A MOLECULAR REARRANGEMENT OF TERTIARY AMINES.

Thesis submitted by W.F. Cockburn
for the degree of Doctor of Philosophy.

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With three additional papers.

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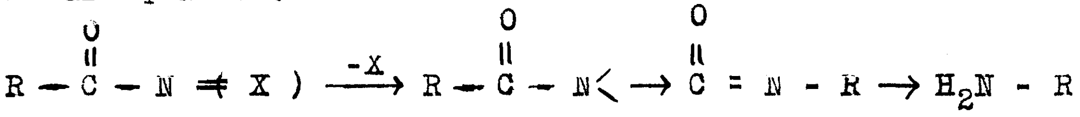
A MOLECULAR REARRANGEMENT OF TERTIARY AMINES.

SUMMARY.

The rearrangement of phenacylbenzylaniline to α-anilino-β-phenylpropiophenone, first achieved by T.S. Stevens, has been confirmed, and the reaction conditions more fully investigated. Further proof of rearrangement has been obtained in the identification of β-phenylpropiophenone as a by-product. Experiments have been carried out with a number of other tertiary amines, and in the case of two, namely, phenacyl-α-phenethylaniline, and phenacylallylaniline, strong indications of rearrangement have been observed. In the case of the other amines investigated, general decomposition has been found to occur under the reaction conditions employed.

INTRODUCTION.

Many examples are known of the "1:2" type of molecular rearrangement. Although these involve a variety of compounds of apparently unrelated type, most of them can be assigned to one of a relatively small number of groups; and indeed, an attempt has been made to include all intramolecular rearrangements in one general reaction(1). A typical group is that which includes such well-known changes as the Hofmann, Lossen and Curtius degradations, and which can be given the general equation:

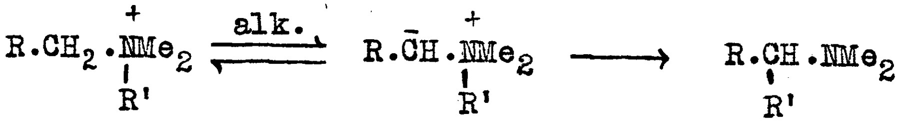


$$R-\overset{\overset{O}{\|}}{C}-N \neq X\ ) \xrightarrow{-X} R-\overset{\overset{O}{\|}}{C}-N\langle \longrightarrow \overset{\overset{O}{\|}}{C}=N-R \longrightarrow H_2N-R$$

The significant step in this process is the migration of the radical R from the carbon atom of the carbonyl group to the nitrogen atom. According to Whitmore, the molecule loses the atoms or group (X) with its own bonding electrons, leaving the nitrogen atom with only a sextet; in fact, he postulates that an atom with an incomplete electronic group is a prerequisite for any rearrangement(1), though there is evidence to the contrary. 'R' then migrates from carbon to nitrogen, thus enabling the latter to complete its octet of electrons, and giving an isocyanate, which is finally hydrolysed by the alkaline medium to an amine. Stereochemical evidence, such as the retention of asymmetry when 'R' is an optically active group linked to the rest of the molecule by the asymmetric carbon atom, shows the reaction to be truly intramolecular, and the migrating group is never entirely free$^{(2,3,4)}$.

Whitmore states that the necessity for completing the octet of electrons about nitrogen is the driving force behind the reaction, but Jones takes the view that this is a subsidiary process, the essential factor being "the tendency of the system ... to pass to one in which the carbon atom is as fully oxidised as possible, and the nitrogen atom as fully reduced as possible."$^{(5)}$ In other words, the reaction is essentially a process of intramolecular oxidation-reduction.

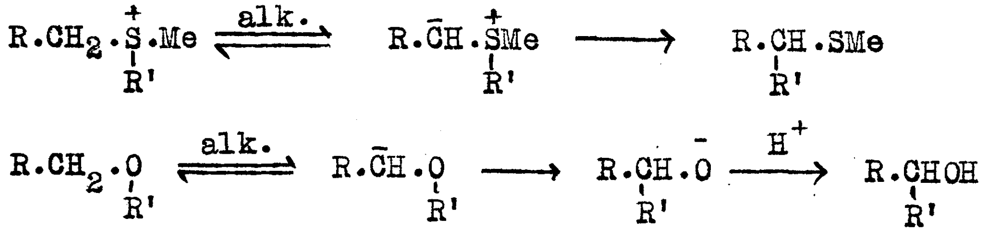
In the Stevens Rearrangement of quaternary ammonium salts, the picture is slightly different. This reaction may be represented by the general equation below$^{(6a-g)}$



$$R.CH_2.\underset{R'}{\overset{+}{N}}Me_2 \xrightleftharpoons{alk.} R.\bar{C}H.\underset{R'}{\overset{+}{N}}Me_2 \longrightarrow R.\underset{R'}{C}H.NMe_2$$

In this case, the migration is from nitrogen to carbon, and all the atoms involved have their octets complete, both before and after the migration. It has one feature in common with those just mentioned, however - the migrating group moves to an atom which possesses unshared electrons, and its attachment by these electrons can be envisaged as occurring simultaneously with the release of the pair by which it was linked originally; a theory which readily explains the intramolecular nature of the reaction(7). Closer examination reveals, in fact, that this rearrangement involves essentially the same process as the previous group - that is, an "intramolecular oxidation and reduction, or an exchange of negative electrons between the carbon atom and the nitrogen atom."(5)

Other examples of the "Stevens" type of reaction are the analogous rearrangements of sulphonium compounds(8) and ethers(9-13), represented by the equations:

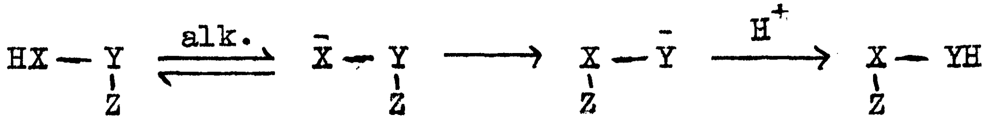


$$R.CH_2.\underset{R'}{\overset{+}{S}}.Me \xrightleftharpoons{\text{alk.}} R.\bar{C}H.\underset{R'}{\overset{+}{S}}Me \longrightarrow R.\underset{R'}{CH}.SMe$$

$$R.CH_2.\underset{R'}{O} \xrightleftharpoons{\text{alk.}} R.\bar{C}H.\underset{R'}{O} \longrightarrow R.\underset{R'}{CH}.\overset{-}{O} \xrightarrow{H^+} R.\underset{R'}{C}HOH$$

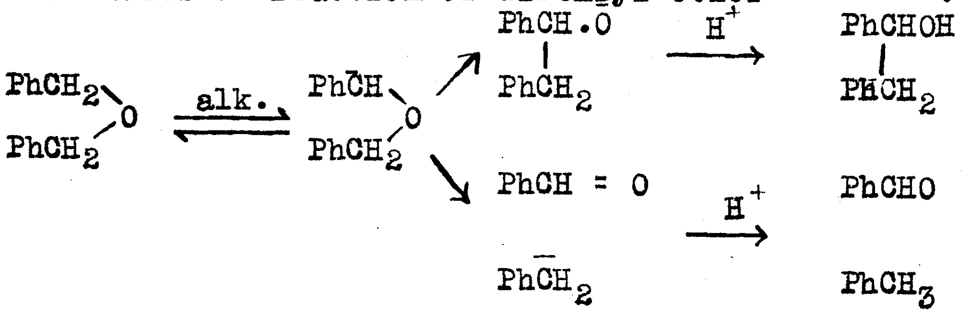
Since, for certain purposes, tertiary amines can be regarded as the nitrogen analogues of ethers, they might therefore be expected to undergo a similar rearrangement reaction; provided that "nitrogen-ethers" of a suitable type were chosen. Such a reaction would satisfy the condition postulated by Jones, namely, the reduction of the nitrogen atom by the adjacent carbon atom(5).

This second group of rearrangements may be given the general equation:



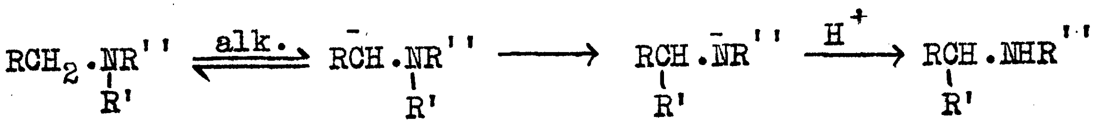
$$HX-\underset{Z}{\underset{|}{Y}} \xrightleftharpoons{\text{alk.}} \bar{X}-\underset{Z}{\underset{|}{Y}} \longrightarrow \underset{Z}{\underset{|}{X}}-\bar{Y} \xrightarrow{H^+} \underset{Z}{\underset{|}{X}}-YH$$

The first stage, the removal of a proton by the alkaline reagent, is rapid, and the reaction rate is determined by the migration stage(6e). In some cases, however, the situation is complicated by the occurrence of a fission reaction in place of, or simultaneous to, the migration. A case in point is found in the alternative modes of reaction of dibenzyl ether(9,11,12).



It is to be noted that changes in the covalencies of the atoms concerned are involved. In both reactions, the covalency of 'X', the "recipient" atom, increases by one; and since in most cases, this is from a highly unstable to an intrinsically stable condition for that atom, the tendency for this change can be considered to be the driving force for the reaction(6e).

If migration occurs, the covalency of 'Y' is diminished by one unit, while that of 'Z' remains constant, and we might therefore expect the relative stabilities of the two valency states of 'Y' to be a controlling factor in the ease of rearrangement. Hence, ethers rearrange much less readily than do ammonium salts, since, in the significant step, the oxygen atom passes from the bi-covalent to the less favoured uni-covalent condition; whereas with ammonium salts, the quaternary nitrogen changes to the at least equally congenial tertiary state. Moreover, the methylene group in $RCH_2.O.R'$, being less acidic than that in $RCH_2.\overset{+}{N}R'_3$, demands a more energetic alkaline reagent for removal of a proton. Assuming the same factors to be operative, therefore, it is to be expected that tertiary amines will undergo rearrangement with even less facility than ethers. In the essential step, the nitrogen atom will change from the stable tertiary to the unwonted di-covalent state, and in addition, exerts no activating effect on the adjacent methylene group.



$$RCH_2\cdot\underset{R'}{N}R'' \overset{alk.}{\rightleftharpoons} R\underset{R'}{\bar{C}}H\cdot NR'' \longrightarrow R\underset{R'}{C}H\cdot\bar{N}R'' \xrightarrow{H^+} R\underset{R'}{C}H\cdot NHR''$$

Since in the fission reaction referred to above, the covalency of 'Y' remains constant while that of 'Z' is lowered by one unit, we might expect fission to make a significant contribution in the case of tertiary amines, depending on the relative stabilities of $\bar{R}'$ and $R\cdot CHR'\cdot\bar{N}R''$. Previous work by S.F. Marrian on this aspect of the general problem(14) has indicated fission to be intrinsically more facile than rearrangement, the latter only occurring if '$\bar{Z}$' is much less stable than $Z - X - \bar{Y}$, as indicated by the relative acidities of ZH and Z - X - YH; a fact which reduces still further the probability of achieving the desired reaction.

In view of the analogy between the hypothetical rearrangement of tertiary amines and the Stevens Rearrangement, it seemed reasonable to expect that information gained from a study of the latter might be applied in choosing the most suitable conditions for the former. The rearrangement of quaternary ammonium salts has been very fully studied, and certain regularities observed.

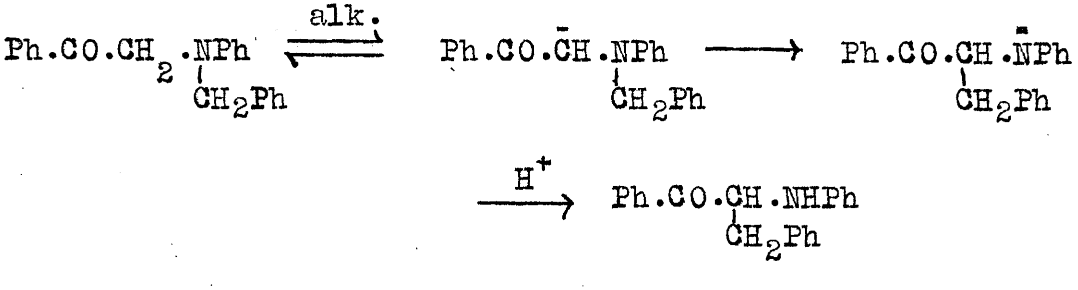
The change normally takes place under relatively mild alkaline conditions, such as warm aqueous alkali; though some of the less acidic recipient radicals require more drastic conditions, such as hot alkoxide solution, or even fusion with sodamide(6f). The most acidic α-hydrogen atom is removed by the reagent, so that the most effective recipient groups are phenacyl and 9-fluoryl, while fluoryl, α-phenethyl, benzhydryl and allyl have been found to be the most mobile; indeed the benzhydryl and fluoryl radicals wander so readily that the intermediate quaternary salt often cannot be isolated(6b). The migration of simple alkyl or aryl groups is not excluded *a priori*, but is evidently less easy than Hofmann degradation where this is structurally possible, or than the breakdown:

$$R_4\overset{+}{N} + \overset{-}{O}H \longrightarrow ROH + R_3N.$$

Little is known about the influence of the non-participating groups.

The reaction has been shown to be intramolecular, since no exchange of radicals could be detected between the molecules of two different compounds undergoing rearrangement in a mixed solution(6b), and has been found to follow a unimolecular course in alcoholic alkoxide solution(6b,d). Although an ionic mechanism was at first suspected(6b,d,g), the reaction, in common with the other rearrangements already mentioned, is now thought of as a continuous electronic process(7), essentially similar to bimolecular substitution as visualised by Polanyi(15).

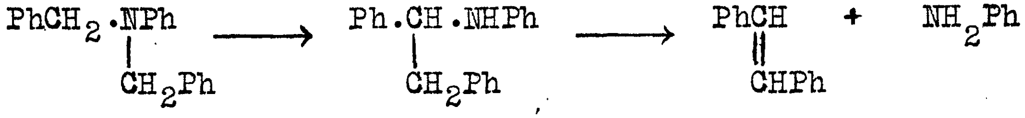
Preliminary experiments by Dr. Stevens confirmed that tertiary amines rearrange only with comparative difficulty. Phenacylbenzylaniline was found to undergo rearrangement on mild potash fusion (130°) to α-anilino-β-phenylpropiophenone (unpublished work), the product being confirmed by synthesis from α-bromo-β-phenylpropiophenone and aniline(16,18).



$$\mathrm{Ph.CO.CH_2.\underset{\displaystyle CH_2Ph}{N}Ph} \xrightleftharpoons{\text{alk.}} \mathrm{Ph.CO.\bar{C}H.\underset{\displaystyle CH_2Ph}{N}Ph} \longrightarrow \mathrm{Ph.CO.\underset{\displaystyle CH_2Ph}{CH}.\bar{N}Ph}$$

$$\xrightarrow{H^+} \mathrm{Ph.CO.\underset{\displaystyle CH_2Ph}{CH}.NHPh}$$

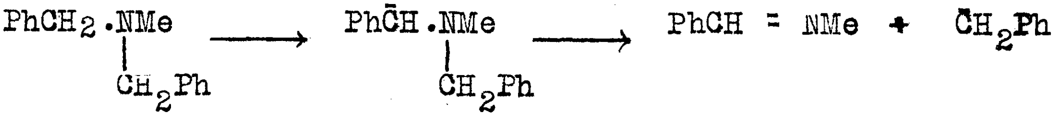
Dibenzylaniline, after heating with sodamide at 250-270°, yielded aniline and toluene, while the higher fractions, on hydrolysis, gave further quantities of aniline along with benzaldehyde, both presumably formed from benzaldehyde anil, and some stilbene. Although the "fission" reaction was predominant, the production of stilbene is strong evidence for migration, since it could not have been formed from dibenzylaniline directly.



$$PhCH_2.\underset{\displaystyle CH_2Ph}{\underset{|}{N}}Ph \longrightarrow Ph.\underset{\displaystyle CH_2Ph}{\underset{|}{C}}H.NHPh \longrightarrow \underset{\displaystyle CHPh}{\underset{\|}{PhCH}} + NH_2Ph$$

This cannot be considered conclusive, however, in view of the drastic conditions of the experiment.

Dibenzylmethylamine, on the other hand, on refluxing with metallic potassium (300^0) apparently underwent fission exclusively, yielding toluene and benzalmethylamine: no evidence of rearrangement was detected.



$$PhCH_2.\underset{\displaystyle CH_2Ph}{\underset{|}{N}}Me \longrightarrow Ph\bar{C}H.\underset{\displaystyle CH_2Ph}{\underset{|}{N}}Me \longrightarrow PhCH = NMe + \bar{C}H_2Ph$$

Several other amines of varying type were subjected to treatment with various reagents (sodamide, sodium alkoxides, alkali metals, metal alkyls and aryls, etc.) but indefinite or negative results, frequently mere pyrolytic decomposition, were achieved. The results obtained are summarised in Table I, p.10.

TABLE I.

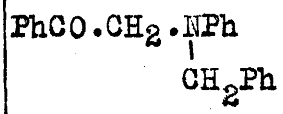
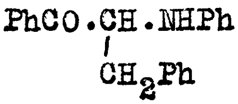
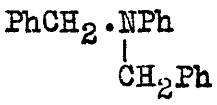
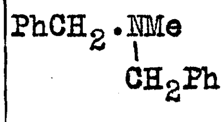
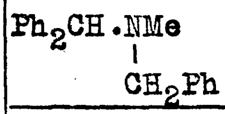
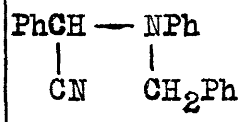
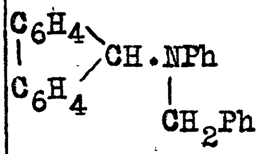
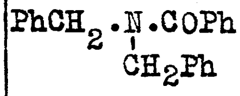
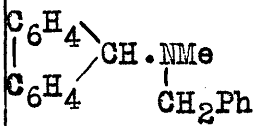
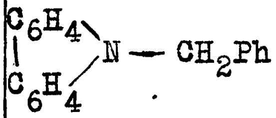
Tertiary amine	Treatment	Products
 $\mathrm{PhCO.CH_2.\underset{CH_2Ph}{N}Ph}$	KOH at 130°	 $\mathrm{PhCO.\underset{CH_2Ph}{C}H.NHPh}$
 $\mathrm{PhCH_2.\underset{CH_2Ph}{N}Ph}$	$NaNH_2$ at 250-270°	PhCH = CHPh, $PhNH_2$, $PhCH_3$, Ph.CHO
 $\mathrm{PhCH_2.\underset{CH_2Ph}{N}Me}$	K at 300°	PhCH = NMe, $PhCH_3$, Ph.CHO
 $\mathrm{Ph_2CH.\underset{CH_2Ph}{N}Me}$	$NaNH_2$ at 250°	Ph_2C = NMe,(?) $PhCH_3$, Ph_2CH_2, Ph.CHO
$PhCH_2.NPh_2$	$NaNH_2$ at 400°	Ph_2CO (?), Ph_2CH_2(?)
 $\mathrm{\underset{CN}{PhCH}-\underset{CH_2Ph}{N}Ph}$	K_2CO_3 at 260°	$PhCH_2.COPh$ (?)
 $\mathrm{\begin{matrix}C_6H_4\\ \vert\\ C_6H_4\end{matrix}\!\!>CH.\underset{CH_2Ph}{N}Ph}$ (14)	NaOEt at 200°	unchanged
	$NaNH_2$ at 200°	$PhCH_3$, difluoryl
	NaOH at 300°	fluorenone (?) $PhCH_3$, $PhNH.CH_2Ph$
	MeLi at 240° PhLi at 110° K boiling decalin	tar
 $\mathrm{PhCH_2.\underset{CH_2Ph}{N}.COPh}$	Na at 180-200°	$PhCH_2.NH.COPh$
$PhCH_2.NPh.COPh$		Ph.NH.COPh

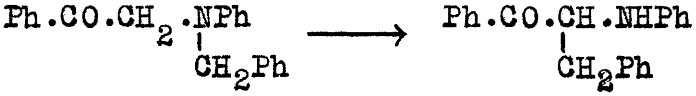
Table I (Contd.)

Tertiary amine	Treatment	Products
 (14)	PhLi at 210°	amorphous products
	NaOH at 300°	difluoryl
	various reagents	carbazole

DISCUSSION.

By analogy with the rearrangement of quaternary ammonium salts, the compounds most liable to exhibit radical migration would be amines of the type phenacyl-α-phenethylaniline, phenacyl allylaniline, phenacylbenzhydrylaniline, and the corresponding 9-fluoryl compounds. Samples of these were accordingly prepared and subjected to strong alkaline treatment. As a preliminary, however, a more thorough examination was made of the one "normal" rearrangement achieved by Dr. Stevens.

Phenacylbenzylaniline.



$$\mathrm{Ph.CO.CH_2.}\underset{\mathrm{CH_2Ph}}{\underset{|}{\mathrm{NPh}}} \longrightarrow \mathrm{Ph.CO.}\underset{\mathrm{CH_2Ph}}{\underset{|}{\mathrm{CH}}}\mathrm{.NHPh}$$

The maximum yield of rearrangement product was obtained by fusion with moist potassium hydroxide at 160° for two hours, about 30% of pure α-anilino-β-phenylpropiophenone being obtained. This compound forms an insoluble hydrochloride with 50% hydrochloric acid, and is yellow like the starting compound, but melts 4° lower. Below 125°, the tertiary amine was unaltered by this treatment, while at higher temperatures or with prolonged heating, deamination occurred, with the formation of β-phenylpropiophenone. Since the latter can only have been formed from the rearrangement product, its isolation constitutes a further proof of the migration.

Huntress and Seikel employed powdered potassium hydroxide in refluxing diphenyl ether for the alkaline fission of substituted fluorenones(17), and this technique was applied to the present reaction, xylene (b.p. 140°) being chosen from temperature considerations. Refluxing with powdered potash in this solvent was found to be without effect, however, and in an attempt to obtain a homogeneous reaction mixture, the amine was treated with sodium amyloxide in boiling amyl alcohol (135°) for varying lengths of time. The products were all oily, only benzylaniline being identified, which indicates decomposition rather than rearrangement. Since this result may have been due to too high a reaction temperature, the experiment was repeated using sodium methoxide in methanol (65°). This again gave benzylaniline, and a 30% yield of a colourless crystalline compound, m.p. 112°, with the analysis C, 79.91%; H, 5.27%; N, 5.21%. $C_{21}H_{17}O_2N$ requires C, 79.98%; H, 5.43%; N, 4.44%, and since the original amine has the formula $C_{21}H_{19}ON$, this would correspond to the replacement of CH_2 by CO, a most unusual oxidation under these reaction conditions.

This compound, in spite of its nitrogen atom, had practically no basic properties, and was not extracted from ligroin by 50% hydrochloric acid; a fact which indicates an acid amide rather than an amine. This is supported by the absence of colour, since the only other colourless phenacyl amine encountered so far is phenacylbenzylbenzamide, also an acid amide (see, however, Appendix, p. 55). The first possibility that suggests itself is phenacylbenzanilide ($Ph.CO.CH_2.NPh.COPh$), which, however, has a melting point of 144°. The identity of this compound is still unknown.

The experiments with phenacylbenzylaniline are summarised in Table II, p.15.

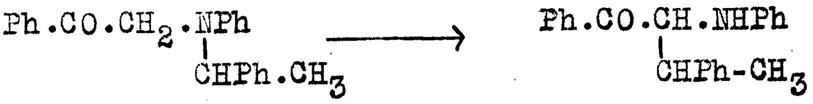
In view of these results, it was decided to employ potash fusion with the other amines to be examined, at least in the preliminary runs. The following series of experiments was designed to assess the effect of replacing the migrating benzyl radical by one of the more "mobile" groups.

TABLE II.

Experiments with phenacylbenzylaniline.

Treatment	Result
KOH at 125° for 1½ hours	unchanged
KOH at 130° for 2 hours	10% rearrangement product traces β-phenylpropiophenone
KOH at 160° for 2 hours	30% rearrangement product 5% of ketone
KOH at 175-185° for 3 hours	10% of ketone
KOH in xylene	unchanged
NaOAm in AmOH for 15 min., 1 hour	benzylaniline
NaOMe in MeOH for 2 hours	benzylaniline 112° compound

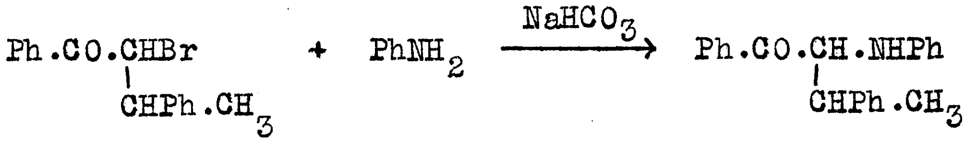
Phenacyl-α-phenethylaniline.



$$\underset{\displaystyle \quad\quad\quad\quad CHPh.CH_3}{Ph.CO.CH_2.NPh} \longrightarrow \underset{\displaystyle \quad\quad CHPh\text{-}CH_3}{Ph.CO.CH.NHPh}$$

Fusion with potassium hydroxide at 145-155° for two hours, or 120° for fifteen minutes, yielded some benzoic acid, α-phenethylaniline, and various oily and tarry materials, indicating dephenacylation of the unrearranged amine. A repeat experiment was carried out in which air was excluded by 40-60° petroleum ether, and heating carried out at 100° for four hours. This gave, in addition to the above compounds, about 10% of the weight of starting material of a green basic compound, m.p. 118-120°, and 20% of buff crystals, m.p. 140°. The former depressed the melting point of the tertiary amine (127°) and had the correct analysis for the "normal" rearrangement product. Found: C, 84.04%; H, 6.37%; N, 4.53%. $C_{22}H_{21}ON$ requires C, 83.75%; H, 6.71%; N, 4.44%. In addition, it formed an insoluble hydrochloride, melted about 6° below the unrearranged amine, and had the same yellow-green colour; all of which properties were to be expected by analogy with the rearrangement product of phenacylbenzylaniline.

An attempt was therefore made to synthesise the expected compound by an independent route, namely, the interaction of α-bromo-β-phenylbutyrophenone and aniline in the presence of sodium bicarbonate(18,19). (See Appendix, p. 55).

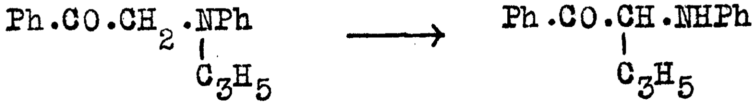


$$\underset{\text{CHPh.CH}_3}{\text{Ph.CO.CHBr}} + \text{PhNH}_2 \xrightarrow{\text{NaHCO}_3} \underset{\text{CHPh.CH}_3}{\text{Ph.CO.CH.NHPh}}$$

The main product of this reaction was a colourless solid, m.p. 122°, which appeared to be an isomeric form of the bromoketone, possibly produced by some form of keto-enol change(cf.20), but in addition, a small amount of a green basic substance, m.p. 121°, was obtained, which did not depress the melting point of the "rearrangement product" described above. There was insufficient of the "synthetic" material for an analysis, but both compounds yielded a red insoluble hydrochloride, and appeared to have similar general characteristics. Further comparison was impossible, however, due to the small quantities involved. Since both the bromoketone and the desired secondary amine contain two asymmetric carbon atoms, the situation may be further complicated by the existence of diastereomeric forms(cf.20), and indeed, a considerable quantity of a green oily base was obtained along with the "synthetic" rearrangement product (see also Appendix p. 55). Further work on this aspect of the problem is necessary, however.

The buff compound, m.p. 140°, was not identified. It blackened on boiling in petroleum ether, and would not crystallise satisfactorily, so that an analysis could not be obtained. In this last run, 20% of the starting material was recovered unchanged.

Phenacylallylaniline.



$$Ph.CO.CH_2.\underset{\displaystyle C_3H_5}{\underset{|}{N}}Ph \longrightarrow Ph.CO.\underset{\displaystyle C_3H_5}{\underset{|}{C}}H.NHPh$$

Fusion with potash at 130-160° for one hour caused extensive tarring, which was aggravated by treatment with acid during the working-up, making investigation impossible. To obviate this difficulty, the next two runs, at 100° and 150° respectively, were carried out in an atmosphere of petroleum ether, and the time of heating shortened to 30 minutes. In addition, the organic portion of the melt was quickly separated and hydrogenated in ethanol, in the presence of palladium black, when the theoretical amount of hydrogen for complete saturation of the allyl group was absorbed.

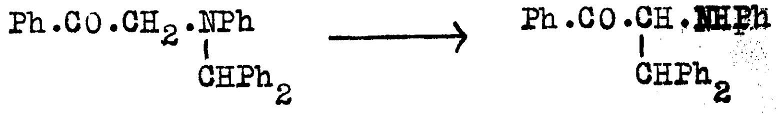
The hydrogenated mixture yielded, in addition to phenacylpropylaniline m.p. 96° (corresponding to unrearranged starting material), a small amount of a yellow oily base, very similar in appearance (colour, viscosity, odour, etc.) to synthetic α-anilinovalerophenone, prepared from α-bromovalerophenone and aniline (see p. 48). Both gave a white insoluble hydrochloride on shaking a petroleum ether solution of the base with 50% hydrochloric acid, whereas phenacylpropylaniline is soluble under these conditions, forming a yellow solution. The synthetic material, however, was readily converted to a benzoyl derivative by heating with benzoyl chloride in pyridine, while the compound obtained from the potash fusion appeared to be unchanged by this treatment. No satisfactory explanation for this has yet been found.

The neutral part of the melt from the 150° run yielded, on steam-distillation, an oily compound smelling strongly of valerophenone, which would correspond to deaminated rearrangement product. Treatment with 2:4-dinitrophenylhydrazine yielded an orange substance, m.p. 243-245°, which appeared to be the hydrazone of acetophenone. This cannot be considered conclusive, however, since a large proportion of acetophenone was certain to be present, and separation was difficult on the small scale employed.

In the 100° run, about 60% of the tertiary amine remained unchanged, while at the higher temperature, the

the figure was only 10%, and a much larger proportion of tarry material was formed. The yellow oily base described above constituted about 10% of the organic material in both cases.

Phenacylbenzhydrylaniline.



$$\mathrm{Ph.CO.CH_2.\underset{\underset{\displaystyle CHPh_2}{|}}{N}Ph} \longrightarrow \mathrm{Ph.CO.\underset{\underset{\displaystyle CHPh_2}{|}}{CH}.NHPh}$$

This amine yielded no identifiable fragments on heating with potash at 100° for two hours in an inert atmosphere. The only pure substance isolated was a yellow crystalline solid, m.p. 225°, in insufficient quantity for an analysis.

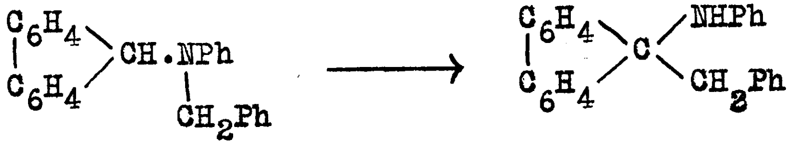
Phenacyldiphenylamine.

$$\mathrm{Ph.CO.CH_2.NPh_2} \longrightarrow \mathrm{Ph.CO.CHPh.NHPh}$$

As in the previous case, decomposition was very extensive, potash fusion at 100° and 140° giving rise to large quantities of highly coloured tar. A quantity of diphenylamine was isolated, but no desylaniline, the expected product, again indicating dephenacylation rather than rearrangement.

Since the phenacyl radical appeared to be sensitive to the reaction conditions employed, it seemed of interest to investigate the effect of replacing it by fluoryl group.

Fluorylbenzylaniline.



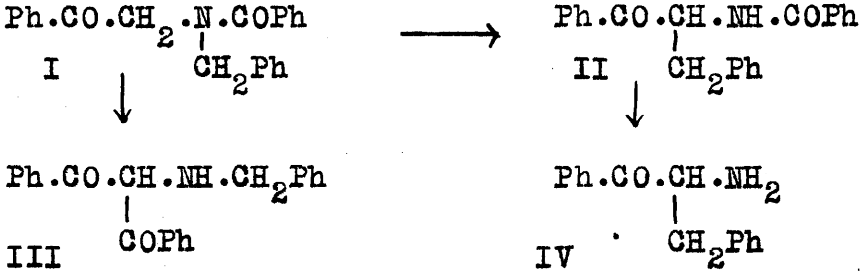
As has already been noted in Table I, p.10, previous experiments with this amine under a variety of conditions(14) had yielded toluene, benzylaniline, difluoryl and possibly fluorenone, which last might indicate that in this compound, rearrangement had given place to the fission reaction already noted in the introduction. In the present investigation, fusion with potassium hydroxide at 150° and 200° gave benzylaniline, fluorenone, an unidentified acid, m.p. 91°, and a large amount of tar, as well as some unchanged starting material. When the reaction was repeated in an atmosphere of nitrogen, most of the tertiary amine was recovered, which would appear to indicate that the fluorenone in the earlier experiments had been formed by atmospheric oxidation of starting material, rather than from intermediately formed anil. More drastic conditions are obviously required with this compound. It is interesting, however, to note the failure to synthesise the expected rearrangement product

9-benzyl-9-anilinofluorene (see p. 48). If this is due to steric hindrance, then it is unlikely that the same compound would be formed by rearrangement of fluorylbenzylaniline.

The unidentified acid referred to above was obtained in buff-coloured needles melting sharply at 91°, and having the analysis C, 79.87%; H, 4.42%; O, 15.71% (by diff.). There was no nitrogen present. Fluorene-9-carboxylic acid, $C_{14}H_{10}O_2$ requires C, 79.98%; H, 4.79%; O, 15.22%, but has a melting point of 225°(21). Potash fusion of fluorenone at 180-200°, either alone(22) or in an inert solvent such as diphenyl ether(17) is reported to give o-phenylbenzoic acid, $C_{13}H_{10}O_2$, which has a melting point of 110-111°, and the analysis C, 78.77%; H, 5.09%; O, 16.15%. The buff acid appeared to be quite pure, however, and this possibility is largely discounted. $C_{13}H_8O_2$ requires C, 79.58%; H, 4.11%; O, 16.31%, but this does not suggest any likely compound.

In an attempt to assess the effect of a change in the non-participating radical, some experiments were carried out in which the phenyl group in phenacylbenzylaniline had been replaced by benzoyl. The latter, due to the presence of the carbonyl group, can be classed as electron-attracting, which should tend to increase the acidity of the phenacyl methylene group, and to weaken slightly the bond between the nitrogen atom and the benzyl group; both of which effects should facilitate radical migration. Under the strong alkaline conditions employed, the benzoyl group would almost certainly be split off, but it was hoped that migration would be sufficiently rapid as to occur before debenzoylation.

Phenacylbenzylbenzamide.



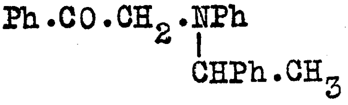
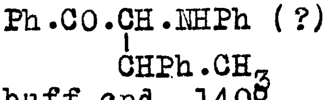
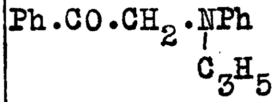
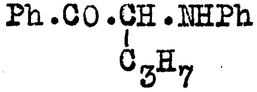
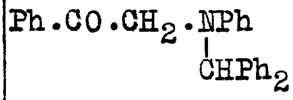
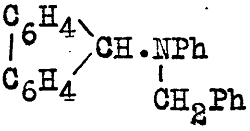
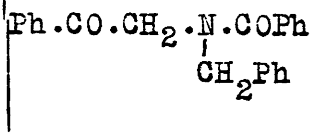
$$\begin{tikzcd} Ph.CO.CH_2.N(CH_2Ph).COPh \arrow[r] \arrow[d] & Ph.CO.CH(CH_2Ph).NH.COPh \arrow[d] \\ Ph.CO.CH(COPh).NH.CH_2Ph & Ph.CO.CH(CH_2Ph).NH_2 \end{tikzcd}$$

Potash fusion at 100° in an inert atmosphere merely gave 85% unchanged starting compound, and a small amount of benzoic acid. At 150° and 175°, the theoretical amount of benzoic acid corresponding to complete debenzoylation was isolated. It is unlikely that the symmetrical compound (III) resulting from migration of the benzoyl radical would yield exactly one equivalent of benzoic acid at both temperatures, so that this mode of reaction is precluded.

Debenzoylation of the "normal" rearrangement product (II) would yield α-amino-β-phenylpropiophenone (IV) which should undergo hydrogenolysis on treatment with zinc and sulphuric acid to β-phenylpropiophenone. A sparingly soluble hydrochloride was isolated from the melt, from which the free base was obtained as a brown gum. Treatment with zinc and dilute sulphuric acid followed by steam-distillation or benzene extraction yielded an oil with the ester-like smell of β-phenylpropiophenone. It refused to solidify, however, and failed to give a derivative with semicarbazide.

The attempted rearrangements are summarised in Table III, p. 25. The results obtained confirm the predictions made on theoretical grounds as to the expected reluctance of tertiary amines to exhibit radical migration. There seems little doubt, however, that a closer study of the necessary experimental conditions would prove this reaction, within limits, to be of fairly general application.

TABLE III.

Amine	Potash fusion	Products
 $\mathrm{Ph.CO.CH_2.\underset{CHPh.CH_3}{N}Ph}$	145-155° for 2 hrs. 120° for 15 mins.	Ph.COOH, $\mathrm{Ph.NH.CHPh.CH_3}$ tarry products
	100° for 4 hrs. inert atmosph.	 $\mathrm{Ph.CO.\underset{CHPh.CH_3}{CH}.NHPh}$ (?) buff cpd. 140° Ph.COOH, $\mathrm{Ph.NH.CHPh.CH_3}$
 $\mathrm{Ph.CO.CH_2.\underset{C_3H_5}{N}Ph}$	130-160° for 1 hr.	tar
	100° for 30 mins. 150° for 30 mins. inert atmosph. hydrogenation	$\mathrm{Ph.CO.CH_3}$ yellow oily base similar to synth.  $\mathrm{Ph.CO.\underset{C_3H_7}{CH}.NHPh}$
 $\mathrm{Ph.CO.CH_2.\underset{CHPh_2}{N}Ph}$	100° for 2 hrs. inert atmosph.	yellow compd. m.p. 225°
$\mathrm{Ph.CO.CH_2.NPh_2}$	140° for 1½ hrs. 100° for 3 hrs.	$\mathrm{Ph_2NH}$, tarry products.
	150°, 200° for 1 hr. 150° for 3 hrs.	$\mathrm{Ph.NH.CH_2Ph}$, fluorenone, buff acid m.p.91°.
	150° for 3 hrs. inert atmosph.	mostly unchanged, some "91°" acid
 $\mathrm{Ph.CO.CH_2.\underset{CH_2Ph}{N}.COPh}$	100°, 150° for 1 hr. 175° for 15 mins. inert atmosph.	Ph.COOH gummy base

EXPERIMENTAL.

All melting points are uncorrected.

The general method of carrying out attempted rearrangements was as follows. The powdered tertiary amine was intimately mixed in a 6 x 1" pyrex tube with a large excess of potassium hydroxide which had been finely ground in an open mortar. The smell of carbylamine was usually immediately noticeable, this being a general property of phenacylanilines(23). The tube was heated in a bath of heavy paraffin, the melt being in most cases stirred with a glass rod to maintain a uniform temperature. Where an inert atmosphere was required, the tube was closed with a cork stopper fitted with a glass capillary, and a few ml. of 30-40° petroleum ether added before heating, stirring being dispensed with.

After cooling, the melt was dissolved in water and 60-80° petroleum ether, filtered from any tarry material present, and the two layers separated. The aqueous solution was acidified and extracted with ether in order to obtain any acidic compounds present. The petroleum was extracted with dilute (5%) hydrochloric acid to remove strong bases such as primary and some secondary amines, then with 50% hydrochloric acid to remove the weaker bases. This frequently gave rise to an insoluble hydrochloride, which was removed by filtration. The petroleum ether solution was then carefully concentrated, and the residue steam-distilled. The first runnings of the distillate were extracted with pentane and heated with nitrating mixture in an attempt to detect such hydrocarbons as toluene, while the main part was examined for other neutral products, such as ketones. The residue in the distillation flask was then examined for non-volatile compounds.

This procedure could be readily adapted to the investigation of other types of reaction mixtures also, and unless otherwise stated, was the method of examination used in all the experiments described in this section. Many of the details will therefore be omitted in the following account, to avoid needless repetition, and only those features of especial interest will be described.

Phenacylbenzylaniline.

(1) 3 g. amine was fused with 9 g. potassium hydroxide at 130° for 2 hours.

The petroleum ether solution, on shaking with 4N hydrochloric acid, yielded a gummy, insoluble hydrochloride, the free base from which could be crystallised from methanol in large yellow rhombs, m.p. 104°

(0.2 g.). This melting point was not depressed by admixture with a synthetic sample of α-anilino-β-phenylpropiophenone obtained from Dr. Stevens(16,18).

Steam distillation of the neutral part of the petroleum ether extract gave a few mgms. of colourless crystals melting diffusely about 50°, which smelled of dibenzyl, but depressed the melting point of a pure sample of the latter (m.p. 52°). This substance was not identified in this experiment.

(2). 3 g. amine was fused with 10 g. potash at 125° for 1½ hours. No rearrangement product was detected, most of the amine being recovered unchanged.

(3). The above was repeated at 160° for 2 hours.

The same treatment yielded 0.8 g. of pure rearrangement product, while steam-distillation yielded the same substance as before. This could be recrystallised from ethanol in colourless square plates, m.p. 71°, which did not depress the melting point of an authentic sample of β-phenylpropiophenone. This compound formed a crystalline semicarbazone, m.p. 144°, either alone or in admixture with genuine β-phenylpropiophenone semicarbazone.

(4). Repeat experiment at 175-185° for 3 hours.

Extensive charring occurred, and no rearrangement product or starting material could be isolated. 0.2 g. of β-phenylpropiophenone was obtained from the neutral steam-distillate, however, proving the intermediate formation of α-anilino-β-phenylpropiophenone.

(5). 1 g. amine and 5 g. powdered potassium hydroxide were heated in refluxing xylene for 1½ hours.

This experiment yielded no useful result, most of the amine being recovered unchanged, and this line of investigation was discontinued.

(6). 1 g. amine was added to a solution of 0.5 g. sodium in moist isoamyl alcohol, and the solution refluxed for 1 hour.

The yellow reaction mixture turned orange on cooling, and green on being acidified with hydrochloric acid. The amyl alcohol was removed by steam-distillation, and the acid solution extracted with ether to remove neutral products. This extract yielded only an unidentified brown oil. The aqueous solution was then basified and again extracted. The residue obtained by concentration of this second extract was also a brownish oil, which slowly solidified. After recrystallisation from ethanol, this solid melted at 37°, either alone or in admixture with pure benzylaniline. Benzoylation in pyridine gave a yellow derivative with a melting point of 102-103°, which was unaltered by admixture with benzoylbenzylaniline.

(7). The above was repeated using dry amyl alcohol, and a reflux time of 15 minutes, but no new result was obtained.

(8). 1 g. amine was added to a solution of 1 g. sodium in methanol, and the mixture refluxed for 2 hours.

On cooling, the solution smelled strongly of methyl benzoate. It was diluted with its own volume of water, and extracted with 60-80° petroleum ether. This extract, on shaking with 50% hydrochloric acid, deposited a greenish, sparingly soluble hydrochloride, m.p. 200-205° (decomp.). The free base from this salt was identified as benzylaniline by its melting point and that of its benzoyl derivative, both alone and in admixture with authentic samples.

The petroleum ether, after the above treatment with acid, slowly deposited a spontaneous crop of greenish-white feathery sheaves of needles, which could be recrystallised from ethanol in white burrs, m.p. 112° (0.3 g.). Found: C, 79.91%; H, 5.27%; N, 5.21%. This substance has not been identified (see p. 13).

No other pure compounds were isolated.

Phenacyl-α-phenethylaniline.

(9) 0.3 g. amine was fused with 3 g. potash at 145-155° for 2 hours.

Substantial charring occurred, making examination difficult. Acid extraction of the petroleum solution gave only α-phenethylaniline, while the aqueous solution, on acidification, yielded benzoic acid. Steam-distillation of the neutral residue yielded no identifiable compound.

(10) The above was repeated at 120° for 15 minutes.

Traces of a yellow crystalline solid were obtained in the steam-distillate, but otherwise no new result was obtained.

(11) 0.5 g. amine was heated with 5 g. potash at 100° for 4 hours in an inert atmosphere.

The melt was dissolved in water and petroleum ether as usual, about 0.05 g. of pure benzoic acid being obtained from the aqueous portion. The petroleum, on shaking with 50% hydrochloric acid, gave a red insoluble hydrochloride and a yellow acid solution; the latter on basification yielding about 0.1 g. of starting material. The hydrochloride was decomposed with sodium hydroxide solution, the free base extracted with ether, and the solvent distilled off. The residue was crystallised in fractions from petroleum ether, the first fraction consisting of yellow-green crystals, m.p. 118-120°, with the analysis C, 84.04%; H, 6.37%; N, 4.53%. This compound suffered a depression in melting point in admixture with the starting tertiary amine (m.p. 127°) but not with the synthetic α-anilino-β-phenylbutyrophenone, m.p. 121° reported on p.48.

From the later crystal fractions was obtained a buff crystalline solid, m.p. 140°. This substance blackened on boiling in petroleum ether, however, and could not be purified for analysis. No β-phenylbutyrophenone could be detected in the steam-distillate.

Phenacylallylaniline.

(12) 0.5 g. amine was fused with 5 g. potash at 130-160° for 1 hour.

The melt was tarry and unworkable, and the standard procedure described above was found to be ineffective, only tarry and amorphous products being isolated. The basic portion smelled of allylaniline, but its presence could not be verified.

(13) 0.7 g. amine was heated with 5 g. potash at 100° for 30 minutes in an inert atmosphere.

Tarring was much less pronounced than in the previous run. The melt was dissolved in water and ether, the organic layer separated, dried with potassium carbonate, and the ether removed by distillation. The residue was quickly dissolved in 20 ml. of absolute ethanol, and hydrogenated in the presence of palladium black, when 60 ml. of hydrogen was absorbed; which is approximately correct for complete saturation of the allyl group. The alcoholic solution was filtered to free it from catalyst, and, after evaporation of the solvent, the residue again dissolved in ether, and shaken with concentrated hydrochloric acid. This gave a yellow acid solution which was basified and extracted in the usual way to yield 0.4 g. of pale yellow needles, m.p. 95-96°. This melting point was unaltered by admixture with phenacylpropylaniline (m.p. 96°), obtained by direct hydrogenation of the starting tertiary amine. The mother liquors yielded a further quantity of this compound, contaminated with a yellow oil, very similar in appearance to α-anilinovalerophenone (see p. 48) and the last fractions were therefore treated with benzoyl chloride in pyridine on a boiling water bath. The product was dissolved in ether and extracted with concentrated hydrochloric acid to remove pyridine and phenacylpropylaniline, but no N-benzoyl-α-anilinovalerophenone could be detected in the remaining ether solution.

Steam-distillation of the neutral material yielded no identifiable product.

(14) The above was repeated with 0.5 g. amine at 150° for 30 minutes, slight tarring being noticeable.

The hydrogenated product was again dissolved in ether, and the solution shaken with concentrated hydrochloric acid, giving a reddish acid solution, and 0.05 g. of a white insoluble hydrochloride. These were examined separately, the former yielding 0.05 g. of phenacylpropylaniline, and the latter the same yellow oily base obtained in the previous run. Several attempts were made to benzoylate this compound in pyridine, but in every case, the oil was recovered unchanged, even after prolonged treatment.

Steam-distillation of the neutral products yielded an oil which smelled strongly of valerophenone. The 2:4-dinitrophenylhydrazone was prepared, and obtained in orange crystals, m.p. 243-245°, which did not depress the melting point of acetophenone 2:4-dinitrophenylhydrazone. No valerophenone was detected.

Phenacylbenzhydrylaniline.

(15) 0.1 g. amine was fused with 3 g. potash at 100° for 2 hours in an inert atmosphere.

The melt did not dissolve completely in water and petroleum, a small quantity of yellow solid material remaining. This crystallised from methanol in orange crossed needles, m.p. 225°, but was insufficient for analysis. The usual examination yielded no identifiable compound.

Phenacyldiphenylamine.

(16) and (17). 0.3 g. amine was heated with 3 g. potash at 140° for 1½ hours, and 100° for 3 hours.

In both runs, large quantities of purple tar were produced. Acid extraction of the petroleum ether solution yielded a small amount of diphenylamine, m.p. 54°, while the residue from the steam-distillation was found to be mainly unchanged tertiary amine.

Fluorylbenzylaniline.

(18). 1 g. amine was heated with 3 g. potash at 150° for 1 hour.

Charring was fairly extensive, making investigation difficult. Much of the starting material was recovered as the residue from the steam-distillation, but no products could be isolated.

(19). The above was repeated at 200° for 1 hour.

In this run, the aqueous solution, on acidification, yielded traces of a crystalline solid which could not, however, be obtained pure. The basic part of the melt consisted mainly of benzylaniline, m.p. 37°, confirmed by its benzoyl derivative, m.p. 102°. Steam-distillation of the neutral residue gave 20-30 mg. of a yellow solid, m.p. 83-84°. This melting point was depressed by admixture with fluorenone anil (m.p. 89°) but not with fluorenone itself (m.p. 84°).

The residue from the steam-distillation again consisted largely of unchanged starting material.

(20). The same reaction was carried out at 150° for 3 hours.

Besides the products isolated from the previous run, there was obtained about 0.1 g. of the acid compound referred to above. After several recrystallisations from petroleum ether, this consisted of buff needles, melting sharply at 91°. Found: C, 79.87%; H, 4.42%; N, zero (see p.22).

(21). 1 g. amine was fused with 3 g. potash at 150° for 3 hours in an atmosphere of nitrogen.

A few mgms. of the "91°" acid were obtained, but most of the starting material was recovered unchanged.

Phenacylbenzylbenzamide.

(22). 2 g. amide was heated with 5 g. potash at 100° for 1 hour in an inert atmosphere.

1.7 g. of the tertiary amine was recovered unchanged, while 0.1 g. benzoic acid was obtained from the aqueous solution.

(23). 1 g. amine was fused with 5 g. potash at 150° for 1 hour in hydrocarbon vapour.

The aqueous solution, on acidification, yielded 0.4 g. of pure benzoic acid, corresponding to complete hydrolysis of the benzoyl group. The petroleum solution, on treatment with 50% hydrochloric acid, gave a solid hydrochloride, from which the free base could only be obtained as an oily gum, of which no derivatives could be obtained. It was refluxed with zinc and dilute sulphuric acid, in order to split off the amino-group, but the oily product which appeared on the surface of the solution was rapidly charred by the acid, and could not be identified.

(24). 2 g. amine was fused with 5 g. potash at 175° for 15 minutes in an inert atmosphere.

As in the previous experiment, complete debenzoylation occurred, 0.8 g. of benzoic acid being isolated. The same gummy base was obtained, and was treated with zinc and dilute sulphuric acid, the solution being continuously distilled. The distillate smelled strongly like β-phenylpropiophenone, and was extracted with ether. The residue from this extract was treated with semicarbazide, but failed to give a derivative.

PREPARATIVE WORK.

Owing to the fact that this project was interrupted, some of the compounds described in this section were never used for experimental work. Their inclusion here is intended to serve as a guide to later workers in this field.

The yields of tertiary amines by the general method described for phenacylbenzylaniline were in general very low (5-20%), owing to slow reaction rate and side-reactions. In the case of the fluorylamines, the analysis results tended to be low in carbon, and since the compounds were in all cases satisfactorily crystalline, with sharp melting points, this is possibly due to faulty combustion.

The following intermediates were prepared:-

Phenacyl bromide. Acetophenone was brominated in presence of aluminium chloride(24).

Benzhydryl bromide. Direct bromination of diphenylmethane(25,26) yielded only high-boiling products, mainly tetraphenylethylene. Better results were obtained by refluxing benzhydrol with constant-boiling hydrobromic acid(27). The product was purified by distillation, b.p. 172° at 11 mm. pressure, and solidified to white crystals, m.p. 45°.

Phenacylamine. Isonitrosoacetophenone, prepared by a Claisen condensation from acetophenone and isoamyl nitrite, in presence of sodium ethoxide(28), was reduced by means of stannous chloride in fuming hydrochloric acid, and after precipitation of the tin with hydrogen sulphide, the product isolated as the hydrochloride(29).

Benzylamine(30). An intimate mixture of phthalimide and potassium carbonate was heated with benzyl chloride to give benzylphthalimide. The latter, after purification, was warmed in alcoholic suspension with hydrazine hydrate, the insoluble phthalylhydrazide removed by filtration, and the product extracted with ether and distilled, b.p. 185-187°.

Benzylmethylamine. Benzalmethylamine was prepared from methylamine hydrochloride, benzaldehyde and potash in aqueous solution, and the product reduced with sodium in ethanol.

Benzylaniline. Aniline (2 mols.) was treated with benzyl chloride (1 mol.) in benzene. A fairly vigorous reaction ensued, during which the excess aniline was precipitated as hydrochloride, and removed by filtration. The benzene solution was dried, concentrated, and the residue vacuum-distilled, yielding the product as a brownish oil which slowly solidified, and could be crystallised from ethanol, m.p. 37°. Benzoylation in pyridine gave benzoylbenzylaniline in yellow crystals, m.p. 102-103°.

Allylaniline. This was prepared by the same general method, from aniline and allyl bromide, being obtained as a reddish-brown aromatic liquid, b.p. 220°.

Phenacylaniline(31). This was prepared from phenacyl bromide and aniline (2 mols.) in ethanol, with chilling in an ice-salt bath. The product crystallised spontaneously, and was recrystallised from ethanol, m.p. 93°.

α-Phenethylaniline(32). Benzaldehyde anil, prepared from benzaldehyde and aniline in the presence of excess potassium hydroxide, was added to an ethereal solution of methylmagnesium iodide. The product was purified by recrystallisation of the sparingly soluble nitrate from water, and the free base liberated and distilled in vacuo. The oil was found to solidify slowly, and could be recrystallised from ethanol, in white nodules, m.p. 27-28°.

Benzhydrylaniline (i). Benzhydryl bromide was treated with aniline (2 mols.) in benzene. Some aniline hydrobromide separated on warming, but vacuum-distillation yielded only high-boiling products.

(ii). Benzophenone anil was prepared in presence of a zinc chloride catalyst, being obtained in square yellow plates, m.p. 117°(33). This was reduced with sodium in ethanol(34,35), the product purified by precipitation of the hydrochloride from methanol with ether, and the free base distilled, b.p. 224° at 12 mm. pressure. A very poor yield was obtained with this method.

(iii). One equivalent of benzaldehyde anil was added to an ethereal solution of phenylmagnesium iodide(32). The product was purified by recrystallisation of the hydrochloride from ethanol (m.p. 199-202°) and vacuum-distilled. The oil slowly solidified, and could be recrystallised from ethanol, in white nodules, m.p. 55-56°.

From the above intermediates, the following tertiary amines were prepared:-

Phenacylbenzylmethylamine. Phenacyl bromide was treated with benzylmethylamine (2 mols.) in benzene, and the product obtained by vacuum-distillation as a yellow oil, b.p. 160° at 0.5 mm. pressure (known compound).

Phenacylbenzylaniline. This was prepared by the same standard method; that is, by the interaction of phenacyl bromide (1 mol.) and benzylaniline (2 mols.) in benzene at room temperature, for several days. The precipitated benzylaniline hydrobromide was filtered off, the benzene removed by distillation, and the residue recrystallised from ethanol. The product was obtained in yellow nodules, and could be purified by crystallisation from chloroform and methanol in pale yellow needles, m.p. 108°.. Found: C, 83.81%; H, 6.41%; N, 5.45%. $C_{21}H_{19}ON$ requires C, 83.65%; H, 6.36%; N, 4.65%.

According to Bauer and Bühler(36), this compound is 1-benzyl-3-phenylindole, formed from the tertiary amine by ring-closure. This is disproved by the analysis results, however, since $C_{21}H_{17}N$ requires C, 89.04%; H, 6.01%; N, 4.94%.

Phenacylallylaniline. A small amount of this compound was obtained by the direct action of phenacyl bromide on allylaniline, but very extensive tarring reduced the yield to a few percent. The latter was raised to 50%, however, by the method of Verkade and Janetsky(19). Equimolecular quantities of allylaniline and phenacyl bromide were refluxed with excess sodium bicarbonate in ethanol, with vigorous stirring for 30 hours. The solution was filtered hot from sodium bromide and excess sodium bicarbonate, and allowed to cool, when a crop of yellow crystals separated. These were purified by recrystallisation from ethanol, being obtained as flat yellow plates, m.p. 91°. Found: C, 81.20%; H, 6.77%; N, 6.27%. $C_{17}H_{17}ON$ requires

C, 81.20%; H, 6.83%; N, 5.58%. This compound is fairly rapidly oxidised in air to a red tar, but keeps well under ethanol. Indole formation is again disproved by the analysis figures, and the presence of a free phenacyl group was further demonstrated by hydrogenolysis with zinc and dilute sulphuric acid to acetophenone (isolated as the 2:4-dinitrophenylhydrazone).

<u>Phenacylpropylaniline.</u> Phenacylallylaniline was hydrogenated in ethanol, in the presence of palladium black. The product was a pale yellow solid, m.p. 96°, soluble in concentrated hydrochloric acid, giving a yellow solution. Found: C, 80.80%; H, 7.43%; N, 5.47%. $H_{17}H_{19}ON$ requires C, 80.63%; H, 7.51%; N, 5.53%.

<u>Phenacyl-α-phenethylaniline.</u> This was prepared by both the methods described for phenacylallylaniline, the second of which again gave a much improved yield. Benzene was employed in place of alcohol, and after filtration from sodium salts, the solution was extracted with 5% hydrochloric acid to remove unchanged α-phenethylaniline. The benzene solution was dried, diluted with ether, and the product isolated by precipitation with hydrogen chloride gas. The hydrochloride was decomposed with sodium hydroxide, and the free base extracted and crystallised

* Treatment of phenacyl bromide with alcoholic potash is reported to give " β-bromodiphenacyl", m.p. 161°(45). Calcd. for $C_{16}H_{13}O_2Br$, C, 60.57%; H, 4.10%. These data are in good agreement with those of the unknown compound.

from 60-80° petroleum ether, being obtained as yellow-green rhombs, m.p. 127°. Found: C, 83.56%; H, 6.48%; N, 5.16%. $C_{22}H_{21}ON$ requires C, 83.75%; H, 6.71%; N, 4.44%.

The reaction between α-chloroethylbenzene (1 mol.) and phenacylaniline (2 mols.) in benzene was found not to yield the required product.

Phenacylbenzhydrylaniline. Phenacylaniline (1 mol.) and benzhydrylbromide (1 mol.) were refluxed with sodium bicarbonate in alcohol, but did not yield the desired product. Similarly unsatisfactory results were obtained by treating phenacyl bromide with benzhydrylaniline (2 mols.) in benzene at room temperature for several days. Refluxing equivalent amounts of benzhydrylaniline and phenacylbromide with sodium bicarbonate in benzene for several days yielded a small quantity of the desired compound, however. The benzene solution was filtered, and shaken with 50% hydrochloric acid, causing the separation of some benzhydrylaniline hydrobromide. The benzene solution was then dried, the solvent distilled off, and the residue crystallised from alcohol-petroleum ether in several fractions. The first consisted of buff needles, m.p. 160-161° (quick heating) with the analysis C, 60.90%; H, 4.23%, and is obviously the wrong substance.* The third crop of crystals was obtained as greenish-yellow needles, m.p. 148-149°, with the analysis, C, 86.10%; H, 5.98%; N, 3.88%. $C_{27}H_{23}ON$ requires C, 85.94%; H, 6.10%; N, 3.71%.

Phenacyldiphenylamine. This was obtained from diphenylamine (2 mols.) and phenacyl bromide (1 mol.), in benzene. Extensive side-reactions gave rise to highly coloured by-products. The product crystallised from petroleum ether in orange-yellow flakes, m.p. 144°. Found: C, 83.27%; H, 6.18%; N, 5.10%. $C_{20}H_{16}ON$ requires C, 83.60%; H, 5.95%; N, 4.88%.

Phenacylbenzylbenzamide. Phenacyl bromide (1 mol.) was added to benzylamine (2 mols.) in anhydrous ether, causing an immediate rise in temperature. After 30 minutes, most of the benzylamine hydrobromide had precipitated, and was filtered off. Benzoyl chloride (1.2 mol.) and excess pyridine were added to the ether solution, which was then heated on a boiling water bath for 30 minutes, (the ether being allowed to distil off) and poured into water. An oil separated which rapidly solidified, and was purified by recrystallisation from ethanol. An 80% yield of white crystals was obtained, m.p. 127-128°. Found: C, 80.49%; H, 5.57%; N, 4.94%. $C_{22}H_{19}O_2N$ requires C, 80.20%; H, 5.82%; N, 4.25%.

The tertiary fluoryl amines were all prepared from fluoryl bromide (1 mol.) and the corresponding substituted aniline (2 mols.) in benzene.

<u>Fluorylbenzylaniline.</u> White needles, m.p. 144° (sample available).

<u>Fluorylallylaniline.</u> Buff needles with a sweet vanilla-like odour, m.p. 102°.

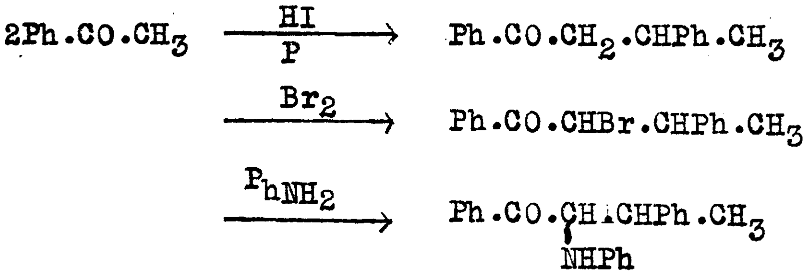
Found: C, 87.83%, 87.78%; H, 6.29%, 6.45%; N, 5.53%, 5.42%. $C_{22}H_{19}N$ requires C, 88.83%; H, 6.44%; N, 4.71%.

<u>Fluoryl-α-phenethylaniline.</u> Crystallised from ethanol in silver-grey plates, m.p. 132°.

Found: C, 88.83%; H, 6.58%; N, 4.68%. $C_{27}H_{23}N$ requires C, 89.70%; H, 6.42%; N, 3.88%.

Several attempts were made to synthesise three of the expected rearrangement products, namely, α-anilino-β-phenylbutyrophenone, α-anilinovalerophenone and 9-benzyl-9-anilinofluorene.

<u>α-Anilino-β-phenylbutyrophenone.</u>



$$2Ph.CO.CH_3 \xrightarrow[P]{HI} Ph.CO.CH_2.CHPh.CH_3$$

$$\xrightarrow{Br_2} Ph.CO.CHBr.CHPh.CH_3$$

$$\xrightarrow{PhNH_2} Ph.CO.\underset{NHPh}{CH}.CHPh.CH_3$$

The first stage, a condensation followed by a reduction, was accomplished by Graebe by heating acetophenone in a sealed tube with hydriodic acid and red phosphorus at 150° for 8-10 hours(37). This was modified to 15 hours refluxing, giving an excellent yield. The product was purified by vacuum-distillation followed by crystallisation from ethanol. This ketone was brominated in carbon tetrachloride, and the product recrystallised from methanol in white needles, m.p. 76°(20). The bromoketone (1 mol.) was refluxed in benzene with aniline (2 mols.) for several days, when a quantity of aniline hydrobromide had separated. Acid extraction gave only aniline, however, and concentration of the remaining solution gave white bromine-containing crystals, m.p. 122°. Found: C, 63.46, 63.72%; H, 5.09, 5.26%; N, zero. This analysis is correct for the bromoketone ($C_{16}H_{15}OBr$ requires C, 63.40%; H, 4.95%), and since the latter contains two asymmetric carbon atoms, it was concluded that the diastereomeric form had been obtained by some kind of keto-enol change(cf. 20).

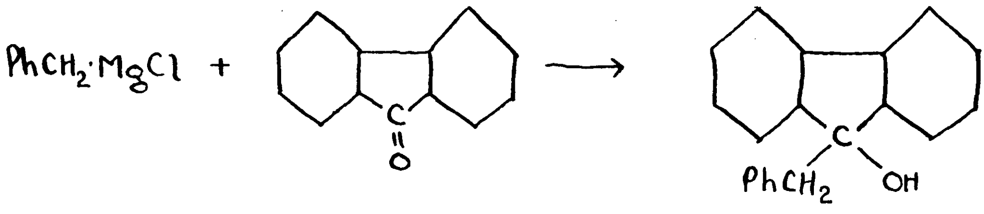
The bromoketone was then refluxed for several days with excess aniline and sodium bicarbonate in ethanol(18,19). The solution was diluted with water, extracted with ether, and the extract shaken with 5% hydrochloric acid to remove excess aniline. Treatment with 50% acid then gave a red gummy hydrochloride, from which were obtained a few mgms.

of a crystalline base, m.p. 121°, which did not depress the melting point of the "rearrangement product" from phenacyl-α-phenethylaniline (see p.16). There was insufficient for analysis, however, and repeat experiments yielded only a green oily base from the insoluble hydrochloride. This may be due to the existence of diastereomeric forms of the aminoketone (see also Appendix, p.55).

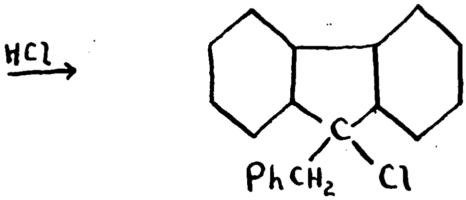
α-Anilinovalerophenone. Valerophenone was brominated directly in carbon tetrachloride, the bromoketone being obtained as a yellow oil. This halide was treated with aniline and sodium bicarbonate as in the previous preparation, and the reaction mixture worked up similarly. Treatment of the ether solution with concentrated hydrochloric acid gave a white insoluble hydrochloride, from which the free base was obtained as a thick yellow oil. The bemzoyl derivative of this compound was prepared in pyridine, being obtained as colourless prisms, m.p. 87°. Found: C, 80.78%; H, 6.28%; N, 4.13%. $C_{24}H_{23}O_2N$ requites C, 80.67%; H, 6.44%; N, 3.92%.

9-Benzyl-9-anilinofluorene.

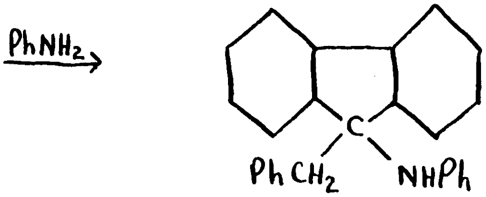
Method A.



I



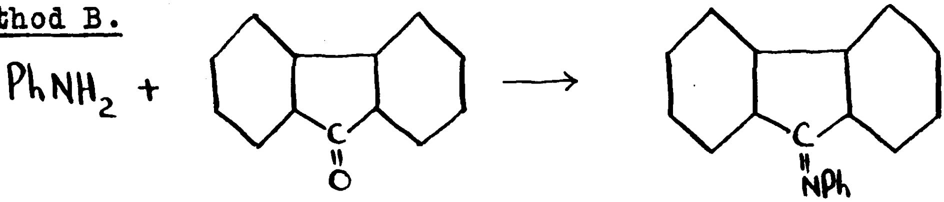
II



III

The first stage is a Grignard reaction(38). The halide (II) was obtained by the action of hydrogen chloride in ether(cf.39) as white crystals melting with decomposition at 99-102°. The analysis was unsatisfactory. Found: C, 85.23%; H, 5.26%. $C_{20}H_{15}Cl$ requires C, 82.60%; H, 5.20%. This may have been due to loss of hydrogen chloride, or admixture with unchanged benzylfluorenol. The halide was treated with aniline (2 mols.) in ether, but only reacted very slowly, as indicated by the separation of a few crystals of aniline hydrochloride. None of the desired product could be isolated.

Method B.



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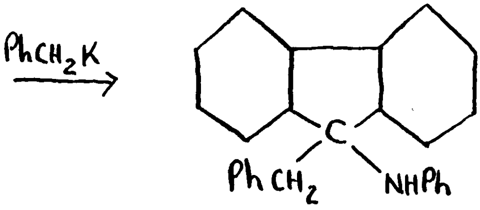
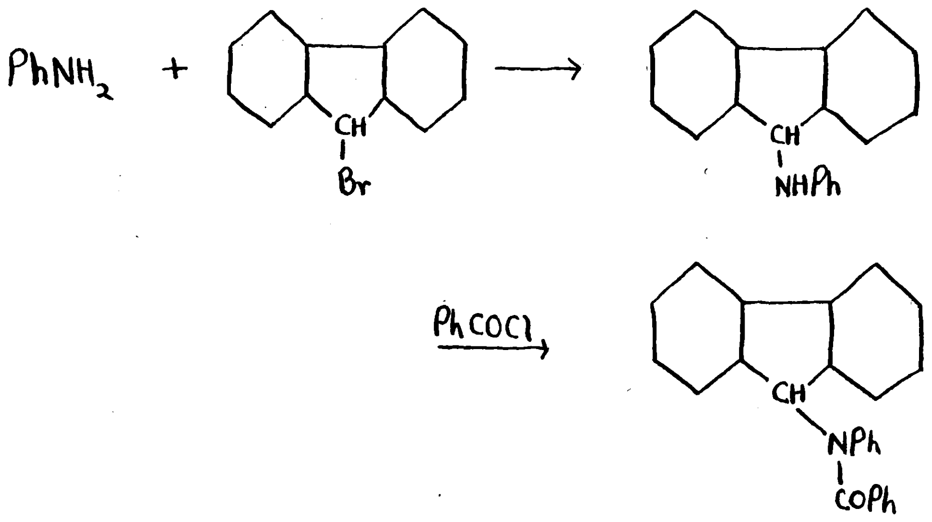


II

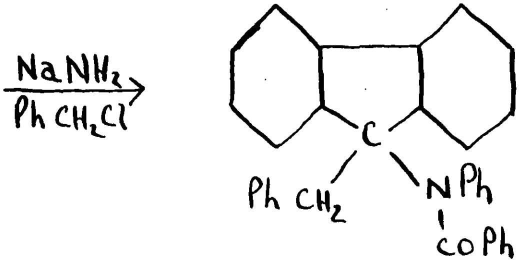
The formation of the anil was catalysed by zinc chloride(33). Since Grignard reagents have been found to give 1:4-addition to this type of system(40), the action of benzyl potassium was investigated(41). This reagent is prepared by the action on toluene of phenyl potassium, prepared in situ from chlorobenzene and potassium sand in an atmosphere of nitrogen. The anil was added to this mixture, and refluxed for 3 hours. The complex was decomposed with ice, excess toluene removed in steam, and the residue crystallised from ethanol. Although this reaction was carried out twice, only fluorylaniline could be obtained, which is possibly due to the reduction of the anil by unchanged potassium sand. Some diphenylmethane was also obtained by the steam-distillation, probably formed from benzyl potassium and unchanged chlorobenzene.

Method C.



I

II



III

Fluorylaniline was prepared by refluxing fluoryl bromide, aniline and anhydrous sodium acetate in amyl alcohol$^{(42)}$. It was thought necessary to "block" the -NH- group by benzoylation. Product was a colourless solid, m.p. 147°, with the analysis, C, 86.07%; H, 5.35%; N, 4.29%. $C_{26}H_{19}ON$ requires C, 86.39%; H, 5.30%; N, 3.88%. The final stage is a condensation with benzyl chloride in presence of sodamide in liquid ammonia$^{(43)}$, but this has not been achieved.

A plausible explanation for the failure of these three routes to yield the desired compound is that steric hindrance is preventing the attachment of two relatively large groups to the No.9 carbon atom.

β-Phenylpropiophenone. Benzalacetophenone (chalkone), prepared by alkaline condensation of benzaldehyde and acetophenone, was hydrogenated catalytically with palladium on strontium carbonate in ethanol. The product was recrystallised from ethanol in colourless square plates, m.p. 71°.

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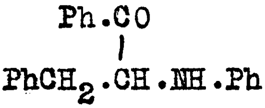
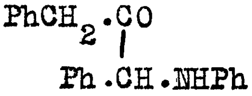
APPENDIX.

Julian has given a thorough treatment of the interaction of α-bromoketones and arylamines(18). The reaction may not be a simple substitution, since addition to the carbonyl group followed by loss of hydrogen bromide, may be involved(44). In many cases, two products are obtained: for example, α-bromo-β-phenylpropiophenone (1 mol.) and aniline (2 mols.) interact to form two anilinoketones, one yellow and the other colourless, with the structures below(16):



$$\begin{array}{c} \mathrm{Ph.CO} \\ | \\ \mathrm{PhCH_2.CH.NH.Ph} \end{array}$$

I, yellow.



$$\begin{array}{c} \mathrm{PhCH_2.CO} \\ | \\ \mathrm{Ph.CH.NHPh} \end{array}$$

II, colourless.

The yellow colour of I is apparently due to the extended, conjugated unsaturation, absent in II. These compounds are formed in varying proportions by the above reaction. When the method of Verkade and Janetsky is used(19), employing equimolecular quantities of bromoketone and arylamine in presence of an excess of sodium bicarbonate, only the yellow isomer is formed, which would seem to suggest that halogen acid is responsible for the formation of the colourless isomer. This was confirmed by the fact that either isomer was converted into a mixture of both on heating with halogen acids (18). Since the yellow isomer is that which corresponds to the required "rearrangement product", Verkade and Janetsky's method was used in this work.

THE HYDROLYTIC FISSION OF FURFURYL ALCOHOL.

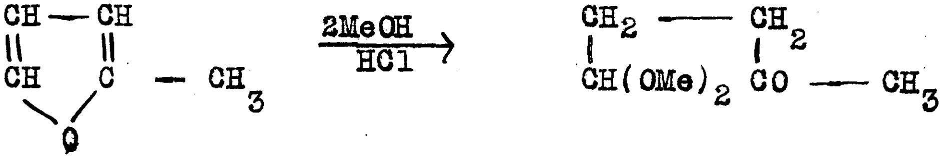
The Hydrolytic Fission of Furfuryl Alcohol.

SUMMARY.

Attempts have been made to determine the structure of two compounds obtained by the acid fission of furfuryl alcohol in the presence of 2:4-dinitrophenylhydrazine. Some of the work of previous investigators has been repeated, with similarly inconclusive results, and additional experiments have yielded little information.

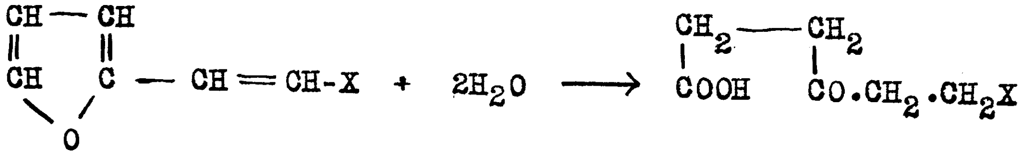
INTRODUCTION.

The furan ring possesses the property of undergoing cleaveage by acidic reagents. Thus Dietrich and Paal(1) obtained the acetal of laevulinaldehyde by the action of methyl alcoholic hydrochloric acid on α-methylfuran.

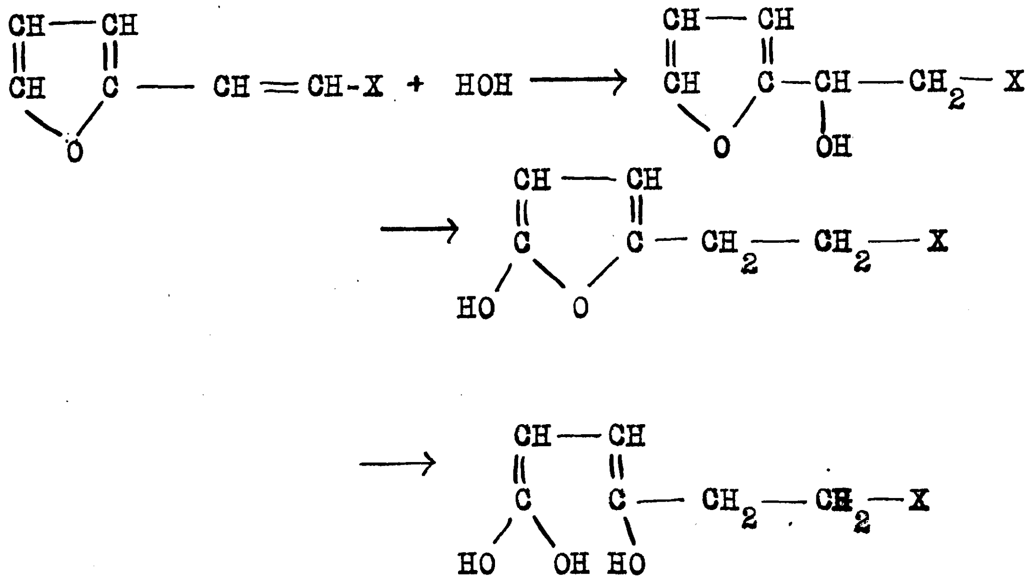


When the furan compound has an ethylenic bond in the α-position, a keto-acid is obtained, rather than an aldehyde(2),

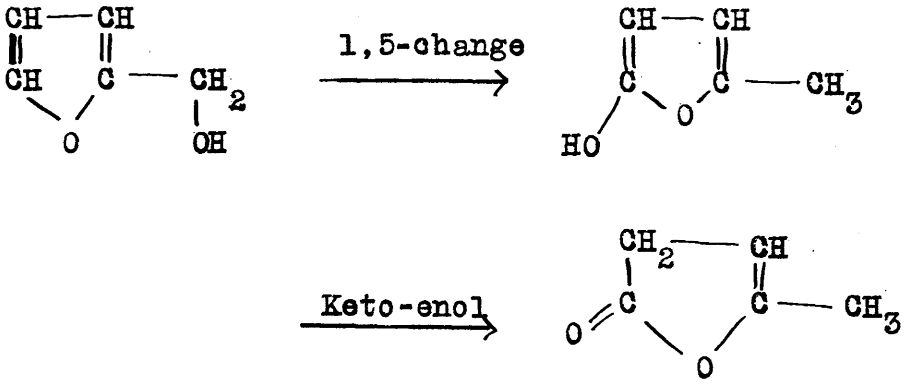
e.g.



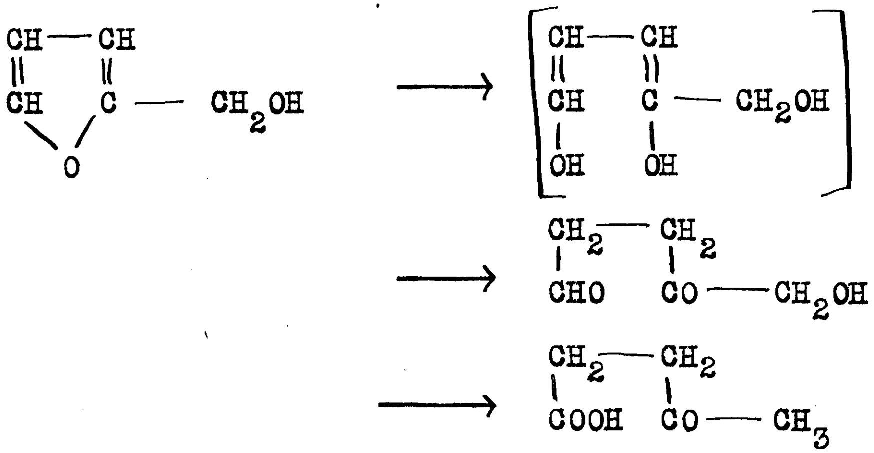
This was explained by Tchitchibabine(3) as addition of HCl or HOH to the ethylenic bond, followed by interchange of No.1 hydrogen atom, and Cl or OH



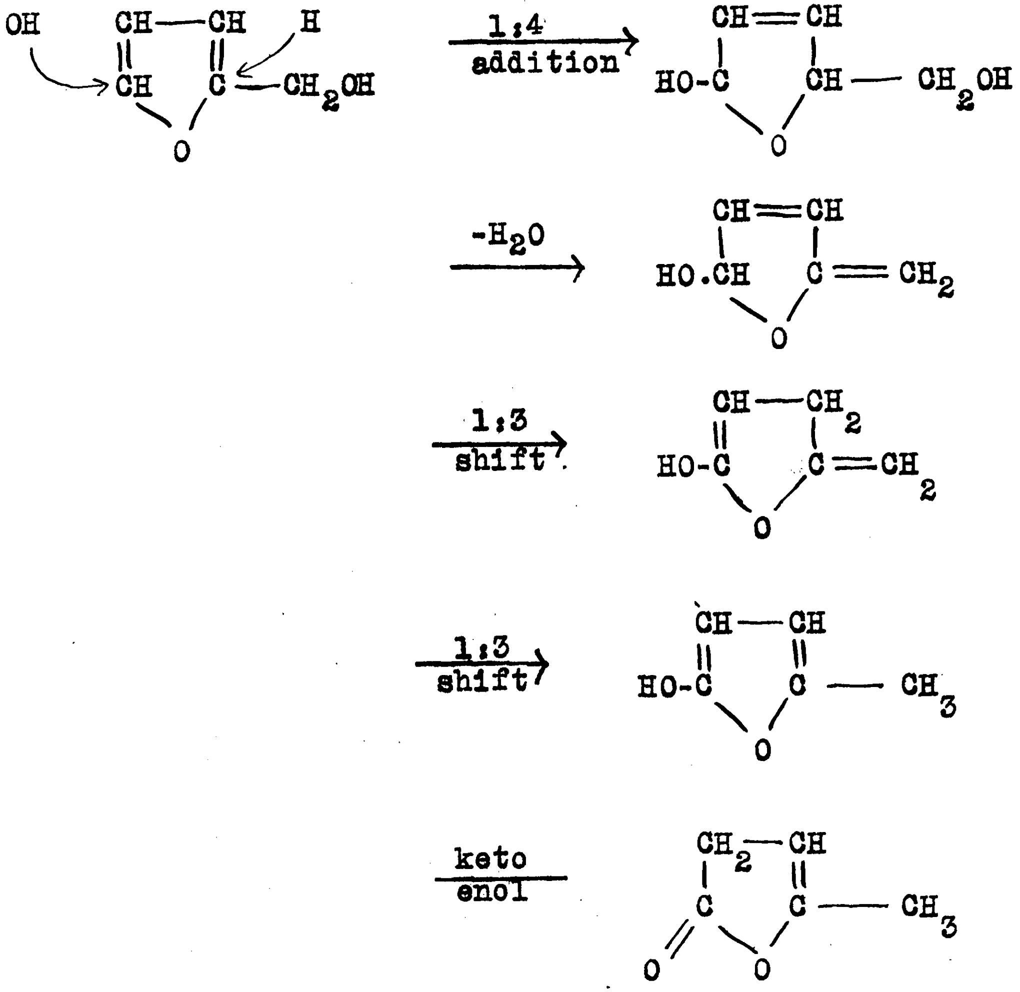
When furfuryl alcohol is heated with hydrochloric acid, laevulinic acid is obtained(4), and Tchitchibabine explained this result according to the above scheme for ethylenic compounds.



The product of the postulated migration, angelicalactone, is readily hydrolysed, in the presence of mineral acids, to laevulinic acid. Pummerer and Gump's theory(4) of the mechanism was that the furfuryl alcohol first gave δ-hydroxylaevulinaldehyde (cf. Dietrich and Paal) which then underwent what they regarded as an intramolecular Cannizzaro reaction between the aldehyde group and the δ-hydroxy group, to give laevulinic acid



These proposed mechanisms, simple though they be, have little in the way of chemical analogy or experimental backing, however, and Scott and Johnson(6) and Hibbert and Leger(5) have offered convincing evidence to support the theory of a preliminary 1:4 addition of HOH, HCl, or MeOH, followed by loss of water from the side-chain, and a double 1:3-migration of hydrogen, to give angelicalactone, which then cleaves to give laevulinic acid as before:



In order to "freeze" any intermediate carbonyl compounds, Wright and Leger (unpub.) carried out the reaction between furfuryl alcohol and methanolic hydrochloric acid, in the presence of 2:4-dinitrophenylhydrazine, and isolated three products: namely, methyl laevulinate 2:4-dinitrophenylhydrazone, a yellow compound, m.p. 226° (hereafter called "A") and a red compound, m.p. 274° (hereafter called "B"). 'A' was the main product when two molecules of the hydrazine and of acid were refluxed with one of furfuryl alcohol for one hour, while 'B' was obtained when equimolecular quantities of all three were used, and the reaction time extended to six hours.

The problem was further investigated by Downing (unpub.) and Woods (unpub.). Downing obtained what appeared to be an acetyl derivative of 'A', m.p. 216-217°, and by the action of potassium permanganate on'B', he isolated a yellow oil which gave the reactions of a free carbonyl group, and which he believed regenerated 'B' on treatment with 2:4-dinitrophenylhydrazine. (This has now been disproved, however).

Woods found that the same products were obtained when the solvent was ethanol, and/or sulphuric acid replaced hydrochloric acid. He ascertained that 'A' is converted to methyl laevulinate DNP* by the action of methanolic hydrochloric acid, and that this is then converted to 'B' by the action of excess furfuryl alcohol and hydrochloric acid. Methyl laevulinate DNP therefore appears to be an intermediate between 'A' and 'B'. Refluxing 'A' in ethanol 0.4N in hydrochloric acid gave a 25% yield of ethyl laevulinate DNP, and 40% of a substance melting sharply at

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* In this account the letters "DNP" after the name of a compound will be understood to mean "2:4-dinitrophenylhydrazone".

80°, but which had the properties of a eutectic mixture.

The more important of Downing's and Woods's results are summarised in Tables I and II. It is interesting to note that the striking royal blue colour obtained by dissolving 'B' in sodium hydroxide in aqueous acetone is reported by Strain(7) as being typical of bis-DNP's of such compounds as glyoxal, methyl glyoxal, or diacetyl.

The average analyses of these compounds as obtained by Downing are as follows:

	Yellow	Red
Carbon	44.74	45.88
Hydrogen	3.69	3.06
Nitrogen	23.26	24.48
Oxygen (diff.)	28.31	26.58
Methoxyl	Nil	Nil
Mol. Wt.	727 ± 30	-

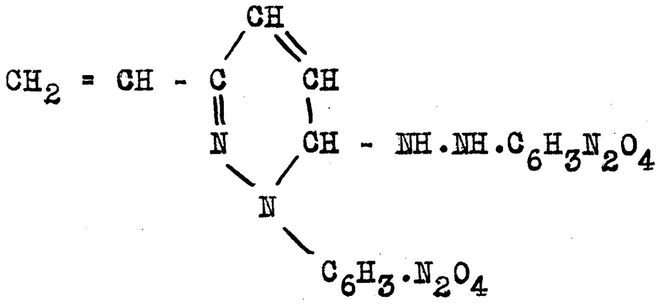
Calculation of empirical formulae gives:-

Yellow	$C_{36}H_{35}O_{17}N_{16}$	(approx.)
Red	$C_{39}H_{31}O_{17}N_{18}$	

Table I	Yellow Compound (A)
Treatment	Result
Ac_2O in the cold	Acetyl deriv. m.p. 216°
Na in pyridine or glycol dimethyl ether	No action
Test for methoxyl	Negative
Furfuryl alc. and EtOH/HCl	Gives 'B' and ethyl laevulinate
Dilute NaOH	Soluble - red solution
Conc. acid	Soluble - yellow solution
Reflux in EtOH/HCl	Ethyl laevulinate DNP, and "80° compound".
Reflux in MeOH/HCl	Methyl laevulinate DNP
Methyl ethyl ketone, MeOH/HCl	Methyl ethyl ketone DNP methyl laevulinate DNP
Hydrogenation, PtO_2	Red gum, soluble in water and solvents. Gave black amorph. ppt. with NaOH. No deriv. with picric acid.

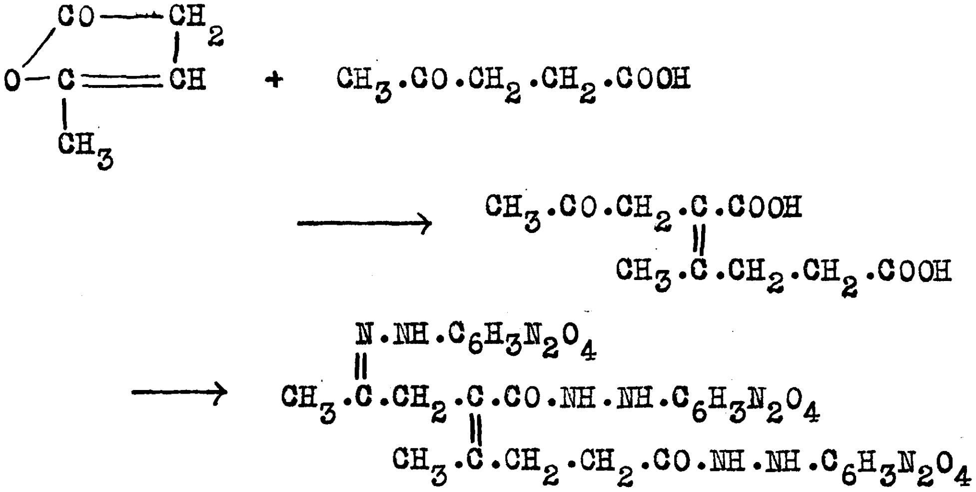
Table II	Red Compound (B)
Treatment	Result
Ac_2O in the cold	Mostly unchanged.
NaOH in aqueous acetone	Royal blue solution
Reflux with 7% NaOH	Unchanged
Reflux with MeOH/HCl	Unchanged
Alkaline $KMnO_4$	Yellow oil, positive carbonyl test

Downing and Woods both proposed several hypothetical structures for 'A' and 'B', but these were all disproved, either by the analysis figures, or the reactions of the two compounds. Downing's first suggestion as to the structure of 'A' was the tetrahydrazone of a trimeric form of δ-hydroxylaevulinaldehyde. Abstraction of dinitrophenylhydrazine from this by laevulinic acid, followed by cyclisation of the laevulinic acid DNP gave a pyridazine derivative which was 'B'. These structures, however, did not agree with the analysis results. His next suggestion for 'A' was the bis-DNP of δ-methoxylaevulinaldehyde. This might lose the terminal DNP residue, and dismute to methyl laevulinate DNP, or might cyclise to form various ring structures, of which the most likely was



This theory was untenable because of the absence of methoxyl radical in 'A', and also because the same products are obtained when the reaction is carried out in ethanol solution.

Woods demonstrated that 'A' is neither an amino-acid salt nor an ester. He suggested that the furfuryl alcohol first forms angelicalactone, according to the mechanism of Tchitchibabine$^{(3)}$, part of which is converted to laevulinic acid. An aldol condensation between the two occurs, followed by opening of the lactone ring to give a dibasic keto-acid, which then reacts with three molecules of dinitrophenylhydrazine to form a hydrazone hydrazide.



$$+ \; CH_3.CO.CH_2.CH_2.COOH$$

$$\longrightarrow \; CH_3.CO.CH_2.\underset{\underset{CH_3.C.CH_2.CH_2.COOH}{\|}}{C}.COOH$$

$$\longrightarrow \; CH_3.\overset{\overset{N.NH.C_6H_3N_2O_4}{\|}}{C}.CH_2.\underset{\underset{CH_3.C.CH_2.CH_2.CO.NH.NH.C_6H_3N_2O_4}{\|}}{C}.CO.NH.NH.C_6H_3N_2O_4$$

This formulation also failed to explain the experimental facts. Woods made no suggestion as to the structure of 'B'.

DISCUSSION.

This investigation has added little to the elucidation of the problem. Both the compounds 'A' and 'B' are of high molecular weight, and probably possess complex structures, which appear to be completely broken down by most of the degradative methods employed, yielding fragments from which little information can be gained.

Since both compounds are almost certainly dinitrophenylhydrazones or hydrazides, a fact which explains their insolubility and high molecular weights, an attempt was made to simplify the reaction by replacing 2:4-dinitrophenylhydrazine with phenylhydrazine itself, but only tarry products were obtained, much of the phenylhydrazine being recovered unchanged. This suggests that the original reaction is "frozen" by the insolubility of the products in methanol.

Some of Woods's and Downing's work was repeated, but with similarly inconclusive results. Hydrolytic decomposition of 'A' by refluxing with methanolic hydrochloric acid was found, as in Woods's experiments, to yield methyl laevulinate DNP. When the latter was chromatographed on an alumina column in an attempt to isolate impurities, decomposition occurred on the adsorbent, and not even the methyl laevulinate DNP could be isolated from the eluate. Refluxing in ethanolic hydrochloric acid gave ethyl laevulinate DNP and Woods's "80^{0} compound". This almost certainly contains ethyl laevulinate DNP, probably a proportion of unchanged 'A', and possibly the yellow volatile compound m.p. 124.5^{0} obtained by chromatographic adsorption; although, in view of the above result with methyl laevulinate DNP, the yellow compound may be a decomposition product formed on the adsorbent.

When the acid hydrolysis was repeated using n-propanol, the main product was propyl laevulinate DNP. In aqueous dioxane, however, the only isolable compound was a very high melting amorphous brown solid, which gave a weak positive reaction with Pechmann's test(8) for osazones, and possessed the interesting "indicator" characteristics described on p.84 , and exhibited also by the similar compound obtained by dichromate oxidation of 'A'. The other products of this oxidation were 2:4-dinitrophenol, m-dinitrobenzene, and a yellow gum which, although isolated by means of Girard's carbonyl reagent, appeared to give no derivative with dinitrophenylhydrazine. Secondary oxidation of products was relatively slow, and a very small excess of the reagent was sufficient to oxidise all the amount of 'A' used. 'B', on the other hand, was completely broken down by this treatment, and reduced a much greater proportion of dichromate than was necessary to cleave the hydrazone links. Alkaline permanganate, however, yielded dinitrophenol, and a yellow oil as reported by Downing. Contrary to his report, this was found not to regenerate 'B' on treatment with dinitrophenylhydrazine, the product melting at 312-314°.

Since the presence of the DNP residue appeared to be complicating the problem, an attempt was made to remove this part of the molecule with an α-dicarbonyl compound, as recommended by Strain(7). It was hoped in this way to obtain a free aldehyde or ketone. Diacetyl was found to be without effect, and glyoxal only reacted in presence of hydrochloric acid, which is a complicating factor in view of the results already obtained with this reagent alone, and the possibility of "aldol" type condensations as a secondary reaction. No carbonyl compound was identified, but the results suggest that one of the four DNP residues in 'A' is an integral part of the molecule, and is unaffected both by glyoxal and by alcoholic hydrochloric acid. Additional experiments failed to shed any light on the situation, however, and in view of these confusing results, further discussion at this point can be of little value.

A condensed account of the experimental work follows:

EXPERIMENTAL.

All melting points are corrected, unless otherwise stated.

Preparation of Yellow Compound(A).

Following Woods's procedure, 58.82 g. (0.297 mole) of 2:4-dinitrophenylhydrazine and 25 ml. of 37% hydrochloric acid (0.297 mole) were refluxed in 1900 ml. of methanol in a 5 l. three-necked balloon flask fitted with a stirrer and reflux condenser, and 14.5 g. (0.148 mole) of freshly distilled furfuryl alcohol added. Refluxing was continued for 1 hour, during which an orange flocculent precipitate separated, which was filtered cold and washed with methanol - 40 g., m.p. 208-216°. 20 g. of this precipitate was extracted in a Soxhlet with 400 ml. of acetone for several days, yielding a dark red solution, and an orange flocculent solid. Repeated crystallisation of the solid from acetone, and decolourisation with charcoal gave 8 g. of relatively pure 'A', m.p. 223-224° (with decomposition).

In later preparations, a greater yield of crude product was obtained by adding the furfuryl alcohol dropwise, and cutting reaction time to 35 minutes.

Also, a greater recovery of pure 'A' (35 g. from 50 g. of crude) was obtained by substituting repeated crystallisation from acetone for the Soxhlet extraction.

Preparation of Red Compound (B).

Again following Woods' directions, 36.6 g. (0.36 mole) of furfuryl alcohol was added to the refluxing mixture of 72 g. (0.36 mole) of 2:4-dinitrophenylhydrazine, 30.3 ml. of concentrated hydrochloric acid (0.36 mole) and 1800 ml. of methanol, and refluxing continued for 6 hours. The mixture was filtered cold, yielding 58 g. of a brown-red powder, m.p. 132-220°. This was partially purified by Soxhlet extraction with acetone, the extract yielding methyl laevulinate DNP in quantity. This treatment failed to raise the melting point sufficiently, however, and the purification was continued by repeated boiling out with acetone, followed by repeated crystallisation from pyridine, with decolourising charcoal. This finally yielded 10 g. of apparently pure 'B', melting with decomposition at 262-263° (uncorrected).

Phenylhydrazine Run.

14.5 g. (0.1 mole) of phenylhydrazine hydrochloride and 8.5 ml. (0.1 mole) of concentrated hydrochloric acid were refluxed in 500 ml. of methanol, and 4.9 g. (0.05 mole) of freshly distilled furfuryl alcohol added dropwise. The solution rapidly darkened, becoming almost black, and no precipitate had appeared after 1½ hours' refluxing. Addition of ether precipitated phenylhydrazine hydrochloride, and only tarry, non-distillable products could be obtained from the mother liquors.

Action of Bromine in Carbon Tetrachloride.

No decolourisation was observed when a few drops of 5% bromine in carbon tetrachloride were added to pyridine solutions of 'A' and 'B'. With 'B', the solution slowly turned very dark red, but no further change occurred. This seems to indicate that there is no non-aromatic unsaturation in either of the molecules, although interaction with the pyridine to form pyridine perbromide may be complicating the situation.

Degradation of 'A' by EtOH/HCl Reflux.

(1) Since Woods considered this to be his most promising line of attack, his work was repeated. 1.5 g. of 'A' was refluxed for 18 hours in 150 ml. of 95% ethanol 0.4 N in hydrochloric acid, giving an orange-red solution. After cooling 8 hours in the refrigerator,

0.7 g. of orange crystals was obtained, m.p. 77-78.5°. This was presumably Woods's "80° compound". It was dissolved in 25 ml. of hot alcohol, filtered from a brown amorphous residue, boiled with charcoal and filtered hot. The solution deposited 0.45 g. of orange needles which melted diffusely from 77.5° to 100.5°. These were recrystallised from alcohol in three fractions:-

(i) Orange needles, m.p. 78-98°
(ii) Yellow-orange needles, m.p. 79-79.5°
(iii) Yellow prisms, m.p. 92-96°.

(ii) was apparently the eutectic mixture of the compounds approximating to (i) and (iii). The latter, after several recrystallisations, proved to be ethyl laevulinate DNP, m.p. 97-98°, thus confirming Woods's findings.

Exhaustive attempts were made to purify fractions (i) and (ii) by crystallisation and extraction with various solvents, but in all cases, mixtures were obtained, melting over the range 75-105°. Sometimes orange and yellow crystals were deposited together, but both were apparently mixtures, and no pure compounds could be obtained. A micro melting point determination showed that the orange component of the mixture of crystals melted at 82-110°, while the yellow crystals melted from

106-122°. The latter were present in too small quantity to make manual separation practicable, however. An attempt was made to separate them by vacuum sublimation at 118°C and 7 m.m. pressure, but the mixed crystals actually yielded homogeneous orange sublimates.

Since separation seemed impossible by these methods, a chromatographic separation was attempted. A separation of dinitrophenylhydrazones is reported by Strain(7) on a column of alumina, and accordingly, a glass tube, 25 x 1 cms., was packed with "Alorco" 80-200 mesh activated alumina. The various crystal fractions obtained above were combined, dissolved in 60-70° ligroin and benzene (10:1) and dried with potassium carbonate. The latter appeared to adsorb one of the components, but only a slight yellow scum was obtained by dissolving the carbonate in acid and extracting with ether.

The solution was run on to the column, giving a black adsorbate, and developed with pure benzene. A slow separation into two dark brown bands and a yellow area at the top, was obtained. Pure methyl laevulinate DNP was found to be adsorbed on alumina from benzene, giving a similar dark brown adsorbate, turning yellow in ethanol. The same behaviour was noted with dinitrophenylhydrazine itself, and these colours may be fairly general for this class of compounds. The first brown band was washed through with benzene, its colour lightening in the process (Band I).

During this development, the second brown band slowly became lighter in colour, and by the time Band I was washed clear, had become almost imperceptible, and appeared to have stopped moving. Since it had not yet separated from the yellow area, development was continued, the solvent being changed to 95% alcohol. The second band became yellow in the ethanol, and a slow separation into two yellow bands was achieved. The lower one (originally the second brown band) was washed through (Band II).

The column was then extruded and eluted with aqueous alcohol, giving a yellow solution (Band III).

Band I. The benzene was distilled off at 40 m.m. pressure, and the residue crystallised from 60-70° ligroin, giving a mixture of orange and yellow needles, m.p. 119-125°. Recrystallisation from twice the volume of ligroin gave a mixture of:-

(i) clear yellow prisms

(ii) small yellow needles

(iii) large orange needles.

A micro melting point determination showed that (i) melted with sublimation at 120-124.5°, (ii) slowly disappeared completely at 110°, and (iii) melted from 118-124.5°. The mixture was again crystallised from ligroin, but the proportion of orange needles seemed even greater, possibly indicating a chemical change on refluxing in ligroin.

Owing to their small size, manual separation of the crystals was impossible, so the mixture was divided into two parts, A and B.

A. This portion was dissolved in 60-70° ligroin, run on to another column of alumina, and developed very slowly with ligroin. A dark brown band was obtained, slowly turning dirty yellow, while a purple-grey band separated from it. The column was extruded, the bands removed and eluted with alcohol. The purple-grey band yielded a mixture of yellow needles and tufts melting diffusely, while the brown band gave the same mixture of orange and yellow crystals as before.

In view of these results, it is thought certain that some chemical change is occurring on the alumina, causing the slow change in colour noted above.

B. These crystals were vacuum-sublimed at 7 m.m. pressure in a bath of refluxing acetic acid (118°).

Nearly all the substance had sublimed after 10 hours, leaving traces of a black amorphous dirt. The sublimate consisted of a fine yellow powder, on which were stuck a mixture of large orange prisms and yellow needles.
These were easily detached and separated manually. In a micro melting point, the yellow crystals started subliming at 112°, melting sharply at 124.5°, while the orange ones melted from 121-124.5°. The yellow substance looked perfectly homogeneous under the polarising microscope, and is apparently a pure compound, but there was insufficient material for a micro-analysis.

Band II. The alcohol solution was concentrated to 24 ml. Addition of water caused a greenish cloudiness, but no precipitate, while one drop of concentrated hydrochloric acid yielded a bluish opalescence. Heating the alcoholic solution turned it from yellow to deep orange.

Addition of ether precipitated 30 mg. of a bright yellow flocculent substance, which exploded with a yellow flash when heated on a nichrome spatula. This was found, by rapid heating in an air-bath, to occur at c. 320°.
If it was first moistened with a drop of concentrated sulphuric acid, the explosion was prevented, and the compound burned away, leaving a dark solid residue, which indicates the presence of inorganic material.

The substance was found to be soluble in water, giving a yellow solution which became colourless on acidification. The bulk of it was therefore dissolved in 5 ml. of water, and acidified with concentrated hydrochloric acid, when 10 mg. of a pale flocculent precipitate was obtained. This substance now exploded at 195° with rapid heating, and could be crystallised from alcohol in long buff needles.

A similar substance is reported by Strain(7) as being formed by heating dinitrophenylhydrazine in sodium carbonate solution, and acidifying. His experiment was repeated, when 406 mg. of the hydrazine was found to yield 343 mg. of a buff compound with all the properties of that obtained from the chromatogram. This compound is therefore derived solely from dinitrophenylhydrazine. There remains the question as to whether the decomposition occurred on the column, or whether Strain's compound was present in the original "80°-compound". Since it is obtained by alkaline, rather than by acid decomposition of the hydrazine, the former suggestion seems the more feasible. Strain himself recommends alumina for the separation of DNP's, adding that basic columns such as magnesium oxide cause decomposition, but since this chromatogram was so slowly developed, alkaline decomposition could have occurred here also.

Since this compound was first obtained as a salt, the acid aqueous solution, after ether extraction, was tested for aluminium ion, but a negative result was obtained.

Band III. Concentration gave 50 mg. of a yellow solid m.p. 188-204^{o} (decomp.). It dissolved in ether, and if the solution was shaken with caustic soda solution, a wine-coloured aqueous layer was obtained, a reaction characteristic of the pure "yellow compound" (m.p. 226^{o}). Recrystallisation only raised the melting point to 200-205^{o}, while a mixture with 'A' melted at 180-198^{o}. The identity of this impure yellow substance is still unknown, but it is believed to contain a proportion of 'A'.

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(2). It was decided to repeat the chromatographic separation in an attempt to obtain more of the yellow compound melting at 124.5^{o}. Accordingly, 1 g. of 'A' was refluxed for 50 hours in 100 ml. of 95% ethanol 0.5 N in hydrochloric acid. 50 ml. of benzene was added, the mixed solvents distilled off till 20 ml.

remained, then more benzene added and distillation continued till no water appeared in the distillate. The benzene solution was filtered and run on to an "Alorco" column, and developed with benzene, then alcohol, giving three bands as before. None of these bands yielded a pure compound, however, and this method of separation was abandoned.

(3). It was thought possible that no decomposition would occur on an acid adsorbent such as silicic acid. Accordingly, 0.5 g. of 'A' was refluxed for 100 hours in ethanolic hydrochloric acid as before, concentrated to 25 ml., and cooled in the refrigerator, giving 250 mg. of orange crystals m.p. 94-96°. These were dissolved in 30 ml. benzene, and run on to a column composed of Merck's silicic acid and "Hyflo Super Cel" brand of celite (2:1 by weight), and developed under strong suction with benzene. Several orange and yellow bands were obtained, but could not be fully separated. The solution of the first two rough bands was run on to a column of pure silicic acid, but owing to the very strong adsorption, this column could not be developed with any solvent. This method had also finally to be abandoned.

Degradation of 'A' by MeOH/HCl Reflux.

(1). 0.5 g. of 'A' was refluxed for 20 hours in 50 ml. of methanol 0.5 N in hydrochloric acid, and allowed to stand overnight, when 0.25 g. of orange crystals, m.p. 127-130° separated. Crystallisation from methanol with charcoal raised the melting point to 140-141°, and a mixed melting point showed this substance to be pure methyl laevulinate DNP. This confirms the result obtained by Woods. A further crop of impure ester DNP was obtained from the reaction mother liquors, but the "impurity" could not be isolated by crystallisation methods.

(2). 1 g. of 'A' was refluxed for 50 hours in 100 ml. of acid methanol. The methanol was replaced by benzene, and the solution run on to a column of alumina, and developed with benzene, then ethanol. As with the ethanol runs, development was very slow, and although several bands were obtained, none of them yielded a pure compound. In view of the fact that methyl laevulinate DNP was easily isolated from the previous run, this is taken as further evidence that chemical decomposition is occurring on the alumina, and experiments with this technique were abandoned.

Degradation of 'A' by n-PrOH/HCl Reflux.

0.5 g. of 'A' was refluxed for 18 hours in 50 ml. of n-propanol 0.5 N in hydrochloric acid. Concentration and cooling yielded a crop of propyl laevulinate DNP, m.p. 62-63°, but nothing further could be isolated from the reaction mixture.

Degradation of 'A' by Aqueous HCl Reflux.

0.5 g. of 'A' was added to 50 ml. of 0.5N hydrochloric acid, a clear solution being obtained by addition of 50 ml. of dioxane, and the mixture refluxed for 22 hours. The solution turned black-brown, and deposited 0.15 g. of a dark amorphous precipitate, m.p. 360°. This was treated with charcoal in hot dioxane and filtered, giving a clear amber solution. Addition of 60-70° ligroin precipitated what appeared to be the same brown amorphous substance as before. This was moistened with ethanol, heated with a crystal of ferric chloride, and extracted with ether, giving a red-brown solution; which indicates that the brown substance may be an osazone(8), though the colour obtained was not distinctive enough to be conclusive.

This substance dissolved readily in sodium hydroxide solution, giving a deep wine-red colour, quite different from, and more intense than that obtained with pure 'A'. The solution was turned pure yellow by hydrochloric acid at pH9-pH7, the colour change being indefinitely reversible. These "indicator" characteristics were shown by a similar brown amorphous substance obtained by dichromate oxidation of 'A' (see p. 86), though, of course, this does not prove their identity.

Concentration of the reaction mother liquor gave more of this brown substance, plus traces of crystalline material which could not, however, be obtained pure.

Dichromate Oxidation of 'A'.

Compounds 'A' and 'B' are apparently phenylhydrazones of some kind, which can often be split across the hydrazone linkage by oxidising agents, giving free carbonyl or carboxy groups.

(1). Preliminary run. 0.989 g. of potassium dichromate (0.01 atoms of O_2) was dissolved in 100 ml. of water and 50 ml. of concentrated sulphuric acid, and 1 g. of 'A' (approx. 0.004 carbonyls) was added, causing the solution to change colour slowly with effervescence from orange to green. It was then heated for 30 minutes on the hot plate to 90°, when the smell of acetic acid became noticeable, indicating considerable decomposition. An orange precipitate which settled overnight was found to consist mainly of 2:4-dinitrophenol.

(2). It was decided to omit the heating in this run to reduce secondary oxidation of the reaction products.

1.5 g. of potassium dichromate (0.015 atoms of O_2) was dissolved in 40 ml. of water, 25 ml. of concentrated sulphuric acid added, and the solution cooled in ice-water. 1 g. of 'A' (c. 0.004 carbonyls) was added, dissolving with a brisk effervescence, which was followed by a further slow effervescence, probably indicating slow secondary oxidation of the products of the first rapid reaction. After 20 minutes, the solution was diluted to 200 ml., cooled in ice and filtered from a crystalline precipitate (a). It was then extracted with three 50 ml. portions of ether (b) and the aqueous solution set aside for 1 hour; after which a further quantity of crystals had separated and were added to (a). The combined precipitates weighed 160 mg. and were almost pure 2:4-dinitrophenol. The aqueous solution was then continuously extracted with ether for 48 hours, and the yellow ether solution added to solution (b).

The combined ether solutions were shaken with 50 ml. of 2% NaOH solution, which, on acidification, yielded a further 90 mg. of dinitrophenol, along with traces of a red acid substance. (0.25 g. of dinitrophenol isolated altogether.) Extraction with a further 20 ml. of NaOH solution gave a red aqueous layer, which was turned yellow on addition of acid. Ether extraction of the acid solution yielded an extract which, on concentration, was found to contain a brown, amorphous high-melting solid, very similar to that obtained by refluxing 'A' in aqueous acid, and giving the same colour changes at the same pH values (see p.84).

The remaining ether solution, after alkaline extraction, was found to give a positive test for the carbonyl group, and was therefore evaporated to dryness, and the residue treated with Girard's reagent "P", and the aqueous solution extracted with ether (c). The Girard complex, on decomposition, yielded a small quantity of yellow gum, which, surprisingly, appeared to give no reaction with 2:4-dinitrophenylhydrazine, and could not be characterised.

The ether solution (c) was concentrated and the solid residue (168 mg.) dissolved in alcohol. After three crystallisations, the melting point became constant at 89-90°. The substance consisted of long pale-yellow fibrous needles, which burnt with a smoky flame. It gave a positive test for nitrogen on sodium fusion, and yielded a purple colour with sodium hydroxide in aqueous acetone, indicating two nitro-groups. It caused no depression in the melting point of a sample of pure m-dinitrobenzene, and the compounds are concluded to be identical.

Dichromate Oxidation of 'B'.

5 g. of potassium dichromate (0.05 atoms of O_2) was dissolved in 100 ml. of water and 50 ml. of concentrated sulphuric acid, and 4 g. of 'B' added (c. 0.017 carbonyls). A brisk effervescence ensued, lasting for several minutes. A red solid was still present, and this was dissolved by addition of another 80 ml. of sulphuric acid. No further reaction occurred, however, and the solution was poured into 300 ml. of water, giving a bright scarlet precipitate, and a pure green solution, indicating that all the dichromate had been reduced. The red precipitate proved to be 2.1 g. of starting material, and since an apparent excess of oxidising agent had been used, this indicated that much more extensive oxidation than simple fission of the hydrazone links had occurred. The solution was extracted continuously with ether for 50 hours, giving a red extract. This ether solution was shaken with sodium hydroxide solution, to remove acidic compounds, which caused such extensive

tarring that this experiment had to be ultimately abandoned.

Permanganate Oxidation of 'B'.

Following Downing's procedure, 1.175 g. of 'B' (c. 0.0045 carbonyls) was dissolved in 80 ml. of acetone, 25 ml. of 10% sodium hydroxide solution and 90 ml. of water, and the acetone removed under vacuum. The resulting 110 ml. of red liquid was cooled to 0°. 1.1 g. of potassium permanganate (0.01 atoms of O_2) in 1% aqueous solution was added from a burette with stirring, during 2 hours, and stirring continued for a further hour. The solution was still red, possibly indicating incomplete oxidation.

The mixture was continuously extracted with ether for 63 hours, and the extract washed with a little dilute sodium hydroxide solution, then water, and dried with potassium carbonate. The ether was removed under partial vacuum in a fractionating Claisen flask, giving 7.5 mg. of yellow-brown oil. This gave a positive test for the carbonyl group, and was therefore treated with 20 mg. of 2:4-dinitrophenylhydrazine in ethanolic hydrochloric acid, giving 7.3 mg. of a yellow flocculent precipitate, m.p. 310-313° (decomp.). After boiling out with 15 ml. ethanol, it melted at 312-314°. A mixture with glyoxal bis-DNP (m.p. 309-310°) melted at 303-305° (all uncorrected), but this is not considered conclusive of identity or non-identity. According to Downing, this oil gave back pure 'B' (m.p. 274°) on treatment with dinitrophenylhydrazine, but this is obviously not the case.

Only dinitrophenol could be isolated from the aqueous solution.

Hydrogenolysis of 'A'.

Preparation of Copper Chromite(9). Prepared from 26 g. (0.1 mole) of barium nitrate, 218 g. (0.9 mole) of copper nitrate, 126 g. (0.5 mole) of ammonium dichromate and 150 ml. of concentrated ammonia, in 1400 ml. of water. The red precipitate was ignited in a muffle at 500°, and the crude product purified by leaching with 10% acetic acid and washing with water.

Purification of Dioxane. 1500 ml. of crude dioxane was refluxed with 10% of its weight of N hydrochloric acid for 12 hours, a stream of air being led through the solution to expel the acetaldehyde formed. It was then extracted with strong sodium hydroxide solution, and dried overnight with sodium hydroxide pellets. Several pieces of sodium were added to the decanted dioxane, and the liquid refluxed till a blue colour was obtained with benzophenone. The pure solvent was finally distilled under nitrogen into a bottle containing sodium wire.

Standardisation of Hydrogenator. A steel bomb of about 250 ml. capacity was employed, fitted with an electric heating coil and a mechanical rocker, and hydrogen was taken from a cylinder without extra boosting, giving a pressure of about 1200 p.s.i. 58 g. (1 mole) of acetone was employed as a standard with 1.5 g. catalyst. Quantitative hydrogenation occurred in 10-15 minutes at 130°C. and 1200 lbs. Pressure drop per mole of hydrogen absorbed for 73 ml. contents was found to be about 550 lbs. at 25°C. when initial pressure was 1200 lbs.

Hydrogenolysis.

10 g. (c. 0.014 moles) of 'A' and 1.5 g. of copper chromite in 75 ml. of dioxane were placed in the bomb, and hydrogen introduced at 1200 p.s.i. The shaker was started, and the pressure fell 50 lbs., then remained constant. It was again raised to 1200 lbs. and the heater switched on. The pressure was found to fall 200 lbs. at 25°C., equal to c. 0.5 mole of hydrogen absorbed, the reaction taking just under 1 hour. The

reaction mixture smelled strongly of ammonia, and was opaque brown after filtration from the catalyst.

The dioxane was taken off at 12 mm. pressure, and the brown residue dissolved in 200 ml. of 95% acetic acid, giving a deep ruby red solution. A portion of this red liquid was diluted with a little water, and solid sodium hydroxide added, causing the solution to turn yellow. This colour change is, however, the opposite of that noted previously with the high melting brown substance isolated in the dichromate oxidation of 'A'.

About 10 g. of chromium trioxide was added to the acetic acid solution with stirring, during 5 hours, the solution heating up during the process. It was filtered, and the acetic acid removed through a column, leaving a black, and apparently highly polymerised residue. This was shaken up with water, giving 250 ml. of a black solution, and a tarry residue. It was made alkaline with sodium hydroxide, when the whole mixture rapidly set to a thick jelly. The experiment had to be abandoned at this point when the entire investigation was discontinued.

Action of Diacetyl on'A'.

(1). 200 mg. of 'A' in 80 ml. of methanol plus 25 ml. of dioxane was refluxed for 2 hours with 475 mg. (0.005

mole.) of freshly distilled diacetyl, but no change was noted after 2 hours. A further 2 g. of diacetyl was added, and refluxing continued for 30 hours, but no reaction was observed.

(2). 200 mg. of 'A' was heated in a sealed tube at 180-200° for 3 hours with 0.5 g. (0.006 mole) of diacetyl in 30 ml. of dioxane, but no diacetyl bis-DNP was isolated from the reaction mixture.

Action of Glyoxal on'B'.

3 mgs. of 'B' was dissolved in 10 ml. of boiling benzyl alcohol, two drops of 30% glyoxal in 3 ml. benzyl alcohol added, and the solution refluxed, but no action could be detected either then or after addition of 10 drops of concentrated hydrochloric acid.

Action of Glyoxal on 'A'.

(1). In preliminary tests, no measurable reaction between 'A' and glyoxal was found to take place in methanol-dioxane unless the solution was made fairly strongly acid with hydrochloric acid. Under these conditions, the glyoxal is rapidly destroyed, and it was therefore necessary to add this reagent slowly, giving each lot time to react. It was also found impracticable to run the reaction in concentrated hydrochloric acid due to the colloidal nature of the precipitate obtained.

(2). It was decided to make this run roughly quantitative in order to estimate the proportion of "DNP residue" removable as such, in an attempt to see if this residue retained its identity in the molecule of 'A'. 223.6 gm. of 'A' was dissolved in 25 ml. of 95% ethanol and 2 ml. of concentrated hydrochloric acid on the steam-bath, and 0.4 g. of 30% glyoxal (0.002 mole) added dropwise during the course of 30 minutes, with frequent shaking. The orange precipitate was filtered off, and washed with ethanol. The mother liquors were again refluxed, and several drops of glyoxal added, when a further small quantity of osazone was obtained. The precipitates were combined and dried, and found to weigh 138.0 mg. After boiling with 100 ml. of ethanol, drying 40 minutes in the 100° oven and cooling in a dessicator, the weight was found to be 137 mg. The melting point was 309-310°, whereas an authentic sample melted at 315-316°. A mixture of the two melted at 310-311° (all uncorrected), however, and their identity is assumed.

138 mg. glyoxal DNP contains 126 mg. DNP residue.

$\therefore$ 'A' contains $\frac{126 \times 100}{223} = \underline{\underline{56.5\%}}$ "removable" DNP residue. Analysis of 'A' gives the empirical formula $C_{36}H_{35}N_{16}O_{17}$. Assuming four DNP residues, the proportion of DNP should be $\frac{784 \times 100}{963} = \underline{\underline{81.4\%}}$.

Among the possibilities for this discrepancy, are (i) handling losses, (ii) incomplete reaction, (iii) not quantitative reaction, (iv) all dinitrophenylhydrazine not present as such in the molecule of 'A'. For example, if only three of the residues were removable as such, the proportion would be $\frac{588 \times 100}{963} = 61.06\%$, which is in fairly good agreement with the experimental value, considering the crudeness of the experiment, and the fact that the formula of 'A' may be only approximate. This would seem to indicate that at least one of the DNP residues no longer retains its hydrazone character in the molecule of 'A', and is probably part of some form of stable ring structure. It also helps to fix the molecular weight of 'A', since it is presumably impossible to remove half of a DNP residue.

No compound corresponding to the remaining part of the molecule could be isolated, however. The reaction mother liquors were concentrated under reduced pressure to 7 ml., and filtered from a dark brown solid of high melting point. This gave a royal blue colour with sodium hydroxide in aqueous acetone, a reaction given by glyoxal bis-DNP. It weighed just over 1 mg.

The filtrate was shaken with solid sodium bicarbonate till effervescence ceased, filtered, and the alcohol removed on the steam-bath. The residue was then heated under vacuum, when a few drops of an oily liquid distilled. This smelled strongly ketonic, like benzylacetophenone, but treatment with dinitrophenylhydrazine yielded only glyoxal bis-DNP.

The residue was placed in a Hickmann molecular still, fitted with a butyl phthalate diffusion pump, and heated on a sandbath to 110° at 0.2-0.5μ pressure. A few yellow oily drops distilled during the course of an hour, and were dissolved in ether, but again, only glyoxal could be detected (as DNP).

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THE ALKALOIDS OF BAPTISIA MINOR, LEHM.

The Alkaloids of Baptisia Minor, Lehm.

SUMMARY.

Baptisia Minor, Lehm.has been found to contain six alkaloids, one of which, baptifoline, appears to be new. This alkaloid content is different from that of B. australis, and the non-identity of the two plants is considered proved.

DISCUSSION.

There has long existed some confusion, on purely taxonomical grounds, as to the identity or otherwise of Baptisia minor, Lehm., and B. australis. B. minor is blue-flowered like B. australis, but smaller-leaved, and although the two had been originally considered as specifically distinct, they were for many years thought to be identical. Recently (1) B. minor has again been claimed to be a species (B. vespertina), then a variety of B. australis(2), and finally, it has been restored to specific rank(3). It therefore seemed of interest to compare the alkaloids of this plant with those found in B. australis(4), already investigated. The results of the chemical study now reported support the recent taxonomical evidence that the plants are specifically distinct.

In common with B. australis, B. minor contains d-sparteine, cytisine, and N-methyl cytisine, but it also contains anagyrine, alkaloid P4, and baptifoline, all of which are absent in the former. While alkaloid P4 is present in insufficient amount to permit satisfactory characterisation, baptifoline, a new alkaloid which was simultaneously discovered in B. perfoliata(5), seems to be the main alkaloid of B. minor, and has been characterised by the preparation of a number of derivatives. The base itself is difficult to crystallise, seeming to undergo some decomposition during the process, and is therefore best purified by means of one of its salts, particularly the perchlorate. Analysis figures were obtained for the free base and a number of salts, but failed to distinguish conclusively between three possible formulae (see table p.100). The molecular weight of the free base was found to be about 244 (as compared with 260 for $C_{15}H_{20}O_2N_2$) as obtained from the vapour pressure of an alcoholic solution, measured in a sensitive differential manometer(7); and indeed, this formula is considered more probable than the two of higher molecular weight.

A simplified account of the experimental work follows.

Deriv.	Found	Calc. for $C_{15}H_{20}O_2N_2$	Calc. for $C_{32}H_{42}O_5N_4$	Calc. for $C_{33}H_{44}O_5N_4$
Free Base	C, 68.83, 68.63 H, 7.44, 7.60 N, 10.74, 10.60	69.18 7.74 10.76	68.29 7.53 9.96	68.73 7.69 9.72
Perchlorate	C, 50.75, 50.55 H, 6.00 5.93 N, 7.25, 7.14	49.91 5.86 7.76	50.31 5.80 7.34	50.95 5.96 7.21
Hydrochloride	C, 60.68, 60.86 H, 6.98, 7.02 N, 8.83, 8.68	60.67 7.12 9.44	60.45 6.97 8.82	61.01 7.14 8.63
Picrate, solvated	C, 50.82 H, 5.01 N, 12.38, 12.54	50.66 5.22 13.44	50.91 5.20 12.91	51.36 5.32 12.75
Picrate, after drying	C, 51.30, 51.45 H, 4.33, 4.43 N, 12.69, 12.83	51.52 4.73 14.31	51.75 4.74 13.72	52.23 4.87 13.54

EXPERIMENTAL.

All melting points are corrected, unless otherwise stated. Since many of the compounds involved, such as perchlorates, melt with decomposition, the "melting points", though reproducible, may vary as much as 20° according to conditions, or even with the individual operator. The figures quoted may therefore differ from those given by other workers, but identity was in all cases confirmed by a melting point determination of a mixture with an authentic sample.

The dried and ground plant material (2157 g.) was extracted in Soxhlets with methanol, and the extract concentrated on the steam bath to a thick oil. This was digested with hot 10% hydrochloric acid, and the solution filtered through a charcoal pad. Non-basic material was removed by ether extraction (A), the solution basified with ammonia, and extracted with chloroform (B), to yield a solution of crude alkaloids.

Isolation of a neutral substance.

The ether extract (A) on evaporation, yielded a compound which crystallised from boiling methanol in rosettes of pale yellow needles, m.p. 231°. This substance, which is soluble in aqueous sodium hydroxide, was not further investigated. Found: C, 50.70, 50.86;

H, 5.17, 5.05. $C_{12}H_{14}O_8$ requires C, 50.35; H, 4.82.

The chloroform extract (B) was concentrated to a thick oil, the crude alkaloids (14 g.) digested with 1 l. of 10% hydrochloric acid on the steam bath, and the solution extracted thoroughly with ether. The acid solution was again filtered through a charcoal pad, basified with ammonia, and extracted repeatedly with chloroform, finishing up with 30 hours on a continuous liquid-liquid extractor. Removal of chloroform from the extract left the bases as a brown gum (6 g.) which was subjected to fractionation in a Späth distillation apparatus at c. 0.1 mm. pressure, to yield the following fractions:-

I b.p. up to 130°
II b.p. 130-165°
III b.p. 165-185°
IV b.p. 185-230°
V a tarry residue.

The residue was redissolved in acid, purified by extraction and filtration as before, and the free bases liberated and redistilled, yielding a further considerable distillate, the fractions of which were combined to the corresponding fractions of the first distillation.

d-Sparteine.

Fraction I consisted of a yellow oil, which on cooling, separated into two layers, the upper one colourless, the lower one yellow. No mechanical separation was attempted, but the oil was dissolved in methanol, and treated with a methanolic solution of twice its own weight of picric acid. A solid picrate separated immediately, which, after several recrystallisations from a large volume of boiling methanol, was obtained as long yellow needles, m.p. 207-208°. Admixture with an authentic sample of l-sparteine dipicrate lowered the melting point by 12°, but no depression was observed on mixing with d-sparteine dipicrate.

A portion of the picrate was decomposed with hydrochloric acid, and the picric acid removed by ether extraction. The free base was liberated with ammonia, extracted with chloroform and redistilled at 80-90°/0.1 mm., being obtained as a water-white oil, having α_D^{20} = +17.01° (c = 1.029 in abs. ethanol). This is in agreement with the known value for d-sparteine.

A small quantity of the free base was dissolved in methanol, and the solution made just acid to congo red by the dropwise addition of 65% perchloric acid.

The solution was evaporated almost to dryness on the steam bath, and a few ml. of water added, followed by a few drops of concentrated ammonia. d-Sparteine perchlorate crystallised almost immediately, and was purified by recrystallisation from methanol. Melting point either alone or after admixture with an authentic sample was 173°.

Further quantities of d-sparteine were obtained on refractionation of the mother liquors and residues from all the higher fractions. Total weight isolated - 390 m. (0.021%).

Cytisine.

Fraction II was obtained as an almost colourless oil, which crystallised in white needles on cooling. It dissolved slowly in refluxing ether, from which the free base crystallised on cooling in white needles, m.p. 150-155°. After recrystallisation from ether, the melting point was 155-156°, and was not depressed by admixture with an authentic sample of cytisine.

The ether mother liquors were evaporated to dryness, the residue dissolved in methanol, and treated with excess picric acid. The picrate which separated was recrystallised several times from boiling water, being finally obtained as feathery aggregates of yellow

crystals, melting at 288-289°, if introduced into the bath at 270° with fairly rapid heating. Admixture with authentic cytisine picrate failed to depress the melting point. Found: C, 48.54, 48.62; H, 4.18, 4.07. Calcd. for $C_{11}H_{14}ON_2,C_6H_3O_7N_3$: C, 48.70; H, 4.08
Total weight of cytisine = 270 mg. (0.015%).

Anagyrine.

Fraction III, a thick, yellow oil, was dissolved in methanol, and the solution neutralised to congo red with 65% perchloric acid. A colourless crystalline perchlorate started to separate before neutralisation was complete, which, after several crystallisations from methanol, was obtained as fine white needles, m.p. 299-301°, either alone or in admixture with an authentic sample of anagyrine perchlorate(6).
Found: C, 52.14; H, 6.24. Calcd. for $C_{15}H_{20}ON_2,HClO_4$: C, 52.23; H, 6.13.

The base from a small quantity of perchlorate was converted to the picrate, which was obtained as yellow prisms, m.p. 249-251°. The mixture with genuine anagyrine picrate (m.p. 252-253°) melted at 251-252°, and the two are considered to be identical.

Total weight of anagyrine = 34 mg. (0.002%).

Baptifoline.

Fraction IV was obtained as a viscous yellow oil which solidified to a glass on cooling. It was dissolved in methanol, and the solution neutralised to congo red with 65% perchloric acid. Addition of ether caused the separation of a brown oil, from which the supernatant liquid was decanted. A mixture of ether-ethyl acetate was added, and the flask cooled in dry ice with stirring, until the oil had solidified. The brown amorphous solid so obtained was boiled with a small quantity of methanol, which extracted the brown colour, leaving a white crystalline solid, m.p. 288-289°. This dissolved slowly in boiling methanol, from which it crystallised in hexagonal or triangular plates, m.p. 289.5° if introduced into the bath at 275°.
α_D^{16} = -89.05° (c = 1.415 in water). Found: C, 50.55, 50.75; H, 5.93, 6.00; N, 7.25, 7.14. $C_{15}H_{20}O_2N_2,HClO_4$ requires C, 49.91; H, 5.86; N, 7.76.

Some of the perchlorate was decomposed with ammonia and the free base extracted with chloroform and distilled, being again obtained as a yellow glass. On treatment with its own weight of picric acid in methanol, it yielded a crop of fine yellow needles which melted at 145° with evolution of gas, resolidified, and melted again at 256°. Both melting points remained unchanged after recrystallisation from methanol.

Found: C, 50.82; H, 5.01; N, 12.38, 12.54.

$C_{15}H_{20}O_2N_2.C_6H_3O_7N_3.CH_3OH$ requires C, 50.66; H, 5.22; N, 13.44.

Part of the sample was dried in vacuo in an Abderhalden pistol at 140°, to remove solvent of crystallisation.

Found: C, 51.30, 51.45; H, 4.33, 4.43; N, 12.69, 12.83. $C_{15}H_{20}O_2N_2.C_6H_3O_7N_3$ requires C, 51.52; H, 4.73; N, 14.31.

A portion of the picrate was decomposed with hydrochloric acid, and the picric acid removed by ether extraction. The solution was basified with ammonia, extracted repeatedly with chloroform, and the residue left after concentration of the extract distilled in vacuo. The distillate, which consisted of a mixture of a yellow glass and some white crystals, was dissolved in methanol. Addition of ether caused the separation of rosettes of small needles, which, after repeated crystallisation from methanol-ether, were obtained as rectangular prisms, m.p. 322-323°. A mixed melting point with a similar compound isolated directly from the higher distillation fractions showed the two to be

identical, and this was at first thought to be the free base corresponding to the two salts described above. Its solution in water gave the reactions for chloride ion, however, and preparation of the base hydrochloride showed them to be the same (see below). The hydrochloride is thus chloroform-soluble and distillable.
Found: C, 60.68, 60.86; H, 6.98, 7.02; N, 8.83, 8.68. $C_{15}H_{20}O_2N_2$·HCl requires C, 60.67; H, 7.12; N, 9.44.

The mother liquors from the hydrochloride deposited an obvious mixture of crystals from which the free base could not be obtained pure. The latter was isolated by decomposition of the perchlorate with ammonia, followed by chloroform extraction and distillation, and crystallised from acetone-ligroin in parallelogram-shaped plates, m.p. 210°. Further crystallisation tended to cause slow decomposition, and no purification could be achieved in this way. The base obtained by decomposition of the pure perchlorate had a sharp melting point, however, and appeared to be pure.
Found: C, 68.83, 68.63; H, 7.44, 7.60; H, 10.74, 10.60. $C_{15}H_{20}O_2N_2$ requires C, 69.18; H, 7.74; N, 10.76.
$\alpha_D^{18} = -147.7^{\circ}$. (c = 0.325 in abs. ethanol).

Some of the free base was dissolved in methanol and neutralised to congo red with methanolic hydrogen chloride, the solution concentrated to small volume and diluted dropwise with acetone to incipient turbidity. On standing, the solution deposited the base hydrochloride referred to above, in rosettes of small, colourless needles, m.p. 322-323°.

This base and its salts, in admixture with baptifoline isolated from B. perfoliata, and its corresponding salts, showed no depression in melting point.

The total weight of base isolated was 380 mg. (0.020%) but, as already noted, it appears to be rather difficult to purify in the free state, and this fact combined with the high temperature of distillation suggests that it constituted a much larger proportion of the total alkaloids, and is probably, in fact, the predominant base present.

N-Methyl Cytisine.

The mother liquors from the purification of the sparteine and cytisine fractions were combined, and the free bases redistilled, giving, besides further quantities of sparteine and cytisine, a yellow oil distilling at 130-145°/0.1 mm. This was treated with picric acid in methanol, giving a picrate which, after purification, melted at 235°, either alone or after admixture with authentic N-methyl cytisine picrate.

The base from a portion of the picrate was converted to the perchlorate, which was obtained as fine white needles with a melting point of 265-266°, which was not depressed by admixture with an authentic sample of N-methyl cytisine perchlorate.

An analysis was not obtained on this alkaloid.

Total weight of base = 17 mg. (0.001%).

Alkaloid P4.

Refractionation of the bases from the baptifoline mother liquors gave a yellow oil distilling at 175-200°, from which a perchlorate was obtained in white sheaves of needles, m.p. 286°, this melting point being depressed by admixture with the perchlorates of anagyrine, cytisine and baptifoline. Insufficient material was obtained for further investigation, however.

The mother liquors from the purification of the various fractions were systematically worked up and refractionated, but no bases other than those already described could be isolated. The yields given are the final figures after complete examination of the residues. Slightly over one-third of the total distillable alkaloids was obtained in the pure state either as such or as crystalline derivatives, (0.059% of dried plant material).

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SYNTHESIS OF PSEUDOCONHYDRINE.

Synthesis of Pseudoconhydrine.

SUMMARY.

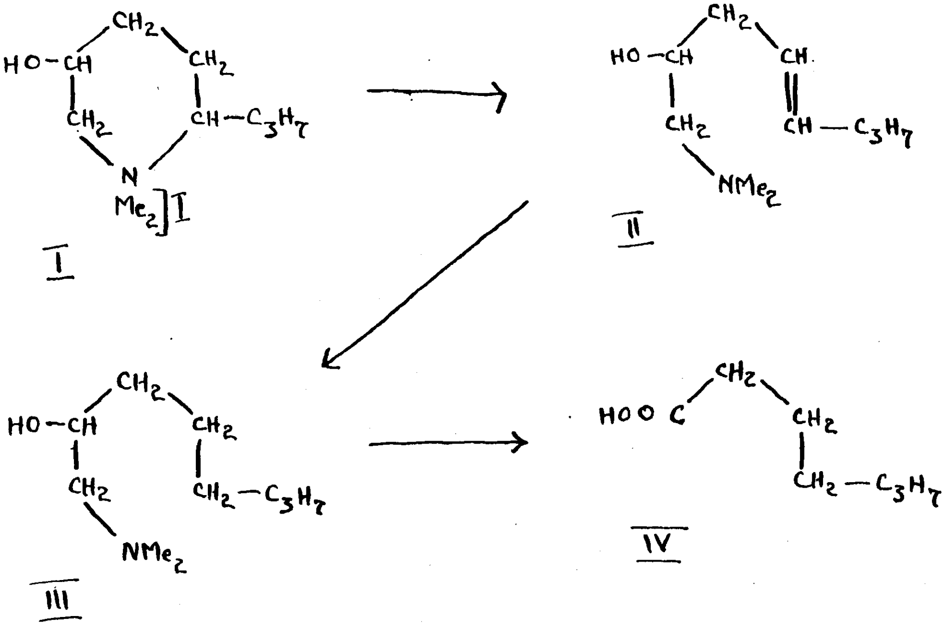
A total synthesis of the racemic compound corresponding to Späth's formula for pseudoconhydrine has been achieved. Final proof of identity with the natural product awaits completion of the optical resolution.

INTRODUCTION.

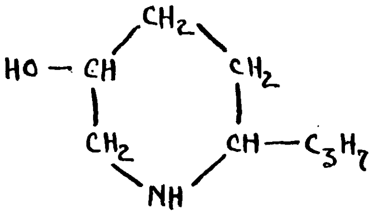
Pseudoconhydrine, one of the Hemlock group of alkaloids, is found in the poison hemlock (Conium maculatum L.) along with coniine, N-methyl coniine, γ-coniceine and conhydrine. It was discovered by Merck in the residues from the preparation of coniine, and studied by Ladenburg and Adam(1), who found it to be an isomer of conhydrine, with the empirical formula $C_8H_{17}ON$. It is a strong secondary base, giving rise to an oily nitrosamine(1), and a crystalline N-benzoyl derivative(2). Like conhydrine, it contains an hydroxyl group, and can be converted to coniine, either by dehydration with P_2O_5 and catalytic hydrogenation(2), or by treatment with hydriodic acid and red phosphorus, followed by reduction of the resulting iodo derivative(3).

These results show it to be an hydroxy coniine, the hydroxyl group being proved by oxidative degradation to be in the piperidine ring(2).

The position of the hydroxyl group in the nucleus can be found by Hofmann degradation(2). The methiodide of pseudoconhydrine (I) when treated with silver oxide and distilled in vacuo yields a methine $C_{10}H_{21}ON$ (II) which on catalytic hydrogenation takes up two atoms of hydrogen, being converted to dihydropseudoconhydrine methine (III). Oxidation of the latter with potassium permanganate yields n-heptylic acid (IV).



This confirms the fact that the alkaloid contains an unbranched chain of eight carbon atoms, and shows that the hydroxyl group cannot be in the side-chain, or positions 2, 3 and 4 of the nucleus. Position 6 can also be eliminated because dihydropseudoconhydrine methine (III) would then be an aldehyde-ammonia, readily hydrolysable by acid, whereas this compound is stable towards acids. The hydroxyl group can therefore occupy only position 5 of the nucleus, and the alkaloid is represented by formula V below, that is, 5-hydroxy-2-n-propylpiperidine.

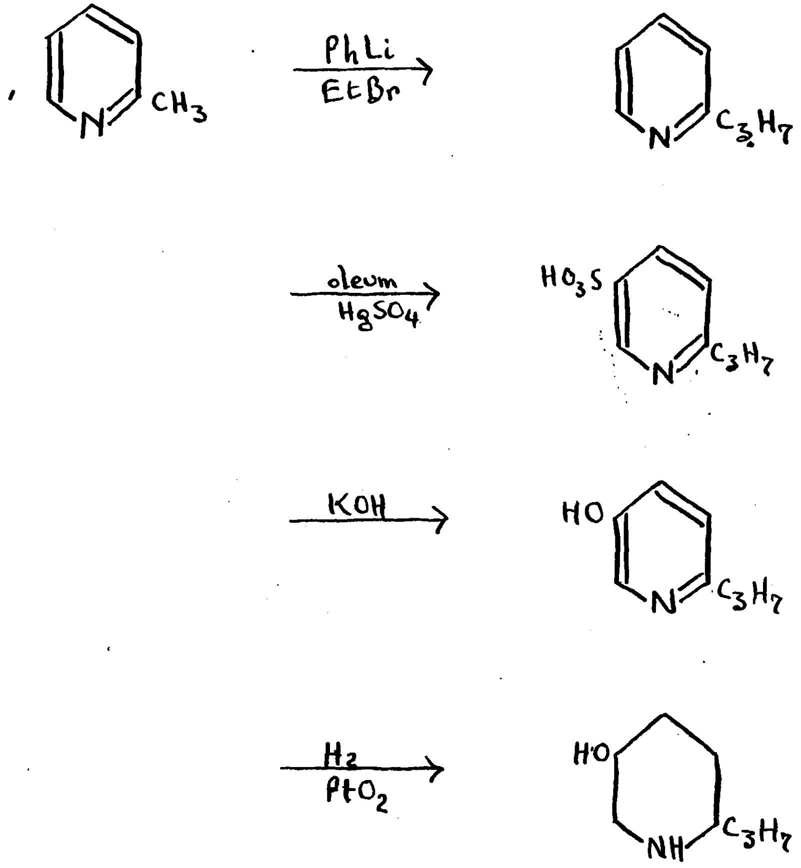


V

DISCUSSION.

Several routes suggest themselves for the synthesis of this compound, using either aliphatic or aromatic methods. Of the two attempted, the first proved unsatisfactory because of low yields, while the second is as yet unfinished, the optical resolution still awaiting completion.

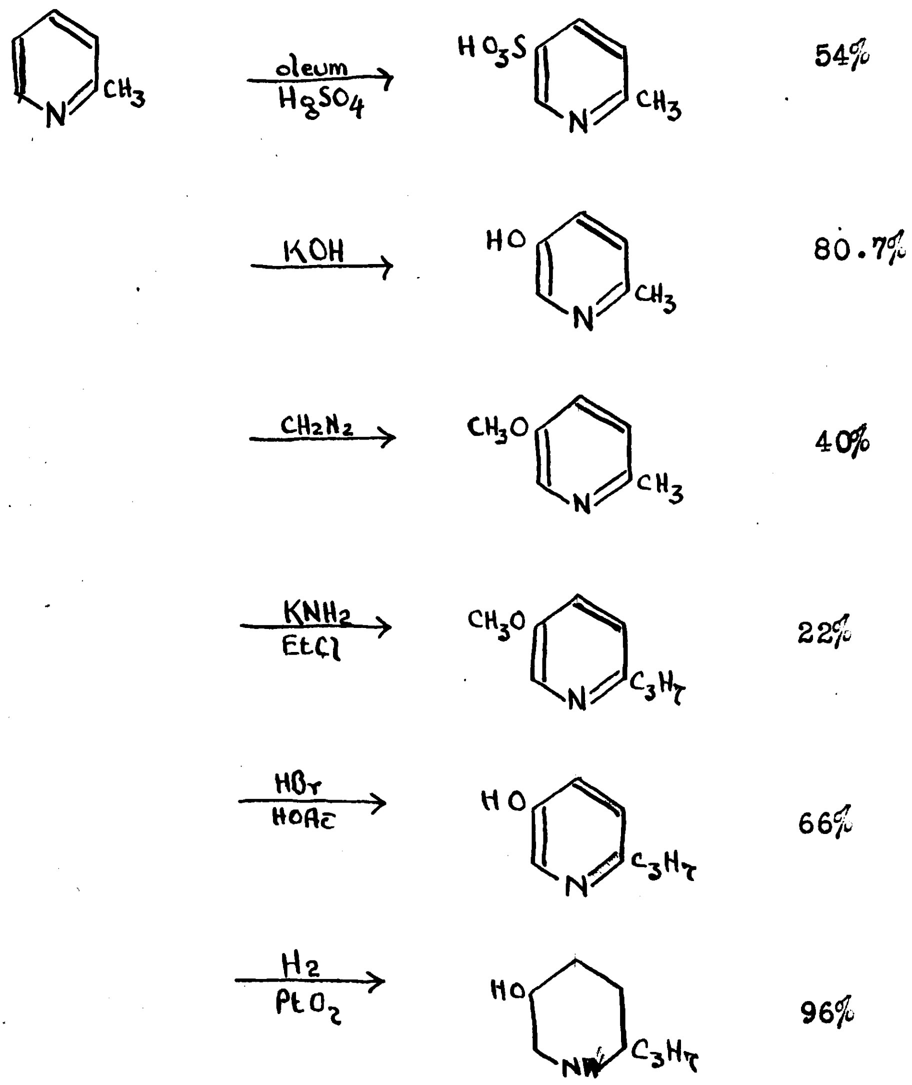
Route I.



A good yield of 2-propyl pyridine (conyrine) was obtained by the phenyl lithium reaction, but sulphonation of the product was quite unsatisfactory. Since picoline itself sulphonates in the presence of a mercury catalyst fairly readily(4,5), this failure is presumably due to the presence in the molecule of the propyl side-chain. Indeed, the reaction mixture effervesced continuously, a phenomenon not observed in the parallel reaction with α-picoline. A small amount of crystalline material with the expected properties was isolated, although it was insufficiently pure for analysis. On fusion with potassium hydroxide, it yielded a gum which gave a deep red colour with aqueous ferric chloride, probably indicating formation of the desired phenolic compound, but the method was not considered sufficiently profitable, and was abandoned.

Route II.

Maximum
yields

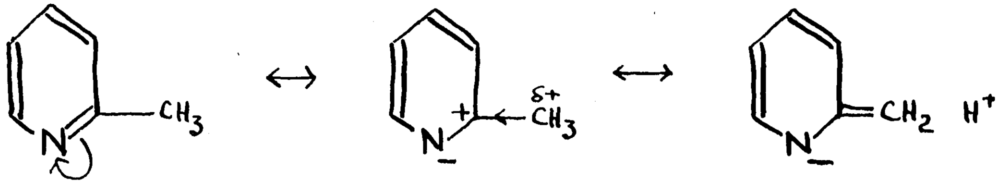


The sulphonation of α-picoline was found to be very sensitive to the grade of oleum used. For example, a change in density from 1.905 (19% SO_3) to 1.916 (21% SO_3) raised the yield from 35% to 54%. The method due to McElvain(5) was employed, it being unusual in that the acid is not neutralised prior to working-up, but is distilled off under reduced pressure, and the product isolated as free sulphonic acid by precipitation with ethanol. It can be purified by filtration in aqueous solution through celite, followed by concentration and reprecipitation with alcohol. The sulphonic acid so obtained is a tan-coloured crystalline solid, with no apparent hygroscopic tendency.

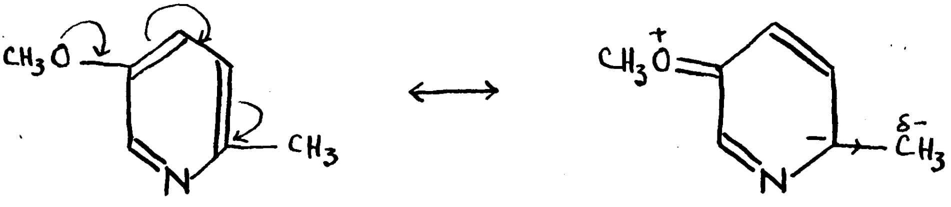
For the formation of the phenolic compound, the free sulphonic acid was fused with excess potash in a nickel crucible, with a few iron filings as catalyst(6). It was found impossible to work with more than 15 g. of the acid, however, since on a larger scale, the reaction was difficult to control, and tended to foam out of the reaction vessel. The product was readily purified by sublimation in vacuo.

Methylation of the phenol with diazomethane proved to be disappointing. A negligible quantity of methyl ether was formed on treatment of a dioxane suspension of the phenol with an ethereal solution of the reagent, while the reaction in methanol gave only 20% of the desired product, about 30% of unchanged phenol being recoverable. The remainder was accounted for by the formation of basic tars, presumably due to interaction of the phenol with unsaturated polymeric self-condensation products from the diazomethane. Addition of water to the point of turbidity, and frequent evaporation of accumulated ether increased the yield to 40%, but also brought about increased formation of tarry by-products, and a correspondingly lower recovery of starting material. An attempt to methylate with "nascent" diazomethane(17) did not increase the yield significantly. The poor results are probably due to the fact that β-hydroxy pyridines are less acidic than benzenoid phenols. This is borne out by the increase in yield with increasing polarity of the solvent.

The lengthening of the side-chain by a condensation reaction with ethyl halide also proved to be much more difficult than had been anticipated. There are several possible explanations for this, the most plausible being the adverse electromeric effect of the methoxyl group para to the reactive methyl group. The activation of the latter is due to the retention of electronic charge by the ring nitrogen atom, thereby causing a decreased electron availability in the ring, particularly in the γ and α positions, and consequently, in the carbon atom of the methyl group.



This in turn facilitates removal of the methyl hydrogen atoms as protons. The methoxyl group, however, is classed by Ingold as having a (+T) effect, that is, it tends to donate electrons to the ring, especially to the ortho and para positions, thereby counteracting the activating effect of the N atom.



A further consequence of this reduced reactivity is that side-reactions, always troublesome in this type of condensation, might be expected to be much more pronounced than with picoline itself. For example, there is the possibility of metalation of the nucleus, ortho to the methoxyl group, rather than of the methyl side-chain(7), while demethylation of the ether grouping must be considered as a possibility(8,15). In addition the ethyl halide can react with the pyridine derivative to form a quaternary salt, or may be dehydrohalogenated by the condensing agent to yield an unsaturated compound(9). It can also condense with the condensing agent itself, rather than with the metalated pyridine derivative, this tendency depending on the particular condensing agent employed.

By analogy with the successful condensation of α-picoline with ethyl bromide by the action of phenyl lithium, a similar run was attempted with the 5-methoxy-2-picoline. Only a small yield (5%) of the desired product was obtained, however, in spite of the vigorous reaction. An attempt to cut down side-reactions by the substitution of ethyl chloride for the bromide raised the yield to 10%, but the product, as in the previous run, was still impure, as shown by the analysis figures. The rather small difference in boiling points (22°) of product and starting compound made fractionation difficult on the small scale employed.

In an attempt to obtain a purer product, triphenylmethyl sodium was employed as condensing agent(10), but gave an entirely negative result. 80% of the methoxy picoline was recovered unchanged, but no fraction corresponding to the desired product. The slow discharge of the red colour was presumably due to interaction of the triphenylmethyl sodium with the halide, but this was not investigated further.

Much better results were obtained with potassamide, however, both as regards increased yield (22%) and purity of product. In addition, up to 67% of the unchanged starting material was recoverable, and could be recycled, which raised the "conversion" to 66%. The reagent was prepared in liquid ammonia by the general method of Nieuwland(11), but since Bergström had obtained unsatisfactory results when he attempted to carry out an analogous condensation in the ammonia solution(12), the general method of Chichibabine(9) employing the solid reagent in the absence of any added solvent was followed.

The potassamide was obtained, by evaporation of the ammonia, as a hard solid cake, which had to be cautiously broken up under nitrogen with a spatula, this resulting, on several occasions, in breakage of the reaction flask, and the subsequent rapid oxidation of the reagent. The reaction was otherwise satisfactory, however. The product was rather difficult to separate from unchanged starting material, and after one distillation in vacuo through a small Vigreux column, was still only 85-90% pure. The combined yield from several runs was finally separated from starting material by careful fractionation in vacuo in a gauze-packed, jacketed column.

Demethylation of the 5-methoxy-2-propyl pyridine with alcoholic potassium hydroxide in a sealed tube according to the general method of Robinson(18) was found to be unsatisfactory, but reasonably good results were obtained by refluxing with 48% hydrobromic acid in glacial acetic acid. The reaction was slow, however, and even after 90 hours refluxing, the yield was only 66%.

The hydrogenation of the pyridine ring was carried out at 50 lbs. pressure in presence of Adams platinum catalyst, the synthetic dl-pseudoconhydrine so obtained being a yellowish semi-crystalline solid. Since there are two active centres in the molecule, preliminary separation of the diastereomeric forms, before resolution with an active acid, is necessary. This was achieved by distillation in vacuo, followed by repeated crystallisation from ether, and from ethyl acetate/ligroin. Since natural pseudoconhydrine readily forms a hydrate in moist solvents, the compound obtained by the above procedure still possessed an unsharp melting point, presumably due to partial hydration. One distillation in vacuo yielded a pure compound, however, consisting of fine white needles, m.p. 91.5-92°. The natural alkaloid melts at 105-106°, and while it is impossible to draw conclusions before resolution has been carried out, it seems probable that the above compound is the required diastereomer.

EXPERIMENTAL.

All melting points are corrected, unless otherwise stated.

α-n-Propyl pyridine (Conyrine)(13).

Purification of reagents; The lithium (B.D.H.) was pressed into wire with the aid of a 20-ton hydraulic press, the wire weighed out under petroleum ether, and cut into short lengths with a pair of scissors before use. The bromobenzene and ethyl bromide were dried with "drierite" and fractionated, the fractions used having a boiling range of less than 1°C. α-picoline (E.K.) was dried with potassium hydroxide and fractionated. The ether was of the usual Grignard quality.

7 g. (1 atom) of lithium wire was placed with 200 ml. of ether in a 1 l. three-necked flask. The flask had four large indentations to serve as vortex baffles, and was fitted with a sealed high-speed stirrer, condenser and dropping funnel, all equipped with ground glass joints. 25 ml. of a solution of 86 g. (0.55 mole) of bromobenzene in 100 ml. ether was added and the stirrer started. A vigorous reaction set in immediately, and the solution was maintained at reflux temperature

by the slow addition of the remainder of the bromobenzene. When all of the lithium had dissolved, 35 g. (0.4 mole) of α-picoline was added dropwise, causing the ether to reflux again, while the colour of the solution changed to a darker brown. 50 g. (0.45 mole) of ethyl bromide was then added, causing a further change in colour, accompanied by evolution of heat. When the reaction had subsided, the lithium compounds remaining were decomposed by the cautious addition of water, till two clear liquid layers were obtained, which were separated. The ether layer was extracted with 10% hydrochloric acid, the extract added to the acidified aqueous layer, and the combined solution exhausted with ether to remove neutral by-products. It was then basified with sodium hydroxide, and again extracted with ether, and the extract, after removal of solvent, distilled through a Vigreux column at atmospheric pressure. The fraction boiling up to 190° was refractionated in a 6 x $\frac{3}{4}$" helix-packed column at 100 mm. pressure, and the fraction distilling at 97-100° collected. This had a boiling point of 174° at atmospheric pressure, as determined by the Siwoloboff method, and gave a picrate m.p. 74°. These are in agreement with the data given by Chichibabine(9). Yield was 18 g. (37%).

2-Propylpyridine-5-sulphonic acid(4).

To 30 g. of fuming sulphuric acid (s.g. 1.920) containing 0.5 g. of mercury subsulphate was added with stirring 8 g. (0.066 mole) of conyrine, the temperature rising to 130°. The mixture was heated with stirring, in an oil bath, at 200° for 3½ hours, cooled, and poured on to ice. The acid solution was neutralised with powdered calcium carbonate, and the calcium sulphate filtered off. It was then heated to boiling, and potassium carbonate added till a permanent alkaline reaction was obtained, and the precipitated calcium carbonate removed by filtration. The solution was concentrated on the steam bath to about 50 ml., poured into four times its volume of saturated aqueous potassium chloride solution at 0°, and left for 48 hours in the refrigerator, but only inorganic material could be isolated. Substitution of barium carbonate for the calcium carbonate gave no better results.

The working-up procedure was then varied as follows. The diluted reaction mixture was neutralised with barium hydroxide, and the excess alkali removed by addition of dry ice. The solution of the barium sulphonate was heated, and the barium precipitated by addition of potassium carbonate, and filtered off. The solution of the potassium sulphonate was then concentrated under reduced pressure, and taken down to dryness in a vacuum desiccator. The semi-crystalline residue was crystallised several times from methanol, but could not be obtained pure. The brownish crystals charred and burned when heated on a spatula, leaving a residue which gave a strongly alkaline reaction when moistened with water. A sodium fusion test was positive for sulphur and nitrogen, while fusion with potassium hydroxide at 220° for 20 minutes yielded a brownish gum, which gave a red colour with aqueous ferric chloride, but which could not be purified further.

Yield was about 0.35 g. (2%) and could not be increased by variation in either the time or temperature of heating.

2-Methyl pyridine-5-sulphonic acid.

(i). (4) To 30 g. of fuming sulphuric acid (s.g. 1.920) containing 0.5 g. of mercury subsulphate, was added 6 g. (0.065 mole) of α-picoline, with frequent cooling and shaking. The mixture was heated for 3 hours at 225°, and after pouring on to ice, the acid solution neutralised with barium carbonate. After removal of the precipitated barium sulphate, the hot solution was treated with potassium carbonate till permanently alkaline, filtered from barium carbonate, and evaporated to dryness. No charring occurred, and the product was an almost white powder. It appeared to be largely contaminated with inorganic salts, however, and the method was abandoned in favour of that devised by McElvain(5), which employs mercuric sulphate as catalyst, and an entirely different method of working-up.

(ii). 93 g. (1 mole) of α-picoline was slowly added with cooling and swirling to 400 g. of fuming sulphuric acid (Mallinckrodt s.g. 1.916 ≡ 21% SO_3), followed by 2.5 g. of mercuric sulphate, and the mixture was heated on an oil bath at 230-235° for 10 hours. The stirrer was replaced by an all-glass distillation set-up, and the apparatus connected to an oil pump. The excess sulphuric acid was distilled off at 0.5 mm. pressure and 200°, about 230 g. being recovered. The black oily residue was cooled, diluted with 200 ml. of absolute alcohol, with cooling and shaking, and left overnight in the refrigerator. The precipitated sulphonic acid was obtained as a mass of black crystals, which, after filtration, were redissolved in 500 ml.

of water, and the mercury salts precipitated with hydrogen sulphide. Owing to the colloidal nature of the sulphide precipitate, the solution was filtered through a celite pad at 80°, and concentrated on the steam bath till crystallisation commenced. The aqueous solution was then diluted with 150 ml. of ethanol, and cooled overnight in the refrigerator. The sulphonic acid was obtained as tan-coloured crystals, m.p. 334-338° (uncorr.). McElvain reports this as 338-341° (corr.).

Great variation in yield was encountered, depending on the strength of acid used, time of heating, and precise method of working-up. The maximum obtained was 54%.

5-Hydroxy-2-methyl pyridine(4).

40 g. (0.7 mole) of potassium hydroxide was melted at 160° in a nickel crucible with a few drops of water and some iron filings, and 15 g. (0.087 mole) of 2-methyl pyridine-5-sulphonic acid added slowly with stirring. The temperature was then raised gradually, causing the liquid melt to become pasty and semi-solid. At 240°, a vigorous reaction set in, the melt once more becoming liquid, and effervescing strongly

causing a great increase in volume. After about ten minutes at this temperature, it commenced to crystallise, and finally became solid, indicating the end of the reaction. After cooling, the melt was dissolved in 100 ml. of water, and partly neutralised with hydrochloric acid. Then, while still alkaline, it was placed on the steam bath, and neutralisation completed by the addition of excess dry ice. When the solution had cooled, the precipitated phenolic compound was filtered off, dried in a desiccator, and extracted in a Soxhlet extractor with ether. Yellow crystals soon started to separate from the boiling solution. The aqueous mother liquors were also extracted overnight in a liquid-liquid extractor, and the two ether extracts combined, and concentrated. The crude 5-hydroxy-2-methyl pyridine which crystallised was purified by sublimation in a large pyrex tube at 130° and 0.1 mm. pressure, being obtained as an almost white crystalline solid, m.p. 167-169°. This is reported as 164-166°(4). It gave a red colour with aqueous ferric chloride. Found: C, 66.22, 66.34%; H, 6.40, 6.30%. Calcd. for C_6H_7ON, C, 66.06%; H, 6.46%.

5-Methoxy-2-methyl pyridine.

(i). 20 g. (0.2 mole) of nitrosomethyl urea(15) was decomposed under ether with 50% aqueous potassium hydroxide, and the reaction mixture distilled to yield an ethereal solution of c. 5.5 g. (0.13 mole) diazomethane(16). This was slowly added with stirring and cooling in ice water, to a slurry of 13 g. (0.12 mole) of 5-hydroxy-2-methyl pyridine in 200 ml. of dioxane. No evolution of gas was noticeable, and addition of small quantities of water and methanol was without effect. On standing overnight in the refrigerator, the solution slowly turned brown and deposited a basic polymer, from which the phenolic compound could not be recovered.

(ii)(17) 2 g. (0.018 mole) of the phenol was dissolved in 50 ml. of methanol, cooled, and 4 g. (0.04 mole) of nitrosomethyl urea added. A solution of 5 g. of potassium hydroxide in 30 ml. of methanol was cautiously added with cooling and shaking, causing strong effervescence. After standing overnight in the refrigerator, the solution was acidified with hydrochloric acid and extracted with ether. It was then concentrated on the steam bath, basified with sodium hydroxide, and again extracted, and the extract worked up for 5-methoxy-

2-methyl pyridine. Yield was 0.6 g. (25%).

(iii). 5.5 g. (0.13 mole) of diazomethane in ether was slowly added with cooling and stirring to a solution of 10 g. (0.10 mole) of 5-hydroxy-2-methyl pyridine in 150 ml. of methanol. A fairly brisk effervescence accompanied the addition, and persisted for a considerable time afterwards. After 30 minutes, the excess diazomethane was destroyed by addition of dilute hydrochloric acid. The ether solution was thoroughly extracted with dilute hydrochloric acid, the combined acid solutions freed from neutral compounds by ether extraction, basified with sodium hydroxide, and extracted with ether again. This latter extract was dried over potassium hydroxide pellets, the ether removed by distillation, and the residual oil distilled in vacuo. The product was a colourless oil, b.p. 43-45°/1 mm., or 188-189°/760 mm. $n_D^{25} = 1.5088$.
Found: C, 68.30, 68.37%; H, 7.17, 7.35%. C_7H_9ON requires C, 68.28%; H, 7.36%.

A Zeisel estimation gave the methoxyl content as 22.20, 22.53%. C_7H_9ON requires 25.20%, but this low result may be due to volatility.

The yield was 2.5 g. (20%). By bringing the aqueous mother liquors to pH 6 with dry ice, and continuous extraction overnight with ether, 3.5 g. (35%) of the phenol was recovered unchanged. In subsequent runs, the yield was raised to 40% by the addition of 5-10% of water to the methanol, and interrupting the addition of diazomethane several times to boil off the ether accumulated in the solution. Both these expedients presumably serve to keep the polarity of the solvent at a maximum, thereby increasing the acid character of the phenolic compound.

5-Methoxy-2-propyl pyridine.

I. Phenyl lithium as condensing agent(13).

(i). The purification of the reagents was as in the preparation of conyrine. Phenyl lithium was prepared from 0.28 g. (0.040 atom) of lithium wire and 3.42 g. (0.022 mole) of bromobenzene in a 50 ml. three-necked flask. When the reaction was complete, 1.95 g. (0.016 mole) of 5-methoxy-2-methyl pyridine was added dropwise, causing the solution to turn from brown to dark red, with evolution of heat. This was followed with 1.86 g. (0.017 mole) of ethyl bromide, causing a darkening of the red colour, accompanied by violent refluxing. The remaining organic lithium compounds were decomposed by the cautious addition of water, the colour changing successively to green, yellow and orange, two clear liquid layers being finally obtained, with a penetrating, sweetish odour. The layers were separated, the ether layer extracted repeatedly with dilute hydrochloric acid, and the acid solution combined with the aqueous layer. The combined solutions were freed from neutral compounds by ether extraction, basified with sodium hydroxide, and extracted again with ether. This second extract was dried with potassium carbonate, the ether "flashed off", and the residue distilled in vacuo. The product was a yellow oil of somewhat indefinite boiling point.

Found: C, 68.69%; H, 7.73%. $C_9H_{13}ON$ requires C, 71.48%; H, 8.66%.

(ii). This result was apparently due to poor fractionation, and the preparation was repeated on a larger scale, using 7.80 g. (0.063 mole) of 5-methoxy-2-methyl pyridine. The product was distilled in a 25 ml. Claisen flask fitted with a 3-inch Vigreux column on the side-arm, at a pressure of 25 mm. Three fractions were taken. I. b.p. 90-95°, II. 95-110°, III. 110-112°.

The analyses of these fractions were as follows:-

I. C, 66.27; H, 7.32. C_7H_9ON requires C, 68.28; H, 7.36.

II. C, 64.27; H, 7.60.

III. C, 70.31; H, 8.77 $C_9H_{13}ON$ requires C, 71.48; H, 8.66.

All these fractions are apparently contaminated with some by-product of low carbon content. Yield of fraction III was 0.45 g. (4.7%), while recovery of starting material (fraction I) was 4 g. (52%).

(iii). Phenyl lithium was made from 0.83 g. (0.119 atom) of lithium wire and 10.26 g. (0.066 mole) of bromobenzene. 4.4 g. (0.036 mole) of 5-methoxy-2-methyl pyridine was added as before, and when the reaction had subsided, the Liebig condenser replaced by a worm condenser, the water for which was precooled by passage through a copper coil immersed in crushed ice. 3.4 ml. (0.048 mole) of ethyl chloride was then added from a cooled graduated pipette in 0.3 ml. portions, at 5 minute intervals, and the mixture left stirring for 40 hours in an atmosphere of nitrogen, with cooling in an ice bath.

The reaction mixture was worked up as before, to yield 0.5 g. (9.2%) of the product, 45% of the starting material being recovered.

II. Triphenylmethylsodium as condensing agent(10).

Triphenylmethylsodium was made from 5.5 g. (0.24 atom) of sodium sand and 14 g. (0.05 mole) of trityl chloride, and the red solution decanted from excess sodium into a 300 ml. three-necked flask in a counter-stream of nitrogen. The flask was fitted with a sealed stirrer, and a dry ice cold-finger condenser, the third neck being closed with a stopper, and the apparatus placed in a Dewar flask filled with crushed ice. 5.7 g. (0.046 mole) of 5-methoxy-2-methyl pyridine was added, followed by 3.8 ml. of ethyl chloride in 0.3 ml. portions at 5 minute intervals, and the solution left stirring overnight under nitrogen. The colour of the solution slowly changed during the reaction from dark red to opaque orange-yellow.

The reaction mixture was worked up as in the runs in which phenyl lithium was employed as condensing agent, but no fraction corresponding to the expected product could be isolated, while 80% of the starting material was recovered unchanged. The slow discharge of the red colour of the condensing agent is assumed to be due to interaction with the ethyl chloride, to form triphenyl propane, but no attempt was made to verify this.

III. Potassamide as condensing agent.

5 g. (0.128 atom) of potassium was converted to potassamide in 80 ml. of liquid ammonia, with an iron catalyst, in a 100 ml. three-necked flask equipped with a stirrer, and a cold-finger condenser with nitrogen inlet, the third neck being closed with a stopper, and used for the addition of reagents. The entire apparatus was equipped with all-glass joints. When all the metal had been converted to amide, the ammonia was allowed to evaporate, the last traces being driven off by warming under nitrogen in a water bath. The solid cake of potassamide was carefully broken up with a spatula, in a strong stream of nitrogen, and the cold-finger condenser filled with dry ice. 10 g. (0.081 mole) of 5-methoxy-2-methyl pyridine was added with stirring, and allowed to stand for 15 minutes, during which time, the solution developed a deep purplish-red colour. 9.5 ml. (0.135 mole) of ethyl chloride was then added in 0.3 ml. portions, at 5 minute intervals, the condenser being kept cold by fresh additions of dry ice. The flask was immersed in an ice bath, and stirring continued overnight, after which the ice bath was removed, fresh dry ice added

to the condenser, and stirring continued at room temperature for a further 10 hours. The total reaction time was about 30 hours.

The reaction mixture was worked-up as in previous runs, and the product distilled in a fractionating Claisen flask at 0.7 mm. pressure. The product was obtained as a water-white oil, with a penetrating odour reminiscent of oil of aniseed, b.p. 60-61°/0.7 mm. Yield was 2.6 g. (22%), 67% of the starting material being recovered. Since the latter can be recycled, the "conversion" is over 65%. The analysis results were still low - Found: C, 70.68%; H, 8.61% as compared with theoretical values of 71.48% and 8.66% respectively. This is presumably due to the presence of 10-15% of 5-methoxy-2-methyl pyridine, so the product of several runs was carefully fractionated at about 1 mm. pressure in a 9 x 3/8 inch column packed with wire gauze, and equipped with a heated jacket and a Whitmore and Lux total condensation - variable take-off still head. Two relatively sharp fractions were obtained at 37-40° and 60-62°, corresponding to unchanged starting material and the desired product.

Found: C, 71.45, 71.48, 71.50%; H, 8.87, 8.76, 8.63%.
$C_9H_{13}ON$ requires C, 71.48%; H, 8.66%.
Refractive index, n_D^{25} = 1.5012.

Treatment with the theoretical amount of picric acid in methanol gave a picrate, in pale greenish-yellow needles, m.p. 113-114°.

Found: C, 47.47, 47.67%; H, 4.24, 4.30%.
$C_{15}H_{16}N_4O_8$ requires C, 47.37%; H, 4.24%.

5-Hydroxy-2-propyl pyridine.

(i)(18). As a test run, 0.5 g. (0.004 mole) of 5-methoxy-2-methyl pyridine was heated with 2 g. (0.036 mole) of powdered potassium hydroxide in 5 ml. of absolute ethanol in a sealed pyrex tube at 215°. It was found that the glass tube would not withstand heating for longer than 15 hours. On opening the tube, a pungent amine-like odour was very noticeable, indicating considerable decomposition. The solution was diluted with water, filtered from a bulky precipitate, and acidified with hydrochloric acid. Neutral and acidic compounds were removed by ether extraction, the solution basified with sodium hydroxide, and again extracted with ether. It was then brought to pH 6 with dry ice, and exhausted on a continuous liquid-liquid extractor with ether. The product obtained on concentration of the ether extract was very impure, and the yield of crude material did not exceed 40%. The working-up was impeded by the presence of bulky, flocculent and colloidal inorganic precipitates derived from the pyrex glass, and the method was considered unsatisfactory. The use of a stainless steel bomb would probably give much better results, however.

(ii). 4.30 g. (0.028 mole) of 5-methoxy-2-propyl pyridine was refluxed for 90 hours with 200 ml. of glacial acetic acid containing 90 ml. of 48% hydrobromic acid. After cooling, the solution was diluted with its own volume of water, and extracted several times with twice its own volume of ether. It was then basified with sodium hydroxide pellets and extracted with ether again. This second extract yielded 0.13 g. of recovered 5-methoxy-2-propyl pyridine (3%).

The aqueous solution was divided into two, and one part neutralised with dry ice and extracted continuously overnight. The ether solution was dried with "drierite" and concentrated to 5 ml. on the steam bath. A white crystalline solid separated on cooling, and a further quantity could be obtained from the mother liquors by slow addition of 50-60° ligroin.

The other part of the aqueous solution was made just acid with hydrochloric acid, then excess ammonium hydroxide added, and the solution continuously extracted as before. This method seems preferable to the first, giving a higher recovery and a purer product. The phenol obtained by the first method is apparently contaminated with oily products from the dry ice.

The product was readily purified by crystallisation from ether-ligroin, being obtained as a white crystalline solid, m.p. 93-93.6°. It gave a deep red colour with aqueous ferric chloride.

Found: C, 70.01, 70.20%; H, 7.84, 7.93%.

$C_8H_{11}ON$ requires C, 70.06%; H, 8.08%.

The yield was 2.60 g. (66%).

<u>dl-Pseudoconhydrine.</u>

1 g. (0.0073 mole) of 5-hydroxy-2-propyl pyridine was hydrogenated at 44 lbs. pressure in 50 ml. of glacial acetic acid containing 250 mg. of Adam's platinum catalyst, for 16 hours.

The solution was diluted with its own volume of distilled water, filtered from the catalyst, acidified with hydrochloric acid, and most of the acetic acid removed by ether extraction. The solution was then basified with sodium hydroxide, and extracted continuously overnight with ether. The extract was dried with potassium carbonate and concentrated, leaving a yellow oil which crystallised on cooling. The crystals had a pleasant, sweetish smell reminiscent of crushed leaves.

Yield, 1.008 g. (96.4%).

Separation of diastereomeric forms.

Distillation. A fairly wide (10-12 mm.) tube was used, well insulated to provide a temperature gradient. The compound distilled at $70\text{-}75^{o}/0.1$ mm., giving white crystals towards the hotter part of the tube, and an oil in the cooler part.

Elution. Much of the oil could be removed by washing with cold ether.

Crystallisation. The crystals were dissolved in ether, and crystallised twice from that solvent, and twice from ethyl acetate-ligroin. This was unsatisfactory since they separated in a mat of invisibly small needles, which gave the appearance of cotton wool. Also, hydrate formation made it impossible to obtain a pure compound by this method, and the melting point remained unsharp.

Redistillation. The recrystallised product was distilled as before, giving a white crystalline solid, m.p. 91.5-92°. This gave no colour with aqueous ferric chloride, and depressed the melting point of 5-hydroxy-2-propylpyridine by over 50°.

Found: C, 67.30, 67.24%; H, 11.71, 11.76%.

$C_8H_{17}ON$ requires C, 67.11%; H, 11.96%.

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