THE STRUCTURE OF DIPYRROLES
AND INDOLE FORMATION
FROM PYRROLES

STEREOCHEMISTRY OF LINALOOL

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A Thesis

by

M. R. Gilbert

Submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science.

McGill University

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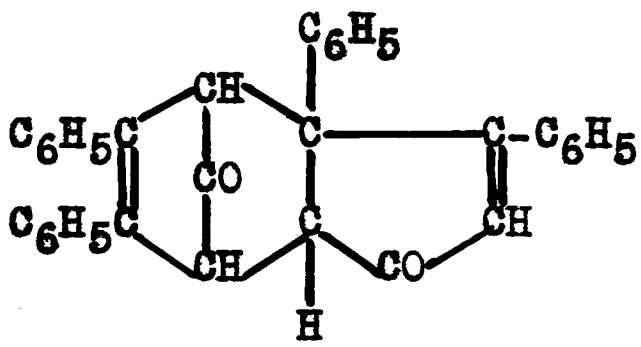
THE STRUCTURE OF DIPYRROLES AND INDOLE FORMATION FROM PYRROLES

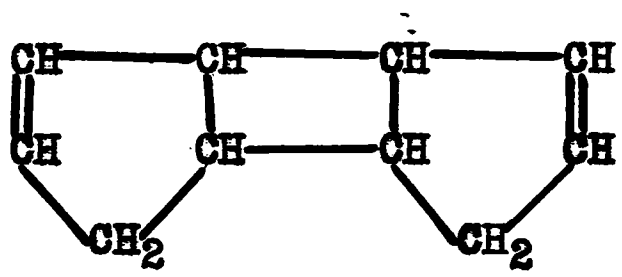
A. Structure of Dipyrroles

Part 1. Historical

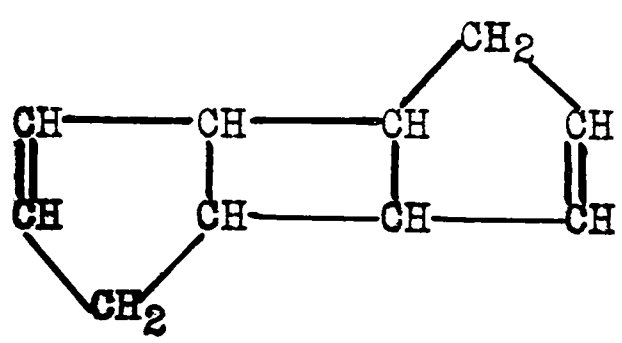
By analogy with the structure (I) assigned to the dimeric form of diphenylcyclopentadienone in 1933 (1) and with structures IIa, IIb, IIIa, IVa assigned to the dimeric forms of dicyclopentadiene (2,3) a few years ago, Allen and Spanagel suggested at that time (1) that the dipyrroles had a similar ring system, formed by a diene synthesis, and that they should be represented as IV, instead of being written as one of the possible cyclobutane derivatives V in current use.



I



IIa



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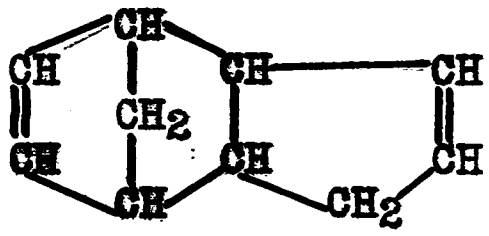
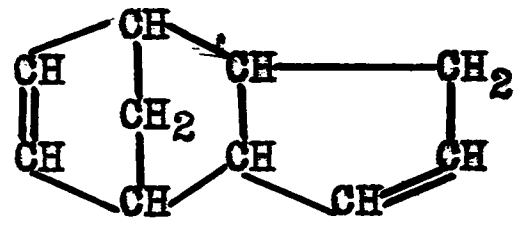


IIIa



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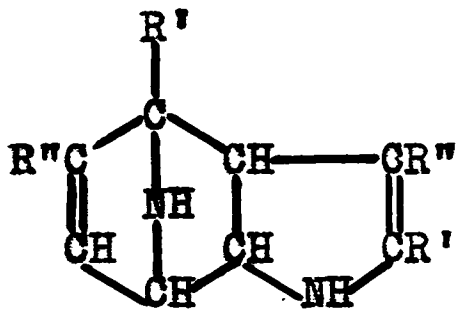
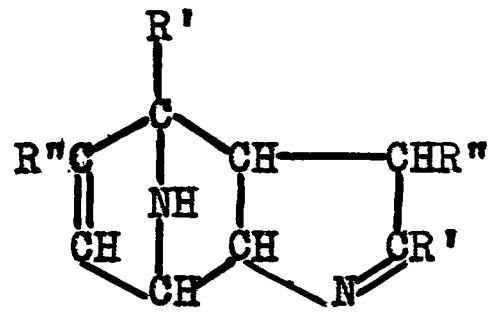
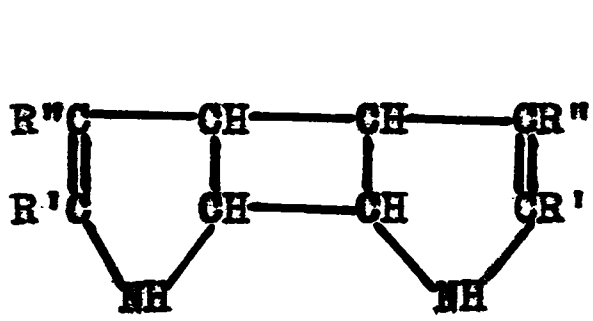


IVa

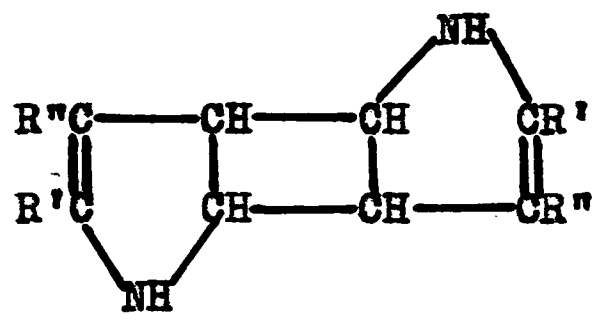


IVb

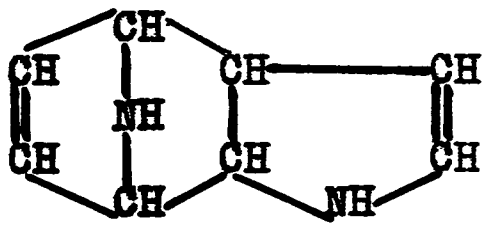
In 1935, Robinson (4) evidently unaware of the previous paper, suggested similar structures VI and VII for di- and tripyrrole.



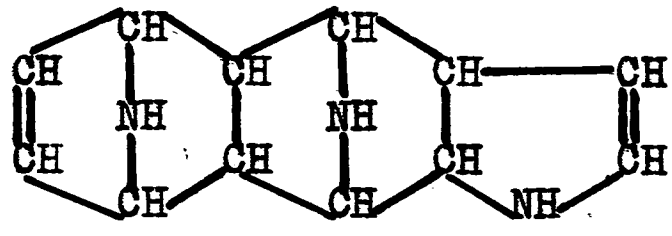
Va



Vb



VI

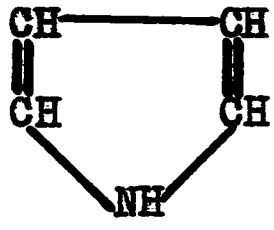


VII

The usual tautomerism of unsaturated nitrogen compounds, as in IVb, does not affect the position of the linkage of the carbon rings. To secure evidence that would en-

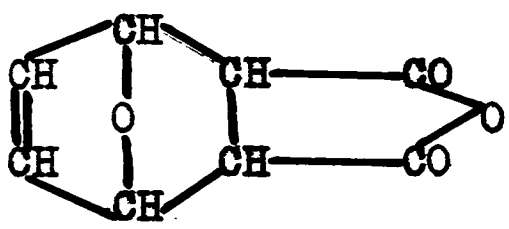
able a structure to be assigned to the dipyrroles, whether V, IV, or some other, Young (46) studied the reactions and properties of diphenyldipyrrole; he showed that II was untenable and that IV seemed to be highly probable.

The structural formula of pyrrole (VIII) shows that this substance contains a diene linkage and would be capable of taking part in the "Diene Synthesis".

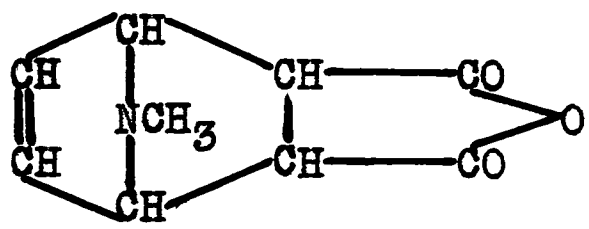


VIII

Since it is known that furan adds to form IX, by analogy N-methylpyrrole should give X.



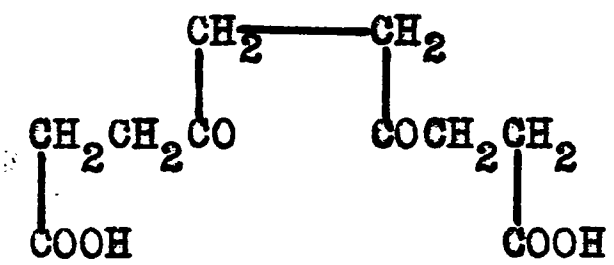
IX



X

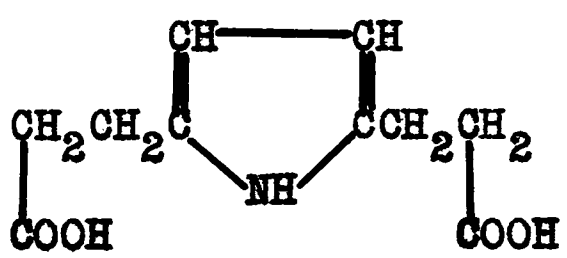
However, Diels (4) found that the reaction between alpha,beta-unsaturated acids and anhydrides and pyrrole and its homologs did not give the anticipated 1,4-addition products. In these investigations an aqueous solution of maleic acid was generally used, to avoid the experimental difficulties encountered with the dry acid. In aqueous solution,

maleic acid and pyrrole reacted at room temperature. When the reaction mixture was gently heated two molecules of carbon dioxide and one molecule of ammonia were split off forming a nitrogen-free diketocarboxylic acid. This acid, which was identical with the one obtained by Kehrer and Hofacker(5) from delta-furfural-levulinic acid, was dilevulinic acid (XI).



XI

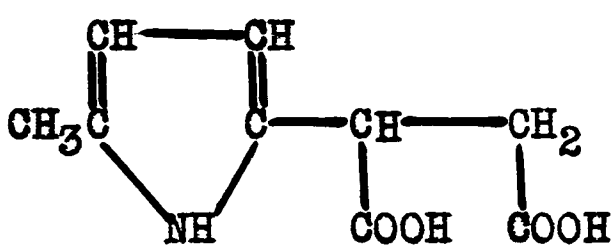
Reduction of the new acid gave sebacic acid; since this was a straight chain acid the carbonyl groups were assumed to be in a 1,4-position. In the reaction mixture, there was also found a small amount of pyrrole-2,5-dipropionic acid (XII), identical with the acid obtained by Kehrer (5) from dilevulinic acid and ammonia.



XII

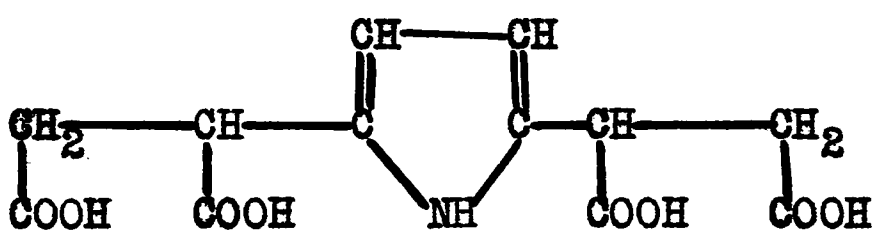
This acid (XII) might have been produced by the action of free ammonia upon dilevulinic acid, but it was believed to have been formed directly from the starting materials. The mechanism of this reaction was cleared up by studying the

addition of maleic acid to 2-methylpyrrole in acqueous solution. In this case, the addition product was isolated and was found to contain both substances in the ratio of 1:1.It was 2-methylpyrrole-5-succinic acid (XIII), and furnished 2-methylpyrrole-5-propionic acid upon gentle heating.



XIII

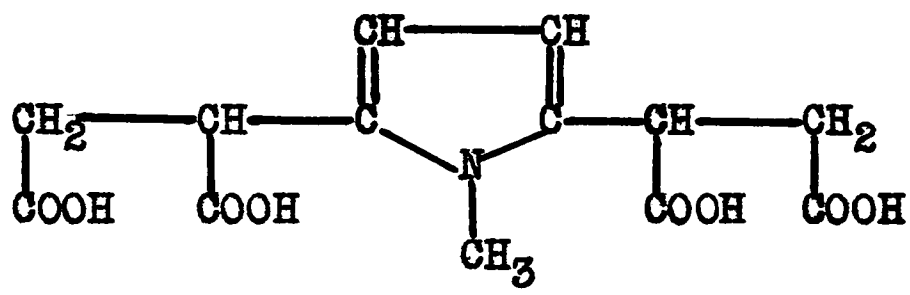
Kehrer(6) has shown that alcoholic hydrochloric acid converted furfural acetone into acetonyl-levulinic acid,which in turn formed 2-methylpyrrole-5-propionic acid when it was treated with ammonium acetate solution. From these facts it was evident that pyrrole and aqueous maleic acid first formed pyrrole-2,5-disuccinic acid (XIV) which then lost two molecules of carbon dioxide to give pyrrole-2,5-dipropionic acid (XII); hydrolysis of the latter yielded ammonia and dilevulinic acid (XI).



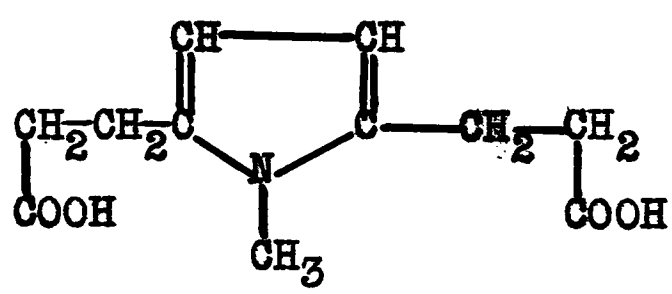
XIV

In the same way, N-methylpyrrole and aqueous maleic acid furnished N-methylpyrrole-2,5-disuccinic acid (XV),

which lost two molecules of carbon dioxide on gentle heating to produce N-methylpyrrole-2,5-disuccinic acid (XVI).

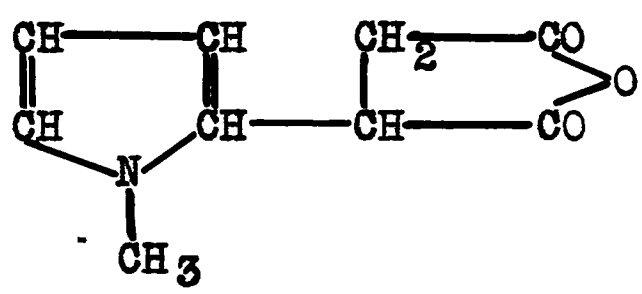


XV



XVI

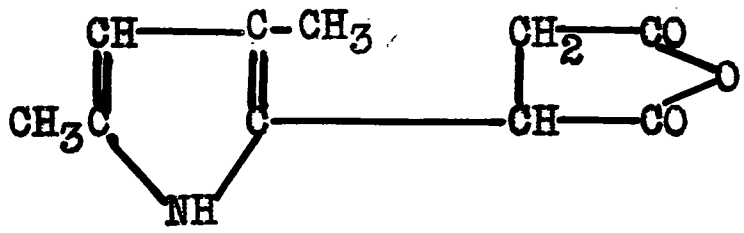
Since this acid proved to be much more resistant to hydrolysis than XII, the proportion of dilevulinic acid (XI) formed was very small. The constitution of XVI was known, for its ester was identical with that obtained from the ester of dilevulinic acid and methylamine. It should be noted that in a non-aqueous solvent N-methylpyrrole and maleic anhydride formed N-methylpyrrole-5-succinic anhydride (XVII).



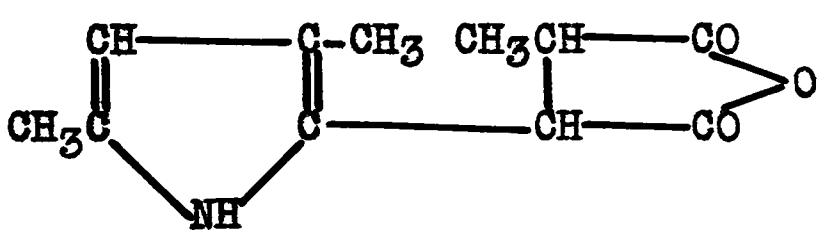
XVII

Likewise, 2,4-dimethylpyrrole and maleic anhydride in a non-

aqueous solvent yielded 2,4-dimethylpyrrole-5-succinic anhydride (XVIII), whereas with citraconic anhydride 2,4-dimethylpyrrole-5-methylsuccinic anhydride (XIX) resulted.

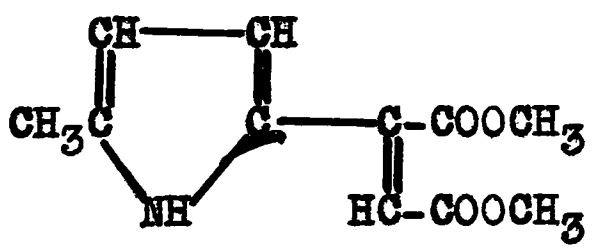


XVIII

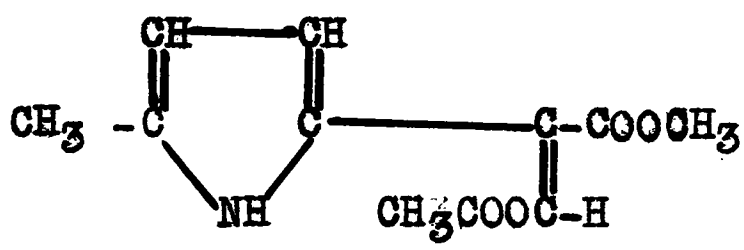


XIX

To the same catagory belongs the addition of acetylenedicarboxylic acid and its esters to pyrroles (7), 2-Methylpyrrole and methyl acetylenedicarboxylate combined additively at room temperature to yield two stereoisomeric dimethylesters (XX, XXI).



XX



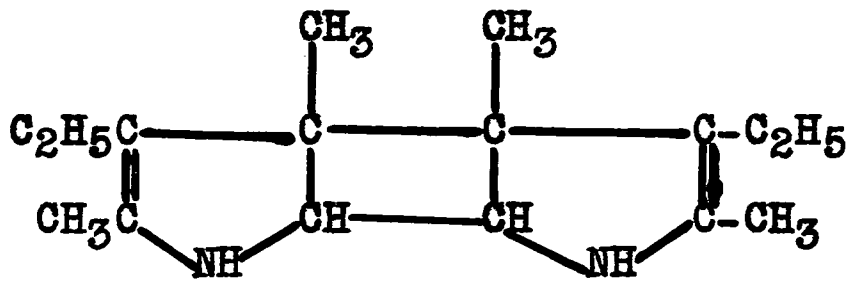
XXI

These esters stand in a cis-trans relationship to one another since on catalytic reduction they both yield 2-methylpyrrole-5- succinic acid.

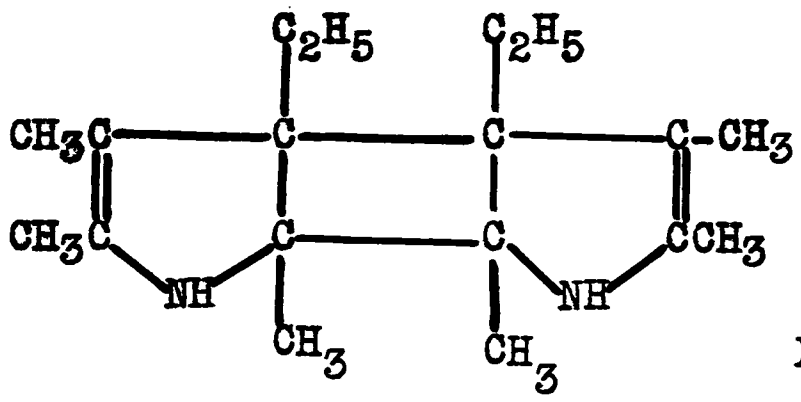
In 1886, it was first shown by Dennstedt (8, 9) that some pyrroles formed hydrochlorides of bases when treated with dry hydrogen chloride in dry ether; in most cases, however, the position of the substituent groups in the starting pyrrole was not definitely known, and the description of the resulting bases (or polymers) was largely of an indefinite, qualitative nature. The dipyrrole salts thus formed, were converted by alkali into the free polypyrroles (10, 11). Thus, it was observed that dipyrroles gave monoacidic salts.

Working in this manner, Dennstedt isolated a dipyrrole by polymerization of 2,3-dimethylpyrrole. Piloty (12, 13) showed that this dipyrrole distilled unchanged in vacuum, and could be converted into an indole by removal of ammonia.

Hans Fischer (14) converted 2,4-dimethyl-3-ethylpyrrole (crytopyrrole) into XXIII and 2,4,5-trimethyl-3-ethylpyrrole (phyllopyrrole) into XXIV.



XXIII

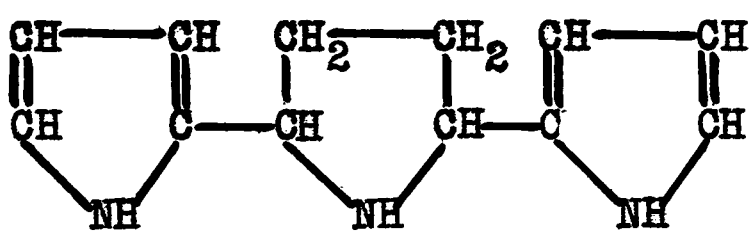


XXIV

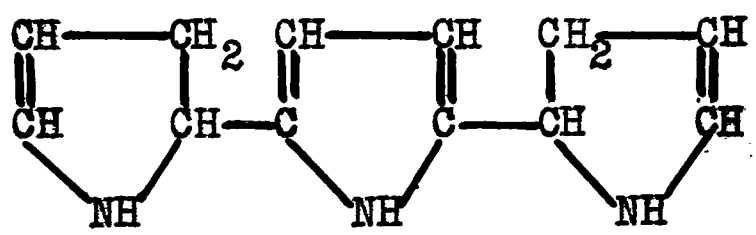
These reactions were brought about by the older hydrogen chloride method or by a new one, which consisted in heating the mono-pyrrole picrate in ethyl acetate. When XXIII was heated above 200° in vacuum, it was depolymerized. The "bis-phyllopyrrole" (XXIV) was much more easily depolymerized, i.e. by steam distilling or by heating to 150° in vacuum. From these examples it is seen that the dipyrroles from tri- and tetra-alkylated pyrroles differ from those of the mono- and di-alkylated pyrroles of Dennstedt in that they can be depolymerized by heating, and also, as will become evident, in that there is no formation of corresponding indoles, Fischer (15) has obtained indoles directly from pyrroles by treatment of the pyrrole either with hydrogen chloride in absolute alcohol or with hydrogen bromide in formic acid. From 2-methyl-5-carboxypyrrole-3-propionic acid, he obtained 2,4-dimethylindole-3,5-dipropionic acid. The latter is an apparent exception since it is a tri-substituted pyrrole, however, in this instance the loss of the group in the 5-position in the pyrrole by decarboxylation, makes it equivalent to a pyrrole with groups on but one side of the ring.

In acid media (16) the aromatic properties of pyrrole were destroyed to a large extent and the compound showed a marked tendency to polymerize. A large number of complex polymers could be obtained, but the majority were mixtures and were not single substances. The best known definite polymer was tripyrrole (XXVa), isolated as the hydro-

chloride, by treating a dry ethereal solution of pyrrole with dry hydrogen chloride; the free base was thrown down as colourless crystals by neutralizing a solution in dilute hydrochloric acid with ammonia.



XXVa



XXVb

When tripyrrole was heated to 300°, it decomposed into pyrrole, indole, and ammonia. These products could be obtained without isolating the tripyrrole if the polymerization mixture was subjected to dry distillation (17). This reaction may be viewed as a case of reversibility of a diene synthesis. Schmitz-Dumont has recently claimed to have isolated the dimer of pyrrole itself, as a result of some work on the addition product of stannic chloride and pyrrole, $SnCl_4 \cdot 2C_4H_5N$.

From the history of dipyrroles the following facts are evident:

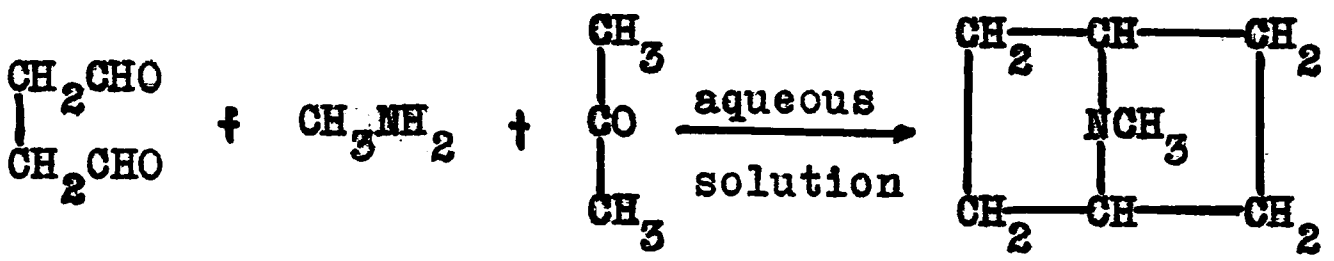
(1) Tripyrrole should be written as an open-chain compound (XXV).

(2) In the "Diene Synthesis" pyrroles do not react like other dienes, but rather as HA[1] compounds.

---

[1] An HA compound consists of H and some such radical as:
-H, -CN, $-NH_2$, -NHR, $-CH_2CHO$, $-NaSO_3$, -OH (as in HOCl),
$-C_6H_5$, $-OCH_3$, -MgCl, -NHOH, $-CH(COOR)_2$, $-C_6H_5CHCN$, $-CH_2NO_2$.

The exact mechanism of Robinson's (19) tropinone synthesis is unknown, but it seems highly probable that it is a true diene synthesis at some step in the reaction.



The yield in this synthesis was small, but an improvement followed on the replacement of the acetone by a salt of acetone dicarboxylic acid. In this case, the initial product was a salt of tropinone dicarboxylic acid, which lost two molecules of carbon dioxide with the formation of tropinone when the solution was acidified and heated. Tropinone was also obtained by the hydrolysis of the product of condensation of succinic dialdehyde with ethyl acetonedicarboxylate and methylamine in alcoholic solution.

(3) Polymerization in the pyrrole series takes place as follows:

(a) Pyrrole itself gives tripyrrole except under special conditions when dipyrrole results.

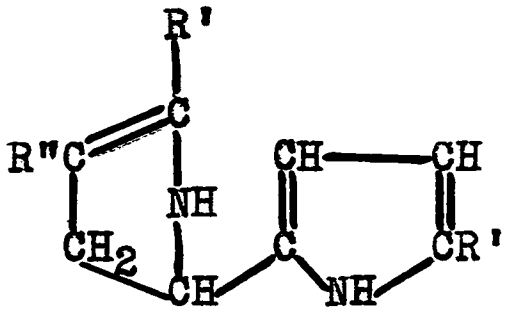
(b) Pyrroles substituted unilaterally (or their equivalent) give relatively stable dipyrroles.

(c) Other pyrroles give dipyrroles that dissociate to the monomeric form on heating.

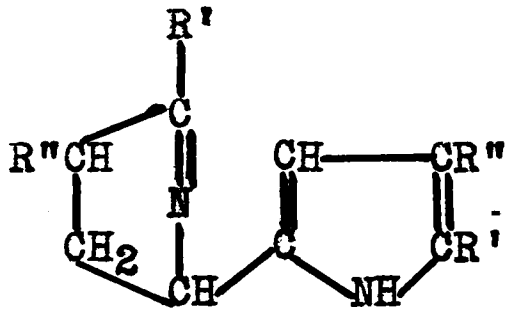
(4) Dipyrroles form monoacidic salts.

Part II. Introduction

From the examples cited in the historical section it was seen that pyrroles reacted with themselves to form dimeric addition products. It was also pointed out that pyrroles did not enter into what is considered to be the usual type of diene synthesis hence some structure other than IV seems more probable for dipyrroles. Such possibilities are illustrated in XXIIa and XXIIb; these are only two of the five theoretically possible forms, and the only ones which present any new complications.



XXIIa



XXIIb

Formulas IV and XXII are very similar; the latter may be considered as a very probable intermediate in the formation of IV in a stepwise diene synthesis. The evidence that has led us to adopt XXII and discard IV is outlined below.

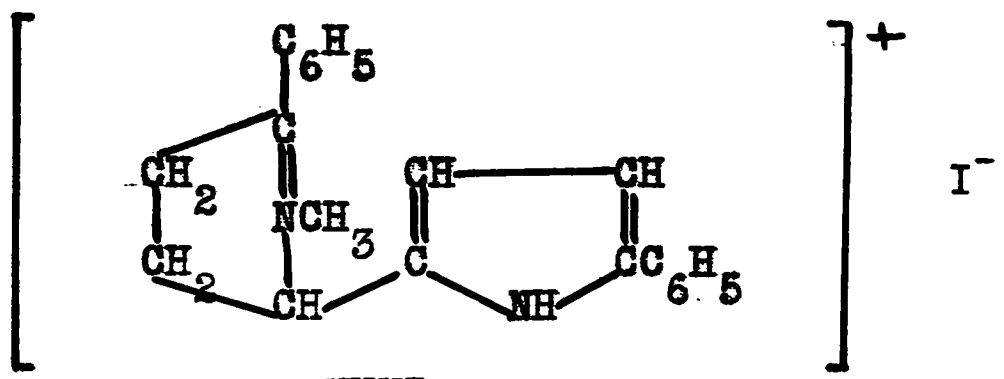
Pyrroles seldom form salts with acids, and methiodides are practically unknown. Since dipyrroles form salts with one equivalent of acid, at least one of the nitrogen atoms must be different, hence one of the characteristic pyrrole linkages has disappeared. Both nitrogen atoms are

alike in V, but are different in Formulas IV and XXII, so V can be excluded from consideration. The pyrrole ring system is still present in XXII, hence monoacidic salts would be expected; nothing is known of substances like IV, so it is impossible to predict the behavior of the nitrogen atoms.

For the purpose of securing solid substances, facilitating manipulation, and simplifying degradation products, Young (46) investigated some of the reactions of 2-phenylpyrrole. It did not give a methiodide but readily formed a dipyrrole, which gave salts with three acids, as well as a monomethiodide. This methylation involved refluxing in methyl iodide as a solvent (over twenty equivalents). With sodium hydroxide an oil resulted, which again added methyl iodide to give a salt, insoluble in water, and unaffected by potash. Refluxing with a suspension of silver oxide in aqueous alcohol brought about a decomposition and deposition of silver iodide, but it was impossible to recognize any of the organic material.

Pyrroles do not form methiodides, whereas the reduced pyrroles or pyrrolidines are completely methylated by excess methyl iodide. In XXIIa, the -NH- should undergo exhaustive methylation under Young's treatment, which involved refluxing with twenty-three moles of methyl iodide, whereas actually only <u>one</u> methyl iodide molecule added. This behavior makes possible the exclusion of all the tautomeric forms of IV and XXIIa except those of the type XXIIb. In this, the

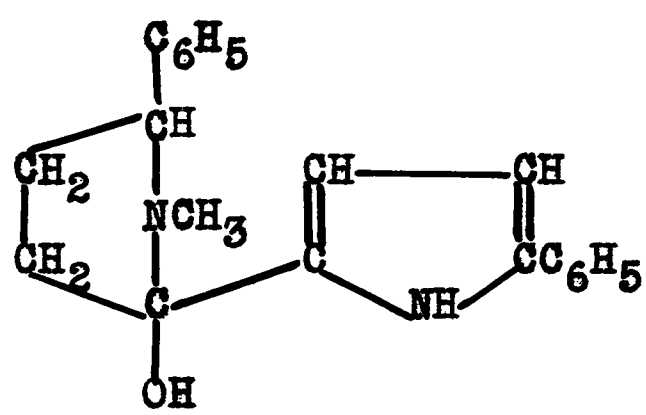
nitrogen atoms are dissimilar; one is still a pyrrole, incapable of forming salts, whereas the other is like a Schiff base, it could add but one molecule of methyl iodide (XXVI) (20) or methyl sulfate (21).



XXVI

It might be thought possible to differentiate between XXIIa and XXIIb, even though XXll a is excluded, by a determination of the number of active hydrogen atoms. Hydrogen atoms undergo a tautomeric shift is pyrroles, in that the usual reagents give derivatives of either possible form, i.e. HNO_2 gives β-nitroso derivatives only, even with pyrrole itself; and acylating agents usually attack the carbon alpha to the nitrogen atom. The Grignard reagent should show the presence of two active hydrogen atoms, but the use of this reagent as a method for determining structure in pyrrole series is known to be unreliable. For example Young treated the condensation product of 2,5-dimethylpyrrole and acetone with methyl magnesium iodide in the "Grignard machine" and found three active hydrogen atoms where normally one would expect two active hydrogen atoms. Therefore, the use of this reagent here would be of no value.

The reaction with alkali, followed by addition of one more molecule of methyl iodide, as found experimentally by Young, is best explained by Corwin (22) which is that the true base, primarily formed, at once rearranges to the more likely form of the pseudo base (XXVII). This now contains a nitrogen atom capable of further methylation, as Young verified experimentally.



XXVII

These reactions render highly probable the new skeletal structure of dipyrroles, and indicate that the nitrogen atom is connected to an adjacent carbon by a double bond. In the particular example the phenyl group was placed at the top by analogy with the reaction of 2-methylpyrrole to form 2,4-dimethylindole with mineral acid. The fact that the only recognizable oxidation product was benzoic acid indicated that probably the phenyl group was attached to a doubly-bound carbon. The cyclobutane structures V have to be discarded, for in not a single point are they in agreement with the above evidence. It was always difficult to explain indole formation from them,

whereas all that is necessary with the new structure was to have the diene synthesis continue to give a substance of the type IV.[2] Diels and Alder (23) have shown that the addition product from furan and maleic acid can be converted into phthalic acid by a series of five reactions involving four intermediate products, whereas VanCampen and Johnson (24) have removed water from similar addition products and obtained phthalic anhydride in one step.

From the examples cited, it seems evident that like any substance of the type HA pyrroles should add to the conjugated system of a second reactant. When there is nothing else present for the pyrrole to combine with, it should add to itself for it contains the necessary conjugated system. Since pyrroles can be kept unchanged for long periods of time, this tendency cannot be very great. The addition,however,takes place in the presence of strong acids or zinc salts which remove the dipyrrole from the equilibrium by formation of an insoluble salt, or by elimination of ammonia yield the indole. As described under indole formation Young excluded the possibility of a hydrolysis mechanism in the formation of indoles directly from pyrroles by showing that there was no evidence that the pyrrole ring was opened by acidic reagents.

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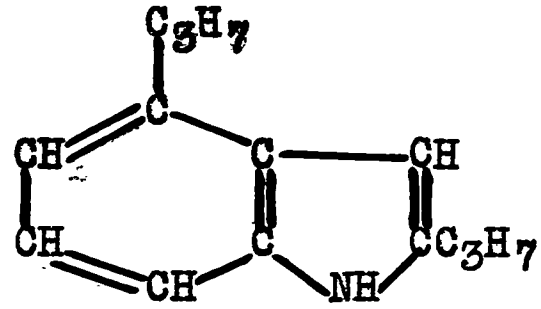
[2]Since nothing like IV is known, its properties cannot be predicted by analogy with the furan-maleic anhydride addition products in which the elements of water are easily removed, the loss of ammonia should be easy.

The reason that a dipyrrole does not lose ammonia in its preparation by Dennstedt's method with hydrogen chloride (25) is due to the strictly anhydrous conditions of the experiment; the indole preparations were invariably done in the presence of water. The function of the zinc acetate in Plancher's method for preparing indoles (26) is probably merely to eliminate ammonia from the dipyrrole which was first formed. This is comparable to the use of zinc chloride in eliminating a molecule of ammonia from a hydrazone in Fischer's indole synthesis (27). That the presence of zinc salts was not essential, however, was demonstrated by the fact that the removal of ammonia had been accomplished by many other methods. Among these might be mentioned, treatment of the hydrazone with sulfuric acid (28) or with a mixture of hydrochloric and acetic acids (29).

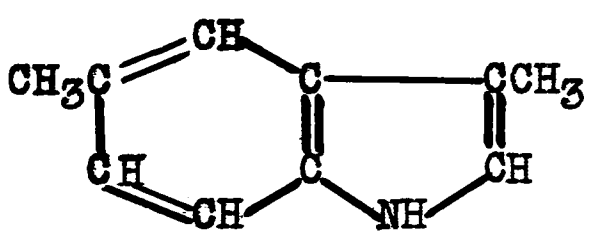
B. Indole Formation from Pyrroles.

Part 1. Historical

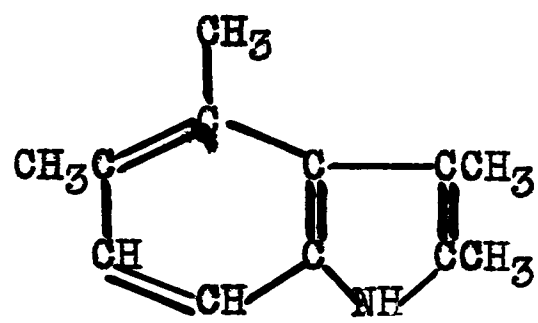
In 1888, Dennstedt (9, 10, 11, 25) found that certain pyrroles dimerized in the presence of acids and that subsequent treatment of the resulting dipyrroles with dilute sulfuric acid affected the elimination of ammonia. He obtained 2,4-diisopropylindole (XXIX) from 3-isopropylpyrrole (now known to be 2-isopropylpyrrole)(11); 3,5-dimethylindole (XXX) from 2-methylindole; and 2,3,4,5-tetramethylindole (XXXI) from 2,3-dimethylindole.[3]



XXIX



XXX



XXXI

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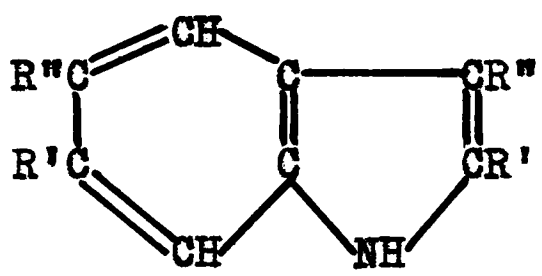
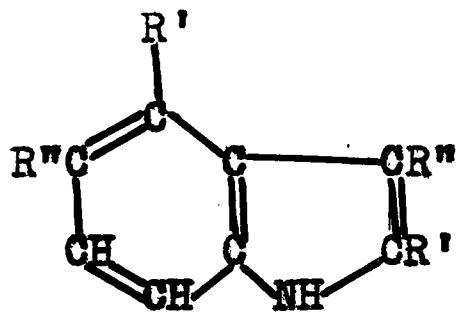
[3] Dennstedt wrote his intermediate dipyrrole with a cyclobutane structure V and numbered accordingly, this has been shown in this thesis to be erroneous. The numbers are corrected on the basis that the intermediate dipyrrole has an open-chain structure (XXIIb).

Dennstedt, however, did not prove the position of the substituent groups in these indoles by synthesis. He merely assumed that the dipyrrole formed had the cyclobutane structure V which formed an indole by ring splitting and evolution of ammonia. If this mechanizm were true, the resulting indole would have structure (XXXII).



XXXII.

Earlier in this thesis, it was shown that a dipyrrole has the structure XXIIb, hence the resulting indole would be expected to have the arrangement of groups in XXXIII.



XXXIII.

Conversely, if the position of the groups in the indole is established, the structure of the dipyrrole can be deduced.

In this series, there are three methods for preparing indoles, none of which give high yields:

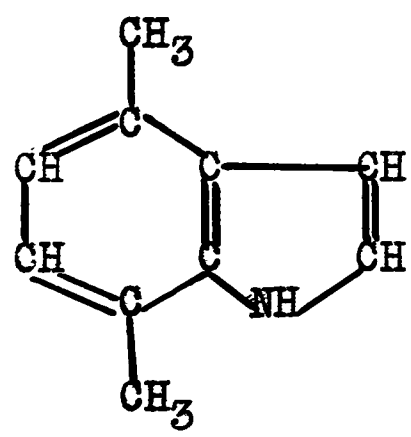
(1) From the pyrroles by long heating with zinc salts and acetic acid.

(2) From the dipyrrole and sulfuric acid.

(3) From acetonylacetone and pyrroles.

Starting with 2-methylpyrrole and procedure (2) Dennstedt (9) prepared a dimethylindole which he represented as the 2,6-isomer assuming the dimethyldipyrrole had a cyclobutane structure.

Plancher (26, 30) found that a dimethylindole was formed by procedure (1) from 2-methylpyrrole. He believed that the first stage consisted in the hydrolysis of the starting material to levulinic aldehyde, which then reacted with a further quantity of 2-methylpyrrole to give 2,4-dimethylindole and two molecules of water. This view was supported by the fact that acetonyl acetone, which is a 1,4-diketone, was shown to condense with pyrrole to give 4,7-dimethylindole(XXXIV); and by the known ease of ring opening of 2,5-dimethylpyrrole by acids (31).

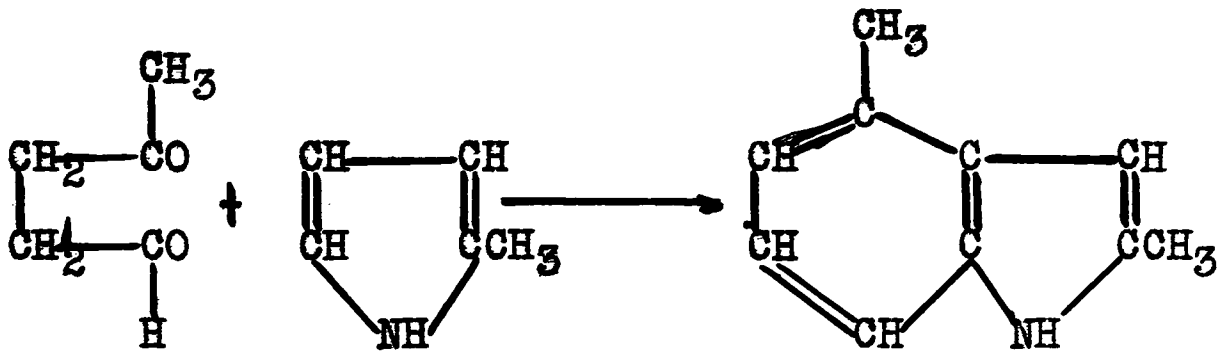


XXXIV

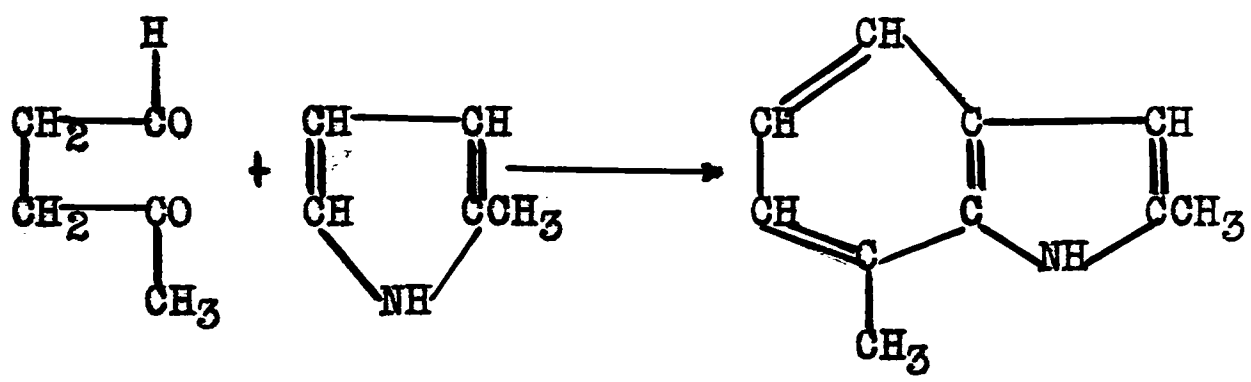
If such a mechanism were true, either a 2,4- or a 2,7-dimethylindole would be expected from the condensation of levulinic aldehyde and 2-methylpyrrole, depending upon whether the

levulinic aldehyde reacted so that in the product the methyl group was in the 4- or 7- position as indicated in (a) and (b).

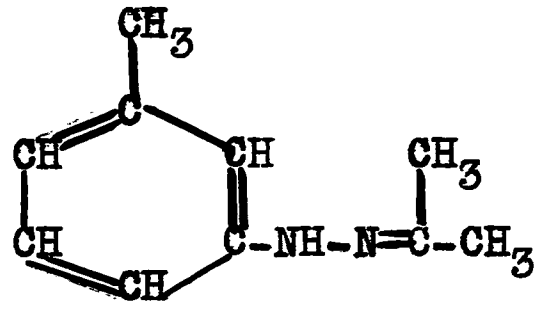
(a)



(b)



Plancher synthesized an indole from the m-tolylhydrazone of acetone (XXXV), which could give either a 2,4- or a 2,6-dimethylindole, depending upon which of the two positions ortho to the nitrogen was involved in ring closure; this indole was found to be identical with the one prepared from 2-methylpyrrole.



XXXV

Since the same substance resulted from both procedures,

Plancher considered it to be the 2,4-isomer. He also stated that his 2,4-dimethylindole was probably identical with Dennstedt's product, obtained from the dipyrrole of 2-methylpyrrole (9). If Plancher's mechanism was correct, it follows that the dipyrrole must have first dissociated into the monomeric form, and hydrolyzed; Young showed that the hydrolysis was extremely improbable if not non-existent and that there was no dissociation in the case of diphenyldipyrrole. The reasons that led Young to discard such a mechanism are outlined in the following paragraph.

To establish the ring opening reaction as the mechanism, it should be shown that pyrroles are hydrolyzed under the conditions necessary for ring formation. With a view to securing evidence on this point, a considerable variety of pyrroles was treated by Young in acid solution under such conditions in the presence of 2,4-dinitrophenylhydrazine. This reagent was selected because it is known to combine with carbonyl compounds with great rapidity and because of the relative insolubility of the expected products (32,47). As the formation of an indole from pyrrole and acetonylacetone is a slow reaction, one would expect to be able to detect any hydrolysis product (carbonyl compound) produced by ring opening. The necessary conditions involved 24-48 hours of refluxing, during which time most of the reactants were lost by tar formation; by interrupting after varying intervals it was possible to isolate unchanged pyrrole and hydrazine.

Only in one instance, that of 2,5-dimethylpyrrole, was there detectable ring opening. When a mineral acid was used, the bis-dinitrophenylhydrazone of acetonylacetone was formed instantly (33); the rate was slower in acetic acid, but the product was the same. The ketones 2-acetyl- and 2,4-dimethyl-3-acetyl-5-carbethoxypyrroles gave dinitrophenylhydrazones without ring opening, but the others were unaffected. Finally 2-methylpyrrole was converted into 2,4-dimethylindole with the same yield in the presence and absence of dinitrophenylhydrazine. Thus there was not the slightest indication that ring opening was a step in the reaction.

The validity of the reasoning depends upon the assumption that the pH most favourable for reaction is the same for dinitrophenylhydrazone and indole formation. Pyrroles are so easily resinified by moderate concentrations of acid that it is impractical to operate in other than dilute solutions. Under these conditions carbonyl compounds actually form dinitrophenylhydrazones, and in the absence of proof to the contrary, the above assumption seems reasonable. 2,5-Dimethylpyrrole is hydrolyzed, but as it does not form an indole, this behavior cannot be interpreted in favour of the hydrolysis mechanism. Sparingly soluble bis-dinitrophenylhydrazones form almost instantly and quantitatively with most dicarbonyl compounds. It is difficult to regenerate the carbonyl compound from its dinitrophenylhydrazone and the procedure involving simple reversal of the reaction has been successful

In a very few instances (34). Reversal by replacement of different carbonyl is of no value. Strain (35) has recommended the use of relatively inaccessible glyoxals or diacetyl; Rupe (36), a 5-hour treatment with alcoholic m-nitrobenzaldehyde; and Cuisa (37), picryl chloride. It has been observed by Collatz and Neuberg that the regeneration of such substances as glyceric aldehyde and dihydroxyacetone from their dinitrophenylhydrazones could be accomplished by heating in a pressure bottle with a larg excess of acetaldehyde, acetone or furfural. Macbeath and Price (38) have shown that in general 2,4-dinitrophenylhydrazones are unstable to alkaline reagents and Wright (39) has been successful in reversing a few reactions using such reagents. Thus it is concluded that such reactions are non-reversible and that any ketone, if formed, would be detected.

From this historical account of indole formation from pyrroles several facts may be noted:

(1) Dennstedt's structure for indoles derived from a dipyrrole written as cyclobutanes are probably incorrect.

(2) Plancher's mechanism for indole formation, which involves (a) Hydrolysis of the starting material to levulinic aldehyde, and (b) Reaction of the aldehyde with one molecule of the pyrrole giving an indole, is highly improbable.

(3) 2,4-Dinitrophenylhydrazine has been used to show that ring opening is not an intermediate step in the formation of an indole from a dipyrrole.

Part II. Introduction

The first point to be settled was the identity or otherwise of Dennstedt's and Plancher's dimethylindoles. This was done by synthesising both, by the described procedures, and comparing their properties. They agreed in all respects; further a mixed melting point of the picrates was not depressed.

It was next essential to determine the location of the methyl groups. One is unquestionably in position 2. The most applicable indole syntheses are those of Salway (40) and Verley[4] (41,42) which consist of acetylation of a xylidine followed by treatment of the resulting acetyl-derivative with sodium ethoxide or sodium amide in the absence of air. This required the xylidines having one of the methyl groups next the amino-group. All were secured, except the most desirable member, 2,3-dimethylaniline. When the syntheses were performed, the dimethylindoles formed were different from each other, and from the Dennstedt-Plancher-isomer. Hence, by exclusion, the latter must be the 2,4-dimethylindole as originally proposed by Plancher.

Since this work was done, the 2,3-dimethylaniline was secured and the synthesis performed; It gave, 2,4-dimethyl-

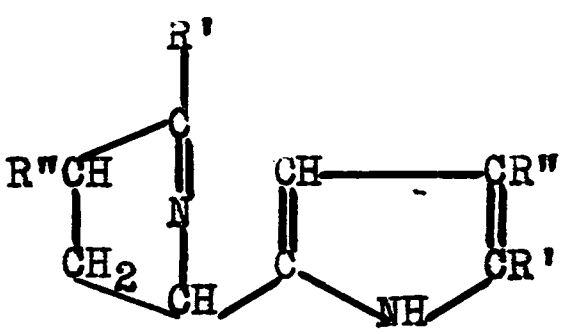
[4] Verley found that in cases where the usual dehydrating reagents such as anhydrous phosphorous pentoxide, zinc chloride, and aluminium chloride gave negative results that sodium amide brought about the dehydration. He showed that the acetyl derivatives of toluidines where heated to a high temperature with sodium amide yielded 2-indoles. He applied this synthesis to the preparation of 2-ethylindole, 2-propylindole, and 2-isobutylindole.

indole, which agreed in all properties with the available sample of Plancher and Dennstedt, thus proving definitely its structure. This therefore, locates the position of the methyl groups in the dimethyldipyrrole, and removes the only arguement that Dennstedt had to support his cyclobutane formula.

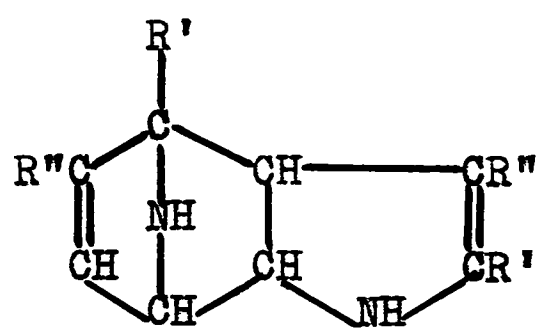
By analogy, then, the diphenyldipyrrole would be XXVII. Likewise, tripyrrole, as shown in another part of this thesis, should be written as an open-chain structure (XXVa or XXVb).

Young showed that indole formation from dipyrroles required no assumption of depolymerization, or ring opening,and it appeared that an indole was formed directly from a dipyrrole, the latter being an intermediate in the reaction, starting from a simple pyrrole. In this thesis it has been shown that the formation of dimethylindole from dimethyldipyrrole is almost instantaneous, which corroborates Young's conclusion that there is no depolymerization.

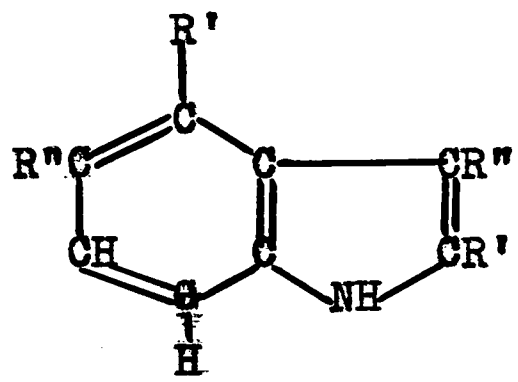
The question then arises as to the mechanism by which indoles are formed from dipyrroles. An inspection of the formulae below reveals that if the diene synthesis, begun in XXXVIII, were completed, a substance XXXIX would result.



XXXVIII



XXXIX



XL

This structure is analogous to the furan-maleic anhydride addition products, which lose water to give an aromatic structure (24) to members of the tropane series, which give dienes on exhasutive methylation (43), and to carbonyl bridge compounds which lose carbon monoxide relatively easily (44). No substances like XXXIX are known, hence their properties can be predicted only by analogy with the instances cited. Now, if XXXVIII and XXXIX were in an equilibrium, which normally favours XXXVIII, indole formation by loss of ammonia from XXXIX would displace the equilibrium, and the reaction would proceed to the right. The procedures for securing indoles involve treatment with mineral acids or zinc salts, both of which enter into chemical combination with ammonia, thus favouring the direction of reaction leading to an aromatic structure. Owing to the many possibilities for side reactions, a low yield would be anticipated.

Young found it impossible to convert the dimer from 2-phenylpyrrole into an indole. This fact is indirectly in favour of structure XXII, for although the position occupied by the phenyl group on the pyrroline ring is uncertain, it is be-

lieved to occupy position R' in XXII, by analogy with the corresponding product from 2-methylpyrrole and because at that point it would be expected to offer the maximum hinderance to the necessary ring closure.

Two diphenylindoles were prepared by Bischler's method, in order to show that this was not due to the instability of the expected indole. Bischler's (45) procedure involved refluxing a xenylamine with its phenacyl derivative, or better, by heating at a high temperature in a sealed tube. p-Xenylamine gave an indole which from the method of synthesis probably has the phenyl groups in the 2 and 5 positions. The synthesis from m-xenylamine is, on the other hand, somewhat ambigous; but is presumed to be the 2,4-compound by analogy with the dimethyl series. These diphenylindoles are high melting, unreactive solids, which form neither picrates nor methiodides.

Experimental

I. Diphenylindoles.

An attempt was made to prepare a series of diphenylindoles from 2,3, and 4-aminodiphenyl by Bischler's method (45) or by heating a xenylamine with its phenacyl derivative at a high temperature in a sealed tube with the intention of ascertaining their properties. Only in the case of the 3-amino compound and the 4-amino compound was the preparation accomplished successfully; the 2,4-diphenylindole and the 2,5-diphenylindole presumably obtained did not form picrates, methiodides, or addition products with trinitrotoluene.

A. 2-Aminodiphenyl.[5]

1. Treatment with Phenacyl Bromide.

One gram of phenacyl bromide and 1.2 g. of 2-aminodiphenyl were dissolved in 5 cc. of ethyl alcohol and allowed to stand at room temperature. No phenacyl derivative was formed and the starting materials were recovered unchanged. When the same amounts of starting materials were heated in a sealed tube for 1 hour on a water bath, a white precipitate was formed which melted at 232-4° and was insoluble in chloroform. This high melting compound was not further investigated, but was assumed to be o-aminodiphenyl hydrobromide. However, no phenacyl-aminodiphenyl could be isolated.

2. Picrate Formation

2-Aminodiphenyl formed a picrate which separated from

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[5] The Monosanto Chemical Company kindly supplied a sample of this amine.

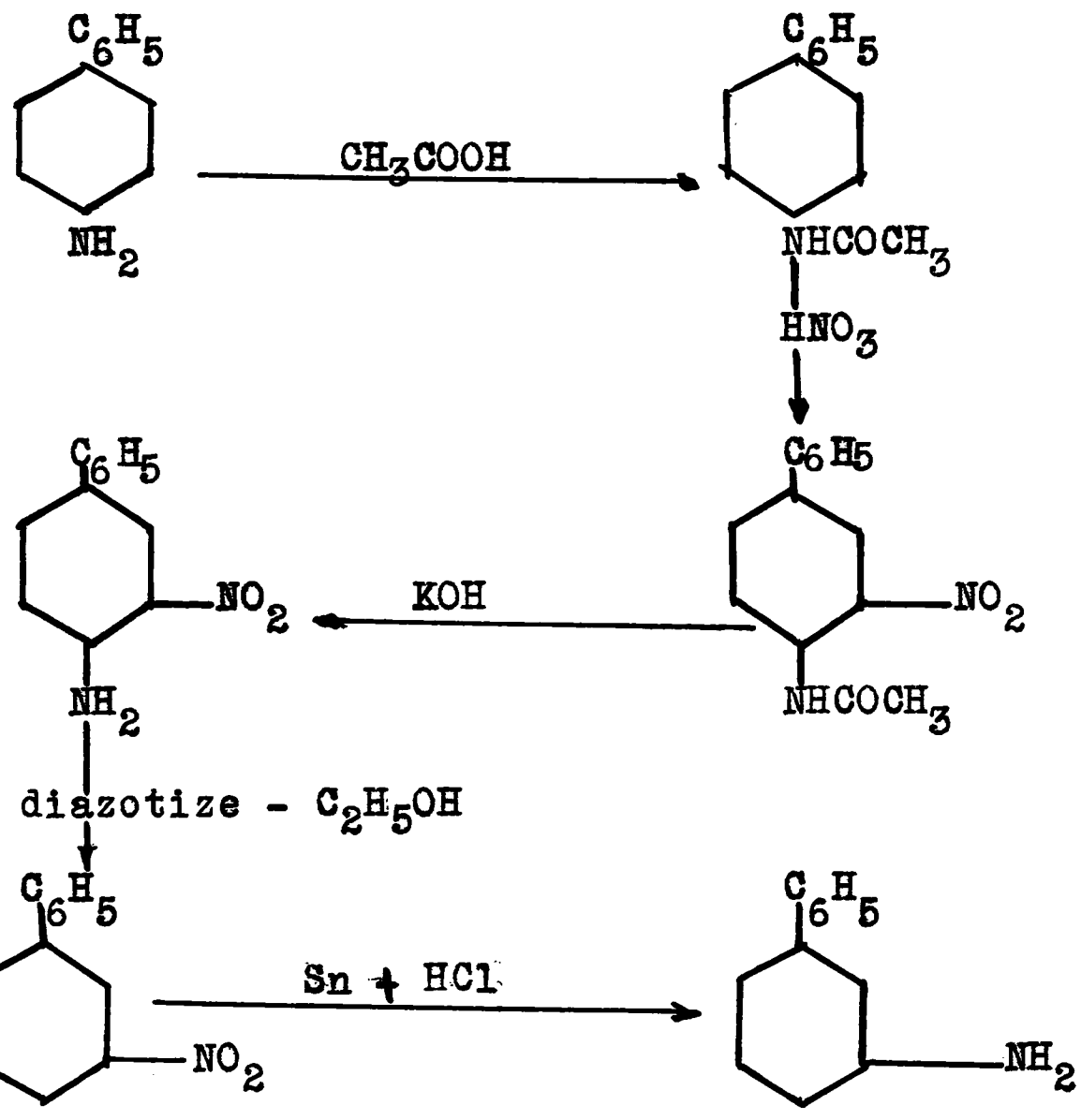
alcohol in bright yellow prisms m.p. 163-4°. This picrate did not lose water upon being dried in vacuum at 76°.

Anal. Calcd. for $C_{18}H_{14}O_7N_4 \cdot H_2O$: N, 13.5. Found N. 13.5.

B. 3-Aminodiphenyl.

1. Preparation.

This amine was prepared from 4-aminodiphenyl[5] by the following series of reactions:



All steps, except the diazotization and the final one, in the above reactions were carried out by employing modifications of the method by Fichter and Sulzberger (48). The diazotization

procedure was carried out according to directions given by DeMilt and Van Zandt (49) and the procedure for the final reduction is due to Jacobson and Loeb (50).

(a) 4-Acetaminodiphenyl.

A mixture of 50 g. of 4-aminodiphenyl and 36 g. (2 equivs.) of glacial acetic acid was refluxed for 15 hours in a flask fitted with an air condenser. The product was poured into 200 cc. of water containing a small amount of hydrochloric acid while still hot. The solid which precipitated was filtered and crystallized from alcohol; its melting point was 172°. The yield was 57 g., or 90% of the theoretical amount.

This substance formed a picrate which separated from alcohol in light red prisms m.p. 123° whose mixed m.p. with picric acid (m.p. 116-7°) was 110-3°.

Anal. Calcd. for $C_{20}H_{16}O_8N_4$: N, 12.7. Found: N, 12.8.

(b) 3-Nitro-4-Acetaminodiphenyl.

Twenty-five grams of the acetaminodiphenyl were dissolved in 250 cc. of glacial acetic acid; the solution was heated to and kept at 70°, while a mixture of 25 g. (17 cc.) of fuming nitric acid (sp. gr., 1.51) and 17 cc. of glacial acetic acid was introduced dropwise over a period of an hour. The solution was stirred during the addition and for an hour after, the temperature being maintained at 70°. It was then cooled and enough water added to precipitate all the nitro compound. After filteration, the product was crystallized from alcohol; it separated in yellow

needles, m.p. 134-5°. The yield was 23g. or 77%.

This substance does not form a picrate.

(c) 3-Nitro-4-Aminodiphenyl.

A solution of 50 g. of 3-nitro-4-acetaminodiphenyl in 800 cc. of alcohol was refluxed with 11 g. of potassium hydroxide. The yellow compound went into solution and almost immediately a bright red solid separated. Heating was continued for 5 minutes, and then the solution was cooled and filtered. The yield, including some product obtained from the filtrate by distilling off the alcohol was practically quantitative. The 3-nitro-4-aminodiphenyl separated from alcohol in bright red needles with a yellow-green fluorescence, m.p. 173-4°.

This substance does not form a picrate.

(d) 3-Nitrodiphenyl.

In 250 cc. of ethyl alcohol were placed 10 g. of the nitro amine and 12 g. of concentrated sulfuric acid.The mixture was stirred and cooled to 0° in an ice bath; the red solid remained largely undissolved. A solution of 5 g. of sodium nitrite in a minimum amount of cold water was then run into the mixture slowly over a period of an hour; a yellow solid was now evident. Stirring was continued for another hour,after which the bath was heated and the solution brought to boiling in half an hour, and then refluxed for the same length of time. The alcohol was removed from the resulting solution by distillation and 400 cc. of water were added to the residue. The solid

which separated was filtered, and on crystallization from alcohol, it formed light yellow plates, m.p. 60-1°. The yield of 3-nitrodiphenyl was 8 g., or 87% of the theoretical amount.

In addition to the above procedure, diazotization was carried out as follows: a mixture of 90 cc. of concentrated sulfuric acid and 45 cc. of water were stirred and cooled to 0°. Then 9 g. of sodium nitrite were carefully added keeping the temperature at 0°. In the same manner 12.02 g. of 3-nitro-4-aminodiphenyl in 60 cc. of pyridine (cooled to 0° and completely dissolved) were added. The reaction will not occur if the amine is not completely dissolved in the pyridine. It was found best to allow it to stand overnight and to filter several times before using. (The addition required 3-4 hours.) Stirring was continued for another hour. Then 300 cc. of alcohol at 0° were added and the mixture was stirred at 0° for an additional hour, after which it was slowly heated to boiling on a water bath and refluxed for 30 minutes. The alcohol was removed from the resulting solution by distillation and 400 cc. of water were added to the residue. The 3-nitrodiphenyl which separated out was filtered off and crystallized from alcohol. This process gave the same yield as the first one.

3-Nitrodiphenyl does not form a picrate.

(e) 3-Aminodiphenyl.

For some unexplained reason the 3-nitrodiphenyl was not reduced to 3-aminodiphenyl with iron and hydrochloric acid but tin gave the desired result.

Five grams of 3-nitrodiphenyl and 9 g. of granulated tin were placed in 50 cc. of ethyl alcohol. The mixture was gently refluxed while 100 cc. of concentrated hydrochloric acid were added in small portions through a dropping funnel. This solution was allowed to stand overnight, for this increased the yield of the final product. The resulting solution was cooled to 0^{o}; made alkaline with potassium hydroxide; and steam distilled. The distillate was collected until it had become clear. The first small portion contained only pyridine and water, and was discarded. The oil was extracted with ether, and then dried over calcium chloride. After distilling the ether, the last traces of ether and pyridine were removed by heating the 3-aminodiphenyl very gently over a smoky flame and the amine was cooled to crystallize it. The procedure gave 3 g. of the amine m.p. 30^{o}, (70% yield), which was white, but rapidly turned to a dark purple due to oxidation. The 3-aminodiphenyl could be obtained directly from the reaction mixture after neutralization by extraction with ether, but the product was not as pure and the separation from the tin salts was very laborious.

2. <u>3-Acetaminodiphenyl.</u>

Refluxing this amine with acetic acid by the same procedure used in the case of 4-aminodiphenyl, yielded 3-acetaminodiphenyl, as expected. After recrystallization from alcohol, its melting point was 149^{o}.

3. <u>Picrate Formation.</u>

3-Aminodiphenyl formed a picrate; this separated from ethyl alcohol in yellow prisms, which decomposed at 196^{o}.

Anal. Calcd. for $C_{18}H_{14}O_7N_4$: N, 14.1. Found : N, 13.9.

4. Treatment with Phenacyl Bromide.

Treatment of 3-aminodiphenyl with an equivalent amount of phenacyl bromide in the manner previously described under A, resulted in the formation of 3-phenacylaminodiphenyl. The substance separated from alcohol in pale yellow leaflets, m.p. 134°.

Anal. Calcd. for $C_{20}H_{17}ON$: N, 4.9. Found: N, 4.7.

5. Treatment with 3-Phenacylaminodiphenyl.

The phenacyl derivative and an excess of the amine were heated at 200° for an hour, and the resulting mixture poured into dilute hydrochloric acid while still hot. Extraction with ether and evaporation of the latter, yielded a residue which was decolourized with charcoal in alcohol. Treatment with picric acid gave the picrate of 3-aminodiphenyl;there was no depression of the mixed melting point with the known sample mentioned above.

When 1.2 g. of 3-aminodiphenyl and 1.7 g. of 3-phenacylaminodiphenyl were heated at 300° for an hour in a sealed tube and allowed to stand for 12 hours, a greenish mass was obtained. This mass was extracted with ether, after the solvent had been allowed to evaporate at room temperature, the resulting mass was recrystallized from chloroform using Nu-Char. After crystallization and filtration, the filtrate was poured into methyl alcohol. The white solid, 2,4-diphenylindole, separated from the chloroform-methyl alcohol mixture in prisms

m.p. 208-9°.

Anal. Calcd. for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.1.

C. 4-Aminodiphenyl.

1. Treatment with Phenacyl Bromide.

This reaction was carried out as described under A. A mixture of the hydrobromide and the phenacyl derivative was obtained. Separation was accomplished by treating the mixture with chloroform, the hydrobromide remaining undissolved.After evaporation of the chloroform, the 4-phenacylaminodiphenyl crystallized from alcohol separated in pale yellow rods,m.p.148°.

Anal Calcd. for $C_{20}H_{17}ON$: N, 4.9. Found: N, 4.9.

This compound formed a picrate which separated from alcohol in prisms, m.p. 130-1° - mixed m.p. with picric acid (116-7°) is 105-10°.

Anal. Calcd. for $C_{26}H_{20}O_8N_4$: N, 10.8. Found: N, 10.7.

The 4-aminodiphenyl hydrobromide was recrystallized from water, in which it was sparingly soluble. It formed white leaflets, which decomposed at 340°.

Anal. Calcd. for $(C_{12}H_{11}N)_2HBr$: N, 6.7. Found: N, 6.7.

2. Treatment with Phenacyl Chloride.

4-Aminodiphenyl and phenacyl chloride react much more slowly than this amine and the bromide. The solution has to stand overnight before the 4-phenacylaminodiphenyl and the 4-aminodiphenyl hydrochloride separate out. The latter separated from water in finely divided gray needles which decomposed at 290°.

3.Treatment with 4-Phenacylaminodiphenyl.

The phenacyl derivative and an excess of the amine were heated at 200° for an hour, and the resulting mixture poured into dilute hydrochloric acid while still hot. Ether extraction of the acid solution yielded a solid, which was fairly insoluble in alcohol. It separated from an alcohol-chloroform mixture in fine needles, which shrank at 200°and melted at 210°. This product did not form a picrate and analysis corresponded to that of 2,5-diphenylindole.

Anal. Calcd. for $C_{20}H_{15}N$: C, 89.2; H, 5.6; N, 5.2.

Found: C, 88.8; H, 5.6.; N, 5.3.

The same indole was obtained by the sealed tube method described under B. It gave a positive Ehrlich's Test i.e. a pale pink colour upon addition of hydrochloric acid which changed to a faint yellow colour upon addition of one drop of sodium nitrite solution. It also gave a positive pine shaving test. It formed no picrate, no methiodide, no addition product with trinitrotoluene, and no acetyl derivative. When the mass from the sealed tube was extracted with warm glacial acetic acid and water was added to precipitate the indole, the filtrate yielded a small amount of a solid which separated in prisms, m.p.272°. Found:N,10.3. This solid was not further investigated.

4. Picrate Formation.

4-Aminodiphenyl formed a picrate which separated from alcohol in pale yellow needles, m.p. 198-9°.

Anal. Calcd. for $C_{18}H_{14}O_7N_4$: N, 14.1. Found: N, 13.9.

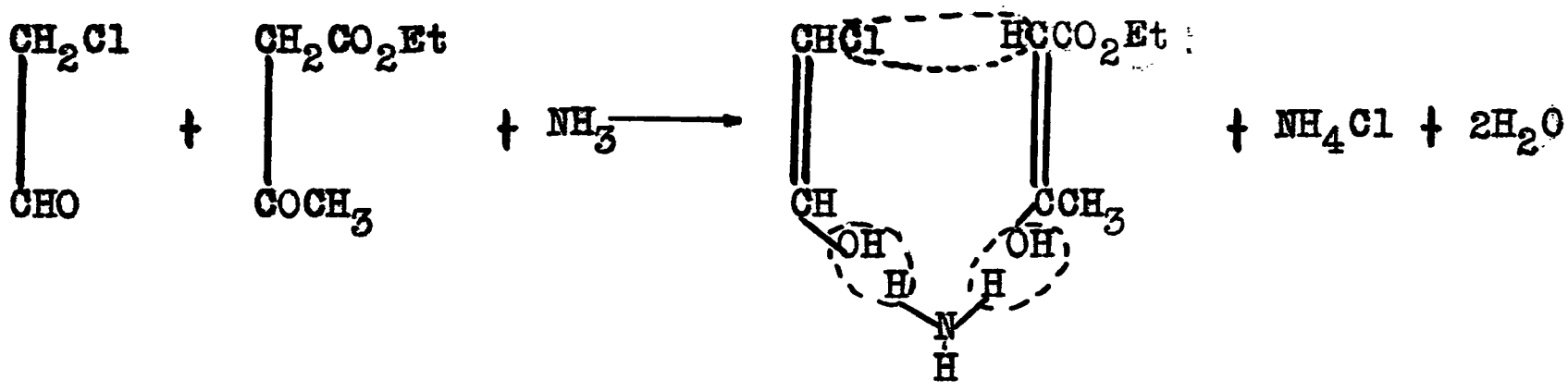
D. Results of Ehrlich's Test Using Indoles (51).

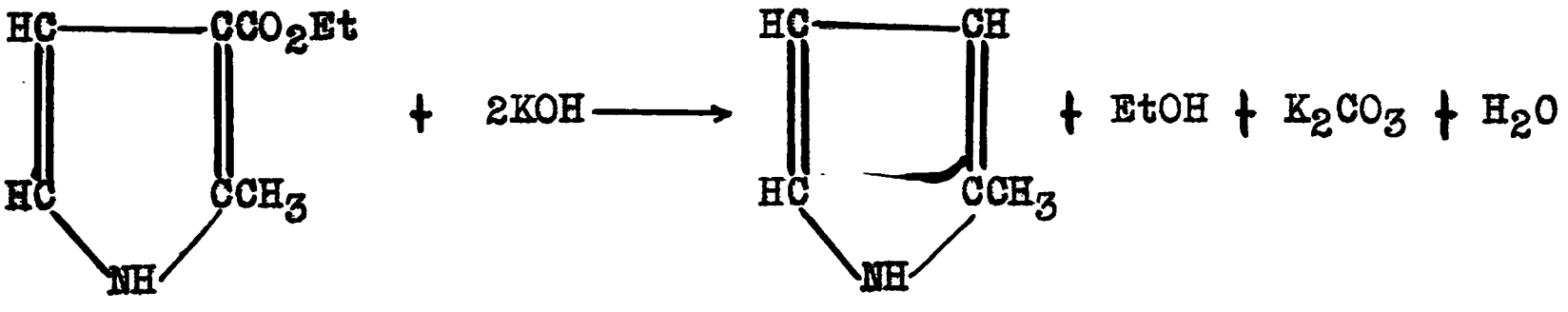
Indole	Colour with HCl	Colour with $NaNO_2$	Colour after standing 12 hours
Indole	Very pale pink violet	Deep Crimson	———
2,4-Diphenylindole	Very pale pink	Pale Yellow	Deeper Yellow
2,5-Diphenylindole	Very pale pink	Pale Yellow	Deeper Yellow
2,4,7-Dimethylindole	Deep purple	Reddish Purple	Red

II. Pyrroles.

A. 2-Methylpyrrole.

1. Preparation.





Twenty grams of freshly distilled α,β-dichloro-diethyl ether and 13 g. of ethyl acetoacetate were placed in a clean 500 cc. flask. (It was found that this reaction took place more quickly when a clean flask was used for each run.) Then 100 cc. of 10% ammonium hydroxide solution were added as quickly as poss-

ible while the mixture was rapidly stirred. The reaction soon took place with the evolution of a considerable amount of heat. The mixture was stirred rapidly until it had cooled to room temperature. Then it was poured into a beaker and cooled in an ice-bath and a heavy dark-coloured oil separated, which partly solidified. More solid could be obtained when it was seeded out with a few crystals of ethyl 2-methylpyrrole carboxylate. The solid was filtered from the oil by suction and the cooling was repeated until crystallization ceased.

The solid from five preparations carried out as described above, was collected and the mother liquors, which still contained a considerable amount of the desired product, were mixed with an equal volume of 10% sodium hydroxide solution and left for 48 hours. After cooling and seeding out, the crystals were filtered out and the resultant mother liquors kept until nothing more crystallized. The various crops of crystals were pressed as free from oil as possible, and recrystallized from alcohol. The weight of ethyl 2-methylpyrrole 2-carboxylate, m.p. 81-2°was 25-30 g., i.e. 32-9% of the theoretical quantity calculated on the ethyl acetoacetate taken. Crystallization from alcohol was found an unnecessary procedure at this point.

Fifty-two grams of this ester were boiled under a reflux condenser for 2 hours with a solution of 40 g. of potassium hydroxide in 200 cc. of 50% alcohol. When hydrolysis was complete, a test portion remained clear on dilution with water. The alcohol was removed by distillation in vacuo and

the residue in the flask was steam distilled. When no more 2-methylpyrrole passed over, the distillate was saturated with salt and extracted twice with ether. The ethereal solution was well dried with anhydrous sodium sulfate and the solvent removed by slow distillation under ordinary pressure, in a flask fitted with a long fractionating column. The residue was distilled in vacuo and the 2-methylpyrrole boiled at 76-7°/24mm. Practically no residue remained in the flask and the weight of pure 2-methylpyrrole was 19 g., i.2. 66% theoretical calculated on ethyl 2-methylpyrrole 3-carboxylate.

The above method of making ethyl 2-methylpyrrole 3-carboxylate is due to Benary (52), while the conversion of this ester into 2-methylpyrrole was taken from H. Fischer, Beller, and Stern (53).

Other methods of preparation are those from pyrrole 2-aldehyde by reduction with sodium ethylate (53), from the conversion of N-methyl into 2-methylpyrrole (54), and from levulinic aldehyde and ammonia (55).

2. Conversion into 2,4-Dimethylindole.

(a) With Zinc Acetate in Acetic Acid.

A mixture of 3g. of 2-methylpyrrole, 5 g. of zinc acetate, and 20cc. of 90% acetic acid was refluxed for 16 hours and then submitted to steam distillation. The acid in the distillate was neutralized by sodium hydroxide. This distillate was extracted with chloroform; the extract dried over anhydrous calcium chloride; and the solvent distilled off. When a saturated alcohol solution of picric acid was added to the residue, the

2.4-dimethylindole was converted into a picrate which crystallized from dilute alcohol in red-brown needles, m.p.158° as described by Plancher (26).

(b) By Acid Treatment of Dimethyldipyrrole Hydrochloride.

When dry gaseous hydrogen chloride was passed into 2-methylpyrrole, dimethyldipyrrole hydrochloride was formed as a reddish sticky mass.

When a portion of the sticky hydrochloride was dissolved in water and made alkaline with sodium hydroxide solution, a flocculent precipitate appeared. This amorphous substance had an indefinite melting point and was not further studied. It was at once dissolved in water by addition of a little sulfuric acid and the mixture steam distilled. The indole came over very rapidly and a strong odour like acetamide was noticed. A portion was treated with cold aqueous maleic acid, but no solid separated as indicated by Diel's work, hence the amount of 2-methylpyrrole present, if any, must have been very small. The steam distillate was extracted with chloroform and the solvent evaporated. An immediate red precipitate formed on the addition of a saturated alcoholic solution of picric acid. This decomposed at 145° before recrystallization.

A mixed melting point of the above picrate and the one prepared from 2-methylpyrrole, as described above under 2.(a) was not depressed, indicating their identity. Their

colour and crystal form were indistinguishable.

A similar distillation of the hydrochloride after addition of a little sulfuric acid at once gave the indole.

The same reaction also occured when 1 g. of the hydrochloride was allowed to stand for 24 hours at room temperature with 19 cc. of water and 1 cc. of concentrated sulfuric acid.

B. 2-Phenylpyrrole.[6]

1. Solubility.

One gram of 2-phenylpyrrole dissolved in 15 cc. of boiling Skelly Solve C.

2. Colour.

Unless completely substituted, pyrroles rapidly turn red or purple on keeping; this has usually been attributed to oxidation. The following experiments were carried out to determine the cause of the colour production.

(a) Crystallization in Air.

Two grams of this pyrrole were recrystallized from Skelly Solve C in air, yielding a dull coloured product similar to that in the reagent bottle.

Two grams of the pyrrole were recrystallized from Skelly Solve C in air after purification in bone charcoal. The resulting crystals were definitely lighter in colour and of a pearly pink nature. These remained white for two months;

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[6] The effect of light, air, moisture, and acid was studied in part by Mr. W. J. Poyner. His assistance is gratefully acknowledged.

in sunlight they acquired a faint pink tinge which soon changed to brown.

(b) Crystallization in a Nitrogen Atmosphere.

Three grams of the pyrrole were recrystallized from 50 cc. of Skelly Solve C in a nitrogen atmosphere. The resultant crystals were a dark violet hue, which intensified on standing. This result was obtained several times.

(c) Crystallization in the Absence of Light.

Three grams of the pyrrole were crystallized from Skelly Solve C at night in an amber beaker. The resultant crystals were white and a specimen in an open beaker (amber glass) exposed to all the laboratory fumes for three weeks, acquired a very faint pink tinge.

(d) Exposure to Sunlight.

Solutions of 2-phenylpyrrole in Skelly Solve C and in ethyl alcohol exposed to sunlight for a week acquired a deep pink colour and contained a small quantity of a precipitate which was diphenyldipyrrole.

Some of the crystals obtained from the charcoal purification in air were placed in test-tubes, tightly stoppered after adding the following constituents, and placed in the direct sunlight for three weeks (April).

(1) Dry Air.

(2) Dry Nitrogen.

(3) Moist Nitrogen.

(4) Nitrogen plus one drop of hydrochloric acid.

The last three turned a pale pink in a few minutes but the colour changed to tan in a day; the first one became tan without a pink colour. There was no further visible change except with the last one, the container wall of which appeared much browner. The melting point of each except the last had dropped about 5^{o}; all were found to be essentially unchanged 2-phenylpyrrole by mixed melting points, whereas admixtures with the diphenyldipyrrole were depressed over 20^{o}.

From these observations it is concluded that the production of colour is associated with traces of an impuriety that is affected by sunlight.

3. Conversion into Diphenyldipyrrole.

The 2-phenylpyrrole was recrystallized in an atmosphere of nitrogen[1] and the saturation with hydrogen chloride was performed in the same apparatus.

A solution of 10 g. of 2-phenylpyrrole in 50 cc. of dry peroxide-free ether was saturated with hydrogen chloride, the gas being passed through at the rate of one bubble per second, while the reaction flask was cooled in ice-water. After closing the flask and allowing it to stand overnight the ether was decanted from 9.8 g. of a brownish resinous deposit. After several washings with acetone, 5.4 g. of a yellow-

[1] The apparatus for working in an atmosphere of nitrogen was built by Mr.W.J.Poyner.Commercial nitrogen from a cylinder was passed successively over heated copper gauze,and through absorption towers containing Fieser's solution,lead acetate,sulfuric acid,and Dessichlora,and finally bubbled through sodium benzophenone in p-cymene. The hydrogen chloride was generated by dropping concentrated sulfuric acid into concentrated hydrochloric acid,dried by passage through concentrated sulfuric acid, and passed over heated copper gauze.

bronze leaflets, m.p. 202-3°.with decomposition.

Anal. Calcd. for $C_{20}H_{19}ClN_2$: N, 8.7; Cl, 11.0; HCl, 11.3.

Found: N, 8.6;Cl, 11.1; HCl, 11.3.

The actual yield was variable, the above being an average value, whether done in air or nitrogen. The presence of moisture may be beneficial, for the best yields were obtained from air-dried pyrrole; a specimen from the same lot carefully dried in a Fischer pistol for 3 hours and run at the same time under the same conditions gave no salt. The resinous by-product is greater if the ether contains peroxide, or if the pyrrole contains N-phenylpyrrole.

C. Results of Ehrlich's Test Using Pyrroles (51).

Pyrrole	Colour with HCl	Colour with $NaNH_2$	Colour after standing 12 hours
2-Phenylpyrrole	Bluish purple	_____	_____
2,5-Dimethyl-pyrrole	Pinkish orange	Deep Red	_____
2,4-Dimethyl-3-acetyl-5-carbethoxy pyrrole	Medium Pink	Pale Yellow	Deeper Yellow
Pyrrole	Deep Pink	Nearly Black	_____
2-Acetylpyrrole	Very Pale Pink	Slightly Deeper	Deep Purple
Diphenlydipyrrole	Very Deep Pink	Slightly Deeper	_____
3-Methyl-3-carbethoxy pyrrole	Pale Pink	Deepens to same shade as diphenyl-dipyrrole	_____

III. Synthesis of Dimethylindoles Related to the Dipyrroles

1. 2,4-Dimethylindole from 1,2,3-o-Xylidine.

(a) Attempt to isolate 1,2,3-o-Xylidine from Technical o-Xylidine[8] (56).

Technical o-xylidine is supposedly a mixture of 1,2-dimethyl-3-aminobenzene and 1,2-dimethyl-4-aminobenzene. The formyl derivative of the 1,2,3-isomer is a solid at room temperature and should crystallize out on standing.

When 9 g. of technical o-xylidine and 13.6 g. of 25% formic acid (25 g. of 85% formic acid and 60cc. of water) were mixed, heat was generated. This mixture was heated to the boiling point with a free flame and then warmed for 3 hours on a water bath with an air condenser. It soon became cloudy and an oily formyl derivative separated which floated on top-then settled to the bottom of the flask. When this was chilled and allowed to stand 12 hours, no change occurred. After it had stood for one month, no solid separated. When concentrated formic acid was used in this procedure, a similar result was obtained.

Thus it is seen that technical o-xylidine contains too small an amount of the 1,2,3-isomer to be isolated by this technique.

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[8] This was very kindly supplied by E. I. Dupont de Nemours Company Incorporated.

(b) 2,4 Dimethylindole (41, 42)[9].

2. 2,5-Dimethylindole from 1,3-Dimethyl-4-Xylidine.

(a) Preparation of the Acetyl Derivative(57).

Into 250 cc. of water, 8.3 cc. of concentrated hydrochloric acid and 12 g. of 1,3-dimethyl-4-xylidine were poured. The oil was brought into solution by stirring and decolourized by stirring for 5 minutes with 3 g. Nu-Char and filtering. The colourless solution was warmed to 50°, 11.6 g. of acetic anhydride were added and 15 g. of sodium acetate in 50 cc. of water were immediately added. The acetyl derivative, m.p.128-9° separated out and was filtered off after the solution had been cooled.

(b) Conversion of Acetyl Derivative into 2,5-Dimethylindole (40).

The acetyl derivative of 1,3-dimethyl-4-xylidine was placed in a 3-necked flask with an equal weight of dry sodium ethoxide. Nitrogen was passed through the system for a few minutes. This was slowly heated up to 280° using a metal bath and held at that temperature for an hour. It was found necessary to pass nitrogen through the apparatus all the time, for otherwise the reaction would not go. This reaction was not

[9] This compound was kindly prepared by C. F. H. Allen of the Eastman Kodak Company, Rochester, New York.

vigorous, for only a few white fumes were given off. Then water was added and the whole mass was steam distilled. The solid, 2,5-dimethylindole, m.p. 114°, was filtered off. It gave a positive pine shaving test.

(c) Conversion of the Indole into the Picrate.

2,5-Dimethylindole gave a dark red picrate, m.p. 155°.

3. 2,6-Dimethylindole from 1,4-Dimethyl-5-Aminobenzene[10].

(a) Preparation of 2,6-Dimethylindole.

Twenty cc. of 1,4-dimethyl-5-aminobenzene were converted into 23.2 g. of the acetyl derivative by Fieser's procedure(57) from which 2,6-dimethylindole was prepared by Verley's procedure (41,42). Eight grams of the acetyl derivative were put in a 100cc. distilling flask, 16 g. of coarsely pulverized sodium amide were added, and the air displaced by illuminating gas. This was heated with a smoky flame and ammonia was evolved. After 10 minutes it was put in a metal bath and gradually heated to 275° when foam nearly filled the flask. After this had cooled, 5cc. of 95% alcohol were added, 20cc. of benzene, and 50% alcohol-water in small portions as the reaction permitted. The sodium amide dissolved slowly. The solvents, the unused amine, and finally the

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[10]This compound was kindly furnished by E. I. Dupont de Nemours Company Incorporated.

indole were removed by steam distillation. The indole solidified in the condenser. It was extracted with chloroform, dried over calcium chloride, filtered, and the solvent evaporated. It separated from Skelly Solve B (dissolved only at b.p.) in white transparent hexagonal leaflets, m.p. 85°.

Anal. Calcd. for $C_{10}H_{11}N$: N, 9.7 Found: N,9.6.

(b) Conversion of the Indole into the Picrate.

2,6-Dimethylindole gave a picrate which was dull red in colour and melted at 132°.

Anal. Calcd. for $C_{16}H_{14}O_7N_4$: N,15.0. Found: N, 15.0.

4. 2,7-Dimethylindole from 1,3-Dimethyl-2-Aminobenzene.

(a) Preparation of 2,7-Dimethylindole.

1,3-Dimethyl-2-aminobenzene was converted into its acetyl derivative, m.p. 163-4° by Fieser's procedure, using acetic anhydride in water. The reaction went very smoothly, and the solid separated in less than a minute. Fourteen grams of the starting material yielded 16 g. of the acetyl derivative. This was subjected to Verley's procedure as described above (41,42). In this case, the air was displaced by nitrogen and the fusion temperature was 300°. The 2,7-dimethylindole prepared in this manner boiled at 129-131°/2mm.[11] After three weeks this compound crystallized, m.p. 35°.

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[11] Micro boiling point by Dr. G. F. Wright.

(b) Conversion of the Indole into the Picrate.

The 2,7-dimethylindole yielded a carmine coloured picrate, m.p. 149° (shrank at 135°).

Anal. Calcd. for $C_{16}H_{14}O_7N_4$: N, 15.0. Found: N, 15.2, 15.2.

The picrates of dimethylindoles prepared in this way were identical with the picrates prepared from the hydrolysis products of dipyrroles.

SUMMARY

(1) 2,4-Diphenylindole and 2,5-diphenylindole were prepared and their reactions investigated.

(2) 2-Methylpyrrole was prepared and converted into 2,4-dimethylindole by two different procedures.

(3) 2-Phenylpyrrole was converted into diphenyldipyrrole.

(4) A number of pyrroles were submitted to Ehrlich's test and their colour reactions compared.

(5) 2,4-Dimethylindole, 2,5-dimethylindole, 2,6-dimethylindole, and 2,7-dimethylindole related to the dipyrroles studied were synthesized.

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STEREOCHEMISTRY OF LINALOOL

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STEREOCHEMISTRY OF LINALOOL

Theoretical

For a long time it has been known that optically active straight chain secondary alcohols can be converted into optically active secondary halides. Pickard and Kenyon (1) have converted a great many optically active carbinols into the corresponding optically active halides and expressed the belief that there was little or no racemization. They found that the conversion in every case investigated was accompanied by a change in the sign of rotation. For example: methylethylcarbinol, $\alpha_D^{17.8}$: + 14.03 yielded the iodide α_D^{17} :-31.98 and d-methyl-n-propylcarbinol, α_D^{19} : + 13.86; the iodide α_D^{17} : -37.15. Their attempts to reconvert these halides back into the optically pure alcohols were however unsuccessful.

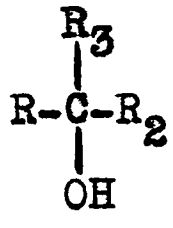
Later, McKenzie and Clough (2) prepared d-phenylethyl chloride, α_D^{20} ; + 50.6 from d-phenylethyl alcohol and thionyl chloride. They believed that no racemization occured, for they always obtained the same rotation from various preparations.

More recently however Hughes, Ingold, and Masterman (3) have prepared halides of straight chain aliphatic secondary carbinols such as methylhexylcarbinol under a variety of conditions such as saturation with the dry gaseous hydrogen halides and treatment with thionyl halides. They found that there was always some racemization, for the ac-

tivity of their halides varied with the method of conversion. The amounts of racemization varied from 50% to as little as 3%.

Now during the conversion of any carbinol into its halide, at some time the hydroxyl group must be removed from the rest of the molecule. The remaining positive fragment $R_1-\overset{+}{C}H-R_2$, if really an intermediate as postulated by Whitmore (4), Jones (5), and Stieglitz and Stagner (6), must therefore be sufficiently stable to retain its asymmetry, although in most cases a change of configuration occurs due to Walden Inversion. Very little work has been done with tertiary alcohols, because of the difficulty in resolving them. The only type studied extensively so far is the triphenyl-carbinol type resolved by Wallis and Adams (7),which were found to yield completely racemized halides.

In order to avoid this complex type so bound up with possible free radical formation, an investigation was made of the simple optically active tertiary alcohols. As there were no methods for resolving them, natural substances had to be considered. Linalool seemed to be well adapted to this work as it was readily available in an optically active form and could be reduced to the simplest type of optically active tertiary-carbinol possible-

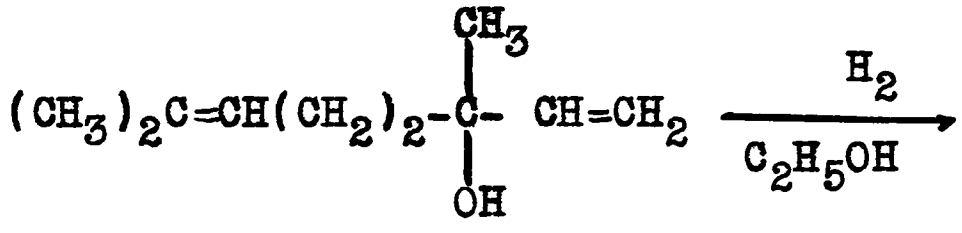


where all the Rs are simple alkyl groups. To be sure lin-

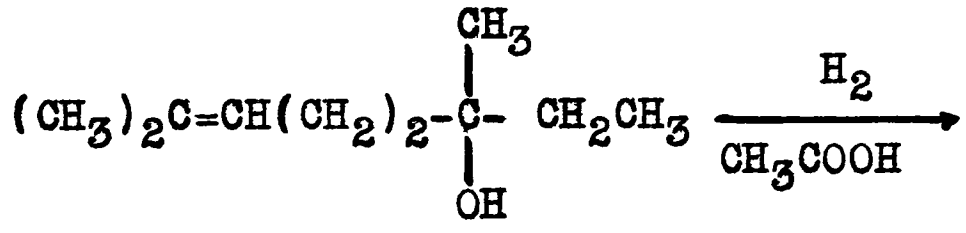
alcol is a tertiary alcohol itself and has been reported as having been converted into an optically active chloride by Vanin and Chernoyarova (8). These results may not however be entirely reliable. It is well known that α,β-unsaturated alcohols rearrange readily when converted to their halides; and in the case of linalool many other different rearrangement products are possible. For example: Ikeda and Takeda (9) found that linalool with both dry gaseous hydrogen chloride and hydrogen bromide gave among other products an optically active terpene, presumably monocyclic, which must have been the result of a deep seated rearrangement.

In order to avoid this complication, l-linalool(I) was first reduced to a saturated compound before conversion into its halide derivative. Complete reduction was possible in glacial acetic acid using Adams platinum catalyst. Several other methods were tried, but this was the only one which gave the desired result. When the reduction was carried out in ethyl alcohol using Adams platinum catalyst, the hydrogenation stopped after addition of two hydrogen atoms-that is, with the formation of dihydrolinalool (II) - the terminal double bond alone having been reduced. The remaining double bond was reduced in glacial acetic acid using Adams platinum catalyst. Dupont (10) with essentially the same process recorded this same stepwise reduction and obtained first dihydrolinalool and then tetrahydrolinalool (III). The structures of the optically active reduced derivatives were proven

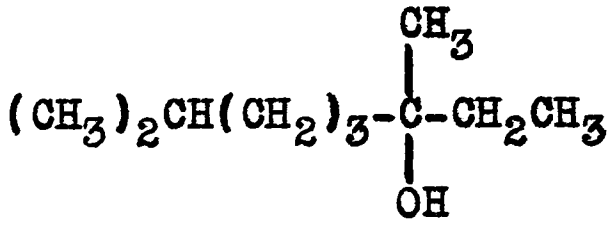
by comparison with synthetic dihydro- and tetrahydro-linalool. Unfortunately Dupont failed to record the optical activity of his tetrahydrolinalool.



I



II



III

Barbier and Locquin (11) and Paal (12,13) reported tetrahydrolinalool (III) (from l-linalool) as being levorotatory, whereas on the other hand some of the samples of tetrahydrolinalool prepared here were dextrorotatory.

In as much as the dihydrolinalool (II) is reduced only with difficulty-and as it has a comparatively high levo rotation-it is not improbable that the levo readings recorded may have been due to incomplete reduction. Indeed there were found in several cases after what app-

eared to be complete reduction, considerable amounts of unsaturated compounds, These were removed by potassium permanganate oxidation.

However, the rotations of the purest sample of tetrahydrolinalool (III) were so low as to be on the border line of experimental error. Therefore a number of attempts were made to make sure that optically active tetrahydrolinalool actually was at hand, by conversion to a derivative of possibly much higher rotation-but all to no avail. It was necessary to conclude, therefore, that as it is highly unlikely that racemization occurred during hydrogenation, simple aliphatic tertiary alcohols must have very low rotations and in the case of tetrahydrolinalool (III) the maximum $(M)_D$ is probably in the neighborhood of + 0.25^o. On the other hand, the maximum values found for methyl- and ethylhexyl carbinols, which are typical secondary alcohols, were 12.7^o and 10.6^o.

Due to this low activity, at first it was thought that it would be better to employ the dihydrolinalool (II) for this study of the preparation of optically active tertiary chlorides. However, this substance gave no definite products. It was necessary therefore to turn to the optically active tetrahydrolinalool.

In this case it was possible to prepare with ease a very pure chloride using hydrochloric acid. The activity, however, while higher than that of the original carbinol,was

still very low α_D^{20} : + 0.23, and of the same sign of rotation.

Hydrolysis of this chloride yielded a carbinol of the same sign and value as the original alcohol, but again due to the low values, it was clear that the results were not conclusive enough to make any definite statement as to the amount of racemization taking place either during halogenation or during hydrolysis.

Experimental

Purification of Linalool.

The sample of linalool(I) used in this work was obtained from Dr. Theodor Schuchardt Company, and had the following physical constants:

d_4^{20} : 0.8632; n_D^{20} : 1.4650; M.R.: Calc. 48.97. Found: 49.24;

$[\alpha]_D^{23.5}$: -14.07; $M_D^{23.5}$: -25.2.

Dispersion.

1. Homogenous.

λ			
6438	$[\alpha]_{Cd}^{28}$	: -11.55;	M_{Cd}^{28} : -20.8
5890	$[\alpha]_{D}^{28}$	: -13.70;	M_{D}^{28} : -24.6
5461	$[\alpha]_{Hg}^{29}$	: -16.20;	M_{Hg}^{29} : -29.1
5209	$[\alpha]_{Ag}^{29}$	: -18.01;	M_{Ag}^{29} : -32.4
5086	$[\alpha]_{Cd}^{29}$	: -18.99;	M_{Cd}^{29} : -34.1
4722	$[\alpha]_{Zn}^{29}$	: -22.71;	M_{Zn}^{29} : -40.9

M_{Zn}^{29} / M_{D}^{28} = -40.9/-24.6 = 1.66

2. In Solvents (Concentration 0.8412 g. / 10cc.)

a. Carbon Disulfide.

λ		
6438	α^{24}_{Cd} : -1.50;	M^{24}_{Cd} : -2.68
5890	α^{24}_{D} : -1.75;	M^{24}_{D} : -3.12
5461	α^{24}_{Hg} : -2.11;	M^{24}_{Hg} : -3.78
5209	α^{24}_{Ag} : -2.28;	M^{24}_{Ag} : -4.07
5086	α^{24}_{Cd} : -2.50;	M^{24}_{Cd} : -4.47
4722	α^{24}_{Zn} : -2.76;	M^{24}_{Zn} : -4.93

$$M^{24}_{Zn} / M^{24}_{D} = -4.93/-3.12 = -1.57$$

b. Chloroform.

λ		
6438	α^{24}_{Cd} : -1.15;	M^{24}_{Cd} : -2.05
5890	α^{24}_{D} : -1.22;	M^{24}_{D} : -2.18
5461	α^{24}_{Hg} : -1.39;	M^{24}_{Hg} : -2.48
5209	α^{24}_{Ag} : -1.52;	M^{24}_{Ag} : -2.72
5086	α^{24}_{Cd} : -1.71;	M^{24}_{Cd} : -3.06

c. Benzene.

λ		
6438	α^{24}_{Cd} : -1.29;	M^{24}_{Cd} : -2.30
5890	α^{24}_{D} : -1.46;	M^{24}_{D} : -2.60
5461	α^{24}_{Hg} : -1.69;	M^{24}_{Hg} : -3.02
5209	α^{24}_{Ag} : -1.93;	M^{24}_{Ag} : -3.44
5086	α^{24}_{Cd} : -2.04;	M^{24}_{Cd} : -3.64
4722	α^{24}_{Zn} : -2.25;	M^{24}_{Zn} : -4.02

$$M^{24}_{Zn} / M^{24}_{D} = -4.02/-2.60 = 1.54$$

d. Ethyl Ether.

λ		
6438	α^{24}_{Cd} ; -1.28;	M^{24}_{Cd} : -2.28
5890	α^{24}_{D} : -1.34;	M^{24}_{D} : -2.39
5461	α^{24}_{Hg} : -1.59;	M^{24}_{Hg} : -2.84
5209	α^{24}_{Ag} : -1.67;	M^{24}_{Ag} : -2.98
5086	α^{24}_{Cd} : -1.94;	M^{24}_{Cd} : -3.46
4722	α^{24}_{Zn} : -2.16;	M^{24}_{Zn} : -3.86

$$M^{24}_{Zn} / M^{24}_{D} = -3.86/-2.39 = -1.61$$

This linalool(I) was now purified by fractional distillation, using a 60cm. packed total reflux column. The following fractions were obtained, and their physical constants determined.

Fraction	B. P.	Temp.of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found	α_D^{24}	M_D^{24}
1	83-6°/14mm.	134-6°	0.8634	1.4642	48.97	49.28	-13.99	-25.1
2	86-7°/14mm.	134-6°	0.8624	1.4630	48.97	49.25	-15.23	-27.3
3	Residue	-----	0.8775	1.4680	48.97	48.82	-11.73	-20.6

Reduction of Linalool.

1. In Glacial Acetic Acid.

A. Pure Linalool.

As linalool(I) would not reduce in a homogenous state, it was necessary to reduce it in a solvent.

Eighteen and one half grams of linalool(I), α_D^{24} :-15.23, 20cc. of pure glacial acetic acid, and 0.1 g. of Adams(14) freshly prepared platinum catalyst were shaken under ±50 pounds pressure in an atmosphere of hydrogen until no more hydrogen was absorbed. Then 0.1 g. more catalyst was added, and the mixture was shaken for three additional hours. The absorption of hydrogen conformed to that required for 4 hydrogens.

After the catalyst had settled, the liquid was carefully pipetted off and washed with a large quantity of distilled water, and finally extracted with a good grade of ether (distilled from a small amount of sodium hydroxide) and dried over anhydrous

potassium carbonate. After drying the ether was removed in vacuo. The crude linalool(I) was stable to potassium permanganate indicating complete reduction. Upon distillation, the following fractions were separated and their physical constants determined:

Fraction	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found	Amount
1	Up to 77°/8mm.	-----	--	1.4339	--------		2.5 g.
2	77-8°/8mm.	114°	0.8396	1.4354	51.6.	49.7	12.5 g.
3	Residue-viscous and yellow in colour.				---	---	1.5 g.

<u>The Rotary Dispersion of Fraction 2 Was As Follows</u>:

λ				
6438	α_{Cd}^{28}	: -0.12;	M_{Cd}^{28}	: -0.229
5890	α_{D}^{28}	: -0.08;	M_{D}^{28}	: -0.153
5461	α_{Hg}^{29}	: -0.09;	M_{Hg}^{29}	: -0.171
5209	α_{Ag}^{29}	: -0.05;	M_{Ag}^{29}	: -0.095
5086	α_{Cd}^{29}	: -0.03;	M_{Cd}^{29}	: -0.057
4722	α_{Zn}^{29}	: -0.09;	M_{Zn}^{29}	: -0.171

$$M_{Zn}^{29}/M_{D}^{28} = -0.171/0.153 = 1.12$$

B. Crude Linalool.

Twenty-eight grams of linalool(I), $\alpha_D^{23.5}$: -14.07, 30cc. of pure glacial acetic acid, and 0.1 g. Adams(14) freshly prepared catalyst were subjected to the above procedure, which was repeated until seven 28 g. samples of linalool(I) had been hydrogenated.

These eight hydrogenations were immediately worked up as before and the ether extracts were all dried over anhydrous potassium carbonate. After removing the greater part of the ether in vacuo, the liquid was found to be slightly unsaturated as evident by reduction of potassium permanganate. The material was therefore further purified by the following procedures.

(a) Distillation.

Fraction	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found	α_D^{24}	M_D^{24}
1	Up to 78°/8mm.	-------	0.8620	1.4359	51.6	50.03	+0.33	+0.634
2	78°/8mm.	118°	0.8317	1.4374	51.6	49.7	+0.09	+0.171
3	Residue - Fairly viscous and dark in colour.							

The tetrahydrolinalool(III) purified in this way did not reduce potassium permanganate.

The Rotary Dispersion of Fraction 2 Was As Follows:

λ			
6438	α_{Cd}^{27}	: +0.02;	M_{Cd}^{27} : +0.038
5890	α_D^{27}	: +0.09;	M_D^{27} : +0.171
5461	α_{Hg}^{27}	: +0.13;	M_{Hg}^{27} : +0.248

5209 α^{27}_{Ag} : +0.15; M^{27}_{Ag} : +0.285

5086 α^{27}_{Cd} : +0.19; M^{27}_{Cd} : +0.362

4722 α^{27}_{Zn} : +0.27; M^{27}_{Zn} : +0.514

$$M^{27}_{Zn} / M^{27}_{D} = +0.514/+0.171 = +3.01$$

Tetrahydrolinalool(III) prepared in this way gave a dispersion of ±0.00 in anhydrous carbon disulphide, chloroform, benzene, and ethyl ether.

(b) Potassium Permanganate Treatment.

The crude linalool(I)before distillation was shaken with equal volumes of ice-cold potassium permanganate until the latter was no longer decolourized after standing for 10 minutes. After separating the layers, the remaining tetrahydrolinalool(III) was washed thoroughly with distilled water; extracted with ether distilled from sodium hydroxide; and the latter after being washed with an aqueous solution of potassium carbonate was dried in ether over anhydrous potassium carbonate and distilled:

Fraction	B. P.	Temp. of Oil Bath	d^{20}_{4}	n^{20}_{D}	M. R. Calc.	M. R. Found	α^{24}_{D}	M^{24}_{D}
1	Up to 78°/8mm	------	----	1.4355	----	-----	±0.00	±0.00
2	78°/8mm.	114°	0.8333	1.4364	51.6	49.7	-0.02	-0.0381
3	Residue - pale yellow in colour and very turbid.			1.4355	-----	-----	-----	-----

Tetrahydrolinalool(III) prepared in this way gave a silver mirror with Tollen's reagent only upon prolonged heating and a positive test with Schiff's Reagent after standing overnight.

(c) Potassium Permanganate and Sodium Bisulfite Treatment.

The crude linalool(I) before distillationwas previously shaken in a separatory funnel with an aqueous solution of potassium permanganate until the latter was no longer decolourized. Then solid sodium bisulfite was carefully added until the potassium permanganate colour was destroyed. The tetrahydrolinalool(III) was extracted from this and the washings with ether which was washed thoroughly with an aqueous solution of potassium carbonate and dried over anhydrous potassium carbonate and distilled:

Fraction	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found	α_D^{24}	M_D^{24}
1	Up to 78°/8mm	---	---	1.4355	----	-----	---	---
2	78-9°/8mm	114°	0.8146	1.4632	51.6	50.8		
3	Residue - Pale yellow in colour and very turbid.							

The Rotatory Dispersion of Fraction 2 Was As Follows:

λ		
6438	α_{Cd}^{27} : ±0.00	M_{Cd}^{27} : ±0.00
5890	α_{D}^{27} : +0.05	M_{D}^{27} : +0.097

5461	α^{27}_{Hg}	: +0.13;	M^{27}_{Hg}	: +0.252
5209	α^{27}_{Ag}	: +0.19;	M^{27}_{Ag}	: +0.368

This gave the same results with Schiff's reagent as the tetrahydrolinalool(III) treated with only potassium permanganate solution.

2. <u>In Ethyl Alcohol</u>.

Twenty-eight grams of the crude linalool(I), $\alpha^{23.5}_{D}$: -14.07, were shaken with 30cc. of pure ethyl alcohol and 0.1 g. Adams (14) platinum catalyst in an atmosphere of hydrogen under ±50 pounds pressure until no hydrogen was further absorbed. The amount of hydrogen absorbed amounted to approximately two hydrogens. This procedure was repeated using 56 g. and 60 g. linalool, respectively.

After the catalyst had settled, the liquid was pipetted and washed several times with a large quantity of water in order to remove the alcohol. Finally it was extracted with a good grade of ether, and dried over anhydrous potassium carbonate. After the ether had been removed in vacuo, the liquid was distilled, and then the physical constants of the different fractions were determined:

Fraction	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found	α_D^{24}	M_D^{24}	Amt.
1	85-7°/15mm	118°	0.8575	1.4570	49.44	49.5	-0.80	-1.45	50.5 g.
2	87°/15mm	118°	0.8575	1.4567	49.44	49.5	-1.24	-2.25	55.6g.
3	87-8°/15mm	118°	0.8575	1.4569	49.44	49.5	-1.33	-2.29	20.4g.
4	Residue	---	------	1.4712	----	----	----	----	4.45g.

The Rotatory Dispersion of Fraction 3 Was As Follows:

λ		
6438	α_{Cd}^{27} : -1.14;	M_{Cd}^{27} : -2.08
5890	α_{D}^{27} : -1.34;	M_{D}^{27} : -2.44
5461	α_{Hg}^{27} : -1.53;	M_{Hg}^{27} : -2.78
5209	α_{Ag}^{27} : -1.63;	M_{Ag}^{27} : -2.96
5086	α_{Cd}^{27} : -1.72;	M_{Cd}^{27} : -3.13
4722	α_{Zn}^{27} : -1.85;	M_{Zn}^{27} : -3.37

$$M_{Zn}^{27}/M_{D}^{27} = -3.37/-2.44 = 1.38$$

The Rotatory Dispersion of Fraction 3 In Anhydrous Solvents Was As Follows:

1. Carbon Disulfide.

λ		
6438	α_{Cd}^{23} : -0.19	M_{Cd}^{23} : -0.346

5890	α^{23}_{D}	: -0.22;	M^{23}_{D} : -0.401
5461	α^{23}_{Hg}	: -0.30;	M^{23}_{Hg} : -0.546
5209	α^{23}_{Ag}	: -0.36;	M^{23}_{Ag} : -0.655
5086	α^{23}_{Cd}	: -0.39;	M^{23}_{Cd} : -0.710

---

2. Chloroform.

6438	$\alpha^{23.5}_{Cd}$	: -0.05;	$M^{23.5}_{Cd}$: -0.091
5890	$\alpha^{23.5}_{D}$	: -0.08;	$M^{23.5}_{D}$: -0.124
5461	$\alpha^{23.5}_{Hg}$	: -0.11;	$M^{23.5}_{Hg}$: -0.199
5209	$\alpha^{23.5}_{Ag}$	: -0.17;	$M^{23.5}_{Ag}$: -0.310
5086	$\alpha^{23.5}_{Cd}$	: -0.20	$M^{23.5}_{Cd}$: 0.364

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3. Benzene.

All the polariscope readings with this solvent were ±0.00.

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4. Ethyl Ether.

All the polariscope readings with this solvent were ±0.00.

Reduction of Dihydrolinalool.

The dihydrolinalool, α_D^{27}: -1.34,(II) was converted into tetrahydrolinalool(III) in the usual way in glacial acetic acid, and the product distilled:

Fraction	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found
1	Up to 78°/8mm	-----	----	1.4353	-----	------
2	78-9°/8mm	114°	0.8317	1.4361	51.6	49.7
3	Residue					

Tetrahydrolinalool(III) prepared in this way did not reduce potassium permanganate.

The Rotatory Dispersion of Fraction 2 Was As Follows:

6438	α^{28}_{Cd} : -0.11;	M^{28}_{Cd} : -0.209
5890	α^{28}_{D} : -0.08;	M^{28}_{D} : -0.153
5461	α^{28}_{Hg} : -0.09;	M^{28}_{Hg} : -0.171
5209	α^{28}_{Ag} : -0.05;	M^{28}_{Ag} : -0.095
5056	α^{28}_{Cd} : -0.02;	M^{28}_{Cd} : -0.038
4722	α^{28}_{Zn} : +0.06;	M^{28}_{Zn} ; +0.114

$$M^{28}_{Zn} / M^{28}_{D} = \frac{+0.114}{-0.153} = 0.746$$

Preparation of Synthetic Dihydrolinalool.

Ethyl magnesium bromide was prepared in the usual manner from 61 g. of ethyl bromide, b.p. 38-9°, and 15 g. of magnesium in anhydrous ether, and then 47 g. of methyl heptenone, b.p. 171-2°/769mm, in anhydrous ether were added to the 50% excess of the Grignard reagent. After this had stood for a week, the reaction product was decomposed in the cold with 10% ammonium chloride; extracted with ether; dried over anhydrous potassium carbonate; and distilled. The pure compound had the following physical constants: b.p. 83°/9mm, d_4^{20} : 0.8596; n_D^{20} : 1.4569; M. R. Calc. 49.44, Found: 49.4. The physical constants of the optically active dihydrolinalool(II) were: b.p. 87°/15mm; d_4^{20} : 0.8575; n_D^{20} : 1.4567; M. R. Calc. 49.44, Found: 49.5; α_D^{21} : -1.24.

Preparation of Synthetic Tetrahydrolinalool.

Ethyl magnesium bromide was prepared in the usual manner from 33 g. of ethyl bromide, b.p. 38-9°, and 9 g. of magnesium in anhydrous ether, and then 17 g. of methyl isohexylketone, b.p. 159-63°/758mm, in anhydrous ether were added to the 50% excess of the Grignard reagent. After this had stood for a week, the reaction product was decomposed in the cold with 10% ammonium chloride; extracted with ether; dried over anhydrous potassium carbonate; and distilled. The pure compound had the following physical constants: b.p. 83-4° /10mm; d_4^{20} : 0.8182; n_D^{20} : 1.4340 M. R. Calc. : 51.6, Found: 50.3. The physical constants of the tetrahydrolinalool(III) prepared by different methods were:

Method	B. P.	Temp. of Oil Bath	d_4^{20}	n_D^{20}	M. R. Calc.	M. R. Found
Linalool: α_D^{24} : -15.23 in Pure Glacial Acetic Acid	77-8°/8mm	114°	0.8296	1.4354	51.6	49.7
Linalool: $\alpha_D^{23.5}$: -14.07 in Pure Glacial Acetic Acid						
1.Distilled	78°/8mm	118°	0.8317	1.4374	51.6	49.7
2.$KMnO_4$	78-9°/8mm	114°	0.8333	1.4364	51.6	49.7
3.$KMnO_4$ & $NaHSO_3$	78-9°/8mm	114°	0.8146	1.4361	51.6	50.8
Dihydrolinalool: α_D^{27} :-1.34 in Pure Glacial Acetic Acid	78-9°/8mm	114°	0.8317	1.4361	51.6	49.7

Attempts to Prepare Derivatives of Tetrahydrolinalool.

Phthalic Anhydride Derivative.

Five grams of tetrahydrolinalool(III), α_D^{28} :+0.09, 5.2g. of finely powdered phthalic anhydride, and 23 g. of dry pyridine were mixed and allowed to stand in a well-stoppered flask until only a small amount of phthalic anhydride remained. The solution became bright yellow. The liquid was carefully pipetted off and the pyridine removed in vacuo. The residue was unchanged phthalic

anhydride as shown by a mixed melting point and conversion into fluorescein.

Phenyl Urethane.

One gram of tetrahydrolinalool(III), α_D^{28} : +0.09, and 1.1 equivalents of phenylisocyanate were allowed to stand for several days in a well-stoppered flask. Then the solid was removed, washed with a small amount of Skelly Solve F, and found to be diphenylurea by a mixed melting point. The reaction did not take place when the mixture was warmed for one hour on the steam bath.

α-Naphthyl Urethane.

An attempt to prepare this derivative yielded the same result as that with phenylisocyanate.

p-Nitrobenzoyl Ester (15).

Two grams of tetrahydrolinalool(III), α_D^{28} :+0.09, and 2 g. of p-nitrobenzoyl chloride in 15cc. of dry pyridine were allowed to stand at room temperature for two days. A white solid separated out which was soluble in water and did not melt upon being heated at 350°.

2,4-Dinitrobenzoyl Ester.

The same result as with p-nitrobenzoyl chloride was obtained when 2,4-dinitrobenzoyl chloride was used.

Tetrahydrolinalool Chloride.

A. Preparation from Saturated Hydrochloric Acid.

Twelve cc. of concentrated hydrochloric acid in a tube were cooled to-20° surrounded by ice and hydrochloric acid in a

Dewar flask. Then the acid was saturated with dry hydrogen chloride gas at such a rate that the temperature was maintained at -20°. Three cc. of tetrahydrolinalool(III), α_D^{28} : +0.09, was added; the tube was sealed; and placed in a water bath at 20°. After it had reached the temperature of the bath, it was shaken vigorously every five minutes for several hours. After standing overnight, the tube was cooled at -20° and opened. The top layer was drawn off; washed with ice-cold 5% sodium bicarbonate and then with ice-cold water; dried over anhydrous potassium carbonate; and filtered. The liquid gave a positive Beilstein test and a precipitate of silver chloride with alcoholic silver nitrate. The physical constants were as follows:

n_D^{20} : 1.4392; Dispersion Angle: 41.2; $\alpha_D^{24.5}$: +0.21.

Anal. Calcd. for $C_{10}H_{21}Cl$: Cl, 20.1. Found: Cl, 19.8.

A larger quantity of tetrahydrolinalool chloride, α_D^{23} : +0.20, was prepared as outlined above and distilled to determine its stability.

Fraction	B. P.	d_4^{20}	n_D^{20}	Dispersion Angle	M. R. Calc.	M. R. Found	α_D	M D
1	30-1°/0.07mm	---	1.4386	40.5	----	----	----	---
2	31-2/0.06-0.08mm	0.8695	1.4390	40.9	53.3	53.4	+0.23	0.468
3	Residue	----	1.4370	40.6	----	----	-----	----

Anal. Calcd. for $C_{10}H_{21}Cl$: Cl,20.1. Found Cl, 19.9.

Fraction 2 on re-distillation boiled at 73°/8mm and the physical constants were as follows:

d_4^{20} : 0.8708; n_D^{20} : 1.4388; M.R. Calc. 53.3, Found: 53.3.

The Rotatory Dispersion of Fraction 2 Was As Follows:

6438	α_{Cd}^{23} : +0.15;	M_{Cd}^{23} : +0.303
5890	α_{D}^{23} : +0.23;	M_{D}^{23} : +0.465
5461	α_{Hg}^{23} : +0.26;	M_{Hg}^{23} : +0.525

Anal. Calcd. for $C_{10}H_{21}Cl$: Cl, 20.1. Found : Cl, 19.7, 19.8.

B. Preparation by Saturation of Tetrahydrolinalool with Gaseous Hydrogen Chloride.

Five cc. of tetrahydrolinalool(III), α_D^{28} : +0.09, were cooled to -20° and saturated with dry hydrogen chloride. After it had stood at this temperature for six hours; it was treated as stated above. The chloride had the following physical constants:

n_D^{20} : 1.4390; Dispersion Angle; 40.3; $\alpha_D^{22.5}$: +0.21.

Anal. Calcd. for $C_{10}H_{21}Cl$: Cl, 20.1. Found : Cl, 19.6.

Hydrolysis of Tetrahydrolinalool Chloride.

Five cc. of tetrahydrolinalool chloride, α_D^{23} : +0.23, were shaken with 2,700cc. of distilled water. At intervals the entire amount was titrated with sodium hydroxide using methyl orange as an indicator. Due to the great insolubility of the chloride in water, the hydrolysis was complete only after 21 hours

Time in Hours	cc. 0.1 N NaOH	%Tetrahydrolinalool Chloride Hydrolyzed
1	37.4	15.5
2	73.2	30.5
5	161.1	67.3
6	188.3	78.8
8	214.3	89.5
10	221.9	92.7
17	232.9	97.5
21	239.1	100.04

Each 250 cc. was extracted with three small volumes of ether. After drying the ether extracts over anhydrous potassium carbonate, the ether was removed in vacuo, and the carbinol distilled. It gave no test for chlorine with alcoholic silver nitrate. The following figures indicate that the carbinol obtained by hydrolysis of the chloride was the original carbinol unchanged.

	B. P./8mm	d_4^{20}	n_D^{20}	α_D^{28} -	Odour
Original Tetrahydro-linalool	77°	0.8317	1.4374	+0.09	same
Tetrahydro-linalool from Tertia-ry Chloride	76°	0.8314	1.4370	+0.08	same

Attempt to Prepare Dihydrolinalool Chloride.

Twelve cc. of concentrated hydrochloric acid were cooled to -20° in a tube surrounded by a freezing mixture of ice and hydrochloric acid in a Dewar flask. Three cc. of dihydrolinalool α_D^{21} : -1.33 were carefully added. After sealing the tube it was placed in a water bath at 21°. Upon shaking the top layer became very viscous. It was allowed to stand over night at 21°. Then it was cooled to -20° and opened. The top layer was pipetted off, washed with ice-cold 5% sodium bicarbonate solution and then with ice-cold water, dried for a few minutes over anhydrous potassium carbonate, and filtered. The dark yellow liquid gave a positive Beilstein test, reduced potassium permanganate solution, and gave a precipitate of silver chloride with alcoholic silver nitrate. After decolourizing with Nu-Char, it was found to be optically inactive.

Anal. Calcd. for $C_{10}H_{19}Cl$: Cl, 20.3%. Found : Cl, 26.3%.

SUMMARY

(1) Pure l-linalool was reduced to dihydrolinalool in ethyl alcohol using a platinum catalyst and then was further reduced to tetrahydrolinalool in glacial acetic acid using the same catalyst. Linalool was converted into the completely saturated carbinol in the same way as dihydrolinalool was reduced. The compound obtained was identical in both cases. This reduction was carried out to avoid rearrangements in the preparation of derivatives which would have occurred if the unsaturated carbinol had been used. Tetrahydrolinalool was slightly dextrorotatory, whereas all previous preparations by other investigators had yielded a levorotatory product.

(2) Attempts to prepare derivatives of tetrahydrolinalool of higher optical activity failed. Therefore, it was not definitely proven that the low dextrorotation of the carbinol was not due to impurities, or almost complete racemization.

(3) Tetrahydrolinalool chloride was prepared and found to be slightly more dextrorotatory than the starting material, and appeared to yield by hydrolysis the original carbinol with undiminished activity.

(4) An attempt to convert dihydrolinalool into the corresponding chloride was unsuccessful.

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