hindered. Similar observations have been made by Fieser and co-workers,[1, 21] and recently by Hill, Short, and Stromberg.[22]

Diazomethane and 2-methylnaphthoquinone (*XI*, *X* = *H*).—The quinone[23] (3 g.) was kept with ethereal diazomethane solution (10 moles) at 0° for 24 hours. Then the solution was evaporated, the residue, which solidified almost completely, was recrystallized from methyl alcohol, and the mixture of white and yellow crystals so obtained was separated mechanically. The white needles, from benzene-light petroleum (b.p. 80-100°), m.p. 114°, were the true addition product.

Anal. Calc'd for $C_{12}H_{16}N_2O_2$: C, 67.3; H, 4.7; N, 13.1.
Found: C, 67.5; H, 4.8; N, 13.1.

The yellow prismatic needles were recrystallized from butanol and had m.p. 242° (XI, X = H). Ferric chloride in alcoholic solution caused no change.

Anal. Calc'd for $C_{23}H_{16}O_4$: C, 77.5; H, 4.5.
Found: C, 77.4; H, 4.7.

The original mother-liquor of both these substances was distilled under high vacuum, and the distillate was treated with methyl alcohol. Yellow needles (m.p. 122°) separated, and the melting point was not depressed on admixture of 2,3-dimethylnaphthoquinone. We cannot confirm the statement of Marbeth and Winzor[24] that 2-methylnaphthoquinone is resistant toward diazomethane.

Diazomethane and 2,6-dimethylnaphthoquinone (→*XI*, *X* = CH_3).—The quinone[25] (7.5 g.) was kept at 0° with diazomethane (3 g.) for 24 hours, and, after addition of another gram of diazomethane, one day more. The precipitate was collected and recrystallized several times from boiling xylene. Yellow, lancet-shaped crystals; m.p. 293° (slight dec.). Concentrate sulfuric acid gives a brilliant-red, methyl alcoholic potash solution a greenish-blue, solution. The substance has been assumed by Fieser[1] to be a diquinone, $C_{25}H_{20}O_4$; our analyses accord very well with the formula $C_{25}H_{22}O_4$.

Anal. Calc'd for $C_{25}H_{22}O_4$: C, 77.6; H, 5.7; active H, 0.52.
Found: C, 78.4, 78.4; H, 5.8, 5.8; active H, 0.38.

Dehydrogenation with alcoholic ferric chloride solution, yields dark-yellow crystals, from a mixture of benzene-light petroleum; m.p. 249°.

Anal. Calc'd for $C_{25}H_{20}O_4$: C, 77.2; H, 5.2.
Found: C, 77.8, 77.6; H, 5.7, 4.8.

The mother liquor, from which the described substance had separated, was distilled several times under high vacuum. The oil, distilling finally at 140°/1 mm., crystallized from alcohol on standing; m.p. 100°. The analysis of the crystals pointed definitely to the formula of a 2,3,6-trimethylnaphthoquinone.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 78.0; H, 6.0.
Found: C, 77.5; H, 5.7.

In some cases, an additional reaction product, from butyl acetate, m.p. 228.5°, was secured; due to the scarcity of material available, its structure was not investigated.

2,6-Dimethyl-1,4-naphthalenediol and its dimethyl ether: In connection with the

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[21] FIESER AND PETERS, *J. Am. Chem. Soc.*, **53**, 4080 (1931).
[22] HILL, SHORT, AND STROMBERG, *J. Chem. Soc.*, **1937**, 937.
[23] MADINAVEITIA AND DE BURUAGA, *Chem. Zentr.*, **1930**, I, 684.
[24] MARBETH AND WINZOR, *J. Chem. Soc.*, **1935**, 334.
[25] WEISSGERBER AND KRUBER, *Ber.*, **52**, 356 (1919).

reported experiments, 2,6-dimethylnaphthoquinone has been reduced. The quinone (15 g.) and zinc dust (30 g.) were suspended in boiling alcohol (100 cc.), and a few cubic centimeters of glacial acetic acid was added. After fifteen minutes' boiling, the solution was filtered while still hot, and the product was precipitated with dilute sulfuric acid. The white crystals, after recrystallisation from benzene, had m.p. 187–188°.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4.
Found: C, 76.5; H, 6.4.

Dimethyl ether.—The hydroquinone (10 g.) and methyl *p*-toluenesulphonate (15 g.) were heated with methyl alcohol (50 cc.) and 10% potash solution (40 cc., after 1 hour's boiling another 50 cc.) was added. After two more hours, the reaction mass was cooled to 0°C, the crystals collected, dissolved in ether, treated with dilute potash solution and finally purified by distillation: b.p. 129°/0.5 mm. The distillate solidified immediately and was recrystallized from light petroleum (b.p. 80–100°). Long, colorless needles, m.p. 75–76°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.4.
Found: C, 77.9; H, 7.3.

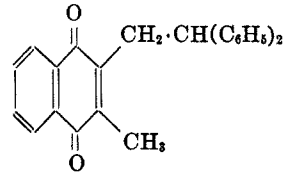
Experiments with 2,3-dimethylnaphthoquinone.—(*a*) 2,3-dimethylnaphthoquinone[26] (2 g.) in methyl alcohol was kept for 10 minutes with a few drops of 15% methyl alcoholic potash solution. The brown-red liquid was acidified with alcoholic hydrochloric acid, filtered, and evaporated. From butyl acetate, ligroïn, or xylene, yellow needles, m.p. 227–228° (XIII), which dissolve in concentrated sulfuric acid with dark-violet coloration.

Anal. Calc'd for $C_{24}H_{18}O_4$: C, 77.8; H, 4.2; active H, 0.54; mol. wt., 370.
Found: C, 78.3; H, 4.7; active H, 0.54; mol. wt. (camphor), 319.

Oxidation.—The foregoing substance (200 mg.) was suspended in alcohol and for some minutes boiled with an alcoholic solution (5 cc.) of ferric chloride (1 g.). The substance passed into solution, and the reaction product had to be precipitated with water. From xylene, stout prisms, from ligroïn plates, m.p. 184°. Analysis points to the formula $C_{24}H_{16}O_5$.

Anal. Calc'd for $C_{24}H_{16}O_5$: C, 75.0; H, 4.2.
Found: C, 74.7; H, 5.6.

(*b*) Benzohydrylsodium, prepared from benzohydryl methyl ether[27] (4.2 g.) was added to 2,3-dimethylnaphthoquinone (1.9 g.). The green mass, after 24 hours' standing, was decomposed with alcohol, and poured out into water. The ethereal layer contained tetraphenylethane, which was identified by melting point and mixture melting point (207°), and a yellow substance, which had to be separated mechanically and then was recrystallized several times from light petroleum (80–100°). Eventually, it formed needles, which melted at 167°, and according to the analysis represented 2-(β, β-diphenylethyl)-3-methylnaphthoquinone.



[26] Preparation: SMITH AND WEBSTER, *J. Am. Chem. Soc.*, **59**, 664 (1937).

[27] ZIEGIER AND THIELMANN, *Ber.*, **56**, 1740 (1923); SCHLENK AND BERGMANN, *Ann.*, **464**, 18 (1928).

Anal. Calc'd for $C_{25}H_{20}O_2$: C, 85.2; H, 5.7.
Found: C, 84.8; H, 5.7.

Its formation is explained by 1,4 addition of benzohydrylsodium to the enolic form (XIV) of 2,3-dimethylnaphthoquinone, and subsequent dehydrogenation by means of air or some constituent of the reaction mixture.

Through the red alkaline aqueous solution a stream of air was passed, whereby a lighter red solution was obtained. A yellow crystalline mass precipitated, partly spontaneously, partly on acidification. From butyl acetate beautiful needles, m.p. 261–262°, which gave a gold-red solution in concentrate sulfuric acid (XII).

Anal. Calc'd for $C_{24}H_{18}O_4$: C, 77.8; H, 5.0.
Found: C, 77.7, 77.8; H, 5.5, 5.3.

In some runs, without discernible reason, the previously-mentioned isomer, m.p. 228°, was obtained instead.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS CO., RIVERSIDE, ILL.]

REACTIONS OF PARAFFINS WITH AROMATIC HYDROCARBONS. I. VARIOUS PARAFFINS WITH BENZENE

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The reaction of paraffins with aromatic hydrocarbons in the presence of a catalyst according to the general equation:

$$\underset{\text{Paraffin}}{C_{(m+n)}H_{2(m+n)+2}} + \underset{\substack{\text{Aromatic Hydrocarbon}\\(\text{Ar} = \text{aryl radical})}}{\text{Ar}\cdot\text{H}} \xrightarrow{\text{Catalyst}} \underset{\substack{\text{Lower}\\\text{Paraffin}}}{C_nH_{2n+2}} + \underset{\substack{\text{Alkyl}\\\text{Aromatic}\\\text{Hydrocarbon}}}{\text{Ar}\cdot C_mH_{2m+1}} \quad (1)$$

has been described in an earlier paper[1] for the case of benzene and 2,2,4-trimethylpentane. In the present investigation, a number of hydrocarbons ranging from pentanes to *n*-hexadecane have been allowed to react with benzene in a tube for eight to twenty-four hours in the presence of aluminum chloride.*

The reaction with aromatic hydrocarbons other than benzene will be described in a later paper.

At present, the assumed mechanism for the reaction is as follows:

$$(a) \quad RR' + HCl \xrightarrow{AlCl_3} RCl + R'H \quad (2)$$

$$(b) \quad RCl + ArH \xrightarrow{AlCl_3} ArR + HCl. \quad (3)$$

The assumption that reaction *a* takes place is warranted by the fact that no reaction occurs in the complete absence of hydrogen chloride. The second reaction, *b*, is justified by the knowledge that hydrogen chloride in excess will reverse the reaction with consequent dealkylation of the hydrocarbon.[2]

[1] GROSSE AND IPATIEFF, *J. Am. Chem. Soc.*, **57**, 2415 (1935); see also V. N. Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," MacMillan Co., New York, **1936**, p. 720.

* It should be stressed that the research about to be described was carried out mainly for orientation in the new field of catalytic reactions between paraffins and aromatic hydrocarbons. It is realized that for the purpose of ascertaining with certainty the primary reaction products, and obtaining a more accurate comparison of the reactivity of different paraffins, a study of the reaction by means of a flow method would be advantageous, albeit more complicated and time-consuming.

[2] Data on dealkylation with hydrogen chloride will be published at a later date; See JACOBSEN, *Ber.*, **18**, 338, (1885).

The nature of the products formed is influenced by several factors. Primarily, of course, the points of scission are determined by the structure of the paraffin. Further, however, certain secondary products may be isolated which are probably due to isomerization of the original paraffin and to certain secondary reactions which produce by-products. We consider these factors in order.

The scission of a pair of carbon atoms (in the form of ethyl chloride (see equation above)), seems to be the predominant reaction of the paraffins. There seems to be no rupture of aliphatic carbon to hydrogen bonds since in no case has hydrogen been noted in the gaseous products, save in traces (below 0.001 mole). Moreover, in all cases where scission of the paraffin occurred in such a way as to sever the terminal carbon atom or pair of carbon atoms no methane or ethane was formed, but invariably toluene or ethylbenzene.

In the case of normal and isopentanes the reaction may be represented in the equations:

$$C_5H_{12} + C_6H_6 \begin{cases} \nearrow C_3H_8 + C_2H_5 \cdot C_6H_5 & (4a) \\ \searrow C_4H_{10} + CH_3 \cdot C_6H_5 & (4b) \end{cases}$$

Similarly, *n*-hexane and 2-methylpentane react according to the scheme:

$$C_6H_{14} + C_6H_6 \rightarrow C_4H_{10} + C_2H_5 \cdot C_6H_5 \qquad (5)$$

The reaction of *n*-heptane is more complex:

$$C_7H_{16} + C_6H_6 \begin{cases} \nearrow C_6H_{14} + CH_3 \cdot C_6H_5 & (6a) \\ \rightarrow C_5H_{12} + C_2H_5 \cdot C_6H_5 & (6b) \\ \searrow C_4H_{10} + C_3H_7 \cdot C_6H_5. & (6c) \end{cases}$$

The isomeric octanes show marked differences in behavior. While *n*-octane, like *n*-heptane, may be cleaved at various points along the chain, mainly as follows:

$$n\text{—}C_8H_{18} + C_6H_6 \begin{cases} \nearrow C_6H_{14} + C_2H_5 \cdot C_6H_5 & (7a) \\ \searrow C_5H_{12} + C_3H_7 \cdot C_6H_5, & (7b) \end{cases}$$

2,2,3-trimethylpentane, like 2,2,4-trimethylpentane,[1] shows scission at but one point,

$$\begin{array}{l} \mathrm{CH_3\ CH_3} \\ \mathrm{|\ \ |\ \ H\ H} \\ \mathrm{CH_3—C—C—C—CH} \\ \mathrm{|\ \ H\ H\ H} \\ \mathrm{CH_3} \end{array} + C_6H_6 \rightarrow C_4H_{10} + \begin{array}{l} \mathrm{CH_3} \\ \mathrm{| } \\ \mathrm{CH_3—C—C_6H_5.} \\ \mathrm{| } \\ \mathrm{CH_3} \end{array} \qquad (8)$$

With the long-chain paraffins, *n*-decane and *n*-hexadecane, no single reaction predominates. That cleavage occurs at most points on the chain is indicated, in the latter case at least, by isolation, from the reaction with benzene, of paraffin hydrocarbons ranging from butanes to undecanes.

That isomerization of the paraffins is a factor in the reaction may be demonstrated by the fact that rarely do the paraffins produced have structures corresponding to the original paraffin. It has been shown that under conditions similar to those prevalent in the reaction under discussion *n*-pentane will isomerize to isopentane, and *n*-butane to isobutane.[3] Therefore, in cases where *n*-butane might be expected from the simple scission of the original paraffin, isobutane will usually appear; *n*-hexane and benzene produce isobutane and ethylbenzene; 2,2,3-trimethylpentane and benzene produce isobutane and *tert*-butylbenzene.†

Another sort of rearrangement, which may be regarded in this case as a side-reaction, and which is invariably encountered, even at low temperatures, is the migration of side-chains attached to the aromatic nucleus. This reaction can be generally expressed by the following equation:

$$m\mathrm{R}\cdot\mathrm{C_6H_5} \xrightarrow{\mathrm{AlCl_3}} \mathrm{R}_m\cdot\mathrm{C_6H_{6-}}_m + (m-1)\ \mathrm{C_6H_6}\cdot \qquad (9)$$

A side-reaction to be expected but which obviously cannot be demonstrated is that involving the lower paraffins formed during the reaction with unreacted benzene.

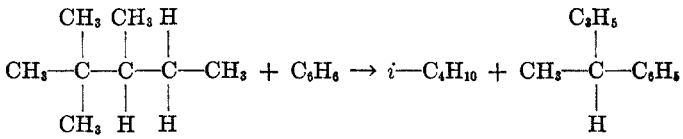
A reaction which probably explains the formation of paraffins in excess of the amounts demanded by equation (1) is the hydro-dehydrogenation reaction represented in

$$\mathrm{R}\cdot\mathrm{R}' + 2\mathrm{C_6H_6} \rightarrow \mathrm{RH} + \mathrm{R}'\mathrm{H} + \mathrm{C_6H_5}\cdot\mathrm{C_6H_5} \qquad (10)$$

Yet, another source of by-products lies in the reactions which benzene

[3] Investigations on the isomerization of paraffins will be published separately by PINES, GROSSE, AND IPATIEFF; see *Ind. Eng. Chem.*, **28**, 463 (1936).

† It might be argued that isobutane is produced in the latter reaction directly according to the reaction,



2,2,3-trimethylpentane *sec.*-butylbenzene

The fact that tertiary rather than secondary butylbenzene is actually found militiates against this explanation. In a separate experiment it was found impossible to demonstrate isomerization of sec.-butylbenzene to the tertiary compound in the presence of aluminum chloride, though intermolecular migration of the butyl groups did occur.

itself undergoes in the presence of aluminum chloride. As we have noted hereafter (see experimental part), one of the products formed by the reaction of benzene alone in the presence of aluminum chloride is ethylbenzene, our main indentifiable reaction product. From this source, under the conditions of our experiments, the yield is only of the order of 0.01 mole per mole of benzene; very small in relation to the products formed from other reactions. However, when ethane, propane, or the butanes are caused to react with benzene in the presence of aluminum chloride or bromide, the reaction conditions must be made so drastic that complete cleavage of the benzene nucleus may occur. For that reason, these paraffins are not discussed in the present paper: they do not react in accordance with the general equation 1.

TABLE I

EFFECT OF SIDE REACTIONS ON PRODUCT YIELDS

PRODUCTS	*n*-PENTANE		*i*-PENTANE		*n*-HEXANE	2-METHYL-PENTANE
	125°	175°	125°	175°	175°	125°
Propane found, g.	3.66	7.2	2.71	7.2		0
Butanes found, g.					13.4	22.1
Ethylbenzene, g. (Calc'd)	8.8	17.3	6.5	17.3	24.5	40.4
Ethylbenzene, g. (Found)	15.2	18.1	15.4	18.1	18.3	28.3

Because of all the possible side-reactions which we discuss above, while in some cases the yields of the hydrocarbons do correspond to the quantities expected, in most cases they do not. In Table I we illustrate this point for pentanes and hexanes; we compare the yields of ethylbenzene expected and actually obtained. The calculated yields of ethylbenzene are found from the amounts of propane and butane obtained.

Although the error which obtains in the analysis of a complex hydrocarbon mixture may be considerable, we believe that much of the discrepancy lies in the side reactions which occur.

We have mentioned in passing that the conditions necessary for the reaction of ethane, propane or the butanes are so drastic that the benzene nucleus is disrupted. It is further true that there is not appreciable reaction between benzene and straight-chain paraffins below 100° under our conditions. On the other hand, 2,2,4-trimethylpentane will react with benzene in the presence of aluminum chloride readily and with practically complete conversion between 25° and 50°—and even below 0° during longer reaction times.

EXPERIMENTAL

In most cases the materials (ordinarily present in the ratio of one mole of paraffin and two moles of benzene to 0.1 mole of aluminum chloride) were placed in a Pyrex

tube containing glass Raschig rings, and saturated with dry hydrogen chloride. The tube was then sealed and heated in a rotating Ipatieff bomb. In some cases the Pyrex liner was equipped with a ground-glass stopper opening to the exterior through a coil of capillary tubing,[4] thus making it possible to compress into the bomb any desired quantity of dry hydrogen chloride. In the case of the reaction involving 2,2,3-trimethylpentane the reaction vessel was Pyrex and was fitted with a mechanical stirrer, an inlet tube for nitrogen or hydrogen chloride, a burette for the admission of liquid, and a reflux condenser with an outlet tube.

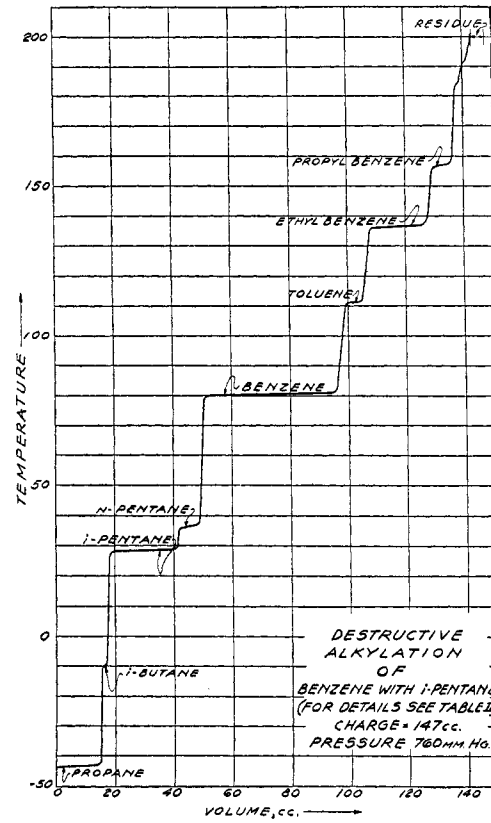


FIG. 1

Benzene was obtained from the J. Baker Chemical Co., C.P., thiopene-free grade. n-*Pentane* (b.p.‡ 35.8°; n_D^{20} 1.3580) and *isopentane* (b.p. 27.6°; n_D^{20} 1.3539) were obtained from Phillips Petroleum Co. and were over 99.5% pure. n-*Decane* (b.p. 172–4°; n_D^{20} 1.4104) and synthetic n-*hexane* (b.p. 68–9°; n_D^{20} 1.3770) were supplied by Eastman Kodak Co.; n-*heptane* (m.p. −90.8°; b.p. 98.4°; n_D^{20} 1.3878; d_4^{20} 0.6835) by the California Chemical Co., and n-*hexadecane*, (m.p. 17.5°; n_D^{20} 1.4350) by E. I. Du

[4] GROSSE, *J. Am. Chem. Soc.*, **60**, 212 (1938).

‡ All boiling points are at 760 mm.

TABLE II

Alkylation of Benzene

Experimental conditions and products	Paraffins investigated												
	n-Pentane		*i*-Pentane		*n*-Hexane	2-Methylpentane	*n*-Heptane		*n*-Octane		2,2,3-Trimethylpentane	*n*-Decane	*n*-Hexadecane
Conditions of reaction:													
Temperature	125°	175°	125°	175°	175°	125°	125°	175°	125°	150°	80–90°	125°	125°
Time, hours	8	8	8	8	8	8	8	8	10	14	11	23	8
Maximum pressure, atm.	Sealed tube	Sealed tube	Sealed tube	Sealed tube	Sealed tube	Sealed tube	Sealed tube	Sealed tube	10.5	12	1	8	4.5
Reactants charged:													
Paraffin, g.	45.23	45.9	45.63	46.2	50.0	54.90	51.09	51.0	57.0	56.3	28.5	36.3	113.0
Benzene, g.	99.67	100.4	100.26	100.0	91.0	100.24	78.13	78.06	78.0	77.0	39.0	48.2	78.0
Aluminum chloride, g.	8.51	8.50	8.49	8.48	7.73	8.56	6.69	6.61	6.66	10.1	3.33	3.28	6.7
Hydrogen chloride, g.	1.16	0.33	1.20	1.18	0.16	1.75	0.06	0.19	2.31	1.8	0.40	2.72	0.9
Total, g.	154.57	155.1	155.58	155.9	148.9	165.45	135.97	135.86	144.0	145.2	71.2	90.5	198.6
Gross distribution of products:													
Gas,[a] g.	8.07	12.2	9.12	13.16	15.7	22.99	6.90	9.39	6.7	8.4	11.6	3.8	0.8
Upper layer, g.	120.05	115.6	120.6	110.72	105.0	115.35	108.69	104.83	103.6	108.4	46.1	62.8	175.0
Lower layer (including $AlCl_3$), g.	24.9	25.7	24.4	30.86	26.9	25.6	19.61	20.80	27.1	26.2	12.4	15.2	20.3
Losses,[k] g.	1.55(0.70)[k]	1.6	1.46(0.54)[k]	1.2	1.3	1.51(0.78)[k]	0.77	0.84	6.6	2.2	1.1	8.7	2.5
Total, g.	154.57	155.1	155.58	155.9	148.9	165.45	135.97	135.86	144.0	145.2	71.2	90.5	198.6
Gas composition (vol. %):													
Propane	56.3	69.2	38.5	64.2		0.0	28.9	57.2	(*b*)	18.2[c]		(*d*)	(*e*)
n-Butane	13.8				4.1					3.8			
i-Butane		10.8	30.3	15.5	87.9	96.9	67.4	39.7		66.2	98.8		
Pentanes	26.3	18.0	28.7	17.4	8.0		3.7	1.5		11.5	1.2		
Hexanes	3.6	2.0	2.5	2.9		3.1		1.6					
Paraffin (or isomer) recovered, g.	27.0	20.8	27.1	21.0	19.0	13.5	31.3	24.0	29.6	32.6	9.7	20.1	83
Benzene recovered, g.	71.5	51.2	71.7	42.7	44.0	56.4	64.8	45.7	43.7	37.2	29.5	25	57.0
Mole ratio reacting $\frac{\text{paraffin}}{\text{aromatic}}$	0.69	0.56	0.72	0.48	0.71	0.86	1.18	0.66	0.55	0.39	1.42	0.40	0.21

Identified reaction products:													
Propane, g.		3.66	7.2	2.71	7.2	0	0.0	1.6	4.7	6.5[b]	1.2	0		(g)
i-Butane, g.		1.18	1.5	2.79	2.3	13.4	22.1	5.0	4.3		5.8	11.5	3.6[d]	0.42
Pentanes, g.							0.98	2.5	2.9			0		
Hexanes, g.		0	0	0	0		3.1	0.3		0.4		0		1.2
Toluene, g.		2.5	8.15	2.7	8.0	8.4	5.8	1.4	4.6	2.6	6.7	0		2.2
Ethylbenzene,[h] g.		15.2	18.1	15.4	18.1	18.3	28.3	7.4	12.7	9.8	9.6	0	4.9	5.8
n-Propylbenzene,[i] g.		2.7	5.9	2.5	6.3	4.8	0.0	3.3	3.9	4.0	4.5			2.2
Other alkyl-	175–200°	0.9	4.6	0.8	4.6	3.5	2.9		3.3	3.3	4.5	(f)		1.6
benzenes from	200–225°	1.0	0.8	1.0	3.1		1.2	3.0	0.2					2.9
upper layer,[j] g.	>200°	2.3	7.0	2.5	8.6	5.2	4.6		5.6	4.0	7.1		4.0	

[a] All material boiling below 25° has been considered as gas.

[b] Gas analyzed by absorption and combustion methods only. At N.T.P.; paraffins—3400 cc. (index 3.0).

[c] Gas analysis indicates 0.3% methane + ethane.

[d] Gas analyzed by absorption and combustion methods only. At N.T.P.; paraffins—1550 cc. (index 4.0).

[e] Quantity of gas too small for accurate fractionation. Analysis indicates the following: paraffins with index 2.3, 220 cc.; C_4-paraffins, 160 cc.; C_5-, C_6-paraffins, 60 cc.

[f] Chief alkylation product *tert.*-butylbenzene. Yield 5.7 g.

[g] Aromatic hydrocarbons were removed from several of the fractions by $H_2SO_4 - SO_3$ and the residual paraffins characterized by boiling range and elementary analysis. These data along with the yields are as follows:

PARAFFIN	YIELD GRAMS	BOILING RANGE AT 757 MM.	FOUND % C	FOUND % H	CALC'D % C	CALC'D % H
Hexanes	1.2	49–66	82.66 82.21	16.00 16.09	83.61	16.39
Octanes	1.0	111–118	84.28	15.32	84.11	15.89
Nonanes	0.8	135.5–147	84.25	15.45	84.27	15.73
Decanes	0.6	167.5–176	84.42	15.27	84.41	15.59

[h] The aromatic constituent of the upper layer fraction in the boiling range 125–150° was always chiefly ethylbenzene. Any xylenes (which were shown to be present in small amounts in a few cases) are included in the yield of ethylbenzene.

[i] The aromatic constituent boiling in the range 150–175° is reported as *n*-propylbenzene since this is the chief constituent and since *i*-propylbenzene was never found to be present. This does not necessarily exclude small amounts of polyalkylbenzenes boiling in this range.

[j] All upper layer fractions were water-white and stable toward permanganate at room temperature.

[k] Figures in parentheses indicate hydrogen chloride recovered in the gas phase.

Pont de Nemours Co. n-*Octane* (b.p. 124.9–125.4°; n_D^{20} 1.3970) was prepared by catalytic hydrogenation of caprylene, which in turn was derived from capryl alcohol by catalytic dehydration over aluminum oxide. The *2,2,3-trimethylpentane* (b.p. 110.2–111.0°; n_D^{20} 1.4030) was prepared by Dr. B. S. Friedman by catalytic hydrogenation of 2,2,3-trimethyl-3-pentanol. The *2-methylpentane* (b.p. 60.19 ±0.05°; n_D^{20} 1.3716; d_4^{20} 0.6527) we owe to the courtesy of Dr. J. H. Bruun of the Sun Oil Company.[5] Merck's reagent-grade sublimed and powdered *aluminum chloride* was used without further purification. *Hydrogen chloride* was taken from a cylinder containing the pure, dry, compressed gas.

For analysis the *gaseous reaction products* were passed through a tared absorber filled with soda lime (to remove the hydrogen chloride) into a receiver cooled to −78° with a solid carbon dioxide-acetone mixture. The gas which did not condense was collected in a graduated gas holder over a saturated salt solution. The condensed gases were analyzed by a low-temperature Podbielniak distillation supplemented by absorption methods. The gases which had not been condensed were analyzed by conventional combustion and adsorption methods.

The *liquid reaction products* consisted of a water-white or slightly yellow upper layer and a lower layer varying in color from dark-brown to black as the temperature of the reaction was increased. The *upper layers* were washed with water, dried, and fractionated in a high-temperature Podbielniak column. A typical result is shown in the accompanying figure. The fractions, containing both paraffins and aromatic hydrocarbons, were analyzed by shaking (in a volume ration of 1:1) first, with 100% sulfuric acid and, then, with sulfuric acid containing 15% of free sulfuric anhydride until the residual hydrocarbon gave no reaction with nitration mixture. In the experiment with hexadecane, the residual hydrocarbons were analyzed for carbon and hydrogen for positive identification. Individual aromatic hydrocarbons were usually identified in the fractions of narrow-boiling range by the preparation of solid derivatives and the melting points of mixtures of the derivatives with known samples. The derivatives used are as follows:

AROMATIC HYDROCARBON	DERIVATIVE
Benzene	*m*-Dinitrobenzene
Toluene	Trinitrotoluene
Ethylbenzene	Benzoic acid
p-Xylene	Terephthalic acid and its dimethyl ester
n-Propylbenzene	2,4-Diacetamido-*n*-propylbenzene[6]
tert.-Butylbenzene	*p*-Di-*tert.*-butylbenzene,[7] does not decolorize bromine
Biphenyl	Melting point and mixture melting point

The *lower layers* were dark brown or black liquids containing the combined catalyst. Their color deepened with the temperature at which the reaction was carried out. They always gave a vigorous reaction with water or ice to form an oil. In general, if the reaction was carried out at temperatures of 125° or lower, this oil was completely ether-soluble. At reaction temperatures of 175° only 30–50% of the hydrocarbon portion of the lower layer was soluble in ether, the rest consisting of tarry, dehydrogenated materials. The lower fractions of these oils consisted mainly of benzene, toluene, and ethylbenzene, and were free of unsaturated hydrocarbons. The higher-boiling fractions, 175°–200°, were always unsaturated to permanganate

[5] See BRUUN, HICKS-BRUUN, AND FALCONER, *J. Am. Chem. Soc.*, **59**, 2355 (1937).

[6] IPATIEFF AND SCHMERLING, *J. Am. Chem. Soc.*, **59**, 1056 (1937).

[7] IPATIEFF AND PINES, *ibid.*, **58**, 1056 (1936); J. ORG. CHEM., **1**, 476 (1936).

solutions (*cf.* upper layer fractions) although they represented, substantially, aromatic hydrocarbons (n_D^{20} = 1.495 to 1.62). They were free of paraffins.

The *experimental data* for each reaction, showing the quantities of starting materials and the yields of the various reaction products, are to be found in Table II.

Reaction between benzene and aluminum chloride.—We have reinvestigated the behavior of benzene alone in the presence of aluminum chloride[8] under our experimental conditions.

Benzene was heated to 125° for eight hours in a sealed Pyrex tube placed in an Ipatieff bomb.

REAGENTS (GRAMS)		PRODUCTS (GRAMS)	
Benzene	150.19	Gas	0.0
Aluminum chloride	13.07	Upper Layer	125.3
Hydrogen chloride	0.43	Lower Layer	38.4
Total	163.69	Total	163.7

The upper layer consisted of 96.0 weight per cent. of pure benzene and about 0.5% toluene, 1.6% ethylbenzene, 0.5% diphenyl, and about 1.4% of unidentified aromatic hydrocarbons boiling between 150–250°/760 mm. and having an n_D^{20} = 1.501–1.567.

The ethylbenzene yield amounted to only 0.009 mole per mole of original benzene.

The oil obtained from the lower layer (d_4^{20} = 1.08), containing the aluminum chloride, after decomposition with ice contained 71 weight per cent. of pure benzene and 29% of higher aromatic hydrocarbons boiling at 760 mm. as follows:

RANGE	PER CENT. BY WEIGHT	n_D^{20}	REMARKS
100–125°	3.4	1.4970	Water-white, no unsaturated hydrocarbons
125–175°	1.7	1.4980	Water-white, no unsaturated hydrocarbons
175–200°	1.1	1.5130	Slightly yellow, traces of unsaturates.
200–225°	4.7	1.5356	Slightly yellow, traces of unsaturates.
225–250°	1.7	1.5625	Slightly yellow, traces of unsaturates.
250–275°	4.0	1.5835	Yellow, traces of unsaturates.
275–300°	16	1.5958	Lemon-yellow, traces of unsaturates.
>300°	67		Partly crystalline; probably $C_6(C_2H_5)_6$.

SUMMARY

The destructive alkylation reaction between benzene and various paraffins ranging from pentanes to *n*-hexadecane in the presence of aluminum chloride was investigated. The reaction products consist of lower-molecular-weight paraffins, such as propane, butanes, pentanes, etc., and alkylated aromatic hydrocarbons, such as ethylbenzene, toluene, and others.

ACKNOWLEDGEMENTS

The authors wish to express their appreciation to J. Grutka and R. A. Klett, who made the low-temperature Podbielniak distillations, and to R. W. Moehl for carbon and hydrogen analyses.

[8] FRIEDEL AND CRAFTS, *Bull. soc. chim.*, **39**, 195, 306 (1883); GUSTAVSON, *Compt. rend.*, **146**, 640 (1908); FISCHER AND NIGGEMANN, *Ber.*, **49**, 1475 (1916); IPATIEFF AND KOMAREWSKY, *J. Am. Chem. Soc.*, **56**, 1926 (1934).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT]

GUANIDINE STRUCTURE AND HYPOGLYCEMIA:* SOME CARBOCYCLIC DIGUANIDINES

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INTRODUCTION

Certain reports in the literature on guanidine structure and hypoglycemic activity suggested the preparation of three carbocyclic diguanidines, *p*-phenylenediguanidine (I), 4,4′-diguanidobiphenyl (II) and 4,4′-diguanidodiphenylmethane (III), in order to compare their physiological action with 1,6-diguanidohexane which Kumagai, Kawai and Shikinami[1] reported as equal to synthalin (1,10-diguanidodecane) in hypoglycemic activity.

Para phenylenediguanidine (I) was of interest because in it the six skeletal carbon atoms of 1,6-diguanidohexane are combined in a benzene nucleus while the two guanido groups occupy comparable positions of maximum distance from each other. Previously it was shown by one of us[2] that when *p*-phenylenediamine was condensed with an *S*-alkylisothiourea salt only one amino group reacted, and a salt of *p*-aminophenylguanidine was obtained instead of *p*-phenylenediguanidine. The fact that *p*-aminophenylguanidine was physiologically inactive[3] made it even more desirable to obtain the corresponding guanyl derivative, *p*-phenylenediguanidine (I), for physiological study.

In 1928 Bischoff[4] obtained impure 4,4′-diguanidobiphenyl sulfate and made the observation that it lowered the blood sugar of normal rabbits. In view of the fact that his compound was admittedly impure, the question arises as to whether the hypoglycemic effects were due to 4,4′-diguanidobiphenyl (II) itself, or to some impurity. This issue could be settled only if pure 4,4′-diguanidobiphenyl (II) were available. Not only was the reported magnitude of the hypoglycemic effect[5] sufficiently great to justify

* For other papers in this series see BRAUN AND LUDWIG, J. ORG. CHEM., **2**, 442 (1937); **3**, 16 (1938).

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[1] KUMAGAI, KAWAI, AND SHIKINAMI, *Proc. Imp. Acad.* (Japan), **4**, No. 1, 23 (1928).

[2] BRAUN, *J. Biol. Chem.*, **89**, 97 (1930); *J. Am. Chem. Soc.*, **54**, 1511 (1932).

[3] PARKS, AND BRAUN, *J. Biol. Chem.*, **91**, 629 (1931).

[4] BISCHOFF, *ibid.*, **80**, 345 (1928).

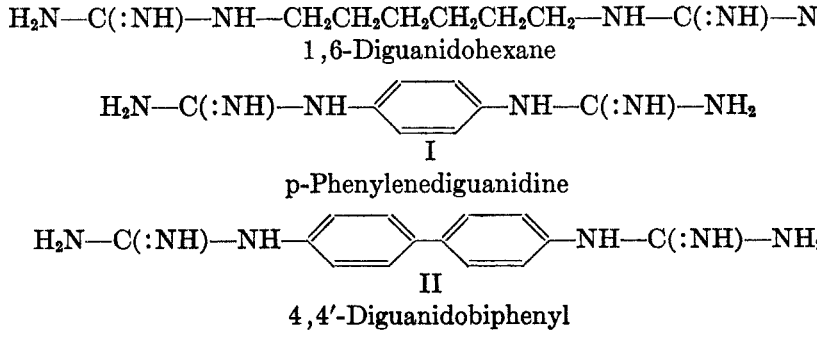
[5] BISCHOFF, SAHYUN, AND LONG, *ibid.*, **81**, 325 (1929).

attempts to prepare pure 4,4′-diguanidobiphenyl (II) and to study its hypoglycemic effects, but this compound would also offer the opportunity for direct comparison of its hypoglycemic activity with that of neosynthalin (1,12-diguanidododecane). In 4,4′-diguanidobiphenyl (II) the twelve skeletal carbon atoms are combined into two attached benzene nuclei, and in neosynthalin they are in a straight chain, while in both compounds the two guanido groups are at maximum distances from each other.

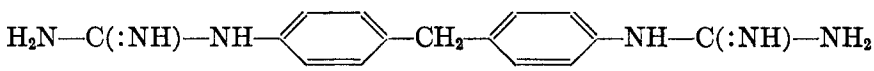
The attempted preparation of 4,4′-diguanidobiphenyl (II) by the Ullmann reaction[6] necessitated the synthesis of certain new salts of *p*-bromophenylguanidine and a new monoguanidine, *p*-iodophenylguanidine. All efforts to couple either *p*-bromophenylguanidine or *p*-iodophenylguanidine by means of copper or silver failed to produce any traces of II. In the case of *p*-iodophenylguanidine appreciable amounts of the starting compound were recovered from the reaction mass as well as some *p*-iodoaniline, the latter probably having been formed by decomposition of *p*-iodophenylguanidine, as evidenced by the continuous evolution of ammonia throughout the attempted coupling even under mild conditions.

The availability of 4,4′-diguanidodiphenylmethane (III) for physiological study offers interesting considerations. In this compound (III) the two guanido groups are attached directly to aromatic nuclei as they are in 4,4′-diguanidobiphenyl (II). However, in III the two benzene residues are not directly attached as they are in II, but are separated by a single methylene group. It seems of interest to study the physiological action of 4,4′-diguanidodiphenylmethane (III) in order to determine to what extent, if any, the slight but very significant structural change of introducing one methylene group between the two benzene nuclei holding the guanido groups would have upon the hypoglycemic properties as compared directly with those of 4,4′-diguanidobiphenyl (II).

The details of the syntheses of these mono- and diguanidines and a brief comparison of the physiological activity of the latter with that of 1,6-diguanidohexane are presented in this paper. The structural relationships between the compounds under discussion are shown below.



[6] ULLMANN, *Ann.*, **332**, 38 (1904).



III

4,4′-Diguanidodiphenylmethane

EXPERIMENTAL

Synthetic Part

Preparation of 1,6-diguanidohexane sulfate.—Suberic acid (Kahlbaum) was converted in the usual manner through the dichloride into its diamide (m.p. 218–219° uncorr.).* The diamide through a double Hofmann degradation after the method of Van Breukeleveen[7] yielded hexamethylenediamine. 1,6-Diguanidohexane sulfate was obtained in 14.4% yield (purified compound) from the diamine and *S*-methylisothiourea sulfate according to Heyn[8]. The purified crystalline sulfate was discolored but not molten at 340°. (Heyn reported that this compound melts above 280°.)

Anal. Calc'd for $C_8H_{22}N_6O_4S$: S, 10.75; Found: S, 10.85.

Preparation of p-*phenylenediguanidine* (*I*).—Twenty-five grams (0.138 mole) of *p*-phenylenediamine dihydrochloride (Eastman Kodak Co.) and 18 g. (0.429 mole) of cyanamide (Eastman Kodak Co.) in 570 cc. of absolute ethyl alcohol were heated under reflux on a steam bath for ten hours. The resulting dihydrochloride (12.8 g.) was filtered off, washed with ether and dried. The crude salt was dissolved in 50 cc. of hot water, boneblacked, and to the cold filtrate was added 60 cc. of a 10% solution of sodium hydroxide. *p*-Phenylenediguanidine precipitated as lustrous white plates which were filtered off, washed with cold water and dried *in vacuo*. The base, after recrystallization from hot water, melted at 258–259° uncorr. with decomposition. The yield (purified crystalline compound) was 9.0 g. or 34.0%.

Anal. Calc'd for $C_8H_{12}N_6$: N, 43.79; Found: N, 43.55 (micro-Kjeldahl).

The base when first formed appeared as large lustrous white plates and probably was a hydrate. After standing *in vacuo* over sulfuric acid the lustre entirely disappeared and the material changed into a dull finely crystalline powder which was not a hydrate as shown by analysis. The base was soluble in hot absolute alcohol and hot water. Its aqueous solutions were strongly alkaline.

The picrate of *p*-phenylenediguanidine, after recrystallization from a large volume of boiling water, was bright golden yellow. It darkened at about 290° but was not molten at 317°.

Seven and one-half grams (0.039 mole) of the base was suspended in 470 cc. of warm 70% ethyl alcohol, and dry hydrogen chloride passed in until complete solution had been effected. The hot solution was boneblacked, filtered, and cooled, and dry ether was added until permanent turbidity was obtained. Upon standing in an ice-chest the dihydrochloride crystallized out. The white crystalline salt was filtered off, washed with dry ether and dried *in vacuo* at room temperature. The dihydrochloride was very soluble in cold water and melted at 315° uncorr. The yield (purified compound) calculated from the base was 7.3 g. or 70.9%.

Anal. Calc'd for $C_8H_{14}Cl_2N_6$: N, 31.70; Cl, 26.75.
Found: N, 31.39 (micro-Kjeldahl); Cl, 26.68.

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* The melting point reported for suberic diamide in Beilstein, 4th Ed., II, 694, is 216–217°.

[7] VAN BREUKELEVEEN, *Rec. trav. chim.*, **13**, 34 (1894).

[8] HEYN, *U. S. Patent* 1,737,192 (Nov. 26, 1929).

(In carrying out the chloride determinations, the silver chloride precipitates were removed by filtration at 60–70° to prevent the precipitation of *p*-phenylenediguanidine nitrate which is insoluble in cold water.)

Preparation of p-*bromophenylguanidine.*†—Thirty-six grams (0.173 mole) of *p*-bromoaniline hydrochloride and 8 g. (0.190 mole) of cyanamide in 100 cc. of absolute ethyl alcohol were heated for thirteen hours under reflux on a steam bath. The resulting solution, after being cooled, was treated with dry ether until permanent turbidity resulted. After standing in an ice-chest a crystalline mass of *p*-bromophenylguanidine hydrochloride formed. The product was filtered off, washed with dry ether, and dried *in vacuo* over sulfuric acid. After purification by re-solution in absolute alcohol and slow precipitation with petroleum ether the hydrochloride melted at 175° uncorr. The yield (purified crystalline salt) was 33 g. or 76.3%.

Anal. Calc'd for $C_7H_8BrClN_3$: Cl, 14.20; Found: Cl, 14.18.

The free base (m.p. 121–123° uncorr.), produced by the addition of a dilute solution of sodium hydroxide to an aqueous solution of the hydrochloride, gradually absorbed carbon dioxide from the air and formed the normal carbonate. After recrystallization from hot water the carbonate was obtained as small clusters of fine colorless needles, melting at 145–149° uncorr. with decomposition.

Anal. Calc'd for $(C_7H_8BrN_3)_2 \cdot H_2CO_3$: Br, 32.61; Found: Br, 32.48 (micro-Carius).

The picrate *of p-bromophenylguanidine, after recrystallization from boiling* dilute ethyl alcohol, was deep yellow and melted at 220° uncorr.

Preparation of p-*iodophenylguanidine.*—Twelve and one-half grams (0.049 mole) of *p*-iodoaniline hydrochloride and 3.5 g. (0.083 mole) of cyanamide in 50 cc. of absolute ethyl alcohol were heated under reflux on a steam bath for seventeen hours. The resulting solution was boneblacked, filtered hot, and then diluted with water. After the alcohol had been distilled off, the remaining aqueous solution was treated with a dilute solution of sodium hydroxide, whereupon an oily layer formed at once. The latter solidified after standing in the cold. The solid material was collected by filtration and treated with 100 cc. of boiling water. The oily layer of unreacted *p*-iodoaniline was allowed to settle, and the clear supernatant liquid was removed by decantation. After concentration to about 70 cc. the aqueous layer upon standing in the cold deposited white crystalline *p*-iodophenylguanidine, which was collected on a filter, washed with ice water and dried. The free base, as in the case of *p*-bromophenylguanidine, absorbed carbon dioxide and formed a stable normal carbonate. The latter, after purification by repeated recrystallizations from hot water, melted at 147–149° uncorr. The yield (purified compound) was 3.5 g. or 12.2%.

Anal. Calc'd for $(C_7H_8IN_3)_2 \cdot H_2CO_3$: I, 43.46; Found: I, 43.69 (Carius).

The picrate of *p*-iodophenylguanidine, after recrystallization from boiling dilute ethyl alcohol, was bright yellow and melted at 235° uncorr.

Some of the carbonate was suspended in absolute ethyl alcohol, and dry hydrogen chloride was passed in until all of the solid had dissolved. The resulting solution was boneblacked, filtered hot, and concentrated to a small volume (5 cc.). After cooling, anhydrous ether was added until permanent turbidity resulted. Upon

† Harwood[9] first prepared the free base (m.p. 122–124°) and the nitrate (m.p. 185–186°) of *p*-bromophenylguanidine by heating under pressure an alcoholic solution of *p*-bromoaniline hydrochloride and cyanamide, but did not isolate the hydrochloride, carbonate or picrate.

[9] HARWOOD, Thesis, Iowa State College, **1931.**

standing in the ice-chest for several hours the white *p*-iodophenylguanidine hydrochloride crystallized. It was purified by re-solution in absolute alcohol and reprecipitation with dry ether. The pure hydrochloride melted at 151–153° uncorr.

Anal. Calc'd for $C_7H_9ClIN_3$: Cl, 11.92; Found: Cl, 12.01.

Preparation of 4,4'-diguanidobiphenyl (II).—Twelve grams (0.0467 mole) of benzidine dihydrochloride and 5 g. (0.119 mole) of cyanamide in 75 cc. of freshly distilled isoamyl alcohol were heated under reflux on an oil bath for twenty-three hours. (There was never complete solution of the reactants during the condensation.) The white, insoluble reaction product was filtered off, washed with ether, and dried *in vacuo* at room temperature. The free base was obtained from the crude dihydrochloride by treating the latter in hot aqueous solution with an excess of dilute sodium hydroxide. The base, after three recrystallizations from a large volume of boiling water and drying at 100° *in vacuo*, melted at 234–236° uncorr. with decomposition. The yield (crystalline base) was 4.5 g. or 36%.

Anal. Calc'd for $C_{14}H_{16}N_6$: N, 31.33; Found: N, 30.64‡ (Semimicro-Dumas).

The picrate of 4,4'-diguanidobiphenyl (II) was obtained from a large volume of boiling water as an orange, finely crystalline material which, upon being heated, gradually discolored (badly discolored at 290°) and finally decomposed without melting at 308° uncorr. This orange picrate presents an interesting contrast with the picrates of the other diguanidines described in this paper, all of which were bright yellow.

The dihydrochloride was prepared by suspending the free base in boiling absolute ethyl alcohol and adding dilute hydrochloric acid until complete solution had been effected. The hot solution was boneblacked, filtered, and cooled. Acetone and ether were then added until permanent turbidity resulted. Upon standing in the cold, the white crystalline dihydrochloride precipitated out. It was filtered off, washed with dry acetone and ether and dried at 100° *in vacuo*. It did not melt up to 300°.

Anal. Calc'd for $C_{14}H_{18}Cl_2N_6$: N, 24.64; Cl, 20.79.
Found: N, 24.13 (Kjeldahl); Cl 20.60.

The sulfate was obtained by adding dilute sulfuric acid to a suspension of the free base in warm water. The crude sulfate, after being washed free of sulfuric acid with cold absolute ethyl alcohol, was recrystallized from boiling water. The purified sulfate (glistening prisms) melted at 318–320° uncorr., with decomposition.

Anal. Calc'd for $C_{14}H_{16}N_6 \cdot H_2SO_4$: S, 8.75; Found: S, 8.73.

Preparation of 4,4'-diguanidodiphenylmethane (III).—4,4'-Diaminodiphenylmethane (Eastman Kodak Co.) was converted into its dihydrochloride by heating it on a steam bath with concentrated hydrochloric acid. The dihydrochloride, recrystallized from hot concentrated hydrochloric acid, melted at 282° uncorr.§

Anal. Calc'd for $C_{13}H_{16}Cl_2N_2$: Cl, 26.16; Found: Cl, 26.02.

Twenty-three grams (0.0848 mole) of 4,4'-diaminodiphenylmethane dihydrochloride and 10 g. (0.238 mole) of cyanamide in 40 cc. of absolute ethyl alcohol were heated under reflux on the steam bath for five hours. The resulting solution was

‡ This compound was very difficult to burn. Although the nitrogen analysis was only in fair agreement with the calculated value, subsequent analyses on the dihydrochloride and sulfate salts prepared from this base left no doubt as to its identity.

§ The melting point reported for 4,4'-diaminodiphenylmethane dihydrochloride in Beilstein, 4th Ed., XIII, 239, is 285°.

filtered, diluted with water and made alkaline by the addition of an excess of dilute aqueous sodium hydroxide solution, whereupon the free base, 4,4′-diguanidodiphenylmethane (III), precipitated out at once. It was collected by filtration, washed with ice water until free of alkali and dried at 105–110°. After four recrystallizations from boiling water (200 cc.) the base was obtained as small colorless plates which melted at 199–200° uncorr., with decomposition. The yield (purified base) was 8 g. or 34%.

The picrate, slender, light-yellow needles from boiling dilute ethyl alcohol, softened and turned orange at 200–202° and melted at 229–230° uncorr.

The sulfate was prepared by the addition of dilute sulfuric acid to a hot aqueous solution of the free base (III). Upon concentrating the solution and cooling, the sulfate crystallized in glistening, colorless prisms. These were filtered off, washed with absolute ethyl alcohol, and recrystallized from boiling dilute alcohol. The purified sulfate melted at 254–256° uncorr., with decomposition.

Anal. Calc'd for $C_{15}H_{18}N_6 \cdot H_2SO_4$: S, 8.43; Found: S, 8.44.

Both 4,4′-diguanidobiphenyl (II) and 4,4′-diguanidodiphenylmethane (III) absorbed carbon dioxide from the air and formed stable carbonates.

The free base and the salts of 4,4′-diguanidodiphenylmethane (III) were much more readily soluble in water than the corresponding derivatives of 4,4′-diguanidobiphenyl (II).

Physiological Part

The physiological assays of 1,6-diguanidohexane, *p*-phenylenediguanidine (I), 4,4′-diguanidobiphenyl (II) and 4,4′-diguanidodiphenylmethane (III) were carried out in part at The Lilly Research Laboratories and in part at the Department of Physiology, College of Physicians and Surgeons, Columbia University, normal rabbits serving as the experimental animals in all of the work. The compounds were administered subcutaneously, and at various time intervals following injection the blood sugar was determined by the micro method of Shaffer and Somogyi[10] or by the macro procedure of Shaffer and Hartmann[11] using the conversion tables of Duggan and Scott.[12] In the micro procedure 0.25 cc. of blood was diluted 1 to 15 with the zinc reagent, and 2 cc. of the filtrate was used for each determination.

1,6-Diguanidohexane was hypoglycemic in doses greater than 30 mg.* per kilo of body weight but in smaller doses produced no hypoglycemia up to five hours following administration. This agreed with the observations of Kumagai, Kawai, and Shikinami[1].

Para phenylenediguanidine (I), in doses as high as 50 mg. per kilo, exhibited no hypoglycemic activity but was hyperglycemic at half this dosage, the hyperglycemia being especially marked shortly (up to about two hours) after injection of the compound. It appeared therefore, that cyclization of the six carbon atoms of 1,6-diguanidohexane into a benzene nucleus, as in *p*-phenylenediguanidine (I), destroyed the hypoglycemic properties and imparted hyperglycemic activity but without apparent increase in toxicity.

Pure 4,4′-diguanidobiphenyl (II) produced hypoglycemia in doses of 35 mg. per kilo. This definitely established the hypoglycemic properties of this compound, and confirmed the work of Bischoff[4] and Bischoff, Sahyun, and Long[5], who, after

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[10] Shaffer, and Somogyi, *J. Biol. Chem.*, **100**, 695 (1933).

[11] Shaffer, and Hartmann, *ibid.*, **45**, 365 (1920).

[12] Duggan, and Scott, *ibid.*, **67**, 287 (1926).

* All of the doses reported are calculated as free base.

working with impure 4,4′-diguanidobiphenyl sulfate (they named this compound diguanylbenzidine and also guanylbenzidine) reported that "certain of these fractions had a physiological action similar to synthalin." Unfortunately, however, 4,4′-diguanidobiphenyl proved to be very toxic and caused death with hypoglycemia in most of the animals.

4,4′-Diguanidodiphenylmethane (III) showed practically no hypoglycemic activity but was about as toxic as 4,4′-diguanidobiphenyl (II). It was interesting to compare the physiological properties of 4,4′-diguanidodiphenylmethane (III) with those of two similar aromatic diguanidines, 4,4′-diguanidodiphenyldisulfide and 4,4′-diguanidodiphenylsulfide[13] which were shown to produce no hypoglycemia and were not toxic in doses of 100 mg. per kilo. These observations suggested that the presence of the biphenyl nucleus is essential to the hypoglycemic properties of 4,4′-diguanidobiphenyl (II) since rupture of this nucleus through the introduction of a methylene group, a dithio linkage or a sulfide linkage between the two benzene residues destroyed the activity despite the presence of the two guanido groups in comparable positions in the molecules.

The physiological results indicated that the three carbocyclic diguanidines, *p*-phenylenediguanidine (I), 4,4′-diguanidobiphenyl (II) and 4,4′-diguanidodiphenylmethane (III), possessed less hypoglycemic activity, and, with the exception of *p*-phenylenediguanidine (I), were much more toxic than the straight-chain diguanidine, 1,6-diguanidohexane.

The major part of the synthetic work presented in this paper was supported by funds from a Sigma Xi Research Grant.

The authors wish to thank Mr. H. A. Shonle and Dr. E. D. Campbell of the Lilly Research Laboratories, and Professor E. L. Scott and Dr. L. B. Dotti of the Department of Physiology, College of Physicians and Surgeons, Columbia University, for carrying out the physiological assays.

SUMMARY

1. The methods of synthesis for *p*-phenylenediguanidine, *p*-bromophenylguanidine, *p*-iodophenylguanidine, 4,4′-diguanidobiphenyl, 4,4′-diguanidodiphenylmethane, and certain of their salts have been described.

2. The effects of *p*-phenylenediguanidine, 4,4′-diguanidobiphenyl and 4,4′-diguanidodiphenylmethane upon the blood sugar of normal rabbits have been studied and compared directly with the hypoglycemic properties and toxicity of a compound of the synthalin type, 1,6-diguanidohexane, and the results are briefly discussed from the point of view of hypoglycemia and chemical constitution in the guanidine field.

[13] BRAUN, AND LUDWIG, J. ORG. CHEM., **3**, 16 (1938).

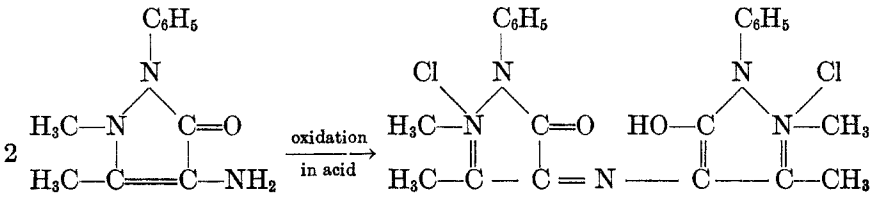
[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY, THE UNIVERSITY OF CHICAGO]

THE CONDENSATION OF AMINOANTIPYRINE WITH AROMATIC AMINES IN THE PRESENCE OF OXIDIZING AGENTS*†‡

EDGAR EISENSTAEDT

Received June 20, 1938

Aminoantipyrine can be oxidized to antipyrine red.[1] During the reaction one mole of ammonia is eliminated from two moles of aminoantipyrine.



This reaction suggested to the writer the possibility of producing indamine-type dyes by oxidizing mixtures of aminoantipyrine and an aniline. With this idea in mind, the oxidation of aminoantipyrine was carried out in the presence of various aromatic amines. New dyes were formed ranging in color from orange-red, through blue, to green, depending on the amine used. Phenols also were found to give color reactions with aminoantipyrine, but the conditions under which the phenols react are entirely different from those under which the amines react. The research reported in this paper is confined to the reaction of aminoantipyrine with aromatic amines.

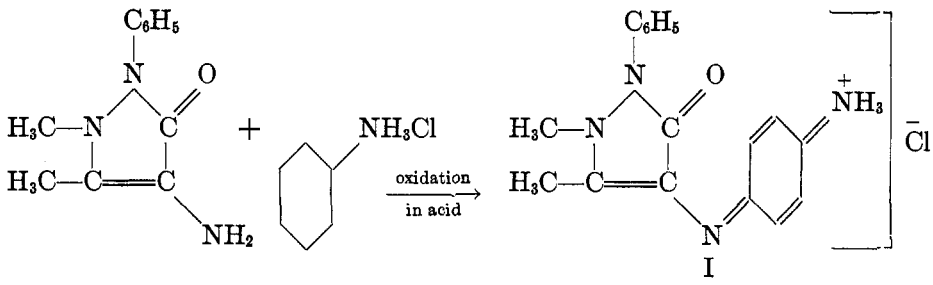
When aminoantipyrine, in solution with an equivalent of aniline hydrochloride, is oxidized with four equivalents of ferric chloride a blue-red dye is produced.

* The Dissertation submitted to the graduate faculty of The University of Chicago, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

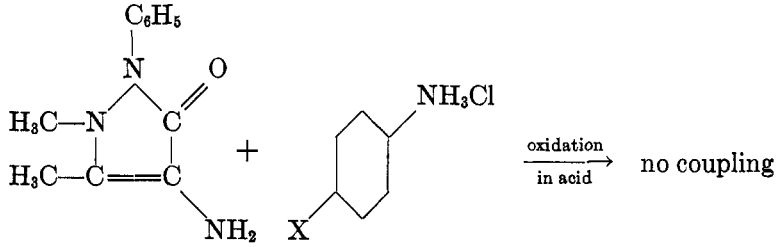
† It has been my great privilege to have worked on this research under the inspiring guidance of Professor Julius Stieglitz. I wish to express my appreciation to Dr. R. W. Johnson for his interest and criticisms in this work, and also I wish to thank Professor M. S. Kharasch for his suggestions during the last stages of this research. During the work I have had the advantage of the help and suggestions of my friend Dr. John Cryer.

‡ I wish to express my gratitude for a Julius Stieglitz Fellowship, the money for which was donated by the Chemical Foundation.

[1] MICHAELIS, *Ann.*, **352**, 157 (1907).

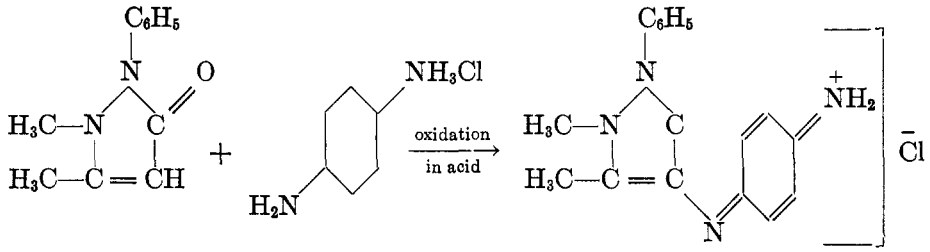


If *p*-toluidine, *p*-phenylenediamine or sulfanilic acid is used in place of aniline the reaction does not take place.



This evidence indicates that the dye formation involves the para hydrogen rather than the aromatic amine hydrogen. This view is supported by the fact that dimethylaniline with aminoantipyrine gives the color reaction, whereas *p*-bromodimethylaniline with aminoantipyrine does not.

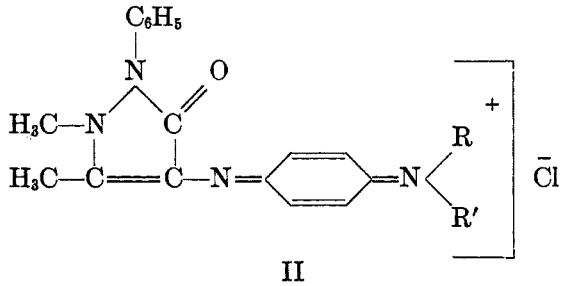
One might expect the oxidation of a mixture of antipyrine with *p*-phenylenediamine to produce the same colored compound as aminoantipyrine and aniline.



The indicated reaction does not take place. Dimethylaniline and antipyrine fail to give a distinguishing color reaction. If dimethylaminoantipyrine (pyramidon) is used in place of aminoantipyrine with a para-unsubstituted amine hydrochloride, only the blue color characteristic of oxidized pyramidon is produced. These facts indicate that the primary amino group in aminoantipyrine is involved in the color production.

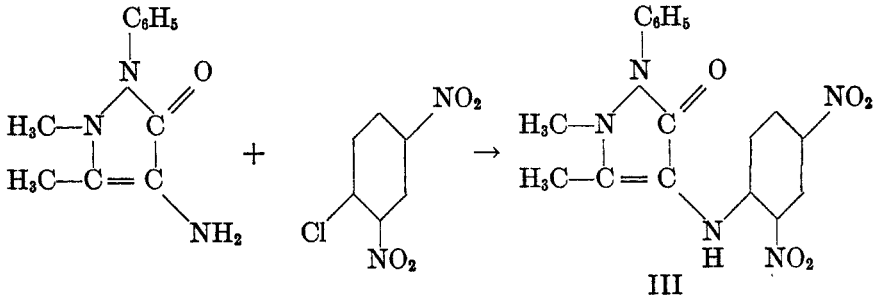
The results of these various reactions led to the belief that the dyes

might have the structure exemplified by the following formula (II), in which R and R′ may be aryl or alkyl groups or hydrogen.



II

The formation of the nitrogen-to-carbon linkage was established by the reaction between aminoantipyrine and 2,4-dinitrochlorobenzene. Analysis of the product formed in the reaction§ corresponded to the composition $C_{17}H_{15}N_5O_5$ (formula III).



III

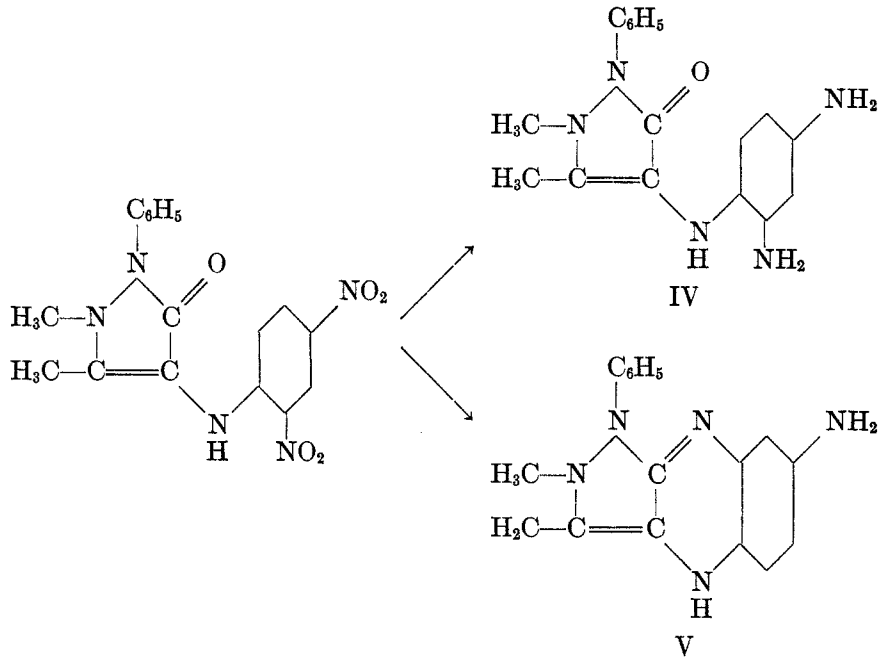
The reduction of the nitro groups in 2,4-dinitrophenylaminoantipyrine (formula III) would be expected to yield either or both of two possible compounds.

The analysis of the compound isolated corresponded to the composition $C_{17}H_{19}N_5O$ (formula IV), and not to $C_{17}H_{17}N_5$ (formula V).

It may be argued that cyclization occurred, as represented by formula V, but that the compound crystallized with a molecule of water of crystallization. The compound recrystallized from benzene was heated for two hours at 100° in a vacuum over phosphorus pentoxide without loss of weight. No indication of evolution of water was observed in the process of determining the melting point, even though the latter was 164.9–167.9°, well above the boiling point of water.

The results obtained from the analysis of the hydrochloride of the compound, recrystallized from alcohol and ether, did not indicate ring forma-

§ All the analyses shown in this paper were made by a professional analyst, Mr. Kurt Eder.



IV

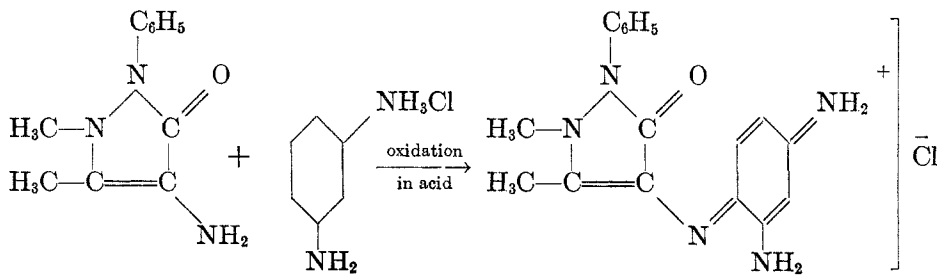
V

tion. Furthermore, no evolution of water was observed during the melting of the hydrochloride at 259.5–260.5°.

Finally, the dye produced by the oxidation of 2,4-diaminophenylaminoantipyrine hydrochloride was identical with the dye produced from the oxidation of a mixture of aminoantipyrine with *m*-phenylenediamine. The results obtained from the analysis of the dye did not indicate ring closure.

On the basis of evidence derived from the analysis of 2,4-diaminophenylaminoantipyrine, the leuco base of the dye, and its derivatives, formula IV should be assigned to the compound.

Oxidation of a mixture of *m*-phenylenediamine and aminoantipyrine forms a dye which dyes silk and wool directly a fast shade of burnt sienna.



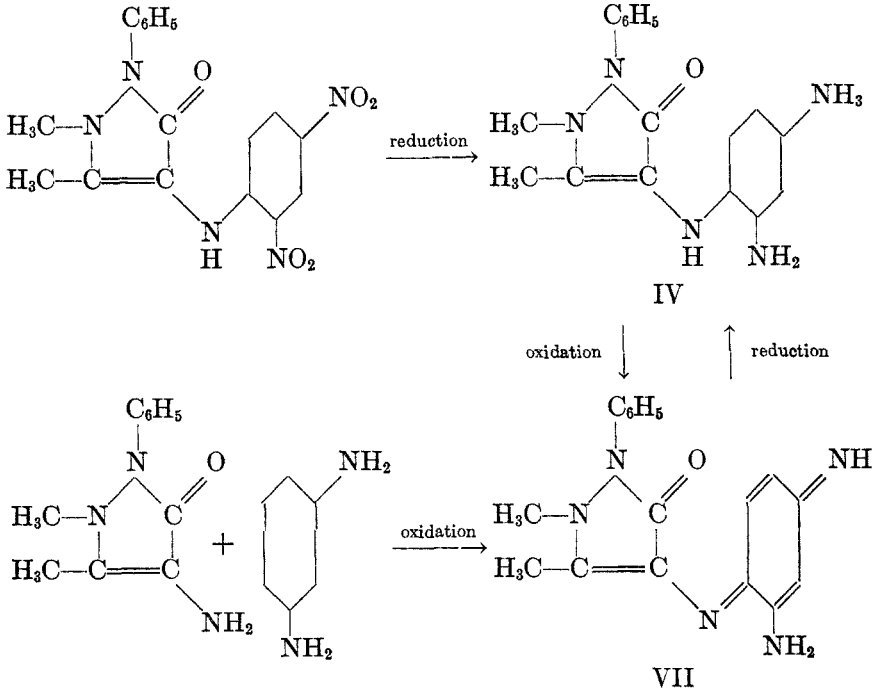
VI

The hydrochloride of the dye crystallizes from water, without the necessity of adding salt, and is easily purified in this manner. The analysis of the hydrochloride of the dye corresponds to that of the substance represented by formula VI. As the dye burns with difficulty a nitrogen analysis was unobtainable.

The absorption spectrum of the dye gives a peak of maximum absorption at 4800 ± 25 Å. (Figure 1.) The dye made from the reduction product of 2,4-dinitrophenylaminoantipyrine matches the color of the dye described above and gives an absorption curve that is identical with that obtained from the product of the reaction of aminoantipyrine with *m*-phenylenediamine. Thus it may be concluded that the two substances are identical.

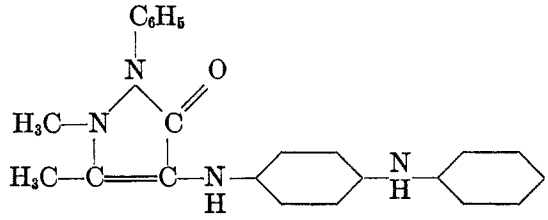
The analysis of the hydrochloride of the leuco compound prepared from the dye derived from *m*-phenylenediamine and aminoantipyrine gave results from which the formula $C_{17}H_{20}ClN_5O$ can be calculated.

The melting point of the compound was 258.6–259.1°. A mixture of the two leuco compounds prepared by different methods melted at 260.0–260.5°, which is the same temperature, or slightly higher, than the melting points of the substances taken separately. Thus it appears that the leuco compounds are identical.



Since the leuco compound made by reducing 2,4-dinitrophenylaminoantipyrine establishes the nitrogen-to-carbon bond, it follows that during the oxidation of aminoantipyrine and *m*-phenylenediamine a nitrogen-to-carbon bond is formed.

The predicted composition of the compound formed by the oxidation of a mixture of aminoantipyrine and diphenylamine would be $C_{23}H_{20}N_4O$. The dye was never obtained in a form sufficiently pure for analytical purposes but the leuco compound produced from the impure dye was easily purified. Results obtained from the analyses indicate the composition $C_{23}H_{22}N_4O$ (formula VIII).



VIII

Failure of di-*p*-tolylamine to produce the color reaction, when oxidized, in the presence of aminoantipyrine, is contributory evidence in support of the conclusion that the condensation produces a compound having a nitrogen-to-carbon bond, rather than a nitrogen-to-nitrogen bond.

The dye as represented in formula VI is a para quinoid. It is possible that it should be written as an ortho quinoid or as an equilibrium between the two types. This detail of the structure is still open to question, but by analogy no doubt is left as to the structure of the dyes formed from the aromatic monamines which may be represented, in general, by formula II.

The conditions necessary for the production of the antipyryl dyes, herein described, are strikingly similar to the conditions necessary for the production of the indamines. The indamines were discovered in 1877 by Nietzki,[2] who established their constitution[3] in 1883. He discovered that in order to obtain indamine dyes the amines should fulfill the following conditions:[4] The *p*-diamine must contain one free amino group, while the other may be primary, secondary, or tertiary; the monamine may be primary, secondary, or tertiary, but the position para to the amino group must be free. These conditions are exactly the same as those necessary

[2] NIETZKI, *Ber.*, **10**, 1157 (1877).

[3] NIETZKI, *ibid.*, **16**, 464 (1883).

[4] NIETZKI, "Chemie der Organischen Farbstoffe," Verlag von Julius Springer, Berlin, 5th Ed., **1906**, pp. 198–9.

for the production of the antipyryl dyes. The primary amine group in aminoantipyrine functions like the free amine group in the *p*-diamines.

The analogy of aminoantipyrine to the *p*-diamines extends beyond the reactions of the former with aromatic amines. It was mentioned in the first paragraph of this paper that phenols also give color reactions with aminoantipyrine. While the chemistry of this reaction has not been thoroughly investigated, sufficient work has been done to convince the writer that the reactions of aminoantipyrine with phenols are analogous to the reactions of the *p*-diamines with phenols in which indophenols[5] are formed.

Finally, it may be mentioned that nitrosoantipyrine reacts with diphenylamine to produce a dye the solutions of which appear to be identical in color with solutions of the dye produced from the reaction of aminoantipyrine and diphenylamine. If the dyes are identical, then the latter reaction is analogous to the reaction of *p*-nitrosoamines with secondary or tertiary, para-free, amines. Sufficient work has not been done on the reaction to make definite claims but the work done up to date indicates that the analogy is complete.

EXPERIMENTAL

Preparation of nitrosoantipyrine.—Nitrosoantipyrine was prepared by the method described by Rodinow[6] with but slight modification. Antipyrine (188 g.) was dissolved in 1500 cc. of water. After the addition of 100 cc. of concentrated hydrochloric acid the solution was cooled to 5–0°. With good mechanical stirring over a period of one hour, 75 g. of sodium nitrite dissolved in 300 cc. of water was introduced below the surface of the liquid. The resulting green solution was kept between 0° and 5° throughout the reaction. The stirring was continued for fifteen minutes after the last of the nitrite had been added. The copious green precipitate of nitrosoantipyrine which formed during the reaction was separated by filtration and washed with two liters of cold distilled water.

Preparation of aminoantipyrine.—The following modification of the procedure described by Rodinow[6] was found to give, not only better yields, but also the free base directly instead of the hydrochloride of aminoantipyrine. The wet nitrosoantipyrine, produced as described above, was transferred to a two-liter filter flask, fitted with a mercury seal for stirring. (The mercury in the seal was protected from the action of hydrogen sulfide by a layer of glycerin.) Distilled water (1500 cc.) containing 5 cc. of concentrated ammonium hydroxide was added, and the resulting suspension was stirred. Hydrogen sulfide was then passed into the reaction mixture until the green color changed to pale yellow (from one and a half to two hours). When the reduction was complete the mixture was heated on a steam bath for fifteen minutes, during which time the stirring and the passage of a slow stream of hydrogen sulfide were continued. The heating was for the purpose of coagulating the colloidally suspended sulfur. The hot solution was quickly filtered into a two-liter

[5] KOCHLIN, *Bull. Soc. ind. de Mulhouse*, **1882**, 532; O. WITT, *J. Soc. Chem. Ind.*, **1882**, 225.

[6] RODINOW, *Bull. soc. chim.*, **39**, 321 (1926).

filter flask. A small amount of sulfur passed through the filter, but this was removed in the subsequent filtration. The sulfur on the filter was washed with two 25-cc. portions of water containing hydrogen sulfide. These washings and 5 cc. of concentrated ammonium hydroxide were combined with the filtrate. The resulting solution was evaporated on a steam bath in a slow stream of hydrogen sulfide under reduced pressure. The vacuum was produced by means of a water pump. When the volume was reduced to 600–700 cc., the vacuum was broken with hydrogen sulfide and the liquid was filtered into a one-liter filter flask. The evaporation was continued under reduced pressure to dryness. The last trace of water was removed by the use of an oil pump pulling through a calcium chloride tower. This treatment yielded a viscous syrup which, after about thirty-six hours, crystallized to a pale yellow compact mass which weighed 183 g., and melted at 100.0–103.1°. This was a 90% yield based on antipyrine.

The product was purified by crystallization from an equal weight of boiling benzene; m.p. 109.0–109.5°.

Preparation of Antipyryl Red B-3.—Aminoantipyrine (4.1 g.) and *m*-phenylenediamine dihydrochloride (3.6 g.) were dissolved in 100 cc. of water. The resulting solution was cooled by the addition of 200 g. of crushed ice. To this mixture 22 g. of ferric chloride hexahydrate in 40 cc. of water was added at once, and then 300 cc. of saturated sodium chloride solution. After ten minutes the precipitated dye was brought on a filter and washed with saturated sodium chloride solution until the wash water no longer gave a test for iron with ammonium thiocyanate.* When all the iron salts had been removed by washing, as much of the wash water as possible was pressed from the dye on a suction filter. The cake formed on the filter was transferred to 500 cc. of water at 80° and stirred at that temperature for five minutes. The solution was then filtered hot, and as the filtrate cooled, red needles were deposited. The product was purified by crystallization from water, and dried in a vacuum desiccator over phosphorus pentoxide. As the drying proceeded, the dye became darker in color until it was a dark garnet red. The garnet red crystals when rubbed on a watch glass with a glass rod showed a bright green reflex.

The dye is soluble in water, alcohol, acetone, and dioxane, and insoluble in hydrocarbon solvents, chloroform, and ether.

Anal. Calc'd for $C_{17}H_{18}ClN_5O$: C, 59.38; H, 5.28; Cl, 10.33.
Found: C, 59.29; H, 5.30; Cl, 10.29.

Since these analyses are for the compound produced by the above procedure, that method of necessity was described. However, the procedure was subsequently improved, to increase the yield, in the following manner. Aminoantipyrine (4.1 g.) and *m*-phenylenediamine (3.6 g.) were dissolved in 60 cc. of water. When solution was complete, 2.1 g. of anhydrous sodium carbonate was added. The solution was filtered, the filtrate was diluted with water to 100 cc., and 100 g. of crushed ice was added. To the reaction mixture a filtered solution of 22 g. of ferric chloride hexahydrate in 15 cc. of water was added at once. From this point on the procedure was the same as that described above.

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* The iron test was carried out in the following manner. To 2 to 3 cc. of wash water was added one drop of hydrogen peroxide, followed by the addition of 0.5 cc. of ten per cent ammonium thiocyanate solution. The solution was shaken with about 2 cc. of ether. Since the mineral acid salts of the dye are insoluble in ether any red color appearing in the ether layer is due to the presence of iron. This test can be used regardless of the intensity of the color of the dye solution.

Reduction of Antipyryl Red B-3 to the leuco compound.—To four grams of Antipyryl Red B-3, suspended in 100 cc. of water was added 4 g. of sodium hydrosulfite in 40 cc. of water. The solution was shaken until all the red color was discharged. Hydrogen sulfide was passed into the solution, which was then filtered. After 5 cc. of 6*N* sodium hydroxide was introduced into the filtrate, silky white needles were deposited. When the deposition was complete, the crystalline precipitate was brought on a sintered glass filter, and washed with two 10 cc. portions of water saturated with hydrogen sulfide. The crystals were quickly transferred to a vacuum desiccator filled with nitrogen over phosphorus pentoxide. The desiccator was exhausted, and the product was allowed to dry for twelve hours. All operations with the leuco compound must be performed quickly, and contact with air must be avoided as much as possible to prevent undue oxidation.

The dry leuco compound was refluxed for fifteen minutes in 200 cc. of benzene. The hot benzene solution was filtered to remove a reddish sludge. On cooling, the filtrate deposited silky white needles which soon turned pink on exposure to the air.

Soluble in benzene, ether and chloroform; slightly soluble in water; m.p. 264.9–267.9°.

Anal. Calc'd for $C_{17}H_{19}N_5O$: C, 66.02; H, 6.15; N, 22.65; O, 5.18.
Found: C, 66.52; H, 6.08; N, 22.23; O (by difference), 5.17.

Preparation of the leuco hydrochloride of Antipyryl Red B-3.—One-half gram of leuco Antipyryl Red B-3 was treated with 1 cc. of concentrated hydrochloric acid. After the addition of 15 cc. of alcohol, the mixture was warmed to complete the solution of the hydrochloride. The solution was then filtered through a sintered glass filter. When the filtrate was sufficiently cool 15 cc. of ether was added. The solution was allowed to cool for one hour at about 5°, during which time a white crystalline precipitate formed. The crystals were brought on a filter and washed with 1:1 alcohol-ether. The washed crystals were dissolved in 50 cc. of boiling alcohol. Dissolution was slow and not all of the material dissolved. The solution was then filtered, and 50 cc. of ether was added to the filtrate, which was allowed to cool at 5°. The crystals formed were separated by filtration and washed as described above. This process was repeated three more times, and the crystals were finally dried in a vacuum desiccator over phosphorus pentoxide.

Soluble in hot water and hot alcohol; insoluble in ether, benzene and chloroform; m.p. 258.6–259.1°.

Anal. Calc'd for $C_{17}H_{18}ClN_5O$: Cl, 10.26. Found: Cl, 10.29.

Preparation of 2,4-dinitrophenylaminoantipyrine.—Aminoantipyrine and 2,4-dinitrochlorobenzene, when heated to 110°, were found to react directly to form 2,4-dinitrophenylaminoantipyrine. It was further found that, in the presence of sodium carbonate, the reaction occurred at a lower temperature and gave a product more readily soluble in alcohol.

Two parts, by weight, of aminoantipyrine were ground with two parts of 2,4-dinitrochlorobenzene and one part of anhydrous sodium carbonate. This mixture was warmed on a steam bath until the melt solidified to an orange-red solid. This was refluxed with one hundred parts of alcohol, until all the organic material dissolved. The alcoholic solution was filtered, and the residue was extracted with twenty-five parts of boiling alcohol. The extract and filtrate were then combined and evaporated to one-tenth the original volume. This mixture was cooled and the orange crystalline product was brought on a filter and washed with cold alcohol.

Yield, about 70% of pure material; m.p. 213.1–213.9°.

Anal. Calc'd for $C_{17}H_{15}N_5O_5$: C, 55.28; H, 4.09; N, 18.96; O, 21.67.
Found: C, 55.27; H, 3.91; N, 19.04; O (by difference), 21.78.

Slowly soluble in hot alcohol, soluble in acetic acid and hydrochloric acid. Insoluble in ether and water. Best crystallized from hot chlorobenzene. Alkaline solutions added to alcoholic solutions of 2,4-dinitrophenylaminoantipyrine turn them deep red.

Reduction of nitro groups in 2,4-dinitrophenylaminoantipyrine.—Iron, tin, or zinc will reduce both nitro groups of 2,4-dinitrophenylaminoantipyrine in acid solution. Two and a half grams of the nitro compound was dissolved in 25 cc. of concentrated hydrochloric acid. Over a period of three hours, 7.5 g. of granulated tin were added. It was necessary for stirring to be efficient to keep the heavy yellow precipitate that formed at first from caking. After the first hour the reaction mixture was heated to boiling, from time to time, to keep the reaction going briskly. When the reduction was complete, as indicated by the disappearance of the yellow color, the solution was filtered from the excess tin and the filtrate poured into 75 cc. of 6*N* sodium hydroxide solution, which was then extracted with ten 20-cc. portions of chloroform. The extract was boiled to assure solution of all organic material. During the boiling the solution was protected by an atmosphere of carbon dioxide, which served to prevent exposure of the leuco compound to atmospheric oxygen. The extract was filtered, and the filtrate was evaporated to dryness in a stream of carbon dioxide. To the syrupy residue, 2 cc. of concentrated hydrochloric acid was added, and then 50 cc. of alcohol. This mixture was boiled in a stream of carbon dioxide, and when solution was complete the solution was filtered. To the filtrate 50 cc. of ether was added, and the solution was allowed to cool for twelve hours at about 5°. The white crystalline solid which formed during the cooling was then separated by filtration, and the residue was washed with 1:1 alcohol-ether. The 2,4-diaminophenylaminoantipyrine hydrochloride was purified by crystallization from a minimum amount of air-free water. The almost-white crystals were dried in a vacuum desiccator over phosphorus pentoxide; m.p. 259.5–260.5°. The melting point of the mixture of these crystals and the crystals of the previously described leuco hydrochloride is 260.0–260.5°.

Anal. Calc'd for $C_{17}H_{18}ClN_5O$: C, 59.00; H, 5.84; N, 20.25; Cl, 10.27; O, 4.64.
Found: C, 59.63; H, 5.67; N, 19.30; Cl, 10.79; O (by difference), 4.61.

The compound is the leuco hydrochloride of Antipyryl Red B-3.

Oxidation of leuco hydrochloride made from 2,4-dinitrophenylaminoantipyrine.—To 10 cc. of water, 0.20 g. of the leuco hydrochloride made from the reduction of 2,4-dinitrophenylaminoantipyrine was added. The mixture was boiled to complete dissolution, then cooled to about 50°, and 0.50 g. of ferric chloride hexahydrate in 1 cc. of water was added. Next, 20 cc. of saturated sodium chloride solution was added. The precipitated red dye was separated by filtration and washed with saturated sodium chloride solution until the test for iron† with ammonium thiocyanate was negative. The dye was pressed on the filter and washed with 3 cc. of water, after which it was dissolved in 3 cc. of water at 65°. The hot solution was filtered through a sintered glass filter, and the filtrate allowed to stand at about 5° for one-half hour, after which the dye was brought on a filter and washed with 3 cc. of cold water. The product was dried in a vacuum desiccator over phosphorus pentoxide.

The absorption spectrum of Antipyryl Red B-3 made by two different methods.‡—Samples of Antipyryl Red B-3 prepared by the two methods described above were

† See previous footnote.

‡ The absorption spectra measurements were made by Dr. Albert E. Sidwell, Jr., in this laboratory.

used to determine absorption spectra. Weighed portions were dissolved in Sörensen's phosphate buffer of pH 6.73,[7] and were examined spectrophotometrically.[8] The solutions were compared with a portion of the diluent buffer solution. Quartz absorption cells two centimeters in length were employed. The results of the determination of the specific absorption, in the region 4000 Å. to 7000 Å., of the two samples are shown graphically in the accompanying figure.

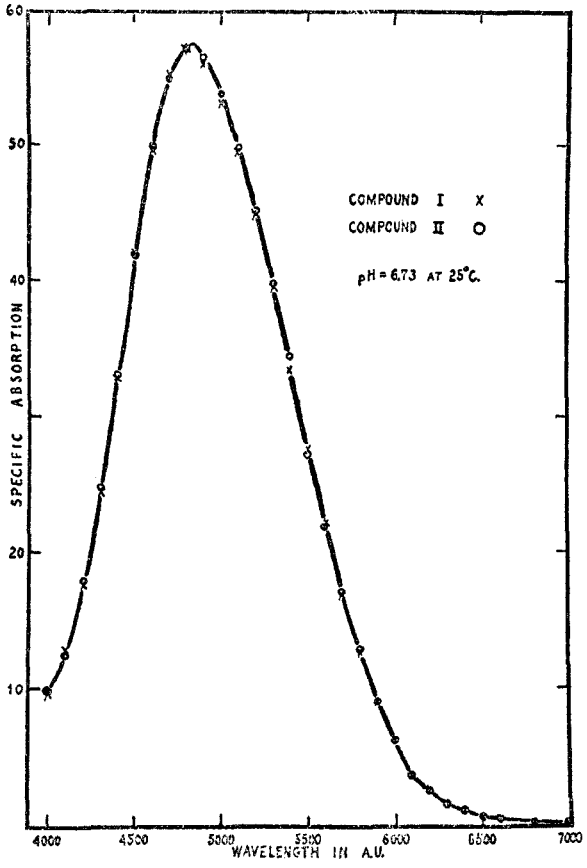


FIGURE.—ABSORPTION SPECTRA OF TWO SAMPLES OF ANTIPYRYL RED B-3

Preparation of Antipyryl Blue A-93.—Two solutions were prepared as follows. Solution I contained 2.0 g. of potassium dichromate, 2.0 cc. of concentrated sulfuric acid, and 25 cc. of water. Solution II contained 2.0 g. of aminoantipyrine, 1.7 g. of diphenylamine, and 25 cc. of glacial acetic acid. Solution II was cooled in an ice bath, and while it was being stirred Solution I was added. After the reaction

[7] CLARK, "The Determination of Hydrogen Ions," Williams & Wilkins Co., Baltimore, 3rd Ed., **1928**, p. 210, Table 41.

[8] HOGNESS, ZSCHEILE, AND SIDWELL, *J. Phys. Chem.*, **41**, 379 (1937).

mixture was poured into 500 cc. of water the resulting solution was filtered. The filtrate, cooled in an ice-salt bath, was well stirred while 200 g. of sodium chloride was added. After fifteen minutes, the precipitated blue dye was separated by filtration and washed with saturated sodium chloride solution. As much of the sodium chloride solution as possible was pressed out, and the dye was dried in a vacuum desiccator over phosphorus pentoxide.

The dried material is difficultly soluble in water; it dissolves in alcohol, acetic acid, or formic acid to form beautiful pure-blue solutions. It is also soluble in concentrated sulfuric acid, forming an intense cerise solution.

Reduction of Antipyryl Blue A-93.—One-half gram of Antipyryl Blue A-93 was dissolved in 50 cc. of acetone. The solution was filtered and to the filtrate five per cent. sodium carbonate solution was added until the color changed from blue to bright red. A freshly prepared ten per cent. solution of sodium hydrosulfite was added drop by drop to this solution until the red color was discharged. The colorless liquid was poured into 1500 cc. of water containing a trace of ammonium sulfide. The flocculent precipitate was brought on a filter and washed with water, in which was dissolved a few drops of ammonium sulfide solution. The residue on the filter was dissolved in 50 cc. of boiling acetone, and one liter of water containing a trace of ammonium sulfide was added to precipitate the leuco base. This procedure was repeated eight times. Finally, the product was dissolved in a minimum amount of boiling acetone, and the solution allowed to cool. The white crystals, which were fairly stable towards air oxidation, were separated from the solution by filtration; m.p. 220.3–221.8°.

Difficultly soluble in hot acetone, alcohol, or benzene; insoluble in water.

Anal. Calc'd for $C_{23}H_{22}N_4O$: C, 74.55; H, 5.99; N, 15.14; O, 4.32.
Found: C, 74.61; H, 5.84; N, 15.17; O (by difference), 4.38.

SUMMARY

(1) A new color reaction between 4-aminoantipyrine and para-unsubstituted aromatic amines has been described.

(2) Several of the dyes obtained by the above reaction have been described.

(3) The structures of these dyes have been determined.

(4) The limiting conditions for the reaction have been discussed.

(5) An analogy between 4-aminoantipyrine and the *p*-phenylenediamines has been drawn, based on the color reaction.

(6) The analogy has been made more complete by mention of the following facts:

(*a*) phenols react with 4-aminoantipyrine to produce dyes similar to the indophenols.

(*b*) nitrosoantipyrine reacts with diphenylamine in a manner similar to para nitrosoamines.

(7) The following new compounds have been prepared:§

§ Ap- is used to represent the antipyryl radical.

(*a*)	Ap—N=$C_6H_3(NH_2)$=NH_2Cl (2, 4)	Antipyryl Red B-3 (Formula VI)
(*b*)	Ap—N(H)—$C_6H_3(NH_2)$—NH_3Cl (2, 4)	2,4-Diaminophenylaminoantipyrine hydrochloride (Hydrochloride of Formula IV)
(*c*)	Ap—N(H)—$C_6H_3(NH_2)_2$ (2,4)	2,4-Diaminophenylaminoantipyrine (Formula IV)
(*d*)	Ap—N(H)—$C_6H_3(NO_2)_2$ (2,4)	2,4-Dinitrophenylaminoantipyrine (Formula III)
(*e*)	Ap—N=C_6H_4=N—$C_6H_5\cdot HCl$	Antipyryl Blue A-93
(*f*)	Ap—N(H)—C_6H_4—N(H)—C_6H_5	*N*, *N'*-Antipyryl phenyl *p*-phenylenediamine (Formula VIII)

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THE CHEMISTRY OF UNSATURATED STEROIDS. IV. THE PREPARATION AND PHOTOCHEMICAL OXIDATION OF 2,4-CHOLESTADIENE*

EVALD L. SKAU AND WERNER BERGMANN

Received June 20, 1938

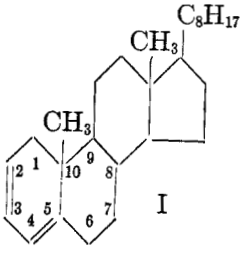
In order to investigate the photochemical oxidation of 2,4-cholestadiene (I), it was necessary to prepare considerable quantities of this compound in a pure state. The procedure for the preparation of this hydrocarbon by the dehydration of cholesterol with aluminum oxide was described in a previous communication[1]. It was there pointed out that this method gave inconsistent results. In some instances the yield was very poor, and occasionally only cholesterol or a hydrocarbon of a negative rotation was obtained. An improved method has now been found by which 2,4-cholestadiene can always be obtained in good yields.

The crude hydrocarbon prepared by the improved method invariably shows a specific rotation of +90 to +100°. For the purification of the diene it was found necessary to modify the method of recrystallization recommended in our previous communication. The tendency of the partially purified hydrocarbon to revert to an oily material which would not crystallize indicated the possibility of a rearrangement or oxidation in solution. It was found that the purification of the hydrocarbon was best carried out by recrystallization from very small amounts of ether. This procedure was greatly facilitated by the use of an improved type of the centrifugal filtration tube.[2] On repeated recrystallization from ether the specific rotation of the diene first rose rapidly to about +160° and then slowly to +168.5°. This value was not exceeded by further recrystallizations. The pure 2,4-cholestadiene crystallized in well-shaped, heavy blocks and melted sharply at 68.5°. The absorption spectrum of the pure hydrocarbon showed maxima at 267mμ and 275mμ. It has thus been demonstrated that the sample of diene (m.p. 63°, $[\alpha]_D^{27} = +114°$) previously reported[1] was not pure. The comparison of the absorption spectrum of such an impure sample with that of the pure 2,4-cholestadiene

* Aided by grants from the International Cancer Research Foundation and The Jane Coffin Childs Memorial Fund for Medical Research.

[1] STAVELY AND BERGMANN, J. ORG. CHEM., **1**, 576 (1936).

[2] SKAU, *J. Phys. Chem.*, **33**, 951 (1929); SKAU AND ROWE, *Ind. Eng. Chem., Anal. Ed.*, **3**, 147 (1931).



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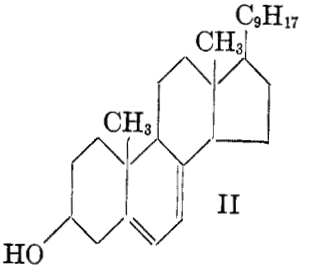

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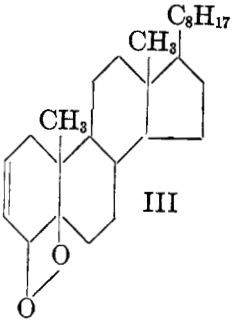

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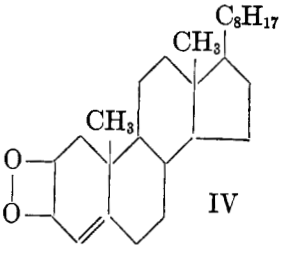

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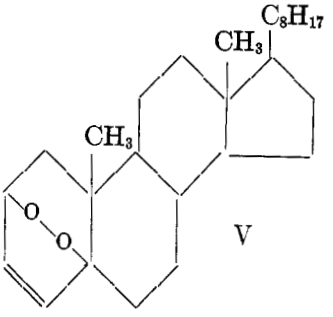

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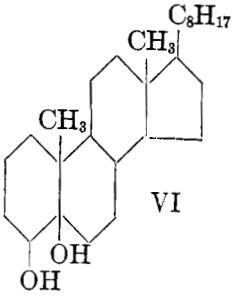

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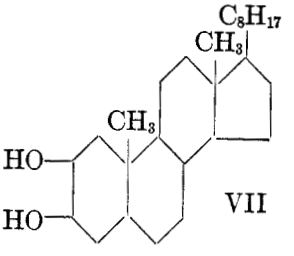

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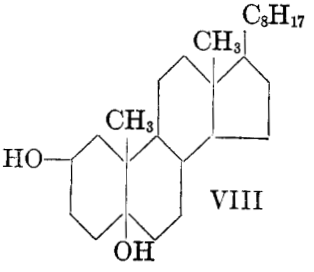

VIII

(see Fig. 1) showed the presence of an impurity having an absorption maximum in the region of 230–240mμ. The position of this maximum indicated that the impurity was a hydrocarbon possessing a pair of conjugated double bonds extending over two rings. Such a hydrocarbon has been isolated. (See Fig. 1). It seemed to be the main product when

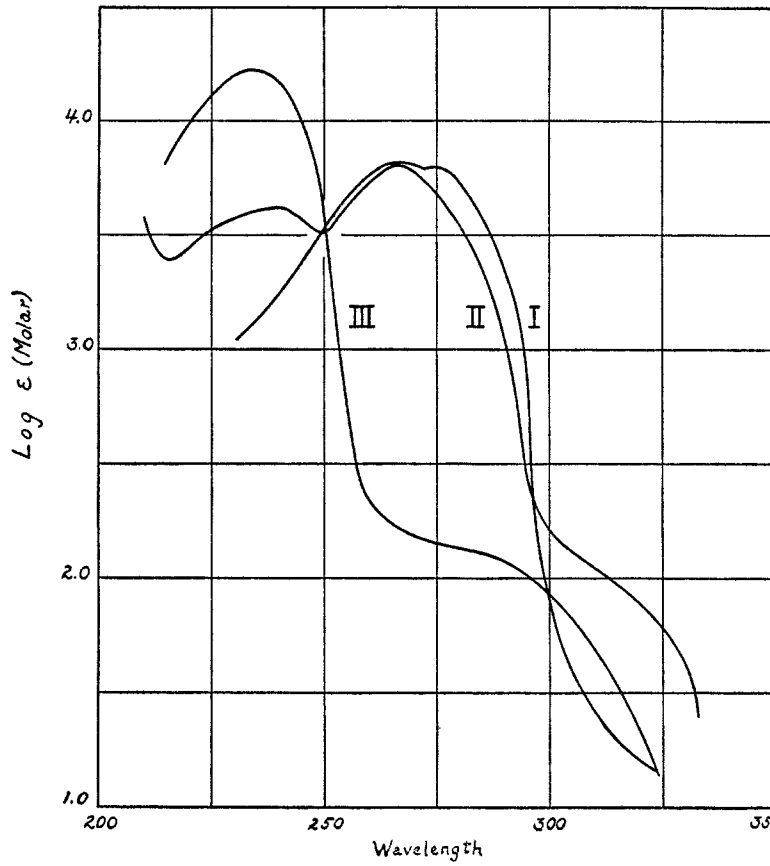

FIG. I. I. 2,4-Cholestadiene. II. Impure 2,4-Cholestadiene, $[\alpha]_D = +114°$. III. Cholestadiene, $[\alpha]_D = -51°$.

the dehydration of cholesterol was carried out at a higher temperature and pressure than recommended for the preparation of 2,4-cholestadiene. The hydrocarbon melted at 80.0–80.5°, showed an optical rotation of $[\alpha]_D^{20} = -51.3°$ and had a maximum of absorption at 234mμ.†

† The authors are greatly indebted to the Misses Marshall and Paddock, Mount Holyoke College, South Hadley, Mass., for their measurements of the absorption spectra.

The carcinogenic activity of the 2,4-cholestadiene has been tested by Dr. Leonell C. Strong of the Yale Medical School. Twenty mice of the Strong CBA strain were given six subcutaneous injections of a 1 per cent solution of 2,4-cholestadiene in sesame oil at weekly intervals. Each injection consisted of 0.2 cc. of the solution, so that each mouse received a total of 12 mg. of the hydrocarbon. The tests were begun twelve months ago. No obvious tumors have yet been observed, and all the mice are still in excellent health.

Like ergosterol[3] (II), 2,4-cholestadiene is easily photo-oxidized by bubbling oxygen through an alcoholic solution containing eosin during exposure to the light of a 200-watt bulb. The oxidation product is a crystalline peroxide of the melting point 113–114° and specific rotation + 48.3°. If this compound is repeatedly recrystallized from ethyl acetate a slow rise of the melting point and of the specific rotation is observed. This phenomenon is due to the tendency of the peroxide to undergo a gradual rearrangement, the exact nature of which has not yet been fully established. The previously reported sample of the peroxide[4], melting over a range of 118.5–120.5° and having a specific rotation of +52.8°, had already undergone partial transformation of that type.

The peroxidic nature of the pure 2,4-cholestadiene peroxide of the m.p. 113–114° is evidenced by the fact that it liberates an exactly equimolecular quantity of iodine from a solution of potassium iodide in glacial acetic acid. The readiness with which 2,4-cholestadiene adds one mole of oxygen indicates that the reactive system of two conjugated double bonds in one ring is very favorable to the formation of peroxides. It also shows that a pair of conjugated double bonds, each of which is connected with a quaternary carbon atom, as in ergosterol (II), is not a prerequisite for the formation of peroxides in the steroid series.

The addition of one mole of oxygen to 2,4-cholestadiene might conceivably lead to one of three peroxides (structures III–V). On catalytic hydrogenation the peroxide adds two moles of hydrogen to give a saturated diol, $C_{27}H_{48}O_2$, having one of the structures VI–VIII. On acetylation with acetic anhydride the diol gives a monoacetate, indicating the presence of an unreactive tertiary hydroxyl group at C_5. This observation eliminates structure VII for the diol and structure IV for the peroxide. Of the remaining two possible structures for the diol one (VI) represents a glycol. According to Criegee[5] such a substance would be expected to react with lead tetraacetate. The diol obtained on hydrogenation of the peroxide, however, gives absolutely no reaction with this reagent. Conse-

[3] WINDAUS AND BRUNKEN, *Ann.*, **460**, 225 (1928).
[4] SKAU AND BERGMANN, *J. Am. Chem. Soc.*, **60**, 986 (1938).
[5] CRIEGEE, *Ber.*, **64**, 264 (1931).

quently structures VI for the diol and III for the peroxide can also be eliminated. The peroxide of 2,4-cholestadiene therefore must be 2,5-peroxidocholestene-3 (V), and its hydrogenation product a 2,5-dihydroxy-compound having structure VIII.

An interesting rearrangement takes place when 2,4-cholestadiene peroxide of m.p. 113–114° in alcoholic solution is exposed to sunlight. The irradiation product melts at 166–168° and has a specific rotation of +141°. The same product can be obtained directly from 2,4-cholestadiene if the photo-oxidation of this substance is carried out in sunlight instead of in the light of a 200-watt bulb. This compound seems to be identical with the "2,4-cholestadiene peroxide" recently described by Butenandt and Kudssus[6]. It is uncertain, however, that this compound is a true peroxide, because it does not liberate iodine from a solution of potassium iodide in glacial acetic acid.

Further studies on the irradiation products of 2,4-cholestadiene are in progress. The carcinogenic activity of the various compounds is being tested by Dr. Leonell C. Strong of the Yale Medical School.

EXPERIMENTAL

Dehydration of cholesterol with aluminum oxide.—The aluminum oxide used for the dehydration of cholesterol was "Activated Alumina, Grade A, 40 to 80 mesh," obtained from the Aluminum Ore Co. It was found to be advantageous to reactivate it immediately before use by heating it in a shallow pan at 200° for four hours and then cooling it in the absence of moisture. Ten grams of cholesterol were melted and allowed to solidfy in a 125-cc. Pyrex retort. A mixture of 20 g. of cholesterol and 34 g. of alumina was then introduced, and a plug of glass wool was inserted into the curved part of the neck. After evacuation to 1 mm. pressure the retort was heated on a metal bath at 220–230°. The heating was continued until most of the cholesterol had reacted. When this stage was reached the refluxing droplets remained glassy-clear when they were cooled locally by a jet of air and allowed to come back to the original temperature. Depending on the activity of the alumina, from one to six hours of heating was required. The retort was then removed from the bath, and cooled rapidly with a stream of air. After the vacuum had been broken the glass wool was pushed into the retort, and 10 g. of alumina was introduced. The heating was now continued as before for thirty minutes more. The retort was then lowered until the bath level was a few mm. above the level of the reaction mixture and covered by a metallic hood, which was heated gently from time to time. An ordinary inverted tin can was used for this purpose. Distillation was carried out with the bath temperature as low as possible, preferably not exceeding 230°. It is advantageous to use a mercury vapor diffusion pump during distillation. The distillation product was a clear oily liquid which slowly crystallized. It was always obtained in yields from 70 to 75 per cent., and had a specific rotation of +90 to +100°. The crude product was recrystallized from small amounts of ether with the help of a slightly modified centrifugal filtration tube designed by one of us.

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[6] BUTENANDT AND KUDSSUS, *Z. physiol. Chem.*, **253**, I (1938).

Modified centrifugal filtration tube.—The centrifugal filtration tube (see Fig. 2) consists of the crystallization chamber, *A*, and the receiver of the mother liquor, *B*. The parts are connected by an interchangeable ground joint. A perforated porcelain disc, *C*, is ground into the ground joint of *B*, deep enough so as to permit a tight connection between the two chambers. In order to facilitate the removal of the disc, a nichrome wire, *D*, is attached to it. For the filtration the disc is covered tightly by a piece of filter paper which has been slit where the wire is fastened to the disc.

Purification of 2,4-cholestadiene.—The crude distillation product was transferred into the crystallization chamber and dissolved in half its weight of ether. The sides of the chamber were washed down with a few drops of ether which thus formed a separate layer on top of the solution. The tube was then assembled and allowed to cool very slowly to 0°, when the hydrocarbon crystallized out in large crystals. The tube was now inverted, placed in a centrifuge cup‡ and centrifuged for twenty

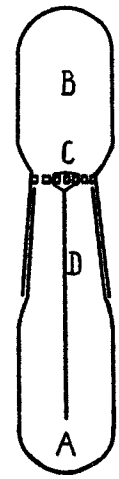

FIG. II

minutes at a speed not exceeding 1100 r.p.m. The crystals were then removed by carefully withdrawing the disc. This procedure was then repeated two or three times until the specific rotation of the crystals was above +150°. Eight parts of the hydrocarbon of such a degree of purity were recrystallized from ten parts of ether, and the procedure was continued until a product of a specific rotation above +160° was obtained. This product is suitable for general use. By continuing this procedure pure 2,4-cholestadiene was prepared, which melted sharply at 68.5°; $[\alpha]_D^{23}$ = +168.5° (45.0 mg. in 3.04 cc. ether, 1 dm. tube).

Anal. Calc'd for $C_{27}H_{44}$: C, 87.96; H, 12.04.
Found: C, 88.03; H, 11.88.

The mother liquors from the various recrystallizations contained considerable quantities of 2,4-cholestadiene which were recovered by one of two methods. They

‡ Tubular pieces of wood are used to adapt the filtration tubes to the size of the centrifuge cups.

were evaporated to dryness in a stream of nitrogen, or were centrifuged, as described above, after cooling slowly to −78° in a large test tube immersed in a carbon dioxide-alcohol bath. The recovered material was then again subjected to fractional crystallizations from small amounts of ether. Inasmuch as the diene, when dissolved in ether, is prone to undergo oxidation it is advisable to work up the mother liquors immediately.

Subjected to this procedure, 180 g. of cholesterol yielded 52 g. of 2,4-cholestadiene of a specific rotation over +160°. This yield could be further improved by a systematic recrystallization of the residues.

Titration with perbenzoic acid.—By titration with perbenzoic acid in the usual manner, 71.0 mg. of diene took up 6.22 mg. of oxygen in 72 hours, an amount corresponding to 2.02 double bonds.

Crystallography and optical properties of 2,4-cholestadiene [*By W. E. Ford and J. P. Sickels*].—2,4-Cholestadiene is monoclinic, the crystals being elongated parallel to the ortho axis and showing a prismatic development. The principal forms have been taken as {100} and {001}; in addition there are smaller faces of the unit prism {110} and pyramid {111}; the orthodome {201} occurs as a very narrow truncation. The crystal faces were not of such a quality as to permit of accurate measurement of the interfacial angles. The approximate angles were as follows: (100) ∧ (001) = 75°45′,

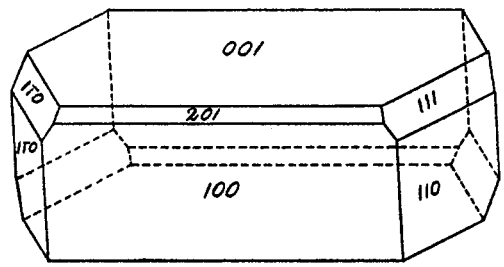

FIG. III

(100) ∧ (110) = 60°, (001) ∧ (111) = 51°30′, (001) ∧ (201) = 46°45′. From these angles the following approximate crystal constants were derived by plotting methods: $a:b:c$, 1.78:1:1.34; β = 75°45′. Figure 3, drawn by Charles M. Warren, represents one habit of crystal development. Another habit was observed in which the prism-like crystals were terminated by prominent faces of the unit pyramid.

Two cleavages were observed, parallel to {100} and {001}. The substance is biaxial, optically negative. The optical axial plane is parallel to the 010 plane. Cleavage plates parallel to {100} show the emergence of an optic axis near the center of the microscope field, while cleavage plates parallel to {001} show an optic axis emerging near the edge of the field. The optic angle $2V$ is very large. The substance shows strong dispersion, $r > v$. The indices of refraction were not measured since the material is soluble in the usual immersion media.

Isolation of cholestadiene, $[\alpha]_D^{23} = -51°$.—The dehydration of cholesterol with activated alumina was carried out as described above. The product was then distilled at 2 mm. pressure and at 290 to 315°. The distillate was recrystallized from an equal weight of ether in a centrifugal filtration tube. After one recrystallization the hydrocarbon had a specific rotation of −38° and after four additional recrystallizations it melted at 80.0–80.5°, $[\alpha]_D^{23} = -51.3°$ (47.0 mg. in 3.04 cc. ether, 1 dm. tube).

Titration with perbenzoic acid.—By titration with perbenzoic acid in the usual manner, 95.7 mg. of diene took up 8.56 mg. of oxygen in 72 hours, an amount corresponding to 1.99 double bonds.

Photo-oxidation of 2,4-cholestadiene.—Nine grams of the diene, $[\alpha]_D = +164°$, was dissolved in one liter of warm absolute alcohol, and 14 mg. of eosin was added to the solution. The photo-oxidation was then carried out at 25° in the apparatus described by Windaus and Brunken[3]. A 200-watt Mazda bulb was used as a source of light. After nine hours of irradiation the solution was evaporated to dryness *in vacuo* below 35°. The crystalline residue after one recrystallization from dilute acetone yielded a crude peroxide of m.p. 110–112°. One further recrystallization from dilute acetone and three recrystallizations from 95 per cent. alcohol brought the melting point to 113–114°, $[\alpha]_D^{24} = +48.3°$ (63.2 mg. in 3.06 cc. $CHCl_3$, 1 dm. tube). The yield of peroxide was 60–70%. Additional quantities could be obtained from the mother liquors.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 81.15; H, 10.94.

Determination of active oxygen.—A sample of the peroxide was introduced into a glass-stoppered bottle, and 20 cc. of a saturated solution of potassium iodide in glacial acetic acid was added. The mixture was kept in the dark at room temperature for 24 hours. The liberated iodine was then titrated with $N/10$ thiosulfate solution. A sample containing 54.1 mg. of 2,4-cholestadiene peroxide required 6.51 cc., and the blank, 3.71 cc. of 0.0990 N thiosulfate solution. The difference corresponded to 1.03 atoms of active oxygen. The corresponding values for 31 mg. of ergosterol peroxide were 5.70 cc. and 3.71 cc., or 0.96 atoms of active oxygen.

Catalytic hydrogenation.—One gram of peroxide was dissolved in 75 cc. of ethyl acetate and shaken with platinum catalyst, prepared from 150 mg. of PtO_2, in an atmosphere of hydrogen. After two hours, 2 moles of hydrogen had been absorbed. The solution was then filtered and evaporated to dryness *in vacuo*. The residue was recrystallized several times from acetone. The diol crystallized in long silky needles, and melted at 155°, $[\alpha]_D^{27} = +19.6°$ (34.2 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube). The substance did not react with perbenzoic acid, and it distilled without decomposition in a high vacuum.

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.12; H, 11.97.
Found: C, 80.24; H, 12.30.

Titration with lead tetraacetate.—Ten cc. of a saturated solution of lead tetraacetate in glacial acetic acid was added to 26 mg. of the diol. After 20 hours the excess of lead tetraacetate was determined by the method described by Criegee[5]. The solution containing the sample used 14.59 cc. of $N/10$ thiosulfate solution, and two blanks 14.60 and 14.61 cc. respectively. No reaction had taken place.

Acetylation of the diol.—The monoacetate was prepared by refluxing the diol with acetic anhydride for 90 minutes. It was recrystallized several times from acetone. The acetate crystallized in the form of small needles, and melted at 141–142°, $[\alpha]_D^{27} = -9°$ (27.6 mg. in 3.0 cc. ether, 1 dm. tube).

Anal. Calc'd for $C_{29}H_{50}O_3$: C, 77.96; H, 11.30.
Found: C, 78.04; H, 11.44.

On saponification of the acetate the diol of m.p. 155° was recovered.

Photochemical rearrangement of 2,4-cholestadiene peroxide.—One part of the peroxide, m.p. 113–114°, was dissolved in 250 parts of absolute alcohol in a large Erlenmeyer flask, and 0.005 part of eosin was added. The solution was then exposed to sunlight in the open air. After a few hours of exposure the solution had become colorless, and after 2 days dense crystals began to separate. One week later the crystalline material was filtered off, washed with small amounts of absolute alcohol,

and recrystallized from boiling absolute alcohol. The material melted at 166–168°, $[\alpha]_D^{25} = +141°$ (30.0 mg. in 3.06 cc. $CHCl_3$, 1 dm. tube). The same substance was obtained in almost quantitative yield when the irradiation was carried out in the absence of eosin and oxygen.

Sunlight irradiation of 2,4-cholestadiene.—2,4-Cholestadiene, $[\alpha]_D = +165°$, was subjected to irradiation in sunlight, using the same proportions as in the case of the peroxide. After half a day the solution had become colorless, and after 3 days dense crystals began to separate in a considerable quantity. Two days later they were collected by filtration, washed with absolute alcohol, and recrystallized from boiling absolute alcohol. The material melted at 168°, $[\alpha]_D^{25} = +140°$ (30.0 mg. in 3.04 cc. $CHCl_3$, 1 dm. tube). It was identical with the product obtained by irradiation of the peroxide.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 81.13; H, 11.05.

SUMMARY

1. An improved method for the preparation and purification of 2,4-cholestadiene has been presented. Pure 2,4-cholestadiene melts at 68.5°, and has a specific rotation of +168.5°.

2. 2,4-Cholestadiene is photo-oxidized in an alcoholic solution containing eosin during exposure to the light of a 200-watt bulb. The photo-oxidation product was identified as 2,5-peroxidocholestene-3.

3. 2,4-Cholestadiene peroxide rearranges during exposure to sunlight to a compound of m.p. 166–168° and specific rotation +141°.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

THE PEROXIDE EFFECT IN THE ADDITION OF REAGENTS TO UNSATURATED COMPOUNDS. XVIII. THE ADDITION AND SUBSTITUTION OF BISULFITE*

M. S. KHARASCH, ERNEST M. MAY,† AND FRANK R. MAYO

Received June 28, 1938

INTRODUCTION

The addition of bisulfite in aqueous solution to unsaturated compounds has been investigated by many workers with varying degrees of success.[1] Table I lists the unsaturated compounds studied, and summarizes the results of the investigations.

ADDITION OF BISULFITE TO UNSATURATED COMPOUNDS

Evidence has now been obtained which indicates that the reaction of bisulfite with ethylene compounds is best interpreted on the basis of a free-radical mechanism. In harmony with this hypothesis, we find that oxidizing agents such as oxygen, which are capable of producing free radicals from bisulfite, are essential for the reaction, and that in the absence of such a reagent no addition occurs. Of especial interest is the fact that small amounts of nitrite and nitrate cause the addition of bisulfite to propylene in the absence of oxygen. In the light of these observations, the discordant results exhibited in Table I (*viz.*, those relating to pinene, cinnamyl alcohol, allyl alcohol, and styrene) can readily be explained. Table II summarizes the results obtained in the present research.

In the investigation of those substances which are gases at room temperature, the oxygen effect was easily demonstrated, and was very striking. The reactions were carried out in an apparatus similar to that often used

*This paper records preliminary work on the reactions of sodium and ammonium bisulfites with ethylene derivatives. Further work on addition and substitution reactions of ethylene and acetylene derivatives, and on substitution reactions of saturated aromatic compounds is in progress. For contribution XVII see Kharasch, May, and Mayo, *Chemistry and Industry*, **57**, 774–5 (1938).

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[1] (*a*) MILLER, *Ann.*, **189**, 338 (1877); (*b*) MUELLER, *Ber.*, **6**, 1442 (1873); (*c*) ROSENTHAL, *Ann.*, **233**, 38 (1886); (*d*) MARCKWALD AND FRAHNE, *Ber.*, **31**, 1864 (1898); (*e*) LABBE, *Bull. soc. chim.*, [3], **21**, 1077 (1899); (*f*) DUPONT, *Sci. Ind. Bull. Roure-Bertrand Fils*, [3], **7**, 3 (1913); (*g*) KOLKER AND LAPWORTH, *J. Chem. Soc.*, **1925**, 307; (*h*) ASHWORTH AND BURKHARDT, *ibid.*, **1928**, 1791; (*i*) HEDÉN AND HOLMBERG, *Chem. Zentr.*, **1937**, I, 1156.

for catalytic hydrogenation, the reservoir being filled with the olefin. In each case there was an initial rapid pressure drop, but absorption of the olefine by the aqueous bisulfite solution practically ceased after twenty to thirty minutes. When the pressure bottle was opened, flushed out with air, and refilled with olefin, this phenomenon was repeated.

TABLE I

PREVIOUS WORK ON THE ADDITION OF BISULFITE TO UNSATURATED COMPOUNDS

COMPOUND	CONDITIONS	RESULT	REFERENCE
Ethylene	0.25 *N* bisulfite and kieselguhr at 25° for 10 days	Addition	1*g*
Cyclohexene		Addition	1*g*
Trimethylethylene		Addition	1*g*
Pinene		Addition	1*g*
Dipentene		Addition	1*g*
Styrene		Addition	1*h*
Styrene	25–130°; S. T.[a]	Negative[b]	1*a*, *e*, *f*, *i*
Pinene	25°; S. T.[a]	Negative	1*f*
Allyl alcohol	Reflux 10–20 hours	Addition	1*b*, *d*
Allyl alcohol	100°; S. T.[a]	Allyl sulfate[c]	1*c*
Cinnamyl alcohol	Reflux	Addition	1*e*
Cinnamyl alcohol	25°; S. T.[a]	Addition	1*f*
Cinnamyl alcohol	130°; S. T.[a]	Negative	1*i*
Limonene	25°; S. T.[a]	Negative	1*f*
Geraniol		Addition	1*f*
Linaloöl		Addition	1*f*
Rhodinol		Addition	1*f*
Esters and ethers of geraniol, linaloöl and cinnamyl alcohol		Negative	1*f*

[a] Sealed tube.

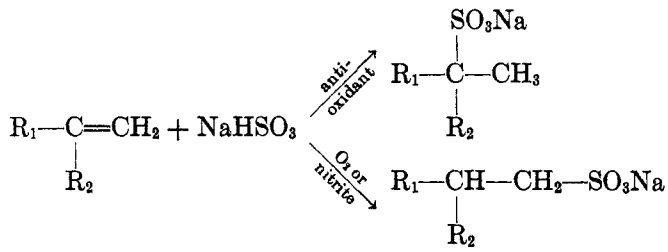
[b] These workers obtained traces of a water-soluble organic product which was not characterized. Miller[1a] obtained sufficient material for analysis.

[c] A possible explanation of this result is that the hydroxyl group of allyl alcohol is acted upon by bisulfite at higher temperatures. This, we believe, should be a characteristic reaction of carbinols of weakly electronegative radicals[1i].

As in the autoxidation of bisulfite, hydrogen-ion concentration has a profound effect on the rate of the reaction. The effect of pH was studied with propylene and 2*N* ammonium bisulfite buffered with ammonia to the desired pH value. The reaction proceeded at the maximum rate in the pH range of 5.1 to 6.1. In the case of ethylene no addition took place at a pH of 4.8, while at a pH of 5.9, a 12 per cent yield was obtained. Whether or not this was the optimum was not determined.

In every case in which the rule elaborated by Kharasch, Engelmann, and

Mayo[2] could be tested, the addition product was found to have the structure predicted for the free radical chain reaction:



"Normal" addition product. There is no indication that this product is formed.

Product of the free-radical mechanism.

TABLE II

ADDITION OF BISULFITE TO UNSATURATED COMPOUNDS

UNSATURATED COMPOUND	CONDITIONS	PER CENT RECOVERED		YIELD[a] OF ORGANIC SULFONATE
		Unsaturated Compound	Bisulfite	
Ethylene	Evac. to 10 mm.		98	0
Ethylene	Oxygen present			12
Propylene	Antioxidant		100	0
Propylene	Nitrite present[c]			30
Propylene	Oxygen present		21	55
Isobutylene	Oxygen present			62
Styrene	Evac. to 1 mm.	100	95	0
Styrene[b]	Oxygen present	27		55
Allyl alcohol	Antioxidant	90	95	0
Allyl alcohol	Oxygen present		5	65
Cinnamyl alcohol	Evac. to 15 mm.	95	95	3
Cinnamyl alcohol	Oxygen present	30		90

[a] The yields represent crude organic sulfonates actually isolated, and were calculated on the basis of the amount of bisulfite or unsaturated compound consumed in the reaction. They were checked at least once.

[b] The main yield in the case of styrene was the substitution product (*vide infra*).

[c] In the absence of oxygen.

[2] KHARASCH, ENGELMANN, AND MAYO, *J. Org. Chem.*, **2**, 299 (1937).

Briefly stated, this rule declares that under antioxidant conditions the bromide ion of hydrogen bromide attaches itself to the carbon atom of the double bond having the lesser electron density, (*i.e.*, in general, the carbon atom possessing the smaller number of hydrogen atoms); whereas under peroxide conditions, the bromine atom becomes linked to the carbon atom about which there is the greater electron density, through a free radical chain mechanism.

Thus, propylene yielded the propane-1-sulfonate, isobutylene the 2-methylpropane-1-sulfonate, allyl alcohol the 1-hydroxypropane-3-sulfonate and styrene the 1-phenylethane-2-sulfonate.

The structures of all these products were established by comparison of the physical properties of their derivatives with those of synthetic samples of known structure. These had all been previously prepared, except in the case of allyl alcohol. In this instance a new crystalline derivative, namely the 1-chloropropane-3-sulfonamide, was synthesized. This type of derivative should prove useful for the characterization of hydroxyalkanesulfonic acids in general.

INTERACTION OF BISULFITE AND STYRENE IN THE PRESENCE OF OXYGEN

By analogy with the other bisulfite addition reactions studied, the styrene addition product to be expected is 1-phenylethane-2-sulfonic acid. However, while a small amount of this compound was formed in the reaction, the product under all conditions, including those employed by Ashworth and Burkhardt[1h], consisted chiefly of 1-phenylethylene-2-sulfonic acid. The latter compound was first prepared by Quilico and Fleischner[3] from styrene and aminosulfonic acid. Their assignment of structure was made on the basis of the facts that cold permanganate oxidation yields benzoic acid, and that fusion with sodium formate yields cinnamic acid. We have further confirmed the structure by catalytic hydrogenation and conversion to 1-phenylethane-2-sulfonamide, in conjunction with the syntheses outlined in Figure I.

The hypothesis that this product was formed by dehydrogenation of the addition product is not tenable, for it was found that sodium 1-phenylethane-2-sulfonate is not affected by bisulfite and oxygen. The unsaturated sulfonic acid must therefore have been formed by substitution.

The presence of the addition product in the reaction between styrene, bisulfite, and oxygen was proven by treating a solution of the sulfonamide obtained from the crude reaction product with potassium permanganate. The unsaturated sulfonamide was destroyed, permitting the isolation of a pure saturated sulfonamide which was shown to be identical with 1-phenylethane-2-sulfonamide.

It is to be noted that these results are not in accord with the conclusions of Ashworth and Burkhardt[1h], who reported that the styrene-bisulfite addition product is the 1-phenylethane-1-sulfonate.

$$C_6H_5CH = CH_2 \xrightarrow{NH_4HSO_3} (C_6H_5C_2H_4)SO_3NH_4 \rightarrow (C_6H_5C_2H_4)SO_2NH_2 \qquad (I)$$

$$C_6H_5CHBrCH_3 \xrightarrow{(NH_4)_2SO_3})C_6H_5C_2H_4)SO_3NH_4 \rightarrow (C_6H_5C_2H_4)SO_2NH_2 \qquad (II)$$

$$C_6H_5CH_2CH_2Br \xrightarrow{(NH_4)_2SO_3} (C_6H_5C_2H_4)SO_3NH_4 \rightarrow (C_6H_5C_2H_4)SO_2NH_2 \qquad (III)$$

[3] QUILICO AND FLEISCHNER, *Atti. accad. Lincei*, [6], **7**, 1050 (1929).

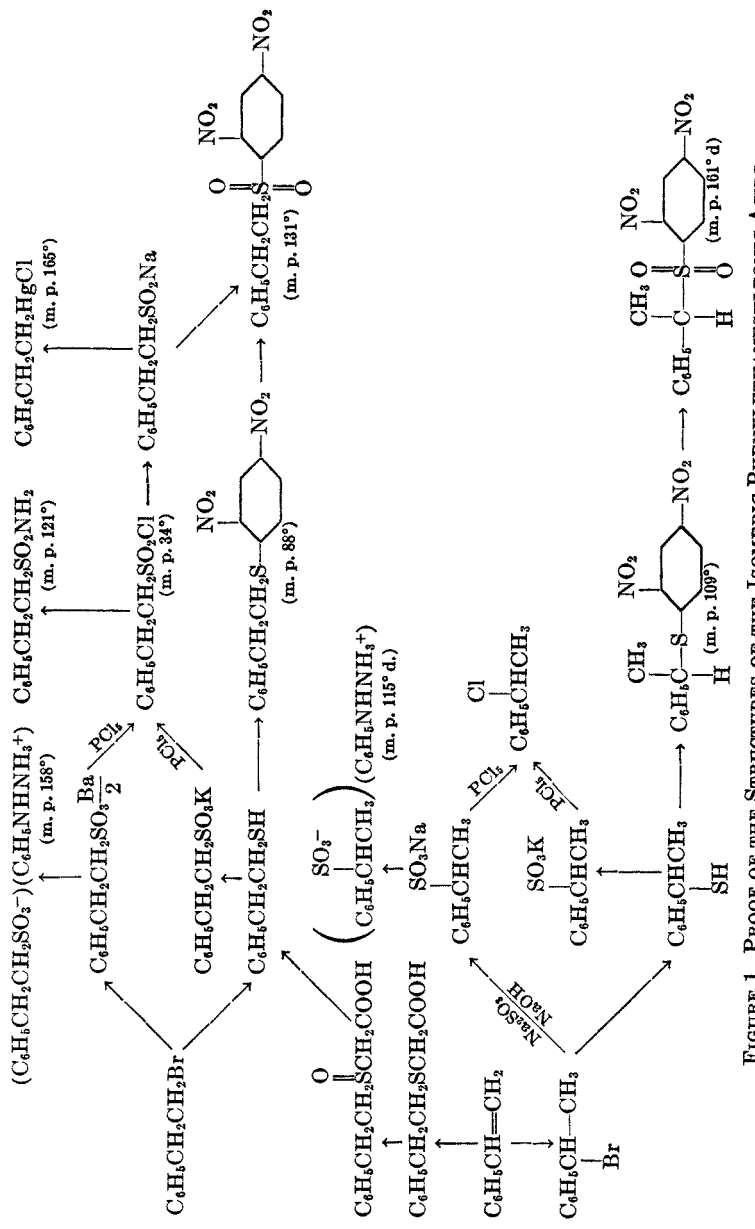


FIGURE 1. PROOF OF THE STRUCTURES OF THE ISOMERIC PHENYLETHANESULFONIC ACIDS

Their assignment of structure was made upon the basis of the identity of the sulfonamide derived from the addition product (I) with that derived from the sulfonate obtained by refluxing secondary phenylethyl bromide with concentrated aqueous ammonium sulfite (II), together with the supposed non-identity of sulfonamides I and II with the sulfonamide derived from phenethyl bromide (III). For sulfonamides I and II and for their mixtures a melting point of 121° was reported; for sulfonamide III, a melting point of 124°. The melting-point behavior of mixtures including the latter product was not reported. Other workers record for the melting point of the sulfonamide derived from phenethyl halide 121.5 — 122.5°[4] and 119°.[5]

However, repetition of these syntheses in our laboratories yielded three apparently identical sulfonamides, all melting, together with their respective mixtures, at 121°. A thorough re-investigation of the structures and properties of the isomeric phenylethanesulfonic acids was therefore undertaken.

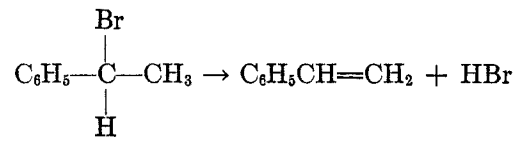
Authentic 1-phenylethane-1-sulfonic and 1-phenylethane-2-sulfonic acids were prepared by oxidation of the respective mercaptans. The structures of these substances were established beyond reasonable doubt by the preparation of a series of corresponding derivatives, the non-identity of which is apparent from their melting points and those of their mixtures (Figure I). No sulfonyl chloride or sulfonamide could be prepared from 1-phenylethane-1-sulfonic acid, the compound which Ashworth and Burkhardt believed they had obtained through bisulfite addition to styrene and from the secondary bromide. On treatment with phosphorus pentachloride, sodium 1-phenylethane-1-sulfonate was rapidly converted into secondary phenylethyl chloride, with the evolution of sulfur dioxide. 1-Phenylethane-2-sulfonic acid, prepared either from the mercaptan or the bromide, gave the sulfonamide of melting point 121°. It can readily be seen on the basis of this evidence that the sulfonamide of melting point 121° is actually 1-phenylethyl-2-sulfonamide and that, therefore, the structure of the addition product of styrene and bisulfite corresponds to 1-phenylethane-2-sulfonic acid.

It remains to be shown how secondary phenylethyl bromide could yield 1-phenylethane-2-sulfonic acid on refluxing with aqueous ammonium sulfite. It was observed by Evans and his co-workers[5] and also in this laboratory* that on refluxing such a mixture the following reaction took place:

[4] JOHNSON AND SPRAGUE, *J. Am. Chem. Soc.*, **58**, 1348 (1936).

[5] EVANS, MABBOTT, AND TURNER, *J. Chem. Soc.*, **1927**, 1159.

* The high yields (40 per cent.) of sulfonic acid reported by Evans and co-workers (*loc. cit.*) for this reaction could not be reproduced. In more than a dozen experiments, we consistently obtained yields of only 5 per cent.



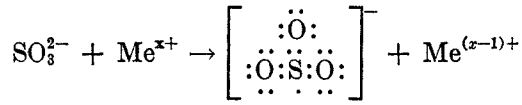
The hydrogen bromide formed was absorbed by the aqueous layer, causing the evolution of sulfur dioxide. *Under such conditions, the active reagents were styrene and bisulfite, and the reaction, therefore, on the basis of which Ashworth and Burkhardt identified the addition product of styrene and bisulfite, was actually the addition of bisulfite to styrene.*

$$C_6H_5CH{=}CH_2 + NH_4HSO_3 \rightarrow C_6H_5CH_2CH_2SO_3NH_4$$

In order to avoid the formation of styrene, with the attendant formation of bisulfite, the reaction was carried out at room temperature, with a strongly ammoniacal solution of ammonium sulfite. An excellent yield (50 per cent) of the sulfonic acid was obtained. This material was identical in its properties with the 1-phenylethane-1-sulfonic acid obtained by the oxidation of the corresponding mercaptan. A poorer yield of the acid was obtained by refluxing secondary phenylethyl chloride with aqueous sodium sulfite containing one-half molar equivalent of sodium hydroxide.

MECHANISM OF THE ADDITION REACTIONS

The end-products of the reaction between bisulfite and unsaturated substances in the presence of oxygen are sulfate ion and alkansulfonate, and the ratio of the two depends on the organic compound in question. The facts outlined point strongly to a chain reaction whereby the free radicals[6] or free radical ions[7] postulated in the autoxidation of bisulfite attack the unsaturated compound.† It is proposed that this reaction proceeds through a chain similar to that suggested to account for the free-radical addition of hydrogen bromide[2] and of thioglycollic acid[8]:

1. a.‡ 

[6] FRANCK AND HABER, *Ber. Berl. Akad.*, **1931**, 250.

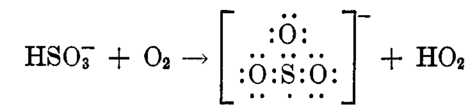
[7] BÄCKSTRÖM, *Z. physik. Chem.*, **B25**, 122 (1934).

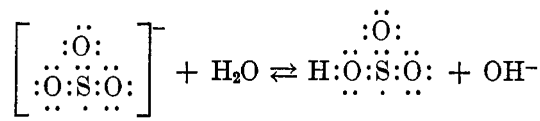
† Strong evidence for a free radical chain mechanism in the autoxidation of sulfite has been adduced by Bäckström and Haber and their respective co-workers. The literature on this subject is well summarized in the recent publication of Bäckström (*loc. cit.*).

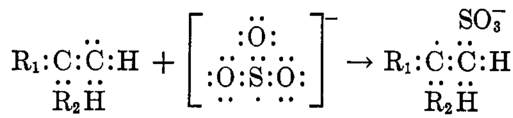
[8] KHARASCH, READ, AND MAYO, *Chem. & Ind.*, **57**, 752 (1938).

‡ This initial step in the autoxidation of sulfite (thermal reaction) is postulated by both Bäckström and Haber (*loc. cit.*).

or

b. 

2. 

3. a. 

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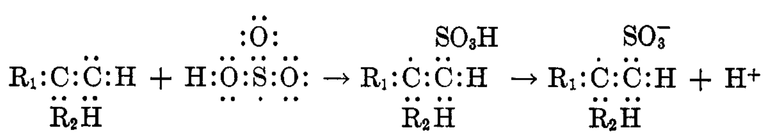
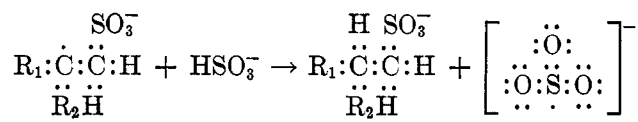
b. 

4. 

Various details of the experimental data lend themselves to interpretation on the basis of this mechanism. Thus, when the solubility of unsaturated substance in the bisulfite solution was low, the chains were necessarily short and a rigorous oxygen-exclusion technique was not needed to inhibit the reaction. With allyl alcohol, however, both a high degree of evacuation and the presence of an antioxidant were necessary to inhibit the reaction, as shown in the experimental part, (Table III). This, we believe, is due to the long chains produced by the presence of a high concentration of unsaturated compound.

Franck and Haber[6] have proposed that neutral bisulfite free radicals ($\cdot HSO_3$) are the chain-carriers in the autoxidation of bisulfite, postulating for them such an acid strength that they would exist only in the pH range of autoxidation. Bäckström[7], on the other hand, considers sulfite ion free radicals ($\cdot SO_3^-$) to be the chain-carriers, and claims that the dependence of the rate of autoxidation on pH is due to the fact that bisulfite ion is involved in the chains. He bases his assumption on the fact that the inhibitory action of alcohols (which, in breaking the chains, are dehydrogenated) is lost in more acid solutions in which the concentration of bisulfite ion is high, this latter species then being preferentially dehydrogenated to sulfite ion free radicals.

Baumgarten[9] has shown that pyridine, when present in high concentration during the autoxidation of bisulfite, is oxidized in small yield to dipyridyl compounds, whereas in the absence of oxygen no such reaction occurs. We have found that a small amount of styrene or 1-phenylethylene-2-sulfonate is oxidized to benzoic acid during the interaction of styrene and bisulfite in the presence of oxygen.

TABLE III

ADDITION OF BISULFITE TO ALLYL ALCOHOL

EXPT. NO.	CONDITIONS	ADDED REAGENTS	PER CENT BISULFITE UNREACTED	REMARKS
5	Vacuum	None	10	*a*
7	Vacuum	Hydroquinone	91	*b, g*
8	Vacuum	Hydroquinone	100	*b*
13	Oxygen	Ascaridole	3	*c, d*
14	Oxygen	None	5	*d*
15	Oxygen	Hydrogen peroxide	10	*d*
16	Oxygen	None	100	*d, e*
36	Oxygen	None		*d, f*

(*a*) Allyl alcohol not distilled *in vacuo*.

(*b*) Allyl alcohol distilled *in vacuo*.

(*c*) Ascaridole recovered unchanged.

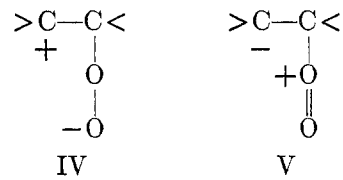
(*d*) In the oxygen runs oxygen was bubbled through the solution for two minutes.

(*e*) No allyl alcohol added. Titrated immediately after oxygen was bubbled through.

(*f*) Addition product isolated in 65% yield.

(*g*) Eight cc. of water used. On cooling, allyl alcohol separated and was recovered in 90% yield.

Winstein and Lucas[10] have suggested a mechanism by which one form (V) of a resonating oxygen complex (IV and V) with the double bond is



IV V

responsible for the directing influence of oxygen (and peroxides) in the addition of hydrogen bromide to double bonds. Although this mechanism accounts as satisfactorily as our own for the direction of addition of hydrogen bromide, it offers no explanation of the non-reversal of the direction

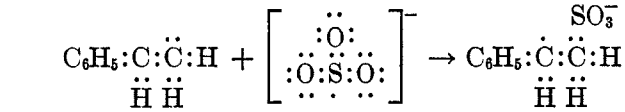
[9] BAUMGARTEN, *Ber.*, **69**, 229 (1936).

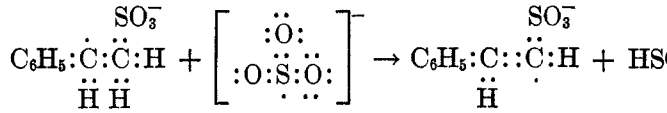
[10] WINSTEIN AND LUCAS, *J. Am. Chem. Soc.*, **60**, 843 (1938).

of addition of such acids as hydrochloric, hydriodic, and sulfuric in the presence of oxygen. If, as we believe, the oxygen-catalyzed hydrogen bromide addition and the bisulfite addition are essentially similar, the fact that nitrate and nitrite ions in the absence of oxygen cause the addition of bisulfite to propylene may be regarded as additional evidence of a free-radical chain mechanism.

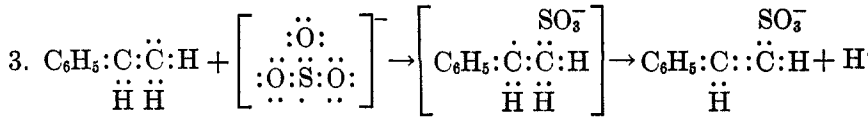
MECHANISM OF THE SUBSTITUTION REACTION WITH STYRENE

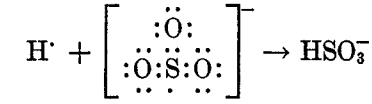
Two alternative mechanisms present themselves for the formation of the substitution product: the first may be represented by equations 1 and 2.

1 

2. 

The alternative mechanism implies a similarity between the complex H_3 described by Eyring and his co-workers[11] and the activated complex formed in equation 1. By analogy to the hydrogen atom-hydrogen molecule collision, the mechanism would then be:

3. 

4. 

Thus, the two mechanisms are the same insofar as the overall result is concerned and differ only in the manner in which hydrogen is lost by the hypothetical complex between styrene and the sulfite-ion free radical. In either case the reaction chain is broken and the slowness of the substitution reaction is thus explained.

EXPERIMENTAL*

Materials.—Isobutylene was prepared in the usual manner from *tert.*-butyl alcohol and hydrated oxalic acid. Cinnamyl alcohol was the Eastman product. Constant-

[11] HIRSCHFELDER, EYRING, AND ROSEN, *J. Chem. Phys.*, **4**, 121 (1936).

* New compounds are indicated by asterisks.

boiling 60–70% allyl alcohol was redistilled, b.p. 87°. Styrene was obtained through the courtesy of the Bakelite Corporation, from cinnamic acid,[12] and from phenethyl alcohol and solid sodium hydroxide.[13] It was freshly distilled *in vacuo* before use.

Addition to ethylene and propylene was carried out in a low-pressure hydrogenator, the reservoir tank of which was filled with the olefin to a pressure of 35 to 40 pounds. One hundred cc. of 2*N* ammonium bisulfite buffered with ammonia to a pH of 5.9 was added to the pressure bottle. The solution was shaken until the rate of absorption of gas by the solution, as indicated by the pressure drop, was negligible. The bottle was then removed, flushed with air, and the procedure was repeated. In general, air was added to the system every half-hour, and after nine to twelve additions the reaction was complete. The product was worked up according to the method of Kolker and Lapworth.[12]

Barium ethanesulfonate.—The yield of crude product was 2.8 grams or 12% of the bisulfite used. It was recrystallized once from water.

Anal. Calc'd: C, 13.56; H, 2.83.
Found: C, 13.53; H, 2.93.

Barium propane-1-sulfonate.—The yield of crude product varied from 11.5 to 13.8 grams. The ratio of sulfate to alkanesulfonate formed was approximately 0.8. After one recrystallization from water, the product was analytically pure.

Anal. Calc'd: C, 18.85; H, 3.67.
Found: C, 18.75; H, 3.83.

Vacuum runs with ethylene and propylene were made by evacuating the system to 20 mm. before admitting the olefin. This did not eliminate all oxygen from the system. However, very little gas was absorbed by the solutions after 10 hours' shaking. Ethylene yielded no addition product, while in the case of propylene 0.2 gram was isolated. When a small amount of hydroquinone was added to the bisulfite solution, the reaction with propylene was completely inhibited.

The effect of pH on the rate of the addition of bisulfite to propylene was studied qualitatively by observing the rate of absorption of the gas over the solution as measured by a pressure gauge which recorded the pressure in the pressure bottle when the valve to the reservoir was closed. pH was measured with a Beckman "pHmeter."

Addition of bisulfite to propylene in the presence of nitrite and nitrate.—One hundred cc. of 2*N* ammonium bisulfite (pH 5.9) containing 1.2 grams each of sodium nitrate and sodium nitrite was shaken under twenty pounds pressure of propylene, the system having been previously evacuated several times to 1 mm. and flushed with propylene. The initial rate of absorption was approximately the same as in the oxygen reaction. After two hours, absorption was negligible, due to the fact that the solution had become alkaline. The product was separated from inorganic sodium salts by extraction with alcohol and evaporation to dryness. The yield was 6 grams. The material was characterized by conversion through the sulfonyl chloride (yield 4.5 grams) to the sulfonamide as described below.

Identification of the propylene addition product.—The two isomeric propanesulfonic acids were prepared from the bromides in the form of their barium salts, according to the method of Hemilian,[14] and converted into the sulfonamides as described by

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[12] *Organic Syntheses*, Coll. Vol. I, p. 430, John Wiley and Sons, New York, **1932.**

[13] SABETAY, *Bull. soc. chim.*, [4], **45**, 69 (1929). This method gives the excellent yields reported by this author, and is far superior to the *Organic Syntheses* method. Due to an unfortunate mistranslation of alcoholic potassium hydroxide for "potasse a l'alcohol," the editors of *Organic Syntheses* apparently rejected this method.

[14] HEMILIAN, *Ann.*, **168**, 146 (1873).

Duguet.[15] Propane-1-sulfonamide melted at 51–2°, and when mixed in any proportion with the sulfonamide obtained from the addition product, no depression was noted. When either of these amides was mixed with propane-2-sulfonamide (m.p. 63°) melting began at room temperature.

Anal. (Propane-1-sulfonamide, addition product) Calc'd: C, 29,27; H, 7.32.
Found: C, 29.40; H, 7.31.

Isobutylene in excess was poured onto 20.8 grams of sodium bisulfite and 2.0 grams sodium hydroxide in 100 cc. of water in the pressure bottle, which was immersed in a cooling bath at −20°. The pressure bottle was then attached to the evacuated hydrogenator and allowed to warm to room temperature. At this point a pressure of 30 pounds was exerted by the system. The addition was then carried out as in the case of ethylene and propylene, any excess liquid isobutylene condensed in the pressure bottle being allowed to escape before the first flushing with air. The solution was evaporated to dryness at 45° under a stream of air. The residue was extracted first with 250 cc. of boiling 95% alcohol, then with 250 cc. of boiling 50% alcohol. The first alcoholic extract, upon evaporation to dryness yielded 9 grams of the sodium sulfonate free from inorganic material. The second extract, on treatment with an equal volume of 95% alcohol, yielded a precipitate of inorganic material. After this had been removed, the solution on evaporation to dryness yielded a further 10.5 grams of the sodium sulfonate which contained a very small amount of inorganic impurity. Total crude yield was 19.5 grams or 62% theoretical. The product may readily be purified by crystallization from alcohol.

The identification of the addition product of isobutylene and bisulfite was carried out by converting the crude product to 2-methylpropane-1-sulfon-α-naphthylamide according to the method of Duguet.[15] This product melted at 103–5°, and when mixed with an authentic specimen prepared according to the method of this author from isobutyl bromide, no depression in melting point was noted.

Allyl alcohol.—Five grams of sodium bisulfite, 5.0 cc. of constant-boiling allyl alcohol, and 10.0 cc. water were sealed off in bomb tubes with added reagents as noted in Table III. The tubes were heated 3 to 5 hours in a steam bath. The contents were then diluted to 250 cc. and titrated in weakly acid solution with standard iodine. Allyl alcohol was found not to affect the titer. An oxygen run was not so diluted, but drowned in alcohol, and the heavy viscous layer was extracted with alcohol until all the organic material had been removed. The inorganic residue weighed 1.2 grams. The alcoholic extract on evaporation to dryness yielded 6.0 grams of sodium 1-hydroxypropane-3-sulfonate which ash test showed to contain 15% sodium sulfate. The yield of addition product was therefore 65%. In order to prepare larger amounts of material for identification purposes, one part of pure allyl alcohol, 2.2 parts of potassium metabisulfite and ten parts of water were refluxed ten hours and then allowed to stand overnight. A slow stream of air was allowed to bubble through. Alcohol was added to complete precipitation of inorganic salts, which were filtered off, and the solution was evaporated on the steam bath to first signs of crystallization, filtered hot through carbon, and allowed to crystallize in the ice box. The crystals were separated by filtration from the viscous liquid, stirred in 95% alcohol and collected by filtration. In this manner, 260 grams of allyl alcohol yielded 60 grams of fairly pure crystals. The filtrates on evaporation to dryness yielded 300 grams of less pure material. Either sample was satisfactory for identification purposes. *Vacuum runs* were made according to the technique

[15] DUGUET, *Rec. trav. chim.*, **25**, 216 (1906).

described by Kharasch and Mayo.[16] In order to inhibit the reaction completely, it was found necessary not only to distil the allyl alcohol in high vacuum but also to add ten mole per cent. of hydroquinone.

Sodium 1-hydroxypropane-3-sulfonate.—Forty-five grams of trimethylene bromohydrin (Eastman Kodak) was refluxed with an equal weight of anhydrous sodium sulfite in a concentrated aqueous solution until the organic layer had disappeared. The solution was then evaporated to a small volume and filtered from sodium bromide. Four hundred cc. of alcohol was added to the filtrate, precipitating 10 grams of the sodium sulfonate containing only a small amount of bromide. Evaporation of the mother liquor to one-half its original volume yielded an additional 9 grams of sodium sulfonate of similar quality.

1-Chloropropane-3-sulfonamide.—Nine grams of the second crop of sodium 1-hydroxypropane-3-sulfonate was dried for two hours at 120°, was finely ground, and was added to 12 grams of phosphorus pentachloride in 35 cc. of dry carbon tetrachloride. Violent decomposition occurred when the solvent was not used. After three hours' refluxing, and standing overnight, the suspension was filtered. The filtrate was evaporated at the pressure of the water pump at a temperature not exceeding 40°. Approximately two grams of oil was obtained. This material was taken up in ether, washed with water, and dried over calcium chloride. It was extremely lachrymatory. Conversion to 1-chloropropane-3-sulfonamide was effected by adding the ether solution to a solution of ammonia in ether at 0°. After standing 1 hour, the solution was filtered, evaporated to 25 cc., diluted to faint turbidity with ligroïn, and allowed to stand in the icebox overnight. A precipitate of fine needless contaminated with oily material was obtained. After two further recrystallizations from ether-ligroïn, the melting point was constant at 63°. The material gave a strong Beilstein test.

Anal. Calc'd: N, 8.89; Found: N, 8.91.

Identification of the addition product of allyl alcohol and bisulfite was carried out by conversion to the chloropropanesulfonamide as described above. This material melted at 63°, and gave a strong Beilstein test. When mixed in all proportions with the authentic sample, no depression in melting point was noted.

Anal. Calc'd: N, 8.89.
Found: N, 8.81.

Treatment of cinnamyl alcohol and of styrene with bisulfite.—Equivalent amounts of unsaturated compound and 1 to 2*N* ammonium bisulfite solution were shaken in a vessel connected to an oxygen reservoir with rubber tubing. The reservoir was refilled with oxygen every 1 to 2 hours. After oxygen absorption ceased, the unsaturated substance was separated and weighed. The aqueous solution was worked up according to the method of Kolker and Lapworth.[1g] *Vacuum runs* were conducted side by side with oxygen runs on the shaker, with identical amounts of material and vessels of the same shape and size.

Styrene.—The yields varied from 30 to 70%, but yields of 50–60% were usual. The time required for reaction varied from 20 to 30 hours with air above the shaken reaction mixture to 10 hours with pure oxygen at 5 to 10 lbs./sq. in. above atmospheric pressure. The effect of alcohol as a common solvent was to decrease the yield and induce the formation of polystyrene, which was never noted in the absence of this solvent. The recovered styrene had the same boiling point as the freshly distilled material. Larger runs were conducted on the hydrogenator, with 25 grams of

[16] KHARASCH AND MAYO, *J. Am. Chem. Soc.*, **55**, 2468 (1933).

styrene, 100 cc. of 2*N* ammonium bisulfite (pH 5.9), and oxygen under five to ten pounds pressure. It was found necessary toward the end of the reaction to add small amounts of ammonia. The substitution product, in the form of the barium sulfonate, was readily purified by a single crystallization. No attempt was made to isolate the addition product, except in the form of the sulfonamide. Benzoic acid was isolated in small quantity from the residues of a number of runs, by acidification, extraction with ether, and recrystallization from water. It was identified by its melting point and that of its mixtures with an authentic sample.

Cinnamyl alcohol.—The reaction was practically complete in 10 hours. The relative proportion of sulfate to organic sulfonate formed in the reaction was 2 to 1. The barium salt of the reaction product was not readily crystallizable. It was therefore converted to the sodium salt, which was crystallized from dilute alcohol.

Anal. Calc'd: Na, 9.63.
Found: Na, 9.62.

Secondary phenylethyl bromide, (b.p. 88° at 15 mm), was prepared by bubbling dry hydrogen bromide through ice-cooled styrene.

Secondary phenylethyl chloride, (b.p. 69–70° at 13 mm.), was prepared by hydrolyzing secondary phenylethyl bromide in cold alcoholic potassium hydroxide, adding water, and shaking the separated phenylmethylcarbinol with concentrated hydrochloric acid.[17]

Secondary phenylethyl mercaptan, (b.p. 83° at 15 mm.), was prepared according to Sontag.[18]

Potassium 1-phenylethane-1-sulfonate was prepared according to Levene[19] by oxidizing secondary phenylethyl mercaptan with potassium permanganate.

Barium 1-phenylethane-1-sulfonate was prepared by shaking 50 grams of secondary phenylethyl bromide, 100 cc. of 42% ammonium bisulfite solution and 50 cc. of concentrated aqueous ammonia for 10 hours. The oil was removed, an excess of barium hydroxide was added, and the ammonia was boiled out. Sulfuric acid was then added to bring the solution almost to neutrality, and the insoluble barium salts were collected by filtration and washed. The filtrates were then concentrated to crystallization. The yield was 35 grams or 50%.

Sodium 1-phenylethane-1-sulfonate was prepared by refluxing a mixture of 42 grams of secondary phenylethyl chloride and 300 cc. of a solution containing 45 grams of anhydrous sodium sulfite and 7.2 grams of sodium hydroxide for 20 hours, with stirring. The product was worked up according to Houlton and Tartar.[20] The yield was 3.5 grams.

*Phenylhydrazinium 1-phenylethane-1-sulfonate** was prepared by the method of Latimer and Bost.[21] It melted at 115° in a preheated bath. On slow heating it decomposed gradually below its melting point to give a high-melting substance.

*α-Phenylethyl 2,4-dinitrophenyl sulfide** was prepared according to the method of Bost, Turner and Norton.[22] Care must be taken to avoid excess alkali. Stout canary-yellow needles; m.p. 109°.

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[17] NORRIS, WATT, AND THOMAS, *ibid.*, **38**, 1078 (1916).
[18] SONTAG, *Ann. chim.*, [11], **1**, 428 (1934).
[19] LEVENE, *J. Biol. Chem.*, **70**, 365 (1926).
[20] HOULTON AND TARTAR, *J. Am. Chem. Soc.*, **60**, 544 (1938).
[21] LATIMER AND BOST, *ibid.*, **59**, 2500 (1937).
[22] BOST, TURNER, AND NORTON, *ibid.*, **54**, 1985 (1932).

*α-Phenylethyl 2,4-dinitrophenyl sulfone** was prepared as by Bost, Turner and Norton.[22] M.p. 161°, with decomposition.

Anal. Calc'd: N, 8.34.
Found: N, 8.44.

Attempted preparation of 1-phenylethane-1-sulfonyl chloride.—The well-dried and ground sodium, potassium, lead and barium salts of 1-phenylethane-1-sulfonic acid prepared from secondary phenylethyl bromide, chloride or mercaptan as described above, were treated with a 10% excess of phosphorus pentachloride in the presence and absence of carbon tetrachloride. In the absence of the solvent, an instantaneous vigorous reaction took place and the only product isolated was secondary phenylethyl chloride in good yield. In the presence of the solvent, the reaction was less vigorous, with, however, the same result. Phosphorus oxychloride and phosphorus trichloride gave oily products which did not react with ammonia in ether solution; thionyl chloride yielded only polystyrene.

Phenethyl alcohol was obtained through the courtesy of Van Ameringen-Haebler, Inc.

Phenethyl bromide, (b.p. 95.5° at 18 mm.), was prepared by the method of Schroeter, Lichtenstadt, and Irineu.[23]

Phenethyl mercaptan (b.p. 93° at 14 mm.) was prepared as by Sontag.[18]

Potassium 1-phenylethane-2-sulfonate was prepared by the oxidation of the mercaptan as in the case of the isomeric sulfonate.

Barium 1-phenylethane-2-sulfonate was prepared from phenethyl bromide by the method of Ashworth and Burkhardt.[14]

*Phenylhydrazinium 1-phenylethane-2-sulfonate** was prepared according to the method of Latimer and Bost;[21] m.p. 154°.

1-Phenylethane-2-sulfonyl chloride was prepared by mixing the dried and powdered barium or potassium sulfonates with a 10% excess of phosphorus pentachloride. After heating for thirty minutes on the steambath and standing for several hours, the mixture was poured into ice-water, shaken in a separatory funnel and extracted with ether. The ether extract was dried overnight in the refrigerator over calcium chloride. The solution was filtered through carbon, and the ether was removed *in vacuo*. The residual oil was taken up in ligroïn, filtered through carbon if cloudy, and allowed to crystallize in the ice box. A 75% yield of material melting at 34°[4,5] was obtained.

1-Phenylethane-2-sulfonamide, (m.p. 121°) was prepared by passing dry ammonia into an ether solution of the sulfonyl chloride, filtering, evaporating to dryness and recrystallizing the residue twice from water. Carbon must be used on the first recrystallization to remove oily impurity.

Anal. Calc'd: C, 51.89; H, 5.94.
Found: C, 51.93; H, 5.91.

Zinc 1-phenylethane-2-sulfinate.—Ten grams of 1-phenylethane-2-sulfonyl chloride in 200 cc. of 98% alcohol and 10 grams of zinc dust, purified by sludging with diluted ammonia and drying *in vacuo*, were shaken for 10 hours. The mixture was then heated to 60° and allowed to stand overnight. It was filtered hot, and the precipitate was extracted twice with 100-cc. portions of boiling alcohol. From the combined filtrates was obtained on cooling 6.5 grams of white needles, or 65% theoretical. A small sample, on removal of the zinc with sodium carbonate, and acidification, yielded with ferric ion the characteristic orange-yellow insoluble ferric sulfinate.

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[23] SCHROETER, LICHTENSTADT, AND IRINEU, *Ber.*, **51**, 1599 (1918).

Phenethyl 2,4-dinitrophenyl sulfone.—Four and four-hundredths grams of zinc 1-phenylethane-2-sulfinate was suspended in 40 cc. of 50% alcohol, and 1.06 grams sodium carbonate in 10 cc. water was added. The zinc carbonate was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 50 cc. of 90% alcohol, and filtered, and 4 grams of 2,4-dinitrochlorobenzene in 15 cc. alcohol was added. The solution was refluxed for thirty minutes, and filtered hot, and the precipitate was washed with boiling alcohol. The yield, after recrystallization, was 4 grams; m.p. 131°.[22]

Anal. Calc'd: N, 8.34.
Found: N, 8.12.

Phenethyl 2,4-dinitrophenyl sulfide was prepared by the method of Bost, Turner, and Norton[22] from the mercaptan. It melted at 88°, and on oxidation[22] yielded a material, m.p. 131°, which showed no depression in melting point when mixed with phenethyl 2,4-dinitrophenyl sulfone prepared from the sulfinate.

Phenethyl carboxymethyl sulfide was obtained through the courtesy of Dr. Read of this laboratory. It was prepared by the addition of thioglycollic acid to styrene, in the presence of ascaridole.

Phenylethyl carboxymethyl sulfoxide was prepared as by Holmberg.[24] On steam distillation with 1*N* sulfuric acid it yielded phenethyl mercaptan, which, on treatment with 2,4-dinitrochlorobenzene[22] gave the sulfide, m.p. 88°, which mixture melting point determinations showed to be identical with the material prepared from phenethyl bromide.

Phenethylmercuric chloride was prepared by refluxing an alcoholic solution of 1-phenylethane-2-sulfinate with 1.5 molar equivalents of mercuric chloride until no further sulfur dioxide was evolved. The solution was filtered hot, the precipitate was extracted with boiling alcohol, and the filtrates were poured into water. The crude product thus precipitated was recrystallized once from alcohol, and then melted at 165°. Kharasch and Flenner[25] give 165° for the melting point of phenethylmercuric chloride.

Proof of structure of barium 1-phenylethylene-2-sulfonate.—Ten grams of barium 1-phenylethylene-2-sulfonate was converted to the sodium salt in 150 cc. of water. One-half gram of platinic oxide monohydrate was added, and the mixture shaken for six hours at room temperature under two atmospheres of hydrogen. The solution was freed of catalyst and evaporated to dryness. The yield was 8 grams of material which did not react with potassium permanganate. On conversion to the sulfonyl chloride as described in the preparation of 1-phenylethane-2-sulfonyl chloride, a crystalline material could not be obtained. The oil was therefore dissolved in ligroïn, and dry ammonia was passed in. The precipitate was filtered, washed with ligroïn and recrystallized several times from water; carbon was used to remove oily impurities. The resulting crystals melted at 118° and were shown to be 1-phenylethane-2-sulfonamide by determination of the melting point of a mixture with an authentic specimen.

Proof of the presence of addition product in the interaction of styrene and bisulfite.—Two runs were made according to the method of Ashworth and Burkhardt,[1h] one at a pH of 5.0, the other at 5.9. The former yielded 4 grams of crude product in 4 days, the latter yielded in two days 6.5 grams of material of which 2.5 grams was isolated as pure barium 1-phenylethylene-2-sulfonate. The crude residues were

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[24] HOLMBERG, *J. prakt. Chem.*, [2], **141**, 93 (1934).

[25] KHARASCH AND FLENNER, *J. Am. Chem. Soc.*, **54**, 674 (1932).

treated separately with phosphorus pentachloride, the crude sulfonyl chloride being extracted with ether, dried, and treated with ammonia. The crude product in each case yielded after two recrystallizations a sulfonamide melting at 131–2° which corresponds to one part of 1-phenylethane-2-sulfonamide with six of 1-phenylethylene-2-sulfonamide (assuming that these are the only components of the system). The mother-liquors from the recrystallizations were then combined and potassium permanganate was added in slight excess. The filtered solution was then extracted with an equal volume of ether. The ether layer was evaporated on the steam bath. The residue was taken up in boiling water and the solution was filtered with carbon. Upon cooling there was a small yield of crystals, m.p. 119°. No depression in melting point was noted when this substance was mixed with 1-phenylethane-2-sulfonamide.

1-Phenylethylene-2-sulfonyl chloride.—Seventeen grams of barium 1-phenylethylene-2-sulfonate and 17 grams of phosphorus pentachloride were mixed in an Erlenmeyer flask fitted with a calcium chloride tube, and the mixture was heated on the steam bath until the mass became viscous; it was then allowed to stand overnight. It was then poured into ice-water and shaken with 250 cc. of ligroïn. The whole mass was filtered; the ligroïn layer was separated, and placed in the ice box. The aqueous layer was discarded. The precipitate on the filter was extracted with 150 cc. of ether, and was dried over calcium chloride. Upon the removal of the ether *in vacuo*, 6.5 grams of the sulfonyl chloride was obtained; m.p. 87°.[3] The ligroïn solution yielded an additional 2.3 grams of crystals; m.p. 87°. The total yield was 75% of the theoretical. The ligroïn mother-liquor contained only highly impure material.

*Phenylhydrazinium 1-phenylethylene-2-sulfonate** was prepared according to the method of Latimer and Bost;[21] m.p. 148°.

*Zinc 1-phenylethylene-2-sulfinate.**—Six grams of 1-phenylethylene-2-sulfonyl chloride was treated in the same manner as described for 1-phenylethanesulfonyl chloride, yielding 1.2 grams of the zinc salt.

*Styryl 2,4-dinitrophenyl sulfone** was prepared in the same manner as phenethyl 2,4-dinitrophenyl sulfone; 1.2 grams of the zinc sulfinate yielded 0.7 grams of sulfone; m.p. 158°.

Anal. Calc'd: N, 8.38.
Found: N, 8.39.

*Styrylmercuric chloride** was prepared in the same manner as phenethylmercuric chloride; m.p. 207°.

Anal. Calc'd: Hg, 59.2.
Found: Hg, 59.0.

1-Phenylethylene-2-sulfonamide, m.p. 142°,[3] was prepared in the same manner as 1-phenylethane-2-sulfonamide.

Anal. Calc'd: C, 52.46; H, 4.92; N, 7.75.
Found: C, 52.90, 52.77, 52.85; H, 4.93, 4.87, 5.08; N, 7.58, 7.46.

SUMMARY

1. The interaction of bisulfite with ethylene, propylene, styrene, allyl alcohol and cinnamyl alcohol has been shown to proceed only in the presence of oxygen, or such oxidizing agents as nitrite and nitrate ions.

2. The products of addition of bisulfite to propylene, isobutylene, sty

rene, and allyl alcohol are those predicted by the rule for free-radical additions to double bonds.

3. The interaction of bisulfite and styrene yields mainly 1-phenylethylene-2-sulfonate.

4. A chain mechanism involving free radicals has been proposed to explain the addition of bisulfite to unsaturated compounds.

5. New derivatives of 1-phenylethane-1-sulfonic acid, 1-phenylethane-2-sulfonic acid, 1-phenylethylene-2-sulfonic acid, and 1-hydroxypropane-3-sulfonic acid have been prepared.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

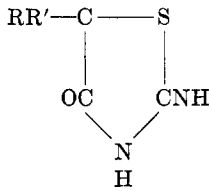
DIALKYL THIAZOLIDIONES

WILBUR J. DORAN AND H. A. SHONLE

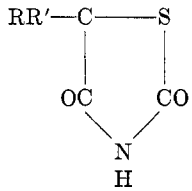
Received May 17, 1938

It seems significant that a wide group of organic compounds exhibiting sedative action, such as the dialkylacetyl ureas, the halogenated dialkylacetamides, the alkaryl hydantoins,* the dialkyl homophthalimides,[1] the dialkyl barbituric acids, the dialkyldiketotetrahydro oxazoles,[2] the dialkyl-dioxotetrahydro pyridines,[3] and dialkyl rhodanines,[4] contain the group $RR'{=}\overset{|}{C}{-}CO{-}NH{-}$. Although many series of organic compounds exhibiting sedative action which do not contain this group exist, the synthesis and pharmacological study of additional compounds containing such a group seemed desirable.

At the time this investigation was completed, little chemical data and no pharmacological reports were available concerning the 5,5-dialkyl-2-imino-4-thiazolidones or the 5,5-dialkyl-2,4-thiazolidiones.



5,5-Dialkyl-2-imino-4-thiazolidone



5,5-Dialkyl-2,4-thiazolidione

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* Of the many hydantoins described, only phenylethyl hydantoin possesses sufficient hypnotic action to come within the range of clinical usefulness.

[1] LUMIERE AND PERRIN, *Bull. soc. chim.* [4], **35**, 1022 (1924) describe diethyl-, ethylpropyl-, dipropyl-, and diallyl homophthalimide.

[2] (*a*) ALTWEGG AND EBIN, *U. S. Patent* 1,375,949, describe phenylmethyl-, phenylethyl-, dipropyl-, and diallyl-2,4-diketotetrahydro oxazole; and (*b*) ERLENMEYER AND KLEIBER, *Helv. Chim. Acta*, **21**, 111 (1938), describe the diethyl-2,4-diketotetrahydro oxazole.

[3] SCHNIDER, *U. S. Patent* 2,090,237, and PREISWERK AND SCHNIDER, *U. S. Patent* 2,090,068, describe a large group of 3,3-dialkyl-2,4-dioxotetrahydro pyridines.

[4] (*a*) LEONARD, *Medd. K. Vetenskapsakad. Nobelinst.* **4**, No. 14, 1–13 (1921), describes 5,5-diethyl rhodanine, and (*b*) ERLENMEYER AND KLEIBER, *Helv. Chim. Acta*, **21**, 111 (1938), describe 5,5-dimethyl and 5,5-diethyl rhodanine.

This paper, which covers the synthesis and pharmacological study of certain of the thiazolidones and thiazolidiones, is a report on a portion of a research directed to increasing our knowledge on the relationship of chemical structures and hypnotic action. This study was directed chiefly to the preparation and evaluation of unsymmetrical thiazolidiones, since it has been our experience in the field of barbituric acids that the unsymmetrically substituted derivatives are more effective than the symmetrically substituted ones. Inasmuch as the corresponding 5,5-dialkyl-2-imino-4-thiazolidones were the intermediates from which the thiazolidiones were prepared, they also were pharmacologically tested.

After our experimental work was completed, Erlenmeyer and von Meyenburg[5] reported the preparation of 5,5-diethyl-, 5,5-dipropyl-, 5,5-diallyl-, and 5,5-phenylethyl-2,4-thiazolidiones. These investigators state that several of these compounds had been pharmacologically tested and found to have a sedative action which was comparable to that of the dialkyl barbituric acids.

Our pharmacological studies show that the thiazolidiones have a marked sedative and anesthetic action of brief duration. Only the data obtained after the intravenous administration of the sodium salts of the 2,4-thiazolidiones are reported, although these compounds also were administered orally and intraperitoneally. The brevity of the effect is indicative of rapid destruction by the body. Critical animal tests, however, brought out the fact that these dialkyl 2,4-thiazolidiones do not give particular promise of clinical usefulness, at least after intravenous administration, due to the fact that they either produce tremors or convulsions. While it is impossible to make a broad prediction that all of the possible dialkyl 2,4-thiazolidiones will produce convulsions or tremors, their presence following administration of these five representative members leads us to believe that such a response may be expected from the other members. No statement is made by Erlenmeyer and von Meyenburg as to whether their compounds produced tremors or convulsions, although our study included one of the compounds which they tested.

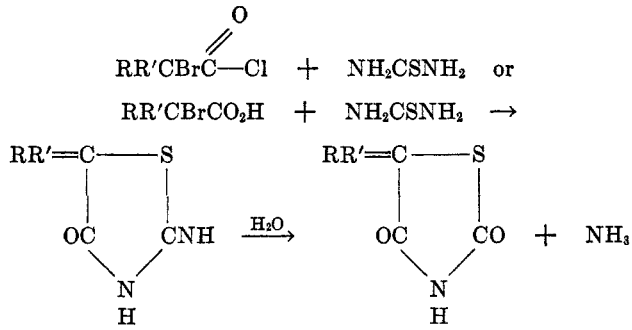
The imino derivatives, which are soluble in both dilute acids and in dilute alkalis, contrary to what might be expected, exhibited a moderate amount of sedative action when administered orally to white rats. The effectiveness of the imino derivatives of this series is in marked contrast to the lack of activity of the imino barbituric acids.

It was concluded, on the basis of the above study, that dialkyl derivatives of the 2,4-thiazolidione nucleus are less satisfactory than the corresponding barbituric acid derivatives for the production of sedation.

[5] ERLENMEYER AND VON MEYENBURG, *Helv. Chim. Acta*, **20**, 1388 (1937).

EXPERIMENTAL

The 5,5-dialkyl-2-imino-4-thiazolidones were prepared either by condensing thiourea with dialkyl substituted bromoacetic acids or with dialkyl substituted bromoacetyl chlorides, and hydrolyzed to form the corresponding thiazolidione.



The substituted acetic acids were obtained by hydrolyzing the corresponding substituted malonic esters in dilute potassium hydroxide solution. After refluxing for several hours, the alcohol was removed by distillation *in vacuo*, and the residue was treated with water. The aqueous solution was acidified, and the substituted malonic acid which separated was extracted with ether. The malonic acids were heated to about 170°, in order to split out carbon dioxide, and thus form the corresponding acetic acids.

The dialkyl-substituted α-bromoacetic acids were obtained by heating the acetic acids with bromine following the general procedure given for the preparation of α-bromo-*n*-caproic acid.[6] Two of the α-bromoacetic acids prepared have not been described in the literature. They are ethylisobutylbromoacetic acid, which boils at 121–125° at 2.5 mm., and ethyl-1-methylbutylbromoacetic acid, which boils at 120–125° at 1 mm.

The dialkyl-substituted bromoacetyl chlorides were prepared by converting the acetic acids into their acid chlorides by means of thionyl chloride and treating the acetyl chlorides with bromine.[7]

5,5-Ethyl-*n*-propyl-, 5,5-ethylisobutyl-, and 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidones were prepared by condensing the corresponding substituted bromoacetic acids with thiourea, using the method which Markley and Reid[8] employed in the preparation of diphenylisothiohydantoin. This is illustrated in the following preparation of 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone.

A mixture of 23.5 g. (0.1 mol) ethyl 1-methylbutylbromoacetic acid, 7.6 g. (0.1 mol) thiourea, 3.8 g. (0.046 mol) anhydrous sodium acetate and 110 cc. absolute ethyl alcohol was refluxed for three hours. The alcohol was removed by distillation *in vacuo*, the residue was treated with water, and sodium bicarbonate was added until the mixture was neutral to litmus. The solid 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone was filtered, washed with water, dried *in vacuo*, and weighed

[6] *Organic Syntheses*, Coll. Vol. I, p. 108.

[7] *D.R.P.* 158,220; *Chem. Zentr.*, **1905**, I, 635.

[8] MARKLEY AND REID, *J. Am. Chem. Soc.*, **52**, 2137 (1930).

TABLE

CONSTANTS OF 2-IMINO-4-THIAZOLIDONES AND OF 2,4-THIAZOLIDONES

5, 5-ALKYL SUBSTITUENTS	2-IMINO-4-THIAZOLIDONE			2,4-THIAZOLIDIONE			INTRAVENOUS ADMINISTRATION OF SODIUM SALT OF DISUBSTITUTED 2,4-THIAZOLIDIONES IN WHITE RATS		
	M.p., °C.[a]	% Nitrogen		M.p., °C.[a]	% Nitrogen		M.E.D., mg./kg.	M.L.D., mg./kg.	Average duration of M.E.D., min.
		Calc'd	Found		Calc'd	Found			
Diethyl	237–238[b]	16.27	16.05 16.15	78.0–78.5[c]	8.09	8.14 8.22	200[d]	600	120
Ethyl-*n*-propyl	220–222	15.04	14.98 14.91	oil	7.49	7.58 7.62	100[e]	400	75
Ethyl-isobutyl	225–227	14.00	14.08 14.08	oil	6.97	7.01 7.13	100[e]	325	30
Ethyl-*sec.*-butyl	215–216	14.00	14.01 13.91	70–72	6.97	6.89 7.03	100[e]	300	60
Ethyl-1-methylbutyl	229–231	13.08	13.00 13.07	105–107	6.51	6.52 6.69	50–100[e]	250	30

[a] Anschütz thermometer used. [b] CLEMMENSEN AND HEITMAN, *Am. Chem. J.*, *40*, 280 (1908), report the m.p. as 224°, while ERLENMEYER AND VON MEYENBURG, *Helv. Chim. Acta*, *20*, 1388 (1937), give 233.5° (corr.).

[c] ERLENMEYER AND VON MEYENBURG report this compound melts at 76°. [d] Produces tremors. [e] Convulsions.

16 g. (79% yield). After several recrystallizations from dilute alcohol it melted at 229–231°.

Diethyl-2-imino-4-thiazolidone[9] and ethyl-sec.-butyl-2-imino-4-thiazolidone were prepared by condensing the dialkyl substituted bromoacetyl chlorides with thiourea. A mixture of the bromoacetyl chloride and thiourea was warmed to initiate the reaction, which was then allowed to proceed spontaneously. All of the 2-imino-4-thiazolidones were crystalline solids which were purified by crystallization from dilute alcohol. They are but slightly soluble in water but dissolve in dilute acids and bases. The constants of the five 2-imino-4-thiazolidones which were prepared, are given in the accompanying table.

The 5,5-dialkyl-2,4-thiazolidones were obtained from the 2-imino-4-thiazolidones by hydrolysis of the 2-imino group. The method used is illustrated in the hydrolysis of 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone. Four and one-half grams (0.021 mol) of the latter was dissolved in a solution of 10 cc. of 1:1 hydrochloric acid and 90 cc. of distilled water. The solution was refluxed for two hours, and on cooling, the oil which had formed solidified. The crude 2,4-thiazolidione was filtered, washed with petroleum ether; it weighed 3.0 g. and melted at 99–100°. After several recrystallizations from dilute alcohol it melted at 105–107° and weighed 2.5 g. (55%). The crystalline 2,4-thiazolidiones described in the accompanying table were purified by recrystallization from alcohol.

Ethyl-*n*-propyl- and ethylisobutyl-2,4-thiazolidiones would not crystallize on standing for some time. They were purified by extracting them from their chloroform solutions with dilute sodium hydroxide solution. The pH of the solutions was then lowered to about 9.0 (colorimetrically), decolorizing carbon was added, and the solutions were filtered. On acidification, oils were obtained, which were extracted with chloroform, and after the chloroform solutions had been washed free of mineral acid, the thiazolidiones recovered by evaporation of the chloroform.

CONCLUSION

Two additional series of compounds containing the group $RR'{=}\overset{|}{C}{-}CO{-}NH{-}$ as part of a heterocyclic ring, the 5,5-dialkyl-2-imino-4-thiazolidones, and the 5,5-dialkyl-2,4-thiazolidiones were found to exert hypnotic action when administered orally to white rats.

The prevalence of tremors or convulsions after the intravenous administration of sodium salts of the thiazolidiones makes it unlikely that they will be of practical importance.

The following new compounds were prepared: ethylisobutyl- and ethyl-1-methylbutyl-bromoacetic acids; ethyl-*n*-propyl-, ethylisobutyl-, ethyl-*sec.*-butyl-, and ethyl-1-methylbutyl-2-imino-4-thiazolidones; and ethyl-*n*-propyl-, ethylisobutyl-, ethyl-*sec.*-butyl-, and ethyl-1-methylbutyl-2,4-thiazolidiones.

[9] CLEMMENSEN AND HEITMAN, *Am. Chem. J.*, **40**, 280 (1908).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

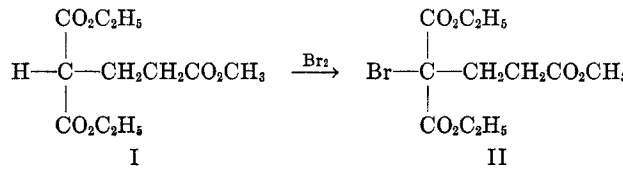
A CONVENIENT SYNTHESIS OF *dl*-GLUTAMIC ACID

C. S. MARVEL AND M. PALMER STODDARD

Received June 2, 1938

Although *dl*-glutamic acid can be obtained easily and cheaply by the racemization of the natural *d*-isomer,[1] there is a demand for a method of preparation which excludes the possibility of other naturally-occurring products as contaminants. It is especially important to use synthetic products in determining the nutritional requirements of microörganisms since very small amounts of impurities may seriously affect the results of such studies. In this communication we are reporting some experiments which have enabled us to prepare synthetic *dl*-glutamic acid easily and at a reasonable price.

We first tried to use the addition product (I) of ethyl malonate and methyl acrylate[2] as a starting material for the preparation of the amino



I II

acid. Bromination proceeded smoothly to give the bromo ester (II).[3] Treatment of this bromo ester with ammonia converted the organic bromine to bromide ion but the amount of amino nitrogen produced was very slight. Thorpe[3] has shown that diethylaniline converts the corresponding bromo derivative of the triethyl ester to a mixture of the carbethoxy glutaconic ester and the cyclopropane triester but it is surprising to find no replacement of the bromine by the amino group when ammonia is used.

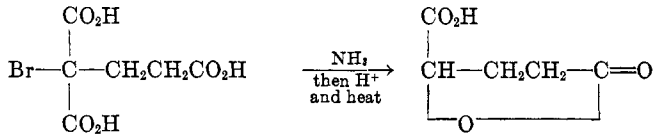
When the bromo ester (II) was treated with potassium phthalmide, there was an apparent reaction. Hydrolysis of the reaction mixture produced glutaric acid but no glutamic acid could be found in the mixture. This removal of bromine by alkaline reagents has been reported for similar

[1] DUNN AND STODDARD, *J. Biol. Chem.*, **121**, 521 (1937).

[2] The triethyl ester corresponding to this diethylmethyl ester has been prepared by the condensation of ethyl malonate and ethyl β-halopropionate. (*a*) EMERY, *Ber.*, **24**, 282 (1891); (*b*) THORPE, *J. Chem. Soc.*, **101**, 249 (1912); (*c*) RUZICKA, ALMEIDA, AND BRACK, *Helv. Chim. Acta*, **17**, 183 (1934).

[3] THORPE, *J. Chem. Soc.*, **101**, 249 (1912), has described the corresponding triethyl ester.

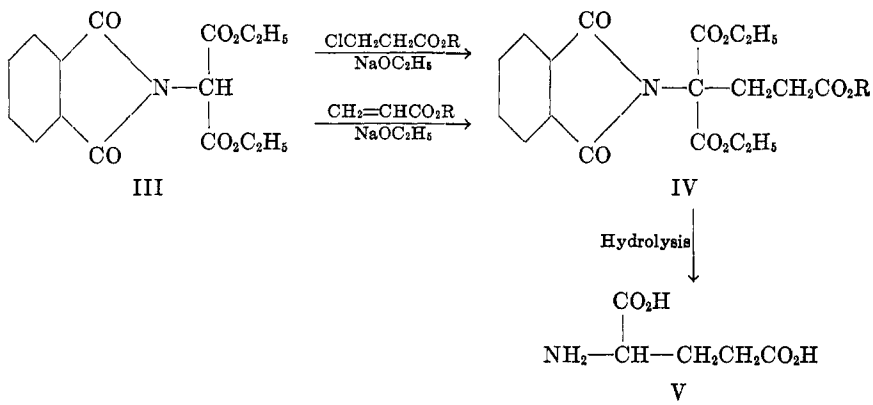
halogen derivatives.[4] The triester was hydrolyzed to the tricarboxylic acid and brominated to give III. This bromo acid was treated with ammonia, and the reaction mixture acidified and heated. The main product isolated from this reaction was γ-carboxy-γ-butyrolactone (IV).[5]



III IV

When it became apparent that none of the above methods would prove satisfactory for the production of glutamic acid, we decided to study again the reaction between ethyl phthalimidomalonate (V) and ethyl β-chloropropionate which Sörenson[6] and also Dunn and Smart[7] have suggested as a possible route to *dl*-glutamic acid. Dunn and Smart[7] were unsuccessful in getting this condensation to take place, but shortly afterward Dunn, Smart, Redemann, and Brown[8] perfected an admirable synthesis of the amino acid from ethyl benzoylaminomalonate and ethyl β-bromopropionate.

When exactly equivalent amounts of sodium ethoxide, ethyl phthalimidomalonate and β-chloropropionic ester were used the yield of glutamic acid (V) was very low. However, when



III IV V

[4] For example, WILLSTÄTTER AND HOTTENROTH, *Ber.*, **37**, 1775 (1909); NORRIS AND THORPE, *J. Chem. Soc.*, **119**, 1202 (1921).

[5] (*a*) WOLFF, *Ann.*, **260**, 128 (1890); (*b*) EMERY, *Ber.*, **24**, 282 (1891).

[6] SÖRENSON, *Compt. rend. des Travaux du Laboratoire de Carlsberg*, **6**, 1 (1903–06).

[7] DUNN AND SMART, *J. Biol. Chem.*, **89**, 41 (1930).

[8] DUNN, SMART, REDEMANN, AND BROWN, *ibid.*, **94**, 599 (1931).

the molar ratio of sodium ethoxide to chloro ester was greater than one the yield was improved. This suggested that probably the first reaction was the removal of hydrogen chloride from the β-chloro ester followed by a Michael condensation between the acrylic ester thus formed and the ethyl phthalimidomalonate. When this latter reaction was tried it was found to go very smoothly. The addition product was not isolated as such but was hydrolyzed directly to glutamic acid. The overall yield was 75–80 per cent., based on the ethyl phthalimidomalonate. This reaction is especially useful since methyl acrylate may now be obtained in 60 per cent. solution in methanol as a commercial product.*

EXPERIMENTAL

Condensation of ethyl phthalimidomalonate and ethyl β-chloropropionate.—In a 500-cc. round-bottomed flask a solution of sodium ethoxide was prepared from 53 cc. of absolute alcohol and 2.3 g. (0.1 gram atom) of sodium. To this solution was added 30.5 g. (0.1 mole) of ethyl phthalimidomalonate and 14 g. (0.102 mole) of ethyl β-chloropropionate. The reaction mixture was refluxed for nine hours, and then by use of an oil bath the volatile material was removed by distillation under reduced pressure at 150°. The dark residue was extracted twice with hot water, and then hydrolyzed by boiling with 75 cc. of concentrated hydrochloric acid and 25 cc. of water for about twelve hours. After the first four hours of boiling an additional 25 cc. of concentrated hydrochloric acid was added to the reaction mixture to replace that used in the reaction. After the hydrolysis was complete, the solution was cooled in an ice bath and most of the phthalic acid was removed by filtration. The filtrate was evaporated to dryness under reduced pressure to remove the excess hydrochloric acid. The residue was taken up in about 40 cc. of water and concentrated ammonium hydroxide solution (about 12 cc.) was added until a pH of 3 was reached. The solution was seeded with *dl*-glutamic acid monohydrate crystals and cooled. An equal volume of alcohol was added, and the crystals were collected on a filter. This product was then recrystallized from water and alcohol. The yield of *dl*-glutamic acid monohydrate was 2.8 g. (17 per cent.). Some glycine (2.4 g., 32 per cent.) was also isolated.

A similar run using 2.7 g. (0.117 gram atom) of sodium gave 9.4 g. (57 per cent.) of *dl*-glutamic acid.

dl-*Glutamic acid monohydrate.*—In a dry 2-l. round-bottomed flask were placed 373 cc. (2.34 moles) of the commercial 60 per cent. solution of methyl acrylate in methanol, 595 g. (1.95 moles) of ethyl phthalimidomalonate, and a solution of 3.2 g. of sodium in 65 cc. of commercial absolute alcohol. The solution was boiled under a reflux condenser about five and one-half hours. The reaction is slightly exothermic and while it is in no way violent, it was found to be inadvisable to apply excessive outside heat to the reaction mixture during the initial fifteen minutes.

The deep red reaction mixture was distilled under reduced pressure on a water bath to remove the volatile material. The residue was transferred to a 5-l. three-necked flask with the aid of hot 6*N* hydrochloric acid and refluxed with stirring with 700 cc. of 6*N* hydrochloric acid for fifteen and one-half hours. During the first

* The Röhm and Haas Company, Philadelphia, Pennsylvania market this chemical.

part of the hydrolysis 700 cc. of concentrated hydrochloric acid was added in 100-cc. portions as the acid was depleted by formation of ethyl chloride and glutamic acid hydrochloride. During the course of the hydrolysis the separation of phthalic acid from the reaction mixture made it necessary to use rapid stirring in order to avoid bumping.

At the end of the reaction the solution, while being stirred, was allowed to cool overnight. The mixture was then cooled in an ice bath and the dark-colored granular phthalic acid was removed by filtration and washed well with water. The phthalic acid amounted to 307 g. (theoretical, 324 g.). The deep red clear filtrate and washings were treated with 30 g. of Norite. The excess hydrochloric acid was removed from the resulting yellow solution by distillation under reduced pressure on a water bath. The thick residue was dissolved in 200 cc. of hot water and neutralized to pH 3 with concentrated ammonium hydroxide (about 200 cc.). The solution was seeded with *dl*-glutamic acid monohydrate after half of the ammonia had been added. Alcohol was added (400 cc.) and the mixture cooled in an ice bath to 15°. The granular precipitate of glutamic acid was removed by filtration and washed twice using a total of 600 cc. of alcohol.

The crude glutamic acid was crystallized by dissolving in 800 cc. of boiling water in a 2-l. beaker. The yellow solution was filtered and again heated in a covered beaker until the small amount of separated glutamic acid had redissolved. The hot solution was seeded with the hydrated glutamic acid, allowed to cool to about 80° and again seeded. Then 700 cc. of alcohol was added and the solution stirred frequently during the subsequent crystallization. After cooling in an ice bath the purified product was collected on a Buchner funnel, washed once with 250 cc. of alcohol and dried at 45° in air for fifteen hours.

This product was recrystallized by dissolving in 1500 cc. of boiling water, filtering and cooling the solution. About 1500 cc. of ethyl alcohol was added to cause complete separation of the amino acid. The solution was seeded with crystalline *dl*-glutamic acid monohydrate to insure the separation of the hydrated form. The total yield of air-dried *dl*-glutamic acid monohydrate was 225–240 g. (70–75 per cent. based on the ethyl phthalimidomalonate). Unless care was used in the crystallization the product consisted of a mixture of the anhydrous acid and its monohydrate.[1] By careful recovery of glutamic acid from the filtrates the yield can be increased by at least 5 per cent., but from a practical point of view this is not worth doing.

A sample of *dl*-glutamic acid monohydrate prepared by this method had a nitrogen content of 8.73 per cent., whereas the theoretical percentage of nitrogen is 8.48.

1,1-Dicarbethoxy-3-carbomethoxypropane.—A 500-cc., three-necked, round-bottomed flask was equipped with a reflux condenser, a dropping funnel, and a mercury-sealed mechanical stirrer. A solution of sodium ethoxide was prepared by adding 1.4 g. (0.04 gram atom) of clean sodium to 130 cc. of commercial absolute alcohol in the above flask. As soon as the last of the sodium had dissolved 189 cc. (1.18 moles) of redistilled ethyl malonate was added to the hot sodium ethoxide solution, and then by the dropwise addition to the refluxing mixture over a period of one-half hour, 100 cc. (0.626 mole) of the commercial preparation of a 60 per cent. solution of methyl acrylate in methanol was introduced. The solution was then refluxed for one-half hour and neutralized with the calculated quantity of glacial acetic acid.

The excess alcohol was removed from the resulting mixture by distillation under reduced pressure on a water bath, and enough distilled water was added to the hot residue to dissolve the sodium acetate. The resulting mixture was then extracted three times with carbon tetrachloride, the extract washed twice with water, and the

washings extracted with carbon tetrachloride. A total of about 170 cc. of carbon tetrachloride was used.

The combined extract was fractionated through an 18-inch Vigreaux column on an oil bath at 18 mm. pressure. The malonic ester was collected up to 110°; the remaining distillate, which was collected as the ester, amounted to 133.5 g. Upon refractionation the 1,1-dicarbethoxy-3-carbomethoxy-propane distilled at 156–162°/18 mm. and amounted to 124.8 g. (80 per cent. of the theoretical amount, based on the methyl acrylate).

1,1-Dicarbethoxy-1-bromo-3-carbomethoxypropane.—One hundred fifty cubic centimeters of carbon tetrachloride containing 217.9 g. (200 cc.; 0.876 mole) of the 1,1-dicarbethoxy-3-carbomethoxypropane was placed in a 500-cc., round-bottomed, three-necked flask equipped with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel dipping below the surface of the liquid. A trap was used to dispose of the hydrobromic acid gas arising from the bromination. Bromine (140.2 g.; 45.0 cc.; 0.876 mole) was added through the dropping funnel to the ester solution as rapidly as the hydrobromic acid could be absorbed. After the addition of all the bromine the reaction mixture was refluxed for twenty minutes at the end of which time the solution was practically colorless.

Most of the carbon tetrachloride was removed by distillation through an 18-inch Vigreaux column at atmospheric pressure and then the remainder by distillation under reduced pressure with the aid of a water pump. The residue was then fractionated. The slightly yellow product had a boiling range of 128–144°/2 mm. Upon refractionation 265.1 g. (92.5 per cent.) of a clear colorless liquid boiling at 129–133°/2 mm. was obtained. For analysis and physical constants this product was refractionated. The following values were obtained: n_D^{20} 1.4624; d_{20}^{20} 1.354; M_R calc'd 65.73; M_R found, 63.71.

Anal. Calc'd for $C_{11}H_{17}BrO_6$: Br, 24.43. Found: Br, 24.14.

Reaction of 1,1-dicarbethoxy-1-bromo-3-carbomethoxypropane with ammonia.—One typical experiment will be described. A solution of 16.35 g. of the bromo ester in 100 cc. of 2.34*N* ammonia in methanol was allowed to stand for about nineteen hours. Aliquot portions were withdrawn from time to time and titrated with standard silver nitrate to determine the amount of bromide ion formed. An aliquot portion of the solution was also titrated with standard acid to follow the disappearance of the ammonia. At the end of one hundred ninety hours, 97 per cent. of the bromine was present as bromide ion. For each mole of bromo ester taken 3.45 moles of ammonia had been used. The excess ammonia and alcohol were removed and the residue was analyzed for amino nitrogen. The results showed that less than 5 per cent. of the bromine could have been replaced by $-NH_2$. Similar experiments using concentrated aqueous ammonia and liquid ammonia gave essentially the same results.

Action of potassium phthalimide on 1-bromo-1,1-dicarbethoxy-3-carbomethoxypropane.—In a 500-cc., three-necked, round-bottomed flask was placed 65.6 g. (0.200 mole) of 1-bromo-1,1-dicarbethoxy-3-carbomethoxypropane and 41.0 g. (0.222 mole) of potassium phthalimide. The mixture was stirred for twenty hours in an oil bath kept at 150–160°. The black mixture was then extracted four times with hot water, dissolved in alcohol (about 200 cc.), and filtered. The volatile material was removed from the black filtrate by distillation under reduced pressure. The residue (62 g.) was hydrolyzed by refluxing with concentrated hydrochloric acid for sixteen hours. The reaction mixture was treated with 8 g. of Norite, cooled in an ice bath, and filtered. The excess hydrochloric acid was removed by distillation under reduced pressure on a water bath. The residue was dissolved in hot

water (75 cc.) and neutralized to pH 3 with concentrated ammonium hydroxide (about 8 cc.). No precipitate of glutamic acid formed even upon seeding and placing in the ice box overnight. After removal of the ammonium salts from a sample of the solution, an amino nitrogen determination (Van Slyke) showed a possible presence of 8 per cent. of the theoretical amount of glutamic acid.

The solution was made strongly acidic (pH 2–3) with hydrochloric acid, and the volatile material was removed by distillation under reduced pressure. The residue was heated to boiling with warm acetone, and then cooled, and the ammonium salts were removed by filtration. The acetone was removed by distillation, and the residue was extracted with ether in which it is very soluble. By the partial evaporation of the ether there was obtained a crop of crystals which were rich in glutaric acid. By recrystallization from toluene the glutaric acid was obtained pure. The yield was 8 g. (m. p. 96–98°). The identification was completed by preparation of the anhydride (m. p. 53°) and the monoanilide (m. p. 123–124°), and comparison of these derivatives with authentic specimens of the compounds. The melting points recorded in the literature for these derivatives are glutaric acid, 97.5°;[9] anhydride, 56–57°;[10] and monoanilide, 126–127°.[11]

In another experiment using the same starting materials the reaction mixture was heated at 160–165° for twelve hours. It was then cooled and taken up in ether. The ether solution was extracted six times with 10 per cent. sodium hydroxide solution and then three times with water to remove phthalic acid, phthalimide, and potassium bromide. The ether layer was dried and distilled. The residue was fractionated under diminished pressure; the main fraction consisted of 26.9 g. (54 per cent.) of 1,1-dicarbethoxy-3-carbomethoxypropane boiling at 157–160°/18 mm.

Action of aqueous ammonia on 1-bromo-1,1,3-propanetricarboxylic acid.—The tricarboxylic acid (35.2 g.) was obtained by saponification of the corresponding ester with alkali and was then brominated in a mixture of dry carbon tetrachloride and ether. The bromo acid was not purified but after removal of the solvent was treated directly with 450 cc. of concentrated aqueous ammonia. After standing for eight days the solution was evaporated to dryness under reduced pressure. The residue was boiled with hydrochloric acid and then treated with ammonia to cause precipitation of any glutamic acid. None was obtained, although an equal volume of alcohol was added and the solution was seeded with *dl*-glutamic acid monohydrate.

The alcoholic solution was then made strongly acidic with hydrochloric acid and evaporated to dryness. The residue was extracted with acetone and distilled. The main portion boiled at 155–162°/19.5 mm. When cooled it formed hygroscopic crystals which melted at 53–59°. It was identified as γ-carboxy-γ-butyrolactone.[5a] The yield was 17 g. (65 per cent. based on the tricarboxylic acid used).

SUMMARY

A convenient synthesis of *dl*-glutamic acid from methyl acrylate and ethyl phthalimidomalonate has been described.

Several other possible methods of preparing glutamic acid have been investigated, and some reactions of 1-bromo-1,1-dicarbethoxy-3-carbomethoxypropane have been recorded.

[9] MARKOWINKOFF, *Ann.*, **182**, 341 (1876).

[10] MARKOWINKOFF, *Bull. soc. chim.*, [2], **28**, 349 (1877).

[11] BALBIANO AND ANGELONI, *Gazz. chim. ital.*, **35**, [1], 150 (1905).

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE ADDITION OF ORGANOMAGNESIUM HALIDES TO PSEUDOCODEINE TYPES. IV. NUCLEAR-SUBSTITUTED MORPHINE DERIVATIVES*

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In a recent communication from this laboratory[1] the preparation of nuclear-methylated derivatives of the morphine series was described. One of these compounds, methyldihydromorphinone, exhibits in man an analgesic action considerably greater than that of morphine, and in contrast to the latter drug, has little or no emetic or respiratory depressant effect in therapeutic doses. From clinical experiments that are still in progress, there appears to be some evidence that methyldihydromorphinone has less tendency than morphine to develop tolerance or to produce addiction in man, or to support an already established condition of morphine addiction.

Since we do not know what structural features are responsible for the favorable action of methyldihydromorphinone, beyond the general connections between analgesic action and structure that we have already pointed out,[2] and since any dissociation of analgesic action from addiction potentiality, however slight, is of great interest to us in our search for an "ideal narcotic," the extension of the study of methyldihydromorphinone to its analogs is of some importance. It may be stated here that as far as studied, the ethyl, isopropyl, and normal amyl analogs show less favorable pharmacological action than the methyl derivative; the data will be communicated in more detail in the pharmacological literature (N. B. Eddy).

The process described in the second paper of this series[1] for the preparation of methyldihydromorphinone through reaction of dihydrothebaïne

* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

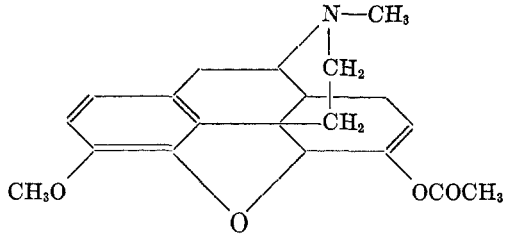
† Merck Fellow in Alkaloid Chemistry, 1936; E. I. DuPont Fellow, 1937.

‡ Squibb Fellow in Alkaloid Chemistry, 1936.

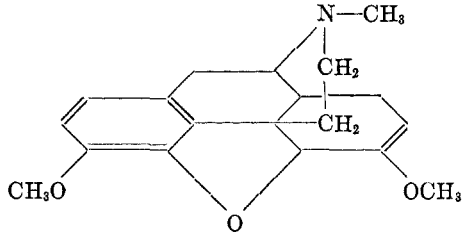
[1] SMALL, FITCH, AND SMITH, *J. Am. Chem. Soc.*, **58**, 1457 (1936).

[2] SMALL, EDDY, MOSETTIG, AND HIMMELSBACH, "Studies on Drug Addiction," Supplement 138 to the Public Health Reports, U. S. Government Printing Office, in press.

with methylmagnesium iodide, followed by bromination, closure of the 4,5-phenanthrylene oxide ring, debromination, and demethylation, has the disadvantage of utilizing thebaïne as the starting material. Thebaïne, in comparison with morphine or codeïne, is a rare alkaloid, and the yields realized in the conversion to dihydrothebaïne are far from satisfactory. For the production of methyldihydromorphinone on an industrial scale, apart from other difficulties, thebaïne could scarcely come into serious consideration. The solution to this dilemma has now been found in the utilization of dihydrocodeïnone enol acetate. By catalytic rearrangement in strongly acid solution, codeïne can be converted in 95% yield to dihydrocodeïnone,[3] and this ketone, in the presence of acetic anhydride and sodium acetate, is transformed in nearly quantitative yield to the enol acetate.



I. Dihydrocodeïnone enol acetate



II. Dihydrothebaïne

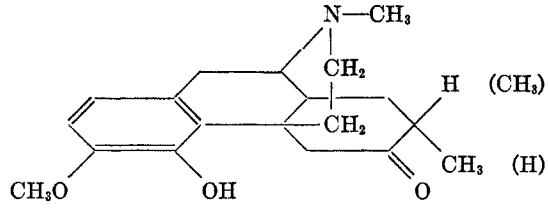
Dihydrocodeïnone enol acetate (I) possesses the pseudocodeïne type of structure, like dihydrothebaïne (II), and reacts with methylmagnesium iodide not like an ester, as might be expected, but like the other pseudocodeïne types that we have studied. The oxide ring is opened, and a methyl group is introduced into ring III; the enol ester group is probably not affected until the magnesium complex is decomposed with acid, at which point hydrolysis takes place, with formation of a ketone group at

[3] KNOLL, A.-G. CHEMISCHE FABRIKEN, *German Patents* 607,931 (Jan. 11, 1935); 617,238 (Oct. 2, 1935); 623,821 (Jan. 6, 1936).

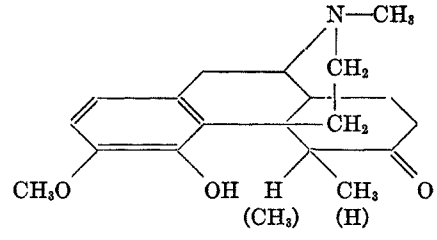
carbon-6 in the end-product. The failure of the reaction to proceed in the manner expected of an ester with Grignard's reagent may be due to the size of the esterified group, but is more probably a result of the speed with which the alternative reaction involving the 6,7 double bond and the cyclic ether group takes place. This reaction is so vigorous that caution must be exercised in adding the enol acetate to the organomagnesium compound, in contrast to the dihydrothebaïne reaction, which requires many hours at the boiling point of benzene to come to completion.

With the discovery of this reactivity of the enol acetates, the possibility of introducing organic nuclear substituents is opened for any of the dihydro-6-ketones of the morphine series that contain the oxygen bridge, as for example acetyldihydrohydroxycodeïnone and dihydrometacodeïnone. These reactions will be described in later papers.

We have also attempted to utilize the enol acetate reaction to determine the nature of the isomerism of methyldihydrothebaïnone and the simultaneously-formed isomethyldihydrothebaïnone. Three explanations of this isomerism come into consideration. (*1*) Methylmagnesium iodide has added to dihydrothebaïne exclusively in the 1,4 manner, to produce diastereoisomers differing in the configuration of the alkyl group on the new asymmetric carbon atom 7 (Formula III). (*2*) The addition has taken place only in the 1,2 manner, and the isomerism is due to a configurational difference at C-5 (Formula IV). (*3*) Competing 1,2 and 1,4 addition have resulted in isomers of which one has the methyl group on C-5, and the other has this group on C-7 (X and VII).

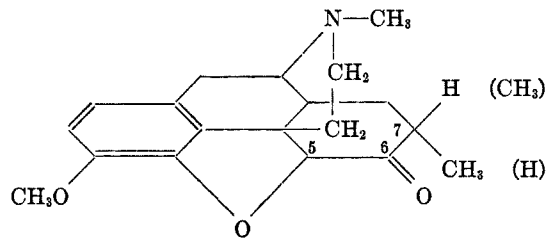


III

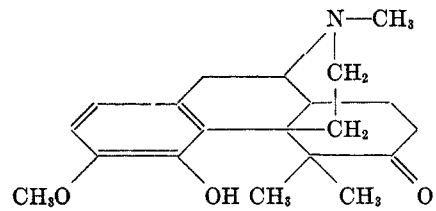


IV

From the fact that the enol acetates of methyldihydrocodeïnone and isomethyldihydrocodeïnone were not identical, Small, Fitch, and Smith concluded that the first possibility could be eliminated, for if the isomeric methyldihydrocodeïnones had the structure V, the asymmetry at C-7 would be destroyed in the establishment of the 6,7 double bond, and both isomers should yield the same enol acetate. This conclusion was, however, subject to the reservation that the hydrogen atom on carbon-5 might have been involved in the enolization. This reservation can now be withdrawn, for we find that the two enol acetates react readily with methylmagnesium iodide, with rupture of the ether ring and introduction of a second methyl group. Such a reaction is possible only if the enol acetates have a double bond in conjugation with the ether oxygen, *i.e.* between C-6 and C-7. The isomerism of the enol acetates and of the parent ketones cannot, therefore, be due to spatial differences at C-7.



V



VI

From the reaction of either of the isomeric enol acetates with methylmagnesium iodide the same dimethyldihydrothebaïnone (together with another, unidentified, crystalline product) is obtained. This fact alone does not permit a decision between the second and third possibilities mentioned above, for 1,2 addition to epimeric 5-methyl compounds might lead to such a result, as would also 1,2 addition to a 7-methyl isomer and 1,4 addition to a 5-methyl isomer. Further evidence on this point, though negative in character has developed in the attempted preparation of dimethyldihydrocodeïnone. Dimethyldihydrothebaïnone appears to react with two moles of bromine (complete decolorization) like the mono-

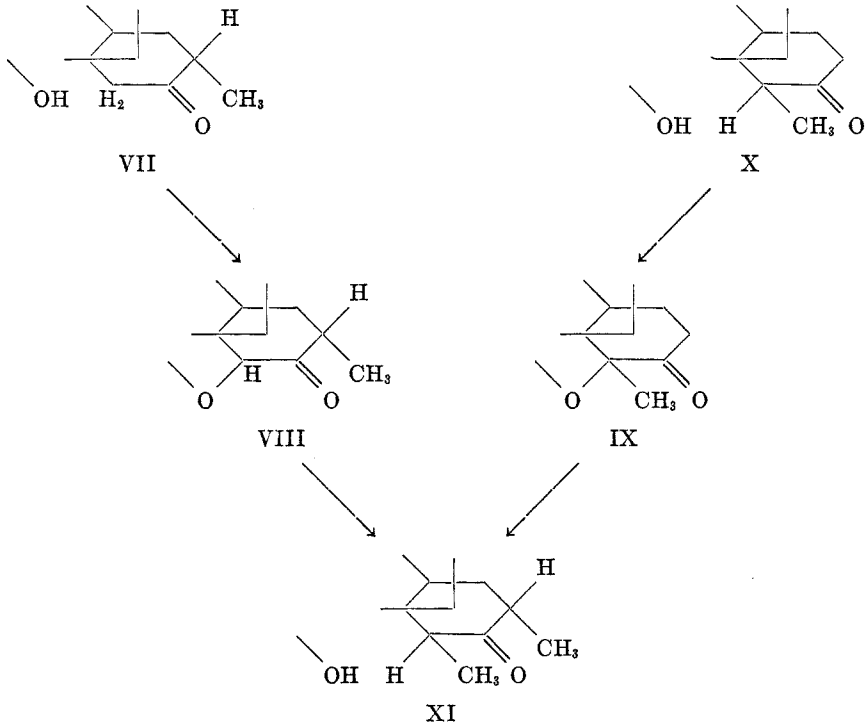
methyldihydrothebaïnones, but when the (liquid) bromination product is treated with alkali, only a monobromodimethyldihydrothebaïnone results, from which, by catalytic debromination, the starting material is regained. The failure of the oxide ring to close suggests that the 5-position is occupied by two methyl groups, which block bromination at this point (VI). If this is so, the isomerism of the methyldihydrothebaïnones must be due to a configurational difference at C-5 (IV). The apparent absorption of two moles of bromine can be explained by the assumption that a portion of the bromine was used in the formation of a perbromide, or of a 1,7-dibromo derivative[4] that may be present in hydrolyzed form as the diketo-compound in the oily by-products.

This negative evidence is, however, not very convincing, and does not exclude the third possibility above, for it may be argued that the bromodimethyldihydrothebaïnone is actually brominated at position-5, but in a configuration sterically unfavorable for the ring closure. This is rather improbable, as it is known from several examples that bromination of the aromatic ring in the dihydrothebaïnone types precedes bromination at C-5, so that we consider the single bromine atom in bromodimethyldihydrothebaïnone to be located in the aromatic ring. Moreover, unless a Walden inversion takes place in the Grignard reaction leading to dimethyldihydrothebaïnone, we must conclude that the product that would result from a reaction proceeding according to the third possibility would necessarily have a configuration favorable for ring closure (see VII–XI). Namely, if dimethyldihydrothebaïnone has a structure according to part-formula XI, resulting from 1,2 addition to the enol acetate of VIII and 1,4 addition to the enol acetate of IX, then the hydrogen atom on C-5 in XI would be in a configuration permitting ring closure, since ring closure in X (whichever of the methyldihydrothebaïnone isomers it be assumed to represent) takes place easily. On the basis of the structures postulated in formulas VIII and IX for methyl- and isomethyldihydrocodeïnones, if an inversion does not take place in the step IX to XI, then it must do so in the step VIII to XI, else the one compound could not be obtained from the two sources. Of the alternatives, a configurational change in the step IX to XI seems most probable, since by the 1,4 addition mechanism assumed, the asymmetry at C-5 would be eliminated in the intermediate addition product and regenerated on hydrolysis of the enol ester group. Thus, in XI, the replaceable hydrogen on C-5 might well be in a configuration unfavorable to ring closure.

The hypothesis that the methyl group in both methyldihydrothe-

[4] It has been demonstrated by SCHÖPF, PFEIFER, AND HIRSCH, [*Ann.*, **492**, 213 (1932)] that the bromination of dihydrothebaïnone involves as a side-reaction the formation of 1,5,7-tribromodihydrothebaïnone.

baïnones is located at C-5 receives some support from the observation of Small, Fitch, and Smith that the corresponding isomeric methyldihydrocodeïnones both behaved in the Claisen ethyl oxalate reaction as though a methylene group were adjacent to the carbonyl. Furthermore, from treatment of isomethyldihydrothebaïnone with more than 2 moles of bromine, what appears to be a 7-ketoisomethyldihydrothebaïnone* has now been isolated; we have not yet determined whether a similar analog forms in the "normal" series. The chief argument against the above



theory lies in the large change in optical properties observed for isomethyldihydrocodeïnone, but not for methyldihydrocodeïnone, when these compounds are transformed to their respective enol acetates, which we have heretofore explained as possibly being due to a change in an asymmetric center present at C-7 in the iso series but not in the normal series.

The stereochemical speculations of Schöpf and Pfeifer[5] led these investigators to the conclusion that a closure of the 4,5-ether ring in but one

* The 7-keto structure has been assumed in analogy with the 7-ketodihydrothebaïnone of Schöpf, Pfeifer, and Hirsch, *loc. cit.*

[5] Schöpf and Pfeifer, *Ann.*, **483**, 157 (1930).

way was sterically possible. This conclusion, if correct, makes our results difficult to explain. With the elimination of possibility 1 for the isomerism of the methyldihydrothebaïnones, it is apparent that in at least one of the isomers, a methyl group must be on C-5, yet both isomers undergo ring closure with equal facility. This methyl group presumably occupies the linkage formerly held by the ether oxygen, which is necessarily in the spatial position favorable to closure of the ring again, unless a Walden inversion has taken place in the Grignard reaction, as mentioned above. Inversion in the bromination or subsequent alkali treatment is equally or more probable, and might explain ring-closure in one configuration if the isomers are related as 5- and 7-methyl derivatives, but not if they are both 5-methyl derivatives, for in the latter case the codeïnone derivatives would be necessarily identical. The transformation of dihydrothebaïnone into dihydrocodeïnone to the extent of at least 80% in one configuration at C-5 seems to us best explained by the hypothesis advanced and discarded by Schöpf, that there is an equilibrium, or a rapid transformation of one (5-bromo-) epimer into the other in the presence of alkali, that epimer having the most favorable configuration of the bromine atom being removed irreversibly by the ring closure. The explanation ultimately favored by Schöpf, while supported by a molecular model designed to show that ring closure is possible in only one configuration, offers no explanation of the corollary fact that out of two otherwise equivalent hydrogen atoms on C-5 of dihydrothebaïnone, only or predominantly that one occupying the spatial position favorable to ring closure is replaced by bromine.

If our conclusion is valid, that at least one of the methyldihydrothebaïnones has the methyl group on C-5, the ethanamine chain, as depicted in the Knorr-Wieland morphine formula, cannot be attached at this point, for no linkage would be available for closure of the ether ring.

The reaction of ethylmagnesium iodide with dihydrothebaïne proceeds parallel to that described for the methyl series. Because of the difficulty of preparing ethylmagnesium iodide entirely free from ethyl iodide, the device of distilling a little anhydrous trimethylamine into a benzene solution of the Grignard reagent was utilized. The amount of water-soluble product (probably the ethiodide of dihydrothebaïne or of the ethyl derivative) otherwise observed in the reaction is thus greatly diminished. The main product is ethyldihydrothebaïnone, a phenolic ketone. By reaction with two moles of bromine and subsequent treatment with alkali, this is converted to bromoethyldihydrocodeïnone, which yields ethyldihydrocodeïnone on catalytic debromination. Like its lower homolog, ethyldihydrocodeïnone can be reduced at the ketone group, to ethyldihydrocodeïne. By demethylation with hydrobromic acid, on the other

hand, ethyldihydrocodeïnone passes into ethyldihydromorphinone, the desired homolog of methyldihydromorphinone. We were unable to effect reduction of ethyldihydromorphinone to ethyldihydromorphine.

As a by-product from the ethylmagnesium iodide reaction, a cryptophenolic base, isoethyldihydrothebaïnone is obtained. It appears to correspond to the already described isomethyldihydrothebaïnone, but was formed in such small yield that its conversion to the codeïnone and morphinone types was not undertaken.

In order to obtain information on the effect of a branched chain substituent upon physiological action, the isopropyl series was investigated. The Grignard reaction proceeds with formation of isopropyldihydrothebaïnone, but none of the expected isomeric compound could be found. In addition to the main reaction product a small amount of a phenolic base having the formula $C_{18}H_{21}NO_3$ was isolated. This will be referred to later as dihydromorphinone methyl enolate. Isopropyldihydrothebaïnone was transformed easily to isopropyldihydrocodeïnone and isopropyldihydromorphinone, but neither of the last named substances could be reduced at the ketone group by the catalytic method. By Clemmensen reduction, isopropyldihydrocodeïnone gave isopropyldihydrothebaïnone through reductive scission of the ether ring, instead of the desired desoxy derivative.

To observe the effect of increasingly heavy groups, both on the course of the chemical reaction and on physiological action, *n*-amyldihydrothebaïnone and benzyldihydrothebaïnone were prepared. The ring closure to amyldihydrocodeïnone took place as in the previously described analogs. Benzyldihydrothebaïnone seemed to show some reluctance in bromination, but the brominated product closed the ether ring with great ease, even with concentrated ammonia. By demethylation with hydrobromic acid the codeïnones yielded the corresponding *n*-amyldihydromorphinone and benzyldihydromorphinone. In addition to the latter substance, the demethylation process in the benzyl series gave a small amount of a non-phenolic base isomeric with benzyldihydrocodeïnone; this was probably formed by a rearrangement of unknown nature. Neither amyldihydromorphinone nor amyldihydrocodeïnone could be reduced catalytically; reduction in the benzyl series was not attempted. As in the other series, Clemmensen reduction of amyldihydrocodeïnone resulted in conversion back to amyldihydrothebaïnone.

The reaction of phenylmagnesium bromide with dihydrothebaïne resembled that in the methyl and ethyl series, in that isomeric compounds having the formula of phenyldihydrothebaïnone were produced. Because of certain relationships in physical properties and chemical reactiv-

ity parallel to those of the isomers of the methyl series, the higher-melting isomer has been designated as phenyldihydrothebaïnone, the lower-melting as isophenyldihydrothebaïnone.

Neither of the phenyldihydrothebaïnones is strongly phenolic in properties, yet both can be converted through bromination and cyclization to the corresponding phenyldihydrocodeïnones. Phenyldihydrocodeïnone undergoes demethylation to yield phenyldihydromorphinone. The substance designated as isophenyldihydrocodeinone, like isomethyldihydrocodeïnone, cannot be demethylated to the corresponding morphinone type.

Isophenyldihydrothebaïnone methyl ether suffered an unexpected degradation when the methochloride was distilled in high vacuum in an attempt to prepare the methyl ether base by the usual procedure. The only crystalline product that could be isolated was nitrogen-free, and had a composition corresponding to that of a 3,4-dimethoxy-5 (or -7) -phenyl-6-keto-5,6,7,8-tetrahydrophenanthrene. There seems to be no obvious explanation of the unusual ease with which the entire ethanamine chain was split out of the saturated base, although similar degradations have been observed with unsaturated bases of the morphine series.

As a by-product from the reaction of phenylmagnesium bromide with dihydrothebaïne, the same phenolic substance of composition $C_{18}H_{21}NO_3$ was isolated in modest amount, as has been mentioned in the discussion of isopropyldihydrothebaïnone. The appearance of the base in both the alkyl and aryl Grignard reactions, together with its composition, immediately led to its identification as the methyl enolate of dihydromorphinone, obviously formed by demethylation of dihydrothebaïne by the Grignard reagent. Although organomagnesium halides have been observed to effect demethylation at higher temperatures[6] such action at the boiling point of benzene is unexpected (see II, XII–XIII).

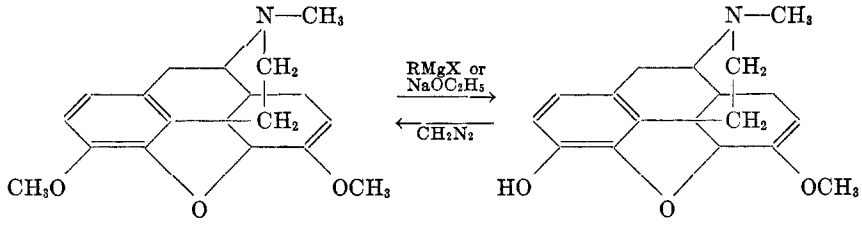
The nature of the new base could be proved conclusively by converting it with diazomethane to dihydrothebaïne, or with cold concentrated hydrochloric acid to dihydromorphinone. Dihydromorphinone methyl enolate can also be prepared by demethylation of dihydrothebaïne with sodium ethoxide in a sealed tube. Attempts at the parallel demethylation of thebaïne were not successful.

In extension of our studies on the behavior of Grignard's reagent with pseudocodeïne types, we wish to report at this time the reaction of pseudocodeïne methyl ether. While the product is not of significance to the problem discussed in the main portion of this paper, it presents at least one unusual feature worthy of mention.

The structure of pseudocodeïne methyl ether as in formula XIV seems

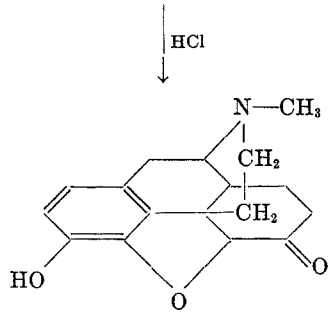
[6] GRIGNARD, *Compt. rend.*, **138**, 1048 (1904); *ibid.*, **151**, 322 (1910); SPÄTH, *Monatsh.*, **35**, 319 (1914).

adequately established by the typical course of catalytic hydrogenation under varying conditions,[7] and by the fact that we have been able to ob-



II. Dihydrothebaïne

XII. Dihydromorphinone methyl enolate



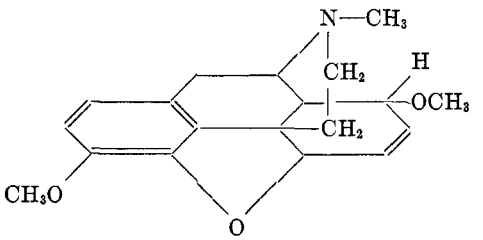
XIII. Dihydromorphinone

tain the same compound by methylation of pseudocodeïne (Mannich procedure[8]) as results from the usual preparative method, methanolysis of α-chlorocodide[9] (see XIV–XVII).

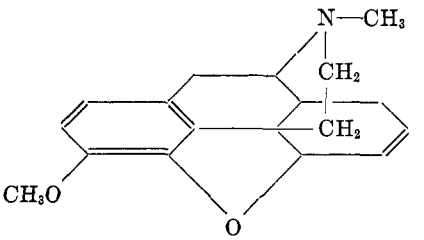
Pseudocodeïne methyl ether reacts slowly with boiling ethereal methylmagnesium iodide to yield a crystalline phenolic base having the composition $C_{20}H_{27}NO_3$ expected for methyldihydropseudocodeïne methyl ether. According to the theoretical speculations offered in the first part of this paper, the new product might be expected to have the structure shown in formula XVI or XVII. On the basis of either formula, and to agree with analytical results, methyldihydropseudocodeïne methyl ether should contain one vulnerable double bond, but all our attempts to saturate this double bond by catalytic hydrogenation have failed. This inertness of the unsaturated center recalls the similar behavior of the Grignard reaction product derived from pseudocodeïnone, which Lutz and Small[10]

[7] Small and Lutz, *J. Am. Chem. Soc.*, **57**, 361 (1935).
[8] Mannich, *Arch. Pharm.*, **254**, 349 (1916).
[9] Knorr and Hartmann, *Ber.*, **45**, 1354 (1912).
[10] Lutz and Small, *J. Am. Chem. Soc.*, **57**, 2651 (1935).

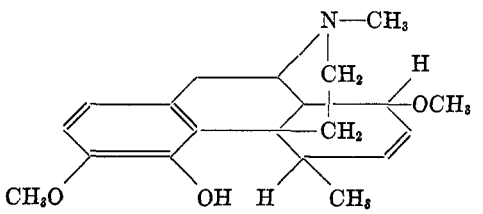
were unable to reduce, either catalytically or by metal combinations. As far as reactivity of the double bond is concerned, there is no reason to



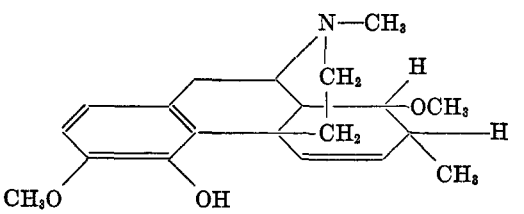
XIV. Pseudocodeïne methyl ether



XV. Desoxycodeïne-C



XVI



XVII

Methyldihydropseudocodeïne methyl ether (?)

expect the nuclear methylation product from pseudocodeïne methyl ether to show any marked difference from the analogous series of compounds obtained from reaction of Grignard's reagent with desoxycodeïne-C (XV),[11]

[11] SMALL AND YUEN, *ibid.*, **58**, 192 (1936).

none of which resisted catalytic hydrogenation, even those members into which such heavy groups as phenyl and cyclohexyl had been introduced. The abnormal behavior of the two alkylated pseudocodeïne derivatives cited leads to the suspicion that the Grignard reaction may have taken a more complex course than expected, as already suggested by Small and Fry in an attempt to account for the extraordinary properties of the methyldihydrothebaïnes.[12]

When the reaction between methylmagnesium iodide and pseudocodeïne methyl ether is conducted in boiling isopropyl ether, in addition to the above described compound another, weakly phenolic, base can be isolated. This has the formula $C_{19}H_{27}NO_3$, *i.e.* is isomeric with tetrahydropseudocodeïne methyl ether. Although the new base showed no depression in melting point when mixed with tetrahydropseudocodeïne methyl ether, it differed from this substance in specific rotation and other properties. The Grignard reagent is known to be capable of effecting reduction, but such a reduction as that of pseudocodeïne methyl ether to its tetrahydro derivative would be most unexpected. The structure of this base must for the present remain uncertain.

We are indebted to Merck and Co., Rahway, N. J., for the gift of the large amount of thebaïne used in this investigation, and to Merck and Co., E. R. Squibb and Sons, and E. I. du Pont de Nemours and Co. for generous fellowship support.

EXPERIMENTAL

Dihydrocodeïnone enol acetate and methylmagnesium iodide.—A solution of 15 g. of dihydrocodeïnone and 1.5 g. of anhydrous sodium acetate in 75 cc. of acetic anhydride was boiled under reflux for 105 minutes. Most of the acetic anhydride was removed at 100° under diminished pressure (water pump), and the remainder was decomposed with ice. The clear aqueous solution was treated cautiously with excess ammonia, and the crystalline base was collected by filtration; yield, 16.4 g. of m. p. 152–153°. It crystallized from methanol as white needles, m.p. 153–153.5°.

As much ether as possible was distilled from 120 cc. of molar ethereal methylmagnesium iodide on the water bath, and a solution of 10 g. of dihydrocodeïnone-enol acetate in 200 cc. of anhydrous benzene was added to the oily Grignard reagent. A vigorous reaction ensued, with formation of a copious white precipitate. The mixture was refluxed for 24 hours, although the reaction was probably complete within 30 minutes. The reaction mixture was decomposed with 400 cc. of cold 3 *N* hydrochloric acid, and all of the alkaloidal material was brought into solution in this medium. The crude crystalline methyldihydrothebaïnone, isolated as previously described, weighed 6.6 g. The reaction of dihydrothebaïne with Grignard's reagent likewise proceeds more smoothly in benzene than in ether or in isopropyl ether.

The following derivatives of the isomethyl series have not been previously described.

[12] SMALL AND FRY, J. ORG. CHEM., to be published.

Isomethyldihydrothebaïnone hydriodide.—The salt was prepared in dilute acetic acid with potassium iodide, and was recrystallized from absolute alcohol; it has the m. p. 259–260° (evac. tube, gas evolution) and $[\alpha]_D^{21}$ −28.0° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{26}INO_3$: I, 28.64. Found: I, 28.90.

Isomethyldihydrothebaïnone methiodide crystallizes from acetone in long needles as the hydrate, m. p. 194–196° (evac. tube, gas evolution, sintering at 185°), and shows $[\alpha]_D^{21}$ −18.6° (water, c = 1.02).

Anal. Calc'd for $C_{20}H_{28}INO_3 + H_2O$: I, 26.72; H_2O, 3.8.
Found: I, 26.45; H_2O, 4.2.

The anhydrous compound is exceedingly hygroscopic.

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.77. Found: I, 27.83.

Isomethyldihydrocodeïnone hydrochloride.—The salt was prepared in alcoholic hydrogen chloride, and crystallized from alcohol in long needles. When dried in air, it sinters at 182°, m. p. 191–193° (evac. tube, gas evolution), and shows $[\alpha]_D^{21}$ −122.1° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{24}ClNO_3 + 1.5\ H_2O$: Cl, 9.42; H_2O, 7.17.
Found: Cl, 9.49; H_2O, 6.79, 7.80.

The anhydrous salt, obtained by drying in a vacuum at 100°, is very hygroscopic.

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.03.

Isomethyldihydrocodeïnone hydriodide.—The salt was prepared in the usual way, and was purified from alcohol; long needles of the monohydrate, which soften at 205° and melt at 209–210° (evac. tube, gas evolution); it shows $[\alpha]_D^{21}$ −102.1° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{24}INO_3 + H_2O$: H_2O, 3.9. Found: H_2O, 3.7.
Calc'd for $C_{19}H_{24}INO_3$: I, 28.77. Found: I, 28.83.

1-Bromoisomethyldihydrothebaïnone.—When less than 2 moles of bromine is used in the bromination of isomethyldihydrothebaïnone, or when bromine is added too rapidly, the alkaline mother liquors from the extraction of 1-bromoisomethyldihydrocodeïnone yield considerable amounts of 1-bromoisomethyldihydrothebaïnone. It is cryptophenolic, and may be extracted from alkaline solution with ether. It crystallizes from acetone or alcohol, m. p. 237–239° (evac. tube), $[\alpha]_D^{21}$ −66.2° (absol. ethanol, c = 0.31). In spite of the unsatisfactory analysis, the nature of the compound seems certain, as it yields isomethyldihydrothebaïnone on catalytic debromination.

Anal. Calc'd for $C_{19}H_{24}BrNO_3$: C, 57.85; H, 6.14; Br, 20.28.
Found: C, 58.15; H, 5.74; Br, 19.53.

Isomethyl-7-ketodihydrothebaïnone.—When isomethyldihydrothebaïnone is treated with 2.5 moles of bromine, followed by alkali and catalytic debromination, the only crystalline product (25% yield) is a substance that appears to be the (debrominated) nuclear methylated analog of the (−) bromosinomeninone obtained by Schöpf in the dihydrothebaïnone series. The supposed isomethyl-7-ketodihydrothebaïnone crystallizes from ethyl acetate, m. p. 172°, $[\alpha]_D^{21}$ −67.3° (ethanol, c = 0.35); sparingly soluble in alkali and precipitated by carbon dioxide; no ferric chloride test. The crystallized material did not give satisfactory analyses (Calc'd for $C_{19}H_{23}NO_4$: C, 69.26; H, 7.04. Found: C, 70.59, 70.00; H, 7.36, 7.09), but on sublimation in high vacuum at 160° the compound melted, bubbled, and then solidified; sublimed material, m. p. 258–259° (evac. tube), $[\alpha]_D^{21}$ −97.4° (ethanol, c = 0.35). Schöpf observed a loss in weight of the analog mentioned.

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.26; H, 7.04.
Found: C, 69.26; H, 7.17.

Isomethyldihydrocodeïne.—A solution of 1.0 g. of isomethyldihydrocodeïnone in 25 cc. of alcohol with 0.1 g. of platinum oxide absorbed 95 cc. of hydrogen (calc'd for 1 mole, 94 cc.) with great rapidity, in contrast to the corresponding reduction in the normal series. The product precipitated crystalline with water (yield 0.8 g.), and was purified from alcohol. It melts at 103–104°, and shows $[\alpha]_D^{21}$ −126.9° (ethanol, c = 0.64). Analysis indicates one-fourth molecule of water, probably due to partial loss of water from a monohydrate.

Anal. Calc'd for $C_{19}H_{25}NO_3 + 0.25\ H_2O$: C, 71.32; H, 8.04; H_2O, 1.41.
Found: C, 71.40; H, 7.82; H_2O, 1.26.

Isomethyldihydrocodeïne salicylate is prepared in absolute alcohol and may be used to purify the base. It crystallizes well from absolute alcohol, m. p. 235–237° (evac. tube, gas evolution) and shows $[\alpha]_D^{21}$ −87.3° (ethanol, c = 0.31).

Anal. Calc'd for $C_{26}H_{31}NO_6$: C, 68.84; H, 6.88.
Found: C, 68.64; H, 6.69.

Isomethyldihydrocodeïne methiodide was prepared by warming the base with methyl iodide; it was purified from 75% alcohol, m. p. 252–254° (evac. tube, gas evolution), $[\alpha]_D^{21}$ −56.8° (water, c = 0.77).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.77. Found: I, 27.64.

Ethyldihydrothebaïnone.—Molar ethylmagnesium iodide (360 cc.), to which had been added 30 cc. of 2-molar anhydrous ethereal solution of trimethylamine, was freed from ether as far as possible on the water bath, and a solution of 40 g. of dihydrothebaïne in 800 cc. of anhydrous benzene was added. The clear solution was heated for 48 hours under reflux, during which time a copious white precipitate separated. The magnesium complex was dissolved in 1000 cc. of warm 3 *N* hydrochloric acid. The acid solution was divided into four portions, and each was covered with four liters of ether, treated with excess concentrated ammonia containing a little sodium hydrosulfite, and extracted. On concentration, the ether solution yielded red, oily crystals; combined yield from 200 g. of dihydrothebaïne, 87.9 g. (41.8%). Three recrystallizations from alcohol gave 18.2 g. of pure ethyldihydrothebaïnone. The mother liquors, concentrated and treated with alcoholic hydrogen chloride, gave the hydrochloride, which was purified from absolute alcohol, and yielded 23.2 g. more of the pure base; total yield of pure ethyldihydrothebaïnone 41.4 g. (19.6%). The mother liquors from purification of the hydrochloride were worked for the isomer.

Ethyldihydrothebaïnone crystallizes well from alcohol or acetone, and sublimes in high vacuum at 170°; m. p. 190.5–191.5°, $[\alpha]_D^{25}$ + 10.9° (alcohol, c = 1.00).

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.90; H, 8.27.
Found: C, 73.05; H, 8.31.

The hydrochloride, prepared in absolute alcohol, crystallizes in long needles, m.p. 280–282° (evac. tube, gas evolution), $[\alpha]_D^{21}$ + 17.8° (water, c = 1.01).

Anal. Calc'd for $C_{20}H_{28}ClNO_3$: Cl, 9.70. Found: Cl, 9.67.

The hydriodide is precipitated from an acetic acid solution of the base by potassium iodide, and crystallizes from absolute alcohol. It has the m. p. 253–255° (evac. tube, gas evolution) and shows $[\alpha]_D^{22}$ +14.0° (water, c = 1.00).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.77. Found: I, 27.68.

Ethyldihydrocodeïnone.—A solution of 23.2 g. of ethyldihydrothebaïnone in 230 cc. of glacial acetic acid, treated with bromine and sodium hydroxide, as described for the methyl analog, gave 24.7 g. of the liquid 1-bromoethyldihydrocodeïnone. On hydrogenation, this absorbed 1322 cc. of hydrogen (calc'd, 1384 cc.) and yielded 16.9 g. of crude ethyldihydrocodeïnone. It was dissolved in hydrochloric acid and

precipitated crystalline with alkali, 13.3 g. (57.7%); the alkaline mother liquors gave 2.7 g. of pure ethyldihydrothebaïnone.

Ethyldihydrocodeïnone crystallizes in needles from ethyl acetate, and sublimes at 150° in high vacuum. It melts at 163–164° and shows $[\alpha]_D^{25}$ −100.9° (alcohol, c = 0.99).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.40; H, 7.68.

The *methiodide* crystallizes from ethanol as the hemihydrate of m. p. 255–257° (evac. tube, gas evolution) and $[\alpha]_D^{21}$ −48.8° (water, c = 1.02).

Anal. Calc'd for $C_{21}H_{28}INO_3 + 0.5\ H_2O$: I, 26.54; H_2O, 1.88.
Found: I, 26.64; H_2O, 1.54.

Ethyldihydrocodeïnone enol acetate.—Ethyldihydrocodeïnone was converted to the enol acetate as described for the methyl analog, except that acetylation was more difficult, and longer heating was required. The ester, purified from 50% alcohol, had the m. p. 129–130°, and $[\alpha]_D^{25}$ −124.1° (alcohol, c = 1.00). It sublimed at 120° in high vacuum.

Anal. Calc'd for $C_{22}H_{27}NO_4$: C, 71.50; H, 7.37.
Found: C, 71.20; H, 7.17.

Ethyldihydrocodeïne.—A solution of 2.0 g. of ethyldihydrocodeïnone in 20 cc. of alcohol with 0.1 g. of platinum oxide slowly absorbed 182 cc. of hydrogen (calc'd, 181 cc.). The product (2.0 g.) was not crystalline, but gave a crystalline perchlorate (1.4 g. after purification from alcohol), from which the base was liberated and distilled in high vacuum at 120°. The oily base has $[\alpha]_D^{22}$ −84.8° (alcohol, c = 0.69).

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.90; H, 8.27.
Found: C, 72.82; H. 8.03.

Ethyldihydrocodeïne perchlorate, crystallized from absolute alcohol, melts with decomposition at 275–276° (evac. tube) and has $[\alpha]_D^{22}$ −60.5° (absol. alcohol, c = 0.31).

Anal. Calc'd for $C_{20}H_{28}ClNO_7$: Cl, 8.25. Found: Cl, 8.22.

The hydriodide crystallizes from absolute alcohol, m. p. 274–275° (evac. tube), $[\alpha]_D^{22}$ −50.6° (water, c = 1.00).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.77. Found: I, 27.66.

Ethyldihydromorphinone.—A solution of 9.0 g. of ethyldihydrocodeïnone in 45 cc. of 48% hydrobromic acid was boiled under reflux for 14 minutes. The red solution was diluted with twice its volume of water, treated with an excess of sodium hydroxide, and extracted with ether, which removed colored and nonphenolic material. After addition of excess ammonium chloride, the solution was extracted with 4 liters of ether. The product was 8.4 g. of faintly colored crystals, which were purified from alcohol. The m. p. is 213–214°, $[\alpha]_D^{25}$ −103.5° (absol. alcohol, c = 0.97). The compound sublimes in high vacuum at 170°, and in contrast to methyldihydromorphinone, is quite soluble in acetone, ethyl acetate, or alcohol.

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40.
Found: C, 72.41; H, 7.32.

The *hydriodide* crystallizes in needles from absolute alcohol; it softens at 278°, and melts at 285–286° (evac. tube, gas evolution); $[\alpha]_D^{22}$ −49.1° (water, c = 0.98).

Anal. Calc'd for $C_{19}H_{24}INO_3$: I, 28.77. Found: I, 28.79.

The *methiodide* crystallizes hydrated from absolute alcohol, and appears to lose a portion of the hydrate water on drying in air. It melts at 263–265° (evac. tube, gas evolution) and shows $[\alpha]_D^{22}$ −42.2° (water, c = 0.40).

Anal. Calc'd for $C_{20}H_{26}INO_3 + 0.5\ H_2O$: I, 27.35; H, H_2O, 1.94.
Found: I, 27.44; H_2O, 1.54, 1.43.

The *anhydrous methiodide*, prepared by drying in vacuum, is very hygroscopic.

Anal. Calc'd for $C_{20}H_{26}INO_3$: I, 27.88. Found: I, 27.76.

1-Bromoethyldihydrothebaïnone.—The alkaline mother liquor from the preparation of bromoethyldihydrocodeïnone was treated with excess ammonium chloride, and extracted with ether. 1-Bromoethyldihydrothebaïnone, 4.0 g., was obtained, and purified from alcohol, from which it crystallizes solvated. It has the m. p. 201.5–202.5° (evac. tube) and $[\alpha]_D^{23}$ −6.8° (absol. alcohol, c = 0.29). It yields ethyldihydrothebaïnone on catalytic debromination.

Anal. Calc'd for $C_{20}H_{26}BrNO_3 + 0.5\ C_2H_5OH$: Br, 18.54; C_2H_5OH, 5.34.
Found: Br, 18.79; C_2H_5OH, 5.55.

Isoethyldihydrothebaïnone.—The alcoholic mother liquors from the preparation of ethyldihydrothebaïnone hydrochloride were freed of solvent, and the resulting oil was dissolved in water, excess of sodium hydroxide was added, and the solution was exhaustively extracted with ether. The ether solution was extracted with 8 portions of dilute sodium hydroxide; with ammonium chloride and ether, fractions 2 and 3 gave 3.2 g. of ethyldihydrothebaïnone, fractions 5 to 8 gave 1.0 g. of pure isoethyldihydrothebaïnone. This compound crystallizes from alcohol, and sublimes in high vacuum at 150°. It melts at 188–189° (mixed m. p. with ethyldihydrothebaïnone shows 30° depression) and has $[\alpha]_D^{22}$ −36.2° (alcohol, c = 1.00). It is a cryptophenol, and is extracted from its solution in alkali by ether.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.90; H, 8.27.
Found: C, 72.55; H, 8.44.

The hydriodide crystallizes from alcohol as the monohydrate, m. p. 191–193° (evac. tube), $[\alpha]_D^{23}$ −4.1° (water, c = 0.98).

Anal. Calc'd for $C_{20}H_{28}INO_3 + H_2O$: I, 26.73; H_2O, 3.79.
Found: I, 26.88; H_2O, 3.53.

The methiodide crystallizes from absolute alcohol as the hemihydrate, m. p. 237–240° (evac. tube, sintering at 218°), $[\alpha]_D^{23}$ −5.8° (water, c = 1.00).

Anal. Calc'd for $C_{21}H_{30}INO_3 + 0.5\ H_2O$: I, 26.43; H_2O, 1.88.
Found: I, 26.45; H_2O, 2.13.

Isopropyldihydrothebaïnone.—The Grignard reaction between 40 g. of dihydrothebaïne and 200% excess of isopropylmagnesium bromide was carried out in benzene as described for the methyl series. The reaction was complete after 12 hours heating. The magnesium complex was decomposed with dilute hydrochloric acid, from which the product was precipitated with ammonia containing a little sodium hydrosulfite, and brought into 9 liters of ether. The ether was extracted several times with 50-cc. portions of 0.3 *N* sodium hydroxide and gave on concentration 34.2 g. of oily crystals. Crystallization from ethanol yielded 9 g. of isopropyldihydrothebaïnone. From 112 g. of dihydrothebaïne 24.5 g. of pure isopropyldihydrothebaïnone (20.6%) was obtained. The sodium hydroxide extracts gave only oily products, excepting in one run of 10 g. of dihydrothebaïne that was carried out using a little trimethylamine in the Grignard reaction. The alkali in this instance yielded 0.4 g. of dihydromorphinone methyl enolate.

Isopropyldihydrothebaïnone is soluble in dilute alkali, but is not appreciably extracted from ethereal solution by alkali. It was purified from hot alcohol (1 g. in 15 cc.), needles of m. p. 217.5–219.5°, $[\alpha]_D^{23}$ −31° (chloroform, c = 0.64). It sublimes in high vacuum at 170°.

Anal. Calc'd for $C_{21}H_{29}NO_3$: C, 73.42; H, 8.51.
Found: C, 73.17; H, 8.47.

The hydrochloride, prepared in absolute alcohol, crystallizes from this solvent in rectangular rods, m. p. 273–275° (evac. tube), $[\alpha]_D^{25}$ −18.3° (water, c = 0.22).

Anal. Calc'd for $C_{21}H_{30}ClNO_3$: Cl, 9.34. Found: Cl, 9.36.

The *hydrobromide* was prepared with 10% hydrobromic acid and recrystallized from water; m. p. 277–277.5° (evac. tube), $[\alpha]_D^{24}$ −12.6° (water, c = 0.87).

Anal. Calc'd for $C_{21}H_{30}BrNO_3$: Br, 18.84. Found: Br, 19.00.

The *salicylate*, prepared in absolute alcohol crystallizes in needles of m. p. 165–185° (evac. tube), $[\alpha]_D^{25}$ −8.9° (acetone, c = 0.67).

Anal. Calc'd for $C_{28}H_{35}NO_6$: C, 69.81; H, 7.33.
Found: C, 69.42, 69.62; H, 7.16, 6.84.

The *perchlorate*, prepared with 25% perchloric acid, crystallizes from alcohol, m. p. 236–238° (evac. tube), $[\alpha]_D^{25}$ −16.0° (acetone, c = 1.13).

Anal. Calc'd for $C_{21}H_{30}ClNO_7$: C, 56.79; H, 6.81.
Found: C, 56.75; H, 6.85.

Numerous other salts, *e.g.*, the fumarate, succinate, hydriodide, and picrate, crystallize well.

Isopropyldihydrothebaïnone oxime.—The oxime hydrochloride separates crystalline when isopropyldihydrothebaïnone is warmed with excess hydroxylamine hydrochloride. The salt melts at 213–215° (evac. tube, gas at 228°) and has $[\alpha]_D^{26}$ +43.8° (water, c = 1.095).

Anal. Calc'd for $C_{21}H_{31}ClN_2O_3$: N, 7.10. Found: N, 7.01.

Sodium carbonate precipitates the oxime base, which crystallizes as the dihydrate in white needles from alcohol. It melts partially at 130–137°, solidifies, and remelts at 199–201°; in ethyl acetate, $[\alpha]_D^{25}$ +13.5° (c = 0.29).

Anal. Calc'd for $C_{21}H_{30}N_2O_3 + 2\ H_2O$: N, 7.11; H_2O, 9.14.
Found: N, 7.24, 7.18; H_2O, 9.24.

1-Bromoisopropyldihydrocodeïnone.—Bromination of 10.5 g. of isopropyldihydrothebaïnone with 2 moles of bromine during 18 hours, as already described, was followed by removal of acetic acid in a vacuum and treatment with 10 *N* sodium hydroxide. The product was 13.8 g. of yellow crystals, and was purified from acetone or ethyl acetate; yield of pure material 70%. It was found that concentrated ammonia will also effect the ring closure to yield the same product. 1-Bromoisopropyldihydrocodeïnone melts at 164–167° and has $[\alpha]_D^{24}$ −79.4° (acetone, c = 1.16).

Anal. Calc'd for $C_{21}H_{28}BrNO_3$: C, 60.00; H, 6.24.
Found: C, 60.29, 59.84; H, 6.44, 6.25.

1,5-Dibromoisopropyldihydrothebaïnone hydrobromide.—This intermediate in the bromoisopropyldihydrocodeïnone synthesis was obtained as shimmering white crystals when the vacuum-concentrated bromination solution was rubbed up with a little water. The salt may be recrystallized from absolute alcohol, or from water. It decomposes at 230–232° (evac. tube) and has $[\alpha]_D^{24}$ −2.7° (alcohol, c = 0.74). The hydrate water was difficult to determine because of the extremely hygroscopic nature of the dehydrated salt.

Anal. Calc'd for $C_{21}H_{28}Br_3NO_3 + 2\ H_2O$: C, 40.78; H, 5.22; H_2O, 5.83.
Found: C, 40.70, 40.61; H, 4.95, 5.27; H_2O, 4.72.

Isopropyldihydrocodeïnone.—Catalytic debromination of 15.3 g. of bromoisopropyldihydrocodeïnone in 170 cc. of 2 *N* acetic acid with 4 g. of potassium acetate, 8 cc. of 1% palladous chloride solution, and a little gum arabic, took place with absorption of 872 cc. of hydrogen (calc'd, 833 cc.), and yielded 12.6 g. of white, crys-

talline isopropyldihydrocodeïnone. It crystallizes in needles from alcohol and sublimes in a high vacuum at 155°; m. p. 175–177°, $[\alpha]_D^{26}$ −110.5° (alcohol, c = 0.87).

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.97. Found: C, 74.05; H, 7.82.

The *hydrobromide* crystallizes from water in needles or rods of m. p. 202–203° (evac. tube) and $[\alpha]_D^{25}$ −58.3° (water, c = 0.81).

Anal. Calc'd for $C_{21}H_{28}BrNO_3$: Br, 18.93. Found: Br, 19.08.

The hydriodide monohydrate crystallizes from water in long rods, m. p. 196–198° (evac. tube), $[\alpha]_D^{25}$ −67.2° (alcohol, c = 1.16).

Anal. Calc'd for $C_{21}H_{28}INO_3 + H_2O$: I, 26.05; H_2O, 3.70.
Found: I, 25.93; H_2O, 3.59.

The *methiodide* crystallizes from dilute alcohol, m. p. with decomp. (evac. tube), 274–275°, $[\alpha]_D^{25}$ −66.0° (acetone, c = 0.51).

Anal. Calc'd for $C_{22}H_{30}INO_3$: C, 54.64; H, 6.26.
Found: C, 54.94; H, 6.10.

The *oxime* crystallizes in lozenges from ethyl acetate, m. p. 224–226° (evac. tube), $[\alpha]_D^{25}$ −25.0° (alcohol, c = 0.40).

Anal. Calc'd for $C_{21}H_{28}N_2O_3$: N, 7.87. Found: N, 8.15.

Reduction of isopropyldihydrocodeïnone.—Attempted catalytic reduction with platinum oxide in alcohol failed, as did reduction by the method of Brown, Durand, and Marvel[13]. Sodium hydrosulfite, as used by Hill[14] for the reduction of codeïnone, and stannous chloride, used by Schöpf and Hirsch[15] for the same reduction, likewise failed to act. Clemmensen reduction of 1.8 g. of isopropyldihydrocodeïnone gave 0.9 g. of isopropyldihydrothebaïnone of m. p. 219–220° and $[\alpha]_D^{25}$ −27°.

Isopropyldihydromorphinone.—A solution of 4.5 g. of isopropyldihydrocodeïnone in 22 cc. of 48% hydrobromic acid was heated under reflux for 25 minutes. Two such runs were joined and diluted with 100 cc. of water, which caused precipitation of the crystalline hydrobromide. Without regard to this, the solution was made strongly alkaline, and extracted with ether; the material in the ether was negligible. With ammonium chloride and ether the alkaline solution yielded 8.7 g. (99%) of white crystals, which were purified from alcohol. The compound sublimes in high vacuum at 180°, and has the m. p. 236–238°, $[\alpha]_D^{26}$ −107.5° (alcohol, c = 0.40).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.61; H, 7.66.

The *hydrochloride* was prepared in acetone with alcoholic hydrogen chloride and was purified from absolute alcohol (monohydrate, rectangular plates); from acetone it crystallizes in prisms; m. p. 340–341° (evac. tube, decomp.), $[\alpha]_D^{25}$ −64.2° (water, c = 0.87).

Anal. Calc'd for $C_{20}H_{26}ClNO_3 + H_2O$: Cl, 9.29; H_2O, 4.72.
Found: Cl, 9.32; H_2O, 4.74.

The *hydrobromide* crystallizes from water in needles of m. p. 215–220° (evac. tube) and $[\alpha]_D^{23}$ −56.4° (water, c = 0.85).

Anal. Calc'd for $C_{20}H_{26}BrNO_3$: Br, 19.58. Found: Br, 19.51.

The *hydriodide* crystallizes from water as the monohydrate, m. p. 199–201° (evac. tube), $[\alpha]_D^{25}$ −61.5° (acetone, c = 1.33).

Anal. Calc'd for $C_{20}H_{26}INO_3 + H_2O$: I, 26.83; H_2O, 3.81.
Found: I, 27.05; H_2O, 4.43.

The *perchlorate* was prepared with 25% perchloric acid and was purified from 33%

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[13] Brown, Durand, and Marvel, *J. Am. Chem. Soc.*, **58**, 1594 (1936).

[14] Karl A. T. Hill, Dissertation, Frankfurt a/M., **1925.**

[15] Schöpf and Hirsch, *Ann.*, **489**, 224 (1931).

alcohol, rectangular plates of m. p. 168–170° (evac. tube); $[\alpha]_D^{25}$ −69.9° (alcohol, c = 1.13). The salt is probably a dihydrate or sesquihydrate when freshly crystallized.

Anal. Calc'd for $C_{20}H_{26}ClNO_7$ + 1.25 H_2O: C, 53.31; H, 6.38; H_2O, 5.00.
Found: C, 53.13; H, 6.43; H_2O, 5.01.

Isopropyldihydromorphinone was unaffected by catalytic hydrogenation with platinum oxide or palladous chloride. By Clemmensen reduction an amorphous solid was obtained, which was for the most part involatile in high vacuum at 210°. It is probably dimolecular in nature. The volatile material crystallized in needles from alcohol, and decomposed (evac. tube) at 277–280°, $[\alpha]_D^{25}$ −117.6° (alcohol, c = 0.068). It did not have the composition expected of isopropyldihydromorphine, or of isopropyldihydrodesoxymorphine.

Anal. Found: C, 68.86, 69.90; H, 7.74, 7.89.

Amyldihydrothebaïnone.—The ether-free Grignard reagent from 380 cc. of molar ethereal *n*-amylmagnesium bromide was brought into reaction with 40 g. of dihydrothebaïne in anhydrous benzene, as described in the foregoing experiments. A white precipitate began to form after about 45 minutes of heating. The solution was boiled under reflux for 22 hours, cooled, and treated with 275 cc. of 1.8 *N* sulfuric acid; the sparingly soluble sulfate was brought into solution by heating and diluting. The base was precipitated from the acid layer with ammonia and brought into six liters of ether, and the ether was worked with small portions of 0.3 *N* sodium hydroxide solution containing hydrosulfite until the alkaline washings were no longer red. From these only a small amount of red oil could be isolated. The ether yielded 34.7 g. of crystals and oil, from which 16.4 g. of crystals were obtained by crystallization from acetone. The yield of pure amyldihydrothebaïnone from a total of 110 g. of dihydrothebaïne was 36.3 g. (27.8% of the calculated amount). Amyldihydrothebaïnone is soluble in most organic media, sparingly soluble in warm dilute sodium hydroxide, from which it is precipitated by carbon dioxide. It crystallizes from acetone in needles, and sublimes in the oil-pump vacuum at 150°; m. p. 153–155°, $[\alpha]_D^{26}$ −12.8° (alcohol, c = 0.586).

Anal. Calc'd for $C_{23}H_{33}NO_3$: C, 74.34; H, 8.96. Found: C, 74.54; H, 8.92.

The *hydrochloride* forms in dilute hydrochloric acid and can be purified from water. When precipitated from absolute alcohol with ether it forms triangular plates of the monohydrate; m. p. 203–205°, $[\alpha]_D^{24}$ +2.8° (alcohol, c = 0.72).

Anal. Calc'd for $C_{23}H_{34}ClNO_3$ + H_2O: C, 64.82; H, 6.52; H_2O, 4.23.
Found: C, 65.07; H, 8.36; H_2O, 3.89.

The *hydrobromide* crystallizes from water in six-sided plates, m. p. 223–224.5° (evac. tube), $[\alpha]_D^{25}$ +1.5° (alcohol, c = 0.99).

Anal. Calc'd for $C_{23}H_{34}BrNO_3$: Br, 17.67. Found: Br, 17.92.

The *hydriodide* crystallizes from 50% alcohol in parallelogram plates, or from 50% acetone; m. p. 238–239° (evac. tube), $[\alpha]_D^{25}$ −1.4° (alcohol, c = 0.72).

Anal. Calc'd for $C_{23}H_{34}INO_3$: C, 55.29; H, 6.86.
Found: C, 55.11; H, 6.56.

The *perchlorate* crystallizes from 25% alcohol in square plates, or in trigonal plates. It melts at 235–236° (evac. tube) and has $[\alpha]_D^{25}$ −2.13° (alcohol, c = 1.08). The water of hydration could not be determined directly.

Anal. Calc'd for $C_{23}H_{34}ClNO_7$ + 0.5 H_2O: C, 57.41; H, 7.34.
Found: C, 57.63; H, 7.32.

The *sulfate* was prepared in 10% sulfuric acid; it crystallized hydrated from water as short rods of m. p. 95–105°; $[\alpha]_D^{24}$ 0° (alcohol, c = 0.24).

Anal. Calc'd for $C_{46}H_{68}N_2O_{10}S + 2.5\ H_2O$: C, 62.33; H, 8.31; H_2O, 5.1.
Found: C, 62.49; H, 8.11; H_2O, 5.1.

Amyldihydrothebaïnone oxime crystallizes from alcohol in rectangular plates melting at 113–115°, $[\alpha]_D^{25}$ +18.6° (alcohol, c = 0.43).

Anal. Calc'd for $C_{23}H_{34}N_2O_3 + 1.5\ H_2O$: N, 6.77; H_2O, 6.5.
Found: N, 6.77; H_2O, 6.9.

1-Bromoamyldihydrocodeïnone.—Twelve grams of amyldihydrothebaïnone in 120 cc. of glacial acetic acid was treated dropwise under mechanical stirring with 2 moles of bromine in glacial acetic acid, time of addition 21 hours. The product, after removal of acetic acid and treatment with 10 *N* sodium hydroxide, was isolated as previously described, and consisted of 15.4 g. of crystals, with some brown oil. Purification from alcohol yielded 11.5 g. of white crystals. From the alcohol mother liquors 0.6 g. of 1-bromoamyldihydrothebaïnone was obtained. The total yield of pure product from the ring closure was 64.8% of the calculated amount.

1-Bromoamyldihydrocodeïnone is insoluble in alkali, and is best recrystallized from alcohol. It melts at 143–145° and has $[\alpha]_D^{24}$ −76.7° (alcohol, c = 0.81).

Anal. Calc'd for $C_{23}H_{30}BrNO_3$: C, 61.59; H, 6.75.
Found: C, 61.26; H, 6.91.

The *oxime* crystallizes from methanol in needles that appear to be hydrated, and which melt partly at 121–123°, resolidify, and melt at 170–174°; $[\alpha]_D^{24}$ −29.7° (alcohol, c = 0.45).

Anal. Calc'd for $C_{23}H_{31}BrN_2O_3 + 0.25\ H_2O$: N, 5.99; H_2O, 0.96.
Found: N, 5.91; H_2O, 1.3.

1-Bromoamyldihydrothebaïnone.—This base was isolated as described above from the ring closure reaction, and was purified from alcohol. It dissolves with difficulty in dilute alkali, from which it is precipitated by carbon dioxide. It crystallizes in rods of m. p. 241–242° (evac. tube), $[\alpha]_D^{25}$ −30.6° (alcohol, c = 0.36).

Anal. Calc'd for $C_{23}H_{32}BrNO_3$: C, 61.31; H, 7.16.
Found: C, 61.21; H, 6.89.

Amyldihydrocodeïnone.—Reduction of 17 g. of bromoamyldihydrocodeïnone in 170 cc. of 2 *N* acetic acid with 5 g. of potassium acetate, 10 cc. of 1% palladous chloride, and a little gum arabic resulted in absorption of 1 mole of hydrogen. The product, isolated in the usual way, was 16.5 g. of yellow oil, which rapidly solidified. It was exceedingly soluble in organic media, with the exception of ligroïn, and was recrystallized from a 2:1 mixture of 70–90° ligroïn and ethyl acetate. It has the m. p. 153–155°, $[\alpha]_D^{26}$ −9.3° (alcohol, c = 0.21).

Anal. Calc'd for $C_{23}H_{31}NO_3$: C, 74.75; H, 8.46.
Found: C, 74.44; H, 8.53.

The *picrate* crystallizes from absolute alcohol in rectangular yellow plates that sinter at 130°, and melt at 174–177°; $[\alpha]_D^{24}$ −52.8° (acetone, c = 0.96).

Anal. Calc'd for $C_{29}H_{34}N_4O_{10}$: N, 9.37. Found: N, 9.57.

The *styphnate* crystallizes from absolute alcohol in rectangular yellow plates of m. p. 142–145° (gas evolution); $[\alpha]_D^{25}$ −45.4° (acetone, c = 0.94).

Anal. Calc'd for $C_{29}H_{34}N_4O_{11} + 0.75\ H_2O$: N, 8.93; H_2O, 2.1.
Found: N, 8.71; H_2O, 1.9.

The *salicylate* can be prepared in absolute alcohol, from which it crystallizes in needles.

Amyldihydromorphinone.—A solution of 14.4 g. of crude amyldihydrocodeïnone in 75 cc. of 48% hydrobromic acid was boiled under reflux for 20 minutes. The solution was diluted (precipitation of a crystalline hydrobromide), treated with excess sodium

hydroxide, and extracted with ether, which removed some colored by-products. With ammonium chloride and ether the alkaline layer yielded 13.6 g. of semi-liquid product which was purified from a mixture of equal amounts of 70–90° ligroïn and ethyl acetate. The purified base crystallized from ethyl acetate as the hemihydrate in short rods of m. p. 113–116° (gas evolution) and had $[\alpha]_D^{25}$ −97.3° (alcohol, c = 0.96).

Anal. Calc'd for $C_{22}H_{29}NO_3 + 0.5\ H_2O$: C, 72.48; H, 8.30; H_2O, 2.4.
Found: C, 72.77; 72.69; H, 8.35, 8.27; H_2O, 2.2.

The *hydrochloride* was prepared in acetone with alcoholic hydrogen chloride. It crystallized from water in lozenges or six-sided plates, from alcohol as the hydrate in needles. It melts with decomposition at 322–325° (evac. tube) and has $[\alpha]_D^{25}$ −63.9° (water, c = 1.08).

Anal. Calc'd for $C_{22}H_{30}ClNO_3 + H_2O$: C, 64.43; H, 7.87; H_2O, 4.4.
Found: C, 64.72; H, 7.75; H_2O, 4.1.

The *hydrobromide* crystallizes hydrated from alcohol in flattened prisms of m. p. 189–190° (evac. tube) and $[\alpha]_D^{25}$ −66.0° (alcohol, c = 0.56).

Anal. Calc'd for $C_{22}H_{30}BrNO_3 + H_2O$: C, 58.13; H, 7.10; H_2O, 4.0.
Found: C, 58.41; H, 6.93; H_2O, 4.0.

The *hydriodide* crystallizes as the monohydrate in needles from alcohol, and melts at 182–184° (evac. tube), $[\alpha]_D^{25}$ −59.8° (alcohol, c = 0.77).

Anal. Calc'd for $C_{22}H_{30}INO_3 + H_2O$: C, 52.68; H, 6.43; H_2O, 3.6.
Found: C, 52.48; H, 6.39; H_2O, 3.5.

Neither amyldihydrocodeinone nor amyldihydromorphinone could be reduced with platinum oxide or palladium-platinum catalyst. On Clemmensen reduction amyldihydrocodeïnone was converted to amyldihydrothebaïnone, and amyldihydromorphinone yielded an amorphous product that may have been dimolecular in nature.

Benzyldihydrothebaïnone.—The reaction of excess benzylmagnesium chloride (3 moles) with dihydrothebaïne in anhydrous benzene proceeded like that of the alkylmagnesium halides, but more slowly, so that heating was continued for 40 hours. The reaction product was brought into dilute hydrochloric acid, from which it was precipitated and redissolved by addition of excess of 0.5 N sodium hydroxide solution. On seeding this solution with benzyldihydrothebaïnone obtained from the more tedious ether extraction procedure, benzyldihydrothebaïnone separated as brown crystals in nearly quantitative yield. The crude product was purified by conversion to the hydrochloride with alcoholic hydrogen chloride and recrystallization of the salt from absolute alcohol. The base, obtained from the hydrochloride and purified from alcohol, represented a yield of 33% of the calculated amount. No trace of an isomer, or of dihydromorphinone methyl enolate could be found.

Benzyldihydrothebaïnone crystallizes from alcohol in needles of m. p. 227–229°, and has $[\alpha]_D^{25}$ −51.6° in chloroform (c = 0.83). It does not dissolve easily in alkali, but when an acid solution is treated with excess of very dilute alkali the base precipitates momentarily and redissolves; from the alkaline solution it is precipitated by carbon dioxide or ammonium chloride.

Anal. Calc'd for $C_{25}H_{29}NO_3$: C, 76.68; H, 7.47.
Found: C, 76.66; H, 7.51.

The *hydrochloride*, prepared and purified as described above, has the melting point 243–244° (evac. tube, gas evolution) and shows in aqueous solution $[\alpha]_D^{25}$ −29° (c = 0.84).

Anal. Calc'd for $C_{25}H_{30}ClNO_3$: Cl, 8.29. Found: Cl, 7.98.

Benzyldihydrothebaïnone oxime was prepared in the usual way, and was purified from benzene. It melts at 135–142°, and has $[\alpha]_D^{25}$ +5.5° (chloroform, c = 0.55).

Anal. Calc'd for $C_{25}H_{30}N_2O_3$: N, 6.90. Found: N, 7.22.

1-Bromobenzyldihydrocodeïnone.—A 10% solution of benzyldihydrothebaïnone in glacial acetic acid was treated dropwise with a 10% solution of bromine in glacial acetic acid (2 moles of bromine), and the product, after treatment with 10 *N* sodium hydroxide, was isolated by extraction into ether, and crystallization of the resulting oil from alcohol. It consisted of white needles of m. p. 167–168°, $[\alpha]_D^{23}$ −101.4° (alcohol, c = 0.83); it exhibited no phenolic properties. Closure of the 4,5-oxide ring can also be accomplished using concentrated ammonia instead of sodium hydroxide.

Anal. Calc'd for $C_{25}H_{26}BrNO_3$: Br, 17.07. Found: Br, 16.80, 16.73.

The salicylate, fumarate, perchlorate, and sulfate of bromobenzyldihydrocodeinone crystallize well, but because of scarcity of material were not further investigated.

1-Bromobenzyldihydrothebaïnone.—This base was isolated from the alcoholic mother liquors from the purification of bromobenzyldihydrocodeïnone. It is much less soluble in organic media than the codeïnone derivative, and the two may thus be easily separated. Its nature was demonstrated not only by its cryptophenolic properties and analysis, but also by catalytic debromination to benzyldihydrothebaïnone. It obviously results from incomplete bromination of benzyldihydrothebaïnone, and by further treatment with bromine (1 mole) and ammonia it yields bromobenzyldihydrocodeïnone. Bromobenzyldihydrothebaïnone crystallizes from alcohol in needles of m. p. 230–232° (evac. tube), $[\alpha]_D^{23}$ −59.4° (alcohol, c = 0.37).

Anal. Calc'd for $C_{25}H_{28}BrNO_3$: Br, 17.00. Found: Br, 17.34.

Benzyldihydrocodeïnone.—Catalytic reduction of 3.3 g. of bromobenzyldihydrocodeïnone, as described for the amyl series resulted in absorption of one mole of hydrogen. The product was 2.7 g. of a colorless oil that could not be induced to crystallize, but could be distilled in high vacuum at 160°; in chloroform it showed $[\alpha]_D^{25}$ −114.3° (c = 0.50).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.07; H, 6.99.
Found: C, 76.72; H, 7.14.

Benzyldihydromorphinone.—Demethylation of benzyldihydrocodeïnone was accomplished by boiling a solution of 2.7 g. of the base in 15 cc. of 48% hydrobromic acid for 20 minutes. The solution was made alkaline and extracted with ether. From the ether layer 0.5 g. of material was obtained; this is an isomer of benzyldihydrocodeïnone, and appears to have been formed by a rearrangement of unknown nature. It crystallized from alcohol in prisms of m. p. 166–167.5°, $[\alpha]_D^{24}$ −439° (chloroform, c = 0.52).

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.07; H, 6.99.
Found: C, 77.38; H, 6.81.

The alkaline solution from the demethylation was treated with ammonium chloride and extracted with ether, from which 1.8 g. of oily product was obtained. This crystallized reluctantly from ethyl acetate, but since our chief interest lay in the preparation of pharmacologically applicable derivatives, it was all converted to the hydrochloride. Benzyldihydromorphinone hydrochloride was prepared with alcoholic hydrogen chloride and was purified from absolute alcohol, from which it separated in hydrated prisms. It melts at 241–242° (evac. tube) and has $[\alpha]_D^{24}$ −100.6° (water, c = 0.30).

Anal. Calc'd for $C_{24}H_{26}ClNO_3 + H_2O$: C, 67.02; H, 6.57; Cl, 8.25; H_2O, 4.2.
Found: C, 67.00; H, 6.34; Cl, 8.07; H_2O, 5.6, 6.0.

Phenyldihydrothebaïnone.—A solution of 40 g. of dihydrothebaïne in anhydrous benzene was added to 3 moles of ether-free phenylmagnesium bromide, and the solution was boiled under reflux for 15 hours (reaction evident after 45 minutes). The white Grignard complex was decomposed with dilute hydrochloric acid. The acid solution was treated with excess ammonia and a little sodium hydrosulfite, and extracted with 24 liters of ether. The purple ether extract was shaken out with 0.5 *N* sodium hydroxide until the alkali was no longer colored red. The ether yielded 34.1 g. of colored oil and crystals. The alkaline extracts from two 40-g. experiments gave with ammonium chloride and ether 6.6 g. of oily crystals of dihydromorphinone methyl enolate. The alkali-insoluble material from two 40-g. experiments was warmed with 150 cc. of ethyl acetate, and the crystalline, insoluble product was filtered out; yield 14 g. of white crystals, m. p. 191–210°. By laborious fractional crystallization from alcohol, this was separated into pure phenyldihydrothebaïnone and isophenyldihydrothebaïnone.

Phenyldihydrothebaïnone is moderately soluble in most organic solvents, and crystallizes best from alcohol. It behaves like a cryptophenol in regard to solubility in alkali. It melts at 230–232°, and has in chloroform $[\alpha]_D^{24}$ −165.9° (c = 0.64).

Anal. Calc'd for $C_{24}H_{27}NO_3$: C, 76.35; H, 7.21.
Found: C, 76.13; H, 7.00.

The *perchlorate* was prepared in 30% alcohol with 25% perchloric acid, and was recrystallized from 95% alcohol. It melts at 201° (evac. tube, gas evolution) and has $[\alpha]_D^{25}$ −97.6° (acetone, c = 0.41).

Anal. Calc'd for $C_{24}H_{28}ClNO_7$: Cl, 7.42. Found: Cl, 7.55.

The *methiodide* is very soluble in alcohol or acetone, but can be crystallized from 30% alcohol. It melts at 245–248° (evac. tube, decomp.) and has in alcohol $[\alpha]_D^{25}$ −96.5° (c = 1.09).

Anal. Calc'd for $C_{25}H_{30}INO_3 + H_2O$: I, 23.63; H_2O, 3.3.
Found: I, 23.37; H_2O, 3.3.

Phenyldihydrothebaïnone oxime was prepared by treating an aqueous suspension of the base with twice its weight of hydroxylamine hydrochloride at 80° for one hour, and precipitating with sodium carbonate. The oxime, purified from absolute alcohol, melts at 198–200° and has $[\alpha]_D^{24}$ −106.7° (alcohol, c = 0.07).

Anal. Calc'd for $C_{24}H_{28}N_2O_3$: N, 7.14. Found: N, 7.06.

Phenyldihydrocodeïnone.—Bromination of 4 g. of phenyldihydrothebaïnone and subsequent treatment with alkali, as described for the alkyl analogs, yielded 5.4 g. of a yellow non-phenolic oil, from which no crystalline derivatives could be prepared. Five grams of this oil, subjected to catalytic reduction, absorbed 1 mole of hydrogen and gave 4.0 g. of white crystalline phenyldihydrocodeïnone, which crystallized in short needles from a mixture of 3 parts of 60–90° ligroïn with 1 part of ethyl acetate. It has the melting point 149–151°, $[\alpha]_D^{24}$ −166.2° (alcohol, c = 0.39).

Anal. Calc'd for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.72.
Found: C, 77.04; H, 6.72.

Phenyldihydromorphinone.—Demethylation of 2 g. of phenyldihydrocodeïnone with 48% hydrobromic acid for 30 minutes gave a nearly quantitative yield of phenyldihydromorphinone (0.15 g. of starting material was recovered). It crystallizes from alcohol in short prisms of m. p. 278–280° (evac. tube, decomp.); $[\alpha]_D^{24}$ −164.5° (acetone, c = 0.29).

Anal. Calc'd for $C_{23}H_{23}NO_3$: C, 76.41; H, 6.42.
Found: C, 76.55; H, 6.34.

The *hydrochloride* was prepared with alcoholic hydrogen chloride, and was purified from 90% alcohol. It crystallizes in long needles having the m. p. 334–337° (evac. tube, decomp.) and $[\alpha]_D^{24}$ −126.9° (water, c = 0.53).

Anal. Calc'd for $C_{23}H_{24}ClNO_3$: Cl, 8.92. Found: Cl, 9.28.

The *hydrobromide* crystallizes in rods from 90% alcohol; it melts at 281–284° (evac. tube) and has $[\alpha]_D^{25}$ −97.4° (acetone, c = 0.58).

Anal. Calc'd for $C_{23}H_{24}BrNO_3 + 1.25\ H_2O$: Br, 17.20; H_2O, 4.85.
Found: Br, 16.94; H_2O, 4.85.

The *hydriodide* crystallizes in large prisms from 90% alcohol, and melts at 273–276° (evac. tube); $[\alpha]_D^{25}$ −95.1° (acetone, c = 0.35).

Anal. Calc'd for $C_{23}H_{24}INO_3 + H_2O$: I, 25.03; H_2O, 3.5.
Found: I, 24.97; H_2O, 3.3.

Isophenyldihydrothebaïnone.—This base resembles phenyldihydrothebaïnone in solubility, but is noticeably less soluble in chloroform. It crystallizes from alcohol in needles of m. p. 213–215°, and has in chloroform $[\alpha]_D^{24}$ +34.8° (c = 0.69). It does not dissolve in alkali from the solid state, but does so when precipitated from a solution in acid, and is reprecipitated by carbon dioxide.

Anal. Calc'd for $C_{24}H_{27}NO_3$: C, 76.35; H, 7.21.
Found: C, 76.00; H, 7.42.

The *methiodide* is very soluble in methanol, and was best purified by addition of a little methanol to a suspension in boiling ethyl acetate. It separated in small rectangular plates of m. p. 214–215° (evac. tube), $[\alpha]_D^{24}$ 0° (alcohol, c = 0.34).

Anal. Calc'd for $C_{25}H_{30}INO_3 + 1.75\ H_2O$: C, 54.48; H, 6.13; I, 23.05; H_2O, 5.7.
Found: C, 54.24; H, 5.90; I, 23.04; H_2O, 5.5.

Isophenyldihydrothebaïnone oxime, prepared in the usual way, crystallizes from ethyl acetate in needles of m. p. 230–232° and $[\alpha]_D^{24}$ −157° (alcohol, c = 0.09).

Anal. Calc'd for $C_{24}H_{28}N_2O_3$: N, 7.14. Found: N, 7.32.

Isophenyldihydrothebaïnone methyl ether methiodide was prepared in order to demonstrate conclusively the presence of the phenolic hydroxyl group. A suspension of 7.6 g. of isophenyldihydrothebaïnone in 38 cc. of methanol was treated with 0.7 g. of sodium dissolved in 13 cc. of methanol, and 3.5 cc. of methyl iodide. After being boiled under reflux for 45 minutes, the purple solution was concentrated, and the crystalline product was triturated with a mixture of equal parts of methanol and ether; yield, quantitative. Purified from methanol-ethyl acetate mixture, the methyl ether methiodide had the m. p. 264–265° and $[\alpha]_D^{24}$ +49.3° (alcohol, c = 0.193).

Anal. Calc'd for $C_{26}H_{32}INO_3$: C, 58.52; H, 6.05.
Found: C, 58.51; H, 6.14.

Degradation of isophenyldihydrothebaïnone methyl ether.—Isophenyldihydrothebaïnone methyl ether methiodide was converted to the methochloride by stirring in aqueous solution at 80° for one hour with excess of silver chloride. By concentration of the solution in vacuum and trituration of the residue with acetone, the methochloride was obtained crystalline. Because of unfavorable solubility, the compound was difficult to purify, but could be recrystallized from a 9:1 mixture of ethyl acetate and methanol. It melted at 239–243° (evac. tube), but was so unstable that a satisfactory analytical sample could not be obtained.

The methochloride was distilled in one-gram portions at 200–205° in an oil-pump vacuum. The glass-like distillate was dissolved in chloroform and washed with

dilute hydrochloric acid. From the chloroform a partly crystalline product was isolated, which was triturated with alcohol to remove color, and was recrystallized from ethyl acetate. It forms flat, colorless plates, insoluble in acids, and nitrogen-free; m. p. 227–230°, $[\alpha]_D^{22}$ −130° (benzene, c = 1.02). The analytical results indicate that the compound is the expected degradation product, 3,4-dimethoxy-5 (or -7) -phenyl-6-keto-5,6,7,8-tetrahydrophenanthrene.

Anal. Calc'd for $C_{22}H_{20}O_3$: C, 79.48; H, 6.07.
Found: C, 79.40; H, 6.27.

Attempted preparation of isophenyldihydromorphinone.—To 6 g. of isophenyldihydrothebaïnone in 80 cc. of glacial acetic acid, 2 moles of bromine in glacial acetic acid was added dropwise, with mechanical stirring, over a period of nine hours. The resulting dibromoisophenyldihydrothebaïnone could not be obtained crystalline, and was converted to 1-bromoisophenyldihydrocodeïnone by the action of 10 N sodium hydroxide. The yield was 7.5 g. of a viscous, nonphenolic yellow oil, that did not crystallize nor give crystalline salts. This material was subjected to catalytic debromination under the conditions described for the other members of the series, and gave 5.3 g. of oily product containing a trace of crystalline material (isophenyldihydrothebaïnone). The oil (4 g.) gave no crystalline derivatives, and was demethylated with 48% hydrobromic acid. The demethylation was unsuccessful, as with the isomethyldihydrocodeïnone analog; most of the material was decomposed, but 0.9 g. of crystalline material was isolated. This was non-phenolic in nature, and we believe it to be a rearrangement product of isophenyldihydrocodeïnone, to which it corresponds in empirical formula. It crystallizes from alcohol in six-sided plates of m. p. 189–190° (evac. tube) and shows in alcohol $[\alpha]_D^{24}$ +127.5° (c = 0.26).

Anal. Calc'd for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.72.
Found: C, 76.73; H, 6.52.

Dihydromorphinone methyl enolate.—The unexpected appearance of a demethylation product of dihydrothebaïne in the Grignard reactions involving isopropylmagnesium bromide and phenylmagnesium bromide has been mentioned in the preceding paragraphs. From the empirical formula, and strongly phenolic nature of the substance, it is obvious that the methoxyl group at the 3-position has been hydrolyzed, while the enolic methoxyl at C-6 is unchanged. This is proved by the following experiments. Dihydromorphinone methyl enolate, treated with cold concentrated hydrochloric acid for 5 minutes gave a good yield of dihydromorphinone, m. p. 264–266.5° (evac. tube, decomp.), which did not depress the melting point of a known sample (courtesy of Bilhuber-Knoll and Co.).

A suspension of 0.5 g. of dihydromorphinone methyl enolate in absolute ether with a little methanol was treated with an excess of diazomethane for 20 hours. From the clear ether solution, 0.52 g. of dihydrothebaïne was isolated, melting point and mixed melting point 162–163°. On hydrolysis with warm concentrated hydrochloric acid the methylation product yielded dihydrocodeïnone of m. p. 194.5–195°, mixture melting point 195°.

A solution of 4 g. of dihydrothebaïne in 55 cc. of absolute methanol containing 2 g. of dissolved sodium was heated in a bomb-tube at 125–140° for 36 hours. The products, isolated without the use of acids, were 3.6 g. of unchanged dihydrothebaïne, and 0.4 g. of dihydromorphinone methyl enolate, identical in melting point and specific rotation with that obtained from the Grignard reactions. As might be expected from the relative instability of thebaïne, an attempt to prepare the methyl

enolate of the unknown base morphinone by parallel demethylation of thebaïne resulted only in decomposition products.

Dihydromorphinone methyl enolate is soluble in alkali, and moderately soluble in organic media. It crystallizes from ethanol in long needles and four-sided rods. It has the melting point 233–235°, and shows in alcohol $[\alpha]_D^{24}$ −206.5° (c = 0.94).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.07; N, 4.68; mol. wt. 299.2.
Found: C, 72.32, 72.12; H, 7.21; 7.13; N, 4.52; mol. wt. 285.

The *hydrochloride* was prepared from a suspension of the base in water by adding hydrochloric acid to faint acidity; the salt crystallizes in prisms from alcohol or water, and has the m. p. 309–310° (evac. tube, decomp.), and shows $[\alpha]_D^{25}$ −180.6° (water, c = 0.53).

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: Cl, 10.56. Found: Cl, 10.87.

The *hydriodide*, prepared like the hydrochloride, crystallizes from water or alcohol, and has the m. p. 274–275° (evac. tube, decomp.); $[\alpha]_D^{25}$ −140.5° (water, c = 0.42).

Anal. Calc'd for $C_{18}H_{22}INO_3$: I, 29.72. Found: I, 29.53, 30.16.

The *benzoate* was prepared in alcohol solution with the calculated amount of benzoic acid. It crystallizes from alcohol in large four-sided rods of m. p. 229–230° (evac. tube) and $[\alpha]_D^{25}$ −150.7° (alcohol, c = 0.49).

Anal. Calc'd for $C_{25}H_{27}NO_5$: C, 71.22; H, 6.46.
Found: C, 70.93; H, 6.36.

The *salicylate*, prepared like the benzoate, crystallizes from dilute alcohol in the form of small needles; m. p. 268–270° (evac. tube); $[\alpha]_D^{25}$ −130.8° (acetone, c = 0.26). The analytical data indicate the presence of 0.25 molecule of hydrate water, but this was retained even after drying at 130°.

Anal. Calc'd for $C_{25}H_{27}NO_6 + 0.25\ H_2O$: C, 67.92; H, 6.27.
Found: C, 67.91, 67.92; H, 5.93, 6.09.

The *methiodide* was prepared by boiling a solution of the base in methanol with methyl iodide under reflux for 3 hours. The methiodide is soluble in acetone, insoluble in cold water or ethanol. It crystallizes from methanol as small needles of the monohydrate, m. p. 259–261° (evac. tube), $[\alpha]_D^{25}$ −123.6° (acetone, c = 1.19).

Anal. Calc'd for $C_{19}H_{24}INO_3 + H_2O$: I, 27.64; H_2O, 3.9.
Found: I, 26.91, 27.48; H_2O, 3.8.

Dimethyldihydrothebaïnone.—To the residue from removal of the ether from 280 cc. of molar methylmagnesium iodide was added a solution of 20 g. of methyldihydrocodeïnone enol acetate in 450 cc. of anhydrous benzene. A vigorous reaction took place, with formation of a white precipitate. Although the reaction appeared to be complete after about 15 minutes boiling under reflux, heating was continued for several hours. The product was decomposed with dilute hydrochloric acid, and the acid layer was extracted once with a little ether. By treatment of the aqueous portion with ammonia and ether, 15.3 g. of red oil was obtained. This was dissolved in 50 cc. of absolute alcohol, and 6 g. of fumaric acid was added; the fumarate crystallized immediately and was purified from absolute alcohol; yield 11 g. From the mother liquors, 2 g. more was obtained. Further manipulation of the mother liquors gave 4.8 g. of oil of unknown nature. The two crops of fumarate were converted separately to the base; from the larger crop, an oil was obtained, from the smaller, crystals of the "X compound." The oil, on extraction into ether and concentration, gave 8.3 g. of white crystals with some oil. By recrystallization from 50% acetone, 1.3 g. of dimethyldihydrothebaïnone was obtained. The base obtained from the

acetone mother liquors was isolated as the salt, "X-fumarate." The nature of the base "X", the main product of the reaction, will be discussed in a later paper. The parallel reaction of isomethyldihydrocodeïnone enol acetate with methylmagnesium iodide gave a comparable yield of dimethyldihydrothebaïnone, although we are not certain where the main product from this reaction, also isolated as the fumarate, is identical or not with the above-mentioned "X-fumarate."

Dimethyldihydrothebaïnone crystallizes well from acetone, and has the m. p. 199–202°, $[\alpha]_D^{26}$ +3.52° (alcohol, c = 0.85). The material from the isomethyl series has the melting point 199–201° (no depression in mixture melting point) and $[\alpha]_D^{26}$ +3.50°. The base dissolves readily in alkali, from which it is precipitated by carbon dioxide; it forms a crystalline hydrochloride.

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.90; H, 8.27.
Found: C, 73.31; H, 8.49.

The *oxime* is very soluble in organic media but can be crystallized from a mixture of ligroïn and ethyl acetate. It melts unsharp, 70–90°.

Anal. Calc'd for $C_{20}H_{28}N_2O_3$: N, 8.14. Found: N, 7.88.

To 0.64 g. of dimethyldihydrothebaïnone in 10 cc. of glacial acetic acid, 2 moles of bromine in a 10% solution in the same medium was added over a period of 3 hours. In the initial stages, a red precipitate formed (perbromide?), which dissolved as the reaction proceeded. The final solution was pale yellow. The solution was diluted and made strongly alkaline with 10 *N* sodium hydroxide. The product, from ether extraction was 0.8 g. of oil that crystallized from acetone. The bromodimethyldihydrothebaïnone so obtained had the m. p. 218–221°, and behaved as a cryptophenol, soluble with reluctance in very dilute alkali and precipitated by carbon dioxide; ferric chloride test blue-green. The compound was apparently not quite pure, but analysis shows without question the presence of only one bromine atom.

Anal. Calc'd for $C_{20}H_{25}Br_2NO_3$: Br, 32.82.
Calc'd for $C_{20}H_{26}BrNO_3$: Br, 19.58. Found: Br, 17.59.

Reduction of bromodimethyldihydrothebaïnone proceeded with absorption of one mole of hydrogen to give dimethyldihydrothebaïnone.

Methyldihydropseudocodeïne methyl ether.—The investigation of the action of methylmagnesium iodide on pseudocodeïne methyl ether involved unexpected difficulties in the preparation of pure starting material. The reaction of purest α-chlorocodide, carried out according to the method of Knorr and Hartmann, gave a yield of 55% of the calculated amount of crude product, of which, however, 10% was β-chlorocodide. This can be removed only by fractional extraction, so that the yield of pure pseudocodeïne methyl ether (m. p. 134–136°) does not exceed 20%. The α-chlorocodide was shown to be free of the β-isomer, so that the latter must be produced by rearrangement under the experimental conditions (100° for 7 hours). We have observed the same phenomenon during the purification of α-chlorocodide from ethanol. Modifications in concentration, temperature, and time of heating did not improve the yield of desired product. It was further demonstrated that the losses in the preparation are not due to decomposition of the end-product, for pseudocodeïne methyl ether was recovered unchanged after 116 hours at 100° in methanol. Methylation of pseudocodeïne methyl ether-*N*-oxide with 10 *N* sodium hydroxide and methyl sulfate gave, after reduction of the *N*-oxide, pseudocodeïne methyl ether in poor yield.

Ten grams of pseudocodeïne methyl ether was heated under reflux with 75 cc. of an 0.8 molar ethereal solution of methylmagnesium iodide for 18 hours. The ether was removed, and the residue was treated cautiously with water. The semi-crystal-

line product was washed twice by decantation with 500 cc. of boiling water and dried. It was dissolved in 100 cc. of boiling ethanol, freed from 0.5 g. of inorganic material, and treated with alcoholic hydrogen chloride. The yield was 5.5 g. (47%) of pink crystals. After recrystallization from alcohol, the hydrochloride was converted to the base, 3.4 g. (32%) of crystals from ether. Methyldihydropseudocodeïne methyl ether crystallizes best from ethyl acetate, m. p. 182.5–183°; it sublimes unchanged in high vacuum at 150°. It is not strongly phenolic but dissolves readily when an acid solution is treated with excess alkali; ferric chloride reaction, blue-green. In alcohol, $[\alpha]_D^{28}$ +121.0° (c = 1.00).

Anal. Calc'd for $C_{20}H_{27}NO_3$: C, 72.90; H, 8.27.
Found: C, 72.87; H, 8.54.

The *hydrochloride* crystallizes from alcohol in white needles that melt at 247–251° (evac. tube, decomp.) and show $[\alpha]_D^{25}$ +125.9° (water, c = 1.00).

Anal. Calc'd for $C_{20}H_{28}ClNO_3$: Cl, 9.70. Found: Cl, 9.37.

The *hydriodide* crystallizes from alcohol as white needles, m. p. 256–257° (evac. tube. gas evolution), $[\alpha]_D^{25}$ +91.5° (alcohol, c = 1.00).

Anal. Calc'd for $C_{20}H_{28}INO_3$: I, 27.77. Found: I, 27.62.

The *perchlorate* was prepared in alcohol and purified from the same solvent. It melts at 285–287° (evac. tube, decomp.) and has $[\alpha]_D^{25}$ +103.1° (alcohol, c = 0.40).

Anal. Calc'd for $C_{20}H_{28}ClNO_7$: Cl, 8.25. Found: Cl, 8.06.

The *methiodide* crystallizes from alcohol as white needles of m. p. 273–276° (evac. tube, gas evolution) and $[\alpha]_D^{25}$ +98.1° (alcohol, c = 1.00).

Anal. Calc'd for $C_{21}H_{30}INO_3$: I, 26.94. Found: I, 27.15.

When the Grignard reaction was carried out in isopropyl ether, by extracting the pseudocodeïne methyl ether from a Soxhlet extractor into the reaction flask, 10 g. of starting material yielded only 1 g. of methyldihydropseudocodeïne methyl ether. In addition, 2.3 g. of sparingly soluble crystals were isolated from ethyl ether. This product was purified from ethyl acetate and sublimed in high vacuum at 110°. It melted at 132–132.5° and did not depress the melting point of tetrahydropseudocodeïne methyl ether. It showed, on the other hand, $[\alpha]_D^{25}$ −57.4° (alcohol, c = 1.00), whereas tetrahydropseudocodeïne methyl ether crystallizes only as the hemihydrate (m. p. 125–130°), cannot be sublimed crystalline, and has $[\alpha]_D^{30}$ −5°.

Anal. Calc'd for $C_{19}H_{27}NO_3$: C, 71.90; H, 8.58.
Found: C, 71.96, 71.86; H, 8.58, 8.68.

SUMMARY

1. Organomagnesium halides react with morphine derivatives of the pseudocodeïne type, *i.e.*, those having an unsaturated linkage in the 6,7 position, with scission of the ether ring, and introduction of an organic group into the nucleus. This reaction can likewise be applied to the enol esters of the dihydroketones of the morphine group.

2. The preparation of methyl, ethyl, isopropyl, *n*-amyl, benzyl, and phenyl derivatives of dihydrothebaïnone is described. In the methyl, ethyl, and phenyl series, pairs of isomeric substituted dihydrothebaïnones are formed, in the isopropyl, *n*-amyl, and benzyl series, no isomers have been found.

3. By closure of the 4,5-oxide ring, the alkyl, aralkyl, and aryl dihydrothebaïnones can be transformed to the corresponding dihydroco-

deïnone derivatives, and demethylation of these leads to organic substituted dihydromorphinones.

4. The nuclear methylated dihydrocodeïnone isomers can be converted to the enol acetates, and these derivatives brought into reaction with methylmagnesium iodide, whereby a second methyl group is introduced. The same dimethyldihydrothebaïnone is formed from both isomers. The significance of this fact for speculations concerning the structure of the alkyl dihydrothebaïnones is discussed.

5. The action of isopropyl- or phenylmagnesium bromide on dihydrothebaïnone results to some extent in demethylation at the phenolic ether group, whereby dihydromorphinone methyl enolate is formed. This compound can also be prepared by demethylation of dihydrothebaïne under alkaline conditions.

6. Pseudocodeïne methyl ether reacts with methylmagnesium iodide to give a phenolic product containing a new methyl group. Analysis shows that methylpseudocodeïne methyl ether must contain an alicyclic unsaturated linkage but the compound shows the same extraordinary resistance to hydrogenation exhibited by phenyldihydrothebaïne and the methyldihydrothebaïnes.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

DIRECT INTRODUCTION OF THE AMINO GROUP INTO THE AROMATIC AND HETEROCYCLIC NUCLEUS. IV. THE ACTION OF THE ALKALI AND ALKALINE EARTH AMIDES ON SOME SUBSTITUTED QUINOLINES*

F. W. BERGSTROM

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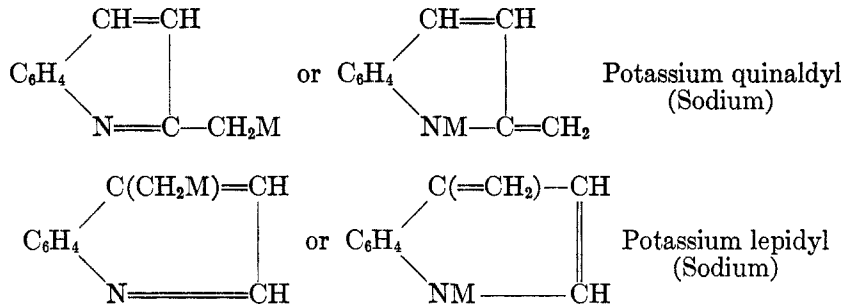
In continuation of previous work[1] a study has been made of the action of potassium amide on a number of substituted quinolines, with the ultimate goal in mind of determining the effect of various radicals on the rate of introduction of an amino group.

The methyl quinolines.—The alkali amides (MNH_2) react with solutions of 2- and 4-methylquinolines in liquid ammonia to form soluble salts of the formulas,[2]



These salts did not react with an excess of potassium amide, alone, or in the presence of potassium nitrate, to form amino derivatives. The presence of the anionic charge in or near the nucleus has doubtless prevented the introduction of an amino group.

Potassium amide (in excess) reacts with 6-, 7- or 8-methylquinolines in liquid ammonia to form tars or resins, even when the reaction is carried out in the presence of potassium nitrate. Poor yields of 2-amino-8-

* Presented in part at the Pittsburgh meeting of the American Chemical Society, 1936.

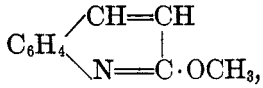
[1] (*a*) BERGSTROM, *J. Am. Chem. Soc.*, **56**, 1748 (1934); (*b*) BERGSTROM, *Ann.*, **515**, 34–42 (1934); (*c*) BERGSTROM, J. ORG. CHEM., **2**, 411–430 (1937).

[2] (*a*) BERGSTROM, *J. Am. Chem. Soc.*, **53**, 3027 (1931); (*b*) CHICHIBABIN, *Ber.*, **60**, 1607 (1927), first suggested that quinaldine and lepidine are tautomeric substances.

methylquinoline and of amino-6-methylquinoline are obtained by the action of barium amide on 8- and 6-methylquinoline, respectively, in spite of the fact that approximately the theoretical amount of hydrogen is evolved. It has proven impossible to prepare amino-7-methylquinoline.

The alkoxy- and dimethylaminoquinolines.—6-Methoxyquinoline appears to be converted to two amino-6-methoxyquinolines by potassium amide and potassium nitrate in liquid ammonia, although probably only a single product is formed with barium amide. It will be recalled[1c] that under similar conditions a mixture of 2- and 4-aminoquinolines is obtained by the action of potassium amide and potassium nitrate on quinoline, while barium amide yields only 2-aminoquinoline.

Amino-6-dimethylaminoquinoline is prepared from 6-dimethylaminoquinoline with the use either of barium amide or of potassium amide and potassium nitrate at a slower rate than 2-aminoquinoline is similarly formed from quinoline.

2-Methoxyquinoline,  contains the grouping, —C(=N—)OCH_3, present also in the imido ethers of Pinner, and is therefore to be regarded as a neutral cyclic aquo ammono ester.[3] In accordance with expectation, it is readily saponified by a solution of potassium amide in liquid ammonia to potassium-2-aminoquinoline and potassium methylate, that is, to a salt of a cyclic ammono acid ester and to an aquo alcoholate. It has been found impossible to prepare an amino-2-methoxyquinoline, because of the greater rapidity of the saponification just described.

An amino-8-ethoxyquinoline is obtained in fairly good yield by the action of barium amide on 8-ethoxyquinoline in liquid ammonia, although practically none is formed when potassium amide and potassium nitrate are used. In the latter case, 8-hydroxyquinoline was the only definite product obtained. The removal of a methoxyl group in position 2 is a much more rapid reaction.

The hydroxy- and aminoquinolines.—Neither 2-hydroxyquinoline, 8-hydroxyquinoline nor 2-aminoquinoline can be converted to amino derivatives by potassium amide, potassium amide and potassium nitrate, or barium amide in liquid ammonia at temperatures up to 110°. The hydroxy and amino groups therefore decrease the rate of introduction of an amino group into the quinoline nucleus, even though they increase the rate of bromination, nitration and sulfonation of the benzene ring.

[3] FRANKLIN, "The Nitrogen System of Compounds." The Reinhold Publishing Co., New York, **1935**, p. 263.

To explain this difference in behavior, it has been assumed that bromine the nitro and sulfonic acid groups are positively polarized when introduced into a molecule while the amino group is negatively polarized.[4] Nitric and sulfuric acids are kationoid reagents, whereas potassium amide is anionoid.

The quinoline carboxylic acids.—Quinaldic acid and cinchoninic acid react with potassium amide and potassium nitrate in liquid ammonia to form, respectively, 4-amino-quinoline-2-carboxylic acid and 2-amino-quinoline-4-carboxylic acid. Competition experiments, to be described in a subsequent article, have shown that the carboxyl group increases the rate of introduction of the amino group into the quinoline nucleus. Cinchoninic acid does not appear to react with barium amide, beyond the formation of a barium salt of very low solubility in ammonia. An amino-quinoline-6-carboxylic acid of unknown orientation is obtained by treating quinoline-6-carboxylic acid with potassium amide and potassium nitrate in liquid ammonia.

Quinolinesulfonic acids.—Quinoline-2-sulfonic acid reacts readily with potassium amide or with a mixture of potassium amide and potassium nitrate to form 2-aminoquinoline and potassium sulfite. It is known that 2-hydroxyquinoline is easily made by heating quinoline-2-sulfonic acid with dilute aqueous alkali.[16] It will be recalled that chlorine in the 2-position also has an enhanced reactivity, since 2-chloroquinoline is a cyclic acid chloride-ester of the ammonia system.

An aminoquinoline-6-sulfonic acid is readily obtained by treating quinoline-6-sulfonic acid with barium amide, or with potassium amide and potassium nitrate in liquid ammonia. It is isolated as the monohydrate.

EXPERIMENTAL

Reactions were carried out in liquid ammonia solution at room temperatures, unless otherwise mentioned, and in accordance largely with the methods of references 1*a* and 1*c*. All temperatures are uncorrected. Microanalyses were made by Weiler and Straus, Oxford.

Amino-6-methylquinoline.—Eleven and nine-tenths millimoles of barium amide and 10.2 millimoles of 6-methylquinoline† reacted for thirty days at room temperature[1a]. Six and five-hundredths millimoles of hydrogen was collected (59%). The tarry hydrolysate was boiled with sodium sulfate solution and filtered hot, colorless crystals, m.p. 142–145°, separating from the filtrate. Yield, 1.72 millimoles or 16.9%; m.p. 145.7–146.7°, after several recrystallizations from water.

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[4] INGOLD, *Rec. trav. chim.*, **48**, 809–810 (1929); BRADLEY AND ROBINSON, *J. Chem. Soc.*, **1932**, 1254.

[16] BESTHORN AND GEISZELBRECHT, *Ber.*, **53**, 1021–3 (1920).

† Obtained from the Eastman Kodak Company.

Anal. Calc'd for $C_{10}H_{10}N_2$: C, 75.89; H, 6.38; N, 17.72.
Found: C, 75.54; H, 6.30; N, 18.33.

Reaction also occurs with an excess of 6-methylquinoline, but more tar is formed.

Amino-8-methylquinoline.[6]—Fifteen and eight-tenths millimoles of barium amide reacted for 22 days with 10 millimoles of 8-methylquinoline.[1a] Seven and eighty-five-hundredths millimoles of hydrogen (78.4%) was obtained, the product being isolated as described above. Yield, 3.51 m. moles (35.1%); m.p. 85–7° crude, and 86.0–86.3°, after recrystallizations from water.

Anal. Calc'd for $C_{10}H_{10}N_2$: C, 75.89; H, 6.38; N, 17.72.
Found: C, 76.03; H, 6.29; N, 17.54.

The picrate was prepared in alcohol and crystallized from the same solvent; m.p. 242–243.5°.

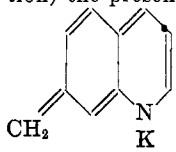
Anal. Calc'd for $C_{16}H_{13}N_5O_7$: C, 49.58; H, 3.38.
Found: C, 49.78; H, 3.52.

Amino-8-methylquinoline was diazotized in 25% sulfuric acid, and converted to hydroxy-8-methylquinoline by boiling; m.p. 214–215°, uncorr., as compared with 219–220° (corr.?) as given by Späth[5] for 2-hydroxy-8-methylquinoline. O. Fischer[6] prepared 2-amino-8-methylquinoline from 2-chloro-8-methylquinoline, but gave no melting point.

The rate of formation of hydrogen in the barium amide-8-methylquinoline reaction is somewhat increased by the addition of barium thiocyanate.

Barium amide reacts with an excess of 8-methylquinoline to form hydrogen and amino-8-methylquinoline, although more slowly than above.

7-Methylquinoline.—With a twofold excess of barium amide, hydrogen is formed (84.5%) but no amino derivative, or other definite product. Potassium amide reacts with 7-methylquinoline to form a solution which assumes several different colors, but no definite products were obtained therefrom. Attempts to prove (by alkylation) the presence of a potassium salt of a tautomeric form of 7-methylquinoline,



failed. No definite product was obtained by the action of an excess of potassium amide and potassium nitrate on 7-methylquinoline.

Amino-6-methoxyquinoline.—Seventeen and two-tenths millimoles of barium amide reacted for 26 days with 9.62 millimoles of 6-methoxyquinoline.†[1a] The hydrolysate of the reaction product was dissolved in dilute hydrochloric acid, and sulfuric acid added to precipitate barium. A crop of gray needles slowly separated from the filtrate of the barium sulfate upon addition of ammonia; m.p. 162–163°, crude, but 178.7–179.4° after several crystallizations from water (large volumes are required) and benzene. Yield, crude, 7.30 m. moles, or 75.9%; pure, 2.6 m. moles. The product is soluble in alcohol, and appears to be slowly oxidized by air.

Anal. Calc'd for $C_{10}H_{10}N_2O$: C, 68.93; H, 5.79; N, 16.09.
Found: C, 69.26; H, 5.89; N, 16.18.

Thirty-seven and six-tenths millimoles of potassium amide, 10.74 millimoles of 6-methoxyquinoline, and 18.0 millimoles of potassium nitrate reacted for 11 days (ref. 1*c*, expt. 11–15). The product, obtained in poor yield, and crystallized from

[5] SPÄTH, *Monatsh.*, **40**, 125 (1919).
[6] FISCHER, *Ber.*, **35**, 3679 (1902).

water, consisted of two products, partially separated by further crystallizations into material melting at 119–121.5° (colorless needles), and at 160–175°. It is probable that both 2- and 4-amino-6-methoxyquinolines are formed.

2-Methoxyquinoline.—Addition of potassium amide (17.2 millimoles) to 2-methoxyquinoline[7] (6.75 millimoles) in a two-legged tube gave an opaque red solution from which much colorless precipitate (CH_3OK) separated on standing. Although the reaction appeared to be complete in about half an hour, the tube was allowed to stand for twelve hours before evaporation of the solvent. The 2-aminoquinoline (3.44 millimoles, or 51%, m.p. 127.8–129.1°) obtained from the hydrolysate was purified by crystallization from water and identified by the melting point of a mixture with authentic material.

In a repetition of this reaction, with the addition of potassium nitrate, a slightly lower yield of 2-aminoquinoline was obtained, but no other product was isolated.

Amino-8-ethoxyquinoline.—Potassium amide (25.3 millimoles) was added to a liquid ammonia solution of anhydrous barium thiocyanate (26.1 millimoles) and 8-ethoxyquinoline[8] (10.39 millimoles) with continual shaking until the precipitate, at first very voluminous, had become more compact. It is necessary to have all of the barium thiocyanate in solution before the addition of the potassium amide. To prevent or minimize caking, the ammonia is distilled into both legs of the reaction tube at once, but if a cake is formed, it may be slowly dissolved by evaporating some solvent into the other leg of the reaction tube, distilling ammonia back into the leg containing the thiocyanate, and repeating as long as necessary. Although the reaction was apparently complete at the end of about nine hours (no hydrogen evolution), the tube was allowed to stand for one day.

The hydrolysate was dissolved in hot dilute hydrochloric acid (about 1:3) and filtered. The nearly colorless crystals obtained on cooling consisted largely of aminoethoxyquinoline, formed by hydrolysis of the hydrochloride. These were filtered and treated with excess ammonia. An additional small amount of product was obtained by addition of ammonia to the hydrochloric acid filtrates. Yield, 7.90 millimoles, or 76.1%, m.p. 211–212° after recrystallization from benzene (in which it is not very soluble).

Anal. Calc'd for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9.
Found: C, 70.08; H, 6.51; N, 14.77.

Less satisfactory results were obtained by using the coarser barium amide made from barium metal.

Thirty-nine and four-tenths millimoles of potassium amide, 12.19 millimoles of 8-ethoxyquinoline and 14.9 millimoles potassium nitrate reacted for two weeks (ref. 1c, expts. 11–15). A trace of amino-8-ethoxyquinoline was obtained, together with 2.02 millimoles of 8-hydroxyquinoline, m.p. 72.5–74°.

Amino-6-dimethylaminoquinoline.—6-Dimethylaminoquinoline[9] dissolves in liquid ammonia at room temperatures, but partially crystallizes at 0°. Potassium amide (27.8 millimoles) was added to a liquid ammonia solution of barium thiocyanate (13.8 millimoles) and 6-dimethylaminoquinoline (11.50 millimoles), in accordance with the method of the preceding section. The reaction was allowed to continue for 27 days. The hydrolysate of the reaction mixture was extracted several times with boiling benzene, the extracts being filtered and concentrated, whereupon silvery-

[7] FRIEDLÄNDER AND OSTERMAIER, *ibid.*, **15**, 336 (1882).
[8] VIS, *J. prakt. Chem.*, [2], **45**, 530 (1892).
[9] KNUEPPEL, *Ber.*, **29**, 706 (1896). M.p. 59–61°; Knueppel found 56°.

gray needles separated; yield, 3.90 millimoles, or 33.9%, m.p. 162.5–165°; m.p. after several crystallizations from dilute alcohol, 168.5–169.5° (water is also a suitable solvent for crystallization). The product is soluble in dilute hydrochloric acid.

In a repetition of the above reaction, in the presence of excess barium thiocyanate, a 22.4% yield of aminodimethylaminoquinoline was obtained in a ten-day reaction. About half of the dimethylaminoquinoline was recovered as crude material. Quinoline then appears definitely to react more rapidly with barium amide than does 6-dimethylaminoquinoline.

Anal. Calc'd for $C_{11}H_{13}N_3$: C, 70.54; H, 7.00; N, 22.46.
Found: C, 70.29; H, 7.04; N, 22.4.

Considerable tar was formed in the reaction of excess potassium amide and potassium nitrate with 6-dimethylaminoquinoline, together with a trace (1%) of aminodimethylaminoquinoline. (Method of ref. 1*c*, expts. 11–15.)

8-Hydroxyquinoline.—8-Hydroxyquinoline† reacts with ammonia gas to form a yellow ammonium salt, which is sparingly soluble in liquid ammonia, but readily soluble in an excess of potassium amide, forming a yellow solution. Potassium amide (40 millimoles), 8-hydroxyquinoline (11 millimoles) and potassium nitrate (15 millimoles) did not react to form an amino derivative (10 days); 4.6 millimoles of 8-hydroxyquinoline was recovered unchanged.

2-Hydroxyquinoline.—2-Hydroxyquinoline,† although not very soluble in liquid ammonia at room temperatures, dissolves readily in an excess of potassium amide. In a 130-day reaction between 42.5 millimoles of potassium amide, 10.4 millimoles of 2-hydroxyquinoline and 14.6 millimoles of potassium nitrate, no amino derivative was formed, 9.25 millimoles (89%) of the hydroxyquinoline being recovered at the end. Considerable nitrogen was formed.‡ Similar results were obtained (but no nitrogen was evolved) when the potassium nitrate was omitted

2-Aminoquinoline.—2-Aminoquinoline[1a] (9.80 millimoles) was added to barium amide (14.0 millimoles) prepared in a straight tube in accordance with the method of reference 1*c*, this being followed by 8.19 millimoles of anhydrous barium thiocyanate to serve as a catalyst; 5.50 millimoles of 2-aminoquinoline was recovered at the end, and no other product was isolated. A slight reaction was indicated by the collection of 0.12 millimole of hydrogen.

Potassium amide (59.6 millimoles), 2-aminoquinoline (17.4 millimoles) and potassium nitrate (21.0 millimoles) were heated for four days at 100–125°,[12] in the presence of the iron oxide catalyst used in making the potassium amide. Nitrogen was formed,‡ and most of the aminoquinoline (12.9 millimoles) was recovered at the end of the experiment.

4-Aminoquinoline-2-carboxylic acid.—Potassium amide (36.0 millimoles), potassium nitrate (16.7 millimoles), and quinoline-2-carboxylic acid† (8.84 millimoles) reacted in a two-legged tube (ref. 1*c*, expts. 11–15) for 0.9 day. The iron-iron oxide catalyst was filtered from the cold hydrolysate of the reaction product, and the filtrate acidified with acetic acid. Cream-colored needles were obtained when this filtrate was concentrated; m.p. about 280.5–281°, (decomp., CO_2 evol.); yield, 7.19 millimoles or 81.4%. The product was soluble in dilute pyridine, or in aqueous alkalies, but insoluble in cold or hot ethyl alcohol, butyl alcohol, acetone, or anhydrous pyridine. It can be crystallized from water.

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‡ $3KNH_2 + 3KNO_3$ $(+Fe_2O_3)$ $= 3KNO_2 + 3KOH + N_2 + NH_3$. Bergstrom, unpublished work.

[12] Blair, *J. Am. Chem. Soc.*, **48**, 90–2 (1926).

The 4-aminoquinoline-2-carboxylic acid was not obtained entirely free from water. Drying *in vacuo* at 100° resulted in slight decomposition.

Anal. Calc'd for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9.
Calc'd for $C_{10}H_8N_2O_2 \cdot 0.25\ H_2O$: C, 62.3; H, 4.45; N, 14.55.
Found (dried *in vacuo* at room temps.): C, 62.59; H, 4.50; N, 14.7.

Thirty-five-hundredths gram was heated in a test-tube just above the melting point for a few moments. The cooled melt was ground in a mortar, extracted with hot benzene, and filtered. From the cooled extracts, 0.12 g. of white crystals separated, m.p. 150–150.5°. Anhydrous 4-aminoquinoline melts at 154–155°.[10]

Anal. Calc'd for $C_9H_8N_2$: C, 75.0; H, 5.6; H, 19.4.
Found: C, 75.10; H, 5.64; N, 19.28.

Kynurenic acid—Fifty-two-hundredths gram of the amino acid was dissolved with warming in sulfuric acid (4 cc. of 1:1) and diazotized by slow addition of 0.25 g. sodium nitrite in 1 cc. of water. After half an hour at 0°, and an equal time at 100°, the solution was diluted with water, and the resultant light-yellow precipitate was collected by filtration. It was dissolved through the filter by dilute ammonia water, and reprecipitated by adding acetic acid; yield, 0.25 g.; m.p. within 2°, between about 260° and 290°,[11] depending upon the rate of heating.

Anal. Calc'd for $C_{10}H_7NO_3 \cdot H_2O$: C, 58.0; H, 4.3; N, 6.8.
Found: C, 58.25; H, 4.46; N, 6.57.

2-Aminoquinoline-4-carboxylic acid.—In accordance with the method of reference 1c, expts. 11–15, 52.4 millimoles of potassium amide, 16.7 millimoles of potassium nitrate and 13.05 millimoles of quinoline-4-carboxylic acid[13] were allowed to react for five days. The aqueous solution of the hydrolysate was filtered to remove the iron and iron oxide, and the filtrate was cooled and acidified with acetic acid. The light-brown precipitate was collected by filtration, and dissolved through the filter with dilute ammonia, leaving a small reddish residue. The filtrate was acidified with acetic acid, the resulting precipitate being dissolved in hot dilute hydrochloric acid. The hydrochloride separated as colorless needles which underwent partial hydrolysis when recrystallized from water. It was therefore dissolved in dilute ammonia, and the base was reprecipitated by addition of acetic acid; yield, 9.15 millimoles or 70.1%; m.p. 350–352°, crude.

Anal. Calc'd for $C_{10}H_8N_2O_2$: C, 63.80; H, 4.28; N, 14.90.
Found: C, 63.61; H, 4.39; N, 15.04.

The ethyl ester was prepared by refluxing the acid with a saturated alcoholic solution of hydrogen chloride gas, and crystallizing from alcohol; m.p. 191–2°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.60.
Found: C, 66.59; H, 5.50.

A small amount of the acid was decomposed just above its melting point, the cooled melt being crystallized from water; the melting point 127–128°, as was the melting point of a mixture with authentic 2-aminoquinoline[1a], showing their identity. Koenigs[14] prepared 2-hydroxyquinoline-4-carboxylic acid by heating cinchoninic acid with potassium hydroxide.

Potassium amide (29.9 millimoles) was added to barium thiocyanate (18.55 milli-

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[10] KOENIGS, *Ber.*, **40**, 2880 (1907).

[11] SPÄTH, *Monatsh.* **42**, 92 (1921), observed the same behavior.

[13] KOENIGS, *Ber.*, **12**, 97 (1879); PFITZINGER, *J. prakt. Chem.*, [2], **56**, 311 (1897). Prepared by W. L. Coffin and H. A. Rooney.

[14] KOENIGS, *Ber.* **12**, 99 (1879); **16**, 2152 (1883).

moles) and cinchoninic acid (7.40 millimoles), in a two-legged tube, the reaction being allowed to continue for 26 days. The hydrolysate of the reaction product was treated with excess dilute ammonia and filtered. Aminocinchoninic acid was precipitated from the filtrate by addition of a slight excess of acetic acid; yield, 0.915 millimoles, or 12.4%; m.p. 349–52°, crude. In a repetition (49-day reaction), the isolable product was a small amount of colorless solid; m.p. 211.4–212.4°.

Anal. Calc'd for $C_{10}H_9N_3O$: C, 64.2; H, 4.8; N, 22.4.
Found: C, 63.54; H, 5.03; N, 22.47.

Possibly this is the amide of 2-aminoquinoline-4-carboxylic acid.

Aminoquinoline-6-carboxylic acid.—Potassium amide (29.2 millimoles) potassium nitrate (10.5 millimoles) and quinoline-6-carboxylic acid[15] (6.59 millimoles) reacted for three days, in accordance with the method of reference 1*c*, expts. 11–15. The filtered, cold aqueous hydrolysate was acidified with acetic acid, the light-brown precipitate being collected and dried at 110°; yield, 4.17 millimoles, or 60.4%; m.p. 322–4°. It was purified by dissolving in dilute ammonia, filtering, and reprecipitating by addition of dilute acetic acid; it then melted at 323–324°.

Anal. Calc'd for $C_{10}H_8N_2O_2 \cdot 0.5\ H_2O$: C, 60.88; H, 4.60; N, 14.22.
Found (dried *in vacuo* at 80°): C, 60.77; H, 4.67; N, 14.13.

Loss in weight when dried *in vacuo* at 80° (referred to weight when dried *in vacuo* over concentrated sulfuric acid at 20°), 4.26%; calc'd for loss of 0.5 H_2O from $C_{10}H_8N_2O_2 \cdot H_2O$, 4.37%.

The product is soluble in dilute hydrochloric acid, ammonia or alkali hydroxides, but insoluble or very slightly soluble in hot or cold alcohol or pyridine or in dilute acetic acid, although it may be crystallized from glacial acetic acid. Attempts to decarboxylate it failed.

Quinoline-2-sulfonic acid.—Quinoline-2-sulfonic acid (7.27 millimoles)[16] reacts with ammonia to form an ammonium salt, moderately soluble at 0°. This salt reacts rapidly with potassium amide (24.6 millimoles; ref. 1*c*, expts. 11–15, potassium nitrate omitted) to form a finely-divided yellow precipitate. At the end of a half-day, ammonia was evaporated from the reaction tube, the product was hydrolyzed, and the hydrolysate was filtered hot. 2-Aminoquinoline crystallized, and was identified by the melting point of a mixture with authentic material (m.p. 128–129°); yield, 5.36 millimoles, or 73.8%. The filtrate of the last crop was evaporated to dryness and extracted with boiling benzene, leaving a residue of potassium sulfite. From the benzene, a substance of unknown structure was obtained, which, after several recrystallizations from this solvent, melted at 209–210°.

Anal. Calc'd for $C_{18}H_{12}N_2O_2$: C, 69.84; H, 6.19; N, 13.59.
Found: C, 69.81; H, 6.11; N, 13.59.

No product other than 2-aminoquinoline was obtained when the above reaction was carried out in the presence of potassium nitrate.

Aminoquinoline-6-sulfonic acid.—Quinoline-6-sulfonic acid[17] (crystallized twice from water and dried at 120–140°) reacts with ammonia gas to form an ammonium salt which is moderately soluble in liquid ammonia at room temperatures. A small insoluble residue indicates that the original sulfonic acid was not quite homogeneous. Potassium amide (44.0 millimoles) and potassium nitrate (14.9 millimoles) react with the sulfonic acid (10.5 millimoles) (ref. 1*c*, expts. 11–15) to form a deep-brown or yellow-brown solution, from which a solid (potassium hydroxide?) is slowly deposited. The reaction appears to be relatively rapid (time of reaction, 1.1 days).

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[15] SCHLOSSER AND SKRAUP, *Monatsh.*, **2**, 526 (1881).
[17] KNUEPPEL, *ibid.*, **29**, 707 (1896); HEPP, *ibid.*, **17**, 191 (1884).

The aqueous solution of the reaction product was filtered to remove the catalyst. An excess of ammonium chloride was added, and the solution was held near the boiling point for several hours to precipitate the aminoquinolinesulfonic acid (the ammonium salt is slowly hydrolyzed). The procedure was repeated twice. Yield, 4.19 millimoles, or 39.8%, m.p. above 354°. The product is insoluble or very slightly soluble in cold or hot glacial acetic acid, or absolute pyridine, although it may be crystallized from water (large volumes are required).

Anal. Calc'd for $C_9H_8N_2O_3S \cdot H_2O$: C, 44.57; H, 4.16; N, 11.56; S, 13.24.
Found: C, 44.72; H, 4.10; N, 11.27; S, 12.98 (dried *in vacuo* at 100°).

Potassium amide (28.6 millimoles) was added to a solution of quinoline-6-sulfonic acid (9.56 millimoles) and barium thiocyanate (20.4 millimoles). Hydrogen was visibly formed, the reaction appearing sensibly complete in a day or less, though the tube stood for 6 days before the product was worked up. The hydrolysate was treated with excess sodium carbonate, the barium carbonate being filtered and washed with water. To the filtrate, an excess of ammonium chloride was added, and the aminoquinolinesulfonic acid hydrate was slowly precipitated by heating. Purification was accomplished as described in the previous section; yield, 7.95 millimoles, or 83.1%.

SUMMARY

(1) Substituted quinolines have been converted to amino derivatives by the following methods: (*a*) treatment with barium amide alone or in the presence of barium thiocyanate in liquid ammonia at room temperatures, and (*b*) treatment with potassium nitrate and an excess of potassium amide under the same conditions. Potassium amide alone converts many of the substituted quinolines studied into tars and resins.

(2) The following compounds have been prepared for the first time (the amino group is probably in the 2 position, unless otherwise stated): amino-6-methylquinoline, amino-8-methylquinoline, amino-6-methoxyquinoline, amino-8-ethoxyquinoline, amino-6-dimethylaminoquinoline, 4-aminoquinoline-2-carboxylic acid, 2-aminoquinoline-4-carboxylic acid, aminoquinoline-6-carboxylic acid monohydrate, aminoquinoline-6-sulfonic acid monohydrate. 7-Methylquinoline could not be converted to an amino derivative.

(3) Potassium amide, or potassium amide and potassium nitrate together, react with quinoline-2-sulfonic acid, or with 2-methoxyquinoline to form 2-aminoquinoline. It is considered that the reaction with 2-methoxyquinoline is analogous to saponification of an ester.

(4) The hydroxyl and amino groups in position 2 prevent the introduction of an amino group into quinoline. 8-Hydroxyquinoline cannot be converted to an amino derivative by any of the methods described in this article. The 2- or 4-carboxyl group, on the other hand, increases the rate of introduction of an amino group.

[CONTRIBUTION FROM THE SCHOOL OF CHEMICAL TECHNOLOGY OF NORTH DAKOTA AGRICULTURAL COLLEGE]

PREPARATION AND USE OF COPPER-CHROMIUM-OXIDE CATALYSTS IN DEHYDROGENATIONS

RALPH E. DUNBAR

Received June 15, 1938

Investigations involving the dehydrogenation of various alcohols to the corresponding aldehydes have been reported from time to time. Bouveault[1] in 1908 reported the use of a copper catalyst but Conant, Webb, and Mendium[2] later found that while this catalyst was suitable for trimethylacetaldehyde and dimethylacetaldehyde, it was easily susceptible to poisoning. Oxide catalysts are less easily poisoned but require a higher temperature, induce a greater amount of dehydration, and do not retain their activity over as long a period. Among such catalysts are zinc oxide, zinc-chromium-oxide[3] and copper-chromium-oxide.[4] Adkins, Kommes, Struss, and Dazler[5] report a special type of equipment for these dehydrogenations using the copper-chromium-oxide catalyst. In this equipment the alcohol was fed by gravity through a horizontal tube at the rate of one to two ml. per minute. The unchanged alcohol was recovered by fractionation and again passed through the equipment. The yields of aldehyde, based upon the amount of alcohol passed once over the catalyst, ranged from 28 to 35 per cent. In using this equipment the catalyst was pressed into pellets of approximately 0.15 gram each.

In the dehydrogenation of alcohols there are at least four rather important types of reactions which occur when alcohols are passed over catalysts of this type, *i.e.*, (I) dehydrogenation; (II) dehydration; (III) aldol condensation, possibly followed by dehydration; and (IV) ester formation by the Tischtchenko reaction, *i.e.*,

(I) $$n\text{-}C_4H_9OH \rightarrow n\text{-}C_3H_7CHO + H_2$$

(II) $$n\text{-}C_4H_9OH \rightarrow C_4H_8 + H_2O$$

(III) $$2\ n\text{-}C_3H_7CHO \rightarrow CH_3CH_2CH_2CH(OH)CH(C_2H_5)CHO$$
$$\rightarrow CH_3CH_2CH_2CH{=}C(C_2H_5)CHO + H_2O$$

(IV) $$2\ n\text{-}C_3H_7CHO \rightarrow n\text{-}C_3H_7COOC_4H_9\text{-}n$$

[1] BOUVEAULT, *Bull. soc. chim.*, [4], **3**, 119 (1908).
[2] CONANT, WEBB, AND MENDIUM, *J. Am. Chem. Soc.*, **51**, 1250 (1929).
[3] ADKINS, FOLKERS, AND KINSEY, *ibid.*, **53**, 2714 (1931).
[4] WESTON, AND ADKINS, *ibid.*, **50**, 1930 (1928).
[5] ADKINS, KOMMES, STRUSS, AND DAZLER, *ibid.*, **55**, 2292 (1933).

The various types of equipment previously described for these dehydrogenations are either unnecessarily complicated or possess limited possibilities. The formation of the catalyst into pellets is also extremely laborious and time-consuming. For these reasons it seemed advisable to modify and improve, if possible, the type of equipment, and to find a suitable support for the catalyst that would eliminate the operation of forming pellets from the catalyst. It was also hoped that the yields might be increased.

EXPERIMENTAL

The best results in the preparation of this catalyst have been achieved by precipitating and decomposing with heat the catalyst in the presence of finely divided porous material that might serve as a carrier for the catalyst. The following method has been found to be most satisfactory, after experimenting with numerous possibilities. Two solutions were prepared as follows. (*A*) Three hundred milliliters of a solution containing 87 g. of cupric nitrate trihydrate and 10.4 g. of barium nitrate. The barium nitrate was first dissolved in the least amount of water possible at a temperature near the boiling point of the water. The cupric nitrate trihydrate was then added, and the solution was diluted to 300 ml. Solution (*B*) was prepared from 300 ml. of a solution containing 50.4 g. of ammonium dichromate and 75 ml. of a twenty-eight per cent. solution of ammonium hydroxide. Solution (*A*) was heated to 80°, and 177 g. of the carrier was added. Thus far three of these inert carriers have been used, namely acid-washed Italian pumice of mesh 20; Activated Alumina, Grade A, 8 to 14 mesh size, supplied by the Aluminum Ore Company, of East St. Louis, Ill.; and Johns-Manville Celite, Grade C-12, 212 supplied by the Johns-Manville Co., of Manville, N. J. This solution (*A*) was then digested for several hours on a steam bath in the presence of the carrier and with frequent stirring. Water was added to compensate for evaporation. While solution (*A*) was still at a temperature of approximately 80° solution (*B*) was slowly added with thorough stirring. Solution (*B*) at no time was heated above room temperature. The precipitate formed and the carrier were then separated by suction filtration, and dried with frequent stirring over a period of 24 hours in an oven at a temperature of 70–80°. The treatment from this point on was similar to that of Connor, Folkers, and Adkins[6] except that the product was thoroughly stirred in the moist condition each time to obtain a uniform distribution of the catalyst over the carrier, and also in that the final decomposition was carried out in five portions with very slow, cautious heating and continual stirring. Lazier and Vaughen[7] have found that the final heat treatment materially affects the activity of the catalyst. The material was then leached with 600 ml. of ten per cent. acetic acid and washed with six 600-ml. portions of water. The catalyst, after drying at 125°, was sifted on a twenty-mesh sieve before use to remove the fine material. The material that did not pass through the sieve was used for the dehydrogenation of the normal butanol. The yields of catalyst using this method averaged 220 g.

The equipment used in these dehydrogenations was similar to that described by Conant[8]. The tube of the dehydrogenator was a 15-mm. Pyrex tube with four

[6] CONNOR, FOLKERS, AND ADKINS, *ibid.*, **54**, 1138 (1932).

[7] LAZIER AND VAUGHEN, *ibid.*, **54**, 3080 (1932).

[8] CONANT, "The Chemistry of Organic Compounds," The Macmillan Co., New York City, **1933**, p. 106.

indentations near the bottom to support the catalyst. A side-arm was sealed to the upper end. The capacity of the tube for catalyst was approximately 50 ml. The dehydrogenator was wrapped with one layer of asbestos paper, then with 30 feet of B. and S. gauge No. 22 chromel wire (22 ohms), and finally with six layers of asbestos paper. The ends of the chromel wire were attached to binding posts, firmly imbedded in the asbestos paper. The whole was held in place by wrapping with electrician's tape. For the final separation of the products from each determination an eight-inch Widmer column was used.

Representative determinations for the three carriers previously suggested are tabulated in Table I. All values included are the average of several determinations. One hundred grams of *n*-butanol was used in each determination. The temperature of the catalyst at all times was maintained at 330° to 350°. The values for butylene

TABLE I

PRODUCTS RECOVERED BY THE DEHYDROGENATION OF 100 G. *n*-BUTANOL

PRODUCTS	PUMICE	ALUMINA	CELITE
n-Butraldehyde (b.p. 72.5–77°)	54.6 g.	31.5 g.	56.7 g.
n-Butanol (b.p. 113–117°)	14.3 g.	19.9 g.	30.0 g.
n-Butyl butrate (b.p. 160–163°)	10.5 g.	17.1 g.	1.0 g.
Condensation products (above 180°)	1.8 g.	6.4 g.	1.5 g.
Gases collected	26.1 l.	18.0 l.	17.9 l.
Water	2.7 g.	4.8 g.	0.7 g.
Butylene	3.2 l.	5.8 l.	0.9 l.
	8.0 g.	14.6 g.	2.2 g.
Hydrogen, by difference	22.9 l.	12.2 l.	17.0 l.
Theoretical hydrogen	17.0 l.	9.8 l.	17.6 l.
	1.6 g.	0.9 g.	1.6 g.
Total products recovered	93.5 g.	95.2 g.	93.7 g.
Mechanical loss	6.5 g.	4.8 g.	6.3 g.

are derived theoretically from the amount of water recovered, although they agree closely with values obtained by the analysis of the escaping gas, from representative runs.

All values tabulated in Table I represent actual amounts of material obtained directly or by fractionation from the reaction mixture. *n*-Butanol was selected for a study of the effectiveness of this equipment and catalyst, largely because of its tendency to give consistent yields of aldehyde and a minimum yield of unsaturated hydrocarbon and ester. The yields of butyraldehyde reported do not necessarily represent maximum yields possible but merely averages under normal operating conditions. High percentages of *n*-butyl butrate and other condensation products are of course undesirable, and the Celite is definitely superior in this respect. The rates and amounts of gases collected, which is normally and predominately hydrogen, may be used as a measure of the effectiveness of the catalyst while the equipment is in actual operation. The greater the amount of water, naturally, the greater the amount of butylene, since both result from the dehydration of the butanol. The

dehydration of any aldol formed would also produce a proportionate amount of water. When all facts and products are considered it is quite obvious that the Celite catalyst is definitely the superior catalyst. The 56.7 g. of aldehyde collected does not necessarily represent the maximum yield possible, because of the large amount of unreacted butanol yet available, and the small amounts of the condensation products produced. It has also been found that the ester produced can be easily saponified by the use of solid potassium hydroxide at the conclusion of each run, and thus noticeably increase the amount of the aldehyde produced. No final information is yet available as to the possible life of these catalysts. Runs with each varying from 3 to 15 hours continuous use show little if any deterioration either in terms of noticeable reduction or decreased activity.

SUMMARY

Copper-chromium-oxide catalysts can be conveniently precipitated upon inactive material as an adequate support where this catalyst is used in the dehydrogenation of *n*-butanol, and other similar alcohols. The supporting materials studied can be arranged in the increasing order of effectiveness as alumina, pumice, and celite. The catalyst retains its activity well over prolonged periods.

A satisfactory arrangement of equipment for such dehydrogenations has been described.

Temperatures of 330° to 350° appear to be superior to lower temperatures, previously used by other investigators, with this catalyst and equipment for the dehydrogenation of *n*-butanol.

An efficient fractionating column for the separation of the aldehyde and alcohol during the dehydrogenation is extremely desirable for the maximum yields of aldehyde.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE,
REHOVOTH, PALESTINE]

REMARKS ON THE FINE-STRUCTURE DETERMINATION OF AROMATIC COMPOUNDS

ERNST BERGMANN AND TOBIAS BERLIN

Received May 25, 1938

Wilson Baker[1] in a series of remarkable papers, has shown that the formation of chelate structures in aromatic *o*-hydroxyketones involves a rigid double bond between the nuclear carbon atoms bearing the hydroxyl and the carboxyl groups, respectively, as in I. This fact can be understood in terms of the electronic theory of aromatic substitution.

In the same way, the ability of aromatic *o*-hydroxyaldoximes and ketoximes to form insoluble complex cupric derivatives, will be ascribed to energy considerations favoring a system like II. (This is the more general aspect of the argument advanced by Feigl and Bondi[2] that the difference in behavior of salicylaldoxime and of, *e.g.* $CH_3 \cdot CHOH \cdot CH_2 \cdot C(=NOH) \cdot CH_3$, is due to "differences in spatial structure and acidity, caused by the aromatic bonds"). The formation, for example, of an insoluble oxime-copper derivative from ethyl 1-acetyl-2-hydroxy-3-naphthoate, will be expressed satisfactorily by the formula III in which one of the naphthalenic double bonds is fixed in the 1,2 position. That this is the normal structure of the naphthalene nucleus, has been proved before by Fieser and Lothrop,[3] and by Bergmann and Hirshberg.[4] There seems to be an exception, already classic, to that rule: 2-naphthol is carbonated at higher temperatures in the 3 position. As the Kolbe synthesis proceeds via an acid carbonate by intramolecular rearrangement—it is completely analogous to the Fries reaction—and as migration in such rearrangements proceeds along a double bond, the above synthesis involves a double bond between the carbon atoms 2 and 3 of the naphthalene nucleus. On the basis of that exceptional structure it is easily explained that 2-hydroxy-3-naphthoic acid and 2-hydroxy-3-acetylnaphthalene are yellow: an *o*-quinonoid system is terminated by a hydroxyl group (*e.g.* IV). This formulation appears to be proved by our observa-

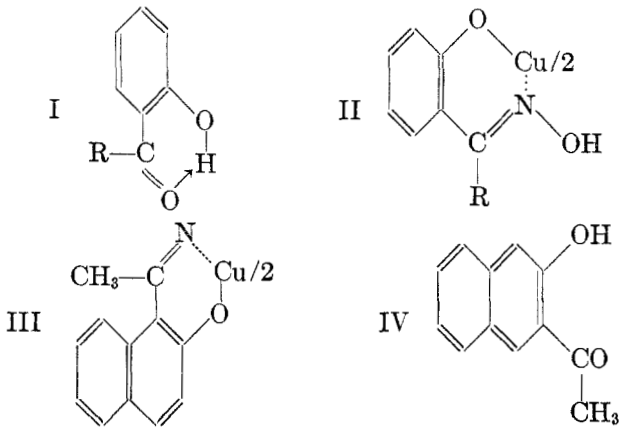
[1] BAKER, *J. Chem. Soc.*, **1934**, 1684; **1935**, 628; **1936**, 274, 346.

[2] EPHRAIM, *Ber.*, **63**, 1928 (1930); **64**, 1210 (1931); MEISENHEIMER, THEILACKER, AND BEISSWENGER, *Ann.*, **495**, 249, (1932). Compare PFEIFFER, BUCHHOLZ, AND BAUER, *J. prakt. Chem.*, [2], **129**, 163 (1931).

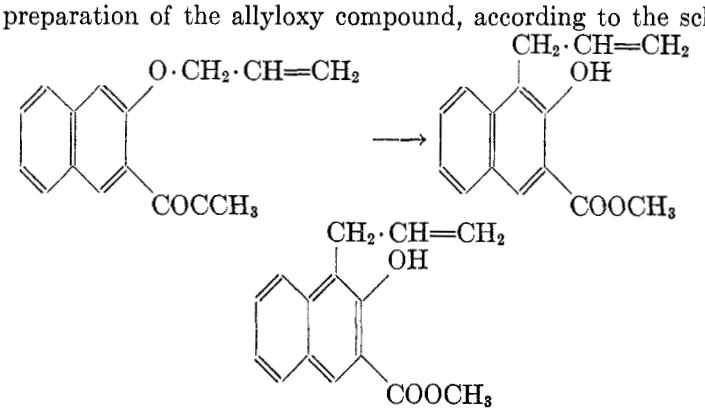
[3] FIESER AND LOTHROP, *J. Am. Chem. Soc.*, **57**, 1459 (1935).

[4] BERGMANN AND HIRSHBERG, *J. Chem. Soc.*, **1936**, 331.

tion, that 2-hydroxy-3-acetylnaphthalene oxime gives an insoluble, brownish-yellow copper derivative.[5]



This anomalous structure of the naphthalene system, which most probably occurs not only in the above oxime, but also in the corresponding ketone and in 2-hydroxy-3-naphthoic acid, is apparently stabilized by the formation of a chelate system as in I and II. Accordingly, in a derivative containing no free hydroxyl group, the double bonds should extend from C_1 to C_2 and C_3 to C_4, as usual. This conclusion has been verified in studying the rearrangement of methyl 2-allyloxynaphthalene-3-carboxylate. It is known[6] that allyl ethers rearrange exclusively via a double bond; were the double bond therefore extended between C_2 and C_3 in the above allyloxy compound, no rearrangement could take place. Actually, methyl 1-allyl-2-naphthol-3-carboxylate is formed, in the course of the preparation of the allyloxy compound, according to the scheme:

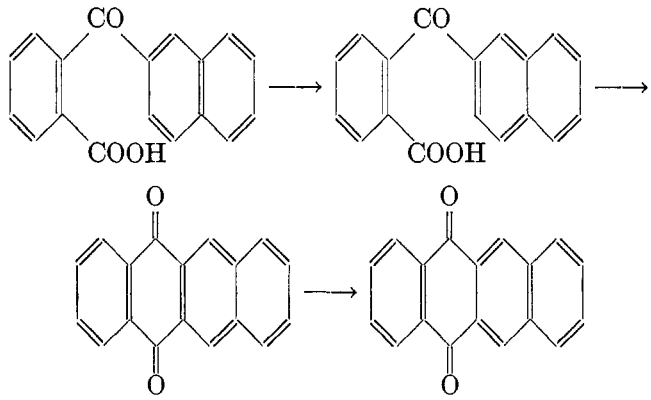


[5] According to JAFFE AND KRYLOWA (*Chem. Zentr.*, **1937**, I, 2590), 2-hydroxy-3-naphthoic acid forms a complicated complex compound on reaction with ferric chloride.

[6] FIESER AND CO-WORKERS, *J. Am. Chem. Soc.*, **53**, 4120 (1931); **57**, 1459 (1935); **58**, 749 (1936). Compare CLAISEN, *Ber.*, **45**, 3157 (1912).

The constitution of the rearrangement product was proved by decarboxylation in boiling quinoline; instead of 1-allylnaphthol-2, the isomeric coumarane was obtained, similar observations having been reported recently by Hill, Short, and Stromberg.[7]

In other instances, the anomalous distribution of double bonds may occur as a transitory intermediate stage. The formation, *e.g.*, of 2,3-benzanthraquinone from *o*-(2-naphthoyl)benzoic acid, which we found to occur under the drastic conditions of an aluminum chloride-sodium chloride melt, or the synthesis of hydroxynaphthacenequinones according to the method of Ch. Weizmann,[8] involves that during the ring closure the double bond of the non-acidic part of the molecules extend between the bridge heads of the newly-formed ring system—but we know at least in the case of 2, 3-benzanthraquinone[9] that the double bond after cyclization rearranges into its "normal" position:



The above results suggest the utilization of the Ephraim reaction not only for the determination of copper by means of aromatic structures, but for the determination of aromatic structures by means of copper, also in the case of other polycyclic ring-systems.[10,11]

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[7] HILL, SHORT, AND STROMBERG, *J. Chem. Soc.*, **1937**, 937.

[8] WEIZMANN AND CO-WORKERS, *Ber.*, **36**, 547 (1903); *J. Chem. Soc.*, **91**, 1588, 1622 (1907); **95**, 279 (1909); 1938, in press.

[9] ALLEN AND GILMAN, *J. Am. Chem. Soc.*, **58**, 937 (1936).

[10] Compare, for other methods, FIESER AND CO-WORKERS, *ibid.*, **53**, 4120 (1931); **58**, 749, 2050 (1936).

[11] In two recent papers (*J. Chem. Soc.*, **1937**, 476, 479), WILSON BAKER has applied his method set out above to the systems of hydrindene and naphthalene. His experiments with 2-hydroxy-3-acetylnaphthalene are in complete accordance with the above-reported results.

EXPERIMENTAL

Copper derivative of 2-hydroxy-3-acetylnaphthalene oxime.—For the preparation of the oxime, a solution of 2-hydroxy-3-acetylnaphthalene[12] (0.50 g.) and anhydrous sodium acetate (0.23 g.) in the minimum amount of alcohol was mixed with a concentrated aqueous solution of hydroxylamine hydrochloride (0.20 g.) and kept at room temperature for 12 hours. Then, the alcohol was distilled off, the residue was extracted with ether, the ethereal layer was washed with soda solution and evaporated, and the residue was recrystallized from benzene; m.p. 151°. (Found: C, 71.6; H, 5.9. $C_{12}H_{11}O_2N$ requires: C, 71.6; H, 5.5.) To the solution of the oxime in dioxane was added a few drops of glacial acetate acid and the necessary quantity of aqueous cupric acetate solution. The brown precipitate was collected, washed with alcohol and ether and dried. Found: C, 62.4; H, 4.7; Cu, 13.6 (the ash was considered as cupric oxide). $C_{24}H_{20}O_4N_2$ requires: C, 62.1; H, 4.3; Cu, 13.8.

Methyl 1-allyl-2-naphthol-3-carboxylate.—Methyl 2-hydroxy-3-naphthoate[13] (5 g.) in acetone (25 cc.) was boiled for 2 hours with allyl bromide (4.6 g.) and sodium hydroxide (1.08 g.) dissolved in a few drops of water. The acetone was evaporated, the residue was taken up in ether, and the solution freed of phenolic and acidic substances by means of sodium hydroxide solution, and then evaporated. The product, after distillation *in vacuo* (b.p. 162–164°/0.4 mm.) crystallized on trituration with methyl alcohol. From the same solvent or from light petroleum (b.p. 40–80°), prisms, m.p. 60°. (Found: C, 74.6; H, 6.1. Calc'd for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8.) As can be seen from the insolubility in alkali, the substance is cryptophenolic in character, but it exhibits an intense dark-blue color-reaction with alcoholic ferric chloride solution, exactly like the allyl-free compound. That the substance still contains the allyl group, and has not been rearranged into a propenyl compound, follows from the observation that it gives no precipitate with mercuric acetate.[14]

The acetyl derivative, prepared by boiling the ester with 10 times its weight of acetic anhydride for 5 hours, is a viscous oil, b.p. 170°/0.3 mm., which gives no ferric chloride reaction. (Found: C, 72.0; H, 5.9 Calc'd for $C_{17}H_{16}O_4$: 71.9; H, 5.6.)

1-Allyl-2-hydroxy-naphthalene-3-carboxylic acid.—The ester (4g.) was refluxed with 25% alcoholic potash solution (4g.) for 15 minutes.[15] The mass was poured out into water, and the solution was acidified. From ligroin long needles, m.p. 203°; yield 2.2 g. (Found: C, 73.9; H, 5.6 Calc'd for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3.)

1-Methyl-1,2-dihydro-α-naphthofuran.—The acid (1.8 g.) was refluxed for 3 hours with quinoline (10 cc.) and basic cupric carbonate[16] (0.15 g.), and the mass was poured out into cold dilute hydrochloric acid. The precipitate was dissolved in ether, washed with soda solution, and distilled; b.p. 125°/2 mm.; n_D^{29} 1.6177. According to its non-reaction with bromine, the yellowish oil has no double bond (Found: C, 84.7; H, 7.0. Calc'd for $C_{13}H_{12}O$: C, 84.8; H, 6.5). The same substance was obtained when 1-allyl-2-naphthol (1 g.) was refluxed with quinoline (6 cc.) and basic cupric carbonate (0.1 g.) for 3 hours; $n_D^{29.2}$ = 1.6160. This experiment supports our

[12] FRIES AND SCHIMMELSCHMIDT, *Ber.*, **58**, 2838 (1925). The m.p. of the hydroxyketone has been found at 121°, not at 112°.

[13] COHEN AND DUDLEY, *J. Chem. Soc.*, **97**, 1748 (1919); m.p. 79°.

[14] Compare BALBIANO AND TAOLINI, *Ber.*, **35**, 2994 (1902); **36**, 3575 (1903).

[15] CLAISEN, *ibid.*, **45**, 3165 (1912).

[16] FIESER, *J. Am. Chem. Soc.*, **58**, 2322 (1936).

view that the above coumarane is formed in a secondary reaction from 1-allyl-2-naphthol.

Methyl 1-cinnamyl-2-hydroxy-3-naphthoate.—Methyl 2-hydroxy-3-naphthoate (5 g.) was refluxed with cinnamyl bromide (9.8 g.) and sodium hydroxide (1.08 g.) in acetone solution (25 cc.) and worked up as above. The resulting oil was distilled *in vacuo*, and then crystallized, on trituration with methyl alcohol and a little acetone. From methyl alcohol, long, slender needles, m.p. 132°; yield, 0.5 g. (Found: C, 78.7; H, 6.1. Calc'd for $C_{21}H_{18}O_3$: C, 79.2; H, 5.6.)

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY
MICHIGAN STATE COLLEGE]

CONDENSATION OF ALIPHATIC ALCOHOLS WITH AROMATIC COMPOUNDS IN THE PRESENCE OF ALUMINUM CHLORIDE. II. TERTIARY ALIPHATIC ALCOHOLS AND BENZENE

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It has been shown that unsaturation of the *alpha* carbon atom of alcohols favors condensation of these compounds with aromatic hydrocarbons or phenols in the presence of anhydrous aluminum chloride. The unsaturation may be due to an aromatic ring[1], a simple double bond[2], or strain in a polymethylene ring[3].

A second factor which was found to influence the ease with which an alcoholic hydroxyl will combine with the hydrogen of an aromatic ring is the accumulation of alkyl radicals on the carbinol carbon. Under the experimental conditions described saturated primary aliphatic alcohols do not condense, simple secondary alcohols give a 25–30 per cent. yield of the secondary alkyl benzene, while *tert.*-butyl alcohol gives a 60–70 per cent. yield of trimethylphenylmethane[4, 5].

The following alcohols were condensed with benzene: *tert.*-butyl alcohol, *tert.*-amyl alcohol, the three *tert.*-hexyl alcohols, and the seven *tert.*-heptyl alcohols. Physical constants were carefully determined and are discussed in their relationship to structure.

EXPERIMENTAL

The technique used in all condensations was similar to that described in an earlier paper[4]. One-eighth of a mole (0.5 equivalent) of $AlCl_3$ (C.P. white) was suspended in 1.25 mole (5 equivalents) of thiophene-free benzene in a three-necked round-bottomed flask provided with mercury-sealed mechanical stirrer, a reflux condenser, and a dropping funnel. The mixture was vigorously stirred while 0.25 mole (1 equivalent) of the carbinol was added drop by drop. The temperature was maintained at 20–30°. The usual reaction phenomena were exhibited: hydrochloric acid was evolved, and the reaction mixture turned a deep red. After standing overnight, the mixture was decomposed with ice and a little hydrochloric acid. The benzene layer was removed, and the aqueous portion was extracted with ether.

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[1] HUSTON AND FRIEDEMANN, *J. Am. Chem. Soc.*, **38**, 2527 (1916); **40**, 785 (1918); HUSTON, *ibid.*, **46**, 2775 (1924).

[2] HUSTON AND SAGER, *ibid.*, **48**, 1955 (1926).

[3] HUSTON AND GOODEMOOT, *ibid.*, **56**, 2432 (1934).

[4] HUSTON AND HSIEH, *ibid.*, **58**, 439 (1936).

[5] TZUKERWANIK, *J. Gen. Chem.* (U. S. S. R.), **5**, 117, 764, 767 (1935).

Ether and benzene were removed from the combined extract by distillation and the residue was fractionated through a 30-cm. column, generally under reduced pressure.

Trimethylcarbinol.—Yield of 2-methyl-2-phenylpropane,[6] 65–70%.

The residues from several condensations, boiling above 170°, were combined and fractionated. That portion which came over at 230–240° (736 mm.) solidified, and melted after recrystallization from alcohol at 77–78° (white plates). It was identified as *p*-di-*tert.*-butylbenzene.

Dimethylethylcarbinol.—After about half of the alcohol had been added, there was formed a dark-colored coagulum which made stirring difficult. When the temperature was allowed to rise to 30–32° this mass broke up, and the reaction proceeded with the elimination of much hydrochloric acid. The yield of 2-methyl-2-phenylbutane[7] was approximately 60%. The small residue did not yield a constant-boiling fraction.

Dimethyl-n-*propylcarbinol.*—The 2-methyl-2-phenylpentane[8], was collected at 86–88° (15 mm.) in a yield of approximately 55%. At atmospheric pressure (745 mm.) it boiled at 205–206°.

Dimethylisopropylcarbinol[9].—Fractionation was carried out at 15 mm. A somewhat smaller yield of condensation product, 2-3-dimethyl-2-phenylbutane (b. p. 86–87° 15 mm.), was obtained (35%). This decrease in yield is attributed to the accumulation of radicals on a carbon adjacent to the carbinol carbon.

Anal. Calc'd for $C_{12}H_{18}$: C, 88.81; H, 11.19; mol. wt., 162.
Found: C, 88.69; H, 11.13; mol. wt., 165.

Methyldiethylcarbinol.—This carbinol was prepared from ethylmagnesium bromide and ethyl acetate[10]. Condensation with benzene gave a 40% yield of 3-methyl-3-phenylpentane[11] which came over at 86–88° (15 mm.).

Dimethyl-n-*butylcarbinol*[12].—During the extraction of the aqueous portion of the reaction product with ether an emulsion was formed, which was broken up by the addition of hydrochloric acid. After removal of the ether and benzene from the combined extracts, fractionation was carried out at 20 mm. The first fraction (30–106°) gave positive tests for unsaturation and for chloride. From it was isolated a small amount of 2-chloro-2-methylhexane[13]; b.p. 132° (740 mm.), 39–40° (20 mm.); n_D^{20}, 1.4210. As a check the chloride was prepared from the carbinol by saturation with dry hydrochloric acid.

The main product of the condensation, 2-methyl-2-phenylhexane, came over at 106–109° (20 mm.); yield 45%.

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37; mol. wt., 176.
Found: C, 88.61; H, 11.44; mol. wt., 169.

Dimethylisobutylcarbinol[14].—A considerable fraction came over at 33–40° (20 mm.).

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[6] VERLEY, *Bull. soc. chim.*, [3], **19**, 72 (1898); BOEDTKER, *ibid.*, [3], **31**, 966 (1904); SCHRAMM, *Monatsh.*, **9**, 615 (1888); SHOESMITH AND MACKIE, *J. Chem. Soc.*, 2334 (1938).

[7] GLEDITSCH, *Bull. soc. chim.*, [3], **35**, 1094 (1906).

[8] SCHREINER, *J. prakt. Chem.*, [2], **82**, 293 (1910).

[9] DELACRE, *Bull. acad. roy. Belg.*, **1906**, 7; LINDER, *Monatsh.*, **32**, 419 (1911).

[10] HENRY, *Rec. trav. chim.*, **26**, 94 (1907).

[11] SCHREINER, *J. prakt. Chem.*, [2], **82**, 295 (1910).

[12] WHITMORE AND CHURCH, *J. Am. Chem. Soc.*, **55**, 1119 (1933).

[13] DEWAEL, *Bull. acad. roy. Belg.*, **1908**, 957.

[14] EDGAR, CALINGAERT, AND MARKER, *J. Am. Chem. Soc.*, **51**, 1483 (1929).

This gave a positive test for unsaturation but consisted for the most part of 2-chloro-2,4-dimethylpentane which boiled after repeated fractionation at 33–34° (20 mm.). When boiled at atmospheric pressure it decomposed[15], liberating hydrochloric acid; n_D^{20}, 1.4239. The condensation product of the carbinol and benzene came over at 100–102° (20 mm.), 216–218° (746 mm.); $n_D^{1.65}$, 1.4940. The yield of 2,4-dimethyl-2-phenylpentane[16] was approximately 30%.

Dimethyl-sec.-*butyl-carbinol*[14].—From the first fraction, which contained some unsaturated compounds, there was isolated 2-chloro-2,3-dimethylpentane boiling at 38–39° (20 mm.); n_D^{20}, 1.4264; yield, 10%.

The main product of condensation, 2,3-dimethyl-2-phenylpentane, came over at 105–107° (20 mm.); yield, 20%.

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37; mol. wt. 176.
Found: C, 88.03; H, 11.33; mol. wt. 167.

Dimethyl-tert.-*butylcarbinol*[17].—Between 60° and 104° (20 mm.), a considerable fraction came over which gave positive tests for unsaturation and chloride. The condensation product, 2,3,3-trimethyl-2-phenylbutane was formed in the smallest yield (7%) of any of the isomers. It came over at 105–108° (20 mm.), and was purified with difficulty.

Anal. Calc'd for $C_{12}H_{20}$: C, 88.63; H, 11.37; mol. wt., 176.
Found: C, 88.34; H, 11.47; mol. wt., 169.

Methylethyl-n-*propylcarbinol*[17].—A small amount (3 g.) of 2-chloro-2-ethylpentane[18] was isolated from the low-boiling unsaturated fraction; b. p. 41° (20 mm.); n_D^{20}, 1.4283. This was also prepared from the carbinol and hydrochloric acid.

2-Ethyl-2-phenylpentane was produced in 40% yield; b.p. 100° (15 mm.); 106–107° (20 mm.); n_D^{20}, 1.4964; n_D^{25}, 1.4985. Since these constants do not agree with those given in the literature[19] the compound was analyzed.

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37.
Found: C, 88.23; H, 11.44.

Methylethylisopropylcarbinol[20].—A 14% yield of 3-chloro-2,3-dimethylpentane[21] was isolated from the low-boiling fraction; b. p. 41–42° (20 mm.). A 22% yield of 2,3-dimethyl-2-phenylpentane came over at 105–107° (20 mm.).

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37; mol. wt., 176.
Found: C, 88.26; H, 11.42; mol. wt., 166.

Trimethylcarbinol[22].—A small amount of 3-chloro-3-ethylpentane[23] (2%) was recovered; b.p. 43–44° (20 mm.); n_D^{20}, 1.4320.

The condensation product, 3-ethyl-3-phenylpentane, came over at 107–108° (20 mm.). It boiled at 225–226° (745 mm.); n_D^{20}, 1.4975; n_D^{25}, 1.4953. These constants do not agree with those given by Schreiner[23]. The yield was 40%.

Anal. Calc'd for $C_{13}H_{20}$: C, 88.63; H, 11.37.
Found: C, 88.37; H, 11.41.

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[15] SCHREINER, *J. prakt. Chem.*, [2], **82**, 294 (1910).
[16] SCHREINER, *ibid.*, [2], **82**, 294 (1910).
[17] WHITMORE AND BADERTSCHER, *J. Am. Chem. Soc.*, **55**, 1559 (1933).
[18] SCHREINER, *J. prakt. Chem.*, [2], **82**, 296 (1910).
[19] HALSE, *ibid.*, [2], **89**, 452 (1914).
[20] WHITMORE AND EVERS, *J. Am. Chem. Soc.*, **55**, 812 (1933).
[21] KASCHIRSKY, *J. Russ. Phys.-Chem. Soc.*, **13**, 90 (1883).
[22] MOYER AND MARVEL, *Organic Synthesis*, Vol. XI, p. 98.
[23] SCHREINER, *J. prakt. Chem.*, [2], **82**, 296 (1910).

TABLE I

BOILING POINTS, DENSITIES AND MOLECULAR VOLUMES

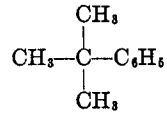
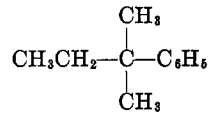
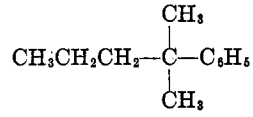
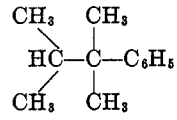
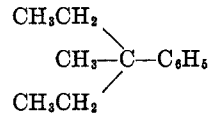
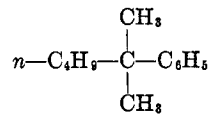
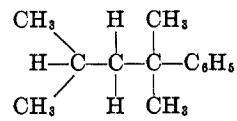
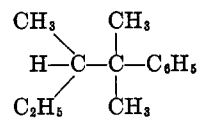
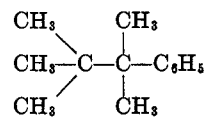
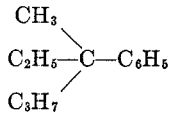
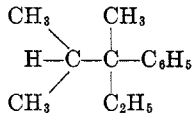
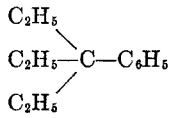
SUBSTANCE	B.P.	d_4^{20}	V_M		YIELD %
			Calc'd	Found	
	168–170° 740 mm.	.8659	155.68	154.87	70
	189–191° 740 mm.	.8720	171.95	169.88	60
	205–206° 745 mm.	.8718	188.22	185.97	55
	209–210° 745 mm.	.8814	188.22	183.95	35
	205–206° 745 mm.	.8778	188.22	184.71	40
	223.5–224.5° 745.6 mm. 107–107.5° 20 mm.	.8737	204.49	201.44	45
	216–217° 745.7 mm. 101–102° 20 mm.	.8724	204.49	201.74	30
	222–223° 745 mm. 105–107° 20 mm.	.8801	204.49	199.97	20
	224–226° 746 mm. 107–108° 20 mm.	.8867	204.49	198.78	7

TABLE I—*Concluded*

SUBSTANCE	B.P.	d_4^{20}	V_M		YIELD %
			Calc'd	Found	
	224–226° 745.6 mm. 106–107° 20 mm.	.8786	204.49	200.32	40
	224–226° 745 mm. 105–107° 20 mm.	.8803	204.49	199.93	22
	225–226° 745.6 mm. 107.5° 20 mm.	.8807	204.49	199.83	40

DISCUSSION

A comparison of yields of condensation products obtained from the isomeric *tert.*-hexyl and heptyl alcohols would seem to indicate that the accumulation of alkyl groups on the carbon atom adjacent to the carbinol carbon has a marked depressing influence on the condensing capability of the compound. The same structural character appears to favor the formation of unsaturated compounds and *tert.*-alkyl chlorides.

Boiling points, densities and molecular volumes.—These constants were accurately determined and are assembled in Table I.

The molecular volumes are calculated by the formulae developed by Kauffman[24] for unbranched homologues of benzene. In the *n*-alkyldimethylphenylmethanes, the difference between calculated and observed values may be taken as the effect of the accumulation of two methyl groups on the carbon atom adjacent to a ring carbon, which is also an accumulation center. This effect appears to increase slightly as the length of the normal chain increases.

A comparison of the molecular volumes of the isomeric propyldimethylphenylmethanes and the butyldimethylphenylmethanes gives a clear-cut picture of the effect of accumulation of radicals on adjacent and on non-adjacent carbons.

These same groups show the highest boiling points in the compounds of greatest density and the lowest boiling points in the compounds having

[24] KAUFFMAN, "Beziehungen zwischen physikalischen Eigenschaften und chemisher Konstitution," Verlag F. Enke, Stuttgart, Germany, **1920**, p. 98.

TABLE II

SURFACE TENSIONS AND PARACHORS

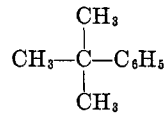
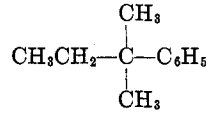
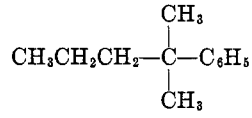
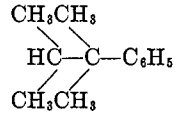
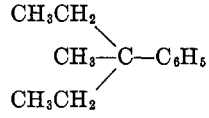
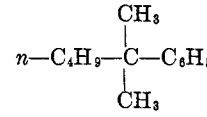
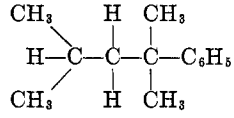
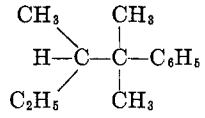
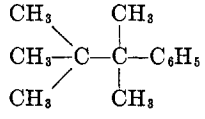
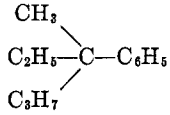
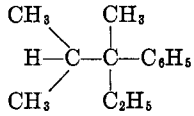
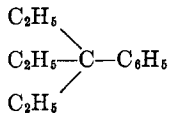
SUBSTANCE	SURFACE TENSION		PARACHOR		
	Drop-wt.	DuNouy Tensiom-eter	Calc'd	Drop-wt.	DuNouy Tensiom-eter
	28.04	28.52	356.4	356.4	357.9
	28.88	29.73	396.4	393.9	396.6
	28.95	30.54	436.4	431.4	437.1
	29.59	31.82	436.4	429.	436.8
	29.30	31.16	436.4	429.7	436.4
	29.45	31.52	476.4	469.36	476.5
	28.63	30.80	473.4	466.6	475.3
	29.26	31.52	473.4	465.2	473.2
		31.84	470.4		471.9

TABLE II—*Concluded*

SUBSTANCE	SURFACE TENSION		PARACHOR		
	Drop-wt.	DuNouy Tensiom-eter	Calc'd	Drop-wt.	DuNouy Tensiom-eter
	29.60	31.93	476.4	466.6	476.1
	29.47	31.83	473.4	465.8	474.8
	29.66	32.13	476.4	464.0	475.8

the smallest density. This relationship between density and boiling point is not clear-cut in the other isomers.

Surface tension and parachor.—Surface tension was determined by the drop-weight method of Harkins, and by means of the DuNouy tensiometer, both at 20°.

In calculating parachors, the constants of Mumford and Phillips[25] were used, together with the suggested decrement of −3.0 for branched groups of the type $-CHR_2$ and double this value for the group $-CR_3$. In addition a decrement of −3.0 was used for the attachment of the alkyl group on the benzene ring.

The agreement between the calculated values and those determined by means of the tensiometer are very close. The greatest deviation is found in the case of 2,4-dimethyl-2-phenylpentane, in which case the density is relatively low. It is noteworthy that, although this compound has a higher V_M than 2-methyl-2-phenylhexane, its parachor is slightly lower.

Index of refraction and molecular refraction.—Indices of refraction were determined by the Abbé refractometer. Molecular refractions were calculated from the Lorentz-Lorenz formula.

To eliminate any doubt as to the correctness of the formulae assigned to the *tert.*-alkylbenzenes attention is called to the following:

(*a*) All alcohols were prepared by standard methods and were checked as to properties with the literature.

(*b*) In the rearrangement of alkyl groups during processes of condensa-

[25] MUMFORD AND PHILLIPS, *J. Chem. Soc.*, **33**, 2112 (1929).

TABLE III

INDICES OF REFRACTION AND MOLECULAR REFRACTIONS

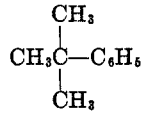
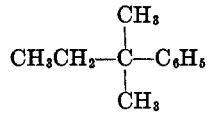
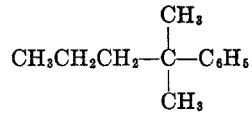
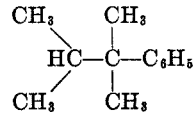
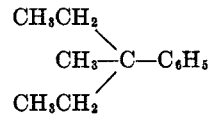
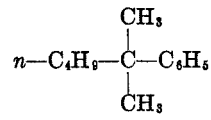
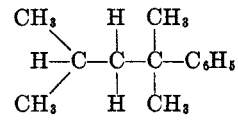
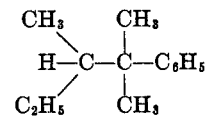
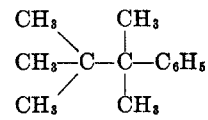
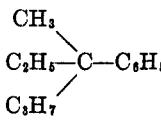
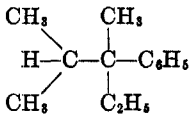
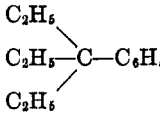
SUBSTANCE	n_D^{20}	MR_D^{20}	
		Calc'd	Found
	1.4923	44.79	44.94
	1.4924	49.40	49.29
	1.4934	54.02	54.02
	1.4988	54.02	54.00
	1.4955	54.02	53.99
	1.4943	58.65	58.68
	1.4928	58.65	58.67
	1.4966	58.65	58.48
	1.5019	58.65	58.62

TABLE III—*Concluded*

SUBSTANCE	n_D^{20}	MR_D^{20}	
		Calc'd	Found
	1.4964	58.65	58.53
	1.4974	58.65	58.54
	1.4975	58.65	58.53

tion, primary groups may change to secondary or tertiary, and secondary groups may change to tertiary[26]. We were unable to find instances of the reverse processes in which appreciable yields of primary or secondary groups are formed from groups of higher branching. It was found that isobutyl alcohol does not condense with benzene in the presence of aluminum chloride at room temperature; above 50°, it reacts to form *tert.*-butylbenzene[27].

(*c*) The properties of *tert.*-butyl- and *tert.*-amylbenzenes agree with those recorded in the literature[6, 7].

The three possible *tert.*-hexylbenzenes were prepared, two of which have been prepared by other methods[8, 11].

All *seven* possible *tert.*-heptylbenzenes were prepared, three of which are recorded[16, 21, 24].

(*d*) Differences in the physical properties of the isomeric *tert.*-alkylbenzenes, as recorded in the tables are in accord with accepted rules.

(*e*) All *tert.*-alkylbenzenes listed have been used in the preparation of *p-tert.*-alkylphenols of different and characteristic properties[4, 28].

[26] KONOWALOW, *J. Russ. Phys.-Chem. Soc.*, **27**, 457 (1896); ESTREICHER, *Ber.*, **33**, 439 (1900); SCHRAMM, *Monatsh.*, **9**, 613, 615 (1888); GROSSIN, *Bull. soc. chim.*, [2], **41**, 446 (1884); VERLEY, *ibid.*, [3], **19**, 72 (1898); MEYER AND BERNHAUER, *Monatsh.*, **53**, 721 (1929); GILMAN AND CALLOWAY, *J. Am. Chem. Soc.*, **55**, 4197 (1933); LAUGHLIN, NASH, AND WHITEMORE, *ibid.*, **56**, 1395 (1934); IPATIEFF, PINES, AND SCHMERLING, *ibid.*, **60**, 353, (1938), etc.

[27] TCHITCHIBABINE, *Bull. soc. chim.*, [5e], **2**, 498 (1935).

[28] HUSTON AND HEDRICK, *J. Am. Chem. Soc.*, **59**, 2001 (1937).

Attempts to prepare the alkylbenzenes by the Wurtz-Fittig method gave only diphenyl and dialkyl. Partial oxidation of the *tert.*-alkyl side-chains did not yield information helpful in the determination of structure.

SUMMARY

1. Tertiary aliphatic alcohols up to and including the isomeric heptyl alcohols were condensed with benzene by means of aluminum chloride to form *tert.*-alkylbenzenes.

2. The straight-chain carbinols, such as dimethyl-*n*-butylcarbinol, methylethyl-*n*-propylcarbinol and triethylcarbinol, condense readily to give good yields of the corresponding hydrocarbons.

3. Branched-chain carbinols, especially those in which branching occurs on the carbon adjacent to the carbinol carbon, condense much less readily. In these compounds there is a greater tendency to form unsaturated compounds and *tert.*-alkyl chlorides.

4. Boiling points, densities, indices of refraction, and surface tensions were determined. Molecular volumes, molecular refractions, and parachors were calculated.

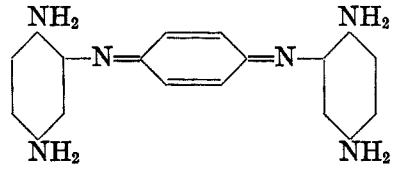
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND THE DEPARTMENT OF CHEMISTRY OF THE NORTH DAKOTA AGRICULTURAL COLLEGE]

THE STRUCTURE AND MECHANISM OF FORMATION OF THE BANDROWSKI BASE*

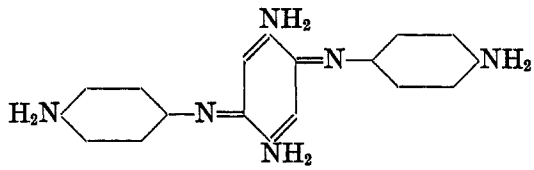
W. M. LAUER AND C. J. SUNDE

Received June 6, 1938

The oxidation of *p*-phenylenediamine under certain conditions leads to the formation of the compound, $C_{18}H_{18}N_6$, which is known as the Bandrowski base.[1] Two different structures have been proposed for this base; one by Bandrowski (structure I) and the other by Green (structure II).[2]



I



II

Ritter and Schmitz[3] in a brief, critical summary of the previous work on the structure of this base, showed that oxidation yields quinone. Since not more than one mole of quinone was isolated for each mole of the Bandrowski base, they favored structure I. However, in the present work, evidence is introduced which points to structure II as the correct one.

The hydrolysis of the Bandrowski base with 10 per cent. hydrochloric acid gives *p*-phenylenediamine hydrochloride.[4] Furthermore, on the basis

* Abstracted from the Ph.D. thesis of C. J. Sunde, submitted to the Graduate Faculty of the University of Minnesota, August 1937.

[1] BANDROWSKI, *Ber.*, **27**, 480 (1894); see also MATTHEW KIESS, M. S. Thesis, University of Minnesota, 1928.

[2] GREEN, *J. Chem. Soc.*, **1913**, 933.

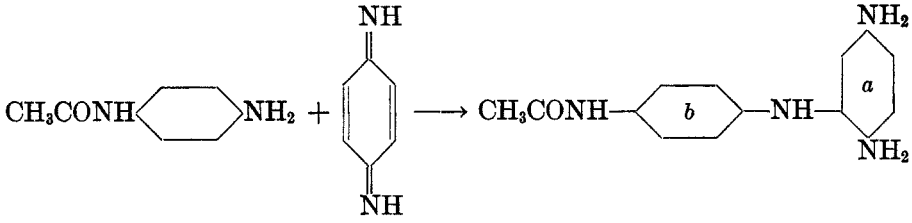
[3] RITTER AND SCHMITZ, *J. Am. Chem. Soc.*, **51**, 1587 (1929).

[4] COX, *Analyst*, **59**, 3 (1934); **60**, 360 (1935).

of 1 mole of Bandrowski base giving 2 moles of *p*-phenylenediamine, an 87 per cent. yield of *p*-phenylenediamine hydrochloride was obtained.

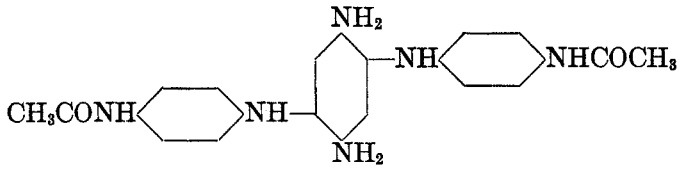
Also, a diacetate of the Bandrowski base has been obtained by adding quinonediimine, prepared either according to the method of Willstätter[5] in ether solution, or according to the method of Erdmann[6], to a solution of *p*-aminoacetanilide in aqueous methyl alcohol containing a small amount of hydrochloric acid. On acetylation, this diacetate gives the tetraacetate of the Bandrowski base.

The diacetate is very likely formed in steps, the first step being the addition of *p*-aminoacetanilide to quinonediimine as follows:

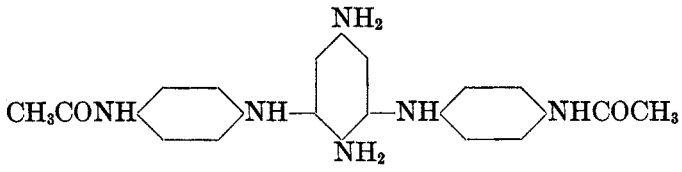


III

The intermediate III in the presence of quinonediimine may: (1) add to quinonediimine, or (2) be oxidized to the quinoid form. If the former takes place several products are possible, but since none of these can be diacetates, this possibility must be excluded. In the second instance four products are possible, IV and V by oxidation of ring *a* followed by the addition of *p*-aminoacetanilide, and VI and VII if ring *b* is involved in the

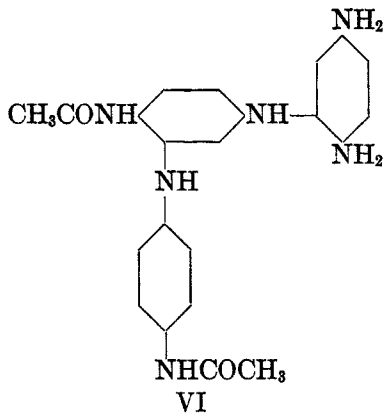


IV

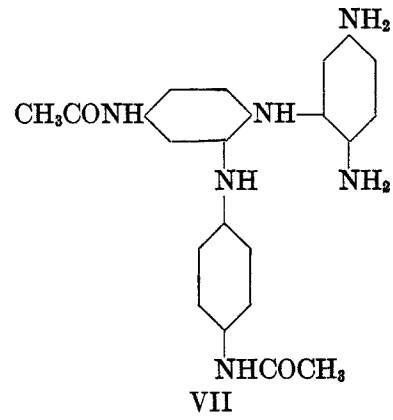


V

[5] WILLSTÄTTER AND PFANNENSTIEL, *Ber.*, **37**, 4605 (1904).
[6] ERDMANN, *ibid.*, **37**, 2906 (1904).

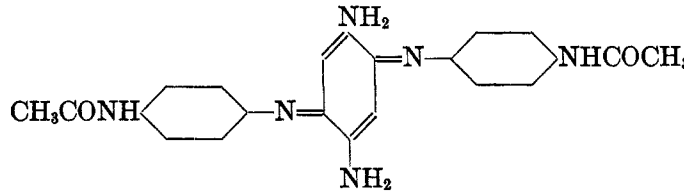


VI



VII

oxidation. Of these V, VI, and VII are easily excluded on the ground that if the leuco base of the Bandrowski base has any of these structures oxidation to the quinoid form followed by hydrolysis would not give two molecules of *p*-phenylenediamine. On the other hand, if the leuco base has the structure corresponding to IV, two moles of *p*-phenylenediamine would be expected on hydrolysis of the quinoid form (VIII).



VIII

Bandrowski did not formulate any mechanism for the formation of the base. Erdmann assumed that quinonediimine was the primary oxidation product of *p*-phenylenediamine and that 3 moles of the diimine polymerized to yield the Bandrowski base. It has been shown[7], however, that the polymer of quinonediimine differs from the base. The mechanism for the formation of the diacetate of the Bandrowski base, proposed in the present paper requires a ratio of three moles of quinonediimine to two moles of *p*-aminoacetanilide. It is of interest to point out that an increase in the amount of *p*-aminoacetanilide over the above ratio did not increase the yield of diacetate whereas a decrease led to a lower yield. Since the diacetate is readily converted to the tetraacetate of the Bandrowski base, it is reasonable to suppose that the mechanism adopted for the formation of the diacetate will also be the mechanism of formation of the base itself.

[7] WILLSTÄTTER AND MAYER, *ibid.*, **37**, 1494 (1904); see also reference 4.

EXPERIMENTAL

Hydrolysis of the Bandrowski base.—One gram of the base (m.p. 242–243°), prepared by the oxidation of *p*-phenylenediamine with potassium ferricyanide, was refluxed for two hours with 20 ml. of 10% hydrochloric acid. After removal of a black residue by filtration, the solution was evaporated until crystals appeared. The solution was then cooled to room temperature and several ml. of concentrated hydrochloric acid were added. One gram of crude product was obtained after cooling in an ice-salt bath. Purification by crystallization from dilute hydrochloric acid yielded a colorless product (0.90–0.95 g.). The hydrochloride upon treatment with sodium hydroxide was converted to the free base, which was identified as *p*-phenylenediamine (m.p. and mixture m.p. 139–140°).

Synthesis of the diacetate of the Bandrowski base.—(*a*) A filtered solution of quinonediimine in *ether* prepared from one gram of *p*-phenylenediamine according to the method of Willstatter[5] was added dropwise with mechanical stirring to a solution of *p*-aminoacetanilide (2.8 g.; m.p. 162–163°) in 20 ml. of water and 40 ml. of methyl alcohol containing 0.4 ml. of 12*N* hydrochloric acid, keeping the temperature at 0°. After standing for one hour at room temperature, the reaction mixture was made alkaline by the addition of water (100 ml.) containing 4 to 5 ml. of 15*N* ammonium hydroxide. The ether was then removed by evaporation, and after filtration the solid product was digested for a short time with about 100 ml. of boiling methyl alcohol. The average yield of crude product (ochre yellow, m.p. 296–298°) was 0.52 g.

This substance is difficultly soluble in methyl alcohol, but after extracting in a Soxhlet apparatus for a considerable period, the product isolated from the alcohol melts at 310–311°.

Anal. Calc'd for $C_{22}H_{22}N_6O_2$: C, 65.67; H, 5.47; mol. wt., 402.
Found: C, 64.89; H, 5.81; mol. wt. (Rast camphor method), 381.

The same diacetate with an identical yield was obtained using 0.95 g. of *p*-aminoacetanilide (*i.e.*, one-third of the amount used in the experiment described). The use of 0.48 g. of *p*-aminoacetanilide decreased the yield of the diacetate to 0.20 g.

(*b*) The diacetate of the base was also prepared using an *aqueous* solution of quinonediimine and *p*-aminoacetanilide. The quinonediimine was prepared according to the method of Erdmann.

Tetraacetate of the Bandrowski base.—The *diacetate* was acetylated with excess acetic anhydride at the temperature of the steam bath. It was crystallized once from dilute acetic acid and twice from nitrobenzene; m.p. 293–294°. The tetraacetate prepared in this way is identical with that obtained by the acetylation of the Bandrowski base.

SUMMARY

Evidence has been presented in support of Green's structure for the Bandrowski base, and a mechanism for the formation of this base has been discussed.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

α,β-UNSATURATED KETONES OBTAINED FROM ACETOPHENONE, AND THEIR REACTION WITH PHENYLHYDRAZINE

L. CHAS. RAIFORD AND GLEN V. GUNDY

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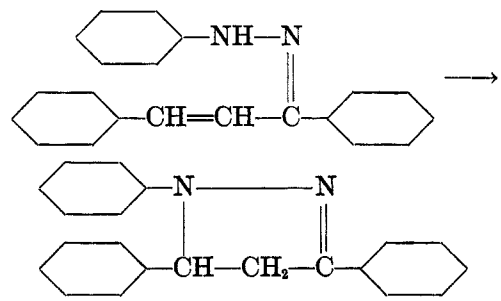
In a previous paper[1] it was reported that when the bromine and chlorine substitution products of vanillin were condensed with acetophenone in the presence of sodium hydroxide, as indicated by Schmidt[2] and extended by Claisen and collaborators[3], both mono- and diacetophenone derivatives were obtained, regardless of the relative amounts of aldehyde and ketone used. It was clearly of interest to test this behavior when a substituent is present in the acetophenone used. The earlier experiments have therefore been repeated with various substituted acetophenones, and it may be stated at once that although several modifications of the method of condensation were tried[4] no diacetophenone derivatives were obtained. In a few cases condensation failed with every method tried. No reaction product could be isolated in attempts to condense 5-bromovanillin with *o*-nitroacetophenone and none from 2-bromovanillin and *p*-chloroacetophenone. Steric hindrance does not explain these failures.

A second purpose of this work was to use these monoacetophenone derivatives in a continuation of our studies[5] on the rearrangement of the phenylhydrazones of α,β-unsaturated ketones into the isomeric pyrazolines as indicated below. Here it was desired particularly to test further Straus'



[1] RAIFORD AND GUNDY, *J. Am. Chem. Soc.*, **54**, 1191 (1932).

[2] SCHMIDT, *Ber.*, **14**, 1459 (1881).

[3] CLAISEN AND OTHERS, *Ann.*, **223**, 137 (1884); *Ber.*, **20**, 657 (1887).

[4] GLASER AND TRAMER [*J. prakt. chem.*, **116**, 331 (1927)] used a mixture of glacial

claim[6] that "when halogen or the nitro radical is present in either the ketone or the hydrazine residue of such hydrazones the closing of the pyrazoline ring occurs readily; but that when both are substituted with such groups the hydrazone is quite stable and energetic treatment is required to rearrange it".

In the present study the behavior of several of these unsymmetrical ketones toward phenylhydrazine and the *p*-nitro compound has been examined. Some of them failed to react with the nitro compound. Thus, when 3-nitrobenzal- and 5-bromovanillal-*m*-nitroacetophenones, and also 2-nitro- and 6-bromovanillal-*p*-chloroacetophenones, respectively, were treated with *p*-nitrophenylhydrazine, as indicated below, more than 90 per cent. of each ketone was recovered, and no reaction product could be isolated.

The most suitable solvent in which to conduct the reaction is glacial acetic acid. In a few cases it was possible to bring about the reaction at room temperature, but in most instances it was necessary to heat the mixture. In those cases where both methods could be used they gave the same product, which indicated that the latter was a pyrazoline rather than a hydrazone*. Phenylhydrazine was added to an acetic acid solution of 5-bromovanillalacetophenone, and the liquid was divided into two portions. One was boiled for half an hour and the other was allowed to remain at room temperature for forty-eight hours. The same product crystallized from each mixture. This substance was also obtained when the reactants were dissolved in 70 per cent. alcohol and the mixture was allowed to stand, though the separation of crystals was much slower than when acetic acid was the solvent.

The identity of the above product was further established by failure to obtain aniline in attempts to reduce it by the method described by Tafel[7] and used extensively by Auwers and Kreuder[8,9]. They found that, in general, the phenylhydrazones of α,β-unsaturated ketones can be reduced

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acetic and concentrated hydrochloric acids, while RAO, SRIKANTIA, AND IYENGAR [*Helv. Chim. Acta.*, **12**, 581 (1929)] used an acetic acid solution of ammonium acetate at the room temperature, and also at the boiling point.

[5] RAIFORD AND DAVIS, *J. Am. Chem. Soc.*, **50**, 156 (1928); RAIFORD AND ENTRIKIN, *ibid.*, **55**, 1125 (1933); RAIFORD AND HILL, *ibid.*, **56**, 174 (1934).

[6] STRAUS, *Ber.*, **51**, 1458 (1918).

* The phenylhydrazones of α,β-unsaturated ketones are usually rearranged to the isomeric pyrazolines by boiling acetic acid, but there are exceptions. AUWERS AND VOSS [*Ber.*, **42**, 4418 (1909)] failed to rearrange the product obtained from cinnamic aldehyde and *p*-nitrophenylhydrazine, although the compound was shown by reduction to be a hydrazone.

[7] TAFEL, *Ber.*, **22**, 1854 (1889).

[8] AUWERS AND KREUDER, *ibid.*, **58**, 1983 (1925).

[9] RAIFORD AND DAVIS, Reference 5.

to give aniline as one product. In the present work it has been found that some hydrazones from this and other classes of ketones undergo the change indicated, but that pyrazolines do not. For example, when a boiling absolute alcoholic solution of the hydrazone of benzalacetophenone[10] was treated with sodium†, 38 per cent. of the required aniline was obtained and some of the hydrazone was recovered. Treated in the same way, the phenylhydrazone of 5-bromovanillin[11] gave 54 per cent. of the required aniline. On the other hand, when 1,3,5-triphenylpyrazoline was suspended in alcohol at 50–60° and treated with excess of sodium amalgam while the mixture was kept acid with acetic acid, as directed by Tafel, 94 per cent. of the pyrazoline was recovered. In a second experiment, where the method was modified to the extent that the mixture was stirred vigorously, and a constant stream of carbon dioxide was passed in, the amount of starting material recovered was 90 per cent. In a third experiment where Schlenk's[12] method was employed, the pyrazoline recovered represented 92 per cent. of the starting material.

With more highly substituted pyrazolines the results were similar to the extent that no aniline was obtained. Thus, with the compounds obtained by action of 4-nitrophenylhydrazine on 5-bromo- and 6-bromovanillalacetophenone, respectively, 86 per cent. of starting material was recovered in each case. In some instances this treatment caused loss of halogen from a portion of the material and gave rise to mixtures. For example, when the pyrazoline obtained by the action of phenylhydrazine on benzal-4-bromoacetophenone was tested it gave 12 per cent. of 1,3,5-triphenylpyrazoline and 72 per cent. of the starting material, while that one obtained from 5-bromovanillal-4-bromoacetophenone gave 10 per cent. of 1,3-diphenyl-5-(3-methoxy-4-hydroxyphenyl)-pyrazoline and 63 per cent. of starting material. On this ground one may question the value of reduction methods for identification of the phenylhydrazones of the type under consideration.

EXPERIMENTAL

Preparation of ketones.—These were obtained by one of the general methods indicated above with such modification as the individual case required. The reaction of 5-nitrovanillin with acetophenone gives the products to be expected when the starting ketone is unsubstituted, and illustrates the difficulty in purification of these compounds. To a solution containing 15 g. of 5-nitrovanillin and an equal weight of acetophenone in 100 cc. of alcohol 35 cc. of a 25 per cent. solution of sodium hydroxide was added and the mixture was heated to boiling under reflux for ninety minutes. When the liquid was acidified with acetic acid a mixture of gum and

[10] This was found to be more suitable than Tafel's method.

[11] RAIFORD AND HILMAN, *J. Am. Chem. Soc.*, **49**, 1572 (1927).

[12] SCHLENK, *J. prakt. chem.*, [2] **78**, 57 (1908).

TABLE I

DERIVATIVES OBTAINED BY CONDENSATION OF VANILLIN SUBSTITUTION PRODUCTS WITH ACETOPHENONE

SUBSTITUENT IN VANILLAL RESIDUE	YIELD,[a] %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
2,5-Dichloro-[d]	Low	Acetone	Pale yellow[b] needles	139–141	$C_{16}H_{12}Cl_2O_3$	21.98	20.85		
2-Nitro-[e]	52[c]	Acetone	Yellow needles	175–178	$C_{16}H_{13}NO_5$			4.68	4.60
5-Nitro-[d]	Very low	Acetone	Yellow needles	139–140	$C_{16}H_{13}NO_5$			4.68	5.16
2-Nitro-5-bromo-[e]	42[c]	Acetic acid	Pale brown flakes	185–187 (decomp.)	$C_{16}H_{12}BrNO_5$			3.70	3.68

[a] These refer to purified material.

[b] The experiment in which these were formed gave also the diacetophenone derivative which, after repeated crystallization from alcohol, was obtained as short colorless needles that melted at 160–161°. *Anal.* calc'd for $C_{24}H_{20}Cl_2O_4$: Cl, 16.02. Found Cl, 16.07.

[c] In accordance with previous experience it was expected that some diacetophenone derivative would be formed here, but none could be isolated.

[d] The condensing agent was sodium hydroxide.

[e] Glaser and Tramer's method (Ref. 4) was used.

TABLE II

DERIVATIVES OBTAINED BY CONDENSATION OF 5-BROMOVANILLIN WITH ACETOPHENONE SUBSTITUTION PRODUCTS

SUBSTITUENT IN ACETOPHENONE	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
4-Methyl-[f]	19[a]	Alcohol	Cream prisms	146–147	$C_{17}H_{15}BrO_3$	23.05	22.77		
4-Methoxyl-[f]	67[b]	Alcohol[c]	Yellow hexagonal plates	138–140	$C_{17}H_{15}BrO_4$	22.04	22.12		
4-Hydroxy-[g]	46	Acetic acid	Yellow needles	229–230	$C_{16}H_{13}BrO_4$	22.92	22.79		
3-Nitro-[g]	92	Acetic[d] acid	Yellow needles	270 (decomp.)	$C_{16}H_{12}BrNO_5$			3.70	3.63
4-Bromo-[h]	15[a]	Alcohol	Yellow parallelopipeds	154–155	$C_{16}H_{12}Br_2O_3$	38.83	38.70		
2-Chloro-[f]	38	Acetic acid	Yellow nodules	120–121	$C_{16}H_{12}BrClO_3$	31.42	31.42		
4-Chloro-[f]	31[a]	Alcohol	Pale yellow needles	164–167[e]	$C_{16}H_{12}BrClO_3$	31.42	31.09		

[a] This refers to purified material. Separation from the gum, which was nearly always formed, caused loss of much material.

[b] The yield may be increased by evaporation of solvent from the mother liquor.

[c] From acetic acid this product separated with solvent of crystallization; 1.2506 g. of air dried material heated at about 120° for two hours lost 0.1947 g. Calc'd for $C_{17}H_{15}BrO_4 \cdot C_2H_4O_2$: acetic acid, 14.18. Found, acetic acid, 15.57.

[d] No suitable crystallizing solvent was found. Foreign matter was extracted with acetic acid.

[e] Repeated crystallizations did not change this.

[f] Glaser and Tramer's method (Ref. 4) was used.

[g] The condensing agent was ammonium acetate.

[h] Aqueous-alcoholic solution of sodium hydroxide was used here.

TABLE III

CONDENSATION PRODUCTS FROM 6-BROMOVANILLIN AND ACETOPHENONE DERIVATIVES

SUBSTITUENT IN ACETOPHENONE	YIELD,[a] %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
4-Chloro-[d]	76	Acetic acid	Yellow prisms	201–203	$C_{16}H_{12}BrClO_3$	31.42	31.56		
4-Bromo-[b]	32	Alcohol	Yellow prisms	190–191	$C_{16}H_{12}Br_2O_3$	38.83	38.97		
4-Methyl-[d]	55	Alcohol	Yellow rods	156–158	$C_{17}H_{15}BrO_3$	23.05	22.92		
4-Hydroxy-[c]	30	Dilute alcohol	Yellow needles	228–229	$C_{16}H_{13}BrO_4$	22.92	22.72		
4-Methoxy-[d]	22	Acetic acid	Yellow prisms	146–148	$C_{17}H_{15}BrO_4$	22.04	22.11		
3-Nitro-[c]	49	Acetic acid	Yellow needles	185–186.5	$C_{16}H_{12}BrNO_5$	21.16	21.14	3.70	3.61

[a] These values represent purified products.

[b] Condensation was brought about by aqueous-alcoholic solution of sodium hydroxide.

[c] Ammonium acetate was present in the reaction mixture, which was dissolved in acetic acid.

[d] Glaser and Tramer's method (Ref. 4) was used.

TABLE IV

PYRAZOLINES

SUBSTITUTED PHENYL GROUPS			YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
Position 1	Position 3	Position 5						Calc'd	Found
Phenyl (unsubs.)	Phenyl (unsubs.)	3-Methoxy-4-hydroxy-5-bromo-	93	Dilute alcohol	Nearly colorless plates	139–141	$C_{22}H_{19}BrN_2O_2$	18.91	19.05
Phenyl (unsubs.)	4-Bromo-	3-Methoxy-4-hydroxy-5-bromo-	85	Acetic acid	Pale[a] yellow needles	195–197	$C_{22}H_{18}Br_2N_2O_2$	31.87	31.96
4-Nitro-	Phenyl (unsubs.)	3-Methoxy-4-hydroxy-5-bromo-	49	Acetic acid	Yellow needles	211–213	$C_{22}H_{18}BrN_3O_4$	17.09	17.29
4-Nitro-	4-Chloro-	3-Methoxy-4-hydroxy-5-bromo-	75	Acetic acid	Yellow needles	214–215	$C_{22}H_{17}BrClN_3O_4$	22.98	22.88
4-Nitro-	4-Tolyl-	3-Methoxy-4-hydroxy-5-bromo-	52[b]	Acetic acid	Orange-red prisms	231–232	$C_{23}H_{20}BrN_3O_4$	16.61	16.69
4-Nitro-	4-Hydroxy-	3-Methoxy-4-hydroxy-5-bromo-	6[b]	Dilute[c] acetone	Red plates	255–256	$C_{22}H_{18}BrN_3O_5$	16.52	16.32
4-Nitro-	Phenyl (unsubs.)	3-Methoxy-4-hydroxy-6-bromo-	89	Acetic acid	Red needles[d]	210–212	$C_{22}H_{18}BrN_3O_4$	17.09	17.31
4-Nitro-	3-Nitro-	3-Methoxy-4-hydroxy-6-bromo-	21	Acetic acid	Orange nodules	237–238	$C_{22}H_{17}BrN_4O_6$	15.59	15.39
4-Nitro-	Phenyl (unsubs.)	2-Nitro-3-methoxy-4-hydroxy-5-bromo-	46	Acetic acid	Orange needles	220 (decomp.)	$C_{22}H_{17}BrN_4O_6$	15.59	15.53

[a] Obtained by allowing an acetic acid solution of the reactants to stand in the cold. An acetone solution of the product showed blue fluorescence, and boiling its acetic acid solution caused no change in melting point.

[b] This refers to purified material.

[c] The boiling acetone solution was treated with a small amount of water and allowed to cool.

[d] These were yellow when first deposited, but they became red on standing in contact with the mother liquor or air.

crystalline material separated. Ten crystallizations from dilute acetic acid were required to remove the gum, but the remaining crystals still represented a mixture which was separated as follows. Cold acetone in too small a portion to dissolve all material was poured on the solid and allowed to drain through it. The solution obtained was heated almost to boiling and then diluted with water. The precipitate that formed was collected and subjected again to the treatment described. Ten repetitions sufficed to give a rough separation of the products. The less soluble portion was then recrystallized several times from dilute acetone and was obtained in small yellow plates that melted at 150–151°. Analysis indicated that it was 5-nitrovanillaldiacetophenone.

Anal. Calc'd for $C_{24}H_{21}NO_6$: N, 3.34. Found, N, 3.44.

The more soluble portion, recovered from the mother liquors indicated above turned out to be the monoacetophenone derivative. Analytical data for this and others are given in Table I. Products obtained from substituted acetophenones are given in Tables II and III.

Formation of pyrazolines.—These compounds were obtained by treatment of an acetic acid solution of the required ketone with phenylhydrazine. When the latter was unsubstituted the reaction sometimes took place at room temperature. But, due to the low solubility of many of the ketones in acetic acid, it was usually necessary to carry out the reaction at the boiling point. This was always done when *p*-nitrophenylhydrazine was used. In most cases the product that separated from the reaction mixture was nearly pure. Analytical data and other properties for these compounds are given in Table IV.

SUMMARY

1. Several α,β-unsaturated unsymmetrical ketones were prepared by condensing chloro, bromo and nitro derivatives of vanillin with acetophenone and several of its substitution products. In no case was a diacetophenone derivative obtained when the starting ketone contained a substituent. No reaction product could be isolated in attempts to condense 5-bromovanillin with *o*-nitroacetophenone and none from 2-bromovanillin and *p*-chloroacetophenone.

2. These ketones were treated with phenylhydrazine and its *p*-nitro substitution product. Under the conditions of these experiments the rearrangement from hydrazone to pyrazoline occurred so readily that the latter only were isolated.

3. Further work is in progress.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY,
INDIANA UNIVERSITY]

REARRANGEMENT IN THE BENZOIN SERIES*

FLOYD L. JAMES WITH ROBERT E. LYONS

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The rearrangement of benzoin to diphenylacetic acid was discovered by Lachman.[1] By long heating in sealed tubes in the presence of aqueous solutions of phosphoric or sulfuric acids at temperatures up to 230° he was able to convert as high as 9 per cent. of the benzoin to diphenylacetic acid. Considerable decomposition to diphenylmethane and carbon dioxide occurred, however.

$$C_6H_5CHOHCOC_6H_5 \begin{cases} \nearrow (C_6H_5)_2CHCOOH \\ \searrow (C_6H_5)_2CH_2 + CO_2 \end{cases}$$

This reaction is of interest from a theoretical standpoint because the alpha-hydroxy ketone benzoin is intermediate structurally between the diketone benzil and the glycols hydrobenzoin and pinacol. The benzil and glycolic rearrangements are usually almost quantitative under suitable conditions, and have attracted repeated consideration.[2, 3]

The benzoin rearrangement is closely related also to the rearrangement of other alpha-hydroxy ketones and alpha-hydroxy aldehydes. Danilov and Venus Danilova[4] found that alpha-hydroxyisobutyraldehyde could be changed to isobutyric acid in alkaline solution in the presence of hydroxides of heavy metals such as copper and lead. Heating the same aldehyde with very dilute mineral acid brought about a reaction of another type.

$$(CH_3)_2COHCHO \begin{cases} \nearrow (CH_3)_2CHCOOH \\ \searrow CH_3CHOHCOCH_3 \end{cases}$$

Other examples of this second type of rearrangement have been discussed recently as "interconversion of mixed benzoins"[5] where R'CHOHCOR'' → R''CHOHCOR'.

* Compiled from a thesis submitted by Floyd L. James in partial fulfillment of the requirements for the degree Doctor of Philosophy.

[1] LACHMAN, *J. Am. Chem. Soc.*, **45**, 1529 (1923).

[2] SCHÖNBERG AND KELLER, *Ber.*, **56**, 1638 (1923).

[3] TIFFENEAU AND CO-WORKERS, *Bull. soc. chim.*, **49**, 1595–1851 (1931).

[4] DANILOV AND DANILOVA, *Ber.*, **67**, 24 (1934).

[5] LUIS, *J. Chem. Soc.*, **1932**, 2547.

The present investigation was carried out with two objects in view—(1) to find a method for obtaining more complete conversion of benzoin to diphenylacetic acid, and (2) to study the effect of substituting groups upon the rearrangement.

The more complete conversion of benzoin to diphenylacetic acid should be possible under favorable conditions, since the closely related benzil[2] and pinacol[3] rearrangements both are almost complete. However, as Lachman found[1], at the high temperatures necessary to bring about the benzoin rearrangement, side reactions predominate. We tried adding several substances to aid the acid catalyst in the rearrangement. The results are summarized in Table I.

TABLE I

ADDITIONAL REAGENTS IN THE REARRANGEMENT OF BENZOIN BY ACID CATALYSIS WITH 20 ML. OF 60% PHOSPHORIC ACID

SUBSTANCE ADDED	GRAMS ADDENDUM	GRAMS BENZOIN	TEMP., °C.	TIME, HOURS	DIPHENYLACETIC ACID, %	GAS PRESSURE
None[a]		5	230	4	6	Moderate
Pumice[a]	2.5	5	230	4	5	Moderate
Activated charcoal	2.5	5	230	4	6	None
Activated charcoal	1.5	3	260	4	11	Moderate
Silica gel	1.5	3	240	4	18	None
Silica gel	1.0	2	270	24	54	Moderate
Activated alumina	1.5	3	250	4	27	None

[a] Twenty milliliters of 1.5 molar sulfuric acid was used instead of 20 ml. of 60% phosphoric acid.

Silica gels prepared from sodium silicate and (1) acetic acid, (2) hydrochloric acid, (3) carbon dioxide, (4) ferric chloride, and (5) sulfur dioxide, and activated at temperatures from 150 to 450° we found to be of about equal effectiveness in this rearrangement.

Heating benzoin with zinc chloride or with cobalt chloride in an open test-tube for 4 hours at 230° gave no diphenylacetic acid.

The effect of variations in time and temperature is shown in Tables II and III.

In an attempt to accomplish the benzoin rearrangement by less drastic treatment, we tried the method which Gomberg and Bachmann[6] found to be effective in the pinacol rearrangement. The pinacol rearrangement, like the benzoin rearrangement, is ordinarily brought about by heating with mineral acid in sealed tubes. We found that their process of refluxing in glacial acetic acid with a little iodine was totally ineffective in bringing

[6] GOMBERG AND BACHMANN, *J. Am. Chem. Soc.*, **49**, 246 (1927).

about the benzoin rearrangement. When 5 g. benzoin was thus treated we recovered 4.6 g. unchanged benzoin, along with 0.26 gm. benzil.

The following substituted benzoins were prepared and their rearrangement attempted: furoin, 4-methoxybenzoin*, 4-dimethylaminobenzoin, 4,4′-dimethoxybenzoin (anisoin), 4-methoxy-2′-chlorobenzoin, 4,4′-dimethylbenzoin (toluoin), 4,4′-diisopropylbenzoin (cuminoin), and alpha-phenyl benzoin [$(C_6H_5)_2COHCOC_6H_5$].

TABLE II

REARRANGEMENT OF BENZOIN IN THE PRESENCE OF SILICA GEL AND 60% PHOSPHORIC ACID IN 24 HOURS

TEMP., °C.	DIPHENYL-ACETIC ACID, %	COMMENTS
240	38.3	No pressure
250	46.1	Slight pressure
260	50.3	No pressure
270	53.9	Slight pressure
280	50.5	Slight pressure, some darkening
290	15.3	Much pressure, contents almost black

TABLE III

REARRANGEMENT OF BENZOIN IN THE PRESENCE OF SILICA GEL AND 60% PHOSPHORIC ACID AT 250°

TIME, HOURS	DIPHENYL-ACETIC ACID, %	COMMENTS
4	37	No pressure
24	46.1	Slight pressure
48	52.2	Slight pressure, some darkening
72	50.6	No pressure, contents almost black

When the substituted benzoins furoin, 4-methoxybenzoin, 4-dimethylaminobenzoin, 4,4′-dimethoxybenzoin, and 4-methoxy-2′-chlorobenzoin were heated with phosphoric acid and silica gel or alumina, in every case severe charring occurred and in most cases pressure was developed. None of the expected substituted diphenylacetic acids were obtained. Using acid of lower concentration did not reduce decomposition appreciably.

With the alkyl-substituted benzoins better results were obtained. With

* In accordance with the usage of *Chemical Abstracts* since 1927, in naming mixed benzoins, primes are given to the numbered constituents on the benzene ring next to the CHOH group. Buck and Ide [*J. Am. Chem. Soc.*, **54**, 3304 (1932)] suggest and use a system exactly opposite—giving primes to the numbered constituents on the benzene ring next to the CO group. These conflicting usages make the literature rather confusing, since some authors do not specify which system they use.

4,4′-dimethylbenzoin and 4,4′-diisopropylbenzoin, decomposition did not occur, but the extent of rearrangement was less than with benzoin; with 4,4′-dimethylbenzoin about 25 per cent. of ditolylacetic acid was produced, while with 4,4′-diisopropylbenzoin only 5 per cent. was converted to organic acids. This was shown not to be pure dicuminylacetic acid, so the amount of actual rearrangement was less than 5 per cent.

A chain-substituted benzoin was prepared to find out whether the conversion of the secondary hydroxyl of benzoin to a tertiary hydroxyl would encourage rearrangement. Alpha-phenylbenzoin $[(C_6H_5)_2COHCOC_6H_5]$ remained unchanged when heated with phosphoric acid and silica gel or alumina.

EXPERIMENTAL

The variables involved in the rearrangement of benzoin are temperature, time, kind of acid, acid strength, and the presence of additional catalysts. Lachman[1] found that sulfuric and phosphoric acids were about equally effective, and that variation in acid strength did not affect the reaction greatly. After a few preliminary experiments we selected 60% phosphoric acid as a suitable catalyst.

Procedure.—The specified materials were placed in combustion tubes, which were then sealed. An electric resistance furnace of the Carius type provided the high temperatures. After the tube was cool, the end was broken off and an ether extraction was made directly from the combustion tube. To the ether extract was added 40 ml. of 5% aqueous sodium carbonate solution. After shaking and letting stand, the aqueous layer was run off and acidified with concentrated hydrochloric acid. This brought down a heavy white precipitate which, after collection on a weighed filter paper, washing with distilled water, and drying at 110° was weighed. This crude diphenylacetic acid melts at 143 to 145° and may be recrystallized readily from hot water in long white needles of the pure acid melting at 148°. A second and very much smaller portion may be obtained by extracting the mother liquor and wash waters with ether, shaking with 10 ml. of 5% sodium carbonate solution, and separating and acidifying the aqueous layer.

Preparation of materials.—The benzoin was prepared by the usual cyanide condensation and was recrystallized several times from hot ethyl alcohol until it was almost white and had a melting point of 135 to 136°.

Furoin[7], m.p. 135°; 4-dimethylaminobenzoin[8], m.p. 163°; 4-methoxy-2′-chlorobenzoin[9], m.p. 82°; 4-methoxybenzoin[10], m.p. 102 to 103°; 4,4′-dimethoxybenzoin[11], m.p. 113; 4,4′-dimethylbenzoin[12], m.p. 88 to 89°; and 4,4′-diisopropylbenzoin[13], m.p. 101 to 102°, were all prepared by cyanide condensations of the respective aldehydes in essentially the manner described in the references, and purified by recrystallization from ethyl alcohol.

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[7] FISCHER, *Ann.*, **211**, 218 (1881).
[8] STAUDINGER, *Ber.*, **46**, 3535 (1913).
[9] BUCK AND IDE, *J. Am. Chem. Soc.*, **52**, 4107 (1930).
[10] KINNEY, *ibid.*, **51**, 1595 (1929).
[11] BÖSLER, *Ber.*, **14**, 327 (1881).
[12] STIERLIN, *ibid.*, **22**, 380 (1889).
[13] WIDMAN, *ibid.*, **14**, 609 (1881).

Alpha-phenylbenzoin, m.p. 88°, was prepared by the method of Acree[14], in which phenylmagnesium bromide reacts with benzil.

Rearrangement of 4,4'-dimethylbenzoin.—When 2 g. of 4,4'-dimethylbenzoin was heated with 1 g. silica gel and 20 ml. of 60% phosphoric acid for 11 hours at 250°, the procedure outlined above for separation of organic acids gave 0.491 g. (24.6%) of white ditolylacetic acid melting after recrystallization at 143.5 to 144° and giving on titration an equivalent weight of 242.2 (calc'd, 240.1).

Rearrangement of 4,4'-diisopropylbenzoin.—Samples of 4,4'-diisopropylbenzoin were treated as follows: (1) 1.5 g. with silica gel and 60% phosphoric acid 24 hours at 250°; (2) 1 g. with silica gel and 60% phosphoric acid 24 hours at 270°; (3) 1.5 g. with alumina and 50% phosphoric acid 24 hours at 250°.

The acidic material obtained from these three experiments was so scanty that the three portions were combined, giving a total of only 0.21 g. before purification, or 5% of the starting material. Titration after recrystallization gave a value of 353 for the equivalent weight instead of the 296 calculated for $[(CH_3)_2CHC_6H_4]_2CHCOOH$. The acidified titration solution was ether-extracted, and the ether was allowed to evaporate. The white residue did not completely dissolve in aqueous 5% sodium carbonate solution, indicating the presence of some non-acidic material which gave too high a value for the equivalent weight.

Attempted rearrangement of alpha-phenylbenzoin.—Two grams of alpha-phenylbenzoin, 1 g. of silica gel, and 20 ml. of 60% phosphoric acid were heated for 8 hours at 245°. There was no increase in pressure, but the contents changed in color from almost white to almost black. After ether extraction the ether was shaken with 10% aqueous sodium carbonate solution. Acidification of the aqueous layer with hydrochloric acid gave no precipitate of triphenylacetic acid. Evaporation of the ether layer gave balls of white alpha-phenylbenzoin melting at 87.5° alone or mixed with alpha-phenylbenzoin.

A second attempt was made to rearrange alpha-phenylbenzoin by heating 2 g. with 1 g. of silica gel and 20 ml. of 50% phosphoric acid at 260° for 10 hours. The blackened contents of the reaction tube were extracted with benzene, and the extract was shaken with 10% aqueous sodium hydroxide solution, since triphenyl acetic acid is referred to as a very weak acid. On acidification of the aqueous layer with hydrochloric acid, however, there was no precipitate of triphenylacetic acid. Evaporation of the acidified solution to dryness left a white residue which was almost completely insoluble in boiling benzene, while triphenylacetic acid is soluble in this solvent. So once again, no triphenylacetic acid had been produced.

DISCUSSION

Inspection of Tables I, II, and III shows that the rearrangement of benzoin will proceed to the extent of about 50 per cent. on heating for 24 hours with 60 per cent. phosphoric acid and silica gel or alumina at 250 to 260°. This method of producing diphenylacetic acid is more direct than the ordinary preparation from benzoin through benzil and benzilic acid, but it has the disadvantages of lower yields and of requiring the use of sealed tubes.

Lachman[1] had found that a great deal of carbon dioxide pressure developed even at 230° when benzoin was heated with 6-molar phosphoric acid. He believed the formation of at least part of this carbon dioxide to be due

[14] ACREE, *ibid.*, **37**, 2758 (1904).

to decarboxylation of diphenylacetic acid at 230°. We heated diphenylacetic acid with 60 per cent. (8.6-molar) phosphoric acid at 240° for 4 hours and found no carbon dioxide. This shows that the carbon dioxide is produced by a side reaction during the rearrangement rather than from diphenylacetic acid after rearrangement. The presence of silica gel or alumina retards the side reaction, permitting the use of higher temperatures where rearrangement is more complete.

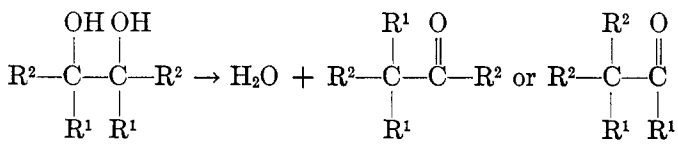
The benzil and pinacol rearrangements have been studied extensively, the benzoin and hydrobenzoin less so, with two chief theoretical considerations in view: (1) devising a satisfactory mechanism to explain these and related rearrangements, and (2) determining the relative migratory aptitudes of various radicals.

Among the most acceptable mechanisms of rearrangement are those of Lachman[15] and Whitmore[16]. Lachman assumes that a hydroxyl radical migrates to an adjacent carbon, creating an unstable structure which is readjusted by a shift of the phenyl group to give diphenylacetic acid.
$C_6H_5\text{-}CHOH\text{-}CO\text{-}C_6H_5 \rightarrow C_6H_5\text{-}CH \div COOH\text{-}C_6H_5 \rightarrow (C_6H_5)_2CH\text{-}COOH$
The division sign indicates the unstable structure.

Whitmore suggests that the formation of an "open electron sextet" by loss of a negative group, such as hydroxyl, with its two electrons may cause a group such as phenyl to move in to complete the octet, but at the same time leaving another atom with an open sextet. The negative hydroxyl radical then returns to the structure to complete an octet, giving the rearranged product.

The principal difference between these two mechanisms seems to be in the timing of the various steps. Lachman's theory calls for (1) detachment of hydroxyl, (2) reattachment, and (3) rearrangement by transfer of phenyl. Whitmore's specifies (1) detachment of hydroxyl, (2) transfer of phenyl, and (3) reattachment of hydroxyl. We see no reason why migration of the phenyl group with its pair of electrons and reattachment of hydroxyl with its pair could not take place simultaneously, making the two mechanisms identical.

Comparison of migratory aptitudes of radicals by the extent of rearrangement has been made chiefly in the symmetrical pinacol series, where only the relative migratory aptitudes of the radicals is the determining factor in deciding which product will appear in greater amount.



[15] LACHMAN, *J. Am. Chem. Soc.*, **44**, 330 (1922); **45**, 1509 (1923).
[16] WHITMORE, *ibid.*, **54**, 3274 (1932).

Bachmann[17] found that except for the ortho-substituted radicals the relative migratory aptitudes follow the order of electronegativity as determined by Kharasch and Reinmuth[18]. In unsymmetrical pinacol, benzil, and benzoin rearrangements the factors influencing rearrangement become more complex and the relation between the migratory aptitude and the electronegativity of a radical is less exact.

We succeeded in rearranging, besides unsubstituted benzoin, the 4,4′-dimethyl and the 4,4′-diisopropyl derivatives. Bachmann[17] gives the relative migratory aptitudes of phenyl, 4-isopropylphenyl, and 4-methylphenyl respectively as 1 (arbitrarily assigned), 9, and 15.7. If this alone were the determining factor in the benzoin rearrangement, it should proceed most readily with 4,4′-dimethyl, next most readily with 4,4′-diisopropyl, and least readily with unsubstituted benzoin. But we found unsubstituted benzoin to rearrange most completely, 4,4′-dimethylbenzoin next, and 4,4′-diisopropyl hardly at all under the conditions tried.

To find out whether the ease of losing a hydroxyl determines the extent of rearrangement, as Lachman's and Whitmore's mechanisms might suggest, we prepared alpha-phenylbenzoin [$(C_6H_5)_2COHCOC_6H_5$], and attempted its arrangement. Here the secondary hydroxyl of benzoin is replaced by tertiary to give a more negative carbon. Koopal,[19] in a generalization from rearrangements in the glycol series (pinacol, hydrobenzoin, etc.), showed that in such rearrangements a tertiary hydroxyl is invariably more mobile than a secondary or primary hydroxyl. So one might hope for the rearrangement of alpha-phenylbenzoin to triphenylacetic acid to take place more readily than that of benzoin to diphenylacetic acid. We found that this was not the case. Upon subjecting alpha-phenylbenzoin to the conditions of the benzoin rearrangement, unchanged alpha-phenylbenzoin but no triphenylacetic acid was recovered. This failure was not entirely unexpected, since Weissberger[20, 21] showed that the speed of oxidation of benzoins to arylacetic acids with air in alkaline solution increased with increasing dissociation constants of the acids formed, and that the same relationship holds true in the Cannizzaro oxidation-reduction of aromatic aldehydes. Since the benzoin rearrangement is essentially an intramolecular oxidation-reduction, and since triphenylacetic acid is known to be an extremely weak acid[22], on the basis of Weissberger's findings we would not expect this acid to be produced readily by rearrangement.

[17] BACHMANN AND CO-WORKERS, *ibid.*, **56**, 2081 (1934), and earlier papers.
[18] KHARASCH AND REINMUTH, *J. Chem. Educ.*, **8**, 1713 (1931).
[19] KOOPAL, *Rec. trav. chim.*, **34**, 115 (1915).
[20] WEISSBERGER, *Ber.*, **65**, 1815 (1932).
[21] WEISSBERGER AND HAASE, *J. Chem. Soc.*, **1934**, 535.
[22] SCHMIDLIN AND HODGSON, *Ber.*, **41**, 441 (1908).

SUMMARY

1. The presence of alumina or silica gel in the rearrangement of benzoin to diphenylacetic acid by acid catalysis allowed the use of high temperatures without decomposition.

2. Approximately 50 per cent. rearrangement was attained in 24 hours with 60 per cent. phosphoric acid and silica gel or alumina at 250 to 260°.

3. Treatment of furoin, 4-methoxybenzoin, 4-dimethylaminobenzoin, 4,4′-dimethoxybenzoin, and 4-methoxy-2′-chlorobenzoin in the same manner resulted only in their decomposition.

4. The alkyl-substituted benzoins 4,4′-dimethylbenzoin and 4,4′-diisopropylbenzoin rearranged under the conditions stated in (2), but not so completely as benzoin.

5. Alpha-phenylbenzoin [$(C_6H_5)_2COHCOC_6H_5$] was found to remain unchanged under the conditions stated in (2).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

THE REACTIVITY OF PARA-FLUORINE IN TRIARYLMETHYL CHLORIDES

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Soon after the discovery of triphenylmethyl it was found that para halogens in the triphenylmethyl group may be removed or replaced under conditions which indicate a quinoidation in the benzene nucleus containing the reacting halogen. The behavior of halogenated triarylmethyl chlorides in liquid sulfur dioxide alone and in the presence of silver chloride, and also in benzene solution in the presence of finely divided silver will be discussed in this paper.

p-Bromotriarylmethyl chlorides rearrange in liquid sulfur dioxide solution to yield *p*-chlorotriarylmethyl bromides. Gomberg[1] investigated numerous examples of this rearrangement, obtaining for example, an 85 per cent. yield of *p*-chloro-di-*p*-bromotriphenylmethyl bromide from tri-*p*-bromotriphenylmethyl chloride. Long agitation of *p*-bromotriarylmethyl chlorides or bromides in this solvent with silver chloride results in their conversion into *p*-chlorotriarylmethyl chlorides[2]. The mechanism of these reactions must involve the quinoidation of the triarylmethyl halide (or the corresponding positive ion), placing the halogen atom from the methyl carbon and the nuclear halogen in the same position in the para-quinoidal structure. In the case of direct rearrangement, the halogen which was on the aromatic nucleus goes to the methyl carbon when the compound reverts to the benzenoidal form. Replacement is explained by ionization of the quinoidal form which permits either or both of the halogen atoms on the para quinoidal carbon to be replaced by chlorine atoms from the silver chloride.

Gomberg and Cone[3] found that when a triarylmethyl chloride containing chlorine, bromine, or iodine on an aromatic nucleus is shaken with silver, the chlorine atom is quantitatively removed from the methane carbon atom in about half an hour. After several weeks, more or less of the halogen on the aromatic nucleus is removed if it was present in the para position. Halogen atoms in the ortho or meta position do not react. The

[1] GOMBERG, *Ber.*, **42**, 406 (1909).

[2] GOMBERG, *Ber.*, **40**, 1847 (1907); GOMBERT AND CONE, *Ann.*, **370**, 142 (1909).

[3] GOMBERG AND CONE, *Ber.*, **39**, 3274 (1906).

experiments of Gomberg and Blicke[4] showed rather conclusively that in the case of several para-brominated triarylmethyl chlorides, exactly one-half atom of bromine per molecule is removed by prolonged shaking and free radicals of the "second order" result. These reactions may be formulated as follows for the case of *p*-bromotriphenylmethyl chloride:

$$2(BrC_6H_4)(C_6H_5)_2CCl + 2Ag \longrightarrow 2(BrC_6H_4)(C_6H_5)_2C + 2AgCl$$

$$2(BrC_6H_4)(C_6H_5)_2C \rightleftharpoons 2(C_6H_5)_2C{=}\langle\rangle{-}Br + Ag \longrightarrow$$

$$(BrC_6H_4)(C_6H_5)_2C{-}\langle\rangle{=}C(C_6H_5)$$

The present investigation was undertaken to study the reactivity of fluorine as compared to the other halogens in these reactions. For this purpose, the mono-, di-, and tri-*p*-fluorotriphenylmethyl chlorides were synthesized, the last two for the first time. In the first series of experiments, solutions of these compounds in liquid sulfur dioxide were agitated for a considerable number of days. Analysis of the products after evaporation of the sulfur dioxide for ionizable fluorine indicated that rearrangement had taken place to the extent of about one to eight per cent. A similar series of experiments carried out in the presence of silver chloride gave results of the same order, indicating that the silver chloride was without any appreciable effect.

Agitation of the fluorinated triphenylmethyl chlorides in benzene solution with finely divided silver yielded from 0.13 to 0.43 atoms of ionizable fluorine per molecule in the ten experiments conducted. The results and conditions were rather irregular and the differences between the average results for the three compounds were small as compared to the deviation between individual experiments. The fact that ionizable fluorine was found in appreciable amounts indicates the formation of radicals of the second order such as Gomberg and Blicke[4] showed to result from similar treatment of *p*-bromotriphenylmethyl chloride.

The results obtained in the three groups of experiments vary widely and have little quantitative significance, but they show positively that fluorine in the para position in triarylmethyl chlorides has reactions similar to the other halogens, although it does not react as readily.

EXPERIMENTAL

Methyl p-*fluorobenzoate.*—*p*-Fluorobenzoic acid was prepared by the method of Schiemann and Winkelmüller[5] and recrystallized from 25% alcohol. The product

[4] GOMBERG AND BLICKE, *J. Am. Chem. Soc.*, **45**, 1765 (1923).

[5] SCHIEMANN AND WINKELMÜLLER, *Organic Syntheses*, **13**, 52 (1933).

was dissolved in a large excess of methyl alcohol, saturated with dry hydrogen chloride, and allowed to stand for one day. The resulting solution was distilled under 8 mm. pressure, and the fraction boiling at 73–79° was collected. This material gave a capillary boiling point of 197°. Meyer and Hub[6] give 197°.

p-*Fluorotriphenylmethyl chloride.*—A Grignard reaction was carried out with 37 g. of bromobenzene and 5.9 g. of magnesium turnings in 100 cc. of ether and 44 g. of *p*-fluorobenzophenone (prepared by the method of Dunlop and Gardner[7]) in 100 cc. of benzene. The product was decomposed with ice and hydrochloric acid, and extracted with ether. The extract was concentrated, and some impurities removed by steam distillation. The residue, which solidified in a brown sticky mass, was recrystallized twice from carbon tetrachloride with the use of calcium chloride and an activated charcoal, yielding 10.5 g. of yellowish material. This was dissolved in benzene, placed over calcium chloride, and treated with dry hydrogen chloride for several hours. The solution was filtered and concentrated until the boiling point reached 100°. An equal volume of petroleum ether was added, and crystals were obtained by holding at a temperature below 0° for two days. The product was recrystallized from petroleum ether in which it dissolves very slowly. Yield, 6.5 g. (10%), m.p. 90–91°. Nixon and Branch[8] give 87°.

Anal. Calc'd for $C_{19}H_{14}ClF$: Cl, 11.95. Found: Cl, 11.81, 12.26.

Di-p-*fluorotriphenylmethyl chloride.*—Di-*p*-fluorotriphenylcarbinol was prepared similarly to *p*-fluorotriphenylcarbinol from 175 g. of *p*-fluorobromobenzene in 500 cc. of ether, 27 g. of magnesium, and 62 g. of methyl benzoate in 150 cc. of ether. Two recrystallizations from carbon tetrachloride yielded 37.7 g. of yellowish crystals of impure carbinol. A solution of 10 g. of this material in petroleum ether was placed over calcium chloride and treated for four hours with dry hydrogen chloride. The resulting solution was decolorized by boiling with fresh calcium chloride and an activated charcoal, was filtered, concentrated on the steam bath, then held below 0° over night after seeding with a minute crystal of *p*-fluorotriphenylmethyl chloride. White crystals of di-*p*-fluorotriphenylmethyl chloride separated. Yield, 5.5 g. (14%), m.p. 56–57°. This compound is much more soluble in benzene and petroleum ether than *p*-fluorotriphenylmethyl chloride.

Anal. Calc'd for $C_{19}H_{13}ClF_2$: Cl, 11.27. Found: Cl, 11.11, 11.31.

Tri-p-*fluorotriphenylmethyl chloride.*—Tri-*p*-fluorotriphenylcarbinol was prepared similarly to *p*-fluorotriphenylcarbinol from 36.5 g. of *p*-fluorobromobenzene in 120 cc. of ether, 5. g. of magnesium, and 15 g. of methyl *p*-fluorobenzoate in 60 cc. of ether. The product was recrystallized three times from petroleum ether with the aid of an activated charcoal and powdered calcium chloride. White crystals resulted. A solution of these crystals in petroleum ether was placed over calcium chloride and treated for six hours with dry hydrogen chloride. The resulting solution was boiled with an activated charcoal and powdered calcium chloride, then filtered and concentrated on a steam bath. A small portion of this liquid when exposed to the air in a thin film solidified, and when this solid was scraped into the main portion of liquid, it solidified completely. The solid mass was recrystallized from petroleum ether with the use of an activated charcoal and calcium chloride. Crystals with a slight yellowish tinge separated after seeding with a reserved crystal. Yield, 1.1 g. (4%), m.p. 81–82°. The slight coloration and low analysis indicate that some impurity was still present.

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[6] Meyer and Hub, *Monatsh.*, **31**, 935 (1910).

[7] Dunlop and Gardner, *J. Am. Chem. Soc.*, **55**, 1665 (1933).

[8] Nixon and Branch, *Ibid.*, **58**, 492 (1936).

Anal. Calc'd for $C_{19}H_{12}ClF_3$; Cl, 10.67. Found: Cl, 9.96, 9.90, 10.02.

Rearrangement of fluorinated triphenylmethyl chlorides in liquid sulfur dioxide.—This was studied by dissolving approximately 20-mg. portions of the compounds in about 0.5 cc. of liquid sulfur dioxide in sealed tubes, agitating the tubes for a number of days, and then analyzing the contents for ionizable fluorine. The sulfur dioxide was permitted to vaporize slowly from each tube at the end of its period of agitation, and the residue was dissolved in 50 cc. of 50% alcohol. Fluorine was determined in this solution by the Willard and Winter titration[9] using sodium alizarin sulfonate alone as indicator. A sample of triphenylmethyl chloride which had been dissolved in and recovered from liquid sulfur dioxide gave an appreciable titer, indicating that a little sulfur dioxide remained, and precipitated thorium. Experiments with known solutions showed that in the presence of triphenylmethyl chlorides the error of the method is never more than 10% of the correct value. The data and results for these experiments are shown in Table I.

TABLE I

BEHAVIOR OF TRIPHENYLMETHYL CHLORIDES IN LIQUID SULFUR DIOXIDE

TRIPHENYLMETHYL CHLORIDE	WEIGHT, MG.	TIME, DAYS	FINAL COLOR	0.0128 *N* $Th(NO_3)_4$ cc.	ATOMS IONIZABLE F PER MOL.
Unsubstituted	20.2	0	Yellow	0.04	0.007
p-Fluoro-	20.5	56	Orange	0.10	0.019[a]
Di-*p*-fluoro	21.6	46	Orange	0.16	0.030
Di-*p*-fluoro-	21.3	59	Orange	0.26	0.049
Di-*p*-fluoro-	21.8	59	Orange	0.20	0.037
Di-*p*-fluoro-	19.5	63	Dp. Or.	0.40	0.080
Tri-*p*-fluoro-	20.9	19	Orange	0.08	0.016
Tri-*p*-fluoro-	20.3	19	Orange	0.09	0.019
Tri-*p*-fluoro-	19.9	23	Orange	0.13	0.026
Tri-*p*-fluoro-	20.2	23	Orange	0.19	0.037

[a] This value was low because a portion of the sample was lost.

Behavior of the fluorinated triphenylmethyl chlorides in liquid sulfur dioxide in the presence of silver chloride.—The procedure here was the same as in the study of rearrangement in sulfur dioxide except that 99–107 mg. of silver chloride was added to each tube on filling, and this silver chloride had to be filtered out of the product before titrating the fluorine. The data and results for these experiments are given in Table II.

Behavior of the fluorinated triphenylmethyl chlorides in benzene in the presence of silver.—The procedure here was similar to that used in the study of rearrangement in liquid sulfur dioxide. The compounds were dissolved in about 0.5 cc. of benzene in the presence of 99–103 mg. of finely divided silver, and this mixture was sealed in the tube under an atmosphere of carbon dioxide. At the conclusion of its period of agitation, the contents of each tube were mixed with 35 cc. of alcohol, then filtered to remove the excess silver and the silver chloride formed. The filtrate was diluted

[9] WILLARD AND WINTER, *Ind. Eng. Chem., Anal. Ed.*, **5**, 7 (1933); REYNOLDS, KERSHAW, AND JACOB, *J. Assoc. Official Agr. Chem.*, **19**, 159 (1936).

with 15 cc. of water and then titrated. Titration of known sodium fluoride samples in the presence of benzene showed that the error does not exceed 10% of the correct value under these conditions. In the presence of benzene and triphenylmethyl chloride, but no fluoride, the first drop of titrating solution gave the end-point. The data and results for these experiments are given in Table III.

TABLE II

TREATMENT OF TRIPHENYLMETHYL CHLORIDES IN LIQUID SULFUR DIOXIDE WITH SILVER CHLORIDE

TRIPHENYLMETHYL CHLORIDE	WEIGHT, MG.	TIME, DAYS	FINAL COLOR	0.0128 *N* $Th(NO_3)_4$ cc.	ATOMS IONIZABLE F PER MOL.
Unsubstituted	20.7	0	Yellow	0.04	0.007
p-Fluoro-	20.9	56	Orange	0.09	0.016
p-Fluoro-	21.4	56	Orange	0.26	0.046
p-Fluoro-	19.0	73	Lt. Or.	0.10	0.020
p-Fluoro-	21.0	77	Orange	0.16	0.027
Di-*p*-fluoro-	19.1	59	Orange	0.18	0.038
Di-*p*-fluoro-	20.9	59	Orange	0.20	0.039
Tri-*p*-fluoro-	20.3	19	Orange	0.06	0.012
Tri-*p*-fluoro-	20.7	23	Orange	0.14	0.027

TABLE III

TREATMENT OF TRIPHENYLMETHYL CHLORIDES IN BENZENE SOLUTION WITH SILVER

TRIPHENYLMETHYL CHLORIDE	WEIGHT, MG.	TIME, DAYS	FINAL COLOR	0.0128 *N* $Th(NO_3)_4$ cc.	ATOMS IONIZABLE F PER MOL.
p-Fluoro-	21.5	56	Lt. Yel.	0.92	0.16
p-Fluoro-	20.6	56	Lt. Or.	1.6	0.30
p-Fluoro-	23.1	77	Orange	1.26	0.21
Di-*p*-fluoro-	20.8	42	Lt. Yel.	1.00	0.19
Di-*p*-fluoro-	21.6	42	Dp. Or.	1.46	0.28
Di-*p*-fluoro-	20.3	57	Dp. Or.	1.1	0.22
Di-*p*-fluoro-	20.5	57	Purple	0.86	0.17[a]
Tri-*p*-fluoro-	20.5	23	Colorl.[b]	1.18	0.25
Tri-*p*-fluoro-	20.6	23	Orange	1.0	0.21
Tri-*p*-fluoro-	20.0	23	Lt. Or.	2.2	0.43
Tri-*p*-fluoro-	20.6	29	Orange	0.66	0.13

[a] In this experiment the solvent was nitrobenzene instead of benzene.

[b] An orange color first developed in this experiment, then disappeared after several days.

SUMMARY

1. Di- and tri-*p*-fluorotriphenylmethyl chlorides have been prepared and described, and *p*-fluorotriphenylmethyl chloride has been prepared by a new method which leaves no doubt as to its structure.

2. It has been shown that these three compounds rearrange in liquid sulfur dioxide to the extent of 1 to 8 per cent., depending on specific conditions, to yield chloro- and fluorochlorotriphenylmethyl fluorides, and that the presence of silver chloride has little or no effect on this reaction.

3. It has been shown that silver removes, on the average, 0.24 atoms of fluorine per molecule from the fluorinated triphenylmethyl chlorides in benzene solution and that a reaction resulting in the formation of "radicals of the second order" which goes halfway to completion is thus indicated.

4. These findings show that fluorine in a para position of the triphenylmethyl group has a mobility like that of the other halogens but in a lesser degree.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

THE SEPARATION OF STEROLS BY THE CHROMATOGRAPHIC ADSORPTION METHOD

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The separation of complex sterol mixtures as found in nature is often difficult, due to the close relationship of the substances. In search for isolation procedures adsorption methods have been applied.

In a review on the preparation and purification of organic compounds, Winterstein[1] has mentioned the successful application of adsorption methods to sterols in spite of the difficulty that separate zones of colorless substances cannot be recognized as such and that dissection has to be done empirically. When a mixture of cholesterol and ergosterol was adsorbed on aluminum oxide, it was found that the upper layers contained most of the ergosterol whereas the cholesterol concentrated in the lower layers. Evidently, the number of double bonds influences strongly the degree of of adsorption.

Windaus[2] has used this method with slight variation for the isolation of provitamin from cholesterol, obtained from egg-yolk. He adsorbed the sterol on aluminum oxide and washed until the cholesterol appeared again in the filtrate. The filtrate was collected in separate fractions. The first fraction was found to contain pure cholesterol. In the last fraction the provitamin was concentrated and was then identified as ergosterol.

Another possible way of separating adsorbed sterols is by means of fluorescence, produced by irradiation of the column with ultraviolet light. Karrer and Nielsen[3] separated ergosterol from a mixture of cholesterol and ergosterol. The fluorescence, however, is rather weak and we have found that when Karrer's experiment is repeated with a more complex mixture, it is not possible to distinguish between the zones of the ultrachromatogram. When this method is used one must consider also the possible formation of irradiation products, especially when quartz adsorption tubes are used.

* Research Assistant on Special Funds from Merck and Company, Inc., Rahway, New Jersey.

[1] WINTERSTEIN AND STEIN, *Zeit. physiol. Chem.*, **220**, 247 (1933).

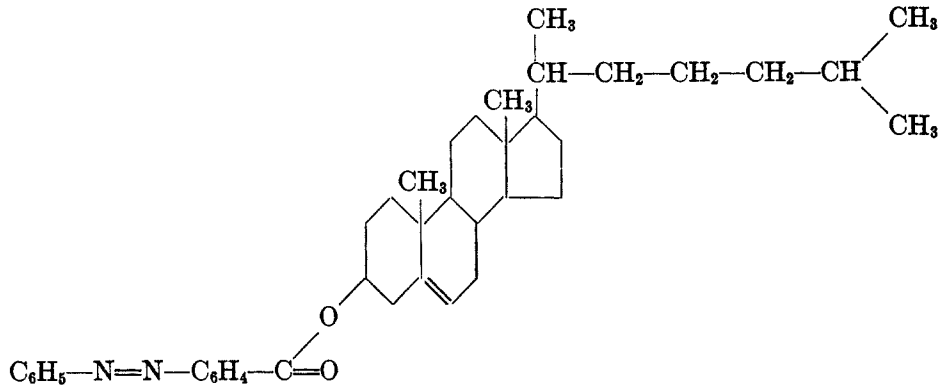
[2] WINDAUS AND STANGE, *ibid.*, **244**, 218 (1936).

[3] KARRER AND NIELSEN, *Ber. ges. Physiol. exptl. Pharmakol.*, **86**, 529; *Zangger-Festschrift*, 954 (1934).

A somewhat different technique was employed by Brockmann[4] in his work on the isolation of vitamin D_3. Winterstein[1] had formerly suggested that it might be possible, in some cases at least, to add to colorless mixtures which are to be separated small amounts of dyes the adsorption coefficients of which are known with respect to those of the colorless substances. Following this suggestion, Brockmann used a dye of the same adsorption coefficient as the vitamin itself, and thus was able to locate the adsorption zone.

Another method of obtaining chromatograms of colorless substances was investigated by Strain[5] who separated colorless carbonyl compounds by converting them into their colored dinitrophenylhydrazones before adsorption. In similar manner Brockmann[4] investigated the adsorption of mixtures of dinitrobenzoic acid esters of sterols. The color of these sterol esters, however, is not pronounced, and distinct adsorption zones were not easily observed.

Therefore, it seemed advisable to investigate the possibility of preparing bright-colored sterol derivatives which could be employed advantageously for chromatographic adsorption. Sterol esters of azobenzenemonocarboxylic acid were found to have suitable properties, and their separation was studied. Apart from the obvious advantage of having visible adsorption zones, they also offered the possibility of regenerating the original sterol by simple saponification.



CHOLESTERYL ESTER OF AZOBENZENEMONOCARBOXYLIC ACID

The azobenzenemonocarboxylic acid was prepared according to Angeli[6]. Chlorination of the acid with thionyl chloride presented some difficulty at first, but if an excess of solid sodium carbonate is mixed with the acid

[4] BROCKMANN, *Zeit. physiol. Chem.*, **241**, 104 (1936).
[5] STRAIN, *J. Am. Chem. Soc.*, **57**, 758 (1935).
[6] ANGELI AND VALORI, *Atti. accad. Lincei*, **22**, I, 132 (1913).

before the addition of the thionyl chloride, an almost quantitative yield of the chloride can be obtained. The pure acid chloride forms beautiful red crystals, melting at 93–94° (uncorr.), and when kept dry is stable at room temperature. A number of sterols were esterified in pyridine solution with the use of a slight excess of the acid chloride. The esters are orange- to red-colored, crystalline compounds.

The preparation of the (*a*) cholesteryl ester, m.p. 188–9°, (*b*) β-sitosteryl ester, m.p. 173–4°, (*c*) stigmasteryl ester, m.p. 191–2°, and (*d*) ergosteryl ester, m.p. 200–1°, of azobenzenemonocarboxylic acid is described in the experimental part of this paper. Mixtures of $a + c$, $c + d$, $a + d$, and $a + c + d$ can be separated easily and quantitatively into their components, provided the proper technique is employed.

Mixtures of $a + b$, however, give a continuous chromatogram, and no separate zones can be distinguished. When the column is cut into several sections, the fractions obtained from each section by elution all melt within the same range of temperature, corresponding to the mixture melting point of the cholesteryl and β-sitosteryl esters. Apparently no separation has taken place.

Mixtures of $b + c$, $b + d$, and $b + c + d$ cannot be separated into their components as successfully as the combinations listed above. One obtains long, continuous chromatograms. If, however, the chromatogram is cut into several pieces one finds that the sitosteryl ester always concentrates in the lowest layers, and pure sitosteryl ester could be obtained by elution of the lowest part of the chromatogram.

All these results are in accordance with the theory that the number of double bonds is responsible for the degree of adsorption. The more double bonds a compound has, the stronger is its adsorption and the slower is its rate of downward movement on development of the chromatogram; therefore, it concentrates in the upper zone. The fact that β-sitosterol and cholesterol seem to have the same adsorption coefficient is in agreement with these conclusions. Both of these compounds have one double bond in the molecule and differ only in the nature of their side-chains. This difference, however, is not sufficient to cause enough variation in the respective adsorption coefficients. Therefore, it may be concluded that with aluminum oxide this method of separation is only applicable to sterols which differ in the number of double bonds, the position of which does not seem to exert any important influence.

Other interesting facts should be noted. Sterols in general are by no means as strongly adsorbed as many other substances, for example, the carotinoids the adsorption of which is illustrated by Zechmeister[7]. Here

[7] ZECHMEISTER AND CHOLNOKY, "Die Chromatographische Adsorptionsmethode," Julius Springer, Wien, 1937.

beautiful sharp rings are obtained in rather short columns. In our work on the sterols it was found necessary to employ long, narrow tubes to insure fair development of the chromatogram. The expectation that the azobenzenemonocarboxylic group would increase the degree of adsorption of the sterols does not seem to have been realized to any extent.

The technique of packing the adsorption column and the manner in which the adsorbed substances are washed down have a great influence on the production of a good chromatogram. The apparatus used in our experiments was devised according to descriptions by Zechmeister[7]. It was found that it is best to use anhydrous aluminum oxide, standardized according to Brockmann, to introduce the adsorbent in small portions into the tubes, which had a length of 70–80 cm. and a diameter of 1–1.5 cm., and to pack each portion separately. Benzene is most conveniently employed as a solvent for the sterol esters. For the development of the chromatogram, however, benzene cannot be used, since the esters are much too soluble and will travel down the column much too fast. Mixtures (1:10) of benzene and high-boiling petroleum ether may be used. Petroleum ether alone, however, is more effective for this purpose. It is important that all of the substance be adsorbed in as small a layer as possible before the development. Therefore, no unnecessary excess of benzene should be used.

A slow and even travelling rate is the ideal condition. No suction should be applied throughout the development. This necessarily involves a long period of time for a single run, but if a sufficiently large funnel be used, and if it be fastened to the tube in an airtight manner, a constant level of solvent is automatically maintained over the aluminum oxide column and only occasional observation is necessary. Pushing out the whole column after development was never very successful. As a consequence the glass tubes were always cut into the desired sections. For elution a mixture of benzene, ether and alcohol was used, from which the esters could be regained easily.

EXPERIMENTAL

Preparation of the acid chloride of azobenzenemonocarboxylic acid.—Two grams of dry azobenzenemonocarboxylic acid was thoroughly mixed with 5 grams of anhydrous sodium carbonate. To this 25 cc. of thionyl chloride was added and the mixture was then refluxed for 1.5 hours. The product was taken up in low-boiling petroleum ether. The sodium carbonate was filtered, and the clear red solution was evaporated to dryness on the steam bath. Crystallization of the residue from petroleum ether at 0° gave bright red crystals which melted at 93–94° (uncorr.); yield, 90% of the theoretical.

Preparation of sterol esters of azobenzznemonocarboxylic acid.—(*a*) Five-tenths of a gram of cholesterol (dried in vacuum at 100°) and 0.4 gram of the acid chloride were dissolved in 15 cc. of pyridine (dry), and the solution was heated on the steam bath

for 1 hour. The ester was then precipitated with cold water, filtered, and washed. The dried product was recrystallized from benzene and absolute alcohol. Beautiful red needles which melted at 188–189° were obtained.

Anal. Calc'd for $C_{40}H_{54}N_2O_2$: C, 80.76; H, 9.15; N, 4.71.
Found: C, 80.94; H, 9.02; N, 4.81.

(*b*) β-Sitosteryl ester of azobenzenemonocarboxylic acid was prepared in a manner similar to that described for cholesteryl ester. Crystals which melted at 173–174° were obtained.

Anal. Calc'd for $C_{42}H_{58}N_2O_2$: C, 80.97; H, 9.39; N, 4.50.
Found: C, 80.93; H, 9.53; N, 4.69.

(*c*) Crystals of stigmasteryl ester of azobenzenemonocarboxylic acid melted at 191–192°.

Anal. Calc'd for $C_{42}H_{56}N_2O_2$: N, 4.52. Found: N, 4.59.

(*d*) Preparation of ergosteryl ester of azobenzenemonocarboxylic acid by the above method gave a product which melted at 200–201°.

Anal. Calc'd for $C_{41}H_{52}N_2O_2$: C, 81.40; H, 8.67; N, 4.64.
Found: C, 81.38; H, 8.64; N, 4.84.

Separation of cholesteryl and ergosteryl esters of azobenzenemonocarboxylic acid.— Filling of the adsorption tube was carried out as follows. Cotton was placed in the lower end of the glass tube (70 cm. long, 1.4 cm. in diameter) mounted vertically. This was covered with a layer of sand about 3 cm. in height. Anhydrous aluminum oxide was then introduced in small portions. Each portion was packed firmly. The last 10 cm. of the tube was left empty. During the filling suction was applied, and after each portion had been packed the tube was tapped lightly to smooth out the surface. A mixture of benzene and petroleum ether (1:1) was poured into the tube and allowed to run through the column until only a small layer of solvent remained over the aluminum oxide. A solution of 0.05 gram of the above described cholesteryl ester and 0.05 gram of the ergosteryl ester in 10 cc. of benzene was then added, and the suction was turned off. When only a small amount of solution was left on top of the column, a few cubic centimeters of pure benzene was added to wash down the mixture. A liter funnel was then stoppered tightly into the tube, and pure high-boiling petroleum ether was allowed to drop onto the column at the same rate as it was running through the adsorption tube (10–20 drops per minute). The petroleum ether should only be introduced after all colored solution has disappeared from the top of the column. Care must be taken not to allow the surface of the column ever to become dry once the experiment has been started.

Before the development of the chomatogram, the adsorbed ester mixture formed a red-brown zone at the top of the column (about 6 cm. in length). On washing with petroleum ether this zone began to travel down, slowly lengthening and decreasing in color intensity. After 3 hours it had reached a length of 15 cm., having travelled about halfway down the column. About that time a break in the middle became noticeable, and widened as the washing was continued. After 4 hours the development was stopped, and the glass tube was cut in the middle of the non-colored zone which had reached a length of about 7 cm. The upper and the lower layers were eluted separately by shaking with a mixture of benzene, ether, and alcohol (5:5:1). The filtered solutions were evaporated, and the residues were dried.

Upper layer: 0.048 gram, melting at 199–201° (ergosteryl ester).

Lower layer: 0.047 gram, melting at 187–189° (cholesteryl ester).

All other mixtures which were studied were treated in a similar manner. The results are described in the theoretical part of the paper.

The authors at this time wish to express their thanks to Merck and Company, Inc. of Rahway, New Jersey for a grant-in-aid, and for the analyses published in this article.

SUMMARY

Preparations of the acid chloride of azobenzenemonocarboxylic acid and of its cholesteryl, β-sitosteryl, stigmasteryl, and ergosteryl esters have been described.

A study of the separation of the above sterol esters by means of the chromatographic adsorption method has been made.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE RELATIVE PROPORTIONS OF STEREOISOMERIC OXIMES FORMED IN THE OXIMATION OF UNSYMMETRICAL KETONES

W. E. BACHMANN AND SISTER M. XAVERIA BARTON, I. H. M.*

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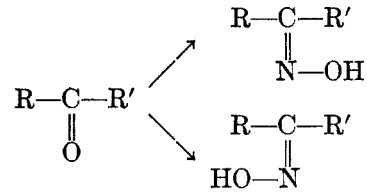
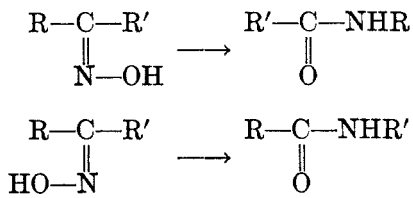
It is well known that interaction of hydroxylamine and an unsymmetrical ketone may yield a mixture of two stereoisomeric oximes.



In a number of instances it has been possible to isolate the two forms of the oxime from the mixture. The configurations of the oximes have usually been determined by means of the Beckmann rearrangement. The latter reaction has received ample discussion from others[1]. For our discussion it suffices to point out that, provided no isomerization of the oxime occurs, each oxime gives rise to a single rearrangement product, this product being different for each oxime. Moreover, according to Meisenheimer[2], the group *trans* with respect to the hydroxyl group migrates from the carbon to the nitrogen atom.



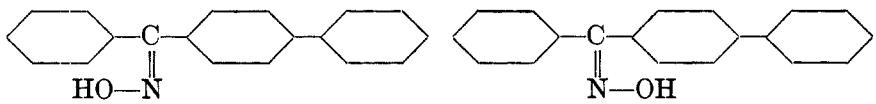
* From part of the Ph.D. dissertation of Sister M. Xaveria Barton, I.H.M.

[1] Excellent reviews of the Beckmann rearrangement have been presented by BLATT, *Chem. Rev.* **12**, 215-260 (1933), and by MEISENHEIMER AND THEILACKER in FREUDENBERG, "Stereochemie," Franz Deuticke, Leipzig, **1933**, Part III, pp. 1002-1094. See also GILMAN, "Organic Chemistry," John Wiley and Sons, New York, **1938**, Vol. I.

[2] MEISENHEIMER, *Ber.*, **54**, 3206 (1921).

Although a large amount of work has been done on the Beckmann rearrangement itself, little attention has been directed to the quantitative estimation of the relative amounts of the two stereoisomeric oximes that are formed under a given set of conditions. Recently, Bachmann and Boatner[3] investigated the oximation of the structurally isomeric acetylphenanthrenes and benzoylphenanthrenes and determined the relative amounts of the two oximes that were produced in each case. We have now extended this investigation to include the oximation of a number of simple diaryl ketones and alkyl aryl ketones. Having determined the proportions of the two stereoisomeric oximes that are produced from a ketone, we were next interested in knowing what this ratio really means. Is it a measure of the relative rates of two competing reactions leading to the two different oximes, or does it represent the proportions of the two stereoisomers in an equilibrium mixture? To answer these questions we studied the oximation of phenyl *p*-biphenyl ketone in detail, for it was found that the two stereoisomeric oximes produced from this ketone could be separated readily and be obtained in pure form.

Phenyl *p*-biphenyl ketone was oximated by heating a mixture of the ketone, hydroxylamine hydrochloride, and pyridine in absolute alcohol[4] for two hours. By the method to be described subsequently, it was found that the two oximes were formed in approximately equal amounts. By fractional crystallization we next isolated the two stereoisomeric oximes in pure, crystalline form[5]. One of the oximes, which crystallized in large prisms melting at 173°, rearranged under the influence of phosphorus pentachloride to *N*-(*p*-biphenyl)benzamide, $C_6H_5CONHC_6H_4C_6H_5$, exclusively; hence, on the principle of a *trans* migration, this oxime must be *syn*-phenyl *p*-biphenyl ketoxime† (I). The other oxime, crystallizing in fine needles melting at 200°, rearranged to give *N*-phenyl-*p*-phenylbenzamide, $C_6H_5C_6H_4CONHC_6H_5$, exclusively; hence this oxime must be *anti*-phenyl *p*-biphenyl ketoxime (II).



(I) (II)

[3] BACHMANN AND BOATNER, *J. Am. Chem. Soc.*, **58**, 2097 (1936).

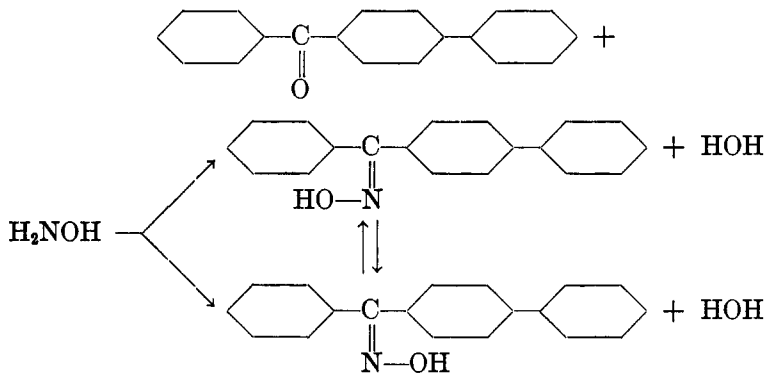
[4] Compare HOUBEN AND PFANKUCH, *Ber.*, **59**, 2394 (1926), BUCK AND IDE, *J. Am. Chem. Soc.*, **53**, 1541 (1931), BRYANT AND SMITH, *ibid.*, **57**, 57 (1935), and BACHMANN AND BOATNER, *ibid.*, **58**, 2097 (1936), for the pyridine method of preparing oximes.

[5] KOLLER, *Monatsh.*, **12**, 501 (1891), was able to isolate only one of the oximes, although, as will be shown in the experimental part, the product prepared according to his procedure actually contained both oximes.

† The prefix, *syn* or *anti*, refers to the position of the first group named relative to the hydroxyl group. This oxime (I) could also be called *anti*-*p*-biphenyl phenyl ketoxime.

The fact that only one rearrangement product was obtained in each case is of importance in demonstrating that pure oximes had been isolated, and, secondly, that no isomerization of one stereoisomer to the other occurred under the conditions employed for the rearrangement.

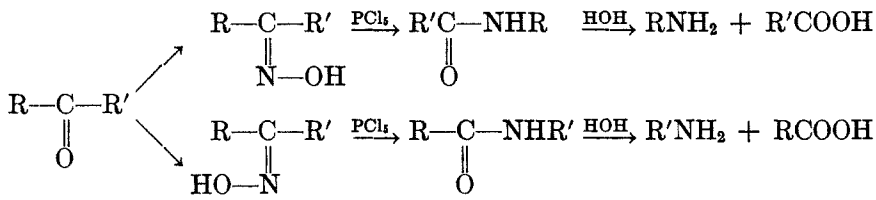
Each of the pure oximes was now heated with a mixture of hydroxylamine hydrochloride, pyridine, absolute alcohol and a few drops of water for two hours. Under these conditions, which simulated those used for the oximation of the ketone, each of the oximes was converted to a 1:1 mixture of the *syn* and *anti* forms, the identical mixture that was obtained when the ketone was oximated. This means that each oxime is convertible to its geometrical isomer under the conditions employed for oximation, and it follows that the 1:1 mixture represents an *equilibrium* mixture of the *syn* and *anti* forms. The oximation of the ketone can, therefore, be formulated as follows,



Although the rate of formation of one oxime may be greater than that of the other, this factor will have no effect on the final proportions if sufficient time is allowed for equilibrium to be established. That the conversion of one oxime to the other is fairly rapid was shown by running the reaction for only twenty-five minutes; even in this time a single, pure oxime was converted to the equilibrium mixture. As was expected, the ratio of the two oximes in the equilibrium mixture remained unchanged when the oximation mixture was heated for two days.

It should be borne in mind that the scheme shown above represents the over-all state of affairs and does not attempt to account for the mechanism by which the change from one oxime to the other takes place. There may be an equilibrium between the oximes themselves, or through intermediate oxime salts, or the mechanism might involve hydrolysis of the oximethrough a reversible reaction with re-oximation of the regenerated ketone. These points as well as the speed of the interconversion and the reagent catalyzing the change await solution from further experiments.

In order to determine the relative amounts of the two stereoisomeric oximes produced from a given ketone, we employed the procedure of Bachmann and Boatner[3]. The crude mixture of oximes was subjected to rearrangement, without any purification of the oximes by recrystallization, for it would be impossible to avoid some loss if this were done. Other investigators have been content to recrystallize the mixture of oximes and isolate the isomer present in the larger amount. Following the rearrangement, we hydrolyzed the mixture of substituted amides, and the relative proportion of the two different acids (or amines) which were produced was taken as a measure of the amounts of the original oximes in the mixture. The complete scheme may be represented as follows,



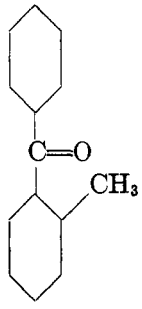
The relative amount of the acid RCOOH represents the relative proportion of the oxime having the group R *syn* to the hydroxyl group.

In general, oximation was accomplished by the method already mentioned, namely, heating the ketone with hydroxylamine hydrochloride and pyridine in absolute alcohol for two hours. With all of the ketones listed in Table II, except 2-benzoylfluorene, the oximes remained in solution. By this method we were able to obtain quantitative oximation of all of the ketones which we studied with the exception of the 9-anthryl ketones. The failure in these cases is attributed to steric hindrance around the carbonyl group. Steric hindrance had already been encountered in the *o*-tolyl aryl ketones, for longer periods of time were required in order to oximate them completely. Smith[6] endeavored to prepare the oxime of mesityl phenyl ketone but even the most drastic conditions failed to yield the oxime. A comparison of the structures of 9-anthryl phenyl ketone with the *o*-methyl substituted ketones shows why the negative results obtained with the 9-anthryl ketones were not entirely unexpected, for two ortho groups are present to hinder the formation of the oxime.

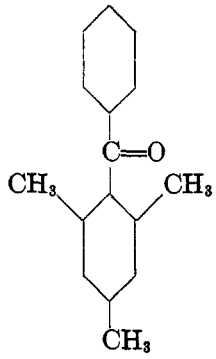
The second requirement for our investigation was quantitative rearrangement of the ketoximes. Phosphorus pentachloride in anhydrous benzene was selected as the best reagent for carrying out the Beckmann rearrangement, because in all cases it was possible to obtain at room temperature a quantitative yield of the substituted amide in a relatively pure condition. Phosphorus trichloride and sulfuric acid-acetic acid were

[6] SMITH, *Ber.*, **24**, 4025 (1891).

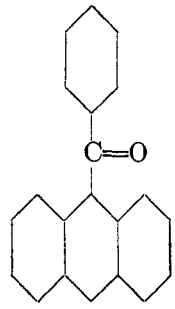
found to be less satisfactory for our purpose. Although we obtained only partial rearrangement with phosphorus trichloride, the latter can now be added to the list of reagents capable of inducing the Beckmann rearrangement. Other reagents were less desirable because they frequently re-



PHENYL *o*-TOLYL KETONE
Slow oximation



PHENYL MESITYL KETONE
No oximation



PHENYL 9-ANTHRYL KETONE
No oximation

quired heating or were incomplete in their reaction. It has been reported that certain oximes, particularly the aliphatic ketoximes, isomerize to some extent during the process of rearrangement, especially under the influence of heat. We feel that under our conditions, there is practically no conversion of one form of the oxime to the other—and this was definitely shown to be true with the phenyl *p*-biphenyl ketoximes.

The mixtures of substituted amides produced on rearrangement of the oximes were generally resistant to hydrolysis. Best results were obtained by refluxing the mixture with a methanol solution of potassium hydroxide for four days or longer. The removal of the acids from the hydrolysis mixture and the analysis of the mixture of acids varied with the particular mixture involved. In Table I is given a typical set of data obtained with one ketone, *p*-biphenyl *m*-tolyl ketone, which shows the agreement obtained on different runs. The yield of acids is calculated on the basis of the ketone. The proportion of *p*-phenylbenzoic acid represents the relative amount of the *syn*-*p*-biphenyl *m*-tolyl ketoxime (53 per cent.) and the quantity of *m*-toluic acid corresponds to the proportion of *anti*-*p*-biphenyl *m*-tolyl ketoxime (47 per cent.) in the mixture of the *syn* and *anti* oximes.

In Table II are summarized the results obtained with thirteen ketones, of which all but one (*o*-tolyl *p*-biphenyl ketone) gave yields of acids corresponding to 88–98 per cent. of the theoretical amount. Not listed are the ketones which failed to give satisfactory results in some stage of the

process; mention of these is made in the experimental part. The figures representing the proportions of *syn* and *anti* oximes in the mixtures obtained on oximation are accurate only to 5–10 per cent. In nearly all cases two hours of heating was employed for the oximation, so that the

TABLE I

PROPORTIONS OF ACIDS PRODUCED BY HYDROLYSIS OF THE AMIDES FORMED BY REARRANGEMENT OF THE OXIMES OF *p*-BIPHENYL *m*-TOLYL KETONE

p-PHENYLBENZOIC ACID		*m*-TOLUIC ACID		TOTAL ACID	
g.	% by moles	g.	% by moles	g.	% by moles
2.01	53.5	1.20	46.5	3.21	95
1.00	55.6	0.55	44.5	1.55	91
0.99	51.5	0.65	48.7	1.64	98
Average	53	Average	47		

TABLE II

PROPORTIONS OF *Syn* AND *Anti* OXIMES IN THE MIXTURES PRODUCED BY OXIMATION OF THE KETONES

KETONE R–C(=O)–R′		% R–C(=N–OH)–R′	% R–C(=N–OH)–R′
R	R′		
Phenyl	*p*-Biphenyl	49	51
Phenyl	*p*-Tolyl	48	52
Phenyl	*m*-Tolyl	50	50
Phenyl	*o*-Tolyl	23	77
Phenyl	*p*-Anisyl	51	49
Phenyl	*p*-Chlorophenyl	44	56
Phenyl	2-Fluoryl	46	54
o-Tolyl	*p*-Biphenyl	66	34[a]
m-Tolyl	*p*-Biphenyl	47	53
p-Tolyl	*p*-Biphenyl	34	66
Methyl	1-Naphthyl	99	1
Methyl	2-Naphthyl	99	1
Methyl	*p*-Biphenyl	99	1

[a] These values are based on a 75% yield of acids.

results indicate the proportions of the two forms of the oxime in the mixture at the end of this time. Whether or not an equilibrium mixture was obtained in each case cannot be stated with certainty. This can be ascertained by isolating the two oximes as was done for the phenyl *p*-biphenyl ketoximes and determining whether conversion of one form to the other

takes place under the conditions of the oximation. Once the interconversion of the oximes has been established for all cases, the position of equilibrium could be determined by running the oximation reaction for varying periods of time.

From the table it is seen that most of the diaryl ketones yielded the *syn* and *anti* oximes in an approximately 1:1 ratio. The methyl aryl ketones gave nearly entirely the *syn*-methyl form, although about 1 per cent. of the other form was present in the mixture. This result is in agreement

TABLE III

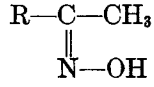
NEW SUBSTITUTED AMIDES

(All of the compounds are colorless.)

AMIDE	RECRYST. SOLVENT	CRYST. FORM	M.P., °C.
N-Methyl-*p*-phenylbenzamide[a]	Alcohol	Needles	167
N-(*o*-Tolyl)-*p*-phenylbenzamide[b]	Benzene	Needles	179.5–180
N-(*p*-Biphenyl)-*o*-methylbenzamide[c]	Benzene	Needles	256
N-(*m*-Tolyl)-*p*-phenylbenzamide[d]	Acetone	Plates	165–166
N-(*p*-Biphenyl)-*m*-methylbenzamide[e]	Acetone	Flakes	270
N-(*p*-Tolyl)-*p*-phenylbenzamide[f]	Acetone	Flakes	230–231
N-(*p*-Biphenyl)-*p*-methylbenzamide[g]	Alcohol	Plates	236–237
N-Methyl-1-naphthamide[h]	Benzene	Needles	159–160
N-Methyl-2-naphthamide[i]	Benzene	Plates	108–109.5
N-Phenyl-*m*-methylbenzamide[j]	Benzene	Rhombs	125–125.5
N-(2-Fluoryl)benzamide[k]	Benzene	Flakes	215
N-Phenyl-2-fluorenecarboxylic acid amide[l]	Acetone	Flakes	255–256

[a] Calc'd for $C_{14}H_{13}NO$: N, 6.3. Found: N, 6.3. [b] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.9. [c] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.8. [d] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.6. [e] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.8. [f] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.7. [g] Calc'd for $C_{20}H_{17}NO$: N, 4.9. Found: N, 4.6. [h] Calc'd for $C_{12}H_{11}NO$: N, 7.6. Found: N, 7.4. [i] Calc'd for $C_{12}H_{11}NO$: N, 7.6. Found: N, 7.5. [j] Calc'd for $C_{14}H_{13}NO$: N, 6.6. Found: N, 6.5. [k] Calc'd for $C_{20}H_{15}NO$: N, 4.9. Found: N, 4.9. [l] Calc'd for $C_{20}H_{15}NO$: N, 4.9. Found: N, 4.9.

with the results obtained by Bachmann and Boatner with the acetylphenanthrenes. They found that the 1-, 2-, 3-, and 9-phenanthryl groups oriented themselves nearly entirely *anti* to the hydroxyl group. In all of these methyl aryl ketones, then, the configuration of the oxime is principally



No ketone which we could successfully oximate failed to give two stereoisomers. This is particularly noteworthy in the case of the methyl aryl

ketones, for only one oxime has been reported before for these ketones. It is probable that two oximes are always formed from a given ketone, but the one present in small amount has escaped detection by the ordinary methods of separation. By our procedure we have demonstrated the existence of the following new oximes: *syn-p*-biphenyl methyl ketoxime, *syn*-phenyl *p*-biphenyl ketoxime, *syn-o*-tolyl *p*-biphenyl ketoxime, *anti-o*-tolyl *p*-biphenyl ketoxime, *syn-m*-tolyl *p*-biphenyl ketoxime, *anti-m*-tolyl *p*-biphenyl ketoxime, *syn-* or *anti-p*-tolyl *p*-biphenyl ketoxime*, *syn-* or *anti-m*-tolyl phenyl ketoxime*, *syn-* or *anti-* phenyl 2-fluoryl ketoxime*, *syn*-1-naphthyl methyl ketoxime, *syn*-2-naphthyl methyl ketoxime, *syn*-methyl 1-anthryl ketoxime, *anti*-methyl 1-anthryl ketoxime. For the oximes marked with an asterisk, one form of the oxime has already been reported in the literature but the configuration has not been established; our work shows that both forms of these oximes exist.

A number of the substituted amides, which were obtained as products of the rearrangement of the oximes, have not been prepared before. These new amides have now been synthesized in quantitative yield by mixing equimolar quantities of the acid chloride and the amine in benzene or acetone solution. The properties of these new amides are shown in Table III.

EXPERIMENTAL

Oximation of the ketones.—In all cases a mixture was made of 0.01 gram mole of the ketone and 0.011 gram mole of hydroxylamine hydrochloride in enough pyridine and absolute alcohol (usually 4 to 5 cc. of each) to dissolve all of the reactants when warm. After the mixture had been heated on a steam bath for two hours, the solvents were evaporated in a current of air, and the residue, which was usually crystalline, was treated with water, filtered, washed well with water, and dried. The products so obtained were entirely satisfactory for the rearrangement reaction.

Beckmann rearrangement of the oximes.—The mixture of the dry oximes was suspended in 25 cc. of anhydrous, thiophene-free benzene and treated portionwise with excess of powdered phosphorus pentachloride, usually 3 g. After two to three hours water was added, and the mixture was allowed to stand for three hours more. The solvent was then evaporated in a current of air, and the mixture of amides was collected by filtration, washed with water, and dried.

Hydrolysis of the substituted amides.—The general procedure for hydrolysis consisted in refluxing the mixture of amides with 100 cc. of a 25% solution of potassium hydroxide in pure methanol, the condenser being provided with a drying tube containing calcium chloride. A 1-liter round-bottomed flask fitted to a condenser by a ground-glass connection was used. When the hydrolysis was complete, the methanol was distilled from the mixture. Distilled water and benzene were added to the residue in the flask, and the mixture was warmed until two clear layers resulted. After separation of the two solutions, the aqueous solution was extracted three times with benzene in order to remove the amine. Acidification of the filtered aqueous solution yielded the mixture of acids, which were isolated by filtration and/or extraction by benzene. The benzene extract of the amines was shaken with several por-

tions of dilute hydrochloric acid in order to extract the amines, and the benzene solution was evaporated in order to determine if any non-saponfiable material was present.

The mixtures of acids which were obtained were analyzed by the methods worked out in the study of the pinacol-pinacolone rearrangement.[7] Thus, digestion with hot water served to separate benzoic acid (soluble) from *p*-phenylbenzoic acid (insoluble), *m*-toluic acid from *p*-phenylbenzoic acid, *o*-toluic acid from *p*-phenylbenzoic acid, *p*-toluic acid from *p*-phenylbenzoic acid, and benzoic acid from *p*-chlorobenzoic acid. The proportion of *p*-anisic acid in the mixture of this acid and benzoic acid was determined by means of a methoxyl determination, performed according to the method of Vieböck and Schwappach[8]. The mixtures of benzoic acid and the toluic acids were analyzed by oxidizing the toluic acids to the corresponding phthalic acids, which could be separated readily from the soluble benzoic acid. As a rule synthetic mixtures of the acids were analyzed at the same time for comparison.

Isolation of the two stereoisomeric phenyl p-*biphenyl ketoximes.*—Fifteen grams of phenyl *p*-biphenyl ketone was oximated, and the mixture of oximes was recrystallized from methanol. The first crop of crystals consisted principally of fine, gleaming needles of the *anti*-phenyl *p*-biphenyl ketoxime, which is less soluble than its stereoisomer. By further recrystallization this oxime was obtained perfectly pure; m. p. 200°. The filtrate from which this oxime had been separated was concentrated and allowed to stand for several days so that some evaporation took place. Under these conditions the solution deposited the *syn*-phenyl *p*-biphenyl ketoxime as stout, monoclinic prisms along with fine needles of the isomer and a fine mixture of both forms. The large prisms were separated from the mixture mechanically and purified by recrystallization from methanol; m.p. 173°.

Rearrangement of anti-*phenyl* p-*biphenyl ketoxime.*—Rearrangement of the oxime in the usual manner by means of phosphorus pentachloride in anhydrous benzene yielded an anilide, which on hydrolysis gave a quantitative yield of *p*-phenylbenzoic acid and aniline; no *p*-aminobiphenyl or benzoic acid could be detected.

Conversion of anti-*phenyl* p-*biphenyl ketoxime to the equilibrium mixture of the oximes.*—A 1.0-g. portion of the oxime, 0.4 g. of hydroxylamine hydrochloride, 2 cc. of absolute alcohol, 2 cc. of pyridine and 2 drops of water were heated on a steam bath for two hours. Rearrangement of the product which was isolated from the solution, followed by hydrolysis of the rearrangement product yielded 53.5% of *p*-phenylbenzoic acid and 44% of *p*-aminobiphenyl.

Rearrangement of syn-*phenyl* p-*biphenyl ketoxime.*—Rearrangement of a sample of this oxime in the usual manner gave only *N*-(*p*-biphenyl)benzamide, for hydrolysis of the amide yielded benzoic acid and *p*-aminobiphenyl; no trace of *p*-phenylbenzoic acid was found.

Conversion of syn-*phenyl* p-*biphenyl ketoxime to the equilibrium mixture of the oximes.*—A sample of this oxime treated in the manner described for the *anti* isomer gave a mixture of oximes, which on rearrangement, followed by hydrolysis of the amides, yielded 54% of *p*-phenylbenzoic acid and 46% of benzoic acid.

Rearrangement of the phenyl p-*biphenyl ketoximes prepared by Koller's method.*—Koller oximated phenyl *p*-biphenyl ketone in an alkaline aqueous-alcoholic solution.

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[7] BACHMANN AND MOSER, *J. Am. Chem. Soc.*, **54**, 1124 (1932); BACHMANN, *ibid.*, **54**, 2112 (1932); BACHMANN AND STERNBERGER, **56**, 170 (1934); BACHMANN AND FERGUSON, *ibid.*, **56**, 2081 (1934).

[8] VIEBÖCK AND SCHWAPPACH, *Ber.*, **63**, 2818 (1930).

Since he was able to isolate only one oxime from his product, we have repeated his procedure. To a solution of 1.26 g. of the ketone in 25 cc. of alcohol was added an aqueous solution of 0.84 g. of hydroxylamine hydrochloride and 2.1 g. of potassium hydroxide. In order to dissolve all of the ketone, 11 cc. of alcohol was added and the mixture was refluxed for sixteen hours. The mixture of oximes was isolated and rearranged, and the products of the rearrangement were hydrolyzed; in this manner a mixture of *p*-phenylbenzoic acid (48%) and benzoic acid (39%) was obtained, an indication that both oximes were present in the product of oximation.

Rearrangement by other reagents.—Ten cc. of concentrated sulfuric acid was added to 50 cc. of glacial acetic acid containing the mixture of oximes obtained from 0.005 gram mole of phenyl *p*-biphenyl ketone. The solution was heated for twenty minutes on a steam bath and then kept at the boiling point for fifteen minutes. In one run, 1.19 g. (90%) of the theoretical weight of the substituted amides was obtained. Hydrolysis of the mixture of amides yielded 53% of *p*-phenylbenzoic acid (in addition to benzoic acid), in good agreement with the experiments in which phosphorus pentachloride was employed. In a number of runs the yields of products were rather low.

Rearrangement of the phenyl *p*-biphenyl ketoximes by phosphorus trichloride in anhydrous benzene was incomplete even after twenty-four hours at room temperature. The reagent was also tried on benzophenone oxime. Two g. of phosphorus trichloride was added to a mixture of 2 g. of benzophenone oxime and 25 cc. of benzene. After three days at room temperature, the benzene was evaporated and the solid was collected by filtration, washed with water and dried. After digestion with hot 60–70° petroleum ether, 0.87 g. (44%) of benzanilide remained. From the petroleum ether extract was isolated 1.0 g. of benzophenone.

Methyl p-*biphenyl ketoximes.*—By hydrolysis of the products obtained by rearrangement of the oxime mixture from 0.01 gram mole of methyl *p*-biphenyl ketone, 0.04 g. (1%) of *p*-phenylbenzoic acid was obtained. In addition 3.23 g. (95.6%) of *p*-aminobiphenyl was isolated, thus accounting for 96.6% of the products.

Ingersoll and White[9] obtained an 80–82% yield of the *anti*-*p*-biphenyl methyl ketoxime in the form of yellow plates melting at 186° by oximation of methyl *p*-biphenyl ketone with hydroxylamine hydrochloride and 30% sodium hydroxide. We isolated this oxime in nearly quantitative yield by the pyridine method, and by recrystallization from alcohol obtained it as colorless needles which melted at 186–187°.

Phenyl o-*tolyl ketoximes.*—Forty hours of heating was found to be necessary to oximate phenyl *o*-tolyl ketone completely. Rearrangement of the mixture of oximes gave a 98% yield of the substituted amides. The proportion of *o*-toluic acid in the mixture of benzoic acid and *o*-toluic acid obtained by hydrolysis of the amides was determined by oxidizing the *o*-toluic acid to phthalic acid by alkaline permanganate solution, and separating the benzoic acid and phthalic acid by means of hot carbon tetrachloride, in which the phthalic acid is nearly insoluble.

o-*Tolyl* p-*biphenyl ketoximes.*—Even forty-eight hours of heating proved to be insufficient for complete oximation of *o*-tolyl *p*-biphenyl ketone. In the best runs only a 75% yield of acids was obtained in the final step. The mixture of *o*-toluic acid and *p*-phenylbenzoic acid was readily separated by digestion with hot water, which dissolved the former but not the latter.

Methyl 1-anthryl ketoximes.—1-Acetylanthracene was prepared according to the method of the German patent 492,247; our product melted at 106.5–108° instead of

[9] INGERSOLL AND WHITE, *J. Am. Chem. Soc.*, **54**, 274 (1932).

the reported 103–105°. During the oximation process, the solution turned dark-green, and the oil remaining after evaporation of the solvent retained the dark color. After the customary treatment with water, the oximes crystallized. During the rearrangement with phosphorus pentachloride the mixture became very dark and the products refused to crystallize. By hydrolysis a 20% yield of 1-aminoanthracene (m.p. 118–119°) and a small amount of 1-anthroic acid were isolated. Since quantitative yields of the products could not be obtained the work on this ketone was abandoned. 9-Acetylanthracene, likewise, gave unsatisfactory results.

9-Benzoylanthracene.—This ketone was prepared by the Perrier modification of the Friedel-Crafts reaction. A mixture of 3.5 g. of aluminum chloride and 3.5 g. of benzoyl chloride was warmed gently over a free flame until a clear solution resulted. The cooled product was dissolved in 20 cc. of warm carbon disulfide, and to the cooled solution was added 4.5 g. of anthracene. The red-black precipitate which formed slowly during the course of one-half hour of cooling by ice and water was filtered, dried and hydrolyzed by dilute hydrochloric acid. The ketone which resulted was recrystallized from alcohol in order to free it from anthracene. Sublimation and recrystallization from ethyl acetate gave bright-yellow, diamond-shaped crystals of 9-benzoylanthracene; m.p. 145.5–146°; yield, 85%. Heating a mixture of 0.564 g. of the ketone, 0.2 g. of hydroxylamine hydrochloride, 1.5 cc. of pyridine and 1.5 cc. of absolute alcohol for two hours, for twenty-four hours, and even for three weeks failed to give any of the oxime.

Phenyl 2-fluoryl ketoximes.—Phenyl 2-fluoryl ketone (2-benzoylfluorene) was prepared by adding 16.6 g. of anthracene to a solution of the complex from 14 g. of benzoyl chloride and 14 g. of aluminum chloride in 80 cc. of carbon disulfide. The bright-yellow solid which resulted was filtered off and washed with carbon disulfide in order to free it from a red by-product. The precipitate was hydrolyzed with dilute hydrochloric acid and the colorless ketone, after being freed from traces of carbon disulfide, was recrystallized from alcohol (450 cc.); m.p. 124–124.7°; yield, 24 g. (89%). By sublimation at 0.4 mm. the ketone was obtained as colorless, glistening needles which melted at 124.5–125°. Ray and Levine,[10] using the Perrier method (no details given), reported a 61% yield of ketone melting at 122°.

When 2.7 g. of the ketone was oximated, precipitation of the oximes started after about twenty minutes of heating. The mixture of substituted amides obtained by rearrangement of the oximes proved to be very resistant to hydrolysis by potassium hydroxide in methanol. The amide, which was particularly difficult to hydrolyze, was found to be *N*-phenyl-2-fluorenecarboxylic acid amide (m. p. 255–256°); this compound could be readily isolated after partial hydrolysis had been effected, and its structure was established by synthesis. The isomeric amide, *N*-(2-fluoryl-benzamide (m.p. of a synthetic sample, 215°) was more readily hydrolyzed.

Complete hydrolysis of the mixture of amides was finally accomplished by refluxing them for four weeks with a 5% solution of hydrochloric acid in ethanol. After removal of the amine hydrochlorides (from which a 46% yield of 2-aminofluorene was isolated), the residue was heated with potassium hydroxide in order to hydrolyze any esters that had been formed. The mixture of acids which was isolated consisted of 54% (by moles) of 2-fluorenecarboxylic acid and 46% of benzoic acid. The two acids were separated by digestion with hot water, which dissolved the benzoic acid.

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[10] RAY AND LEVINE, J. ORG. CHEM., **2**, 267 (1937).

SUMMARY

Pure *syn*- and *anti*-phenyl *p*-biphenyl ketoximes have been isolated from the mixture of the two oximes produced on oximation of phenyl *p*-biphenyl ketone.

Under the conditions employed for making the oximes from the ketone, each of the stereoisomeric phenyl *p*-biphenyl ketoximes is converted to the same mixture of the two oximes that is formed on oximation of the ketone.

The relative proportions of the *syn* and *anti* oximes produced on oximation were determined for thirteen ketones.

The existence of a number of new oximes has been established by means of the quantitative methods employed in the investigation.

Twelve new substituted amides have been synthesized.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

ACID CATALYSIS IN LIQUID AMMONIA. III. EFFECT OF α-SUBSTITUENTS ON THE AMMONOLYSIS OF ESTERS

L. F. AUDRIETH AND J. KLEINBERG

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Since ammonium salts behave as acids in liquid ammonia it was to have been expected that the presence of compounds yielding the ammonium ion would accelerate ammonolytic reactions. This theoretical premise has been confirmed experimentally in a number of studies on the ammonolysis of esters, not only by Shatenshtein[1] in the case of diethyl tartrate, but also in this laboratory in the case of ethyl benzoate[2] and of diethylmalonate.[3] This concept has also been extended to apply to the ammonolysis of esters derived from polyhydric alcohols and long-chain saturated or unsaturated fatty acids.[4] In all of these instances the addition of ammonium salt has caused a tremendous increase in the velocity of the reaction between esters and liquid ammonia. An increase in the concentration of ammonium salt has also been found to give proportionately greater yields of the corresponding acid amides over comparable time intervals.

These reactions presumably represent examples of *acid catalysis* in liquid ammonia. Experimental work now in progress in this laboratory indicates that solvolytic reactions are in general, susceptible to catalysis by the corresponding *onium* ion, *id est*, the solvated proton. The concept of onium-ion catalysis is therefore applicable to a wide variety of protophyllic solvents.

It is well-known that the ease of hydrolysis of esters varies considerably with the nature of the α-substituent. It was therefore considered to be of distinct theoretical interest to determine if this same order of reactivity held qualitatively for the corresponding ammonolytic reactions. The experimental results of a study of the ammonolysis of the ethyl esters of acetic, cyanoacetic, malonic, malonamic, lactic, mandelic, phenylacetic and ethoxyacetic acids at 0° are presented in the first part of this paper. The catalytic effect of the addition of ammonium chloride was also deter-

[1] SHATENSHTEIN, *J. Am. Chem. Soc.*, **59**, 432 (1937).

[2] FELLINGER AND AUDRIETH, *ibid.*, **60**, 579 (1938).

[3] SLOBUTSKY AND AUDRIETH, *Trans. Ill. Acad. Sci.*, **29**, 104 (1936); *Proc. Nat. Acad. Sci.*, **23**, 611 (1937).

[4] BALATY, FELLINGER, AND AUDRIETH, In press (*Ind. Eng. Chem.*)

mined in each case. In the course of this investigation it was found that the treatment of certain classes of esters with liquid ammonia afforded a very simple and convenient method for the preparation of the corresponding acid amides. Consequently, reactions between ammonia and the ethyl esters of lactic and of mandelic acids were carried out at higher temperatures and pressures in order to investigate in more detail, than previously reported by Glattfeld and MacMillan[5], the usefulness of this method for the preparation of α-hydroxy acid amides.

EXPERIMENTAL

I. Effect of α-Substituents on the Ammonolysis of Esters

Preparation of materials.—All liquid esters were carefully dried over anhydrous sodium carbonate and then distilled fractionally under reduced pressure. Especial care was taken to remove any free acid contaminating the esters, in view of the fact

TABLE I

AMMONOLYSIS OF ESTERS AT 0°

($XCH_2COOC_2H_5$ = 0.025 mole in 25 cc. NH_3)

ESTER	RELATIVE SAPONIFICATION CONSTANTS (OLSSON)	PERCENTAGE YIELDS OF AMIDES			
		24 hours		48 hours	
		No catalyst	0.2 g. NH_4Cl	No catalyst	0.2 g. NH_4Cl
$CN CH_2COOEt$ / $CONH_2$		97	96	99	100
CH_2 \ $COOEt$		67	91	93	98
$CH_2(COOEt)_2$	2070	9	79	63	95
$C_6H_5CHOHCOOEt$	1015	44	63	62	79
$CH_3CHOHCOOEt$	968	26	53	38	77
$C_2H_5OCH_2COOEt$	985	5	53	12	86
$C_6H_5CH_2COOEt$	191	0.6	2	1.2	4.7
CH_3COOEt	100	0	1	0	3

that the acids would be converted into the ammonium salts by liquid ammonia and by their presence exert a catalytic effect on the reaction. Ethyl malonamate was purified by recrystallization from benzene.

Procedure.—Pyrex tubes (16 × 350 mm.) were sealed at one end to form elongated test-tubes. A definite quantity of pure ester (0.025 mole) was placed in each reaction tube. Where the experiments were carried out in the presence of catalyst, a weighed amount (0.2 g.) of ammonium chloride was next added. The tubes were then cooled thoroughly in a solid carbon dioxide-acetone bath, and liquid ammonia was siphoned into each tube to give a total volume of 25 cc. With the contents of the tube entirely below the surface of the cooling bath, the upper end was sealed off. The sealed tubes were allowed to warm slowly to 0° and the contents mixed thoroughly to produce a

[5] GLATTFELD AND MACMILLAN, *J. Am. Chem. Soc.*, **58**, 898 (1936).

homogeneous solution. The starting time of the reactions was taken as the time of mixing.

After 24- or 48-hour interval tubes were removed from the ice-water bath and immediately cooled in a carbon dioxide-acetone bath. After the seals had been broken, the tubes were inserted through closely fitting rubber stoppers into filter flasks, and the contents were allowed to drain into the containers. The ammonia was allowed to evaporate spontaneously, and the alcohol was removed by drawing warm dry air through the container. A suitable solvent, either low-boiling petroleum ether or absolute ether, was added to extract the unreacted ester. The residues were filtered through tared sintered-glass crucibles, washed with the solvent used in extracting the unreacted ester, dried and weighed. The known weights of catalyst were deducted to determine the net yields of amides. The identity of the ammonolytic products was verified in each case either by a check of the physical properties as recorded in the literature or by analysis.

Typical experimental results are recorded in Table I. Percentage yields of amides are given for runs with and without ammonium chloride for 24- and 48-hour reaction periods. The error in these determinations is, on the average, not greater than ± 5 per cent., except in those cases where relatively small quantities of amide were isolated and weighed. Here the slight, but definite solubility of the amides in the solvent mixture containing the unreacted ester, introduced an appreciable error.

Discussion.—The relative saponification constants for these same esters, as calculated by Olsson[6], taking the reactivity of ethyl acetate as equal to 100, are given in the second column of Table I. It may seem illogical to compare the reactivity of esters towards alkaline hydrolysis with findings based upon their susceptibility to ammonolysis. However, both types of reactions are solvolytic, and it is apparent from our results (1) that the nature of the α-substituent exerts a profound effect upon the reactivity of esters towards ammonia, and (2) that this effect is qualitatively in the same order as in the case of water.

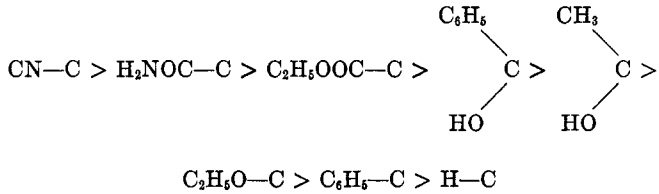
The one apparent exception to this generalization, among the uncatalyzed reactions, is diethyl malonate. Previous study in this laboratory had shown that the reaction between ammonia and diethyl malonate[3] is autocatalytic in nature. Both the intermediate product, ethyl malonamate, and the end product, malonamide, behave as acids in liquid ammonia. A relatively long induction period is necessary in order to build up a sufficiently high concentration of these products to give enough ammonium ions (from $RCONH_2 + NH_3 \rightleftharpoons NH_4^+ + RCONH^-$) to catalyze the reaction. While the yields of malonamide under the given experimental conditions, in the absence of catalyst, are slight after 24 hours, they become appreciable after a 48-hour reaction period.

All of the esters listed in Table I are quite soluble in liquid ammonia at 0°. This may in part account for the fact that the ammonolysis of esters, even in the absence of catalyst, proceeds more rapidly than the corresponding uncatalyzed hydrolytic reactions. Furthermore, liquid ammonia is recognized as a strongly basic solvent and as such enhances the acid strength of weak acids. The reaction products, as pointed out above in the case of diethyl malonate, serve to catalyze ammonolytic reactions of this type. In addition, it is possible that the acidity of a methylenic hydrogen is enhanced in liquid ammonia—and this factor may serve to increase the rate of ammonolysis. In line with these considerations it is also apparent why the α-hydroxy esters are ammonolyzed so readily. Compounds of the type ROH are

[6] OLSSON, *Z. physik. Chem.*, **133**, 233 (1928).

more acidic in ammonia than in water, due to the greater basicity of the solvent and because of the fact that competition for the proton is displaced in the direction of formation of the ammonium ion ($ROH + NH_3 \rightleftharpoons RO^- + NH_4^+$).

The effect of α-substituents upon the reactivity of the ethyl esters of acetic and related acids may be given by the following series:



$$C_2H_5O{-}C > C_6H_5{-}C > H{-}C$$

The magnitude of the catalytic effect of addition of ammonium chloride varies with different esters. In every case, however, addition of ammonium salt, brings about a marked increase in yields of the corresponding acid amides. Since ammonium chloride is the ammonia analogue of hydrochloric acid our results may be considered as further confirmation of the original premise that ammonolytic reactions of this type are susceptible to catalysis by ammono acids.

II. Preparation of α-Hydroxy Acid Amides

The data given in Table I indicate that many amides may be prepared readily and in good yields by reaction with liquid ammonia. However, only in the case of the α-hydroxy acid amides does this method possess particular advantages over accepted procedures.

McKenzie and Wren[7], prepared *dl*-mandelamide by reaction of the methyl ester with alcoholic ammonia. They point out that the reaction is a very slow one. Ôeda[8] prepared a number of α-hydroxy amides in 85–90% yields by treating the acetone derivatives of the corresponding acids with liquid ammonia. Twenty-five to thirty moles of liquid ammonia per mole of acetone compound was employed. This latter method involves the intermediate preparation of the acetone derivatives from the respective acids. Glattfeld and MacMillan[5] studied the action of liquid ammonia at its boiling point upon various lactates and mandelates and found these esters to undergo ammonolysis readily. They give no specific details.

In studying this method for preparation of the amides of lactic and mandelic acids use was made of a steel autoclave to enable the synthesis of larger quantities and permit operation at room temperature. It is interesting to note that the addition of catalyst does not cause enough of an increase in yield of these amides over a 24-hour period at room temperature to warrant its use.

*Preparation of mandelamide.**—Forty grams (0.22 mole) of ethyl mandelate was placed in a large Pyrex tube and cooled in a solid carbon dioxide-acetone bath. One

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[7] McKenzie and Wren, *J. Chem. Soc.*, **93**, 311 (1908).

[8] Ôeda, *Bull. Chem. Soc.* (Japan), **11**, 385 (1936).

* Through the courtesy of H. A. Shonle of the Lilly Research Laboratories samples of the amide were subjected to pharmacological study. An abstract of his report follows: "Mandelamide was tested for toxicity by intravenous injection on mice and for rate of excretion on a single dog. The doses for the excretion experiments

hundred cc. of liquid ammonia was added, and the mixture was stirred to effect solution. The solution was placed in the steel bomb and allowed to remain in the autoclave for 24 hours. The excess ammonia was then allowed to escape from the bomb, and the reaction product was treated with 100 cc. of absolute ether to remove unchanged ester. The product was filtered, washed with ether, and dried. The yield of mandelamide was 27 g. (80.5% theoretical).

Preparation of lactamide.—Fifty-nine grams (0.5 mole) of ethyl lactate and 200 cc. of liquid ammonia were allowed to react as described above. The yield of lactamide was 31.5 g. (70.8 % theoretical). Similar experiments with 4 g. ammonium chloride gave slight increases in yield (74 and 76% theoretical), indicating that under the given conditions a catalyst is not desirable, since it necessitates additional purification of the reaction product.

SUMMARY

1. The concept of acid catalysis has been shown to be generally applicable to the ammonolysis of esters in liquid ammonia.

2. The reactivities of esters toward ammonolysis in liquid ammonia parallel, qualitatively, the reactivities of esters toward alkaline hydrolysis in aqueous solution.

3. The relative influence of various α-substituents on the reactivity of the ester toward ammonolysis in liquid ammonia is given by the following series:

$$CN{-}C > H_2NOC{-}C > C_2H_5OOC{-}C > \begin{matrix} C_6H_5 \\ \diagdown \\ \quad C \\ \diagup \\ HO \end{matrix} > \begin{matrix} CH_3 \\ \diagdown \\ \quad C \\ \diagup \\ HO \end{matrix} >$$

$$C_2H_5O{-}C > C_6H_5{-}C > H{-}C$$

4. A convenient method for the preparation of α-hydroxy amides, by the action of anhydrous liquid ammonia on the esters, has been developed.

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were made proportional to twice the equivalent of a dose of 12 g. of mandelic acid for a 70 kg. man. Mandelic acid was tested in a similar way and at the same time. Both the amide and the acid were found to have a M.L.D. of 610 mg. per kg. of body weight. The urine had neither bactericidal or bacteriostatic action on cultures of Staphylococcus aureus and Bacillus coli. With a dose equivalent to twice the effective dose of mandelic acid for man, mandelamide in dogs showed less than 50% recovery and no appreciable decrease in the pH of the urine from these treated dogs."

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

STUDIES IN THE PHENANTHRENE SERIES. XIX. NAPHTHOQUINOLINES SYNTHESIZED FROM AMINOPHENANTHRENES*,[1]

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The considerations that led us to undertake the synthesis of compounds derived from condensed ring systems consisting of a phenanthrene nucleus and a pyridine ring, have been stated in the first communication on naphthoquinolines.[1] In this paper we shall set forth the structural proof of the previously described naphthoquinoline prepared from 3-aminophenanthrene, and the synthesis and the structural proof of the naphthoquinolines and their derivatives that were prepared from 2-aminophenanthrene and 2-amino-9,10-dihydrophenanthrene.

We obtained our starting materials, the various aminophenanthrenes by the Beckmann rearrangement of the oximes of the corresponding acetylphenanthrenes. This rather simple and very convenient method for large-scale preparation of aminophenanthrenes has been employed recently and independently by Adelson and Bogert,[2] Bachmann and Boatner,[3] Fieser and Price,[4] and in our laboratory.[1] These authors used phosphorus pentachloride in ether or benzene, while we employed as rearranging agent hydrogen chloride in a mixture of glacial acetic acid and acetic anhydride. Furthermore we used only sterically homogeneous oximes. Although 2-amino-9,10-dihydrophenanthrene may be prepared analogously,[5] we found a quicker and more convenient way to this amine through the corresponding nitro compound which, itself, was obtained in a yield of 65 per cent. by nitration of 9,10-dihydrophenanthrene.[6]

In the Skraup quinoline synthesis, applied to 3-aminophenanthrene

* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

[1] First paper on naphthoquinolines, MOSETTIG AND KRUEGER, *J. Am. Chem. Soc.*, **58**, 1311 (1936).

[2] ADELSON AND BOGERT, *ibid.*, **58**, 653 (1936).

[3] BACHMANN AND BOATNER, *ibid.*, **58**, 857, 2097 (1936).

[4] FIESER AND PRICE, *ibid.*, **58**, 1838 (1936).

[5] BURGER AND MOSETTIG, *ibid.*, **59**, 1302 (1937).

[6] See following communication (XX).

(I), naphtho[1,2-*f*]quinoline (II) was produced in a yield of 45 per cent.[1],† Careful examination, in several experiments, of the reaction mixture indicated that no isomeric naphthoquinoline had been formed. Ring closure had taken place only in one position, namely in position 4.

The reduction of this naphthoquinoline was studied under a variety of experimental conditions. Electrolytic reduction, reduction with tin and hydrochloric acid, and with sodium and alcohol did not give satisfactory results. The substance was either incompletely reduced, or partly resinous products that could neither be separated nor characterized appeared. When platinum oxide was used as catalyst and glacial acetic acid as solvent in the hydrogenation, the base (II) absorbed hydrogen exceedingly slowly, in contrast to its isomers IX and XXII. The reaction mixture contained at least two hydrogenation products, a tetrahydro derivative (III) and an octahydro derivative (IV). The pure tetrahydro compound, under the same conditions, was much more quickly hydrogenated than the naphthoquinoline itself. When the hydrogenation of the naphthoquinoline was allowed to go to completion, only the octahydro derivative could be isolated. The tetrahydro compound is most readily prepared by high-pressure hydrogenation at 140° using Adkins' chromite catalyst.[7] When the temperature was raised to 170°, the yield dropped to 45 per cent.; however, no octahydro derivative could be isolated in such an experiment. The latter compound was rather conveniently obtained by hydrogenation of the tetrahydro compound, using platinum oxide as catalyst. 4-Methyl-1,2,3,4-tetrahydronaphtho[1,2-*f*]quinoline (VI) was prepared by thermal decomposition of the methiodide (V) which itself was obtained by complete methylation of 1,2,3,4-tetrahydronaphtho[1,2-*f*] quinoline (III).

The methiodide (V), when boiled in aqueous solution with sodium amalgam (Emde degradation), gave an ether-soluble oily reaction product which was not homogeneous. A partial separation was effected by slow vacuum distillation. The oily base in the distillate was converted to the hydrochloride, which was further purified by crystallization. Of the three theoretically possible fissions in the degradation,[8] apparently the one be-

† The orientation, numbering and names of the heterocyclic compounds included in this paper have been recommended to us by Dr. Capell through the kindness of Dr. Crane. *Cf.* PATTERSON, *J. Am. Chem. Soc.*, **50**, 3074 (1928).

[7] The wide usefulness of this catalyst, particularly in selective hydrogenation, has been repeatedly demonstrated by Adkins and his co-workers. See the monograph "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts" by HOMER ADKINS, The University of Wisconsin Press, **1937**.

[8] (*a*) *Cf.* EMDE AND KULL, "Degradation of Quaternary Ammonium Compounds with Sodium Amalgam, a Review," *Arch. Pharm.*, **272**, 469 (1934). (*b*) See also MOSETTIG AND ROBINSON, *J. Am. Chem. Soc.*, **57**, 902 (1935).

tween the nitrogen atom and the adjacent benzene nucleus predominated. Analyses of the degradation product and its salts for carbon and hydrogen do not indicate clearly whether or not, simultaneously with ring opening, reduction of the 9,10-double bond of phenanthrene (7,8 of the naphthoquinoline derivative) had taken place. The degradation product was different in every respect from 2-[3-(dimethylamino)-*n*-propyl] phenanthrene and also from 2-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene. To the degradation product, therefore, must be assigned the formula of a 4-[3-(dimethylamino)-*n*-propyl] phenanthrene (VII), or the less probable formula of a 4-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene. Ring closure in the Skraup synthesis had taken place in position 4, yielding naphtho[1,2-*f*]quinoline (II). Although 4-acetylphenanthrene, which might serve as starting material in the synthesis of the propylamino derivative (VII), is known through the work of Fieser,[9] the synthesis of VII was not attempted on account of the difficult and long route to this ketone.

The remote possibility that the degradation product might be a 3-dimethylamino-4-*n*-propylphenanthrene (or 3-dimethylamino-2-*n*-propylphenanthrene or a corresponding 9,10-dihydro derivative) can be excluded through the known facts that such compounds form methiodides only with difficulty[10] and that, in our experience, salts of phenanthrene derivatives carrying the dimethylamino group directly on the nucleus hydrolyze strongly. In contrast to such behavior, the degradation product forms the methiodide readily, and its hydrochloride does not hydrolyze. It is, of course, not impossible that such compounds carrying the dimethylamino group directly on the nucleus, and also the tertiary base VI, are present in the residue from the first vacuum distillation of the crude degradation products.

The structure of the tetrahydro compound (III) seems to be sufficiently supported by the empirical rule that in the hydrogenation of quinolines by various means, the pyridine portion is attacked first, further, by the formation of an *N*-methyl derivative (VI) and by the course of the degradation. More difficult is the assignment of a structural formula to the octahydro compound. Neglecting the possibility of a shift of hydrogen atoms during the hydrogenation from the tetrahydro compound to the octahydro compound, formulas IV-*a* and IV-*b* have to be considered first, since they appear to be the only theoretically possible formulas that do not contain isolated double bonds. Without experimental evidence, we prefer formula IV-*a* to formula IV-*b*.

[9] FIESER, FIESER, AND HERSHBERG, *J. Am. Chem. Soc.*, **58**, 2322 (1936).
[10] VON BRAUM AND AUST, *Ber.*, **49**, 501 (1916).

Somewhat similar compounds were obtained by Bamberger and co-workers[11] in the sodium-amyl alcohol reduction of "β-naphthoquinolines" or their tetrahydro derivatives to the corresponding octahydro compounds. (A "β-naphthoquinoline" which is, in the nomenclature used in this paper, a benzo[*f*]quinoline, may be visualized by omitting from formula II the terminal benzene nucleus.) The relatively strong basicity of octahydronaphtho[1,2-*f*] quinoline would speak, on the basis of Bamberger's experiments for formula IV-*b*, this being the analog of the "ac. octahydro-β-naphthoquinoline." The stronger basicity, however, of IV in comparison with III does not necessarily imply that the benzene nucleus C in III had been hydrogenated. Any higher degree of hydrogenation, irrespective of the location of the additional hydrogens, may increase the basicity. Furthermore the fact that in Bamberger's experiments the "ac. octahydro-β-naphthoquinolines" are formed only in minimal yields, the "ar. octahydro-β-naphthoquinolines" being the main products, and finally the difference between Bamberger's reducing agents and ours apparently do not permit drawing analogies from this author's experiments as a support in the decision between formulas IV-*a* and IV-*b* for octahydronaphtho[1,2-*f*]quinoline.

The hydrochloride of the octahydro compound does not hydrolyze, in contrast to the hydrochloride of the tetrahydro compound and of the naphthoquinoline itself. Under the conditions imposed in the Emde degradation of the tetrahydro derivative, the methiodide of the *N*-methyl-octahydro compound was hardly attacked. By prolonged boiling with sodium amalgam, chiefly ether-insoluble products were obtained. The thermal decomposition of the methiodide does not result in the formation of an *N*-methyl derivative, but rather in a deep-seated decomposition.

In the Skraup synthesis applied to 2-aminophenanthrene (VIII) a homogeneous naphthoquinoline was obtained in a yield of 80–90 per cent., to which the structure of a naphtho[2,1-*f*]quinoline (IX) must be assigned on the basis of the following evidence. A tetrahydro compound (X) was readily obtained by catalytic hydrogenation, using platinum oxide as catalyst. The same compound was obtained by high pressure hydrogenation at 140°, using chromite catalyst. By employing a higher temperature, a homogeneous hydro derivative could be isolated from the reaction mixture, to which we assigned the structure of a hexahydronaphthoquinoline (XI).

The Emde degradation of the 1-methyl-1,2,3,4-tetrahydronaphtho-[2,1-*f*]quinoline methiodide (XIII) was carried out as in the 1,2-*f* series. The carbon-hydrogen analyses of the final, carefully purified degradation product do not decide the question whether or not simultaneous hydrogenation of the 9,10 double bond (of the phenanthrene nucleus) has taken place. The degradation product (XVII) is obviously different from 1-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene (XVIII) obtained by degradation of the methiodide (XV) of 1-methyl-1,2,3,4,5,6-hexahydronaphtho[2,1-*f*]quinoline (XVI). Furthermore it is different from

[11] BAMBERGER AND MÜLLER, *ibid.*, **24**, 2648 (1891). BAMBERGER AND STRASSER, *ibid.*, **24**, 2662 (1891).

synthetic 3-[3-(dimethylamino)-*n*-propyl]phenanthrene (XXX) and from 3-[3-(dimethylamino)-*n*-propyl]9,10-dihydrophenanthrene (XXIX), which was obtained in the degradation of the methiodide (XXVII) of 8-methyl-5,6,8,9,10,11-hexahydronaphtho[1,2-*g*]quinoline, as was shown by comparison of the respective hydrochlorides and picrates. Degradation product XVII must therefore be a 1-[3-(dimethylamino)-*n*-propyl]phenanthrene. Ring closure in the Skraup synthesis with 2-aminophenanthrene had taken place in position 1. We did not attempt the preparation of XVII from 1-acetylphenanthrene that has been synthesized recently by Bachmann and Boatner[3] through a long and difficult series of reactions. A final structural proof of IX is found in the fact that IX is not identical with naphtho[1,2-*g*]quinoline (XXII), which was obtained by dehydrogenation of 5,6-dihydronaphtho[1,2-*g*]quinoline (XXI).

To the tetrahydronaphthoquinoline compound in this series, formula X must be assigned on the basis of the results of catalytic hydrogenation, and the course of degradation. For the more highly hydrogenated derivative, which appears to be, from its carbon-hydrogen analyses, a hexahydro derivative, we assume as most likely the structure of a 1,2,3,4,5,6-hexahydro compound (XI). As next most probable might be considered the structure of a 1,2,3,4,11,12-hexahydro compound (XII). If this were correct, the Emde degradation of the methiodide of the 1-methyl derivative of XII should lead to a 1-[3-(dimethylamino)-*n*-propyl]-3,4-dihydrophenanthrene (XIX) which, very likely, would be further hydrogenated to a tetrahydrophenanthrene derivative during degradation. This did not take place. It is worthy of mention that the methiodide (XV), when boiled in aqueous solution, partially decomposed into the *N*-methyl derivative (XVI) and methyl iodide.

By application of Skraup's method to 2-amino-9,10-dihydrophenanthrene (XX) a dihydronaphthoquinoline (XXI) was obtained in a yield of 50 per cent. The hydrogenation of this compound, using platinum oxide catalyst proceeds moderately rapidly, yielding the hexahydronaphthoquinoline (XXIV). In the high-pressure hydrogenation this hexahydro derivative is formed in surprisingly low yields, not exceeding 40 per cent. It was converted to the methiodide (XXVII) of 8-methyl-5,6,8,9,10,11-hexahydronaphtho[1,2-*g*]quinoline which in the Emde degradation yielded 3-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene (XXIX). This amine could be dehydrogenated (in one experiment only) to 3-[3-(dimethylamino)-*n*-propyl]phenanthrene (XXX).

By palladium dehydrogenation of the dihydronaphthoquinoline (XXI) a naphthoquinoline (XXII) was obtained in an average yield of 50 per cent., which was different in every respect from the naphthoquinoline (IX) prepared from 2-aminophenanthrene. In hydrogenation under atmospheric pressure, using platinum oxide catalyst, it absorbs two moles

of hydrogen, decidedly faster than its isomers II and IX, to produce the tetrahydro derivative (XXV).

It is suggestive that this difference in speed of hydrogen absorption is based on the structural difference of II and IX on the one hand, and XXII on the other hand. In II and IX, the original phenanthrene structure, in respect to the location of the double bonds, has not been changed, both structural formulas containing a naphthalene and quinoline nucleus in which the double bonds are symmetrically arranged. This is not the case in naphtho[1,2-*g*]quinoline, which may be depicted as XXII or XXIII. In formula XXII the double bonds are arranged as in the analogous isocyclic 1,2-benzanthracene formula advanced by Fieser and Lothrop.[12]

The methiodide (XXVIII) of 8-methyl-8,9,10,11-tetrahydronaphtho[1,2-*g*]quinoline, obtained by complete methylation of XXV gave, in the Emde degradation, a product XXX that proved to be identical with synthetic 3-[3-(dimethylamino)-*n*-propyl]phenanthrene. This constitutes a direct structural proof of naphtho[1,2-*g*]quinoline (XXII) and its dihydro derivative (XXI), and consequently an indirect proof of the structure of naphtho[2,1-*f*]quinoline (IX).

3-[3-(Dimethylamino)-*n*-propyl]phenanthrene and 2-[3-(dimethylamino)-*n*-propy]-9,10-dihydrophenanthrene were synthesized as follows:

$$\mathrm{RCOCH_3} \xrightarrow{\mathrm{CH_2O,NH(CH_3)_2}} \mathrm{RCOCH_2CH_2N(CH_3)_2} \xrightarrow{\mathrm{Pt,H_2}} \mathrm{RCHOHCH_2CH_2N(CH_3)_2} \xrightarrow{\mathrm{PCl_5}}$$

$$\mathrm{RCHClCH_2CH_2N(CH_3)_2} \xrightarrow{\mathrm{Pd,H_2}} \mathrm{RCH_2CH_2CH_2N(CH_3)_2}$$

$\mathrm{R} = \mathrm{C_{14}H_9}-$ or $\mathrm{C_{14}H_{11}}-$

Assuming a symmetrical arrangement of double bonds in naphthalene and analogously in quinoline, Marckwald[13] formulated the rule that a condensation of a pyridine nucleus to a benzene nucleus takes place only when the two condensing carbon atoms are connected by a double bond. Apparently this rule has been upheld with rare exceptions[14] up to the present. If one adopts, furthermore, a phenanthrene structure with fixed double bonds, as postulated by Fieser and Young[15] it is to be expected that in the Skraup synthesis, starting from 2-aminophenanthrene, ring closure will take place in position 1, and starting from 3-aminophenanthrene, in position 4, since positions 2 and 1 and positions 3 and 4 are connected by double bonds.

On the other hand there exists apparently and quite consistently a

[12] FIESER AND LOTHROP, *J. Am. Chem. Soc.*, **58**, 749 (1936). See also FIESER AND HERSHBERG, *ibid.*, **59**, 2502 (1937).

[13] MARCKWALD, *Ann.*, **274**, 331 (1893). Compare LELLMANN AND SCHMIDT, *Ber.*, **20**, 3154 (1887); FIESER AND LOTHROP, *J. Am. Chem. Soc.*, **57**, 1459 (1935); FIESER, in GILMAN, "Organic Chemistry," Wiley, New York, **1938**, Vol. I, 89.

[14] FRIES, WALTER, AND SCHILLING, *Ann.*, **516**, 248 (1935).

[15] FIESER AND YOUNG, *J. Am. Chem. Soc.*, **53**, 4120 (1931).

parallelism between the fusion of the isocyclic carbon ring and the heterocyclic nitrogen-containing ring to a benzene nucleus. Thus, in the Skraup synthesis on 2-aminonaphthalene,[16] as well as in the ring closure of γ-(2-naphthyl)-*n*-butyric acid,[17] the angular tricyclic ring systems are formed. Like the pyridine ring, the isocyclic carbon ring needs, or at least prefers, the double bond for the condensation.[18] In the dehydration of γ-(2-phenanthryl)-*n*-butyric acid and β-(2-phenanthryl)propionic acid ring closure, forming the six- and five-membered rings, takes place exclusively, or to a very large extent, in position 1,[19] as in the application of the Skraup synthesis to 2-aminophenanthrene. Surprisingly, however, all ring closures of side-chains located in position 3 and involving the attachment of a *six*-membered carbon atom ring take place exclusively, or to a very large extent, in position 2. From γ-(3-phenanthryl)-*n*-butyric acid[19a] and γ-(3-phenanthryl)-α-methyl-*n*-butyric acid[20] only 1,2-benzanthracene derivatives were obtained. Equally, by hydrogenation and subsequent cyclization of methyl-(3-phenanthryl)itaconic acid[21] cyclization takes place with the formation of a 1,2-benzanthracene derivative. In this instance, however, a very small amount of the isomeric 3,4-benzophenanthrene derivative was isolated. We expected, therefore, that the ring closure of the pyridine nucleus, in the Skraup synthesis applied to 3-aminophenanthrene, also would extend to position 2. This, however, was not the case, as we have shown in this investigation. It is of interest that β-(3-phenanthryl)propionic acid[19b] and β-(3-phenanthryl)-*n*-butyric acid[22] cyclize principally at position 4, forming the cyclopenteno ring along the double bond. We believe that the difference, in respect to cyclization, of the three-carbon side chains —C—C—C— and the side chain —N—C—C— on the one hand, and the four-carbon side chain —C—C—C—C— on the other hand must be attributed to steric influences.[23] It has been shown by Burger and Mosettig[5] that, in the 9,10-

[16] SKRAUP AND COBENZL, *Monatsh.*, **4**, 436 (1883); *J. Chem. Soc. Abstracts*, **44**, 1010 (1883).

[17] SCHROETER, MÜLLER, AND HUANG, *Ber.*, **62**, 645 (1929); HAWORTH, *J. Chem. Soc.*, **1932**, 1125.

[18] See the ring closure of α-(2-naphthyl)-o-amino-cinnamic acid in the Pschorr phenanthrene synthesis [COOK, *J. Chem. Soc.*, **1931**, 2524] and the low yield in the ring closure of γ-(8-methyl-2-naphthyl)-n-butyric acid to 1-keto-5-methyl-1,2,3,4-tetrahydroanthracene where a phenanthrene ring closure is sterically inhibited [HAWORTH AND SHELDRICK, *J. Chem. Soc.*, **1934**, 1950.]

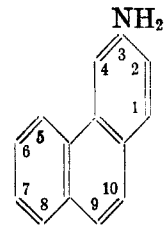
[19] (*a*) HAWORTH AND MAVIN, *J. Chem. Soc.*, **1933**, 1012. (*b*) BACHMANN AND KLOETZEL, *J. Am. Chem. Soc.*, **59**, 2207 (1937). (*c*) BERGMANN AND HILLEMANN *Ber.*, **66**, 1302 (1933).

[20] COOK AND HASLEWOOD, *J. Chem. Soc.*, **1934**, 428.

[21] COOK AND ROBINSON, *ibid.*, **1938**, 505.

[22] HILLEMANN, *Ber.*, **69**, 2610 (1936).

[23] Compare BERGMANN AND BLUM-BERGMANN, *J. Am. Chem. Soc.*, **59**, 1574 (1937).



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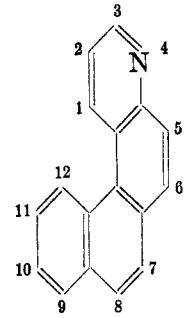
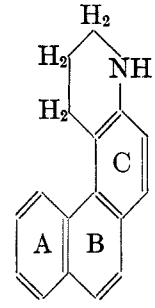


II, Naphtho[21,2-*f*]quinoline

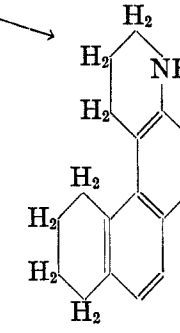
Chromite or PtO_2

PtO_2



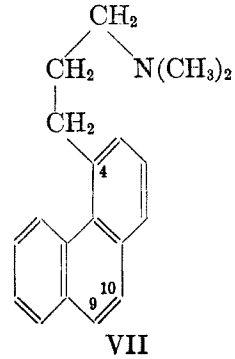
III

PtO_2

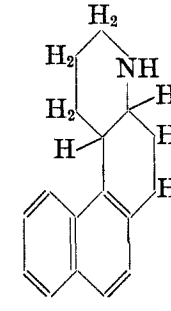


IV*a*

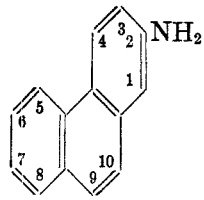
V, Methiodide of *N*-methyl derivative ⇌ VI, *N*-Methyl derivative of III



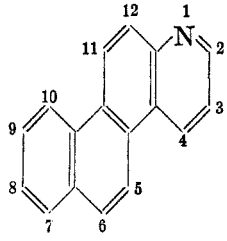
VII



IV*b*



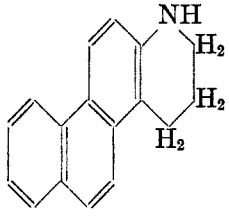
VIII



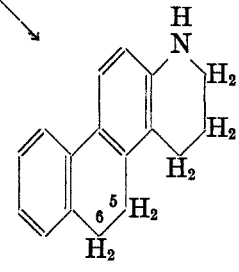
IX, Naphtho[2,1-*f*]quinoline

Chromite or PtO_2

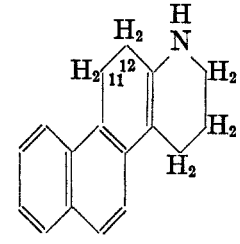
Chromite



X



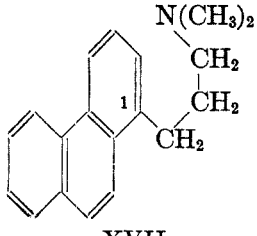
XI



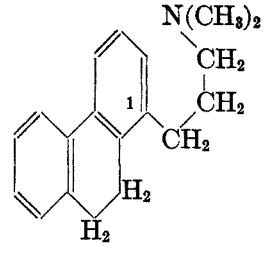
XII

XIII, Methiodide ⇌ XIV, *N*-Methyl derivative of *N*-methyl derivative of X

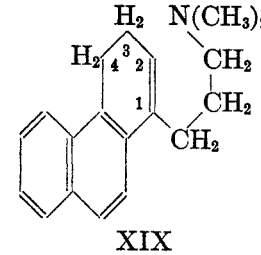
XV, Methiodide ⇌ XVI, *N*-Methyl derivative of *N*-methyl derivative of XI



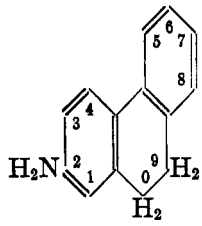
XVII



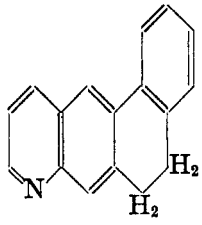
XVIII



XIX

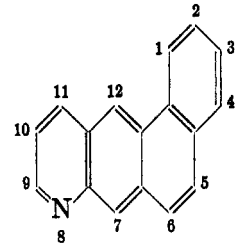


XX

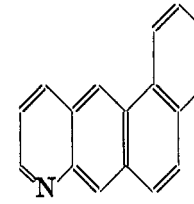


XXI

Pd



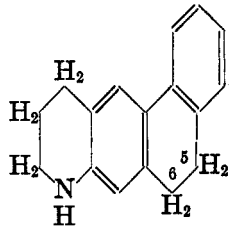
XXII, Naphtho[1,2-*g*]-quinoline



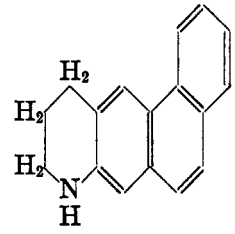
XXIII

Chromite or PtO_2

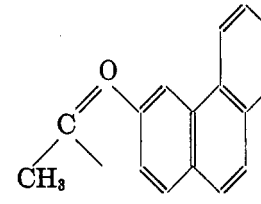
PtO_2



XXIV



XXV



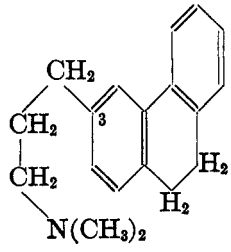
XXVI

XXVII, Methiodide of *N*-methyl derivative of XXIV

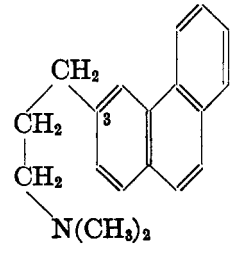
XXVIII, Methiodide of *N*-methyl derivative of XXV

4 steps

Pd



XXIX



XXX

dihydrophenanthrene series, three- and four-carbon side-chains attached to position 2, when forming five- and six-membered rings, will be directed entirely or chiefly to position 3. In striking analogy to this fact, in the quinoline synthesis applied to 2-amino-9,10-dihydrophenanthrene, ring closure takes place entirely in position 3. Furthermore, such analogy can be adduced in the tetrahydronaphthalene series. In application of the Skraup synthesis to *ar.*-tetrahydro-2-naphthyl amine, ring closure takes place in position 1 (30 per cent.), as well as in position 3 (60 per cent.).[24] Ring closure of the analogous γ-[7-(1,2,3,4-tetrahydro)naphthyl]-*n*-butyric acid, similarly takes place in positions 6 and 8, the anthracene and phenanthrene derivatives being formed in about equal amounts.[25] This discussion is not intended to be a support to any of the structural formulas that have been proposed for di- or polycyclic ring systems, but rather, points out the striking regularities and analogies in the attachments of rings to such systems which are satisfactorily expressed by the customary formulas with alternating single and double bonds.

4-Methyl-1,2,3,4-tetrahydronaphtho[1,2-*f*]quinoline (VI) and 1-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]quinoline (XIV) were investigated pharmacologically by Dr. N. B. Eddy at the University of Michigan. VI showed only a slight analgesic action (200 mg. per kg.) in the cat, while XIV shows no analgesic action at all at this dosage. Both substances cause slight depression in doses of 200 mg.[26]

On account of the structural analogy of naphtho[1,2-*f*]quinoline (II), naphtho[2,1-*f*]quinoline (IX), and naphtho[1,2-*g*]quinoline (XXII) to 3,4-benzophenanthrene, chrysene, and 1,2-benzanthracene respectively, Dr. Carl Voegtlin of the National Institute of Health suggested the investigation of the naphthoquinolines II, IX, XXI, and XXII for carcinogenic activity.[27] The result of the tests will be reported elsewhere.

EXPERIMENTAL

Preparation of 2- and 3-Aminophenanthrene

A sterically nearly homogeneous oxime of 3-acetylphenanthrene, melting at 142–144° (the pure *trans* form melts at 144–145°) was conveniently prepared by the method employed by Bachmann and Boatner.[3] The yield was quantitative.

The preparation of a sterically homogeneous oxime of 2-acetylphenanthrene has been described previously.[1]

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[24] VON BRAUN AND GRUBER, *Ber.*, **55**, 1711 (1922).

[25] SCHROETER, *ibid.*, **57**, 2003, 2017 (1924); KROLLPFEIFFER AND SCHÄFER, *ibid.*, **56**, 628 (1923).

[26] EDDY, unpublished results.

[27] Some ring-nitrogen-containing analogs of polycyclic hydrocarbons, as dibenzacridines, are known to show some carcinogenic activity. See COOK, *Ber.*, **A69**, 38 (1936).

3-Aminophenanthrene.—Fifty grams of the pure 3-oxime was dissolved in a mixture of 240 cc. of glacial acetic acid and 100 cc. of acetic anhydride. Dry hydrogen chloride was passed through the reaction mixture, with occasional shaking, for twelve hours. After the mixture stood for twelve hours longer a thick paste-like crystalline mass of 3-acetylaminophenanthrene (m. p. 195–200°) had separated. The acetylamino compound was hydrolyzed, according to Werner and Kunz,[28] by boiling it with a mixture of 400 cc. of glacial acetic acid and 400 cc. of 20% aqueous hydrochloric acid, until the amine hydrochloride precipitated. The hydrochloride, after being triturated with acetone, gave a practically pure amine (m. p. 86–87°). The yield calculated on oxime was 70%.

Obviously the acetyl derivative of the oxime was an intermediate in the rearrangement. This compound precipitated almost immediately when hydrogen chloride was passed into the reaction mixture. It was isolated in a preliminary experiment, and crystallized from alcohol in needle-like prisms; m. p. 140–142°.

Anal. Calc'd for $C_{18}H_{15}NO_2$: C, 77.94; H, 5.46.
Found: C, 77.81; H, 5.60.

2-Aminophenanthrene.—Fifty-three grams of the pure 2-oxime was suspended in a mixture of 200 cc. of glacial acetic acid and 150 cc. of acetic anhydride. Dry hydrogen chloride was passed through the mixture for six hours, and the thick paste was then transferred to several Lintner pressure bottles and heated at 100° for three hours. The 2-acetylaminophenanthrene melted at 220–224°. It was hydrolyzed like the corresponding 3-isomer. The yield of amine (m. p. 85–86°) was 86% (based on oxime).

When the rearrangement mixture was filtered before heating, a compound of m. p. 144–146° was obtained. This substance could be hydrolyzed in the presence of acid to 2-acetylphenanthrene, and is, most likely, the acetyl derivative of the oxime.

Naphtho[1,2-f] quinoline Series

The preparation of naphtho[1,2-*f*] quinoline (II) has been described by us in a previous communication.[1] It was named there "naphthoquinoline." We simplified somewhat the former preparative procedure. The mixture of the reactants was heated in an oil bath for an hour at 135–150°, and then kept at a gentle boil on a hot plate for three hours. The boric acid may be omitted.

Hydrogenations

Naphtho[1,2-f]quinoline (II) to octahydronaphtho[1,2-f]quinoline (IV).—To this previously described experiment may be added: the octahydro compound can be conveniently purified by distillation in an oil-pump vacuum. The product is so strongly basic that when carbon dioxide is passed into a suspension of the base in water, the base goes partly into solution and may be reprecipitated with alkali. The aqueous alcoholic solution of the base turns litmus paper blue. The hydrochloride is sparingly soluble in water and does not hydrolyze.

In the hydrogenation from II to IV, 5 g. of base and 60 cc. of glacial acetic acid and 0.5 g. of platinum oxide were employed; the hydrogen absorption (2600 cc., calc'd for 4 moles, 2230 cc.) came to a standstill in two days. The yield of IV was approximately the same as in the previous experiment. Hydrogenation of base or hydrochloride, using platinum oxide catalyst, could not be effected in alcoholic solution.

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[28] WERNER AND KUNZ, *Ann.*, **321**, 314 (1902).

Tetrahydronaphtho[1,2-f]quinoline (III) to octahydronaphtho[1,2-f]quinoline (IV).—Five grams of III of m. p. 74–76°, dissolved in 62 cc. of glacial acetic acid, absorbed 1300 cc. of hydrogen (calc'd for 2 moles, 1150 cc.) in fifteen hours (0.5 g. of platinum oxide). The yield of hydrochloride of the octahydro compound (IV) was 3.2 g.

N-Methyltetrahydronaphtho[1,2-*f*]quinoline (VI) of m. p. 77–78.5° absorbs approximately 2 moles of hydrogen under similar conditions. It was, however, impossible to isolate any well-defined compound from the reaction mixture.

Naphtho[1,2-f]quinoline (II) to tetrahydronaphtho[1,2-f]quinoline (III).—In an experiment employing 9 g. of II, 0.46 g. of platinum oxide, and 125 cc. of glacial acetic acid, the hydrogen absorption was interrupted when, after sixty hours, 2600 cc. of hydrogen had been taken up (calc'd for 2 moles, 2000 cc.). Sodium chloride was added to the filtered solution of the reaction mixture, whereby a hydrochloride of m. p. 225–250° precipitated. This salt yielded 2.4 g. of the rather unstable tetrahydro derivative of m. p. 74–75°. (The hydrochloride crystallized from alcohol in white leaflets of m. p. 255–260°.) The mother liquor from the crude hydrochloride was neutralized with sodium carbonate and extracted with ether. Three and one-tenth grams of an oil was obtained from the ether. No individual substances could be isolated from this oily material. Furthermore there was formed a crystalline precipitate, insoluble in the aqueous or ethereal layer, which was obviously a carbonate of the octahydro compound. By treating this precipitate with 10% potassium hydroxide and extracting the mixture with ether, 1.4 g. of octahydronaphtho[1,2-*f*]quinoline (IV), melting at 109–110°, was obtained.

The most convenient method of preparing the tetrahydro compound (III) has been described in the previous paper.[1] It may be added that by employing a higher temperature (170°) the yield of tetrahydro compound drops to about 40%. No other hydrogenated derivative could be isolated.

Degradations

Methiodide (V) and methochloride of 4-methyl-1,2,3,4-tetrahydronaphtho[1,2-f]-quinoline (VI).—To an ice-cold mixture of 11 g. of 1,2,3,4-tetrahydronaphtho-[1,2-*f*]quinoline, 40 cc. of acetone, and 10 cc. of methyl iodide was added 6 g. of sodium hydroxide in 10 cc. of water. The mixture was allowed to stand at room temperature for nine hours with occasional shaking. Five cubic centimeters of methyl iodide was added, and after twenty hours the precipitate was separated by filtration and boiled with a little water in order to remove inorganic material. The crude methiodide was recrystallized from alcohol; colorless slabs, m. p. 185–187° (decomp.); yield, 15.2 g.

Anal. Calc'd for $C_{19}H_{20}IN$: I, 32.61. Found: I, 32.19.

This methiodide may be obtained quantitatively by allowing VI and methyl iodide to react in acetone solution for several hours at room temperature. The precipitation is completed by addition of ether.

The methochloride of VI was obtained nearly quantitatively by heating the methiodide in aqueous suspension, with stirring, with freshly precipitated silver chloride. The silver halides were filtered off and the filtrate was evaporated to dryness in a vacuum. The substance crystallized from alcohol in long needles or little cubes of m. p. 174–176° (decomp.).

Anal. Calc'd for $C_{19}H_{20}ClN$: Cl, 11.91. Found: Cl, 12.24.

4-Methyl-1,2,3,4-tetrahydronaphtho[1,2-f]quinoline (VI).—Fifteen grams of methiodide (V) was slowly heated in a water-pump vacuum using a luminous flame. The distillate was redistilled in an oil-pump vacuum. The C-H analyses of this

product of m. p. 75–77.5° (yield 90%) were consistently too high (0.5–1%). Recrystallization from ether yielded clusters of flat rods of m. p. 77–78.5° (corr.).

Anal. Calc'd for $C_{18}H_{17}N$: C, 87.40; H, 6.93; N, 5.67.
Found: C, 87.59; H, 7.32; N, 5.88.

The hydrochloride was prepared by adding alcoholic hydrochloric acid to an acetone solution of the base. It crystallizes from alcohol-ether in colorless tablets, m. p. 215–217° (decomp.).

Anal. Calc'd for $C_{18}H_{18}ClN$: C, 76.16; H, 6.40.
Found: C, 76.08; H, 6.51.

Methiodide of 4-methyl-1,2,3,4,9,10,11,12-octahydronaphtho[1,2-f]quinoline.—To a solution of 2.0 g. of base (IV) in 10 cc. of acetone was added 1.5 g. of sodium hydroxide and 5 cc. of methyl iodide. The reaction mixture was allowed to stand for two hours. The precipitate was collected by filtration and washed well with water. The methiodide crystallized from water in white needles, m. p. 275–280 (decomp.), yield 75%.

Anal. Calc'd for $C_{19}H_{24}IN$: I, 32.28. Found: I, 31.89.

Emde degradation of the methochloride and methiodide of 4-methyl-1,2,3,4-tetrahydronaphtho[1,2-f]quinoline (VI) to 4-[3-(dimethylamino)-n-propyl]phenanthrene (VII).—To a solution of 2.2 g. of methochloride in 20 cc. of water was added 25 g. of 4% sodium amalgam. The mixture was boiled for fifteen minutes, although an oil precipitated immediately at the beginning of boiling. The oil was extracted with ether, the ether solution was filtered and dried with sodium sulfate. The residue remaining after removal of the ether was distilled in an oil-pump vacuum at 120° until about three-fourths of the material has passed over. From this distilled oil 0.6 g. of hydrochloride of m. p. 115–122° was obtained. It was recrystallized from 3 cc. of absolute alcohol, and melted, air-dried, at 123–125° with softening at 115°.

Anal. Calc'd for $C_{19}H_{22}ClN + C_2H_5OH$: C, 72.90; H, 8.16.
Found: C, 73.26; H, 7.51.

The hydrochloride was dried fifteen minutes in a water-pump vacuum over phosphorus pentoxide at room temperature, when it melted at 125–127°.

Anal. Calc'd for $C_{19}H_{22}ClN + C_2H_5OH$: C, 72.90; H, 8.16.
Found: C, 72.71; H, 7.80.

The hydrochloride was dried for two hours over calcium chloride at 103°; m. p. 157–159°.

Anal. Calc'd for $C_{19}H_{22}ClN$: C, 76.09; H, 7.40.
Calc'd for $C_{19}H_{24}ClN$: C, 75.58; H, 8.02.
Found: C, 75.42, 75.14; H, 7.19, 7.38.

The hydrochloride was dried for two hours in an oil-pump vacuum at 160°, at which temperature it begins to sublime; m. p. 157–159°. (The sublimed portion melts at the same temperature.)

Anal. Calc'd for $C_{19}H_{22}ClN$: C, 76.09; H, 7.40.
Calc'd for $C_{19}H_{24}ClN$: C, 75.58; H, 8.02.
Found: C, 75.48; H, 7.49.

The oily free base was liberated from the hydrochloride with ammonia and distilled in an oil-pump vacuum.

Anal. Calc'd for $C_{19}H_{21}N$: C, 86.63, H, 8.04.
Calc'd for $C_{19}H_{23}N$: C, 85.97; H, 8.74.
Found: C, 85.91, 85.59; H, 8.54, 8.70.

Six and five-tenths grams of methiodide was degraded with 3% sodium amalgam. By treatment of the reaction mixture as described above, 1.4 g. of a hydrochloride,

melting at 115–120° was obtained. It was recrystallized from absolute alcohol and dried in an oil-pump vacuum at 125°; m. p. 159–160°; yield, 0.8 g.

Anal. Calc'd for $C_{19}H_{22}ClN$: C, 76.09; H, 7.40.
Found: C, 75.96, 76.03; H, 7.74, 7.78.

The oily base was obtained as described above.

Anal. Calc'd for $C_{19}H_{21}N$: C, 86.63; H, 8.04.
Found: C, 86.53, 86.41; H, 7.52, 7.72.

Methiodide of 4-[3-(dimethylamino)-n-propyl]phenanthrene.—This compound precipitated almost immediately when the oily amine VII and methyl iodide were combined in acetone—ether solution. It crystallized from alcohol in white slabs of melting point 208–208.5° (corr.).

Anal. Calc'd for $C_{20}H_{24}IN$: C, 59.24; H, 5.97.
Found: C, 58.84; H, 5.79.

Naphtho[2,1-f]quinoline Series

Preparation of naphtho[2,1-f]quinoline (IX).—Thirty grams of 2-aminophenanthrene, 30 cc. of dry nitrobenzene, 60 g. of dry glycerine, and 6 g. of ferrous sulfate were well mixed in an Erlenmeyer flask. Twenty-nine cc. of C.P. sulfuric acid was added with thorough stirring, whereby considerable heat was evolved. The mixture was heated in an oil bath for one hour at about 145°, and was then transferred to a hot plate and gently boiled for two and one-half hours. The reaction mixture was steam-distilled, diluted with water, heated, and filtered. Addition of saturated sodium chloride solution to the filtrate caused precipitation of yellow crystals, which were suspended in hot water and treated with 10% ammonia with thorough stirring, whereupon the free base separated as a grayish precipitate. It was purified by sublimation in an oil-pump vacuum at 180° and by crystallization from toluene; colorless leaflets of m. p. 226–227° (corr.), yield 80–90%.

Anal. Calc'd for $C_{17}H_{11}N$: C, 89.04; H, 4.84; N, 6.11.
Found: C, 88.79; H, 4.82; N, 6.10.

The hydrochloride crystallized from alcohol, in which it is sparingly soluble, in tiny bright yellow needles of m. p. 296–300° (evac. tube).

Anal. Calc'd for $C_{17}H_{12}ClN$: Cl, 13.35. Found: Cl, 13.24.

Hydrogenations

Naphtho[2,1-f]quinoline (IX) to tetrahydronaphtho[2,1-f]quinoline (X).—A solution of 2.7 g. of IX in 75 cc. of glacial acetic acid absorbed 680 cc. of hydrogen (calc'd for 2 moles, 600 cc.) in seven and one-half hours, in the presence of 0.15 g. of platinum oxide catalyst. To the yellow reaction solution was added a concentrated sodium chloride solution, whereby a hydrochloride was precipitated. The free base was liberated by sodium carbonate and extracted with ether. The ether solution yielded 2.3 g. of white prisms of m. p. 153–155°. The base crystallized from chloroform or ethyl acetate in pale yellow tablets, m. p. 157–159° (corr.).

Anal. Calc'd for $C_{17}H_{15}N$: C, 87.51; H, 6.49; N, 6.01.
Found: C, 87.60; H, 6.24; N, 6.06.

The hydrochloride crystallizes from alcohol, in which it is sparingly soluble, in white blades of m. p. 310–313° (decomp.).

Anal. Calc'd for $C_{17}H_{16}ClN$: Cl, 13.15. Found: Cl, 13.00.

Twenty grams of the naphthoquinoline (IX), 2 g. of chromite catalyst (37 KAF) and 50 cc. of absolute alcohol were heated to 130° during one hour and kept for two hours at 136° at a hydrogen pressure of 162 atm. The filtrate from the reaction mix-

ture gave 1.2 g. of base of m. p. 149–153°. The precipitate consisting of catalyst and crystalline reaction product was treated with acetone. The acetone solution yielded 19 g. of base, melting at 149–153°. This practically pure compound gave no melting-point depression with the tetrahydro base obtained in the previous hydrogenation experiment.

Naphtho[2,1-f]quinoline (IX) to hexahydronaphtho[2,1-f]quinoline (XI).—Ten grams of the naphthoquinoline, 1 g. of chromite catalyst and 30 cc. of absolute alcohol were heated during two hours to 230° under a hydrogen pressure of 217 atm. From the crystalline material and from the original mother liquor were obtained a fraction of 2.6 g., melting at 110–115°, and a fraction of 1.2 g., melting at 105–111° respectively. By recrystallization from ethyl acetate a hexahydronaphthoquinoline was obtained in large white prisms that melted at 115–116° (corr.).

Anal. Calc'd for $C_{17}H_{17}N$: C, 86.76; H, 7.29; N, 5.96.
Found: C, 86.81, 86.56; H, 7.56, 7.37; N, 6.13.

The hydrochloride crystallized from alcohol in white leaflets of m. p. 274–285° (corr., evac. tube).

Anal. Calc'd for $C_{17}H_{18}ClN$: C, 75.11; H, 6.67.
Found: C, 75.11; H, 6.92.

When the high-pressure hydrogenation using chromite catalyst was carried out at 172° a mixture containing the hexahydro base and the tetrahydro base, the latter predominating, was obtained.

An impure hexahydro base (probably containing some tetrahydro compound) was obtained by hydrogenating the tetrahydro compound in glacial acetic acid, employing platinum oxide catalyst. It is noteworthy that this hydrogenation proceeds exceedingly slowly. Five grams absorb 1160 cc. of hydrogen (calc'd for 1 mole, 620 cc.) in 85 hours, giving 2.7 g. of crystalline material of m. p. 104–105°.

Degradations

Methiodide (XIII) of 1-methyl-1,2,3,4-tetrahydronaphtho[2,1-f]quinoline (XIV).—(*a*) A mixture of 5 g. of X, 25 cc. of acetone, 8 cc. of methyl iodide, and 3 g. of sodium hydroxide was allowed to react for two hours and shaken occasionally. After the addition of 2 cc. of methyl iodide the mixture was allowed to stand for two days. Six and seven-tenths grams of crude methiodide was obtained. It crystallized from water in white lozenges of melting point 204–205° (decomp.).

Anal. Calc'd for $C_{19}H_{20}IN$: I, 32.61. Found: I, 32.28.

(*b*) This methiodide is also obtained quantitatively by combining methyl iodide and the base XIV in acetone solution and allowing the reaction mixture to stand for one day.

The corresponding methochloride of m. p. 188–190° was prepared by treating the methiodide with silver chloride as described in the 1,2-*f* series.

1-Methyl-1,2,3,4-tetrahydronaphtho[2,1-f]quinoline (XIV).—Six grams of the methiodide gave, on heating in a vacuum and redistillation of the first distillate, 3.2 g. of a base melting at 164–166°. By repeated recrystallization from ethyl acetate the *N*-methyltetrahydro base was obtained in the form of large flat tablets of melting point 170–171° (corr.).

Anal. Calc'd for $C_{18}H_{17}N$: C, 87.40; H, 6.93; N, 5.67.
Found: C, 87.44; H, 6.95; N, 5.89.

The hydrochloride was prepared like the corresponding compound in the 1,2-*f* series, m. p. 240–260° (decomp.).

Anal. Calc'd for $C_{18}H_{18}ClN$: C, 76.16; H, 6.40.
Found: C, 76.07; H, 6.49.

Methiodide (XV) of 1-methyl-1,2,3,4,5,6-hexahydronaphtho[2,1-f]quinoline (XVI).—(*a*) This methiodide was prepared from (XI) in the usual manner (0.7 g. of XI, 2 cc. of methyl iodide, 0.1 g. of sodium hydroxide, 5 cc. of acetone). When the precipitate was boiled with water, it was observed that the salt decomposed partly, whereby the tertiary base XVI was formed. This was separated by filtration, and the methiodide XV (0.5 g.) was precipitated from the filtrate by potassium iodide. It crystallized from alcohol in flat rods, m. p. 189–192° (decomp.).

Anal. Calc'd for $C_{19}H_{22}IN$: C, 58.29; H, 5.69.
Found: C, 58.03; H, 5.47.

(*b*) This methiodide was also readily formed when methyl iodide was added to the acetone solution of the *N*-methylhexahydro base (XVI) (from the decomposition of the methiodide); m. p. 193–195°.

The 1-methyl-1,2,3,4,5,6-hexahydronaphtho[2,1-*f*]quinoline (XVI), obtained by boiling the methiodide (XV) with water, was purified by recrystallization from absolute alcohol and sublimation in an oil-pump vacuum at 120°; m. p. 129–131°. The methiodide had been thoroughly washed with ether in order to eliminate the possibility of the presence of the tertiary base XVI before decomposition.

Anal. Calc'd for $C_{18}H_{19}N$: C, 86.69; H, 7.68.
Found: C, 86.45; H, 7.65.

Emde degradation of the methiodide and methochloride of 1-methyl-1,2,3,4-tetrahydronaphtho[2,1-f]quinoline (XIV) to 1-[3-(dimethylamino)-n-propyl]phenanthrene (XVII).—Five and six-tenths grams of the methochloride of XIV was boiled in 200 cc. of water with 100 g. of 5% sodium amalgam for fifteen minutes. The oily basic reaction product was extracted with ether, distilled in an oil-pump vacuum and converted into a hydrochloride of m. p. 195–200°. This hydrochloride appeared to be unstable, turning gray and brown on standing. The base liberated from it was redistilled in an oil-pump vacuum.

Anal. Calc'd for $C_{19}H_{21}N$: C, 86.63; H, 8.04.
Calc'd for $C_{19}H_{23}N$: C, 85.97; H, 8.74.
Found: C, 85.84; H, 8.47.

Further distillation of the crude Emde degradation products yielded 0.2 g. of the *N*-methyltetrahydro base (XIV), identified by mixture melting point.

In another degradation, carried out in the same manner, but with 3% sodium amalgam, 0.2 g. of methochloride gave 0.1 g. of a hydrochloride melting at 200–202°. It was converted with sodium picrate solution to the picrate, which crystallized from alcohol in clusters of short needles, m. p. 164.5–166.5° (corr.).

Anal. Calc'd for $C_{25}H_{26}N_4O_7$: C, 60.70; H, 5.30.
Calc'd for $C_{25}H_{24}N_4O_7$: C, 60.95; H, 4.91.
Found: C, 60.68; H, 4.81.

In mixture with the picrate of 1-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene (XVIII), of m. p. 144–145°, it softens at 135° and melts at 139–143°.

Another degradation was carried out using the methiodide instead of the methochloride. The degradation product was purified by fractional liberation of the base with insufficient amounts of ammonia and by crystallization of the hydrochloried from alcohol-ether. The salt was obtained in clumps of white rectangular plates of m. p. 210–213° (slight softening at 198°). When recrystalized from alcohol-acetone-ether, it precipitated in form of fine white needles of m. p. 206–207°. The

mixture melting point of this hydrochloride with the hydrochloride of the degradation product (XVIII) (m. p. 207–209°) from the methiodide (XV) of 1-methyl-1,2,3,4,5,6-hexahydronaphtho[2,1-*f*]quinoline (XVI) was at 205–206°. They are, however, not identical (see Table I).

Emde degradation of the methiodide (XV) of 1-methyl-1,2,3,4,5,6-hexahydronaphtho[2,1-f]quinoline (XVI) to 1-[3-(dimethylamino)-n-propyl]-9,10-dihydrophenanthrene (XVIII).—A solution of 0.4 g. of XV in 20 cc. of water was boiled for twenty minutes with 3% sodium amalgam. The hydrochloride (0.1 g.) of the purified degradation product was recrystallized from alcohol and ether, and melted at 207–209° (uncorr.).

Anal. Calc'd for $C_{19}H_{24}ClN$: C, 75.57; H, 8.02.
Found: C, 75.33; H, 7.90.

The hydrochloride was converted with sodium picrate solution to the picrate, which crystallized from alcohol in pale yellow prisms, m. p. 145.5–146.5° (corr.).

Anal. Calc'd for $C_{25}H_{26}N_4O_7$: C, 60.70; H, 5.30.
Found: C, 60.73; H, 5.08.

TABLE I

MELTING POINTS OF HYDROCHLORIDES AND PICRATES

	M. P. OF HYDROCHLORIDE, °C	M. P. OF PICRATE (CORR.), °C
XVII	206–207 (210–213)	164.5–166.5
XVIII	207–209	145.5–146.5
XXX	160.5–162 (corr.)	150.5–151.5
XXIX	150–151 (corr.)	101.5–103

In Table I the non-identity of the degradation products XVII and XVIII and of each of them with synthetic 3-[3-(dimethylamino)-*n*-propyl]phenanthrene (XXX) and 3-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene (XXIX) is illustrated by the melting points of the respective hydrochlorides and picrates.

Naphtho[1,2-g]quinoline Series

Preparation of 5,6-dihydronaphtho[1,2-g]quinoline (XXI).—To a mixture of 30 g. of 2-amino-9,10-dihydrophenanthrene, 30 cc. of nitrobenzene, 6 g. of ferrous sulfate, and 60 g. of glycerine was added 29 cc. of C.P. sulfuric acid. The mixture was heated at 150–160° for five hours in a metal bath. The black product was poured into 1500 cc. of water and extracted with ether. The naphthoquinoline hydrochloride precipitated from the aqueous solution in the form of hair-like yellow crystals when saturated sodium chloride solution was added. The free base was liberated with ammonia, extracted with ether and distilled in an oil-pump vacuum at 150°. It crystallized from ethyl acetate in large white prisms, m. p. 72–74° (corr.), yield 50%.

Anal. Calc'd for $C_{17}H_{13}N$: C, 88.27; H, 5.67.
Found: C, 87.89; H, 5.85.

The hydrochloride crystallized from alcohol as a yellow powder, m. p. 258–262° (corr., evac. tube).

Anal. Calc'd for $C_{17}H_{14}ClN$: Cl, 13.26. Found: Cl, 12.83.

Hydrogenations

5,6-Dihydronaphtho[1;2-g]quinoline (XXI) to 5,6,8,9,10,11-hexahydronaphtho-[1,2-g]quinoline (XXIV).—Five grams of XXI in 62 cc. of glacial acetic acid with 0.5 g. of platinum oxide catalyst absorbed 1400 cc. of hydrogen (calc'd for 2 moles, 1150 cc.) within six hours. The base was liberated with sodium carbonate solution, extracted with ether, and distilled at 150° in an oil-pump vacuum. The oily, pale yellow base was converted into the hydrochloride (4.6 g.) which was recrystallized from alcohol and reconverted to the base which, eventually, became crystalline. It was obtained by recrystallization from ethyl acetate as colorless prisms, m. p. 72–73° (corr.) (the mixture melting point with XXI was 65°).

Anal. Calc'd for $C_{17}H_{17}N$: C, 86.76; H, 7.29; N, 5.96.
Found: C, 86.95; H, 7.44; N, 5.72.

The hydrochloride crystallized from alcohol in minute white needles, m. p. 240–244° (evac. tube).

Anal. Calc'd for $C_{17}H_{18}ClN$: C, 75.11; H, 6.68.
Found: C, 74.75; H, 7.01.

Ten grams of XXI, 30 cc. of absolute alcohol and 1 g. of chromite catalyst were heated during three hours to 150°, during an hour and a half to 170° and finally to 197° for half an hour under a hydrogen pressure of 183 atm. By readings on the pressure gauge, the temperature at which hydrogenation took place could not be determined. As far as could be judged by plotting pressure against temperature for both heating and cooling of the bomb, the hydrogenation appeared to have taken place between 150–160°. The reaction product yielded 7 g. of a hydrochloride of m. p. 215–217°, from which finally 4.2 g. of hexahydro base (XXIV) of m. p. 70–73° was obtained.

Methiodide (XXVII) of 8-methyl-5,6,8,9,10,11-hexahydronaphtho[1,2-g]quinoline.—Four and two-tenths grams of XXIV in 30 cc. of acetone, 5 cc. of methyl iodide, and 1 g. of potassium hydroxide in 2 cc. of water were allowed to react for two days. The heavy precipitate that formed did not give a clear solution when boiled with water. Potassium iodide was added, and the dry precipitate (consisting of methiodide and *N*-methylhexahydro base ?) was suspended in ether containing methyl iodide. Finally the methiodide was recrystallized from alcohol; large, slightly yellow needles, m. p. 196–200° (decomp.), yield 65%.

Anal. Calc'd for $C_{19}H_{22}IN$: N, 3.58. Found: N, 3.67.

Emde degradation of XXVII to 8-[3-(dimethylamino)-n-propyl]-9,10-dihydrophenanthrene (XXIX).—An aqueous solution of 6.3 g. of XXVII was boiled for one hour with 3% sodium amalgam. The oily reaction product gave, after distillation in an oil-pump vacuum at 130°, 3.2 g. of a hydrochloride melting at 138–142°. The base was liberated again, distilled, and reconverted to the hydrochloride, which crystallized from alcohol in white needles of melting point 150–151° (corr.).

Anal. Calc'd for $C_{19}H_{24}ClN$: C, 75.57; H, 8.02; Cl, 11.76.
Found: C, 75.68; H, 8.07; Cl, 12.13.

The picrate crystallized from alcohol in pale yellow prisms of m. p. 101.5–103° (corr.).

Anal. Calc'd for $C_{25}H_{26}N_4O_7$: C, 60.70; H, 5.30.
Found: C, 60.32; H, 5.15.

In only one of several dehydrogenation experiments was the transformation of XXIX to XXX accomplished. A mixture of 1.2 g. of base XXIX and 50 mg. of

palladium black[29] was heated in a nitrogen atmosphere at 190–200° for thirty minutes. Only a small amount of hydrochloride, approximately 10 mg., insoluble in acetone and melting at 155–157° could be isolated from the reaction mixture. The mixture melting point with 3-[3-(dimethylamino)-*n*-propylphenanthrene of m. p. 157–159° was at 156–158°. The hydrochloride from the dehydrogenation experiment was converted to the picrate which melted after four recrystallizations from alcohol at 147–148.5°.

Preparation of naphtho[1,2-g]quinoline (XXII) by dehydrogenation of 5,6-dihydronaphtho[1,2-g]quinoline (XXI).—Two grams of XXI and 0.1 g. of palladium black were placed in a wide test-tube and heated gradually in a nitrogen atmosphere. The evolution of hydrogen began at about 300°. The temperature was raised to 350–360° and maintained there for two hours. The contents of the tube were subjected to distillation in an oil-pump vacuum at 170°, yielding a distillate (1.6 g.) that melted at 135–149°. The naphthoquinoline crystallized from benzene or ethyl acetate in fine white needles of m. p. 159–160° (corr.), yield 50%.

Anal. Calc'd for $C_{17}H_{11}N$: C, 89.04; H, 4.84.
Found: C, 88.99; H, 5.21.

The hydrochloride crystallized from alcohol in yellow needles, m. p. 280–295° (evac. tube).

Anal. Calc'd for $C_{17}H_{12}ClN$: C, 76.82; H, 4.55.
Found: C, 76.74; H, 5.03.

In a series of twelve experiments, no more than 3 g. of substance was dehydrogenated in one run. Increase of the amount of catalyst increases the yield to some extent. (Two and seven-tenths grams of dihydro compound, 0.5 g. of palladium, and 25 minutes of heating yielded 1.8 g. of a naphthoquinoline, melting at 154–156°.)

Hydrogenation of naphtho[1,2-g]quinoline (XXII) to 8,9,10,11-tetrahydronaphtho[1,2-g]quinoline (XXV).—Two and six-tenths grams of XXII with 0.2 g. of platinum oxide in glacial acetic acid absorbed in one hour and twenty minutes 680 cc. of hydrogen (calc'd for 2 moles, 590 cc.). The hydrochloride was precipitated with saturated sodium chloride solution and the base obtained from the hydrochloride (ammonia and ether) was distilled in an oil-pump vacuum at 180°. The pale yellow oil could not be induced to crystallize.

Anal. Calc'd for $C_{17}H_{15}N$: C, 87.51; H, 6.49.
Found: C, 87.23; H, 6.67.

Methiodide of 8-methyl-8,9,10,11-tetrahydronaphtho[1,2-g]quinoline (XXVIII).—A mixture of 0.9 g. (not distilled) of tetrahydro base (XXV), 10 cc. of acetone, 3 cc. of methyl iodide, and 1 g. of potassium hydroxide was allowed to stand for two days. The precipitate was filtered out, and 2 cc. of methyl iodide and 1 g. of potassium hydroxide were added to the mother liquor. The total yield of methiodide, recrystallized from water, was 0.8 g. It melted after recrystallization from alcohol at 200–203° (white needles). The distilled base yielded a slightly purer methiodide melting at 203–205° (decomp.).

Anal. Calc'd for $C_{19}H_{20}IN$: C, 58.60; H, 5.18.
Found: C, 58.53; H, 5.38.

Emde degradation of XXVIII to 3-[3-(dimethylamino)-n-propyl]phenanthrene (XXX).—An aqueous solution of 0.7 g. of XXVIII was boiled with 5% sodium amalgam for one hour following the usual procedure. A hydrochloride (0.08 g.) of m. p. 156–157° was obtained by treating the crude hydrochloride with acetone and

[29] WILLSTÄTTER AND WALDSCHMIDT-LEITZ, *Ber.*, **54**, 123 (1921).

ethyl acetate. By extremely slow crystallization from alcohol this hydrochloride was obtained in small white needles melting at 160–160.5° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClN$: C, 76.09; H, 7.43.
Found: C, 75.48; H, 7.71.

The mixture melting point with the hydrochloride of XXIX was 143–147°.

The following derivatives were obtained from various degradation experiments in which XXX was obtained in essentially the same manner:

The picrate crystallized from alcohol in clusters of pale yellow needles of m. p. 150.5-151.5° (corr.).

The methiodide of XXX precipitated immediately when an acetone-ether solution of XXX was mixed with methyl iodide. It crystallized from alcohol in white prisms of m. p. 173–174°.

The perchlorate of XXX precipitated in white glistening leaflets, melting point 84.5–89° (corr.), when ethereal perchloric acid was added to an ethereal solution of XXX.

TABLE II

MELTING POINTS OF DERIVATIVES OF 3-[3-(DIMETHYLAMINO)-*n*-PROPYL] PHENANTHRENE

DERIVATIVE	BY SYNTHESIS, °C	BY DEGRADATION, °C	MIXTURE, °C
Base	Oily	Oily	
Hydrochloride	160.5–162	160–160.5	160–161
Picrate	150–150.5	150.5–151.5	150–150.5
Methiodide	164–165	174–175	164–165
Perchlorate	86–89	84.5–89	85–89

In Table II are listed melting points and mixture melting points of the corresponding derivatives of XXX obtained by degradation and by synthesis. All melting points are corrected. No explanation of the difference in melting points of the methiodide can be offered.

*Synthesis of Dimethylamino-*n*-propyl-phenanthrenes*

The hydrochloride of 3-[3-(dimethylamino)-1-hydroxy-*n*-propyl]phenanthrene is hygroscopic and apparently undergoes changes in the presence of free hydrochloric acid (either by loss of water or by chlorination). It can be obtained by evaporation to dryness of the alcoholic solution resulting from the catalytic hydrogenation of the corresponding amino ketone hydrochloride.[30]

*3-[3-(Dimethylamino)-1-chloro-*n*-propyl]phenanthrene hydrochloride.*—Seven-tenths of a gram of amino alcohol hydrochloride was added to a suspension of 1 g. of phosphorus pentachloride in 10 cc. of chloroform. After half an hour the excess of phosphorus pentachloride was destroyed with alcohol, and ether was added to precipitate the salt. The air-dried product melted at 150–155°, solidified and finally melted at 238–240°.

Anal. Calc'd for $C_{19}H_{21}Cl_2N$: C, 68.24; H, 6.34.
Found: C, 68.13; H, 6.91.

[30] VAN DE KAMP AND MOSETTIG, *J. Am. Chem. Soc.*, **58**, 1568 (1936).

3-[3-(Dimethylamino)-n-propyl]phenanthrene.—A suspension of 0.4 g. of palladous hydroxide-calcium carbonate catalyst[21] (palladium content 1%) and 1.2 g. of the hydrochloride of the chloro compound were shaken in a hydrogen atmosphere. Absorption was complete in thirty minutes. The catalyst was filtered off, the solvent was evaporated, and the residue was treated with ammonia, extracted with ether, and distilled in an oil-pump vacuum at 140°. The oily base (ca. 0.75 g.) was converted to the hydrochloride, which crystallized from alcohol—ethyl acetate in small white prisms of m. p. 160.5–162° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClN$: C, 76.09; H, 7.40; Cl, 11.83.
Found: C, 75.73; H, 7.34, Cl, 11.81.

The picrate crystallized from alcohol in pale orange needles of m. p. 149.5–151° (corr.).

Anal. Calc'd for $C_{25}H_{24}N_4O_7$: C, 60.95; H, 4.91.
Found: C, 61.03; H, 5.06.

The methiodide crystallized from alcohol in small white prisms of m. p. 163–164°.

Anal. Calc'd for $C_{20}H_{24}IN$: C, 59.24; H, 5.97.
Found: C, 59.52; H, 6.06.

The perchlorate was prepared exactly as described for this derivative of the degradation product XXX, and melted at 86–89° (corr.).

The preparation of 2-[3-(dimethylamino)-*n*-propyl]phenanthrene hydrochloride of m. p. 222–227° has been described in the previous communication.[1] The base of this hydrochloride is apparently little attacked when boiled in aqueous alcoholic solution with 5% sodium amalgam for four hours. The hydrochloride prepared from the reaction mixture melted at 210–213°. Boiling the base for four hours with sodium and alcohol yielded finally a mixture of hydrochlorides melting at 170–180° from which no individual compound could be isolated.

2-[3-(Dimethylamino)-1-oxo-propyl]-9,10-dihydrophenanthrene.—Seven grams of 2-acetyl-9,10-dihydrophenanthrene, 1.9 g. of trioxymethylene, 6.3 g. of dimethylamine hydrochloride, and 26 cc. of isoamyl alcohol were boiled under reflux for twelve minutes. The reaction mixture was poured into water, and the base was liberated from the aqueous solution with ammonia, extracted with ether, and recrystallized from ligroin; m. p. 69–70°, yield 5.0 g. It crystallized from ethyl acetate in white prisms of melting point 70–71° (corr.).

Anal. Calc'd for $C_{19}H_{21}NO$: C, 81.67; H, 7.58.
Found: C, 81.79; H, 7.73.

The hydrochloride crystallized from acetone-alcohol in long flat rods, m. p. 162–163° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClNO$: Cl, 11.23. Found: Cl, 11.67.

2-[3-(Dimethylamino)-1-hydroxy-n-propyl]-9,10-dihydrophenanthrene.—The amino alcohol was prepared by reducing 4.7 g. of the amino ketone hydrochloride in 100 cc. of 60% alcohol, using 0.2 g. of platinum oxide catalyst. It melted, after recrystallization from ether-petroleum ether, at 72–74° (corr.), yield 80%.

Anal. Calc'd for $C_{19}H_{23}NO$: C, 81.08; H, 8.24.
Found: C, 80.69; H, 8.29.

The hydrochloride crystallized from alcohol-ether in small white needles of m. p. 159–161° (corr.).

Anal. Calc'd for $C_{19}H_{24}ClNO$: Cl, 11.16. Found: Cl, 11.43.

2-[3-(Dimethylamino)-1-chloro-n-propyl]-9,10-dihydrophenanthrene hydrochloride.—The chloro compound was obtained by chlorinating the amino alcohol hydrochloride

[21] Busch and Schulz, *Ber.*, **62**, 1460 (1929).

in chloroform with phosphorus pentachloride. The hydrochloride was recrystallized from alcohol and dried over calcium chloride in the desiccator. It melted around 160°, solidified, and remelted at 214–216° (decomp.).

Anal. Calc'd for $C_{19}H_{23}Cl_2N$: C, 67.83; H, 6.89.
Found: C, 67.53; H, 7.09.

2-[3-(Dimethylamino)-n-propyl]-9,10-dihydrophenanthrene hydrochloride.—The elimination of the chlorine was effected by catalytic hydrogenation employing palladous hydroxide—calcium carbonate catalyst. The propyl amino compound was obtained in a yield of 75%. The hydrochloride melted at 204–206° (corr.).

Anal. Calc'd for $C_{19}H_{24}ClN$: C, 75.57; H, 8.02; Cl, 11.76.
Found: C, 75.29; H, 8.05; Cl, 11.59.

SUMMARY

By application of the Skraup method to 3-aminophenanthrene, 2-aminophenanthrene, and 2-amino-9,10-dihydrophenanthrene, naphthoquinolines were obtained in satisfactory yields.

Various hydro derivatives of the naphthoquinolines were obtained by catalytic hydrogenation using platinum oxide catalyst under normal conditions and chromite catalyst at elevated temperature and hydrogen pressure.

The constitutional proof of the naphthoquinolines was established by degradation of the respective *N*-methyltetrahydronaphthoquinolines to dimethylamino-*n*-propylphenanthrenes, which were compared with the corresponding phenanthrene derivatives of known structure.

3-[3-(Dimethylamino)-*n*-propyl]phenanthrene and 2-[3-(dimethylamino)-*n*-propyl]-9,10-dihydrophenanthrene were synthesized from 3-acetylphenanthrene and 2-acetyl-9,10-dihydrophenanthrene respectively.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

STUDIES IN THE PHENANTHRENE SERIES. XX. NITRATION OF 9,10-DIHYDROPHENANTHRENE*

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The nitration of phenanthrene is known to be an unsatisfactory procedure for preparing nitrophenanthrenes, first, on account of the interference of the 9,10-double bond—formation of addition products with the nitrating agent—[1] and second, because of the tediousness involved in the separation of the isomeric nitro products.[2]

Our expectation that the nitration of 9,10-dihydrophenanthrene, which has no double bond of "olefinic character", would proceed quite normally was realized. This nitration gave an easily separable mixture of two mononitrophenanthrenes, the one being formed in a yield of 65 per cent., the other in a yield of 3–4 per cent. We have pointed out previously that 9,10-dihydrophenanthrene behaves like diphenyl rather than like phenanthrene.[3] Therefore we assumed that, in analogy to the nitration of diphenyl,[4] the main product(*A*) would be the 2-nitro-9, 10-dihydrophenanthrene (corresponding to *para*-nitrodiphenyl) and the by-product (*B*) the 4-nitro-9,10-dihydrophenanthrene (corresponding to *ortho*-nitrodiphenyl). This assumption was correct. *A* was reduced to an amino compound which was identical with 2-amino-9,10-dihydrophenanthrene prepared from 2-acetyl-9,10-dihydrophenanthrene.[5, 3b] *B*, also, was first reduced to an amino compound which by diazotization and subsequent methylation of the resulting hydroxy compound was converted to a methoxydihydrophenanthrene. We attempted to dehydrogenate this compound to one of the known methoxyphenanthrenes, but the only crystalline material that could be isolated from the dehydrogenation

* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, The University of Virginia, and the University of Michigan.

[1] SCHMIDT, *Ber.*, **33**, 3251 (1900); WIELAND AND RAHN, *ibid.*, **54**, 1770 (1921).

[2] (*a*) SCHMIDT, *ibid.*, **12**, 1153 (1879); (*b*) SCHMIDT AND HEINLE, *ibid.*, **44**, 1488 (1911).

[3] (*a*) BURGER AND MOSETTIG, *J. Am. Chem. Soc.*, **57**, 2731 (1935); (*b*) *ibid.*, **58**, 1857 (1936).

[4] JENKINS, MCCULLOUGH, AND BOOTH, *Ind. Eng. Chem.*, **22**, 31 (1930).

[5] BURGER AND MOSETTIG, *J. Am. Chem. Soc.*, **59**, 1302 (1937).

mixture was phenanthrene. The methoxyl group had been eliminated largely or entirely in this process. The ease of elimination of the methoxyl group was strongly suggestive of its location in position-4, since it is known that substituents so located in phenanthrene are relatively easily eliminated.[6]

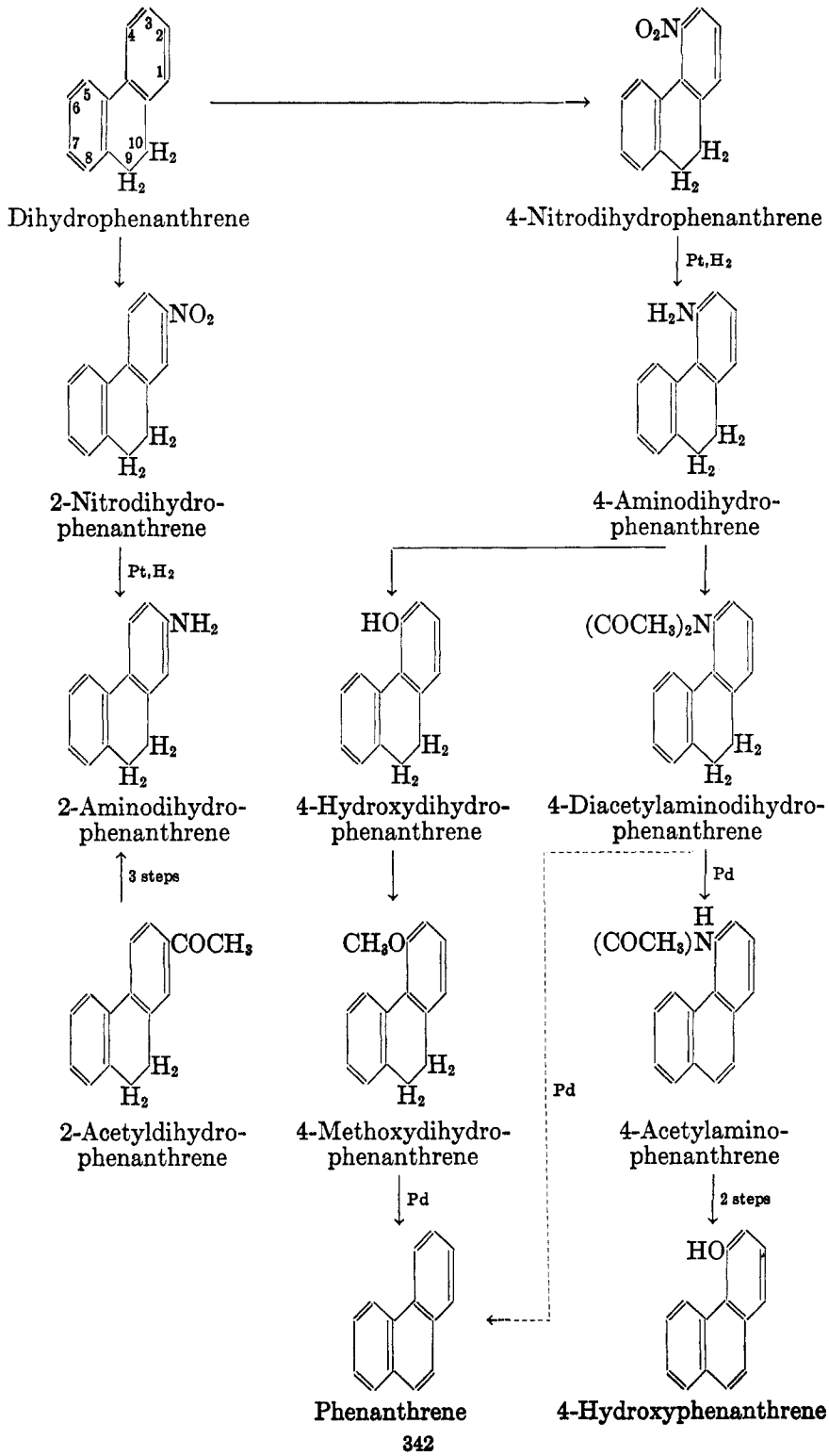
The dehydrogenation of the diacetylaminodihydrophenanthrene (obtained from *B*) was more successful, and a monoacetylphenanthrene of m. p. 196–197° could be isolated in relatively good yields. It was hydrolyzed to an aminophenanthrene of m. p. 62.5–63.5° (benzoyl derivative of m. p. 216–218°) which on diazotization and subsequent methylation gave successively 4-hydroxy- and 4-methoxyphenanthrene, whose identities were established by direct comparison with authentic samples of these phenanthrene derivatives. Schmidt and Heinle[2b] described a 4-aminophenanthrene as melting at 104–105° (acetyl derivative, m. p. 190°, benzoyl derivative, m. p. 224°). Although these authors state that they did not observe two modifications of their 4-aminophenanthrene (in analogy with 3-aminophenanthrene[7] and 9-aminophenanthrene) we believe that the discrepancy in the melting points of these apparently different 4-aminophenanthrenes may be accounted for by the existence of this amine in two forms. (The hydrolysis of their 4-acetylaminophenanthrene was not described by Schmidt and Heinle.) Schmidt's structural proof for 4-aminophenanthrene rests upon the conversion of his 4-nitrophenanthrene to 4-nitro-9,10-phenanthrene quinone. Our attempts to oxidize 4-nitro-9,10-dihydrophenanthrene with chromic acid were unsuccessful, since it proved to be unexpectedly stable towards this reagent.

It seems worthy of mention, that we were not able, in various experiments, to obtain a naphthoquinoline by applying the Skraup method to 4-amino-9,10-dihydrophenanthrene. This failure, together with the empirical fact (see foregoing paper) that side-chains attached to position 2 of 9,10-dihydrophenanthrene cyclize entirely or largely in position 3, might indicate a fixed arrangement of double bonds in 9,10-dihydrophenanthrene (the double bond connecting positions 2 and 3, the single bond connecting 3 and 4) different from that in the terminal nuclei of phenanthrene. A more complete study of the empirical rule† mentioned above,

[6] WERNER AND KUNZ, *Ber.*, **35**, 4419 (1902); MOSETTIG AND BURGER, *J. Am. Chem. Soc.*, **55**, 2981 (1933); COOK AND HEWETT, *J. Chem. Soc.*, **1933**, 403; MOSETTIG AND DUVALL, *J. Am. Chem. Soc.*, **59**, 368, footnote *m* (1937).

[7] WERNER AND KUNZ, *Ber.*, **34**, 2524 (1901); SCHMIDT, *ibid.*, **34**, 3531 (1901).

† The ring closure of γ-[2-(9,10-dihydrophenanthryl)]-*n*-butyric acid resulted in only 30% yield of the benzanthracene derivative [BURGER AND MOSETTIG, *J. Am. Chem. Soc.*, **59**, 1302 (1937)] and the yield of dihydronaphtho[1,2-*g*]quinoline from 2-amino-9,10-dihydrophenanthrene was only 50% (see foregoing paper). But in both instances there was no indication of the formation of an isomeric compound.


Dihydrophenanthrene
4-Nitrodihydrophenanthrene
Pt,H2
2-Nitrodihydro-phenanthrene
4-Aminodihydro-phenanthrene
Pt,H2
2-Aminodihydro-phenanthrene
4-Hydroxydihydro-phenanthrene
4-Diacetylaminodihydro-phenanthrene
3 steps
Pd
2-Acetyldihydro-phenanthrene
4-Methoxydihydro-phenanthrene
4-Acetylamino-phenanthrene
Pd
Pd
2 steps
Phenanthrene
4-Hydroxyphenanthrene

and the application of the Skraup synthesis to 4-aminophenanthrene, which is not available in sufficient quantity at present, appear necessary to substantiate such speculations.

EXPERIMENTAL

2-Nitro- and 4-nitro-9,10-dihydrophenanthrene.—To a mechanically stirred mixture of 20.5 g. of dihydrophenanthrene and 120 cc. of glacial acetic acid, 30 cc. of nitric acid (Merck Reagent "Acid Nitric Fuming" sp. gr. 1.5) was added during two hours, the temperature being kept between 29° and 33°. The red solution was poured into three liters of water, and the oily precipitate solidified overnight sufficiently to be separated by filtration (20 g., m. p. 70–75°). It was dissolved in acetone and carefully precipitated with alcohol, m. p. 77–81°, yield 63%. 2-Nitro-9,10-dihydrophenanthrene crystallized from ether in very small, pale pink prisms of m. p. 81–82°.

Anal. Calc'd for $C_{14}H_{11}NO_2$: N, 6.22. Found: N, 6.62.

The acetone-alcohol mother liquors from a series of reactions in which 200 g. of hydrocarbon had been nitrated and from which 147 g. of pure 2-nitro-9,10-dihydrophenanthrene had been obtained, were concentrated to a small volume and allowed to stand in a refrigerator for several days. Six grams of impure 2-nitro compound of m. p. 72–78° was filtered off. The remaining solvent was evaporated, and the oily residue was distilled in an oil-pump vacuum through a Vigreux column wrapped in asbestos paper (metal bath). The fraction distilling at 180°, approximately 20 g. of a yellow oil, was dissolved in ethyl acetate and yielded 8.7 g. of 4-nitro-9,10-dihydrophenanthrene of m. p. 82–94°. By another crystallization, 7 g. of well-defined, large yellow cubes, melting at 97–98° was obtained.

Anal. Calc'd for $C_{14}H_{11}NO_2$: C, 74.64; H, 4.93; N, 6.22.
Found: C, 74.74; H, 4.66; N, 6.03.

2-Amino-9,10-dihydrophenanthrene.—A suspension of 25 g. of 2-nitro-9,10-dihydrophenanthrene in 200 cc. of absolute alcohol with 0.05 g. of platinum oxide absorbed slightly more than the calculated amount of hydrogen in five hours. It was necessary to cool the reduction vessel from time to time in ice water and to work up the reaction mixture immediately after hydrogenation came to a standstill. The amine was isolated as hydrochloride by adding alcoholic hydrogen chloride to the solution filtered from the catalyst. The free base could be distilled readily in an oil-pump vacuum. To a suspension of the hydrochloride in water ammonia was added, and the mixture was extracted with ether. The ether solution was concentrated and cooled in an ice-salt mixture, whereby the amine (described by Burger and Mosettig[5] as an oil) crystallized out. The crystalline product liquified when allowed to stand at room temperature, but resolidified after some time and melted at 48–90°. Two days later the melting point had changed to 49–52°. The free amine prepared in exactly the same way from a hydrochloride obtained by Beckmann rearrangement (and subsequent hydrolysis) of the oxime of 2-acetyl-9,10-dihydrophenanthrene behaved in exactly the same way and melted finally at 49–52°. The mixture melting point of the two samples was at 49–52°. In later experiments only the melting point 49–52° was observed.

Anal. Calc'd for $C_{14}H_{13}N$: N, 7.18. Found: N, 7.62.

Diazotization of the amine (from the nitro compound) gave a hydroxy derivative identical with 2-hydroxy-9,10-dihydrophenanthrene described by Burger and Mosettig.[5]

4-Amino-9,10-dihydrophenanthrene.—The catalytic reduction of 4-nitro-9,10-

dihydrophenanthrene was carried out like that of the 2-isomer. The base crystallized from ethyl acetate in large, pale pink prisms of m. p. 53–54° (corr.).

Anal. Calc'd for $C_{14}H_{13}N$: C, 86.11; H, 6.71.
Found: C, 85.95; H, 6.94.

The hydrochloride crystallized from alcohol in white needles, m. p. 270-273° (corr., decomp.) in vacuo.

Anal. Calc'd for $C_{14}H_{14}ClN$: Cl, 15.31. Found: Cl, 15.27.

4-Diacetylamino-9,10-dihydrophenanthrene was obtained by boiling under reflux 3 parts of the amine in 10 parts of acetic anhydride for twenty minutes. It crystallized from acetone-water in small tablets of m. p. 100–103°.

Anal. Calc'd for $C_{18}H_{17}NO_2$: C, 77.38; H, 6.14.
Found: C, 77.60, 77.58; H, 6.25, 5.84.

4-Hydroxy-9,10-dihydrophenanthrene.—The diazotization of 4-amino-9,10-dihydrophenanthrene was carried out according to the method of de Milt and Van Zandt.[8] Four grams of the amine, dissolved in 20 cc. of pyridine, was added with stirring, during the course of one hour, to a solution of nitrosyl sulfuric acid cooled to −3° with ice and salt. The nitrosyl sulfuric acid solution was prepared by first adding 3 g. of sodium nitrite to an ice-cold mixture of 15 cc. of water and 30 cc. of concentrated sulfuric acid, and then carefully warming the mixture to 40° until a clear solution resulted. The stirring was continued at this temperature for one hour, and the reaction mixture was then diluted to 400 cc. with ice and water. A solution of 2 g. of urea in 50 cc. of water was added, and stirring was continued another hour. The solution of the diazonium sulfate was filtered and poured slowly into boiling water. A red oil precipitated, from which the aqueous solution was decanted. The oil was dissolved in a 1% potassium hydroxide solution and filtered. By acidification was obtained 1.7 g. of crystalline phenolic product, which distilled readily (at 130°) in an oil-pump vacuum. The distillate was recrystallized from benzene-petroleum ether; prisms, m. p. 72–74° (corr.)

Anal. Calc'd for $C_{14}H_{12}O$: C, 85.67; H, 6.17.
Found: C, 85.53, 85.26; H, 6.14, 6.01.

One and three-tenths grams of 4-hydroxy-9,10-dihydrophenanthrene was methylated in the usual manner with potassium hydroxide and dimethyl sulfate. The oily methoxy compound was dehydrogenated without further purification. It was heated in a nitrogen atmosphere with 0.1 g. of palladium black at 300° for one-half hour. By distillation of the reaction mixture in an oil-pump vacuum, 0.8 g. of crystalline material that melted from 42–76° was obtained. One crystallization from benzene-petroleum ether and three crystallizations from alcohol yielded 0.2 g. of phenanthrene melting at 99–101°, which showed no depression in melting point upon admixture with an authentic sample.

Conversion of 4-Diacetylamino-9,10-dihydrophenanthrene into 4-Hydroxyphenanthrene

4-Acetylaminophenanthrene.—One and eight-tenths grams of 4-diacetyl-amino-9,10-dihydrophenanthrene and 0.5 g. of palladium black were heated, in a nitrogen atmosphere, to 250° within fifteen minutes and kept for another fifteen minutes between 250° and 260°. (A violent gas evolution began at 230°.) A very slow distillation of the reaction mixture in an oil-pump vacuum (twelve hours at 120° and approximately one-half hour at 170°) gave as the first fraction a pasty crystalline

[8] DE MILT AND VAN ZANDT, *J. Am. Chem. Soc.*, **58**, 2044 (1936). See also BACHMANN AND BOATNER, *ibid.*, **58**, 2194 (1936).

mass and then fine white needles. The latter were separated mechanically; they weighed 0.5 g. and melted at 190–192°. This material crystallized from alcohol as fine white needles of melting point 196–197°.

Anal. Calc'd for $C_{16}H_{13}NO$: C, 81.66; H, 5.57.
Found: C, 81.50; H, 5.91.

In another dehydrogenation experiment, 0.5 g. of the diacetylamino compound was heated at 250–280° for twelve minutes. The reaction mixture yielded by vacuum distillation and recrystallization 50 mg. of phenanthrene of m. p. 94–96° and 20 mg. of an impure 4-acetylaminophenanthrene that softened at 180° and melted at 192–194°.

4-Aminophenanthrene.—One gram of the acetylamino compound in 50 cc. of 15% alcoholic hydrogen chloride was boiled under reflux for eight hours. On cooling, 0.6 g. of amine hydrochloride separated, from which, by liberation with ammonia and extraction with ether, 0.4 g. of the base was obtained in white warts of m. p. 60.5–62°. Five cubic centimeters of concentrated hydrochloric acid was added to the alcoholic mother liquor from the first crop of amine hydrochloride, and the mixture was boiled for six hours. (A flocculent precipitate appeared after three hours boiling.) The hydrochloride was collected by filtration, and gave 0.35 g. of amine base melting at 60–62°. The 4-aminophenanthrene crystallized from petroleum ether in fine, white needles, m. p. 62.5–63.5° (corr.).

Anal. Calc'd for $C_{14}H_{11}N$: N, 7.25. Found: N, 7.32.

A mixture of 30 mg. of the amine in 3 cc. of ether, 3 cc. of 5% sodium hydroxide solution, and 0.1 cc. of benzoyl chloride was shaken at room temperature for three and one-half hours. Enough ether was added to dissolve the heavy white precipitate. The ether solution was evaporated to dryness, and the residue was heated in a watch glass on the steam bath in order to sublime off any benzoic acid. It crystallized from alcohol in fine white needles of m. p. 216–218° (corr.), yield 13 mg.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.71. Found: N, 4.76.

A solution of 0.4 g. of 4-aminophenanthrene in 2 cc. of pyridine was added dropwise (forty-five minutes) with stirring to a cold solution (approximately −5°) of nitrosyl sulfuric acid, which was prepared as described above, from 0.3 g. of sodium nitrite, 1.6 cc. of water, and 3.2 cc. of concentrated sulfuric acid. The mixture was maintained at 0°, stirred forty-five minutes longer, and was then diluted to 40 cc. with ice and water. After addition of 0.2 g. of urea, stirring was continued at 0° for one hour. The diazonium sulfate solution was filtered and poured slowly into boiling water. The entire reaction mixture was extracted with ether, and the ether residue was treated with 10% potassium hydroxide solution. The filtered alkaline solution gave on acidification 135 mg. of pale yellow 4-hydroxyphenanthrene. After sublimation at 100° in an oil-pump vacuum, it melted at 112–113.5°. A mixture melting point determination with an authentic sample of 4-hydroxyphenanthrene of melting point 112–112.5°, showed the melting point 112–113°. In all the three melting point determinations a slight sintering at 109° was observed. The product, mixed with 3-hydroxyphenanthrene, melted below 85°.

A mixture of 20 mg. of sublimed 4-hydroxyphenanthrene (from the diazotization), 0.1 cc. of 5% sodium hydroxide solution, and 0.1 cc. of methyl iodide was allowed to stand at room temperature for one-half an hour. The reaction mixture was diluted with water, extracted with ether, and the ether residue was distilled in an oil-pump vacuum. The oily distillate (18 mg.) became crystalline when seeded with 4-methoxyphenanthrene, and melted at 64.5–66° (sintering at 60°). The mixture melting point with an authentic sample of 4-methoxyphenanthrene (of m. p. 64.5–66.5°, sintering at 63°) was at 64–65.5° (sintering at 60°). The mixture with 3-methoxyphenanthrene was liquid at room temperature.

SUMMARY

In the nitration of 9,10-dihydrophenanthrene, 2-nitro- and 4-nitro-9,10-dihydrophenanthrene are formed in yields of 65 per cent. and 4 per cent. respectively.

The structure of these nitro compounds has been proved by converting them into phenanthrene derivatives of well-established structure, namely 2-amino-9,10-dihydrophenanthrene, and 4-hydroxyphenanthrene.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE DECOMPOSITION OF UNSYMMETRICAL ORGANOMERCURIC COMPOUNDS: A METHOD OF ESTABLISHING THE RELATIVE DEGREE OF ELECTRONEGATIVITY OF ORGANIC RADICALS. III*

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The previous paper[1] in this series defined the more electronegative of two organic radicals as the one cloven from the mercury atom by hydrogen chloride in the following reaction:

$$RHgR' + HCl \rightarrow RHgCl + R'H$$

That paper summarized the procedures for the preparation, proof of structure, and cleavage of unsymmetrical mercury compounds, and presented a table of the results obtained up to that time. The present work is concerned with the effects of halogens and the trifluoromethyl group on the electronegativity of the phenyl radical, and with the relative electronegativities of the benzyl and *o*-, *m*-, and *p*-chlorobenzyl radicals. Further evidence establishing the validity of the above method of determining the relative electronegativities of organic radicals is presented. It is shown in Table I that in all cases tested the cleavage of phenylethylmercury is independent of the halogen acid and solvent employed.

Phenylethylmercury was treated with halogen acid under the following conditions: with hydrogen chloride in alcohol, with hydrogen bromide in alcohol, glacial acetic acid, and benzene, and with hydrogen iodide in the two latter solvents. In all cases the product was shown by melting point to be ethylmercuric halide. It is thus shown that the phenyl radical is more easily cloven from the mercury atom than the ethyl radical, irrespective of the solvent or halogen acid used. Since the phenylmercuric halides are less soluble than the corresponding ethylmercuric halides, it is clear that the more soluble of the organomercuric halides is formed, and, therefore, that the course of the reaction is not determined by the insolubility of one of the two possible products.

* This paper is condensed from the Doctorate Thesis of Herman Pines, the University of Chicago, 1935, and from the Master's Thesis of Janice H. Levine, the University of Chicago, 1933.

[1] KHARASCH AND FLENNER, *J. Am. Chem. Soc.*, **54**, 674 (1932).

The treatment of suitable monohalogenated diphenylmercury compounds with hydrogen chloride leads to the following conclusions: the *p*-fluorophenyl radical is somewhat more electronegative than the phenyl radical; the *p*-chlorophenyl, *p*-bromophenyl, *o*-bromophenyl, *m*-bromophenyl, and *m*-fluorophenyl radicals are somewhat less electronegative than the phenyl radical. The phenylmercury derivatives of the last three radicals gave exclusively benzene and the substituted phenylmercuric chloride on cleavage but the three *p*-halogenated diphenylmercury compounds all gave mixtures of the possible cleavage products. We conclude that the *p*-halogenated radicals are very close to the phenyl radical in electronegativity. Thus, the *p*-fluorophenyl radical (although the difference is slight) appears to be the only known exception to the rule of Kharasch and Flenner that direct substitution decreases the electronegativity of the phenyl radical.

Other experiments indicate that the *m*-(α,α,α-trifluoro)tolyl radical is less electronegative than the phenyl and *m*-chlorophenyl radicals, but mixtures of cleavage products were obtained in both cases. This result shows that such substitution in the side-chain decreases the electronegativity of the tolyl radical, and that a trifluoromethyl group in the *m*-position has a greater effect than a chlorine atom in decreasing the electronegativity of the phenyl radical.

Cleavage of *o*-, *m*-, and *p*-chlorodibenzylmercury with hydrogen chloride showed that all the chlorobenzyl radicals are less electronegative than the unsubstituted benzyl radical. 2,3′-Dichlorodibenzylmercury was cloven to give an equimolecular mixture of *o*- and *m*-chlorobenzylmercuric chlorides. 2,4′-Dichlorodibenzylmercury also gave a mixture of chlorobenzylmercuric chlorides on cleavage, but the proportion of isomers in the mixture was not determined. It is concluded that the three chlorobenzyl radicals are of approximately the same relative electronegativity and that all are less electronegative than the benzyl radical.

Subsequent papers in this series will be published soon.

EXPERIMENTAL

Analytical methods for the determination of mercury.—Three methods were used for the determination of mercury in the organomercuric compounds. Two have already been described by Kharasch and Flenner, and by Whitmore and Sobatski.[2] The third is the method of Smith[3] for inorganic compounds, modified for use in the case of organic compounds by Kharasch, Legault, and Sprowls. A quantity of the organomercuric compound (0.4 g.) is weighed into a tall, narrow beaker with a bulb in the bottom, and is dissolved in 5 cc. of glacial acetic acid by warming on the steam bath. Two cc. of bromine is added to convert the organic to inorganic mercury. The mixture is warmed again on the steam bath and then allowed to

[2] WHITMORE AND SOBATZKI, *ibid.*, **55**, 1128 (1933).

[3] SMITH, "Electro-Analysis," P. Blakiston's Sons, Phila., **1918**, p. 99.

stand for half an hour. When the organic radical attached to mercury is weakly electronegative, overnight standing is necessary for complete conversion. Eight cc. of amylene is then added to destroy excess bromine. The amylene bromide collects in the bulb in the bottom of the beaker; otherwise it might coat and poison the electrodes. The solution is neutralized by the addition of 85 cc. of 6.67% sodium bicarbonate solution and 15 cc. of 10% sodium carbonate solution, then acidified with 8 cc. of concentrated nitric acid. The solution is then electrolyzed for two hours with a currect of 3.5 amperes. The temperature rises to (and remains at) about 80°. The mercury is deposited on a previously weighed, perforated, cylindrical gold electrode, which is washed with water, alcohol, and ether, and dried

TABLE I

CLEAVAGE WITH VARIOUS HALOGEN ACIDS AND SOLVENTS

GRAMS $C_6H_5HgC_2H_5$	SOLVENT CC.	CLEAVAGE REAGENT		PRODUCT[a]		RECORDED MELTING POINTS, °C.
		Solvent, cc.	Saturated with	Softens, °C.	Melts, °C.	
1.3	Ethanol, 25–30	Ethanol, 7	HCl		192	C_2H_5HgCl, 192 C_6H_5HgCl, 251
1.5	Benzene[b], 25–30	Benzene, 15	HBr		189	C_2H_5HgBr, 193
1.0	Glacial acetic acid, 20	Glacial acetic acid, 7–10	HBr	187	189	C_6H_5HgBr, 276
1.0	Ethanol, 20	Ethanol, 7	HBr	187	189	
1.3	Benzene	HI gas from H_3PO_4 and		162	175[c]	C_2H_5HgI, 182
1.3	Glacial acetic acid	NaI		179	181	C_6H_5HgI, 266

[a] Products precipitated from the reaction mixture and were washed with ether and/or petroleum ether. Benzene solutions were concentrated in an air stream to effect crystallization.

[b] Cleavage carried out at 15°; others at room temperature.

[c] Ethylmercuric iodide was separated from mercuric iodide by extraction with acetone and evaporation of acetone solution.

over phosphorus pentoxide. The electrode is cleaned for subsequent use by heating to 600° in an electric furnace.

Preparation of halides.—The preparation of a few uncommon halides used as starting materials for the required organomercuric chlorides is indicated below.

The three isomeric bromofluorobenzenes were prepared from the corresponding bromoanilines by diazotization and formation and decomposition of the borofluorides, essentially according to the procedure of Balz and Schiemann.[4] The yields and boiling points of the bromofluorobenzenes thus obtained were: *ortho*, 37%, 157–60°; *meta*, 50%, 148–51°; *para*, 52%, 150–2°.

m-Bromochlorobenzene was prepared from *m*-bromoaniline by diazotization and treatment with cuprous chloride. The yield was 72% of a compound which boiled at 192°.

[4] BALZ AND SCHIEMANN, *Ber.*, **60**, 1186 (1927).

Two chlorobenzyl bromides were prepared by bromination of the appropriate chlorotoluenes. Fifty grams of bromine was added slowly to 35 g. of boiling chlorotoluene. The product was washed with sodium carbonate, dried, and distilled.

TABLE II

PREPARATION AND PROPERTIES OF ORGANOMERCURIC CHLORIDES

R IN RHgCl	PREPARATION			M.P., °C.	MERCURY ANALYSIS		
	Method[a]	Starting Material	Yield, %		Calc'd	Found	Method[b]
C_6H_5-	MN	$C_6H_5NH_2$	18	252			
m-FC_6H_4-	G	*m*-FC_6H_4Br		243[c]	60.4	58.8 58.9	K & F
p-FC_6H_4-	G	*p*-FC_6H_4Br		291	60.4	58.7 58.5	K & F
p-ClC_6H_4-	N	*p*-$ClC_6H_4NH_2$	25	238	57.8	57.1 57.2	K & F
o-BrC_6H_4-	H	*o*-$BrC_6H_4NH_2$	44	155			
	N	*o*-$BrC_6H_4NH_2$	0[d]				
m-BrC_6H_4-	H	*m*-$BrC_6H_4NH_2$	50	194			
p-BrC_6H_4	H	*p*-$BrC_6H_4NH_2$	60	250			
	N	*p*-$BrC_6H_4NH_2$	28	248			
	MN	*p*-$BrC_6H_4NH_2$	55	255			
m-$CF_3C_6H_4$-	MN	*m*-$CF_3C_6H_4NH_2$	20	151	52.6	53.2	Elec.
$C_6H_5CH_2$-	G	$C_6H_5CH_2Cl$	74	107			
o-$ClC_6H_4CH_2$-	G	*o*-$ClC_6H_4CH_2Cl$	25	115	55.5	55.56[e]	W & S
m-$ClC_6H_4CH_2$-	G	*m*-$ClC_6H_4CH_2Br$	40	141	55.5	54.8 54.8	W & S
p-$ClC_6H_4CH_2$-	G	*p*-$ClC_6H_4CH_2Br$	55	141			

[a] G, H, N, and MN indicate the Grignard, Hanke, Nesmejanow, and modified Nesmejanow methods, respectively.

[b] Elec., K & F, and W & S indicate the electrolytic, Kharasch and Flenner, and Whitmore and Sobatzky methods, respectively.

[c] The original melting point of 239° was raised to 243° by shaking with freshly-precipitated silver chloride.

[d] Preparation in either acetone or alcohol solution gave tars from which none of the desired mercury compound could be obtained.

[e] This analysis was made on a sample melting at 111° which had been prepared from di-*o*-chlorobenzylmercury and mercuric chloride. Di-*o*-chlorobenzylmercury was prepared by the addition of mercuric chloride to three equivalents of *o*-chlorobenzylmagnesium bromide in ether. It was a white crystalline solid, melting at 100°, and containing 44.31% mercury by the Whitmore and Sobatzky method (calculated, 44.49% Hg).

o-Chlorobenzyl bromide, $b.p._{10}$ 103–4°, was obtained in 72% yield; *m*-chlorobenzyl bromide, $b.p._8$ 105–8°, in 63% yield.

Preparation and properties of the organomercuric chlorides.—(Summarized in Table II.) Three methods of preparing the organomercuric chlorides were employed. The first method involved the reaction of a sulfinic acid (prepared from a

diazonium salt by Gatterman's method[5]) with mercuric acetate in glacial acetic acid to give an arylmercuric acetate.[6] Aqueous or alcoholic solutions of the acetate were converted to chloride by reaction with sodium chloride. The second method is the decomposition of an aryldiazonium chloride-mercuric chloride double salt in the presence of copper bronze, according to Nesmejanow.[7] When his procedure was followed as closely as possible, we could not attain his yield of phenylmercuric chloride, and considerable tar was obtained. Less tar and improved yields of

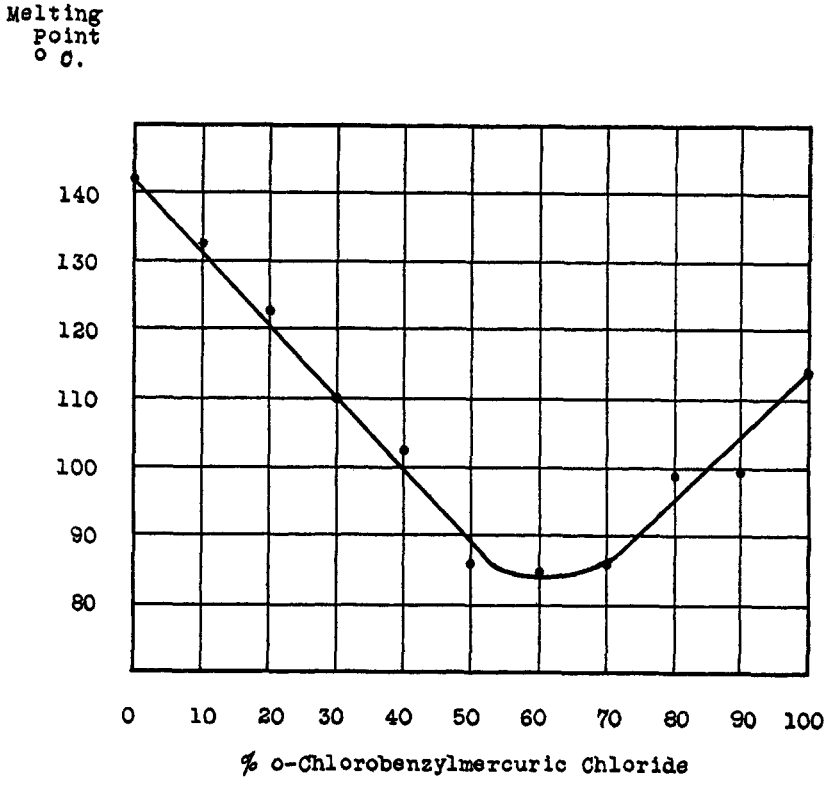

FIGURE I. MELTING POINT CURVE OF MIXTURES OF *o*- AND *m*-CHLOROBENZYLMERCURIC CHLORIDES

phenylmercuric chloride were obtained in a less vigorous reaction when metallic mercury was substituted for the copper. The third method is by reaction of a Grignard reagent with mercuric chloride. One mole of Grignard reagent in ether solution was heated for one to two hours with 1.2 moles of mercuric chloride. The product was poured into water, and the solid organomercuric chloride was washed

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[5] GATTERMAN, *ibid.*, **32**, 1136 (1899).
[6] HANKE, *J. Am. Chem. Soc.*, **45**, 1321 (1923).
[7] NESMEJANOW, *ibid.*, **62**, 1010 (1929).

TABLE III

PREPARATION AND CLEAVAGE OF UNSYMMETRICAL MERCURY COMPOUNDS

UNSYMMETRICAL MERCURY COMPOUND					CLEAVAGE PRODUCT: RHgCl and/or R'HgCl		
R and R' in RHgR'[a]	M. p., °C.	Hg Anal. Calc'd. %	Hg Anal. Found %	ANAL. METHOD[b]	Hg Anal., %	M.p., °C.	Composition
C_6H_5- m-FC_6H_4-	107–11	53.8	52.6 52.4	K & F	60.7 60.0	234–6	m-FC_6H_4HgCl
C_6H_5- p-FC_6H_4-	111–5	53.8	53.3 53.4	K & F	63.4 63.1	258–61	C_6H_5HgCl, 80% p-FC_6H_4HgCl, 20%
p-FC_6H_4- C_6H_5-	115–8	53.8	53.4 53.3	K & F	63.3 63.7	254–7	C_6H_5HgCl, 80% p-FC_6H_4HgCl, 20%
C_6H_5- p-FC_6H_4-	106–11			W & S	62.34 62.09 62.50	259–61	C_6H_5HgCl, 57% p-FC_6H_4HgCl, 43%
p-ClC_6H_4- C_6H_5-	165–205	51.4	50.2 50.7	K & F	59.3 59.1	250–2	p-ClC_6H_4HgCl, 78% C_6H_5HgCl, 22%
p-ClC_6H_4- C_6H_5-	172–200			K & F	59.5 59.6	245–9	p-ClC_6H_4HgCl, 70% C_6H_5HgCl, 30%
o-BrC_6H_4- C_6H_5-	73–5	46.1	45.8 45.4	K & F	52.2	145–7	o-BrC_6H_4HgCl
m-BrC_6H_4- C_6H_5-	Liquid	46.1	45.15	K & F	51.9 51.1	183–6	m-BrC_6H_4HgCl
p-BrC_6H_4- C_6H_5-	151–75	46.1	46.2 46.5	K & F	54.5 54.0	238	p-BrC_6H_4HgCl, 76% C_6H_5HgCl, 24%
p-BrC_6H_4- C_6H_5-	136–76			K & F	54.5 54.3	233–5	p-BrC_6H_4HgCl, 74% C_6H_5HgCl, 26%
m-$CF_3C_6H_4$- C_6H_5-	100–3	47.8	47.4	Elec.	53.6	159–60	m-$CF_3C_6H_4HgCl$, 91% C_6H_5HgCl, 9%
m-$CF_3C_6H_4$- m-ClC_6H_4-	130–43	43.6	44.0	Elec.	56.8 56.6	164	m-$CF_3C_6H_4HgCl$, 82% m-ClC_6H_4HgCl, 18%

m-$CF_3C_6H_4$- *m*-ClC_6H_4-	130–40	43.6	43.5 43.7	W & S	54.5 54.3	159–63	*m*-$CF_3C_6H_4HgCl$, 65% *m*-ClC_6H_4HgCl, 35%
m-$CF_3C_6H_4$- *m*-ClC_6H_4-	130–9			W & S	54.0 54.2	164–6	*m*-$CF_3C_6H_4HgCl$, 70% *m*-ClC_6H_4HgCl, 30%
$C_6H_5CH_2$- *o*-$ClC_6H_4CH_2$- *o*-$ClC_6H_4CH_2$- $C_6H_5CH_2$-	Liquid	48.09	44.47[c]	W & S	55.5	96–103	*o*-$ClC_6H_4CH_2HgCl$[d,e]
m-$ClC_6H_4CH_2$- $C_6H_5CH_2$-	Liquid			W & S	55.9	132	*m*-$ClC_6H_4CH_2HgCl$[i]
$C_6H_5CH_2$- *p*-$ClC_6H_4CH_2$-	80–2	48.09	48.41 48.29	Elec.	57.2 56.7	131–7	*p*-$ClC_6H_4CH_2HgCl$,[d,f] 75% $C_6H_5CH_2Cl$, 25%
o-$ClC_6H_4CH_2$- *m*-$ClC_6H_4CH_2$-	Liquid	44.3	42.8[c] 42.9	W & S	54.7	87	*o*-$ClC_6H_4CH_2HgCl$, 50%[d,g] *m*-$ClC_6H_4CH_2HgCl$, 50%
p-$ClC_6H_4CH_2$- *o*-$ClC_6H_4CH_2$-	90–113	44.3	43.9 43.8	W & S			
p-$ClC_6H_4CH_2$- *o*-$ClC_6H_4CH_2$-	98–129			W & S	54.9	99–110	*o*-$ClC_6H_4CH_2HgCl$[d,h] *p*-$ClC_6H_4CH_2HgCl$

[a] The unsymmetrical mercury compound was prepared from the organomercuric chloride of the first-named radical and the organomagnesium bromide of the second-named radical.

[b] Both the unsymmetrical mercury compound and the cleavage product were analyzed by the same method, designated as in Table II.

[c] Low mercury content is probably due to difficulty of removing solvents.

[d] The unsymmetrical compound was not decomposed by alcoholic hydrogen chloride at room temperature and so the reaction mixture was heated to 60° for 20 minutes.

[e] The addition of known *o*-chlorobenzylmercuric chloride to the solid cleavage product raised its melting point to 98–108°; addition of benzylmercuric chloride lowered the melting point of the cleavage product to 85–8°. These facts, together with the mercury analysis, indicate that the cleavage product is fairly pure *o*-chlorobenzylmercuric chloride.

[f] The melting point of the solid cleavage product was lowered by the addition of benzylmercuric chloride but not by the addition of *p*-chlorobenzylmercuric chloride. Thus, by melting point the product is fairly pure *p*-chlorobenzylmercuric chloride but mercury analysis indicates the presence of about 25% benzylmercuric chloride.

[g] The melting point of the product corresponds to 50–70% of *o*-chlorobenzylmercuric chloride and 30–50% of *m*-chlorobenzylmercuric chloride, as can be seen from Figure I. Addition of 10% *m*-chlorobenzylmercuric chloride to the product raised the melting point of the mixture to 100°. Hence the original cleavage product consisted of equal proportions of the two chlorobenzylmercuric chlorides.

[h] The proportion of *o*- and *p*-chlorobenzylmercuric chlorides in the cleavage product is not known.

[i] This result is taken from the Master's Thesis of Willard R. Sprowls, the University of Chicago, 1935.

with water until no trace of mercuric chloride remained (test with sodium hydroxide). When the Grignard reagent was made from an organic bromide, the product was sometimes a mixture of organomercuric bromide and chloride. This mixture was converted to chloride by shaking with freshly precipitated silver chloride.

Attempts to prepare *o*-fluorophenylmercuric chloride by treatment of *o*-bromofluorobenzene with magnesium (reaction finally took place in a sealed tube at 120°) and then with mercuric chloride failed to give any organic compound containing mercury.

Preparation, properties, and cleavage of unsymmetrical organomercuric compounds.—The unsymmetrical mercury compounds were prepared from an organomercuric chloride and a Grignard reagent, and treated with mercuric chloride and alcoholic hydrogen chloride as described by Kharasch and Flenner. The analyses and the results are summarized in Table III.

SUMMARY

1. A number of new organomercuric compounds of the type RHgCl and RHgR′ have been prepared.

2. The relative electronegativities of some halogenated phenyl radicals, the *m*-(α,α,α-trifluoro)tolyl, the benzyl, and the three chlorobenzyl radicals have been determined.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE REACTIONS OF EPOXY COMPOUNDS WITH REAGENTS. I. THE INTERACTION OF PHENYLEPOXYETHANE (STYRENE OXIDE) AND ARYLMAGNESIUM HALIDES*

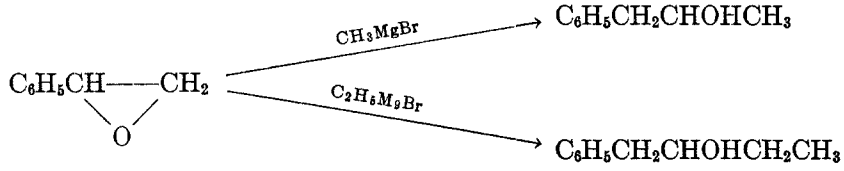
M. S. KHARASCH AND HOUGHTON GEORGE CLAPP

Received August 1, 1938

Some years ago we became interested in formulating an explanation for the peculiar behavior of epoxy compounds with various reagents. Due to pressure of other work, this project was not pursued actively. However, since we expect to engage again in this work, it seems best to publish some of our results. We also wish to correct a prevalent impression[1] that appropriate epoxy compounds upon cleavage with Grignard reagents give exclusively the corresponding tertiary and secondary alcohols rather than secondary and primary ones. We have shown that styrene oxide can be made to react with phenylmagnesium bromide to yield a primary alcohol, namely 2,2-diphenylethanol.

PREVIOUS WORK

Tiffeneau and Fourneau[2] treated styrene oxide with methyl- and ethylmagnesium bromides and obtained 1-phenyl-2-propanol and 1-phenyl-2-butanol, respectively. These results were interpreted on the assumption that the styrene oxide first rearranged to phenylacetaldehyde and that the



latter compound then condensed with the Grignard reagent to yield the final products of the reaction. This interpretation has also been used to explain the behavior of highly substituted epoxyalkanes with Grignard reagents.[3]

* This report is an abstract, in part, of a dissertation submitted by H. G. Clapp in 1929 in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry of the University of Chicago.

[1] NORTON AND HASS, *J. Am. Chem. Soc.*, **58**, 2147 (1936).

[2] TIFFENEAU AND FOURNEAU, *Compt. rend.*, **146**, 697 (1908).

[3] SCHLENK, "Houben-Weyl," 2d Ed., Vol. IV, 1924, p. 781.

DISCUSSION OF RESULTS

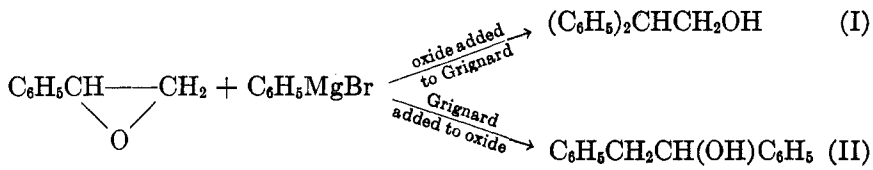
Our working hypothesis of the behavior of epoxy compounds led us to believe that the mode of interaction of styrene oxide with Grignard reagents would depend (in the same solvent) upon two factors: (1) the identity of the Grignard reagent, and (2) the order of addition of reagents. The first factor, presumably of minor importance, has not been investigated as yet. The second factor, however, should dominate the course of the reaction. Our expectations were fully justified. Thus different products resulted when styrene oxide was added slowly to an ether solution of phenylmag-

TABLE I

BEHAVIOR OF CONDENSATION PRODUCTS OF PHENYLMAGNESIUM BROMIDE AND STYRENE OXIDE

ORDER OF ADDITION OF REAGENTS	PHYSICAL STATE	$KMnO_4$	OXALIC ACID (HEAT)	3,5-DINITROBENZOYL CHLORIDE	DISTILLATION AT REDUCED PRESSURE
Styrene oxide added to Grignard reagent (I).	Oil	1 g. of (I) gave: 0.4 g. benzophenone, 0.1 g. benzoic acid.	Oxalate, m.p. 160.5°	Derivative, 135°	Distills unchanged
Grignard reagent added to styrene oxide (II).	Oil	1 g. of (II) gave: 0.8 g. benzoic acid, 0.1 g. benzophenone.	Stilbene		Decomposes into stilbene and water

nesium bromide, and when the addition of reagents was in the reverse order. This schematic representation of the course of the reactions holds for about



eighty to ninety per cent. of the reactants. In each case, we have been able to demonstrate the presence of small quantities of the isomeric alcohol. In Table I are collected the series of reactions which, in our estimation, prove fairly conclusively that oil (I) is mostly the 2,2-diphenylethanol. The structure of the oxalic ester of the alcohol was proved by hydrolysis with potassium hydroxide in ethyl alcohol solution. The oxalic acid was identified by conversion into calcium oxalate, and by its p-toluidine derivative. The 2,2-diphenylethanol was identified by conversion into the 3,5-dinitrobenzoate, m.p. 135°, which did not depress the melting point of a known sample of the 3,5-dinitrobenzoate of 2,2-diphenylethanol.

While the data presented are highly suggestive of the structures assigned

by us it was felt that a direct synthesis of 2,2-diphenylethanol, and a comparison of the oxalate and 3,5-dinitrobenzoate of the synthetic alcohol with those of compound I, was necessary. Accordingly, one of us (M.S.K.) and Ziels[4] prepared the 2,2-diphenylethanol by the following series of reactions.

(1) $$HOCH_2COOC_2H_5 + 3C_6H_5MgBr \xrightarrow{HOH} C_6H_6 + (C_6H_5)_2COH\cdot CH_2OH + C_2H_5OH + 3\,MgBrOH$$[5]

(2) $$(C_6H_5)_2COH\cdot CH_2OH \xrightarrow[\text{Heat 4 hrs.}]{0.5N\,HCl} (C_6H_5)_2CH\cdot CHO$$[6]

(3) $$(C_6H_5)_2CH\cdot CHO \xrightarrow[Pt]{H_2} (C_6H_5)_2CH\cdot CH_2OH$$[7]

The oxalate and 3,5-dinitrobenzoate of the 2,3-diphenylethanol thus prepared had the same melting point as the compounds obtained in our study. Furthermore, there was no depression of the melting point upon mixing the respective derivatives of the known synthetic alcohol with those obtained from the alcohol formed when styrene oxide was added to the Grignard reagent of phenylmagnesium bromide.

An interesting observation was made[8] when 2,2-diphenylethanol, dissolved in benzene, was treated with phosphorous pentoxide and heated for about ten minutes; an excellent yield of stilbene was obtained. The formation of stilbene when both isomeric alcohols are treated with phosphorous pentoxide is of course readily explained on the basis of the Wagner rearrangement.

$$C_6H_5CH_2\cdot CHOH\cdot C_6H_5 \xrightarrow{P_2O_5} C_6H_5CH{=}CHC_6H_5$$

$$(C_6H_5)_2CH\cdot CH_2OH \xrightarrow{P_2O_5} C_6H_5CH{=}CHC_6H_5$$

A few experiments were made to ascertain whether the interaction of styrene oxide with anisylmagnesium bromide would give two different products also, depending upon the order of addition of the reagents. As indicated in the experimental part, the results with this reagent were analogous in all details to those obtained with phenylmagnesium bromide.

EXPERIMENTAL

Preparation of 1,2-diphenylethanol.—In all the hereafter-described preparations involving the use of the Grignard reagent, the reaction vessel consisted of a small, three-necked flask, equipped with a condenser, a mercury-sealed stirrer, and a

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[4] NORBERT W. ZIELS, Master's Dissertation, **1933**, University of Chicago.

[5] PAAL AND WEIDENKAFF, *Ber.*, **39**, 2062 (1906).

[6] EUNICE FLOCK, Master's Dissertation, **1931**, University of Chicago.

[7] This alcohol was prepared by RAMART AND AMAGAT, *Ann. chim.*, [10] **8**, 263 (1927), by reduction of the ester.

[8] KHARASCH AND ZIELS, *loc. cit.* This observation has already been made by REMART AND AMAGAT, *loc. cit.*, except that these investigators subjected the reaction mixture to distillation.

dropping funnel. The condenser and dropping funnel were equipped with calcium chloride tubes, and the apparatus was scrupulously clean and dry at all times. Absolute ether was used throughout.

The Grignard reagent† was prepared from 7.2 g. of phenyl bromide and 1.1 g. of magnesium and added slowly, with vigorous stirring, to a solution of 5 g. of styrene oxide dissolved in ether and cooled with an ice bath. After all the material was added the reaction mixture was refluxed for one hour, again cooled with an ice bath and then decomposed, first with ice water and then with a small amount of dilute sulfuric acid. The ether solution was then separated, and the water solution was extracted twice more with ether. The extracts were combined, washed with water, and the ether was removed by evaporation in a vacuum desiccator. A yellow oil which remained was dissolved in a small amount of hot alcohol. Upon cooling, long white needles separated from the solution. The melting point of the material was 62°. A further quantity of this material was obtained by evaporation of the alcohol from the mother-liquor and addition of a few crystals of the substance of melting point 62°. Within a few days a large quantity of the oil was converted into a crystalline material. A single crystallization of this material from alcohol was sufficient to obtain the pure compound. The solid (m.p. 62°) upon oxidation with potassium permanganate yielded benzoic acid, and no benzophenone.

A second lot of the oil was prepared, and an attempt made to purify the oil by fractional distillation. Although a very high vacuum was used, the oil decomposed, yielding a large quantity of stilbene.

A third lot of the oil was prepared in the same manner as before. Upon oxidation with alkaline potassium permanganate solution one gram of the oil gave 0.8 g. of benzoic acid and 0.1 g. of benzophenone. Some of the oil was heated with oxalic acid. When the reaction was over, water was added to remove the unchanged acid. The solid which separated was crystallized from alcohol. The solid was identified as stilbene (m.p. 122°).

Preparation of 2,2-diphenylethanol.—In the preparation of this material, the procedure was the same as described for the symmetrical diphenylethanol, except that in this case the oxide was added slowly to the solution containing the Grignard reagent. Upon removal of the solvent, the product remained behind in the form of a yellow oil. The material was extremely soluble in ether, alcohol, acetone, benzene, petroleum ether, chloroform, and glacial acetic acid. It was impossible to crystallize the material from any of these solvents. The oil was fractionated at 2 mm. pressure and collected; boiling point 125–135°. From 7.5 g. of styrene oxide 11.1 g. of this oil was obtained.

A second lot of the same material was prepared in the manner outlined above, except that two moles of Grignard reagent were used for one mole of the oxide. The same thick yellow oil was obtained.

Reactions of 2,2-diphenylethanol.—Attempts to oxidize this oil with chromic anhydride-glacial acetic acid mixture, or with neutral potassium permanganate, gave very poor results. For this reason one gram of the oil was refluxed with an alkaline permanganate solution for three hours. The solution was then extracted with ether, which, upon evaporation, yielded 0.4 g. of benzophenone, melting point 46°. The water solution upon acidification, yielded 0.1 g. of benzoic acid. The benzoic acid was obtained by ether extraction and evaporation of the ether in a vacuum desiccator.

† The same results were obtained with two moles of the Grignard reagent to one mole of styrene oxide.

One gram of the oil (presumably 2,2-diphenylethanol) was heated with one gram of anhydrous oxalic acid. At first a double layer formed but this disappeared when the reaction mixture was heated for five minutes. The mixture solidified upon cooling and was washed twice with water and once with alcohol. The remaining solid was crystallized from glacial acetic acid. A solid was obtained which melted at 160.5°.

Anal. Calc'd for $C_{30}H_{26}O_4$: C, 80.00; H, 5.80.
Found: C, 79.81; H, 6.00.

The analytical data, however, do not differentiate between a formate of 2,2-diphenylethanol and a di-2,2-diphenylethanol oxalate. For this reason, 0.4 g. of the solid (m.p. 160.5°) was refluxed for four hours with alcoholic potassium hydroxide. The alcohol was then evaporated, water was added, and the solution was filtered. Calcium chloride solution was added to a small quantity of the filtrate. A white precipitate, insoluble in dilute acetic acid, separated. This test was fairly good evidence for the presence of oxalate ion. The remainder of the solution was concentrated, acidified with dilute sulfuric acid, and extracted four times with ether. Upon evaporation of the ether a white crystalline material remained. This was heated with *p*-toluidine, and the resulting product crystallized from hot alcohol. A solid which melted at 266–267° was obtained. The melting point of a mixture of this material with an authentic sample of *p*-toluidine oxalate showed no depression.

The oil obtained during the saponification was then warmed with 3,5-dinitrobenzoyl chloride, and the product was crystallized from hot alcohol. Upon recrystallization the material melted at 135°. The original oil (2,2-diphenylethanol) when treated with 3,5-dinitrobenzoyl chloride, also gave a product, m.p. 135°. This indicated that there had been no decomposition of the alcohol during the treatment with oxalic acid.

Preparation of 2,2-diphenylethanol 3,5-dinitrobenzoate.—A mixture of 0.2 g. of 3,5-dinitrobenzoyl chloride and one gram of 2,2-diphenylethanol (prepared from diphenylacetaldehyde) was heated at 100° for ten minutes. The mixture was allowed to cool, and 10 cc. of ice water was added to it. The solid which separated was collected on a filter and crystallized from methyl alcohol. The melting point of this compound was 135°. It was identical in every respect with the material prepared by condensing 3,5-dinitrobenzoyl chloride with the oil obtained from the addition of styrene oxide to one or two moles of phenylmagnesium bromide.

Anal. Calc'd for $C_{21}H_{16}N_2O_6$: N, 7.14. Found: N, 6.98.

Preparation of 1-(p-*anisyl*)*-2-phenylethylene.*—This material was prepared by the general procedure outlined above. The Grignard reagent from 8.6 g. of *p*-bromoanisole was added to 5.0 g. of the oxide. The product was isolated as a viscous brown oil, which would not crystallize from alcohol or ether. When kept for a month, the material separated into a mass of crystals contaminated with an oil. These were isolated by absorbing the oil on a porous plate. The material was crystallized from hot alcohol, and melted at 132°. The melting point of phenylanisylethylene is recorded as 136°. Furthermore, the alcohol which should be formed from the Grignard reagent of benzyl chloride and anisaldehyde has never been isolated. An attempt to obtain it in pure form resulted in decomposition into water and the unsaturated compound.

Upon oxidation of the oily residue obtained by removal of the 1-(*p*-anisyl)-2-phenylethylene, none of the corresponding ketone was obtained, but merely a mixture of benzoic and anisic acids and a small quantity of unoxidized material.

Preparation of 2-(p-*anisyl*)*-2-phenylethanol.*—The Grignard reagent was prepared from 8.6 g. of the *p*-bromoanisole and 1.1 g. of magnesium. The oxide was added

slowly, and the procedure from then on was the same as previously described. A thick brown oil, which was readily soluble in most organic solvents, and which could not be obtained from any solvent in a solid form, was the product. The yield was 8 g. Although this oil stood three weeks a trace only of crystalline material had separated [probably the 1-(*p*-anisyl)-2-phenylethylene].

One gram of the oil was oxidized with alkaline permanganate solution, and extracted with ether. Upon removal of the solvent, 0.4 g. of a light-yellow oil was obtained. Upon seeding with a little phenyl *p*-anisyl ketone the oil was converted to a white crystalline product which melted at 50–55°. This material did not depress the melting point of an authentic sample of phenyl *p*-anisyl ketone.

SUMMARY

1. It has been shown that the order of addition of the reagents determines the nature of the products formed when styrene oxide reacts with an arylmagnesium halide.

2. It has been shown that when phenylmagnesium bromide is added to styrene oxide 1,2-diphenylethanol is obtained.

3. If styrene oxide is added slowly to one or two mole equivalents of phenylmagnesium bromide, 2,2-diphenylethanol is formed.

4. Results similar to those noted with phenylmagnesium bromide were obtained with *p*-anisylmagnesium bromide.

5. An oxalate and 3,5-dinitrobenzoate of 2,2-diphenylethanol have been prepared.

6. It was observed that 2,2-diphenylethanol rearranges into stilbene when a benzene solution of it is treated with phosphorous pentoxide and heated for ten minutes.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

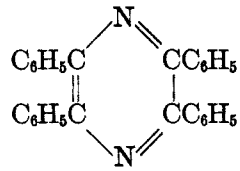
AN EXTENSION OF KNORR'S PYRROLE SYNTHESIS

DAVID DAVIDSON

Received August 17, 1938

INTRODUCTION

In a recent study of the action of ammonia in acetic acid on benzoin,[1] it was observed that the mother liquors yielded a fugitive green color when treated with nitric acid. In attempting to trace the progenitor of this color it was kept in mind that the formation of tetraphenylpyrazine (amarone) (I) which is the principal product of the reaction involves the loss of two atoms of hydrogen, the removal of which cannot be attributed to the action of aerial oxygen. It seemed possible, therefore, that this mole of hydrogen is removed by one of the components of the reaction mixture; hence an effort was made to examine the reduction products of the known components of the reaction mixture.



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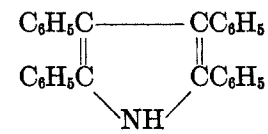


II

THE REDUCTION OF AMARONE

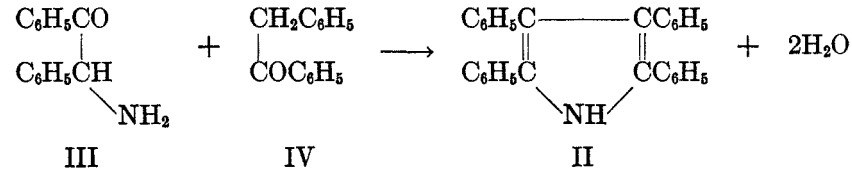
Amarone (I) was selected for the first test. When reduced with zinc in acetic acid it yielded a neutral, colorless, nitrogenous product melting at 214° which gave a fleeting green color when suspended in glacial acetic acid and treated with a trace of nitric acid. This product proved to be identical with tetraphenylpyrrole (II),[2] which Robinson and Robinson had found to give a brilliant green color with nitric or nitrous acid in sulfuric acid. Nitrosylsulfuric acid gave a lasting deep green color with the reduction product of amarone.

[1] DAVIDSON, WEISS, AND JELLING, J. ORG. CHEM., **2**, 328 (1937).

[2] (*a*) GARRETT, *Ber.*, **21**, 3107 (1888); (*b*) ROBINSON AND ROBINSON, *J. Chem. Soc.*, **113**, 644 (1918).

DESOXYBENZOIN IN KNORR'S PYRROLE SYNTHESIS

Although it thus appeared likely that tetraphenylpyrrole is responsible for the green color observed in the preparation of amarone it seemed desirable to explore simpler routes to its formation than the reduction of amarone. It seems plausible that the hydrogen eliminated in the formation of amarone hydrogenates benzoin to desoxybenzoin (IV). Since the reaction mixture is known to contain desylamine (III) (formed by the action of ammonia on benzoin) there is a possibility for the condensation of these two molecules as in Knorr's pyrrole synthesis.[3]



III IV II

Opposed to this hypothesis was the statement of Knorr and Lange[3b] that desoxybenzoin does not enter into the pyrrole synthesis. Nevertheless the experiment was tried with the following results. In acetic acid solution desylamine condensed with desoxybenzoin in the presence of ammonium acetate to give a 74 per cent. yield of tetraphenylpyrrole in one hour. The replacement of the ammonium acetate by sodium acetate lowered the yield to 33 per cent. In the presence of ammonium acetate the desylamine could be replaced by an equivalent amount of benzoin with little effect on the yield of tetraphenylpyrrole. Apparently a fairly activated methylene group such as that between carbonyl and phenyl groups or between two carbonyl groups is required under the conditions described in the present paper since acetophenone failed to behave like desoxybenzoin, although methyl benzyl ketone, dibenzyl ketone, and ethyl acetoacetate did.

A simple modification of this preparation of tetraphenyl pyrrole dispenses with the use of desoxybenzoin. Benzoin and ammonium acetate are heated in glacial acetic acid solution with sufficient zinc dust to produce desoxybenzoin or to reduce any amarone that may form.

The results reported in the present paper point to an explanation for the failure of Fritsch's attempted papaverine synthesis.[4] His reagents were

[3] (*a*) KNORR, *Ann.*, **236**, 317 (1886); (*b*) KNORR AND LANGE, *Ber.*, **35**, 2998 (1902); (*c*) KNORR AND HESS, *ibid.*, **44**, 2758 (1911); (*d*) PILOTY, *ibid.*, **43**, 489 (1910); (*e*) PILOTY AND WILKE, *ibid.*, **45**, 2586 (1912); (*f*) PILOTY AND BLOMER, *ibid.*, **45**, 3749 (1912); (*g*) PILOTY AND HIRSCH, *Ann.*, **395**, 63 (1913).

[4] FRITSCH, *Ann.*, **329**, 37 (1903).

aminoacetal and desoxyveratroin. It seems possible that instead of following the course he expected, the reaction led to the formation of 2,3-diveratrylpyrrole.

EXPERIMENTAL

The reduction of amarone.—One gram of amarone was suspended in 50 cc. of boiling glacial acetic acid, and 3.0 g. of zinc dust was added gradually. The boiling was continued until the solution was again colorless after passing through an orange stage. The mixture was then filtered to remove the excess of zinc, and 25 cc. of hot water added. This caused the crystallization of 0.29 g. (30% theoretical yield) of satiny needles melting at 214° (corr.). This melting point was not changed by recrystallizing the product from alcohol nor by mixing with the product obtained by condensing desylamine with desoxybenzoin as described below. Addition of a

TABLE

PYRROLES FROM BENZOIN

REAGENT	PRODUCT	RECRYSTALLIZED FROM	M.P. (CORR.)	YIELD OF CRUDE	ANALYSIS	
					Calc'd N	Found N
Methyl benzyl ketone*	2-Methyl-3,4,5-triphenyl pyrrole	Methanol	164°	72%	4.5%	4.3%
Dibenzyl ketone*	2-Benzyl-3,4,5-triphenyl pyrrole	Methanol	151°	43%	3.6%	3.5%
Ethyl acetoacetate	2-Methyl-4,5-diphenylpyrrole-3-carboxylic ethyl ester[5]	Ethanol	203°	87%	4.6%	4.6%

crystal of this product to a little nitrosylsulfuric acid (1.0 g. of sodium nitrite in 30 cc. of concentrated sulfuric acid) gave an immediate deep green color.

Condensation of desylamine with desoxybenzoin.—A mixture of 0.62 g. (0.0025 mole) of desylamine hydrochloride,[6] 0.54 g. (0.0028 mole) of desoxybenzoin,[7] 3.0 g. of ammonium acetate, and 25 cc. of glacial acetic acid was refluxed for one hour. The solution became orange-colored at first but the color lightened to straw at the end of the heating period. The addition of 5 cc. of boiling water caused the precipitation of colorless needles which were filtered and washed with 50% acetic acid. Yield, 0.69 g. (74% theoretical), m. 214° (corr.). Recrystallization from ethyl alcohol did not alter the melting point, nor did mixing with the product obtained by the reduction of amarone as described above. The product gave a deep

* The author is indebted to Dr. David Perlman for samples of these ketones.

[5] FEIST AND STANGER, *Ber.*, **35**, 1558 (1902); see also KNORR AND LANGE (ref. 3*b*).

[6] PSCHORR AND BRUGGEMANN, *Ber.*, **35**, 2740 (1902).

[7] BALLARD AND DEHN, *J. Am. Chem. Soc.*, **54**, 3970 (1932).

green color with nitrosylsulfuric acid. With sodium acetate in place of ammonium acetate the yield of tetraphenylpyrrole was 0.31 g. (33% theoretical).

Condensation of benzoin and ammonia with desoxybenzoin.—A mixture of 0.53 g. (0.0025 mole) of benzoin, 0.54 g. (0.0028 mole) of desoxybenzoin, 3.0 g. of ammonium acetate, and 25 cc. of glacial acetic acid was refluxed for one hour. The addition of 5 cc. of boiling water precipitated 0.68 g. (73% theoretical yield) of tetraphenylpyrrole, m. 212° (corr.) which was collected by filtration and washed with 50% acetic acid. Recrystallization from alcohol yielded a product, m. 213° (corr.), which was analyzed.

Anal. Calc'd for $C_{28}H_{21}N$: N, 3.8. Found: N, 4.0.

Preparation of tetraphenylpyrrole from benzoin.—A mixture of 1.06 g. (0.005 mole) of benzoin, 0.32 g. (0.005 g. atom) of zinc dust, 3.0 g. of ammonium acetate and 25 cc. of glacial acetic acid were refluxed until the solution became colorless (about 1.5 hours). The addition of 5 cc. of boiling water precipitated the product as colorless, silky needles which were filtered and washed with 50% acetic acid. Yield, 0.46 g. (50% theoretical), m. 214° (corr.).

The preparation of other pyrroles from benzoin.—In a manner similar to that described for the condensation of desoxybenzoin with benzoin and ammonia the reactions tabulated below were carried out.

SUMMARY

1. Contrary to the statement of Knorr and Lange, desoxybenzoin enters into Knorr's pyrrole synthesis.

2. Tetraphenylpyrrole may be prepared by the action of ammonia in acetic acid on (*a*) desylamine + desoxybenzoin, (*b*) benzoin + desoxybenzoin, (*c*) benzoin + zinc.

3. Under the same conditions other benzyl ketones and ethyl acetoacetate condense with benzoin and ammonia to give good yields of pyrroles.

4. Amarone (tetraphenylpyrazine) is reduced to tetraphenylpyrrole by zinc and acetic acid.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

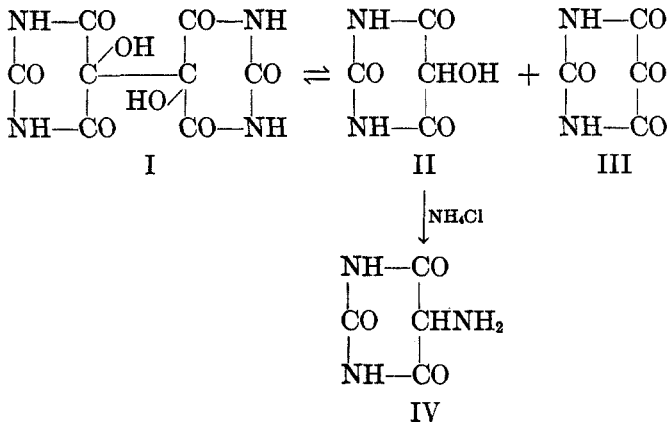
THE FORMATION OF URAMIL FROM DIALURIC ACID

DAVID DAVIDSON AND HAROLD SOLOWAY

Received September 9, 1938

INTRODUCTION

During their classical researches on the chemistry of uric acid, Wöhler and Liebig[1] observed that when a solution of alloxantine was boiled with ammonium chloride, uramil was rapidly formed as an insoluble precipitate, leaving alloxan in the mother liquors. In reëxamining this reaction, Biltz and Damm[2] considered the mechanism of the reaction to involve the dissociation of alloxantine (I) into dialuric acid (II) and alloxan (III) followed by a metathesis of the resulting dialuric acid with ammonium chloride to form uramil (IV). Since this left the alloxan moiety of alloxantine unutilized for the production of uramil, these authors suggested the more economical procedure of reducing alloxantine to dialuric acid before treating it with ammonium chloride.

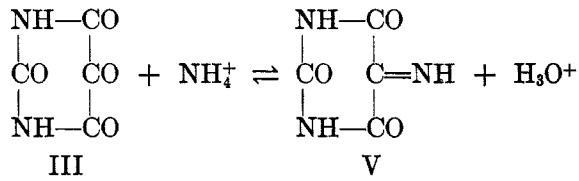


This work fixed the impression that alloxan has but a passive part in the formation of uramil from alloxantine. Recently, however, Davidson and Epstein[3] have demonstrated that alloxan plays a rôle in the reverse reac-

[1] WÖHLER AND LIEBIG, *Ann.*, **26**, 310 (1838).
[2] BILTZ AND DAMM, *Ber.*, **46**, 3662 (1913).
[3] DAVIDSON AND EPSTEIN, J. ORG. CHEM., **1**, 305 (1936).

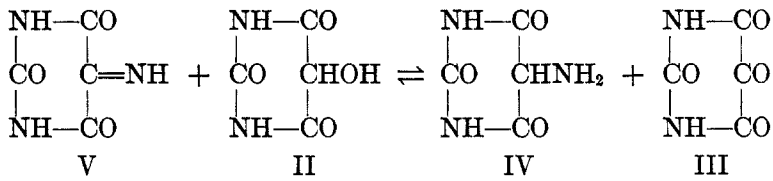
tion; that is, the hydrolysis of uramil to dialuric acid and ammonia. They proposed the hypothesis that both the formation and the hydrolysis of uramil involve a reversible oxidation-reduction process as well as a metathetical change, the latter involving not dialuric acid but alloxan. The composite reversible reaction may be represented by means of the following reversible steps.

Step 1. Metathesis: Alloxan (III) + Ammonium Ion $\rightleftharpoons$ Alloxan-Imine (V) + Oxonium Ion



III V

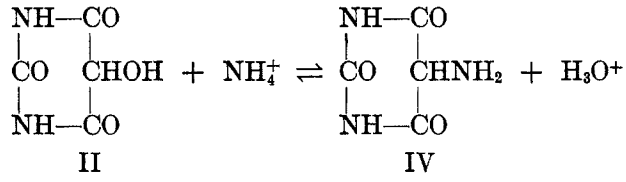
Step 2. Oxidation-Reduction: Alloxan-Imine (V) + Dialuric Acid (II) $\rightleftharpoons$ Uramil (IV) + Alloxan (III)



V II IV III

Thus the products disappearing and appearing in the first step respectively appear and disappear in the second step so that the resultant becomes:

Sum of Steps 1 and 2. (Apparent Metathesis): Dialuric Acid (II) + Ammonium Ion $\rightleftharpoons$ Uramil (IV) + Oxonium Ion



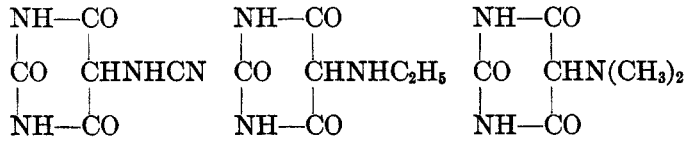
II IV

EVIDENCE SUPPORTING THE PROPOSED MECHANISM

The mechanism proposed above is supported by certain facts already recorded in the literature. Thus, Biltz and Beck[4] found that 7-cyanouramil (VI) could be prepared by heating alloxantine solution (*i.e.*, dialuric acid plus alloxan) with cyanamide, but that this product was not

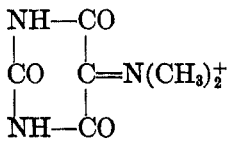
[4] BILTZ AND BECK, *J. prakt. Chem.*, [2], **118**, 151, 162 (1928).

obtainable from the action of cyanamide on dialuric acid alone. In the absence of alloxan, of course, the primary metathesis could not occur. This result appears all the more remarkable in view of the ease with which dialuric acid is autoxidized to alloxan (or alloxantine).[5]



VI VII VIII

Likewise, while Piloty and Finckh[6] prepared 7-ethyluramil (VII) from alloxantine and ethylammonium acetate, Biltz, Marwitsky, and Heyn[7] had difficulty in obtaining this uramil derivative from dialuric acid. The salt, ethylammonium dialurate, appeared instead of 7-ethyluramil, unless a large excess of ethylammonium acetate was employed. Furthermore, Piloty and Finckh[6] were unable to produce 7,7-dimethyluramil (VIII) from alloxantine and dimethylammonium acetate under the same conditions which succeeded for the formation of 7-methyluramil from alloxantine and methylammonium acetate. According to the proposed hypothesis the formation of 7,7-dimethyluramil would require the occurrence of a quaternary ion derivative of alloxan-imine as an intermediate (IX). Presumably the stability of such an ion, and hence the conditions for its formation, would be quite different from those for alloxan-imine or its 7-monoalkyl derivatives.



IX

In the present study it was attempted to demonstrate that the formation of uramil from dialuric acid and ammonium chloride is catalyzed by alloxan and that the success of the method of Biltz and Damm[2] depends upon the formation of some alloxan by the autoxidation of dialuric acid. The problem of obtaining pure dialuric acid (free from alloxan or alloxantine) was solved by utilizing isodialuric acid[8] (X), which resists autoxidation.

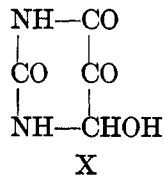
[5] HILL, *J. Biol. Chem.*, **85**, 713 (1930); **92**, 471 (1931).

[6] PILOTY AND FINCKH, *Ann.*, **333**, 64 (1904).

[7] BILTZ, MARWITSKY, AND HEYN, *ibid.*, **423**, 148 (1923).

[8] (*a*) BEHREND AND ROOSEN, *Ann.*, **251**, 235 (1889); (*b*) DAVIDSON AND BAUDISCH, *J. Biol. Chem.*, **64**, 621 (1925); (*c*) BOGERT AND DAVIDSON, *J. Am. Chem. Soc.*, **55**, 1667 (1933).

This was rearranged to dialuric acid by alkali[9] in the absence of air. The subsequent addition of potassium bisulfate served to neutralize the alkali employed as well as to furnish sufficient acidity to prevent the precipitation of alkali dialurate.



X

APPARATUS AND PROCEDURE

The apparatus employed in the present experiments consisted of a test-tube (30 × 150 mm.) the open end of which was fused to a narrower tube (20 mm. wide) which in turn bore three side-tubes (20 × 80 mm.) arranged one above the other and fixed at successively more acute angles to the main tube. Radially the upper two side-tubes were 90° apart, the lowermost tube falling in between. This reaction vessel was charged as indicated in the accompanying sketch, some of the solid reagents being weighed out in glass "shoes" (made from 8-mm. tubing) which were then introduced into the reaction vessel by means of a glass hook at the end of a string. Granular ammonium chloride was introduced by means of a delivery tube (10 mm. wide) which had a short right-angle at one end and an enlargement at the other. Potassium bisulfate was formed into rod, which could be slipped into the reaction vessel, by fusing the salt in a test-tube and then drawing the molten salt into a length of 8-mm. glass tubing. After cooling, the glass was broken away leaving the bisulfate stick.

The charge consisted of 0.180 g. of isodialuric acid dihydrate (0.001 mole) plus 15 cc. of water, two pellets of sodium hydroxide (approximately 0.20 g. or 0.005 mole), 1.4 g. of potassium bisulfate (0.010 mole), 1.0 g. of ammonium chloride (0.017 mole), and a varying amount of alloxan monohydrate.[10] When the charging was complete, the open end of the reaction tube was drawn out in the blast lamp. The tube was then immersed in a water bath (a large museum jar served for this bath) to a point well above the side-tubes. Hot water was poured into the upper part of the bath so that while the lower part of the reaction tube was at about 35° the side-tubes were considerably warmer. This arrangement prevented condensation in the side-tubes during the boiling out which was effected by connecting to an efficient water pump. Five minutes' pumping was adequate for the present purpose and avoided excessive evaporation of the water charged into the tube (about 2 cc. was lost).

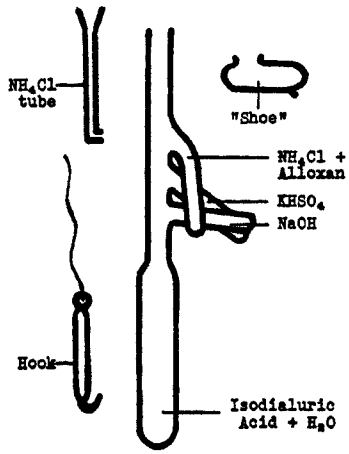
The reaction vessel was then sealed off with a blast lamp and manipulated further. The tube was tilted and tapped so that the alkali "shoe" fell into the test-tube. The apparatus was then carefully shaken for a few minutes until the isodialuric acid and the sodium hydroxide were completely dissolved. The bisulfate was then moved into the test-tube. As this dissolved, a precipitate appeared (potassium dialurate), which could be inhibited or redissolved by occasionally immersing the tube in a boiling water bath. The ammonium chloride and any alloxan present were

[9] BEHREND AND KOECH, *Ann.*, **315**, 246 (1901).

[10] MCELVAIN, *J. Am. Chem. Soc.*, **57**, 1303 (1935).

then added by inverting and reinverting the tube several times. If the mixture was not homogeneous at this point, gentle warming on the water bath for a minute or two was sufficient to produce a clear, colorless solution consisting of acidulated dialuric acid and ammonium chloride, ready for observations on the effect of alloxan on the formation of uramil from dialuric acid.

When uramil was produced in an experiment it was filtered by suction and washed with water and alcohol. Filtrates were tested for unconverted dialuric acid by heating. The crude uramil was dried by continuing the suction while a lighted 60-watt bulb fitted with a reflector rested on the rim of the funnel. Purification of uramil was effected by suspending the crude precipitate in 10–20 cc. of water containing a little sodium sulfite, adding 2 cc. of 2*N* sodium hydroxide, filtering quickly, and turning the filtrate into 50–100 cc. of boiling water containing 6 cc. of 2*N* hydrochloric acid. Uramil separated at once from the boiling solution as fine, colorless,



silky needles, which were filtered and dried as described above. The identity of the uramil preparations was checked by means of nitrogen determinations (Kjeldahl).

DISCUSSION OF RESULTS

The rôle of air—In one experiment, two tubes containing no alloxan were prepared as described above. (See table; tubes Nos. 1 and 2.) Air was then admitted to No. 1 by cutting off the capillary tip. Both tubes were then heated on the water bath, the second (sealed) tube being inverted to prevent the collection of liquid in the side-tubes. Uramil began to precipitate in the open tube after eleven minutes of heating, and the process was complete within an hour. The sealed tube, however, remained clear even after five hours' heating and then standing overnight. That this second tube nevertheless had the potentiality of producing uramil was shown by later admitting air to it, whereupon it produced a precipitate of uramil of about the same quantity and quality as in the first tube.

Alloxan, a catalyst—In another experiment three tubes were charged as usual, one containing one millimole of alloxan (tube no. 3), a second containing one-tenth millimole of alloxan (tube no. 4), and a third, as a control, no alloxan (duplicate of tube no. 1). All three tubes were heated on the water bath. The first assumed a faint wine color (murexide) and evidenced a precipitate of uramil within five minutes, the second remained colorless and produced a precipitate in about fifteen minutes, while the third was unchanged after an hour's heating and three weeks' standing

TABLE OF RESULTS

(Each tube contained one millimole of dialuric acid in water in the presence of potassium bisulfate and ammonium chloride)

TUBE NO.	ALLOXAN EMPLOYED MILLIMOLE	CONDITIONS OF EXPERIMENT	TIME FOR PRECIPITATE TO APPEAR	YIELD (THEORETICAL: 0.143 g.)		ANALYSIS (THEORETICAL: N, 29.4%) FOUND: (%)
				Crude, g.	Recryst'd, g.	
1	0.0	Opened tube after mixing; heated 1 hour.	11 min.	0.082	0.066	29.2
2	0.0	Heated 5 hours; stood overnight.	—	None	None	—
2 (cont.)	0.0	Opened tube #2; stood 5 days.	Overnight	0.076	0.057	29.1
3	1.0	Heated 25 min.	3–5 min.	0.125	0.094	29.3
4	0.1	Heated 3 hours.	14–17 min.	0.110	0.097	29.3
5	0.0	At room temp. for 3 weeks.	—	None	None	—
6	0.0	Opened tube after standing overnight; stood 5 days longer.	Overnight	0.086	0.057	29.4
7	1.0	At room temp. for 24 hours.	15–20 min.	0.122	0.056[a]	29.1
8	0.1	At room temp. for 5 days.	Overnight	0.086[b]	0.054	29.7

[a] This shrinkage on recrystallization was probably due to the presence of alloxantine in the crude precipitate.

[b] The reaction was incomplete as the filtrate yielded a precipitate on being heated.

thereafter. Precipitation of uramil was complete in the first tube within an hour, whereas the second tube required three hours for completion. It is significant that the proportion of alloxan determined merely the rate of formation of uramil but not the ultimate yield which was about 75–85 per cent. of crude product and 65–70 per cent. of recrystallized material which analyzed correctly.

Temperature effects.—Preliminary tests having indicated that uramil could be formed at room temperature, the two sets of experiments just described were repeated in the cold. The results parallel those obtained

on the water bath, confirming the rôle of air in the formation of uramil from dialuric acid and the catalytic action of alloxan.

A NOTE ON THE STRUCTURE OF DIALURIC ACID

Although, in harmony with custom, the structure of dialuric acid has been represented in this paper by means of the carbinol formula (II), it seems worthwhile to point out that the properties of dialuric acid are better represented by the enediol formula (XI). For the sake of brevity these properties are listed below without discussion.

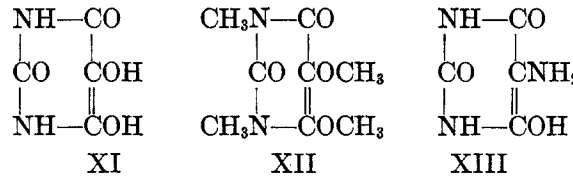
1. Acidity.—Dialuric acid is a fairly strong monobasic acid ($pK = 2.83$)[11] while 5-ethyl-5-hydroxybarbituric acid is weak.[12]

2. Iron salt.—Dialuric acid forms a deep blue ferric salt.

3. Action of diazomethane.—Diazomethane converts dialuric acid to a tetramethyl derivative[13] (XII).

4. Autoxidation.—Dialuric acid is readily oxidized to alloxan or alloxantine by elementary oxygen.[5]

5. Reversible oxidation-reduction.—With alloxan, dialuric acid forms a reversible oxidation-reduction system.[11, 14] According to Conant's view,[15] this suggests a stable enol structure for the reductant, dialuric acid.



XI XII XIII

By analogy, the structure of uramil is better represented by the enolic formula (XIII) than by the carbinamine formula (IV).

SUMMARY

1. The formation of uramil by the action of ammonium chloride on dialuric acid is catalyzed by alloxan.

2. This catalysis is explained by assuming the reaction to occur in two stages; *viz.*, (*a*) *metathesis* between alloxan and ammonium ion to form alloxan-imine and oxonium ion; and (*b*) *oxidation-reduction* between alloxan-imine and dialuric acid producing uramil and regenerating alloxan.

3. Biltz and Damm's preparation of uramil depends upon the production of alloxan, the catalyst, by the autoxidation of dialuric acid.

[11] Richardson and Cannan, *Biochem. J.*, **23**, 68 (1929).
[12] Aspelund, *J. prakt. Chem.*, [2], **136**, 334 (1933).
[13] Biltz and Paetzold, *Ann.*, **433**, 77 (1923).
[14] Hill and Michaelis, *Science*, **78**, 485 (1933).
[15] Conant, *Chem. Rev.*, **3**, 12 (1926).

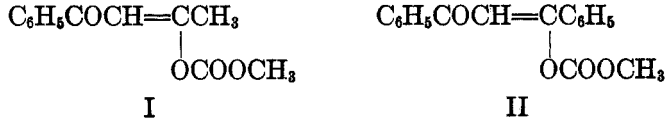
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE PARTITION PRINCIPLE AS APPLIED TO THE STRUCTURES OF ENOLIC SODIUM DERIVATIVES OF β-DIKETONES AND β-KETO ESTERS. III[1]

ARTHUR MICHAEL AND NATHAN WEINER

Received September 9, 1938

Several years ago, Michael and Ross[1a] described the formation of a solid and a liquid *O*-carbomethoxy enol benzoylacetone (I), which were obtained



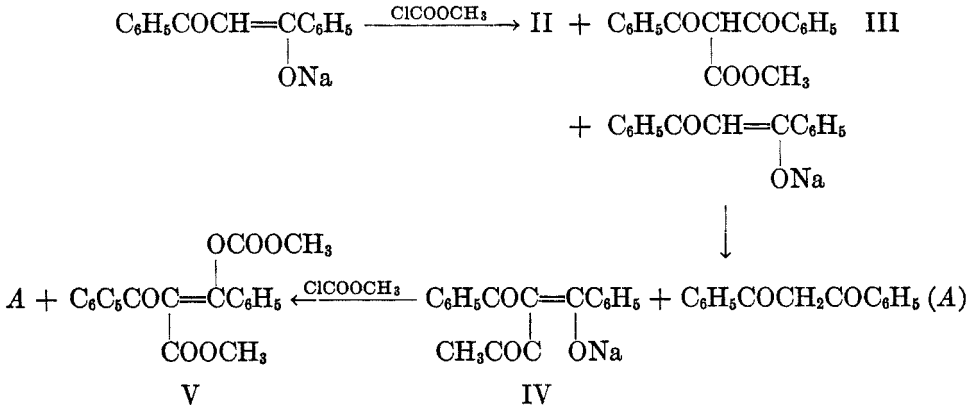
I II

by interaction of equimolar quantities of sodium enol benzoylacetone, in ether suspension, and chloroformic methyl ester. Evidence of stereoisomerism was based on the catalytic reduction of both products to butyrophenone. It was also found[1a] (p. 2403) that sodium enol dibenzoylmethane, made with sodamide, in ether suspension, gave with the chloroester at room temperature a poor yield (30 per cent.) of a solid *O*-carbomethoxy dibenzoylmethane (II), and about 50 per cent. of recovered dibenzoylmethane, along with 20 per cent. of an uncrystallizable and undistillable oil. Poorer yields of II, and a larger recovery of dibenzoylmethane, were obtained when the sodium enolate was prepared from the diketone and either sodium or sodium methoxide in ether suspension.

It seemed probable that the small yield in the latter reaction may have been connected with the slight solubility of the enolate in ether. We therefore used dioxane as a solvent, in which the enolate is fairly soluble (*ca.* one in four parts) at room temperature and extremely soluble at 100°. In that solvent, equimolar quantities of chloroformic methyl ester and sodium enol dibenzoylmethane, prepared either with sodamide or sodium methoxide, in ether suspension, reacted completely at room temperature, as was shown by the quantitative yields of sodium chloride, but twenty to twenty-five per cent. of dibenzoylmethane was recovered. A small quantity of the *O*-carbomethoxy dibenzoylmethane (II) was isolated; treatment with copper acetate yielded a bright green copper derivative, which had

[1] (*a*) I, MICHAEL AND ROSS, *J. Amer. Chem. Soc.*, **53**, 2401 (1931); (*b*) II, *ibid.*, **54**, 387 (1932).

the composition of cupric enol dibenzoylacetic methyl ester. Acidification of this enolate gave the corresponding free ester (III). The reaction, therefore, results partly in the formation of a *C*-derivative; a similar observation had previously been made with acetylacetone.[2] Dibenzoylacetic ester (III) is more acidic than dibenzoylmethane and, as formed, should liberate that compound from its enolate to form sodium enol dibenzoylacetic ester (IV), which could react with the chloroformic ester to yield *O*-carbomethoxy dibenzoylacetic ester (V):



Evidence for this course was found in the analysis of the uncrystallizable syrup, distillable with only slight decomposition, at 204–208° (2 mm.). The carbon and hydrogen values fell between those for II and V. The syrup contained neither enol dibenzoylmethane nor enol dibenzoylacetic ester (III), since it gave no color with ferric chloride, but on brief treatment with dilute alkali, and then with acid, it gave these compounds.

To test this view, sodium enol dibenzoylmethane, in dioxane solution and in ether suspension, was treated at room temperature, with half an equivalent of chloroformic ester. This was done to depress the formation of V, since the sodium of better-neutralized enolate IV, should react with the chloro ester less readily than with the relatively less neutralized sodium in the enolate of dibenzoylmethane.[3] In dioxane solution 52.9 per cent. of dibenzoylmethane was recovered; 26.2 per cent. as enolate, and 26.7 per cent. as free diketone. Of the changed dibenzoylmethane, 25.1 per cent. was accounted for by formation of dibenzoylacetic ester (III), isolated as the enolate, and 17.2 per cent. was used to form a corresponding amount of *O*-carbomethoxy dibenzoylmethane (II). It was not possible to separate completely the mixture of dibenzoylmethane and dibenzoyl-

[2] CLAISEN, *Ann.*, **277**, 182 (1893).

[3] For literature, see 1*a* and 1*b*.

acetic ester, liberated from the enolates, by fractional crystallization, nor through the copper enolates. The separation was effected satisfactorily, however, by extracting the ether solution of the mixture, first with sodium carbonate solution and then with caustic soda. The first treatment eliminated the more acidic dibenzoylacetic ester (III), and the latter removed dibenzoylmethane from the neutral *O*-carbomethoxy derivative (II). In ether suspension, the reaction proceeded much more slowly, and 77.9 per cent. of the dibenzoylmethane was recovered; 71.7 per cent. as enolate and 6.2 per cent. as the free diketone. The remainder was accounted for as dibenzoylacetic ester (III), isolated as enolate, and 13.8 per cent. of *O*-carbomethoxy dibenzoylmethane, (II). It should be emphasized that no syrup was formed in these experiments and the formation of a liquid stereomer of (II) is, therefore, excluded. The change in solvent, from dioxane to ether, had the effect of shifting the relative proportion of *C*- to *O*-derivative; in dioxane approximately three parts of the *C*-derivative to two parts of the *O*-derivative were formed, whereas in ether the *O*-derivative predominated in the ratio of almost two to one.

The formation of *C*-derivatives from β-diketonic enolates and chloroformic ester seems more general than has hitherto been recognized,[4] and the reaction with sodium benzoylacetone was, therefore, again investigated. The occurrence of such a product was indicated by the observation[1a] that the "liquid" isomer of I gave a ferric chloride test. The experiment was repeated as described[1a] and the same proportion of solid and liquid products was obtained; the liquid boiled over a 22-degree range (143–165°/2 mm.), despite repeated fractionation. In contrast, solid *O*-carbomethoxy benzoylacetone, (I), was found to have a boiling point of 142°/2 mm., a divergence which cannot be reconciled with the stereomerism of the two products. Further, sodium carbonate extracted from the liquid product a small quantity of an enolic compound, which yielded a copper derivative of the composition of copper enol benzoylacetoacetic methyl ester. It was identified by its preparation from the hitherto unknown benzoylacetoacetic methyl ester, $C_6H_5CO(CH_3CO)CHCOOCH_3$ (VIII), which was made from sodium enol acetoacetic methyl ester and benzoyl chloride.

To compare the course of this reaction with that of sodium enol dibenzoylmethane and the chloroformic ester, the same experimental procedure was followed. The products were separated in the same manner; benzoylacetoacetic ester was removed by sodium carbonate, and benzoylacetone by caustic soda. The yields of the reaction products are given in Table I.

Although these results do not account for as high a percentage of the

[4] MICHAEL AND CARLSON, *J. Amer. Chem. Soc.*, **57**, 160, footnote 6 (1935).

reaction products as in the experiments with dibenzoylmethane, yet it may be stated with considerable certainty that the change in the solvent affected only slightly the relative proportions of the reaction products. There was no evidence of a liquid isomer of I, although it should have been produced in about the same proportion in these reactions as in the reaction between equimolar amounts of the reagents. The deviations from 100 per cent. are undoubtedly largely due to mechanical losses and to the hydrolysis of benzoylacetoacetic ester, since it has been shown[5] that decomposition occurs in the separation of that ester in ether solution by sodium carbonate.

It remained to be proved experimentally that the "liquid isomer"[6] of I was a mixture of *O*-carbomethoxy benzoylacetone and *O*-carbomethoxy benzoylacetoacetic methyl ester. To separate such a mixture it was necessary to know the properties of the latter compound and, to prepare it, sodium enol benzoylacetoacetic ester, in ether suspension, was allowed to react with an excess of the chloroformic ester. The reaction proceeded

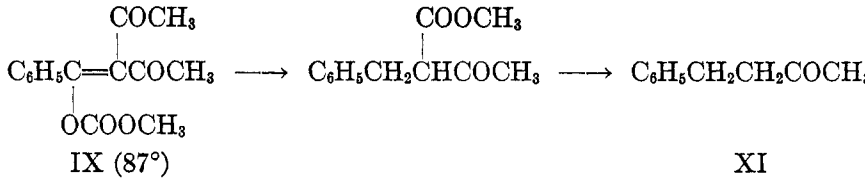
TABLE I

SOLVENT	% BENZOYLACETONE RECOVERED		% VIII FORMED		% I FORMED	TOTAL (%)
Ether	37.9 (enolate) 18.9 (free)	56.8	8 (enolate) 1.8 (free)	9.8	26.3	92.7
Dioxane	33 (enolate) 17 (free)	50	5.5 (enolate) 2.7 (free)	8.2	27.1	85.3

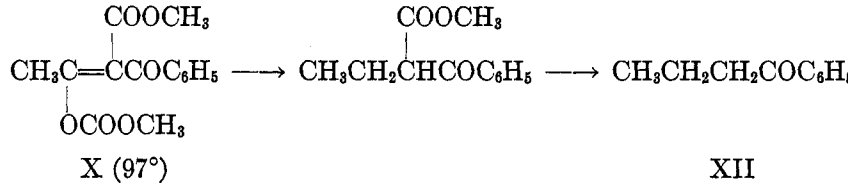
slowly; after two weeks at room temperature, only 85 per cent. was completed. The reaction product was separated into two solids, m.p. 87° and 97°, in the ratio of five parts of the latter to seven parts of the former. Analysis showed that they are isomers of the formula $C_{14}H_{14}O_6$, *i.e.*, they correspond to the composition of *O*-carbomethoxy benzoylacetoacetic methyl ester. It was shown that they are structural isomers IX and X, by hydrogenation in the presence of Adams' catalyst and hydrolysis and decarboxylation of the resulting keto-esters to the isomeric ketones XI and XII, which were identified through their semicarbazones. Therefore, the lower-melting isomer (87°), yielding benzoylacetone, must have structure IX, and the higher-melting (97°) structure X. In contrast to sodium enol benzoylacetone, the reaction takes place with each of the possible enolates of benzoylacetoacetic ester, and in fact, with a slight preponderance at the benzoylenolate, which does not react at all in the benzoylacetone reaction.

[5] MICHAEL AND CARLSON, *Ibid.*, **57**, 168, footnote 27 (1935).

[6] MICHAEL AND ROSS, (1*a*, p. 2410) observed that the solid compound always appeared in the first and last fractions in the distillation of the liquid portion.



IX (87°) XI



X (97°) XII

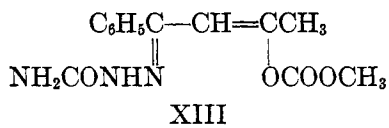
The reaction between equimolar quantities of sodium benzoylacetone and chloroformic methyl ester in ether was also re-examined. The products were separated by carbonate and alkali, as previously described, and the neutral esters, (I, IX, and X), by fractional crystallization. The results of one experiment are given in Table II. There were no other products

TABLE II

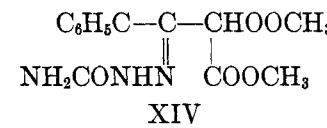
% BENZOYLACETONE RECOVERED	% I	% VIII	% IX AND X	TOTAL (%)
18.5	46.8	10.5	8.3 (87) 7.7 (97)	91.8

and the loss (8.2 per cent.) is no more than may be expected from the numerous manipulations involved in the separation of the reaction products.

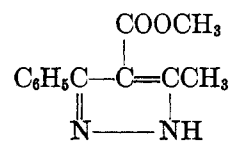
The fact that the "liquid isomer" was a mixture of several substances explains why Michael and Ross[1a] could not isolate definite products from the action of semicarbazide, or its salts, and only derivatives of benzoylacetone, in poor yields, by the action of other weakly alkaline carbonyl



XIII

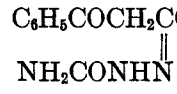


XIV

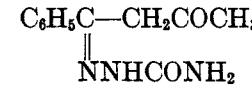


XV

reagents. On the other hand, the solid ketoester (I) with semicarbazide acetate gave a semicarbazone (XIII), which, in the presence of dilute acetic acid, was believed to undergo, first, a rearrangement to the semicarbazone of benzoylacetoacetic ester (XIV), to yield the pyrazole derivative (XV) as final product. Structure (XIV) was based upon an analysis, and the production of color with ferric chloride. However, the conversion of XIII into XIV does not seem theoretically probable. The reaction was therefore repeated, and the same products were obtained. However, the analyses of the compound melting at 166° showed that it has the composition of a semicarbazone of benzoylacetone. It must have been formed through the retrogression of XIII to a semicarbazone and it must have structure XVII, since it was formed by very mild hydrolysis. The blue-green color which it gives with ferric chloride is indistinguishable from that produced by the known semicarbazone of benzoylacetone (XVI), m.p. 127°.[7]

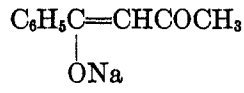


XVI

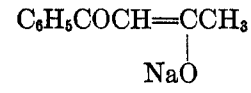


XVII

With the proof that *O*-carbomethoxy benzoylacetone (I), benzoylacetoacetic ester (VIII), and the isomeric *O*-carbomethoxy derivative are the sole products in the action of chloroformic methyl ester upon sodium enol benzoylacetone, the former conclusion[1a] that the reaction leads to a mixture of the stereomeric *O*-carbomethoxy benzoylacetone has been shown unfounded. The extent of the neutralization of the sodium in the isomeric enolates XVIII and XIX, depends mainly upon the relative nega-



XVIII

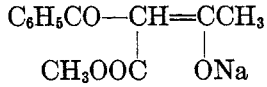


XIX

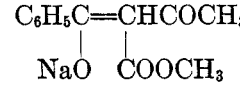
tivity of the benzoyl and acetyl radicals of benzoylacetone and this must stand in a direct relationship to the *K* values of the corresponding acids, *i.e.*, *ca.* 6.5 to 1.8. The exclusive action of the chloro ester, in the formation of the *O*-derivative from the acetyl enolate group, furnishes a quantitative approximation of the extent of negative influence necessary to practically suppress the reactivity of the sodium in the benzoyl enolate group toward the reactive chloroformic ester at room temperature. The formation of isomeric *O*-carbomethoxy derivatives (IX and X) from the

[7] MICHAEL AND ROSS, 1*a*, p. 2412.

enolate of benzoyl acetoacetic ester, in contrast with the single *O*-derivative (I), from sodium benzoylacetone, is an interesting illustration of the partition principle[8] and also of the relation between the extent of neutralization of the sodium of enolates and the facility of its replacement by radicals. It has been demonstrated experimentally,[9] that the reactivity of the sodium in enolates is exceedingly sensitive to the degree of neutralization of the metal, decreasing therewith to an astonishing degree. Thus, although the *K* value of benzoic acid is only 3.5 times greater than that of acetic acid, and the degree of neutralization of the sodium in the $C_6H_5CONa=$ and $CH_3CONa=$ radicals must stand in a direct relation to these values, the fairly reactive chloroformic ester attacks only the less neutralized sodium of the latter group. The introduction of β-$COOCH_3$ into benzoylacetone brings a negative radical in the same structural and stereochemical position to the sodium atoms of the isomeric enolates and, as the sodium atom of XIX is less neutralized than that of XVIII, the sodium of XX undergoes relatively a greater neutralization of its positive



XX



XXI

energy than that of XXI. The polarity of the sodium atoms must now be closer together than before and, accordingly, a mixture of isomeric *O*-carbomethoxy derivatives is formed in the reaction with chloroformic methyl ester. This result proves that the enolate of benzoylacetoacetic ester consists of a mixture of enolates (XX and XXI), in accordance with the principle of partition.[8] The above results lead to conclusions that would not be expected from the current views on substitution. For example, each sodium enolate of *m*- and *p*-toluoylbenzoylmethane (*K* of *m*- and *p*-toluic acids = 5.1×10^{-5}) should yield isomeric *O*-carbomethoxy derivatives with chloroformic ester, whilst the corresponding *o*-toluoyl compound (*K* of *o*-toluic acid = 12.5×10^{-5}) should give only a single *O*-derivative, with the carbomethoxy radical in the enol benzoyl group.

The question of solvent effect in the above reaction is complicated by the appearance of a second energy factor, *viz.*, the slight solubility of the benzoylacetone enolates in ether and the considerable solubility in dioxane. N. Menschutkin[10] first showed that the relation of reaction velocity in

[8] MICHAEL, *J. Prakt. Chem.*, **60**, 341 (1899); *J. Am. Chem. Soc.*, **32**, 1005 (1910); *Ber.*, **39**, 2133, 2569, 2786 (1906); **40**, 140 (1907).

[9] For literature, see *Ber.*, **38**, 222 (1903); *J. Am. Soc.*, **53**, 2394 (1931); **54**, 3871 (1932); **57**, 159 (1935).

[10] MENSCHUTKIN, *Z. physik. Chem.*, **34**, 157 (1900).

certain reactions to solvent effect at different concentrations is complicated and that the specific influence of solvents disappeared only at very high dilutions, but this and other similar investigations concern mainly solvent influence upon reaction velocity in chemical changes proceeding in a single direction. The probable viewpoint, that the above reaction proceeds largely through the soluble part of the enolate, implies a much greater concentration in dioxane, and the increased reaction velocity in that solvent accords with the solubility conditions. However, a difference in reaction velocity should not affect the quantitative relationship between the formed isomeric reaction products. The considerable quantitative differences between the relative proportions of *C*- to *O*-carbomethoxy products should, therefore, be attributed, at least partially, to a direct solvent effect. The relation of solvent effect to the formation of isomers in the addition of hydrogen bromide to monobasic acetylenic, and to the corresponding ethylenic, acids;[11] also, of "oxygen and peroxide effect,"[11] upon the course of addition to certain ethylenic derivatives[12] has been found to appear noticeably only when the difference between the energy degradations, as formulated in the partition principle[8], accompanying the formation of possible isomeric products is relatively small and this relationship should be manifested in all such reactions, if the effect is not covered by larger differences in other energy factors involved in the chemical changes.*

EXPERIMENTAL

A. Action of chloroformic methyl ester on sodium enol dibenzoylmethane.—Sodium enol dibenzoylmethane was prepared by adding an ether solution of dibenzoylmethane to a suspension of an equivalent of sodium methoxide, prepared by Brühl's method, in ether, or to a similar suspension of sodamide.[13] The mixtures were allowed to stand at room temperature, with occassional shaking, for twenty-four hours. They were then filtered, washed with absolute ether until a washing no longer gave a ferric chloride test, and dried at 100° in vacuum. Experiments showed that the enolates by either method gave the same results, and thereafter the enolate was prepared with the more accessible sodium methoxide.

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[11] MICHAEL, unpublished results.

[12] For literature, see KHARASCH, J. ORG. Chem., **2**, 289 (1937).

* Contrary to experimental conclusions[12] that alkene derivatives with nonterminal double bonds do not manifest a "peroxide effect," we find that isoamylene-2 is very susceptible to that influence. According to the above rule, atropic acid should respond to peroxide and solvent effect, although cinnamic acid does not[12]. These, and other, conclusions with respect to the relations to chemical structure, are being investigated.

[13] The fine suspension of sodamide was obtained by preparing a liquid ammonia solution of sodamide by the method of NIEUWLAND, *J. Am. Chem. Soc.*, **56**, 2121 (1934), and evaporation of the ammonia, after addition of ether, at room temperature with stirring.

(*1*) *Equimolar quantities in dioxane.*—Sodium enol dibenzoylmethane (46 g.) was dissolved in 200 cc. of dry dioxane and 18.7 g. of chloroformic methyl ester (1.06 moles) was added slowly. The mixture was kept at room temperature, by immersion in a water bath, for an hour and then in a desiccator for eighteen hours. The solution first became orange-red and deposited a bright yellow solid, probably sodium enol dibenzoylacetic ester, which later dissolved. The reaction mixture was finally a pale yellow solution, with a fine suspension of sodium chloride. It was diluted with 300 cc. of ether, and the solid was separated by filtration; weight 11.75 g. (theoretical for NaCl, 10.95 g.). The filtrate, upon concentration and removal of the dioxane under reduced pressure, left a residue of 51.1 g., which was dissolved in 200 cc. of ether and extracted with small portions of ice-cold, 10% sodium carbonate solution until the latter was only slightly yellow. The extracts were added to ice-cold, dilute hydrochloric acid, which precipitated a slightly yellow oil that soon solidified. The solid was washed with water, pressed out on a porous plate, and dried over calcium chloride. It weighed 11.4 g. and melted at 112°. After recrystallization from methanol it melted at 116–117°.

Anal. Calc'd for $C_{17}H_{14}O_4$ (III): C, 72.35; H, 4.96.
Found: C, 72.60; H, 4.97.

Copper enol dibenzoylacetic ester was precipitated quantitatively by shaking an ether solution of the solid with a saturated solution of copper acetate. It was obtained as bright green needles from benzene-petroleum ether; m.p. 240°.

Anal. Calc'd for $C_{34}H_{26}CuO_8$: Cu, 10.17. Found: Cu, 10.07.

The above ether solution was extracted repeatedly with small portions of ice-cold 10% sodium hydroxide, until the washing was no longer colored deep red. These washings were brought into cold, dilute hydrochloric acid and yielded 8.3 g. of dibenzoylmethane. The ether solution was shaken with copper acetate and gave 1.3 of copper dibenzoylmethane; equivalent to 1.1 g. of the mother substance.

The ether solution was dried, and the solvent was distilled off, when 29.4 g. of a syrupy residue remained. This was dissolved in an equal volume of methanol, the solution was cooled to −20° and, after seeding, 8.1 g. of *O*-carbomethoxy dibenzoylmethane crystallized; m.p. 87–89°; mixture with an authentic sample[1a] (m.p. 90°), m.p. 89–90°.

The mother-liquor was concentrated to 21 g. of syrup, which was distilled and yielded 17 g. of a pale yellow, extremely viscous syrup; b.p. 200–208°/2 mm.

Anal. Found: C, 70.25; H, 4.85.

The syrup was redistilled, and boiled without change. The portion (6 g.), b.p. 204–208°/2mm., gave no test with ferric chloride and was analyzed:

Anal. Found: C, 69.27; H, 5.07.
Calc'd for $C_{19}H_{16}O_6$ (V): C, 67.04; H, 4.75.
Calc'd for $C_{17}H_{14}O_4$ (II): C, 72.35; H, 4.96.

A solution of 1.4 g. of the above syrup in 5 cc. of methanol was added to a solution of 0.2 g. of sodium hydroxide in 5 cc. of methanol and a drop of water. The solution, which became orange, was warmed on the water bath for five minutes, cooled, diluted to 25 cc. with water and acidified with dilute acid. The precipitated oil was extracted with ether, from which 10% sodium carbonate extracted 0.5 g. of dibenzoylacetic ester (III). Evaporation of the dried ether solution gave 0.4 g. of dibenzoylmethane.

(*2*) *One mole of the sodium enolate and one-half mole of the chloro ester.*—The enolate was dissolved in dioxane, or suspended in ether, and treated with chloroformic methyl ester at room temperature. After the mixtures had stood at room temperature for the specified time (see Table III) they were diluted with 400 cc. of petroleum

ether. The precipitated solids were separated by centrifuging, and were washed repeatedly with ether (500 cc. in all). The solids were dried and weighed. The solutions and washings were evaporated to a solvent-free residue and weighed.

The solids were suspended in ether and shaken with cold dilute hydrochloric acid until solution was completed. The ether solutions were washed with cold 10% sodium carbonate solution in 10 cc. portions, until the extracts were only pale yellow. The extracts were brought into cold dilute acid to precipitate the dibenzoylacetic ester, which was filtered, dried, and weighed. The ether solutions contained only pure dibenzoylmethane.

The residues from the centrifuged solutions were dissolved in ether and extracted as above with sodium carbonate solution, which dissolved only a trace of dibenzoylacetic ester. They were then washed with 10-cc. portions of ice-cold, 10% sodium hydroxide, until the last washing was only faintly pink. These washings were added to cold dilute acid to precipitate dibenzoylmethane. The ether solution was

TABLE III

SOLVENT	ETHER		DIOXANE	
Enolate, g	47.5		46.5	
$ClCOOCH_3$, g	9.4		9.0	
Vol. solvent, cc	200		200	
Time	3 days		18 hrs.	
PRODUCTS	SOLID	SOLUTION	SOLID	SOLUTION
Weight, g	41.4	10.4	34.7	20.6
Dibenzoylacetic ester	4.0	None	13.4	None
Dibenzoylmethane	31.0	2.7	11.1	11.3
O-Carbomethoxy dibenzoylmethane	None	7.5	None	9.3

dried and left, after freeing from ether, almost pure *O*-carbomethoxy dibenzoylmethane (II). The semi-quantitative results are given in Table III.

B. Action of chloroformic methyl ester on sodium enol benzoylacetone.—The enolate was prepared, as already described, with sodium methoxide.

(*1*) *One mole of enolate and one-half mole of the chloro ester.*—After the mixtures had stood the specified time (see Table IV) at room temperature, they were diluted with 100 cc. of petroleum ether, the solid and solution were separated, and both were worked up as previously described in the dibenzoylmethane reactions (experiment *A*-2). Benzoylacetoacetic ester and benzoylacetone were isolated by extraction with sodium carbonate (10%) and sodium hydroxide (5%), acidification, and extraction with ether. The extracts were dried, and the residues were weighed. Benzoylacetone and *O*-carbomethoxy benzoylacetone (I) were identified by m.p. and mixture m.p., and the liquid benzoylacetoacetic ester by the quantitative conversion to the copper derivative. The results are tabulated in Table IV.

(*2*) *With excess of chloroformic ester.*—Sodium enol benzoylacetone (40 g.) was suspended in 200 cc. of ether and allowed to react with 25 g. (1.25 moles) of the chloroformic ester at room temperature for forty-eight hours. The mixture was shaken with cold, dilute hydrochloric acid until all the solid had dissolved. The ether solution, extracted with cold, 10% sodium carbonate solution, yielded 5 g. of

benzoylacetoacetic methyl ester, identified by conversion to the copper derivative; and treatment of the ether solution with 5% sodium hydroxide gave 6.5 g. of benzoylacetone.

The ether solution was washed once with dilute acid and, after drying, gave a solvent-free residue of 33 g. This, dissolved in an equal volume of methanol, on standing at room temperature, yielded 2.1 g. of the higher-melting *O*-carbomethoxy benzoylacetoacetic methyl ester, (X) m.p. 95–97°; mixture m.p., 97°. The filtrate, cooled in an ice-bath, gave 15.9 g. of solid, m.p. 48–52°, and the filtrate, on cooling to −20° gave an additional 4 g. (m.p. 51–6°). The crystals were combined and fractionally crystallized from ether-petroleum ether, in which X is only sparingly soluble, and were separated into 2.5 g. of X and 17.4 g. of *O*-carbomethoxy benzoylacetone (I), m.p. 56–57°.

The mother-liquor, freed from the solvent, left a residue of 11 g., which was extracted repeatedly with petroleum ether, (500 cc. in 50-cc. portions), leaving undissolved a little of a dark-red tar. The petroleum ether extract was evaporated,

TABLE IV

SOLVENT	ETHER		DIOXANE	
Enolate, g.	21.0		27.5	
$ClCOOCH_3$, g.	5.4		7.1	
Vol. solvent, cc.	100		100	
Time	24 hrs.		18 hrs.	
PRODUCTS	SOLID	SOLUTION	SOLID	SOLUTION
Weight, g.	13.5	12.8	19.0	15.3
Benzoylacetoacetic methyl ester, g.	2.0	0.4	1.8	0.9
Benzoylacetone, g.	7.0	3.5	8.0	4.1
O-Carbomethoxy benzoylacetone, g.	None	6.6	None	8.9

and the residue was dissolved in 10 cc. of methanol and cooled to −20°; 7 g. of a solid, which melted from 60–80°, crystallized, and the mother liquor, concentrated and cooled, yielded 3 g., m.p., 45–60°. These precipitates were fractionally crystallized separately from methanol and then from ether-petroleum ether until products with the same melting point were obtained. The latter were combined and further fractionally crystallized until a separation into the above two compounds was effected; 5 g. of the lower-melting *O*-carbomethoxy benzoylacetoacetic methyl ester (IX), m.p. 87° and 5 g. of *O*-carbomethoxy benzoylacetone (I), m.p., 56–57°, were obtained. Both compounds could be isolated from the less soluble fractions, I from the more soluble portions, although the solubilities of these two substances lie much closer together than do those of I and X.

The total yields of the products were: benzoylacetone, 6.5 g.; *O*-carbomethoxy benzoylacetone (I), 22.4 g.; benzoylacetoacetic ester (VIII), 5 g.; *O*-carbomethoxy benzoylacetoacetic ester (IX and X), 9.6 g. (5 g., m.p. 87°; 4.6 g., m.p. 97°).

C. Action of chloroformic methyl ester on sodium enol benzoylacetoacetic methyl ester.—Benzoylacetoacetic methyl ester (VIII) was prepared from sodium enol acetoacetic methyl ester and benzoyl chloride by the procedure described by Michael and Carlson (5, p. 172, experiment VII) for the corresponding ethyl ester. It was obtained as a colorless, slightly viscous, liquid, b.p. 136–137°/2mm.

Anal. Calc'd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45.
Found: C, 65.54; H, 5.66.

Three grams, shaken with a saturated copper acetate solution, yielded 3.3 g. of the powder-blue copper derivative. It crystallized from dioxane as blue-green needles, which reverted to the original color on drying; m.p., 226–228°.

Anal. Calc'd for $C_{24}H_{22}CuO_8$: Cu, 12.68. Found: Cu, 12.22.

Dry sodium enol benzoylacetoacetic methyl ester was prepared from the ester and sodium methoxide as described above. The enolate (24.2 g.) was suspended in 100 cc. of dry ether, 15 g. (1.5 moles) of chloroformic methyl ester added, and the mixture, with occasional shaking, was allowed to stand at room temperature for two weeks. The solid weighed 9.2 g. (theoretical for NaCl, 5.85 g.) and the filtrate gave 24 g. of a pale yellow syrup, which, dissolved in an equal volume of ether, diluted with petroleum ether and cooled in an ice bath, yielded 9.8 g. of solid, m.p. 95–96°. After recrystallization from methanol it melted at 97.2–97.7°. The mother-liquor, from which no more solid separated, after evaporation of the solvent, was dissolved in 10 cc. of methanol and allowed to evaporate at room temperature. This resulted in an almost complete crystallization of the residue, which, after recrystallization from methanol, melted at 87°, and depressed the melting point of the 97° compound to about 60°.

Anal. Calc'd for $C_{14}H_{14}O_6$: C, 60.44; H. 5.04.
Found, (97°): C, 60.85; H, 5.66.
(87°): C, 60.82; H, 5.37.

A mixture of the isomers boiled at 165°/2mm., with slight decomposition, which is the boiling point of the supposed liquid stereomer of *O*-carbomethoxy benzoylacetone (164°/2mm.)[1a].

The structures of the isomers were determined as follows. Ten grams was partially dissolved in 50 cc. of absolute methanol and shaken with hydrogen in the presence of Adams' catalyst. As the reduction proceeded the solids dissolved. Absorption of hydrogen was very slow, *ca.* 20–30 cc. per hour, and additional catalyst had to be added after each 200 cc. (approximately) of hydrogen had been absorbed. When two moles of hydrogen had been used, the catalyst was separated by filtration, and the solutions were concentrated to 20 cc. Ten cc. of concentrated hydrochloric acid was added, and the mixtures were boiled for three hours and then poured into water. The precipitated oils were extracted with ether; the ether was washed with sodium carbonate solution, and dried. In this way, practically theoretical yields of benzylacetone (XI) and butyrophenone (XII) were obtained from the 87° and 97° isomers, respectively. Butyrophenone was identified by conversion to its semicarbazone, m.p. 188°;[14] benzylacetone likewise by its semicarbazone, m.p. 143°.[15] A sample of the ketone, prepared by catalytic reduction of benzalacetone, gave the same semicarbazone, m.p. 143°.

Action of semicarbazide acetate on O-*carbomethoxy benzoylacetone.*—The reaction was carried out according to the directions of Michael and Ross (1*a*, p. 2410), and the same products were isolated. The semicarbazone was recrystallized from absolute methanole and melted at 166°.

Anal. Calc'd for $C_{11}H_{13}N_3O_2$: C, 60.30; H, 5.94.
Found: C, 60.65, 60.35, 60.48; H, 6.22, 6.10, 6.15.

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[14] SORGE, *Ber.*, **35**, 1073 (1902).
[15] KLAGES, *ibid.*, **37**, 2313 (1904).

SUMMARY

1. The reaction between sodium enol dibenzoylmethane and chloroformic methyl ester leads to a mixture of dibenzoylacetic methyl ester and *O*-carbomethoxy dibenzoylmethane.

2. The reaction between sodium enol benzoylacetone and chloroformic methyl ester gives a mixture of benzoylacetoacetic methyl ester and *O*-carbomethoxy benzoylacetone.

3. The reaction between sodium enol benzoylacetoacetic methyl ester yields a mixture of structurally isomeric, *O*-carbomethoxy benzoylacetoacetic methyl esters.

4. The liquid product of the reaction between equimolar quantities of sodium enol benzoylacetone and chloroformic methyl ester, which had been considered a stereomer of the solid *O*-carbomethoxy benzoylacetone, has been shown to consist of a mixture of benzoylacetoacetic methyl ester, *O*-carbomethoxy benzoylacetone, and the two structurally isomeric *O*-carbomethoxy benzoylacetoacetic methyl esters.

5. The occurrence of the various products in the above reactions has been interpreted from the standpoint of the partition principle, as applied to the degree of neutralization of the sodium in the respective enolates.

6. In the action of chloroformic methyl ester upon sodium enol dibenzoylmethane in dioxane the ratio of *C*- to *O*-carbomethoxy derivative is approximately three to two, whereas in ether suspension it is about one to two. This difference is attributed to solvent effect, and a general relationship between this, and also "peroxide effect", and chemical structure has been advanced.

7. The supposed rearrangement of the semicarbazone of the *O*- to that of the *C*-carbomethoxy benzoylacetone has been shown to be erroneous. It consists in the hydrolysis of the *O*-carbomethoxy group, with loss of carbon dioxide, and formation of a new, isomeric semicarbazone of benzoylacetone.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE CHEMILUMINESCENCE OF 3-AMINOPHTHALHYDRAZIDE

FRED H. STROSS AND GERALD E. K. BRANCH

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Albrecht[1] first described the bright chemiluminescence accompanying the oxidation of cyclic hydrazides of phthalic acid derivatives, the greatest intensity being shown by 3-aminophthalhydrazide, commonly known as luminol. This substance fluoresces strongly with ultraviolet light in acid and neutral solution, but not in alkaline solution. On the other hand, the chemiluminescence has only been observed in alkaline solutions. The colors of the fluorescence and the luminescence are very similar but according to Albrecht have their maximum intensities at slightly different wavelengths.

The oxidizing agents capable of producing the luminescence may be divided into three classes, (1) those producing a dim glow of short duration, (2) those producing a dim glow of long duration, and (3) those producing a bright glow of short duration. Potassium ferricyanide and hydrogen peroxide belong to the first and second classes respectively, but a mixture of these oxidizing agents belongs to the third class. In view of this interesting fact we have studied the intensities, rates of change of intensity, and total light given out from various mixtures of potassium ferricyanide, hydrogen peroxide, luminol, and sodium hydroxide.

THE CHEMICAL CHANGES

To understand fully the reasons for the variations in the luminescence it seems necessary to have some knowledge of what happens to the reactants in the mixture during the period of luminescence. For this purpose the following experiments were designed.

Under varying conditions of alkalinity and concentration, an alkaline solution of luminol was mixed with an excess of potassium ferricyanide, and after varying periods of time, all greatly in excess of the duration of the luminescence, the mixtures were analyzed for ferricyanide ion. After ten minutes 2.8 and 2.95 equivalents of ferricyanide ion were reduced per mole of luminol, depending on the concentration of alkali. After half an hour these figures rose to 3.1 and 3.2 equivalents per mole. In an oxidation lasting twelve hours, and in one of two days, 3.5 and 4.8 equivalents of

[1] ALBRECHT, *Z. physik. Chem.*, **136**, 32 (1928).

ferricyanide ion were reduced per mole of luminol respectively. This experiment shows that the luminol is reduced in steps, and that a three-unit stage of oxidation is reached long after the glow has ceased; but as long as ferricyanide ion is present the oxidation continues, though slowly, and may exceed the four-unit stage, the formation of 3-aminophthalic acid and nitrogen.

A similar attempt was made to find out how far hydrogen peroxide oxidizes luminol. As hydrogen peroxide decomposes in an alkaline solution it was necessary to perform a control experiment without any luminol. It was found that in the control experiment the loss of hydrogen peroxide was faster than in the mixture containing the luminol. This experiment shows that luminol inhibits the decomposition of hydrogen peroxide, but it was valueless for the elucidation of what happens to luminol when it is luminescing in a hydrogen peroxide solution.

After it had been found that when hydrogen peroxide is decomposed in the presence of ferricyanide ion more oxygen is evolved than corresponds to the equation

$$2H_2O_2 \rightarrow 2H_2O + O_2$$

an alkaline solution of 0.00325 moles of potassium ferricyanide and 0.00279 moles of hydrogen peroxide was allowed to react in an atmosphere of carbon dioxide. The evolved gases were collected over potassium hydroxide solution, and the residual gases were removed by a stream of carbon dioxide, the reaction being allowed to continue until all the hydrogen peroxide was decomposed. The residual solution was analyzed for oxidizing agent and for ferricyanide ion. The amount of oxygen obtained corresponded to the complete reaction of the ferricyanide ion by the reaction

$$2Fe(CN)_6^{---} + H_2O_2 + 2OH^- \rightarrow 2H_2O + O_2 + 2Fe(CN)_6^{----}$$

plus the oxygen from the decomposition of the remaining 0.00117 moles of hydrogen peroxide (found 46.6 cc, calculated 46.4 cc). The residual solution contained no oxidizing agent, and an amount of ferrocyanide equivalent to the initial ferricyanide (found 0.00326 moles, calculated 0.00325 moles).

It was found that in neutral or slightly acid solution the evolution of oxygen from hydrogen peroxide-potassium ferricyanide solutions is very slow. The reaction in an alkaline mixture was allowed to proceed for a short time in an atmosphere of air, at an alkaline concentration in the range used in our subsequent experiments, and then stopped by neutralization. The gases were collected, and the oxygen was measured by absorption with pyrogallol, the volume of residual nitrogen permitting the correction for the air in the reacting vessel. The oxygen evolved corresponded

to the using up of about 75 per cent. of the ferricyanide ion in about one minute. The timing in this experiment was only approximate as the times of mixing and neutralization were indeterminate and correspond to an appreciable fraction of the total time.

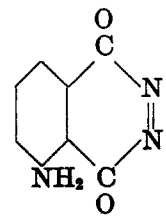
An alkaline mixture of 0.00322 moles of potassium ferricyanide, 0.00186 moles of hydrogen peroxide and 0.000565 moles of luminol was allowed to react in an atmosphere of carbon dioxide to the cessation of gas evolution. The gases were collected over potassium hydroxide and measured. The oxygen was absorbed with pyrogallol and the residual gas, assumed to be nitrogen, was measured; 0.000505 mole of nitrogen was obtained, corresponding to 88 per cent. of the nitrogen in the luminol. The oxygen was less than corresponding to the reaction of all the ferricyanide ion by the reaction

$$2Fe(CN)_6^{---} + H_2O_2 + 2OH^- \rightarrow 2Fe(CN)_6^{----} + 2H_2O + O_2$$

plus the decomposition of the excess of hydrogen peroxide, by the amount necessary to oxidize all the luminol to a two-unit stage of oxidation (found 35.85 cc., calculated 35.84 cc.). In this experiment the luminescence lasts for considerably less than a minute.

Instantaneously mixed solutions similar to those used in our measurements of the luminescence, which contain an excess of hydrogen peroxide over potassium ferricyanide and an excess of potassium ferricyanide over luminol were run through a tube at a rate so that the glow is over before the middle of the tube is reached, and the liquid flows from the tube in a minute. Samples of the liquid coming out of the tube did not glow when treated with a mixture of potassium ferricyanide and hydrogen peroxide, glowed faintly when luminol was added, but brightly when both luminol and potassium ferricyanide were added. When the liquid coming out of the tube was acidified with acetic acid and allowed to stand a few minutes, it glowed brightly on addition of alkali alone.

These experiments show that in solutions with excess of ferricyanide ion and hydrogen peroxide the glow ceases because of the removal of luminol by a two-unit oxidation. In acid solution the product can be reduced back to luminol by ferrocyanide ion, and hence the loss of nitrogen that occurs when luminol is oxidized is a slower reaction following two units of oxidation. The most probable two-unit oxidation of luminol without loss of nitrogen is the formation of

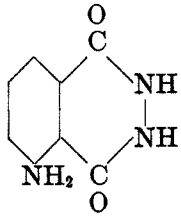


Although this oxidation is the fastest reaction decreasing the luminescence, the reaction

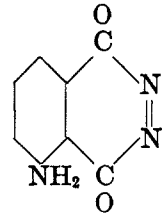
$$2Fe(CN)_6^{---} + 2OH^- + H_2O_2 \rightarrow 2Fe(CN)_6^{----} + 2H_2O + O_2$$

is fast enough to decrease the concentration of ferricyanide ion sufficiently to diminish the glow, and to introduce enough ferrocyanide ion into the mixture to markedly affect the brightness during the glowing period. The decomposition of hydrogen peroxide is not sufficiently fast to have any effect during the luminescence. The following reactions, in which nitrogen is evolved and the further oxidations of the products takes place, are immaterial to the study of the luminescence as they occur chiefly after the luminescence has ceased.

Our statement that the reaction,

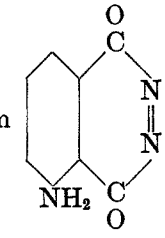


+ 2 equivalents of oxidizing agent ⟶

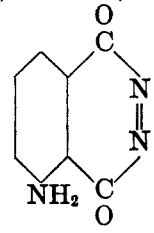


+ H_2O + 2 equivalents of reducing agent,

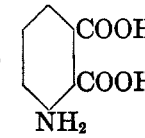
terminates the luminescence is not equivalent to the statement that the light is given off by some step in this process. Provided the efficiency of luminescence is low, the light may be given off by some side reaction of luminol, or of any product of luminol that is not derived from



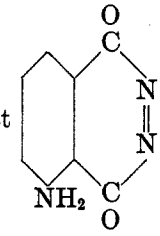
Our statement does, however, contradict the mechanism suggested by Albrecht, in which



hydrolyses to



+ N_2H_2,

and then reacts with N_2H_2 to form nitrogen and activated luminescing luminol; for our experiments seem to show that  is present after the glow has ceased.

THE LUMINESCENCE

Introduction.—The following qualitative experiments are pertinent to or confirmatory of the results of the quantitative experiments.

Two alkaline solutions of luminol were started glowing at the same time, one with potassium ferricyanide alone, the other with the same concentration of potassium ferricyanide and some hydrogen peroxide. After a short time the first solution had practically ceased glowing, and the glow of the second had much diminished in intensity. An amount of hydrogen peroxide equal to that in the second solution was added to the first solution. The two solutions then glowed with about equal intensities, and remained alike until the glows were extinguished. This experiment suggests that the hydrogen peroxide does not have any marked effect on the rate of oxidation of luminol, but greatly increases the amount of light obtained from a given amount of luminol.

When alkaline luminol and hydrogen peroxide were mixed, there was an appreciable interval before the maximum brightness was obtained. This interval does not seem to be due to the time for the eye to accommodate itself. It was much longer than the apparent induction period obtainable, by turning on the lights, and then turning them off, while observing a glowing mixture of luminol and hydrogen peroxide.

When a trace of hydroquinone was added to an alkaline mixture of luminol and hydrogen peroxide, the glow was extinguished, and on long standing the glow returned. The return was eventually complete, and was more rapid the less hydroquinone used.

When a small quantity of hydroquinone was added to an alkaline solution of luminol and a mixture of potassium ferricyanide and hydrogen peroxide was added, the glow obtained was very faint, but belonged to the rapidly fading type characteristic of oxidation by ferricyanide ion alone.

The first of these experiments suggests that when hydroquinone is used to quench the glow, it is used up in the process. The second experiment suggests that the inhibitor acts on a luminescent step in the reaction which is chiefly due to hydrogen peroxide, but does not protect the luminol from oxidation by potassium ferricyanide.

Experimental method.—The oxidation of alkaline solutions of luminol by ferricyanide ion is so fast that it is not possible to use ordinary methods of observing the glow at the start of the reaction or after any measured time. Consequently we used the flow method devised by Roughton for the study of very fast reactions. This method consists of allowing two solutions flowing at a constant speed to come together, mix, and flow together along a tube. Some characteristic of the reacting mixture is then measured at intervals along the tube, which corresponds to times after the mixing of the solutions. The times are calculated from the cross section of the tube, and the volume of liquid delivered from the tube in unit time. The chief difficulty lies in the necessity of very rapid mixing, so that the reaction can be said to start at a nearly definite point in the apparatus.

A strongly luminescent reaction permits one to judge how rapidly the mixing occurs, for during the mixing the light is not given off uniformly through the solution, but chiefly from interfaces of streams of different combinations. This is quite visible to the eye.

We tried various devices for mixing the streams until we obtained one in which the liquid glowed quite uniformly almost immediately after the point of contact of the two streams.

This method had previously been used by Bray and Livingstone,[2] Hartridge and Roughton,[3] and others. It has been claimed that the method can give mixing in .02 seconds, and our observations seemed to indicate an even shorter time. The device used was a junction of a T-tube, with the three openings reduced to capillary size, and a very small compartment left. The two streams entered at opposite sides in line with one another, and the mixed solution entered the main reaction tube at right angles to this line.

The two liquids were an aqueous alkaline solution of luminol and an aqueous mixture of potassium ferricyanide and hydrogen peroxide. They were both in bulk and kept at a temperature of 20°. From their storing vessels they flowed into constant-level vessels, the two levels being the same. The proportions of the two liquids were varied by stopcocks, and measured by taking the rate of flow of each separately. The total flow through the tube was measured at its exit by an electrical device giving the rate over a short interval of time, and by collecting and measuring the liquid flowing out of the tube in a long period. The two measurements agreed, and the rate of flow as measured in short intervals showed a constant rate of flow.

The brightness of the tube was measured with a photoelectric cell (Visitron cell, type 75A) connected to a balanced circuit and galvanometer.

[2] BRAY AND LIVINGSTONE, *J. Am. Chem. Soc.*, **50**, 1654 (1928).

[3] HARTRIDGE AND ROUGHTON, *Proc. Roy. Soc.*, **104**, 376 (1932).

The cell was mounted so that the aperture could be rapidly placed opposite any point of the reaction tube, the distances being always the same. The galvanometer deflections were found to be strictly proportional to the intensity of the light falling on the cell, for they were strictly inversely proportional to the square of the distance between a point source of light and the cell.

To avoid loss of time, the support of the reaction tube was marked at specific distances along the tube, and the cell was always brought to these marks.

The constancy of conditions during a run was assured by taking the measurements from one end of the tube to the other, and then back again to the starting point. Unless good agreement was found between the two sets of measurements the run was not considered satisfactory. No difficulty of this kind was found after filtering was introduced above the regulating stopcocks, except when the concentration of hydrogen peroxide was increased beyond those shown in our tables.

In our measurements some of the light is absorbed by the ferricyanide ion. The error introduced was estimated by putting a bigger tube of known diameter around our reaction tube. A run was then made with water running through this tube, and measurements of the brightness were made at a point along the tube. The water was replaced with a known solution of potassium ferricyanide, and the measurement was repeated. The results indicated that the absorption of light by the ferricyanide ion made a difference of between 5 and 10 per cent. in the most concentrated solutions of potassium ferricyanide we used. We have not included any correction in our measurements for the light absorbed by the ferricyanide ion, since this is about the probable error in our significant results, which involve certain extrapolations.

Results and discussion.—In Figure 1 a typical run is shown, as a plot of the natural logarithm of the galvanometer deflection against the distance along the tube from the point of mixing. The curve is not shown over its full length but includes all the chief characteristics of the experiments.

Were the intensity proportional to the rate of the reaction between luminol and ferricyanide ion and were this the only reaction present this curve would be nearly a straight line, as the ferricyanide is in marked excess over the luminol, but the slope of the curve decreases, more rapidly at first, but even when the light is very dim. This arises because potassium ferrocyanide, one of the products of the reaction, decreases the luminosity. Moreover, the side reaction between hydrogen peroxide and ferricyanide ion is continually lowering the ferricyanide ion concentration and increasing that of ferrocyanide ion. For this reason the analysis of the curve of a single run would require a law which would include the

kinetics of the two reactions mentioned above, and the relationship between the concentrations of the components and the intensity of luminescence. Therefore we have extrapolated the measurements to zero time, when the concentrations of all the components are known. We have also extrapolated the values of the rate of change of the logarithm to zero time, for at this point not only are the concentrations known, but the changes of concentrations are mainly due to the specifically fastest reaction, the oxidation of luminol.

The typical curve we have shown, and those for all the other runs, when extrapolated from the measurements made from 5 cm. on, pass above the point obtained at 2 cm. The persistent lowness of this point could be due to the presence of traces of an inhibitor which is used up almost immediately. If this supposed inhibitor acts like hydroquinone in

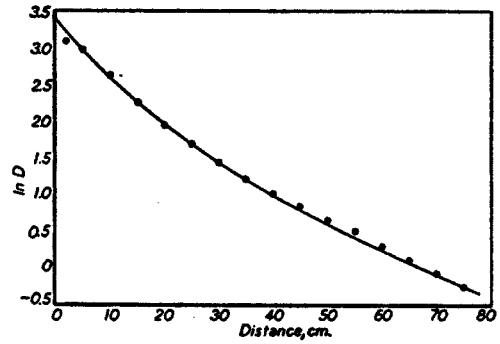


FIG. 1

quenching the brightness rather than stopping the oxidation of luminol by ferricyanide, then extrapolation to zero time gives the brightness which would be obtained if it were absent. We believe, however, that the most probable explanation is that the luminescence occurs in a follow reaction, and a lapse of time is necessary for the luminescing substance to reach a steady state. On this assumption extrapolation gives the brightness that would be obtained from the initial concentrations with the intermediate at its steady-state concentration.

The extrapolations were made to zero time, ignoring the first measurements, those at 2 cm. equivalent to about .2 seconds. The extrapolated values of the brightness and the extrapolated values of the rate of change of the natural logarithms of the brightness for the experiments at 20°, are shown in Table I under the headings B, and $d\ln B/dt$. The units for B are arbitrary, being the galvanometer deflections. In this table the initial concentrations of luminol, hydroxide ion, total hydrogen peroxide, undis-

TABLE I

INITIAL CONCENTRATIONS; INITIAL INTENSITIES; INITIAL RATES OF CHANGE OF INTENSITIES; THE RESPECTIVE CONSTANTS

RUN	LUMINOL	OH^-	TOTAL H_2O_2	UNDISSOCIATED H_2O_2	$K_3FeCy_6 \times 10^3$	K_4FeCy_6	B	$\frac{d\ln B}{dt}$	$K_B \times 10^3$	$K_r \times 10^3$
1	5.13×10^{-4}	2.82×10^{-1}	1.762×10^{-2}	6.04×10^{-4}	6.24		50	3.68	0.9	1.93
2	5.13×10^{-4}	1.32×10^{-1}	1.762×10^{-2}	1.24×10^{-3}	6.24		39	1.6	1.2	1.8
3	5.13×10^{-4}	5.94×10^{-2}	1.762×10^{-2}	2.53×10^{-3}	6.24		28.2	0.677	1.7	1.67
4	5.13×10^{-4}	2.34×10^{-2}	1.762×10^{-2}	4.05×10^{-3}	6.24		11.2	0.445	1.63	2.81
5	5.13×10^{-4}	8.38×10^{-2}	1.762×10^{-2}	1.88×10^{-3}	6.24		33	1.04	1.48	1.83
6	2.57×10^{-4}	8.38×10^{-2}	1.762×10^{-2}	1.88×10^{-3}	6.24		19.5	1.03	1.74	1.89
7	1.28×10^{-4}	8.38×10^{-2}	1.762×10^{-2}	1.88×10^{-3}	6.24		11.4	1.21	2.04	2.32
8	6.41×10^{-5}	8.38×10^{-2}	1.762×10^{-2}	1.88×10^{-3}	6.24		5.7	1.19	2.04	2.25
9	3.21×10^{-5}	8.38×10^{-2}	1.762×10^{-2}	1.88×10^{-3}	6.24		3.1	1.16	2.22	2.21
10	5.13×10^{-4}	1.17×10^{-1}	7×10^{-2}	5.51×10^{-3}	4.71		44.7	1.67	1.66	2.73
11	5.13×10^{-4}	1.17×10^{-1}	3.5×10^{-2}	2.76×10^{-3}	4.71		42.7	1.3	1.66	2.13
12	5.13×10^{-4}	1.17×10^{-1}	1.75×10^{-2}	1.38×10^{-3}	4.71		37.2	1.2	1.58	1.96
13	5.13×10^{-4}	1.17×10^{-1}	8.75×10^{-3}	6.89×10^{-4}	4.71		27.2	1.04	1.36	1.7
14	5.13×10^{-4}	1.17×10^{-1}	4.83×10^{-3}	3.44×10^{-4}	4.71		22	1.25	1.42	2.05
15	5.13×10^{-4}	1.17×10^{-1}	2.19×10^{-3}	1.72×10^{-4}	4.71		15.5	1.23	1.45	2.01
16	5.13×10^{-4}	1.17×10^{-1}	1.09×10^{-3}	8.6×10^{-5}	4.71		11	1.49	1.67	2.44
17	5.13×10^{-4}	1.17×10^{-1}	5.48×10^{-4}	4.3×10^{-5}	4.71		6.6	1.48	1.73	2.43
18	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	7.32		38	1.69	1.61	2.19
19	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	5.49		30.2	1.18	1.54	1.98
20	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	3.66		24	0.785	1.65	1.91
21	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	1.86		16.2	0.47	1.99	2.03
22	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	7.32	7.32×10^{-3}	20	0.95	1.58	2.31
23	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	3.66	3.66×10^{-3}	15.5	0.49	1.65	1.84
24	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	1.83	1.83×10^{-3}	12	0.36	1.92	2.03
25	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	3.66	1.83×10^{-3}	19.8	0.65	1.73	2.01
26	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	1.83	9.15×10^{-4}	15.2	0.416	2.15	2.07
27	5.13×10^{-4}	9.85×10^{-2}	8.67×10^{-3}	7.98×10^{-4}	7.32	9.15×10^{-4}	34.2	1.28	1.61	1.83
									Average	
									$^*K_B \times 10^3$	$K_r \times 10^3$
									1.69	2.09

* Neglecting value of K_B of expt. 1.

sociated hydrogen peroxide, potassium ferricyanide, and potassium ferrocyanide are also given. The values given for OH^-, are calculated from the sodium hydroxide, less that neutralized by the luminol, assuming all the luminol to exist as the monovalent ion, less that neutralized by the hydrogen peroxide, assuming its dissociation constant to be 10^{-12}. Except for experiment 4, a 100 per cent. error in this constant produces no significant change in the hydroxide concentration, the changes varying between 5 per cent. and 0.1 per cent. The concentrations of undissociated hydrogen peroxide are also calculated, assuming a dissociation constant of 10^{-12}. Naturally their values vary greatly with choice of constant, but their relative values are not significantly affected.

Measurements from which the extrapolations were made have a probable error of 1 to 2 per cent. Normally this error is increased to one of 5 to 10 per cent. by extrapolation. But in some experiments the error was greater. In these cases the percentage error is greater in B than in $d\ln B/dt$ when the total light given off per mole of luminol is small, and the error is chiefly in $d\ln B/dt$ when this light is great.

In experiment 1 the brightness changed so rapidly that extrapolation introduced considerable uncertainty, the uncertainty being in B rather than in $d\ln B/dt$. The curve obtained from experiment 4 was not very smooth at the beginning, and $d\ln B/dt$ should be inaccurate. But the curve being flat only a small percentage error could have been introduced in the value of B by the extrapolations. The measurements in experiment 10 did not check as well as in the other runs, and large errors are possible in B and $d\ln B/dt$. The neglect of the absorption by ferricyanide ion artificially enhances the values of B when the concentration of this ion is low (experiments 20, 21, 23, 24, 25, and 26).

In experiments 5 to 9, inclusive, a sixteen-fold change was made. The values of $d\ln B/dt$ were constant within experimental error. The values of B were approximately proportional to the concentration of luminol, but have a trend towards relatively less luminescence at the higher concentrations of luminol. This trend was greater than could be attributed to experimental error. In the preliminary analysis of our results we shall use the approximate law of proportionality between B and luminol concentration.

In experiments 10 to 17 inclusive the concentration of hydrogen peroxide was varied about a hundredfold. There was no definite trend in the values of $d\ln B/dt$. For low concentrations of hydrogen peroxide B varied approximately with the square root of the concentration, but tended to reach a constant value at high concentrations.

In experiments 18 to 21 inclusive a fourfold change of concentration of

potassium ferricyanide was made. The values of B increased approximately as the square root of the concentration and those of $d\ln B/dt$ as its first power.

In experiments 1 to 5 inclusive the hydroxide ion concentration was varied about twelve fold. The values of $d\ln B/dt$ were approximately proportional to the concentration. The values of B increased with the concentration, markedly at first, but tapering off at higher concentrations.

Experiments 22 to 27 duplicated 21, 20, and 18, except that varying quantities of potassium ferrocyanide were added. In all cases both B and $d\ln B/dt$ were decreased by potassium ferrocyanide.

Experiment 28 duplicated experiment 18 except that 7.32×10^{-3} moles per liter of sodium sulfate were added. Within experimental error the results of both runs were the same. This experiment showed that in the range of concentrations used, salt effects are negligible.

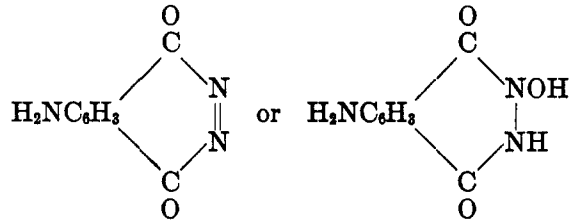
The experimental results can also be made to show the relative amounts of light given off in the oxidation of a given amount of luminol under varying conditions. This is done by drawing the curves for galvanometer deflections against distances along the reaction tube, and measuring the areas under the curves.

Variation of hydrogen peroxide from 3.5×10^{-2} M (experiment 11) to 5.48×10^{-2} M (experiment 17) changed the area from 350 to 40. Variations of potassium ferricyanide from 7.32×10^{-3} M (experiment 18) to 1.83×10^{-3} M (experiment 21) changed the area from 225 to 400. Variation of hydroxide ion from 2.82×10^{-1} M to 5.94×10^{-2} M changed the area from 84 to 400. Experiments 18, 28, 22, and 27 all had the same concentration of ferricyanide ion, but 22 and 27 were started with ferrocyanide ion present. The areas were 225, 211, 206, and 211 respectively. Hydrogen peroxide increases the chance of luminol oxidizing with luminescence, hydroxide and ferricyanide ions decrease it. Ferrocyanide ion has little or no effect on this chance. The most plausible explanation of the changes of B, $d\ln B/dt$ and the chance of luminescing is as follows.

A more and a less luminescent reaction are competing for a product of a preliminary reaction. The more luminescent oxidation is by hydrogen peroxide, the less by ferricyanide ion. Hydroxide ion either hinders the more luminescent oxidation or helps the less. The more rapid preliminary reaction is a reversible oxidation by ferricyanide ion, helped by hydroxide ion. The following scheme represents the suggested mechanism:

$$\text{Luminol} \;\underset{\xleftarrow{\text{Fe(CN)}_6^{4-}}}{\xrightarrow[\text{Fe(CN)}_6^{3-}\ \text{(fast)}]{\text{H}_2\text{O}_2\ \text{(slow)}}}\; \text{Intermediate} \;\xrightarrow[\text{Fe(CN)}_6^{3-}\ \text{(dim)}]{\text{H}_2\text{O}_2\ \text{(bright)}}\; \text{Product}$$

The intermediate is a one-unit oxidation product of luminol, that is $C_8H_6O_2N_3$, or an associated or ionized form of $C_8H_6O_2N_3$. The final substance is a two unit oxidation product of luminol,



Neglecting the slow preliminary oxidation by hydrogen peroxide, which can only result in the dim glows obtained with hydrogen peroxide alone, and the light given off in the follow reaction with ferricyanide ion, which can be no greater than in the dim glows observed with potassium ferricyanide alone, the intensity of the glow is given by the equation

$$I = SR_1 \frac{R_3}{R_3 + R_2 + R_4} \tag{1}$$

In this equation S is a proportionality constant, and R_1, R_2, R_3, and R_4 are rate functions for the preliminary oxidation by ferricyanide ion, the reverse reaction, the follow reaction with hydrogen peroxide, and the follow reaction with ferricyanide ion.

In so far as the side reaction between hydrogen peroxide and ferricyanide ion can be neglected, the rate of change of the brightness can also be expressed as a function of these same rate functions. B and $d\ln B/dt$ are I and $d\ln I/dt$ at a time when the composition is definitely known and the side reaction is most negligible; they are also expressible in terms of R_1, R_2, R_3 and R_4, so that from B or $d\ln B/dt$ the main features of these rate functions may be deduced. The accuracy of the values is not sufficiently great to elucidate such points as the way in which the hydroxide ion changes the chance of luminescence, and why the brightness is not quite proportional to the concentrations of luminol.

We shall assume that hydroxide ion reduces the chance of luminescence because the active reagent in the more luminescent follow reaction is undissociated hydrogen peroxide. These concentrations calculated for $K_a = 10^{-12}$ are given in the table. We shall call this concentration p.

The results show that R, the rate of the preliminary reaction is approximately first-order with respect to luminol, hydroxide ion, and ferricyanide ion, that R_2, the rate of the reverse of the preliminary reaction is first-order with respect to ferrocyanide ion, that R_3, the rate of the more luminescent reaction is first-order with respect to p. It is doubtful whether our values

of B are sufficiently accurate to obtain definitely the order of R_4 with respect to ferricyanide ion, and the orders of R_2, R_3, and R_4 with respect to the concentration of the intermediate. We shall assume all these to be of the first order.

$$B = S \cdot k_1 \cdot l \cdot o \cdot fi \cdot \frac{k_3 \cdot p \cdot m}{k_3 \cdot p \cdot m + k_4 \cdot fi \cdot m + k_2 \cdot fo \cdot m} \tag{2}$$

in which l, o, fi, fo, p, and m are the concentrations of luminol, hydroxide ion, ferricyanide ion, ferrocyanide ion, undissociated hydrogen peroxide, and the intermediate, respectively, and the k's are the rate constants of the reactions. This equation may be simplified to:

$$B = K_B \cdot l \cdot o \cdot fi \cdot \frac{p}{p + a \cdot fi + b \cdot fo} \tag{3}$$

in which K_B, a, and b are combinations of constants.

The constant, a, can be evaluated by using the experiments containing no initial ferrocyanide ion, and plotting calculated values of K_B against assumed values of a for all experiments. These curves pass through a small area in the diagram having values of a between 0.06 and 0.07. We have taken $a = 0.06$.

The constant b can be evaluated by putting equation (3) in the form:

$$\frac{1}{B} = \frac{p + a \cdot fi}{K_B \cdot l \cdot o \cdot fi \cdot p} + \frac{b \cdot fo}{K_B \cdot l \cdot o \cdot fi \cdot p} \tag{4}$$

The first term on the right-hand side of the equation is the reciprocal of B if no ferrocyanide ion were present. So

$$b = \frac{K_B \cdot l \cdot o \cdot fi \cdot p}{fo} \left(\frac{1}{B} - \frac{1}{B'} \right) \tag{5}$$

and b can be calculated from any two experiments which differ only in the presence and absence of initial ferrocyanide. Using experiments 18 and 22, and 20 and 23, $b = 0.154$ and 0.152 respectively. We have used $b = 0.15$.

Using the above values of a and b we have given the values of K_B in Table I.

From equation (3) it follows that:

$$\frac{d \ln B}{dt} = \frac{d \ln l}{dt} + \frac{d \ln fi}{dt} + \frac{d \ln o}{dt} + \frac{d \ln p}{dt} - \frac{d \ln (p + .06fi + .15fo)}{dt} \tag{6}$$

As total alkali and total hydrogen peroxide are in very great excess over luminol, $d\ln o$ and $d\ln p$ are negligible with respect to $d\ln l$; and as ferri-

cyanide ion is in excess over luminol, $d\ln l$ is more important than $d\ln fi$. As long as an appreciable part of the follow reaction is carried by hydrogen peroxide, $d\ln(p + .06fi + 1.5fo)$ is practically negligible. When, as at the beginning of a run, the changes are mainly due to the oxidation of luminol, the changes of fi from other reactions may be neglected, and $\frac{d\ln l}{dt} = \frac{R}{l}$, and $\frac{d\ln fi}{dt} = n \cdot \frac{R}{fi}$. R is equal to dl/dt, and n varies between one and two accordingly as the follow reaction is chiefly with hydrogen peroxide or with ferricyanide ion. As nR/fi is important only at low ferricyanide concentrations, we shall simplify by making n always equal to one, and write the equation:

$$\frac{d \ln B}{dt} = \frac{R}{l} + \frac{R}{fi} \tag{7}$$

In view of the errors introduced with extrapolation, the approximations in the equation for the brightness, the neglect of the side reaction, and the predominance of the term $d\ln l/dt$, refinements beyond this simple equation are hardly worth while.

The mechanism we have suggested for the reaction requires

$$R = R_1 \frac{R_3 + R_4}{R_3 + R_4 + R_2},$$

and if the same functions are used for $d\ln B/dt$ as for B,

$$R = K_r \cdot l \cdot o \cdot fi \frac{p + 0.06fi}{p + 0.06fi + 0.15fo} \tag{8}$$

in which K_r is the rate constant of the preliminary reaction. From equations 7 and 8 it follows that

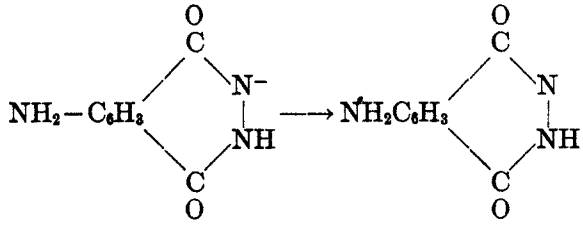
$$K_r = \frac{d \ln B}{dt} \times \frac{p + 0.06fi + 0.15fo}{o(l + fi)(p + 0.06fi)}$$

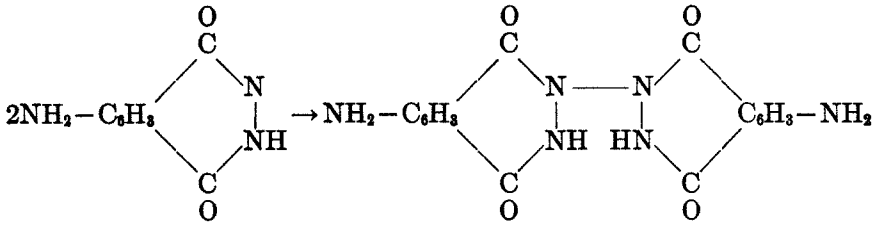
The values of K_r are given in the table.

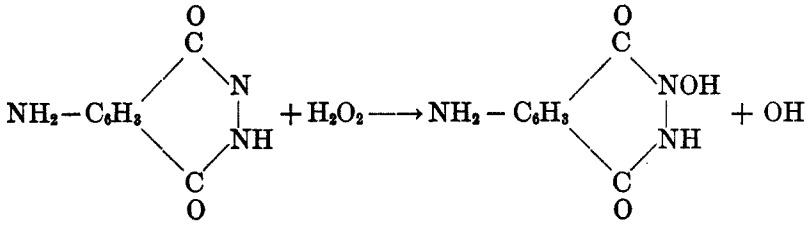
Both K_B and K_r are in general about as constant as the accuracy of measurement and calculation warrant, and this constancy strongly confirms the theory that the mechanism is essentially a preliminary reversible oxidation by ferricyanide ion, followed by a strongly luminescent oxidation by hydrogen peroxide or a dimly glowing one by ferricyanide ion.

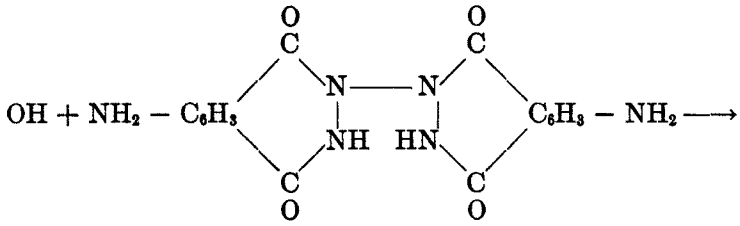
As would be expected, K_B is high when the luminol concentration is low (B not being quite proportional to l), and when the ferricyanide concen-

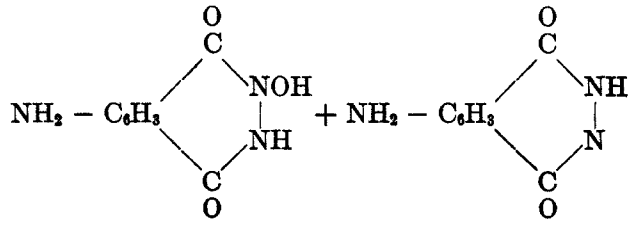
tration is low (the absorption by ferricyanide ion having been neglected). Experiments 4 and 10 in which the accuracy of determination of $d\ln B/dt$ is poor show too high values of K_r.











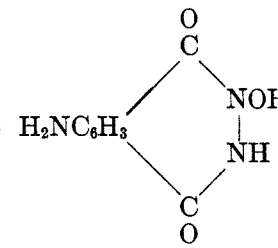
The value of K_B for experiment 1 (a dubious measurement of B) is very low. This should not be attributed to experimental error, as in combination with experiment 2 a definite trend towards low values of K_B at high hydroxide-ion concentrations is shown. This is clearly a lowering of the chance of luminescence rather than a slowing down of the reaction, as K_r for experiment 1 is normal. The effect looks as if the ion of the intermediate does not glow as readily as the undissociated molecule, and that the intermediate is an acid with a dissociation constant somewhat less than 10^{-13}, as the effect comes in as the hydroxide ion concentration increases definitely above 10^{-1} N.

The way in which the hydroxide ion comes into the rate function for the preliminary reaction cannot be attributed to the production of the first ion of luminol. A rough electrometric titration curve made for us by Mr. Jang showed that in our range of alkali concentrations the luminol is practically all present as its first ion. Mr. Jang's results point to a first dissociation constant at about 10^{-6} and no second dissociation constant greater than 10^{-13}.

We have so far neglected two important facts. The brightness is not quite proportional to the luminol concentration, and is quenched by inhibitors, with the using up of the inhibitor, a fact suggesting a chain reaction. This chain mechanism seems to be for the follow rather than the preliminary reaction.

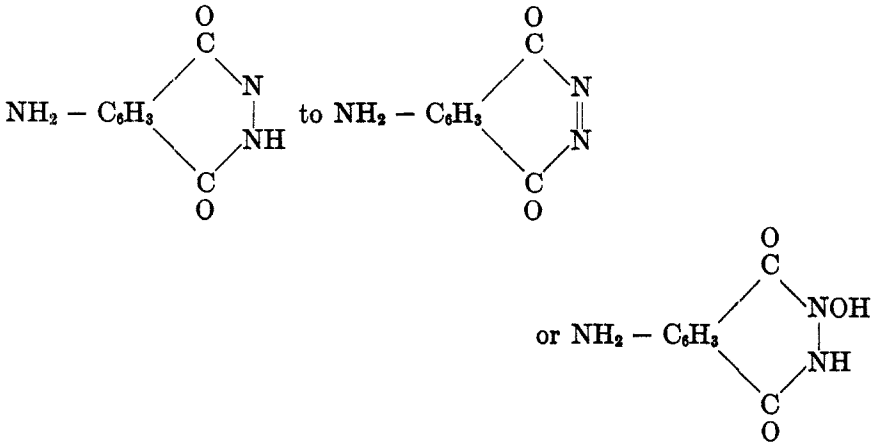
The product of the preliminary one-unit oxidation is a free radical; such are often starting points for chain mechanisms, and tend to associate. The association might well block a luminescent chain mechanism, and would be greater with increase in concentration of luminol.

The more complete mechanism (on p. 399) although speculative would fit the observations.

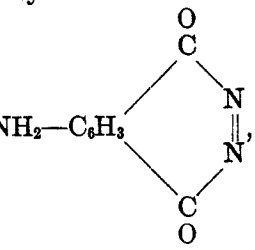
In one of these reactions, probably the last, the 

appears in an activated state, similar to that reached by luminol when it is made to fluoresce, and lose its energy as light, like but not the same as that given by fluorescing luminol.

With ferricyanide ion a similar chain could occur, but with a one-unit oxidizer such as ferricyanide ion the simple oxidation of



would be more probable, and the efficiency would be low.

We have ignored the possibility that the luminescence occurs in a reaction beyond the formation of  , as we have found the efficiency of the luminescence too great to assume a side reaction that we would have missed in our experiments on the chemical changes.

Although our interpretation is very different, our results are somewhat similar to those obtained by Zellner and Dougherty[4] in the oxidation of luminol with sodium hypochlorite. Both sets of investigators have observed the quenching effects of inhibitors, hydroxide ion, and high concentrations of luminol. The most marked difference is the alkali concentration needed to give a maximum brightness (their concentration being lower than ours); this is in large part due to the difference of oxidizing agents used, but may also be partly due to the difference in the method of observation. Had we used a static instead of a flow method we would have found our higher concentrations of alkali giving less brightness than our lower ones, owing to the much smaller efficiency of the luminescence at high concentrations of alkali. We never reached a maximum value for B, though at our highest alkali concentration our intensity half a second after the start was lower than at any other concentration of alkali.

[4] ZELLER AND DOUGHERTY, *J. Am. Chem. Soc.*, **59**, 2580 (1937).

The efficiency of luminescence.—The galvanometer deflection of the photocell 2 m. from a filtered (Corning violet No. 511, 1.5 mm. + Corning Noviol A No. 038, 2.46 mm.) mercury lamp was measured. The light band passing through the filter system was practically the same as that of the luminescence. The intensity of the mercury lamp was calibrated against a standard carbon lamp with a thermopile; knowing the area of the aperture of the photocell we were able to calculate the flow of energy through the aperture of the photocell per unit galvanometer deflection. It was 2.27×10^{-6} watts.

A reading at a point of the luminescing tube was made in our regular manner. The tube was then blackened except for 1 cm. around the point measured, the photocell was removed to 6 cm. and another galvanometer deflection was observed. The two deflections were 9.5 and 1.07. In the second position the photocell was receiving approximately 1.435×10^{-3} of the light given off by a section of the tube 1 cm. long. Hence when in an ordinary measurement a deflection of one unit is obtained, a 1 cm. section of the tube about the point measured is giving off $\frac{2.27 \times 10^{-6} \times 1.07}{1.435 \times 10^{-3} \times 9.5} = 1.78 \times 10^{-4}$ watts of light.

If one makes measurements of the light given out by all the sections of the tube along the whole tube, one would get the same result as if one stopped the flow along the tube and measured the luminescence of the one section at time intervals corresponding to the distances it would have moved with the flowing solution. So the integral under the curve of galvanometer deflections against distance along the tube is proportional to the $\int \frac{dE}{dt}\, dt$ for the little section of the tube luminescing until the luminol is completely removed. This integral is the total amount of light energy given out by the oxidation of the amount of luminol in the little section.

Several of the integrals have been evaluated and have already been mentioned in arbitrary units. These units are little unit squares with one side equal to one unit of deflection, the other side corresponding to 2 cm. along the tube. The side corresponding to one unit of deflection is equivalent to 1.78×10^{-4} watts given out by the solution in the little section in the tube. The rate of flow along the tube is 3.2 cm. per second. The cross section of the tube is .283 cm.^{2}; so one second is equivalent to 11.3 cm. along the tube, or, the other side along the arbitrary unit is equivalent to 1.77×10^{-1} seconds. The arbitrary unit of integration is 3.15×10^{-5} joules or 7.54×10^{-6} cal. of light given by the small section of the tube. The volume of this section is 2.83×10^{-1} cc., the concentration of luminol is 5.13×10^{-4} M, so one arbitrary unit is equivalent to 51.8 cal. radiated

by one mole of luminol. The integral for run 3, a very efficient one, is 400 arbitrary units, or equivalent to 2.07×10^4 cal. per mole of luminol. For the light given out in this reaction (approximately .4570 Å) a molecular quantum of light is equivalent to about 6.24×10^4 cal. per mole. Hence one molecule of luminol gives out about 3.32×10^{-1} quanta of light under the conditions of the experiment. In this reaction the fraction through the hydrogen peroxide follow reaction is .909, so that the efficiency by this path is about 36 per cent., which presumably is about the maximum efficiency obtainable in this reaction. It can be seen from our experiments that very much lower efficiencies can be obtained, as for instance in run 17, where the efficiency is (approximately) 3.3 per cent.

Errors in this calculation arise from the fact that the size of the luminescing section of the tube is not entirely negligible with respect to the distance from the photocell; that the ferricyanide in solution produces an

TABLE II

EFFECT OF TEMPERATURE VARIATION

RUN	TEMPERATURE, °C.	B	$\frac{d\ln B}{dt}$	$\int B dt$
18	20	38	1.69	225
29	10.3	35	1.39	245
30	5.3	33	1.19	260

absorption of some of the light generated; that, if the lowering of the first measurements in most of the runs indicates the necessity of assuming a steady state, the integrals arrived at on the basis of extrapolated values are slightly too high. The first of these errors is small and the other two work in opposite directions; altogether they should not produce more than 10 per cent. deviation from the values given.

The effect of temperature.—Run 18 was repeated at several temperatures obtained by altering the temperature of the supply vessels. The liquids were permitted to flow until thermal equilibrium had been attained in the reaction tube; then the measurements were started. The fluctuation of the temperature during a run was small. Experimental results and average temperatures are given in Table II.

When the concentrations are all the same, $d\ln B/dt$ is proportional to K_r. Using the equation for a bimolecular reaction, $K_r = a \cdot T^{\frac{1}{2}} \cdot e^{-E/RT}$, values of E (the heat of activation) may be calculated. For the rate of change of $\ln K_r$ with $1/T$ the slope of the best straight line through the three points in a plot of $\ln K_r$ against $1/T$ was taken. The heat of activation so

obtained was 3.2×10^3 cal. per mole. This heat of activation is that for the preliminary oxidation by ferricyanide ion.

The chance of a luminol molecule luminescing is increased on cooling. This may be due to the favoring of the follow reaction with hydrogen peroxide over that with ferricyanide, or to an increase of the chance of an activated molecule losing its energy as light rather than heat.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE DECOMPOSITION OF UNSYMMETRICAL ORGANOMERCURIC COMPOUNDS: A METHOD OF ESTABLISHING THE RELATIVE ELECTRONEGATIVITIES OF ORGANIC RADICALS. IV*

M. S. KHARASCH AND SIDNEY SWARTZ

Received August 25, 1938

The more electronegative of two organic radicals was defined by Kharasch and Flenner[1] as the one which is cloven from the mercury atom by hydrogen chloride in the following reaction:

$$RHgR' + HCl \rightarrow RHgCl + R'H$$

The present work is concerned with the determination of the relative electronegativities of the *tert.*-butyl and allyl radicals.

Cleavage of benzyl-*tert.*-butylmercury (benzylmercuritrimethylmethane) with hydrogen chloride gave only *tert.*-butylmercuric chloride. Hence, the benzyl group is more electronegative than the *tert.*-butyl group, and we are led to the interesting conclusion that substitution of a phenyl group in a methyl radical decreases the electronegativity of the methyl radical more than the substitution of two methyl groups but less than the substitution of three methyl groups in the methyl radical.

Our attempts to determine the relative electronegativity of the allyl group were stimulated by the report of Austin[2] that allyltriphenyllead was cloven almost quantitatively by hydrogen bromide to give triphenyllead bromide. Comparisons of the reactivities of their derivatives led us to anticipate that the allyl radical should have approximately the same electronegativity as the benzyl radical (known to be much less electronegative than phenyl) and that the phenyl radical should be more easily cloven from a metal than an allyl group, contrary to the results of Austin.

Allylbenzylmercury (3-benzylmercuripropene) was prepared, and cloven with hydrogen chloride. Half the mercury was recovered as benzylmercuric chloride but the state of the remainder (except that part was inorganic) was not determined.

* This paper is a condensation of the Master's thesis of Sidney Swartz, the University of Chicago, **1932**.

[1] KHARASCH AND FLENNER, *J. Am. Chem.Soc.*, **54**, 674 (1932).

[2] AUSTIN, *ibid.*, **53**, 3514 (1931).

Experiments with allylphenylmercury (allylmercuribenzene) were undertaken to lessen some experimental difficulties. Upon cleavage with hydrogen chloride, about 50 per cent. of the mercury was recovered as phenylmercuric chloride. The remainder was recovered as mercuric iodide by treating the residue with potassium iodide. This demonstrates that the other reaction product was mercuric chloride and not allylmercuric chloride. The formation of mercuric chloride was readily explained when it was found that allylmercuric chloride reacts readily with hydrogen chloride to give mercuric chloride and propylene.

The above results, if accepted without reservation, may be taken to indicate that the phenyl and allyl groups have the same relative electronegativity. Since such a conclusion is wholly inconsistent with the differences in the behavior of phenyl and allyl derivatives, we interpret the results on the basis of a new mechanism for the cleavage of the allyl group from mercury. The normal addition of halogen acids to propylene, allyl chloride, and allyl bromide shows that the proton becomes attached to the terminal carbon atom.[3] Hence the reaction of a proton with allylphenylmercury can be represented schematically as follows:

$$H_2C{:}CHCH_2HgC_6H_5 + H^+ + Cl^- \rightarrow H_3\overset{+}{C}CHCH_2HgC_6H_5 + Cl^-$$
$$\rightarrow H_3CCH{:}CH_2 + C_6H_5HgCl$$

The final products would be phenylmercuric chloride and propylene. In favor of this mechanism is the fact that hydrogen chloride easily removes the allyl group from the mercury in an allylmercury compound. The saturated organomercuric halides are stable under such conditions. That only 50 per cent. of phenylmercuric chloride was formed indicates that only half of the allylphenylmercury was cloven as indicated above and that the other half reacted by the normal mechanism to give allylmercuric chloride as a primary product. Similar interpretetion of our results with allylbenzylmercury is obvious.

Allylphenylmercury was also reacted with iodine, hydrogen chloride in benzene, and hydrogen chloride in petroleum ether. In all cases approximately 50 per cent. of phenylmercuric halide was obtained. Except in the latter experiment in which, after removal of the phenylmercuric chloride, treatment with potassium iodide yielded a small amount of allylmercuric iodide, no indication of any allylmercuric halide was observed.

A mechanism involving addition of a positive ion at the gamma carbon atom of the allyl group is also useful in explaining difficulties in the preparation of allylphenylmercury. Reaction of allylmercuric iodide with excess phenylmagnesium bromide gave a good yield of diphenylmercury.

[3] KHARASCH, KLEIGER, AND MAYO, report in preparation for publication.

With one equivalent of phenylmagnesium bromide, phenylmercuric bromide and a little oil which was probably allylphenylmercury were obtained. Reaction of phenylmercuric bromide with excess allylmagnesium bromide gave allylphenylmercury. Since the saturated unsymmetrical mercury compounds have not been observed to react with the Grignard reagents used in their preparation, and since it is presumed that the primary product in the above three reactions was allylphenylmercury, the differences can be explained by the following sequence of reactions:

$$H_2C{:}CHCH_2HgC_6H_5 + C_6H_5MgBr \rightarrow C_6H_5MgCH_2CH{:}CH_2 + C_6H_5HgBr$$

$$C_6H_5HgBr + C_6H_5MgBr \rightarrow (C_6H_5)_2Hg + MgBr_2$$

$$H_2C{:}CHCH_2HgC_6H_5 + C_3H_5MgBr \rightarrow C_3H_5MgCH_2CH{:}CH_2 + C_6H_5HgBr$$

$$C_3H_5MgBr + C_6H_5HgBr \rightarrow C_3H_5HgC_6H_5 \text{ (regenerated)} + MgBr_2$$

It is obvious, therefore, that cleavage with hydrogen chloride of unsymmetrical organomercuric compounds of the type R-Hg-allyl is not a valid method for comparing the electronegativities of the radicals in question.

EXPERIMENTAL

Analysis for mercury.—The method of analysis for mercury was that described by Koten and Adams.[4] It is not applicable to compounds containing halogens.

Preparation of organomercuric halides.—The two following preparations are new.

tert.-Butylmercuric chloride was prepared from an ethereal solution of *tert.*-butylmagnesium chloride and mercuric chloride. The magnesium compounds were removed on treatment of the mixture with ice and 1–2% sulfuric acid and the *tert.*-butylmercuric chloride was crystallized from alcohol. On heating in an oil bath, a sample sublimed at 124°, but when capillaries containing samples were dipped into previously heated baths, the sublimation point was found to be 131°. The chloride was more stable than the corresponding bromide.

Diallylmercury was prepared from allylmercuric iodide and two equivalents of allylmagnesium bromide in ether solution. After washing with water in the absence of acid and removal of the solvent, a halogen-free oil was obtained. It reacted with one equivalent of mercuric chloride to give allylmercuric chloride quantitatively. The oil gave allylmercuric chloride with hydrogen chloride in alcohol solution but the yield was not quantitative, even though water was added immediately to prevent decomposition of the product. In each case the allylmercuric chloride melted at 110°. Its composition was proved by its reaction with potassium iodide to give the known allylmercuric iodide of m.p. 135°.

Preparation and cleavage of unsymmetrical mercury compounds.—The unsymmetrical mercury compounds were prepared from the organomercuric halides and excess organomagnesium halide as indicated in the table. The products were oils.

[4] KOTEN AND ADAMS, *J. Am. Chem. Soc.*, **46**, 2764 (1924).

When the unsymmetrical organomercuric compounds treated with mercuric chloride, approximately the calculated quantities of the two organomercuric chlorides were obtained in each case, except that allylbenzylmercury gave a mixture which could not be separated because of similar solubilities. The above procedures and the cleavage with alcoholic hydrogen chloride have been described by Kharasch and Flenner.[1] In this work the reaction mixtures from the cleavage reactions were

TABLE

PREPARATION AND PROPERTIES OF UNSYMMETRICAL MERCURY COMPOUNDS

UNSYMMETRICAL MERCURY COMPOUNDS			CLEAVAGE PRODUCTS
Prepared from	Hg content (%)		
	Calc'd	Found	
$C_6H_5CH_2HgCl$, *tert.*-Bu-MgCl	57.52	57.31 57.26	*tert.*-Bu-HgCl[a]
$C_6H_5CH_2HgCl$, Allyl-MgBr	60.24	59.30 59.22	50% $C_6H_5CH_2$-HgCl
C_6H_5HgBr, Allyl-MgBr	62.94	62.58 63.39	50% C_6H_5-HgCl, 50% $HgCl_2$

[a] The melting point, 123°, was lowered by addition of benzylmercuric chloride but not by addition of known *tert.*-butylmercuric chloride, of which the melting point was not lowered by admixture with the cleavage product.

diluted with water to precipitate the organomercuric chloride instead of being evaporated to dryness.

SUMMARY

1. Some new organomercuric compounds of the types RHgCl and RHgR' have been prepared.

2. The benzyl radical is more electronegative than the *tert.*-butyl radical.

3. Anomalous results have been obtained in the determination of the relative electronegativity of the allyl radical and an interpretation of such results is presented.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MARYLAND AND THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE DECOMPOSITION OF UNSYMMETRICAL ORGANOMERCURIC COMPOUNDS: A METHOD OF ESTABLISHING THE RELATIVE ELECTRONEGATIVITIES OF ORGANIC RADICALS. V*

M. S. KHARASCH, R. R. LEGAULT, AND WILLARD R. SPROWLS

Received August 25, 1938

INTRODUCTION

The more electronegative of two organic radicals was defined by Kharasch and Flenner[1] as the one which is cloven from the mercury atom by hydrogen chloride in the following reaction:

$$RHgR' + HCl \rightarrow RHgCl + R'H$$

Reference was also made to the fact that the replacement of a hydrogen atom by a chlorine atom in the phenyl radical decreases the electronegativity of that radical and that for the three positions in the ring the decrease is greatest for the *meta* and least for the *para* position. A tentative hypothesis was advanced that groups capable of causing direct replacement of a hydrogen atom in a benzenoid compound decrease the electronegativity of the initial radical. A subsequent paper[2] showed that this rule holds for the *m*-fluorophenyl radical and the three bromophenyl radicals, but that the *p*-fluorophenyl radical is slightly more electronegative than the phenyl radical. The present paper extends this hypothesis to the 2,4- and 2,5-dichlorophenyl radicals.

DISCUSSION

The results of the present work are summarized in Table I, which lists the radicals newly placed. Our results show that the 2,4-dichlorophenyl radical is less electronegative than *m*-chlorophenyl, and more electronegative than benzyl, and that 2,5-dichlorophenyl is less electronegative than *m*-chlorophenyl and more electronegative than methyl. Another experiment which shows that *m*-chlorophenyl is more electronegative than

* This paper is a condensation of the Master's theses of R. R. Legault, the University of Maryland, **1928**, and of Willard R. Sprowls, the University of Chicago, **1935**.

[1] KHARASCH AND FLENNER, *J. Am. Chem. Soc.*, **54**, 674 (1932).

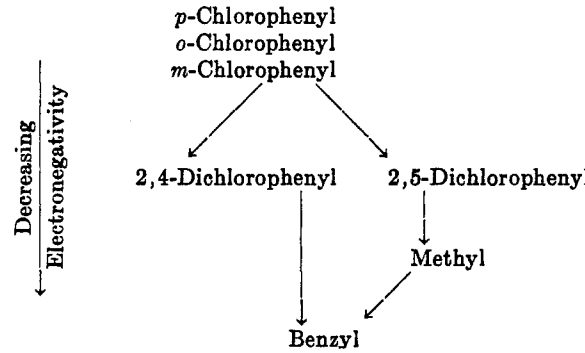
[2] KHARASCH, PINES, AND LEVINE, J. ORG. CHEM., **3**, 347 (1938).

benzyl merely confirms the position of these two radicals. Other cleavage reactions carried out in the present work show that the 2,4- and 2,5-dichlorophenyl radicals are less electronegative than the phenyl radical, and that the former is also less electronegative than *o*-chlorophenyl, but these serve only to confirm previous work which compared the phenyl and chlorophenyl radicals. Previous work also showed that methyl is more electronegative than benzyl.

The present work furnishes further evidence for the rule of Kharasch and Flenner that direct substitution decreases the electronegativity of the phenyl radical. The introduction of a second chlorine atom in the aromatic nucleus decreases still more the electronegativity of the chlorophenyl

TABLE I

RELATIVE ELECTRONEGATIVITIES OF SOME DICHLOROPHENYL RADICALS



radicals. It is also of interest that all the substituted aromatic radicals thus far tested are more electronegative than any of the aliphatic radicals.

EXPERIMENTAL

Analysis for mercury.—Three methods were used for the determination of mercury in its organic compounds. They have been described by Kharasch and Flenner,[1] Kharasch, Pines, and Levine[2] (electrolytic method), and Whitmore and Sobatski.[3] Analysis for chlorine was made by the Carius method.

Preparation of organomercuric chlorides.—(Summarized in Table II.) Chlorophenylmercuric acetates were prepared from the chloroanilines through the sulfinic acids according to the procedure described by Hanke,[4] with the following modifications. 2,4,6-Trichloroaniline was diazotized according to the method of Chattaway, Deighton, and Adair[5] instead of according to that of Hanke. The large excess

[3] WHITMORE AND SOBATZKI, *J. Am. Chem. Soc.*, **55**, 1128 (1933).

[4] HANKE, *ibid.*, **45**, 1321 (1923).

[5] CHATTAWAY, DEIGHTON, AND ADAIR, *J. Chem. Soc.*, **1931**, 1925.

(about 15 moles) of sulfur dioxide required for all these preparations was weighed out in a trap cooled with solid carbon dioxide, and then passed into the cooled (ice and salt) solution of the diazonium salt under a pressure of two atmospheres with agitation. We have found that only one-fifth the quantity of catalytic copper recommended by Hanke is necessary for the satisfactory decomposition of the resulting solution. The separation of the benzenesulfinic acid from the catalytic copper by solution in aqueous sodium carbonate was effected in the case of the 2,4-dichloro derivative, but with the 2,5-dichloro and 2,4,6-trichloro derivatives the separation was more easily carried out with alcohol because of the low solubility of the sodium salts. The arylmercuric acetates in acetic acid solution were converted to arylmercuric chlorides by addition of 10% aqueous sodium chloride. The chlorides precipitated and were crystallized from alcohol.

TABLE II

PREPARATION AND PROPERTIES OF ORGANOMERCURIC CHLORIDES

R IN RHgCl	YIELD (% THEORETICAL)	M.P., °C.	MERCURY CONTENT (%)[a]	
			Calc'd	Found
2,4-$Cl_2C_6H_3$—[b]	50	196	52.51	52.72
2,5-$Cl_2C_6H_3$—[c]		205	52.51	
2,4,6-$Cl_3C_6H_2$—	35	184	48.15	48.6
$C_6H_5CH_2$—	85	104	61.33	
C_6H_5—[d]		250–1	64.06	
o-ClC_6H_4—		147	57.71	
m-ClC_6H_4—		208	57.71	
CH_3—		170	79.89	

[a] By electrolytic method.

[b] One and two-tenths grams of this compound was treated with 0.5 g. of bromine in 10% aq. KBr solution. The product was 1-bromo-2,4-dichlorobenzene; m.p. 27° (recorded m.p. 25°).

[c] Treatment as above gave 1-bromo-2,5-dichlorobenzene; m.p., 35–6° (recorded m.p. 35°).

[d] This and succeeding derivatives are listed only to facilitate identification of cleavage products in Table III.

Benzylmercuric chloride was prepared from benzylmagnesium chloride and mercuric chloride by the method of Hilpert and Grüttner.[6]

Preparation, properties, and cleavage of unsymmetrical mercury compounds.— (Summarized in Table III.) The unsymmetrical mercury compounds were usually prepared by the addition of the organomercuric chloride to 2.5 equivalents of Grignard reagent in ether as described by Kharasch and Flenner.[1] Adding the Grignard reagent to an ether solution of organomercuric chloride gave better results in the preparation of phenyl-2,4-dichlorophenylmercury. In the preparation of benzyl-2,4-dichlorophenylmercury, benzylmagnesium chloride was added to a suspension (instead of a solution) of 2,4-dichlorophenylmercuric chloride in ether; the resulting unsymmetrical compound had a high mercury content, indicating the presence of

[6] HILPERT AND GRÜTTNER, *Ber.*, **48**, 913 (1915).

TABLE III

PREPARATION, PROPERTIES, AND CLEAVAGE OF UNSYMMETRICAL MERCURY COMPOUNDS

R AND R' IN RHgR' [a]	M. p.	MERCURY CONTENT (%)			HCl CLEAVAGE PRODUCTS		
		Calc'd	Found	Method [b]	Hg found (%)	M. p., °C.	Principal Constituent
$2,4\text{-Cl}_2C_6H_3$— C_6H_5—		47.35	47.30 47.19	K. & F.		180–5 [c]	$2,4\text{-Cl}_2C_6H_3HgCl$
$2,4\text{-Cl}_2C_6H_3$— $o\text{-ClC}_6H_4$—	152–62	43.80	43.3 43.27	Elec.	52.68 52.09	182–4	$2,4\text{-Cl}_2C_6H_3HgCl$
$2,4\text{-Cl}_2C_6H_3$— $m\text{-ClC}_6H_4$—	136–42	43.80 (Cl, 23.22)	43.16 42.75 43.28 (Cl, 22.75)	Elec.	53.13 52.21 53.66	158–66 [d] 201–4	$2,4\text{-Cl}_2C_6H_3HgCl$
$2,4\text{-Cl}_2C_6H_3$— $C_6H_5CH_2$—	100–47	45.84	48.39	W. & S.	59.09	106–10	$C_6H_5CH_2HgCl$
$2,5\text{-Cl}_2C_6H_3$— C_6H_5—	120° (Softens at 95°)	47.35	47.06 47.21	K. & F.		200–3	$2,5\text{-Cl}_2C_6H_3HgCl$
$2,5\text{-Cl}_2C_6H_3$— $m\text{-ClC}_6H_4$—	134–8	43.80	43.75	Elec.	53.63 53.04	193	$2,5\text{-Cl}_2C_6H_3HgCl$
$2,5\text{-Cl}_2C_6H_3$— CH_3—	75–80	55.4	55.0 55.1	K. & F.		160 [e]	CH_3HgCl
$C_6H_5CH_2$— $m\text{-ClC}_6H_4$—	Oil					100	$C_6H_5CH_2HgCl$

[a] The unsymmetrical mercury compound was prepared from the organomercuric chloride of the first-named radical and the organomagnesium halide (from aryl bromide, benzyl chloride, or methyl iodide) of the last-named radical.

[b] K. & F., W. & S., and Elec. indicate the Kharasch and Flenner, Whitmore and Sobatzki, and electrolytic methods respectively.

[c] Not lowered by addition of known $2,4\text{-Cl}_2C_6H_3HgCl$.

[d] Melting points of cleavage products from two different preparations are listed.

[e] Raised to 165° by admixture with CH_3HgCl; lowered by admixture with $2,5\text{-Cl}_2C_6H_3HgCl$.

unchanged organomercuric chloride. Several preparations of some of the unsymmetrical compounds were made, but data for only the best preparations are listed.

Cleavages of the unsymmetrical mercury compounds with mercuric chloride and hydrogen chloride were carried out according to the methods of Kharasch and Flenner. On treatment with mercuric chloride phenyl-2,4- and phenyl-2,5-dichlorophenylmercury and methyl-2,5-dichlorophenylmercury gave mixtures from which the expected organomercuric chlorides were isolated. Mixtures obtained from some of the other unsymmetrical compounds could not be resolved. After cleavage with hydrogen chloride, the products obtained by evaporation of the solvents were not recrystallized but were usually washed with ligroïn.

SUMMARY

1. Some new organomercuric compounds of the type RHgCl and RHgR′ have been prepared.

2. The 2,4-dichlorophenyl radical is less electronegative than *m*-chlorophenyl radical, and more electronegative than the benzyl radical.

3. The 2,5-dichlorophenyl radical is less electronegative than the *m*-chlorophenyl radical, and more electronegative than the methyl radical.

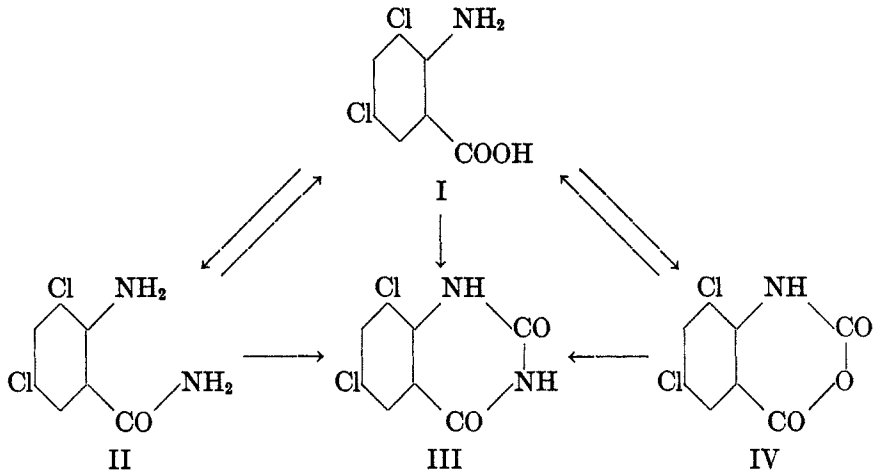
[CONTRIBUTION FROM THE CHEMICAL LABORATORY, CASE SCHOOL OF APPLIED SCIENCE]

6,8-DICHLOROBENZOYLENE UREA, AND THE INTERACTION OF 5,7-DIHALOGEN ISATOIC ANHYDRIDES WITH AMMONIA.—A NEW REAGENT FOR SODIUM

FRED E. SHEIBLEY

Received August 27, 1938

During the course of a series of experiments[1] designed to show the positions of the nitro groups in 6,8-dinitrobenzoyleneurea, it was observed that the key-compound of the demonstration, 6,8-dibromobenzoyleneurea, forms a sodium salt which is sparingly soluble in water and which can be used as a test for sodium in the presence of the other alkali metals. These results suggested that an analogous dichlorobenzoyleneurea might possess similar properties, and an investigation of this point was undertaken.



3,5-Dichloroanthranilic acid (I), like the corresponding dibromo compound,[1] failed to react with aqueous isocyanic acid; on fusing it (I) with urea, however, 6,8-dichlorobenzoyleneurea (III) and appreciable amounts of 3,5-dichloro-2-aminobenzamide (II) were obtained. Attempts to prepare 6,8-dichlorobenzoyleneurea by heating benzoyleneurea with sulfuryl chloride during fourteen hours, and by direct chlorination in

[1] SHEIBLEY AND TURNER, *J. Am. Chem. Soc.*, **55**, 4918 (1933).

hot glacial acetic acid solution were unsuccessful, the benzoyleneurea being apparently unchanged. The amide (II) reverts to 3,5-dichloroanthranilic acid (I) on alkaline hydrolysis, and is identical with the 3,5-dichloro-2-aminobenzamide prepared by Franke[2] from *o*-aminobenzamide and sulfuryl chloride. Phenyl isocyanate and benzoic acid are known to react with loss of carbon dioxide to form benzanilide,[3] and it is possible that the dichloro amide (II) produced in the fusion experiments is formed by an analogous splitting of carbon dioxide between dichloroanthranilic acid and isocyanic acid; but according to J. M. Das-Gupta[4] aromatic monobasic acids do not give amides when fused with urea or heated with it in various solvents. 3,5-Dichloroanthranilic acid, therefore, was heated with urea in glacial acetic acid and in glycerol as recommended[5] for aliphatic acids and phthalic anhydride, but the formation of (II) under these conditions was not realized. Benzoyleneurea is sometimes prepared by fusing anthranilic acid with urea, but *o*-aminobenzamide has not been detected in the melt,[6] and hence cannot be considered an intermediate product, despite the fact that it does give benzoyleneurea on fusion with urea.[7] 3,5-Dichloro-2-aminobenzamide (II), fused with urea at 160–165°, gave 6,8-dichlorobenzoyleneurea (III) in 80 per cent. yield; a comparison of this result with the 67 per cent. yield of the same product (III), obtained in a dichloroanthranilic acid fusion conducted at 160–165°, and the 48 per cent. yield from a similar fusion conducted at 140°, indicates that in this case the dichloro amide (II) is probably a partial intermediate. The ready formation of uramino compounds on reaction of aminobenzoic acids and their amides with urea or isocyanic acid is well known, and the ease of conversion of the ortho isomers into benzoylene ureas affords an explanation of these fusion reactions which applies equally well to the direct acid fusions and those in which an intermediate amide may be involved.[4, 6, 8]

6,8-Dichlorobenzoyleneurea (III) is a high-melting substance with properties analogous to those of the 6,8-dibromo derivative.[1] It dissolves in aqueous potassium hydroxide to give solutions which yield a crystalline precipitate with solutions of sodium salts but are not affected by salts of lithium, rubidium, or cesium. 6,8-Dibromobenzoyleneurea requires lithium hydroxide, which tends to absorb atmospheric carbon dioxide and precipitate lithium carbonate, for its solution, and is altogether a less

[2] FRANKE, *J. prakt. Chem.*, [2], **44**, 431 (1891).
[3] DIECKMANN AND BREEST, *Ber.*, **39**, 3052 (1906).
[4] DAS-GUPTA, *J. Indian Chem. Soc.*, **10**, 117, 169 (1933).
[5] Reference 4, pp. 118, 123.
[6] BOGERT AND SCATCHARD, *J. Am. Chem. Soc.*, **41**, 2056 (1919).
[7] ABT, *J. prakt. Chem.*, [2], **39**, 141 (1889).
[8] JACOBS AND HEIDELBERGER, *J. Am. Chem. Soc.*, **39**, 2437 (1917).

convenient reagent for sodium testing than the dichloro compound. Sodium 6,8-dichlorobenzoyleneurea, precipitated from solutions of the potassium and lithium salts, is a sesquihydrate, in contrast to the previously described sodium 6,8-dibromobenzoyleneurea which is a monohydrate.

In 1886 Robert Dorsch[9] oxidized 5,7-dichloroisatin, prepared by direct chlorination of isatin, with chromic anhydride and obtained 5,7-dichloroisatoic anhydride. This compound he treated with aqueous ammonia and thus arrived at a product which melted at 284° and was assigned the constitution of 3,5-dichloro-2-aminobenzamide. Five years later Franke[2] prepared this amide by the action of sulfuryl chloride on *o*-aminobenzamide; he observed a melting point of 175° and discussed the inconsistency with Dorsch's measurement. Since 5,7-dichloroisatin can be prepared from tetrachloroindigo,[10] and Kolbe[11] obtained isatoic anhydride directly from indigo without isolating the intermediate isatin, 5,7-dichloroisatoic anhydride (IV) was prepared by direct oxidation of tetrachloroindigo with chromic anhydride. The product (IV) possesses the properties described by Dorsch[9] for this compound, and on treatment with ammonium hydroxide yields a substance which melts at 285° and is identical with 6,8-dichlorobenzoyleneurea (III) prepared by the fusion methods. 5,7-Dichloroisatoic anhydride (IV) was also prepared by heating 3,5-dichloroanthranilic acid (I) with ethyl chlorocarbonate, a method which is useful for the preparation of isatoic anhydride.[12] The product (IV), obtained in this manner, is identical with that prepared from tetrachloroindigo and exhibits the same behavior with ammonium hydroxide. By oxidation of tetrabromoindigo the corresponding 5,7-dibromoisatoic anhydride was likewise prepared. Dorsch[13] described this compound and apparently obtained 3,5-dibromo-2-aminobenzamide when he treated it with aqueous ammonia, but in the present experiments 6,8-dibromobenzoyleneurea[1] was produced. A comparison of the melting points recorded by Dorsch[9] for the mono- and dihalogen derivatives of this series indicates that in general the isatoic anhydride has a melting point 30–60° higher than that of the acid, which in turn melts at a temperature approximately 30° above the melting point of the amide. The value of 284° recorded for the dichloro amide is the only anomaly; undoubtedly the product with which this observation was made was 6,8-dichlorobenzoyleneurea (III) and not 3,5-dichloro-2-aminobenzamide (II).

[9] DORSCH, *J. prakt. Chem.*, [2], **33**, 51 (1886).

[10] GRANDMOUGIN AND SEYDER, *Ber.*, **47**, 2366 (1914); ASINGER *Monatsh.*, **63**, 389 (1933).

[11] KOLBE, *J. prakt. Chem.*, [2], **30**, 87 (1884).

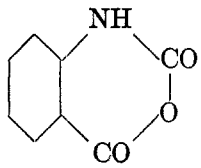
[12] NIEMENTOWSKI AND ROZAŃSKI, *Ber.*, **22**, 1673 (1889).

[13] Reference 9, p. 47.

When 5,7-dichloroisatoic anhydride (IV) is heated with ammonium hydroxide 6,8-dichlorobenzoyleneurea (III) and 3,5-dichloroanthranilic acid (I) are produced in the proportions required by the equation:

$$\underset{\text{Dichloroisatoic anhydride}}{5C_8H_3O_3NCl_2} + 2NH_3 + H_2O \rightarrow \underset{\text{Dichlorobenzoylene urea}}{2C_8H_4O_2N_2Cl_2} + \underset{\text{Dichloroanthranilic acid}}{3C_7H_5O_2NCl_2} + 3CO_2$$

5,7-Dibromoisatoic anhydride behaves in the same manner. Just how this change occurs is not clear; 3,5-dichloro-2-aminobenzamide was not affected by hot aqueous ammonium carbonate, and a mixture of the amide and dichloroisatoic anhydride failed to react when suspended in hot, very dilute sodium hydroxide solution.



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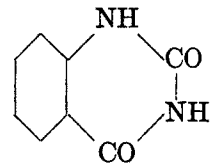

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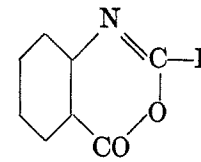
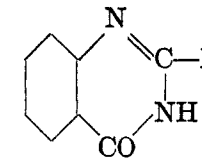


VII



VIII

Isatoic anhydride (V) is a derivative of 3,1,4-benzoxazine, and the ready conversion by ammonia of the alkyl benzoxazones (VII) into the corresponding quinazolones (VIII),[14] sometimes quantitatively, suggests that a quantitative conversion of (V) into benzoyleneurea (VI) on treatment with ammonia would be a normal reaction; and that the actual conversion of (V), under these conditions, into *o*-aminobenzamide[15] is anomalous. The formation of benzoyleneureas by the action of ammonia on isatoic anhydrides has never been reported, although a direct conversion by ammonia of isatoic diazide into benzoyleneurea was observed recently.[16]

EXPERIMENTAL

3,5-Dichloroanthranilic acid (*I*) was prepared by direct chlorination,[17] and by treating anthranilic acid hydrochloride with sulfuryl chloride.[18] The compound is conveniently crystallized from alcohol, but the recovery is poor, and the material in the mother liquors is not easily reclaimed due to the concentration of impurities. Crystallization from benzene is efficient provided the initial material is not too impure. The crude products recovered from mother liquors were dissolved in dilute ammonium hydroxide, and the solutions were boiled until the ammonia was driven off and dichloroanthranilic acid, suitable for recrystallization purposes, began to crystallize.

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[14] BEILSTEIN, "Handbuch der organischen Chemie," 4th ed., Vol. 27, p. 207.
[15] KOLBE, *J. prakt. Chem.*, [2], **30**, 475 (1884).
[16] DARAPSKY AND GAUDIAN, *ibid.*, [2], **147**, 51 (1936).
[17] ELION, *Rec. trav. chim.*, **44**, 1106 (1925).
[18] ELLER AND KLEMM, *Ber.*, **55**, 222 (1922).

The pure acid separates from dilute alcohol in sheaves of small white needles, m.p. 233–233.5° (corr.). It is soluble in ether and insoluble in hot water.

6,8-Dichlorobenzoyleneurea (III) from 3,5-Dichloroanthranilic acid (I).—Three grams each of urea and 3,5-dichloroanthranilic acid were mixed and fused in a flask equipped with a loose-fitting cork stopper carrying a vertical exit tube, and placed in an oil bath at 140°. After periods of heating which varied from four to eight hours, the mass was allowed to cool, was powdered, and extracted with 50 cc. of hot 5% aqueous sodium hydroxide solution in order to remove unchanged acid and any high-melting, alkali-soluble materials. The alkali-insoluble residue, consisting of 3,5-dichloro-2-aminobenzamide and sodium 6,8-dichlorobenzoyleneurea, was collected, washed with water, and suspended in hot dilute sulfuric acid. The resulting acid-insoluble mixture of dichloroaminobenzamide and dichlorobenzoyleneurea was in turn collected, washed with water, and extracted successively with three 50-cc. portions of hot 5% potassium hydroxide solution, each extract being subsequently diluted with 50 cc. of water, reheated, allowed to settle, and decanted from the insoluble material before proceeding with the next extraction. The extracts and insoluble material were combined, reheated to dissolve any dichloroaminobenzamide and potassium dichlorobenzoyleneurea which tended to crystallize, and filtered hot

TABLE I

YIELDS OF CRUDE PRODUCTS FROM FUSIONS OF 3,5-DICHLOROANTHRANILIC ACID AND UREA

TEMPERATURE, °C.	TIME, HOURS	DICHLOROBENZOYLENEUREA, G.	DICHLOROAMINOBENZAMIDE, G.	DICHLOROANTHRANILIC ACID, G.
140	8	0.90	1.21	0.15
140	8[a]	1.63	1.1	0.2
160–165	4	2.25	0.32	0.16

[a] Two heating periods: 5 hours + 3 hours.

from the undissolved residue of crude dichloroaminobenzamide. The clear, colorless to yellow filtrate was acidified with dilute sulfuric acid, and the resulting yellow precipitate was collected, washed, and again extracted with 50 cc. of hot 5% sodium hydroxide. The insoluble residue of sodium salt was removed by filtration, washed with water, and suspended in hot dilute sulfuric acid to give crude dichlorobenzoyleneurea which was collected, washed, and dried. Acidification of the sodium hydroxide filtrate yielded a precipitate of dichloroanthranilic acid, resulting principally from alkaline hydrolysis of the amide.

The yields of crude products varied considerably with the temperature and duration of heating. Some comparable results are given in Table I.

6,8-Dichlorobenzoyleneurea (III) is sparingly soluble in the usual solvents, 1 g. requiring about 135 cc. of boiling alcohol to dissolve it. It is best crystallized from hot glycol or boiling alcohol, and separates from its solutions in the latter solvent in fine needles, usually of a pale yellow color, m.p. 296° (corr.), after sintering and undergoing an apparent change of crystalline form in the neighborhood of 280°.

Anal. Calc'd for $C_8H_4Cl_2N_2O_2$: C, 41.59; H, 1.75; Cl, 30.69.

Found: C, 41.80; H, 2.07; Cl, 31.11.

The color of this product is apparently due to traces of a yellow impurity, small amounts of which remained as an insoluble residue when the crude dichlorobenz-

oyleneurea was dissolved in alcohol. This substance sublimes in yellow needles which are not melted at 300°.

3,5-Dichloro-2-aminobenzamide (II).—The crude amide obtained from the fusion preparations was dissolved in hot alcohol, any insoluble residue of the yellow substance described above being removed by filtration. This compound has marked crystallizing power, and separates readily from its alcoholic solutions in white, glistening, prismatic needles, m.p. 182.5° (corr.). On warming with aqueous potassium hydroxide solution for six hours, the amide was slowly hydrolyzed to 3,5-dichloroanthranilic acid, as described by Franke.[2]

A specimen of 3,5-dichloro-2-aminobenzamide, prepared by the action of sulfuryl chloride on *o*-aminobenzamide at room temperature, and crystallized from benzene, following the procedure of Franke,[2] did not alter the melting point of the fusion product already described, and proved to be identical with the latter in all respects.

The white acicular sublimates which invariably deposited on the upper walls of the flasks during the urea-dichloroanthranilic acid fusions were crystallized from hot water, dilute alcohol, or benzene and found to consist of fairly pure dichloroaminobenzamide. The pure amide, however, shows no tendency to sublime when heated.

The solutions of all three of these compounds, the amide, the acid, and the benzoyleneurea, in alcohol and in aqueous caustic alkalies, exhibit a pale bluish-violet fluorescence, enhanced by impurities, in reflected light.

6,8-Dichlorobenzoyleneurea (III) from 3,5-Dichloro-2-aminobenzamide (II).—A mixture of 1 g. of 3,5-dichloro-2-aminobenzamide and 1 g. of urea was placed in the apparatus already described for the dichloroanthranilic acid-urea fusions, and heated at 160–165° during four hours. The melt gradually solidified throughout the heating period, after which it was allowed to cool, was powdered, and extracted with hot solutions of sodium and potassium hydroxides, following the procedure outlined above. A small amount of dichloroanthranilic acid (0.02 g.) was recovered, the usual acicular deposit of sublimed amide being identified by crystallization from hot water and comparison with an authentic specimen. The yield of crude dichlorobenzoyleneurea was about 0.9 g.; it was crystallized from alcohol and did not depress the melting point of a corresponding preparation from the acid.

Anal. Calc'd for $C_8H_4Cl_2N_2O_2$: Cl, 30.69; N, 12.13.
Found: Cl, 30.82; N, 11.84, 12.07.

6,8-Dichlorobenzoyleneurea as a reagent for sodium.—Like its dibromo analog,[19] 6,8-dichlorobenzoyleneurea dissolves in aqueous lithium hydroxide to give solutions which yield white crystalline precipitates with solutions of sodium salts. Unlike the dibromo compound, however, dichlorobenzoyleneurea is readily soluble in warm potassium hydroxide to solutions which crystallize comparatively slowly on standing and are more useful for purposes of sodium testing, since the possibility of lithium carbonate precipitation is eliminated. These solutions are not precipitated by salts of potassium and lithium respectively, and remain clear when solutions of cesium and rubidium chlorides, or mixtures thereof, are added. Mixtures containing sodium chloride give the characteristic precipitate.

A reagent was prepared by dissolving 0.1 g. of potassium hydroxide and 0.05 g. of dichlorobenzoyleneurea in 10 cc. of water, warming, and allowing to cool. Equal volumes of this reagent and known solutions were mixed and observed, precipitation sometimes being incited by rolling the tubes between the hands. Results of comparative precipitation tests are outlined in Table II.

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[19] Reference 1, p. 4921.

With ammonium chloride the reagent instantly gives a white precipitate of dichlorobenzoyleneurea.

Sodium 6,8-Dichlorobenzoyleneurea.—Two-tenths gram of potassium hydroxide and 0.15 g. of dichlorobenzoyleneurea were dissolved in 40 cc. of hot water; the solution was allowed to cool, was filtered, and 25 cc. of 0.5*M* sodium chloride added with stirring. Precipitation began within one-half minute. After standing for one-half hour the precipitate was collected, washed with water, and dried at 40° during two hours. Yield: 0.14 g. of a white micro-crystalline powder.

The yields of the sodium salt were generally equal to the weight of the dichlorobenzoyleneurea taken. Precipitation from hot solutions, and prolonged drying (25 hours) at 40° did not alter the composition of the product. When crude, uncrystallized dichlorobenzoyleneurea was used an impure sodium salt resulted. The analyses were made with five independent preparations of which the first two were precipitated from solutions in lithium hydroxide.

Anal. Calc'd for $C_8H_3Cl_2N_2NaO_2 \cdot 1\frac{1}{2}H_2O$: Na, 8.21. Found: Na, 8.10, 8.22; 8.20, 8.21, 8.20.

Attempts to determine the total water of hydration by extended drying were unsuccessful. At 230° a drying curve finally passed through the theoretical value

TABLE II

PRECIPITATION OF SODIUM WITH 6,8-DICHLOROBENZOYLENEUREA

SALT	MOLARITY	REMARKS
Sodium chloride	0.5	Heavy white precipitate immediately.
Sodium chloride	0.2	Precipitate within ten minutes.
Sodium chloride	0.1	Precipitate within one hour, later becoming voluminous.
Sodium chloride	0.05	Trace of precipitate after four hours or later.
Rubidium chloride	1.0	Behaves like 0.1*M* sodium chloride.
Cesium chloride	1.0	No precipitate.

(9.65% H_2O), but the weight of the sample did not remain constant at this point. At 125° the weight became constant after a loss of 6.45%, a value agreeing closely with the theoretical (6.43%) for two thirds of the total water present, *i.e.*, for 1 H_2O.

5,7-Dichloroisatoic anhydride (IV) from 3,5-dichloroanthranilic acid (I).—One gram of 3,5-dichloroanthranilic acid and 3 cc. of ethyl chlorocarbonate were mixed in an acetylating flask and gently refluxed over a small flame during 12–14 hours. The reaction mixture was allowed to cool, diluted with alcohol, and the insoluble, gray, sandy solid (0.8 g.) was removed by filtration, washed with alcohol, and dried. This product is a mixture of dichloroisatoic anhydride and a small amount of an unidentified substance which is soluble in benzene. The material was extracted with about 40 cc. of boiling benzene, and the cold extract was separated from the undissolved residue of dichloroisatoic anhydride by filtration. The residue was dissolved in a boiling mixture of acetone and alcohol (1:1), and the resulting solution was filtered and evaporated on a water bath to incipient crystallization. From solutions prepared in this manner, 5,7-dichloroisatoic anhydride separates in glassy, pale-yellow prisms, m. p. 261° (corr.) with evolution of gas but without darkening of the melt. The compound dissolves easily in warm, dilute sodium hydroxide to solutions which yield precipitates of dichloroanthranilic acid on acidification.

Anal. Calc'd for $C_8H_3Cl_2NO_3$: Cl, 30.56. Found: Cl, 30.58.

The unidentified substance mentioned above separated from its solutions in benzene, amyl alcohol, or acetone-alcohol mixtures in white pasty or chalky masses melting in the neighborhood of 220°. Hot aqueous ammonia or, better, sodium hydroxide dissolved it very slowly; and acidification of the resulting alkaline solutions gave white, highly insoluble precipitates which were not melted at 300°.

5,7-Dichloroisatoic anhydride (IV) from tetrachloroindigo.—Five grams of tetrachloroindigo* was suspended in 50 cc. of glacial acetic acid, and with frequent shaking, 9 g. of chromic anhydride was added in small portions during a period of seven hours. The mixture, kept at room temperature by occasional immersions in an ice bath, was finally packed in a small amount of ice and allowed to stand overnight. It was then heated at 50° during one-half hour and at 70° for another half-hour, was allowed to cool, and was poured into a liter of water which had been acidified with 5 cc. of concentrated sulfuric acid. After standing for four hours the yellow brown precipitate, 2.5 g., which had separated was collected, washed with water, dried, and crystallized from an acetone-alcohol mixture in the manner described above, yielding 1.4 g. of brownish crystals, m. p. 254–255° with foaming, as recorded by Dorsch.[9]

5,7-Dichloroisatoic anhydride thus prepared invariably had a darker color than the product obtained from dichloroanthranilic acid and ethyl chlorocarbonate as outlined above, but mixtures of the two products melted at temperatures identical with the melting points of their components.

5,7-Dibromoisatoic anhydride.—On treating a suspension of 1.5 g. of tetrabromoindigo in 15 cc. of glacial acetic acid with 1.8 g. of chromic anhydride, following the procedure just described for tetrachlorindigo, there was obtained 1.0 g. of an orange brown precipitate which, crystallized from acetone-alcohol, yielded 0.7 g. of small, pale brown prisms,[13] m. p. 263.5° (corr.) with gas evolution, and identical in appearance with dichloroisatoic anhydride except for the color. This oxidation proceeds more slowly than that of the corresponding tetrachloro compound; consequently, for cooling purposes cold water is preferable to an ice bath, and a longer heating period (1 hour) at 70° is necessary.

Interaction of 5,7-dichloroisatoic anhydride (IV) with ammonia: 6,8-dichlorobenzoyleneurea (III).—One-half gram of 5,7-dichloroisatoic anhydride was heated with 20 cc. of ammonium hydroxide (28%) on a water bath during one hour, shaking occasionally. The heavy granular anhydride gradually became voluminous and flocculent. The suspension was allowed to cool and the undissolved material (0.20 g.) was removed by filtration, washed with water, and dried. Acidification of the ammoniacal filtrate produced a precipitate, 0.25 g., of 3,5-dichloroanthranilic acid which was identified by crystallization from benzene and determination of the melting point of a mixture with an authentic specimen.

The ammonia-insoluble material was dissolved in a hot solution of potassium hydroxide, filtered, and precipitated with a solution of sodium chloride. The separated sodium salt, collected, washed, and warmed with dilute hydrochloric acid, left a residue of 6,8-dichlorobenzoyleneurea which melted at 285°† after a crystallization from alcohol. Recrystallization from hot glycol gave small, pale-yellow prisms, m. p. 296° corr., alone or mixed with specimens of the same compound prepared by the two fusion methods already described.

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* Courtesy of General Dyestuff Corporation. New York, N. Y.

† Dorsch, reference 9, p. 53, gives m. p. 284° for his product, which was mistaken for the amide of dichloroanthranilic acid.

In a preliminary experiment performed with a sample of dichloroisatoic anhydride prepared from tetrachloroindigo, the ammonia-insoluble residue of 6,8-dichlorobenzoyleneurea was crystallized directly from acetone-alcohol as described by Dorsch.[9] The product was a gray white mass of minute needles having the correct melting point, and without a suggestion of a yellow color.

When 5,7-dibromoisatoic anhydride was similarly treated with ammonia, results contrary to the experience of Dorsch[20] but corresponding closely with those described above for the dichloro compound were obtained. The ammonia-insoluble portion was crystallized from acetone-alcohol and from glycol and found to be identical (mixture melting point) with 6,8-dibromobenzoyleneurea, m. p. 305–306° (corr.), prepared by the fusion method.[21] The 3,5-dibromoanthranilic acid which precipitated on acidifying the ammoniacal solution was repeatedly crystallized from alcohol, m. p. 235–236° (corr.).[22]

In these experiments the weights of the dihalogen isatoic anhydride taken and those of the corresponding benzoyleneurea and anthranilic acid produced bear to

TABLE III

REACTIONS OF 5,7-DIHALOGEN ISATOIC ANHYDRIDES WITH AMMONIA

ISATOIC ANHYDRIDE		BENZOYLENEUREA		ANTHRANILIC ACID	
Grams	Moles	Grams	Moles	Grams	Moles
5,7-Dichloro-					
0.50[a]	5	0.20	2.01	0.25	2.82
0.36[b]	5	0.14	1.95	0.17	2.66
5,7-Dibromo-					
0.65	5	0.20	1.54	0.37	3.10
0.33	5	0.13	1.98	0.185	3.05

[a] Prepared from tetrachloroindigo.

[b] Prepared from 3,5-dichloroanthranilic acid. This specimen proved to be slightly impure.

each other the molecular ratios 5:2:3, respectively. The results, calculated on a basis of five moles of the anhydride, are compared in Table III.

SUMMARY

When 3,5-dichloroanthranilic acid is fused with urea, 6,8-dichlorobenzoyleneurea and 3,5-dichloro-2-aminobenzamide are formed. The amide, fused with urea, likewise gives 6,8-dichlorobenzoyleneurea, and the possibility of its being a partial intermediate in this synthesis is discussed.

6,8-Dichlorobenzoyleneurea, like 6,8-dibromobenzoyleneurea, forms a sodium salt which is sparingly soluble in water and which can be precipi-

[20] Reference 9, p. 48.

[21] Reference 1, p. 4920.

[22] BOGERT AND HAND, *J. Am. Chem. Soc.*, **25**, 939 (1903), give m. p. 235.5–236° for this acid.

tated in the presence of the other alkali metals. As a test for sodium it is more advantageous than the dibromo compound since it dissolves readily in potassium hydroxide, thus eliminating the use of lithium hydroxide and any precipitation of lithium carbonate by atmospheric carbon dioxide.

5,7-Dichloroisatoic anhydride results on heating 3,5-dichloroanthranilic acid with ethyl chlorocarbonate. Treated with ammonia it yields 6,8-dichlorobenzoyleneurea and 3,5-dichloroanthranilic acid. 5,7-Dibromoisatoic anhydride behaves similarly. These anhydrides were previously reported to give, by this treatment, amides of the corresponding anthranilic acids, a reaction supposedly general for isatoic anhydrides.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

THE DIRECT INTRODUCTION OF THE AMINO GROUP INTO AROMATIC AND HETEROCYCLIC NUCLEI. V. THE ACTION OF METALLIC AMIDES ON THE PHENYL AND BENZOQUINOLINES

F. W. BERGSTROM

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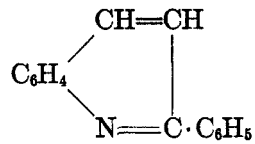
The present article is a continuation of previous work which has dealt with the formation of aminoquinoline and some of its substitution products.[1]

2-PHENYLQUINOLINE

2-Phenylquinoline



may be regarded as a cyclic ketone ether of the ammonia system, because of the grouping, $R(C_6H_5)C{=}N{-}$, a point of view which is in harmony with its properties. It is thus oxidized by acid permanganate[2] to *N*-benzoylanthranilic acid, $C_6H_4\begin{cases}COOH\\NHCOC_6H_5\end{cases}$, the quinoline ring being split on one side of the carbazyl group (C=N), just as aquo ketones are split on one side of the carbonyl group. 2-Phenylquinoline can also be regarded as a "vinylogue"[3] of a cyclic ammonoaldehyde ether, the carbon atom 4 usurping the function of carbon atom 2 in unsubstituted quinoline. In the reactions to be described, the latter viewpoint is the most profitable.

2-Phenylquinoline is only slightly soluble in liquid ammonia at $-33°$ or at room temperatures, although readily soluble in sodium amide or potassium amide to give opaque green solutions, which contain addition com-

[1] (*a*) BERGSTROM, *J. Am. Chem. Soc.*, **56**, 1748–51 (1934); (*b*) *Ann.*, **515**, 34–42 (1934); (*c*) J. ORG. CHEM., **2**, 411–430 (1937); (*d*) *ibid.*, **3**, 233–41 (1938).

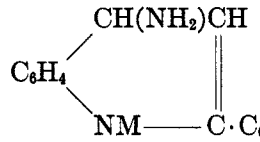
[2] DÖBNER AND VON MILLER, *Ber.*, **19**, 1196 (1886).

[3] FUSON, *Chem. Rev.*, **16**, 1 (1935).

pounds of the type composition, $C_9H_6N(C_6H_5)\cdot NaNH_2$. Treatment with ammonium salts regenerates 2-phenylquinoline in quantities which are the smaller the higher the amide ion concentration, the longer the time of action and the higher the temperature. Thus, while the sodium amide-phenylquinoline addition compound is fairly stable at $-33°$ in the presence of an excess of the sparingly soluble sodium amide, its potassium analogue decomposes almost completely in one day at room temperatures if potassium amide is in excess.

The first decomposition product appears to be a secondary addition compound, of the probable formula,

(A)



(M = Na, K)

in which the alkali amide has added to the vinologous ammonoaldehyde grouping, $—CH=CHC(C_6H_5)=N—$. The evidence for its existence lies in the fact that it reacts with potassium nitrate or mercury, especially readily in the presence of excess amide ions, to form 2-phenyl-4-aminoquinoline, even though 2-phenylquinoline is not regenerated from it by treatment with ammonium salts in liquid ammonia. The overall reaction between 2-phenylquinoline, potassium nitrate and potassium amide, which is expressed by equation 1 below, is accelerated by an excess of amide ions, although it does proceed at an appreciable though much slower rate with an excess of 2-phenylquinoline.

$$(1)\ C_9H_6N\cdot C_6H_5 + 2KNH_2 + KNO_3 = KOH + KNO_2 + C_9H_5N(C_6H_5)NHK + NH_3.$$

When hydrolyzed, $C_9H_5N(C_6H_5)NHK \rightarrow C_9H_5N(C_6H_5)NH_2$. In the discussion of the mechanism of the reaction in a previous article[1c], the possibility was considered that hydrogen and an electron are removed from the addition compound (formula A) in a stepwise manner. No evidence has been obtained in the present work either for or against this alternative.

The formation of 2-phenyl-4-aminoquinoline from potassium amide, mercury and 2-phenylquinoline follows the equation,

$$(2)\ C_9H_6N(C_6H_5) + 3KNH_2 + xHg = C_9H_5N(C_6H_5)NHK + K_2Hg_x + 2NH_3.$$

Again there is no evidence (of either a positive or a negative character) that the reaction takes place in a stepwise manner, since the yield of amino-

phenylquinoline is roughly proportional to the quantity of potassium found in the mercury.

If potassium amide and 2-phenylquinoline are allowed to react in liquid ammonia for periods of a week or two before treatment with potassium nitrate, aminophenylquinoline is formed in quantities which are smaller the longer the time of the initial reaction, showing that the secondary addition compound (formula A) is slowly decomposing.

TABLE

ACTION OF POTASSIUM AMIDE AND MERCURY ON 2-PHENYLQUINOLINE (= PQ) AND ON 5,6-BENZOQUINOLINE (= BQ)

K, MILLIATOMS	PQ OR BQ, MILLIMOLES	TIME OF ROCKING, DAYS	K IN Hg, MILLIATOMS	K, %	AMINO DERIVATIVE		NOTES
					Millimoles	%	
30.4	10.0 PQ	18	11.19	56.0	4.84	48.4	*a*
7.23	8.10 PQ	3.5	0.16	6.5	0.536	22.2	*b*
25.8	6.51 PQ	2.6	12.44	95.5	6.40	98.3	*c*
23.0	7.31 PQ	0.33	9.44	64.5	4.71	64.5	*d*
10.64	11.22 PQ	1.6 at 90° 2 at 25°	0.28	1.2	0.28	2.5	*e*
30.4	6.767 BQ	5.1	11.47	85	6.432	95.0_4	
26.3	6.244 BQ	4.5	10.94	87.8	5.94	95.2	*f*
26.6	6.05 BQ	1.9	6.76	55.9	3.52	58.2	*g*

[a] Intermittent shaking by hand, straight tube. H_2, 0.3 cc.; N_2, 0.2 cc. N.T.P.

[b] Potassium from a sealed capsule. Cf. Kraus and Chiu, J. Am. Chem. Soc., **44**, 2001 (1922). Two legged tube.

[c] Straight tube. In a duplicate, 0.5 cc. H_2, N.T.P., was obtained.

[d] Two legged tube. 0.10 g. of ppt., m.p. 294–8°.

[e] Two cc. N_2, N.T.P.; 0.15 g. ppt., m.p. 292–302°. More 4-amino-2-phenylquinoline formed, but it was hard to separate.

[f] Three and seven-tenths cc. H_2 and 1.3 cc. N_2, N.T.P. Straight tube.

[g] H_2, 4.1 cc; N_2, 1.9 cc., N.T.P.

A high-melting substance of the composition of a tetrahydrodiphenyldiquinolyl, $(C_{15}H_{11}N)_2$, results when 2-phenylquinoline is treated with an excess of potassium amide for periods of about a week or more. In shorter reactions, this seems also to be formed, but it is mixed with other compounds which render the isolation of a chemical individual difficult. Perhaps this compound contains two less hydrogen atoms, and is therefore identical with a product, m. p. 303°, that John obtained by heating metallic salts of cinchophene[4].

Attempts to prepare 2-phenyl-4-anilinoquinoline and 2-phenyl-4-diphenaminoquinoline by treating 2-phenylquinoline with potassium anilide or

[4] JOHN, *Ber.*, **59B**, 2710 (1926).

potassium diphenylamide, respectively, and potassium nitrate, met with failure.

Competition experiments, to be described later, show that 2-phenylquinoline reacts much more rapidly with potassium amide and potassium nitrate than does quinoline itself.

6- AND 8-PHENYLQUINOLINES

8-Phenylquinoline, previously reported as a thick liquid[5], has been obtained as a crystalline solid. Both 6- and 8-phenylquinolines react with potassium amide and potassium nitrate to form (2?)-amino derivatives in fair yield. Better results are obtained with the use of barium amide, gaseous hydrogen then being evolved. Both 6- and 8-phenylquinolines are converted to tars by potassium amide alone, behaving similarly in this respect to the 6-, 7-, and 8-methylquinolines.[1d]

Potassium amide and potassium nitrate react with 2-*p*-tolylquinoline in liquid ammonia to give a substance of high and indefinite melting point, in place of the expected 4-amino-2-*p*-tolylquinoline.

7,8-BENZOQUINOLINE AND 5,6-BENZOQUINOLINE

(α- AND β-NAPHTHOQUINOLINES)

The above-named compounds are converted to mono-(2?)-amino derivatives of unknown orientation by the action on them of potassium amide and potassium nitrate, or of barium amide in liquid ammonia. Lithium amide forms an addition compound of fair stability with 5,6-benzoquinoline.

5,6-Benzoquinoline reacts with potassium amide and mercury to yield the aminobenzoquinoline mentioned above. The reaction follows an equation similar to 2, no evidence being found either for or against the supposition that it is stepwise. The yield of product is always a little greater than corresponds to the amount of potassium in the amalgam, indicating that some reaction has occurred independently of the mercury.

A fair yield (30 per cent.) of amino-5,6-benzoquinoline, along with a little hydrogen, is obtained by treating 5,6-benzoquinoline with potassium amide alone in liquid ammonia.

EXPERIMENTAL

2-Phenylquinoline

Forty grams of 2-phenylquinoline-4-carboxylic acid (cinchophene) was placed in a 125-cc. distilling flask with side-arm near the bulb, and heated a little above the melting point until the greater part of the carbon dioxide had been evolved (5–10 minutes). The temperature was then raised, and the 2-phenylquinoline distilled

[5] LA COSTE AND SORGER, *Ann.*, **230**, (1885); [(*a*) p. 39, (*b*) p. 8].

at atmospheric pressure. Yield of light yellow product, m.p. 80–82.7°, (uncorr.), 28–30 grams (85–91%). Before using, it was crystallized from 75% alcohol. It is therefore of no advantage to use soda-lime as has been recommended.[6]

Action of potassium amide alone on 2-phenylquinoline.—2-Phenylquinoline is slightly soluble in liquid ammonia at −33° or at room temperatures, but readily soluble in potassium amide or sodium amide in proportions of a mole or over, to form opaque green solutions. From the hydrolyzed products of the reaction between 2-phenylquinoline and 2–3 equivalents of potassium amide (reaction period of a week or more) was isolated a cold alcohol- or cold benzene-insoluble portion melting above 280°, together with a tarry alcohol- or benzene-soluble fraction from which a small quantity of 4-amino-2-phenylquinoline was sometimes obtained. The insoluble portion amounted to about 50 or 60% of the total reaction product. After several crystallizations from pyridine or methyl isobutyl ketone it proved to have the composition of a diphenyltetrahydrodiquinolyl.

Anal. Calc'd for $C_{30}H_{22}N_2$: C, 87.8; H, 5.4; N, 6.8.

Found (average of four preparations) C, 87.65; H, 5.31; N, 7.00.

John[4] prepared the same compound, or one with two less hydrogen atoms, by distilling the barium salt of cinchophene; m.p. 303°.

Action of barium amide, potassium anilide, and potassium diphenylamide on 2-phenylquinoline.—The failure of barium amide to react with 2-phenylquinoline over a rather extended period (38 days) in liquid ammonia is probaby due to the formation of an insoluble product which coats the unattacked phenylquinoline.

2-Phenylquinoline reacted to some extent with potassium anilide or potassum diphenylamide in the presence of potassium nitrate, but the expected anilino- and diphenylaminophenylquinolines were not isolated.

Addition compounds formed by the alkali amides and 2-phenylquinoline.—(1) Sodium (0.53 g., two equivalents) was added to a solution of 30 mg. hydrated ferric nitrate in 100 cc. of liquid ammonia contained in a 200-cc. round-bottomed flask. To the resultant sodium amide (this was formed in 5–10 minutes), 2.087 g. of 2-phenylquinoline was added, the reaction being stopped at the end of three hours by the addition of an excess of ammonium chloride. Most of the 2-phenylquinoline (2.031 g.) was recovered in a pure condition.

In a repetition of this experiment at room temperatures in a two-legged tube, about one quarter of the original 2-phenylquinoline was recovered (in the crude state) at the end of a two-week reaction. Three equivalents of sodium was used per mole of 2-phenylquinoline.

(2) 2-Phenylquinoline (1.640 g., 8.00 millimoles) reacted for one day in a two-legged tube (room temperatures) with the potassium amide from 0.96 g. (25 milliatoms) of potassium. Excess ammonium bromide was then introduced, and the solvent was evaporated. No phenylquinoline could be isolated, although a very small amount may have been present. High-melting compounds insoluble in cold benzene, and similar to diphenyltetrahydrodiquinolyl were doubtless formed, but it was impossible in this experiment to isolate anything of definite characteristics.

(3) Thirty-eight-hundredths gram of 2-phenylquinoline reacted for five hours with the sodium amide from 0.14 g. sodium, in a two-legged tube.[7] The solution was partially decanted into the clean leg, the solvent was evaporated, and the solid was dried *in vacuo* at 20° and at 95°, there being no loss in weight at the latter temperature.

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[6] DÖBNER AND GIESEKE, *ibid.*, **242**, 294 (1887); PFITZINGER, *J. prakt. Chem.*, [2], **56**, 298 (1897).

[7] BERGSTROM, *J. Am. Chem. Soc.*, **53**, 3029 (1931).

Anal. Calc'd for $C_9H_6N(C_6H_5)\cdot NaNH_2$; Na, 9.43. Found: Na, 10.2.

The high sodium content is probably due to sodium amide transferred in suspension.

(4) Three hundred eleven thousandths gram (0.311 g.) of 2-phenylquinoline reacted in a two-legged reaction tube[7] for one month with the sodium amide from 0.14 g. sodium. The opaque green solution was analyzed as in experiment 3, described above. Found: Na, 9.69. Therefore, no additional sodium is taken up by the first addition compound on standing with excess sodium amide.

Conversion of the addition compound into 4-amino-2-phenylquinoline.—(5) The preparation of 4-amino-2-phenylquinoline is best accomplished in the following manner. The potassium amide formed from 1.05 g. potassium (26.9 milliatoms) in the presence of ferric oxide catalyst (0.02 g.) was decanted on a mixture of 1.83 g. 2-phenylquinoline (8.93 millimoles) and 1.61 g. potassium nitrate in a two-legged reaction tube.[8a] After four hours at room temperatures, the solution was opaque brown (green when nitrate was omitted), and filled with a white, crystalline precipitate of potassium hydroxide. Ammonia was evaporated at this point, the precipitate was hydrolyzed with benzene and alcohol, water was added, and the first two solvents were distilled. The insoluble solid after collection by filtration and washing with water was almost pure 4-amino-2-phenylquinoline, m.p. 162.4–163.7° (uncorr.); yield, 1.96 g., or 99.7%. In other experiments the yields varied between 93 and 98%. M.p. after several crystallizations from benzene or dilute alcohol, 164.0–164.9° (uncorr.). Molten 4-amino-2-phenylquinoline solidifies to a glass which reverts very slowly to the crystalline form.

Anal. Calc'd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.50; N, 12.73.
Found: C, 81.62; H, 5.67; N, 12.83.

The melting point of a mixture of this material with 4-amino-2-phenylquinoline prepared by the method of Dohrn and Zöllner[9] (m.p. 164.2–164.7°) was 163.9–164.7° (uncorr.), showing their identity.

In a straight-tube experiment[1c], an essential duplicate of the above, 1.5 cc. of hydrogen and 1.4 cc. of nitrogen, N.T.P. were obtained.

(6) In a sealed straight tube[8b] 3.06 g. (14.9 millimoles) of 2-phenylquinoline and 1.53 g. (15.1 millimoles) of potassium nitrate reacted with the potassium amide from 0.51 g. potassium (13 milliatoms) for two months at room temperatures. No water-insoluble gases were given off in the reaction. The hydrolysate was extracted once with boiling ligroïn (b.p. 60–70°), the insoluble portion being crystallized from benzene. Yield, 0.82 g. (3.73 millimoles); m.p. 163–164.5° (uncorr.), or 57% calculated on the basis of the potassium, equation.[1] One and thirty-three-hundredths grams of crude 2-phenylquinoline was recovered fom the ligroïn-soluble portion.

(7) In accordance with the method of experiment 5, 1.453 g. (7.08 millimoles) of 2-phenylquinoline and 1.00 g. sodium nitrate (11.8 millimoles) reacted with the sodium amide from 0.50 g. (21.8 milliatoms) of sodium (0.03 g. ferric oxide as catalyst) for 21 days. Yield (m.p. 164.2–165.3°, twice crystallized from C_6H_6), 0.334 g., or 21.5%. Much 2-phenylquinoline was recovered unchanged. The sodium nitrate appears to decrease the rate of decomposition of the sodium amide-phenylquinoline addition compound into tetrahydrodiphenyldiquinolyl and related substances, as

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[8] Reference 1*c*, pages: (*a*) 423, expts. 11–15; (*b*) 427, note *c*; (*c*) 423, expt. 16; (*d*) 420, expts. 4–6; (*e*) 425, bottom.

[9] Dohrn and Zöllner, Chem. Fabrik auf Aktien, D.R.P. 375, 715; *Chem. Zentr.*, **1924**, I, 967.

judged from comparative reactions in which unchanged 2-phenylquinoline was determined.

(8) *Nitrite formed in the reaction.*—The method used has already been described,[8c] The potassium amide from 0.82 g. (21 milliatoms) of potassum and 2-phenylquinoline (1.292 g., 6.30 m. moles) reacted for a week in the presence of 1.022 g. (10.1 millimoles) of potassium nitrate. Nitrogen from one-tenth aliquot, 13.4 cc., or 95% of the theoretical. Yield of 4-amino-2-phenylquinoline, 1.339 g., or 96.5%.

Potassium amide, potassium nitrite, and 2-phenylquinoline.—(9) 2-Phenylquinoline reacted for three months[8b] with excess potassium amide (three equivalents) in the presence of potassium nitrite (1.5 equivalents) at room temperatures. The reaction products were about the same as in experiments in which the potassium nitrite was omitted—that is to say, a small amount of 4-amino-2-phenylquinoline and a substance, m.p. 302.5–303.0°, (uncorr.) of the composition of a di- or tetrahydrodiphenyldiquinolyl (*cf.* reference 4).

Action of potassium nitrate on the product of the action potassium amide on 2-phenylquinoline.—(10) The potassium amide from 0.798 g. (20.4 milliatoms) of potassium reacted, in the absence of the iron catalyst, for eleven days at room temperatures with 2.052 g. (10.0 millimoles) of 2-phenylquinoline. At the end of this time, 1.53 g. of potassium nitrate was introduced[8d] through the small addition tube, and was allowed to react for two days at room temperatures with the ammonia solution of the addition compound. The product was worked up as in experiment 5. Yield of 4-amino-2-phenylquinoline (crystallized from benzene), m.p. 161.9–162.7°, (uncorr.), 1.608 g. or 73%; 0.07 g. of material m.p. 290–6° was also obtained.

(11) In a repetition of the above experiment, the potassium amide from 2.15 g. potassium (55 milliatoms) reacted for six days with 2.05 g. (10.0 millimoles) of 2-phenylquinoline, and then with 1.60 g. of potassium nitrate. Yield, 1.254 g. (57%); m.p. 164.0–164.7°, (uncorr.). The lower yield in this experiment, as compared with the preceding, is due to a higher concentration of reactants.

(12) Similarly, 1.753 g. of 2-phenylquinoline (8.55 millimoles) reacted for 15 days with the potassium amide from 1.10 g. (28.1 milliatoms) potassium, and then with potassium nitrate (1.50 g., 3 days). Yield, (m.p. 160.7–162.4°), 0.731 g. (38.8%), together with much tar.

Action of potassium amide and mercury on 2-phenylquinoline and 5,6-benzoquinoline.—In the following experiments, potassium amide and 2-phenylquinoline or 5,6-benzoquinoline were rocked continuously in the presence of 3 cc. of mercury (distilled *in vacuo*), since intermittent agitation was found to be insufficient. The reactions were carried out either in two-legged tubes,[8e] or in sealed straight tubes,[8b] in the absence of the iron-wire catalyst used for preparing the potassium amide. In straight-tube reactions, the iron wire was removed before the introduction of the 2-phenylquinoline and the mercury; in two-legged tubes, the wire was wadded up so that it remained in the empty leg. The reaction vessel was placed in a steel container of suitable shape (a capped steel pipe or a narrow steel box with removable lid), which was attached to a rocking apparatus and rocked at room temperatures (20–24°) for the length of time specified.

The amalgam formed in the straight tube could be washed conveniently by the following method. After collection of gases, the top of the tube was cut off, and the solution above the mercury (at −78°) was poured into a beaker (later covered with a watch glass). A few milliliters of liquid ammonia was poured on top of the mercury, the tube was removed from the cooling bath, and the mercury was warmed with the hand until liquid or semi-liquid, and until the ammonia boiled. The tube was shaken gently, then cooled again to −78° to freeze the amalgam, and the ammonia

washings were poured off. The process was repeated until the washings were colorless.

6-Phenylquinoline

(13) In a straight reaction tube, 2.26 g. of barium was converted to amide under the catalytic influence of iron wire. To this was added 1.700 g. of 6-phenylquinoline[5b] (8.29 millimoles), the reaction taking 3 months, a much longer time than necessary. One hundred seventy-three and six-tenths cubic centimeters of hydrogen, N.T.P. (7.748 millimoles, or 93.5%) was obtained. Excess dilute hydrochloric acid was added to the hydrolysate of the reaction product, converting it to a dark-colored oil which soon solidified. This was filtered and combined with a smaller amount of solid obtained by adding ammonia to the filtrates. Yield [crystallized from dilute pyridine, m.p. 239.8–241.3° (uncorr.)], 1.58 g. (86.6%). M.p. pure product, 243–243.5°.

Anal. Calc'd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.48; N, 12.73.
Found: C, 81.65; H, 5.41; N, 12.92.

6-Phenylquinoline is slightly soluble in pure ammonia, but dissolves slowly in potassium amide solution. No definite products were isolated when the two reacted for a month. Better results were obtained by carrying out the reaction in the presence of potassium nitrate, in accordance with earlier directions[8a].

(14) Thus, 2.00 g. of 6-phenylquinoline (9.75 millimoles) and 1.66 g. potassium nitrate reacted for two days in a two-legged tube with the potassium amide from 1.34 g. (34.3 milliatoms) of potassium (*cf.* experiment 5). The hydrolysate of the reaction product, crystallized from dilute pyridine, weighed 0.768 g. (35.8%); m.p. 239–241°, (uncorr.). The reaction did not appear to be complete.

8-Phenylquinoline

As prepared according to the directions of La Coste and Sorger[5a], 8-phenylquinoline is a thick oil. It partly solidified after standing for several months. The mass was triturated with ligroïn (b.p. 60–70°), and then crystallized from petroleum ether (b.p. 35–60°); m.p. 48–9°.

8-Phenylquinoline, like 6-phenylquinoline, reacts with excess potassium amide largely to form tar. An amino-8-phenylquinoline is best prepared in the following manner.

(15) 8-Phenylquinoline (1.470 g., 7.16 millimoles)[5a] reacted for five weeks (a longer time than necessary) with the barium amide from 1.81 g. (13.2 milliatoms) of barium in a two-legged tube. The reaction product was hydrolyzed with water and crystallized as the hydrochloride from dilute hydrochloric acid. The hydrochloride was dissolved in warm water, and made basic with ammonia, the precipitate being crystallized from benzene. Yield (crude, before cryst.) 1.39 g. (88%); m.p. 156–9°.

Anal. (m.p. 165–6°): Calc'd: C, 81.79; H, 5.48; N, 12.73.
Found: C, 82.14; H, 5.69; N, 12.84.

7,8-Benzoquinoline (α-Naphthoquinoline)

(16) The potassium amide from 61.5 milliatoms of potassium reacted for eleven days with 16.8 millimoles of α-naphthoquinoline in a straight tube[8b]. Nine and nine-tenths cubic centimeters (2.6%) of hydrogen, N.T.P., was obtained, together with 4.3 millimoles (26%) of aminonaphthoquinoline, the latter having been extracted from the hydrolysate with ligroïn. The following methods of preparation are better.

(17) In a straight reaction tube[8b], the potassium amide from 1.35 g. potassium (34.5 milliatoms), 2.05 g. of potassium nitrate and 2.00 g. (11.16 millimoles) of 7,8-benzoquinoline[10] reacted for four days at room temperature. Twenty-three cubic centimeters of hydrogen (9.2%) and 15.7 cc. nitrogen were obtained, the latter from the action of potassium amide on potassium nitrate in the presence of ferric oxide. The washed hydrolysate (*cf.* experiment 5) (2.15 g., m.p. 97–100°) was crystallized from dilute alcohol in long colorless silky needles; yield, 1.80 g., 83.1%.

Anal. Calc'd for $C_{13}H_9N_2$: C, 80.37; H, 5.19; N, 14.44.
Found: C, 80.45; H, 5.19; N, 14.60.

(18) The barium amide from 2.32 g. (16.9 milliatoms) of barium reacted in a straight tube[1a] for one month with 1.676 g. of 7,8-benzoquinoline (9.353 millimoles). The reaction appears to be slow, but longer time was allowed than necessary. Of hydrogen, 207.7 cc. (9.268 millimoles, or 99.2%) was formed. The solid remaining after hydrolysis was dissolved in hot dilute hydrochloric acid (250 cc.), fine needles of the hydrochloride (m.p. above 288°) separating on cooling. These were collected by filtration, and were converted to the free base, m.p. 104–105°, by treatment with ammonia; yields, 88% or above. Picrate, prepared by adding aqueous picric acid to a solution of the hydrochloride in water; m.p. 259–62° (dec.).

Anal. Calc'd for $C_{19}H_{13}N_5O_7$:N, 16.55. Found, N, 16.8.

5,6-Benzoquinoline (β-Naphthoquinoline)

β-Naphthoquinoline is slightly soluble in liquid ammonia at room temperatures, but readily soluble in excess sodium amide, potassium amide, or lithium amide to from orange solutions, which change on standing to deep red or reddish brown.

(19) In a straight reaction tube,[1a] the lithium amide from 0.288 g. lithium (41.5 milliatoms, iron-wire catalyst) reacted with 1.804 g. (10.08 millimoles) 5,6-benzoquinoline* for 39 days. Less than 0.5 cc. of gas (N_2 or H_2) was formed; 1.18 g. of 5,6-benzoquinoline was recovered.

(20) 5,6-Benzoquinoline (3.005 g., 16.78 millimoles) reacted for 13 days with the potassium amide from 3.93 g. (100 milliatoms) of potassium in a straight tube[8b]; 2.2 cc. hydrogen and 0.8 cc. nitrogen, N.T.P., were obtained. The precipitate formed by hydrolyzing the solvent-free reaction product in the usual way was extracted several times with cold benzene, the undissolved portion (1.87 g.) being crystallized from methyl isobutyl ketone. Yield, 1.134 g. (34.8%); m.p. 233–235° uncorr.

(21) Better results were obtained in the following procedure. 5,6-Benzoquinoline (2.00 g., 11.17 millimoles) in a two-legged tube[8a] reacted for five days with potassium nitrate (2.00 g., 19.8 millimoles) and the potassium amide from 1.44 g. (36.8 milliatoms) of potassium. The reaction product, hydrolyzed in the usual manner, collected by filtration, and washed with water, melted at 233–235° (uncorr.); yield, 2.12 g. (97.8%). M.p. 234–235° (uncorr.), after crystallization from methyl isobutyl ketone and from pyridine.

The effect of smaller relative proportions of potassium amide is shown in the following, where the reactions consumed about one week, and took place in the presence of about 1.5 moles of potassium nitrate.

(22) Potassium amide (29.2 millimoles) and 14.08 millimoles of 5,6-benzoquinoline yielded 8.32 millimoles, or 59% of aminobenzoquinoline.

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[10] SKRAUP AND COBENZYL, *Monatsh.*, **4**, 460 (1893).

* Obtained from the Eastman Kodak Company.

(23) Potassium amide (15 millimoles) and 11.3 millimoles 5,6-benzoquinoline yielded 4.43 millimoles, or 39.2%, of aminobenzoquinoline.

(24) In a straight tube[1a], 1.117 g. (6.22 millimoles) of 5,6-benzoquinoline reacted for four months with the barium amide from 1.82 g. (13.3 milliatoms) of barium (iron catalyst removed before reaction); 126.1 cc. hydrogen, N.T.P., was obtained (5.63 millimoles, 90.5%). The hydrolysate was extracted with hot hexone, aminobenzoquinoline crystallizing from the extractions on cooling. Yield, 0.755 g. (62.4%); m.p. 235° (uncorr.).

Anal. Calc'd for $C_{13}H_{10}N_2$: C, 80.37; H, 5.19; N, 14.44.
Found: C, 80.65; H, 5.16; N, 14.65.

SUMMARY

(1) 2-Phenylquinoline reacts with the alkali amides in liquid ammonia to form addition compounds of unknown structure, but of the type constitution, $C_9H_6N(C_6H_5)\cdot NaNH_2$. 2-Phenylquinoline is regenerated from them by the action of ammonium salts. On standing, secondary addition compounds are formed which do not react with ammonium salts to form 2-phenylquinoline, but which react with potassium (sodium) amide and potassium (sodium) nitrate to form 4-amino-2-phenylquinoline.

(2) The overall reactions between potassium amide, potassium nitrate (or mercury), and 2-phenylquinoline in liquid ammonia are expressed by the equations;

$$C_9H_6N(C_6H_5) + 2KNH_2 + KNO_3 = KOH + KNO_2 + C_9H_5N(C_6H_5)NHK + NH_3$$

$$C_9H_6N(C_6H_5) + 3KNH_2 + xHg = C_9H_5N(C_6H_5)NHK + K_2Hg_x + 2NH_3.$$

The yields of 4-amino-2-phenylquinoline are excellent. There is no evidence from the present work for or against the assumption that these reactions are stepwise.

(3) By using the same methods, (2?)-amino derivatives of 6-phenylquinoline, 8-phenylquinoline, 7,8-benzoquinoline, and 5,6-benzoquinoline have been obtained. The preparation in these cases may also be accomplished by treating the substituted quinoline with barium amide. Hydrogen is then evolved. 2-*p*-Tolylquinoline has not been converted to an amino derivative.

(4) Potassium amide alone converts 6-phenylquinoline and 8-phenylquinoline to tars. The two benzoquinolines react with potassium amide to form amino derivatives in fair yield (25–35 per cent.), together with small amounts of hydrogen.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF COMPOUNDS RELATED TO 1,2-BENZANTHRACENE AND CHOLANTHRENE

W. E. BACHMANN

Received September 6, 1938

Cholanthrene (VI*) was first synthesized by Cook, Haslewood, and Robinson,[1] using acenaphthene as the starting material. Cook and Haslewood[2] subsequently developed two other synthetic methods for obtaining this carcinogenic hydrocarbon, one starting from *as*-octahydrophenanthrene, and the other employing 1-(β-naphthyl)hydrindene. Fieser and Seligman[3] prepared cholanthrene from 4-(α-naphthoyl)hydrindene by a modified Elbs reaction.

In this paper are described two procedures for synthesizing cholanthrene from phenanthrene. In both methods the phenanthrene is first converted to the well-known 5-ketotetrahydro-1,2-benzanthracene (I). The two extra carbon atoms that are needed in order to obtain the cholanthrene molecule are introduced in one case by means of the malonic ester condensation and in the other procedure through the Reformatsky reaction. The latter procedure is analogous to one of the methods of Cook and Haslewood, who carried out a Reformatsky reaction with 5-ketododecahydro-1,2-benzanthracene. While our investigation was in progress Bergmann and Blum-Bergmann[4] reported the synthesis of methylcholanthrene from phenanthrene. Their method is similar to one of ours, for they employed the Reformatsky reaction on 6-methyl-5-ketotetra-hydro-1,2-benzanthracene, but their procedure differs from ours in certain respects.

Lund[5] has pointed out the advantages of aluminum isopropylate as a reducing agent for obtaining carbinols from aldehydes and from ketones, including cyclic ketones. We have tried the action of aluminum isopropylate on 5-ketotetrahydro-1,2-benzanthracene (I) and have found that the cyclic ketone is reduced nearly quantitatively to 5-hydroxytetrahydro-1,2-benzanthracene (II). The corresponding chloride (VII),

* The numbering system for the cholanthrene molecule is that employed in the index of *Chemical Abstracts*.

[1] COOK, HASLEWOOD, AND ROBINSON, *J. Chem. Soc.*, **1935**, 667.

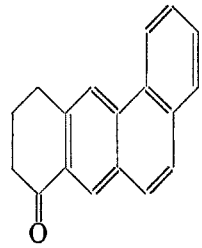
[2] COOK AND HASLEWOOD, *ibid.*, **1935**, 767, 770.

[3] FIESER AND SELIGMAN, *J. Am. Chem. Soc.*, **57**, 2175 (1935).

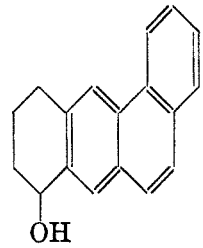
[4] BERGMANN AND BLUM-BERGMANN, *ibid.*, **59**, 1573 (1937).

[5] LUND, *Ber.*, **70**, 1520 (1937).

prepared from this carbinol and hydrogen chloride, was condensed with sodio-malonic ester, the substituted malonic ester was hydrolyzed, and the malonic acid was decarboxylated to yield tetrahydro-1,2-benzanthracene-5-acetic acid (III). The acid chloride, prepared from the acid by means



(I)



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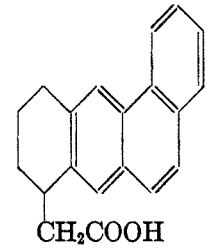

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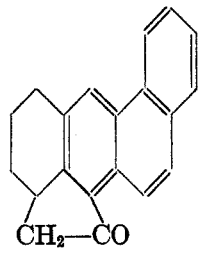

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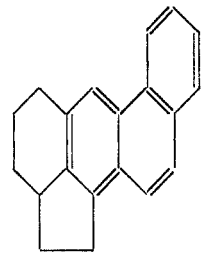

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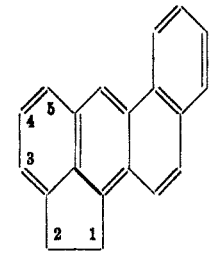


(VI)

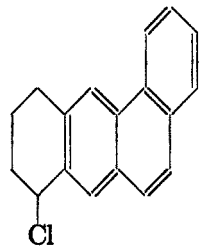
of thionyl chloride, was cyclized by anhydrous stannic chloride in carbon disulfide solution to 1-ketotetrahydrocholanthrene (IV) in yields as high as 90 per cent. Clemmensen reduction of this cyclic ketone gave tetrahydrocholanthrene (V). Dehydrogenation by palladium on charcoal converted the colorless tetrahydro compound to the yellow cholanthrene (VI) in good yield. The over-all yield of cholanthrene varied from 40–45 per cent., based on the 5-ketotetrahydro-1,2-benzanthracene.

The investigation is being continued in order to determine whether the method is applicable to the preparation of substituted cholanthrenes. Moreover, a similar series of reactions is being carried out with other cyclic ketones, including ketotetrahydro-3,4-benzpyrene, ketotetrahydrochrysene and 1- and 4-ketotetrahydrophenanthrene.

In a recent publication[6] we reported that 1-alkylphenanthrenes can be obtained in excellent yields by treatment of the corresponding 1-alkyl-1-hydroxytetrahydrophenanthrenes with palladium-charcoal catalyst at elevated temperatures, the process involving simultaneous dehydration and dehydrogenation. Similarly, the carbinol II is converted to 1,2-

[6] BACHMANN AND WILDS, *J. Am. Chem. Soc.*, **60**, 624 (1938).

benzanthracene by the action of the catalyst. 5-Chlorotetrahydro-1,2-benzanthracene (VII), while relatively stable at room temperature, loses a molecule of hydrogen chloride at its melting point (116°) and gives 7,8-dihydro-1,2-benzanthracene (VIII), and the latter hydrocarbon can be readily prepared by the action of hot pyridine on the chloride. In the reaction between the chloride and sodio-malonic ester some of the chloride is converted to the dihydrobenzanthracene, thereby decreasing the yield



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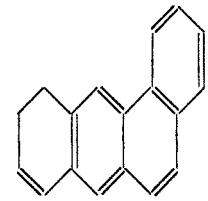
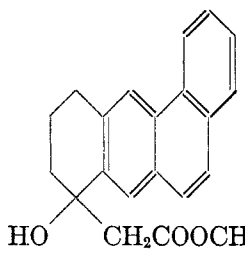


(VIII)

of the substituted malonic ester. The carbinol (II) readily yields a methyl ether when dissolved in cold methanol containing a trace of sulfuric acid, and gives an acetate with acetic anhydride in pyridine.

In the second synthesis of cholanthrene, 5-ketotetrahydro-1,2-benzanthracene was condensed with methyl bromoacetate through the Reformatsky reaction to yield the hydroxy acid ester (IX), which was readily dehydrated by short heating with anhydrous formic acid to the methyl ester of 7,8-dihydro-1,2-benzanthracene-5-acetic acid (X), the over-all yield for the two steps being 95 per cent. Although in the formula the double bond is shown in the ring, it has not been determined whether it is in the ring or in the side chain. A 90 per cent. yield of the methyl ester of 1,2-benzanthracene-5-acetic acid (XII) was obtained by dehydrogenating the ester of the unsaturated ester by means of sulfur at 200°, and the free acid was obtained by hydrolysis of the ester. When the unsaturated acid (XI), obtained from the corresponding ester by hydrolysis, was heated with sulfur, only a small yield (10 per cent.) of 1,2-benzanthracene-5-acetic acid was obtained, the principal product that was isolated being 5-methyl-1,2-benzanthracene, formed by simultaneous decarboxylation and dehydrogenation. The structure of the acid (XII) was proved by its oxidation to 1,2-benzanthraquinone-5-acetic acid (XIV), the product obtained by Cook and Haslewood by oxidation of cholanthrene. The quinone acid is best identified in the form of its methyl ester which, unlike the free acid, has a definite melting point, for it does not undergo decomposition.

Attempts to cyclize 1,2-benzanthracene-5-acetic acid by sulfuric acid



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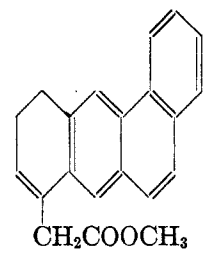

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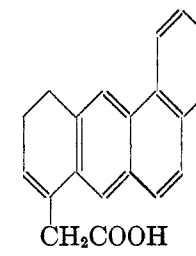

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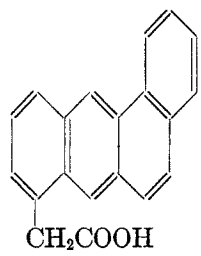
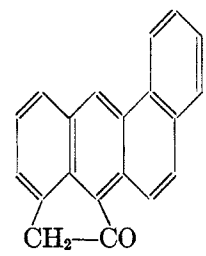
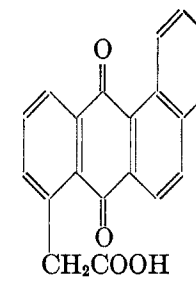


(XII)



(XIII)



(XIV)

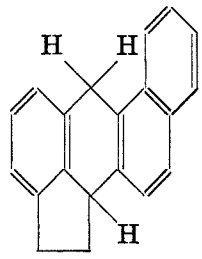
or the acid chloride, by stannic chloride, or by aluminum chloride in nitrobenzene solution were unsuccessful. Cyclization was finally accomplished satisfactorily by treating the acid chloride in carbon disulfide solution with aluminum chloride; in this manner 1-ketocholanthrene (XIII) was obtained in 72 per cent. yield. This ketone can also be obtained from the 1-ketotetrahydrocholanthrene (IV) by dehydrogenation of the latter by means of sulfur. It is of interest to note that while the 1,2-benzanthracene-5-acetic acid is colorless the 1-ketocholanthrene is bright yellow in color. Clemmensen reduction of the ketone gave cholanthrene, but in poor yield, and other methods of reduction are being tried.

For comparison, cholanthrene was also prepared by the method of Fieser and Seligman, involving the pyrolysis of 4-(α-naphthoyl)hydrindene. A variation in their procedure consisted in the preparation of the intermediate ketone by interaction of 4-cyanohydrindene and α-naphthylmagnesium bromide, which gave a better yield (91 per cent.) of the ketone than was obtained by Fieser and Seligman (50 per cent.) from the Grignard reagent of 4-bromohydrindene and α-naphthoyl chloride.

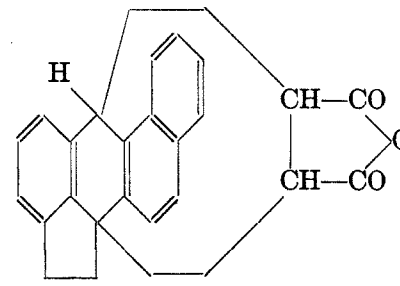
Recently we described the preparation of *meso*-dihydromethylcholanthrene and the *meso*-dihydro derivatives of a number of polycyclic hydrocarbons containing the anthracene nucleus.[7] These dihydro derivatives

[7] BACHMANN, J. ORG. CHEM., **1**, 347 (1936); BACHMANN AND PENCE, *J. Am. Chem. Soc.*, **59**, 2339 (1937).

were obtained from the disodium and dilithium addition products of the hydrocarbons which were prepared by direct addition of sodium and of lithium to the hydrocarbons. Cholanthrene also forms intensely colored addition products with sodium and with lithium by reaction with two atoms of the metal; the disodium compound is purplish-red in color and the dilithium compound is blue. Treatment of the colored addition products with methanol yields colorless *meso*-dihydrocholanthrene (XV). That the two hydrogen atoms are in the *meso* positions as indicated was shown by oxidation of the dihydrocholanthrene to 1,2-benzanthraquinone-5-acetic acid (XIV). Unlike cholanthrene, the *meso*-dihydrocholanthrene does not combine with picric acid in alcohol or in benzene, although the molecule contains a naphthalene nucleus.



(XV)



(XVI)

Like methylcholanthrene,[8] cholanthrene forms an addition product (XVI) with maleic anhydride, the reaction being reversible. The yields of adduct formed under various conditions are shown in Table I; in each case 2 cc. of solvent contained 0.100 g. of cholanthrene and 0.035 g. (1:1) or 1.05 g. (30:1) of maleic anhydride, except in the run in which a 3:1 molar ratio was used, when 10 cc. of benzene was employed for 1.0 g. of cholanthrene.

It is apparent that, while the reaction in boiling xylene is rapid, only a small yield (15 per cent.) of the adduct is obtained when equimolar quantities of the reactants are used, because of the unfavorable position of the equilibrium. By use of a large excess of maleic anhydride, the equilibrium can be shifted in the direction of adduct formation, and a good yield of adduct can be obtained in a short time. In benzene the reaction is slow but the position of equilibrium is more favorable; with three moles of maleic anhydride per mole of cholanthrene a nearly quantitative yield of the adduct was obtained. The reaction in benzene can be speeded up by

[8] BACHMANN AND KLOETZEL, *J. Am. Chem. Soc.*, **60**, 481 (1938).

using a large excess of maleic anhydride, so that a good yield of adduct can be obtained in this solvent also in a relatively short time.

By reaction with aqueous potassium hydroxide, the adduct was hydrolyzed to the water-soluble potassium salt of cholanthrene-6,12*b*-*endo*-α,β-succinic acid, which can be used for testing the carcinogenic properties of the compound. The free dicarboxylic acid was not obtained crystalline; it is readily converted to the original anhydride by short treatment with warm acetic anhydride.

TABLE

YIELDS OF CHOLANTHRENE-*endo*-SUCCINIC ANHYDRIDE

MOLE RATIO MA/CHOL	TIME, HRS.	% ADDUCT	
		Benzene	Xylene
1:1	2.0	9	
1:1	4.0	18	
1:1	0.25		14
1:1	0.50		15
30:1	2.0	93	
30:1	0.50		85
3:1	48.0	99.5	

EXPERIMENTAL

5-Hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene (*II*).—5-Ketotetrahydro-1,2-benzanthracene (I), which has been made previously by the action of stannic chloride on γ-(3-phenanthryl)butyric acid[9] has now been obtained by cyclization of the acid chloride. Ten grams of powdered γ-(3-phenanthryl)butyric acid was added to a mixture of 10 cc. of anhydrous ether, 1 drop of pyridine and 5 cc. of pure thionyl chloride. After thirty minutes at room temperature, all of the acid had gone into solution as the acid chloride. After ten minutes more, the ether and excess of thionyl chloride were removed under reduced pressure, and the acid chloride was dissolved in 50 cc. of dry benzene. The cooled solution was treated with 10 cc. of anhydrous stannic chloride. After standing at room temperature for fifteen minutes, the mixture, which contained a crystalline complex of the cyclic ketone, was poured onto ice, and the benzene was removed by distillation. The crude ketone which remained was digested with warm 40% aqueous potassium hydroxide, the mixture was filtered while hot, and the ketone was washed with hot water; yield of ketone, 8.5 g. (91%). The ketone can be purified by recrystallization from toluene and/or distillation under reduced pressure.

The cyclic ketone was reduced by aluminum isopropylate according to the procedure of Lund.[5] Fifteen grams of the ketone and 50 cc. of anhydrous isopropyl alcohol were added to the aluminum isopropylate solution prepared from 1.5 g. of

[9] COOK, *J. Chem. Soc.*, **1933**, 1597; BACHMANN AND BRADBURY, J. ORG. CHEM. **2**, 179 (1937).

polished aluminum wire (0.8 mm. diameter) and 60 cc. of anhydrous isopropyl alcohol. Fifty cc. of isopropyl alcohol containing acetone formed in the reaction was distilled from the mixture drop by drop. Another 50 cc. of isopropyl alcohol was added and the distillation was continued; after 40 cc. of distillate had been collected, no more acetone could be detected by means of 2,4-dinitrophenylhydrazine. The reaction mixture was treated with cold dilute sulfuric acid, and the crystalline carbinol was collected by filtration and dried. It was dissolved in hot acetone (75 cc.), the solution was boiled with charcoal, filtered, diluted with a little water and concentrated. From the solution 15 g. (99%) of 5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene was obtained as fine, colorless threads; m. p. 124–125°. After recrystallization the carbinol melted at 125.5–126.5°; it gives a purplish-black color with concentrated sulfuric acid.

Anal. Calc'd for $C_{18}H_{16}O$: C, 87.1; H, 6.5.
Found: C, 87.4; H, 6.4.

Conversion of the carbinol to 1,2-benzanthracene.—A mixture of 0.5 g. of 5-hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene and 0.05 g. of the 30% palladium-charcoal catalyst of Zelinsky and Turowa-Pollak[10] was heated at 310° for forty-five minutes. The 1,2-benzanthracene which was formed was extracted with hot benzene, and the solution after being filtered from the catalyst was passed through a tower of aluminum oxide. From the solution 0.32 g. (70%) of pure, colorless, 1,2-benzanthracene was isolated.

5-Hydroxy-5,6,7,8-tetrahydro-1,2-benzanthracene acetate.—A mixture of 0.5 g. of the carbinol, 0.6 cc. of acetic anhydride and 0.6 cc. of pyridine was warmed on a steam bath for one-half hour. After the liquids had been removed by means of a stream of air, the product was dissolved in benzene, and the solution was shaken with dilute ammonium hydroxide. Addition of petroleum ether to the concentrated benzene solution precipitated the crystalline carbinol acetate. By recrystallization from benzene-petroleum ether the ester was obtained as colorless needles; m. p. 136–136.5°; yield, 0.5 g. (81%).

Anal. Calc'd for $C_{20}H_{18}O_2$: C, 82.7; H, 6.2.
Found: C, 82.7; H, 6.0.

5-Methoxy-5,6,7,8-tetrahydro-1,2-benzanthracene.—One gram of the carbinol was added to a solution of 0.05 cc. of concentrated sulfuric acid in 5 cc. of methanol. After one-half hour all of the carbinol had gone into solution as the methyl ether. After two hours more a mixture of benzene and aqueous sodium carbonate was added, the benzene solution was separated, washed with water, dried and evaporated. The crystalline residue of the methy ether was recrystallized from methanol; yield, 0.98 g. (93%). The methyl ether exists in two forms. It was first obtained as colorless plates which melted at 76–77°. When this product was again recrystallized from methanol, it came down in plates; these were not filtered off immediately but were allowed to stand in the mother liquor for twelve hours at room temperature. At the end of this time the plates had disappeared and stout, colorless needles of the methyl ether were present; m. p. 86.5–87.5°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.0; H, 6.9.
Found: C, 87.0; H, 6.6.

5-Chloro-5,6,7,8-tetrahydro-1,2-benzanthracene (*VII*).—Dry hydrogen chloride gas was passed into a cold suspension of 13 g. of 5-hydroxytetrahydro-1,2-benzanthracene in 200 cc. of dry benzene containing 5 g. of anhydrous calcium chloride. In

[10] ZELINSKY AND TUROWA-POLLAK, *Ber.*, **58**, 1295 (1925).

a short time all of the carbinol had reacted, and a solution containing droplets of water resulted. When the solution was clear, it was filtered and evaporated at room temperature, yielding the desired chloride as a crystalline residue. By recrystallization from benzene, petroleum ether being added to the hot solution, the 5-chlorotetrahydro-1,2-benzanthracene was obtained in thin, colorless sheets; m. p. 116°; yield, 12.8 g. (92%).

Anal. Calc'd for $C_{18}H_{15}Cl$: Cl, 13.3. Found: Cl, 13.4.

7,8-Dihydro-1,2-benzanthracene (VIII).—A solution of 0.8 g. of the aforementioned chloride in 5 cc. of pyridine was refluxed for fifteen minutes. Benzene and dilute hydrochloric acid were added, the benzene solution was evaporated and the residue was sublimed at 180–200° at 0.4 mm. Recrystallization of the sublimate from alcohol yielded 0.57 g. (83%) of 7,8-dihydro-1,2-benzanthracene in the form of broad, colorless needles; m. p. 112–113.5°.

Anal. Calc'd for $C_{18}H_{14}$: C, 93.9; H, 6.1.
Found: C, 93.6; H, 6.3.

The same hydrocarbon was obtained by heating the chloride at its melting point or by heating a sample of 5-hydroxytetrahydro-1,2-benzanthracene at 200° for fifteen minutes and then subliming the product under reduced pressure.

The *picrate* of 7,8-dihydro-1,2-benzanthracene was prepared from 0.27 g. of the hydrocarbon and 0.3 g. of picric acid in a mixture of absolute alcohol and acetone. After recrystallization from acetone-absolute alcohol the picrate formed fine, reddish-orange needles; m. p. 138–139°.

Anal. Calc'd for $C_{18}H_{14}\cdot C_6H_3N_3O_7$: N, 9.2. Found: N, 9.2.

5,6,7,8-Tetrahydro-1,2-benzanthracene-5-acetic acid (III).—To the sodium ethylate solution prepared from 0.7 g. of sodium and 15 cc. of absolute alcohol was added 7.5 cc. of diethyl malonate; most of the alcohol was then distilled from the mixture and 10 cc. of benzene and 4.7 g. of 5-chlorotetrahydro-1,2-benzanthracene were added. After the mixture had been kept warm for fifteen hours, 10 cc. of aqueous 45% potassium hydroxide was added and the benzene was distilled off. Water was added to dissolve the potassium salt of the substituted malonic acid and the aqueous solution was extracted with benzene; from this benzene extract was isolated 7,8-dihydro-1,2-benzanthracene. Acidification of the aqueous solution precipitated 4.42 g. (75%) of the substituted malonic acid as colorless crystals. From benzene-acetone the acid crystallized in colorless plates which melted at 175–177° with decomposition.

Decarboxylation of the malonic acid at 180° gave 5,6,7,8-tetrahydro-1,2-benzanthracene-5-acetic acid, which crystallized from benzene-acetone in thin, colorless plates; yield, 96%; m. p. 151–152°. A second recrystallization gave colorless needles of the acid which melted at 153–154°.

Anal. Calc'd for $C_{20}H_{18}O_2$: C, 82.7; H, 6.3.
Found: C, 82.4; H, 6.4.

The *methyl ester* of the acid, prepared by means of diazomethane, crystallized from methanol in colorless needles; m. p. 82–83°.

Anal. Calc'd for $C_{21}H_{20}O_2$: C, 82.9; H, 6.6.
Found: C, 82.8; H, 6.6.

1-Keto-2a,3,4,5-tetrahydrocholanthrene (IV).—In order to prepare the acid chloride it was found necessary to employ a solvent, for when a mixture of the acid and thionyl chloride was heated considerable decomposition took place. To a mixture of 15 cc. of anhydrous ether, 1 drop of pyridine and 6.2 cc. of thionyl chloride was added 3.2 g. of the tetrahydro-1,2-benzanthraceneacetic acid. After the mixture

had been refluxed for fifteen minutes, the ether and excess of thionyl chloride were removed under reduced pressure, the acid chloride was dissolved in 15 cc. of carbon disulfide, the solution was treated with 4.8 cc. of anhydrous stannic chloride, and the mixture was warmed gently for one-half hour. The mixture, which contained a crystalline complex of the ketone, was then cooled and hydrolyzed. After the carbon disulfide had been distilled off, the crystalline residue was collected by filtration, washed well with water, and digested with hot dilute sodium hydroxide in order to remove any unchanged acid. The ketone which was collected by filtration was nearly colorless and weighed 3.1 g. By recrystallization from chloroform-alcohol the ketotetrahydrocholanthrene (2.8 g.) was obtained as colorless plates; m. p. 193–194°. The ketone is little soluble in alcohol or acetone but dissolves readily in hot chloroform. It gives an orange-yellow color with concentrated sulfuric acid.

Anal. Calc'd for $C_{20}H_{16}O$: C, 88.2; H, 5.9.
Found: C, 88.0; H, 6.0.

The ketone combines with picric acid in benzene to form a *semi-picrate*, which crystallizes in clusters of broad, flat, orange needles; m. p. 178–178.5°.

Anal. Calc'd for $2C_{20}H_{16}O \cdot C_6H_3N_3O_7$: N, 5.3. Found: N, 5.3.

Dehydrogenation of 1-ketotetrahydrocholanthrene.—A mixture of 100 mg. of the ketone and 30 mg. of sulfur was heated at 220° for one-half hour. Sublimation of the product yielded 60 mg. of the bright-yellow 1-ketocholanthrene (m. p. 230°), which was identical with the compound obtained by cyclization of the acid chloride of 1,2-benzanthracene-5-acetic acid.

2a,3,4,5-Tetrahydrocholanthrene (*V*).—A mixture of 2.5 g. of 1-ketotetrahydrocholanthrene, 40 g. of amalgamated zinc (20 mesh), 60 cc. of concentrated hydrochloric acid, 10 cc. of acetic acid and 10 cc. of water was refluxed for forty-eight hours; during this time an additional 60 cc. of hydrochloric acid was added. At the end of this time all of the solid ketone had disappeared and a liquid layer of the tetrahydrocholanthrene was present. The latter was recrystallized from acetone-alcohol and was obtained as colorless plates; yield, 2.22 g. (93%); m. p. 101–106°. The product was found to consist of a mixture of two forms of tetrahydrocholanthrene. By recrystallization from acetone-alcohol or *n*-propyl alcohol colorless prisms or plates, which melted at 107°, were obtained. When these crystals were converted to the picrate and the latter was treated with aqueous sodium hydroxide, the regenerated hydrocarbon crystallized in plates which melted at 101–101.5°. The 107° melting form can also be converted to the 101–101.5° melting form by inoculating a concentrated solution of the former with a crystal of the latter form.

Anal. Calc'd for $C_{20}H_{18}$: C, 93.0; H, 7.0.
Found: C, 93.0; H, 6.7.

Both forms yielded the identical *picrate*, which crystallized from alcohol-acetone in reddish-orange needles; m. p. 168–168.5°.

Anal. Calc'd for $C_{20}H_{18} \cdot C_6H_3N_3O_7$: N, 8.6. Found: N, 8.9.

Dehydrogenation of tetrahydrocholanthrene to cholanthrene.—A mixture of 1.0 g. of tetrahydrocholanthrene and 0.2 g. of the palladium-charcoal catalyst was heated at 300° for one-half hour. The cooled mixture was digested with hot benzene and filtered; addition of ether to the concentrated benzene solution precipitated the cholanthrene as light-yellow plates; m. p. 168.5–170°; yield, 0.8 g. (80%).

7,8-Dihydro-1,2-benzanthracene-5-acetic acid (*XI*).—After more than twenty trial runs had been made in which the proportions of reagents and solvent were varied, the following procedure was found to give the most satisfactory results. Two grams of 5-ketotetrahydro-1,2-benzanthracene was added to a mixture of 4 g. of granulated

zinc (20 mesh, cleansed by dilute hydrochloric acid, washed with acetone and dried), 0.1 g. of iodine and 1.2 cc. of methyl bromoacetate in 20 cc. of anhydrous ether and 20 cc. of benzene. After one-half hour of refluxing on a water bath, all of the ketone had gone into solution and a precipitate began to appear. After a total time of one hour, the solution was cooled and sufficient methanol was added to bring the precipitate into solution, and the filtered solution was hydrolyzed with dilute hydrochloric acid. Evaporation of the benzene-ether solution yielded the hydroxy acid ester (IX) which did not crystallize. The latter was heated with 4 cc. of anhydrous formic acid on a steam bath for five minutes. The formic acid was removed from the hot solution by a stream of air, and the residue was dissolved in a mixture of acetone and methanol. On being cooled the soluton immediately deposited the *methyl ester* of *7,8-dihydro-1,2-benzanthracene-5-acetic acid* (X). The crystals were filtered off, washed with methanol, in which the compound is little soluble, and dried; weight, 2.22 g. (91%); m. p. 100–102°. A sample sublimed at 220° at 0.4 mm. and then recrystallized from acetone-methanol formed colorless prisms which melted at 101.5–102°.

Anal. Calc'd for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0.
Found: C, 83.3; H, 6.0.

Hydrolysis of the methyl ester by a hot solution of potassium hydroxide in methanol yielded 7,8-dihydro-1,2-benzanthracene-5-acetic acid. From benzene this acid crystallized in colorless needles. Since this acid decomposes in the neighborhood of its melting point, the melting point depends on the time the melting-point tube is in the hot bath. When the tube was put in the bath at 160° and the temperature was raised slowly, melting with decomposition took place at 187–189°. When the tube was put in the bath at 185°, the substance melted at 193–194°.

Anal. Calc'd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6.
Found: C, 83.3; H, 5.6.

Dehydrogenation of 7,8-dihydro-1,2-benzanthracene-5-acetic acid.—A mixture of 100 mg. of the acid and 20 mg. of sulfur was heated at 210° for one hour. The product was digested with dilute potassium hydroxide and filtered. The alkali-insoluble portion was sublimed under reduced pressure, and the sublimate was recrystallized from acetone-alcohol; a 20% yield of pure 5-methyl-1,2-benzanthracene was obtained. Acidification of the aqueous solution precipitated 1,2-benzanthracene-5-acetic acid, which was obtained as colorless plates by recrystallization from benzene; m. p. 232–234°; yield, 10%.

1,2-Benzanthracene-5-acetic acid (*XII*).—A mixture of 4.95 g. of the methyl ester of 7,8-dihydro-1,2-benzanthracene-5-acetic acid from the Reformatsky reaction and 0.62 g. of sulfur was heated at 200–205° until no test for hydrogen sulfide was obtained with a piece of filter paper moistened with lead acetate solution (5 hours). A small amount of copper powder was added in order to remove unchanged sulfur, and the heating was continued for five minutes more. The product was digested with hot acetone, the solution was boiled with charcoal, filtered, and concentrated. After two crops of ester had been obtained (4.32 g.; m. p. 113–116°) the residue was sublimed at 230° at 0.4 mm. yielding an additional 0.1 g. of ester, total yield, 90%. After further purification by sublimation followed by recrystallization from acetone-methanol, a sample of the *methyl ester* of *1,2-benzanthracene-5-acetic acid* crystallized in broad, colorless needles melting at 116°.

Anal. Calc'd for $C_{21}H_{16}O_2$: C, 84.0; H, 5.3.
Found: C, 83.8; H, 5.5.

Since the acid and its potassium salt are not very soluble the following procedure was used for hydrolysis. Four grams of the methyl ester was heated with a mixture

of 15 cc. of 45% aqueous potassium hydroxide and 50 cc. of methanol on a steam bath for one-half hour. The methanol was boiled off, and the residue was dissolved in a liter of boiling water. Acidification of the solution yielded the 1,2-benzanthracene-5-acetic acid, which crystallized from acetone-benzene as cream-colored needles melting at 232–233°. The pure colorless acid had a melting point of 233–234°.

Anal. Calc'd for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9.
Found: C, 84.4; H, 5.0.

Oxidation of 1,2-benzanthracene-5-acetic acid.—A mixture of 100 mg. of the acid, 150 mg. of pure sodium dichromate dihydrate and 10 cc. of acetic acid was refluxed for forty-five minutes. Dilute sulfuric acid was added, and the solid which precipitated was collected by filtration and digested with 600 cc. of hot dilute potassium carbonate solution. Acidification of the aqueous solution gave 20 mg. of 1,2-benzanthraquinone-5-acetic acid (XIV). After recrystallization from chlorobenzene containing some acetic acid, which gave the acid as yellow needles, the acid was converted to its *methyl ester* by means of diazomethane. The methyl ester formed yellow needles from acetone-methanol which melted at 168–169°. The identical methyl ester was obtained by oxidation of cholanthrene in the same manner, the yield of product being considerably greater. The free quinone acid has been reported previously by Cook and Haslewood.[2]

Anal. Calc'd for $C_{21}H_{14}O_4$: C, 76.3; H, 4.3.
Found: C, 76.4; H, 4.5.

1-Ketocholanthrene (XIII).—A mixture of 0.5 g. of 1,2-benzanthracene-5-acetic acid, 0.37 g. of phosphorus pentachloride and 2 cc. of benzene was heated on a steam bath for twenty minutes; the solution became green and finally light-yellow in color. The phosphorus oxychloride and the benzene were removed by distillation under reduced pressure, and the acid chloride was dissolved in 5 cc. of carbon disulfide. The solution was then treated with 0.8 g. of anhydrous aluminum chloride, and the mixture was refluxed gently for one hour with frequent shaking. The mixture was cooled, and hydrolyzed with ice, the carbon disulfide was distilled off, the cyclic ketone was taken up in hot benzene, the solution was shaken with aqueous potassium hydroxide, and the ketone was obtained by evaporation of the benzene solution; yield 0.34 g. (72%). By sublimation at 240° at 0.05 mm. a canary-yellow product was obtained which crystallized from benzene in fine yellow needles; m. p. 230°. The ketone gives an orange-red color with concentrated sulfuric acid. It does not form a picrate in benzene solution.

Anal. Calc'd for $C_{20}H_{12}O$: C, 89.5; H, 4.5.
Found: C, 89.5; H, 4.6.

A mixture of 100 mg. of the ketone, 1 g. of amalgamated zinc, 15 cc. of concentrated hydrochloric acid, 1 cc. of acetic acid and 1 cc. of toluene was heated for twenty-four hours. During the reduction a considerable amount of dark-red product was formed. From the mixture was isolated 20 mg. of cholanthrene.

o-Chlorohydrocinnamic acid.—A mixture of 50 g. of *o*-chlorobenzaldehyde (Eastman product redistilled before use), 44 g. of malonic acid and 6 cc. of pyridine was heated in a 500 cc. Soxhlet flask on a steam bath. The reaction began in a few minutes as was evidenced by the evolution of carbon dioxide and the formation of crystalline *o*-chlorocinnamic acid. After two hours the porous mass was broken up and digested with a mixture of 50 cc. of water and 10 cc. of concentrated hydrochloric acid. The *o*-chlorocinnamic acid was separated by filtration, washed with water and then with petroleum ether. The latter washing removed a small amount of

unreacted aldehyde, which was treated again with malonic acid to yield 0.5 g. of *o*-chlorocinnamic acid. The product, which was sufficiently pure for reduction, weighed 60 g. (92%) and melted at 204–206°. Fieser and Hershberg[11] obtained a 62% yield of *o*-chlorocinnamic acid by heating *o*-chlorobenzaldehyde, acetic anhydride and potassium acetate for eight hours.

Reduction of the *o*-chlorocinnamic acid was accomplished by dissolving the acid (60 g.) in a solution of 20.4 g. of potassium hydroxide in 500 cc. of water in a strong 1-liter bottle, adding 1100 g. of 2% sodium amalgam, and shaking the mixture vigorously for about twenty to thirty minutes (or until no rise in temperature was observed when the mixture was shaken vigorously). The solution was separated from the mercury, filtered and acidified with hydrochloric acid. The yield of *o*-chlorohydrocinnamic acid melting at 96–97° was 60 g. (99%).

4-Cyanohydrindene.—The preparation of 4-chlorohydrindone has been described by Fieser and Hershberg and by Mayer, Philipps, Ruppert and Schmitt;[12] our procedure varied somewhat from those described. Thirty-five g. of powdered phosphorus pentachloride was added to a suspension of 30 g. of *o*-chlorohydrocinnamic acid in 60 cc. of benzene. In a short time a colorless solution was obtained. After removal of the phosphorus oxychloride by distillation under reduced pressure on a steam bath, the acid chloride was dissolved in 150 cc. of carbon disulfide. To the cold solution was added a total of 36 g. of aluminum chloride in two portions. Immediate reaction set in and the entire mass solidified. After one-half hour at room temperature, the mixture was poured onto ice, the carbon disulfide was removed by distillation, and the 4-chlorohydrindone was collected by filtration. After digestion with hot dilute ammonium hydroxide, the 4-chlorohydrindone weighed 25 g. (92%). A sample sublimed and recrystallized from alcohol formed diamond-shaped plates; m. p. 90–91° (Fieser and Hershberg, 90–90.5°).

Clemmensen reduction of the 4-chlorohydrindone to 4-chlorohydrindene, and the conversion of the latter to 4-cyanohydrindene were carried out according to the directions of Fieser and Hershberg. The 4-cyanohydrindene after distillation under reduced pressure was distilled at atmospheric pressure; b. p. 250–252° at 740 mm.; yield 82%.

Cholanthrene.—A Grignard reagent was prepared from 38 g. of α-bromonaphthalene and 4.4 g. of magnesium in 100 cc. of ether. About 75 cc. of ether was distilled from the solution, 50 cc. of benzene was added and then 17.9 g. of 4-cyanohydrindene. After being refluxed for seventeen hours the mixture was hydrolyzed by ice and ammonium chloride solution. The ether-benzene solution was separated from the aqueous layer, chilled and treated gradually with 100 cc. of concentrated hydrochloric acid. The solid ketimine hydrochloride was filtered off and hydrolyzed to the ketone by heating it with 10 cc. of acetic acid, 100 cc. of water, and 20 cc. of toluene for one hour. The toluene solution was dried and subjected to distillation, the 4-(α-naphthoyl)hydrindene distilling at 215–220° at 0.2 mm.; yield, 31 g. (91%). Pyrolysis of the ketone at 410° for one-half hour gave 12.2 g. (42%) of cholanthrene (Fieser and Seligman,[3] 34%).

meso-*Dihydrocholanthrene* (*XV*).—A mixture of 0.5 g. of cholanthrene and 0.6 g. of lithium wire in 30 cc. of ether and 30 cc. of benzene was shaken with some sharp parti-

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[11] Fieser and Hershberg, *J. Am. Chem. Soc.*, **59**, 396 (1937).

[12] Mayer, Philipps, Ruppert, and Schmitt, *Ber.*, **61**, 1966 (1928).

cles of glass for four days.[7] Sufficient methanol was added to decolorize the deep-blue solution, and the *meso*-dihydrocholanthrene was obtained by concentrating the solution and adding alcohol. The first crop of colorless needles weighed 0.42 g. (84%) and melted at 160–161.5°; recrystallization from benzene-alcohol raised the melting point to 161.5–162.5°.

An intensely purple-red solution was obtained when 1.0 g. of cholanthrene was shaken with 0.5 g. of sodium powder in 20 cc. of benzene and 40 cc. of ether for three days. A cream-colored product (0.92 g.) was obtained by treatment of the colored solution with methanol. The slight amount of color was best removed from the crystals by recrystallization from benzene; yield, 0.5 g.; m. p. 161.5–162.5°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.7; H, 6.3.
Found: C, 93.8; H, 6.2.

*Preparation of cholanthrene-6,12*b-endo-*α,β-succinic anhydride* (*XVI*).—A solution of 1.0 g. of cholanthrene (m. p. 170–171°) and 1.05 g. of maleic anhydride in 10 cc. of benzene was heated on a steam bath for two days. The original red color of the solution, presumably that of a molecular complex, gradually disappeared; after twelve hours the solution was yellow in color and contained a considerable amount of the adduct in the form of colorless prisms. After forty-eight hours the mixture was cooled, and 1.32 g. (92%) of crystalline adduct was collected by filtration. The solution was evaporated to dryness, and the residue was digested with warm 40% potassium hydroxide solution in order to form the water-soluble salt of the dicarboxylic acid. Sufficient water was added to dissolve the latter, and the solution was extracted with benzene; from the benzene solution was obtained only 5 mg. of cholanthrene, an indication that the adduct had been formed to the extent of 99.5%. The cholanthrene-*endo*-succinic anhydride is little soluble in hot benzene, xylene, acetone, or butyl acetate; from the last named solvent it could be recrystallized and obtained as colorless, glistening prisms. The melting point of the compound varies with the conditions of heating since the compound begins to decompose at about 200°; when the melting point tube was put into the bath at 210° the substance melted at 232° with decomposition to an orange-red liquid.

Anal. Calc'd for $C_{24}H_{16}O_3$: C, 81.8; H, 4.6.
Found: C, 82.1; H, 4.6.

In the runs shown in Table I the procedure outlined in a previous paper was employed.[8] The cholanthrene-*endo*-succinic acid which was obtained by acidification of the solution of the potassium salt was found to be readily soluble in ethyl acetate. In one experiment the ethyl acetate solution of the acid boiled down to dryness on a steam bath; the residue soon became crystalline, for the anhydride was formed. When a small amount of acetic anhydride was added to a solution of the dicarboxylic acid in ethyl acetate and the solution was warmed, the anhydride crystallized from the solution. This method would probably be the most convenient procedure for recrystallizing large amounts of the anhydride.

A suspension of 0.137 g. of the cholanthrene-*endo*-succinic anhydride in 2 cc. of xylene was refluxed gently for one hour; most of the solid went into solution in this time. The solution was evaporated, and the unchanged adduct was removed by means of concentrated potassium hydroxide solution. The cholanthrene which remained (0.08 g. or 80%) possessed very little color, being nearly cream colored, and melted at 172–172.5° (174.5–175° corr.), a value somewhat higher than has been reported previously. This procedure constitutes a method for purifying cholanthrene.

SUMMARY

Cholanthrene has been synthesized from phenanthrene by two methods.

A number of derivatives related to 1,2-benzanthracene and cholanthrene have been synthesized, among them 1,2-benzanthracene-5-acetic acid, tetrahydrocholanthrene, *meso*-dihydrocholanthrene and 1-ketocholanthrene.

Conditions have been worked out for preparing the maleic anhydride addition compound of cholanthrene in nearly quantitative yield. Pure cholanthrene can be obtained by dissociation of the maleic anhydride addition product in hot xylene solution.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

REACTIONS OF PARAFFINS WITH AROMATIC HYDROCARBONS. II. VARIOUS AROMATIC HYDROCARBONS AND 2,2,4-TRIMETHYLPENTANE

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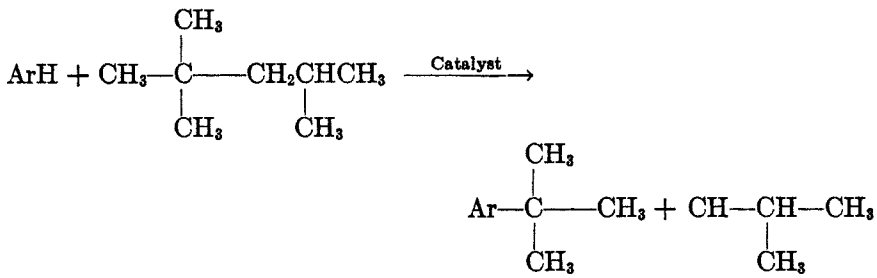
The reaction of various paraffin hydrocarbons with benzene in the presence of catalysts has been described in earlier papers[1, 2]. In the present investigation the reaction of 2,2,4-trimethylpentane with various alkylbenzenes and polynuclear aromatics catalyzed by aluminum chloride has been studied. This particular paraffin was chosen since it has been found to react readily with benzene under mild conditions, and only in one direction—namely, towards the formation of *tert.*-butyl-substituted benzenes and isobutane.[1]

The alkylation reaction can be expressed as follows:



Further reaction may result in the formation of aromatic hydrocarbons containing more than one tertiary butyl group per molecule.

In the present investigation the following aromatics were studied: toluene, ethylbenzene, *p*-xylene, biphenyl, naphthalene, fluorene, and pyrene.

With both *toluene* and *biphenyl*, the normal alkylation reaction was found to proceed quite readily (the reaction was particularly rapid in the case of biphenyl) and the yields of isomeric mono tertiary butyl alkylation products were 34 and 35 per cent., respectively, based on the paraffin reacting. Slightly more than one mole of isobutane per mole of the reacting octane was produced in each case.

[1] GROSSE AND IPATIEFF, *J. Am. Chem. Soc.*, **57**, 2415 (1935).

[2] GROSSE, MAVITY AND IPATIEFF, J. ORG. CHEM., **3**, 137 (1938).

The reactions in the case of *ethylbenzene* and p-*xylene* were complicated by the migration of the alkyl groups[3, 4, 5, 6] giving rise to polyethyl- and polymethylbenzenes, respectively. Although some 2,2,4-trimethylpentane reacted in each case, none of the pure alkylbenzenes formed were isolated from the complex mixtures. The molar ratio of isobutane formed to paraffin reacting (1:1 and 1:3, respectively) indicates that alkylation did occur.

In the case of *fluorene* an interesting hydro-dehydrogenation reaction involving the formation of bifluorenyl and isobutane became predominant.

$$\underset{\text{Fluorene}}{C_{13}H_{10}} + \underset{\text{2,2,4-Trimethylpentane}}{C_8H_{18}} \longrightarrow \underset{\text{Bifluorenyl}}{C_{13}H_9 \cdot C_{13}H_9} + 2\,\underset{\text{Isobutane}}{i\text{-}C_4H_{10}}$$

From each mole of 2,2,4-trimethylpentane which reacted, 1.5 moles of isobutane were produced, indicating that more than half of the paraffin reacted according to the indicated equation.

In the case of hydrocarbons with condensed ring systems no alkylated products were obtained. With *naphthalene* and 2,2,4-trimethylpentane, over 80 per cent. of the latter compound was recovered unchanged although 40 per cent. of the naphthalene was converted to higher-boiling products[7]. This result was unexpected in view of the ease with which naphthalene is alkylated with olefins and alkyl halides. With *pyrene*, over 94 per cent. of the paraffin was recovered unchanged.

Whereas the data of the previous paper[2] showed the dependancy of the reaction on the structure of the particular paraffin used, the present results extend this conclusion to aromatic hydrocarbons and prove that the structure of the aromatic hydrocarbon is a no less important factor.

EXPERIMENTAL

Apparatus

The reactions were carried out in the Pyrex reaction vessel described in an earlier paper.[1] In one experiment with naphthalene at a temperature above 100°, the materials were sealed in a Pyrex tube and heated in an Ipatieff rotating autoclave.

Sources of Reagents

Merck's reagent grade of sublimed *aluminum chloride* was used without further purification. *Hydrogen chloride* was prepared in our laboratory and stored in small steel cylinders *Toluene* and *ethylbenzene*, from J. T. Baker Chemical Company were C.P. products. p-*Xylene*, *fluorene*, and *pyrene*, from the Gesellschaft für Teer-

[3] MUNDICI, *Gazz. chim. ital.*, **34**, II, 121 (1904).
[4] HEISE, AND TÖHL, *Ann.*, **270**, 169 (1892).
[5] ANSHÜTZ, *Ann.*, **235**, 182 (1886).
[6] JACOBSEN, *Ber.*, **18**, 342 (1885).
[7] *Cf.* HOMER, *J. Chem. Soc.*, **91**, 1105 (1907).

verwertung, Duisburg-Meiderich,Germany, were pure products with correct melting points. *Naphthalene*, C.P. and *biphenyl*, practical grade, m.p. 67.5–69°, were from the Eastman Kodak Company. *2,2,4-Trimethylpentane* was from Röhm and Haas Company, b.p. 99.37°, m.p. −107.6°, d_4^{20} 0.6920, n_D^{20} 1.3915.

Reaction Products

Condensible gases were collected in dry-ice traps after removal of excess hydrogen chloride in a weighed soda-lime absorber. These liquefied gases were analyzed by low-temperature fractionation in a Podbielniak column and were always found to be chiefly isobutane containing a trace of higher-boiling liquid carried over with the gas stream. Gases not condensed at −78° were collected in a gas bottle over salt water; these consisted almost entirely of displaced nitrogen from the apparatus.

The products remaining in the reaction vessel always separated into two layers. In case the *upper layer* was liquid at room temperature, it was separated, washed thoroughly with water, dried and fractionated in a high-temperature Podbielniak column. It consisted of a mixture of aromatic hydrocarbons along with any unchanged 2,2,4-trimethylpentane. The quantity of the latter was determined by shaking the appropriate fractions (in a volume ratio of 1:1) first with 100% sulfuric

TABLE I

IDENTIFICATION OF HYDROCARBONS

HYDROCARBON	DERIVATIVE OR METHOD OF IDENTIFICATION
Benzene	Melting point; *m*-dinitrobenzene
m-Diethylbenzene	2,4,6-Trinitro-1,3-diethylbenzene
Durene	Mixture melting point
m-tert.-Butyltoluene	2,4,6-Trinitro-3-tert.-butyltoluene
p-tert.-Butylbiphenyl	Mixture melting point; C and H analysis
Bifluorenyl	C and H analysis

acid, then with acid containing 15% of free sulfur trioxide until the residual hydrocarbon gave no reaction with nitrating mixture.

The *lower layers* were carefully treated with water, the resulting oil was extracted with ether, and distilled. These oils distilled over a wide range, and considerable material remained as residue at 350°. The higher fractions varied in color from yellow to orange and were unsaturated to permanganate solution.

In the reactions where solid aromatic hydrocarbons were used, the upper layers were solid or partially solid at room temperature. In these cases the reaction mixture was first steam-distilled. Any gas evolved during the steam distillation was collected and analyzed. The solid and liquid products were dried and fractionated, the higher-boiling material being distilled under reduced pressure.

The methods used for identifying individual hydrocarbons in narrow boiling fractions are indicated in Table I.

The quantities of starting materials and recovered products as well as the conditions used in each experiment are recorded in Table III.

1. Reaction of 2,2,4-timethylpentane with toluene.—A mixture of toluene (41.4 g.) and aluminum chloride (6.0 g.) was heated by means of a boiling water bath. This was mechanically stirred, while a second mixture consisting of toluene (41.4 g.) and 2,2,4-trimethylpentane (51.4 g.) was introduced dropwise over a period of 3 hours.

Heating was continued for 5 hours. Throughout the entire 8 hours, a slow, continuous stream of dry hydrogen chloride was introduced.

The progress of the reaction, which proceeded gradually, could be followed by observing the rate at which condensible gas was formed.

Low-temperature Podbielniak fractionation of the condensed gas showed the following composition (% by volume): isobutane 90.5%, *n*-butane 5.8%, above butane 3.7%.

High-temperature Podbielniak fractionation of the upper layer gave 17.3 grams of a fraction boiling at 185–190° at 747 mm. and having n_D^{20} 1.4928. Intensive nitration of this material gave a liquid which crystallized on the addition of absolute alcohol. Repeated crystallization gave beautiful pale-yellow crystals having a strong odor of musk and melting at 96–96.5°. The melting point of 2,4,6-trinitro-3-*tert.*-butyltoluene is 96–97°.[8]

Anal. Calc'd for $C_{11}H_{13}N_3O_6$: N, 14.84. Found: N, 14.35.

These results establish the presence of appreciable quantities of *m-tert.*-butyltoluene in this fraction. The remainder of this fraction probably consists of the *p*-isomer.[9]

TABLE II

CHARACTER OF LOWER LAYER

FRACTION	BOILING RANGE, °C.	VOLUME, CC.	n_D^{20}	REMARKS
1	70–132	5.4	1.4827	Saturated to $KMnO_4$. Colorless; aromatic hydrocarbons.
2	132–204	1.0	1.5019	Decolorizes $KMnO_4$ slowly. Yellow; aromatic hydrocarbons.
3	204–368	5.6	1.5799	Decolorizes $KMnO_4$ rapidly. Orange.
Residue		(1.86 g.)		Black

The character of the lower layer is indicated by the data on the oil obtained by treatment of the material with water and extraction with ether (Table II).

2. Reaction of 2,2,4-trimethylpentane with biphenyl.—During a period of 2 hours, 45.6 g. of 2,2,4-trimethylpentane was allowed to fall dropwise into a mechanically-stirred mixture of 123.2 g. of molten biphenyl and 5.3 g. of aluminum chloride, heated in a water bath at 90–95°. A slow, continuous stream of hydrogen chloride was introduced. Reaction proceeded as rapidly as the paraffin was added and the heating and stirring was discontinued 10 minutes after the addition was complete. The major portion of unchanged biphenyl was then steam distilled from the reaction mixture.

The condensed gas (25.5 g.) showed the following composition by low temperature Podbielniak fractionation (% by volume): isobutane 95.5%, butylenes 0.7%, above butane 3.8%. A small quantity of gas (1.2 g.) liberated during the steam distillation was evidently butane, as it was paraffinic and showed a carbon index of 3.9.

The oily residue (80 g.) from the steam distillation was fractionated at diminished pressure to yield 30 g. of biphenyl; 4 g. of intermediate fraction boiling at 100–122°/2

[8] BAUR, *Ber.*, **24**, 2836 (1891).

[9] *Cf.* SHOESMITH AND MCGECHEN, *J. Chem. Soc.*, **1930**, 2231–6.

TABLE III

Destructive Alkylation

Aromatics with 2,2,4-Trimethylpentane. Catalyst: Aluminum Chloride + Hydrogen Chloride

Aromatic	Time, hrs.	Temp., °C.	Maximum pressure, atm.	Quantities of materials charged								Recovered starting materials				Hydrogen chloride		Reacting aromatic		(Diff.) paraffin		Molar ratio of reacting materials paraffin aromatic	Gas, grams (hydrocarbon portion)	Upper layer, grams	Lower layer, grams	Reaction products and approximate yields, grams
				Aromatic		Paraffin		Aluminum Chloride		Hydrogen Chloride		Aromatic		Paraffin												
				Grams	Moles	Grams	Moles	Grams	Moles	Grams	Moles	Grams	Moles	Grams	Moles	Grams	Moles	Moles	%	Moles	%					
Toluene	8	96	1	82.8	0.90	51.4	0.45	6.0	0.045	1.25	0.034	51.5	0.56	9.7	0.085	0.27	0.007	0.34	38	0.365	81	1.1	25.4	90.2	24.5	*i*-Butane, 22.1; *n*-butane, 1.4; monobutyltoluene, 17.3; (*m-tert.*-butyltoluene. identified).
Ethylbenzene	7	100	1	95.4	0.90	51.4	0.45	6.0	0.045	2.02	0.055	34	0.32	18	0.16	1.19	0.033	0.58	64	0.29	64	0.50	20.7	108.4	23.8	*i*-Butane, 18.9; *n*-butane, 0.0; diethylbenzene, 20; benzene, 20; (no individual alkylation prod. definitely identified).
p-Xylene	22.5	100	1	85.0	0.80	45.6	0.40	5.35	0.040	1.10	0.030	42*	0.40	27.5	0.24	0.27	0.007	0.40	50	0.16	40	0.40	13.21	101.82	19.11†	*i*-Butane, 12.1; toluene, 9.6; trimethylbenzene, 9.1; (durene identified; no individual alkylation prod. definitely identified).
Biphenyl	2.2	90–95	1	123.2	0.80	45.6	0.40	5.3	0.040	0.67	0.018	87	0.57	1.8	0.016	0.22	0.006	0.23	29	0.38	95	1.7	26.7	—	—	*i*-Butane, 24.9; isomeric monobutylbiphenyls, 28.5.
Fluorene	22	95–100	1	90.8	0.55	31.2	0.27	3.64	0.027	1.09	0.030	65	0.39	16.6	0.15	0.65	0.018	0.16	29	0.13	47	0.81	11.75	—	—	*i*-Butane, 10.8; bifluorenyl isolated; (no alkylation products identified).

Naphthalene	7	100	1	155.8	1.22	69.4	0.61	8.2	0.061	0.15	0.004	—	—	57.8	0.51	0.12	0.003	—	—	0.10	17	—	0.9	—	—	Butanes, 0.7; (no alkylation products).
Naphthalene	15	125	(Sealed																							
	2	150	tube)	104.3	0.82	46.5	0.41	4.5	0.034	<1.0	<0.03	62.1	0.49	35.6	0.31	—	—	0.33	40	0.10	23	0.30	>2	—	—	*i*-Butane >2; β,β′-binaphthyl identified; (no alkylation products identified).
Pyrene	20	100	1	50.5	0.25	28.5	0.25	3.32	0.025	0.56	0.015	—	—	26.8	0.24	0.18	0.005	—	—	0.01	6	—	0.08	—	—	*i*-Butane, 0.08.

* Includes isomerized xylene (*i.e.* *m*-xylene).

† Black solid.

mm.; 28.5 g. of a water-white liquid boiling at 122–125°/2 mm., n_D^{20} 1.5757; 8 g. of yellow, viscous liquid boiling at 125–162°/2 mm., n_D^{20} 1.5714; and 8.5 g. of a dark-brown, solid residue.

The fraction distilling at 122–125°/2 mm. crystallized to a white solid on standing for several days at −30°, but again liquefied on warming to room temperature. By low-temperature crystallization from pentane, 27% of this fraction was obtained as a white, crystalline solid, which, after several crystallizations from absolute alcohol, melted sharply at 53.1°. A photomicrograph of a single crystal is shown in Figure I.

The well-developed flat prisms show double refraction with straight extinction; their symmetry is probably not greater than rhombic.

Anal. Calc'd. for $C_{16}H_{18}$: C, 91.43; H, 8.57. Found: C, 91.21; H, 8.82.

This compound proved to be identical with a compound synthesized from *p*-bromo-*tert.*-butylbenzene and phenyllithium and is therefore identified as p-tert.-

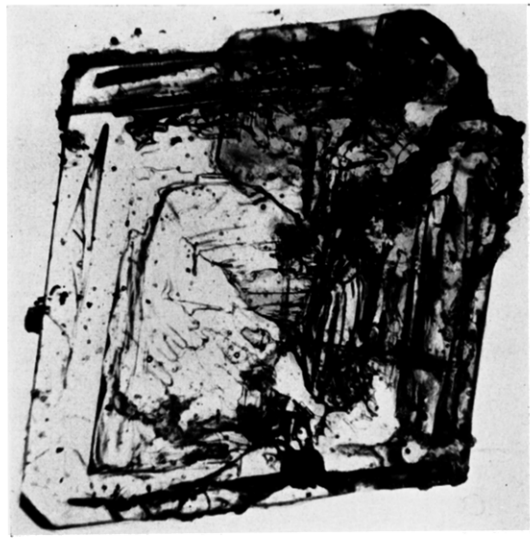


FIGURE I.—*p-tert.*-BUTYLBIPHENYL. MAGNIFICATION 24×

butylbiphenyl. The yield by this latter reaction was poor (about 5%), the chief products being *tert.*-butylbenzene, biphenyl, and a high-boiling resinous material. The synthetic compound melted at 51–2° and this melting point was not depressed by addition of the crystalline alkylation product.

The liquid alkylation product as obtained by distillation is most likely a mixture of isomeric *tert.*-butylbiphenyls. It corresponds to 35% of the reacting 2,2,4-trimethylpentane.

3. Reaction of 2,2,4-trimethylpentane with fluorene.—A mechanically-stirred mixture of 2,2,4-trimethylpentane (31.2 g.), fluorene (90.8 g.) and aluminum chloride (3.64 g.) was heated at a temperature of 95–100°, while a slow continuous stream of dry hydrogen chloride was introduced. Gas evolution was slow, and was apparently complete after 22 hours. At the end of this time the mixture was steam-distilled.

The following composition of the condensed gas (10.65 g.) was indicated by low-temperature Podbielniak fractionation (% by volume): isobutane 91.5, isopentane

5.3, above pentane 3.2. The gas from the steam distillation (1.0 g.) was paraffinic, and had a carbon index of 4.1.

The liquid portion of the steam distillate was identified as unchanged 2,2,4-trimethylpentane, the solid as unchanged fluorene.

The residue from the steam distillation amounted to 25.3 g. of a hard, black solid, which dissolved completely in benzene. It was distilled under diminished pressure to give 2.9 g. of unchanged fluorene; 0.7 g. of an intermediate yellow, liquid fraction distilling at 155–210°/0.2 mm.; 6.8 g. of a clear, red-brown resin boiling at 210–240°/0.2 mm.; and 14.8 g. of residue, consisting of a hard brownish-black resin which deposited crystals from benzene solution.

The fraction boiling at 210–240°/0.2 mm. crystallized readily from benzene, giving, after several crystallizations, pure, white, fine needles melting at 230.2° to 230.7°. The compound is sparingly soluble in benzene. Its composition corresponds to *bifluorenyl*.

Anal. Calc'd for $C_{26}H_{18}$: C, 94.50; H, 5.50.
Found: C, 94.6; H, 5.51.

4. Reaction of 2,2,4-Trimethylpentane with ethylbenzene, p-xylene, naphthalene, and pyrene.—Data on the conditions of the attempted reaction of 2,2,4-trimethylpentane with each of these four aromatic hydrocarbons are included in Table III.

ACKNOWLEDGMENT

The authors wish to acknowledge their indebtedness to R. W. Moehl for the carbon and hydrogen analyses and photomicrograph, and to J. Grutka who made the low-temperature Podbielniak analyses.

SUMMARY

2,2,4-Trimethylpentane has been caused to react with various aromatic hydrocarbons with the use of aluminum chloride as catalyst.

1) With *toluene* and with *biphenyl*, the destructive alkylation reaction occurred, giving isobutane and about 35 per cent. of the mono *tert.*-butyl aromatic. *m-tert.*-Butyltoluene and *p-tert.*-butylbiphenyl have been definitely identified.

2) With *ethylbenzene* and p-*xylene* the alkylation reaction was complicated by migration of the ethyl and methyl groups, giving polyethyl and polymethyl aromatics.

3) *Fluorene* and 2,2,4-trimethylpentane underwent a hydrodehydrogenation reaction, giving bifluorenyl and isobutane.

4) In the case of the polynuclear aromatic hydrocarbons, *naphthalene* and *pyrene*, no alkylation could be established and substantially all of the paraffin could be recovered unchanged.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ACTION OF BENZENE AND ALUMINUM CHLORIDE ON 2,3-DIPHENYLINDONE

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When diphenylindone (I) is boiled with two moles of aluminum chloride in an excess of benzene, the emerald green color of the original complex rapidly changes to a greenish-brown, and from the resulting solution there can be isolated a colorless compound whose weight corresponds to about 109% of that of the diphenylindone used.

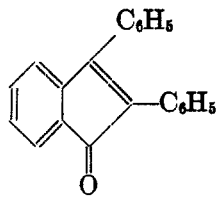
Although this product has finally been shown to be the expected 2,3,3-triphenylhydrindone (II), this formula could not be assumed without proof because (1) the action of benzene and aluminum chloride on quinone stops with the formation of 2,5-diphenylquinone;[1] (2) the action of benzene and aluminum chloride on β,β-diphenylacrylophenone is one of reduction, leading to β,β-diphenylpropiophenone;[2] (3) the properties of the product itself, stability towards fused alkali and towards chromic acid, resistance to phenylation by phenylmagnesium bromide, solubility in Claisen's solution and easy formation of *o*-esters and ethers are not those of the analogous acyclic ketone diphenylacetophenone.

The proof of the structure of the product, reported in this paper, is complicated somewhat by the occurrence of an unusual rearrangement, the generality and mechanism of which will be the subject of future investigations. Although II itself is not attacked by cold permanganate or chromic acid and on more vigorous treatment with these reagents is completely destroyed, its benzoate can be oxidized by chromic acid to IV. On careful treatment of IV with sodium hydroxide it yields sodium benzoate and V, and this, treated more vigorously with the same reagent, is converted into the sodium salt of the acid VI. Dehydration of VI by warming with acetic acid containing a trace of sulfuric acid gives a new acid VII, which can be oxidized with chromic acid to a neutral substance, VIII. When VIII is reduced with potassium iodide in acetic acid, it yields 9,10-diphenylanthracene (IX), the only previously known compound in the series of degradation products.

The presence of the phenyl groups on the *meso* carbon atoms of the final

[1] PUMMERER AND PRELL, *Ber.*, **55**, 3105 (1922).

[2] ALEXANDER, JACOBY, AND FUSON, *J. Am. Chem. Soc.*, **57**, 2208 (1935).



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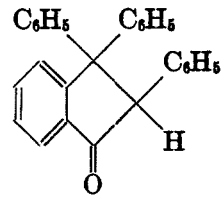

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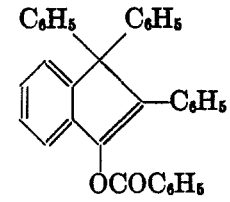

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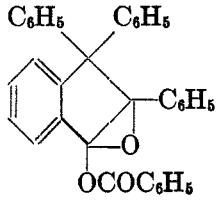

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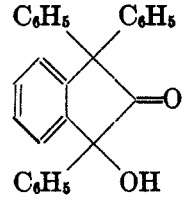

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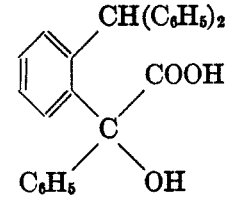

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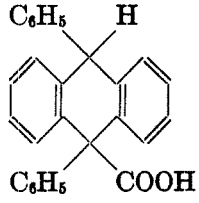

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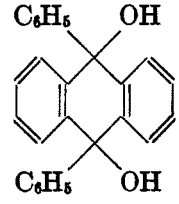

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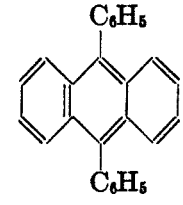

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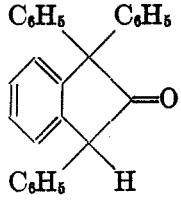

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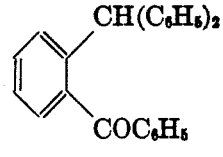

XI

degradation product (IX) points incorrectly to the structure X for the substance (II) obtained from diphenylindone, benzene, and aluminum chloride. The non-occurrence of rearrangements during the two dehydrations by acid is made certain by the fact that acid VI may be oxidized to *o*-benzoyltriphenylmethane, (XI), a known compound. Compound V, the precursor of VI, on account of its reactions and composition must be a triphenylhydroxy ketone with the indene nucleus intact, but it gives on reduction a substance isomeric with but different from II. Thus in the reactions involved in the conversion of II into IX migration of a phenyl

group must have taken place, and accordingly structure II correctly represents the Friedel-Crafts product.

A consideration of the following facts serves to locate the reaction during which the migration takes place. Benzoate III is reconverted into benzoic acid and II on treatment with alcoholic alkali, and benzoate IV may be reduced to benzoic acid and II. If it is assumed that reduction is accompanied by rearrangement of a phenyl group, the improbable conclusion is reached that oxidation involves the migration of both a phenyl and the benzoyloxy groups. If, however, reduction involves no rearrangement, the rearrangement must occur during the hydrolysis of IV to V.

EXPERIMENTAL

The Friedel-Crafts reaction.—A mixture of 20 g. of diphenylindone, 30 g. of aluminum chloride, and 200 ml. of benzene is boiled for ten minutes, the green color of the mixture changing to greenish brown. The addition of dilute hydrochloric acid and removal of the benzene by steam distillation leaves a crystalline residue. This, crystallized once from acetic acid, is white, weighs 21.8 g., and melts at 191–193°.

As evidence of the reversibility of the reaction, 2,3,3-triphenylhydrindone may also be obtained from 2-phenyl-3-*p*-tolylindone, benzene and aluminum chloride in a similar yield.

Anal. Calc'd for $C_{27}H_{20}O$: C, 90.0; H, 5.6.
Found: C, 89.8; H, 5.6.

The ketone is recovered unchanged after treatment with phenylmagnesium bromide, with sodium in butyl alcohol, or with chromic acid in acetic acid at 50°. On fusion with potassium hydroxide at 250° it is converted into a yellow solid which gives back the original hydrindone on treatment with water. The ketone is difficultly soluble in hot alcohol, but readily forms a yellow solution in alcohol containing a little sodium hydroxide.

Acylation and etherification.—A solution of 2,3,3-triphenylhydrindone (5 g.), benzoyl chloride (5 ml.) and pyridine (5 ml.) in chloroform (15 ml.) is warmed for a few minutes, cooled and washed with dilute acid and dilute base. From acetic acid the product, 1,1,2-triphenyl-3-benzoyloxyindene, separates in the form of colorless prisms that melt at 152–154°; yield, 5.3 g.

Anal. Calc'd for $C_{34}H_{24}O_2$: C, 87.9; H, 5.2.
Found: C, 87.5; H, 5.1

A similar procedure using *p*-chlorobenzoyl chloride gives a mixture of *p*-chlorobenzoic anhydride and the p-*chloro-benzoate*, which forms white prisms from acetic acid that melt at 203–204°.

Anal. Calc'd for $C_{33}H_{23}O_2Cl$: C, 81.8; H, 4.62.
Found: C, 81.6; H, 5.13.

On boiling the hydrindone with an excess of acetic anhydride containing potassium acetate it is converted into 1,1,2-triphenyl-3-acetoxyindene, white plates from acetic acid that melt at 147–148°.

Anal. Calc'd for $C_{29}H_{22}O_2$: C, 86.5; H, 5.5
Found: C, 86.0; H, 5.5

1,1,2-Triphenyl-3-benzyloxyindene is obtained in a 70% yield when benzyl chloride (3 ml.) is added to a solution of sodium (0.5 g.) and the hydrindone (1 g.)

in absolute alcohol (20 ml.) and the mixture is boiled until neutral. The ethoxytoluene and alcohol are removed by steam distillation, and the residue is crystallized from acetic acid. It forms white plates that melt at 149–151°.

Anal. Calc'd for $C_{34}H_{26}O$: C, 90.6; H, 5.8.
Found: C, 90.0; H, 5.8.

1,1,2-Triphenyl-3-methoxyindene is obtained by adding 40% aqueous sodium hydroxide and methyl sulfate alternately to a suspension of the hydrindone in alcohol until the addition of the base no longer causes the development of a yellow color. From acetic acid the product forms white plates that melt at 117–119°.

Anal. Calc'd for $C_{28}H_{22}O$: C, 89.8; H, 5.9.
Found: C, 89.4; H, 5.9.

The acyl derivatives are rapidly hydrolyzed on boiling with alcoholic alkali, giving the original hydrindone, while the ethers are completely hydrolyzed to the hydrindone on boiling with a mixture of 40% aqueous hydrobromic acid (1 vol.) and acetic acid (2 vols.) for two hours.

Oxidation of the benzoate.—A suspension of the finely divided benzoate (III) (20 g.) in acetic acid (100 ml.) is treated with a solution of 7 g. of chromic anhydride in 5 ml. of water and 20 ml. of acetic acid. The mixture is kept at 60° for three hours, then cooled and poured into water and ether. The ether solution is washed with aqueous sodium carbonate and evaporated. The residue is crystallized from acetic acid, when there is obtained 16.5 g. of 1,1,2-triphenyl-3-benzoyloxy-2,3-epoxyhydrindene (IV), white prisms that melt at 193–195°.

Anal. Calc'd for $C_{34}H_{24}O_3$: C, 85.0; H, 5.0.
Found: C, 84.7; H, 5.2.

Reduction of the oxide (IV).—A solution of the oxide (0.5 g.) and 50% aqueous hydriodic acid (0.5 ml.) in 10 ml. of acetic acid is boiled for one hour. After working up the mixture there is obtained 0.35 g. of 2,3,3-triphenylhydrindone and 0.1 g. of benzoic acid.

Hydrolysis of the oxide (IV).—The oxide (16.3 g.) is added to a solution of 2.5 g. of sodium in 100 ml. of 95% methanol, and the mixture is boiled until complete solution takes place (about ten minutes). The products are transferred to ether, from which sodium carbonate removes benzoic acid (3.0 g. after crystallization from water). The neutral hydroxyketone (V) is purified by crystallization from toluene-ligroïn. There is obtained 11.85 g. of 1,1,3-triphenyl-3-hydroxyhydrindone-2, fine white needles that melt at 157–159°.

Anal. Calc'd for $C_{27}H_{20}O_2$: C, 86.1; H, 5.3.
Found: C, 85.5; H, 5.4.

Reduction of the hydroxyketone (V).—A solution of 1 g. of the hydroxyketone and 4 ml. of 47% hydriodic acid in 15 ml. of acetic acid is boiled for one minute. The solution is decolorized with aqueous bisulfite, and the product is crystallized from ether. There is obtained 0.8 g. of 1,3,3-triphenylhydrindone-2, white prisms that melt at 106–109°.

Anal. Calc'd for $C_{27}H_{20}O$: C, 90.0; H, 5.6.
Found: C, 90.1; H, 5.7.

Cleavage of the hydroxyketone (V).—The hydroxyketone (5 g.) is boiled for two hours with a solution of 2 g. of sodium hydroxide in 50 ml. of 90% ethanol. The solution is poured into 100 ml. of water, warmed to dissolve the sodium salt, and acidified. The precipitated acid becomes solid on boiling its aqueous suspension; it is filtered and crystallized from dilute acetic acid. There is obtained 4.9 g. of *o*-benzohydrylbenzilic acid (VI), fine white plates that melt at 188–189° with gas evolution.

Anal. Calc'd for $C_{27}H_{22}O_3$: C, 82.2; H, 5.6.
Found: C, 82.3; H, 6.0.

Shaking a suspension of the sodium salt of the acid in warm 5% sodium hydroxide with an excess of methyl sulfate gives the *methyl ester*, white needles from methanol that melt at 121–123°.

Anal. Calc'd for $C_{28}H_{24}O_3$: C, 82.3; H, 5.9.
Found: C, 82.1; H, 5.9.

Dehydration of the acid (VI).—A solution of 1 g. of *o*-benzohydrylbenzilic acid in 10 ml. of acetic acid containing 0.1 ml. of concentrated sulfuric acid is boiled for five minutes and then poured into water and ether. Washing the ether solution with sodium carbonate removes the acidic products in the form of their difficultly soluble sodium salts. These are separated by crystallization into a small amount of the sodium salt of the acid (VI) (more easily soluble) and that of the acid (VII). 9,10-Diphenyl-9,10-dihydroanthracene-9-carboxylic acid crystallizes from acetic acid in white prisms that have a violet fluorescence and melt at 236–238°.

Anal. Calc'd for $C_{27}H_{20}O_2$: C, 86.1; H, 5.3.
Found: C, 86.2; H, 5.7.

The *methyl ester*, obtained from the sodium salt and methyl sulfate in warm alkali, forms a white powder with a violet fluorescence; crystallized from acetic acid it melts at 195–197°.

Anal. Calc'd for $C_{28}H_{22}O_2$: C, 86.1; H, 5.7.
Found: C, 85.5; H, 5.8.

Oxidation of the acid (VII).—A solution of 0.9 g. of 9,10-diphenyl-9,10-dihydroanthracene-9-carboxylic acid and 0.5 g. of chromic anhydride in 10 ml. of acetic acid is kept at 80° for ten minutes. The mixture is poured into water and ether, and the unchanged acid (50 mg.) is removed by washing the ether solution with carbonate. From the ether is obtained 0.5 g. of 9,10-diphenyl-9,10-dihydroxy-9,10-dihydroanthracene (VIII) which melts at 183–185° after crystallization from benzene and drying at 100°.

Anal. Calc'd for $C_{26}H_{20}O_2$: C, 85.7; H, 5.5.
Found: C, 85.6; H, 5.6.

This glycol is distinctly different from the previously known 9,10-diphenyl-9,10-dihydroxy-9,10-dihydroanthracene[3] of m.p. 247°. Since, however, like the latter compound it gives a blue color with sulfuric acid, and on reduction is converted into 9,10-diphenylanthracene, it must be a stereoisomer of the 247° glycol.

Reduction of the glycol is carried out by warming it in acetic acid with an excess of sodium iodide. The resulting 9,10-diphenylanthracene melts at 245–246° alone or mixed with a sample prepared by reduction[4] of the 247° glycol.

Oxidation of the acid (VI).—To a solution of 1 g. of *o*-benzohydrylbenzilic acid warmed to 85° is added a small excess chromic acid in acetic acid. Crystallized from ethanol the neutral oxidation product (0.55 g.) forms white prisms that melt at 84–86° (literature,[5] 88°). On treatment with phenylmagnesium bromide it gives *o*-benzohydryltriphenylcarbinol that melts at 213–215° (literature,[6] 218°). Dehy-

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[3] HALLER AND GUYOT, *Bull. soc. chim.*, [3], **31**, 798 (1904).
[4] SIMONIS AND REMMERT, *Ber.*, **48**, 208 (1915).
[5] SEIDEL AND BEZNER, *ibid.*, **65**, 1566 (1932).
[6] BARNETT, COOK, AND NIXON, *J. Chem. Soc.*, **1927**, 504.

dration of the carbinol so obtained gives 9,9,10-triphenyl-9,10-dihydroanthracene that melts at 223–225° (literature,[7] 223°).

SUMMARY

The action of benzene and aluminum chloride on 2,3-diphenylindone or on 2-phenyl-3-*p*-tolylindone leads to 2,3,3-triphenylhydrindone. The structure of the product is proved by conversion through a series of degradation products into known compounds. The degradation involves a rearrangement, whose mechanism and generality will be investigated.

[7] KOVACHE, *Ann. chim. phys.*, [9], **10**, 227 (1918).

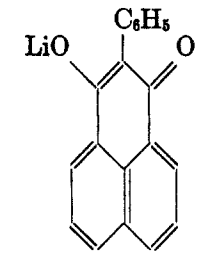
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

STUDIES IN THE *peri*-NAPHTHINDENE SERIES. III. THE ACTION OF PHENYLMAGNESIUM BROMIDE ON 7-ETHOXY-*peri*-NAPHTHINDENONE-9*

C. F. KOELSCH AND R. H. ROSENWALD

Received September 30, 1938

It has been shown in paper II[1] of this series that the addition of phenyllithium to 8-phenyl-*peri*-naphthindandione-7,9, a reaction which undoubtedly proceeds through the primary formation of the lithium enolate (I) of the diketone, involves 1,4 addition, forming II after removal of the metal. Also it was noted that 7-methoxy-8-phenyl-*peri*-naphthindenone-9 (III) reacts with phenylmagnesium bromide in a similar way, leading ultimately to IV.



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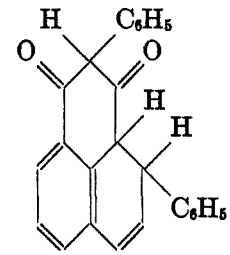

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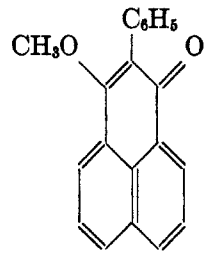

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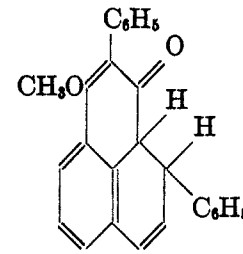


IV

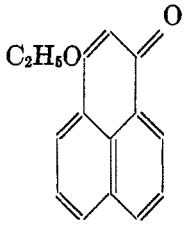
The reaction of phenylmagnesium bromide with 7-ethoxy-*peri*-naphthindenone-9 (V) has been described by Calderaro,[2] who considered the

* A portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy by R. H. Rosenwald, December, 1936.

[1] KOELSCH AND ROSENWALD, *J. Am. Chem. Soc.*, **59**, 2166 (1937).

[2] CALDERARO, *Gazz. chim. ital.*, **42**, II, 464 (1913).

reaction to lead to VI, the product of a 1,2 addition. Analogy with the reactions noted above would suggest that this reaction also might involve a 1,4 addition, unless its course were changed by the phenyl substituent on carbon-8. Since Calderaro's work was done at a time before the possibility that an aromatic unsaturation might take part in a 1,4 addition of this type had been recognized, some doubt naturally attaches to the structures suggested by him. And in fact, as is shown in the present paper, Calderaro's reaction does involve 1,4 addition, his addition product has the structure VII, and his supposed 7,9-dihydroxy-9-phenylnaphthindene is actually VIII.



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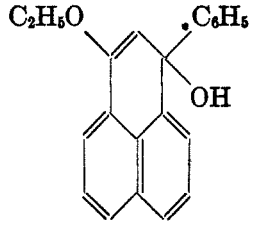

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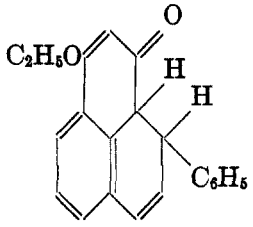

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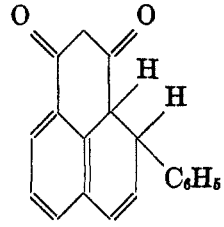
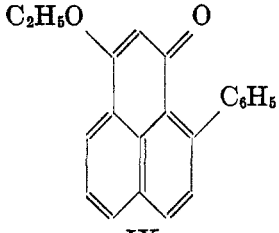
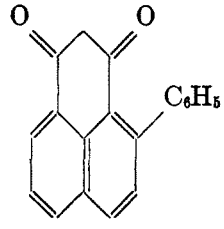


VIII

The position of the phenyl introduced by the Grignard reagent was shown by treating the addition product (VII) with quinone, which yielded IX, hydrolysis of this to the diketone (X), and finally oxidation of the latter to the known 2-phenylnaphthalic anhydride (XI).



IX



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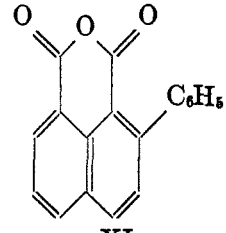


XI

EXPERIMENTAL

peri-*Naphthindandione-7,9.*—The diketone was prepared according to the procedure of Errera.[3] From 60 g. of naphthalic anhydride, 110 g. of malonic ester, and 60 g. of zinc chloride there was obtained 30–60 g. of diketone, m.p. 250–265°.

7-Ethoxy-peri-*naphthindenone-9.*—Treatment of the diketone with alcohol and sulfuric acid according to the procedure of Errera[3] gave the ether in a yield of 45%; it melted at 147–148°. Treatment of the diketone with ethyl sulfate and alkali did not give satisfactory yields of the ether.

Reaction with phenylmagnesium bromide.—A benzene solution of the ethoxyketone (1.3 g.) was added to two molecular equivalents of phenylmagnesium bromide in ether. The dark-blue solution was boiled for four hours, decomposed with dilute hydrochloric acid and worked up as usual. The resulting 1-phenyl-7-ethoxy-1,9*a*-dihydro-*peri*-naphthindenone-9 (VII) melted at 156–157° and weighed 0.3 g. after crystallization from dilute acetic acid. The substance dissolved in aqueous alkali and was reprecipitated unchanged by acids.

On boiling for one hour with acetic acid (7 ml.) containing 40% hydrobromic acid (2.5 ml.) the above addition product (0.35 g.) was hydrolyzed. The yellow 1-phenyl-1,9*a*-dihydro-*peri*-naphthindandione-7,9 (VIII) was crystallized from methanol. Very slowly heated, it melted at about 220°, heated more rapidly at 240–245°, and when placed in a bath pre-heated to 240° it melted at about 250°. Dissolved in toluene, the diketone reacted with quinone to give quinhydrone, but the dehydrogenation product could not be isolated.

1-Phenyl-7-ethoxy-peri-*naphthindenone-9* (IX).—A benzene solution of benzoquinone (0.2 g.) was added to a solution of (VII) (0.2 g.) in benzene. The mixture was washed with dilute alkali and steam-distilled to remove excess quinone. Crystallization from ligroin and then from methanol gave yellow needles (0.13 g.) that melted at 153–154°.

Anal. Calc'd for $C_{21}H_{16}O_2$: C, 83.96; H, 5.37.
Found: C, 83.66; H, 5.61.

1-Phenyl-peri-*naphthindandione-7,9* (*X*).—Compound IX was hydrolyzed by the same procedure as that used for the preparation of the dihydro compound (VIII). Crystallized from toluene, the resulting diketone melted at 240–250°, with decomposition and the formation of a dark sublimate. This behavior serves to distinguish it from VIII which does not melt with this very noticeable decomposition.

Anal. Calc'd for $C_{19}H_{12}O_2$: C, 83.79; H, 4.44.
Found: C, 83.75; H, 4.83.

Oxidation of 1-phenyl-peri-*naphthindandione-7,9.*—An aqueous solution of potassium permanganate (0.2 g.) was added to a solution of X (0.03 g.) in dilute sodium hydroxide. After the mixture had stood for fifteen minutes, the excess permanganate was destroyed with bisulfite and acid, and the precipitated 2-phenylnaphthalic anhydride was crystallized from acetic acid. The anhydride formed characteristic white cubes (0.01 g.) which melted alone or mixed with a known sample[1] at 239–240°.

SUMMARY

It is shown that the reaction between phenylmagnesium bromide and 7-ethoxy-*peri*-naphthindenone-9 involves a 1,4 addition of the Grignard reagent, in analogy with the behavior of the previously studied 7-methoxy-8-phenyl-*peri*-naphthindenone-9.

[3] ERRERA, *ibid.*, **41**, I, 190 (1911).

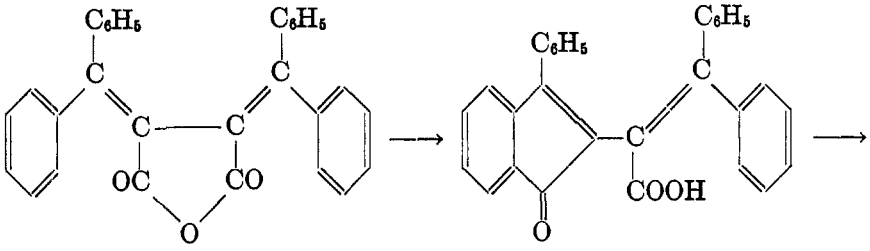
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ACTION OF ALUMINUM CHLORIDE ON CERTAIN PHENYLATED FULGENIC ANHYDRIDES*

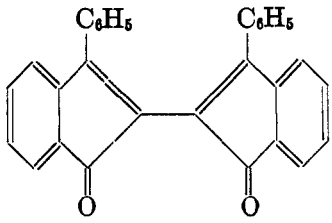
C. F. KOELSCH AND H. J. RICHTER

Received September 30, 1938

One of the methods by which it was hoped to synthesize derivatives of 2,2′-bisindene in connection with a study[1] of the rubrene problem may be summarized in the following reactions:



I II



III

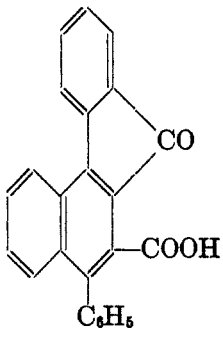
Now although the conversion of tetraphenylfulgenic anhydride (I) into the indone acid (II) was finally accomplished, conditions were never found for conversion of II into III. The results actually obtained in the research were, however, of greater interest than those to be expected had the experiments proceeded as outlined. They are reported in the present paper.

When tetraphenylfulgenic anhydride dissolved in benzene was treated with aluminum chloride, it was converted into a mixture of two sub-

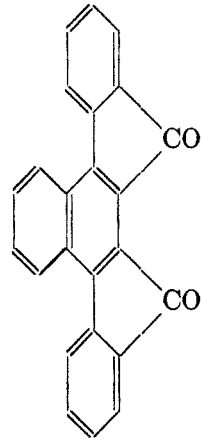
* A portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy by H. J. Richter, June, 1937.

[1] KOELSCH AND RICHTER, *J. Am. Chem. Soc.*, **57**, 2010 (1935).

stances, 2-phenyl-3,4-benzofluorenone-1-carboxylic acid (IV) and the previously known 1,2,3,4-dibenzoylenenaphthalene (V). The latter compound was identified by comparison with a sample prepared according to the method of Weiss and Abeles,[2] and it was found that the anhydride (VI), also prepared by the method of these investigators, could be readily converted into product IV by the action of aluminum chloride in benzene.



IV



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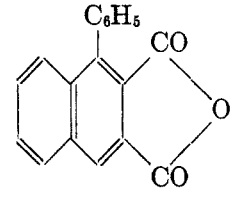
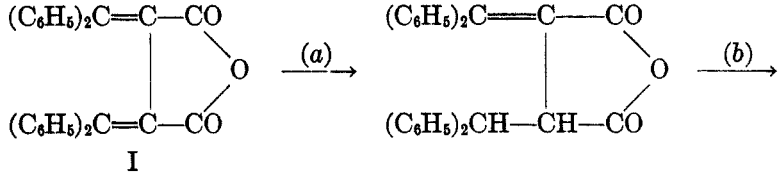
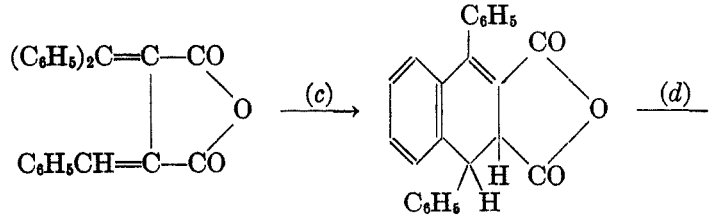


VI

It was apparent that the diketone (V) was a secondary product resulting from the dehydration of the acid (IV), and this dehydration could be carried out readily. But the formation of IV from I, a reaction involving the loss of benzene, was not easily accounted for. A more or less plausible mechanism for this reaction, represented in the accompanying formulas, was first considered.

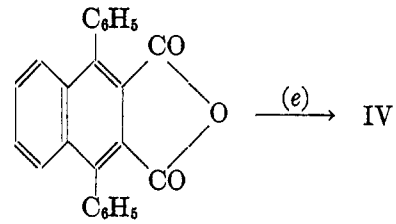


I



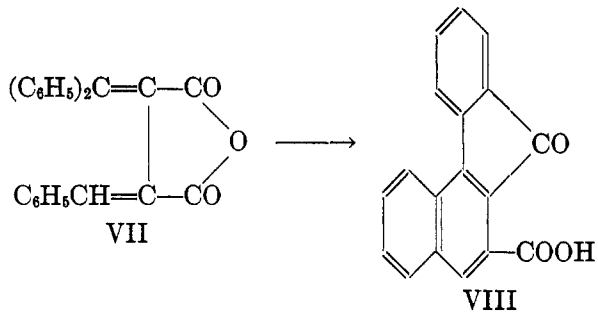
VII

[2] WEISS AND ABELES, *Monatsh.*, **61**, 162 (1932).



None of the reactions involved in this mechanism is without analogy. With *a* is to be compared the conversion of 1,1-diaryl-2-acylethylenes to 1,1-diaryl-2-acylethanes;[3] *b* involves the reversibility of the Friedel-Crafts reaction;[4] while *c* and *d* find an analogy in the conversion by aluminum chloride of 1-cinnamoylnaphthalene into 7-phenyl-*peri*-naphthindone-9.[5,†]

A simple experiment, however, demonstrated the incorrectness of the above mechanism. Treatment of triphenylfulgenic anhydride (VII), an intermediate in the mechanism in question, with aluminum chloride in benzene gave no trace of either IV or V. Instead there was obtained 3,4-benzofluorenone-1-carboxylic acid (VIII).



The true mechanism by which IV was formed from tetraphenylfulgenic anhydride and VIII was formed from triphenylfulgenic anhydride was discovered only after the behavior of these anhydrides towards aluminum chloride in nitrobenzene had been studied. In this solvent, in analogy with diphenylitaconic anhydride (IX) which thus treated yields 3-phenylindone-1-acetic acid[6] (X), tetraphenylfulgenic anhydride gave 3-phenyl-2-

[3] ALEXANDER, JACOBY, AND FUSON, *J. Am. Chem. Soc.*, **57**, 2208 (1935).

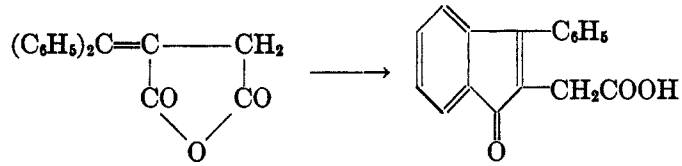
[4] FUSON AND CO-WORKERS, *ibid.*, **56**, 2103 (1934), and previous papers.

[5] KOLISCHER, HONOLD, AND GRENNE, German Patent 491089; *Chem. Zentr.*, **101**, II, 469 (1930).

† Unpublished work carried out in This Laboratory by Mr. J. A. Anthes indicates that cinnamoylnaphthalene gives *peri*-naphthindone and not its 7-phenyl derivative.

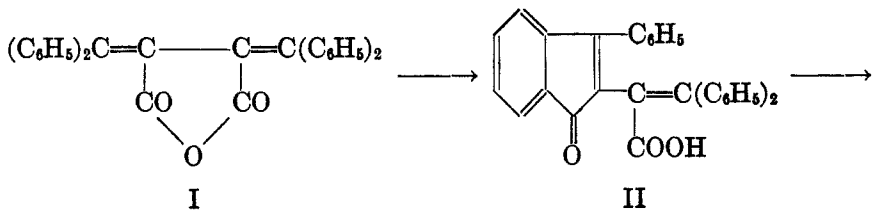
[6] BORSCHE, *Ann.*, **526**, 1 (1936).

(α-carboxy-β,β-diphenylvinyl)indone (II) and triphenylfulgenic anhydride gave 3-phenyl-2(α-carboxystyryl)indone (XI).

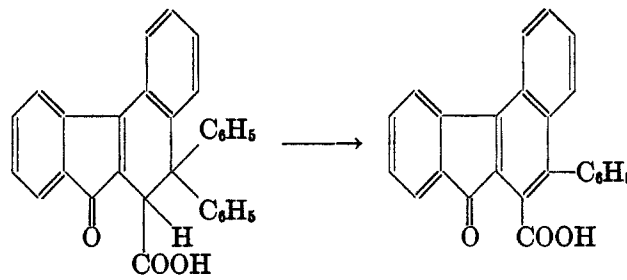


IX X

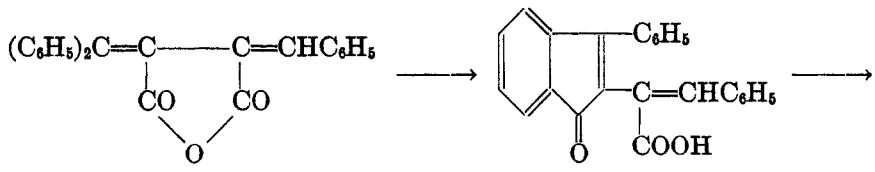
Now when acid II dissolved in benzene was treated with aluminum chloride it was converted into IV; its chloride similarly treated gave V. Analogously acid XI was converted by aluminum chloride in benzene into VIII. The following reactions thus represent the course of the conversion of I into IV, and VII into VIII.



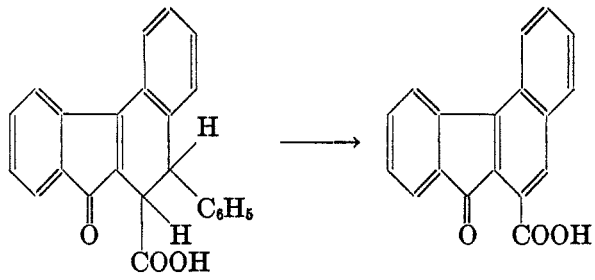
I II



IV

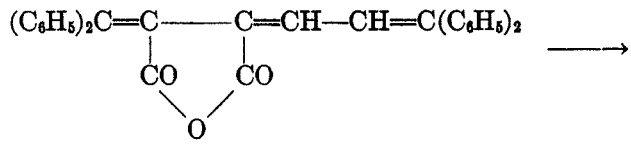


VII XI

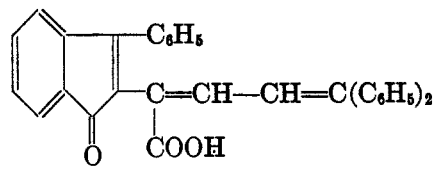


VIII

1,1,6,6-Tetraphenylhexatriene-2,3-dicarboxylic anhydride (XII), either the high- or low-melting form, behaved in a manner analogous to that of tetraphenylfulgenic anhydride when treated with aluminum chloride in nitrobenzene. It gave in good yield α1-(3-phenylindonyl-2)-δ,δ-diphenylbutadiene-α-carboxylic acid (XIII).



XII



XIII

All the acids obtained in this research were found to lose carbon dioxide when their solutions in quinoline containing a little copper acetate were boiled for a few minutes.

EXPERIMENTAL

Tetraphenylfulgenic anhydride and aluminum chloride in benzene.—A solution of tetraphenylfulgenic anhydride[7] (1 g.) in benzene (50 ml.) became deep red on the addition of aluminum chloride (3 g.), and after a short time deep green. It was boiled for thirty minutes, then decomposed with dilute hydrochloric acid, and the benzene was removed with steam. The solid residue was separated by crystallization from acetic acid into the more difficultly soluble dibenzoylenenaphthalene and 2-phenyl-3,4-benzofluorenone-1-carboxylic acid. The diketone formed orange-red needles which melted (copper block) at 308–310° (literature,[2] 295–297°). The compound was

[7] KOELSCH AND RICHTER, J. ORG. CHEM., **3**, 473 (1938).

identified by direct comparison with a sample of the same melting point obtained by the method of Weiss and Abeles.

Anal. Calc'd for $C_{24}H_{12}O_2$: C, 86.7; H, 3.62.
Found: C, 86.5; H, 3.78.

The keto acid was purified through its difficultly soluble orange sodium salt and was recrystallized from acetic acid. The bright red substance melted at 264–266t on a copper block. In a capillary tube it was still solid at 280°.

Anal. Calc'd for $C_{24}H_{14}O_3$: C, 82.3; H, 4.0.
Found: C, 82.2; H, 4.3.

The above procedure gave approximately equal amounts of the two products. When the reaction mixture was boiled for a shorter time (10 minutes) the product (0.86 g.) consisted nearly wholly of the keto acid.

The keto acid gave a purple solution which rapidly became very dark in ice-cold concentrated sulfuric acid. Such a solution allowed to stand for forty-five minutes and then poured into water gave a good yield of dibenzoylenenaphthalene.

The keto acid was decarboxylated by boiling its solution in ten times its weight of quinoline with a few mg. of copper acetate for five minutes. The 2-phenyl-3,4-benzofluorenone so obtained was crystallized from acetic acid, giving fine rusty-orange needles which melted at 191° (literature[2] 187–189°).

The keto acid was synthesized by boiling 1,4-diphenyl-naphthalene-2,3-dicarboxylic anhydride (m.p. 288–289°, literature,[2] 275°) (1 g.) in benzene (100 ml.) with aluminum chloride (2 g.) for fifteen minutes. So obtained it formed red crystals (0.65 g.) which melted at 266–270° alone or mixed with the acid obtained from tetraphenylfulgenic anhydride; its decarboxylation product (m.p. 190–191°) likewise caused no depression in the melting point of the 2-phenyl-3,4-benzofluorenone obtained as above.

Triphenylfulgenic anhydride and aluminum chloride in benzene.—The deep green solution obtained by adding aluminum chloride (3 g.) to triphenylfulgenic anhydride[8] dissolved in benzene (80 ml.) was boiled for fifteen minutes, then decomposed with iced hydrochloric acid, and worked up in the usual way. The 3,4-benzofluorenone-1-carboxylic acid obtained was purified through its sodium salt and crystallized from acetic acid. It formed red needles which melted at 283–286° on a block (literature,[9] 288–289°).

Anal. Calc'd for $C_{18}H_{10}O_3$: C, 78.8; H, 3.65.
Found: C, 78.7; H, 4.24.

By treatment with thionyl chloride and then with methanol the acid was converted into its methyl ester which melted at 148–150° (literature,[9] 146–147°).

Decarboxylated by boiling with quinoline and copper acetate, the acid gave 3,4-benzofluorenone which melted at 161–162° (literature[10] 161°).

Anal. Calc'd for $C_{17}H_{10}O$: C, 88.7; H, 4.35.
Found: C, 88.3; H, 4.71.

3,4-Benzofluorenone oxime melted at 213–215° (literature[10] 215°).

Tetraphenylfulgenic anhydride and aluminum chloride in nitrobenzene.—A solution of tetraphenylfulgenic anhydride (1 g.) in 30 ml. of nitrobenzene was treated with aluminum chloride (3 g.) and warmed to 60° for fifteen minutes. The mixture was decomposed with dilute hydrochloric acid, the nitrobenzene was removed with

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[8] STOBBE, *Ber.*, **37**, 2659 (1904).
[9] SCHAARSCHMIDT, *ibid.*, **48**, 1830 (1915).
[10] SCHAARSCHMIDT, *ibid.*, **49**, 1449 (1916).

steam, and the residue was crystallized from acetic acid. The 3-phenyl-2-(α-carboxy-β,β-diphenylvinyl)indone (II) obtained in a nearly quantitative yield formed orange-red crystals that melted at 237–241°.

Anal. Calc'd for $C_{30}H_{20}O_3$ + CH_3COOH: C, 78.69; H, 4.92.
Found: C, 78.65; H, 5.31.

On decarboxylation in the usual manner the indone acid (II) gave 3-phenyl-2-(β,β-diphenylvinyl)indone, red crystals from acetic acid, m.p. 147–148°.

Anal. Calc'd for $C_{29}H_{20}O$: C, 90.6; H, 5.20.
Found: C, 90.1; H, 5.24.

Boiled with aluminum chloride in benzene for fifteen minutes, the indone acid (II) was converted nearly quantitatively into 2-phenyl-3,4-benzofluorenone-1-carboxylic acid which melted at 264–266° alone or mixed with the same substance obtained directly from tetraphenylfulgenic anhydride.

The indone acid (II) was converted into its chloride by boiling with an excess of thionyl chloride for thirty minutes. The acid chloride obtained by removing the excess thionyl chloride under reduced pressure and crystallization from benzene-ligroïn formed red crystals that melted at 183–186°.

Anal. Calc'd for $C_{30}H_{19}O_2Cl$: C, 80.7; H, 4.25.
Found: C, 80.7; H, 4.45.

Boiling a solution of the acid chloride in benzene with aluminum chloride gave dibenzoylenenaphthalene. With aluminum chloride in nitrobenzene the acid chloride gave an orange-yellow substance of melting point 161–163° which was not investigated further since it was obviously not the desired bisindone (III). Treatment of the acid (II) with cold concentrated sulfuric acid gave only a brown, amorphous substance.

Triphenylfulgenic anhydride and aluminum chloride in nitrobenzene.—Treatment of triphenylfulgenic anhydride[8] (1 g.) with aluminum chloride in nitrobenzene was carried out in the same manner as described for the tetraphenyl compound. There was obtained 0.76 g. of 3-phenyl-2-(α-carboxystyryl)indone (XI), orange-yellow prisms from acetic acid that melted at 196–199°.

Anal. Calc'd for $C_{24}H_{16}O_3$: C, 81.8; H, 4.55.
Found: C, 81.2; H, 5.0.

Decarboxylation of the acid (XI) in the usual way gave 3-phenyl-2-styrylindone. Crystallized from acetic acid this substance formed deep red needles which melted at 144–146°.

Anal. Calc'd for $C_{23}H_{16}O$: C, 89.6; H, 5.2.
Found: C, 89.5; H, 5.23.

1,1,6,6-Tetraphenylhexatriene-2,3-dicarboxylic anhydride and aluminum chloride in nitrobenzene.—When aluminum chloride (1.5 g.) was added to a solution of the anhydride (XII)[7] (m.p. 222–224°) (1 g.) in nitrobenzene (20 ml.) it became bright red. The mixture was warmed for four minutes at 65°, and the resulting green-brown solution was decomposed with iced hydrochloric acid. The α-(β-phenylindonyl-2)-δ,δ-diphenylbutadiene-α-carboxylic acid (XIII) obtained was purified through its sodium salt, and crystallized from acetic acid. It formed orange prisms (0.98 g.) that sintered at 235° and melted at 242–246°.

The isomeric 1,1,6,6-tetraphenylhexatriene-2,3-dicarboxylic anhydride[7] of melting point 212–214° treated in the same way gave the same acid (XIII).

Anal. Calc'd for $C_{32}H_{22}O_3$: C, 84.58; H, 4.85.
Found: C, 84.27; H, 4.99.

Decarboxylated in the usual way the acid (XIII) gave α-(3-phenylindonyl-2)-

δ,δ-diphenylbutadiene which formed dark purple needles that melted at 165–167° when crystallized from acetic acid.

Anal. Calc'd for $C_{31}H_{22}O$: C, 90.7; H, 5.37.
Found: C, 90.6; H, 5.62.

SUMMARY

When tetraphenylfulgenic anhydride dissolved in benzene is treated with aluminum chloride it is converted into 2-phenyl-3,4-benzofluorenone-1-carboxylic acid, and an analogous behavior is shown by triphenylfulgenic anhydride. A mechanism for these changes based on the behavior of these same anhydrides toward aluminum chloride in nitrobenzene is suggested. Attempts to convert tetraphenylfulgenic anhydride into *bis*-2,2′-(1-phenylindenone-3) were unsuccessful.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

ANOMALIES ENCOUNTERED IN THE SYNTHESIS OF TETRAPHENYLFULGENIC ANHYDRIDE*

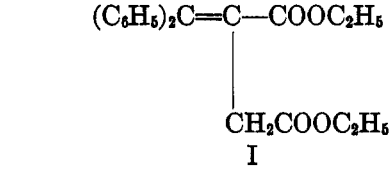
C. F. KOELSCH AND H. J. RICHTER

Received September 30, 1938

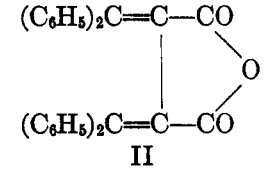
It has been reported[1] that by appropriate treatment of the reaction mixture resulting from the interaction of sodium ethoxide, benzophenone, and ethyl diphenylitaconate (I) there was obtained four different substances, all represented by formula (II). These substances were: tetraphenylfulgenic anhydride A_α, blood-red, triclinic, melting point 219°; tetraphenylfulgenic anhydride A_β, yellow, monoclinic, melting point 219°; *iso*-tetraphenylfulgenic anhydride, brick-red, melting point 187.5°; *allo*-tetraphenylfulgenic anhydride C, garnet-red, rhombic, melting point 274°.

The condensation has been repeated several times in this laboratory, but by following the procedure of Stobbe[2], it has never been possible to isolate more than two substances: (A) a red anhydride of melting point 267–269°, which is the true tetraphenylfulgenic anhydride (II); and (B) an orange-red substance of melting point 192–194° which is a mixture of the anhydrides (IIIa) and (IIIb) described below.

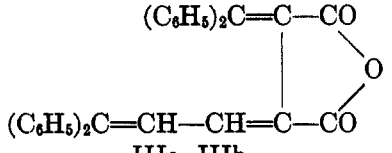
A different method of working up the reaction mixture, however, yielded four different substances: tetraphenylfulgenic anhydride (II), two geometrically isomeric forms of 1,1,6,6-tetraphenylhexatriene-2,3-dicarboxylic anhydride (IIIa and IIIb); and 1,1,6,6-tetraphenylhexadiene-1,2-dicarboxylic anhydride (IV).



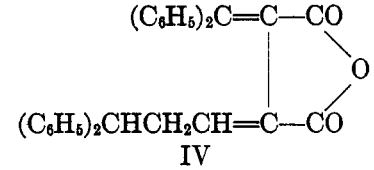
I



II



IIIa, IIIb

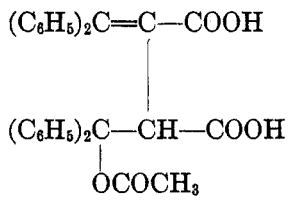


IV

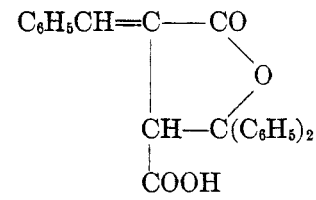
* A portion of a thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy by H. J. Richter, June, 1937.

[1] STOBBE, HOUBEN-WEYL, "Die Methoden der org. Chemie" 2nd ed., Georg Thieme, Leipzig, **1922**, Vol. II, page 1033.

[2] STOBBE AND BADENHAUSEN, *Ber.*, **39**, 769 (1906).



V



VI

The relative amounts of these substances formed in the condensation varied considerably in different experiments. Manipulative losses during their separation could not be avoided, and a variable amount of a red oil from which no definite substance could be obtained accompanied them. The approximate yields were 40 per cent. of (II), 10 per cent. of (IIIa); 10 per cent. of (IIIb), and 1 per cent. of (IV).

Tetraphenylfulgenic anhydride (II) formed deep red crystals that melted at 267–269°; the corresponding acid formed white needles. The structures of these compounds were determined by decarboxylation; either substance gave the known 1,1,4,4-tetraphenylbutadiene when it was boiled with quinoline containing a little copper acetate.

An improved method for the preparation of tetraphenylfulgenic anhydride, consisting of the condensation of benzophenone with methyl diphenylitaconate by the action of sodium methoxide, was devised. In this condensation compounds IIIa, IIIb, or IV were not found, the sole by-product being the acetoxy acid (V). This acetoxy acid, whose formation is analogous to that of γ,γ-diphenyl-α-benzalparaconic acid (VI) from benzophenone, ethyl phenylitaconate and sodium ethoxide, was converted into tetraphenylfulgenic anhydride when it was heated at 220°.

1,1,6,6-Tetraphenylhexatriene-2,3-dicarboxylic anhydride (IIIa) formed orange-red crystals that melted at 222–224°; the corresponding crystalline acid was yellow, melted at 220–222°, and on boiling with acetic acid was reconverted into the anhydride. The isomeric anhydride (IIIb) was orange and melted at 212–213°; the acid corresponding to it was yellow, melted at 232–234°, and was reconverted into the anhydride only on warming with acetyl chloride, not by simple boiling with acetic acid. On this difference in ease of anhydride formation was based the method by which the two acids were separated. The anhydrides mixed in equal amounts formed a compound that melted at 191–193° and could not be separated by crystallization. When boiled with aniline, either of the anhydrides (IIIa or IIIb) gave the same phenylimide.

An assignment of *cis* and *trans* structures to the anhydrides (IIIa) and (IIIb) could not be made, but their gross structures were determined by decarboxylation and confirmed by synthesis. Decarboxylation of either

(IIIa) or (IIIb) by heating with copper acetate in quinoline gave a hydrocarbon melting at 172–174°, and when this substance was reduced catalytically it was converted into the known[3] 1,1,6,6-tetraphenylhexane of melting point 124–125.5°. The 172–174° melting decarboxylation product is probably a stereoisomer of the previously described[4] 1,1,6,6-tetraphenylhexatriene which melts at 203–206°, since on distillation under reduced pressure it is completely converted into the latter.

The synthesis of the anhydrides IIIa and IIIb was carried out through the condensation of methyldiphenylitaconate with β-phenylcinnamaldehyde. From this synthesis there was obtained a 27 per cent. yield of the 222–224° anhydride (IIIa) and a 53 per cent. yield of the 212–213° anhydride (IIIb).

The formation of the two 1,1,6,6-tetraphenylhexatrienedicarboxylic anhydrides† (IIIa and IIIb) in the reaction between benzophenone, ethyl diphenylitaconate and sodium ethoxide obviously involves the intermediate formation of acetaldehyde from the sodium ethoxide. The oxidizing agent here is probably benzophenone, since considerable amounts of benzohydrol were isolated from the reaction mixtures. Similar instances of the unexpected participation of acetaldehyde in condensations involving sodium ethoxide have been recorded,[5] and indeed such reactions simply illustrate the reversibility of the well-known reduction of aldehydes by secondary alkoxides.[6]

The final substance isolated from the benzophenone, ethyl diphenylitaconate, and sodium ethoxide reaction mixture was 1,1,6,6-tetraphenylhexadiene-1,2-dicarboxylic anhydride (IV). This structure was assigned to the substance because the corresponding acid is white, having a shorter conjugated system than the acids corresponding to IIIa and IIIb while the anhydride is bright red, in keeping with its fulgid structure. Decarboxylation of this anhydride gave a colorless hydrocarbon that melted at 196–197°, which should be 1,1,6,6-tetraphenylhexadiene-1,3. A hydrocarbon having this structure but melting at 118–121° has been described;[7] this

[3] WITTIG AND LEO, *ibid.*, **63**, 947 (1930).

[4] WITTIG AND KLEIN, *ibid.*, **69**, 2093 (1936).

† The half-esters of the corresponding acids are actually formed in the condensation, and these are converted into the anhydrides only in the subsequent treatment of the reaction mixtures. The products are discussed as anhydrides as a matter of convenience.

[5] KLIEGL, WENG, AND WIEST, *Ber.*, **63**, 1631 (1930); SCHLENK AND BERGMANN, *Ann.*, **479**, 57 (1930).

[6] MONTAGNE AND VAN CHARANTE, *Rec. trav. chim.*, **31**, 299 (1912); MEERWEIN AND SCHMIDT, *Ann.*, **444**, 221 (1925); LUND, *Ber.*, **70**, 1520 (1937).

[7] Reference 4, p. 2094.

substance may be a stereoisomer of the compound obtained in the present research.

EXPERIMENTAL

Condensation of benzophenone with ethyl diphenylitaconate by sodium ethoxide.— Sodium ethoxide was prepared by treating 17.1 g. of sodium wire covered with dry ether, with 34.5 g. of absolute ethanol. After the sodium had disappeared (twenty-four hours) the ether was distilled and a mixture of 68 g. of benzophenone and 126 g. of ethyl diphenylitaconate[8] warmed to 80° was poured on the sodium ethoxide with stirring. The mixture was warmed for fifteen minutes on a steam bath and then boiled with three liters of water, the material insoluble in hot water being discarded. Sodium hydroxide (50 g.) was added, the mixture was boiled for two hours, then acidified with hydrochloric acid and boiled for an additional five minutes. The hot aqueous solution was decanted, and the red, oily product was boiled for fifteen minutes with two liters of water; from the combined aqueous extracts was obtained unchanged diphenylitaconic acid.

A portion of the red oil was covered with acetyl chloride (Stobbe's procedure[9]). On standing, the solution deposited an orange-red material which after crystallization from acetic acid, melted at 191–193° (mixture of IIIa and IIIb, separation described below). Concentration of the acetyl chloride filtrate gave tetraphenylfulgenic anhydride which melted at 267–269° after crystallization from acetic acid.

Anal. Calc'd for $C_{30}H_{20}O_3$: C, 84.11; H, 4.67.
Found: C, 84.20; H, 5.22.

The remainder of the red oil was boiled for five minutes with enough acetic acid to dissolve it. The solution was then cooled, whereupon the tetraphenylhexatriene dicarboxylic anhydride of melting point 222–224° (IIIa) separated. It was recrystallized from acetic acid.

Anal. Calc'd for $C_{32}H_{22}O_3$: C, 84.58; H, 4.85.
Found: C, 84.94; H, 4.86.

Water was added to the acetic acid filtrate from which the anhydride (IIIa) had separated. The red oil which separated was dissolved in ether and the ether solution was extracted with dilute aqueous sodium carbonate. The resulting suspension of sodium salts was separated, acidified, and warmed on a steam bath for thirty minutes. The precipitated oily acids were washed with water, dried, and dissolved in hot benzene. Cooling this solution gave the tetraphenylhexatriene dicarboxylic acid corresponding to anhydride IIIb; crystallized from ether-ligroïn it formed yellow crystals which melted at 231–233° with vigorous decomposition.

Anal. Calc'd for $C_{32}H_{24}O_4$: C, 81.3; H, 5.1.
Found: C, 80.5; H, 5.8.

The addition of petroleum ether to the benzene filtrate from the above acid caused the slow deposition of a white, crystalline acid. This substance recrystallized from ether-petroleum ether, gave tetraphenylhexadiene dicarboxylic acid (*cf.*, IV) in the form of white prisms which melted at 194–195.5°, to a red liquid.

Anal. Calc'd for $C_{32}H_{26}O_4$: C, 81.0; H, 5.49; Neutr. equiv., 474.
Found: C, 81.3; H, 5.59; Neutr. equiv., 476.

The benzene and petroleum ether was distilled from the above filtrate, and the remaining red oil was covered with acetyl chloride. The resulting solution was

[8] STOBBE, *Ber.*, **44**, 1299 (1911).
[9] STOBBE, *ibid.*, **38**, 3681 (1905).

allowed to stand for several hours, was distilled to a small volume, and the residue was warmed with acetic acid. From this solution was obtained tetraphenylfulgenic anhydride, m.p. 267–269°, and on dilution a mixture of the anhydrides IIIa and IIIb, m.p. 191–194°.

Condensation of benzophenone with methyl diphenylitaconate by sodium methoxide.—Methyl diphenylitaconate was prepared by boiling a mixture of methanol (200 ml.) with diphenylitaconic acid (10 g.) and sulfuric acid (5 ml.) for six hours. From methanol the dimethyl ester separated in the form of colorless crystals that melted at 94–95°; yield, 2 g.

Anal. Calc'd for $C_{19}H_{18}O_4$: C, 73.55; H, 5.81.
Found: C, 73.46; H, 5.76.

The principal product was the acid methyl ester [probably the a-form,[10] $(C_6H_5)_2C{=}C(COOH)CH_2COOCH_3$] which was separated through its sodium salt. Crystallized from methanol it melted at 135–138°.

Anal. Calc'd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.41.
Found: C, 72.60; H, 5.48.

A hot mixture of dimethyl diphenylitaconate (10 g.) and benzophenone (5.8 g.) was poured onto dry sodium methoxide (prepared from 1.5 g. of sodium under ether). The mixture was stirred and heated on a steam bath for thirty minutes, then boiled for ninety minutes with 500 ml. of 5% sodium hydroxide. The solution was acidified, boiled a few minutes, and decanted from the red, oily product. This material (14 g.) was dried, covered with acetyl chloride and allowed to stand for two hours. Removal of the acetyl chloride and crystallization from acetic acid gave tetraphenylfulgenic anhydride (2.7 g., m.p. 267–270°) and the more easily soluble orange α-acetoxy-$\alpha,\alpha,\delta,\delta$-tetraphenyl-$\Delta^{\gamma}$-butene-$\beta,\gamma$-dicarboxylic acid (V) (6 g.) which melted at 134–137°.

Anal. Calc'd for $C_{32}H_{26}O_6$: C, 76.21; H, 5.57.
Found: C, 76.44; H, 5.39.

The acetoxy acid was partially converted into tetraphenylfulgenic anhydride when it was heated at 220° for fifteen minutes. When boiled with quinoline and copper acetate it gave tetraphenylbutadiene. And when it was boiled with acetic anhydride it was converted into its anhydride which formed yellow-orange needles that melted at 163–164°.

Anal. Calc'd for $C_{32}H_{24}O_5$: C, 78.69; H, 4.92.
Found: C, 78.86; H, 5.17.

This anhydride was hydrolyzed back to the acetoxy acid when it was crystallized from dilute acetic acid.

Tetraphenylfulgenic acid.—An ether solution of tetraphenylfulgenic anhydride was shaken with 5% sodium hydroxide until the red color had disappeared. The mixture, in which the sodium salt was suspended, was acidified and shaken until the acid had dissolved. The product, obtained by concentrating the ether solution and adding petroleum ether formed white needles which became red at 240° and melted at 252–255°.

Anal. Calc'd for $C_{30}H_{22}O_4$: C, 80.72; H, 4.93.
Found: C, 80.90; H, 4.96.

1,1,6,6-Tetraphenylhexadiene dicarboxylic anhydride (*IV*).—Tetraphenylhexadiene dicarboxylic acid was warmed with acetyl chloride, and the product was crys-

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[10] *Cf.*, reference 8, p. 1297.

tallized from acetic acid, when it formed deep orange-red needles that melted at 164–167°.

Anal. Calc'd for $C_{32}H_{24}O_3$: C, 84.2; H, 5.26.
Found: C, 84.1; H, 5.24.

When tetraphenylhexadiene dicarboxylic acid was boiled for ten minutes with quinoline containing copper acetate it was decarboxylated. The product, presumably 1,1,6,6-tetraphenylhexadiene-1,3 was crystallized from alcohol; it melted at 196–197°.

Anal. Calc'd for $C_{30}H_{26}$: C, 93.26; H, 6.74.
Found: C, 93.33; H, 6.39.

Condensation of β-phenylcinnamaldehyde with methyl diphenylitaconate by sodium methoxide.—β-Phenylcinnamaldehyde was prepared by essentially the same method as that described by Kohler and Larsen.[11] Its 2,4-dinitrophenylhydrazone melted at 205–206°.

Anal. Calc'd for $C_{21}H_{16}N_4O_4$: C, 64.95; H, 4.12.
Found: C, 64.65; H, 4.12.

Methyldiphenylitaconate (3.1 g.) and β-phenylcinnamaldehyde (2.1 g.) were added to a solution of sodium (0.5 g.) in methanol (35 ml.) and the mixture was boiled for three hours. After the addition of sodium hydroxide solution (50 ml., 5%), the mixture was boiled for an additional hour and then acidified. The product was dried, treated with acetyl chloride, and crystallized from acetic acid; it consisted of the mixture of anhydrides IIIa and IIIb which melted at 192–194°. Separation of this mixture gave 1.2 g. of the orange-red anhydride IIIa, m.p. 222–224°, and 2.5 g. of the yellow acid, m.p. 232–234° (dec.), corresponding to anhydride IIIb.

Separation of the mixture of anhydrides IIIa and IIIb melting at 192–194°.—One gram of the mixture of anhydrides was boiled with 500 ml. of 5% sodium hydroxide until the red color had disappeared. The suspension of sodium salts was acidified with hydrochloric acid and boiled for twenty minutes. The solid material was taken up in ether, and the ether solution was washed with dilute aqueous sodium carbonate. The sodium salt of the 232–234° acid separated in the carbonate extract, while from the ether solution was obtained the orange-red anhydride IIIa of melting point 222–224°.

The anhydride IIIb, obtained from the 232–234° acid by treatment with acetyl chloride, crystallized from acetic acid in the form of orange needles that melted at 212–213°.

Anal. Calc'd for $C_{32}H_{22}O_3$: C, 84.58; H, 4.85.
Found: C, 84.45; H, 4.65.

The acid corresponding to the 222–224° anhydride IIIa was obtained by hydrolyzing the anhydride with aqueous sodium hydroxide. Crystallized from acetic acid the resulting tetraphenylhexatriene dicarboxylic acid formed yellow crystals which became orange-red at 175°, sintered at 184° and melted with decomposition at 220–222°.

Anal. Calc'd for $C_{32}H_{24}O_4$: C, 81.36; H, 5.09.
Found: C, 81.11; H, 5.27.

Appropriate experiments proved that the hydrolysis of the anhydrides and the dehydration of the acids proceeded without apparent inversion. Yet either anhydride IIIa or IIIb when boiled with an excess of aniline for ten minutes gave the same

[11] KOHLER AND LARSEN, *J. Am. Chem. Soc.*, **57**, 1448 (1935).

anil in nearly quantitative yield. Crystallized from acetic acid this substance formed orange-yellow needles which melted at 234–235°.

Anal. Calc'd for $C_{38}H_{27}NO_2$: C, 86.2; H, 5.10.
Found: C, 86.2; H, 5.08.

Similarly either of the anhydrides IIIa or IIIb, or either of the corresponding acids gave the same 1,1,6,6-tetraphenylhexatriene when boiled with guinoline containing a little copper acetate. From acetic acid the resulting hydrocarbon separated in the form of faintly yellow crystals that melted at 172–174°.

Anal. Calc'd for $C_{30}H_{24}$: C, 93.75; H, 6.25.
Found: C, 93.32; H, 6.34.

When it was distilled under reduced pressure this 172–174° tetraphenylhexatriene was quantitatively converted into a form which melted at 203–206°.

Reduced with an excess of sodium in butyl alcohol the 172–174° tetraphenylhexatriene gave 1,1,6,6-tetraphenylhexene-3 which melted at 79–80° after crystallization from ether-methanol.‡

Anal. Calc'd for $C_{30}H_{28}$: C, 92.78; H, 7.22.
Found: C, 92.63; H, 7.32.

Reduced in ether solution with hydrogen in the presence of palladium on barium sulfate, the 172–174° tetraphenylhexatriene gave the known 1,1,6,6-tetraphenylhexane which melted at 124–125.5° (literature,[3] 124.5–126°) after crystallization from ether-ligroïn.

SUMMARY

The condensation of benzophenone with ethyl diphenylitaconate in the presence of sodium ethoxide leads not only to tetraphenylfulgenic acid but also to three other compounds whose structures point to the intermediate formation of acetaldehyde from the sodium ethoxide. These substances are 1,1,6,6-tetraphenylhexa-1,3-diene-1,2-dicarboxylic acid and two geometrically isomeric forms of 1,1,6,6-tetraphenylhexa-1,3,5-triene-1,2-dicarboxylic acid. The structures of these compounds are supported by the behavior of the substances on decarboxylation. An improved method for the preparation of tetraphenylfulgenic anhydride and a synthesis of the two tetraphenylhexatriene acids are described.

‡ The compound previously described as 1,1,6,6-tetraphenylhexene-3 of melting point 124–125° may be a stereoisomer of this hydrocarbon, but more probably is 1,1,6,6-tetraphenylhexane, whose melting point is 124–126°.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE REACTIONS AND ENOLIZATION OF CYCLIC DIKETONES. IV.[1] 1,2-DIKETO-3,4,5-TRIPHENYLCYCLOPENTENE*

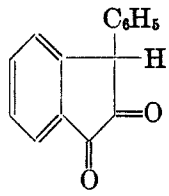
C. F. KOELSCH AND T. A. GEISSMAN

Received September 30, 1938

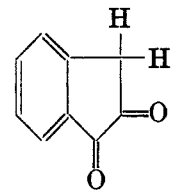
Evidence available from investigations carried out in this laboratory and from data in the literature indicates that among the many factors which affect the enolization of diketocyclopentane derivatives, two are of especial importance. These are (1) the nature of the second substituent on the carbon which bears the hydrogen atom involved in enolization, and (2) the state of saturation of the five-membered ring.

The first effect may be illustrated by a comparison of 1,2-diketo-3-phenylhydrindene (A) (enolic)[2] with 1,2-diketohydrindene (B) (ketonic).[3] From this comparison the conclusion may be drawn that a second hydrogen atom on the carbon bearing the one involved in the tautomerism hinders enolization.

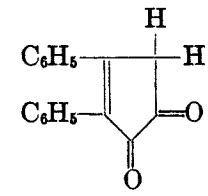
The second effect may be illustrated by a comparison of 1,2-diketo-3,4-diphenylcyclopentene (C) (ketonic)[1] with 1,2-diketo-3,4-diphenylcylopentane (D) (enolic).[4] From this example it may be concluded that a double bond in the five-membered ring hinders enolization.



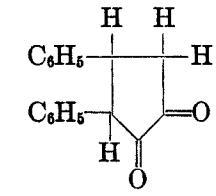
A



B



C



D

In the present paper the preparation and properties of 1,2-diketo-3,4,5-triphenylcyclopentene (V) are described. This diketone is related in

[1] Previous paper in this field, GEISSMAN AND KOELSCH, J. ORG. CHEM., **3**, 489 (1938).

* A portion of a thesis presented in partial fulfilment of the requirements for the degree of Doctor of Philosophy by T. A. Geissman, May, 1937.

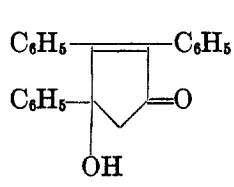
[2] KOELSCH, *J. Am. Chem. Soc.*, **58**, 1321 (1936).

[3] KOELSCH AND HOCHMANN, J. ORG. CHEM., **3**, 503 (1938).

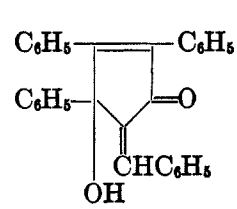
[4] VORLANDER AND SCHROEDTER, *Ber.*, **36**, 1490 (1903).

structure to 1,2-diketo-3-phenylhydrindene (A) but the properties of the two substances are markedly different. The hydrindene derivative is reddish-purple and behaves as an enol, while the cyclopentene is orange yellow and is ketonic. This difference may be explained as an instance of the second effect. In the cyclopentene diketone the double bond is definitely present in the five-membered ring, preventing enolization. In the hydrindene analog, however, the double bond, being part of an aromatic nucleus, is not necessarily within the five-membered ring, and indeed according to the Mills-Nixon hypothesis,[5] it is prevented from entering it.

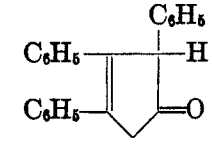
The condensation of benzil with phenylacetone in the presence of alkali gave anhydrophenylacetonebenzil (I).[6] The location of the methylene group in this compound was established by the preparation of the benzal derivative (II) of the condensation product. Partial reduction led to the ketone (III), which was nitrosated, the nitroso compound (IV) being then hydrolyzed to the diketone (V).



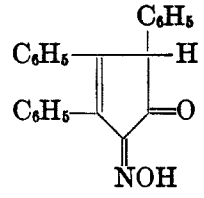
I



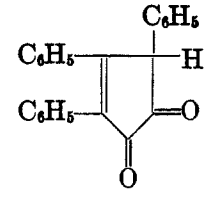
II



III



IV



V

1,2-Diketo-3,4,5-triphenylcyclopentenone formed a phenazine (VI) with *o*-phenylenediamine, and was cleaved readily by hydrogen peroxide with the formation of α,β,γ-triphenylglutaconic anhydride (VII). It reacted with bromine in hot acetic acid, slowly at first, rapidly after some

[5] BROCKWAY AND TAYLOR, "Ann. Reports of the Progress of Chemistry", The Chem. Soc., London, **1937**. Vol. 34, p. 219.

[6] This compound was also reported by DILTHEY AND HURTIG, *Ber.*, **67**, 2004 (1934), while the present research was in progress.

hydrogen bromide had formed. Bromination was somewhat easier than in the case of 1,2-diketo-3,4-diphenylcyclopentenone (C), indicating that although the triphenyl compound is not itself enolic, it is the more easily enolized of the two.

The diketone was not soluble in dilute aqueous alkali, but a drop of aqueous sodium hydroxide added to an alcoholic solution of the compound produced a blue-green coloration which faded almost immediately at room temperature but persisted about a minute at $-10°$. When a solution of sodium methoxide was added to the diketone in methanol, however, a deep blue-green color was produced which faded to yellow only after several hours at room temperature. A similar effect of the solvent on the stabilities of salts in other series has been observed. Thus, the red salts of 2-alkyl-1,3-diketohydrindene decompose to salts of *o*-alkylacetobenzoic acid much more rapidly in water than in alcohols,[7] and the rate at which the blue salts of isatin change into salts of isatinic acid is decreased as the proportion of alcohol in their solutions is increased.[8]

The diketone (V), unlike the diphenyl compound (C)[1] showed no tendency to form an acetal. It could be crystallized unchanged from acidic methanol, although such solutions did not possess the peculiar pink cast of those in non-polar solvents.

That the diketone can react in the enolic form was shown by its reaction with benzoyl chloride in pyridine. The benzoate (VIII) thus formed, in conformity with its cyclopentadienone structure, was deep-red, the color contrasting greatly with that of the diketone itself. Good evidence for the diketonic nature of the latter was found in its behavior towards phenylmagnesium bromide. Two moles of the Grignard reagent added to the diketone, forming the glycol (IX). This substance was not obtained crystalline, but its identity was established by treatment with hydriodic acid which dehydrated and reduced it to the known pentaphenylcyclopentadiene.[9]

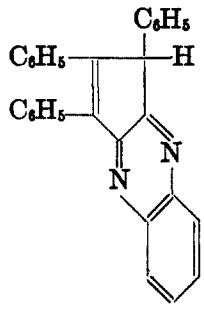
The keto alcohol (X) which would have been formed if the diketone had reacted in its enolic form was obtained by treating the bromodiketone (XI) with phenylmagnesium bromide; this type of reaction is characteristic of α-bromoketones.[10] The product (X) was dehydrated to tetraphenylcyclopentadienone (XII), and reduced to tetraphenylcyclopentenone (XIII), both known compounds.

[7] HANTZSCH AND CZAPP, *Z. phys. Chem.*, **146**, 135 (1930).

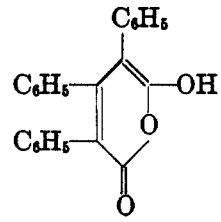
[8] HELLER, "Sammlung Chem. und Chemisch-tech. Vorträge"; Ferdinand Enke, Stuttgart; **1931**, New Series, Vol. 5, p. 56.

[9] ZIEGLER AND SCHNELL, *Ann.*, **445**, 266 (1925).

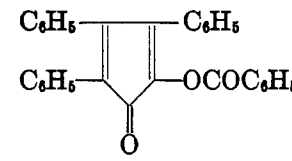
[10] KOHLER AND TISHLER, *J. Am. Chem. Soc.*, **54**, 1494 (1932).



VI



VII



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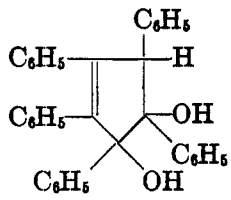

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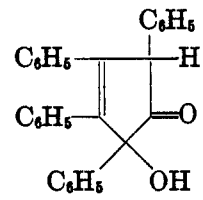

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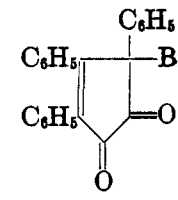

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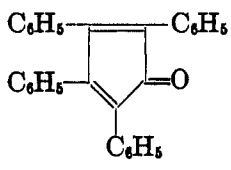

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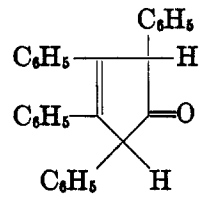

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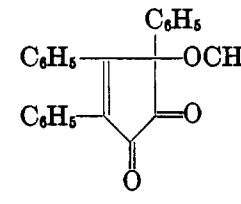


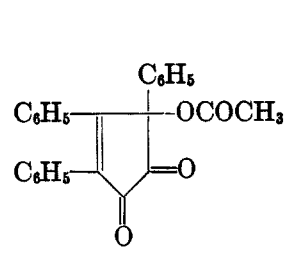
XIV

The bromine atom in the bromodiketone (XI) had a very marked reactivity. It was replaced by methoxyl when the bromodiketone was dissolved in methanol, the methoxydiketone (XIV) being formed. This substance possessed a striking cerise color similar to that of 3-phenyl-3-methoxy-1,2-diketohydrindene. Unlike the latter compound however, it showed no tendency to form an acetal, nor was an acetal of the methoxy compound formed during replacement of the bromine atom by methoxyl. The methoxydiketone (XIV) formed a phenazine, and was cleaved by alkaline hydrogen peroxide.

In contrast to the behavior of the bromodiketone towards methanol, with water the substance was converted into α,β,γ-triphenylglutaconic anhydride. This transformation probably occurred through the hydrolysis of the bromo compound to the diketone (V) and hypobromous acid, followed by oxidation of the diketone by the hypobromous acid to the

anhydride. This mechanism was supported by the observation that hydrolysis of the bromodiketone in the presence of phenol yielded the diketone (V), and not the anhydride.

The bromodiketone showed two reactions which are probably closely related to this abnormal hydrolysis. It reacted with silver acetate in acetic acid with the production of an orange compound (XV or XVI) which by the action of cold concentrated sulfuric acid was converted into (XVII). This substance (XVII) was also obtained by the action of sulfuric acid on α,β,γ-triphenylglutaconic anhydride (VII). There can be little doubt that the compound is 1,2-benzo-3-hydroxy-4-phenylfluorenone, since it gave a red-violet solution in alkali, formed a yellow benzoate, and resembled the fluorenone (XVIII) obtained from α,β-diphenylglutaconic anhydride.[1] When the bromodiketone (XI) was treated directly with sulfuric acid there was obtained a bromine-containing compound (XIX) which acted in every way like the compound XVII. Since XIX was also obtained by bromination of XVII, its structure as x-bromo-1,2-benzo-3-hydroxy-4-phenylfluorenone was confirmed.



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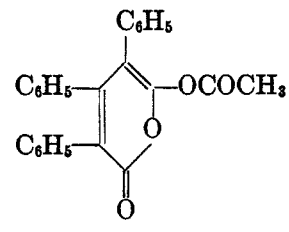

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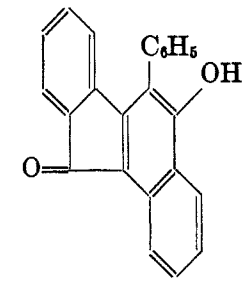

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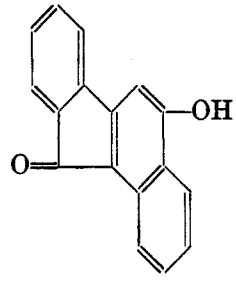

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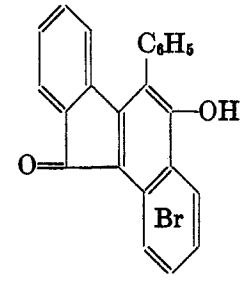


XIX

EXPERIMENTAL

Anhydrophenylacetonebenzil (I).—To 59 g. of phenylacetone, 91 g. of benzil, and 500 ml. of methanol was added 25 ml. of a 20% alcoholic potassium hydroxide solution. The mixture was boiled for thirty minutes, and was poured into water. The

gummy precipitate, which crystallized on standing, was ground in a mortar, washed thoroughly with water, dried and crystallized from benzene-ligroïn. There was obtained 95.5 gm. of a slightly yellow product which melted at 162–164°. For analysis, a portion crystallized from methanol formed silky white needles that melted at 164–165°.

Anal. Calc'd for $C_{23}H_{18}O_2$: C, 84.7; H, 5.5.
Found: C, 84.7; H, 5.3.

The compound formed a phenylhydrazone which melted at 173–174° with decomposition and a *p*-nitrophenylhydrazone which melted at 214–215° with decomposition.

Its benzal derivative (II) was obtained when 1 g. of the cyclopentenolone, 0.5 ml. of benzaldehyde, and 10 ml. of 1% alcoholic potassium hydroxide were allowed to stand for several hours at room temperature. Crystallized from alcohol it formed pale-yellow needles that melted at 217.5–218°.

2,3,4-Triphenylcyclopentenone (III).—Eighty-nine grams of the cyclopentenolone (I) was placed in 500 ml. of acetic acid; 155 g. of 45% hydriodic acid was added in the cold, and the mixture was then boiled under a reflux for five minutes. The solution was poured into aqueous sodium bisulfite, and was extracted once with ether. When the ether solution was washed with water and sodium carbonate, the reduction product separated almost completely. It was filtered, washed with ether, and dried. Crystallized once from alcohol the product formed faintly-yellow flat needles (75 g.) which melted at 142–143°. The pure substance, from alcohol, was white, m. p. 142–143°.

Anal. Calc'd for $C_{23}H_{18}O$: C, 89.0; H, 5.9.
Found: C, 88.5; H, 6.1.

2-Isonitroso-3,4,5-triphenylcyclopentenone (IV).—Attempts to nitrosate the ketone (III) in alcohol gave only poor yields of the desired product, but the use of ether as a solvent led to excellent results. Fifty-four grams of the ketone (III) was boiled for ninety minutes in 1 liter of ether containing 65 ml. of butyl nitrite and 25 ml. of concentrated hydrochloric acid. The nitroso compound (45 g.) was then filtered off and washed. It was obtained as a white, poorly crystalline solid which melted with decomposition at 221–223°. For purification it was best dissolved in hot 2% caustic soda, filtered, precipitated with acid, and crystallized from acetic acid. It then formed small white nodules that melted with decomposition at 228–229°.

Anal. Calc'd for $C_{23}H_{17}NO_2$: C, 81.4; H, 5.05.
Found: C, 83.45, 82.79, 83.05, 83.18; H, 5.23, 5.25, 5.12, 5.04.

The *benzoate* obtained from the nitroso compound and benzoyl chloride in pyridine, and crystallized from dilute acetic acid, formed yellow plates that melted with decomposition at 154–155°.

Anal. Calc'd. for $C_{30}H_{21}NO_3$: C, 81.3; H, 4.7.
Found: C, 81.2; H, 5.2.

1,2-Diketo-3,4,5-triphenylcyclopentene (V).—A mixture of 45 g. of the crude isonitroso compound, 200 ml. of acetic acid, 200 ml. of 40% formalin, and 50 ml. of concentrated hydrochloric acid was boiled under a reflux for one hour. The isonitroso compound did not dissolve, but slowly changed in color and form until at the end of the boiling the liquid was filled with orange needles and small lumps of poorly crystalline orange solid. Water was added, the product was collected, washed with water and dried (41 g., m. p. 157–160°). This impure product was extracted with warm benzene, which left about 10 g. of a white by-product melting at about 235° (dec.) undissolved. The benzene solution was concentrated, and ligroïn was added. On cooling there was obtained 25 g. of orange needles that melted at 157–161°. Recrys-

tallized from benzene, the diketone formed orange needles which melted at 162–163.5°.

Anal. Calc'd for $C_{23}H_{16}O_2$: C, 85.2; H, 5.0.
Found: C, 85.2; H, 4.7.

The diketone dissolved in concentrated sulfuric acid with a clear deep-red color. Its behavior towards aqueous and alcoholic alkali has been described in the first part of this paper, as has its behavior towards alcohol.

The *phenazine* (*VI*) obtained from the diketone and *o*-phenylenediamine in alcohol, crystallized from acetic acid in the form of white prisms that melted at 226–227° with decomposition. It dissolved in concentrated hydrochloric acid with a crimson color, and in sulfuric acid with a deep purple color.

Anal. Calc'd for $C_{29}H_{20}N_2$: C, 87.9; H, 5.1.
Found: C, 88.0; H, 5.1.

Benzoylation of the diketone.—Treatment of the diketone (1 g.) in pyridine (10 ml.) with benzoyl chloride (3 ml.) gave the benzoate (VIII) in good yield. The product was purified by solution in ether, washing with dilute hydrochloric acid and with sodium carbonate, and crystallization from acetic acid. 2,3,4-Triphenyl-5-benzoyloxycyclopentadienone formed copper-red needles which melted with decomposition at 242–243°.

Anal. Calc'd for $C_{30}H_{20}O_3$: C, 84.1; H, 4.7.
Found: C, 83.9; H, 4.7.

Cleavage of the diketone with hydrogen peroxide.—To a suspension of 1 g. of the diketone in 30 ml. of alcohol was added 0.5 ml. of 30% hydrogen peroxide, and then, dropwise, 1 ml. of 20% sodium hydroxide. After the solid had dissolved, the solution was poured into water and washed with ether. Acidification of the aqueous layer gave a α, β, γ-triphenylglutaconic anhydride (0.45 g.) which formed white needles that melted at 166–167° from benzene-petroleum ether. The anhydride gave a green color with alcoholic ferric chloride, and behaved as a monobasic acid, although the end-point of the titration drifted.

Anal. Calc'd for $C_{23}H_{16}O_3$: C, 81.2; H, 4.8; Neut. equiv., 340.
Found: C, 81.2, H, 5.0; Neut. equiv., 334.

Reaction of the diketone with phenylmagnesium bromide.—To the Grignard reagent prepared from 6.2 g. of bromobenzene and 1 g. of magnesium was added a benzene solution of 3.25 g. of the diketone. The mixture was boiled for thirty minutes and then decomposed with iced ammonium chloride. The solvents and biphenyl were removed by steam distillation in the presence of aqueous sodium carbonate, but the product could not be obtained crystalline. The glassy product was boiled for thirty minutes with an excess of hydriodic acid in acetic acid, which gave a good yield of 1,2,3,4,5-pentaphenylcyclopentadiene, yellow needles that melted at 252–254°.

Anal. Calc'd for $C_{35}H_{26}$: C, 94.2, H, 5.9.
Found: C, 94.1; H, 6.3.

This hydrocarbon is described by Ziegler[9] as melting at 244–246°, but a sample prepared by his method was found to melt at 252–254° either alone or mixed with the substance obtained from the diketone.

Bromination of the diketone.—Five grams of the diketone was placed in 30 ml. of acetic acid containing 3 g. of bromine; the mixture was warmed to 65°, a higher temperature causing the formation of a tarry product. The diketone went into solution, and, on scratching, the bromo compound (XI) (4.45 g.) separated. From acetic acid the product formed yellow-orange needles that melted at 145–146°.

Anal. Calc'd for $C_{23}H_{15}BrO_2$: C, 68.5; H, 3.7.
Found: C, 68.5; H, 4.0.

When the bromo compound was boiled in dilute acetic acid it was converted in rather poor yield into α,β,γ-triphenylglutaconic anhydride (m. p. 166–167°), identified by comparison with a sample obtained by hydrogen peroxide cleavage of the diketone (V).

1,2-Diketo-3,4,5-triphenyl-3-methoxycyclopentene (XIV).—A deep red solution was formed when the bromodiketone (XI) (2 g.) was boiled for five minutes with methanol (20 ml.). Boiling was continued for ten minutes, the solution was then poured into water and extracted with ether. The ether solution was washed with sodium carbonate, dried, and concentrated, giving 1.1 g. of a pink solid. The product, crystallized from benzene-petroleum ether and then from methanol, formed small cerise prisms which melted at 148–150°.

Anal. Calc'd for $C_{24}H_{18}O_3$: C, 81.4; H, 5.1; OCH_3, 8.8.
Found: C, 81.2; H, 4.9; OCH_3, 8.9.

The phenazine of the methoxydiketone formed colorless prisms that melted at 200–201° after crystallization from methanol.

Treated with alkaline hydrogen peroxide in methanol-water, the methoxydiketone (0.2 g.) gave a colorless product (0.06 g.) (*α-methoxy-α,β,γ-triphenylglutaconic anhydride*) which formed white needles from acetic acid that melted at 161–162° with gas evolution.

Anal. Calc'd. for $C_{24}H_{18}O_4$; C, 77.8; H, 4.9.
Found: C, 77.2; H, 5.4.

Reaction of the bromodiketone with phenylmagnesium bromide.—The bromodiketone (XI) (4.5 g.) was added to the Grignard reagent prepared from 2 g. of magnesium and 12.5 g. of bromobenzene. The solution was refluxed for thirty minutes, decomposed with iced ammonium chloride, and worked up in the usual way. The product (4.35 g.) after crystallization from benzene-ligroïn and then from acetic acid, formed colorless prisms which melted at 208.5–210°.

Anal. Calc'd for $C_{29}H_{22}O_2$: C, 86.6; H, 5.5.
Found: C, 86.6; H, 5.4.

On warming with acetic acid containing a little sulfuric acid, or on distillation at reduced pressure the tetraphenylcyclopentenolone obtained above gave tetraphenylcyclopentadienone[11] (m. p. and mixture m. p. 217–218°). On boiling with acetic acid containing hydriodic acid the cyclopentenolone yielded tetraphenylcyclopentenone[11] (m.p. and mixture m.p. 162–163°) and with acetic acid, hydrogen chloride and zinc, it yielded tetraphenylcyclopentenol[12] (m.p. and mixture m.p. 174–176°).

Reaction of the bromodiketone with silver acetate.—Silver bromide was rapidly precipitated when the bromodiketone was warmed with an excess of silver acetate in acetic acid. Dilution of the filtered solution resulting gave a good yield of an acetoxy compound (XV or XVI) which formed bright orange prisms that melted at 174–177°.

Anal. Calc'd for $C_{28}H_{18}O_4$: C, 78.5; H, 4.7.
Found: C, 78.2; H, 4.9.

The above compound gave a bright green solution in sulfuric acid, and dilution of this with water precipitated an orange substance. Recrystallized from benzene-ligroïn, this substance formed deep orange needles which melted at 237–238° and gave a deep red-violet solution in aqueous sodium hydroxide.

The same orange compound [1,2-benzo-3-hydroxy-4-phenylfluorenone, (XVII)] was obtained when α,β,γ-triphenylglutaconic anhydride was allowed to stand in

[11] DILTHEY AND QUINT., *J. prakt. Chem.*, **128**, 139 (1930).
[12] DILTHEY, BRAUN, AND TRÖSKEN, *ibid.*, **139**, 12 (1933).

cold concentrated sulfuric acid for a short time. Because of the formation of water-soluble products, the orange fluorenone was not obtained in good yield from either the anhydride or the acetoxy compound.

Anal. Calc'd for $C_{23}H_{14}O_2$: C, 85.7; H, 4.3.
Found: C, 85.6; H, 4.4.

Reaction of the bromodiketone with sulfuric acid.—When 3.0 g. of the bromodiketone (XI) was dissolved in about 25 ml. of concentrated sulfuric acid, the initially red-brown solution rapidly became green, and hydrogen bromide was evolved. The solution was poured into water after five minutes, and the orange precipitate was crystallized from xylene. It formed deep red-orange needles which melted at 287–289°, gave a deep red-violet solution in dilute alkali, and formed a benzoate (m.p. 240–241°) on treatment with benzoyl chloride in pyridine.

x-Bromo-1,2-benzo-3-hydroxy-4-phenylfluorenone was also obtained when a slight excess of bromine in acetic acid was added to the green solution obtained by dissolving α,β,γ-triphenylglutaconic anhydride in sulfuric acid.

Anal. Calc'd for $C_{23}H_{13}BrO_2$: C, 68.8; H, 3.2.
Found: C, 71.3; H, 3.9.

SUMMARY

The preparation and reactions of 1,2-diketo-3,4,5-triphenylcyclopentene are described. It is noted that the ketonic nature of this diketone is in agreement with the postulated hindrance of enolization of such diketones by the presence of a double bond in the five-membered ring. It is also noted that this diketone is apparently more easily enolized than 1,2-diketo-3,4-diphenylcyclopentene. This conforms with the postulated hindrance of enolization in such diketones by a second hydrogen on the carbon atom bearing the hydrogen involved in the enolization.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

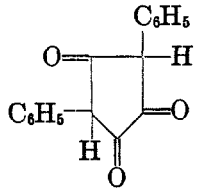
THE REACTIONS AND ENOLIZATION OF CYCLIC DIKETONES. III.[1] 1,2-DIKETO-3,4-DIPHENYLCYCLOPENTENE*

T. A. GEISSMAN AND C. F. KOELSCH

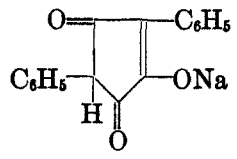
Received September 30, 1938

Numerous examples of acyclic α-diketones, cyclic α-diketones containing a saturated ring, and 1,2-diketohydrindenes have been described, but so far no alicyclic analogs of 1,2-diketohydrindenes have been prepared except those containing acyl groups on the carbon atom corresponding to the 3 position in 3-substituted 1,2-diketohydrindenes. The reactivity of such α-diketones is affected by the acyl substitutent, since it forms a part of a β-dicarbonyl system with one of the α-diketone carbonyl groups, in such a way that no comparison can be made between these compounds and the known 1,2-diketohydrindenes containing a substitutent in the 3 position, such as methyl or phenyl.

One of the earliest examples of a substituted diketocyclopentene is oxalyldibenzyl ketone (I) a yellow compound, prepared by Claisen and Ewan.[2] This substance dissolves in one equivalent of alkali with the formation of a yellow salt and in two equivalents of alkali with the formation of a blue salt. The structures of these were written by Claisen and Ewan as (II) and (III).



I



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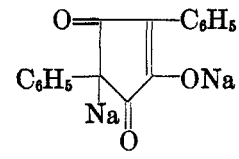

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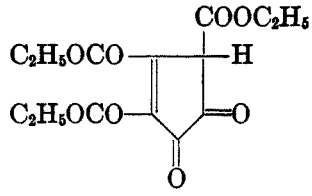

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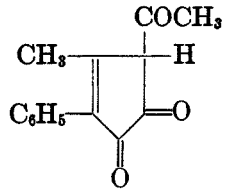


V

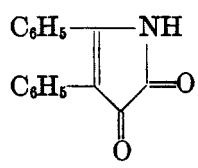
[1] Previous paper in this field, KOELSCH AND HOCHMANN, J. ORG. CHEM., **3**, 503 (1938).

* A portion of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy by T. A. Geissman, May, 1937.

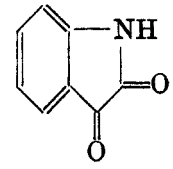
[2] CLAISEN AND EWAN, *Ann.*, **284**, 245 (1895).

Triethyl oxalylaconitate (IV) was prepared later by Ruhemann and Hemmy[3] and acetomethylphenyldiketocyclopentene (V) by Ruhemann and Merriman.[4] These compounds, written as enols by Ruhemann, are red, and they form blue alkali salts.

Ruhemann's final view as to the structures of the blue salts of these compounds and of Claisen and Ewan's triketone, grew out of his study of diketodiphenylpyrroline (VI).[5] This compound is an analog of isatin (VII), and resembles it in many ways. Both substances are red; both dissolve in alkali with the formation of blue salts, the blue color fading in a short time to yellow; and both give phenylhydrazones which are insoluble in acid or in alkali.

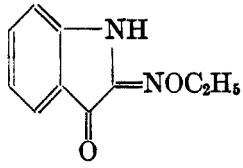


VI

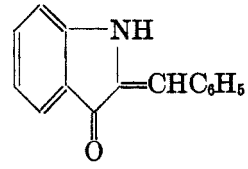


VII

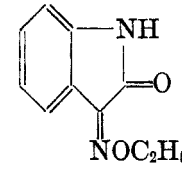
von Baeyer had previously shown[6,7] that the ethyl ether of isatin α-oxime (VIII) dissolved in alkali with the formation of a blue salt, as did benzylidene indoxyl (IX), while no blue salt was formed from the ether of the β-oxime of isatin (X).



VIII



IX

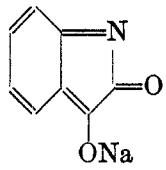


X

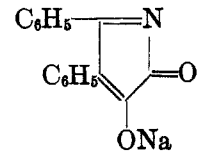
The interpretation placed on these facts by Ruhemann[5,8] was that since replacement of the α-keto oxygen did not interfere with the formation of a blue salt while that of the β-keto oxygen did, the metal must be attached to the β-keto oxygen, so that the structure of the blue salt of

[3] RUHEMANN AND HEMMY, *J. Chem. Soc.*, **71**, 334 (1897).
[4] RUHEMANN AND MERRIMAN, *ibid.*, **87**, 1383 (1905).
[5] RUHEMANN, *ibid.*, **95**, 984 (1909).
[6] V. BAEYER, *Ber.*, **16**, 2192 (1883).
[7] HELLER, "Sammlung chem. und chemisch-tech. Vorträge." Ferdinand Enke, Stuttgart, **1931**, New Series, Vol. 5, pp. 49–62.
[8] RUHEMANN, *J. Chem. Soc.*, **97**, 1438 (1910).

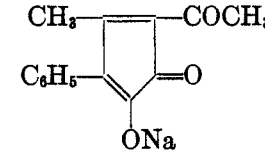
isatin itself would be (XI) and by analogy that of the blue salt of diketodiphenylpyrroline, (XII)



XI



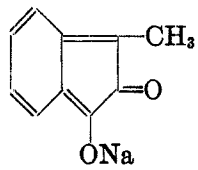
XII



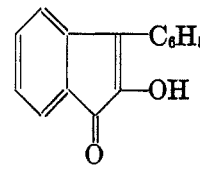
XIII

Analogous structures, for example XIII were assigned to the blue salts of the carbocyclic compounds, V, I, and IV.

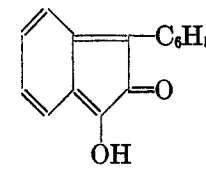
Ruhemann's deduction of an *o*-quinoid structure for the blue salt of isatin led v. Braun[9] to postulate the structure XIV for the blue salts of 3-methyl-1,2-diketohydrindene. But this is probably incorrect, since it has been shown[10] that 3-phenyl-1,2-diketohydrindene enolizes to give XV and not XVI.



XIV

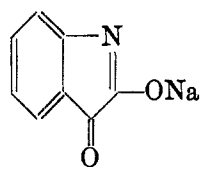


XV

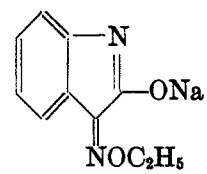


XVI

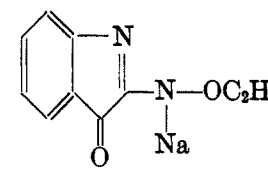
Indeed the evidence for the *o*-quinoid structure of the blue salts of isatin itself is not as conclusive as it at first appears. Whether the salt formation takes place as in XI or as in XVII, the chromophore is a crossed conjugated system. That a blue salt is not formed from isatin β-oxime ether is probably due to replacement of the carbonyl oxygen by the oximino grouping as indicated in formula XVIII, while the blue color of the salt of the α-oxime ether (XIX) is due to the intact carbonyl group.



XVII



XVIII



XIX

That replacement of a carbonyl oxygen in such a system does strongly affect color may be illustrated by diphenylindone and its oxime, which are deep red and yellow respectively.

[9] v. Braun and co-workers. *Ber.*, **46**, 3041 (1912); **49**, 1268 (1916); **64**, 1790 (1931).
[10] Koelsch, *J. Am. Chem. Soc.*, **58**, 1321 (1936).

The question which this formulation of the enolates of isatin raises as to the structure of diketodiphenylpyrroline salts will be the subject of future communications from this laboratory.†

Isatin, diketodiphenylpyrroline, and the cyclopentene derivative (V) are all red compounds, all form blue salts in alkali, all give phenylhydrazones which are not soluble in acid or alkali; and all give phenazines when treated with *o*-phenylenediamine. But the two heterocyclic compounds yield yellow phenazines while that derived from the compound (V) is purple. These and other similarities on the one hand, and differences on the other, between compounds containing an isatin ring and compounds of which the cyclopentene (V) is a representative, led Ruhemann to consider studying the properties of a compound containing an intact methylene group adjacent to the diketone grouping, for example 1,2-diketohydrindene.

Ruhemann's attempt to prepare this substance was unsuccessful, although it led to the discovery of triketohydrindene.[8] 1,2-Diketohydrindene was first prepared by Perkin, Roberts, and Robinson,[11] and later these investigators and others[12] prepared various derivatives of 1,2-diketohydrindene containing substituents in the benzene ring. These derivatives, like the parent substance, are all yellow, but for the most part their properties have not been studied in detail.

So far as chemical behavior is concerned, unsubstituted (except in the benzene ring) 1,2-diketohydrindenes have two structural features of special interest: the carbonyl groups and the methylene group.

1,2-Diketohydrindene reacts[11] with the usual carbonyl reagents, forming an oxime when treated with hydroxylamine, an osazone with phenylhydrazine, and a quinoxaline with *o*-phenylenediamine. The greater reactivity of the carbonyl group adjacent to the methylene group is shown by the fact that oximation of the diketone leads to the formation of the same compound as that obtained by the nitrosation of hydrindone-1; that is, 2-isonitrosohydrindone-1. The diketone reacts with hydrogen cyanide and with sodium bisulfite with the formation of colorless addition compounds. Perkin and co-workers observed that solutions of the diketone in methanol or ethanol are nearly colorless while in non-hydroxylic

† It is recognized that in these salts the metal is ionically bound to the organic part of the molecule and that accordingly the latter may have several forms through resonance. Nevertheless it is believed that inferences drawn from color, preferential reactivity of one carbonyl group, or other properties may indicate which of the forms represents a preferred structure; certainly they are allowable from a pragmatic standpoint.

[11] PERKIN, ROBERTS, AND ROBINSON, *J. Chem. Soc.*, **101**, 232 (1912); **105**, 2405 (1914).

[12] CHAKRAVARTI AND SWAMINATHAN, *J. Indian Chem. Soc.*, **11**, 101 (1934).

solvents the solutions are deep yellow. This behavior points to the formation of acetals, but no acetal has been isolated in this laboratory or by Perkin. Upon evaporation of the alcohol from a solution of the diketone in methanol or ethanol, the solution remains nearly colorless until the solvent has been largely removed. On removal of the last of the solvent, the diketone crystallizes unchanged. The compound is cleaved in the usual way by hydrogen peroxide, the expected homophthalic acid being formed.

1,2-Diketohydrindene dissolves in 5 per cent. sodium hydroxide[11] to give at first a colorless solution which becomes brownish-red, then brownish-yellow. Acidification at that point precipitates a colorless substance. If the alkaline solution is boiled a color change through violet to red is observed. In sodium carbonate, or very dilute sodium hydroxide solution the compound dissolves with an olive-green color which on standing becomes greenish-blue, and on boiling becomes an intense blue.

1,2-Diketohydrindene does not react with bromine[1] except in boiling acetic acid, and then not readily in the absence of a catalyst such as hydrobromic acid. Depending on the amount of bromine used, a dibromo or an unstable monobromo substitution product is formed. This behavior indicates that the compound exists entirely in the keto form, and support for this view is found in absorption spectrum measurements.

The open-chain analog of 1,2-diketohydrindene, phenylbenzylglyoxal, has been studied by Dufraisse and Moureu and by Kohler and Barnes.[13] This substance may be obtained in three forms, two of them stereoisomeric modifications of the enol, and one the diketone. The ketonic and both enolic forms liberate methane when treated with methylmagnesium iodide, the latter yielding 93 per cent. of the theoretical amount, and the former 50 per cent., indicating an enolizing action of the Grignard reagent. No tendency of the diketone to form acetals has been noted.

Whether the marked differences in the characters of 1,2-diketohydrindene and phenylbenzylglyoxal are the result of the effects arising from the presence of the benzene ring in the former, or simply as an effect of the double bond connecting the methylene and carbonyl groups, can be ascertained by a study of a compound containing the double bond in the same position but not as a part of a benzene ring.

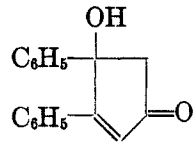
The experimental part of the present paper and the following discussion are devoted to a description of the preparation and properties of such a compound, 3,4-diphenylcyclopentenedione-1,2 (XXIII).

Anhydracetone benzil (XX)[14] was reduced to diphenylcyclopentenone

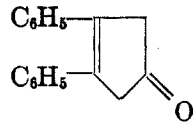
[13] DUFRAISSE AND MOUREU, *Bull. soc. chim.*, **41**, 1607 (1927); KOHLER AND BARNES, *J. Am. Chem. Soc.*, **56**, 211 (1934).

[14] JAPP AND KNOX, *J. Chem. Soc.*, **87**, 673 (1905).

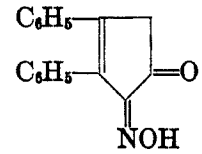
(XXI).[15] Nitrosation of this ketone led to the expected isonitroso compound (XXII) which was then hydrolyzed in the presence of formaldehyde as an hydroxylamine acceptor, giving the diketone (XXIII).



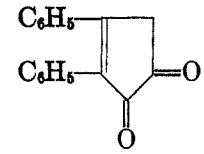
XX



XXI



XXII



XXIII

The diketone (XXIII) is yellow, like 1,2-diketohydrindene, but has an orange tinge. Its solutions in non-polar solvents are yellow, but in thin layers are distinctly pink-tinged by transmitted light.

The compound resembles 1,2-diketohydrindene in most ways, so far as the latter has been investigated. Treated with hydroxylamine it forms a mono-oxime (XXIV). It gives a colorless phenazine (XXV) with phenylenediamine, and is readily cleaved by alkaline hydrogen peroxide to the corresponding glutaconic acid, isolated as its anhydride (XXVI).

Bromine has no effect on the diketone in the cold or in boiling carbon tetrachloride. In boiling acetic acid, however, bromination proceeds smoothly to yield the monobromo compound (XXVII) or the dibromo compound (XXVIII). There is an appreciable period of induction before bromination proceeds, but the subsequent reaction is rapid.

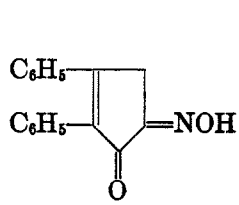
The diketone is insoluble in aqueous alkali in the cold, and on boiling decomposition occurs. Its solution in alcohol becomes greenish yellow on the addition of a drop of alkali. There is no color reaction with ferric chloride.

These facts show clearly that the diketone exists in the keto form and indicate that it has little or no more tendency to react in the enol form than a simple monoketone with two α-hydrogen atoms.

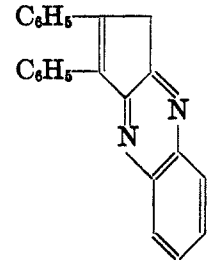
The superior reactivity of the carbonyl group adjacent to the methylene group is shown by the fact that it is preferentially oximated by hydroxylamine with the formation of an isonitrosocyclopentenone (XXIV) different from, but isomeric with, the isonitroso compound (XXII) from which the diketone is prepared. An even more striking example of the pronounced reactivity of this carbonyl group is found in the ease with which the diketone forms an acetal. When a methyl-alcoholic solution of the diketone containing a trace of acid is boiled, the color fades to a pale

[15] JAPP AND LANDER, *ibid.*, 71, 131 (1897).

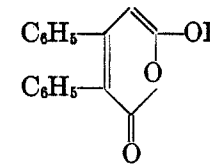
yellow and from the resulting solution there is obtained a colorless crystalline substance, the acetal (XXIX).



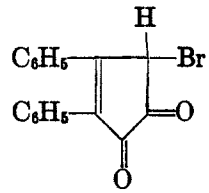
XXIV



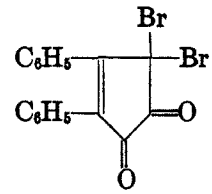
XXV



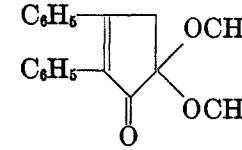
XXVI



XXVII



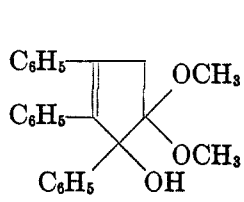
XXVIII



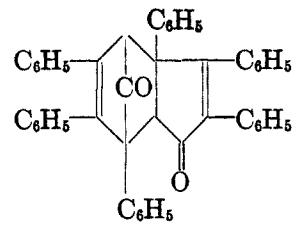
XXIX

That acetal formation takes place on the carbonyl group indicated was shown in two ways. Treatment of the acetal with benzaldehyde in alcoholic alkali produced no change, the compound being recovered. If acetal formation had taken place on the carbonyl group adjacent to the double bond, the methylene group would be activated by the remaining carbonyl group and benzal formation would be expected. This is negative evidence, however, and more conclusive proof was obtained by treating the acetal with phenylmagnesium bromide. The resulting carbinol (XXX) when boiled with acetic acid containing a trace of sulfuric acid underwent hydrolysis and dehydration with the formation of a colorless compound (XXXI). Although the structure of this compound was not rigidly proved, there is little doubt that it has the structure shown and arises as a result of the dimerization of 2,3,4-triphenylcyclopentadienone, since the same substance is obtained when the carbinol (XXXII)[16] is dehydrated in the same manner. Support for the suggested structure (XXXI) is found in the work of Allen and Spanagel[17] on the dehydration of anhydracetone benzil and in the observations of Dilthey and Schommer[18] on the reversible dimerization of 1,2,4-triphenylcyclopentadienone.

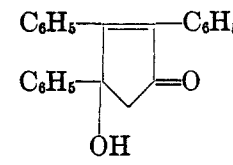
[16] Koelsch and Geissman, J. Org. Chem., **3**, 480 (1938).
[17] Allen and Spanagel, *J. Am. Chem. Soc.*, **54**, 4338 (1932).
[18] Dilthey and Schommer, *J. prakt. Chem.*, **136**, 293 (1933).



XXX



XXXI



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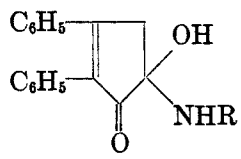
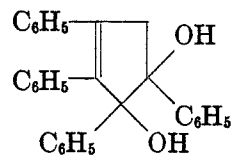
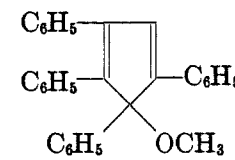


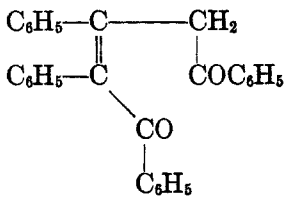
XXXIII



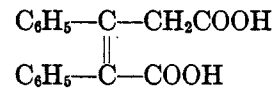
XXXIV



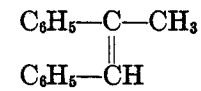
XXXV



XXXVI



XXXVII



XXXVIII

Further evidence for the reactivity of the carbonyl group is found in the reaction of the diketone with aniline and with *p*-toluidine. In ether suspension at room temperature these amines are added, structure XXXIII being suggested for the unstable products by analogy with oximation and acetal formation.

The distinctly ketonic character of the diketone (XXIII) is demonstrated further by its reaction with phenylmagnesium bromide. Two moles of the Grignard reagent add with the formation of a glycol (XXXIV).

This glycol is simultaneously dehydrated and etherified in methanol by a trace of sulfuric acid, with the formation of the methyl ether (XXXV).[19] In acetic acid containing a drop of sulfuric acid dehydration and oxidation occur, leading to the formation, in poor yield, of the known tetraphenylcyclopentadienone.[20] Rigid proof for the structure of the glycol was

[19] The position of the double bonds and of the methoxyl group in this compound are uncertain. Compare KOELSCH, *J. Am. Chem. Soc.*, **56**, 1337 (1934).

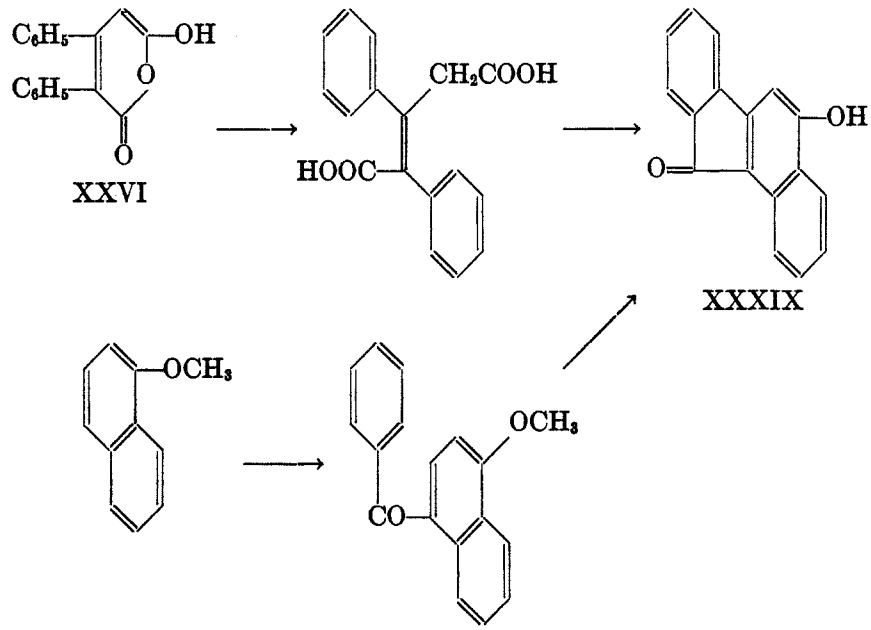
[20] ZIEGLER AND SCHNELL, *Ann.*, **445**, 266 (1925).

obtained by oxidizing it by means of lead tetraacetate to the known 1,2,3,5-tetraphenylpentene-2-dione-1,5 (XXXVI).[21]

The anhydride (XXVI) of α,β-diphenylglutaconic acid, which was obtained by hydrogen peroxide cleavage of the diketone, was found to titrate as a monobasic acid and to give two isomeric dibasic acids (XXXVII) under different conditions of hydrolysis. As Thorpe and Bland[22] have shown, such behavior is characteristic of α,β-disubstituted glutaconic anhydrides, which exist in their enolic forms. The structure of the anhydride was made certain by subjecting it to distillation with soda-lime, producing the known α-methyl stilbene (XXXVIII).

An interesting reaction took place when the anhydride (XXVI) was dissolved in sulfuric acid. Upon the addition of a trace of water the initially yellow-brown solution became green, and on further dilution a red compound was precipitated. This substance was identified as 1,2-benzo-3-oxyfluorenone (XXXIX) by comparison with an authentic sample prepared by the method of Fierz-David[23] and of Scholl and Seer.[24]

The formation of the fluorenone from the anhydride and the method used for its synthesis are shown in the following equations.



[21] DILTHEY, *Ber.*, **52**, 2052 (1919).
[22] THORPE AND BLAND, *J. Chem. Soc.*, **101**, 1563 (1912).
[23] FIERZ-DAVID AND JACARD, HELV. CHEM. ACTA, **11**, 1042 (1928).
[24] SCHOLL AND SEER, *Ann.*, **394**, 154 (1912).

EXPERIMENTAL

3,4-Diphenylcyclopentenone, (XXI).—The following procedure gives a much better yield of the ketone than the original one of Japp and Lander.[15] A mixture of 100 g. of anhydroacetone benzil,[14] 12.5 ml. of 45% hydriodic acid, 22.5 g. of red phosphorus, and 400 ml. of acetic acid was boiled for one hour, then filtered into a cold dilute solution of sodium bisulfite. The precipitate was taken up in ether and washed with water and sodium carbonate. Part of the product separated at once; the remainder was obtained by removal of the ether and distillation at 20 mm. These two parts, combined, and crystallized from benzene, gave a total of 70 g. of white crystals that melted at 108–110°.

2-Isonitroso-3,4-diphenylcyclopentenone, (XXII).—To a solution of 72 g. of diphenylcyclopentenone in 350 ml. of ethanol was added 46 g. of butyl nitrite and 15 ml. of concentrated hydrochloric acid. The mixture was kept at 50–55° for one hour, and then allowed to stand for several hours at room temperature. After collection by filtration and washing with alcohol, the product (67 g.) was yellow, and melted at about 210° with decomposition. The impurities were largely extracted by boiling for fifteen minutes with 200 ml. of benzene and filtering hot. The undissolved, nearly colorless product weighed 52 g., melted at 216–218° with decomposition, and was used for the preparation of the diketone without further purification. An analytical sample of m.p. 223–224° (dec.) was obtained by crystallization from ethyl acetate-acetic acid, and then from alcohol.

Anal. Calc'd for $C_{17}H_{13}NO_2$: C, 77.6; H, 4.9.
Found: C, 77.6; H, 4.8.

The substance is insoluble in aqueous 5% sodium hydroxide, but dissolves in aqueous-alcoholic 3% caustic, giving a deep yellow solution from which it is precipitated unchanged by acids.

On treatment with benzoyl chloride and aqueous sodium hydroxide, or better with benzoyl chloride in dry pyridine, the oxime is converted into its *benzoate*, fine yellow needles that melt at 142–143° with decomposition. The benzoate dissolves in alcoholic alkali giving a yellow solution.

Anal. Calc'd for $C_{24}H_{17}NO_3$: C, 78.4; H, 4.6.
Found: C, 78.0; H, 4.7.

3,4-Diphenylcyclopentendione-1,2 (XXIII).—A mixture of 52 g. of the isonitroso compound (XXII), 300 ml. of acetic acid, 300 ml. of 40% formalin, and 50 ml. of concentrated hydrochloric acid was boiled under a reflux condenser for thirty minutes. During this time the isonitroso compound dissolved, and the diketone started to separate. The mixture was then allowed to stand overnight; the product was filtered off and washed well with water. It was yellow-orange, and weighed 27 g.

The melting point of the diketone varied considerably in different samples. Crystallized from benzene or acetic acid, the substance formed yellow needles that melted with decomposition at 178–182°, while one sample crystallized from bromobenzene and petroleum ether was obtained in the form of deep yellow leaflets that melted at 186–188° with slow decomposition. Possibly dimorphic modifications were in hand; both the high- and low-melting samples gave the same phenazine.

Anal. Calc'd for $C_{17}H_{12}O_2$: C, 82.3; H, 4.8.
Found: C, 82.6; H, 4.6.

The diketone did not dissolve in cold dilute aqueous alkali, and on warming in alkali it was converted into an insoluble red oil. The addition of aqueous sodium hydroxide to an alcoholic solution of the compound caused the formation of a greenish-yellow color.

The *phenazine* (XXV) was obtained by boiling the diketone with a benzene solution of *o*-phenylenediamine. Crystallized from benzene, the substance formed soft white needles that melted at 236–237°. The phenazine dissolved in concentrated hydrochloric acid with a deep-red color and was precipitated unchanged by aqueous ammonia.

Anal. Calc'd for $C_{23}H_{16}N_2$: C, 86.3, H, 5.0.
Found: C, 86.7; H, 5.4.

The *oxime* (XXIV, 2-isonitroso-4,5-diphenylcyclopentenone) was obtained when an alcoholic suspension of the diketone was boiled for fifteen minutes with an excess of hydroxylamine hydrochloride neutralized with sodium hydroxide. It formed pale-yellow needles that darkened at 215° and melted at 237–239° with decomposition. A mixture with XXII (m.p. 223–224) melted at 217–218° with decomposition.

Anal. Calc'd for $C_{17}H_{13}NO_2$: C, 77.6; H, 4.9.
Found: C, 78.0, H, 4.9.

Cleavage with hydrogen peroxide.—To a suspension of 5 g. of the diketone in 50 ml. of alcohol was added 2.5 ml. of 30% hydrogen peroxide and then, dropwise and with shaking, 5 ml. of 20% aqueous sodium hydroxide. The solution was allowed to stand for five minutes, poured into water, and extracted several times with ether, the ether extracts being discarded. Acidification of the aqueous solution precipitated the product, which weighed 4.7 g. and melted at 121–126°. Recrystallized from ether-petroleum ether the α,β-diphenylglutaconic anhydride (XXVI) formed pale yellow needles that melted at 126–127°.

Anal. Calc'd for $C_{17}H_{12}O_3$: C, 77.3; H, 4.6; Neutr. equiv. (monobasic acid), 264.
Found: C, 77.3; H, 4.6; Neutr. equiv., 262.

Crystallized from benzene-petroleum ether, the anhydride separated in pale yellow plates of m.p. 111–112° that contained solvent of crystallization. This solvent was lost on heating at 105° for ten minutes, the residue then melting at 126–127°.

The anhydride can be distilled unchanged at 20 mm. When heated with phenol and sulfuric acid for five minutes at 140° it gave a melt which dissolved in alkali with a wine-red color. When treated with benzaldehyde in alcoholic hydrochloric acid, the anhydride was converted into a compound that melted at 152.5–153.5°. On heating with aniline, the anhydride yields a tan substance crystallizing in needles that melt at 224–225°; this is partly converted into a red substance melting at 246–248° when boiled with methanol.

α-β-Diphenylglutaconic acid (XXXVII).—When the anhydride (XXVI) was boiled with 10% sodium hydroxide, dilute hydrochloric acid, or acetic acid containing phosphorus and iodine (the latter in an attempt to reduce the anhydride), there was obtained an acid which formed white leaflets that melted at 165–166° with decomposition (after crystallization from water). It was reconverted to the anhydride (XXVI) on distillation at 20 mm.

Anal. Calc'd for $C_{17}H_{14}O_4$: C, 72.4; H, 5.0; Neutr. equiv., 141.
Found: C, 72.6; H, 4.9; Neutr. equiv., 142.

An isomeric form of the acid was obtained when the anhydride was boiled for one hour with 10% sodium hydroxide in the presence of zinc dust. Crystallized from dilute alcohol this substance melted with decomposition at 204–205°. This acid was not identical with α,β-diphenylglutaric acid of m.p. 209–210°,[25] since, when it was

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[25] BORSCHE, *Ber.*, **42**, 4496 (1909); AVERY AND MACLAY, *J. Am. Chem. Soc.*, **51**, 2833 (1929).

mixed with a sample of the latter, it softened at 185° and melted with decomposition at 195–199°.

Anal. Calc'd for $C_{17}H_{14}O_4$: C, 72.4; H, 5.0, Neutr. equiv., 141.
Found: C, 72.48; H, 495; Neutr. equiv., 140.

α-Methylstilbene (XXXVIII) from the anhydride (XXVI).—The dry sodium salt prepared from 1 g. of the anhydride was intimately mixed with an equal weight of soda-lime and distilled at 20 mm. The distillate, obtained in poor yield, solidified in the receiver and after crystallization from petroleum ether melted at 80–81.5°. This melting point was unchanged when the substance was mixed with an authentic sample of α-methylstilbene.[26]

1,2-Benzo-3-hydroxyfluorenone (XXXIX) from the anhydride.—The anhydride dissolved in concentrated sulfuric acid with a yellow-brown color, and when the solution was slowly diluted with water it became green and finally deposited a brick red substance. Recrystallized from nitrobenzene, this formed deep-red needles that melted at 307–308° on a copper block, (literature,[23] 305°).

Treated with benzoyl chloride in pyridine, the oxyfluorenone gave its benzoate, yellow needles that melted at 235–236°, (literature,[26] 236°).

The oxyfluorenone and its benzoate were identified by melting point determinations of mixtures with samples prepared by reactions described in the literature.

Reaction of the diketone with phenylmagnesium bromide.—A benzene solution of the diketone (2.9 g.) was added to a Grignard reagent prepared from 6.2 g. of bromobenzene and 0.96 g. of magnesium. The mixture was boiled for thirty minutes, decomposed with iced hydrochloric acid and worked up in the usual way. The 1,2,3,4-tetraphenylcyclopenten-3-diol-1,2 (XXXIV), obtained in a yield of 3 g., formed white needles that melted at 200–201° after crystallization from ethyl acetate-petroleum ether.

Anal. Calc'd for $C_{29}H_{24}O_2$: C, 86.1; H, 6.0.
Found: C, 86.1; H, 5.8.

When the glycol (0.5 g.) was boiled for five minutes with 25 ml. of methanol containing 4 drops of sulfuric acid, it was converted into *1,2,3,5-tetraphenyl-1-methoxycyclopentadiene* (XXXV)[19] in good yield. Crystallized from methanol, the ether formed white needles that melted at 150–151°.

Anal. Calc'd for $C_{30}H_{24}O$: C, 90.0; H, 6.0; OCH_3, 7.75.
Found: C, 89.6; H, 6.0; OCH_3, 7.9.

From the deep-red solution that resulted when the glycol (XXXIV) (0.2 g.) was boiled for fifteen minutes with 2 ml. of acetic acid containing a drop of sulfuric acid there was obtained about 20 mg. of 2,3,4,5-tetraphenylcyclopentadienone, m.p. 216–218°, identified by comparison with an authentic sample.[27] The addition of potassium bichromate to a similar reaction mixture had no effect on the yield of ketone.

Oxidation of the glycol with lead tetraacetate.—To a suspension of 0.5 g. of the glycol (XXXIV) in 20 ml. of acetic acid was added 0.7 g. of lead tetraacetate. The mixture was shaken for ten minutes and poured into water. Crystallization from methanol yielded 0.32 g. of a white product that melted at 110–112°, and gave a red-violet color with alcoholic alkali. It formed a ferric salt that melted at 187–188° when its solution in acetic acid was treated with ferric chloride. These properties are characteristic of the known 1,2,3,5-tetraphenylpenten-2-dione-1,5 (XXXVI).[21]

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[26] HELL, *Ber.*, **37**, 458 (1904).

[27] DILTHEY AND QUINT, *J. prakt. Chem.*, **128**, 139 (1930).

Bromination of the diketone: the monobromo compound (XXVII).—A solution of 2.0 g. of the diketone and 1.3 g. of bromine in 40 ml. of acetic acid was boiled a few minutes, or until the bromine color had disappeared. The solution was cooled, whereupon the product (2.2 g.) separated in the form of soft yellow needles that melted at 181–182.5° with decomposition.

Anal. Calc'd for $C_{17}H_{11}BrO_2$: C, 62.4; H, 3.4.
Found: C, 62.4; H, 3.4.

Treatment of the bromo compound with methanol, sodium methoxide in methanol, sodium acetate in acetic acid, or with phenylmagnesium bromide led to uncrystallizable products in each case.

The dibromo compound (XXVII).—Two grams of the diketone treated as above, but with 2.6 g. of bromine, gave the dibromo compound (2.9 g.), crisp orange needles that melted at 162–165° and decomposed at about 185°.

Anal. Calc'd for $C_{17}H_{10}Br_2O_2$: C, 50.2; H, 2.5.
Found: C, 50.2; H, 2.5.

Treatment of the dibromodiketone with methanol gave no crystallizable product. Aniline reacted with the dibromo compound to give the calculated amount of aniline hydrobromide, but the other product was an uncrystallizable red oil.

Reaction of the diketone with aniline.—A deep-green solution was formed when the diketone (0.5 g.) was boiled with aniline (1 ml.) in benzene (20 ml.). Replacement of half of the solvent with petroleum ether precipitated 0.7 g. of a yellow crystalline powder that melted at 81–83°, but this could not be recrystallized without decomposition, and a satisfactory analysis was not obtained. The analogous compound formed with *p*-toluidine melted at 87.5–89°.

When aniline (1 ml.) was added to an ether solution of 0.3 g. of the diketone in the cold, a product (XXXIII, R = C_6H_5) that crystallized in small yellow needles that melted with decomposition at 108–110° was obtained. This substance decomposed to an oil when its recrystallization was attempted. It regenerated the diketone when treated with dilute hydrochloric acid.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6.
Found: C, 81.2; H, 5.8.

The *p*-toluidine addition product (XXXIII, R = $p - C_7H_7$) had similar properties and melted at 120–122° with decomposition.

Anal. Calc'd for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.9.
Found: C, 81.6; H. 6.2.

Reaction of the diketone with methanol.—One gram of the diketone was boiled for an hour in 15 ml. of methanol containing 5 drops of concentrated hydrochloric acid. The solution was concentrated and cooled, and the product which separated was recrystallized from methanol. There was obtained 0.65 g. of 1,1-dimethoxy-3,4-diphenylcyclopentenone-2 (XXIX): flat white needles that melted at 120–121°.

Anal. Calc'd for $C_{19}H_{18}O_3$: C, 77.6; H, 6.1; OCH_3, 21.1.
Found: C, 77.8; H, 6.7; OCH_3, 21.3.

The diketone was regenerated when the acetal was boiled with acetic acid containing a drop of hydrochloric acid.

1,1-Dimethoxy-2,3,4-triphenylcyclopentenol-2, (XXX).—An ether suspension of the acetal (XXIX) (2.94 g.) was added to a solution of phenylmagnesium bromide containing 0.52 g. of magnesium. The mixture was boiled for fifteen minutes, and was decomposed with iced ammonium chloride. The product, obtained in the usual way and crystallized from methanol, formed white needles which melted at 124–125°; yield 3.2 g.

Anal. Calc'd for $C_{25}H_{24}O_3$: C, 80.6; H, 6.5.
Found: C, 80.5; H, 6.5.

Dimer of 2,3,4-triphenylcyclopentadienone (XXXI).—A solution of 1,1-dimethoxy-2,3,4-triphenylcyclopentenol-2 in acetic acid containing 2% of sulfuric acid was boiled for a few minutes and then poured into water. The product was crystallized from ether, when it formed pale yellow needles that melted at 257–258° with darkening.

Anal. Calc'd for $C_{46}H_{32}O_2$: C, 89.6; H, 5.2.
Found: C, 89.5; H, 5.6.

The same compound was prepared by the action of acetic-sulfuric acid on anhydrophenylacetonebenzil.[16]

SUMMARY

A discussion of some of the properties of previously known cyclic α-diketones is presented.

The preparation and reactions of 1,2-diketo-3,4-diphenylcyclopentendione are described. It is noted that this diketone has little or no tendency to enolize, and that it has one particularly reactive carbonyl group.

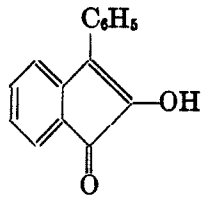
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ENOLIZATION OF 1,2-DIKETOHYDRINDENE AND OF 1,2-DIKETO-3-PHENYLHYDRINDENE*

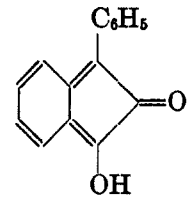
C. F. KOELSCH AND HARRY HOCHMAN

Received September 30, 1938

In a previous paper[1] chemical evidence was presented which indicated that 1,2-diketo-3-phenylhydrindene is completely enolic and that the enolic form has structure I rather than II. Evidence for the structure of this compound and for that of its unsubstituted analog, 1,2-diketohydrindene, III, based on ultraviolet absorption measurements is now brought forward.



I



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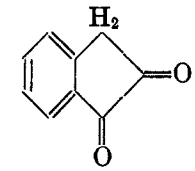


III

The absorption curves of the compounds investigated, given in Figures 1 and 2, fall into two distinct classes. In one of these the maxima (with the exception of that for diphenylindone) are close to 2500Å, while in the other they are close to 2730Å; also, the absorption of the former class is considerably the stronger.

Since the optical properties of 1,2-diketo-3-phenyl-hydrindene[1] (curve 4) are similar to those of 2-methoxy-3-phenylindone[1] (curve 5) and 2,3-diphenylindone[2] (curve 7), the enolic structure I of this compound is indicated.

The absorption of 1,2-diketohydrindene[3] (curve 6) however, places it in a class with 3-methyl-3-phenyl-[4] (curve 1), 3-hydroxy-3-phenyl-[4] (curve 2), and 3,3-dimethyl-1,2-diketohydrindene[4] (curve 3), compounds which

* Abstracted from the thesis of Harry Hochman, presented to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, December, 1935.

[1] KOELSCH, *J. Am. Chem. Soc.*, **58**, 1321 (1936).

[2] Prepared by the action of phenylmagnesium bromide on 2-phenylindandione-1,3. Compare KOELSCH, *J. Am. Chem. Soc.*, **58**, 1328 (1936).

[3] PERKIN, ROBERTS, AND ROBINSON, *J. Chem. Soc.*, **101**, 232 (1912).

[4] Preparation to be described in a future paper from this laboratory.

must have the diketonic structure. The chemical behavior of the unsubstituted diketone also indicates that it is completely ketonic. The compound dissolves in aqueous alkali without the formation of a blue color, and the solution so obtained does not give back the diketone on acidification.[3] Also, the diketone is quite resistant to the action of bromine, even in hot acetic acid, although a dibromo substitution product can be obtained under the proper conditions.

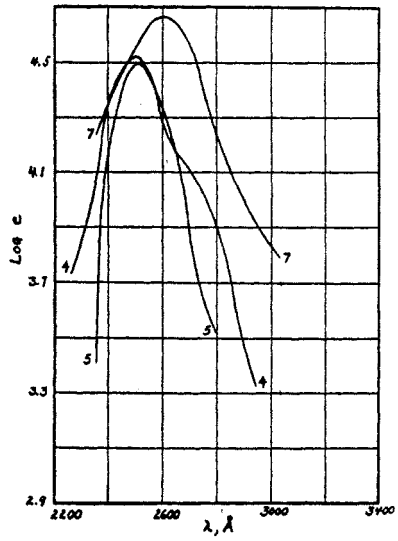


FIG. 1

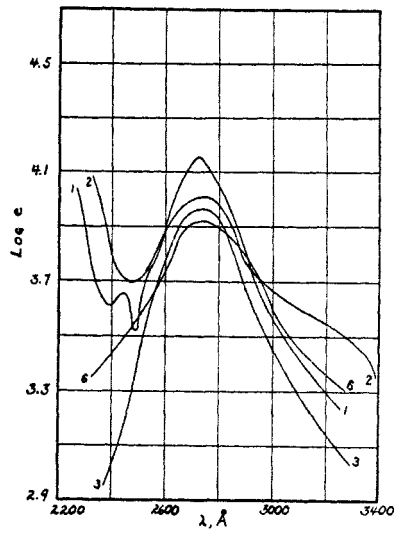


FIG. 2

FIGURE 1.—ABSORPTION CURVES OF INDENONES

Curve 4 = 1,2-Diketo-3-phenylhydrindene. Curve 5 = 2-Methoxy-3-phenylindone. Curve 7 = 2,3-Diphenylindone.

FIGURE 2.—ABSORPTION CURVES OF DIKETONIC SUBSTANCES

Curve 1 = 1,2-Diketo-3-methyl-3-phenylhydrindene. Curve 2 = 1,2-Diketo-3-hydroxy-3-phenylhydrindene. Curve 3 = 1,2-Diketo-3,3-dimethylhydrindene. Curve 6 = 1,2-Diketohydrindene.

EXPERIMENTAL

The compounds used were prepared by methods described in the reference given. Special attention was paid to the purity of the substances, and those compounds which are unstable, 1,2-diketo-3-phenylhydrindene and its enol ether, were prepared immediately before the optical measurements were made.

The absorption curves were determined photographically by means of a Judd-Lewis photometer and a Hilger quartz spectrograph using a hydrogen arc as a light source. Cyclohexene was used throughout as a solvent. In Figures 1 and 2 the logarithm of the molar extinction coefficient is plotted as a function of wave-length in Ångstroms.

Bromination of 1,2-diketohydrindene.—1,2-Diketohydrindene (1 g.) can be boiled

with bromine (2.3 g.) in acetic acid (20 ml.) without change, but it reacts when a little sodium acetate or a few drops of hydrobromic acid is added. The dibromodiketone separates on cooling, and after recrystallization from acetic acid it forms orange plates (1.1 g.) that melt at 141–142°.

Anal. Calc'd for $C_9H_4Br_2O_2$: C, 35.5; H, 1.3.
Found: C, 35.8; H, 1.9.

The bromine is removed completely (0.132 g. subst. gave 0.159 g. AgBr; calc'd 0.163 g.) when the dibromo compound is boiled with alcoholic silver nitrate for one minute. Hence both bromine atoms are in the alicyclic ring.

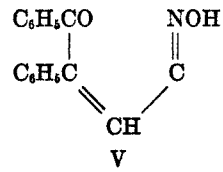
SUMMARY

The ultraviolet absorption of 1, 2-diketo-3-phenylhydrindene indicates that it exists in the enolic form, while that of 1, 2-diketohydrindene indicates that this compound is ketonic. The chemical behaviors of these substances are consistent with these structures.

THE TAUTOMERISM OF OXIMES: CORRECTION

The following corrections should be made in the article of this title in the JOURNAL OF ORGANIC CHEMISTRY 3, 91 (1938).

On page 92



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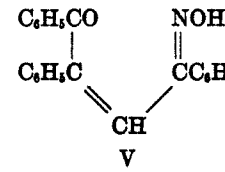

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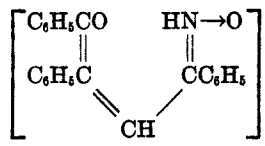

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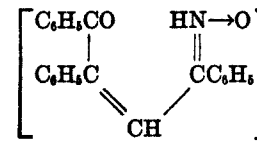

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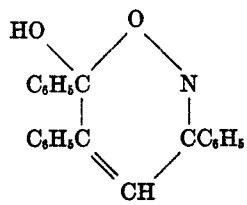

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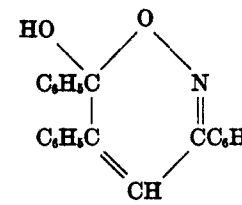

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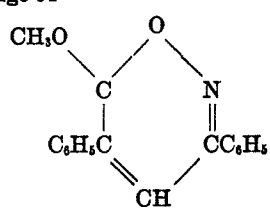

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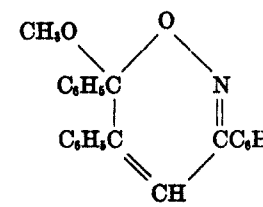

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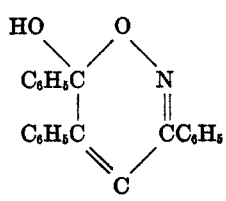

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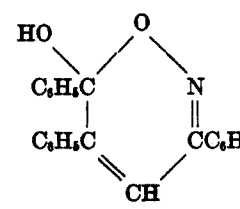

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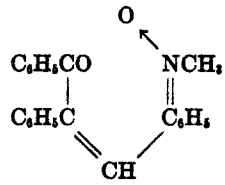

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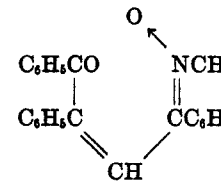


XIX

A. H. BLATT

THE SYNTHESIS OF CONDENSED POLYNUCLEAR HYDROCARBONS BY THE CYCLODEHYDRATION OF AROMATIC ALCOHOLS. VII. CYCLODEHYDRATION INVOLVING THE WAGNER REARRANGEMENT: CORRECTION

In a recent article in THIS JOURNAL [**2**, p. 542 (1938)], by Price, Davidson, and Bogert, we have referred to the synthesis of 1-phenyl-4,4-dimethylpentanol-3 and its phenylurethane as though they were new compounds, having overlooked completely at the time the article was written the fact that Hill and Bruce had described these same compounds a number of years ago [*J. Am. Chem. Soc.*, **52**, 350 (1930)]. One reason why we missed this reference was that the name used for this carbinol by the latter authors was not the same as the one employed by us. We regret this oversight and wish to extend our apologies to Drs. Hill and Bruce.

MARSTON T. BOGERT

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

ADDITION OF GRIGNARD'S REAGENT TO PSEUDOCODEÏNE TYPES. III. THE METHYLDIHYDROTHEBAÏNES*

LYNDON SMALL AND EDWARD M. FRY†

Received April 6, 1938

It has been shown in previous investigations in this laboratory that alkylmagnesium halide reacts more or less readily with a number of derivatives of the morphine alkaloids, namely desoxycodeïne-C,[1] pseudocodeïne methyl ether,[2] pseudocodeïnone,[3] and dihydrothebaïne.[4] The same reaction has most recently been realized with dihydrocodeïnone enol acetate and acetyldihydrohydroxycodeïnone enol acetate.[5] All of these substances have in common the structural feature of an unsaturated linkage in the 6, 7 position, *i.e.*, all are (cyclic) allyl ether types. The participation of both the cyclic-linked ether oxygen and the alicyclic unsaturation (directly, or by virtue of activating influence) in the reaction is obvious, for in every example cited, the ether ring is opened with formation of a phenolic hydroxyl group; furthermore, with no derivative yet studied does such a reaction take place when the unsaturation is not present, or is at a different location than between carbon atoms 6 and 7.‡

Martin Freund observed many years ago that thebaïne and phenylmagnesium bromide react to give a phenolic product, which he designated as phenyldihydrothebaïne.[6a] At the time of Freund's studies, neither the

* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

† Mallinckrodt Fellow in Alkaloid Chemistry, 1936–1937; Squibb Fellow in Alkaloid Chemistry, 1937–1938.

[1] SMALL AND YUEN, *J. Am. Chem. Soc.*, **58**, 192 (1936).

[2] SMALL AND FITCH, unpublished results.

[3] LUTZ AND SMALL, *J. Am. Chem. Soc.*, **57**, 2651 (1935).

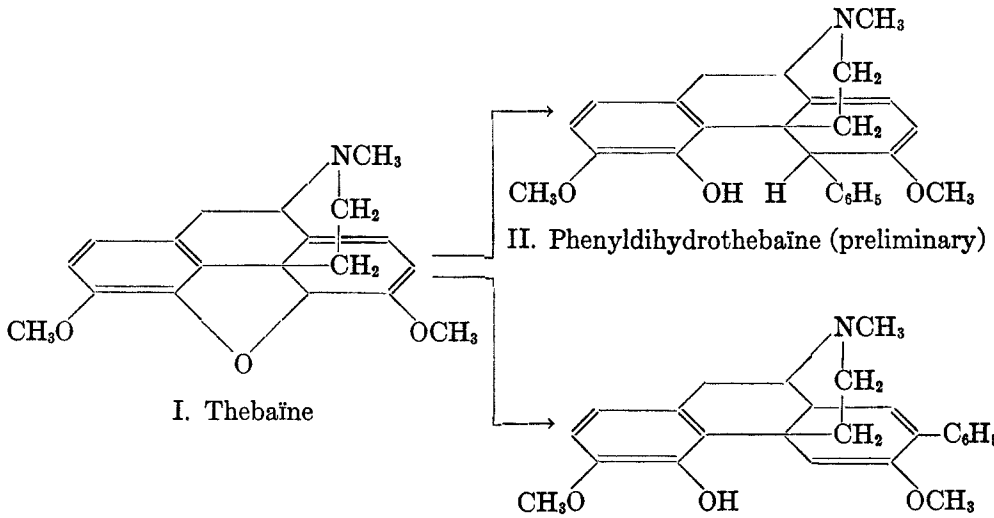
[4] SMALL, FITCH, AND SMITH, *ibid.*, **58**, 1457 (1936).

[5] SMALL AND CO-WORKERS, unpublished results.

‡ The reaction of methylmagnesium iodide with α-chlorocodide [SMALL AND COHEN, *J. Am. Chem. Soc.*, **53**, 2214 (1931)] is of a different type. An organic group is not introduced into the molecule, and the Grignard reagent acts only in a reducing capacity.

[6] (*a*) FREUND, *Ber.*, **38**, 3234 (1905); (*b*) FREUND AND SPEYER, *ibid.*, **49**, 1287 (1916).

structure of thebaïne, nor the connection between the activity of the ether oxygen and the position of the double bond, were known, but it now appears reasonable to regard the reaction of thebaïne with phenylmagnesium bromide as another manifestation of the characteristic behavior of the allyl ether system present in the pseudocodeïne types. Phenyldihydrothebaïne, accordingly, should have the structure of a 1,2- or 1,4-addition product (II or III).



I. Thebaïne

II. Phenyldihydrothebaïne (preliminary)

III. Phenyldihydrothebaïne (preliminary)

The compound presents some extraordinary features, however, which lead us to believe that the reaction is more complicated than that of the simpler structural types, as for example desoxycodeïne-C, and different from that of dihydrothebaïne. The most notable peculiarities are as follows.

(1) Although the empirical formula and derivation of phenyldihydrothebaïne indicate the presence of two alicyclic unsaturated linkages, the compound resists catalytic hydrogenation.[6,7] In fact, the unsaturated linkages are so indifferent that they remain unaffected even under conditions so rigorous that the nitrogen-containing ring is opened reductively (formation of phenyltetrahydrothebaïmine.[6b] Compound II should add at least one mole of hydrogen easily, as does thebaïne; compound III might show some reluctance, since enol ethers are exceedingly difficult to hydrogenate, and the phenyl group at the other unsaturated linkage might influence the ease of reduction at this point.

[7] HOEK, Dissertation, Freiburg, **1926**, p. 24.

(2) Phenyldihydrothebaïne contains two methoxyl groups (Zeisel), one of which should be in an enol ether linkage, yet the compound is unaffected by boiling concentrated hydrochloric acid. Of the numerous enol ethers in the morphine series that we have examined, none has resisted this treatment, and most are hydrolyzed by normal or three-normal hydrochloric acid at room temperature. The products from the reaction of alkyl-, aralkyl-, or arylmagnesium halides with dihydrothebaïne, for example, are so easily hydrolyzed that we have not been able to isolate the enol ether form, even under the gentlest conditions. If the assumption of an enol ether group is rejected, the resistance to hydrogenation becomes even more difficult to explain. Moreover, with the ethanamine chain attached to C-13, it is impossible to arrange two double linkages in ring III without postulating the enol ether structure.

(3) The empirical formula, which seems well established, shows that ring III cannot be aromatic in nature, but if phenyldihydrothebaïne is completely demethylated by sufficiently vigorous treatment, the product, norphenyldihydrothebaïne, has the properties of a triphenol, *i.e.*, contains three acidic hydroxyl groups. The demethylation does not involve any rearrangement, for norphenyldihydrothebaïne gives with diazomethane a trimethyl ether identical with phenyldihydrothebaïne methyl ether. Hoek[7] argues that the inexplicable third acidic hydroxyl group does not behave like an enolic hydroxyl, for he was unable to effect reduction with sodium amalgam; norphenyldihydrothebaïne failed likewise to react like a carbonyl compound with hydroxylamine. This evidence must be accepted with some caution, since morphine derivatives carrying a ketonic group in ring III sometimes behave abnormally. Hydroxythebaïnone, for example, although it forms an oxime, cannot be reduced with sodium, in contrast to most other 6-keto derivatives of the morphine group.[8] Moreover, methyldihydropseudocodeïnone, which should have a carbonyl group at position 8, does not form an oxime, nor can the carbonyl group be reduced by metal combinations or catalytically.[3]

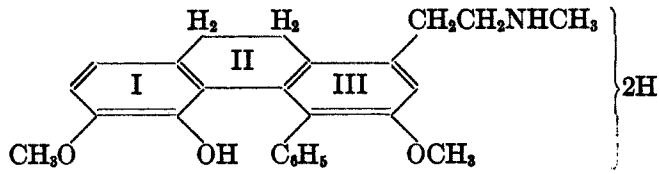
(4) In contrast to thebaïne, phenyldihydrothebaïne does not undergo degradation with boiling acetic anhydride, nor does it behave like thebaïne on alkaline degradation. Whereas most morphine derivatives having the tetrahydrophenanthrene state of unsaturation lose the entire ethanamine side-chain and become aromatic during the Hofmann degradation, phenyldihydrothebaïne retains carbon atoms 15 and 16 in this degradation. The hypothesis that the phenyl group may be located on C-14, and thus hinders aromatization of the nucleus,[9] involves the improbable assumption of a

[8] SMALL AND LUTZ, unpublished studies on hydroxycodeïnone.

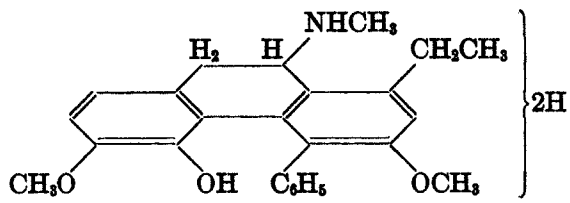
[9] SMALL AND LUTZ, "Chemistry of the Opium Alkaloids," Supplement 103 to the Public Health Reports, **1932**, p. 333.

1,6-addition of phenylmagnesium bromide to thebaïne, and does not in any way facilitate explanation of the other anomalies cited in the preceding paragraphs.

The inviting hypothesis that ring III of the thebaïne system has become aromatic during phenyldihydrothebaïne formation would explain all of the peculiarities of the compound. This idea is untenable, however, for analyses of phenyldihydrothebaïne and its numerous transformation products all show the presence of two hydrogen atoms for which no place other than a position on the ring can be found. It is unfortunate that Freund practically neglected optical properties, so that this valuable criterion of the aromaticity of ring III in his degradation products is not applicable. The one example that can be drawn from his work is indecisive. Phenyltetrahydrothebaïmine was observed to be optically active. If ring III in this compound is aromatic, the conclusion is inevitable that the ethanamine chain must have shifted from its original position in thebaïne. Assuming that such a shift has taken place, and neglecting for the moment the disposal of the two hydrogen atoms, phenyltetrahydrothebaïmine might be expected to have the structure IV (or perhaps with C_6H_5 at C-7 and the ethanamine chain at C-5) and could not be optically active. The alternative formula V for phenyltetrahydrothebaïmine is possible, however, and indeed is favored somewhat by Freund; this point will be decided in a later study on the end-product from degradation of phenyltetrahydrothebaïmine. Several examples of optically active degradation products described in the present communication support the arguments against the aromaticity of ring III.



IV. Phenyltetrahydrothebaïmine, formula illustrative of argument against aromaticity of ring III



V. Phenyltetrahydrothebaïmine, alternative formula

Phenyldihydrothebaïne thus remains one of the few derivatives of the morphine series whose behavior cannot be adequately explained in terms of a structural formula. The phenyl group, as a nuclear substituent, may introduce two unnecessary complications, the steric factor, and a possible "negative" influence. We were therefore led to investigate the simplest possible example, the reaction of methylmagnesium iodide with thebaïne. The results are far more complex than those that have been obtained with the phenyl derivative, but probably only because phenyldihydrothebaïne has not been exhaustively studied.

When thebaïne is brought into reaction with ethereal methylmagnesium iodide by slow extraction from a Soxhlet apparatus, a sensitive, liquid product is obtained, which can be separated through the crystalline perchlorate and hydrochloride into two isomeric methyldihydrothebaïnes, $C_{20}H_{25}NO_3$, that is, thebaïne, $C_{19}H_{21}NO_3$, plus CH_4. The principal product, α-methyldihydrothebaïne, is formed in a yield of 41 to 49 per cent. of the calculated amount the minor product, δ-methyldihydrothebaïne, in a yield of 24 to 26 per cent. Both bases are strongly phenolic in nature and are identical in empirical formula, but differ widely in physical properties, and in the properties of their salts. Neither base can be hydrogenated by catalytic methods, nor hydrolyzed by boiling concentrated hydrochloric acid. When pure α-methyldihydrothebaïne (as perchlorate, in alcohol solution) is heated on the water bath for about twenty-four hours, it is converted to the extent of 10 per cent. into the δ base, the rest of the material being recovered unchanged. In spite of this demonstration of the slow transformation of the α into the δ isomer, it seems probable that the appearance of δ-methyldihydrothebaïne in the original Grignard reaction is independent of, and parallel to, the formation of the α compound, since the reaction conditions are so mild, and the yield of the δ isomer is relatively so high, that a rearrangement of primarily-formed α-methyldihydrothebaïne is scarcely to be expected.*

α-Methyldihydrothebaïne undergoes a different isomerization when distilled slowly in a high vacuum, or when heated in an evacuated sealed tube at 125° for four days. Only about 20 per cent. of the α base can be recovered; two other products, which account for the remainder of the

* An inspection of Freund's experimental work immediately leads to the suspicion that his phenyldihydrothebaïne was a mixture of isomers. This is evident from the indefinite properties of the base itself, and of phenyldihydrothebaïnemethine, phenyldihydrothebaïne methyl ether, phenyldihydrothebaïnemethine methyl ether, acetylphenyldihydrothebaïne, norphenyldihydrothebaïne, and dichloro- and dibromophenyldihydrothebaïne. In exploratory experiments with phenyldihydrothebaïne, we have observed that it gives two distinct perchlorates, which appear to be partly interconvertible.

material, can be isolated. One of these (4 per cent. yield) is an optically inactive methyldihydrothebaïne, and will be later discussed as α,ω-methyldihydrothebaïne racemate. The second product (about 75 per cent. yield), which we shall designate as α,η-methyldihydrothebaïne molecular compound, yields analytical values identical with those of the starting material, but differs from it in physical properties. The new product can be recrystallized many times without change in melting point or rotatory power; like the α base, it is indifferent toward catalytic hydrogenation. The α,η-methyldihydrothebaïne molecular compound, can, however, through the hydrochloride and perchlorate, respectively, be separated into approximately equal amounts of α-methyldihydrothebaïne and the new isomer, η-methyldihydrothebaine.† Conversely, when equal amounts of α-methyldihydrothebaïne (m.p. 89°) and of η-methyldihydrothebaïne (liquid) are mixed in alcohol solution, a 93 per cent. yield of α,η-methyldihydrothebaïne (m.p. 125°) is obtained. The conversion of α-methyldihydrothebaïne to the equimolecular α,η compound appears to be an equilibrium reaction, for if pure η-methyldihydrothebaïne is heated in a sealed tube at 150° for 15 hours, a good yield of the molecular compound is obtained. η-Methyldihydrothebaine has the empirical formula $C_{20}H_{25}NO_3$, and is identical in its physical properties, and those of its salts, with δ-methyldihydrothebaïne and its salts, except that the optical rotation is opposite in direction.

The base designated as δ-methyldihydrothebaïne, a minor product of the Grignard reaction, and a conversion product obtained by heating an alcoholic solution of α-methyldihydrothebaïne perchlorate, undergoes transformations parallel to those described above for the α base. When heated in an evacuated sealed tube at 155° for ten hours, δ-methyldihydrothebaïne is converted in about 78 per cent. yield to an apparently homogeneous isomeric substance, which we designate as δ,ω-methyldihydrothebaïne molecular compound. At the same time, a small amount (1 per cent.) of the above-mentioned α,ω-methyldihydrothebaïne racemate is formed.

δ,ω-Methyldihydrothebaïne molecular compound corresponds in every way to the α,η molecular compound except that its rotation is opposite in direction. By means of salts, it can be separated into δ-methyldihydrothebaïne, and the new isomer, ω-methyldihydrothebaïne. Likewise, when equal amounts of δ-methyldihydrothebaïne (liquid) and ω-methyldihydrothebaïne (m.p. 89°) are mixed in ethanol solution, the δ,ω molecular

† This is reminiscent of the molecular compound of isocodeïne and allopseudocodeïne described by Lees [*J. Chem. Soc.*, **91**, 1416 (1907)], which behaved like a chemical individual but could be separated into its components through the methiodide; see also Speyer and Krauss, *Ann.*, **432**, 248 (1923).

compound (m.p. 124.5°) is obtained. ω-Methyldihydrothebaïne can also be prepared in small yield (about 2 per cent.) by prolonged heating of pure η-methyldihydrothebaïne perchlorate in alcohol solution. The change resembles the partial transformation of the α isomer into the δ isomer under similar conditions.

THE α,ω- AND δ,η-METHYLDIHYDROTHEBAÏNE RACEMATES‡

When equal amounts of α- and ω-methyldihydrothebaïnes (melting points identical, specific rotations respectively +140° and −140°) are dissolved separately in alcohol, in which they are readily soluble, and the alcoholic solutions are mixed, a sparingly soluble crystalline compound separates. This compound has the melting point 179–182°, specific rotation 0°, and gives the same analytical values as the components; it appears to be a racemic compound. It is identical with the optically inactive substance that is isolated in small yield from the isomerization of α- and δ-methyldihydrothebaïnes. The appearance of a small amount of the racemate in the course of the isomerization process is obviously due to transformation of a portion of the η isomer into the ω isomer during the prolonged heating involved in the α-to-η change, and similarly to a transformation of a little of the δ into the α isomer during the δ-to-ω change, the resulting α,ω-racemate being easily isolated because of its slight solubility.§

The δ- and η-methyldihydrothebaïnes likewise behave as optical antipodes. When alcoholic solutions of their perchlorates (specific rotations respectively +50° and −50°) are mixed, a sparingly soluble perchlorate crystallizes. It yields a new base, of empirical formula $C_{20}H_{25}NO_3$, which, in contrast to the oily δ and η bases, is crystalline. It melts at 79–83°, has the specific rotation 0°, and appears to be the δ,η-methyldihydrothebaïne racemate.*

We have described in the foregoing paragraphs two molecular compounds, having the same melting points and empirical formulas, but equal and opposite rotatory power. Each of these molecular compounds consists of two bases, (α + η) and (δ + ω), which, pairwise, (α and ω) and

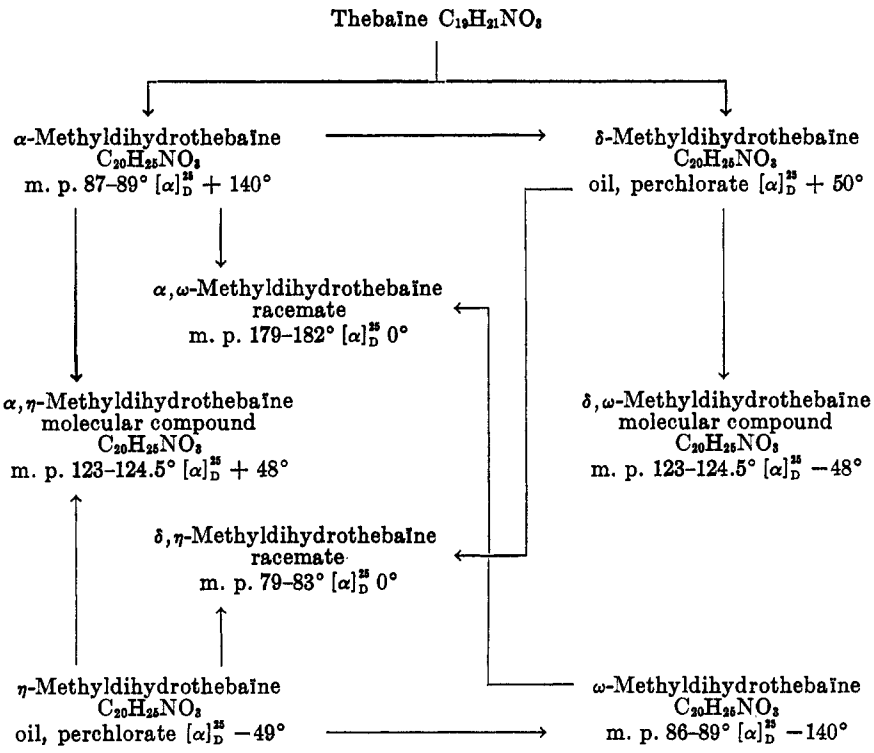
‡ In spite of what we believe to be convincing evidence that the ω- and η-methyldihydrothebaïnes are the optical opposites of the parent α and δ compounds, we prefer for the present to refer to them by the Greek letters assigned during the progress of experiments rather than as the (−) forms of the progenitors.

§ The direct transformation of the δ-methyldihydrothebaïne into the α isomer was not attempted, but is assumed to be possible because the parallel change of the optical opposite, the η isomer, into the ω isomer was realized.

* In analogy with the formation of traces of α,ω-racemate in the isomerization of α- and δ-methyldihydrothebaïnes, some of the δ,η-racemate might be expected in the same reaction. Perhaps because of its low melting point and greater solubility, none of this racemate has been found.

(δ and η) have the physical characteristics of optical antipodes, and which, when mixed, yield new compounds that appear to be racemates. As would be expected from these facts, when solutions of the α,η molecular compound and of the δ,ω molecular compound are mixed, the products that can be isolated are the optically inactive α,ω- and δ,η-methyldihydrothebaïne racemates.

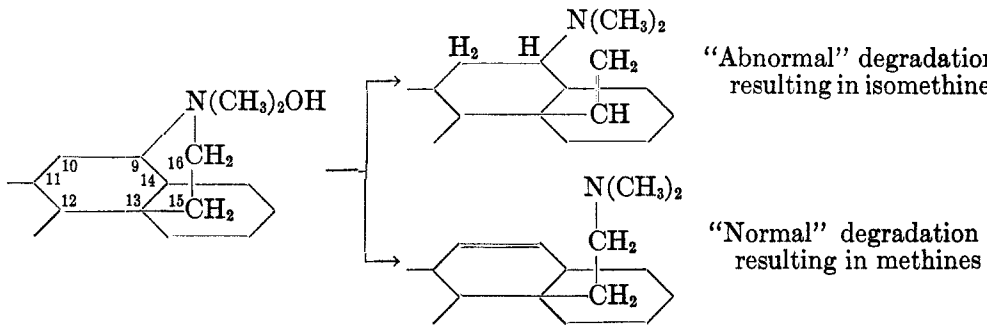
FIG. I



DEGRADATION OF THE METHYLDIHYDROTHEBAÏNES

The degradation of the methyldihydrothebaïnes was undertaken with the object of clarifying the inexplicable transformations and relationships of the several isomers. Because of the difficult accessibility of ω-methyldihydrothebaïne, its degradation was not completed, but there is little doubt that it will proceed parallel to that of the optical opposite, the α isomer. All evidence indicates that the methiodides of the four isomers, on alkaline degradation, suffer rupture of the nitrogen-containing ring in a

manner hitherto unknown for the morphine series,† *i.e.*, between the nitrogen atom and carbon atom 16, whereby carbons 15 and 16 emerge as a vinyl group. The products of this "abnormal" type of degradation we shall designate as "isomethines." On the other hand, for reasons beyond speculation, the acetyl derivatives of the α, δ, and η isomers (the ω isomer was not investigated) break down predominantly in the "normal" way when subjected in the form of methohydroxide to dry distillation, with formation of an unsaturated linkage at the 9,10-position, yielding products that will be described in the usual way as "methines."‡



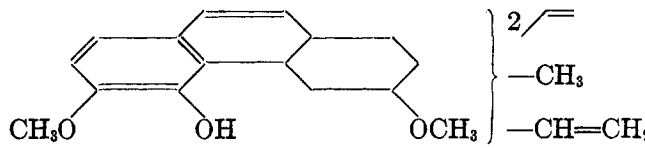
The relationships between the significant degradation products discussed in the following paragraphs are summarized in Figure II. α-Methyldihydrothebaïne methiodide, subjected to the Hofmann degradation, yields a phenolic isomethine base of the expected composition, $C_{21}H_{27}NO_3$. α-Methyldihydrothebaïneisomethine, in contrast to the undegraded base,

† It is not excluded that "abnormal" degradation of the morphine series takes place to some extent in some of the well-known degradations of morphine derivatives. In a great many degradations the basic products produced in the final step have not been identified, and the methine base has been assumed to have the "normal" structure in analogy with the methylmorphimethines, where the formation of β-hydroxyethyldimethylamine by acetolysis indicates plainly the course of the degradation. One conspicuous example of "abnormal" degradation, that of apomorphine dimethyl ether, is discussed in a later paragraph. This compound, however, no longer possesses the true morphine ring skeleton.

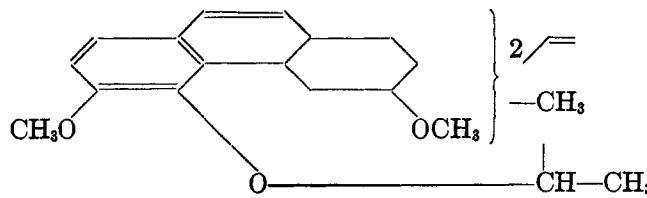
‡ The factor determining type of degradation seems to be the modification of the phenolic hydroxyl at the 4 position rather than the conditions imposed. δ-Methyldihydrothebaïne methyl ether, unlike the unmethylated base, gives largely the "normal" product when degraded by Hofmann's method. This is not the first example of degradation being influenced by the 4-hydroxyl group. Whereas dihydro-des-*N*-methyltetrahydrodesoxycodeïne methohydroxide splits off trimethylamine and water in the expected way on boiling with alkali, the corresponding 4-methyl ether merely loses methanol to give the starting material [CAHN, *J. Chem. Soc.*, **1926**, 2562)]. These reactions have recently been verified in this laboratory.

takes up one mole of hydrogen by the catalytic method. It is especially significant that the dihydro-α-methyldihydrothebaïneisomethine so obtained is recovered unchanged, without loss of its phenolic character, after boiling with concentrated hydrochloric acid.

α-Methyldihydrothebaïneisomethine methiodide undergoes alkaline degradation with some difficulty, giving a phenolic nitrogen-free end-product in which the vinyl group arising from the rupture of the ethanamine chain is still present, as is the methyl group that was introduced by the Grignard reaction. The nucleus of the nitrogen-free product is not completely aromatic, but is that of a dihydrogenated phenanthrene derivative. The compound is optically inactive in consequence of racemization, and will be called racemic vinyldihydro-x-methylthebaöl (VI).§ Racemic vinyldihydro-x-methylthebaöl contains two vulnerable unsaturated centers



VI. Vinyldihydro-x-methylthebaöl



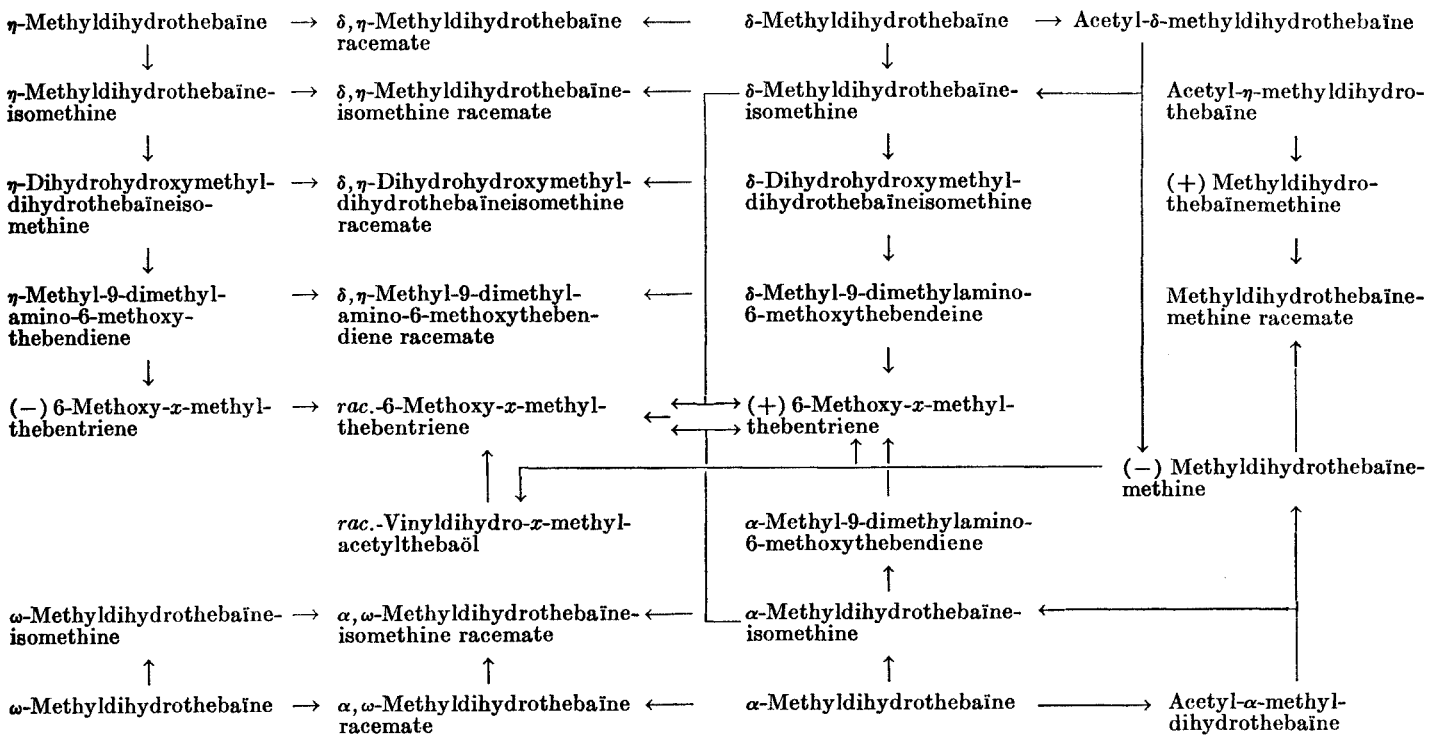
VII. 6-Methoxy-x-methylthebentriene

(the vinyl group and the 9,10-double linkage generated in the final stage of degradation) and absorbs two moles of hydrogen in the presence of catalysts. The two unsaturated linkages believed to be present in ring III resist hydrogenation here, as in the compound before degradation.

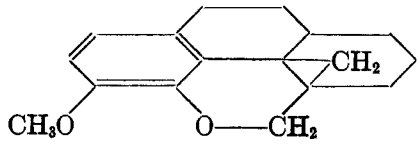
If α-methyldihydrothebaïneisomethine is treated for one minute with hot concentrated hydrochloric acid before degradation, the reaction takes a different course. Two nitrogen-free, non-phenolic products of formula $C_{19}H_{20}O_3$ result, (*i.e.*, isomeric with the above-mentioned *rac.*-vinyldihydro-x-methylthebaöl). These we name tentatively racemic and (+) 6-methoxy-x-methylthebentriene respectively (VII). Although we are by no means certain that the vinyl group is still attached to carbon atom

§ The parent substance thebaöl, from the acetic anhydride or Hofmann degradation of thebaïne, is 3,6-dimethoxy-4-hydroxyphenanthrene.

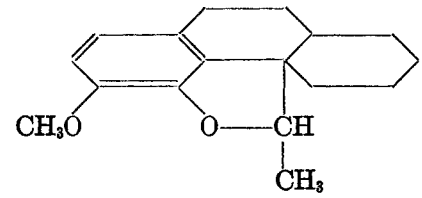
FIG. II


η-Methyldihydrothebaïne
δ,η-Methyldihydrothebaïne racemate
δ-Methyldihydrothebaïne
Acetyl-δ-methyldihydrothebaïne
η-Methyldihydrothebaïne-isomethine
δ,η-Methyldihydrothebaïne-isomethine racemate
δ-Methyldihydrothebaïne-isomethine
Acetyl-η-methyldihydrothebaïne
η-Dihydrohydroxymethyldihydrothebaïneisomethine
δ,η-Dihydrohydroxymethyldihydrothebaïneisomethine racemate
δ-Dihydrohydroxymethyldihydrothebaïneisomethine
(+) Methyldihydrothebaïnemethine
η-Methyl-9-dimethylamino-6-methoxythebendiene
δ,η-Methyl-9-dimethylamino-6-methoxythebendiene racemate
δ-Methyl-9-dimethylamino-6-methoxythebendeine
Methyldihydrothebaïnemethine racemate
(−) 6-Methoxy-x-methylthebentriene
rac.-6-Methoxy-x-methylthebentriene
(+) 6-Methoxy-x-methylthebentriene
(−) Methyldihydrothebaïnemethine
rac.-Vinyldihydro-x-methylacetylthebaöl
α-Methyl-9-dimethylamino-6-methoxythebendiene
ω-Methyldihydrothebaïne-isomethine
α,ω-Methyldihydrothebaïne-isomethine racemate
α-Methyldihydrothebaïne-isomethine
ω-Methyldihydrothebaïne
α,ω-Methyldihydrothebaïne racemate
α-Methyldihydrothebaïne
Acetyl-α-methyldihydrothebaïne

thirteen, there is little doubt that cyclization with the 4-hydroxyl group has taken place, and the nomenclature introduced by Wieland for these cyclic ethers (thebenone) and recently used by Goto[10] for the compound of formula VIII, thebenane, is convenient for description.



VIII. Thebenane



IX. Thebenane, alternative formula

It can be shown that the formation of the cyclic ether system precedes the degradation. Namely, when the degradation of α-methyldihydrothebaïneisomethine is preceded by short treatment with acetyl chloride containing hydrochloric acid, a non-phenolic methine base, which is isomeric with the starting material, is obtained.* This base, α-methyl-9-dimethylamino-6-methoxythebendiene (XII), is unaffected by catalytic hydrogenation, hence the lone reducible unsaturated center (the vinyl group) of α-methyldihydrothebaïneisomethine (X) must be involved in the change. These facts and the parallel observations in the δ and η series are important points of evidence in favor of our hypothesis concerning the "abnormal" scission of the nitrogen-containing ring in the first step of the Hofmann degradation.

Further degradation of α-methyl-9-dimethylamino-6-methoxythebendiene results exclusively in (+) 6-methoxy-*x*-methylthebentriene, indicating that the closure of the thebenane ring blocks the racemization noted above in the transformation of α-methyldihydrothebaïneisomethine (levorotatory) to racemic vinyldihydro-*x*-methylthebaöl. (+) 6-Methoxy-*x*-methylthebentriene contains a new double linkage, generated in the loss

[10] GOTO AND SHISHIDO, *Bull. Chem. Soc. Japan*, **10**, 252 (1935). The alternative formula IX for thebenane, with a ring closed to carbon atom 15, as first proposed by GULLAND AND VIRDEN (*J. Chem. Soc.*, **1928**, 921) for the analogous thebenol types seems more probable to us. This is supported by the isolation from the cyclization reaction in the δ- and η-isomethine series of an intermediate that would be expected to have formula XI if addition of water to the vinyl group follows Markownikoff's rule.

* The mechanism of this change involves addition of a molecule of water or its equivalent at the vinyl group, followed by cyclodehydration, as is demonstrated by the isolation of the intermediate in the δ and η series. We shall, for simplicity, refer to the cyclization between the 4-hydroxyl and the vinyl group as "thebenane ring closure," leaving undecided for the present the nuclear position of the vinyl group.

of the nitrogen atom, and absorbs one mole of hydrogen to give (+) 6-methoxy-*x*-methylthebendiene. The involution of an unsaturated linkage in the thebenane ring formation is demonstrated convincingly in the conversion of *rac.*-vinyldihydro-*x*-methylthebaöl (VI, phenolic, two reducible centers) with concentrated hydrochloric acid to *rac.*-6-methoxy-*x*-methylthebentriene (VII, non-phenolic, one reducible center); and furthermore, by the fact that when the vinyl group is saturated, as in the dihydro-α-methyldihydrothebaïneisomethine mentioned above, thebenane ring closure cannot be accomplished.

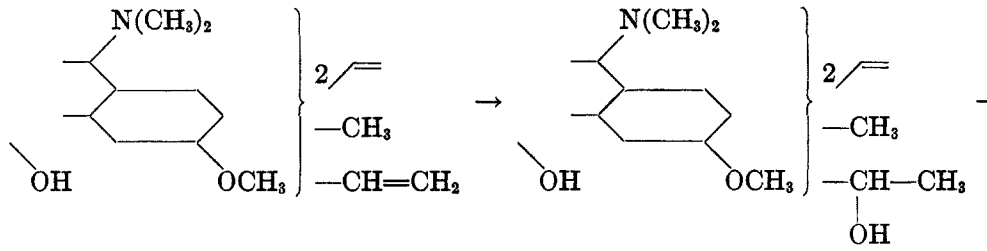
The degradation of acetyl-α-methyldihydrothebaïne through heating the methohydroxide takes two courses. A portion of the material breaks down as in the alkaline degradation, giving α-methyldihydrothebaïneisomethine ("abnormal" degradation). The remainder decomposes to give an isomer, (−) methyldihydrothebaïnemethine, which is phenolic and contains one reducible double bond, but is indifferent toward boiling concentrated hydrochloric acid. The same methine base is also obtained in the parallel degradation of acetyl-δ-methyldihydrothebaïne methohydroxide, *whence it follows that the isomerism of α- and δ-methyldihydrothebaïnes is due only to that asymmetric center which is destroyed in the formation of this methine base.* This conclusion, and our hypothesis concerning the course of the "abnormal" degradation, is supported further by the fact that the first stage of the Hofmann degradation of α- and δ-methyldihydrothebaïnes (opening the nitrogen-containing ring at the N—C-16 bond) results in isomeric α- and δ-methyldihydrothebaïneisomethines, but in the second stage, elimination of the nitrogen atom and consequent destruction of the asymmetric center at C-9, (+) 6-methoxy-*x*-methylthebentriene is obtained from both isomethines. Further degradation of (−) methyldihydrothebaïnemethine leads to a mixture of sodium salts of (+) and racemic vinyldihydro-*x*-methylthebaöls, which can be converted by treatment with hot hydrochloric acid, or with acetic anhydride into (+) 6-methoxy-*x*-methylthebentriene and *rac.*-acetylvinyldihydro-*x*-methylthebaöl respectively.

The evidence adduced above indicates that α- and δ-methyldihydrothebaïnes are diastereoisomers, differing in the configuration at C-9. If this is true, *η-methyldihydrothebaïne, the optical opposite of the δ isomer, must have a configuration opposite to that of the α isomer at the asymmetric center other than C-9.* This conclusion is confirmed by experiment, for degradation of acetyl-η-methyldihydrothebaïne methohydroxide yields (+) methyldihydrothebaïnemethine, which forms a racemate with the corresponding levorotatory compound derived from the α and δ series.

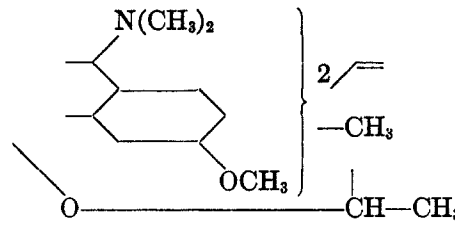
The other degradations of the δ and η isomers proceed parallel, and may be conveniently considered together. Treatment of δ- and η-methyldi-

hydrothebaïne methiodides with hot alkali results in the corresponding δ- and η-methyldihydrothebaïneisomethines (isolated as salicylates), which are isomeric and have the same melting point and solubility, but equal and opposite rotatory power. Crystallization of a mixture of the two isomethine salts gives a racemate that differs from the components in physical properties, and is optically inactive.

When δ- and η-methyldihydrothebaïneisomethines are treated with partially hydrolyzed acetyl chloride, they add a molecule of water, presumably at the vinyl group, giving respectively δ- and η-dihydrohydroxymethyldihydrothebaïneisomethines (XI), which are optical opposites and form a racemate. The dihydrohydroxy compounds are intermediates in the formation of the dimethylaminothebendiene types (XII), which appear simultaneously to some extent in the above transformation. The reaction may be provisionally formulated as follows, and, with the exception of the intermediate XI, applies also to the α series:



X. XI.



XII.

More vigorous treatment of the dihydrohydroxy intermediates with essentially the same reagent results in cyclodehydration and yields the non-phenolic δ- and η-methyl-9-dimethylamino-6-methoxythebendienes (XII), optical opposites that combine to form a racemate.

In the last step of the degradation, conversion of these two dimethylaminothebendienes to the nitrogen-free products, the isomerism still persists. The η series gives (−) 6-methoxy-x-methylthebentriene, the δ series gives the dextrorotatory form; mixture of the (+) and (−) isomers yields the racemic 6-methoxy-x-methylthebentriene, which may also be

obtained as mentioned above, from degradation of α-methyldihydrothebaïneisomethine or thebenane cyclization of racemic vinyldihydro-*x*-methylthebaöl.

The degradation of ω-methyldihydrothebaïne has been carried only to ω-methyldihydrothebaïneisomethine, which, as expected, is the optical antipode of α-methyldihydrothebaïneisomethine. When mixed, the two isomethines form a racemate, which results also from degradation of α,ω-methyldihydrothebaïne racemate methiodide. The conclusion reached for the α and δ series must likewise apply to the optical opposites; ω- and η-methyldihydrothebaïnes must be alike at the asymmetric center which is left undisturbed during the rupture of the nitrogen-to-nucleus linkage. If, for discussion, we assume this asymmetric center (*y*) to be the point of attachment of the vinyl group or of the methyl group, and assign to it the sign of the rotation that it causes in the nitrogen-free derivatives, we arrive at the following arrangements as the only possible configurations for the four isomers:

	C-9	*y*		C-9	*y*
Alpha-	+	+		−	+
Delta-	−	+		+	+
Eta-	+	−	or	−	−
Omega-	−	−		+	−

SPECULATIVE CONSIDERATIONS

With the experimental evidence at hand it is not possible to make a choice between these alternative combinations of the asymmetric centers, nor can we tell which group corresponds to the symbol "*y*." The only evidence that has developed in this connection is the suggestive fact that the vinyl compound, α-methyldihydrothebaïneisomethine, yields *racemic* vinyldihydro-*x*-methylthebaöl on degradation, whereas the corresponding derivative in which the vinyl group has been restricted by cyclization, α-methyl-9-dimethylamino-6-methoxythebendiene, gives entirely an optically active degradation product. In the conversion of the α to the δ isomer, or of the η into the ω isomer, the asymmetric center at C-9 is racemized, and the products, as diastereoisomers, are easily separable. Similarly, when α-methyldihydrothebaïne is transformed into the α,η molecular compound, the asymmetric center "*y*" is racemized, resulting in η-methyldihydrothebaïne, which is a diastereoisomer of the α compound, but is likewise the optical opposite of the δ isomer. This is the only one of the racemizations that has been carried out in the reverse way, *i.e.*, the η-methyldihydrothebaïne prepared by racemization of asymmetric center "*y*" in the α isomer was caused to undergo racemization again at the same center to the α isomer (in the form of the α,η molecular compound). The

α,ω-methyldihydrothebaïne racemate that appears in small amount during the α-to-η racemization may result either from a simultaneous racemization of both asymmetric centers in the α base, or from a racemization of the C-9 center in the primarily-formed η isomer. This change seems to be markedly influenced by temperature, and in epimerization carried out at 160° the α,ω racemate constituted 40 per cent. of the product.

The simultaneous appearance of the α and δ isomers in the Grignard reaction might be explained as a directed addition of the methyl group to generate a new asymmetric carbon atom exclusively in one configuration, with a shift of the ethanamine chain to a new position in two steric arrangements. This hypothesis has the disadvantage of postulating the existence of three asymmetric centers in the methyldihydrothebaïnes, whereas we have evidence of only two, unless the assumption is made that two centers always racemize together. Attempts to determine the nuclear position of the introduced methyl group have been unsuccessful. From zinc-dust distillation of α-methyldihydrothebaïne, a small amount of phenanthrene was isolated. This fact points to a location of the methyl group such that the process of aromatization under these drastic conditions inevitably results in expulsion of the group, *i.e.*, at C-13 or at C-14. As was mentioned in the discussion of phenyldihydrothebaïne, placing the new group at C-14 also offers an explanation of the unexpected retention of the vinyl group in degradations that almost invariably result in loss of carbon atoms 15 and 16 from tetrahydrophenanthrene types in the morphine series. The argument seems reasonable, that the tendency toward aromatization, which according to the Gulland and Robinson theory furnishes the driving force for the extrusion of the ethanamine chain in the normal morphine series, is not strong enough to displace both the vinyl group and a methyl or phenyl group from the compounds under discussion. However attractive the 14 position is from this standpoint, we cannot devise any acceptable mechanism by which the addition of Grignard's reagent to thebaïne can result in such a compound;* moreover, the postulated structure is incapable of explaining the other extraordinary features of the series. The appearance of phenanthrene in the zinc-dust distillation might also indicate the 5 position for the methyl group, as it is known that groups at the phenanthrene 4 (or 5) position are lost with

* Even under favorable conditions, Grignard's reagent does not add in the 1,6-manner to conjugated double bonds terminating with oxygen. See Gilman's "Organic Chemistry," p. 605 (Wiley, New York, 1938), where one exception is cited. As has been shown in previous communications from this and other laboratories, the cyclic-linked oxygen and 6,7 double bond often behave in a way comparable to a conjugated carbonyl group and double bond.

exceptional ease, especially when the ortho (3 or 6) carbon atom carries a methoxyl group. For example, 3,4,5-trimethoxyphenanthrene with hydriodic acid yields 3,5-dihydroxyphenanthrene; 3-methoxyphenanthrene-4-aldehyde is converted to 3-methoxyphenanthrene on distillation; 3-hydroxyphenanthrene-4-carboxylic acid loses carbon dioxide in hot water, and Pschorr[11] comments upon the extraordinary ease with which 3,4,8-trimethoxyphenanthrene-5-carboxylic acid undergoes decarboxylation. In this connection may also be cited the observation of Haworth, that a selenium dehydrogenation that should have yielded 4-methylphenanthrene resulted partially in 1-methylphenanthrene.

The possibility of a shift of the ethanamine chain from its generally accepted position at C-13 during the Grignard reaction deserves some consideration. The relative mobility of this chain in thebaïne is well known, and is exemplified in the transformations that result in morphothebaïne, thebenine, and metathebaïnone. All of these products are formed, however, by comparatively vigorous treatment of thebaïne with acid. Thebaïne is amazingly stable under neutral or alkaline conditions, and a shift of the ethanamine chain under the influence of Grignard's reagent at the temperature of boiling ether would be most unexpected.

If a migration of the C-15 end of the chain be nevertheless assumed, carbon atoms 5 and 8 are most reasonable as possible points of reattachment (the Hofmann degradation shows nitrogen to be still in a ring). While either of these positions may explain retention of the vinyl group, since its expulsion is not necessary to aromatization, they are both open to objection on the score that aromatization unquestionably does not take place as would be expected under these circumstances (excluding the improbable blocking of the process through location of the methyl group at C-13 or C-14). Were the chain attached at C-5, α-methyldihydrothebaïneisomethine and vinyldihydro-x-methylthebaöl should undergo spontaneous ether ring closure with a facility comparable to that observed for thebenine and ethebenol.[12] Location of the ethanamine chain at its supposed original position (C-13) is open to the same objection, for it has been shown by several examples that a vinyl group at C-13 cyclizes with

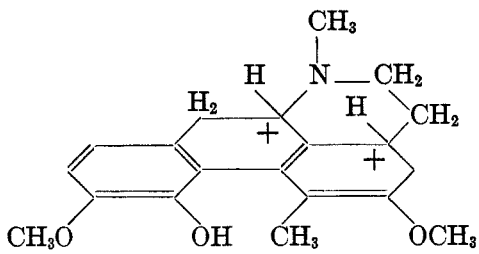
[11] PSCHORR, *Ann.*, **373**, 58 (1910).

[12] FREUND, *Ber.*, **32**, 168 (1899); PSCHORR, *Ann.*, **373**, 51 (1910); PSCHORR AND ZEIDLER, *ibid.*, **373**, 75 (1910). It should be recalled that 3,4,8-trimethoxy-5-vinylphenanthrene displays a tedency for ring closure between the vinyl group and the oxygen at position 4 so strong as to result in splitting the methoxyl group. A similar reaction takes place in the degradation of dihydrothebenine dimethyl ether. [PSCHORR AND MASSACUI, *Ber.*, **37**, 2780 (1904); PSCHORR, *Ann.*, **373**, 59 (1910); SPEYER AND ROSENFELD, *Ber.*, **58**, 1120 (1925)].

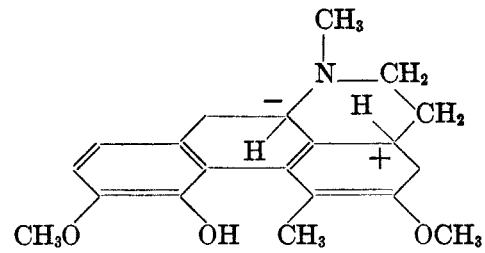
the 4-hydroxyl with extreme ease.† These facts do not by any means exclude C-5 or C-13, for the difference in cyclization is only one of degree, and ring closure does take place under sufficiently strenuous conditions. It may be noted that Freund[6a] observed spontaneous ether-ring closure in the degradation of phenyldihydrothebaïne and dichlorophenyldihydrothebaïne, but was able to show convincingly that the ring closure extended to the oxygen on C-6 with scission of the methoxyl group at this point. Namely, when phenyldihydrothebaïne-4-ethyl ether was degraded, the resulting end-product was found still to contain the ethyl group, and had lost a methyl group (from the methoxyl at C-6) in cyclization. The analyses of our nitrogen-free products, (+), (−), and *rac.*-6-methoxy-*x*-methylthebentriene, exclude this possibility in the methyldihydrothebaïne series.

A shift of the ethanamine chain to C-8, in analogy with the transformation of thebaïne to morphothebaïne, or of morphine to apomorphine, seems least probable. Nevertheless, we wish to point out that the only known case of "abnormal" degradation in a substance derived from the morphine group was observed with a compound of this type. Gadamer[13] obtained from the Hofmann degradation of apomorphine dimethyl ether an optically active methine base, in which the only asymmetric center (C-9) present in apomorphine was still intact.

If the existence of a *trans*-ring is postulated, such an aporphine-like structure might also permit of explaining the appearance of the α and δ isomers in the Grignard reaction, as well as the failure of the isomers to undergo hydrogenation.



XIII. Hypothetical
α-methyldihydrothebaïne



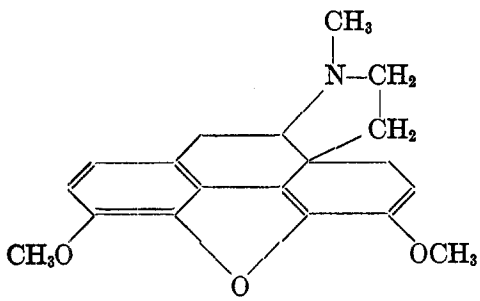
XIV. Hypothetical
δ-methyldihydrothebaïne

† The degradation of dihydro-des-*N*-methyldihydrothebaïnone always yields the cyclic ether, thebenone [WIELAND AND KOTAKE, *Ann.*, **444**, 69 (1925)]; degradation of dihydr-odes-*N*-methyltetrahydrodesoxycodeïne gives the cyclic ether (+) thebenane,[10], [SMALL AND BRALLEY, unpublished results]; the analogous derivative in the sinomenine series behaves in a like manner.

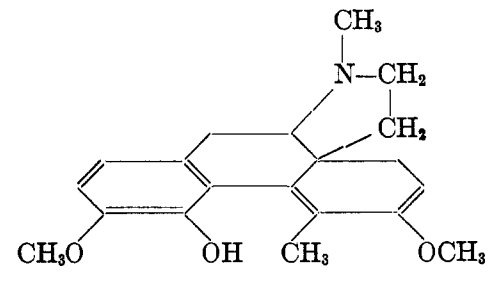
[13] GADAMER, *Arch. Pharm.*, **253**, 266 (1915).

By the further assumption of a most improbable series of shifts of the double bonds in ring III, whereby epimerization at C-8 or C-9 could take place, the interconversion of the isomers might be explained. There is, however, no reason to expect such a superficially simple reaction as that of methylmagnesium iodide with thebaïne to result in such deep-seated changes, and these formulas do not account for the anomalous enol ether group. In particular, closure of the thebenane ring by such a structure would be difficult to explain, and (−) methyldihydrothebaïnemethine would contain a naphthalene nucleus and should not undergo hydrogenation (one mole) with the ease observed. The above formulas, therefore, seem excluded, even as suggestions that might account for a part of the observed phenomena.

Finally, the possibility may be mentioned that the Grignard reagent causes a rearrangement of thebaïne to an intermediate (XV) containing a ring structure of the metathebaïnone type, which then reacts in the 1,2 manner to give a compound as illustrated in formula XVI:



XV. Hypothetical intermediate



XVI. Metathebaïnone-type formula

This formula would explain adequately the difficulty of hydrogenation, the optical activity of phenyltetrahydrothebaïmine and our nitrogen-free products, and might permit an equally facile closure of a 6-membered ether ring to the 4 position (methyldihydrothebaïne series) or to the 6 position (phenyldihydrothebaïne), but fails to account for the indifference of the enol ether group to hydrolysis, or for the retention of the vinyl group in degradation (metathebaïnonemethine methyl ether breaks down readily to dimethylmorphol[14]).

We have at present no formula to offer that will explain satisfactorily all of the observations in the phenyldihydrothebaïne and methyldihydrothebaïne series. It is our intention to re-open the phenyldihydrothebaïne

[14] KNORR AND PSCHORR, *Ber.*, **38**, 3172 (1905).

problem, and to extend the present studies, with the object of locating the points of attachment of the methyl group and of the ethanamine chain.

We are indebted to Merck and Company, Inc., Rahway, N. J., for the gift of the thebaïne used in this work, and to Mallinckrodt Chemical Works, St. Louis, Mo., and E. R. Squibb and Sons, Brooklyn, N. Y., for the fellowships under which the investigation was carried out.

EXPERIMENTAL

The Grignard reaction.—Fifty grams of thebaïne was extracted from a Soxhlet apparatus into twice the equivalent amount of boiling molar ethereal methylmagnesium iodide (325 cc.). About 8 hours was required for the extraction, and the product was subsequently boiled for 5 hours under reflux. At the end of this time, the light-green reaction mixture consisted of an ether layer and a heavy oily layer of the magnesium complex. The complex was decomposed with water and sufficient concentrated ammonium chloride solution to dissolve the magnesium-containing precipitate, and the mixture was extracted several times with ether. The aqueous portion darkened in color rapidly, and tended to emulsify if too much water was used in the decomposition reaction. From the ether was obtained a light-orange oily base, which was rather sensitive, and became darker in color on standing. The oily base was treated with 20% perchloric acid solution (prepared by diluting 60% aqueous perchloric acid with 2 parts of alcohol) to litmus acidity. The crystalline product, consisting principally of α-methyldihydrothebaïne perchlorate, was washed with alcohol until white.

On concentration of the red mother liquor in a vacuum desiccator, crystals consisting principally of δ-methyldihydrothebaïne perchlorate separated from the red oil. These crystals were washed with a small amount of cold alcohol. In four runs the yields of crude α-methyldihydrothebaïne perchlorate varied between 41% and 49% of the calculated amount, crude δ-methyldihydrothebaïne perchlorate between 20% and 26%.

The crude perchlorates were converted separately to the bases, and the bases were treated with 6*N* hydrochloric acid, whereupon the sparingly soluble hydrochloride of the α isomer separated. Its solubility was further reduced by the addition of saturated ammonium chloride solution. The mother liquors from the separation of the α-isomer hydrochloride contained practically all of the δ isomer, which does not form a crystalline hydrochloride.

α-Methyldihydrothebaïne crystallizes best from a mixture of two parts of alcohol with one part of water. It has the melting point 87.5–89.5°, and shows in alcohol $[\alpha]_D^{25}$ +140° (c = 1.0).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70; $(OCH_3)_2$, 18.9.
Found: C, 73.17; H, 7.79; OCH_3, 18.3.

Its perchlorate, crystallized from alcohol, shows $[\alpha]_D^{25}$ +84° (alcohol, c = 0.5).

Anal. Calc'd for $C_{20}H_{26}ClNO_7$: C, 56.12; H, 6.13.
Found: C, 56.15; H, 6.22.

The methiodide crystallizes well from ethanol; m. p. 219–221°, $[\alpha]_D^{20}$ +76° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{28}INO_3$: C, 53.71; H, 6.01.
Found: C, 53.98; H, 6.46.

α-Methyldihydrothebaïne could not be hydrogenated as base or as hydrochloride in alcohol with Adams' catalyst. It was likewise indifferent in the presence of a very active 95% PtO_2-5% PdO_2 catalyst. The α base was recovered unchanged after being boiled for 3 minutes in concentrated hydrochloric acid.

α-Methyldihydrothebaïne dissolves readily in dilute alkali, and is precipitated from the alkaline solution by ammonium chloride or carbon dioxide. The action of acetyl chloride on the perchlorate yielded an alkali-insoluble acetyl derivative [perchlorate, crystals from alcohol, $[\alpha]_D^{25}$ +78° (alcohol, c = 0.6)] whose methiodide hemihydrate, crystallized from ethanol, had the melting point 193–195° and $[\alpha]_D^{28}$ +55° (alcohol, c = 0.4). The hydrate water could not be determined because of a slight tendency of the substance to sublime.

Anal. Calc'd for $C_{23}H_{30}INO_4 + 0.5\ H_2O$: C, 53.06; H, 6.00.
Found: C, 52.93; H, 5.96.

α-Methyldihydrothebaïne methyl ether methiodide was formed in 95% yield when α-methyldihydrothebaïne in methanol with excess of methyl iodide and a little strong sodium hydroxide was warmed gently. The methiodide was recrystallized from a mixture of ethanol and ethyl acetate. A small amount of unidentified, sparingly soluble by-product was separated at this point; m. p. about 60°, resolidifying at about 100°, unmelted then at 230°, optically inactive. The main product, the methyl ether methiodide, was water-soluble, m. p. 177–178°, $[\alpha]_D^{21}$ +43.3° (alcohol, c = 0.5).

Anal. Calc'd for $C_{22}H_{30}INO_3$: 3(OCH_3), 19.2. Found: OCH_3, 18.7.

Degradation of α-methyldihydrothebaïne.—A solution of α-methyldihydrothebaïne methiodide in 40% aqueous sodium hydroxide solution was boiled vigorously for 15 minutes. The degradation product was the water-soluble sodium salt of the isomethine base. The isomethine sodium salt was suspended in ammonium chloride solution and extracted with ether, from which the isomethine base was obtained as a yellow oil. This was converted to the salicylate with alcoholic salicylic acid, and the salt was purified from alcohol, yield, 87%. α-Methyldihydrothebaïneisomethine salicylate melts at 163–164.5°, $[\alpha]_D^{20}$ −90° (alcohol, c = 0.8).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11; H, 6.94.
Found: C, 70.00; H, 7.14.

Its methiodide was prepared in methanol, and was purified by addition of ethanol to a suspension in hot ethyl acetate until solution was complete. It has the melting point 227–230° and $[\alpha]_D^{25}$ −80° (alcohol, c = 0.7).

Anal. Calc'd for $C_{22}H_{30}INO_3$: C, 54.64; H, 6.26.
Found: C, 54.63; H, 6.35.

Dihydro-α-methyldihydrothebaïneisomethine is formed when α-methyldihydrothebaïneisomethine is hydrogenated in alcohol solution with Adams' catalyst (absorption, 1 mole). The hydrogenated base is an oil but forms a crystalline salicylate, purified from ethanol. The base is soluble in sodium hydroxide, and, in contrast to the unhydrogenated isomethine, is unaffected by boiling for 2 minutes in concentrated hydrochloric acid. The salicylate has the melting point 165–167°, and $[\alpha]_D^{25}$ −47.7° (alcohol, c = 0.7).

Anal. Calc'd for $C_{28}H_{34}NO_6$: C, 69.81; H, 7.33.
Found: C, 69.71; H, 7.30.

rac.-*Vinyldihydro*-x-*methylthebaöl.*—α-Methyldihydrothebaïneisomethine methiodide proved to be extremely resistant to the ordinary Hofmann degradation, being practically unaffected by heating under reflux for 2 hours with 40% sodium hydroxide solution. The methiodide was dissolved in hot water and treated with the equivalent amount of 0.15*N* thallous hydroxide. After removal of thallous iodide, sufficient solid sodium hydroxide was added to make a 50% solution (the quaternary base separated as an oil), which was boiled under reflux for 30 minutes. The separated resinous material was extracted with ether in the presence of concentrated ammonium chloride solution. The ammonium chloride solution still contained about half the material in undegraded form, dissolved as the quaternary hydroxide. This solution was returned to the sodium hydroxide solution, whereupon the oily quaternary hydroxide was salted out, and was subjected to degradation with fresh 50% sodium hydroxide. Three such partial degradations resulted in practically complete conversion to the nitrogen-free product.

The thebaöl derivative obtained from ether was not crystalline. When rubbed with 3*N* sodium hydroxide it yielded a crystalline sodium salt, which, in the dry state, was triturated with a little absolute ether to remove colored resins. The sodium salt was suspended in water, whereby it was largely hydrolyzed, and extracted again with ether. From the ether, the thebaöl was again isolated and converted to the sodium salt, which was recrystallized from a solution of 2 parts of 3*N* sodium hydroxide with 1 part of ethanol. The yield of sodium salt was 50–60% of the calculated amount. The purified vinyldihydro-*x*-methylthebaöl obtained from this salt was optically inactive. A solution of 0.5 g. of the sodium salt in 10 cc. of pyridine containing 3 cc. of acetic anhydride was allowed to stand for 42 hours. The pyridine and acetic anhydride were removed under diminished pressure at 40°, water was added, and the acetyl derivative was extracted into ether. The product was recrystallized from ethanol; yield 71% of the calculated amount. *rac.*-Vinyldihydro-*x*-methylacetylthebaöl melts at 103–105.5°, $[\alpha]_D^{25}$ 0° (alcohol, $c = 0.6$).

Anal. Calc'd for $C_{21}H_{22}O_4$: C, 74.51; H, 6.55.
Found: C, 74.38; H, 6.60.

The acetyl derivative, in ethanol with platinum oxide, absorbed 2 moles of hydrogen. The product was not crystalline, nor did it yield a crystalline hydrolysis product.

(+) *and* rac.-6-*Methoxy*-x-*methylthebentriene.*—A solution of α-methyldihydrothebaïneisomethine in concentrated hydrochloric acid was boiled for one minute. The product was precipitated with ammonia (it is now alkali-insoluble), and converted to the methiodide, which was boiled with 40% sodium hydroxide. The degradation was not complete. The nitrogen-free portion was extracted into ether, from which it crystallized on concentration; over-all yield, 44% of the calculated amount. The product was separated by fractional crystallization from ethanol into two components, (+) 6-methoxy-*x*-methylthebentriene, and the corresponding racemic compound, in practically equal amounts. The purified products crystallized best from ethanol containing a little water; both are insoluble in alkali. The mixture of (+) and racemic 6-methoxy-*x*-methylthebentriene was also obtained in 20% yield when δ-methyldihydrothebaïneisomethine was degraded by the above-described procedure.

(+) 6-Methoxy-*x*-methylthebentriene has the melting point 99–101°, $[\alpha]_D^{22}$ +9° (alcohol, $c = 0.6$).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.82.
Found: C, 76.81; H, 6.79.

rac.-6-Methoxy-*x*-methylthebentriene has the melting point 91.5–93.5°, and is optically inactive. It was obtained not only as described above, but by mixing equivalent amounts of the (+) form and the (−) form, which was obtained from degradation of *η*-methyldihydrothebaïne. It likewise resulted from boiling the sodium salt of *rac.*-vinyldihydro-*x*-methylthebaöl with concentrated hydrochloric acid for 2 minutes.

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.82.
Found: C, 77.06; H, 6.97.

(+) 6-*Methoxy*-x-*methylthebendiene.*—(+)6-Methoxy-*x*-methylthebentriene is not racemized or hydrolyzed by concentrated hydrochloric acid; a sample which was boiled for 4 minutes with concentrated hydrochloric acid was recovered unchanged in 80% yield. The compound contains only one reducible double linkage. A solution of (+) 6-methoxy-*x*-methylthebentriene in ethanol with Adams' catalyst absorbed one mole of hydrogen. The product was purified from alcohol, m.p. 56–59.5°, $[\alpha]_D^{29}$ −5° (alcohol, $c = 0.7$).

Anal. Calc'd for $C_{19}H_{22}O_3$: C, 76.47; H, 7.44.
Found: C, 76.74; H, 7.31.

α-Methyl-9-dimethylamino-6-methoxythebendiene.—The salicylate of *α*-methyldihydrothebaïneisomethine (4 g.) in 5 cc. of acetyl chloride was boiled for 4 minutes. The reaction mixture was treated with water, made ammoniacal, and extracted with ether. The oily base from ether was extracted several times with alkali, being largely soluble. From the alkaline solution an oily base was obtained, which formed crystalline salts (salicylate, benzoate, phthalate [m. p. 150–160°], fumarate, and picrate [m. p. 172–180°]). The salts were so difficult to purify that this base remains unidentified. The alkali-insoluble portion could be crystallized from dilute alcohol, yield 11% of the starting material; the alcohol mother liquor gave an additional 20% in the form of methiodide. *α*-Methyl-9-dimethylamino-6-methoxythebendiene melts at 76.5–78° and has $[\alpha]_D^{22}$ −82° (alcohol, $c = 0.5$); it is indifferent toward catalytic hydrogenation.

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 73.96; H, 8.14.

The methiodide crystallizes solvated from ethanol, m. p. 115–117°, $[\alpha]_D^{25}$ −51° (alcohol, $c = 0.6$). From ethanol by addition of ethyl acetate it separates in crystals of m. p. 207°. On degradation with boiling 40% sodium hydroxide the methiodide was transformed in 71% yield to (+) 6-methoxy-*x*-methylthebentriene. None of the racemic form could be isolated from the degradation.

Zinc-dust degradation of α-methyldihydrothebaïne.—Distillation of 25 g. of *α*-methyldihydrothebaïne from 200 g. of zinc dust over zinc dust on pumice at dull red heat, in a hydrogen stream, resulted in a deep brown oil. This was dissolved in ether and extracted with acid and alkali to remove incompletely degraded material. The liquid product was distilled at 17 mm. and 110°, giving oily crystals. These were purified three times from methanol, yielding a small amount of phenanthrene, m. p. 96–97°, no depression in mixture melting point with phenanthrene; the picrate was also identical with phenanthrene picrate. A second degradation carried out at a lower temperature likewise gave some phenanthrene, together with an unidentified compound of m. p. 116–120°, picrate, m. p. 133–134°.

δ-Methyldihydrothebaïne.—This base, as mentioned above, is formed in about 20–26% of the calculated amount in the reaction of thebaïne with methylmagnesium iodide. It may also be prepared from the *α*-isomer. Pure *α*-methyldihydrothebaïne

was converted to the perchlorate, which was washed thoroughly with alcohol and with water, and the damp salt (faintly acid litmus reaction) was dissolved in boiling 95% alcohol. The alcoholic solution was evaporated slowly on the water bath, alcohol added if crystallization took place, and again evaporated. After several repetitions of this treatment the concentrated alcoholic solution was heated in boiling water under reflux for 24 hours. The base was isolated (oily) with ammonia and ether, and was converted to the hydrochloride by addition of 6*N* hydrochloric acid to a suspension of the base in concentrated ammonium chloride solution. The hydrochloride of the unchanged α isomer precipitated crystalline. From the mother liquor the oily δ-methyldihydrothebaïne was isolated, and purified as the perchlorate. The conversion amounted to about 10% of the starting material (average of experiments).

δ-Methyldihydrothebaïne is not crystalline. It cannot be purified by high-vacuum distillation because of partial conversion to the ω isomer under these conditions. It is readily soluble in dilute alkali, from which it is precipitated by ammonium chloride. It is recovered unchanged after being boiled for 2 minutes in concentrated hydrochloric acid. As base or as hydrochloride in alcoholic solution it absorbed no hydrogen with Adams' catalyst. The perchlorate crystallized well from ethanol, and showed in alcohol the specific rotation $[\alpha]_D^{25}$ +50° (c = 0.7).

Anal. Calc'd for $C_{20}H_{26}ClNO_7$: C, 56.12; H, 6.13.
Found: C, 55.92; H, 6.25.

Acetyl-δ-methyldihydrothebaïne was formed when δ-methyldihydrothebaïne perchlorate was dissolved in acetyl chloride and allowed to stand for a short time. The acetyl derivative precipitated from the solution as the crystalline perchlorate, which could be purified from ethanol; $[\alpha]_D^{25}$ +67.5° (alcohol, c = 0.5), yield, 87%. The oily base regained from the salt was insoluble in alkali. It reacted with methyl iodide in methanol to give the methiodide, which was purified by addition of ethyl acetate to a solution in hot ethanol. Acetyl-δ-methyldihydrothebaïne methiodide hydrate sinters at 109°, loses its hydrate water, solidifies, and melts at 198°. In alcohol it has $[\alpha]_D^{25}$ +56° (c = 0.5).

Anal. Calc'd for $C_{23}H_{30}INO_4 + H_2O$: C, 52.16; H, 6.09; H_2O, 3.4.
Found: C, 52.17; H, 6.27; H_2O, 4.2.

The degradation of δ-methyldihydrothebaïne.—δ-Methyldihydrothebaïne in methanol with methyl iodide was converted to the amorphous methiodide, and excess methyl iodide was removed by repeated addition and evaporation of methanol. The methiodide was degraded by boiling with 40% sodium hydroxide and the product isolated in the form of the salicylate, as described under degradation of the α-isomer. The yield was 85–90% of the calculated amount.

The isomethine base is not crystalline. It dissolves readily in dilute alkali, and is precipitated by ammonium chloride. The alkali-soluble base is converted to the non-phenolic δ-methyldimethylamino-6-methoxythebendiene when boiled for 1 minute with concentrated hydrochloric acid.

The salicylate of δ-methyldihydrothebaïneisomethine crystallizes well from ethanol, in which it is sparingly soluble. The salt sinters slightly at 190°, and melts at 209–211°; in alcohol, $[\alpha]_D^{20}$ −16° (c = 0.22).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11: H. 6.94.
Found: C, 69.89; H. 7.19.

The methiodide hydrate crystallizes from water, m. p. 176.5–178.5°, crystallizes again at 180° and remelts at 233°; in alcohol, $[\alpha]_D^{22}$ −30° (c = 0.6).

Anal. Calc'd for $C_{22}H_{30}INO_3 + H_2O$: C, 52.67; H, 6.40; H_2O, 3.6.
Found: C, 52.49; H, 6.14; H_2O, 4.5.

δ-Methyldihydrothebaïneisomethine methyl ether methiodide was prepared by treating δ-methyldihydrothebaïneisomethine in methanol with excess methyl iodide in the presence of 40% sodium hydroxide and boiling the solution until methanol was removed. The product was crystallized from water, and from boiling ethyl acetate by addition of alcohol until solution was complete. It has the melting point 172.5–174°, $[\alpha]_D^{22}$ −25° (alcohol, c = 0.5).

Anal. Calc'd for $C_{23}H_{32}INO_3$: C, 55.51; H, 6.49; $(OCH_3)_3$, 18.7.
Found: C, 55.49; H, 6.44; OCH_3, 18.3.

δ-Methyldihydrothebaïneisomethine methyl ether picrate was obtained by degradation of δ-methyldihydrothebaïne methyl ether methiodide (not crystalline) with 40% sodium hydroxide. The crude oily mixture of methine bases was treated with the calculated amount of tartaric acid, and methyldihydrothebaïnemethine methyl ether tartrate crystallized out in 49% yield. The mother liquors yielded the oily δ-methyldihydrothebaïneisomethine methyl ether base, from which the picrate was prepared and purified from alcohol; yield 23%. The picrate melts at 125–128°; it could be converted to the above-described methiodide of m. p. 172–174°.

Anal. Calc'd for $C_{28}H_{32}N_4O_{10}$: $(OCH_3)_3$, 15.9. Found: OCH_3, 15.7.

Dihydro-δ-methyldihydrothebaïneisomethine.—In contrast to the δ-isomer before degradation, δ-methyldihydrothebaïneisomethine in alcohol solution with platinum oxide absorbed one mole of hydrogen rapidly to give the dihydro derivative, a phenolic oily base, unaffected by boiling with concentrated hydrochloric acid. The base was characterized as the salicylate (84% yield); m. p. 182.5–185.5°, $[\alpha]_D^{20}$ +12.8° (alcohol, c = 0.3).

Anal. Calc'd for $C_{28}H_{35}NO_6$: C, 69.81; H, 7.33.
Found: C, 69.84; H, 7.42.

Degradation of δ-methyldihydrothebaïneisomethine methiodide through the quaternary ammonium base as described for the α-isomer, yielded exclusively the same optically inactive vinyldihydro-x-methylthebaöl (identified as the acetyl derivative) as was obtained in the parallel degradation of α-methyldihydrothebaïneisomethine methiodide. Degradation of δ-methyldihydrothebaïneisomethine which had been boiled with concentrated hydrochloric acid resulted in a 20% yield of the mixture of (+) and racemic 6-methoxy-x-methylthebentriene that has already been described in the degradation of the α-isomer.

Dihydrohydroxy-δ-methyldihydrothebaïneisomethine.—The δ-methyldihydrothebaïneisomethine base liberated from 0.66 g. of the salicylate was dissolved in 1 cc. of acetyl chloride which had been previously treated with 2 drops of water. The solution was evaporated to a viscous oil on the water bath, finally under diminished pressure. The foamy mass was neutralized with 3N sodium hydroxide, and enough excess alkali added to bring the concentration to about 2N. The alkaline solution was boiled for 5 minutes to hydrolyze the acetyl derivatives present, and excess of saturated ammonium chloride solution was added. The ether extract from this partly crystallized on concentration. The crystals, dihydrohydroxy-δ-methyldihydrothebaïneisomethine, were filtered out, and the oily filtrate was washed with a

little alkali. The alkali-insoluble material consists of δ-methyl-9-dimethylamino-6-methoxythebendiene (see parallel conversion in the η-series).

Dihydrohydroxy-δ-methyldihydrothebaïneisomethine, yield 30% of the calculated amount, crystallizes from ethyl acetate. It is phenolic in nature, m. p. 163–165°, $[\alpha]_D^{30}$ +25° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{29}NO_4$: C, 70.15; H, 8.14.
Found: C, 69.97; H, 7.97.

δ-Methyl-9-dimethylamino-6-methoxythebendiene.—Acetyl chloride was added to a solution of dihydrohydroxy-δ-methyldihydrothebaïneisomethine in a little concentrated hydrochloric acid until an excess was present, and concentrated hydrochloric acid was added until all acetyl chloride was decomposed. The solution was made alkaline with 40% sodium hydroxide and the oil that separated was washed with water. The oil crystallized from alcohol in a yield of 30%; further purification was effected from dilute alcohol. The compound was insoluble in alkali; m. p. 101.5–103°, $[\alpha]_D^{23}$ +33° (alcohol, c = 0.2). It was indifferent toward catalytic hydrogenation.

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 74.08; H, 7.82.

The closure of the thebenane ring was accomplished in a single operation when δ-methyldihydrothebaïneisomethine salicylate was boiled for 4 minutes in acetyl chloride. The excess of reagent was decomposed with water, and δ-methyl-9-dimethylamino-6-methoxythebendiene was precipitated with ammonia and extracted into ether; yield 56% of the calculated amount; m. p. 101.5–103°, $[\alpha]_D^{29}$ +30° (alcohol, c = 0.6).

The methiodide was prepared in the usual way and was purified from alcohol. It crystallizes with one-half molecule of water, which could not be determined directly because of slight sublimation. The compound softens at 155° with loss of hydrate water, solidifies, and melts at 207–208°; in alcohol solution, $[\alpha]_D^{25}$ −13° (c = 0.5).

Anal. Calc'd for $C_{22}H_{30}INO_3 + 0.5\ H_2O$: C, 53.64; H, 6.35.
Found: C, 53.34; H, 6.44.

δ-Methyl-9-dimethylamino-6-methoxythebendiene methiodide suffered degradation only slowly in boiling 40% sodium hydroxide, but when the alkali was permitted to become more concentrated, the decomposition proceeded smoothly, giving (+) 6-methoxy-x-methylthebentriene in 86% yield. None of the corresponding racemate could be isolated.

(−) *Methyldihydrothebaïnemethine.*—Acetyl-δ-methyldihydrothebaïne methiodide was dissolved in the minimum amount of hot water and treated with the calculated amount of 0.15N thallous hydroxide. The filtered solution was evaporated to dryness in a vacuum desiccator, and the hygroscopic glass-like quaternary base was redried in a high vacuum and then heated for 10 hours at 98° in an oil-pump vacuum. The material was treated with ammonia and extracted into ether, and the residue from the ether was boiled for two minutes in normal sodium hydroxide, becoming completely soluble through hydrolysis at the acetyl group. The oily base isolated after treatment with ammonium chloride gave a crystalline tartrate, yield 49% of the calculated amount. From the mother liquor, 12.5% yield of δ-methyldihydrothebaïneisomethine salicylate was obtained; considerable water-soluble material, probably undecomposed quaternary base, was present. The degradation of acetyl-α-methyldihydrothebaïne methiodide in similar fashion gave the above-mentioned

tartrate in 14.5% yield, and α-methyldihydrothebaïneisomethine salicylate in 42% yield.

The tartrate of (−) methyldihydrothebaïnemethine was recrystallized from ethanol; m. p. 135–140°, $[\alpha]_D^{25}$ −7° (alcohol, c = 0.5). The methine base regenerated from the tartrate was purified from ethanol. It was alkali-soluble, and this property was not changed by boiling the substance in concentrated hydrochloric acid. The base melts at 106–108° and has $[\alpha]_D^{25}$ −21.3° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 74.03; H, 8.08.

The methyl ether methiodide was formed when the methine base was warmed in ethanol with excess methyl iodide and 3*N* sodium hydroxide. The product was purified by adding ethanol to a suspension in boiling ethyl acetate until complete solution resulted. It has the m. p. 190–192°, $[\alpha]_D^{23}$ +20° (alcohol, c = 0.7).

Anal. Calc'd for $C_{23}H_{32}INO_3$: C, 55.51; H, 6.49; $(OCH_3)_3$, 18.7.
Found: C, 55.46; H, 6.53; OCH_3, 18.6.

The methyl ether tartrate was obtained in 49% yield as described above from the degradation of δ-methyldihydrothebaïne methyl ether methiodide with 40% sodium hydroxide. The salt was purified from water, and has the melting point 135–137° (loss of hydrate water at 100°); $[\alpha]_D^{29}$ +23° (alcohol, c = 0.8). The tartrate could be converted to the above described methiodide.

rac.-*Methyldihydrothebaïnemethine.*—When acetyl-δ-methyldihydrothebaïne methohydroxide was distilled in a high vacuum at 128° instead of at the lower temperature, racemization accompanied the degradation to a small extent. The racemate could be separated easily from the levorotatory form through its slight solubility in ether. It was identified by conversion to the racemic methyl ether methiodide (m. p. 207.5-209.5°) that is obtained when (−) and (+) methyldihydrothebaïnemethine methyl ether methiodides are mixed (see the degradation of η-methyldihydrothebaïne). *rac.*-Methyldihydrothebaïnemethine is soluble in acid or alkali. It was purified from alcohol, m. p. 139.5–141.5°, $[\alpha]_D^{25}$ 0°, (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 74.15; H, 8.04.

(−) *Methyldihydrothebaïne-9,10-dihydromethine methyl ether.*—A solution of (−) methyldihydrothebaïnemethine methyl ether (liquid) in ethanol with platinum oxide absorbed one mole of hydrogen. The hydrogenated base did not crystallize, but formed a tartrate, purified from water, m. p. 106–110°, $[\alpha]_D^{23}$ +32.3° (alcohol, c = 0.5). The methiodide, purified from water, sinters at about 170° and melts at 182–183°; $[\alpha]_D^{29}$ +29.1° (alcohol, c = 0.5).

Anal. Calc'd for $C_{23}H_{34}INO_3$: C, 55.29; H, 6.86.
Found: C, 55.32; H, 6.88.

The base was recovered unchanged after being boiled for 3 minutes in concentrated hydrochloric acid.

Degradation of (−) *methyldihydrothebaïnemethine.*—(−) Methyldihydrothebaïnemethine reacted vigorously with methyl iodide to give a methiodide, which was recrystallized from water, m. p. above 230°. The methiodide was degraded by boiling with 40% sodium hydroxide, extracting with ether from an ammonium chloride suspension, and reheating with alkali several times. The ether yielded an oil, which crystallized from sodium hydroxide solution as the sodium salts of

racemic and (+) vinyldihydro-*x*-methylthebaöl; yield 90%. The sodium salt of (+) vinyldihydro-*x*-methylthebaöl, when triturated with a little hot hydrochloric acid, was converted in poor yield to (+) 6-methoxy-*x*-methylthebentriene. Treatment of the sodium salt (0.2 g.) with acetic anhydride in pyridine for two days gave 30 mg. of *rac.*-acetylvinyldihydro-*x*-methylthebaöl of m. p. 103–106°, identical with that obtained from the degradation of α- or δ-methyldihydrothebaïneisomethines.

Oxidation of vinyldihydro-x-methylthebaöl methyl ether.—Three grams of δ-methyldihydrothebaïnemethine methyl ether tartrate was converted to the methiodide and degraded by boiling for 2 hours with 40% sodium hydroxide. The liquid product was optically active, $[\alpha]_D^{22}$ +20.8°, and probably consisted of a mixture of *rac.* and (+) vinyldihydro-x-methylthebaöl methyl ethers. The oxidation with a solution of 1.5 g. of potassium dichromate in 8 cc. of water with 1.5 cc. of concentrated sulfuric acid proceeded with great vigor. The product was 0.05 g. of an ether-insoluble, yellow crystalline compound, optically inactive, m. p. 191–193°. The same compound (quinone?) was obtained from the parallel degradation and oxidation in the α series.

Anal. Found: C, 70.42; H, 6.52.

η-Methyldihydrothebaïne.—Pure α-methyldihydrothebaïne was heated at 125° for 4 days in an evacuated sealed tube. The product was taken up in hot ethanol, and the sparingly soluble α,ω-racemate (m. p. 179–182°) was separated by filtration; yield about 4%. The remainder of the product was fractionated from alcohol; about 50% yield of an apparently homogeneous substance, the α,η-methyldihydrothebaïne molecular compound, was obtained. From the mother liquors, 25% of the starting material was recovered. The conversion is more rapid at higher temperatures, but the yield of the α,η compound is lower, due to increased formation of α, ω racemate. A high-vacuum sublimation of α-methyldihydrothebaïne at 150° yielded α, ω racemate and α, η compound in the ratio of 5 to 7.

The molecular compound shows constant properties on repeated crystallization from alcohol. The m. p. is 123–124.5°, $[\alpha]_D^{25}$ +48° (alcohol, c = 0.6).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.26; H, 7.68.

α,η-Methyldihydrothebaïne molecular compound dissolves in alkali, and is precipitated by ammonium chloride. All attempts to hydrogenate it failed. It was separated into its components by treating a solution of the base in a little 6*N* hydrochloric acid with concd. ammonium chloride solution and seeding with α-methyldihydrothebaïne hydrochloride. After removal of the crystalline α-isomer hydrochloride, the mother liquor was made ammoniacal, extracted with ether, and the oily residue from the ether was treated with 20% aqueous perchloric acid. The salt was liquid, but crystallized when a little alcohol was added. It was purified from alcohol. η-Methyldihydrothebaïne perchlorate has $[\alpha]_D^{25}$ −49° (alcohol, c = 0.5).

Anal. Calc'd for $C_{20}H_{26}ClNO_7$: C, 56.12; H, 6.13.
Found: C, 56.08; H, 6.13.

The base regenerated from the pure perchlorate is not crystalline. It is soluble in alkali, and like the other isomers is indifferent toward catalytic hydrogenation. The oily base obtained from 0.6 g. of the perchlorate was treated with an alcoholic solution of 0.46 g. of α-methyldihydrothebaïne. Crystallization yielded 0.86 g. (93.5%) of the dimolecular α,η compound. The transformation of the α isomer into the η isomer can be reversed: when the oily η base was heated in an evacuated sealed

tube at 150° for 15 hours, the α,η dimolecular compound was obtained in good yield (75%).

δ,η-Methyldihydrothebaïne racemate.—The perchlorates of δ- and η-methyldihydrothebaïnes (0.5 g. of each) were mixed and dissolved in hot alcohol. The racemate perchlorate crystallized out in 86% yield, $[\alpha]_D^{25}$ 0°. The perchlorate yielded a very soluble base, which was purified from dilute alcohol, m.p. 79–83°.

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.48; H, 7.57.

Degradation of η-methyldihydrothebaïne.—The degradation of the η isomer proceeded parallel to that of the δ isomer, and gave at every step derivatives having the same constitution as, but rotatory power opposite to, those of the δ series, with which compounds having the properties of racemates were formed.

η-Methyldihydrothebaïneisomethine salicylate was prepared as described for the δ series, yield 90%. It has the melting point 209–211° and $[\alpha]_D^{20}$ +14° (alcohol, c = 0.25).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11; H, 6.94.
Found: C, 70.22; H, 7.20.

When this isomethine salicylate was dissolved in ethanol with an equal amount of δ-methyldihydrothebaïneisomethine salicylate, the racemate, δ,η-methyldihydrothebaïneisomethine salicylate crystallized out in 77% yield. It has the m. p. 190–195° (gas evolution), $[\alpha]_D^{25}$ 0° (alcohol, c = 0.2).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11; H, 6.94.
Found: C, 69.98; H, 7.24.

Dihydrohydroxy-η-methyldihydrothebaïneisomethine.—The oily η-methyldihydrothebaïneisomethine was treated with partially hydrolyzed acetyl chloride, as described for the δ isomer. The products were dihydrohydroxy-η-methyldihydrothebaïneisomethine (48.5% yield), purified from ethyl acetate, and η-methyl-9-dimethylamino-6-methoxythebendiene (14% yield), purified from dilute alcohol.

Dihydrohydroxy-η-methyldihydrothebaïneisomethine is a phenolic base, m. p. 163.5–165.5°, $[\alpha]_D^{28}$ −23° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{29}NO_4$: C, 70.15; H, 8.14.
Found: C, 70.24; H, 8.46.

When equal amounts of this isomethine base and the corresponding derivative of the δ series were dissolved in ethanol, the racemate, δ,η-dihydrohydroxymethyldihydrothebaïneisomethine, crystallized in 83% yield. It showed constant properties on recrystallization from ethanol; m. p. 167–168.5°, $[\alpha]_D^{25}$ 0° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{29}NO_4$: C, 70.15; H, 8.14.
Found: C, 70.18; H, 8.44.

η-Methyl-9-dimethylamino-6-methoxythebendiene, obtained as described above, is a non-phenolic base of m. p. 101–103°, $[\alpha]_D^{25}$ −34° (alcohol, c = 0.5).

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 74.03; H, 8.25.

When equal amounts of this compound and the corresponding derivative of the δ series were mixed in alcohol containing a little water, the racemate, δ,η-methyl-9-

dimethylamino-6-methoxythebendiene, crystallized in 86% yield. The new compound had the m. p. 110–112°, $[\alpha]_D^{25}$ 0° (alcohol, $c = 0.6$).

Anal. Calc'd for $C_{21}H_{27}NO_3$: C, 73.85; H, 7.98.
Found: C, 73.96; H, 8.14.

(−) *6-Methoxy-x-methylthebentriene.*—η-Methyl-9-dimethylamino-6-methoxythebendiene was degraded in boiling 80% sodium hydroxide as described for the corresponding δ derivative. The degradation product crystallized readily from ether (yield, 76% of the calculated amount) and was purified from dilute alcohol. (−) 6-Methoxy-x-methylthebentriene has the m. p. 99–101.5° and $[\alpha]_D^{25}$ −7.2° (alcohol, $c = 0.6$).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.82; $(OCH_3)_2$, 20.9.
Found: C, 76.93; H, 6.99; OCH_3, 19.6, 19.4.

When equal amounts of this compound and (+) 6-methoxy-x-methylthebentriene were dissolved in hot alcohol, the racemic compound of m. p. 91.5–94° and $[\alpha]_D^{25}$ 0° was obtained in 91% yield.

(+) *Methyldihydrothebaïnemethine methyl ether methiodide.*—η-Methyldihydrothebaïne was converted to the methyl ether methiodide by the action of methyl iodide and 3*N* alkali on a solution of the base methiodide in methanol. The crude methyl ether methiodide was degraded by boiling with 40% sodium hydroxide, and the oily methine base was converted to the methiodide in the usual way. The methiodide was crystallized from a mixture of ethyl acetate and ethanol, over-all yield based on η-methyldihydrothebaïne, 72% of the calculated amount. By fractional crystallization, the product was separated into the methine methyl ether methiodide (28.5% yield based on η-methyldihydrothebaïne) and η-methyldihydrothebaïneisomethine methyl ether methiodide (26.5% yield).

(+) Methyldihydrothebaïnemethine methyl ether methiodide has the m. p. 190.5–192°, $[\alpha]_D^{25}$ −20° (alcohol, $c = 0.7$).

Anal. Calc'd for $C_{23}H_{32}INO_3$: C, 55.51; H, 6.49.
Found: C, 55.55; H, 6.40.

When this compound was mixed with an equal amount of (−) methyldihydrothebaïnemethine methyl ether methiodide and crystallized from ethyl acetate-ethanol mixture, the racemate was obtained in 93% yield. The racemate has the m. p. 207.5–209.5° and $[\alpha]_D^{25}$ 0° (alcohol, $c = 0.5$).

Anal. Calc'd for $C_{23}H_{32}INO_3$: C, 55.51; H, 6.49.
Found: C, 55.69; H, 6.74.

η-Methyldihydrothebaïneisomethine methyl ether methiodide, obtained from the above described degradation, had the m. p. 172.5–174°, $[\alpha]_D^{25}$ +26.4° (alcohol, $c = 0.9$).

Anal. Calc'd for $C_{23}H_{32}INO_3$: C, 55.51; H, 6.49.
Found: C, 55.54; H, 6.59.

ω-Methyldihydrothebaïne.—δ-Methyldihydrothebaïne, in an evacuated sealed tube, was held at 155° for 10 hours. The yellow oily product was separated, by fractional crystallization from alcohol, into the racemate of δ- and ω-methyldihydrothebaïnes (1% yield), and the apparently homogeneous δ,ω-methyldihydrothebaïne molecular compound. A small amount of ω-methyldihydrothebaïne was isolated from the alcohol mother liquors.

The dimolecular δ,ω-methyldihydrothebaïne is analogous to the α,η-methyl-

dihydrothebaïne that has already been described. It shows a constant melting point, 123–124.5°, (coincident with that of the α,η compound) on repeated recrystallization from ethanol, and has $[\alpha]_D^{25}$ −48° (alcohol, $c = 0.8$), equal and opposite to the rotation of the α,η compound.

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.47; H, 7.81.

When 0.5 g. each of the α, η and δ, ω compounds were dissolved separately in alcohol, and the solutions mixed, crystallization ensued. The product was 0.5 g. of the racemate of α- and ω-methyldihydrothebaïnes. From the mother liquors, 0.17 g. of δ,η-methyldihydrothebaïne racemate was obtained. It seems certain that the racemates were formed in equal amounts, but the δ, η racemate is much more difficult to isolate because of its low melting point and greater solubility.

The δ,ω-molecular compound was converted to the hydrochloride by bringing it into solution in a small amount of 6*N* hydrochloric acid and adding saturated ammonium chloride solution. The hydrochloride of ω-methyldihydrothebaïne that crystallized was converted into the base; yield, including that recovered from the mother liquors, 46% of the weight of the δ,ω compound. The action of perchloric acid on the oily residues gave δ-methyldihydrothebaïne in 22% yield.

ω-Methyldihydrothebaïne is phenolic in nature, and crystallizes well from ethanol; m. p. 86.5–89.5°, $[\alpha]_D^{25}$ −140° (alcohol, $c = 0.7$).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.49; H, 7.66.

Its perchlorate crystallizes from alcohol, and has, in alcohol solution, $[\alpha]_D^{25}$ −81° ($c = 0.5$).

When equal weights of δ-methyldihydrothebaïne (oil) and ω-methyldihydrothebaïne (m. p. 86.5–89.5°) were mixed in ethanol solution, the δ, ω molecular compound (m. p. 123–124.5°) was recovered in 82% yield.

ω-Methyldihydrothebaïne has the same melting point as the α isomer, but an equal and opposite rotatory power. When 0.2 g. each of the α and ω isomers were dissolved in a little ethanol (in which they are very soluble), and the solutions were mixed, the racemate crystallized out immediately in a yield of 97%. α,ω-Methyldihydrothebaïne racemate is only slightly soluble in boiling alcohol. It has the m. p. 179–182°, and $[\alpha]_D^{25}$ 0° (alcohol, $c = 0.13$).

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.35; H, 7.70.
Found: C, 73.32; H, 7.65.

ω-Methyldihydrothebaïne can be prepared from η-methyldihydrothebaïne by a procedure similar to that used in the transformation of α-methyldihydrothebaïne to the δ isomer. A concentrated solution of η-methyldihydrothebaïne perchlorate in ethanol was heated on the water bath under a reflux condenser for 23 hours. The red solution was diluted with a little ethanol, and 78% of the starting material precipitated crystalline. The material in the mother liquors was converted to the base (elimination of colored materials), which was then subjected to fractional crystallization in the form of perchlorate. A little more η perchlorate was then removed. The perchlorate mother liquors, through the base and its hydrochloride, yielded 2.2% of the weight of starting material as ω-methyldihydrothebaïne base of m. p. 85–86.5° and $[\alpha]_D^{25}$ −134°. When mixed with ω-methyldihydrothebaïne it showed no depression in melting point; mixed with the α isomer, it showed the melting point of the racemate.

Partial degradation of ω-methyldihydrothebaïne.—The methiodide of ω-methyldihydrothebaïne was prepared and subjected to degradation in exactly the same manner as its optical opposite, the α isomer. ω-Methyldihydrothebaïneisomethine salicylate was obtained in 82% of the calculated amount. The salt melts at 161.5–165.5°, and has in alcohol solution $[\alpha]_D^{25}$ +85° (c = 0.7).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11; H, 6.94.
Found: C, 69.86; H, 6.91.

A mixture of equal weights of ω-methyldihydrothebaïneisomethine salicylate and α-methyldihydrothebaïneisomethine salicylate was dissolved in hot ethanol. The sparingly soluble racemate salicylate separated immediately; yield after recrystallization from ethanol, 73% of the starting materials. The salt melts at 201–204°, and has $[\alpha]_D^{25}$ 0° (alcohol, c = 0.25).

Anal. Calc'd for $C_{28}H_{33}NO_6$: C, 70.11; H, 6.94.
Found: C, 70.22; H, 6.99.

SUMMARY

1. Thebaïne reacts with methylmagnesium iodide to give the isomeric α- and δ-methyldihydrothebaïnes. These have the formula $C_{20}H_{25}NO_3$, are phenolic, and resemble phenyldihydrothebaïne in their resistance to hydrogenation or hydrolysis.

2. α-Methyldihydrothebaïne, by epimerization at one asymmetric center, can be converted to δ-methyldihydrothebaïne, or by epimerization at a different asymmetric center, to η-methyldihydrothebaïne. The last-named is the optical oppoiste of the δ isomer, with which it forms a racemate.

3. δ-Methyldihydrothebaïne undergoes epimerization to yield ω-methyldihydrothebaïne, which is the optical opposite of the α isomer.

4. Degradation of the isomers by Hofmann's method results in opening the nitrogen-containing ring in such a way that isomeric vinyl derivatives result; in these, the vinyl group cyclizes easily with the 4-hydroxyl to give analogs of thebenane.

5. Elimination of the nitrogen atom from the α and δ isomethines gives the same optically active compound, showing that the α and δ isomers differ only in the configuration at the asymmetric center C-9.

6. Degradation of the δ and η isomers can also be carried to "normal" methine bases, which are optical opposites, showing that these isomers differ at the asymmetric center other than C-9.

7. The methyldihydrothebaïnes retain the vinyl group on complete degradation, in contrast to most other derivatives of the morphine series.

8. Speculations on the structure of the series are offered.

[CONTRIBUTION FROM THE SOILS DEPARTMENT, NEVADA AGRICULTURAL EXPERIMENT STATION, UNIVERSITY OF NEVADA]

THE PREPARATION OF CALCIUM GLUCOSE-3-PHOSPHATE FROM DIBRUCINE GLUCOSE-3-PHOSPHATE*

S. ALLAN LOUGH AND V. E. SPENCER

Received October 13, 1938

In an extension of the work of Spencer and Stewart[1], glucose-3-phosphoric acid of a high degree of purity was desired for study. The preparation of the barium salt of this acid has been described by Raymond and Levene[2] and by Levene and Raymond[3], but the toxic nature of barium precludes its use in plant nutrition. The calcium salt would be satisfactory. Apparently the calcium salt has been prepared only by Spencer and Stewart[1], who obtained an impure sample by adding calcium sulfate to barium glucose-3-phosphate which had been made by the method of Raymond and Levene[2].

Although Raymond and Levene[2] produced the barium salt by adding baryta water to a solution of glucose-3-phosphoric acid, all our efforts to obtain the calcium salt by using calcium hydroxide solution, or milk of lime, resulted in failure. By this procedure one of us[4] has obtained several products, in each of which the calcium exceeded, while the phosphorus fell below, the theoretical amount. These products contained inorganic phosphorus, which increased in amount when purification was attempted. For these reasons we sought a more fruitful procedure for obtaining calcium glucose-3-phosphate of sufficient purity.

The problem was solved by adding the stoichiometrical quantity of solid calcium hydroxide to a water suspension of the dibrucine salt of glucose-3-phosphoric acid, made by the method of Levene and Raymond[3]. The brucine formed in the reaction, as well as any calcium hydroxide which failed to react, were insoluble and were separated from the solution of calcium glucose-3-phosphate by filtration. By this method a sample of calcium glucose-3-phosphate of satisfactory purity was obtained in 66 per cent. yield, based on the amount of the dibrucine salt used.

* Published with the permission of the Director of the Nevada Agricultural Experiment Station.

[1] SPENCER AND STEWART, *Soil Science*, **38**, 65–79 (1934).

[2] RAYMOND AND LEVENE, *J. Biol. Chem.*, **83**, 622–4 (1929).

[3] LEVENE AND RAYMOND, *ibid.*, **89**, 484–7 (1930).

[4] SPENCER, unpublished results.

EXPERIMENTAL

Preparation of dibrucine glucose-3-phosphate.—Dibrucine glucose-3-phosphate was prepared by the method of Levene and Raymond[3]. The diacetone-glucose used was made by a procedure[5] published later. Analysis for nitrogen was by the Kjeldahl method, while that for phosphorus involved combustion in a Parr bomb and the usual molybdate and magnesia treatment.

Anal. Calc'd for $C_{82}H_{65}N_4O_{17}P$: N, 5.34; P, 2.96.
Found: N, 4.92, 4.94; P, 3.07, 3.01.

Preparation of calcium glucose-3-phosphate.—Five hundred milliliters of water and 55.29 g. of dibrucine glucose-3-phosphate were stirred vigorously in a 3-liter beaker until a homogeneous suspension was produced. Then, while stirring was continued, in small portions at intervals of several minutes, 3.90 g. of solid calcium hydroxide was added. Solid brucine separated before all the calcium hydroxide had been added. The brucine was filtered off with suction, removed from the funnel, suspended in water and filtered again with suction. Five volumes of 95% alcohol was added to the combined filtrate and washings, whereupon a white, flocculent solid separated immediately. After the solid had settled, the supernatant liquid was removed and an effort was made to filter the precipitate through a hardened paper on a Hirsch funnel. Cloudy filtrates made centrifugation necessary. The product was suspended in 95% alcohol, centrifuged again, washed twice with absolute alcohol, and finally filtered, without cloudiness of filtrate, through a hardened paper on a Hirsch funnel. The product, partially dried by drawing air through the funnel for 2 hours, was broken into lumps and dried over concentrated sulfuric acid under reduced pressure. Yield, 10.47 g., 66.6% of the theoretical amount.

Anal. Calc'd for $C_6H_{11}O_9PCa$: P, 10.41; Ca, 13.44.
Found: P, 10.14; Ca, 12.93, 13.03.

SUMMARY

The calcium salt of glucose-3-phosphoric acid was prepared by treatment of a water suspension of dibrucine glucose-3-phosphate with the stoichiometrical amount of solid calcium hydroxide.

[5] LEVENE AND RAYMOND, *J. Biol. Chem.*, **92**, 759 (1931).

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE, WASHINGTON, D. C.]

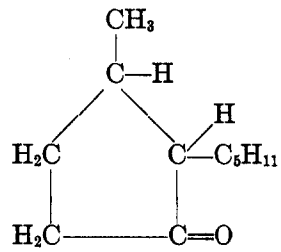
CONSTITUENTS OF PYRETHRUM FLOWERS. XIV.* THE STRUCTURES OF THE ENOLS OF PYRETHROLONE

H. L. HALLER AND F. B. LAFORGE†

Received October 17, 1938

When pyrethrolone is boiled in a dilute methanol solution of sodium methoxide, it is converted into a mixture of two isomeric compounds which are soluble in aqueous alkali and which exhibit the properties of enols.[1] The two compounds can be separated by fractional distillation, and both correspond to the empirical formula $C_{11}H_{14}O_2$. Since this formula contains two hydrogen atoms less than that originally proposed by Staudinger and Ruzicka for pyrethrolone, the enols were regarded by them as oxidation products. They were only superficially studied by these authors, with the following results.

The isomer that boiled at 82° (0.05 mm.), yielded a semicarbazone melting at 255° with decomposition. On hydrogenation it furnished the same cyclic ketone of formula I, 2-amyl-3-methyl-cyclopentanone-1, that had already been obtained by hydrogenation of pyrethrolone.



I

The hydrogenated compound exists in two stereoisomeric forms, the semicarbazones of which melt at 196° and 160°, respectively,[2,3,4] the lower-

* For article XIII of this series see SCHECHTER AND HALLER, *Soap*, **14**, (11), 101 (1938).

† We are indebted to W. G. Rose and F. Acree, Jr., for the microcombustions, and to E. L. Gooden for the optical data.

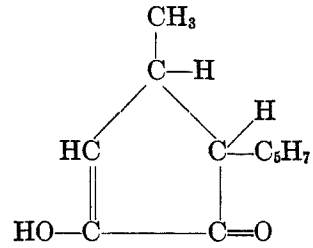
[1] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 220 (1924).

[2] STAUDINGER AND RUZICKA, *ibid.*, **7**, 237 (1924).

[3] TREFF AND WERNER, *Ber.*, **66**, 1521 (1933).

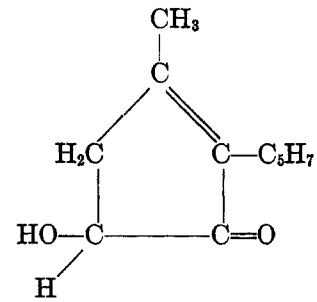
[4] HALLER AND LAFORGE, J. ORG. CHEM., **2**, 49 (1937).

melting form being the more stable. On the basis of these results formula II was assigned to the lower-boiling isomer.



II

In a previous paper[5] the formula for pyrethrolone was revised from one derived from cyclopentanolone to one with a cyclopentenolone nucleus, III.



III

On the basis of this revised formula, the enol of formula II is not an oxidation product but is formed by rearrangement of pyrethrolone.

The second isomeric enolic compound, which is the major product of the action of alkali on pyrethrolone, boiled at 145° (0.05 mm.), and was regarded by Staudinger and Ruzicka as a polymer of the compound of formula II. It yielded no semicarbazone. The results described in the present article now permit an explanation of the nature of this compound.

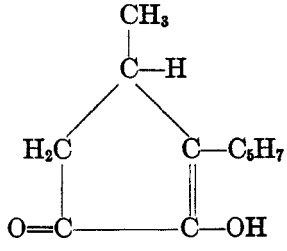
In our first experiments tetrahydropyrethrolone in which the side-chain is saturated was treated with alcoholic alkali in the presence of zinc dust to avoid oxidation. The reaction product consisted of an enolic compound boiling at 150° (0.25 mm.), together with some optically inactive tetrahydropyrethrolone. The enol was found to correspond to the empirical formula $C_{11}H_{18}O_2$. Under the conditions employed no lower-boiling isomer was isolated. That the compound is not a polymer was shown by

[5] LaForge and Haller, *J. Am. Chem. Soc.*, **58**, 1777 (1936).

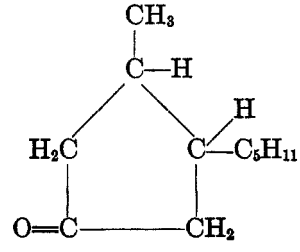
a molecular-weight determination. It yielded a monoacetyl derivative. The higher-boiling enol prepared by the directions of Staudinger and Ruzicka[1] from pyrethrolone furnished a tetrahydro derivative on hydrogenation. This was identical with the enol obtained by alkali treatment of tetrahydropyrethrolone. The monoacetyl derivative was also identical with the corresponding derivative obtained from the hydrogenated pyrethrolone enol. It is hence immaterial whether the pyrethrolone is first subjected to alkali treatment and then hydrogenated or these reactions are carried out in the reverse order.

The nuclear double bond in the higher-boiling enols, unlike that of formula II, is comparatively resistant to hydrogenation. This is not the case with the corresponding acetyl derivatives. On hydrogenation of the acetyl tetrahydropyrethrolone enol 2 moles of hydrogen was absorbed, with saturation of the nuclear double bond and elimination of the acetyl group. As products of the reaction two compounds were formed which were isolated as semicarbazones. One was difficultly soluble in ethanol and melted at 206°, the other very soluble and melted at 143°. Both have the same empirical formula, $C_{12}H_{23}N_3O$, and are different but isomeric with the semicarbazones of the compounds of formula I, which with reference to the revised conception of pyrethrone are designated as hexahydropyrethrones.

The enol of boiling point 155–160° (0.7 mm.), from pyrethrolone furnished a monoacetyl derivative, which on hydrogenation consumed 4 moles of hydrogen and yielded two isohexahydropyrethrones, which were isolated as semicarbazones identical with those obtained from tetrahydropyrethrolone enol acetate. A partial hydrogenation of acetyl pyrethrolone enol, involving only the double bonds in the side-chain, was possible with the use of a platinum oxide catalyst in denatured ethyl acetate, with the formation of the same tetrahydropyrethrolone enol acetate as that derived from tetrahydropyrethrolone enol. From the results described there can be no doubt that the higher-boiling enol obtained from pyrethrolone, which will be designated as isopyrethrolone enol, should be represented by formula IV, and the isohexahydropyrethrones by formula V (3-amyl-4-methylcyclopentanone-1).



IV



V

This conclusion is substantiated by several analogies to be found in the reports of Staudinger and Ruzicka in connection with the synthetic preparation of cyclopentanolones related to pyrethrolone. In several instances where the reactions were expected to lead to compounds analogous to formula II, compounds analogous to formula IV or mixtures of the two were obtained.[6]

EXPERIMENTAL

Conversion of pyrethrolone to the enol forms.—Seven and two-tenths grams of pyrethrolone was treated with sodium methoxide solution according to the directions of Staudinger and Ruzicka[1] except that the solution was refluxed for 20 hours instead of 7 hours. The enolic fraction was distilled at 0.7 mm., and two fractions were collected. The first fraction (1.1 g.) passed over from 90–155°, the second fraction (2.35 g.) from 155–160°.

On redistillation of the first fraction 0.5 g. of distillate boiling at 93° (0.7 mm.) was obtained. This part was used for the preparation of the semicarbazone, the proportions of reagents being ethanol 5 cc., pyridine 1 cc., and semicarbazide hydrochloride 0.75 g. in 1 cc. of water. The semicarbazone separated almost instantly. After standing for several hours it was removed by filtration. The yield was 0.52 g. It melted with decomposition at about 255° after it had sintered at 220°. It was recrystallized from glacial acetic acid and then melted with decomposition at about 255°. The analysis indicates that the compound has the same empirical formula as pyrethrolone semicarbazone.‡

Anal. Calc'd for $C_{12}H_{17}N_3O_2$: C, 61.27; H, 7.23.
Found: C, 61.49, 61.14; H, 7.11, 6.99.

The enolic fraction boiling from 155–160° contained a little of the lower-boiling material. When 0.55 g. was treated with semicarbazide hydrochloride in pyridine-ethanol solution under the above conditions, about 0.025 g. of semicarbazone separated at once. After it has been recrystallized from acetic acid, it melted with decomposition at 255° and was found by a mixture-melting point determination to be identical with the semicarbazone from the lower-boiling fraction.

The enolic fraction boiling from 155–160° (0.7 mm.) (isopyrethrolone enol) has been analyzed by Staudinger and Ruzicka and found to correspond to the formula $C_{11}H_{14}O_2$.

Contrary to the results of Staudinger and Ruzicka,[1] the total enolic product is soluble in alkali carbonate as well as in alkali hydroxide.

Isopyrethrolone enol acetate.—The acetate of isopyrethrolone enol was easily obtained in almost quantitative yield by allowing 1 part of the enol in 4 to 5 parts of acetic anhydride to stand overnight and completing the reaction by warming for 4 hours on the steam bath. After removal of the excess reagent by distillation with

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[6] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 409, 421 (1924).

‡ STAUDINGER AND RUZICKA [(*Helv. Chim. Acta*, **7**, 234 (1924)] report analyses on a semicarbazone melting at about 230–260°, which is always obtained in small amount as a by-product in the preparation of pyrethrolone semicarbazone. The analytical results obtained on this compound indicate that it corresponds to the formula $C_{12}H_{17}N_3O$, *i.e.*, an anhydropyrethrolone semicarbazone. It is evident that the semicarbazone derived from the lower-boiling pyrethrolone enol is different from this product.

the aid of the water pump, the reaction product was distilled. It boiled at 118–120° (0.4 mm.); $n_D^{25} = 1.5047$; $n_F^{25} - n_C^{25} = 0.0146$.

Anal. Calc'd for $C_{13}H_{16}O_3$: C, 70.90; H, 7.27.
Found: C, 70.37; H, 7.77.

Hydrogenation of isopyrethrolone enol.—On hydrogenation of 0.9 g. of isopyrethrolone enol in ethyl acetate solution, with 0.1 g. of reduced platinum oxide as catalyst, 190 cc. of hydrogen was absorbed in 30 minutes. (The theory requires 224 cc. for 2 mols of hydrogen.)

The solvent was removed under reduced pressure, the residue was dissolved in ether, and the ethereal solution was extracted with 5% sodium carbonate solution. On acidification the carbonate solution yielded an oil, which was extracted with ether. The residue from the dried ether solution was distilled, yielding 0.6 g. of viscous oil boiling at 157–160° (0.3 mm.); $n_D^{28} = 1.5054$. $n_F^{28} - n_C^{28} = 0.0147$. These constants are the same as those obtained for tetrahydroisopyrethrolone enol prepared from tetrahydropyrethrolone.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.52; H, 9.89.
Found: C, 72.28, 72.31; H, 9.80, 9.64.

Tetrahydroisopyrethrolone enol.—Fifteen cubic centimeters of a 10% aqueous solution of potassium hydroxide was dropped over a period of 30 minutes into a boiling solution of 2 g. of tetrahydropyrethrolone in 500 cc. of 95% ethanol containing 3 g. of zinc dust. The reaction was carried out with mechanical stirring, and the boiling was continued for 3 hours. The solution was filtered from zinc, which was then washed with ether. After removal of the alcohol the aqueous solution was extracted with ether and the ethereal solutions were combined. About 0.6 g. of oily residue was obtained from these on evaporation. It was distilled under reduced pressure (b.p. 120°C, $p = 0.2$ mm.). The product when treated with semicarbazide yielded the semicarbazone of inactive tetrahydropyrethrolone melting at 170°. The identity of the two semicarbazones was confirmed by the mixture melting point.

The aqueous alkaline solution yielded, on acidification and extraction with ether, a thick, slightly yellow oil, which distilled almost completely at 150° (0.25 mm.). The yield of pure material was 1.4 g.; $n_D^{28} = 1.5050$. The compound is a very viscous liquid with a yellow-green fluorescence. It gives a bright yellow color with tetranitromethane.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89; Mol. wt., 182.
Found: C, 72.25, 72.02; H, 10.07, 10.06; Mol. wt. (Rast), 199.

Acetate of tetrahydroisopyrethrolone enol.—The acetate was readily obtained by heating 1 g. of the tetrahydroisopyrethrolone enol with 4 g. of acetic anhydride for several hours on the steam bath. After removal of the excess acetic anhydride by distillation with the aid of the water pump, the remaining liquid product was distilled. It boiled at 115–120° (0.35 mm.), giving 0.9 g. of a colorless mobile liquid; $n_D^{26} = 1.4724$; $n_F^{26} - n_C^{26} = 0.0102$.

Anal. Calc'd for $C_{13}H_{20}O_3$: C, 69.64; H, 8.93.
Found: C, 69.41, 69.03; H, 9.10, 8.92.

Hydrogenation of tetrahydroisopyrethrolone enol acetate.—One and six-tenths grams of the acetate was hydrogenated in ethyl acetate solution, with reduced platinum oxide as catalyst. The absorption of hydrogen was very rapid, and 355 cc. was taken up in 15 minutes. (The theoretical requirement for 2 moles is 320 cc.) The solvent was removed under reduced pressure, and the residue was dissolved in ether. After the ethereal solution had been washed with dilute sodium carbonate and water, it was dried with sodium sulfate. The ether was then removed, and the residue was

distilled. It boiled at 67–70° (2 mm.). The yield was 1 g.; $n_D^{25} = 1.446$; $n_F^{25} - n_C^{25} = 0.0066$.

Anal. Calc'd for $C_{11}H_{20}O$: C, 78.57; H, 11.90.
Found: C, 78.12, 78.74; H, 11.72, 11.99.

One-tenth gram of the distillate was dissolved in 1 cc. of ethanol, and 0.15 cc. of pyridine and 0.15 g. of semicarbazide hydrochloride in a few drops of water were added. After standing overnight the separated crystals were removed by filtration, washed with water and then with cold ethanol, and dried. The yield was 0.05 g. The product melted at 190–192°, and after recrystallization from ethanol at 206°. The melting point was not further raised by recrystallization. The melting point of the semicarbazone of one of the stereoisomeric forms of normal hexahydropyrethrone is 196°. When a sample of this compound was mixed with an equal quantity of the semicarbazone just described, the melting point was depressed to 176–180°.

Anal. Calc'd for $C_{12}H_{23}N_3O$: C, 64.00; H, 10.22.
Found: C, 63.68, 63.69; H, 9.94, 10.01.

The ethanolic mother liquor from which the semicarbazone of melting point 206° had separated yielded, on dilution with water, 0.07 g. of another semicarbazone which melted at 140–142°. On recrystallization from benzene it melted at 143°. It is a stereoisomer of the higher-melting compound.

Anal. Calc'd for $C_{12}H_{23}N_3O$: C, 64.00; H, 10.22.
Found: C, 64.22; H, 10.31.

Hydrogenation of isopyrethrolone enol acetate.—One and one-tenth grams of isopyrethrolone enol acetate was hydrogenated in 95% ethanol, with reduced platinum oxide as catalyst. The solution absorbed 465 cc. of hydrogen in 11 minutes. (The theoretical requirement for 4 moles is 448 cc.)

The solution was concentrated under reduced pressure to a volume of about 10 cc., and 1 cc. of pyridine and 1 g. of semicarbazide hydrochloride in 1 cc. of water were added. The solution, on standing overnight, deposited crystals, which were removed by filtration. The yield was 0.26 g. On recrystallization from ethanol the product melted at 206°. It was identical with the semicarbazone of hexahydroisopyrethrone of the same melting point obtained by hydrogenation of tetrahydroisopyrethrolone enol acetate, as was shown by a mixture melting-point determination.

The ethanolic mother liquor from the first crystallization was diluted with water, and the precipitated material was recrystallized from a very small volume of ethanol. It melted at 140°, and after crystallization from benzene at 143°. This compound was found by the mixture melting point to be identical with the corresponding compound obtained from the hydrogenation product of the tetrahydroisopyrethrolone enol acetate.

Partial hydrogenation of isopyrethrolone enol acetate. The acetate of isopyrethrolone enol can be hydrogenated to the tetrahydroisopyrethrolone enol acetate without affecting the double bond in the nucleus or the acetate group if the solvent employed is denatured ethyl acetate.§

One and three-tenths grams of isopyrethrolone enol acetate was reduced in denatured ethyl acetate solution, with reduced platinum oxide as catalyst. The solution absorbed 220 cc. of hydrogen in 40 minutes, when the reaction ceased. (The theory for 2 mols requires 265 cc.) The residue obtained on removal of the solvent was distilled. It boiled at 110–120°, p = 3 mm. The yield was 1.05 g. $N_D^{25} = 1.4735$. $N_F^{25} - N_C^{25} = 0.0102$. The constants are the same as those of tetrahydroisopyrethrolone enol acetate.

§ The denaturant was probably an oxidized petroleum distillate containing a trace of sulfur-containing product.

SUMMARY

Pyrethrolone is converted, on treatment with alcoholic alkali, into a mixture of two isomeric enols, having the same empirical formula ($C_{11}H_{14}O_2$) as pyrethrolone and therefore also isomeric with it.

The lower-boiling enol yields on hydrogenation 3-methyl-2-amylcyclopentanone-1, which is also obtained on hydrogenation of pyrethrolone. Therefore, the relative positions of the hydroxyl and ketone groups in the enol are the same as in pyrethrolone.

The higher-boiling enol yields an acetyl derivative that is hydrogenated to 3-amyl-4-methylcyclopentanone-1, which compound is also the product of hydrogenation of the acetate of the corresponding enol obtained by the action of alcoholic alkali on tetrahydropyrethrolone.

It follows that the positions occupied by the hydroxyl and ketone groups in the higher-boiling enol, designated isopyrethrolone enol, are reversed with respect to the positions that obtain in pyrethrolone and in the lower-boiling enol.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY, EVANSTON, ILLINOIS]

MECHANISMS FOR THE REARRANGEMENTS OF ETHERS: γ-ETHYLALLYL PHENYL ETHER AND γ-ETHYLALLYL VINYL ETHER

CHARLES D. HURD AND MAXWELL A. POLLACK

Received October 19, 1938

The type of thermal rearrangement represented by the change at about 200° of phenyl allyl ether into *o*-allylphenol has been studied considerably[1] in the past decade. Phenyl allyl ether contains the skeleton C=C—O—C—C=C, but the simplest compound to contain this skeleton, namely, vinyl allyl ether, was not investigated till very recently. Its rearrangement[2] at 250° into allylacetaldehyde establishes the fact that this is the essential skeleton for the rearrangement.

$$CH_2{=}CHOCH_2CH{=}CH_2 \rightarrow CH_2{=}CHCH_2CH_2CHO$$

Vinyl allyl ether, besides being the simplest ether of its type, also is simpler than phenyl allyl ether in its mode of pyrolysis. Rearrangement of the latter is followed by migration of hydrogen, but no such enolization occurs with the former.

It is characteristic of the rearrangement of allyl aryl ethers to involve the ortho position if available, otherwise the para position, but never the meta. When the ortho position is involved, it has been demonstrated conclusively[3] that the process is intramolecular and that there is inversion of the "wandering" allyl group. It seems, however, that no such inversion occurs[4] when rearrangement is forced to the para position.

Rearrangement of α-substituted or γ-substituted allyl ethers is similar to that of the allyl ethers, but the α,α-disubstituted allyl ethers behave differently. Instead of rearranging, the last-named types split into phenols and dienes,[5] but a certain amount of splitting into phenol[6] has been shown

[1] For a summary of the early work in this field see HURD, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Company, New York, **1929**, pp. 214–228.

[2] HURD AND POLLACK, *J. Am. Chem. Soc.*, **60**, 1905 (1938).

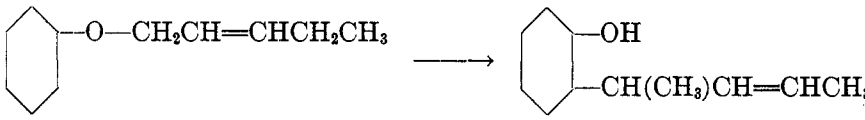
[3] (*a*) HURD AND SCHMERLING, *J. Am. Chem. Soc.*, **59**, 107 (1937); (*b*) CLAISEN AND TIETZE, *Ber.*, **58**, 275 (1925).

[4] MUMM AND MÖLLER, *Ber.*, **70**, 2214 (1937).

[5] CLAISEN AND COWORKERS, *J. prakt. Chem.*, **105**, 67 (1922); HURD AND COHEN, *J. Am. Chem. Soc.*, **53**, 1919 (1931).

[6] HURD AND PUTERBAUGH, J. ORG. CHEM., **2**, 381 (1937).

to take place also with the allyl ether types that do undergo rearrangement. Other pertinent facts are the non-rearrangement of the corresponding propargyl ethers,[7] and the evolution of propylene from allyl 2,4,6-trialkylphenyl ether.[8] A related fact is that the ammono analog of phenyl allyl ether, namely, diallylaniline, pyrolyzes[9] into propylene and aniline instead of rearranging. Unusual interest attaches itself to the behavior of γ-ethylallyl phenyl ether because of its anomalous rearrangement[10] into *o*-(α-methylcrotyl)phenol:



The same substance was produced by the normal rearrangement of α-methylcrotyl phenyl ether. These two rearrangements were effected by heating in diethylaniline solution.

Since this reaction was not covered by any of the existing mechanisms, it seemed important to study it further. To start with, it was necessary to demonstrate the purity of the ether in question. If α-methylcrotyl phenyl ether were present in quantity in Lauer and Filbert's material it would remove the anomaly. These workers did prove that their material contained γ-ethylallyl phenyl ether because on oxidation it gave rise to a 28 per cent yield of phenoxyacetic acid (0.32 g. from 1.2 g.), but they did not demonstrate the absence of the isomeric α-methylcrotyl phenyl ether. Their ether was prepared from phenol by reaction with 1-chloro-2-pentene which in turn was synthesized from ethylvinylcarbinol and dry hydrogen chloride. 1-Chloro-2-pentene and 3-chloro-1-pentene were formed and were separated by distillation. A third isomer, 2-chloro-3-pentene, which would have produced α-methylcrotyl phenyl ether, was not mentioned. If the hydrogen chloride functioned as a dehydrating agent, its formation could be anticipated by these steps:

$$\begin{array}{l} CH_2{=}CH{-}CHOH{-}CH_2CH_3 \xrightarrow{-H_2O} CH_2{=}CH{-}CH{=}CHCH_3 \xrightarrow{HCl} \\ \qquad\qquad\qquad\qquad\qquad\qquad CH_3CH{=}CH{-}CHCl{-}CH_3 \end{array}$$

Some of this chloride was found in the present work, but in quantity insufficient to account for the bulk of the abnormality.

The pentenyl chlorides were synthesized according to Lauer and Fil-

[7] HURD AND COHEN, *J. Am. Chem. Soc.*, **53**, 1068 (1931).
[8] HURD AND YARNALL, *ibid.*, **59**, 1686 (1937).
[9] CARNAHAN AND HURD, *ibid.*, **52**, 4586 (1930).
[10] LAUER AND FILBERT, *ibid.*, **58**, 1388 (1936).

bert's directions. The following procedure was developed to analyze each fraction for the three possible chlorides:

$$CH_3CH_2CH{=}CHCH_2Cl\ (A), \quad CH_3CH_2CHClCH{=}CH_2\ (B), \quad \text{and} \quad CH_3CHClCH{=}CHCH_3\ (C)$$

Ozonization followed by hydrolytic oxidation with water and silver oxide would yield as volatile acids propionic, formic, and acetic respectively, from A, B, and C, which could be separated by steam distillation from the concurrently formed, non-volatile hydroxy acids (glycolic, α-hydroxybutyric, and lactic acids). The steps with A are illustrative:

$$A + O_3 \longrightarrow CH_3CH_2CH\underset{\diagdown\,O_3\,\diagup}{}CHCH_2Cl \xrightarrow[Ag_2O]{H_2O} CH_3CH_2COOH + HOCH_2COOH$$

ANALYSIS OF MIXTURE OF FORMIC, ACETIC, AND PROPIONIC ACIDS

The problem of analyzing the distillate, which contained a mixture of formic, acetic and propionic acids, was solved as follows. Formic acid was determined by oxidation with chromic acid.[11] Propionic and acetic acids, not touched by this reagent, were distilled off, and the aqueous distillate was analyzed by the Duclaux method.[12] These operations were practically quantitative.

Since the acetic acid represented C it was important to demonstrate its presence or absence even more conclusively. The method selected was based on the fact that propionic acid may be oxidized quantitatively to oxalate by hot alkaline permanganate,[13] whereas acetic acid is relatively unaffected. The latter was distilled off and identified by Duclaux values and by conversion to *p*-bromophenacyl acetate.

ANALYSIS OF THE PENTENYL CHLORIDES

Once the analytical method was established, the pentenyl halides (A and B) were synthesized. Lauer and Filbert's directions were followed closely. Analysis of the higher-boiling fraction, which had been assumed to be pure A, showed it to be 89 per cent A, 11 per cent B, with only a trace of C. Obviously, the anomalous rearrangement could not be traceable to C in the starting material.

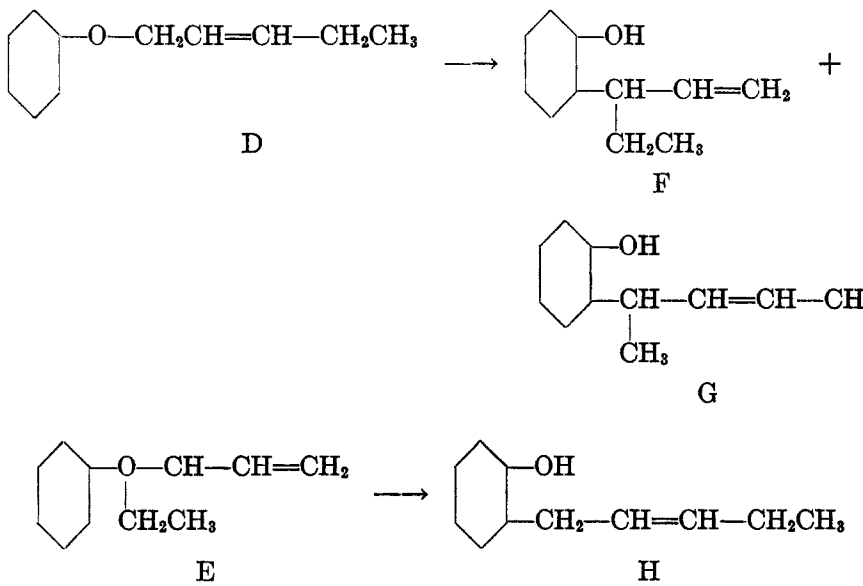
The lower-boiling fraction (assumed to be pure B) when analyzed similarly was found to contain 62 per cent B, 36 per cent A and 2 per cent C.

[11] MACNAIR, *Chem. News*, **55**, 229 (1887).
[12] VIRTANEN AND PULKKI, *J. Am. Chem. Soc.*, **50**, 3138 (1928).
[13] MCNAIR, *J. Am. Chem. Soc.*, **54**, 3249 (1932).

The presence of 2 per cent of C indicates that a slight dehydration occurred as pictured. The considerable quantity of A explains the isolation by Lauer and Filbert of a sizeable yield of γ-ethylallyl phenyl ether in the reaction of this chloride with phenol.

The anomalous rearrangement.—The higher-boiling chloropentene fraction (89 per cent A, 11 per cent B), on condensation with phenol, gave rise to a mixture of pentenyl phenyl ethers which was shown by ozonolysis to consist of 90 per cent of γ-ethylallyl phenyl ether (D), and 10 per cent of α-ethylallyl phenyl ether (E).

The rearrangement product obtained by heating this mixture of ethers was found to contain 56 per cent of *o*-(α-ethylallyl)phenol (F) from the normal "gamma" rearrangement, 42 per cent of the isomer, *o*-(α,γ-dimethylallyl)phenol (G) from the abnormal rearrangement, and a small amount of *o*-(γ-ethylallyl)phenol (H) from E.



D F G E H

In an independent check run, a pentenyl phenyl ether mixture (87 per cent D, 13 per cent E), gave rise to phenols in approximately the same proportions (59 per cent of F, 35 per cent of G, and 6 per cent of H).

It should be noted that Lauer and Filbert also obtained evidence for the normal rearrangement of D, but failed to recognize it as such. The formaldehyde observed by them among the ozonolysis products of their methylated rearrangement material undoubtedly arose from some *o*-(α-ethylallyl)-anisole, but was attributed instead to "deep-seated changes."

γ-ETHYLALLYL VINYL ETHER

Since the rearrangements of vinyl allyl ethers were found to proceed smoothly on heating,[2] it seemed desirable to investigate the behavior of vinyl γ-ethylallyl ether in order to determine whether the normal or abnormal type of rearrangement would occur.

The pentenyl bromide used in the synthesis of vinyl γ-ethylallyl ether was a mixture of 1-bromo-2-pentene (81.5 per cent) and 3-bromo-1-pentene (18.5 per cent) as determined by the ozone method of analysis. It was condensed with sodium glycolate to form the β-hydroxyethyl pentenyl ether. The latter was converted into the β-bromo ether with phosphorus tribromide, after which the elements of hydrogen bromide were detached with powdered alkali:

$$HOCH_2CH_2ONa \xrightarrow{C_5H_9Br} HOCH_2CH_2OC_5H_9 \xrightarrow{PBr_3}$$

$$BrCH_2CH_2OC_5H_9 \xrightarrow{KOH} CH_2{=}CH{-}O{-}C_5H_9$$

It was assumed that the ratio of isomeric products remained unaltered during these steps and that the ether obtained was a mixture of the two isomers: $CH_2{=}CH{-}O{-}CH_2CH{=}CHC_2H_5$ (J) and $CH_2{=}CH{-}O{-}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}{-}CH{=}CH_2$ (K), in the ratio of 81.5:18.5. This ether was found to hydrolyze readily into acetaldehyde and pentenyl alcohol:

$$CH_2{=}CH{-}O{-}C_5H_9 + H_2O \xrightarrow{acid} CH_3CHO + C_5H_9OH$$

The thermal stability of this ether was about the same as that of vinyl allyl ether. Short heating of the vapors at 255° produced a 35 per cent conversion into heptenaldehyde. Practically complete conversion was effected by heating in a sealed tube at 220°. Ozonolysis of the unsaturated aldehyde yielded a mixture of formic, propionic and acetic acids in molar ratios, respectively, of 76.5:18.9:4.6. This indicated that the aldehyde was a mixture of 76.5 parts of 3-ethyl-4-pentenal (L), 18.9 parts of 4-heptenal (M), and 4.6 parts of 3-methyl-4-hexenal (N). The normal rearrangement of K is to M:

$$CH_2{=}CH{-}O{-}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}{-}CH{=}CH_2 \longrightarrow C_2H_5CH{=}CHCH_2CH_2CHO$$

The fact that an 18.5 per cent mixture of K gave rise to a mixture containing 18.9 per cent of M is evidence that this reaction occurred.

The normal rearrangement of J is to L:

$$CH_2{=}CH{-}O{-}CH_2CH{=}CHC_2H_5 \longrightarrow CH_2{=}CH{-}\underset{\displaystyle C_2H_5}{\underset{|}{CH}}{-}CH_2CHO$$

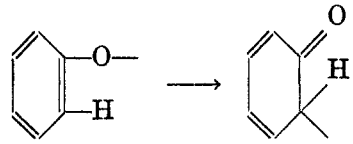
but J is the ether from which abnormal rearrangement to N might occur:

$$CH_2{=}CH{-}O{-}CH_2CH{=}CHCH_2CH_3 \rightarrow CH_3CH{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_2CHO$$

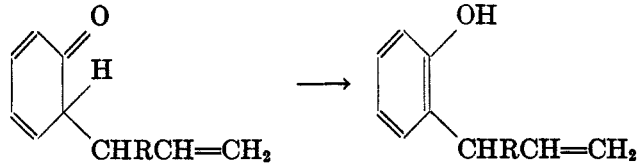
Both of these effects occurred but the chief effect was the former (76.5 per cent of L and 4.6 per cent of N from 81.5 per cent of J). Thus, the abnormal effect which was so prominent in the case of phenyl γ-ethylallyl ether resulted also with vinyl γ-ethylallyl ether but to a much lesser extent.

PREVIOUS MECHANISMS

From a consideration of the facts at his disposal, chief of which were the inversion of the allyl group and the impossibility of considering chromanes as intermediates, Claisen[3b] suggested that increase of temperature loosened and finally broke the bond between the allyl group and the oxygen atom. The phenoxy radical was then assumed to resonate to a keto modification:



The new bond on the ortho carbon then seized the γ-carbon atom of the allyl group, since that atom was considered to be nearest it in space, after which tautomerization to the phenol occurred:



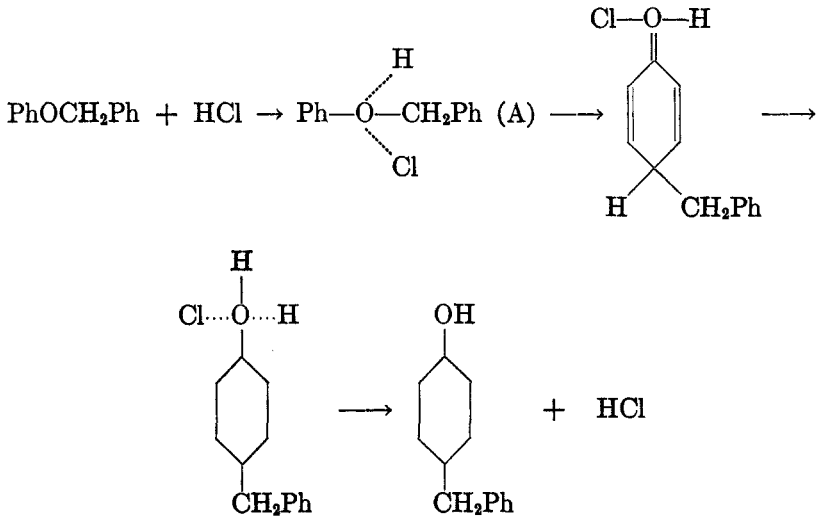
This mechanism carries the unjustifiable assumption that radicals retain their positions after formation. Since the γ-C of the radical need not necessarily be the "nearest atom," this becomes an inadequate explanation of the inversion of the allyl group. Hurd and Cohen[14] pointed out that if scission into radicals were the first step, inversion might be ex-

[14] HURD AND COHEN, *J. Am. Chem. Soc.*, **53**, 1917 (1931).

plained by assuming resonance of both the phenoxy and the allyl radicals, followed by recombination of the two new radicals.

One objection to radicals as intermediates is the relatively low reaction temperature. Another objection, made by Niederl,[15] is the absence of by-products, reference being made to the absence of such a compound as phenyl peroxide, PhOOPh, in the reaction products (from combination of two PhO radicals).

Niederl proposed a mechanism, based on the oxonium mechanism proposed by van Alphen[16] to explain the catalytic effect of hydrogen chloride in bringing about the rearrangement of benzyl phenyl ether into *p*-benzylphenol.



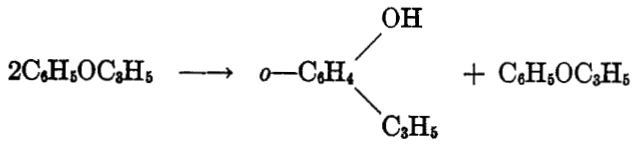
Structure A must be polar, namely, $(Ph—\underset{\underset{H}{|}}{\overset{\cdot\cdot}{O}}—CH_2Ph)^+ \; :\ddot{Cl}:^-$ and the other oxonium formulas must be regarded similarly.

In extending this mechanism to allyl phenyl ether where heat alone effects the rearrangement, Niederl assumed "the formation of oxonium compounds between identical molecules, then the succeeding transitory bimolecular addition compounds of the quinhydrone type may be formed

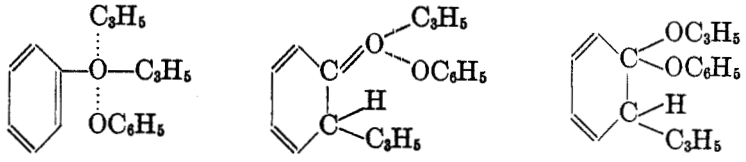
[15] NIEDERL AND NATELSON, *ibid.*, **54**, 1067 (1932); NIEDERL AND STORCH, *ibid.*, **55**, 288 (1933).

[16] VAN ALPHEN, *Rec. trav. chim.*, **46**, 799 (1927).

and finally the substituted phenol is obtained." This would be summarized in the equation:

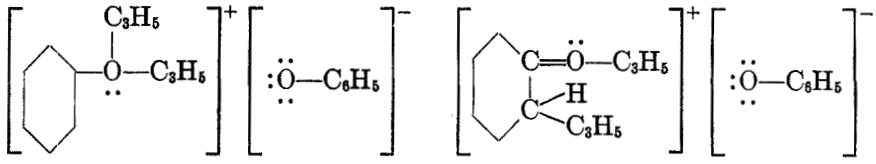


with I, II and III as intermediate steps.



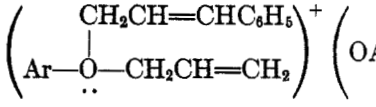
I II III

In terms of electron theory, the structures for I and II must be ionic, *i.e.*, IV and V respectively.



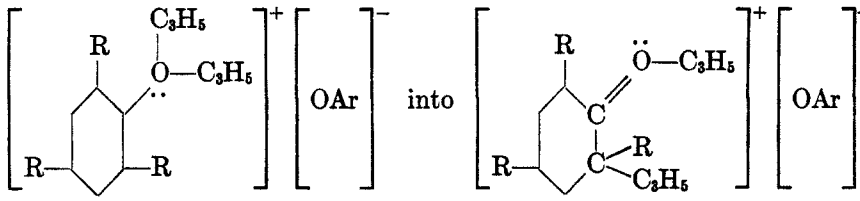
IV V

There are several serious objections to this hypothesis. (1) It ignores the actual process of rearrangement, the mechanism of the change of I into II. (2) It does not explain the inversion of the wandering radical. (3) If phenyl allyl ethers depend on oxonium structures to bring about rearrangement, then any phenyl alkyl ether should do the same because oxonium formation should be general for ethers rather than specific for the allyl ethers. (4) If V is an intermediate, part of it at least should decompose to yield allyl *o*-allylphenyl ether, *o*-$C_3H_5C_6H_4$—O—C_3H_5, which has not been observed. (5) A mixture of aryl allyl ether and aryl cinnamyl ether should give rise to a mixed addition product



but if so the allyl and the cinnamyl groups should compete for the privilege of rearrangement. The evidence[3a] reveals no such competition. (6)

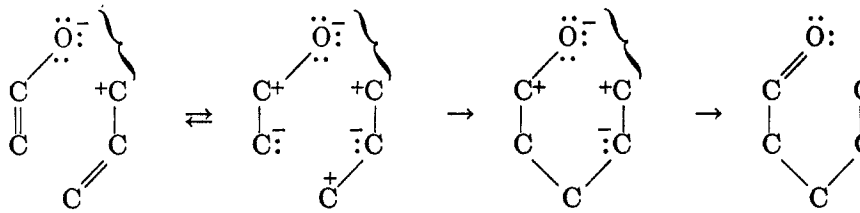
Allyl 2,4,6-trialkylphenyl ether should be able to rearrange, because the step from I to II (or IV to V) is not inhibited, *i.e.*,



This is not what occurs.[8]

PROPOSED MECHANISM

It may be assumed that the initial effect of heat on the system C=C—O—C—C=C is to alter the position of the pair of electrons which bind the allyl group to the oxygen so that a semi-ionization occurs, such as C=C—O—C—C=C. Actual separation into ions does not occur, but the semi-ionization promotes other ionic disturbances at the double bonds. This effect, combined with the spatial proximity of the atoms at the end of the systems, brings about temporary ring closure and readjustment of electrons as shown in the following sequence of steps.



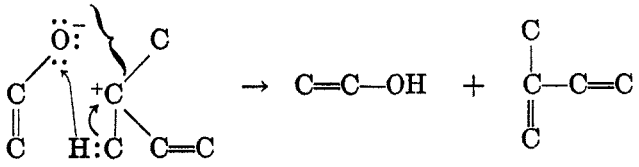
(or its enol)

It should be emphasized that the unstable, cyclic intermediate is not a chromane.

This mechanism provides an explanation for the intramolecular nature of the reaction and for the inversion of the "wandering" radical. The semi-ionic, positive carbon seeks to satisfy its electron deficiency by appropriating electrons from the neighboring double bond. This process is reversible but the next step which involves cyclization is irreversible.

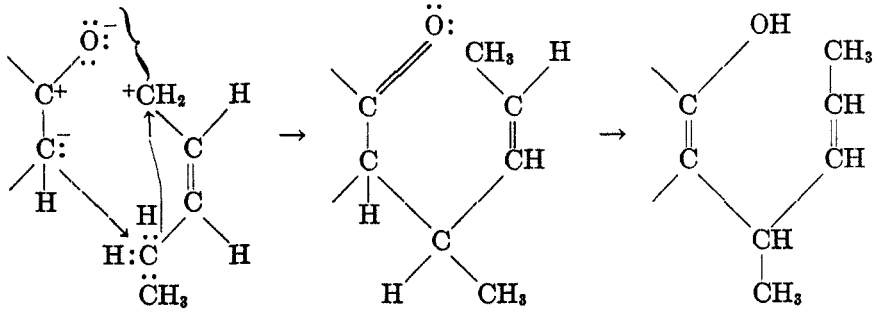
To obtain cyclization calls for free rotation of the bonds. This condition is met in the simple cases. If, however, it be assumed that there

is restricted rotation with α,α-dialkylallyl aryl ether then a satisfactory picture for its scission into a diene and phenol may be constructed. In the following formulation it shows that the positive α-C of the allyl group may satisfy its electron deficiency not only by appropriating electrons



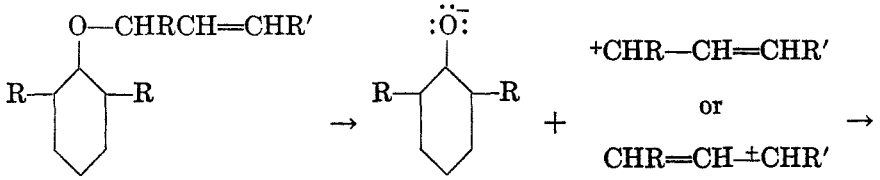
from the neighboring double bond (reversible) but also from a neighboring C—H bond (irreversible), the released proton being attracted to the oxygen. This gives rise to phenol and a diene.

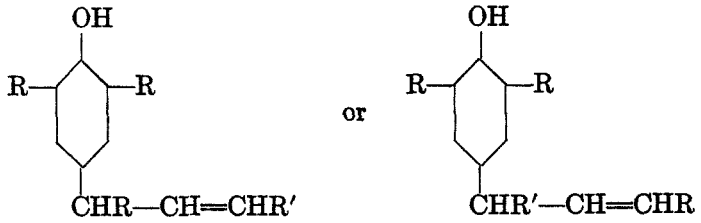
γ-Ethylallyl phenyl ether is capable of existing in *cis* and *trans* modifications. The *trans* form, and to a certain extent the *cis* form as well, should rearrange normally to *o*-(α-ethylallyl)phenol by the mechanism developed for simple allyl ethers. With the *cis* form, however, a consideration of space models shows that the δ-C of $\overset{o}{C}{=}C{-}O{-}\overset{\alpha}{C}{-}\overset{\beta}{C}{=}\overset{\gamma}{C}{-}\overset{\delta}{C}{-}\overset{\epsilon}{C}$ may be in the vicinity of the *o*-C. Under these circumstances, the combined attractions of the positive α-C for the δ-H with its electrons, and the negative *o*-C for the positive δ-C may be sufficient to bring about the abnormal rearrangement which has been observed. It is important to note that the δ-C is "allylic" and, therefore, inherits a tendency to lose an electron pair.



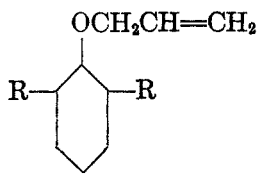
Para rearrangements.—Two mechanisms suggest themselves for rearrangements which are forced to the para position. Present evidence is not sufficient to decide between them, but both lend themselves to experi-

ment. One possibility is that of complete ionization. The other is a modification of the above-described, semi-ionic cyclization. In the former, namely,

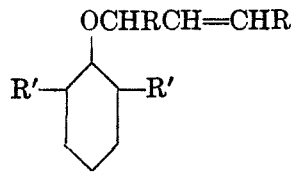




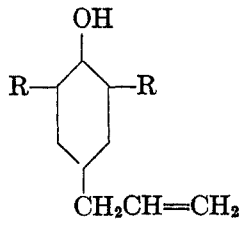
it is apparent that inversion of the wandering radical may or may not occur. Also, it is evident that by heating a mixture of VI and VII there should be formed both VIII and IX from VI, and the equivalent pair from VII.



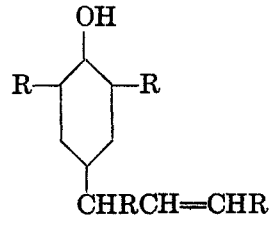
VI



VII

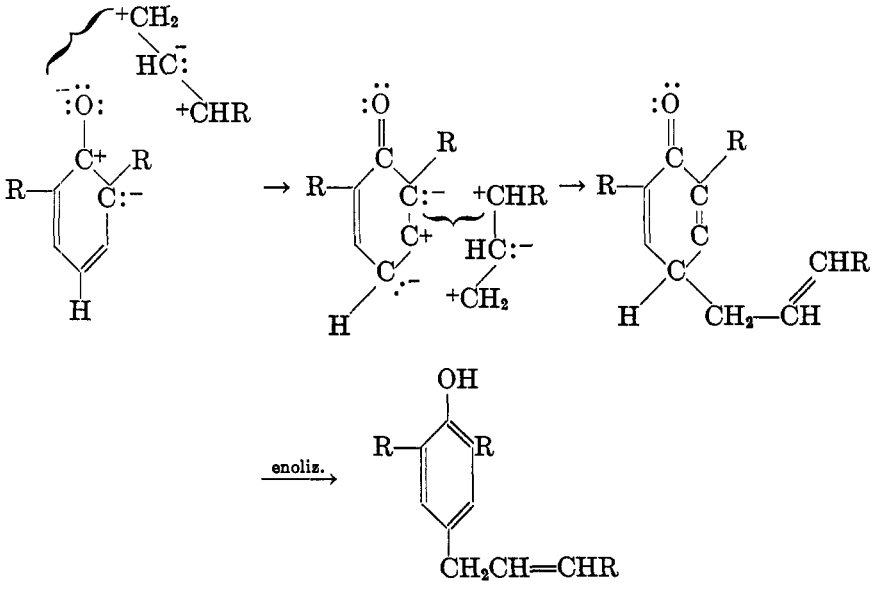


VIII



IX

The following steps are visualized in the semi-ionic mechanism.



The first step is rearrangement with inversion to the ortho position by way of semi-ionic linkages, to be followed by another semi-ionic cyclization and final enolization. The double inversion demanded by this mechanism gives the final effect of no inversion. In the ethers of this type which have been tested, it will be recalled that inversion did not occur.[4] Also, the mechanism would not permit of intermolecular interchange by heating such a mixture as VI and VII.

It would seem reasonable to believe that the mechanism involving complete ionization is involved in the thermal rearrangement of *tert.*-butyl phenyl ether[17] into *p-tert.*-butylphenol, or of phenyl $\alpha,\alpha,\gamma,\gamma$-tetramethylbutyl ether[18] into *o*-($\alpha,\alpha,\gamma,\gamma$-tetramethylbutyl)phenol, or of benzyl phenyl ether[19] at 250° into a mixture of *o*- and *p*-benzylphenol. It is characteristic that one of the groups of these thermolabile ethers is related to allyl, benzyl, or *tert.*-alkyl which are known to be of a low order of electron attraction.

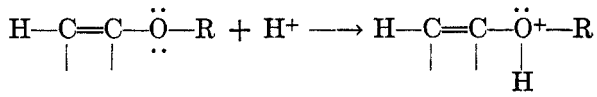
α-Methylvinyl phenyl ether is typical of the ethers for which Niederl's oxonium mechanism[15] was devised. Essentially, the medium is acidic

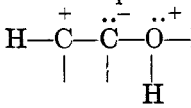
[17] SMITH, *J. Am. Chem. Soc.*, **55**, 3718 (1933).

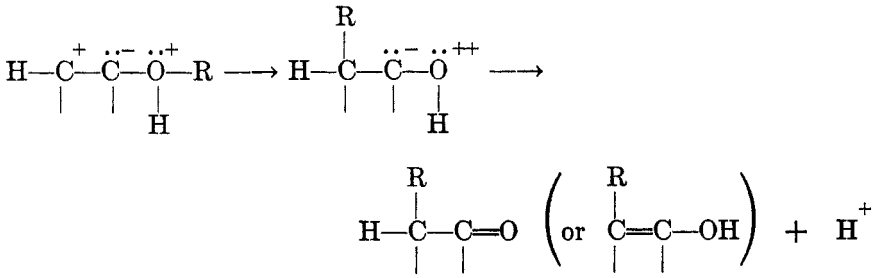
[18] NIEDERL, NATELSON, AND BEECKMAN, *ibid.*, **55**, 2571 (1933); NATELSON, *ibid.*, **56**, 1583 (1934).

[19] BEHAGHEL AND FREIENSEHNER, *Ber.*, **67**, 1368 (1934).

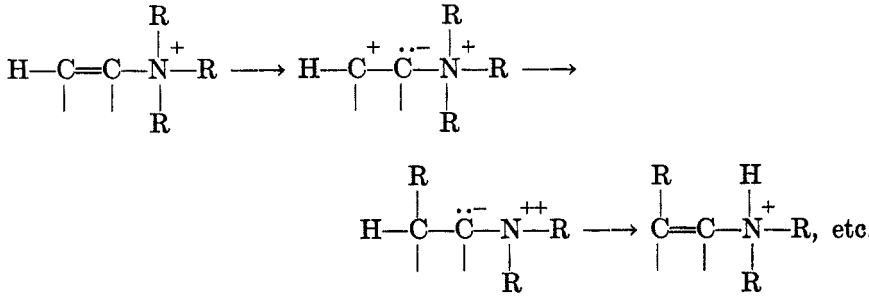
(sulfuric acid, or boron trifluoride, or similar reagents), and addition yielding an oxonium salt is the first step:



It seems plausible that the next step is resonance at the double bond to  following which the C^+ (sextet) may attract either the R or the H from the oxygen. The latter would be reversible and not noticed, but the former would be an irreversible rearrangement.



This modification of Niederl's mechanism explains not only the rearrangements of aryl alkyl ethers to alkylphenols by BF_3 or $AlCl_3$ or $CH_3COOH—H_2SO_4$ but also, by extension to the "ammonia system," explains the Hofmann rearrangement of substituted aniline salts:



The acidic nature of these reactions, with ions involved necessarily, is another supporting factor in the belief that ions are involved in this type of rearrangement.

EXPERIMENTAL

Estimation of Mixtures of Volatile Acids

Quantitative determination.—Chromic acid was used to oxidize formic acid from the mixture of formic, acetic, and propionic acids. Macnair's[20] chromic acid solution (distilled water, 100 cc.; potassium dichromate, 12 g.; concentrated sulfuric acid, 30 cc.) was used. It was found that volatile acids could be distilled quantitatively from such a solution, or from one containing considerable sodium sulfate. In such cases, it was necessary to distil slowly until crystals began to separate.

Definite volumes of 0.1*N* solutions of formic, acetic, and propionic acids were mixed and refluxed for twenty minutes with an equal volume of the chromic acid solution. Then the solution was distilled, and the distillate was adjusted to a total volume of 110 cc. for Duclaux analysis:[21] Run 1: Ten cc. required 5.45 cc. of 0.0994*N* sodium hydroxide for neutralization, and the first 30 cc. of distillate required 14.95 cc. of the alkali. Run 2: Ten cc. required 4.22 cc. of 0.0994*N* alkali, and the first 30 cc.

TABLE I

ANALYSIS OF MIXTURE OF ACIDS

RUN	ACID	NORMALITY	VOL. TAKEN, CC.	VOL. FOUND, CC.	ERROR
1	Formic	0.118	13.0	14.5	1.5
	Acetic	0.117	30.5	30.0	−0.5
	Propionic	0.114	22.5	21.5	−1.0
2	Formic	0.118	19.7	20.1	0.4
	Acetic	0.117	22.1	22.0	−0.1
	Propionic	0.114	18.2	17.9	−0.3

of distillate required 11.76 cc. of this alkali. In run 1, since the acidity of the original mixture was 0.00767 equiv., and that of the distillate from the oxidation was 0.00596 equiv., the formic acid content was found by difference. The data and findings are assembled in Table I.

Isolation of acetic acid.—In the following oxidation by permanganate both formic and propionic acids were affected. The propionic acid[22] was oxidized quantitatively to an oxalate.

To a mixture of 9.2 cc. of 0.118*N* formic acid 9.6 cc. of 0.117*N* acetic acid and 8.9 cc. of 0.114*N* propionic acid was added 16 cc. of a 25% sodium hydroxide solution and 60 cc. of a 3% potassium permanganate solution. The 250-cc. Erlenmeyer container was capped with a small glass beaker and the whole was heated on the steam bath for six hours. After cooling, 32 cc. of a 1:2 sulfuric acid solution was added slowly and the resulting solution was distilled. The distillate was made up to 110 cc. The Duclaux values found on this material were 7.0, 7.0, 7.4, which indicated acetic acid only. The 110 cc. of distillate contained 80% of the original acetic acid. In another run, lactic acid (1.2 g.) and anhydrous sodium sulfate (10 g.) were added to a mixture

[20] MACNAIR, *Chem. News*, **55**, 229 (1887).

[21] VIRTANEN AND PULKKI, *J. Am. Chem. Soc.*, **50**, 3138 (1928).

[22] MCNAIR, *ibid.*, **54**, 3249 (1932).

of 12.0 cc. of 0.118*N* formic acid, 24.6 cc. of 0.117*N* acetic acid, 18.9 cc. of 0.114*N* propionic acid and the resulting solution was distilled. To the distillate, now containing only formic, acetic and propionic acids, was added 12 g. of anhydrous potassium carbonate and 45 cc. of a 6.7% potassium permanganate solution (prepared and added while hot). The whole was heated as above for six hours on the steam bath. Thirty-two cc. of a 1:2 sulfuric acid solution was used to acidify and the acid solution was distilled. This distillate was refluxed for a short time to eliminate any dissolved carbon dioxide, cooled and made up to 110 cc. Duclaux values, 6.9, 7.2, 7.6, again indicated only acetic acid.

After neutralization of the distillate in the Duclaux determination, the solutions were evaporated to dryness. Treatment of the resulting sodium salt with *p*-bromophenacyl bromide yielded *p*-bromophenacyl acetate, m.p. 85°.

The Pentenyl Halides

Ethylvinylcarbinol and hydrogen chloride.—Ethylvinylcarbinol[23] was prepared from acrolein and ethylmagnesium bromide, was freshly distilled (b.p. 111–113.5°) and treated with dry hydrogen chloride according to Lauer and Filbert's directions.[10] The weight of carbinol taken was 33.7 g. and the total gain in weight was 20.7 g. It was twice fractionally distilled through a 33-cm. Widmer column, constant pressure being maintained by use of the Munch pressure regulator.[24] These fractions were collected, all at 149 mm.: (1) b.p. 42–45.5°, 1.7 g.; (2) 45.5–51°, 9.1 g.; (3) 51–59.5°, 3.0 g.; (4) 59.5–62°, 6.2 g.; (5) 62–62.5°, 5.7 g.; residue, 1.7 g.

Fractions 4 and 5 should be pure 1-chloro-2-pentene, and fraction 2 has been regarded as pure 3-chloro-1-pentene. It was not found possible to limit the boiling range of fraction 2 to less than five degrees although Lauer and Filbert reported a 0.2° range. Refluxing under atmospheric pressure for one hour produced no observable change in composition. All the material distilled at 43–48° (147 mm.). From the work of Winstein and Young[25] it would be expected that either of the allylic isomers would rearrange into an equilibrium mixture if heated briefly at atmospheric pressure. Since the boiling range of fraction 2 did not change appreciably on refluxing, its composition probably approximated that of the equilibrium mixture.

Ethylvinylcarbinol and hydrobromic acid.—To a mixture of 272 g. of 48% hydrobromic acid and 80 g. of concentrated sulfuric acid was added slowly with stirring, 94 g. of ethylvinylcarbinol. The mixture was stirred at 20–25° for twenty-four hours; the upper layer was separated, washed thrice with water, and dried over sodium sulfate. It was twice vacuum-distilled through an efficient column.

FRACTION	B.P., °C.	PRESSURE, MM.	WT., G.	n_D^{20}
1	23–30	20	9.5	1.4654
2	30–34	20–19	118.2	1.4769

Structure of the Pentenyl Halides

Pentenyl chloride, fraction 5.—An excess of a 5% ozone-in-oxygen stream was passed through an ice-cold solution of 100 cc. of dry carbon tetrachloride and 1.4 g.

[23] HURD AND MCNAMEE, *ibid.*, **59**, 104 (1937).
[24] MUNCH, *J. Chem. Educ.*, **9**, 1275 (1932).
[25] WINSTEIN AND YOUNG, *J. Am. Chem. Soc.*, **58**, 104, (1936).

of pentenyl chloride, fraction 5 (b.p. 62–62.5° at 149 mm.). Then the ozonide was hydrolyzed by refluxing one hour with 100 cc. of pure water, distilling off the carbon tetrachloride, refluxing another thirty minutes, and then refluxing for four hours in the presence of freshly-prepared silver oxide. It was cooled, filtered, the alkaline filtrate was evaporated to half-volume, and acidified with phosphoric acid. Then 2 g. of anhydrous sodium sulfate was added, the volatile acids were distilled off, and the distillate was divided into two equal parts of 30.5 cc. each.

Titration of one part showed it to contain 0.00405 equivalent of acid. After refluxing with chromic acid mixture and distillation, 0.00362 equivalent of volatile acid remained. From this, 0.00043 equivalent of formic acid was oxidized away. Duclaux values (11.9, 11.6, 11.1) on the distillate indicated practically pure propionic acid.

The other part was refluxed for six hours with the alkaline permanganate solution, acidified, and distilled. The Duclaux values (8.2, 8.4, 7.9) indicated slightly impure acetic acid. This acid was neutralized; the sodium salt solution was evaporated to dryness and treated with *p*-bromophenacyl bromide. The ester thus produced, after three recrystallizations from alcohol, melted at 77–79°. When mixed with authentic *p*-bromophenyl acetate, m.p. 85°, the m.p. was 82–84°.

The three acids were present in these amounts: propionic 89%, formic 11%, and a trace of acetic acid.

Pentenyl chloride, fraction 2.—A part of this fraction (1.85 g., b.p. 43–48° at 147 mm.) was subjected to ozonolysis as described above. There was 0.00630 equivalent of total volatile acids. The formic acid content, determined by the chromic acid method, was 0.00393 equivalent. The unoxidized volatile acids, made up to 110 cc. for Duclaux titrations with 0.0314*N* acid, gave these data: 10 cc. of the 110 cc. required 6.86 cc. of alkali; the first three 10-cc. portions of distillate required 7.96, 7.92, 7.53 cc. of the alkali. Duclaux values: 11.6, 11.5, 11.0. The 30% distillation values indicated the presence of 0.00224 equivalent of propionic acid and 0.00013 equivalent of acetic acid. The percentage of acids present in the original distillate, therefore, was formic 62.3, acetic 2.1, and propionic 35.6.

Pentenyl bromide, fraction 2.—One gram of the higher-boiling fraction (b.p. 30–34° at 20–19 mm.) was subjected to the same technique of ozonolysis. The volatile acids produced were diluted to 110 cc., of which 10 cc. required 14.43 cc. of 0.0314*N* sodium hydroxide. The first three 10-cc. portions of distillate from the remaining 100 cc. required successively 15.12, 14.94, 14.44 cc. of the alkali. Duclaux values: 10.5, 10.3, 10.0. By calculation, these data show 18.5% formic acid (0.00092 equiv.) and 81.5% propionic acid (0.00406 equiv.).

The portions of volatile acids were combined, neutralized, evaporated to 30 cc., and oxidized by the chromic acid procedure. The volatile acid which remained after this treatment was practically pure propionic acid, judged by the Duclaux values of 12.0, 11.7, 11.3 which were obtained. Pure propionic acid gives 11.9, 11.7, 11.3.

γ-Ethylallyl Phenyl Ether

Preparation from pentenyl chloride (89% 1-chloro-2-pentene).—Lauer and Filbert's directions[10] were followed exactly with one-third quantities. A 61% yield was collected at 123–125° (25 mm.). This ether will be referred to as X.

Preparation from pentenyl bromide (82% 1-bromo-2-pentene).—The same general directions of synthesis were followed. The sample investigated had these properties: b.p. 109–110° (17 mm.), n_D^{20} 1.5176, d_D^{24} 0.975, M.R. (found) 50.39, M.R. (calc'd) 59.57. This ether will be referred to as XI.

Ozonolysis.—Essentially the same technic of ozonization, hydrolysis and oxidation with silver oxide as that described earlier was applied to 0.7 g. of X and to 1.0 g. of XI. From the former, phenoxyacetic acid, m.p. and mixture m.p. 98–99°, was isolated from the residue after distilling off the aliphatic acids. The distillate was redistilled from 5 g. of anhydrous sodium sulfate. Titration revealed 0.00256 equivalent (or 60% yield) of volatile acids. The total quantity was refluxed for half an hour with Macnair's chromic acid mixture; the remaining volatile acids were distilled and redistilled from sodium sulfate. There was 0.00230 equivalent of acid: Duclaux values 11.9, 11.9, 11.2. It was, therefore, practically pure propionic acid. The formic acid lost by oxidation was 0.00026 equivalent. Formic and propionic acids were present in the ratio 10:90.

From XI there was obtained 0.00498 equivalent (81% yield) of total volatile acid, shown by Duclaux analysis to be 86.9% propionic and 13.1% formic from the following data. When the acid was made up to 110 cc., 10 cc. required 14.71 cc. of 0.0308*N* sodium hydroxide and the first three 10-cc. portions of distillate (of the remaining 100 cc.) required 16.07, 15.91, 15.09 cc., from which 10.9, 10.7, 10.3 are the Duclaux values. After the chromic acid treatment the Duclaux values were 11.9, 11.9, 11.6 indicating practically pure propionic acid.

Pyrolysis.—The rearrangement of 4.1 g. of X (in nitrogen atmosphere) or 4.0 g. of XI (in carbon dioxide atmosphere) was carried out after the directions of Lauer and Filbert by heating with 2.1 g. of diethylaniline. These investigators extracted the pentenylphenol from ether solution with 20% sodium hydroxide solution but we obtained much more effective extraction with 4% solution. The pentenylphenol prepared from X was collected at 72–74° (1 mm.); n_D^{20} 1.5337; d_4^{20} 0.990; M.R. 50.86 (calc'd 50.46). That from XI was collected in 55% yield at 122° (20 mm.); n_D^{24} 1.5320.

Ozonolysis of the pentenylphenol.—The pentenylphenols from both X and XI were ozonized, 0.8 g. in 80 cc. of dry carbon tetrachloride at 0° being used with an excess of ozone in each case. After hydrolysis of the ozonide and oxidation by silver oxide, the volatile acids were prepared for Duclaux analysis by distillation and redistillation from sodium sulfate. Total acid in distillate: 0.00395 equivalent, or 80% yield, from X, and 0.00338 equivalent, or 69% yield, from XI. Duclaux analysis of acid from X: 5.3, 5.5, 5.8, 6.0, 6.3; that from XI was 5.2, 5.8, 6.2. These results indicated formic acid, mixed with others. The total acid of each was neutralized, concentrated to 60 cc., the formic acid was removed by refluxing with an equal volume of chromic acid mixture. The distillate of the remaining volatile acids was made up to 110 cc. and analyzed. Ten cubic centimeters of the solution from X required 5.06 cc. of 0.0314*N* alkali. The first three 10-cc. distillates required 3.58, 3.69, 3.91 cc. from which Duclaux values of 7.1, 7.3, 7.7 are obtained. Ten cubic centimeters of the solution from XI required 4.03 cc. of 0.0308*N* alkali. The first three 10-cc. distillates required 3.01, 3.13, 3.18 cc. from which follow the Duclaux values of 7.5, 7.8, 7.9.

The data from X point to the presence of 0.00165 equivalent of acetic acid and 0.00010 equivalent of propionic acid. The formic acid oxidized was 0.00220 equivalent. Therefore, formic, acetic and propionic acids existed in the relative amounts of 55.7, 41.8, 2.5.

The data from XI show 0.00118 equivalent of acetic acid, 0.00019 equivalent of propionic acid. The formic acid lost by oxidation was 0.00201 equivalent. Hence, formic, acetic, and propionic acids were in the proportions: 59.4, 35.0, 5.6.

The sodium salt from the Duclaux determinations was treated with *p*-bromophenacyl bromide. The ester obtained melted at 78–80°. The melting point of a mixture with authentic *p*-bromophenacyl acetate (m.p. 85°) was 82–84°.

γ-Ethylallyl Vinyl Ether

β-Hydroxyethyl γ-ethylallyl ether.—Twenty grams of sodium in small pieces was added slowly to 145 g. of redistilled ethylene glycol, with gentle heating on the steam bath. When the reaction was over, 117 g. of "1-bromo-2-pentene" (18.5% of 3-bromo-1-pentene) was added slowly with constant stirring and gentle heating on the steam bath. After the addition, the heating and stirring were continued for two hours, and the reaction mixture then allowed to stand for four hours. After removal of the sodium bromide by filtration, the filtrate was distilled under reduced pressure. Since refractionation did not suffice for the complete separation of the hydroxy ether and ethylene glycol, advantage was taken of the relative solubilities of the two in ether and water.

All of the material was shaken with 400 cc. of water and 100 cc. of ether. The ether layer was extracted with 100 cc. of water. The combined aqueous solutions were then extracted three times with ether; the ether portions were combined and dried over anhydrous sodium sulfate. After filtration, and distillation of the ether on the steam bath, the residue was distilled and refractionated through a good column. The yield of this ether (crude) was 72.5 g. (71%). The pure β-hydroxyethyl γ-ethylallyl ether (45.3 g. or 44.3% yield) was collected at 85–87° (13 mm.): n_D^{20}, 1.4452; d_4^{20}, 0.925; M.R. (found), 37.48; M.R. (calc'd), 37.23.

Anal. Calc'd for $C_7H_{14}O_2$: C, 64.57; H, 10.84.
Found: C, 64.67; H, 10.85.

β-Bromoethyl γ-ethylallyl ether.—A mixture of 43.5 g. of pure β-hydroxyethyl γ-ethylallyl ether and 5.9 g. of dry pyridine was added slowly to 36.2 g. of phosphorus tribromide in a fractionating flask at 0°. After thirty minutes the crude bromoether was distilled under reduced pressure. The distillate was washed twice with dilute sodium hydroxide, twice with dilute sulfuric acid, then once with water, and was dried over anhydrous sodium sulfate. After filtration, the pure bromide was obtained by distillation through a 55-cm. electrically-heated Vigreux column with partial condensation head. The yield was 18.4 g. or 28.5%. In other runs, the yield was comparable. Physical constants of β-bromoethyl γ-ethylallyl ether: b.p., 79° at 11 mm.; $n_D^{20} = 1.4705$; $d_4^{20} = 1.234$; M.R. (found) = 43.69; M.R. (calc'd) = 43.47.

Anal. Calc'd for $C_7H_{13}BrO$: Br, 41.39. Found: Br, 41.51.

Since the original pentenyl bromide was a mixture, and all of the intermediate product was used in these runs, the substance here obtained is undoubtedly a mixture of the γ- and the α-ethylallyl β-bromoethers (approximately in the ratio of 80:20).

γ-Ethylallyl vinyl ether.—Into a 50-cc. distilling flask was placed 23.2 g. of the bromoethyl pentenyl ether. Nineteen grams of finely-powdered, technical potassium hydroxide was then added, whereupon an exothermic reaction ensued. The mixture was heated slowly by an oil bath kept at 160–170°. A small amount of material distilled over during the first hour, after which the bath temperature was lowered, and 5 g. more of potassium hydroxide was added. Further heating to 170–174° for one and one-half hours caused only a few more drops of material to come over. Very slight suction was used to assist in the distillation for a small part of the time.

The distillate consisted of two layers; an upper one, weighing 4 g., and a small amount of water. Upon taking up the residue in the flask with water, 6 g. of a dark-brown oil separated, which was mainly unchanged ether.

The water-insoluble distillate was distilled through the 55 cm. Vigreux column to obtain fractions 1 and 2, but fraction 3 was distilled through a short Vigreux column:

FRACTION	B.P., °C.	PRESSURE	WT., G.	n_D^{20}	d_4^{20}
1	94.5–97	Atmos.	0.3		
2	97–101	Atmos.	1.2	1.4317	0.813
3	39–40	15 mm.	0.6	1.4307	0.856
Residue			0.7		

The highest temperature reached by the bath during the distillation was 190°. Fraction 2 was the desired γ-ethylallyl vinyl ether: M.R. (found), 35.77; M.R. (calc'd), 35.24.

Anal. Calc'd for $C_7H_{12}O$: C, 74.93; H, 10.78.
Found: C, 74.24; H, 10.77.

Fraction 3 appears to be the heptenaldehyde rearrangement product of the vinyl ether: M.R. (found), 33.92; M.R. (calc'd), 34.07. That it was somewhat impure was indicated by carbon and hydrogen analyses, wherein the carbon values found were 1.7–2.1% low. The 2,4-dinitrophenylhydrazone of this material melted, after recrystallization, at 94°.

Acid hydrolysis of γ-ethylallyl vinyl ether.—One drop of this ether was dissolved in 5 cc. of alcohol, to which was added 5 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in alcohol and a few drops of hydrochloric acid. The mixture was heated to boiling, and water was added to incipient cloudiness. After two crystallizations from dilute alcohol, the yellow powder melted at 140–145°. Further recrystallization lowered the melting point to 129–131°, where it remained fairly constant. That this was impure acetaldehyde 2,4-dinitrophenylhydrazone, contaminated with some more insoluble impurity, was indicated by the fact that a mixture of this material with authentic acetaldehyde derivative (m.p. 165–166°) melted at 146–149°.

Pyrolysis of γ-ethylallyl vinyl ether.—The apparatus used in previous cases,[26] in which the vapors of the ether were passed through a tube heated to 255°, was employed. One and three-tenths grams of γ-ethylallyl vinyl ether was distilled through the tube during a period of twenty minutes. One gram of material with the constants $n_D^{20} = 1.4307$ and $d_4^{20} = 0.826$ was recovered.

This material was then heated slowly to 220° in a sealed tube and kept at that temperature for eight minutes. Upon cooling, it was observed that only an extremely faint yellow tint had been developed. The constants of this resulting material, which had an odor strongly resembling that of allylacetaldehyde were $n_D^{20} = 1.4314$; $d_4^{20} = 0.850$; M.R. (found), 34.20; M.R. (calc'd for heptenaldehyde), 34.07.

Ozonolysis of the heptenaldehyde.—The reaction of 0.6 g. of the aldehyde with ozone (5%) was carried out with the technic described earlier. The volatile acids produced were made up to 110 cc. and analyzed. The volumes of 0.0314*N* alkali required for 10 cc. of the original 110 cc. and the first three 10-cc. portions of distillate were respectively: 8.12, 4.88, 4.87, 4.97. *Duclaux values:* 6.0, 6.0, 6.1—indicating a mixture of formic with one or more volatile acids. Total acid in distillate, 0.00281 equivalent (62% yield).

All portions used in the determination were combined, neutralized, and evap-

[26] HURD AND POLLACK, *J. Am. Chem. Soc.*, **60**, 1905 (1938).

orated down to a volume of 35 cc. An equal volume of Macnair's chromic acid mixture was added and the whole was refluxed for one-half hour. The volatile acids were distilled and redistilled from sodium sulfate. This distillate was made up to 110 cc. and a Duclaux determination made as before. Cubic centimeters of alkali required (in the same order as before): 1.90, 2.17, 2.05, 1.92. The corresponding Duclaux values (11.4, 10.8, 10.1) indicate propionic acid with a small amount of acetic acid. Using the 30% distillation values and calculating in the usual way, the relative amounts of propionic and acetic acids were found to be 0.00053 and 0.00013 equivalent. Since the total amount of acid here present is 0.00066 equivalent, the amount of formic acid which has been oxidized is 0.00281 − 0.00066 = 0.00215 equivalent.

To confirm the acetic acid, all portions of the Duclaux analysis were combined, neutralized, and evaporated to 30 cc. Two grams of anhydrous potassium carbonate and 30 cc. of a 3% potassium permanganate solution were added, and the mixture was heated on the steam bath in a capped Erlenmeyer flask for five and one-half hours. After cooling, dilute sulfuric acid was used to acidify, and the mixture was distilled. The distillate was refluxed for ten minutes and distilled from sodium sulfate. The final distillate was made up to 110 cc., and a determination of the Duclaux values was made. In these analyses, the indicator used for each titration was one drop of a 1% solution of phenolphthalein in a 1:1 dioxane-water mixture. Cubic centimeters of 0.0314*N* sodium hydroxide required (in same order as above): 0.57, 0.40, 0.41, 0.44. The corresponding Duclaux values are: 7.0, 7.2, 7.7—confirming the presence of acetic acid. Therefore, the proportions of formic, acetic and propionic acids were 76.5, 4.6, 18.9.

SUMMARY

The rearrangement of γ-ethylallyl phenyl ether into *o*-pentenylphenol was subjected to critical study. It was established that the pentenylphenol was a mixture of *o*-(α-ethylallyl)phenol and *o*-(α,γ-dimethylallyl)-phenol in about the ratio of 3:2. The second of these products comes by an "abnormal" type of rearrangement.

The same type of abnormality, but to a far lesser degree, was found in the pyrolytic rearrangement of γ-ethylallyl vinyl ether. The normal and abnormal products, namely, 3-ethyl-4-pentenal and 3-methyl-4-hexenal, were found in a 17:1 ratio.

The analytical method was based on ozonolysis and subsequent determination of the volatile acids which were formed. A reliable analytical method for the determination of a mixture of formic, acetic, and propionic acids was developed.

A survey of the various mechanisms to account for rearrangements of ethers has been presented and the limitations of each have been noted. A mechanism is proposed for these rearrangements which is based on semi-ionic (and sometimes, ionic) intermediates rather than on radicals. This mechanism accounts for both the normal and abnormal effects.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

THE MICHAEL CONDENSATION. V*. THE INFLUENCE OF THE EXPERIMENTAL CONDITIONS AND THE STRUCTURE OF THE ACCEPTOR UPON THE CONDENSATION

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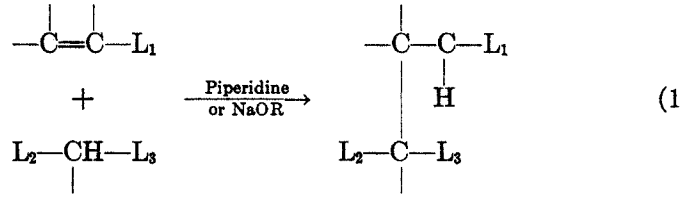
A general representation of the Michael condensation is shown in the following equation, in which L_1, L_2, and L_3 represent labilizing groups:



(1)

Examples† have been reported in which L_1 is —$COOR^1$, —COR^2, —CN^3, —$CONH_2^4$, —NO_2^5 or —SO_2R^6 and in which L_2, L_3, or both are —$COOR^1$, —COR^1, —CN^7, —$CONH_2^8$, —NO_2^9, —SO_2R^{10} or —CHO^{11}. One of the two labilizing groups in the addendum may be aryl[10,12]. If a very effective labilizing group is present in the addendum, a second labilizing group

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† The literature of this field is so extensive that no attempt has been made to include a complete bibliography. The citations given were selected either because of their priority or because of the general interest of their contents.

[1] MICHAEL, *J. prakt. Chem.*, [2], **36**, 349 (1887).

[2] KOHLER, *Am. Chem. J.*, **37**, 385 (1907).

[3] VORLÄNDER, *Ann.*, **320**, 66 (1902).

[4] HERRMANN AND VORLÄNDER, *Abhandlungen der Naturforschenden Gesellschaft zu Halle*, **21**, 251 (1899); *Chem. Zentr.*, **1899**, **1**, 730.

[5] MEISENHEIMER AND HEIM, *Ber.*, **38**, 466 (1905).

[6] KOHLER AND POTTER, *J. Am. Chem. Soc.*, **57**, 1316 (1935).

[7] THORPE, *J. Chem. Soc.*, **77**, 923 (1900).

[8] KOHLER AND SOUTHER, *J. Am. Chem. Soc.*, **44**, 2903 (1922).

[9] KOHLER, *ibid.*, **38**, 889 (1916).

[10] CONNOR, FLEMING, AND CLAYTON, *ibid.*, **58**, 1386 (1936).

[11] MEERWEIN, *J. prakt. Chem.*, [2], **97**, 225 (1918).

[12] BORSCHE, *Ber.*, **42**, 4496 (1909); KOHLER AND ALLEN, *J. Am. Chem. Soc.*, **46**, 1522 (1924); MEERWEIN AND KLINZ, *J. prakt. Chem.*, [2], **97**, 237 (1918).

may be unnecessary[13]. The acceptor may be acetylenic[14], rather than olefinic, or it may be a quinone[15]. Either the acceptor[16] or the addendum[17] may be vinylogs[18] of the structures indicated above. By no means all of the possible combinations of these groups have been studied and many which have been tested have failed; nevertheless, this reaction has made available many types of compounds that would be difficult to obtain by any other methods now available. In addition to the more obvious types of compounds prepared by direct condensation, the products have been used for the following varied types of substances: dihydroresorcinols[19], cyclohexenones[20], terpene derivatives[21], pyridines[22], piperidones[23], pyryllium salts[24], cyclopropanes[25], coumarins[15] and derivatives of hydrogenated polycyclic hydrocarbons[26]. Considering the numerous applications of this reaction it must often be used by investigators who are not familiar with some of its limitations which are probably generally understood by those who have worked in the field. This paper, therefore, is presented to summarize our experiences with the various conditions used for carrying out the reaction and to show, from new data and the work of others, the influence of the structure of the unsaturated compound (*acceptor*) upon its reactivity in the condensation‡.

Experimental conditions.—Secondary amines (for example piperidine) are the safest catalysts in that they seldom cause any reaction other than normal condensation. In reactions in which ring closure, rearrangement,[27] or the formation of trimolecular compounds[28] must be avoided, amines

[13] KOHLER AND ENGELBRECHT, *J. Am. Chem. Soc.*, **41**, 764 (1919); ANDREWS AND CONNOR, *ibid.*, **57**, 895 (1935).

[14] MICHAEL, *J. prakt. Chem.*, [2], **49**, 22 (1894).

[15] SMITH AND JOHNSON, *J. Am. Chem. Soc.*, **59**, 673 (1937).

[16] KOHLER AND BUTLER, *J. Am. Chem. Soc.*, **48**, 1040 (1926).

[17] INGOLD, PERREN, AND THORPE, *J. Chem. Soc.*, **121**, 1771 (1922).

[18] FUSON, *Chem. Rev.*, **16**, 1 (1935).

[19] BREDT, *Ber.*, **24**, 603 (1891); VORLÄNDER, *ibid.*, **27**, 2053 (1894); *Ann.*, **294**, 253 (1897); MICHAEL, *Ber.*, **27**, 2126 (1894); KNOEVENAGEL, *Ber.*, **27**, 2337 (1894).

[20] KNOEVENAGEL AND SPEYER, *Ber.*, **35**, 397 (1902).

[21] BARDHAN, BANERJI, CHATTERJEE, AND CHATTERJEE, *J. Chem. Soc.*, **1935**, 476.

[22] KNOEVENAGEL, *Ann.*, **281**, 33, 35 (1894); **303**, 225 (1898).

[23] BARAT, *J. Ind. Chem. Soc.*, **8**, 699 (1931); ALLEN AND SCARROW, *Can. J. Research*, **11**, 395 (1934).

[24] ALLEN AND BARKER, *J. Am. Chem. Soc.*, **54**, 743 (1932); DILTHEY, *J. Prakt. Chem.*, [2], **94**, 53 (1916).

[25] KOHLER AND DARLING, *J. Am. Chem. Soc.*, **52**, 424, 1174 (1930).

[26] HAWTHORNE AND ROBINSON, *J. Chem. Soc.*, **1936**, 763.

‡ The influence of the structure of the addendum upon its reactivity has been discussed earlier.[29] See also Andrews and Connor.[13]

[27] MICHAEL AND ROSS, *J. Am. Chem. Soc.*, **52**, 4598 (1930).

[28] MICHAEL AND ROSS, *ibid.*, **55**, 1632 (1933).

give satisfactory results. Unfortunately, they often fail to bring about reactions that do occur in the presence of sodium alkoxides (examples will be found in the tables) and even in favorable cases the rate is rather slow with amines. The use of piperidine as a catalyst is described in part A of the experimental part of this paper.

One-sixth to one-third of an equivalent of sodium ethoxide (see part B of the experimental description) may cause condensation in cases where amines do not. This condition is less drastic and is less likely to cause side reactions than the use of *one equivalent of sodium ethoxide.* The equivalent of catalyst (see parts C, D and E of the experimental) is the most likely to cause condensation and also side reactions. If a reactant or

TABLE I

COMPARISON OF LABILIZING GROUPS IN ACTIVATING THE ACCEPTOR

ACCEPTOR	ADDENDUM	YIELD, %	CONDITIONS[a]
$C_6H_5CH=CHCOC_6H_5$	$C_6H_5CH_2COOC_2H_5$	90	A, C
$C_6H_5CH=CHCOOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	0	A
$C_6H_5CH=CHCOOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	85	C
Coumarin	$C_6H_5CH_2COOC_2H_5$	55	C
Coumarin	$C_6H_5CH_2COOC_2H_5$	0	A
$C_6H_5CH=CHCN$	$C_6H_5CH_2COOC_2H_5$	0[b]	C
p-$O_2NC_6H_4CH=CHCOC_6H_5$	$CH_2(COOC_2H_5)_2$	90	A
p-$O_2NC_6H_4CH=CHCOOC_2H_5$	$CH_2(COOC_2H_5)_2$	0	A

[a] In this and the following tables, the letters designating the conditions used for carrying out the reactions refer to the corresponding sections in the experimental part describing the general methods for carrying out the condensation. In making comparisons in the tables it should be borne in mind that C, D and E represent more severe conditions than B, and B represents more severe conditions than A. Therefore, an acceptor which reacts under condition A may be considered more reactive than one which does not react under other conditions; it is not permissible, however, to compare an acceptor which is reactive under condition C, D, or E, with one which is not reactive under condition B or A.

[b] BORSCHE, *Ber.*, **42**, 4496 (1909).

product undergoes alcoholysis readily in the presence of alkoxides or if the sodio derivative of the active methylene compound is not readily formed, the sodio derivative may be prepared by the use of metallic sodium (see part E of the experimental description) or sodamide[26].

The solubility of the reactants is the chief consideration in selecting a *solvent.* Methanol, ethanol, benzene, ether, and dioxane have all given satisfactory results. With sodium alkoxides as catalysts the best results are obtained by allowing the reaction to stand at room *temperature* for twenty to one hundred-fifty hours. Higher temperatures may give lower yields, presumably because they favor retrogression[29] and increase

[29] INGOLD AND POWELL, *J. Chem. Soc.*, **119**, 1976 (1921).

the side reactions. However, if ring closures or the formation of trimolecular compounds are desired, the reaction may be carried out under reflux. With secondary amines the reaction is usually so slow that a long reflux period is necessary.

TABLE II

INFLUENCE OF α AND β SUBSTITUTION UPON THE REACTIVITY OF THE ACCEPTOR[a]

NO.	ACCEPTOR	ADDENDUM	YIELD, %	CONDITIONS[b]
1	$C_6H_5CH=CHCOC_6H_5$	$C_6H_5CH_2COOC_2H_5$	90	B, C
2	$C_6H_5CH=C(COOC_2H_5)COC_6H_5$	$C_6H_5CH_2COOC_2H_5$	0	C
3	$C_6H_5CH=CHCOOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	85	C
4	$C_6H_5CH=C(C_6H_5)COOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	0	C
5	$CH_3CH=CHCOOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	90	C
6	$CH_3CH=C(CH_3)COOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	40	C
7	$(CH_3)_2C=CHCOOC_2H_5$	$C_6H_5CH_2COOC_2H_5$	20	C
8	$C_6H_5CH=CHCOC_6H_5$	$CH_3CH(COOC_2H_5)_2$	42	E[c]
9	$C_6H_5CH=C(CH_3)COC_6H_5$	$CH_3CH(COOC_2H_5)_2$	0	E
10	$CH_3CH=CHCOOC_2H_5$	$CH_3CH(COOC_2H_5)_2$	84	B[d]
11	$CH_3CH=C(CH_3)COOC_2H_5$	$CH_3CH(COOC_2H_5)_2$	15	C
12	$CH_3CH=CHCOOC_2H_5$	$CH_3CH(CN)COOC_2H_5$	50	C[e]
13	$(CH_3)_2C=CHCOOC_2H_5$	$CH_3CH(CN)COOC_2H_5$	17	C[f]
14	$C_6H_5CH=CHCOOC_2H_5$	Anthrone	0	A
15	$C_6H_5CH=C(COOC_2H_5)_2$	Anthrone	91	A[g]
16	m-$O_2NC_6H_4CH=CHCOOCH_3$	$CH_2(COOCH_3)_2$	95	B
17	m-$O_2NC_6H_4CH=C(CH_3)COOCH_3$	$CH_2(COOCH_3)_2$	0	B, D
18	Coumarin	$CH_2(COOC_2H_5)_2$	54	D[h]
19	3-Methylcoumarin	$CH_2(COOC_2H_5)_2$	0	D[h]

[a] For examples of the replacement of the α hydrogen of $CH_2=CHL_1$ by methyl, compare 5 and 6, 8 and 9, 10 and 11, 16 and 17, 18 and 19; for the influence of β substitution compare 5 and 7, 12 and 13. For the influence of phenyl compare 3 and 4; of carbethoxyl, 1 and 2; of benzoyl, 2 and 3.

[b] The explanation of this column is given in footnote *a* of Table I.

[c] This yield represents rearrangement-retrogression products[31] as reported by Holden and Lapworth[32].

[d] Michael and Ross[27] report this result.

[e] This represents the rearrangement product[31] reported by Michael and Ross[33].

[f] This was reported by Thorpe[7] and is a rearrangement product.

[g] This was reported by Gravel[34].

[h] The authors are indebted to Messrs. R. A. Cardinali and R. E. Houghton for these experiments.

The nature of L_1.—An arrangement of labilizing groups in the order of their ability to activate the double bond of the acceptor would be very

[31] CONNOR AND ANDREWS, *J. Am. Chem. Soc.*, **56**, 2713 (1934).

[32] HOLDEN AND LAPWORTH, *J. Chem. Soc.*, **1931**, 2368.

[33] MICHAEL AND ROSS, *J. Am. Chem. Soc.*, **53**, 1150 (1931).

[34] GRAVEL, *Naturaliste canadien*, **57**, 181 (1931); *Chem. Abstr.*, **28**, 169 (1934).

useful. Unfortunately, no such table of reactivities or "negativities" can be made from the data at hand. In some cases, ring closures[14,19,20,22,23] (as in some cases where L_1 is —$COCH_3$ or —$CONH_2$) or rearrangements[27] render the yields of doubtful significance in comparing reactivities; in other cases not enough examples have been studied to justify a comparison. However, it can be said that an unsaturated ketone is more reactive than the corresponding ester and the latter more reactive than the nitrile. Specific examples of these facts are given in Table I and many others are to be found in the literature.

Substitution on the α and β atoms.—This subject has already received some attention in studies on the Michael reaction. In general, the conclusions are similar to those reached by Ingold, Perren, and Thorpe[17]

TABLE III

INFLUENCE OF REMOTE SUBSTITUTION UPON THE REACTIVITY OF THE ACCEPTOR

ACCEPTOR	ADDENDUM	YIELD, %	CONDITIONS[a]
o-$O_2NC_6H_4CH=CHCOOCH_3$	$CH_2(COOCH_3)_2$	70	B
m-$O_2NC_6H_4CH=CHCOOCH_3$	$CH_2(COOCH_3)_2$	95	B
p-$O_2NC_6H_4CH=CHCOOCH_3$	$CH_2(COOCH_3)_2$	0	B
Coumarin	$CH_2(COOC_2H_5)_2$	54	D
6-Bromocoumarin	$CH_2(COOC_2H_5)_2$	0	B, D
$C_6H_5CH=CHCOC_6H_2(CH_3)_3(2,4,6)$	$CH_2(COOCH_3)_2$	70	B
m-$O_2NC_6H_4CH=CHCOC_6H_5$	$CH_2(COOC_2H_5)_2$	95	A, B
p-$O_2NC_6H_4CH=CHCOC_6H_5$	$CH_2(COOC_2H_5)_2$	90	A

[a] The explanation of this column is given in the first footnote of Table I.

on the self-condensation of substituted glutaconic esters. The conclusions may be summarized as follows (for examples, see Table II):

(1) In a system, $CH_2 = CHL_1$, the reactivity of the acceptor decreases as the hydrogens are replaced by larger groups. This is true whether substitution is made on the α or β carbon atom.

(2) The reactivity of the acceptor is decreased if the substituent is alkyl[23,30], aryl, carbethoxyl or acyl. The magnitude of this effect probably is largely dependent upon the size of the substituent[17,23] although, according to Ingold, Perren, and Thorpe[17], in the case of negative groups such as —COOR and —CN the spatial effect may be modified by a polar effect which will render the system less unreactive than might be expected from the size of such groups.

The above generalities are probably adequate for almost all cases; however, at least one exception is known. This is the case of ethylcin-

[30] See also Thorpe[7] and Kohler and Engelbrecht[13].

TABLE IV

PROPERTIES OF NEW COMPOUNDS

COMPOUND	MOLECULAR FORMULA	CALCULATED			FOUND			SOLVENT FOR RECRYSTALLIZATION	M.P. (CORR.)	B.P. (OBS.)
		C	H	N	C	H	N			
$C_6H_4CHCH_2COO$ (ring closed) | $CH(COOC_2H_5)_2$	$C_{16}H_{18}O_6$[a]	62.73	5.93	—	62.93 62.82	6.02 5.84	—	Ethanol	52°	203° (4 mm.)
$(CH_3)_2CCH_2COOC_2H_5$ | $C_6H_5CHCOOC_2H_5$	$C_{17}H_{24}O_4$	69.83	8.28	—	69.80	8.10	—	—	—	160–3° (6 mm.)
m-$O_2NC_6H_4CH{=}CCOOCH_3$ | CH_3	$C_{11}H_{11}O_4N$	59.76	5.01	—	59.97	4.92	—	Methanol	54–5°	—
m-$O_2NC_6H_4CHCH_2COOCH_3$ | $CH(COOCH_3)_2$	$C_{15}H_{17}O_8N$	—	—	4.13	—	—	4.20	Methanol	97–8°	—
o-$O_2NC_6H_4CHCH_2COOCH_3$ | $CH(COOCH_3)_2$	$C_{15}H_{17}O_8N$	—	—	4.13	—	—	4.22	Methanol	82–3°	—
p-$O_2NC_6H_4CHCH_2COC_6H_5$ | $CH(COOC_2H_5)_2$	$C_{22}H_{23}O_7N$	63.91	5.61	—	64.29	5.67	—	Ethanol	97–97.5°	—
$C_6H_5CHCH_2COC_6H_2(CH_3)_3(2,4,6)$ | $CH(COOCH_3)_2$	$C_{23}H_{26}O_5$	72.23	6.85	—	72.21	7.04	—	Methanol	82–3°	—

[a] Messrs. R. A. Cardinali, Philip Tryon and R. E. Houghton have studied the behavior of coumarins in the Michael condensation and report the data on this product.

namate, which does not react with anthrone, although ethyl benzalmalonate (the α-carbethoxy derivative of ethyl cinnamate) gives a good yield[34] of condensation product.

Remote substitution.—Groups which are not attached directly to the double bond of the acceptor probably have a greater influence upon reactivity than is generally appreciated. The magnitude of their influence cannot be estimated but in predicting reactivity the possibility that remote groups may vastly alter the behavior of the acceptor must be borne in mind. Examples are given in Table III.

From the possibility of steric hindrance one might expect the *ortho* isomer to be the least reactive of the nitrocinnamic esters; actually the *para* isomer is the least reactive. Apparently steric influences by ortho substituents are not extremely important—a fact confirmed by the reaction of benzalacetomesitylene. On the other hand, a *p*-nitro group does not always prevent reaction (*cf.* the case of 4-nitrochalcone). In one case studied (6-bromocoumarin) substitution by bromine gave a decrease in reactivity.

EXPERIMENTAL

The general directions for carrying out the Michael condensation under the various conditions used are given below. In the cases in which 0% yield has been reported the recovery of unreacted materials was seldom less than 85% and never below 70%.

A. Piperidine as a catalyst.—To equimolar quantities of the addendum and acceptor dissolved in absolute ethanol or methanol (50 ml. per 0.1 mole of addendum) was added piperidine (2.0 cc. per 0.1 mole of addendum), and the solution was heated seventy-two hours on a steam bath. The reaction mixture was cooled in ice and if a solid appeared it was removed by filtration and recrystallized from the appropriate solvent. When no solid formed the mixture was diluted with water, extracted with ether, and the ethereal washings were dried over sodium sulfate. Removal of the solvent gave a product which was crystallized or distilled.

B. A small amount of sodium alkoxide.—A sodium ethoxide solution was prepared by dissolving sodium in the minimum amount of absolute methanol or ethanol. An amount of addendum corresponding to three to six times the number of moles of catalyst was then added, followed by a solution containing the amount of the acceptor equivalent to the addendum. The solution of the acceptor was prepared by using a minimum of 2 l. of dry ether or thiophene-free benzene per mole of acceptor, plus whatever additional amount was necessary to make a homogeneous solution. The reaction mixture stood at room temperature for at least 20 hours, was acidified with acetic acid, and the organic layer was washed with water. The ethereal or benzene extracts were dried over anhydrous sodium sulfate, the solvent was removed on the steam bath, and the product was recrystallized or distilled.

C. An equivalent of sodium alkoxide (hot).—To a solution prepared by dissolving 2.3 g. (0.1 gram atom) of sodium in 35 ml. of absolute methanol or ethanol was added 0.1 mole of the addendum and 0.1 mole of the acceptor. The mixture was heated on the steam bath for four hours, allowed to stand overnight, and diluted with 200 ml. of water containing 7 g. of acetic acid. The diluted reaction mixture was extracted

twice with ether, the extracts dried over anhydrous sodium sulfate and the ether was removed on the steam bath. The product was recrystallized or distilled.

D. An equivalent of sodium alkoxide (room temperature).—These experiments were carried out exactly like those described under B except that the amount of sodium used was equivalent to the active methylene compound.

E. Use of the sodio-derivative in the absence of alcohol.—Sodium was powdered under xylene, and the xylene was replaced by dry, thiophene-free benzene by repeated decantation. The theoretical amount of the active methylene compound dissolved in dry thiophene-free benzene (300 ml. of benzene per mole of addendum) was added slowly to the sodium suspended in benzene (300 ml. of benzene per mole of sodium). The mixture was heated on the steam bath until reaction had ceased, and a solution of the theoretical amount of the acceptor in dry benzene (175 ml. of benzene per mole of unsaturated compound) was added. The mixture was heated on the steam bath for ten hours, cooled and washed with an equal volume of water containing a slight excess of acetic acid. The benzene layer was dried over magnesium sulfate, the solvent was removed, and the residue was crystallized or distilled under reduced pressure.

Acknowledgment.—The authors are grateful to the Faculty Research Committee of the University of Pennsylvania for a grant to aid this investigation.

SUMMARY

A brief summary has been given of the results to be expected when the Michael condensation is carried out under various experimental conditions. The influence of the structure of the acceptor upon the reactivity of the unsaturated compound has been discussed.

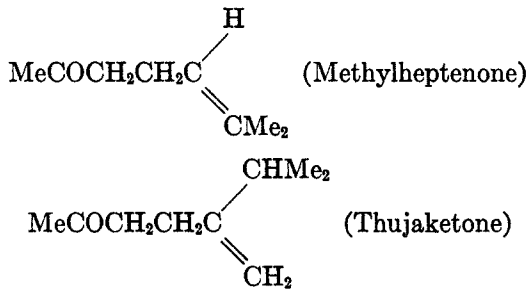
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

THE SYNTHESIS FROM THUJAKETONE OF SOME NEW HYDROTERPENOIDS

JESSE WERNER AND MARSTON TAYLOR BOGERT

Received November 3, 1938

It is rather surprising, in view of the ease with which thujaketone can be obtained from thuja-leaf oil (*Thuja occidentalis*), that this interesting compound has not been used more frequently in recent years for syntheses in the terpene and related fields. Structurally, it resembles quite closely the important methylheptenone:



It is worth noting also that its carbon skeleton is identical with that of the side-chain of ergosterol and calciferol (vitamin D_2), and that one of the products of the oxidation of *alpha*-ergostenol acetate is dihydrothujaketone[1].

Although thuja-leaf oil has been investigated carefully by Jahns[2], Wallach[3], Semmler[4], Tiemann[5], and others, no mention was made in their reports of the fact that pure thujone can be isolated easily and in excellent yield (46.5%) by a single fractionation.

The first series of syntheses is shown in Flow Sheet A and may be described briefly here.

[1] (*a*) GUITERAS, NAKAMIYA, AND INHOFFEN, *Ann.*, **494**, 116 (1932); (*b*) HEILBRON, SIMPSON, AND WILKINSON, *J. Chem. Soc.*, 1699 (**1932**).

[2] JAHNS, *Arch. Pharm.*, **221**, 748 (1883).

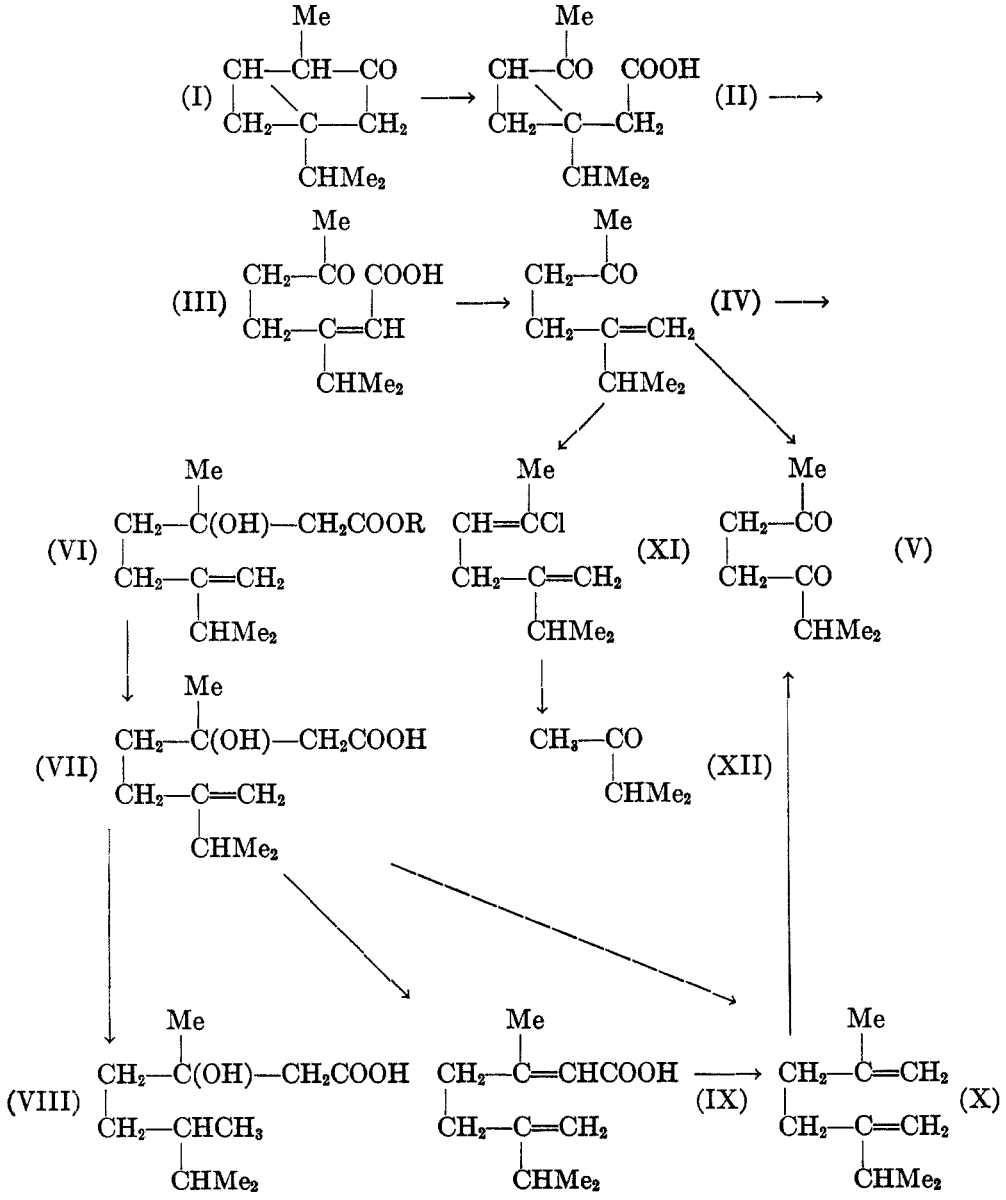
[3] (*a*) WALLACH, *Ann.*, **272**, 99 (1893); (*b*) **275**, 164 (1893); (*c*) **309**, 24 (1899); (*d*) **336**, 263 (1904); (*e*) **381**, 81 (1911).

[4] (*a*) SEMMLER, *Ber.*, **25**, 3343 (1892); (*b*) **33**, 275 (1900).

[5] TIEMANN AND SEMMLER, *Ber.*, **30**, 429 (1897).

In the oxidation of thujone (I) by potassium permanganate, at room temperature, Wallach[3a] obtained both *alpha* (II) and *beta* (III) forms of

Flow Sheet A



thujaketonic acid, whereas Thomson[6] found only the former. Our own results agreed with the findings of Thomson. Distillation of the *alpha* acid (II), at atmospheric pressure, gave a good yield of the thujaketone (IV) desired, presumably through the intermediate formation of the *beta* acid, although Wallach[3b] has claimed that the yield from the *alpha* acid is poor, but good from the *beta* isomer. It was oxidized by permanganate, as described by Tiemann and Semmler[5], and the *omega*-dimethylacetonylacetone (V) isolated as the oxime.

The ketone was next subjected to the usual Reformatsky reaction with ethyl bromoacetate and zinc, and the resulting ester (VI) hydrolyzed to the free acid (VII). Catalytic reduction of this acid, yielded the corresponding saturated hydroxy acid (VIII), the odor of which was more agreeable than that of (VII). The latter was dehydrated by phosphorus pentoxide to the diene acid (IX), distillation of which gave the diolefin (X), a hydrocarbon with sweet, pleasant odor. This same dihydroterpene (X) was prepared by dry distillation of the olefin hydroxy acid (VII). Its structure was established by analysis, physical constants, and oxidation to *omega*-dimethylacetonylacetone (V).

In attempting to prepare an isomeric hydroterpene, following a German patent[7] for the conversion of methylheptenone into an unsaturated chloride, thujaketone was subjected to the action of phosphorus pentachloride and a vinyl chloride (XI) obtained which, on oxidation, yielded methyl isopropyl ketone (XII). Probably because of its tertiary carbon union, this chloride refused to react with either sodiomalonic ester or methylmagnesium iodide.

A second group of reactions, using thujaketone as initial material, is exhibited in Flow Sheet B.

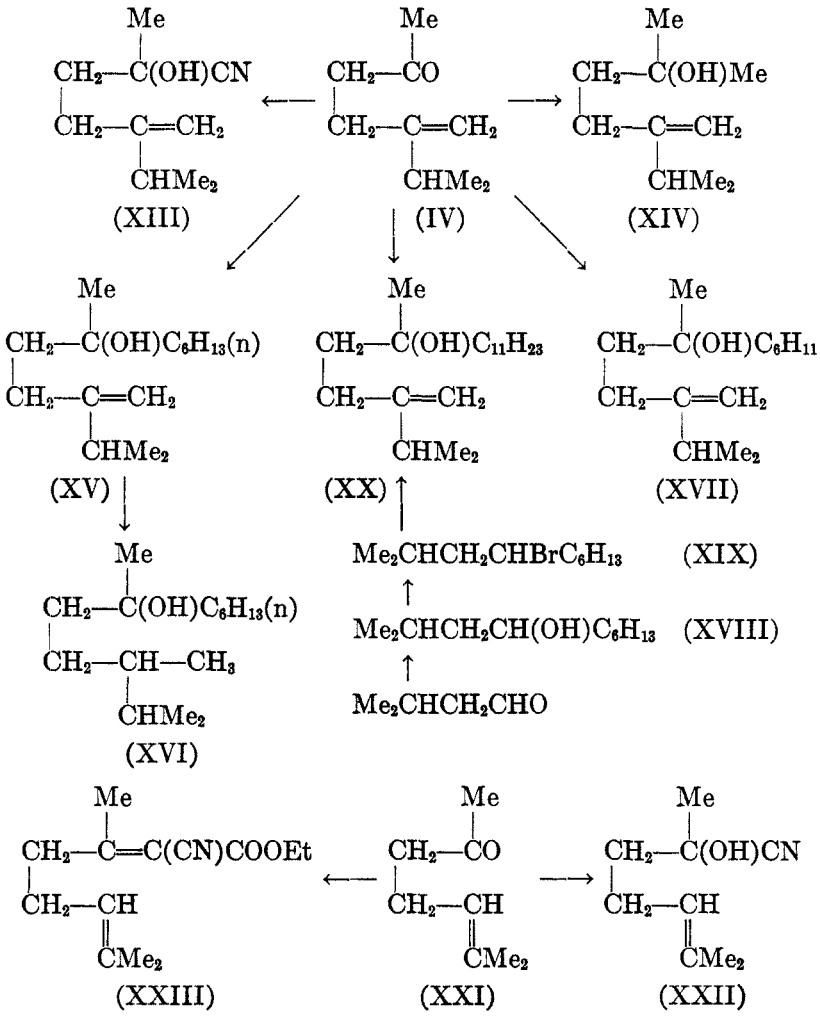
Rupe and Schlochoff[8] have reported that they were unable to obtain a satisfactory yield of the cyanohydrin (XXII) from methylheptenone (XXI), and that the small quantity of impure material secured broke down to methylheptenone again when distilled. We were more fortunate in this reaction and succeeded in preparing the pure cyanohydrin without serious difficulty and in good yield. Further, the product distilled undecomposed under reduced pressure.

The same reaction was therefore applied to thujaketone, with equally good results. Unfortunately, however, this cyanohydrin (XIII) could not be hydrolyzed satisfactorily by either acid or alkali, nor did its dehydration by phosphorus pentoxide yield a pure product. Its aroma strongly

[6] THOMPSON, *J. Chem. Soc.*, **97**, 1502 (1910).
[7] GRIESHEIM-ELEKTRON, *German pat.* 118,351; *Friedlaender*, VI, 1252 (1900–1902).
[8] RUPE AND SCHLOCHOFF, *Ber.*, **38**, 1502 (1905).

resembled that of peach essence, whereas the cyanohydrin of methylheptenone exhaled only a very faint cyanide type of odor.

Flow Sheet B



Since the action of methylmagnesium iodide upon methylheptenone leads to the formation of a useful perfume alcohol[9], five analogous tertiary alcohols (XIV, XV, XVI, XVII, XX) were prepared from thujaketone

[9] (*a*) GRIGNARD, Thèse de Doctorat, Univ. Lyons, p. 81 (1901); (*b*) HARRIES AND WEIL, *Ber.*, **37**, 845 (1904).

for a comparison of their odor values. This comparison showed that the pleasingness of their perfume was decreased by increasing the molecular weight of the hydrocarbon radical introduced by the Grignard reaction, but was increased by hydrogenation of the olefin bond. Thus, of the five, the odor of (XIV) was most agreeable, and (XVI) had a finer aroma than (XV).

Finally, the Knoevenagel reaction was applied to methylheptenone, following in general the method of Cope[10], and the cyanoacetic ester condensation product (XXI) was obtained easily and in excellent yield. Endeavors to saponify this ester, by the action of alcoholic potassium hydroxide solution, under various conditions, failed to yield the corresponding acid, so no attempt was made to apply the same reaction to thujaketone.

Acknowledgment.—Our grateful thanks are due to Mr. Frederick H. Leonhardt, President of Fritzsche Brothers, Inc., New York, N. Y., who generously supplied the thuja-leaf oil and methylheptenone necessary for this research.

EXPERIMENTAL

The thuja-leaf oil used as initial material possessed the following properties: color, straw-yellow, normal; thujone, 61.8%; specific gravity at 15°, 0.920; optical rotation, −12° 39′; refractive index at 20°, 1.4568; ester value, 18.7; ester value after acetylation, 32.1; acid value, 0.5.

In the following experiments, the melting-point determinations were made in a Thiele apparatus; and distillations under reduced pressure were performed with the aid of a barostat[11] which controlled the pressure to ±0.1 mm.

All thermometers were checked against a set of total immersion thermometers calibrated by the U. S. Bureau of Standards.

Densities were measured with a pyknometer of about 1.5 cc. capacity, and were accurate to ± 0.0002.

Refractive indices were determined with an Abbe refractometer, kept at 25° (± 0.01°) by circulating water from the thermostat through the thermoregulator[12] by means of a gear pump. The readings were correct to ± 0.0002.

The analyses were carried out in these laboratories by Mr. Saul Gottlieb.

***d*-Thujone (I).**—Ten pounds of thuja-leaf oil was distilled, with the assistance of a very efficient 25-cm. Vigreux column, and the fraction boiling at 198–203° was collected. It consisted of a pale-yellow oil of piney odor, and amounted to 2110 g., or 46.5% of the original oil, and showed n_D^{25} 1.4521. According to other investigators, the b.p. of pure *d*-thujone is 200–201°[3d], and its n_D is 1.45109[13], 1.45220[14], or 1.45252[15].

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[10] COPE, *J. Am. Chem. Soc.*, **59**, 2327 (1937).
[11] COX, *Ind. Eng. Chem., Anal. Ed.*, **1**, 7 (1929).
[12] HEISIG AND CAMERON, *ibid.*, **5**, 420 (1933).
[13] WALLACH, *Ber.*, **28**, 1965 (1895).
[14] BRÜHL, *ibid.*, **32**, 1224 (1899).
[15] TSCHUGAEFF, *ibid.*, **33**, 3122 (1900).

Tribromide.—Prepared by Wallach's method [3b, 16]. White plates from ligroïn, m.p. 121–122° (corr.) (literature, m.p. 122°).

2,4-Dinitrophenylhydrazone.—Orange needles (from ethanol), m.p. 106–107° (corr.).

Anal. Calc'd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07.
Found: C, 58.06; H, 6.25.

Strain[17] has reported the melting point of such a hydrazone as 106–107.5°, and Macbeth and Price[18] as 116–117°, but in neither article is the origin or form of the thujone stated.

alpha-**Thujaketonic acid (II)** has been prepared by permanganate oxidation of thujone by a number of investigators[3a, 3b, 4a, 5, 6, 19], but we found it desirable to modify these methods in various respects and operated as follows:

After stirring vigorously for 10 minutes a mixture of 490 g. of potassium permanganate with 9310 cc. of water, 350 g. of thujone was added and the stirring was continued for 3 hrs. at room temperature. After removal of the manganese dioxide precipitate, 90 g. of unoxidized thujone was recovered from the mixture by extraction with ether. The residual aqueous solution was made acid to Congo Red by concentrated hydrochloric acid, saturated with salt, and extracted with ether; the extracts were distilled, and the residue was dried by adding dry benzene and distilling it off again. The liquid mass left behind solidified completely to white foliated crystals when cooled and scratched; yield, 239 g., or 75.6%. Recrystallized from an ether-petroleum ether mixture, it melted at 74–75° (corr.); m.p. reported in the literature, 74.5°[4a, 5], and 75–76°[6]. No *beta*-thujaketonic acid was encountered in this process.

Oxime.—M.p. 175–176° (corr.); previously reported, 174–175°[6].

Thujaketone (IV).—The decarboxylation of the thujaketonic acid, as carried out by Wallach[3b], has been modified and the yield greatly improved.

In a 500-cc. distilling flask, 239 g. of *alpha*-thujaketonic acid was heated in a bath of molten Wood's metal the temperature of which was raised slowly from 275° to 325°. To the distillate, benzene was added, the solution was cleared by calcium chloride, and the filtrate was distilled with the aid of a 25-cm. Vigreux column. The fraction boiling at 183–188° consisted of the desired ketone, and more was recovered by redistillation of the fore and after runs. The product was a pale-yellow liquid, of amyl acetate odor; yield, 113.6 g., or 62.4%; n_D^{25} 1.4430. Previously reported: b.p. 184–186°[3a], 182–185°[3b]; n_D^{20} 1.44104[3a].

Semicarbazone.—White plates, m.p. 141–142° (corr.); previously reported, 143°[20].

2,4-Dinitrophenylhydrazone.—Microscopic orange needles (from ethanol), m.p. 73–74° (corr.).

Anal. Calc'd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29.
Found: C, 56.33; H, 6.58.

Oxidation of thujaketone with permanganate, following the directions of Tiemann and Semmler[5], and our own experience in the oxidation of thujone, gave a very poor yield of *omega*-dimethylacetonylacetone (V), which was isolated as its *dioxime*; white microscopic needles, m.p. 128–130° (m.p. previously reported, 132°[5]).

Ethyl 3-hydroxy-3, 7-dimethyl-6-methyleneoctanoate (VI).—A mixture of 140.2 g.

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[16] WALLACH, *Ann.*, **286**, 109 (1895).
[17] STRAIN, *J. Am. Chem. Soc.*, **57**, 760 (1935).
[18] MACBETH AND PRICE, *J. Chem. Soc.*, **1935**, 151.
[19] RUZICKA AND KOOLHAAS, *Helv. Chim. Acta*, **15**, 944 (1932).
[20] WALLACH, *Ber.*, **30**, 423 (1897).

of thujaketone, 167.1 g. of ethyl bromoacetate, 72 g. of zinc (sheet zinc, sandpapered and cut into small pieces), 250 cc. of dry benzene, and 250 cc. of dry toluene, in a flask equipped with an efficient condenser and drying tube, was heated carefully with a free flame until the reaction started. The flame was then removed, and the very vigorous reaction was controlled by cooling with ice water from time to time. When the reaction was over, the mixture was refluxed for 30 minutes, cooled, and decomposed by agitation with 600 cc. of ice-cold 10% sulfuric acid. The upper layer was removed, washed twice with water, filtered, and the solvents were distilled off under diminished pressure. The remaining liquid was distilled in an atmosphere of nitrogen at a pressure of 3 mm., and a fraction was collected at 113–114°, amounting to 173.4 g., or 76%, as a very pale-yellowish liquid of pleasant, fruity aroma; d_4^{25} 0.9440; n_D^{25} 1.4500; M_D calc'd 64.97, obs. 65.02.

Anal. Calc'd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59.
Found: C, 68.65; H, 10.46.

Free acid (VII).—This was secured by saponifying the ester with alcoholic potassium hydroxide solution and distilling the crude product under reduced pressure in an atmosphere of nitrogen. The fraction collected boiled at 144–146° at 3 mm. and was a pale-yellow liquid, of mild, agreeable odor, and amounted to 132.5 g., or 87%. Its constants were: d_4^{25} 0.9904; n_D^{25} 1.4646; M_D calc'd 55.73, obs. 55.86; neutral. equiv. calc'd 200.3, obs. 199.7.

Anal. Calc'd for $C_{11}H_{20}O_2$: C, 65.97; H, 10.07.
Found: C, 66.21; H, 10.23.

3-Hydroxy-3,6,7-trimethyloctanoic acid (VIII).—Ten grams of the above unsaturated acid (VII), 100 cc. of 80% methanol, and 1 g. of palladium on charcoal, were placed in a Parr-Adams hydrogenator, and the hydrogenation was conducted for 24 hrs. at a pressure of two atmospheres. The mixture was filtered, the methanol was distilled from the filtrate, and the residue was extracted with ether. The ether extract was washed with water, dried with sodium sulfate and distilled, with reduction of the pressure after the elimination of the ether. The fraction collected boiled at 164–166° at 6 mm., was a pale-yellow oil of agreeable, sweet odor, amounted to 7 g., or 70%, and showed the following constants: d_4^{25} 0.9952, n_D^{25} 1.4645; M_D calc'd 56.20, obs. 56.15; neutral. equiv. calc'd 202.3, obs. 203.1.

Anal. Calc'd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.71.
Found: C, 65.03; H, 10.57.

3,7-Dimethyl-6-methyleneocten-2-oic acid (IX).—To a solution of 132.5 g. of the methylene octanoic acid (VII) in 200 cc. of dry benzene, there was added 175 g. of phosphorus pentoxide, and the mixture was refluxed for 6 hrs. at 100°. It was then filtered; the residue was extracted twice with 200-cc. portions of dry benzene; the extracts were added to the original filtrate, and the whole was distilled under reduced pressure, under an atmosphere of nitrogen after removal of the benzene. The fraction boiling at 127–128° at 2 mm. was collected. It was a pale-yellow oil, of mild, pear-essence odor; yield, 32.5 g., or 28%; d_4^{25} 0.9611; n_D^{25} 1.4840; M_D calc'd 53.73, obs. 54.25; E_M +0.52, which is similar to that reported by Tiemann[21] for geranic acid; neutral. equiv. calc'd 182.3, obs. 181.8.

Anal. Calc'd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96.
Found: C, 72.55; H, 10.11.

2,6-Dimethyl-5-methyleneheptene-1 (X).—Fifty grams of the octanoic acid (VII) was distilled slowly over a naked flame. The distillate was washed with sodium

[21] TIEMANN, *Ber.*, **31**, 823 (1898).

carbonate solution, dried over calcium chloride, and distilled; the fraction boiling at 158–159° was collected. This was a colorless oil, of very sweet smell; yield, 17.5 g., or 50%; d_4^{25} 0.7698, n_D^{25} 1.4418; M_D calc'd 47.45, obs. 47.50.

Anal. Calc'd for $C_{10}H_{18}$: C, 86.88; H, 13.12.
Found: C, 86.64; H, 13.21.

Distillation of the octenoic acid (IX), gave a 25% yield of the same hydrocarbon.

Oxidation with potassium permanganate, as in the case of thujaketone, yielded only a small quantity of *omega*-dimethylacetonylacetone (V), identified by its dioxime, microscopic white needles, m.p. 128.5–130° (corr.); mixture with the corresponding dioxime from thujaketone, m.p. 128–129.5° (corr.).

2-Chloro-6-methyl-5-methyleneheptene-2 (XI).—To 84 g. of phosphorus pentachloride, cooled by a mixture of ice and salt, there was added dropwise 56 g. of thujaketone. The reaction mixture was left in the ice bath for 15 minutes longer, then maintained at room temperature until the vigorous evolution of hydrogen chloride ceased, and finally heated at 100° for 2.5 hrs. It was next placed in an ice pack, hydrolyzed by the careful addition of water, and distilled with steam. The distillate was extracted with benzene, the benzene was distilled off, and the residue was fractionated at 18 mm. pressure, the cut which boiled at 95–96° was collected. This was a colorless oil, of terpene odor, 25.1 g., or 40%, in amount, with the following constants: d_4^{25} 0.9310, n_D^{25} 1.4730; M_D calc'd 47.72, obs. 47.81.

Anal. Calc'd for $C_9H_{15}Cl$: C, 68.12; H, 9.53; Cl, 22.35.
Found: C, 67.91; H, 9.66; Cl, 22.34.

Oxidation of this compound with potassium permanganate, yielded a small quantity of methyl isopropyl ketone (XII); identified by its semicarbazone, m.p. 110–112° (corr.) [mixed with an authentic sample of m.p. 112–113° the m.p. was 110.5–112° (corr.)], and by its 2,4-dinitrophenylhydrazone, m.p. 115–116° (corr.) [mixed with an authentic sample of m.p. 116–117° the m.p. was 115–116° (corr.)].

2-Hydroxy-2,6-dimethylhepten-5-oic nitrile (XXII).—To 42 g. of methylheptenone, in a flask equipped with sealed stirrer, dropping funnel, and exit tube to the hood, there was added a solution of 34.7 g. of sodium bisulfite in 65 cc. of water. The mixture was stirred for 20 minutes, cooled in ice and water, and a solution of 21.7 g. of potassium cyanide in 35 cc. of water added dropwise with vigorous stirring. At the end of the cyanide addition, the cooling bath was removed, the mixture was stirred for 2 hrs., the upper layer was separated, and the lower layer was extracted twice with ether. The ether extracts and the separated upper layer were united, washed with concentrated sodium bisulfite solution, then twice with dilute sodium chloride solution, dried over sodium sulfate, the ether was distilled off, and the residue was fractionated under 2 mm. pressure; the portion that boiled at 115–117° was collected. This amounted to 28.7 g., or 56.3%, and was a pale-yellow oil of cyanide odor; d_4^{25} 0.9224; n_D^{25} 1.4501; M_D calc'd 44.64, obs. 44.68.

Anal. Calc'd for $C_9H_{15}NO$: C, 70.55; H, 9.87.
Found: C, 70.51; H, 10.14.

2-Hydroxy-2,6-dimethyl-5-methyleneheptanoic nitrile (XIII).—This was prepared from thujaketone and potassium cyanide in essentially the same way as the foregoing nitrile was synthesized from methylheptenone. It was a pale-yellow liquid, b.p. 116–118° at 2 mm., with a sweet odor strongly recalling that of peach essence, and on standing turned red first and then yellow; yield, 14.2 g. from 23.4 g. of the ketone, or 51%; d_4^{25} 0.9103; n_D^{25} 1.4498; M_D calc'd 49.26, obs. 49.41.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25.
Found: C, 71.94; H, 10.24.

The alcohols listed below were synthesized by the standard Grignard reaction, either from thujaketone (XIV, XV, XVII, XX) or isovaleraldehyde (XVIII), or (XVI) by reduction of the corresponding unsaturated alcohol.

2,6-Dimethyl-5-methyleneheptanol-2 (XIV).
2,6-Dimethyl-3-methylenedodecanol-6 (XV).
2-Cyclohexyl-6-methyl-5-methyleneheptanol-2 (XVII).
2,6-Dimethyl-3-methylene-7-isobutyltridecanol-6 (XX).
2,3,6-Trimethyldodecanol (XVI).
2-Methyldecanol-4 (XVIII).
The details are given in the accompanying Table.

TABLE

ALCOHOL	XIV	XV	XVII	XX	XVI	XVIII
Yield (%)	80	69	46.5	45	73	73
Appearance	Pale-yellow oil	Pale-yellow oil	Pale-yellow oil	Pale-yellow oil	Colorless oil	Colorless oil
Odor	Sweet, minty	Agreeable	Sweet, piney	Mildly pleasant	Very pleasant	Slightly sweet
B. p.	97–99° at 19 mm.	150–153° at 15 mm.	122–124° at 3 mm.	157–157.5° at 2 mm.	149–151° at 17 mm.	123–125° at 12 mm.
d_4^{25}	0.8390	0.8375	0.8937	0.8384	0.8351	0.8168
n_D^{25}	1.4453	1.4535	1.4749	1.4542	1.4472	1.4310
M_D calc'd	49.44	72.56	70.36	95.62	73.03	54.55
M_D obs	49.60	72.67	70.68	95.81	73.11	54.60
C calc'd	76.86	79.57	80.28	81.01	78.87	76.67
C found	77.04	79.49	80.36	81.28	78.89	76.43
H calc'd	12.90	13.36	12.59	13.60	14.12	14.04
H found	12.90	13.35	12.77	13.77	13.82	13.90

2,3,6-Trimethyldodecanol-6 (XVI). was obtained from the unsaturated alcohol (XV), by reduction for 2 hrs. in 95% ethanol, in a Parr-Adams hydrogenator, at two atmospheres pressure, in the presence of platinum oxide catalyst. The crude product was fractionated under diminished pressure, and the properties of the pure compound are recorded in the foregoing Table.

2-Methyl-4-bromodecane (XIX).—After refluxing for 5.5 hrs. 43.2 g. of 2-methyldecanol-4 (XVIII) with 136 cc. of 48% hydrobromic acid, the supernatant layer was separated, washed with concentrated sulfuric acid, water, and dilute sodium bicarbonate solution, dried over calcium chloride, and distilled at 17 mm. pressure. The fraction boiling at 115–118° consisted of the bromide sought, and was a colorless oil of agreeable odor; yield, 39.3 g., or 60%; d_4^{25} 1.0439; n_D^{25} 1.4525; M_D calc'd 60.79, obs. 60.85.

Anal. Calc'd for $C_{11}H_{23}Br$: C, 56.17; H, 9.86.
Found: C, 56.43; H, 10.16.

Ethyl 3,7-dimethyl-2-cyanooctadien-2,6-oate (XXIII).—A mixture of 34.7 g. of

methylheptenone, 60 cc. of glacial acetic acid, 5 drops of acetic anhydride, 5 g. of acetamide, and 28.3 g. of ethyl cyanoacetate, was heated so that the temperature of the vapor was maintained at 105–117° and 62 cc. of liquid distilled in 4.75 hrs. The residue in the flask was cooled, washed with two 50-cc. portions of water, and distilled under a pressure of 12 mm. The fraction boiling at 151–152° consisted of the desired condensation product, and was a pale-yellow oil, of sweet, fruity nitrile odor; yield, 47 g., or 85%; d_4^{25} 0.9751, n_D^{25} 1.4820; M_D calc'd 62.77, obs. 64.70; E_M +1.93. Cope[10] has noted a similar exaltation in the case of analogous compounds.

Anal. Calc'd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.79; N, 6.33.
Found: C, 70.38; H, 8.67; N, 6.31.

SUMMARY

1. New hydroterpenoids have been synthesized from thujaketone by application of the Reformatsky, Grignard, Knoevenagel, cyanohydrin, and other standard reactions.

2. Insofar as the odors of these new products are concerned, they differ from, and are more pleasant than, those of the analogously constituted compounds prepared from methylheptenone. In the case of the tertiary alcohols synthesized by the Grignard reaction, the agreeableness of the odor decreased with increase in the molecular weight of the hydrocarbon radical introduced.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA AND DARTMOUTH COLLEGE]

THE PREPARATION OF AMINONITRILES AND THEIR QUATERNARY AMMONIUM DERIVATIVES

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The preparation of the series of aminonitriles and their derivatives, the betaïne nitrile salts, which are described in this article was undertaken in connection with an investigation of the kinetics of the hydrolysis of the nitriles and the amides which are derived from them. The results of that investigation have been published in part[1].

The aminonitriles were prepared either by the method (I) of Knoevenagel and Mercklin[2] which, according to Stewart and Li[3], appears to involve the reactions:

$$\text{(I)}\quad RR'CO + HSO_3^- \rightarrow RR'C(OH)SO_3^- \qquad (1)$$
$$RR'C(OH)SO_3^- + R''_2NH \rightarrow RR'C(NR''_2)OH + HSO_3^- \qquad (2)$$
$$RR'C(NR''_2)OH + HSO_3^- \rightarrow RR'C(NR''_2)SO_3^- + H_2O \qquad (3)$$
$$RR'C(NR''_2)SO_3^- + CN^- \rightarrow RR'C(NR''_2)CN + SO_3^=, \qquad (4)$$

or by a frequently employed method (II) which has been shown by Stewart and Li[3] to depend primarily upon the reactions:

$$\text{(II)}\quad RR'CO + R''_2NH = RR'C(OH)NR''_2 \qquad (5)$$
$$RR'C(OH)NR''_2 + HCN \rightarrow RR'C(NR''_2)CN + H_2O. \qquad (6)$$

While mutual neutralization of the secondary amine and hydrocyanic acid, together with the formation of cyanohydrin, occur to a considerable extent, neither of these reactions leads directly to the formation of the aminonitrile.

The first method is the less satisfactory; by its use good yields of only the aminonitriles derived from formaldehyde and the simpler amines may be obtained. No product was obtained from formaldehyde and diisopropyl amine or dicaprylamine by this series of reactions. The method can be used to secure α-diethylaminopropionitrile (from acetaldehyde),

[1] (*a*) STEWART AND KORPI, *J. Am. Chem. Soc.*, **54**, 3977 (1932).
(*b*) LUTEN AND STEWART, *ibid.*, **56**, 2151 (1934).
[2] KNOEVENAGEL AND MERCKLIN, *Ber.*, **37**, 4081 (1904).
[3] STEWART AND LI, *J. Am. Chem. Soc.*, **60**, 2782 (1938).

and probably α-dimethylaminoisobutyronitrile (from acetone), but not α-diethylaminoisobutyronitrile.[4] In cases where the method is unsuccessful the failure appears to be due to the low rate or adverse equilibrium of reaction 2.

The second method, under the special conditions which were employed, gives a good yield in many cases where the first fails, but there are certain cases where it also fails to give any yield of product. Thus, no product was obtained from the interaction of diethylamine and methyl isopropyl ketone, or from dimethylamine and pinacolone. There seems to be little relation between the molecular weights of the reactants and the ultimate yield; however, diethylamine gives a much lower yield with each of the ketones employed than does dimethylamine. Some of the aldehydic derivatives were obtained in low yields owing to the destruction of the aldehydes by the competing aldol condensation reaction.

Using this method it was noted that with the simpler derivatives considerable heat was evolved upon mixing the reagents, and that the reaction was quickly finished, whereas with the more complex derivatives there was no evolution of heat, and increased time of reaction appeared (although not unambiguously) to give increased yields of product. This is clearly shown in Table I under α-diethylamino-α-methylbutyronitrile.

Although method II has been employed a number of times[5] the experimental conditions used were not adapted to securing the highest yields of product. Stewart and Li[3] have been able, as a consequence of their kinetic investigation of the reactions, to show how better yields might be obtained by modification of the experimental conditions. Unfortunately, these modifications have not yet been employed in the more difficult preparations.

The aminonitriles derived from formaldehyde and the ketones usually have pronounced camphor-like odors, but the aldehyde derivatives are similar to the parent aldehyde in odor, while derivatives of higher amines, such as dicaprylamine, resemble the parent amine. Dimethylaminoacetonitrile acquires a garlic-like odor on a few days' standing. The higher derivatives are more stable, but an odor of hydrogen cyanide appears in all cases on long standing. They are all clear, colorless liquids.

The quaternary derivatives were prepared by adding the appropriate halide to the aminonitrile, or by adding iodoacetonitrile to the appropriate tertiary amine. The substitution of a radical, R_2, for a radical, R_1, on

[4] STEWART AND COOK [*J. Am. Chem. Soc.*, **50**, 1980 (1928)] obtained this substance once by this method but were unable to repeat the preparation.

[5] (*a*) BRUYLANTS, *Bull. sci. acad. roy. Belg.*, [5] **10**, 126 (1924); (*b*) [5] **11**, 261 (1925); (*c*) STEVENS, COWAN, AND MCKINNON, *J. Chem. Soc.*, **1931**, 2568; (*d*) THOMSON AND STEVENS, *ibid.*, **1932**, 2607.

TABLE I

BOILING POINTS AND YIELDS OF AMINONITRILES

NUMBER	SUBSTANCE	BOILING POINT[a], °C$_{p(mm.)}$	METHOD OF PREPARATION AND YIELD, %	LITERATURE BOILING POINT[a] °C$_{p(mm.)}$
1	$(CH_3)_2NCH_2CN$	138	I, 45–79	137–138[9]
		42_{21}		139–140[10]
9	$(C_2H_5)_2NCH_2CN$	70_{23}	I, 70–75	170[10]
		53_{10}		70–71$_{14}$[11]
16	$(n\text{-}C_3H_7)_2NCH_2CN$	96_{23}	I, 72	200–202[10]
		78_9		89–90$_{12}$[12]
20	$(i\text{-}C_3H_7)_2NCH_2CN$	78–79$_{14}$	I, 0	
		55–58$_3$	II, 52–65 (6 hr.)	
22	$(n\text{-}C_4H_9)_2NCH_2CN$	85_4	I, 75	
25	$(i\text{-}C_4H_9)_2NCH_2CN$	87_9	I, 75	95–96$_{11}$[12]
		78–79$_4$	II, 45 (6 hr.)	
26	$(n\text{-}C_5H_{11})_2NCH_2CN$	102–104$_4$	I, 84	
27	$(i\text{-}C_5H_{11})_2NCH_2CN$	93–94$_4$	I, 79	
29	$(n\text{-}C_8H_{17})_2NCH_2CN$	145–150$_3$	I, 0	
			II, 31(9 hr.)	
34	$(CH_3)_2NCH(CH_3)CN$	59–61$_{40}$	II, 28	144[13]
36	$(C_2H_5)_2NCH(CH_3)CN$	55_{11}	II, 68	68_{17}[2]
				47–49$_7$[4]
39	$(CH_3)_2NCH(C_2H_5)CN$	67–68$_{23}$	II, 78 (8 hr.)	156–158[14]
42	$(C_2H_5)_2NCH(C_2H_5)CN$	75.5_{16}	I, 25	
44	$(CH_3)_2NC(CH_3)_2CN$	57_{25}	II, 52–69 (8 hr.)	152[13]
		46_{13}		
47	$(CH_3)(C_2H_5)NC(CH_3)_2CN$	58_{14}	II, 53	
48	$(C_2H_5)_2NC(CH_3)_2CN$	72–74$_{14}$	I, 0	75–77$_{23}$[4]
			II, 30–39 (24 hr.)	73$_{11}$[1a]
51	$(CH_3)_2NCH(n\text{-}C_3H_7)CN$	70_{14}	II	175–176[15]
54	$(C_2H_5)_2NCH(n\text{-}C_3H_7)CN$	95_{15}	II, 44	
		78_4		
56	$(CH_3)_2NCH(i\text{-}C_3H_7)CN$	61_{14}	II	
58	$(C_2H_5)_2NCH(i\text{-}C_3H_7)CN$	69_4	II, 39	
60	$(CH_3)_2NC(CH_3)(C_2H_5)CN$	63_{12}	II, 70 (3–8 hr.)	171[15]
				76–77$_{15}$[5b]
62	$(C_2H_5)_2NC(CH_3)(C_2H_5)CN$	78_{16}	II, 18 (5 hr.)	
64	$(C_2H_5)_2NCH(n\text{-}C_4H_9)CN$	91_9	II, 64 (6 hr.)	
66	$(CH_3)_2NC(CH_3)(n\text{-}C_3H_7)CN$	75_{10}	II, 49 (24 hr.)	

[a] If no figure for pressure is given the boiling point recorded is for atmospheric pressure (750–760 mm. Hg).

[9] ESCHWEILER, *Ann.*, **279**, 44 (1894).

[10] HENRY, *Rec. trav. chim.*, **24**, 173 (1905).

[11] KLAGES, *J. Prakt. Chem.*, (2) **65**, 193 (1902).

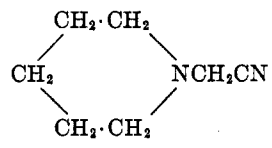
[12] VON BRAUN, *Ber.*, **40**, 3933 (1907).

[13] HENRY, *Bull. sci. acad. roy. Belg.*, **1904**, 741.

[14] MCMEEKING AND STEVENS, *J. Chem. Soc.*, **1933**, 347.

[15] HENRY, *Bull. sci. acad. roy. Belg.*, [3], **36**, 241 (1898).

TABLE I—*Concluded*

NUMBER	SUBSTANCE	BOILING POINT[a], °C$_{p(mm.)}$	METHOD OF PREPARATION AND YIELD, %	LITERATURE BOILING POINT[a] °C$_{p(mm.)}$
68	$(C_2H_5)_2NC(CH_3)(n\text{-}C_3H_7)CN$	103_{21} $80\text{–}85_5$	II, 11.3 (15 hr.) 12.5 (24 hr.) 15.5 (48 hr.)	
70	$(CH_3)_2NC(CH_3)(i\text{-}C_3H_7)CN$	63_7	II, 42 (48 hr.) 49 (24 hr.)	176–177[15]
72	$(CH_3)_2NC(C_2H_5)_2CN$	$69\text{–}73_{10}$	II, 40 (5 hr.) 75 (26 hr.)	176–177[15]
74	$(C_2H_5)_2NCH(n\text{-}C_6H_{13})CN$	$113\text{–}115_{13}$	II, 73	$125\text{–}126_{11}$[2]
75	$(CH_3)_2NC(CH_3)(n\text{-}C_5H_{11})CN$	$104\text{–}105_{10}$	II, 63 (21 hr.)	
77	$(CH_3)(C_6H_5)NCH_2CN$	$138\text{–}141_9$	I, 70–76	266[18] $161\text{–}163_{21}$[16]
80	$(CH_3)_2NCH(C_6H_5)CN$	90_6	I, 29	120_{16}[5c]
81	$(C_2H_5)_2NCH(C_6H_5)CN$	$122\text{–}124_9$	I, 56	$120\text{–}131_{11}$[2] 112_7[4]
82		83_9	I, 94	210^{10} $99\text{–}100_{15}$[17]

[16] WARUNIS AND SACHS, *Ber.*, **37**, 2636 (1904).

[17] KLAGES AND MARGOLINSKY, *ibid.*, **36**, 4188 (1903).

the nitrogen atom influences the rate of quaternization to a degree similar to that found if the same substitution is made in simple amines. If R_2 is substituted for R_1 on the carbon atom adjacent to the nitrile group the rate of the reaction is altered to a similar degree; the effect is not, as might be expected, of a magnitude several-fold smaller. The rates of quaternization of the aminonitriles are much slower than are those of similarly *N*-substituted alkyl amines.

The quaternary derivatives are colorless salts; they vary remarkably in the ease with which they crystallize. While many of the derivatives are strongly crystalline, in other cases the reaction mixtures stood for over a year before any crystals appeared. In a number of cases crystals never were obtained, even though it was obvious that the amine and halide had reacted to a considerable extent. The melting points of the salts range from 85° to 268°.

The results of the preparations are summarized in Tables I and II. The general methods of preparation, the yields and boiling points of the aminonitriles, and the analyses and melting points of the quaternary derivatives are given. In some cases with aminonitriles prepared by method II the time allowed for the reaction is also given. The boiling points and melting points which are recorded in the literature are included.

TABLE II

MELTING POINTS AND ANALYSES OF QUATERNARY SALTS

NUMBER	SUBSTANCE	MELTING POINT, °C.	HALOGEN		LITERATURE MELTING POINT, °C.
			Calc'd, %	Found, %	
2	$(CH_3)_3N^+CH_2CN\ I^-$	228	56.15	56.16	196[18]
				56.19	
3	$(C_2H_5)(CH_3)_2N^+CH_2CN\ I^-$	209	52.88	52.59	
				52.59	
4	$(n\text{-}C_3H_7)(CH_3)_2\overset{+}{N}CH_2CN\ I^-$	95	49.96	49.82	
				49.90	
5	$(i\text{-}C_3H_7)(CH_3)_2\overset{+}{N}CH_2CN\ I^-$	219	49.96	49.82	
				49.81	
6	$(n\text{-}C_4H_9)(CH_3)_2\overset{+}{N}CH_2CN\ I^-$	86.5	47.35	47.36	
				47.38	
7	$(n\text{-}C_{16}H_{33})(CH_3)_2\overset{+}{N}CH_2CN\ I^-$		30.07	28.7	
8	$(CH_3)(C_2H_5)_2\overset{+}{N}CH_2CONH_2\ I^-$	118	46.65	46.16	
				46.15	
10	$(CH_3)(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$	199	49.96	49.92	190–191[17]
				49.91	186[19]
11	$(C_2H_5)_3\overset{+}{N}CH_2CN\ I^-$	187	47.35	47.17	184[17]
				47.20	
11*a*	$(C_2H_5)_3\overset{+}{N}CH_2CN\ Br^-$	209	36.15	35.92	202[20]
				35.93	
12	$(n\text{-}C_3H_7)(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$	195	45.00	44.73	
				44.91	
13	$(n\text{-}C_4H_9)(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$	154	42.87	42.78	
				43.01	
14	$(n\text{-}C_5H_{11})(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$	125	40.94	40.76	
				40.78	
15	$(CH_2{:}CH\cdot CH_2)(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$	157	45.32	44.98	
				45.09	
17	$(CH_3)(n\text{-}C_3H_7)_2\overset{+}{N}CH_2CN\ I^-$	162	45.00	44.72	150[12]
				44.96	
18	$(C_2H_5)(n\text{-}C_3H_7)_2\overset{+}{N}CH_2CN\ I^-$	176	42.87	42.77	
19	$(n\text{-}C_3H_7)_3\overset{+}{N}CH_2CN\ I^-$	179	40.94	40.97	
				40.87	
21	$(CH_3)(i\text{-}C_3H_7)_2\overset{+}{N}CH_2CN\ I^-$	196	45.00	44.87	
				44.87	
23	$(CH_3)(n\text{-}C_4H_9)_2\overset{+}{N}CH_2CN\ I^-$	104	40.94	40.94	
24	$(n\text{-}C_4H_9)_3\overset{+}{N}CH_2CN\ I^-$	131	36.05	35.88	
28	$(CH_3)(i\text{-}C_5H_{11})_2\overset{+}{N}CH_2CN\ I^-$	109	37.54	37.34	
				37.44	
30	$(HOCH_2CH_2)(C_2H_5)_2\overset{+}{N}CH_2CN\ I^-$		44.68	43.97	

[18] VON BRAUN, DEUTSCH, AND SCHMATLOCH, *ibid.*, **45**, 1262 (1912).

[19] KNOEVENAGEL, *ibid.*, **37**, 4073 (1904).

[20] VON BRAUN, *ibid.*, **41**, 2113 (1908).

TABLE II—*Continued*

NUMBER	SUBSTANCE	MELTING POINT, °C.	HALOGEN		LITERATURE MELTING POINT, °C.
			Calc'd, %	Found, %	
31	$(C_2H_5)_2(CH_2CN)\overset{+}{N}CH_2COOC_2H_5\ Br^-$	128	28.63	28.63 28.58	
32	$(CH_3)_2(CH_2CN)\overset{+}{N}CH_2CH_2COOC_2H_5\ Br^-$	102	30.15	30.23 30.17	
33	$(CH_3)_2(CH_2CN)\overset{+}{N}CH_2CH_2COOC_2H_5\ I^-$	122	40.67	40.60 40.56	
35	$(CH_3)_3\overset{+}{N}CH(CH_3)CN\ I^-$	204	52.88	52.53 52.52	
37	$(CH_3)(C_2H_5)_2\overset{+}{N}CH(CH_3)CN\ I^-$	202	47.35	47.16 47.17	195–196[17] 192[2]
38	$(CH_3)_3\overset{+}{N}CH_2CH_2CN\ Cl^-$	230	23.86	23.88	228–229[21]
40	$(CH_3)_3\overset{+}{N}CH(C_2H_5)CN\ I^-$	176	49.96	49.89 49.82	
41	$(C_2H_5)(CH_3)_2\overset{+}{N}CH(C_2H_5)CN\ I^-$	135	47.35	47.41 47.42	
43	$(CH_3)(C_2H_5)_2\overset{+}{N}CH(C_2H_5)CN\ I^-$	184	45.00	44.86 45.02	
45	$(CH_3)_3\overset{+}{N}C(CH_3)_2CN\ I^-$	268	49.96	50.01 49.95	
46	$(C_2H_5)(CH_3)_2\overset{+}{N}C(CH_3)_2CN\ I^-$	*ca.* 250	47.35	47.32 47.30	
49	$(CH_3)(C_2H_5)_2\overset{+}{N}C(CH_3)_2CN\ I^-$	241	45.00	44.96 44.98	
50	$(CH_3)_3\overset{+}{N}CH_2CH_2CH_2CN\ Br^-$	226	38.60	38.42 38.38	
52	$(CH_3)_3\overset{+}{N}CH(n\text{-}C_3H_7)CN\ I^-$	163	47.35	47.46 47.34	
53	$(C_2H_5)(CH_3)_2\overset{+}{N}CH(n\text{–}C_3H_7)CN\ I^-$	121	45.00	45.06 44.91	
55	$(CH_3)(C_2H_5)_2\overset{+}{N}CH(n\text{-}C_3H_7)CN\ I^-$	132	42.87	42.91 42.94	
57	$(CH_3)_3\overset{+}{N}CH(i\text{-}C_3H_7)CN\ I^-$	177	47.35	47.33 47.39	
59	$(CH_3)(C_2H_5)_2\overset{+}{N}CH(i\text{-}C_3H_7)CN\ I^-$	150	42.87	42.77 42.67	
61	$(CH_3)_3\overset{+}{N}C(CH_3)(C_2H_5)CN\ I^-$	216	47.35	47.34 47.32	
63	$(CH_3)(C_2H_5)_2\overset{+}{N}C(CH_3)(C_2H_5)CN\ I^-$	*ca.* 220	42.87	42.74 42.90	
65	$(CH_3)(C_2H_5)_2\overset{+}{N}CH(n\text{-}C_4H_9)CN\ I^-$	116	40.94	40.90 40.86	

[21] EWINS, *Biochem. J.*, **8**, 369 (1914).

TABLE II—*Concluded*

NUMBER	SUBSTANCE	MELTING POINT, °C.	HALOGEN		LITERATURE MELTING POINT, °C.
			Calc'd, %	Found, %	
67	$(CH_3)_3\overset{+}{N}C(CH_3)(n\text{-}C_3H_7)CN\ I^-$	165	45.00	45.09 45.09	
69	$(CH_3)(C_2H_5)_2\overset{+}{N}C(CH_3)(n\text{-}C_3H_7)CN\ I^-$	119	40.94	41.15 41.14	
71	$(CH_3)_3\overset{+}{N}C(CH_3)(i\text{-}C_3H_7)CN\ I^-$	188	45.00	45.30 45.37	
73	$(CH_3)_3\overset{+}{N}C(C_2H_5)_2CN\ I^-$	191	45.00	45.26 45.23	
76	$(CH_3)_3\overset{+}{N}C(CH_3)(n\text{-}C_5H_{11})CN\ I^-$	199	40.94	41.00 40.92	
78	$(p\text{-}CH_3\cdot C_6H_4)(CH_3)_2\overset{+}{N}CH_2CN\ I^-$		42.02	41.81 41.69	100[8]
79	$(C_6H_5\cdot CH_2)(CH_3)_2\overset{+}{N}CH_2CN\ Br^-$	158	31.33	31.28 31.32	
83	$(CH_3)(C_5H_{10})\overset{+}{N}CH_2CN\ I^-$	206	47.71	47.43 47.48	192–193[17]
84	$(C_2H_5)(C_5H_{10})\overset{+}{N}CH_2CN\ I^-$	183	45.32	44.93 45.04	
85	$(n\text{-}C_3H_7)(C_5H_{10})\overset{+}{N}CH_2CN\ I^-$	152	43.16	43.08 42.99	
86	$(CH_2CN)(C_5H_{10})\overset{+}{N}CH_2COOC_2H_5\ Br^-$	154	27.45	27.12 27.23	

For the sake of convenience the aminonitriles and the quaternary salts are tabulated separately, but they are numbered as if they were tabulated in one series. Specific exceptions to the general methods are described in detail in the experimental section.

EXPERIMENTAL

The general methods for the preparations of the aminonitriles are outlined below.

Method I.—A concentrated aqueous solution of the aldehyde bisulfite is prepared by the addition, with cooling, of a slight (5%) excess of solid sodium metabisulfite to a concentrated aqueous solution of the desired aldehyde. After the completion of this reaction as evidenced by the cessation of evolution of heat one equivalent of amine is added to the solution at room temperature, with stirring. In many cases the sodium salt of the aminosulphonic acid precipitates from the solution as a gelatinous mush. The addition of saturated aqueous potassium cyanide dissolves the precipitate (heating is necessary in certain cases) and results in the rapid formation of the aminonitrile as an upper, oily, layer. This is separated, dried over potassium carbonate, and vacuum-distilled.

Method II.—The directions of Immendörfer[6] were adhered to in most cases. To a concentrated aqueous solution of the desired amine hydrochloride an equivalent amount of potassium cyanide was added, following which the desired ketone or aldehyde was added in about 30% excess. The resulting mixture was left on a shaker for a period varying from two to forty-eight hours as indicated in Table I. The appearance of an oily phase in the mixture, and the odor of the mixture indicate roughly the extent to which the reaction has proceeded. The aminonitrile was removed and treated as described above.

No great pains were taken to obtain the aminonitriles in high purity since they served only as intermediates in the preparation of the quaternary derivatives. However, Dr. C. H. Li[7] has prepared a number of the aminonitriles in highly purified form, and has obtained the same values for the boiling points as were obtained by distillation of the crude materials. The yields obtained and boiling points of the aminonitriles are given in Table I.

The quaternization reactions were carried out in dry acetone or *n*-propyl alcohol solution. The simpler derivatives reacted rapidly at room temperature, dilution with solvent being necessary to keep them under control. The slow reactions were carried out in a thermostat at 60°; higher temperatures appeared to favor too much the formation of resinous substances. Well over a month's reaction time was required for a number of the preparations under these conditions. The yields were nearly quantitative for the more rapid reactions, but diminished regularly as the rates decreased.

In a number of cases the quaternary salts were most easily obtained by the reaction of iodoacetonitrile with the desired tertiary amine. This is especially true, owing to the great reactivity of the iodoacetonitrile, when one of the higher alkyl halides must be treated with an aminonitrile. The iodoacetonitrile was prepared by the method described by von Braun.[8] Two preparations of iodoacetonitrile gave yields of 443 grams and 130 grams, 78% and 73%, respectively, boiling from 73° to 78° at 6–9 mm. pressure. Von Braun observed a boiling point of 73–76° at 7 mm. and obtained a yield of 70–75% of a somewhat more carefully purified product.

The crude salts were recrystallized from *n*-propyl alcohol. In this process high yields of the quaternary salts were sacrificed to obtain greater purity. Ordinarily, one recrystallization was sufficient to give a product of more than 99.5% purity, but in a few cases three or four recrystallizations were necessary. Most of the salts are very soluble in hot *n*-propyl alcohol, but some of the ketone derivatives will not dissolve until water to the extent of a few per cent. is added to the alcohol. The temperature coefficient of solubility is high as is usual with iodides. The solubilities of the salts in water may be qualitatively correlated with the melting points and weight of the alkyl radicals; high melting point and high molecular weight both result in diminished solubility.

The iodine content of the salts was determined by titration with silver nitrate, using a chromate indicator. The melting points were determined as described by Luten and Stewart[1b]. They are easily reproducible to within four or five degrees. The analyses and melting points of the quaternary salts are given in Table II.

In the following paragraphs specific points with regard to the preparation or prop-

[6] IMMENDÖRFER, *Ber.*, **48**, 606 (1915).

[7] Private communication.

[8] VON BRAUN, *Ber.*, **41**, 2134 (1908).

erties of certain of the substances described are presented. The italicized number at the beginning of each paragraph refers to the number of the substance used in Tables I and II.

(*4*, *6*) Extremely soluble in *n*-propyl alcohol.

(*5*) Slightly soluble in *n*-propyl alcohol.

(*7*) Obtained as an apparently non-crystalline wax. Very slightly soluble in water.

(*8*) Obtained from the corresponding nitrile by the method described by Luten and Stewart[1b].

(*14*) The yield on quaternization was in the neighborhood of 5%.

(*19*) Prepared from the aminonitrile and *n*-propyl iodide and also from tri-*n*-propylamine and iodoacetonitrile. J. von Braun[20] prepared the bromide but not the iodide.

(*24*) Prepared only from the tertiary amine and iodoacetonitrile.

(*30*) This material decomposed slowly on storage; it probably was never obtained in a very pure condition. It was prepared from iodoacetonitrile and β-diethylaminoethanol.

(*31*) Prepared from the aminonitrile and ethyl bromoacetate.

(*32*, *33*) The iodide was prepared from the aminonitrile and ethyl β-iodopropionate. No difficulties were encountered. In the preparation of the bromide using ethyl β-bromopropionate considerable olefin formation occurred, judging from the fact that a large part of the product was trimethylamine hydrobromide. Repeated crystallization from *n*-propyl alcohol gave a product free of the hydrobromide.

(*34*) The small yield in this reaction is probably due to the removal of acetaldehyde by the competitive aldol condensation reaction.

(*38*) The chloride was prepared without difficulty from trimethylamine and β-chloropropionitrile, as described by Ewins.[21] An attempt was made to prepare the corresponding bromide from β-bromopropionitrile (b.p.$_5$ 58–61°, 15% yield) which in turn was prepared from ethylene cyanohydrin and phosphorus tribromide. The reaction of this substance with trimethylamine was very rapid, although carried out below zero degrees, and gave a product which was 75% trimethylamine hydrobromide and only 25% quaternary salt; the latter substance was never recovered pure from the mixture.

(*46*) This substance decomposes at about 250° without melting.

(*50*) This substance melts at 226° without perceptible decomposition. It was prepared from trimethylamine and γ-bromobutyronitrile. The latter substance was prepared from trimethylene bromide and potassium cyanide by the method described by Derick and Hess.[22]

(*67*) One preparation of this material was impure after the first recrystallization and became more so upon repeated recrystallization; a second preparation, however, was satisfactory after the first recrystallization.

(*68*) Decomposes without melting at about 220°.

(*71*, *73*, and *76*) Considerable difficulty was encountered in the purification of these substances. For recrystallization, dilution of the alcoholic solvent with water gives more satisfactory results.

(*78*) The method of preparation described by J. von Braun[5] (iodoacetonitrile and dimethyl-*p*-toluidine) was employed. This and similar aryl derivatives are unstable under ordinary conditions of storage. The related phenyl derivative becomes

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[22] DERICK AND HESS, *J. Am. Chem. Soc.*, **40**, 546 (1918).

largely decomposed within two months; the *p*-tolyl derivative requires about ten times as long to reach the same condition.

(*79*) This substance was prepared from the aminonitrile and benzyl bromide. The quaternization reaction was rapid and unmarred by resin-forming side reactions. A crystalline product was easily obtained but on analysis it was found to give an acid reaction which was due to contamination by an amine hydrobromide. It could not be purified by recrystallization from *n*-propyl alcohol owing to the fact that the acidic impurity was generated during the process. A satisfactory product was obtained by twice dissolving the salt in cold alcohol and precipitating it with ether.

(*25*, *26*, *74*, *29*, and *47*). The methiodides of the first three of these substances were never obtained in a crystalline form, although it was clear that the quaternization reaction proceeded at a fairly high velocity. In view of the lack of success with these substances no attempt was made to quaternize $(n\text{-}C_8H_{17})_2NCH_2CN$ (*29*). Similarly, in view of the fact that it was much more difficult to prepare the ethiodides than the methiodides of the higher aldehyde and ketone derivatives, no attempt was made to prepare the propiodide of $(CH_3)(C_2H_5)NC(CH_3)_2CN$ (*47*), its methiodide and ethiodide already having been prepared by different routes.

Four other compounds were conspicuous in their failure to crystallize: $(i\text{-}C_4H_9)_3\overset{+}{N}CH_2CN\ I^-$, $(n\text{-}C_5H_{11})_3\overset{+}{N}CH_2CN\ I^-$, $(i\text{-}C_5H_{11})_3\overset{+}{N}CH_2CN\ I^-$, and $(C_6H_5CH_2)_3\overset{+}{N}CH_2CN\ I^-$. In each case the attempt at the preparation was made with iodoacetonitrile and the appropriate tertiary amine, and there was no doubt that the quaternization reaction took place.

I am indebted to Dr. Bernhardt Weidenbaum and Mr. Karl Polifka for the preparation of several of the aminonitriles.

SUMMARY

A series of thirty-three aminonitriles, largely aliphatic derivatives, and fifty-two betaïne nitrile salts, most of which are dervived from the aminonitriles, have been prepared. The limitations of two general methods of preparation of the aminonitriles are outlined.

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE ATLANTIC REFINING COMPANY, PHILADELPHIA, PA.]

REACTION OF ALIPHATIC ETHERS WITH DENIGÈS' REAGENT

E. M. MARKS AND D. LIPKIN*

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In 1898 Denigès[1] showed that tertiary alcohols react with a solution of mercuric oxide in dilute sulfuric acid to form yellow or red precipitates of the type $C_n H_{2n} (SO_4:Hg_2:O)_3$. The tertiary alcohol must be one which is capable of forming an olefin; the reaction fails to take place with those which do not (*e.g.*, triphenylcarbinol). Primary and secondary alcohols, which form olefins less readily than tertiary alcohols, do not react with mercuric sulfate. Recently Kirrmann and Graves[4] demonstrated that various aliphatic ethers behave differently with concentrated sulfuric acid at ordinary temperatures. Straight-chain ethers, as for example ethyl and *n*-propyl ethers, are quite inert and apparently are not attacked by this acid. Ethers containing branched chains (isopropyl, *n*-propyl isopropyl, isopropyl *n*-butyl) react slowly with sulfuric acid. Thus, from a mixture of 4 ml. of isopropyl ether and 5 ml. of 92 per cent sulfuric acid only 1.1 ml. of unchanged ether was recovered after several hours of contacting at room temperature. A consideration of both Denigès' reaction and the results obtained by Kirrmann and Graves suggests that various types of ethers might be characterized to some extent by their behavior towards a solution of mercuric oxide in sulfuric acid. A few simple experiments have shown this to be true.

EXPERIMENTAL

The ethers used in this work were the following: ethyl, *n*-butyl, methyl *n*-amyl, ethyl *n*-butyl, ethyl isobutyl, isopropyl, methyl *tert.*-butyl, ethyl *tert.*-butyl, *n*-propyl *tert.*-butyl, isopropyl *tert.*-butyl, *n*-butyl *tert.*-butyl, methyl *tert.*-amyl, ethyl *tert.*-amyl and di-β-methylallyl ether. In addition, *tert.*-butyl and *tert.*-amyl alcohols were tested for the purpose of determining the effects of replacing hydroxyl hydrogen by alkyl groups. Of the ethers listed above, the following were synthesized by methods described in the literature[2, 3, 5, 6, 8] and carefully purified: methyl *n*-

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[1] DENIGÈS, *Compt. rend.*, **126**, 1277 (1898).

[2] EVANS AND EDLUND, *U. S. Patent* 2010356.

[3] HENRY, *Rec. trav. chim.*, **23**, 329 (1904).

[4] KIRRMANN AND GRAVES, *Bull. soc. chim.*, [5], **1**, 1494 (1934).

[5] LESPIEAU, *Compt. rend.*, **154**, 886 (1912).

[6] MARKS, LIPKIN, AND BETTMAN, *J. Am. Chem. Soc.*, **59**, 946 (1937).

[8] NORRIS AND RIGBY, *J. Am. Chem. Soc.*, **54**, 2088 (1932).

amyl, ethyl isobutyl, and all of the *tert.*-butyl ethers. The remaining compounds were obtained from commercial sources and were also carefully purified before use. All of the ethers were purified by refluxing over sodium ribbon until reaction with the sodium ceased, and were finally distilled through a column of the type recommended by Podbielniak[9]. Before treatment with sodium it is advisable to remove as completely as possible any dissolved alcohol. This may be accomplished either by several washings with a saturated aqueous solution of calcium chloride or more satisfactorily by treatment with sulfuric acid of 30% concentration, followed by water-washing and treatment with solid potassium carbonate or anhydrous calcium sulfate[2].† The tertiary alcohols were of good commercial grades. They were merely refluxed over calcium shavings to remove the last traces of moisture and then were distilled through the Podbielniak column.

The common physical properties of the ethers and alcohols corresponded closely to those recorded in the literature[5, 8, 10, 11, 12].‡ In a few instances, namely with the *tert.*-butyl ethers, the densities were slightly less (0.001–0.003) than those given by Norris and Rigby[8]. Di-β-methylallyl ether, a commercial product, had the following properties after distillation through the Podbielniak column; b.p. 134.4–135.3° (corr. to 760 mm.); d_4^{25}, 0.8100; n_D^{25}, 1.4268.

Denigés' reagent was prepared by dissolving 5 g. of yellow mercuric oxide in 20 ml. of C.P. concentrated sulfuric acid and 100 ml. of distilled water. The testing of the various compounds with this reagent was carried out in the following manner. To 2 ml. of reagent in a test tube (18 by 150 mm.) was added 3 drops of the compound to be examined. Time was recorded by means of a stop watch which was started when the second drop of compound was added. The mixture was then shaken for the required number of minutes and finally was heated to gentle boiling. Reaction was evidenced by the formation of opalescence, coloration and opacity in the mixture. A summary of the results obtained is given in the accompanying table.

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[9] PODBIELNIAK, *Ind. Eng. Chem., Anal. Ed.*, **5**, 135 (1933).

[10] REYCHLER, *Chem. Zentr.*, **1907, I,** 1125.

[11] SENDERENS, *Compt. rend.*, **181,** 698 (1925).

[12] VAN HOVE, *Chem. Zentr.*, **1908, II,** 292.

† In the case of isopropyl *tert.*-butyl ether, essentially complete removal of dissolved alcohol by sulfuric acid was found to be necessary before treatment with sodium. Otherwise, continued decomposition of the ether appeared to take place. In one experiment a quantity of the crude ether (400 ml.) was washed with saturated calcium chloride solution to constant volume (355 ml.). This material was then refluxed over sodium, giving rise to an appreciable amount of a white incrustation on the sodium. The liquid was then distilled, the major portion coming over at 76° (uncorr.), and the last 4% at about the boiling point of isopropyl *tert.*-butyl ether. The distillate (245 ml.) was then treated twice with fresh sodium, each time a considerable incrustation appearing on the sodium, and the liquid distilled mostly at 76°. The volume of distillate was now about 210 ml. Further treatment with sodium showed continued reaction and loss of liquid product. Eventually it was necessary to discontinue this method of treatment. In another experiment a fresh portion of crude ether was washed with 30% sulfuric acid to constant volume, neutralized by dilute sodium hydroxide solution, water-washed and dried by anhydrous calcium sulfate. The recovered liquid did not react appreciably with sodium and showed the correct boiling point for isopropyl *tert.*-butyl ether.

‡ In addition, consult Beilstein.

Whenever coloration was observed, it was yellowish. The test for opacity was that recommended by Mulliken[7]. It consisted in viewing a black line 1 mm. in width on a piece of white paper which was placed in back of, and in actual contact with, the test-tube containing the reactants. When the line became invisible through the mixture, the mixture was considered to be opaque.

DISCUSSION

None of the straight-chain ethers appears to react with Denigès' reagent. Neither the number of carbon atoms nor the position of the oxygen atom in these compounds seems to exert any influence. Compounds containing the *tert.*-butyl radical are, however, quite reactive. *tert*-Butyl alcohol becomes opaque in 4 minutes, as does also methyl *tert.*-butyl ether. It is evident that replacement of hydroxyl hydrogen by methyl does not affect the rate of reaction. In going to ethyl *tert.*-butyl ether the reactivity becomes slightly lower, 5 minutes being required for opacity. Further lengthening of the straight-chain radical influences the reactivity markedly; *n*-propyl *tert*-butyl ether requires 7 minutes for opalescence, develops color after 8 minutes and does not become opaque, while *n*-butyl *tert.*-butyl ether must be heated to boiling before any visible change takes place. Isopropyl *tert.*-butyl ether, on the contrary, is quite reactive, requiring only 4 minutes for opacity. Compounds containing the *tert.*-amyl radical seem to behave like the *tert.*-butyl compounds except that (*a*) their rates of reaction are in general slower, and (*b*) the precipitates formed after the heating period differ in appearance. The *tert.*-amyl ethers form white, needle-like precipitates; the *tert.*-butyl ethers give yellow, curdy deposits. It is suggested that this difference in behavior be used as a test for distinguishing between these two classes of ethers. Considering the *tert.*-amyl compounds more thoroughly, it is seen that *tert.*-amyl alcohol becomes opaque after 2 minutes, the methyl ether requires 9 minutes and the ethyl ether 10 minutes. Replacement of hydroxyl hydrogen in *tert.*-amyl alcohol by alkyl groups therefore brings about a more drastic lowering of reaction rate than that shown in the *tert.*-butyl series.

It should be observed that ethyl isobutyl ether does not react with Denigès' reagent. Apparently the primary carbon atom connecting the oxygen atom with the branched part of the butyl group retards reaction considerably. The compound di-β-methylallyl ether

$$\begin{array}{l} CH_2 = C{-}CH_2{-}O{-}CH_2{-}C = CH_2 \\ \qquad\quad | \qquad\qquad\qquad\quad | \\ \qquad CH_3 \qquad\qquad\quad CH_3 \end{array}$$

[7] MULLIKEN, "Identification of Pure Organic Compounds", 1st Edition, John Wiley and Sons, Inc., New York City, 1904, Vol. I, p. 134.

TABLE

REACTIVITY WITH DENIGÈS' REAGENT

COMPOUND	TIME REQUIRED FOR		AFTER HEATING
	Opalescence (O); Coloration (c)	Opacity	
Ethyl ether	No change after 5 minutes shaking	—	No change
n-Butyl ether	No change after 5 minutes shaking	—	No change
Methyl *n*-amyl ether	No change after 5 minutes shaking	—	No change
Ethyl *n*-butyl ether	No change after 5 minutes shaking	—	No change
Ethyl iso-butyl ether	No change after 5 minutes shaking	—	No change
Isopropyl ether	c, 0.5 min. O, 4 min.	10 min.	Orange precipitate
tert.-Butyl alcohol	O, 1 min. c, 2 min.	4 min.	Dark-yellow, curdy precipitate
Methyl *tert.*-butyl ether	O, 1 min. c, 1.5 min.	4 min.	Dark-yellow, curdy precipitate
Ethyl *tert.*-butyl ether	O, 2 min. c, 3 min.	5 min.	Dark-yellow, curdy precipitate
n-Propyl *tert.*-butyl ether	O, 7 min. c, 8 min.	None	Dark-yellow, curdy precipitate
Isopropyl *tert.*-butyl ether	O, 2 min. c, 3 min.	4 min.	Dark-yellow, curdy precipitate
n-Butyl *tert.*-butyl ether	No change after 10 minutes	None	Dark-yellow, curdy precipitate
tert.-Amyl alcohol	O, 2 min. c, 2 min.	2 min.	Gray, curdy precipitate
Methyl *tert.*-amyl ether	O, 4 min. c, 4 min.	9 min.	White needles
Ethyl *tert.*-amyl ether	O, 6 min.	10 min.	White needles
Di-β-methylallyl ether	O, 2 min. A small amt. of a white curdy ppt. after 5 min.	None	Gray, curdy precipitate

however, is quite reactive, a fact which may be accounted for by the presence of unsaturation in the molecule, since a fully saturated ether with a similar carbon structure (isobutyl ether) should be quite inert towards Denigès' reagent.

In considering the differences in rates of reaction of the various ethers, one should bear in mind that the effect of the solubility of the ether in the reagent has not been taken into account. It is at present a factor of unknown magnitude. We believe, however, that its effect is of only minor significance. For the reaction with mercuric sulfate to take place it appears that at least one of the carbon atoms attached to the oxygen atom must be secondary or tertiary. If both carbons are primary, reaction will not take place. With *n*-alkyl *tert.*-alkyl ethers the reactivity may be reduced appreciably by increasing the length of the *n*-alkyl group.

We desire to thank Mr. J. W. Johnson, Jr. for his capable assistance in the synthesis and purification of the ethers used in this work.

SUMMARY

(1) Denigès' reagent reacts with aliphatic ethers having at least one secondary or tertiary carbon atom joined to the oxygen atom, but not with ethers having only primary carbons attached to oxygen.

(2) The reactivity depends upon the degree of branching. It is greatest when a tertiary carbon atom is attached directly to oxygen.

(3) Mixed ethers, containing both straight- and branched-chain radicals, react with Denigès' reagent at different rates, depending upon the length of the straight-chain radical; the shorter the straight chain, the faster will be the rate of reaction.

(4) Denigès' reagent distinguishes between *tert.*-butyl and *tert.*-amyl ethers.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE ACTION OF DIAZOMETHANE UPON CYCLOHEXANDIONE-1,4*

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Received November 21, 1938

In 1910 Willstätter[1,2] reported the synthesis of cyclooctatetraene. There exists a striking similarity in chemical and physical properties between Willstätter's compound and its derivatives and styrene and its derivatives. Because of this, it was decided to attempt a different synthesis of cyclooctatetraene. As an intermediate in the proposed synthesis cyclooctandione-1,5 was desired, and it was thought that this substance might be prepared by a ring enlargement, using a cyclic ketone and diazomethane. There are several examples of this type of reaction in the literature.[3,4,5,6,7]

With this purpose in mind cyclohexandione-1,4 was treated with diazomethane in ether-methyl alcohol solution, and after repeated fractional distillation four compounds were separated from the reaction product.

I. A white crystalline solid; m.p. 106°–108°.

II. A colorless oil; b.p. 65°–66°/2 mm.; m.p. approx. 10°.

III. A colorless oil, which slowly becomes brown at room temperature, but which is stable indefinitely at 0°; b.p. 84°–88°/2 mm., 107°–111°/10 mm., and 133°–139°/26 mm., with some decomposition.

IV. A rather viscous, colorless oil which becomes colored on standing; b.p. 105°–113°/3 mm.

Because of the complexity of the reaction product, the original purpose of the research was abandoned, and attention was turned to the nature of the compounds formed in the reaction between diazomethane and cyclohexandione-1,4.

* Abstracted from a thesis by John R. Vincent, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, November 1938.

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[1] WILLSTÄTTER AND WASER, *Ber.*, **44**, 3423 (1910).

[2] WILLSTÄTTER AND HEIDELBERGER, *ibid.*, **46**, 517 (1913).

[3] HELLER, *ibid.*, **52**, 741 (1919); **59**, 704 (1926).

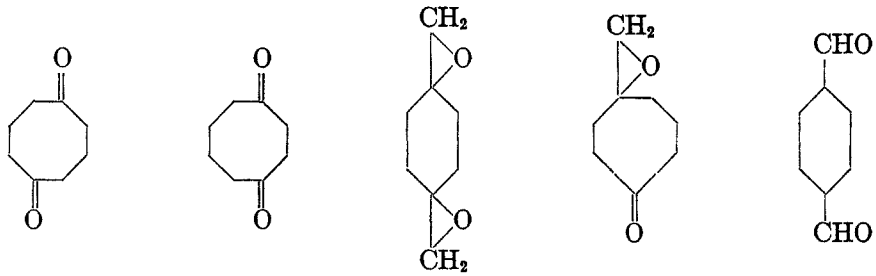
[4] HANTZSCH AND CZAPP, *ibid.*, **63**, 566 (1930).

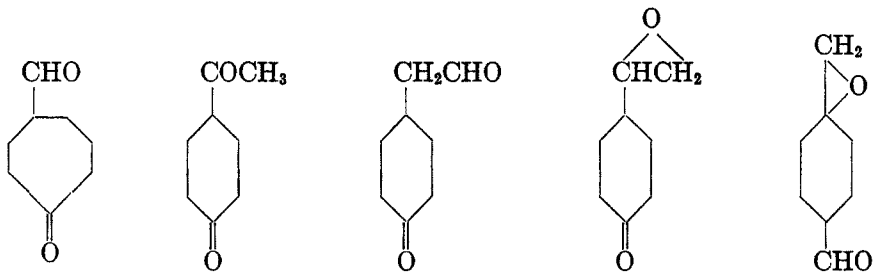
[5] MOSETTIG AND BURGER, *J. Am. Chem. Soc.*, **52**, 3456 (1930).

[6] ROBINSON AND SMITH, *J. Chem. Soc.*, **1937**, 371.

[7] GERAITIS AND BULLOCK, *J. Am. Chem. Soc.*, **59**, 951 (1937).

Compound I has the composition $C_8H_{12}O_2$, showing the introduction of two methylene groups into one molecule of the diketone. This compound on analysis in the Grignard machine‡ shows no active hydrogen and no carbonyl groups. It combines, by addition, with two molecules of hydrogen chloride, two molecules of water and two molecules of piperidine. The piperidine addition product forms a dipicrate. Compound I does not form a semicarbazone, nor does it form a benzal derivative, and it gives no reaction with Fehling's solution or with decolorized fuchsin. After heating I with zinc chloride the fuchsin test is positive. The following chart in analogy with the chart of Arndt, Amende, and Ender,[8] shows the compounds to be expected from the reaction of a carbonyl compound and diazomethane.





Of the above products which are theoretically possible from this reaction and which have the composition $C_8H_{12}O_2$, A, B, D, F, G, H and J all contain a methylene group alpha to a carbonyl group, which would be expected to condense with benzaldehyde. Of the other structures, only one, C, satisfactorily accounts for any of the properties of I, and all these properties together constitute proof that compound I is 1,4-dimethylenecyclohexane dioxide. (C)

‡ We are indebted to Mr. W. W. Prichard for the Grignard analyses reported in this paper.

[8] ARNDT, AMENDE, AND ENDER, *Monatsh.*, **59**, 202 (1932).

The structure of compound II has not been determined. Carbon-hydrogen analyses and molecular weight determinations indicate that its formation involves two molecules of cyclohexanedione and either one or two methylene groups. It forms a semicarbazone and a phenylhydrazone, and reacts with piperidine, forming an oily product. When boiled with very dilute hydrochloric acid II yields two products; one is an organic solid which does not melt below 325°, and the other is a viscous oil.

Compound III has the composition $C_{14}H_{20}O_2$. Attempts to prepare a semicarbazone of III yield the disemicarbazone of 1,4-cyclohexanedione. Further, a sample of this compound, which has been exposed to the air and then cooled with dry ice, precipitates cyclohexanedione. Two facts indicate that the diketone is not present in the oil as an impurity. First, assuming the cleavage of a compound of molecular weight 252, a 67 per cent yield of the semicarbazone of cyclohexanedione is obtained. It is hardly likely that this amount of diketone would be present in the oil as an impurity. Second, if a sample of III is exposed to the air for a short time, cyclohexanedione can be frozen out. After filtering, no more crystallization occurs until the sample has again been exposed to the atmosphere. This process may be repeated several times, until finally no more diketone can be obtained. After this, the remaining oil no longer yields a semicarbazone. From these facts it is concluded that compound III is easily cleaved by moisture, yielding as one of the cleavage products 1,4-cyclohexanedione.

Other properties of III are as follows:

1. Compound III was analysed in the Grignard machine, and showed 1.06 moles of carbonyl and 0.32 moles of active hydrogen per mole of compound, assuming a molecular weight of 252.

2. III reacts with phenylmagnesium bromide giving an oil. This oil is colorless immediately after distillation, but in the presence of air it goes through a very impressive series of color changes, which are repeated on redistillation.

3. III is oxidized by silver oxide or chromium trioxide and is reduced by hydrogen and Raney-nickel or aluminum isopropoxide, to give oily products.

4. III reacts with benzaldehyde in the presence of hydrogen chloride or sodium ethoxide, with malonic acid in the presence of pyridine, and with butyl nitrite in the presence of sodium ethoxide, but in each case the product is an oil.

5. With hydroxylamine and phenylhydrazine compound III reacts to give tarry products.

6. III reacts with bromine with the formation of hydrogen bromide.

7. With dry hydrogen chloride in absolute ether a tar is produced.

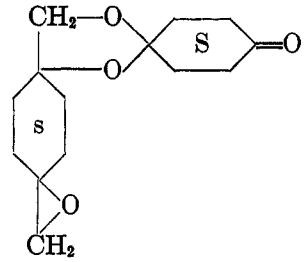
8. Attempts to hydrate III by dissolving it in water and heating, with or without acid catalysts, yielded only oils, from which no solid derivatives could be obtained.

9. With piperidine, III gives a solid dipiperidine addition product, without cleaving.

10. III reacts with phthalic anhydride, but the product is an oil.

11. III does not react with α-naphthyl isocyanate.

The only structure which seems at all reasonable for compound III is



While the reactions given cannot be considered as proof, this structure explains all the properties of III, even the fact that the glycol which would be expected as one of the hydrolysis products (1,4-dihydroxy-1,4-dihydroxymethylcyclohexane) and its derivatives do not crystallize, for this might be expected because of the number of possible stereoisomers.

Some time after this work was completed it was found that O. Pauli[9] in an unpublished dissertation had reported on a study of the action of diazomethane on certain methoxyketones. He obtained two products from each ketone, one of which was the expected ethylene oxide and the other was an oil for which Pauli wrote the cyclic acetal structure, on the basis of the fact that these compounds gave the same glycols on hydrolysis as did the corresponding ethylene oxides. It is interesting that in Pauli's work he was able to isolate only the glycol while in the work described here the cleavage of a similar product led only to the ketone.

Pauli also studied the action of diazomethane on 1,4-cyclohexanedione and obtained compound I, for which he wrote the same structure as is written above, that is, 1,4-dimethylenecyclohexane dioxide, and an oil the structure of which he did not determine.

Compound IV was not investigated because it decomposes in a short time at room temperature.

EXPERIMENTAL

Preparation of 1,4-cyclohexanedione.—Ethyl succinate was prepared by the very useful method of Thielepape[10], in 95% yields. Using the method of Liebermann[11]

[9] PAULI, Dissertation, Marburg, **1935**.

[10] THIELEPAPE, *Ber.*, **66**, 1454 (1933).

[11] LIEBERMANN, *Ann.*, **404**, 272 (1914).

this ester was condensed to ethyl succinosuccinate, in yields of 60–65%. The cyclohexanedione was obtained by heating ethyl succinosuccinate in a small hydrogenating bomb with an equal weight of water and a few small pieces of soft-glass tubing. The bomb was heated to 195°–200° for from 8 to 10 minutes and then cooled rapidly with running water. Several runs of 20–30 g. were always worked up together by distillation under approximately 20 mm. Cyclohexanedione, boiling at 132°/20 mm. and melting at 78°–79.5°, was obtained in yields of 80% to 85%.

Reaction of cyclohexanedione with diazomethane.—To a cold solution of diazomethane (28.0 g.) in ether (1310 cc.), cyclohexanedione (55.4 g.) was added. A very slight evolution of gas began immediately. Then methyl alcohol (415 cc.) was added, and the mixture kept in an ice bath for 15 minutes and then allowed to stand at room temperature until the yellow color had completely disappeared (23.5 hours). After removal of the solvents the product was fractionated through a three-inch column packed with helices. The following fractions were collected:

1. 118–29°/25 mm. Bath temp. 155–60°. Consisted of an oil and a solid. Filtration yielded		
(*a*) Solid	2.08 g.	(3.0%)
(*b*) Oil	17.6 g.	(25.4%)
2. 76–95°/2 mm. Bath temp. 125–30°. Mostly 94–95°	6.2 g.	(8.9%)
3. 95–98°/2 mm. Bath temp. 130°	9.8 g.	(14.2%)
4. 98–05°/2 mm. Bath temp. 130–134°	5.9 g.	(8.5%)
5. 105–08°/2 mm. Bath temp. 134–140°	14.4 g.	(20.8%)
Distillation was stopped at this point to change receivers and then continued.		
6. 98–107°/2 mm. Bath temp. 140–65°	2.0 g.	(2.9%)
7. Residue	4.0 g.	(5.8%)
	61.98 g.	(89.5%)

The yields are based on the assumption of two moles of diazomethane reacting with each molecule of diketone. The yield based on the diazomethane used was 95.8%. The material was fractionated nine more times, during which 0.85 g. of the solid (compound I) was obtained. The tenth distillation gave the following fractions:

1. 65–66°/2 mm. Bath temp. 89–90°	0.42 g.	(0.6%)
2. 66°/2 mm. Bath temp. 90–93°	2.04 g.	(2.9%)
3. 81–84°/2 mm. Bath temp. 100–101°	0.90 g.	(1.3%)
4. 84–85°/2 mm. Bath temp. 101–102°	1.69 g.	(2.4%)
5. 85–86°/2 mm. Bath temp. 102–102.5°	6.32 g.	(9.1%)
6. 86–87°/2 mm. Bath temp. 102.5–103°	3.93 g.	(5.7%)
7. 87–88°/2 mm. Bath temp. 103–104°	9.40 g.	(13.6%)
8. 88°/2 mm. Bath temp. 104–107°	1.61 g.	(2.3%)
9. 101–105°/3 mm. Bath temp. 131–133°	0.91 g.	(1.4%)
10. 105–109°/3 mm. Bath temp. 133–136°	1.80 g.	(2.6%)
11. 109–113°/3 mm. Bath temp. 136°	3.71 g.	(5.4%)
	32.73 g.	(47.3%)

In this way four distinct compounds were obtained:

I. Solid	2.93 g.	(4.2%)
II. Oil, b.p. 65–66°/2 mm	2.46 g.	(3.6%)
III. Oil, b.p. 81–88°/2 mm	23.85 g.	(34.4%)
IV. Oil, b.p. 101–113°/3 mm	6.42 g.	(9.3%)
	35.66 g.	(51.5%)

Properties of compound I

Compound I does not react with semicarbazide hydrochloride, Fehling's solution, or decolorized fuchsin.

Anal. Calc'd for $C_8H_{12}O_2$: C, 68.57; H, 8.57.
Found: C, 68.61; H, 8.91.

Addition of hydrogen chloride to I.—In an attempt to prepare a benzal derivative of I dry hydrogen chloride was passed for 6 hours through an absolute ether solution of 0.3 g. of I and 0.6 g. of benzaldehyde, at 0°. After removal of the ether the resulting product was recrystallized from benzene. It weighed 0.14 g. After two more recrystallizations from benzene it melted at 142.5–143°.

Anal. Calc'd for $C_8H_{14}Cl_2O_2$: C, 45.28; H, 6.66.
Found: C, 45.29, 45.44; H, 7.54, 7.36.

This analysis does not check at all for any of the possible benzal derivatives, but rather indicates the addition of two molecules of hydrogen chloride to I.

Addition of piperidine to I.—When 0.35 g. of piperidine was added to a solution of 0.20 g. of I dissolved in 2 cc. of water the mixture solidified in a few minutes. Two cubic centimeters more of water was added, and the solution was filtered. The white, crystalline solid melted at 124–130° and weighed 0.41 g. After recrystallizing from alcohol, then petroleum ether, and then ether this product melted at 128.5–130°. Molecular weight, by the Rast method, gave 294 and 303.5.

Anal. Calc'd for $C_{18}H_{34}N_2O_2$: C, 69.68; H, 11.05, mol. wt., 310.
Found: C, 69.45; H, 11.16.

This amine forms a picrate melting with decomposition at 222–223.5°.

Anal. Calc'd for $C_{30}H_{40}N_8O_{16}$: C, 46.88; H, 5.21.
Found: C, 46.71; H, 5.23.

Addition of water to I.—A mixture of 0.20 g. of I, 0.5 cc. of water and 2 drops of a 2% solution of acetic acid was heated on the steam bath for 6 hours. The water was removed, leaving a viscous oil. After 10 days in the icebox, partially dissolved in ether-petroleum ether, it had deposited 0.05 g. of crystals of m.p. 190–194°. Approximately half of this solid was recrystallized from alcohol; m.p. 199.5–201.5°.

Anal. Calc'd for $C_8H_{16}O_4$: C, 54.55; H, 9.16.
Found: C, 53.76; H, 9.16.

Though not a first-class analysis, this indicates that two molecules of water have been added rather than one, since the calculated values for $C_8H_{14}O_3$ are C, 60.76; H, 8.86.

Other attempts to hydrate I yielded viscous oils which could not be crystallized.

A small amount of I was heated in a test-tube with freshly fused zinc chloride. A few drops of alcohol was added to extract any organic material. This alcohol solution gave a positive fuchsin test (a blank on the alcohol alone was negative), indicating that some of the aldehyde had been formed.

Properties of compound II

Molecular-weight determinations by the Rast method gave the values 242 and 250 for compound II.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 65.55; H, 7.62; mol. wt., 238.
Found: C, 65.42; H, 7.85.

Semicarbazone of II.—In the usual manner, 0.30 g. of II yielded 0.28 g. of a white solid, which melted with decomposition at 202° after having been twice recrystallized from alcohol.

Anal. Calc'd for $C_{16}H_{26}N_6O_4$: C, 52.46; H, 7.16.
Found: C, 52.33; H, 7.24.

Phenylhydrazone of II.—Compound II forms a phenylhydrazone in the usual manner. After two recrystallizations from alcohol it melts at 121–127°. This derivative is unstable, decomposing into a dark-brown liquid on standing over night.

Reaction of II with piperidine.—When piperidine is added to a water solution of II a colorless oil separates in a few minutes. This oil could not be crystallized. It forms a picrate which melts with decomposition at 200–205° after darkening at about 190°. This picrate is unstable, rapidly decomposing at room temperature.

Hydrolysis of II.—A mixture of 0.4 g. of II, 0.5 cc. of water and 1 drop of concentrated hydrochloric acid was heated for 7 hours on the steam bath, and then 20 cc. of alcohol was added. The mixture was filtered. The insoluble material was organic, but it did not melt below 325°. From the alcoholic solution a viscous oil was obtained, which did not react with semicarbazide or α-naphthyl isocyanate.

Properties of compound III

Molecular-weight determinations by the Rast method gave values of 236, 239, and 241 for compound III.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 66.67; H, 8.00; mol. wt., 252.
Found: C, 66.79; H, 8.21.

Compound III gives positive tests with both Fehling's solution and fuchsin reagent.

Addition of piperidine to III.—A few minutes after dissolving 0.2 g. of III and 0.11 g. of piperidine in 0.5 cc. of water, an oil separates. On standing this oil solidifies and after recrystallization from alcohol, petroleum ether, and finally from ether it melts at 100–101°. The yield was 61%. A molecular-weight determination by the Rast method gave the value 395.

Anal. Calc'd for $C_{24}H_{42}N_2O_2$: C, 68.25; H, 9.95; mol. wt., 422.
Found: C, 67.99; H, 10.58.

The picrate of this compound was obtained as a red oil.

Action of semicarbazide on III.—When III is treated with semicarbazide hydrochloride in the usual way, a 66.7% yield of the semicarbazone of cyclohexanedione is obtained. It melts with decomposition at 228.5° and shows no depression of melting point when mixed with an authentic sample of the disemicarbazone of 1,4-cyclohexanedione.

Anal. Calc'd for $C_8H_{14}N_6O_2$: C, 42.48; H, 6.19.
Found: C, 42.55; H, 6.18.

When the diazomethane from 5 g. of methyl nitroso urea was distilled into a solution of 2 g. of III in 16 cc. of ether and 16 cc. of methyl alcohol, and the solution was allowed to stand at room temperature, it became colorless in 19 hours. The solvents were removed, and the residue was distilled. A small forerun, containing a few crystals, was obtained, but the main fraction boiled at 135–140°/33 mm. This sample of III should contain no cyclohexanedione, but treatment with semicarbazide hydrochloride again yields the disemicarbazone of cyclohexanedione.

Hydrolysis of III by moist air.—A solution of 1 cc. of III in 2 cc. of ether was allowed to stand open to the air for a short time and then was cooled in a bath of carbon dioxide snow and chloroform. Filtration removed the white crystals which melted, after crystallization from petroleum ether, at 79–80°. No depression in melting point resulted when this solid was mixed with known cyclohexanedione. The filtrate was again cooled and filtered, and this was repeated until no crystallization took place. Then the solution was allowed to stand open to the air for 24 hours. The freezing process was repeated and more crystals of cyclohexanedione were obtained. This was repeated every day for 6 days, and then after standing

for 2 days more, no crystals were obtained when the oil or its ether solution was cooled to −80°. Apparently hydrolysis was complete. The remaining oil gave no semicarbazone but it did give a 43% yield of the piperidine addition product of III.

Action of piperidine on 1,4-cyclohexanedione.—When 2.0 g. of cyclohexanedione, 5 g. of piperidine, and 10 cc. of water were allowed to stand in a tightly-stoppered flask, at room temperature, no change was observed after 2.5 hours. After 22 hours the mixture was slightly yellow and possessed a green fluorescence. A small sample poured onto a watch glass became red in a few seconds. After about half the water was removed under reduced pressure the solution was extracted with ether. During the extraction the water layer turned dark red. The ether layer had a green fluorescence. When the ether was removed the residue was a yellow liquid which turned red on contact with air and which possessed a strong ammonia-like odor. When this oil was added to water it solidified (white solid) and then rapidly turned to a red gummy material. The water layer from the extraction was further evaporated and then filtered. This gave a white solid (0.23 g.) that was stable in air, and which melted at 223.5–224° after recrystallization from alcohol.

SUMMARY

Four compounds have been isolated from the reaction between 1,4-cyclohexanedione and diazomethane.

One of these is 1,4-dimethylenecyclohexane dioxide.

Another is probably the cyclic acetal of 1,4-cyclohexanedione and 1-hydroxy-1-hydroxymethyl-4-methylenecyclohexane oxide.

A third compound has been characterized, but its structure has not been determined.

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

CATALYTIC *CIS-TRANS*-ISOMERIZATION AND RESTRICTED ROTATION OF BIPHENYL DERIVATIVES

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It is well known that halogen atoms, halogen halides, oxides of nitrogen oxygen, and colloidal sulfur catalyze *cis-trans*-isomerizations.[1] More recently Kuhn[2] has shown that such transformations can be brought about by certain metals. In his experiments on the isomerization of the dimethyl ester of maleic acid, and of *cis*-stilbene into the *trans* modifications he has observed that the change is catalyzed by alkali metals and catalytic platinum and palladium, but not by bivalent metals such as zinc, cadmium, mercury, magnesium, calcium, strontium, and barium. His results with gallium, indium, and thallium are inconclusive.

Since all the above substances with the exception of the halogen acids have the electron configuration necessary for paramagnetism, Kuhn attempts to correlate his observations by stating that substances which possess a permanent magnetic moment, that is, are paramagnetic, bring about this transformation. Kuhn's theory finds further support in the bromine photosensitized transformation in which the bromine atoms are the active agents. He explains the action of hydrogen iodide and hydrogen bromide as being due to the presence of a small but sufficient concentration of bromine and iodine atoms.[3] To explain the action of hydrogen chloride Kuhn invokes the strong polarizing action of the protons to produce the distortion of the ethylene bond necessary for isomerization.

The first part of this paper deals with an attempt to extend Kuhn's theory to other substances such as chlorides and oxides and to determine whether in these cases also there is a correlation between catalytic activity and magnetic behavior. In Table I in the experimental part of this paper is given the magnetic characteristics of the substances tested and the experimental results obtained. From these observations it can be readily

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[1] For references see GRIGNARD AND BAUD, "Traité de Chimie Organique," I, 1088 (1935), Paris.

[2] R. KUHN, see FREUDENBERG, "Stereochemie," p. 917 (1933), Leipzig.

[3] See also KHARASCH and co-workers, *J. Am. Chem. Soc.*, **55**, 2468 (1933); *ibid.*, **59**, 1405 (1937). J. ORG. CHEM., **2**, 288, 298 (1937). Further references are given in these papers.

seen that there is no direct correlation between the magnetic characteristics of the compound tested and their catalytic activity. Thus, the diamagnetic zinc chloride produces isomerization in five hours while the strongly ferromagnetic magnetite requires fifteen hours to produce a similar change. Furthermore, the paramagnetic ferric oxide and nickel chloride produce no change in the times indicated. The diamagnetic aluminum chloride must be left out of consideration because of the undoubted presence of small traces of hydrogen chloride always associated with this substance, which would catalyze the transformation.

The difficulty of formulating an explanation of the results obtained in this study is one common to any problem in catalysis. At the start one one must assume a definite interaction between the catalyst and the ethylene bond. An examination of the structure of this double bond indicates that it has two types of electrons, the σ electrons, and the π electrons, which are available for bond formation. These latter electrons are also the very electrons which stabilize the special configuration of the molecule (in this case maleic ester). Therefore, in any process of isomerization that does not involve a complete rupture of the ethylene compound into radicals it is these electrons that are involved. During the isomerization process, therefore, the coupling between these two electrons must be affected either by a distortion of their orbits (polarizing action) or by actual bond formation with the catalyst itself. Thus, the catalyst has definite conditions placed upon it.

Kuhn claims that this polarizing action is exerted by the odd electrons present in the catalyst. The presence of an odd electron produces an unsaturation on the catalyst surface which results in the deformation of the orbits of the ethylene π electrons and thus produces the isomerization.

The presence of the odd electron, however, is not necessary. It is to be remembered that the catalyst may have unsaturation in the Werner sense. By that, we mean that the catalyst molecule may have an incomplete octet, as for example, has aluminum chloride, or it may have an octet capable of being expanded into one of higher electron number in which the central atom exhibits its maximum covalency. Such a configuration can also accommodate the two electrons of the ethylene bond, and, thus, form a complex, and make possible the equilibrium.

$$\text{Ethylene bond} + \text{Catalyst} \rightleftarrows \text{Complex},$$

which of necessity will ultimately produce the spacial form which is consistent with the thermodynamic requirements of the system

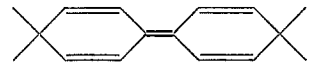
$$cis \rightleftarrows trans.$$

When dealing with heterogeneous systems it is also to be noted that the efficiency of a catalyst depends not only on its electronic structure

but also on the number of catalyst molecules available to the substrate. It is well known that this number can be increased by spreading the catalyst on an inert porous support. On the other hand the number may be increased during the process of isomerization itself. For, if the binding between the substrate and the catalyst is strong enough to overcome the binding between the catalyst molecules themselves, the latter will dissolve in the substrate and thus increase the number of effective catalyst molecules. In other words under such conditions we shall have a very efficient catalyst.

PART II

Quantum mechanical considerations suggest an analogy between the restricted rotation of the ethylene bond and the restricted rotation which gives rise to optical activity in certain diphenyl compounds. Pauling and Sherman in their discussion[4] of the resonance energy of biphenyl postulate a contribution of the following type



to the ordinary structural formula for diphenyl. Theoretical considerations of Lennard-Jones and Turkevich[5] suggest that in biphenyl the carbon-carbon distance between the two rings is not 1.54Å, the value found in aliphatic single carbon-carbon linkages but 1.44Å, involving a shortening of the single bond and an approach to a carbon-carbon double bond.

Finally, X-ray investigations of the structure of biphenyl and related compounds give as the distance of the axial carbon-carbon bond, a value of 1.48Å, again a value intermediate between that observed for the carbon-carbon single bond and the corresponding double bond.[6] Quantum mechanical theories of valence account for this shortening by resonance. Thus, on this basis one would expect to find in the carbon-carbon bond connecting the two rings in biphenyl some of the characteristics of the ethylene double bond, as for example, a shortening of the carbon-carbon distance, a diminished freedom of rotation, and a tendency to assume a planar configuration of the rings.

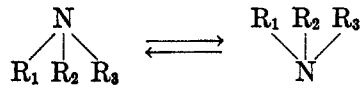
Such double bond characteristics will have two possible effects on the optical stability of the substituted biphenyls.

(1) The presence of asymmetry in biphenyl compounds is generally conceded to be due to a spatial repulsion of the ortho substituents, which does not permit the benzene rings to assume a planar configuration. The fact that the benzene rings do not lie in one plane insures the existence

[4] PAULING AND SHERMAN, *J. Chem. Phys.*, **1**, 633 (1933).
[5] LENNARD-JONES AND TURKEVICH, *Proc. Roy. Soc.*, **A158**, 297 (1936).
[6] PICKETT, *Proc. Roy. Soc.*, **A231**, 213 (1933); DHAR, *Ind. J. Physics*, **7**, 43 (1932).

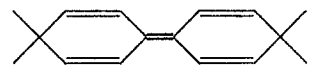
of optical activity. The presence of a double-bond character in the axial carbon-carbon bond tends to counteract this steric repulsion of the ortho substituents in the rings and make the rings co-planar. Such an effect would tend to produce optical instability.

(2) On the other hand, it should be remembered that isolation of the optically active form of a potentially asymmetric compound depends also on the ease of racemization. For instance the molecule $R_1R_2R_3N$ is potentially asymmetric since it has a pyramidal structure. Yet the ease of racemization



is so great that it cannot be isolated in an optically active form. The double bond character of the axial carbon-carbon bond in the biphenyls would decrease the ease of racemization. In the first place it would shorten the carbon-carbon distance and thereby increase the steric repulsion of the ortho substituents. In the second place the process of racemization involves rotation around the carbon-carbon bond. The double bond character of this bond would decrease the ease of rotation and consequently the ease of racemization. This effect would produce optical stability.

In view of these considerations, attempts were made to determine whether those experimental conditions which produce the *cis-trans* isomerization of the ethylene double bond, and which temporarily destroy the double bond character, would racemize an optically active biphenyl derivative. For this study optically active 3,5-dinitro-6-α-naphthylbenzoic acid was chosen. The partially resolved material had a specific rotation $[\alpha]_D^{24} = +8.39°$. From the results of the experiments described in the experimental part of this paper it must be concluded that the existence of the double bond in the carbon-carbon atom linkage between the two phenyl groups in biphenyl derivatives cannot be detected by use of those chemical agents which bring about the *cis-trans* isomerization. Two explanations may be given for this fact. (1) In reality there may be no contribution of the type



to the ordinary structural formula for biphenyl as postulated by Pauling and Sherman[4] in their discussion of resonance energy. (2) This contribution may be present, but, due to the size of the substituents on the phenyl groups, steric factors may come into play and prevent the catalyst from

affecting the coupling between these two π electrons, either by distorting their orbits or by actual bond formation with the catalyst, and thus prevent the formation of the necessary complex which of necessity on decomposition would give an equal number of *d*, and *l* forms. This point of view finds substantiation in certain experimental results of Adkins and his coworkers.[7] In their work on the catalytic hydrogenation of substituted diphenyls these investigators have shown that one may easily hydrogenate all compounds of this type except those which possess the structure necessary for molecular asymmetry. These latter compounds resist hydrogenation even under the most drastic conditions.

TABLE I

"CORRELATION" OF MAGNETIC CHARACTERISTICS WITH CATALYTIC ACTIVITY

SUBSTANCE	MAGNETIC SUSCEPTIBILITY ($X \times 10^6$ e.s.u.)	TIME NECESSARY TO FORM CRYSTALS
Na[a]	+0.51	10 min.
$AlCl_3$	−0.60	1 hour
$FeCl_3$	+86.	3 hours
$ZnCl_2$	−0.47	5 hours
$CrCl_3$	−44.	9 hours
Fe_3O_4	Ferromagnetic	15 hours
$NiCl_2$	−44.7	None in 5 hours
$MgCl_2$	−0.58	None in 5 hours
$HgCl_2$	−0.19	None in 5 hours
Hg_2Cl_2	−0.23	None in 5 hours
H_3O	−0.7	None in 5 hours
Fe_2O_3	+20.	None in 5 hours

[a] It should be noted that our experiments on the interaction of sodium and the dimethyl ester of maleic acid were also carried out in the absence of oxygen. In all cases an appreciable amount of a red, water-soluble sodium derivative was formed. This could be easily isolated by taking up the reaction mixture in anhydrous ether. This fact, which was apparently not noted by Kuhn in his experiments, is significant, and it suggests possibilities which should be further investigated.

EXPERIMENTAL

Experiments on dimethyl maleate—Five-tenths of a gram of dimethyl maleate together with 0.1 g. catalyst was placed in a small glass test-tube, stoppered, and heated at 100° for varying amounts of time. The tube was cooled rapidly and the appearance of solid material was used as a criterion of isomerization since dimethyl fumarate is insoluble in dimethyl maleate. The above table gives the magnetic characteristics of the substances tested and the experimental results obtained.

Experiments with d-*3,5-dinitro-6-α-naphthylbenzoic acid.*—The 3,5 dinitro-6-α naphthylbenzoic acid used in these experiments was prepared and partially resolved

[7] WALDEMAND, ZARTMAN, AND ADKINS, *J. Am. Chem. Soc.*, **55**, 4234 (1933).

according to the directions of Wallis and Moyer[8]. The specific rotation of the partially resolved material was $[\alpha]_D^{24} = +8.38°$.

The ethyl ester of this acid was also made in accordance with directions described in the article referred to above. The ester so prepared was recrystallized from aqueous alcohol. It melted at 94–96°; $[\alpha]_D^{22} = +7.08$.

Effect of Platinum Black.—Two hundred and one milligrams of the acid was dissolved in 25 cc. of absolute alcohol containing 8 mg. of freshly reduced platinum black. The suspension was shaken for twenty-four hours. The optical activity was then measured and found to be $\alpha_D^{25} = 0.08°$. The result for a blank solution containing no platinum black was $\alpha_D^{25} = 0.08°$. No racemization took place under the above conditions.

Action of Metallic Sodium on the Ester.—A dry benzene solution of the ester containing 0.08 g. in 20 cc. was treated with 4 g. of metallic sodium wire. The mixture was thoroughly freed from air by repeated freezing and evacuation and then sealed off in an evacuated tube. The sodium wire turned a brownish-copper color. After shaking for fifteen hours the rotation was $\alpha_D^{25} = +0.06$ while that of the blank was $\alpha_D^{25} = +0.07$. The same experiment was repeated at 100° for forty-eight hours. The sodium in this case was molten and finely divided. There was no evidence of complete racemization under these conditions.

Action of Ferric Chloride on the Ester.—Sixty-three and six-tenths milligrams of the ester in 20 cc. of absolute alcohol was treated with 1 cc. of ferric chloride solution in absolute alcohol (0.1 g. of the salt). A blank containing no iron chloride was similarly prepared. Both solutions were allowed to stand for one day at room temperature. The optical activity was measured and found to be $\alpha_D^{25} = +0.10$ for the ferric chloride solution and $\alpha_D^{25} = +0.09$ for the blank. Thus, no racemization occurred.

Action of Light on the Optically Active Acid.—One hundred and twelve milligrams of the optically active acid was dissolved in 25 cc. of a chloroform-carbon tetrachloride solution, placed in a quartz tube, and exposed to bright summer sunlight for eight hours. No racemization occurred.

Action of Bromine Atoms on Optically Active Acid.—The same solution was treated with 0.1 cc. of a concentrated bromine tetrachloride solution and exposed to sunlight and the strong electric light of a 150-watt lamp for twenty hours. No racemization was observed. A parallel experiment using the dimethyl ester of maleic acid showed that three hours time was sufficient to convert the maleic acid ester into the fumaric acid form.

Other catalysts were studied but in no case was racemization observed under conditions which bring about the *cis-trans* isomerization.

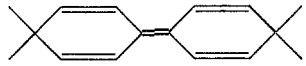
We wish to take this opportunity to express our thanks to the Chemical Foundation for a grant-in-aid for this work.

SUMMARY

The catalytic influence of sodium, and of certain metallic oxides and halides on the *cis-trans* isomerization of dimethyl maleate has been studied. Results have been obtained which show that there is no correlation between catalytic activity and magnetic susceptibility.

[8] WALLIS AND MOYER, *ibid.*, **55**, 2598 (1932).

A study has also been made of possible catalytic effects of these substances on the racemization of *d*-3,5-dinitro-6-α-naphthylbenzoic acid in an attempt to ascertain by chemical means whether there be present in an optically active diphenyl derivative a contribution to the resonance energy of the double bond type,



as suggested by certain quantum mechanical considerations. A theoretical discussion is given of the results so obtained.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

REDUCTION STUDIES IN THE MORPHINE SERIES. VII. THEBAINE*

LYNDON SMALL AND GEORGE L. BROWNING, JR.†

Received October 14, 1938

In the course of experiments in the alkylthiocodide series, it has been shown in this laboratory that the transformation of α-ethylthiocodide (I) into the isomeric β-ethylthiocodide (II) takes place through a shift of one hydrogen atom from the 6 position of the nucleus to the oxygen of the 4,5 ether bridge, with formation of a phenolic hydroxyl group (at C-4) and of a new double bond between carbons 5 and 6. β-Ethylthiocodide has the properties of an enol thio-ether, and undergoes hydrolysis with ease, like an enol oxygen ether, yielding the unsaturated cyclic ketone thebainone (V). Under the conditions imposed for the α-ethylthiocodide rearrangement, it was observed that codeine methyl ether (III), the oxygen (methyl) analog of α-ethylthiocodide, can be caused to undergo a similar rearrangement. The product in this instance is the methyl enol ether (IV) of thebainone (V).[1]

The arrangement of double bonds in ring C of thebainone methyl enolate (IV) is amply demonstrated by the method of preparation, and by the structure of the hydrolysis product, thebainone. There appears to be no satisfactory explanation of the ease with which the ether ring opens in the rearrangement of codeine methyl ether; it can scarcely be ascribed to strain, for the linkage, at least in the saturated series, is re-established even more readily than broken, when the 5-bromodihydrothebainone types are treated with cold dilute alkali.[2] The hydrogen atom on C-6 in codeine methyl ether appears to lie in a configuration with respect to the cyclic

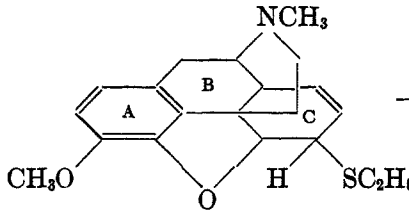
* The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

† Mallinckrodt Fellow in Alkaloid Chemistry, 1936–1937; Merck Fellow in Alkaloid Chemistry, 1937–.

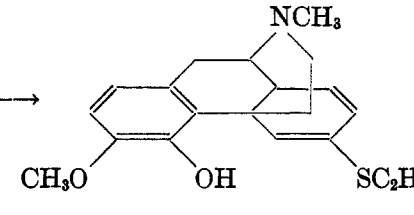
[1] MORRIS AND SMALL, *J. Am. Chem. Soc.*, **56**, 2159 (1934).

[2] (*a*) SCHÖPF AND PFEIFER, *Ann.*, **483**, 157 (1930); (*b*) SCHÖPF AND PERREY, *ibid.*, **483**, 169 (1930); (*c*) SMALL, FITCH, AND SMITH, *J. Am. Chem. Soc.*, **58**, 1457 (1936). See also KONDO AND IKAWA, *Ber.*, **65**, 1214 (1932); *J. Pharm. Soc. Japan*, **52**, 777 (1932); K. K. Shionogi Shoten, Jap. Pat. 101,692 (June 22, 1933), *Chem. Zentr.*, **1933**, II, 3481.

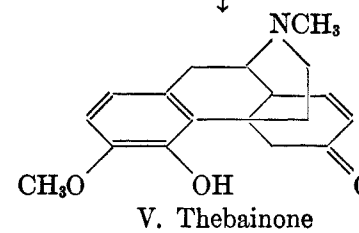
ether oxygen that favors the change, for isocodeine methyl ether, differing from codeine methyl ether only in the configuration at C-6, cannot be caused to rearrange. The C-6 hydrogen atom may also be activated by the 7,8 double linkage, since we have found dihydrocodeine methyl ether (tetrahydrothebaine, IX) to be indifferent. It should be noted, however, that codeine itself is recovered practically unchanged from the reaction.



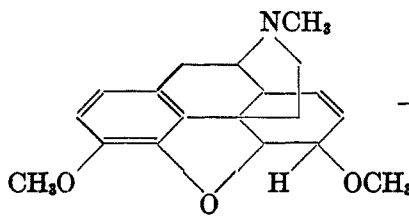
I. α-Ethylthiocodide



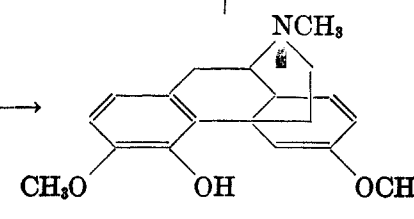
II. β-Ethylthiocodide



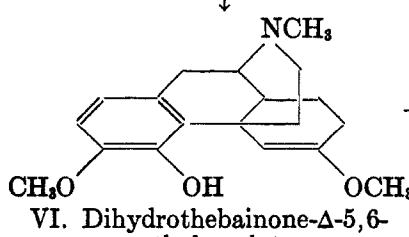
V. Thebainone



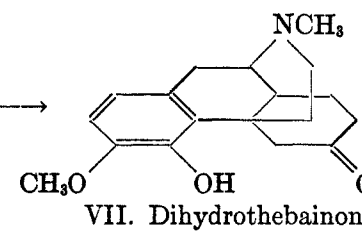
III. Codeine methyl ether



IV. Thebainone methyl enolate



VI. Dihydrothebainone-Δ-5,6-methyl enolate



VII. Dihydrothebainone

Thebainone methyl enolate is so easily hydrolyzed by acids that no salts can be prepared, even in anhydrous media. In neutral or alkaline solution the compound is relatively stable (as shown by the method of preparation, sodium ethoxide solution at 100°), and can be reduced catalytically, or by sodium and alcohol, without alteration of the enol ether group. Both types of reduction yield the same substance, dihydrothebainone-Δ-5,6-methyl enolate (VI). This compound is somewhat less easily hydrolyzed than thebainone methyl enolate. Although it is converted rapidly and quantitatively to dihydrothebainone by dilute aqueous acid solutions, relatively stable salts can be prepared with organic acids

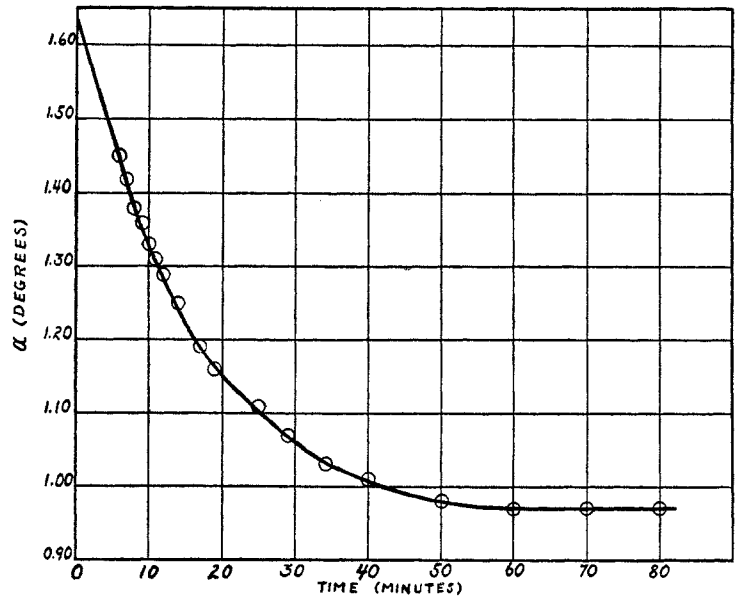


FIGURE 1.—HYDROLYSIS OF DIHYDROTHEBAINONE-Δ-5,6-METHYL ENOLATE FUMARATE

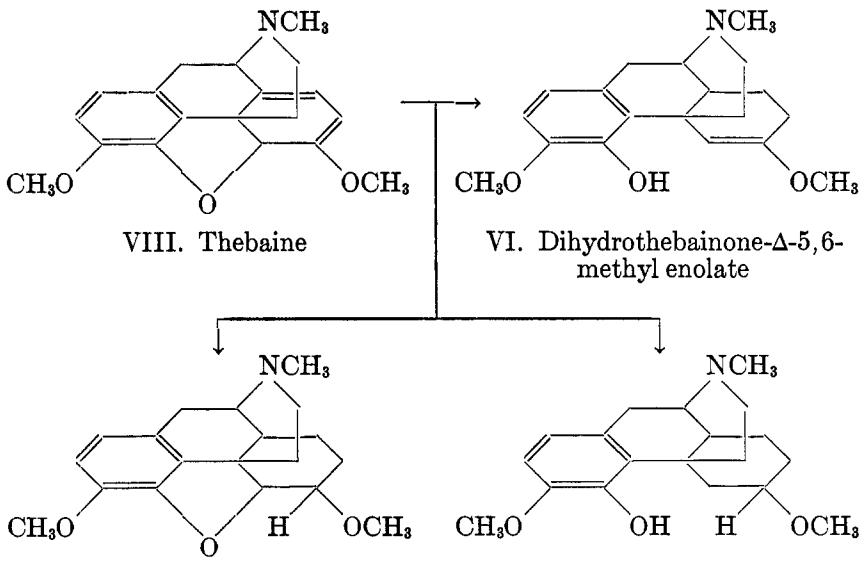
(Water, c = 0.622, l = 4 dm., t = 23°)

in anhydrous media. The fumarate, for example, can be recrystallized from absolute ethanol, but in aqueous solution exhibits a slow change in rotatory power, by which the course of hydrolysis can be followed (Figure 1). In sixty minutes the specific rotation drops from −64.4° (extrapolated to zero time) to −39.0°, the final, constant value being the same as that of dihydrothebainone fumarate.

The structural formula VI that we advance for dihydrothebainone-Δ-5,6-methyl enolate is based on the assumption that the hydrogenation of thebainone methyl enolate (IV) takes place exclusively at the 7,8 unsaturation, in preference to the difficultly reducible enol ether double bond, and in preference to a 1,4 addition of hydrogen. This assumption is supported to some extent by the isolation of the other possible enol ether

isomer (XII) from a different reaction that leaves little doubt concerning the location of the unsaturation.

According to these deductions, dihydrothebainone-Δ-5,6-methyl enolate, a well-crystallized compound of melting point 167°, has a structure identical with that suggested by Wieland and Kotake[3] for an oily product obtained from catalytic hydrogenation of thebaine in neutral solution (alcohol containing suspended sodium bicarbonate). A re-investigation of the Wieland and Kotake reduction shows that it proceeds in a manner more complex than believed by those authors. Hydrogenation takes place with absorption of 2.2 moles of hydrogen, and yields a crude product that is indeed an oil, but which can be separated nearly quantitatively into three crystalline products. The principal one (47 per cent.) is the above-mentioned dihydrothebainone-Δ-5,6-methyl enolate. As secondary products we find tetrahydrothebaine (IX), 31 per cent.) and the hitherto unknown dihydrothebainol alcoholic methyl ether (X, 18 per cent.). The fact that Wieland and Kotake obtained an 80% yield of dihydrothebainone by hydrolysis of their oily product, indicating the presence of a corresponding amount of VI in the mixture, can probably be explained by a difference in the catalyst employed, as even variations between different preparations of catalyst result in as much as 10 to 15 per cent. difference in the yield of dihydrothebainone-Δ-5,6-methyl enolate.



VIII. Thebaine

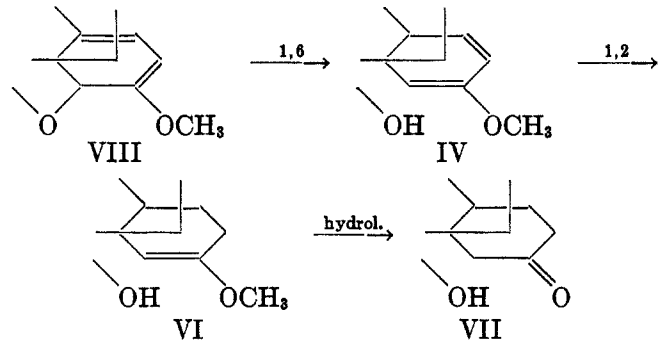
VI. Dihydrothebainone-Δ-5,6-methyl enolate

IX. Tetrahydrothebaine

X. Dihydrothebainol-6-methyl ether

[3] WIELAND AND KOTAKE, *Ber.*, **58**, 2009 (1925); the structure given by these investigators is without double bonds in ring *C*, but is the bridge-ring equivalent of VI or XII with the ethanamine chain attached to C-5.

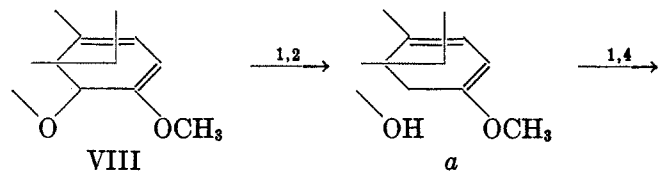
With the demonstration of the reducibility of thebainone methyl enolate to dihydrothebainone-Δ-5,6-methyl enolate, and the positive identification of the latter compound in the thebaine reduction, the Schöpf 1,6 hydrogen-addition mechanism, which postulates the first of these compounds as an intermediate in the reduction of thebaine to dihydrothebainone,[4] gains much in plausibility. The Schöpf mechanism, however, assumes 1,4-hydrogenation as the second step in the reduction process, whereas all of the evidence adduced in the present communication indicates a 1,2-hydrogenation (resulting in VI) in this step. Schöpf's deductions should, therefore, be revised in the sense of the following part-formulas:



VIII IV VI VII

The dihydrothebainol-6-methyl ether that we have isolated from thebaine reduction can be methylated at the phenolic hydroxyl group in position 4 (Rodionov method[5]), but all efforts to prepare the dimethyl ethers of the two known dihydrothebainols[6] were unsuccessful; the steric relationship of the methyl ether X to the dihydrothebainol isomers remains unknown.

The formation of dihydrothebainol-6-methyl ether in the Wieland-Kotake hydrogenation of thebaine is difficult to explain in terms of hydrogenation mechanism. The simplest hypothesis would suggest a primary 1,2 addition of hydrogen to the ether oxygen (activated by the 6,7 double linkage) and C-5, followed by successive 1,4 and 1,2 saturation of the double bonds.

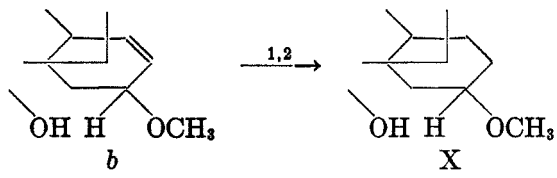


VIII *a*

[4] SCHÖPF AND WINTERHALDER, *Ann.*, **452**, 239 (1927).

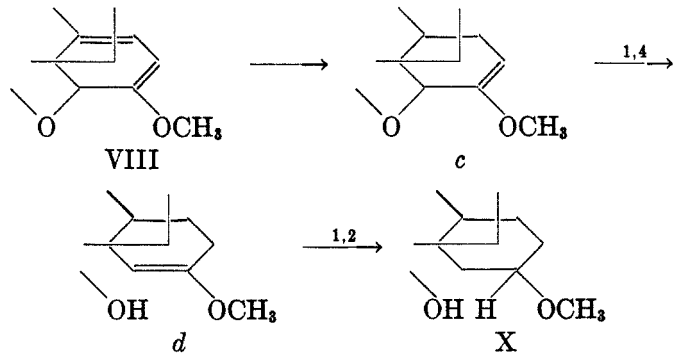
[5] RODIONOV, *Bull. soc. chim.*, **39**, 305 (1926).

[6] (*a*) SPEYER AND SIEBERT, *Ber.*, **54**, 1519 (1921); (*b*) SKITA, NORD, REICHERT, AND STUKART, *ibid.*, **54**, 1560 (1921).



b X

This mechanism, however, postulates a compound of structure *a* as an intermediate. The substance having this structure is known ("phenolic dihydrothebaine"), and, as is set forth in a subsequent paragraph, does not undergo reduction in the manner shown above. A second proposal might assume primary reduction of the 8,14 unsaturation, followed by successive 1,4 and 1,2 reduction. The above mechanism is even less acceptable than the first, for the intermediate *c* is dihydrothebaine, which we

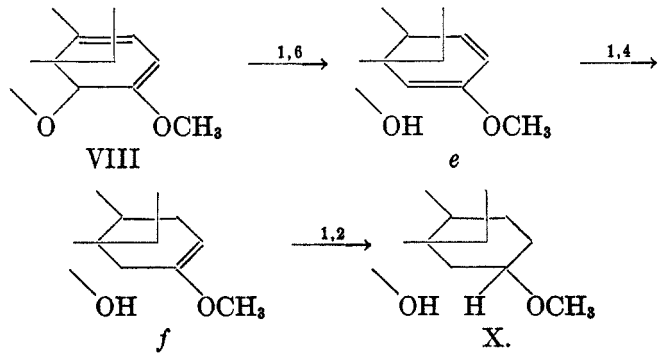


VIII *c*

d X

have found to be completely indifferent under the Wieland-Kotake conditions. The postulated second intermediate *d* is dihydrothebainone-Δ-5,6-methyl enolate, which cannot be hydrogenated further; the reduction stops completely while the product still contains nearly 50 per cent. of this compound.

A third suggestion would involve the Schöpf 1,6 addition hypothesis in its original form, which is incapable also of explaining this phase of the problem. As stated in the discussion of thebainone methyl enolate, we



VIII *e*

f X.

believe that we have evidence that the compound of structure *e* does not add hydrogen in the manner *e* to *f*. The intermediate *f*, however, is dihydrothebainone-Δ-6,7-methyl enolate, a substance that we have isolated from a different series of reactions, and which, as an enol ether, resists hydrogenation under ordinary conditions. We are unable at present to propose any satisfactory mechanism to explain the formation of dihydrothebainol-6-methyl ether.

In 1899, Freund and Holthof[7] accomplished the reduction of thebaine with sodium and alcohol, obtaining a "dihydrothebaine" having the same empirical formula, and approximately the same melting point (154°) as thebainone methyl enolate (IV, m. p. 154–156°). We have examined the compound described by Freund and Holthof, and find it to be different from thebainone methyl enolate. The isomerism appears to be due to a difference in the position of the double bonds in ring C, and the formula XI that we propose for the phenolic† dihydrothebaine rests on the following evidence.

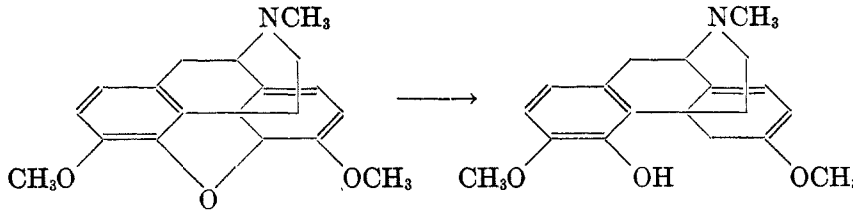
Phenolic dihydrothebaine (XI), in the presence of platinum, adds one mole of hydrogen. The reduction product, which we designate as dihydrothebainone-Δ-6,7-methyl enolate (XII), is an isomer of the above-described dihydrothebainone-Δ-5,6-methyl enolate (VI), and the isomerism must depend solely upon a difference in the enol structure, for XII yields on hydrolysis the same dihydrothebainone as is obtained from hydrolysis of VI. We believe that the 8,14 double linkage assumed in the phenolic dihydrothebaine has been saturated in the hydrogenation, for if the 6,7 linkage were saturated, or if addition of hydrogen to XI took place in the 1,4 manner, the reduction product could not be an enol ether. The possibility that phenolic dihydrothebaine might possess the alternative structure IV that we have assigned to thebainone methyl enolate seems excluded by observations on the hydrolysis of phenolic dihydrothebaine itself, and by the methods of preparation of the two isomers.

Phenolic dihydrothebaine is hydrolyzed with great rapidity by dilute (normal) hydrochloric acid, but other changes appear to take place, for the product is a colored, varnish-like substance. Dilute acetic acid, or cold sulfur dioxide water, on the other hand, cause no change.‡ With

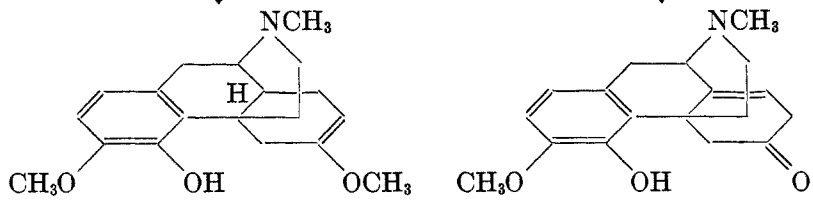
[7] (*a*) FREUND AND HOLTHOF, *Ber.*, **32**, 175 (1899); (*b*) FREUND AND SPEYER, *ibid.*, **49**, 1287 (1916).

† Although Freund mentions the alkali-solubility of phenolic dihydrothebaine, he does not appear to have recognized the presence of the phenolic hydroxyl group. In a potassium hydroxide fusion he obtained the potassium salt, (ref. 7*a*, p. 193), which he believed to be a cleavage product, even though the starting material was regained from it.

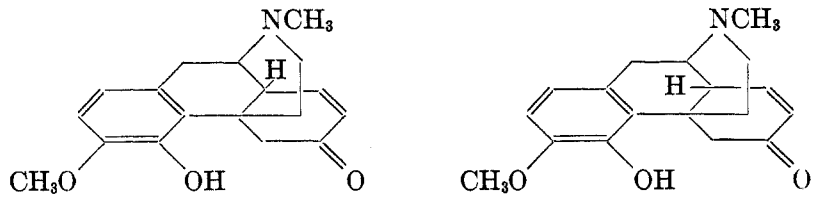
‡ The hydrolysis experiments with sulfur dioxide water have been inconclusive and not always reproducible. One experiment carried out at room temperature was successful, while in others, apparently identical, the starting material was regained.



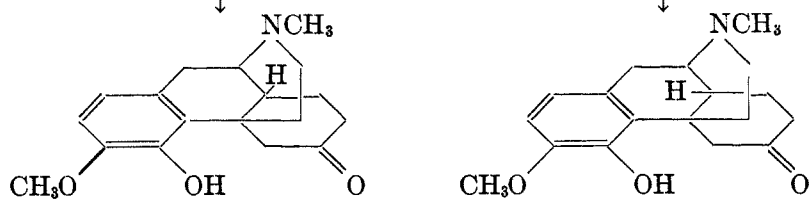
VIII. Thebaine XI. Phenolic dihydrothebaine



XII. Dihydrothebainone-Δ-6,7-methyl enolate XIII. α-Thebainone



XIV. β-Thebainone V. Thebainone



XV. β-Dihydrothebainone VII. Dihydrothebainone

warm sulfur dioxide water, a hydrolysis product (m. p. 184°) that we have named α-thebainone (XIII) is obtained. The yields are so unsatisfactory and erratic that we are delaying the investigation of this compound until a better preparative method is found. The structure XIII is suggested only as a possibility, subject to revision when decisive experiments can be undertaken.

Hydrolysis at the hydrogen-ion concentration of potassium acid sulfate

solution is more successful, and yields three products.§ The known thebainone (V), and α-thebainone are formed in small amounts, but the main product is a new isomer, β-thebainone (XIV). The following discussion will be concerned mainly with the nature of this β-thebainone and its transformation products.

β-Thebainone, $C_{18}H_{21}NO_3$, differs widely in melting point (89–90°) from the known thebainone (m. p. 151–152°), and in specific rotation. The isomerism is apparently not due to a difference in location of the unsaturation (as we have tentatively assumed for the thebainone-α-thebainone relationship), for elimination of the unsaturation by catalytic hydrogenation results in a β-dihydrothebainone (XV),* different from dihydrothebainone.

The appearance of the three isomeric thebainones in the hydrolysis of phenolic dihydrothebaine may be explained as follows. Hydrolysis at the enol ether group, followed by ketonization with saturation of the C-6, C-7 double bond would result in a compound of the structure assigned to α-thebainone. A 1,4 addition of water at C-6 and C-14, with subsequent loss of methanol resulting in the carbonyl group at C-6, would explain the appearance of thebainone.† If the postulated addition of hydrogen at C-14 takes place in both possible configurations, β-thebainone would be explained as a diastereoisomer of thebainone. It seems equally probable that thebainone and β-thebainone might arise from a 1,2 hydrolysis of the enol ether, followed by 1,4 ketonization in two configurations at C-14.

We have not neglected the possibility that β-thebainone might have the structure that we suggest for α-thebainone, and that the isomerism of

§ Freund isolated from the hydrolysis of phenolic dihydrothebaine with dilute hydrochloric acid a small amount of a "poorly characterized compound" that gave analytical values corresponding approximately to the formula $C_{18}H_{21}NO_3$. This was probably a mixture of the three thebainones, and Freund's designation "isocodeine" for the product should be deleted from the literature [Beilstein, Ergänz. III, 677 (1904)], the term isocodeine being correctly applied to one of the hydrolysis products from the halogenocodides.

* The term β-dihydrothebainone was applied by KONDO AND OCHIAI, *J. Pharm. Soc. Japan*, No. **549**, 913 (1927); *Ann.*, **470**, 232 (1929), to a supposedly homogeneous reduction product of metathebainone, that SMALL AND MEITZNER, *J. Am. Chem. Soc.*, **55**, 4602 (1933), showed to be a mixture of metathebainol and dihydrometathebainone. The term β-dihydrothebainone is any event not applicable to a compound derived from the metathebainone series.

† A similar explanation has been offered for the formation of bromocodeinone and hydroxycodeinone, from treatment of thebaine with bromine and hydrogen peroxide, respectively [SCHÖPF AND BORKOWSKY, *Ann.*, **462**, 249 (1927)]. Nothing is known of the configuration of the hydroxyl or bromine atom, except that bromocodeinone can be converted to hydroxycodeinone, or, by reduction, to codeinone or dihydrocodeinone, changes that involve the possibility or probability of inversion.

β-dihydrothebainone and dihydrothebainone might be due to addition of hydrogen at C-14 during the catalytic hydrogenation, in a configuration opposite to that existing naturally in the morphine group. There is, however, no evidence in morphine chemistry for this type of isomerism appearing in the catalytic saturation of the 8,14 double bond beyond the isolation by Schöpf[4, 8] of a supposed "dihydro-*epi*-thebainone" whose structure was never investigated. Certainly, in the series under investigation, the nearest analog, phenolic dihydrothebaine, undergoes hydrogenation at the 8,14 unsaturation to yield a sterically homogeneous product, dihydrothebainone-Δ-6,7-methyl enolate, that gives only dihydrothebainone on hydrolysis and must therefore have the hydrogen atom at C-14 in the ordinary configuration. Dihydrothebainone is known to have the same C-14 configuration as morphine from various methods of preparation, for example the process codeine-codeinone-dihydrocodeinone-dihydrothebainone, furthermore, from the ring closure of Schöpf[2a] that leads from dihydrothebainone through bromodihydrocodeinone to dihydrocodeinone. In neither of these reaction series is there any possibility that C-14 has been affected. Other examples of saturation of the 8,14 double bond in the ordinary configuration may be found in the hydrogenation of β-methylmorphimethine, and of neopine.

The appearance of dihydrothebainone as the product from hydrolysis of dihydrothebainone-Δ-6,7-methyl enolate excludes the possibility that inversion of an asymmetric center, or any deep-seated structural change, might have taken place under the rather drastic conditions imposed in the conversion of thebaine to phenolic dihydrothebaine.

The experiment of Knorr,[9] who was able to hydrolyze thebaine itself to codeinone, demonstrates that such a system as we postulate for phenolic dihydrothebaine can undergo hydrolysis (or ketonization subsequent to hydrolysis) in the 1,4 manner. The fact that the product obtained by Knorr had the morphine configuration at C-14 does not weigh heavily against our hypothesis of the generation of asymmetry at this point in the opposite configuration, for the yield of codeinone was so low (5 per cent.), and the conditions necessary for the thebaine hydrolysis were so vigorous, that it is not surprising that no epimer of codeinone was observed. The discrepancy, if any, lies in the relative resistance of thebaine to hydrolysis, in comparison with phenolic dihydrothebaine. The presence of the 4,5 oxygen bridge seems to stabilize the enol ether group to some extent, for we have observed that dihydrocodeinone methyl enolate (dihydrothebaine) and dihydromorphinone methyl enolate[10] are markedly more resistant to

[8] SCHÖPF AND BORKOWSKY, *Ann.*, **458**, 155 (1927).
[9] KNORR AND HÖRLEIN, *Ber.*, **39**, 1409 (1906).
[10] SMALL, TURNBULL, AND FITCH, J. ORG. CHEM., **3**, 204 (1938).

hydrolysis than the two dihydrothebainone methyl enolates described in this communication. Thebainone methyl enolate (IV) likewise undergoes hydrolysis with extraordinary ease in comparison with thebaine.

The exhaustive methylation of phenolic dihydrothebaine has not yet been undertaken, as it was subordinate to our interest in the hydrogenation and hydrolysis products. The reaction of phenolic dihydrothebaine methiodide with sulfur dioxide water is unusual, and has been taken under investigation. There is but little doubt that the product is the hydriodide of one or more of the thebainonemethines, formed by hydrolysis of the enol ether and rupture of the nitrogen-containing ring. The ring scission probably takes place with such extraordinary ease because of the tendency to form a conjugated system, although a similar tendency would be expected of thebaine. This aspect of the problem will be reported in a later communication.

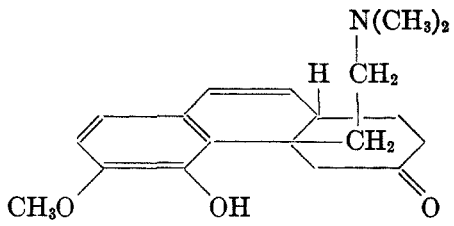
The degradation of β-dihydrothebainone methiodide takes the usual course, and results in β-dihydrothebainonemethine (XVI), an isomer of dihydrothebainonemethine (des-*N*-methyldihydrothebainone), XVII. β-Dihydrothebainonemethine absorbs one mole of hydrogen, giving β-dihydrothebainonedihydromethine, isomeric with the corresponding derivative in the normal dihydrothebainone series.‡

Schöpf and Borkowsky[11] have reported that the degradation product from dihydrohydroxythebainone, namely dihydrohydroxythebainonemethine (des-*N*-methyldihydrohydroxythebainone), suffers loss of water with great ease, apparently from the 8,14 position. The hydrogenation product (not analyzed) derived from the dehydrated methine base was suggested by these investigators as perhaps having the structure that we assign to β-dihydrothebainonedihydromethine. Its melting point (135–137°) does not correspond with that of our base (177–178°), and, in view of the evidence that we have accumulated on the structure of our isomer, we are forced to believe that other changes than those postulated by Schöpf and Borkowsky must have taken place in the decomposition of dihydrohydroxythebainonemethine.

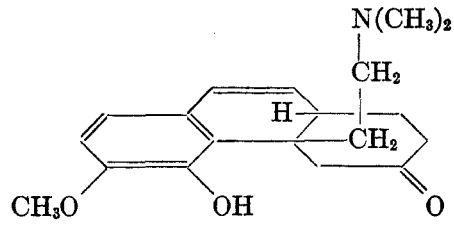
β-Dihydrothebainonedihydromethine methiodide undergoes further degradation with loss of trimethylamine, to yield the non-phenolic ketone, β-thebenone (XX). It is obvious that the vinyl group formed in the degradation has cyclized with the phenolic hydroxyl in the 4 position, as

‡ We have prepared dihydrothebainonedihydromethine several times, and find the melting point to lie at 155–156°, as originally observed by WIELAND AND KOTAKE, *Ann.*, **444**, 88 (1925). The melting point 138–139° reported by CAHN, *J. Chem. Soc.*, **1926**, 2570, and by SCHÖPF, (136–137°), *Ann.*, **452**, 266, footnote, (1927) is that of an unstable modification, as we were able to demonstrate with a sample of the low-melting form generously furnished by Prof. Schöpf.

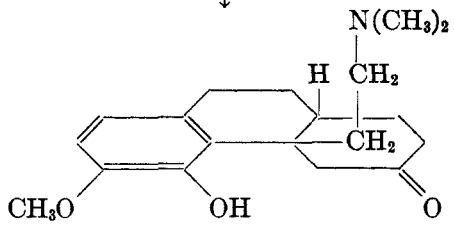
[11] SCHÖPF AND BORKOWSKY, *Ann.*, **452**, 255 (1927).



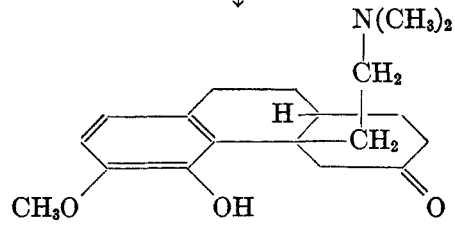
XVI. β-Dihydrothebainonemethine



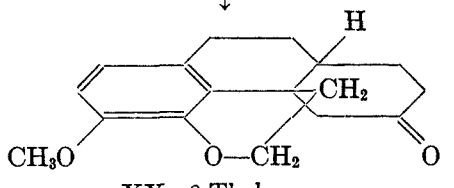
XVII. Dihydrothebainonemethine



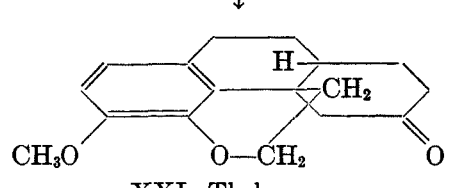
XVIII. β-Dihydrothebainone-dihydromethine



XIX. Dihydrothebainone-dihydromethine



XX. β-Thebenone



XXI. Thebenone

was demonstrated by Wieland and Kotake in the parallel degradation of dihydrothebainonedihydromethine. In β-thebenone, all of the asymmetric centers originally present in thebaine (C-9, C-13, C-5) have been eliminated excepting C-13. This center has been proved to be unchanged in configuration in the phenolic dihydrothebaine through the transformations that result in dihydrothebainone, and in none of the steps leading to β-thebenone is there any reason to suspect a change at this point. The isomerism of β-thebenone and thebenone must therefore depend upon a configurational difference at C-14, the other asymmetric center present, which was generated in the hydrolysis step.

We believe that the series of isomers of dihydrothebainone, dihydrothebainonemethine, dihydrothebainonedihydromethine, and thebenone constitutes the first experimentally substantiated evidence that stereoisomerism of this type can be generated in the morphine group.

Further investigations in this series will include attempts to demonstrate the structure of α-thebainone, and if, as we postulate, it contains the 8,14 double linkage, to close the 4,5 ether ring. This should lead into the neopine series. Ether-ring closure with β-dihydrothebainone may be expected to result in an epimer of dihydrocodeinone having considerable pharmacological interest.

We are indebted to Merck and Co., Inc., Rahway, N. J., for the gift of the thebaine used in this research, and to Merck and Co., Rahway, N. J., and Mallinckrodt Chemical Works, St. Louis, Mo., for fellowship grants under which the work was carried out.

EXPERIMENTAL

Thebainone methyl enolate.—A solution of 10 g. of codeine methyl ether (m. p. 141–142°, $[\alpha]_D^{22}$ −194.5°) in 80 ml. of absolute alcoholic sodium ethoxide (containing 2.4 g. of sodium) was heated in a sealed tube for four hours in boiling water. At the end of the reaction, 150 ml. of water was added, and the alcohol was removed at 25° under diminished pressure in a stream of hydrogen. The product separated as pink crystals, and the precipitation was completed with excess of saturated ammonium chloride solution. The crystals were washed well with water and dried in a vacuum; yield, 9.5 g. After two crystallizations from a small volume of absolute alcohol, the compound consisted of colorless, hard, granular crystals that sintered slightly at 148°, and melted at 154–156°; in 95% alcohol, $[\alpha]_D^{22}$ +9.6° (c = 0.57).

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40; $(OCH_3)_2$, 19.8.
Found: C, 72.65; H, 7.43; OCH_3, 19.3

Thebainone methyl enolate sublimes at 100° in the vacuum of the oil pump without change in melting point or rotatory power. It is soluble in cold dilute sodium hydroxide, and precipitates with ammonium chloride. The ferric chloride reaction in alcohol is deep blue-green, changing rapidly to pure green, probably as a result of hydrolysis. The base is so easily hydrolyzed by acids that no salts could be prepared. In absolute alcohol with alcoholic hydrogen chloride a crystalline hydrochloride was obtained, which represented almost entirely hydrolysis product; calc'd for $C_{19}H_{24}ClNO_3$: $(OCH_3)_2$, 17.7; for $C_{18}H_{22}ClNO_3$: OCH_3, 9.2. Found: OCH_3, 10.2. Thebainone methyl enolate is somewhat unstable; after four years in darkness the crystals are distinctly yellow, and melt over a wider range, 148–154°.

Thebainone.—A solution of 0.5 g. of thebainone methyl enolate in 3 ml. of 3 *N* hydrochloric acid was warmed gently, and treated with excess of potassium iodide. The yield of thebainone hydriodide of melting point 257–260° (decomp.) was 0.5 g.; no depression in mixture melting point. From it was obtained thebainone base, m. p. 145–147°, $[\alpha]_D^{24}$ −46.6°, whose oxime hydrochloride had the melting point 285–287°; both compounds were identified by mixture melting point.

Reduction of thebainone methyl enolate.—1. Sodium.—Four grams of thebainone methyl enolate in 300 ml. of alcohol was heated under reflux in a hydrogen atmosphere, and 20 g. of sodium was added during one hour, with mechanical stirring. After all sodium was dissolved, 300 ml. of oxygen-free water was added to the colorless alcohol solution, and alcohol was removed under diminished pressure (water-pump), with a stream of hydrogen passing through the capillary. The resulting aqueous alkaline solution was treated with excess of carbon dioxide, which precipitated a nearly white crystalline product. This was extracted into ether, and the

product obtained after removal of the ether was purified from alcohol. The yield was 2.1 g. of pure white crystals of m. p. 164–165.5°, $[\alpha]_D^{25}$ −115.7° (absolute alcohol, c = 1.02). It did not depress the melting point of dihydrothebainone-Δ-5,6-methyl enolate (see thebaine reduction), and yielded dihydrothebainone on treatment with acid.

2. Catalytic.—Four grams of thebainone methyl enolate in absolute alcohol with 0.1 g. of platinum oxide absorbed one mole of hydrogen in one hour. The product, purified from alcohol, was 2.4 g. of the above-described dihydrothebainone-Δ-5,6-methyl enolate, m. p. 164–165°.

Isocodeine methyl ether.—This compound has been described previously only in the form of the methiodide.[12] It was prepared by methylation of isocodeine-*N*-oxide, followed by reduction of the *N*-oxide group, according to the procedure of Mannich.[13] The product (50% yield) was liquid, but after distillation at 110° in the oil-pump vacuum it crystallized slowly. The crystals melted at 80–82°, and were so soluble that they could not be purified from solvents. The methiodide crystallized in white leaflets, m. p. 196–198°, $[\alpha]_D^{25}$ −112.1° (Pschorr, m. p. 199–200°, $[\alpha]_D^{22}$ −111.6°). The salicylate crystallized well from absolute alcohol and had the melting point 158–159°; $[\alpha]_D^{24}$ −122.4° (water, c = 0.91).

Anal. Calc'd for $C_{26}H_{29}NO_6$: C, 69.14; H, 6.48; $(OCH_3)_2$, 13.7.
Found: C, 69.19; H, 6.56; OCH_3, 14.2.

Isocodeine methyl ether salicylate was recovered nearly quantitatively from the attempted rearrangement with sodium ethoxide, as were also codeine, isocodeine, and tetrahydrothebaine. At higher temperatures only decomposition products resulted.

Hydrogenation of thebaine.—A suspension of 25 g. of thebaine in 150 ml. of 95% alcohol with 2 g. of palladium-barium sulfate (5% Pd) and 0.5 g. of sodium bicarbonate was shaken under hydrogen until absorption ceased; between 30 and 120 hours was required with different catalyst preparations. The absorption in six experiments averaged 158 ml. (corr.) of hydrogen per gram of thebaine, or 2.2 moles, a quantity that agrees well with the composition of the products. In the early experiments, the catalyst was filtered out, and the alcohol was removed under diminished pressure with a bubble tube at about 35°, until a brittle, fluffy mass remained. When this was rubbed with alcohol, a heavy crop of crystals formed. When once seed was present in the laboratory, it was necessary to filter the catalyst out very rapidly as soon as the hydrogenation flask was opened in order to effect its removal before crystallization started. The alcohol solution was chilled in ice for two hours, the first crop of dihydrothebainone methyl enolate filtered out, and the mother liquor was concentrated under diminished pressure to a thick syrup. When this was brought to a volume of 40 ml. with hot absolute alcohol it crystallized immediately. The total yield of dihydrothebainone-Δ-5,6-methyl enolate was 11.8 g. (47% of the calculated amount).

The alcohol mother liquors were practically free of dihydrothebainone methyl enolate. To the boiling alcohol solution was added sufficient solid fumaric acid (4.8 g.) to combine with all the remaining alkaloidal material (13.2 g.). The crystalline fumarate of dihydrothebainol-6-methyl ether separated immediately, and a small second crop was obtained by cautious addition of ether to the mother liquor. A total of 6.3 g. of fumarate was obtained, equivalent to 4.6 g. of base, or a yield of 18%.

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[12] Pschorr and Dickhäuser, *Ber.*, **45**, 1567 (1912).

[13] Mannich, *Arch. Pharm.*, **254**, 349 (1916).

The mother liquor still contained the equivalent of 8.6 g. of the original 25 g. of thebaine. It was evaporated to a heavy oil, taken up in water, and the base was liberated with ammonia and brought into ether. Evaporation of the ether gave a yellow oil. This was dissolved in 50 ml. of hot alcohol, and treated with a hot saturated alcoholic solution of the calculated amount (6.3 g.) of picric acid. The yield of crystalline tetrahydrothebaine picrate was 13.4 g., equivalent to 7.7 g. of tetrahydrothebaine, or 31%. The total yield of identified products was 24.1 g., or 96% of the starting material. The base isolated from the picrate was tetrahydrothebaine of melting point 81–83°, which was further identified by conversion to the characteristic hydrochloride trihydrate.

Dihydrothebainol-6-methyl ether.—The dihydrothebainol-6-methyl ether fumarate, isolated from the hydrogenation mixture as described above was purified by repeated recrystallization from absolute alcohol. It had the m. p. 198–201° (decomp.) and showed in aqueous solution $[\alpha]_D^{22}$ −28.1° (c = 0.85). The crystalline base regenerated from the fumarate was purified by adding benzene to a suspension in boiling isopropyl ether (peroxide-free) until all material dissolved. The purified material was then sublimed several times in a high vacuum, air-bath temperature 120°; it formed centimeter-long silky white needles, m. p. 140.5–142°, $[\alpha]_D^{21}$ −23.4° (alcohol, c = 1.024). The ferric chloride test is pale emerald, turning to brown.

Anal. Calc'd for $C_{19}H_{27}NO_3$: C, 71.87; H, 8.58; $(OCH_3)_2$, 19.5.

Found: C, 71.83, H, 8.70; OCH_3, 19.5.

The compound was regained unchanged from attempted methylation with diazomethane, but from the action of trimethylphenylammonium hydroxide a liquid methyl ether was obtained, which was not further investigated.

Dihydrothebainone-Δ-5,6-methyl enolate.—The crystalline base that first separated from the thebaine hydrogenation solution was purified by recrystallization from absolute alcohol, in which it is only slightly soluble. It had the melting point 165.5–166° (evac. tube); mixture melting point with dihydrothebaine of m. p. 162° was 135–138°. In absolute alcohol, $[\alpha]_D^{22}$ −118.4° (c = 1.03).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99; $(OCH_3)_2$, 19.7.

Found: C, 72.15; H, 7.91; OCH_3, 19.7.

The enol ether group underwent hydrolysis rapidly. One gram of the base was dissolved in 5 ml. of cold, normal hydrochloric acid; in less than an hour, 0.9 g. of long matted needles of dihydrothebainone hydrochloride had separated. The crude product had $[\alpha]_D^{24}$ −54.1°, dihydrothebainone hydrochloride has $[\alpha]_D^{25}$ −57.7°. By precipitation of the entire hydrolysis solution with ammonia, 0.95 g. of dihydrothebainone was obtained. After recrystallization it melted at 139–142° (no depression in mixture melting point) and had $[\alpha]_D^{25}$ −72.6° in alcohol; dihydrothebainone has $[\alpha]_D^{25}$ −72.5°. The oxime melted at 248–250°, and gave no melting point depression with dihydrothebainone oxime.

A solution of 104 mg. of the methyl enolate in 10 ml. of normal hydrochloric acid showed at 1.5 minutes after mixing the constant rotation value $[\alpha]_D^{23}$ −57.7°. Dihydrothebainone, in normal hydrochloric acid has $[\alpha]_D^{23}$ −58.4° (c = 1.04).

The only crystalline salts of the methyl enolate that could be prepared were the malonate and fumarate (in absolute alcohol). The latter (m. p. with decomp. 215–217°) was selected for optical examination. A solution of 155 mg. in 25 ml. of water required six minutes for preparation, initial value was $[\alpha]_D^{23}$ −58.3°, and this sank slowly to the constant value at sixty minutes $[\alpha]_D^{23}$ −39.0°. Extrapolated to zero time, the rotation value is $[\alpha]_D^{23}$ −64.4°. The constant end value is practically identical with that of pure dihydrothebainone fumarate, $[\alpha]_D^{23}$ −40.5° (water, c =

1.00). Dihydrothebainone fumarate has not been previously described; it remains unmelted up to 220°.

Anal. Calc'd for $C_{22}H_{27}NO_7$: C, 63.27; H, 6.52.
Found: C, 63.30; H, 6.50.

Phenolic dihydrothebaine.—Thirty grams of thebaine in 400 ml. of alcohol (2-liter flask equipped with reflux condenser, mechanical stirrer, and hydrogen inlet) was heated to vigorous boiling (oil bath, 110–130°) under hydrogen, with stirring, and 105 g. of sodium was added during two hours. During this time, addition of 1200 ml. of alcohol was necessary to keep the mixture liquid. When all sodium was dissolved, the oil bath was removed, 50 ml. of water was added, and the solution was saturated with carbon dioxide, alcohol being added when necessary to prevent solidification. The neutralized mixture was filtered through a canvas bag in a press to remove sodium carbonate. If neutralization has not been complete the filtrate turns red rapidly by air oxidation, and should be treated with more carbon dioxide. The filtrate was concentrated under diminished pressure to a thick oily liquid. This was covered with water and allowed to stand several hours or overnight; it solidified to a hard cake, which was crushed, collected by filtration, and washed well with water. The product, crystallized twice from methyl acetate, consisted of four-sided white prisms of melting point 152–154°, $[\alpha]_D^{27}$ +25.5° (alcohol, c = 1.096); ferric chloride test in alcohol, clear emerald green. The yield (average) was 15 g. Some unreduced thebaine, together with resinous products, accounted for the rest of the starting material. Although Freund's analytical values were satisfactory, they were nevertheless verified.

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.80; H, 7.40.
Found: C, 72.64; H, 7.20.

Dihydrothebainone-Δ-6,7-methyl enolate.—Five grams of phenolic dihydrothebaine in 100 ml. of alcohol with 50 mg. of platinum oxide took up one mole of hydrogen rapidly. The alcohol was removed under diminished pressure, yielding a colorless oil that crystallized in rectangular plates when treated with methyl acetate. Three crystallizations from this solvent gave a white product of melting point 127–128°, $[\alpha]_D^{27}$ −8.0° (alcohol, c = 0.503). The yield was nearly quantitative.

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.38; H, 7.94.
Found: C, 72.75; H, 7.95.

One gram of dihydrothebainone-Δ-6,7-methyl enolate was dissolved in 5 ml. of normal hydrochloric acid and precipitated after five minutes with sodium carbonate. The yield of dihydrothebainone was nearly quantitative. After crystallization from alcohol it melted at 139–143° and gave no depression in mixture melting point with dihydrothebainone. The oxime melted at 240–242° (decomp.) and did not depress the melting point of dihydrothebainone oxime.

α-Thebainone.—Three grams of phenolic dihydrothebainone was dissolved in excess of saturated sulfur dioxide water, and the solution was allowed to stand at 25° for thirty minutes. The yellow solution was filtered, neutralized with ammonia, and extracted with ether. Concentration of the ether solution under hydrogen gave an amber oil, which was taken up in alcohol and diluted cautiously with a small amount of water. The product separated as irregular, pointed prisms, yield 0.9 g. After purification from acetone it had the m. p. 184–185°, $[\alpha]_D^{27}$ +158.5° (chloroform, c = 0.511).

Anal. Calc'd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.08.
Found: C, 72.12; H, 7.23.

β-Thebainone.—Twenty grams of phenolic dihydrothebaine was dissolved in

excess dilute aqueous potassium acid sulfate solution, and allowed to stand at 25° for five hours. A small crystalline deposit that had separated was brought into solution by gentle warming, the solution was covered with a thin layer of ether, and saturated aqueous sodium carbonate solution was added dropwise, with scratching. During the neutralization a few milligrams of sodium hydrosulfite was added from time to time to decrease oxidation. Without this precaution, the solution turned deep green, and the yield was lowered. As the neutral point was approached, an amorphous base started to separate, but this could be brought back into solution by vigorous stirring and rubbing. On further very slow addition of carbonate the crystalline base separated, up to a point where precipitation of a light curd-like material could be observed. This was brought back into solution with a few drops of potassium acid sulfate solution, and the crystalline product was separated by filtration; yield 15.4 g. of β-thebainone, containing a little α-thebainone.

The filtrate was treated with excess sodium carbonate, and the curdy precipitate was extracted into ether, from which about 1 g. of thebainone, together with much resinous, brown material, was obtained. This probably does not represent all of the thebainone formed, as its separation from the resins was extremely difficult.

β-Thebainone is exceedingly soluble in organic solvents, and was purified through the hydrobromide or perchlorate. The latter was prepared using 25% perchloric acid, and was purified by five recrystallizations from 50% alcohol; yield 10.7 g., six-sided plates, m. p. 149–157°, $[\alpha]_D^{27}$ +67.3° (methanol, c = 0.505).

Anal. Calc'd for $C_{18}H_{22}ClNO_7 + 2\ H_2O$: C, 49.58; H, 6.02; H_2O, 8.27.
Found: C, 49.38; H, 5.86; H_2O, 8.18.

β-Thebainone base was obtained from the purified perchlorate by precipitation (fine needles) from an aqueous solution in the presence of a little ether, with sodium carbonate. It was recrystallized once from dilute acetone, from which it separated as the monohydrate; this sintered at about 92° and melted at 98–99°. In alcohol it showed $[\alpha]_D^{27}$ +114.9° (c = 0.496).

Anal. Calc'd for $C_{18}H_{21}NO_3 + H_2O$: C, 68.10; H, 7.31; H_2O, 5.68.
Found: C, 68.21; H, 7.61; H_2O, 5.55.

The previously known thebainone of Schöpf, and Pschorr[14] melts at 145–147° (151–152°) and has $[\alpha]_D^{26}$ −45.7° to −46.9°.

β-Thebainone hydrobromide crystallizes in small rods from alcohol m. p. 168–169° (evac. tube, decomp.), and has $[\alpha]_D^{27}$ +61.1° (water, c = 0.516).

Anal. Calc'd for $C_{18}H_{22}BrNO_3$: Br, 21.03. Found: Br, 21.14.

The hydriodide crystallizes in rods from absolute alcohol, m. p. 150–155° (evac. tube, decomp.), and has $[\alpha]_D^{27}$ +55.3° (water, c = 0.452).

Anal. Calc'd for $C_{18}H_{22}INO_3 + 0.5\ H_2O$: I, 29.10; H_2O, 2.07.
Found: I, 29.04; H_2O, 2.12.

The picrate crystallizes in yellow needles from 50% alcohol; it is insoluble in water or alcohol alone, soluble in acetone. It melts at 172–183° with decomp., and has $[\alpha]_D^{27}$ +43.8° (acetone, c = 0.502).

Anal. Calc'd for $C_{24}H_{24}N_4O_{10}$: N, 10.61. Found: N, 10.89.

β-Thebainone oxime is not crystalline, but yields a crystalline salt with fumaric acid, fine needles from alcohol, m. p. 220.5° (evac. tube), $[\alpha]_D^{27}$ +46.0° (water, c = 0.370). β-Thebainone semicarbazone likewise failed to crystallize, and was brought to analysis in the form of the picrate, yellow rods from alcohol, m. p. 203–204° (evac. tube, decomp.).

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[14] SCHÖPF AND HIRSCH, *Ann.*, **489**, 224 (1931); PSCHORR, *ibid.*, **373**, 15 (1910); SMALL AND MORRIS, *J. Am. Chem. Soc.*, **54**, 2122 (1932).

Anal. Calc'd for $C_{28}H_{27}N_7O_{10}$: C, 51.28; H, 4.65; N, 16.75.
Found: C, 51.27; H, 4.68; N, 16.90.

The mother liquors from the purification of β-thebainone perchlorate became colored purple rapidly, probably through oxidation of the α-thebainone, which seems to be rather sensitive. By concentration of the solution, treatment with sodium carbonate, and extraction with ether, a small amount of α-thebainone was obtained.

β-Dihydrothebainone.—A solution of 10 g. of β-thebainone perchlorate in 250 ml. of alcohol with 50 mg. of platinum oxide absorbed one mole of hydrogen rapidly. The solution was freed of catalyst and concentrated under diminished pressure. The product separated as six-sided prisms of melting point 254–255°, in nearly quantitative yield. From the salt, by treatment with ammonia and ether, β-dihydrothebainone was isolated as a colorless oil that could not be induced to crystallize. It was purified by distillation in an oil-pump vacuum; in alcohol it showed $[\alpha]_D^{27}$ −48.1° (c = 0.499).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.71; H, 7.70.
Found: C, 71.33; H, 7.81.

The previously known dihydrothebainone has the m. p. 138–143° and $[\alpha]_D^{16}$ −72.5°.[15]

β-Dihydrothebainone hydrochloride crystallizes from absolute alcohol in rods that melt partly at 183–190°, solidify, and remelt at 245–248° (evac. tube). In water it shows $[\alpha]_D^{27}$ −34.4° (c = 0.494).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: Cl, 10.50. Found: Cl, 10.60.

The hydrobromide forms three-sided prisms from alcohol; it melts at 182–185°, solidifies, and remelts at 225.5–227.5° (evac. tube). In water it shows $[\alpha]_D^{27}$ −31.5° (c = 0.508).

Anal. Calc'd for $C_{18}H_{24}BrNO_3$: Br, 20.91. Found: Br, 21.25.

The perchlorate crystallizes in six-sided prisms from alcohol, or clusters of boat-shaped needles from water. It melts at 254–255° (evac. tube), and has $[\alpha]_D^{24}$ −32.5° (water, c = 0.400).

Anal. Calc'd for $C_{18}H_{24}ClNO_7$: C, 53.78; H, 6.02.
Found: C, 53.73; H, 6.41.

The picrate crystallizes from 50% alcohol as yellow needles, although it is insoluble in water or alcohol alone. It melts at 202–215° (evac. tube, decomp.) and has $[\alpha]_D^{27}$ −16.5° (acetone, c = 0.121).

Anal. Calc'd for $C_{24}H_{26}N_4O_{10}$: N, 10.57. Found: N, 10.78.

The methiodide forms rectangular needles from alcohol, melting point 149–154° (evac. tube). The compound appeared to have lost some of its hydrate water before analysis.

Anal. Calc'd for $C_{19}H_{26}INO_3 + 2\ H_2O$: I, 26.49; H_2O, 7.52.
Found: I, 26.10; H_2O, 5.61.

The oxime crystallizes from dilute alcohol in colorless needles, m. p. 225–226° (evac. tube), and has $[\alpha]_D^{21}$ −100.4° (alcohol, c = 0.438).

Anal. Calc'd for $C_{18}H_{24}N_2O_3 + H_2O$: N, 8.38; H_2O, 5.4.
Found: N, 8.24; H_2O, 6.2.

In the previously known dihydrothebainone series, the following constants have been observed for corresponding derivatives: hydrochloride, $[\alpha]_D^{25}$ −57.7°; methiodide, m. p. 116°[6b,16] and 150°; oxime, m. p. 253–255°, $[\alpha]_D^{20}$ +6.6° (10% acetic acid).

β-Dihydrothebainonemethine (*des*-N-*methyl*-β-*dihydrothebainone*).—Six grams of β-dihydrothebainone methiodide was boiled with 40% sodium hydroxide solution for twenty minutes. The sodium salt of the methine base separated from the cooled

[15] Schöpf and Winterhalder, *Ann.*, **452**, 232 (1927).

[16] Freund, Speyer, and Gutmann, *Ber.*, **53**, 2250 (1920).

solution as a hard cake, which became crystalline when triturated with water, probably as a result of hydrolysis. By extraction of the suspension with ether, 3.6 g. of white needle crystals was obtained. The base was purified from dilute alcohol, or by vacuum sublimation. It had the melting point 183–184° and $[\alpha]_D^{25}$ −257.9° (alcohol, c = 0.473).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.33; H, 7.67.

The previously known dihydrothebainonemethine has the melting point 183°, and we find for it in alcohol $[\alpha]_D^{25}$ +53.8° (c = 0.502). In mixture with β-dihydrothebainonemethine it melts at 156–162°.

β-Dihydrothebainonemethine perchlorate forms crystal rosettes from alcohol and melts at 225.5–226° (evac. tube).

Anal. Calc'd for $C_{19}H_{26}ClNO_7$: Cl, 8.53. Found: Cl, 8.64.

The picrate, fine yellow needles from 66% alcohol, melts at 164–165° (evac. tube) and has $[\alpha]_D^{27}$ −181.1° (acetone, c = 0.475).

Anal. Calc'd for $C_{25}H_{28}N_4O_{10}$: N, 10.30. Found: N, 10.55.

The oxime crystallizes in small rods from 50% alcohol and melts at 160–162° (evac. tube).

Anal. Calc'd for $C_{19}H_{26}N_2O_3$: N, 8.48. Found: N, 8.71.

β-Dihydrothebainonedihydromethine (*dihydro-des*-N-*methyl-β-dihydrothebainone*).—A solution of 2 g. of β-dihydrothebainonemethine in dilute acetic acid with 10 mg. of platinum oxide absorbed one mole of hydrogen in fifteen minutes. The product, obtained by neutralization with sodium carbonate in the presence of ether, crystallized as long white needles. It was purified from alcohol or acetone, or by sublimation in a high vacuum. It melts at 177–178° (evac. tube) and has $[\alpha]_D^{27}$ +63.8° (chloroform, c = 0.502).

Anal. Calc'd for $C_{19}H_{27}NO_3$: C, 71.87; H, 8.58.
Found: C, 72.20; H, 8.45.

The previously known dihydrothebainonedihydromethine (*ex* dihydrothebainone) we find to have the melting point 154–156° and $[\alpha]_D^{25}$ −79.3° (alcohol, c = 0.593). This melting point is the same as that found by Wieland and Kotake, whereas Cahn, and Schöpf observed the melting points 139° and 137°. A sample of the low-melting form kindly supplied by Prof. Schöpf, although many years old and somewhat colored, melted at 134–136°. A portion of this, seeded with a single tiny crystal of the higher-melting form and intimately ground, showed after twelve hours the m. p. 151–153°. Recrystallization of the remainder of Schöpf's sample from 50% alcohol gave a pure white product of m. p. 154–155°; no depression in mixture melting point. It showed $[\alpha]_D^{27}$ −78.2° (alcohol, c = 0.499). It is evident that the lower-melting form is an unstable modification of dihydrothebainonedihydromethine.

β-Dihydrothebainonedihydromethine hydrobromide crystallizes in needles from alcohol, m. p. 260–260.5° (evac. tube); $[\alpha]_D^{28}$ +24.0° (water, c = 0.500).

Anal. Calc'd for $C_{19}H_{23}BrNO_3$: Br, 20.07. Found: Br, 20.38.

The perchlorate crystallizes in four-sided rods from water, m. p. 232.5–233.5° (evac. tube), and has $[\alpha]_D^{28}$ +23.8° (methanol, c = 0.505).

Anal. Calc'd for $C_{19}H_{25}ClNO_8$: Cl, 8.49. Found: Cl, 8.67.

The picrate forms light yellow needles from alcohol, m. p. 203–207° (evac. tube, decomp.), and has $[\alpha]_D^{27}$ +18.2° (acetone, c = 0.495).

Anal. Calc'd for $C_{25}H_{30}N_4O_{10}$: N, 10.26. Found: N, 10.18.

The oxime is not crystalline, and yields no crystalline salts.

β-Thebenone.—A solution of 0.6 g. of β-dihydrothebainonedihydromethine in a

little hot benzene was treated with 0.2 ml. of methyl iodide. The product, 0.85 g. of white powder, was boiled with 40% sodium hydroxide solution until trimethylamine evolution ceased. The suspension was diluted with water, and the apparently crystalline product was extracted into ether. The ether residue, after recrystallization from alcohol, yielded 0.5 g. of white rods, m. p. 189–190°, $[\alpha]_D^{25}$ +113.6° (alcohol, c = 0.559). The compound sublimes readily in a high vacuum at 160°. The ferric chloride test is negative.

Anal. Calc'd for $C_{17}H_{20}O_3$: C, 74.96; H, 7.41.
Found: C, 74.73; H, 7.76.

The oxime crystallizes from dilute alcohol in cubes of m. p. 176–177° (evac. tube), and shows $[\alpha]_D^{23}$ +30.6° (alcohol, c = 0.506).

Anal. Calc'd for $C_{17}H_{21}NO_3$: N, 4.88: Found: N, 5.12.

The thebenone of Wieland and Kotake melts at 134–136°, and we find for it the value $[\alpha]_D^{27}$ +66.9° (alcohol, c = 0.508). Its oxime melts at 201–204°.

SUMMARY

Codeine methyl ether can be caused to rearrange to a phenolic isomer, thebainone methyl enolate. The latter substance undergoes hydrolysis with extreme ease, yielding thebainone, but, under neutral or alkaline conditions, can be reduced to dihydrothebainone-Δ-5,6-methyl enolate. The structure assigned to this compound was already claimed for a liquid product obtained from the hydrogenation of thebaine under neutral conditions. Re-investigation of this hydrogenation shows that three crystalline products are formed: dihydrothebainone-Δ-5,6-methyl enolate, dihydrothebainol-6-methyl ether, and tetrahydrothebaine. The reduction mechanism is discussed.

Reduction of thebaine with sodium results in reductive scission of the ether ring, yielding phenolic dihydrothebaine, an isomer of thebainone methyl enolate. Catalytic reduction of phenolic dihydrothebaine gives dihydrothebainone-Δ-6,7-methyl enolate, which is isomeric with dihydrothebainone-Δ-5,6-methyl enolate; the isomerism is due only to a difference in location of the enolic double bond. Hydrolysis of phenolic dihydrothebaine yields three isomers, thebainone, α-thebainone, and β-thebainone. The last-named appears to differ from the previously known types of morphine derivatives in the configuration of the asymmetric carbon atom 14. It can be converted successively to the following derivatives, all of which are isomeric with the corresponding compounds derived from the previously known thebainone: β-dihydrothebainone, β-dihydrothebainonemethine, β-dihydrothebainonedihydromethine, and β-thebenone. This is the first well established case of isomerism at C-14 in the morphine series.