The Alkylation of 3,4-Dihydro-β-Carbolines

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By

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SCOPE AND CONTENTS:

The structure of anhydro- and pseudobases obtained from N_β-alkyl-3,4-dihydro-β-carbolinium salts is discussed in the light of chemical and spectroscopic evidence.

The behaviour of these compounds on further alkylation and the structure of the alkylation products so obtained has been investigated.

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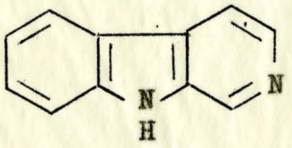
INTRODUCTION

The formation of anhydro- and of pseudobases from 3,4-dihydroisoquinoline and β-carboline derivatives, the structure of these compounds and the structure of their alkylation products has been repeatedly studied and a general pattern of behaviour established.

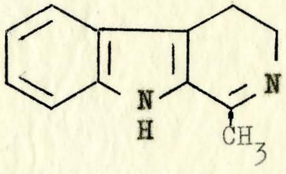
Analogous compounds derived from 3,4-dihydro-β-carbolines have been reported to behave entirely atypically. It was the object of present work to re-investigate the behaviour of the latter group of compounds.

Nomenclature of β-Carbolines

The ring system in structure (I), containing a fused indole-pyridine nucleus, has been named in a number of different ways by different authors. Although the name β-carboline, first introduced by Perkin and Robinson (1919 b), is widely used, the ring index (Patterson, Capell and Walker, 1960) prefers the name pyridoindole for the system.



I



II

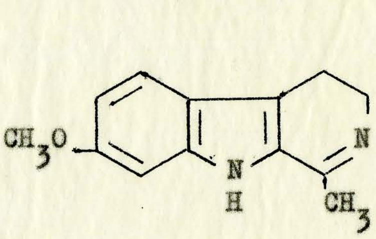
Thus the compound of structure (II) is 1-methyl-3,4-dihydro-9H-pyrido (3,4-b) indole.

In the present study the carboline nomenclature is adhered to with the numbering of individual ring atoms used by Morton (1946). According to this system compound (II) is 1-methyl-3,4-dihydro-β-carboline.

Apart from this mode of nomenclature, the trivial name, e.g. harmalan for compound (II), derived from the names of the harmala alkaloids which were the first members of this heterocyclic group to be described, will be used in some cases for the sake of brevity.

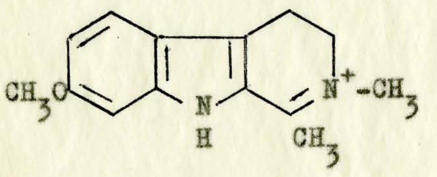
The Alkylation of 3,4-Dihydro-β-Carboline Derivatives

The only dihydro-β-carboline derivative whose chemistry has been investigated in any detail is the alkaloid harmaline which was studied by Perkin and Robinson and their collaborators, who by degradation (Perkin and Robinson, 1912, 1913, 1919 a, 1919 b; Kermack, Perkin and Robinson, 1921, 1922) and synthesis (Manske, Perkin and Robinson, 1927), showed it to be 1-methyl-7-methoxy-3,4-dihydro-β-carboline (III). This formulation of harmaline as a tertiary base was supported by a large body of experimental evidence, including the fact that the compound formed quaternary salts by the addition of only one

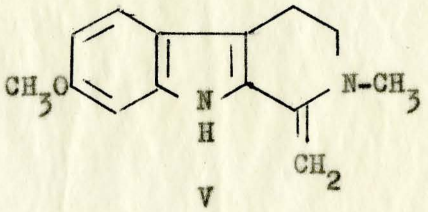


III

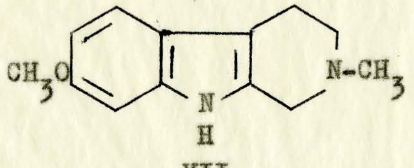
mole of alkyl halide. Two observations, however, the formation of an N_β-acetyl derivative (Fischer and Täuber, 1885) and of an N_β-methyl derivative (Fischer, 1897) could not be immediately reconciled with this formulation. N_β-methyl harmaline (V) derived from harmaline methiodide (IV) by treatment with base (Nishikawa, Perkin and Robinson, 1924) gave on oxidation a neutral compound (VI) which was reduced with sodium in alcohol to N_β-methyltetrahydronorharmine (VII) which was synthesised by an unambiguous method (Kermack, Perkin and Robinson, 1922). Thus the C_1 methyl group present in harmaline was lost in the course of oxidation. The neutral oxidation product was formulated as the lactam (VI) and N_β-methyl harmaline was then represented by (V).



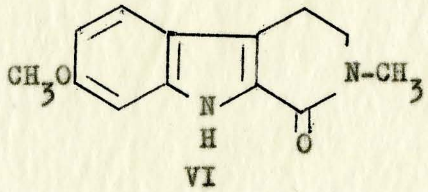
IV



V



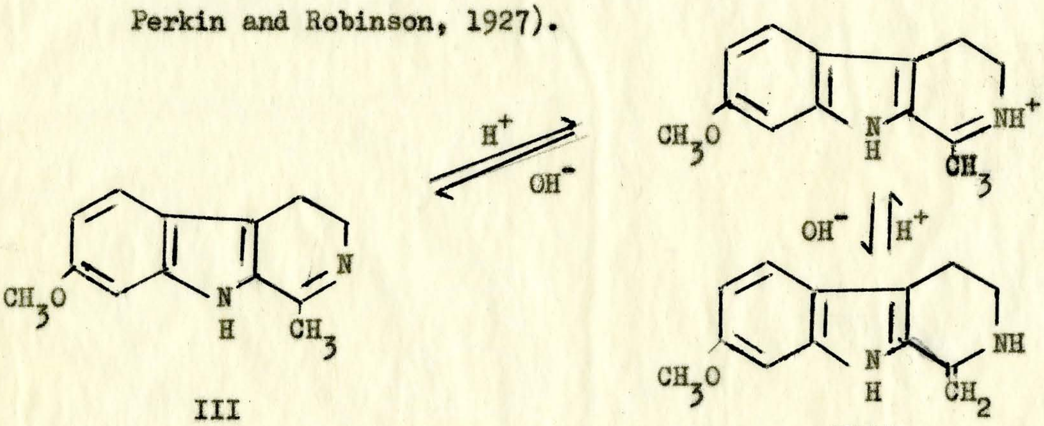
VII



VI

The N_β-acetyl derivative of harmaline was formulated analogously, on the basis of a similar sequence of reactions (Barret, Perkin and Robinson, 1929).

The structure of N_β-acetyl and methyl derivatives thus appeared to indicate that harmaline could behave as a secondary base (VIII). This formulation was, however, rejected (Nishikawa, Perkin and Robinson, 1924) on the basis of the stability of compound towards oxidising agents and its dual behaviour explained by the hypothesis that harmaline existed in two tautomeric forms (III) and (VIII), whose interchange depended on protonation at N_β and decomposition of the harmaline cation (Manske, Perkin and Robinson, 1927).

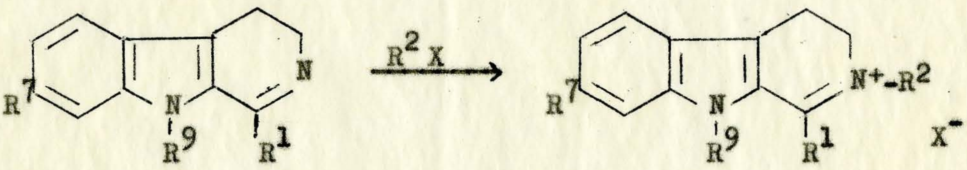


III

VIII

Similar prototropic behaviour is observed in 2-alkyl pyridines. The activity of methyl hydrogens in these compounds has been investigated using a Tschugaef reaction with methyl magnesium iodide (Ploquin, 1950) and the activity is attributed to hyperconjugation effects and not to tautomerism. Additional evidence against the existence of tautomerism in 2-alkyl pyridines is available from spectral data (Anderson and Seeger, 1949). In the dihydro-β-carboline series this type of prototropic behaviour is possible only in 1-alkyl-3,4-dihydro-β-carbolines and not in 1-unsubstituted 3,4-dihydro-β-carboline derivatives. These do not possess a hydrogen atom on the C atom adjacent to position 1, the presence of which is essential for such a change.

When a 3,4-dihydro-β-carboline derivative is treated with alkyl halide, the main product of the reaction is the corresponding mono-alkylated salt. The formation of a dialkylated derivative in small yield as a byproduct has been reported only in one instance when the alkylation was carried out in the presence of base (Fischer, 1914). The alkylation reaction can be represented as follows and the product formulated as a 2-alkyl-3,4-dihydro-β-carbolinium salt (IX).



IX

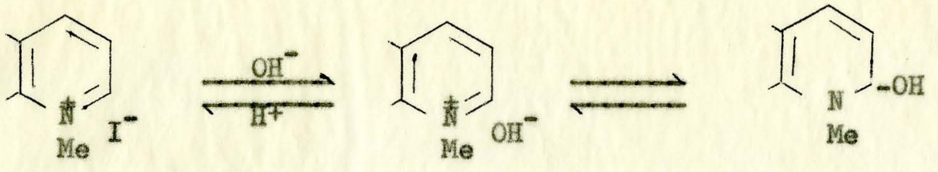
Only a small number of such salts has been described. Several new compounds of this type have now been prepared.

When treated with alkali these compounds do not merely yield the quaternary ammonium hydroxide (IX, $X^- = OH$) but are converted further into substances which are soluble in benzene and therefore non ionic. By analogy with similar conversions in the 3,4-dihydro isoquinoline series, to be discussed in greater detail later, these derivatives might be represented as pseudobases or anhydrobases.

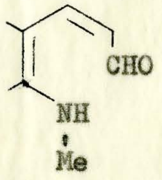
Quaternary hydroxides derived from heterocyclic bases containing a =N- function behave in a different manner from aliphatic quaternary ammonium hydroxides. The latter compounds are relatively stable but on heating with base usually undergo an elimination reaction to yield a tertiary amine and an ethylenic compound. The quaternary hydroxides of heterocyclic aromatic bases do not undergo this "Hofmann degradation" on heating but many of them change on treatment with base at room temperature into isomeric substances which are non electrolytes and whose chemical nature depends upon the substituents attached to the heterocyclic ring α to the nitrogen. There are two main possibilities, formation of pseudobases and formation of anhydrobases.

Pseudobases and Anhydrobases

N-Alkyl ammonium halides of a heterocyclic base such as (X) without alkyl substitution α to the nitrogen atom yield, with sodium or potassium hydroxide the unstable ammonium hydroxide (XI), which re-arranges into non-conducting water-insoluble pseudobase (XII), (Decker and Kaufmann, 1911). Decker compared this process with the dissociation of a quaternary ammonium hydroxide into the tertiary base and an alcohol, e.g. $(CH_3)_4\ N^+\ OH^- \rightleftharpoons (CH_3)_3N + CH_3OH$.



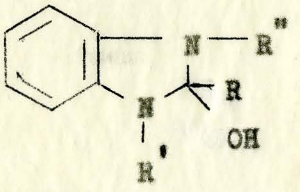
X XI XII



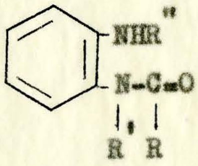
XIII

There is considerable uncertainty as to the equilibrium between the ammonium hydroxide form (XI) and the pseudobase (XII). The quaternary hydroxide (XI) is favoured in the pyridine series where pseudobase formation results in complete loss of aromatic character (Hantzch and Kalb, 1899), but with an increasing number of rings in the molecule the equilibrium shifts towards the pseudobase since the pseudobase formation is accompanied by only a fractional loss of aromaticity. Thus acridine and phenanthridine pseudobases can readily be isolated although this may be attributed in part to their insolubility (Aston, 1931). It is noteworthy that stable pseudobases can be obtained from partially hydrogenated quinoline and isoquinoline derivatives, presumably because here pseudobase formation is unattended by loss of aromaticity (Kröhnke and Vogt, 1956, 1957).

The situation regarding the existence of pseudobases and their structure is further complicated by evidence, very often conflicting, that these compounds may exist in an open chain form (XIII), which has been used to explain certain of their properties which are generally associated with aldehydes. The pseudobases of the benzimidazole series were assumed to possess a carbinolamine structure (XIV) (Fischer and Römer, 1906). Recently it has been shown by infrared spectroscopy that these compounds possess an amide linkage which would indicate structure (XV) (Smith, Rasmussen and Ballard, 1949). Chemical evidence in favour of (XV) has also been provided. On the other hand, in the case of pseudobases of the dihydroisoquinoline series (discussed later), it has recently been shown (Beke and Korobnits, 1959) that cotarnine and hydrastinine are carbinolamines and not open chain aldehydes.



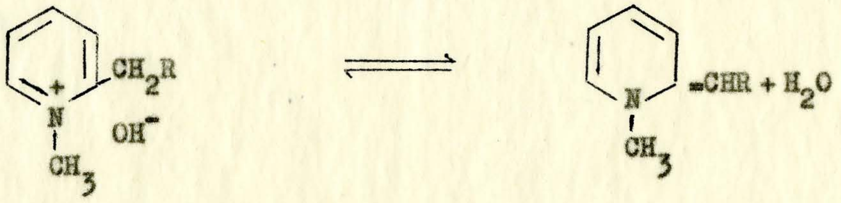
XIV



XV

The formation of pseudobases is an example of nucleophilic addition in the heterocyclic ammonium ion in the position α to the nitrogen.

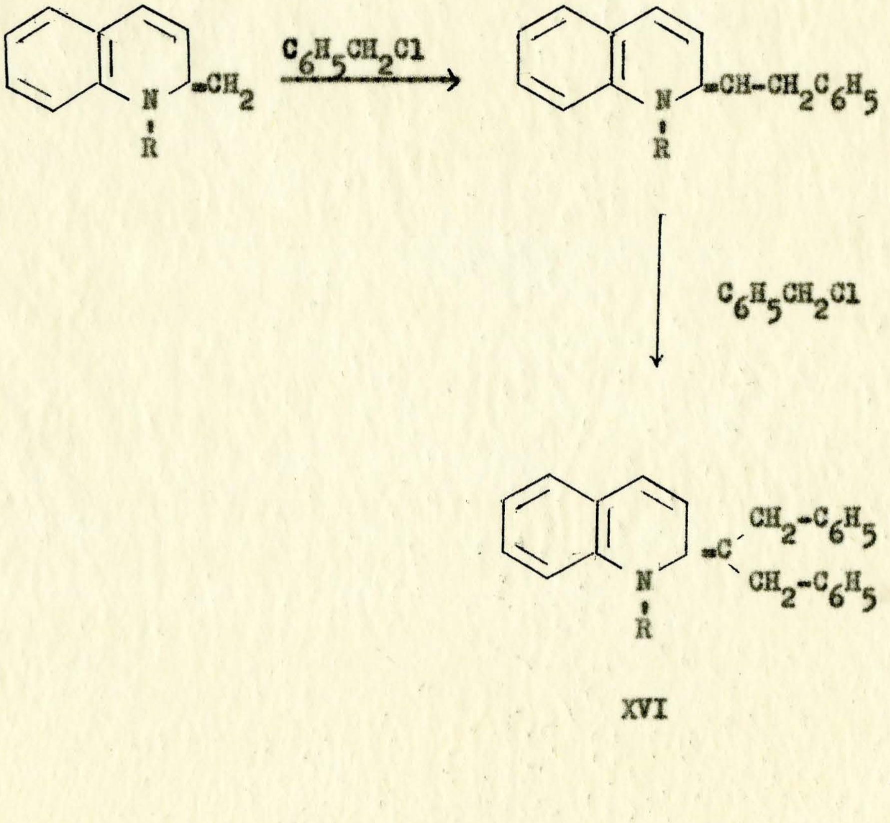
When a quaternary pyridinium salt bears an alkyl group in the 2 or 4 position from which a proton may be lost, the corresponding quaternary hydroxide is in equilibrium with a non ionic base formed by removal of a proton from the alkyl group. Such compounds are called anhydro or methylene bases. Decker (1905) pointed out the structural features necessary for this conversion and some of the properties of the system. For example, 1-methyl-2-benzyl pyridinium iodide produced an orange oil on treatment with sodium hydroxide which was soluble in benzene. Dilution with water led to decolorisation indicating reversal of the reaction. Instability of the anhydrobase prevented its isolation; spontaneous decomposition to 2-benzylpyridine occurred. Conductivity measurements of aqueous solutions of 1-methyl-2-picoline hydroxide indicate that the equilibrium is far towards the quaternary hydroxide (Aston and Lasselle, 1934).



However, structural features increase both the ease of anhydrobase formation and its stability. Thus 1-methyl-2-diphenylmethylpyridinium iodide gives a red crystalline anhydrobase (Chichibabin and Benevolenskaia, 1928). An O- or p-nitro group further increases the stability of the anhydrobase (Königs, Köhler and Blindow, 1925).

Pyridine anhydrobases in inert solvents react readily with a number of reagents, commonly associated with the chemistry of amines but reaction occurs at the methylene carbon atom adjacent to the ring. Thus carbon disulfide, isocyanates and some acid chlorides lengthen the chain. However, these reactions have not been explored extensively and their generality remains to be determined. Some interesting observations on the reactions of pyridine anhydrobases have been made by Baker and McEvoy (1955).

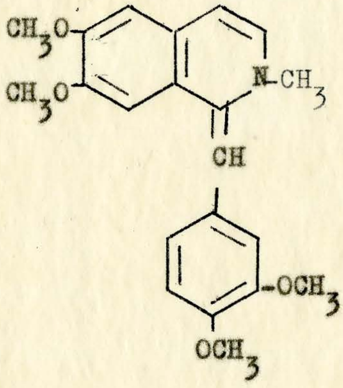
Not only quaternary pyridinium salts but also those of other heteroaromatic bases yield anhydrobases. For example, anhydrobases from N-methylnaphthaquinaldinium salts (Mills and Raper, 1925) and 2-methyl-N-methylquinolinium salts (Rosenhauer, 1926) have been prepared. These bases are highly reactive and susceptible to oxidation, on treatment with alkyl halides they undergo C-alkylation to dialkyl derivative (XVI) (Mills and Raper, 1925; Robinson and Saxton, 1952; Robinson and Hamilton, 1916.)



XVI

Some purely aliphatic examples are known in which either C-alkylation or N-alkylation have been observed (Stork, Terrel and Szmuszkovicz, 1954). In the anhydrobases reaction at the nitrogen atom would result in the loss of ring resonance energy and consequently the methylene carbon reacts exclusively, preserving the aromatic ring.

Similar anhydrobases have also been obtained in isoquinoline systems. For example, papaverine methiodide on treatment with alkali forms N-methyl isopapaverine (XVII) (Decker and Klauser, 1904; Decker, 1904).

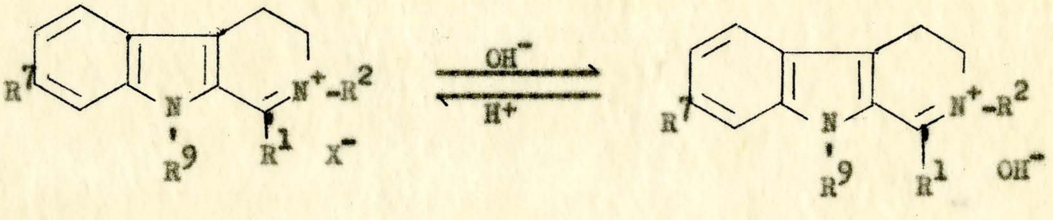


XVII

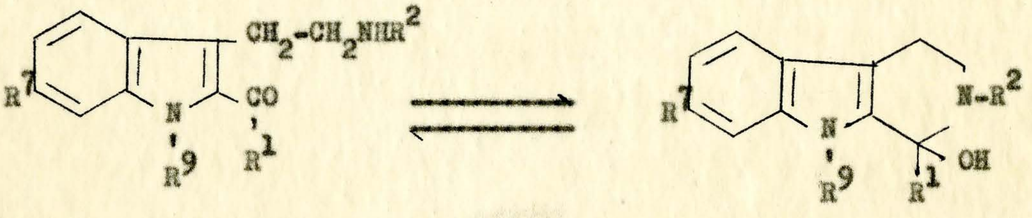
One characteristic property of both pseudo- and anhydrobases is that on acidification they revert to the ion from which they were originally derived. Many of these bases tend to give unsatisfactory analyses (Schwarz and Schlitter, 1951).

The behaviour of quaternary 3,4-dihydro-β-carbolinium salts may be schematically represented as follows.

(a)



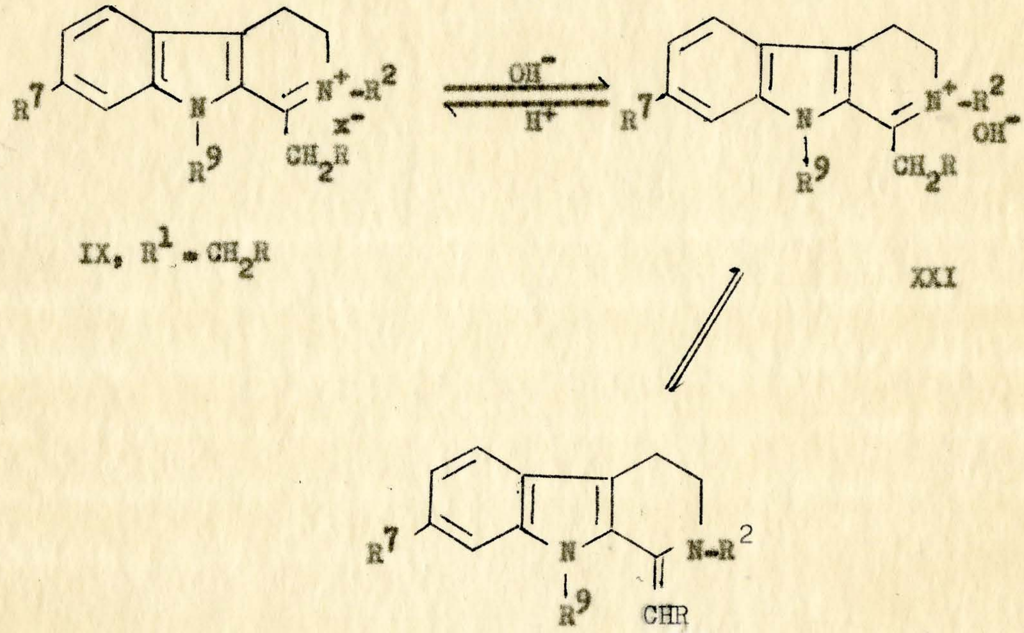
IX XVIII



XX XIX

When R^1 = H or C_6H_5, formation of an anhydrobase is not possible, since no hydrogen is available for the formation of an exocyclic double bond. On the basis of spectroscopic evidence, to be discussed later, the existence of aldehydeamine structure (XX) is excluded. When R^1 is an alkyl group an anhydrobase with an exocyclic double bond can be formed.

(b)

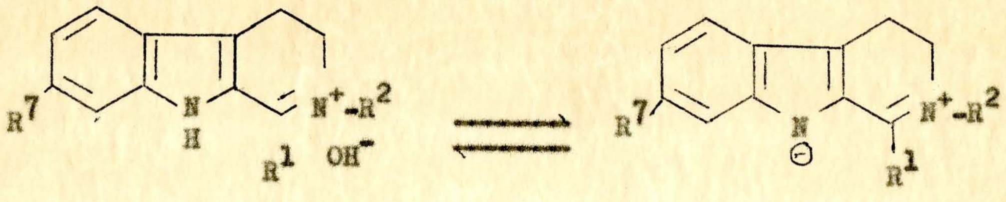


IX, $R^1 = CH_2R$

XXI

XXII

In 2-alkyl-3,4-dihydro-β-carbolinium hydroxides another transformation, involving the indole nucleus would be possible. The hydrogen attached to the pyrrole nitrogen could take part in a dehydration to yield a compound of an "isocarboline structure" (XXIII) (Perkin and Robinson, 1919b). This type of anhydrobase formation is known to occur in the case of 2-alkyl-β-carbolinium hydroxides (Spenser, 1956).



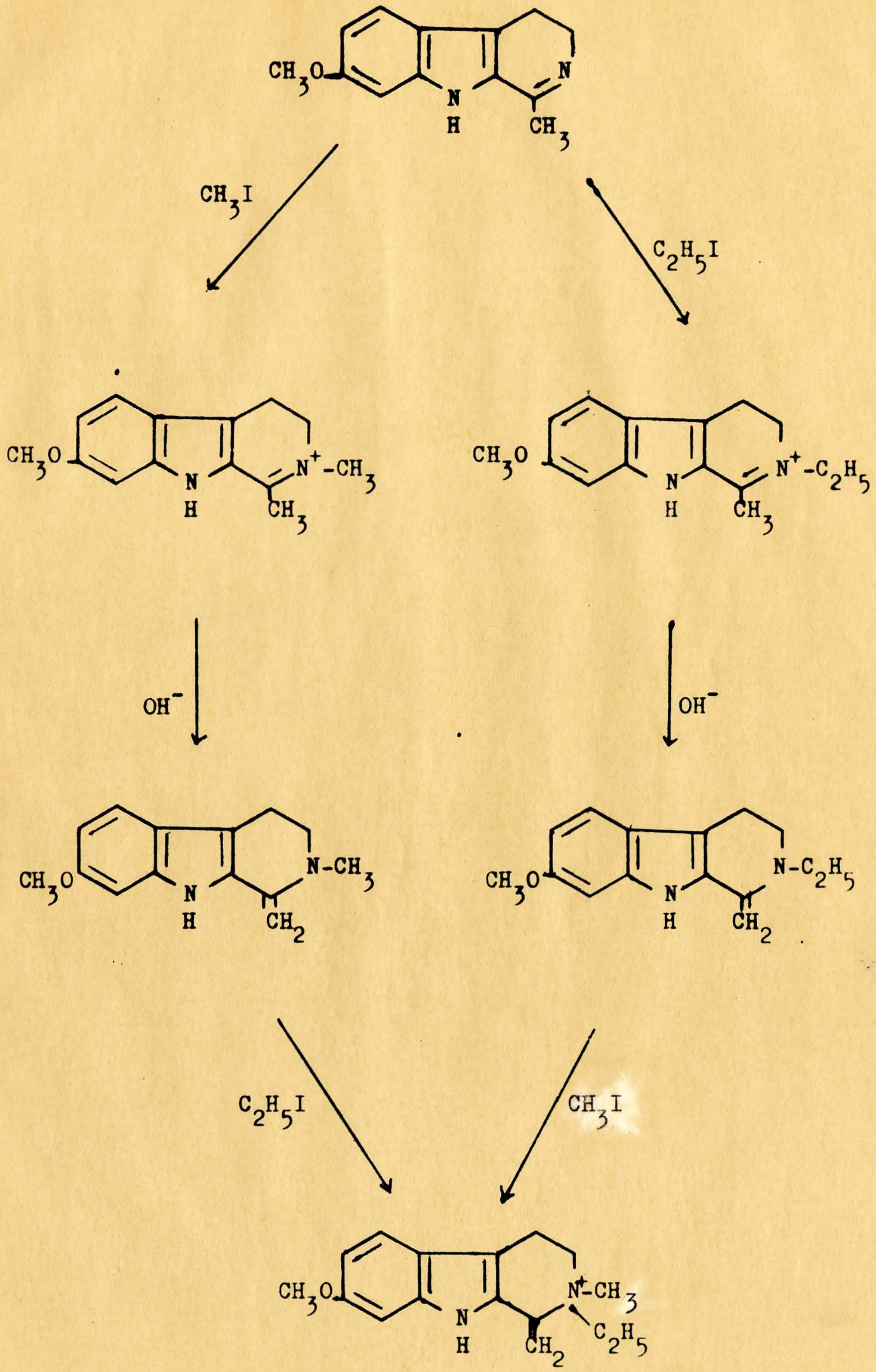
IX, R^9 = H

XXIII

Such a change could take place regardless of the nature of the substituent R^1 on C^1, but requires a replaceable hydrogen at the indole nitrogen. Since 9-substituted 3,4-dihydro-β-carbolinium salts have now been shown to yield anhydro and pseudobases in a manner analogous to 9-unsubstituted compounds, the formation of anhydrobases of the structure (XXIII) is excluded.

Further Alkylation of Dihydro-β-Carboline Anhydro and Pseudobases.

It seems that only one attempt has been made to study the further alkylation of 3,4-dihydro-β-carboline anhydro and pseudobases. Konowalowa and Orechoff (1934) reported that the treatment of 2-methyl harmaline anhydrobase with ethyliodide yielded the same quaternary salt as the reaction of 2-ethyl harmaline anhydrobase with methyliodide. The reaction sequences reported by these authors may be summarised as follows.



CH_3O
N
H
CH_3
CH_3I
C_2H_5I
N^+-CH_3
$N^+-C_2H_5$
OH^-
OH^-
$N-CH_3$
$N-C_2H_5$
CH_2
C_2H_5I
CH_3I
N^+-CH_3
C_2H_5

XXIV

The final product (XXIV) of both sequences was regarded as a 2,2-dialkyl-1-methylene-1,2,3,4-tetrahydro-β-carbolinium salt containing an exocyclic methylene group. The same exocyclic methylene group was deduced to be present in the two monoalkylated bases. The product (XXIV) was reported to be stable to base.

Earlier it had been observed (Fischer, 1914) that alkylation of harmaline with methyl iodide in alkaline solution yielded, in addition to harmaline methiodide, the 2-monoalkylated, 3,4-dihydro-β-carbolinium salt, small amounts of another alkylation product referred to as "dimethyl harmaline iodide" which on treatment with sodium hydroxide gave trimethylamine. The structure of Fischer's compound has not been clarified and the origin of trimethylamine has remained obscure.

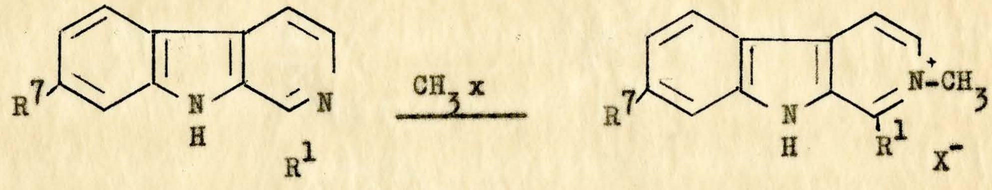
These conflicting observations of Fischer and of Orechoff are in marked contrast to the results of a similar sequence of reactions in the β-carboline series and the 3,4-dihydroisoquinoline series, which will be reviewed in the next section of this introduction. It is well established that 2-alkyl-β-carbolines on further alkylation yield ind-N-alkylated derivatives, i.e., 2,9-dialkylated salts and not 2,2-dialkylated compounds. On the other hand alkylation of 2-alkyl-3,4-dihydroisoquinoline **bases** is accompanied by ring opening and the products are quaternary salts of substituted phenylethylamines, which undergo Hofmann degradation to give tertiary amines.

This striking difference of the behaviour of the 3,4-dihydro-β-carbolines, and of 3,4-dihydro isoquinoline compounds on the one hand

and β-carbolines on the other was thought to warrant re-investigation. In the succeeding pages established knowledge bearing on the structure of the alkylation products of β-carbolines and of dihydroisoquinolines will be briefly reviewed and the results of re-investigation of the alkylation of dihydro-β-carbolines will be reported.

Alkylation of β-Carboline Derivatives

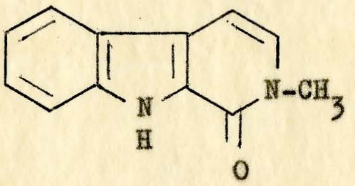
Since it was shown that the alkaloid harmine was 1-methyl-7-methoxy-β-carboline (XXV) (Perkin and Robinson, 1919a), the chemistry of the β-carboline nucleus has been fully investigated (Spenser, 1956 and earlier references quoted therein). Very recently an ever increasing number of newly isolated alkaloids has been found to contain a derived β-carboline nucleus (e.g. Witkop, 1953; Schwarz and Schlitter, 1950; Karrer and Schmid, 1955) and the interest in its properties has consequently been revived. Of the two nitrogen atoms present in β-carboline (XXVI), only one is basic and a quaternary salt (XXVII) is formed with only one mole of alkyl halide. No case of dialkylation by direct treatment of a β-carboline with an alkyl halide is known.



XXV, $R^1 = CH_3$, $R^7 = OCH_3$

XXVI, $R^1 = R^7 = H$

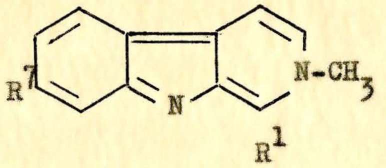
XXVII, $R^1 = R^7 = H$; $x^- = I^-$, $SO_4 Me^-$



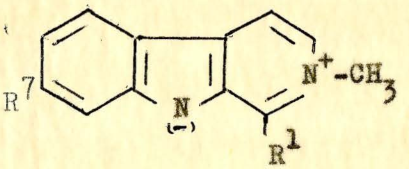
XXVIII

The position of alkylation in the quaternary salt was established by oxidation of norharman methosulfate (XXVII) with potassium ferricyanide in alkaline solution, yielding 1-oxo-2-methyl-1,2-dihydro-β-carboline (XXVIII), the structure of which was proved by independant synthesis (Kermack, Perkin and Robinson, 1922).

On treatment with strong alkali quaternary β-carbolinium salts are converted to yellow or orange anhydrobases whose chemistry has been repeatedly investigated (Spenser, 1956). Their structure is generally believed to be that of a resonance hybrid whose major canonical contributions are (XXIX) and (XXX) (Armit and Robinson, 1925; Woodward and Witkop, 1949; Schwarz and Schlitter, 1951).



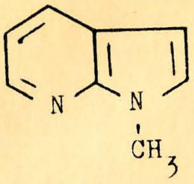
XXIX



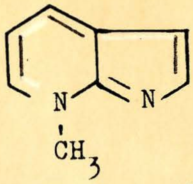
XXX

It has recently been stated, however, that there is no need to consider the polar formula (XXX) of the anhydrobase as a major contributor since the observed behaviour can be satisfactorily explained on the basis of the classical covalent structures (XXIX) (Martini-Bettolo and Paoloni, 1957). This statement was based on a calculation of the charge distribution, a measurement of dipole moment and spectral shift of pyrrolo-pyridines (XXXI) and (XXXII) which possess the fundamental conjugated system of the anhydrobases.

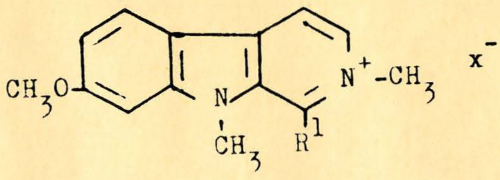
Further alkylation of the N_{β}-alkyl-β-carboline anhydrobases takes place at the indole nitrogen atom when 9-substituted quaternary salts (XXXIII) are formed (Kermack, Perkin and Robinson, 1922). This sequence of alkylation was further established when it was found that treatment of harmine with two different alkyl halides in different order yielded two isomeric compounds (XXXIV) and (XXXV) (Konowalowa and Orechoff, 1934) and has since been confirmed with other β-carboline derivatives (Spenser, 1956).



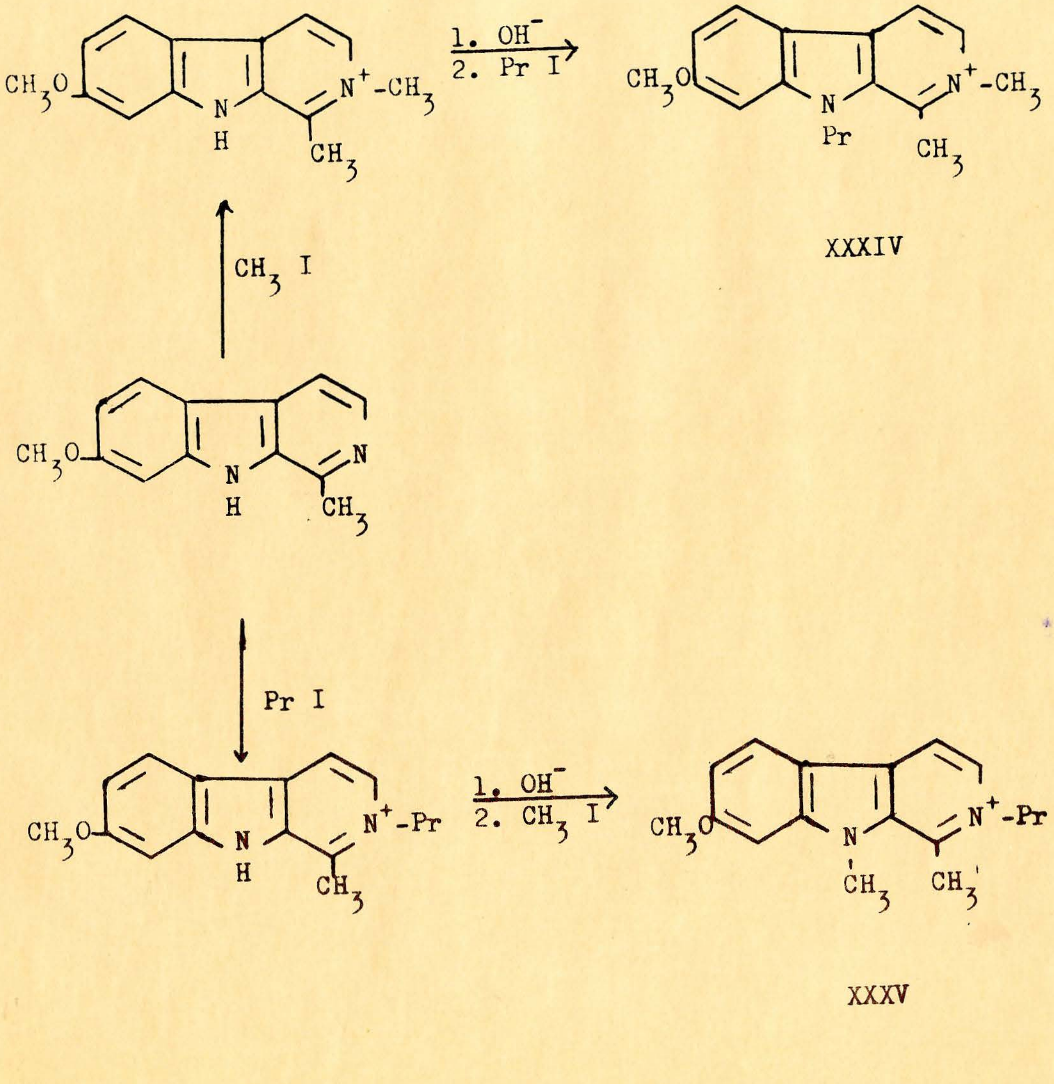
XXXI



XXXII

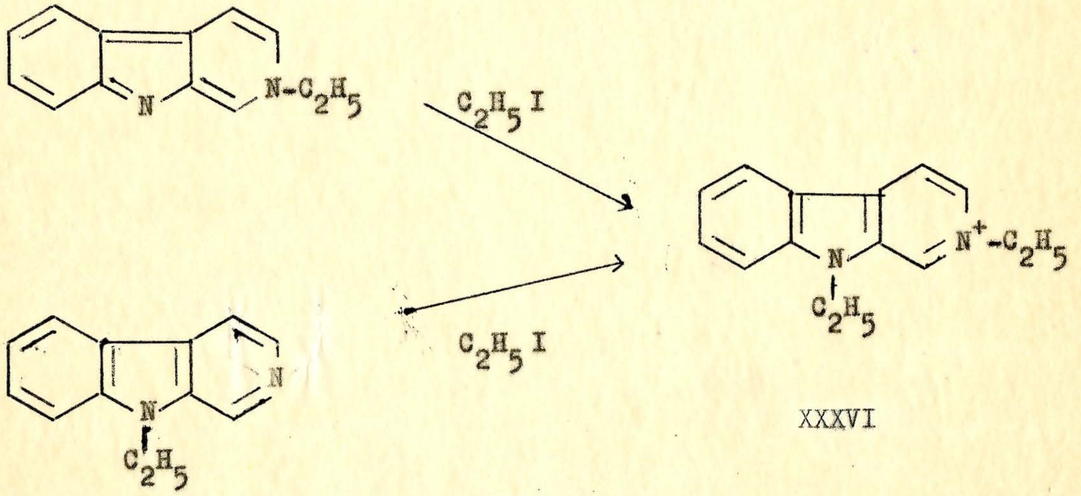


XXXIII



XXXV

Conclusive evidence in support of this alkylation sequence was the finding that both 9-ethyl-β-carboline and 2-ethyl-β-carboline anhydrobase yielded one and the same product 2,9-diethyl-β-carbolinium iodide (XXXVI) on alkylation with ethyl iodide (Leonard and Elderfield, 1942).



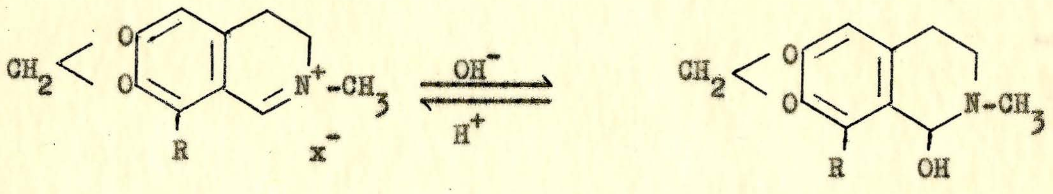
XXXVI

The fact that further alkylation of the β-carboline anhydrobases takes place at the indole nitrogen atom is best explained by regarding the dipolar amphion (XXX) as the reacting form in the alkylation reaction.

Alkylation of 3,4-Dihydroisoquinolines

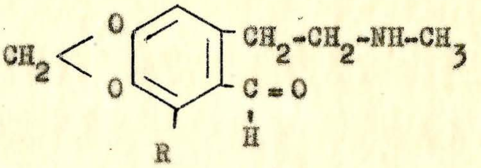
Hydrastinine (XXXVIII, R = H) and cotarnine (XXXVIII, R = OCH_3), typical 3,4-dihydroisoquinoline derivatives, exist in acid solution as (XXXVII, x^- = e.g. Cl^-). From alkaline solution they may be isolated as non ionic and relatively water insoluble pseudobases

(XXXVIII). The compounds have also been reported to exist as the open chain aldehyde amines (XXXIX).



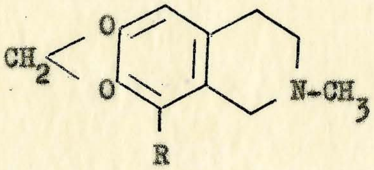
XXXVII

XXXVIII



XXXIX

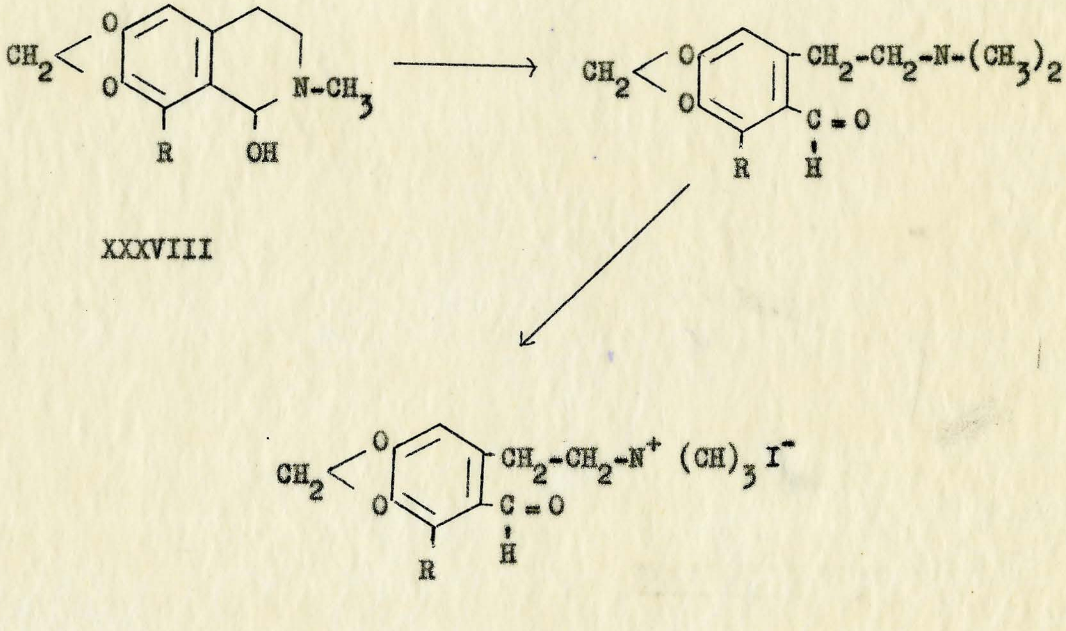
Support for the existence of an equilibrium between a non ionic (XXXVIII) and ionic form (XXXVII, $x^- = OH^-$) was obtained from the studies of the ultraviolet absorption of cotarnine and hydrastinine (Skinner, 1950; Dobbie, Lauder and Tinkler, 1903; Dobbie and Tinkler, 1904). Thus in non polar solvents the spectrum of cotarnine is different from its spectrum in polar solvents. This fact can be readily accounted for by the interpretation that in polar solvents cotarnine exists in the ionic form (XXXVII, $x^- = OH$). In alkaline solution cotarnine shows ultraviolet absorption similar to that of hydrocotarnine (XL, R = OCH_3) and therefore presumably exists as the carbinolamine (XXXVIII). Since



XL

the ultraviolet absorption of a substance with structure (XXXIX) should be different from that of (XL), just as the ultraviolet absorption of benzaldehyde differs from that of N-methyl-benzylamine, it may be concluded that cotarnine does not exist as (XXXIX). Further evidence against the existence of structure (XXXIX) is that the infrared spectra of cotarnine and hydrastinine (Schneider and Müller, 1958; Beke and Korobnits, 1959) do not show absorption due to C = O.

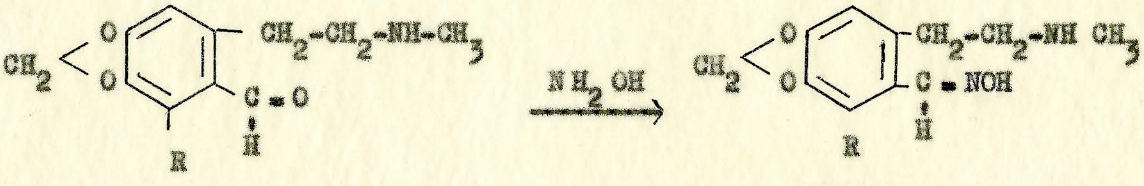
However, certain chemical properties of cotarnine have been explained on the assumption that it exists as aldehydeamine (XXXIX). Thus on treatment with methyl iodide in the presence of alkali, cotarnine gives the quaternary salt (XLI) (Roser, 1888a) which may be regarded as formed by dimethylation of (XXXIX). The formation of (XLI), however, can equally well be explained on the basis of cotarnine existing as carbinolamine (XXXVIII).



XXXVIII

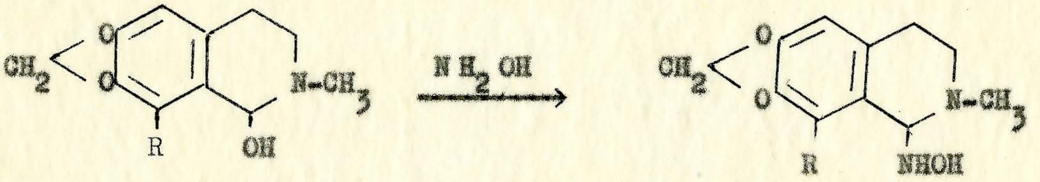
XLI

Another reaction which was interpreted as favouring the existence of the aldehydeamine form of cotarnine was the formation of an oxime to which the structure (XLII) was assigned (Roser, 1889; Dey and Kantam, 1935). As in the last case, however, its formation can be explained on the basis of the carbinolamine (XXXVIII) and the aldehydeamine (XXXIX) structures for cotarnine.



XXXIX

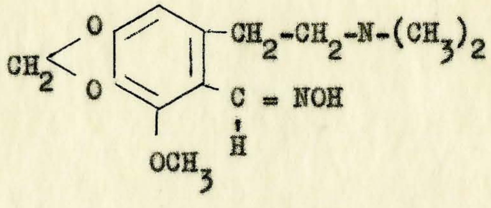
XLII



XXXVIII

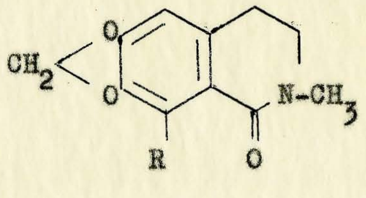
XLIII

Recently the structure of this oxime has been revised on the basis of infrared studies (Schneider and Müller, 1958). By comparison of the infrared absorption spectra of cotarnine oxime and an independantly prepared sample of compound (XLIV), it has been shown that cotarnine oxime does not show absorption at 1680 cm^{-1}, whereas (XLIV) shows absorption at this frequency and that therefore a C = N band is not present in cotarnine oxime which should consequently be represented by (XLIII).

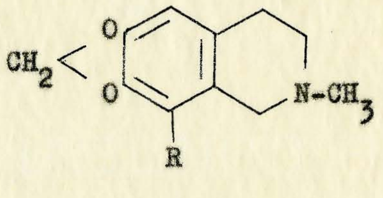


XLIV

Another example of a chemical reaction which has been attributed to the presence of an aldehydic group is the disproportionation of cotarnine on treatment with alkali (Freund and Will, 1887; Pyman, 1909) into a 1-oxo-tetrahydro (XLV) and a tetrahydroderivative (XLVI). A mechanism analogous to that of the Cannizzaro reaction was originally proposed for this disproportionation (Roser, 1888 b). Such a mechanism has since been questioned but not conclusively disproved (McGeoch and Stevens, 1934).



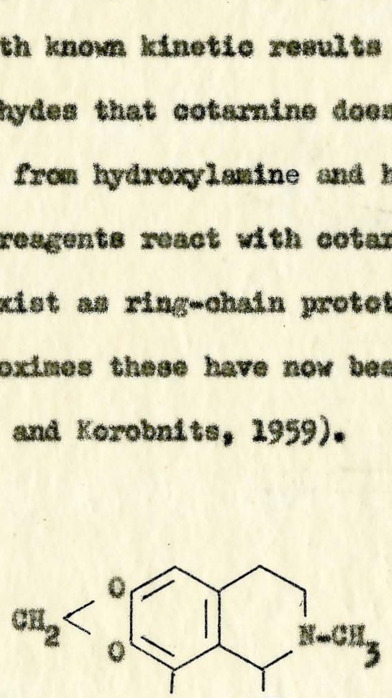
XLV



XLVI

The absence of spectroscopic evidence (both ultraviolet and infrared) does not preclude the possibility that cotarnine exhibits tautomerism between (XXXVIII) and (XXXIX). The concentration of (XXXIX) may be too small for spectroscopic detection. To decide whether cotarnine as (XXXVIII) or (XXXIX) reacts with nucleophilic reagents, its reaction with hydrocyanic acid has been kinetically studied (Beke, Szanty and Barczai, 1960) and it has been shown by comparison with known kinetic results of cyanhydrin formation of aromatic aldehydes that cotarnine does not react as the aldehyde (XXXIX).

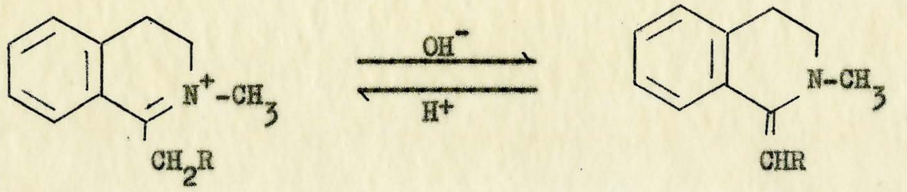
Apart from hydroxylamine and hydrocyanic acid a number of other nucleophilic reagents react with cotarnine and the products were believed to exist as ring-chain prototropic systems (Ingold, 1953), but like the oximes these have now been shown to have cyclic structures (XLVII) (Beke and Korobnits, 1959).



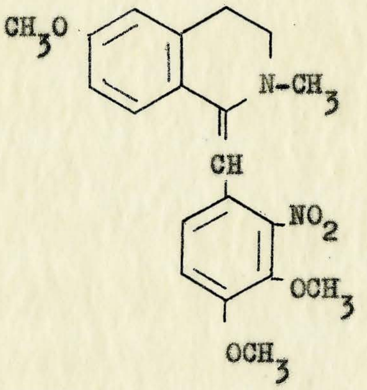
XLVII

X = NHC_6H_5, CH_2COOH, CH_2COCH_3, CH_2NO_2 etc.

Instead of pseudobases of the type (XXXVIII) anhydrobases (XLIX) would be expected from 1-alkyl3,4-dihydro-isoquinolinium alkiodides (XLVIII) on treatment with alkali. Thus a crystalline



XLVIII XLIX

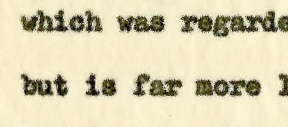


L

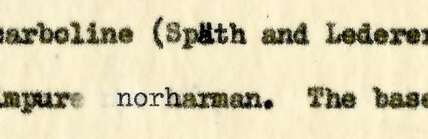
anhydrobase (L) which reverts to the original methiodide on treatment with NaI was reported by Gulland and Haworth (1927). Further alkylation of such anhydrobases does not seem to have been reported.

The Synthesis of 3,4-Dihydro-β-Carbolines and of 2-Alkyl-3,4-Dihydro-β-Carbolinium Salts

The parent base of the dihydro-β-carboline ring system, 3,4-dihydro-β-carboline (I) has not hitherto been characterised in the pure state. It was first obtained by degradation of evodiamine as a tarry mass, was characterised as the picrate (Asahina and Kashiwaki, 1915) and identified by oxidation to β-carboline (Asahina, 1924). Attempted synthesis by cyclodehydration of N_β-formyltryptamine (II) with P_2O_5 in tetralin gave an uncharacterised product in 2% yield which was regarded as 3,4-dihydro-β-carboline (Späth and Lederer, 1930) but is far more likely to have been impure norharman. The base was obtained by cyclisation of N_β-formyltryptamine in toluene as an amorphous powder yielding a picrate and a perchlorate (Schöpf and Steuer, 1947). It has now been obtained in improved yield (52%) as an amorphous powder using polyphosphoric acid as cyclodehydrating agent. Due to its sensitivity, particularly towards acids, it resisted all attempts of crystallisation or purification by chromatography when only intractible polymeric material was recovered.



I

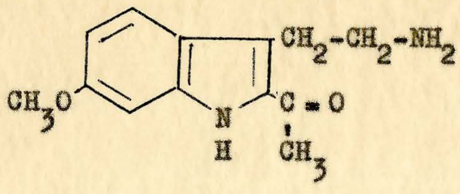


II

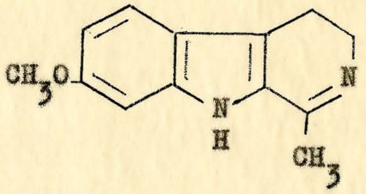
The difficulty encountered in the synthesis and purification of this base is in line with experience with analogous compounds of the isoquinoline series (Späth, Berger and Kuntara, 1930). Trimeric material analogous in structure to N-N'-N'' triphenyl ethylaminomalonamide and obtained as a byproduct in the synthesis of 3,4-dihydroisoquinoline (Decker, Kropp, Hoyer and Becker, 1913) was not detected. Partial purification was achieved on sublimation at 3×10^{-3} mm and 120 - 145°, when 3,4-dihydro-β-carboline was obtained as a glassy solid.

9-Methyl-3,4-dihydro-β-carboline was obtained in a similar way by cyclodehydration of ind-N-methyl-N_{β}-formyltryptamine with polyphosphoric acid.

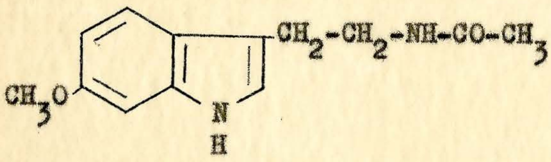
Synthesis of a large number of 1-substituted 3,4-dihydro-β-carbolines has been reported. Harmaline (III) was first synthesised by cyclisation of 2-acetyl-3-aminoethyl-6-methoxyindole (IV) (Manske, Perkin and Robinson, 1927). It was later obtained by Bischler-Napierlaski ring closure of N_{β}-acetyl-6-methoxy tryptamine (V) (Späth and Lederer, 1930) and the latter method has been widely used for the synthesis of other 1-substituted-3,4-dihydro-β-carbolines. Other methods of synthesis, based on controlled oxidation of a suitably substituted 1,2,3,4-tetrahydro-β-carboline (Perkin and Robinson, 1919 a) and on oxidative decarboxylation of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acids (Spenser, 1959) have so far found limited application only.



IV



III



V

Recently harmalan (1-methyl-3,4-dihydro-β-carboline) (VI) was obtained by condensation of glycolaldehyde (VII) with tryptamine (VIII) ($R^9 = H$), followed by dehydration of the resulting (±) 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (IX) ($R^9 = H$) (Spenser, 1959).

In the present investigation both harmalan and 1,9-dimethyl-3,4-dihydro-β-carboline were obtained by this method.

The dihydro-β-carboline derivatives which were prepared in the course of the present work are listed in Table I.

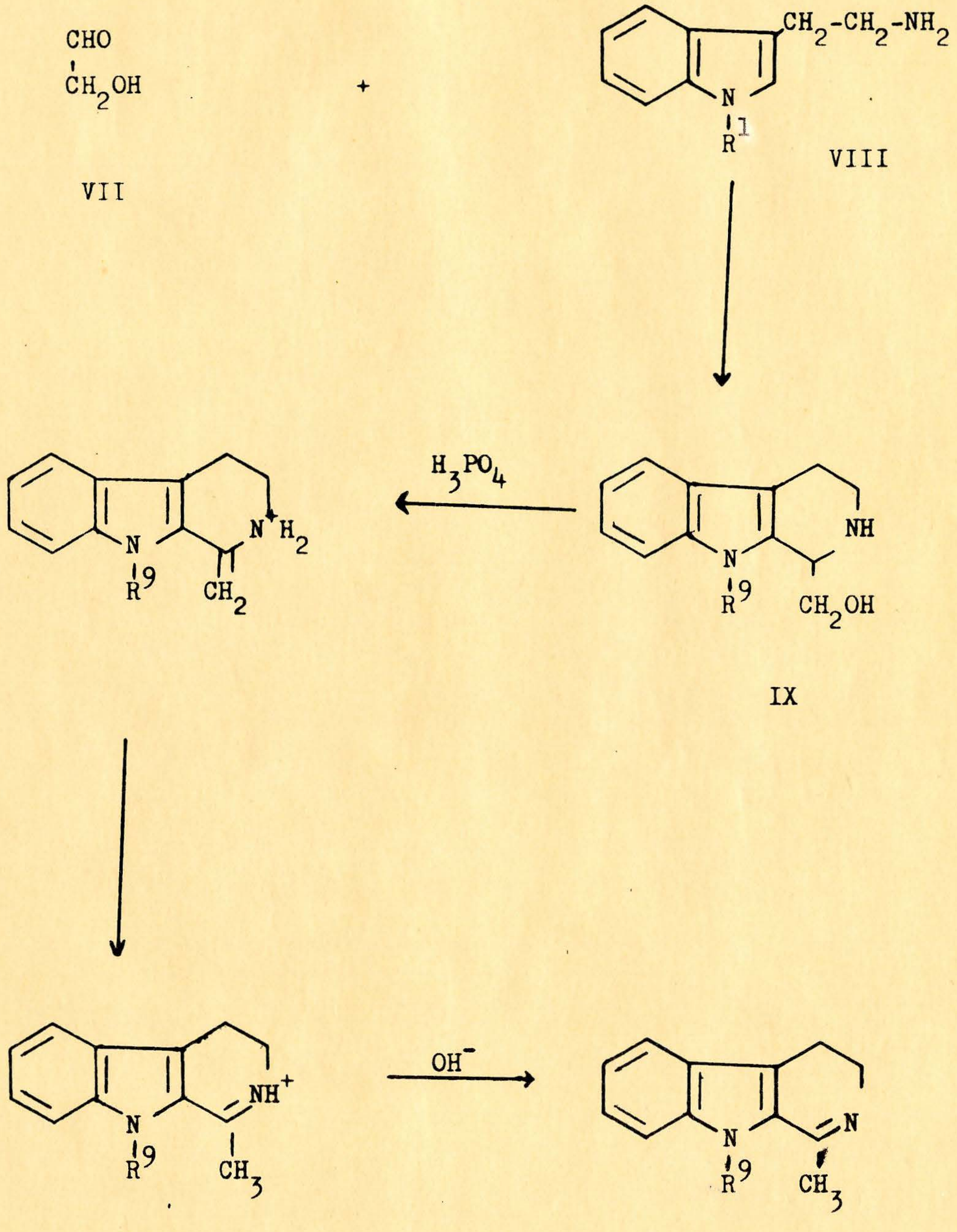
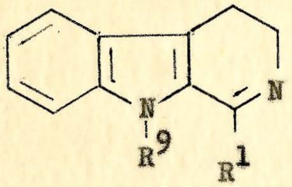
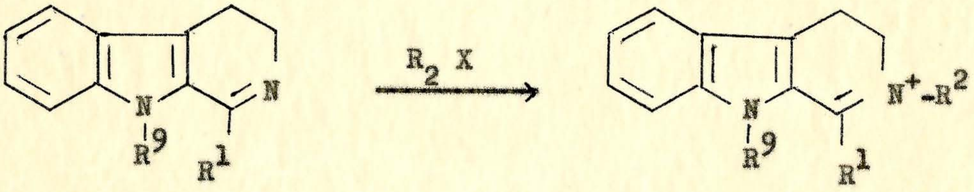

CHO
CH_2OH
VII
+
$CH_2-CH_2-NH_2$
N
R^1
VIII
H_3PO_4
N
R^9
N^+H_2
CH_2
NH
N
R^9
CH_2OH
IX
N
R^9
NH^+
CH_3
OH^-
N
R^9
N
CH_3
VI

TABLE I

3,4-Dihydro-β-Carbolines

Base		Name	M.P.
			
R^1	R^9		
H	H	3,4-dihydro-β-carboline (norharmalan)	120 - 125°
H	CH_3	9-Me-3,4-dihydro-β-carboline	120 - 130°
CH_3	H	1-Me-3,4-dihydro-β-carboline (harmalan) (Spenser, 1959)	180 - 181°
C_2H_5	H	1-Et-3,4-dihydro-β-carboline (Späth and Lederer, 1930)	150 - 160°
CH_3	CH_3	1,9-dimethyl-3,4-dihydro-β-carboline	80 - 84°

Dihydro-β-carbolines behaved as tertiary amines and on alkylation formed yellow to orange quaternary salts (X). These salts were invariably monoalkylated and no trace of dialkylated salts could be detected. The quaternary salts which were prepared are listed in Table II.

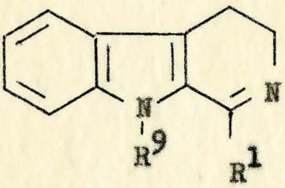
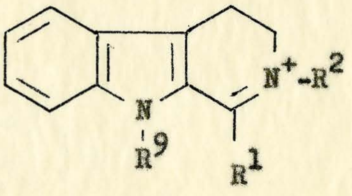


X

$R_2X = CH_3I$ or $n\text{-}C_3H_7I$

TABLE II

2-Alkyl-3,4-Dihydro-β-Carbolinium Iodides

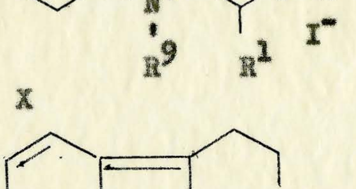
Parent Base	Alkyl Halide	Quaternary Salt	M.P.
			
$R^9 = R^1 = H$	CH_3I	$R^1 = R^9 = H$ $R^2 = CH_3$ (monohydrate)	223 after sintering at 215°
$R^9 = CH_3$ $R^1 = H$	CH_3I	$R^1 = H$ $R^2 = R^9 = CH_3$	228°
$R^9 = H$ $R^1 = CH_3$	CH_3I	$R^9 = H$ $R^1 = R^2 = CH_3$	280°
$R^9 = H$ $R^1 = CH_3$	CH_3 CH_2 CH_3I	$R^9 = H$ $R^1 = CH_3$ $R^2 = n\text{-}Pr$	269°
$R^9 = H$ $R^1 = C_2H_5$	CH_3I	$R^9 = H$ $R^1 = C_2H_5$ $R^2 = CH_3$	224 - 225°
$R^9 = R^1 = CH_3$	CH_3I	$R^9 = R^1 = R^2 = CH_3$ (monohydrate)	216°

The Structure of Dihydro-β-Carboline Anhydro and Pseudobases

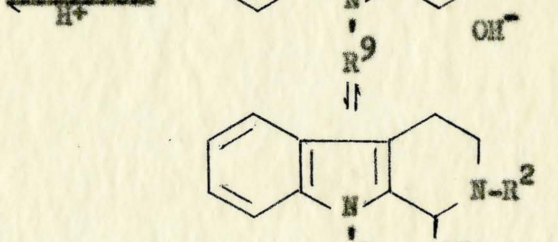
When an aqueous solution of each of the quaternary dihydro-β-carbolinium salts was treated with sodium hydroxide the corresponding pseudo- or anhydrobase formed. Since the structure of the products so obtained from 1-alkyl substituted compounds differed from those obtained from 1-unsubstituted salts the two groups of compounds will be discussed separately.

The Products Derived from 1-Unsubstituted Quaternary 3,4-Dihydro-β-Carbolinium Salts

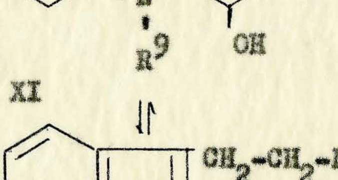
1-Unsubstituted quaternary salts (X, $R^1 = H$) would be expected, by analogy with the behaviour of 3,4-dihydroisoquinolinium salts, to give the pseudobase (XI) on treatment with sodium hydroxide according to the following sequence.



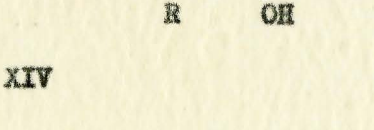
X



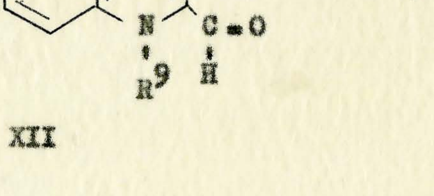
XIII



XI



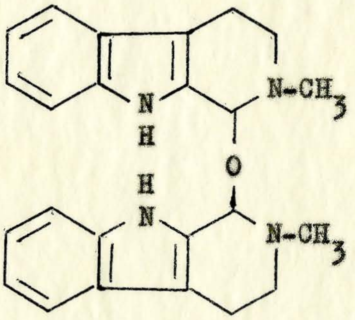
XIV



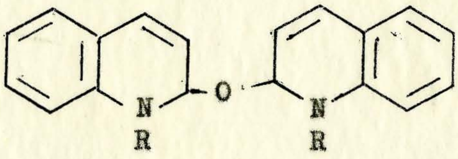
XII

The pseudobase derived from (X, $R^1 = R^9 = H$, $R^2 = CH_3$), which on this basis should be 1-hydroxy-2-methyl-1,2,3,4-tetrahydro-β-carboline, is a colourless solid which is remarkably stable. It crystallises well and can be kept indefinitely without decomposition or darkening. In alkaline or non aqueous solvents the substance shows ultraviolet absorption similar to that of indole, whereas in acidic solution the absorption becomes similar to that of the quaternary salt. This easy reversion to the original quaternary salt is a characteristic property of pseudo and anhydrobases (Sidgwick, 1937). The ultraviolet absorption spectra of the compound are compatible with its formulation as (XI). The infrared absorption spectrum of the compound, however, does not show bands which can be assigned to OH or NH. This lack of OH and NH absorption is not in itself conclusive evidence against formulation (XI). A similar absence of OH absorption has been observed in other pseudobases. Thus hydrastinine (XIV, $R = H$) and cotarnine (XIV, $R = OCH_3$) fail to show OH absorption (Schneider, 1961). Similarly only very weak OH bands were observed in the infrared spectrum of vomalidine, a new alkaloid of the ajmaline group (Hofmann and Frey, 1957). Further, it has now been found that many 1-substituted 3,4-dihydro-β-carbolines do not show NH absorption. More serious evidence against the formulation of the pseudobase as (XI), however, is provided by its elementary analysis which indicates that C, H and N account for the composition of the compound which therefore does not contain oxygen. Structure (XI) cannot therefore represent the compound.

This analytical result also eliminates the possibility that the substance has the structure (XV) of a dimeric ether base analogous to (XVI) obtained in the quinoline series (Hantzsch and Kalb, 1899; Kaufmann and Strubin, 1911).



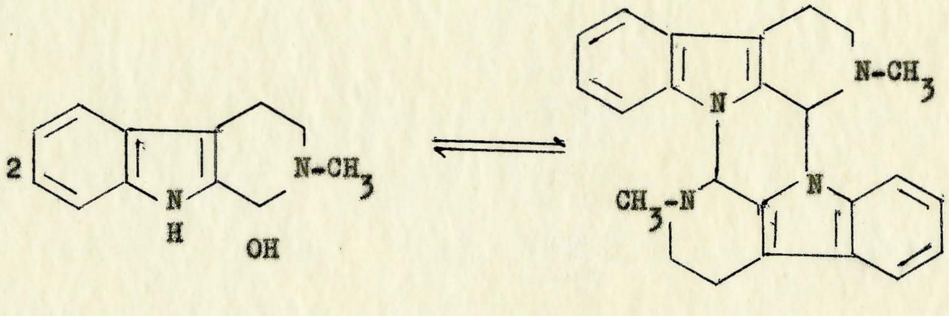
XV



XVI

The aldehydeamine structure (XII) for the compound is eliminated on the basis of ultraviolet, infrared absorption spectra and elemental analysis. The compound does not show any absorption which may be attributed to the presence of a C = O group. Structure (XIII), corresponding to anhydrobases of the β-carboline series, cannot be accepted on the basis of the behaviour of the compound towards further alkylation which is discussed later.

To account for the experimental findings a different formulation is required. A structure which can account for all the observed properties of the product is (XVII), a formulation of the compound as a dimeric anhydrobase, which in solution is in equilibrium with pseudobase (XI).

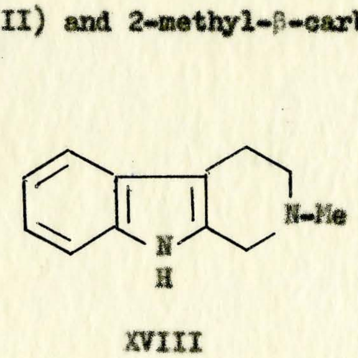


XI

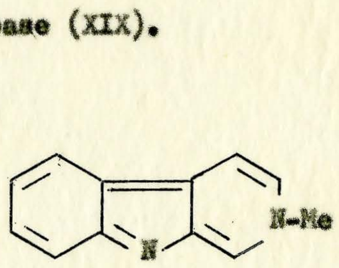
XVII

Such a dimeric structure would account for the observed analytical result, the lack of NH and OH absorption in the infrared and is also in accord with the ultraviolet spectrum. In direct evidence for a dimeric structure a molecular weight of 346 ± 35 was found for the substance by thermoelectric measurement (Schwarzkopf Microanalytical Laboratory). The calculated molecular weight of the dimer is 368. This dimeric structure may also explain the unusual stability of the compound.

Another property of the product which may be accounted for by a dimeric structure is an unusual disproportionation reaction. Pseudobases of the 3,4-dihydroisoquinoline series undergo disproportionation into a tetrahydro and a 1-oxo-tetrahydro derivative on treatment with alkali (Freund and Will, 1887; Pyman, 1909). A mechanism analogous to that of the Cannizzaro reaction was originally proposed for this disproportionation (Roser, 1888 b). Such a mechanism has been questioned but not conclusively disproved (McGeoch and Stevens, 1934). The product, now formulated as a dimeric dihydro-β-carboline anhydrobase, does not undergo this disproportionation on treatment with alkali. This may be related to the fact that indole-2-aldehyde does not appear to undergo the Cannizzaro reaction (Taylor, 1950). However, the dimeric base undergoes another type of disproportionation. On distillation under high vacuum it yielded 2-methyl-1,2,3,4-tetrahydro-β-carboline (XVIII) and 2-methyl-β-carboline anhydrobase (XIX).

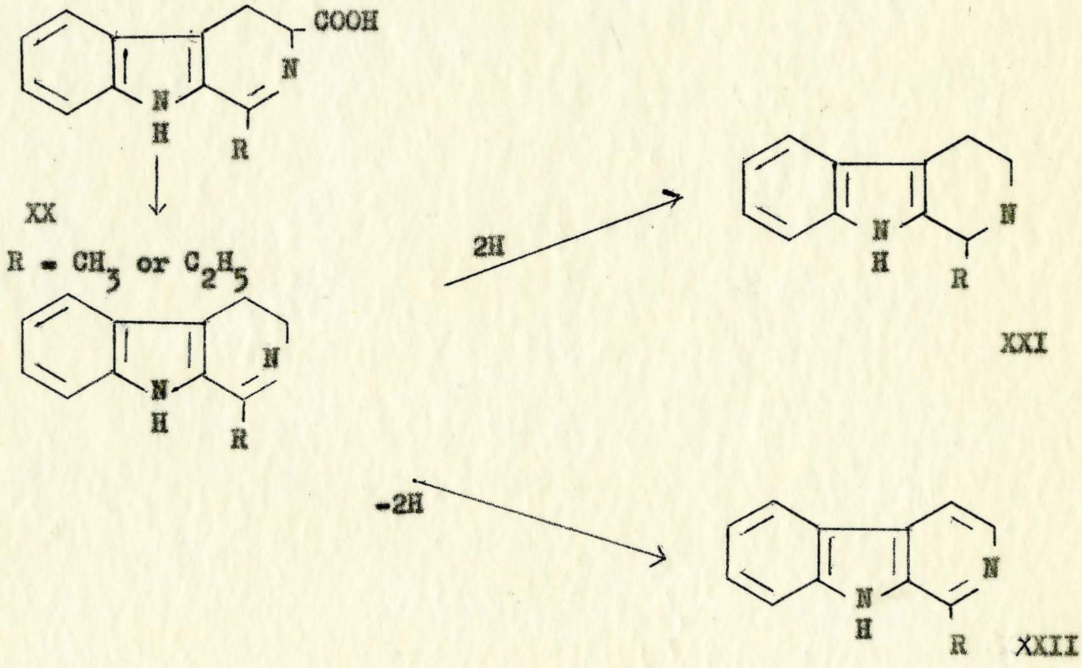


XVIII



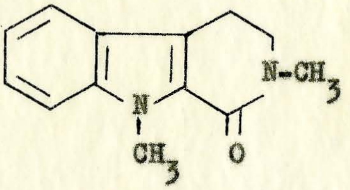
XIX

Similar disproportionations have been observed in the dihydroisoquinoline series. Thus 1-phenyl-3,4-dihydroisoquinoline yields 1-phenyl isoquinoline and 1-phenyl-1,2,3,4-tetrahydroisoquinoline on distillation (Brodrick and Short, 1949). Recently, 3,4-dihydro-β-carboline derivatives have also been reported to behave in this way. Distillation under reduced pressure of 1-alkyl-3,4-dihydro-β-carboline-3-carboxylic acid (XX) yielded 1-alkyl-1,2,3,4-tetrahydro-β-carboline (XXI) and 1-alkyl-β-carboline (XXII) (Jenssen and Tschesche, 1960). This was explained by following reaction sequence according to which the primary product, 1-alkyl-3,4-dihydro-β-carboline, formed by decarboxylation of the parent compound (XX), undergoes disproportionation similar to 1-phenyl-3,4-dihydroisoquinoline.

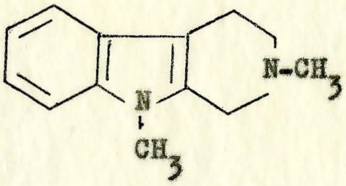


In the present work, however, dihydro-β-carbolines sublimed under high vacuum without any detectable decomposition or disproportionation. These bases were in fact purified by sublimation under high vacuum. It seems therefore that another explanation must be sought for the reported observation.

The product obtained from 9-methyl-3,4-dihydro-β-carboline methiodide by treatment with base differs from its lower homologue in being non crystallisable and susceptible to atmospheric oxidation. The substance cannot be formulated as a dimeric anhydrobase because the indole nitrogen is substituted. The ultraviolet and infrared absorption spectra of the compound are similar to those of the dimeric base. However, these observed ultraviolet and infrared spectra are satisfactorily accounted for by assuming structure (XI, $R^9 = R^2 = CH_3$). When the compound was refluxed with alkali a small amount of a neutral product presumably 1-oxo-2,9-dimethyl-1,2,3,4-tetrahydro-β-carboline (XXIII) was then isolated, but no trace of 2,9-dimethyl-tetrahydro-β-carboline (XXIV) could be detected. The compound therefore does not undergo a cotarnine type disproportionation. The formation of (XXIII) seems to be due to atmospheric oxidation of the compound, which yields traces of (XXIII) also on high vacuum sublimation although most of the starting compound sublimes unchanged. It seems very likely therefore that on the basis of its ultraviolet and infrared spectra, and its susceptibility to oxidation, the compound is pseudobase (XI, $R^9 = R^2 = CH_3$). Since the compound could not be purified, analysis was not attempted.

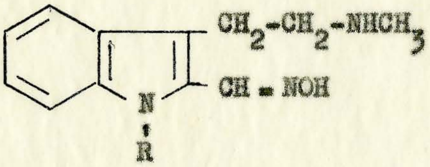


XXIII

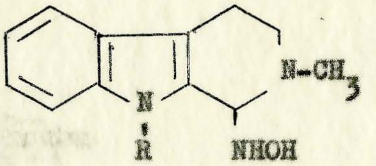


XXIV

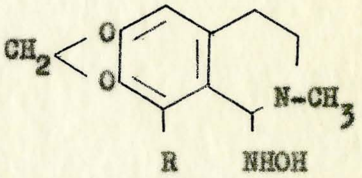
Both the dimeric base (XVII) and the pseudobase (XI, $R^9 = R^2 = CH_3$) react with hydroxylamine. The products formed may have the structure of an open chain oxime (XXV) or of a hydroxylamino substitution product (XXVI). Since in agreement with recent observations in the case of cotarnine oxime (Schneider and Müller, 1958), infrared spectra of solid samples of these compounds do not show oxime bands in the region 1600 - 1700 cm^{-1}, 1-hydroxylamino- 2 -alkyl-1,2,3,4-tetrahydro-β-carboline (XXVI) is the more likely structure of these compounds.



XXV, R = H or CH_3



XXVI, R = H or CH_3

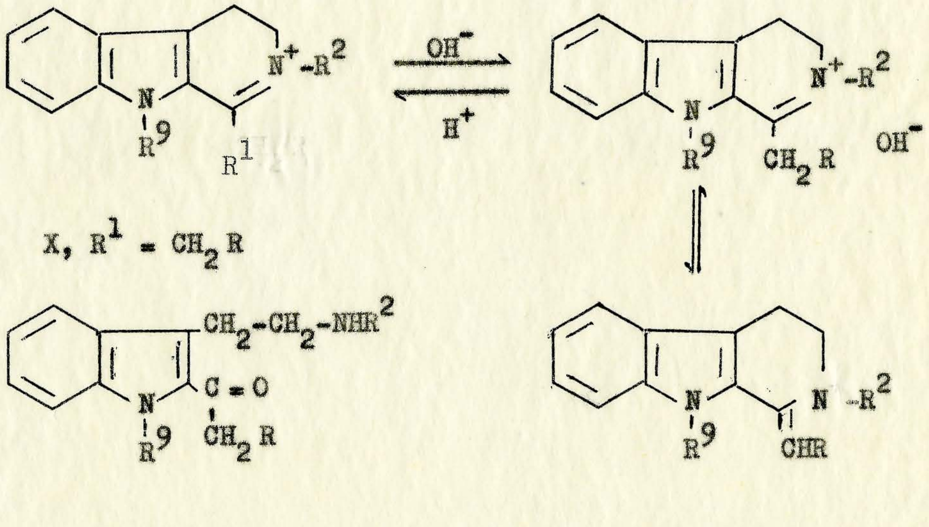


XXVII, R = OCH_3

However, these derivatives give ultraviolet spectra similar to that of 2-formyl indole, unaffected by pH, or by the nature of the solvent. This observation cannot be explained on the basis of structure (XXVI) which should give a spectrum similar to that of indole. The observed spectrum would be more consistent for an aldoxime group conjugated with the indole nucleus, i.e., for the structure (XXV). It is therefore likely that these compounds exist in two different forms in the solid state and in the dilute solution.

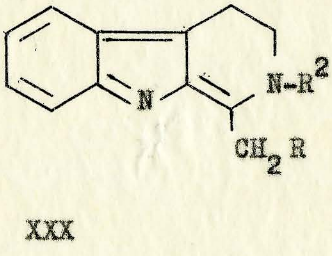
The Products Derived from Quaternary 1-Alkyl-3,4-Dihydro-β-Carbolinium Salts

When 1-alkyl substituted quaternary salts (X, $R^1 = -CH_2R$) are treated with sodium hydroxide in aqueous solution, products are formed which, by analogy with the behaviour of similar dihydroisoquinoline derivatives may be formulated as anhydrobases derived according to the following scheme.



XXIX

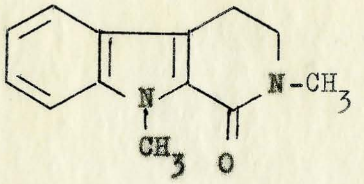
XXVIII



XXX

The observed properties of the products are in best agreement with the anhydrobase structure (XXVIII). Thus the elemental analysis of the product obtained from (X, $R^1 = R^2 = CH_3$; $R^9 = H$) is accounted for by carbon, hydrogen and nitrogen only and the compound therefore does not contain oxygen. The infrared absorption spectrum shows a band in the region 1600 - 1700 cm^{-1}, whose intensity is much lower than that of a $C = O$ band in this region. The observed band may be attributed to $C = C$ and this eliminates the ketoamine structure (XXIX). A structure (XXX) analogous to that of β-carboline anhydrobases is excluded on the basis of infrared spectra which show NH bands (Schwarz and Schlitter, 1951) which would not be expected from (XXX). The study of further alkylation of these compounds which is discussed later also eliminates the structure (XXX).

The anhydrobases derived from harmalan methiodide (X, $R^1 = R^2 = CH_3$; $R^9 = H$) and harmalan propiodide (X, $R^1 = CH_3$; $R^2 = n\text{-}C_3H_7$; $R^9 = H$) sublimed under high vacuum without decomposition or disproportionation to give light yellow solids which darkened on standing. The anhydrobase derived from 9-methyl harmalan methiodide (X, $R^1 = R^2 = R^9 = CH_3$) decomposed in the course of distillation. The small amount of distillate obtained showed an ultraviolet spectrum unaffected by pH similar to that of 2-formyl indole. Quantities obtained were insufficient for characterisation but the change in ultraviolet absorption is consistent with formation of the 1-oxoderivative (XXXI) by air oxidation.



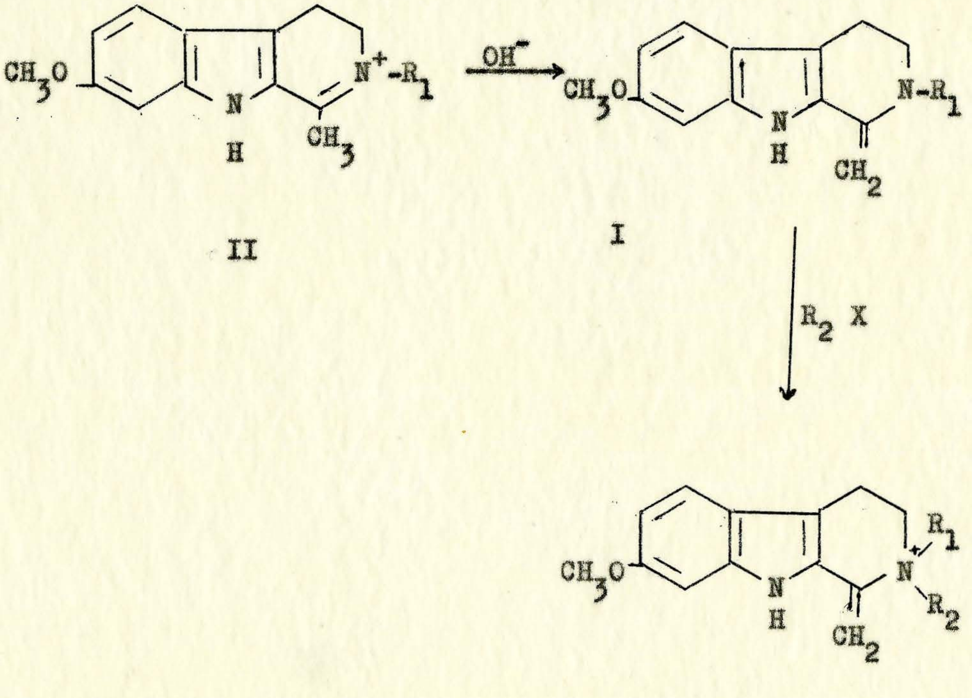
XXXI

These findings confirm the classical formulation of the structure of N_β-methyl harmaline anhydrobase (Nishikawa, Perkin and Robinson, 1924).

Further Alkylation of the Pseudo- and Anhydrobases

The Alkylation of 1,2-Dialkyl-3,4-Dihydro-β-Carboline Anhydrobases

According to Konowalowa and Orechoff (1934), the further alkylation of the anhydrobase of structure (I) obtained from harmaline alkiodide (II) takes place at N_{β}. These authors reported that when (II) was refluxed with alkyl halide in alcoholic solution for six hours a substance of structure (III) was obtained which was stable to treatment with base.



II

I

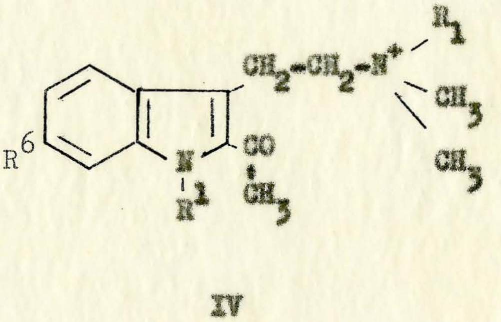
III

Before the constitution of harmaline was fully established Fischer (1914) isolated, from the mother liquors obtained during the methylation of harmaline with methyl iodide in alkaline solution, a quaternary salt which he referred to as "dimethyl harmaline iodide". This compound whose structure has not been clarified gave trimethylamine, identified as the chloroplatinate, on treatment with base at room temperature. One of the aims of the present investigation was to reconcile these conflicting results.

Since harmalan and its derivatives are considerably more accessible than harmaline, and since it is a reasonable assumption that both compounds behave similarly on alkylation, the present work was carried out with the former group of compounds.

It was found that anhydrobases derived from 1-alkyl and 1,9-dialkyl-3,4-dihydro-β-carboline alkiodides do not alkylate to an appreciable extent under the conditions used by Konowalowa and Orechoff. Instead of dialkylated products, 3,4-dihydro-β-carboline alkiodides of the structure of type (I), i.e. the salts of the starting materials to which the anhydrobases had reverted, were recovered. The ultraviolet spectra of the mother liquors from these experiments did, however, show weak additional absorption unaffected by pH, at 310 mμ.

When anhydrobases obtained from harmalan alkiodides were treated with methyl iodide in alcoholic potassium carbonate suspension, however, new quaternary salts were indeed obtained. On the basis of evidence to be presented below, these can be formulated as (IV). The compounds of this type which have now been prepared are summarised in Table III.

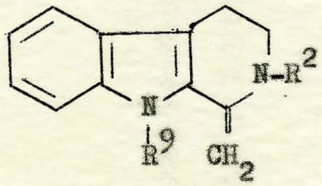
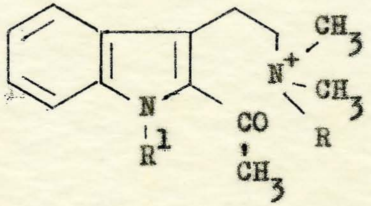
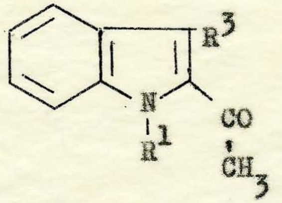


IV

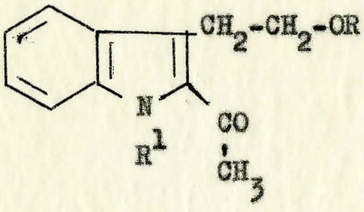
The structure of these compounds was established by analysis, ultraviolet and infrared spectra and Hofmann degradation. These compounds showed very strong C = O absorption in the region 1640 - 1650 cm^{-1} in the infrared, and ultraviolet absorption at 310 mμ similar to that of 2-formyl indole, unaffected by pH. On treatment with base each of these quaternary salts gave a tertiary amine and a neutral fragment. The tertiary amine was isolated in every case as the picrate which was characterised by melting point and analysis. Since in this type of reaction there is always a competition between substitution and elimination, the neutral fragment was invariably a mixture whose composition was dependent upon reaction conditions and the nature of substrate. In most cases either the substitution product, 2-acetyl-3-(β-alkoxyethyl) indole (V) or the elimination product 2-acetyl-3-vinyl indole (VI) was obtained and characterized by ultraviolet and infrared

TABLE III

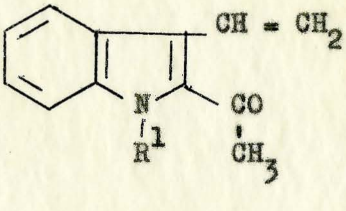
Alkylation of Anhydrobases and Hofmann Degradation of Quaternary Salts

Anhydrobase		Products of Alkylation			Products of Hofmann Degradation of Quaternary Salts			
		Quaternary Salt			Neutral Fragment			Basic Fragment
								
				M.P.			M.P.	
R^9 = H	R^2 = CH_3	R^1 = H	R = CH_3	278°	(a) R^1 = H	R^3 = $CH_2 - CH_2 - OCH_3$	140°	Trimethylamine
					(b) R^1 = H	R^3 = $CH_2 - CH_2 - OC_2H_5$	118°	Trimethylamine
R^9 = H	R^2 = n-C_3H_7	R^1 = H	R = n-C_3H_7	170°	(a) R^1 = H	R^3 = $CH_2 - CH_2 - OCH_3$	140°	Dimethyl-n-propyl amine
					(b) R^1 = H	R^3 = $CH_2 - CH_2 - OC_2H_5$	118°	Dimethyl-n-propyl amine
R^9 = CH_3	R^2 = CH_3	R^1 = CH_3	R = CH_3	215°	R^1 = CH_3	R^3 = - CH = CH_2	54°	Trimethylamine

spectra and analysis. The ethers (V) showed ultraviolet absorption unaffected by pH similar to that of quaternary salt (IV). Besides



V

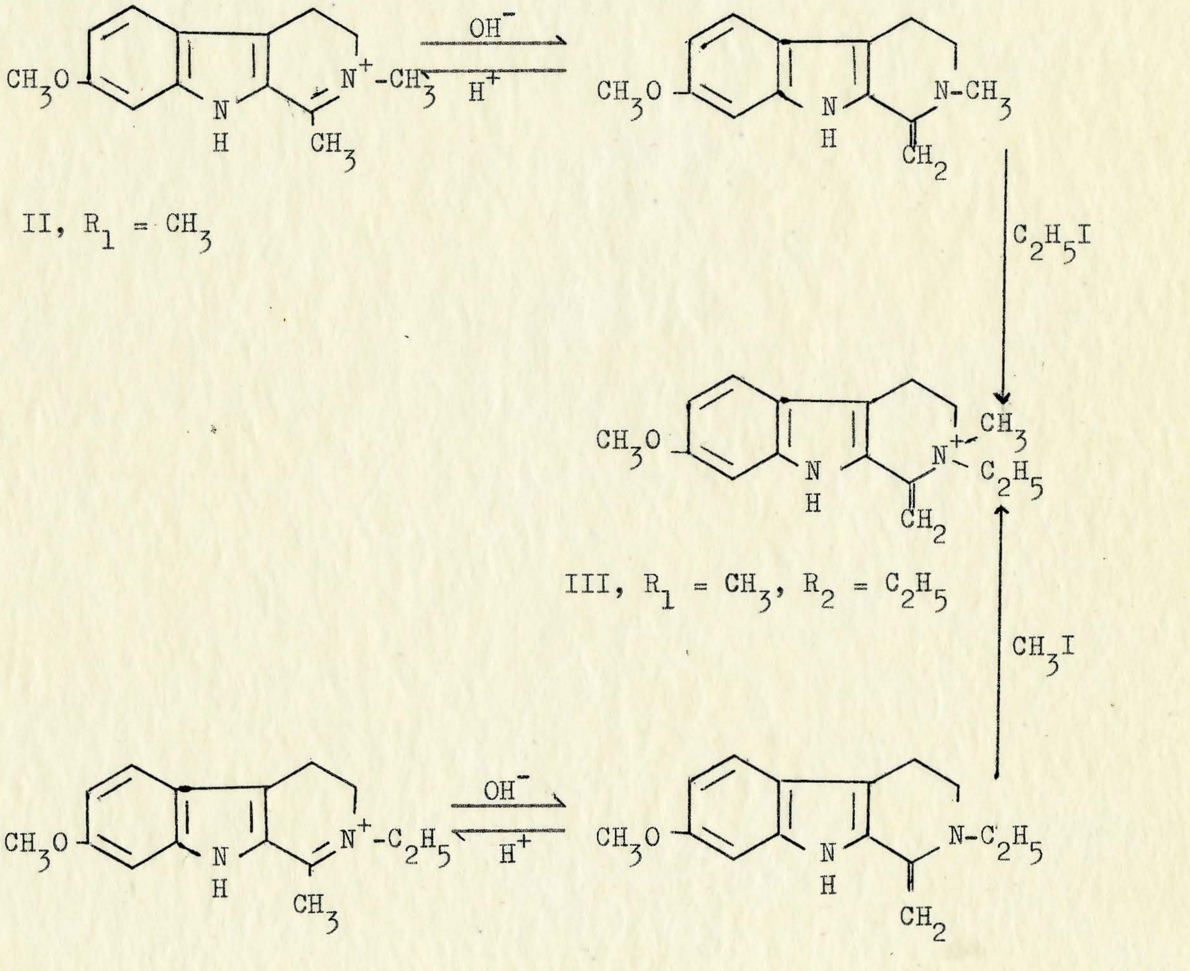


VI

strong absorption due to C = O, bands due to OR in the region 1000 - 1200 cm^{-1} were observed in the infrared spectra of the ethers. When the Hofmann degradation was carried out in two different alcohols (CH_3OH, C_2H_5OH), in each case a different ether was obtained from the same quaternary salt (V, R = CH_3 and R = C_2H_5). The results of O-alkyl determination agreed with the calculated values. The ultraviolet absorption of the vinyl compounds (VI) was shifted to longer wavelengths and in addition to the extended bands due to C = O absorption, bands due to C = C stretching were observed in the infrared absorption spectra.

Since the behaviour of anhydrobases derived from quaternary 9-alkyl substituted 3,4-dihydro-β-carbolinium salts on further alkylation is similar to that of 9-unsubstituted derivatives, these compounds cannot have a structure corresponding to that of the β-carboline anhydrobases. The formation of anhydrobases of the latter type is not possible from 9-substituted compounds.

It has thus been established that the course of further alkylation of 1,2-dialkyl-3,4-dihydro-β-carboline is not as reported by Konowalowa and Orechoff. Their evidence that the reaction led to dialkyl quaternary salts (III) was based on the supposed identity of the products obtained in the following reaction sequences.



II, $R_1 = CH_3$

III, $R_1 = CH_3$, $R_2 = C_2H_5$

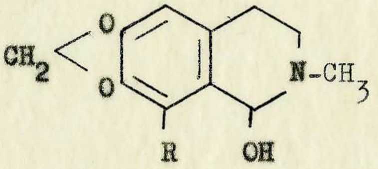
II, $R_1 = C_2H_5$

The sole criteria for this identity were the melting points and iodine analysis of the two products. This evidence is certainly inadequate and it seems that Konowalowa's quaternary salts were in fact the starting alkiodides (II). Hydriodic acid required for the reversion of (I) to (II) is formed by solvolysis of alkyl halide during refluxing.

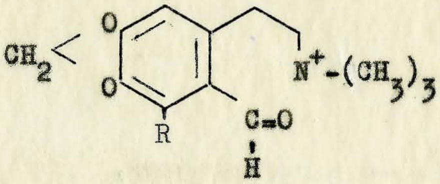
Fischer did not explain the formation of trimethylamine from the quaternary salt which he referred to as "dimethyl harmaline iodide". In the light of the present findings it seems that the uncharacterised "dimethyl harmaline iodide" was presumably the quaternary salt of structure (IV, $R^6 = OCH_3$, $R_1 = CH_3$, $R^1 = H$).

The Alkylation of the Products Obtained from Quaternary 1-unsubstituted 3,4-Dihydro-β-Carbolinium Salts

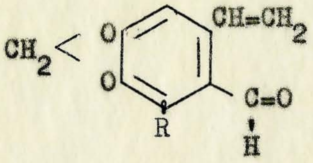
Further alkylation of the bases obtained from 1-unsubstituted 3,4-dihydro-β-carbolinium salts does not seem to have been attempted before, although such studies have been repeatedly made with bases obtained from similar 3,4-dihydro-isoquinolinium salts. Thus cotarnine (VII, $R = OCH_3$) and hydrastinine (VII, $R = H$) on treatment with methyl-iodide in the presence of alkali yield quaternary salts (VIII), the structure of which was established by Hofmann degradation and isolation of trimethylamine and the vinyl piperonal (IX) (Roser, 1888 a; Freund, 1889).



VII

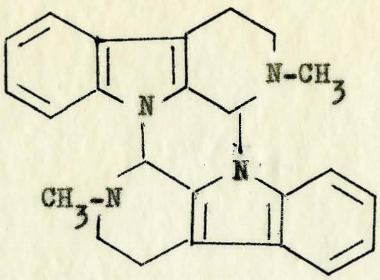


VIII

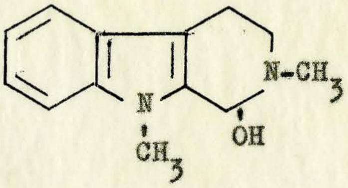


IX

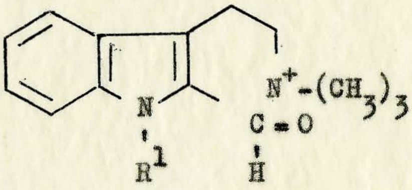
When the dimeric anhydrobase (X) and pseudobase (XI) were treated with methyl iodide in aqueous-alcoholic potassium carbonate suspension, quaternary salts (XII) were obtained which were very similar to quaternary salts (IV), obtained from 1,2-dialkyl-3,4-dihydro-β-carboline anhydrobases. The structure of (XII) was established by the same criteria of analysis, ultraviolet and infrared spectra and Hofmann degradation. Ultraviolet absorption of these compounds was similar to that of 2-formyl indole and their infrared spectra showed strong C = O absorption. On treatment with base both of these compounds



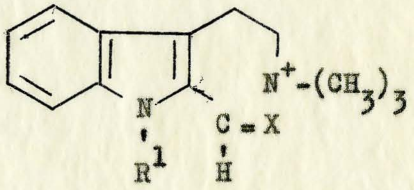
X



XI



XII



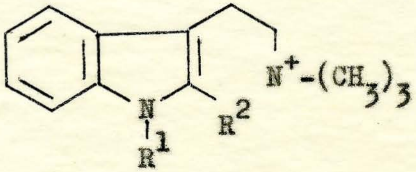
XIII

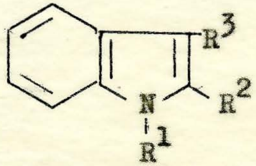
yielded trimethylamine and a neutral fragment. As in the case of Hofmann degradation of 2-acetyl quaternary salts (IV), trimethylamine was isolated and identified as picrate, whereas the neutral fragment was characterised by ultraviolet and infrared spectra and analysis and was found to be either elimination product 2-formyl-3-vinyl-indole or substitution product 2-formyl-3-(β-alkoxyethyl) indole.

When (XII) was treated with hydroxylamine hydrochloride in the presence of potassium carbonate an oxime (XIII, X = NOH) was obtained which further confirmed C = O group in (XII). When the alkylation of the dimeric base (X) and the pseudobase (XI) was carried out in the presence of excess anhydrous potassium carbonate, acetals (XIII, X = $(OR)_2$) of the quaternary salt (XII) were obtained. Different acetals were formed when the alkylation was carried out in the presence of different alcohols. Since acetals are known to be formed from aldehydes on treatment with alcohol containing ammonium iodide (Haworth and Lapworth, 1922), it seems that potassium iodide formed during the reaction plays the role of ammonium iodide in the present case. This formation of acetals also affords further evidence for the aldehydic nature of the quaternary salts (XII). The ultraviolet spectra of these acetals in alkaline solution were similar to those of indole, whereas in acidic solution these compounds showed absorption similar to that of 2-formylindole. This change in absorption was found to be irreversible. Rebasification did not change the latter absorption spectrum back to the former. Acidification had hydrolysed the acetals to aldehyde (XII). The infrared spectra of the acetals did not show absorption due to C = O but bands characteristic of ether absorption appeared in the region 1000 - 1200 cm^{-1}. The acetals also undergo Hofmann degradation and yield trimethylamine. The various quaternary salts prepared and the results of Hofmann degradation are summarised in Table IV.

TABLE IV

Alkylation of Pseudobase and Dimeric Anhydrobase and Hofmann Degradation of Quaternary Salts





Base	Products of Alkylation Quaternary Salts	M.P.	Products of Hofmann Degradation of Quaternary Salts Neutral Fragment	M.P.	Basic Fragment
Dimeric-2-methyl-3,4-dihydro-β-carboline-anhydrobase	(1) R^1=H R^2=$-\underset{H}{C}{=}O$	270°	(a) R^1=H R^2=$-\underset{H}{C}{=}O$ R^3=$-CH{=}CH_2$	126°	Trimethylamine
			(b) R^1=H R^2=$-\underset{H}{C}{=}O$ R^3=$-CH_2-CH_2OCH_3$	110°	Trimethylamine

TABLE IV (CONTINUED)

Alkylation of Pseudobase and Dimeric Anhydrobase and Hofmann Degradation of Quaternary Salts

	Products of Alkylation		Products of Hofmann Degradation of Quaternary Salts		
Base	Quaternary Salt	M.P.	Neutral Fragment	M.P.	Basic Fragment
Dimeric-2-methyl-3,4-dihydro-β-carboline-anhydrobase (continued)	(2) $R^1{=}H\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}(OCH_3)_2$	180°	$R^1{=}H\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}(OCH_3)_2\ R^3{=}{-}CH{=}CH_2$	125°	Trimethylamine
	(3) $R^1{=}H\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}(OC_2H_5)_2$	230°			
2,9-Dimethyl-3,4-dihydro-β-carboline-pseudobase	(1) $R^1{=}CH_3\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}O$	216°	$R^1{=}CH_3\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}O\ R^3{=}{-}CH{=}CH_2$	82°	Trimethylamine
	(2) $R^1{=}CH_3\ R^2{=}{-}\underset{H}{\underset{\mid}{C}}{=}(OCH_3)_2$	233°			

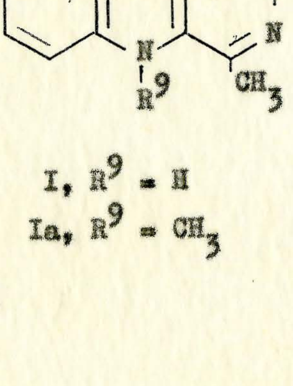
Conclusion

It has thus been found that the behaviour of pseudobases and anhydrobases of the 3,4-dihydro-β-carboline series on alkylation is similar to that of corresponding compounds in the 3,4-dihydroisoquinoline series. A discrepency in the literature has thereby been resolved and the object of the present work achieved.

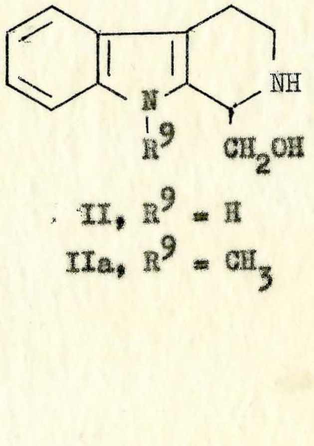
The Ultraviolet Absorption of Dihydro-β-Carboline Derivatives

Due to the presence of the extended indole chromophore, 3,4-dihydro-β-carbolines show strong absorption in the ultraviolet region of the spectrum and this fact was of diagnostic value in structural assignment and product analysis.

Thus during the preparation of 1-methyl-3,4-dihydro-β-carboline (harmalan) (I) and 1,9-dimethyl-3,4-dihydro-β-carboline (Ia), by dehydration of (dl)-1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (II) and (dl)-9-methyl-1-hydroxymethyl-1,2,3,4,-tetrahydro-β-carboline (IIa) respectively, the completion of reaction was determined by observing the changes in ultraviolet absorption of the reaction mixture. An absorption spectrum similar to that of indole is observed in the case of (II), which behaves as a 2,3-disubstituted indole, whereas in (I) the indole chromophore is conjugated with another unsaturation as a result of which λmax is shifted to longer wavelengths as expected.

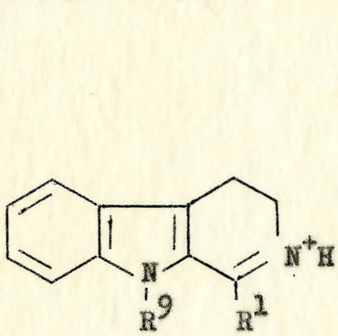


I, R^9 = H
Ia, R^9 = CH_3

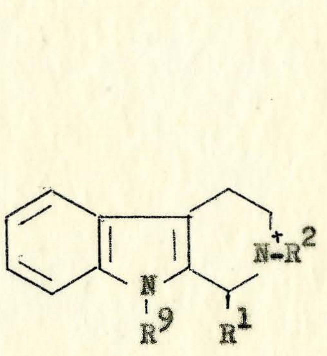


II, R^9 = H
IIa, R^9 = CH_3

The absorption spectra of dihydro-β-carbolines are affected by pH. Dihydro-β-carboline and its c-substituted derivatives show an absorption band at about 315 mμ in alcoholic solution or in the presence of base, whereas in the presence of acid a strong band at about 350 mμ is observed. This change represents the conversion of dihydro-β-carboline bases into dihydro-β-carbolinium ions. The band at 350 mμ is also shown by 3,4-dihydro-β-carboline alkiodides (IV) in acid or alcoholic solution. This behaviour is in general agreement with the observation that there is a bathochromic shift of 1 - 50 mμ when compounds containing C = N are converted into a cation C = N$^+$ (Witkop, 1954).



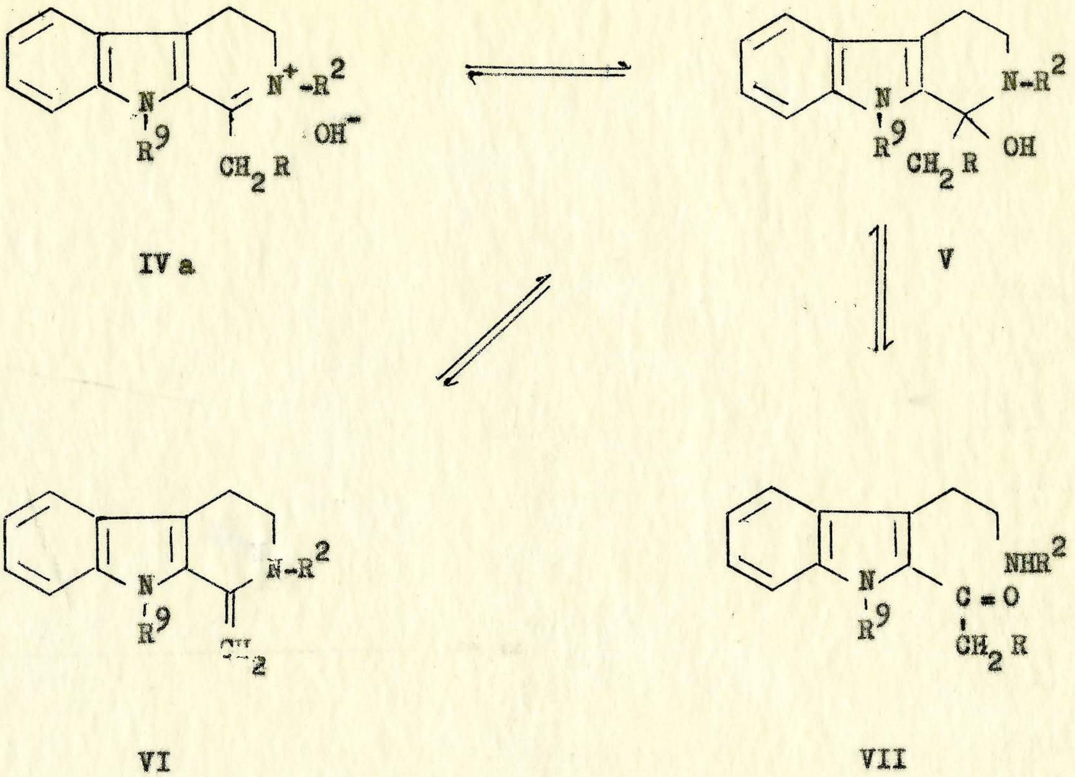
III



IV

In alkaline solution the N$_\beta$-alkyl-dihydro-β-carbolinium ions (IV) undergo structural changes which as already discussed, may be of one of two types, depending on 1-substitution.

The product derived from 1-alkyl substituted-3,4-dihydro-β-carbolinium iodides, by treatment with base, could in principle have any one of the following structures.



IV a

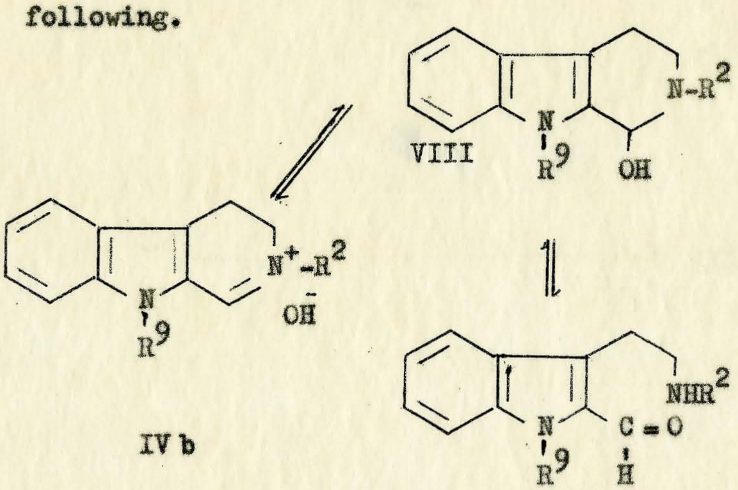
V

VI

VII

From a consideration of the ultraviolet absorption of the product it was possible to eliminate some of these. That there is an isomerisation of quaternary hydroxide (IV a) is shown by the shift of absorption to shorter wavelengths as soon as alkali is added to the solution of quaternary alkiodide. Since the new spectrum is similar to that of 2-formylindole (Taylor, 1950), structure (V), which would be expected to show absorption similar to that of indole, is excluded. The observed absorption does not, however, permit differentiation between (VI) and (VII) which would be expected to show similar ultraviolet absorption.

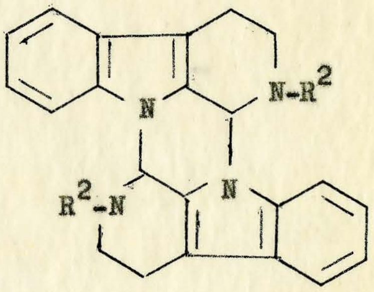
Treatment of 1-unsubstituted 3,4-dihydro-β-carbolinium iodide with alkali yields a product which could be represented as one of the following.



VIII

IV b

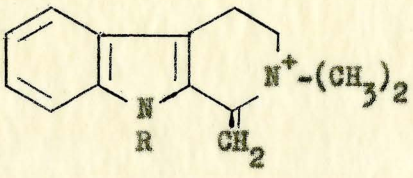
IX



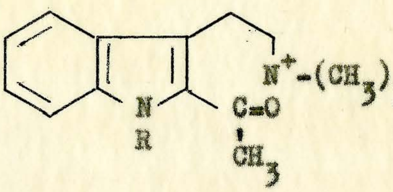
X

The shift of absorption to shorter wavelength as soon as base is added to a solution of the ion shows that quaternary hydroxide (IV b) does not exist. From the observed ultraviolet absorption spectrum, which is similar to that of indole, the aldehydeamine structure (IX) can be excluded while structure (VIII) is favoured. However, a distinction between the pseudobase structure (VIII, $R^9 = H$) and dimeric anhydrobase (X) cannot be made since the latter is also expected to show ultraviolet absorption similar to that of indole.

On further alkylation of the anhydrobases, new quaternary salts are obtained to which structure (XI) had been assigned (Konowalowa and Orechoff, 1934), but which have now been shown to be of structure (XII). Since the ultraviolet absorption spectrum of these structures would be expected to be similar a differentiation on this basis cannot be made.

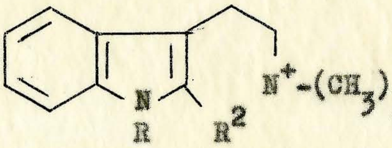


XI



XII

Ultraviolet absorption spectra, nevertheless, proved useful in recognising the products of further alkylation of the pseudo and anhydrobases. When pseudobase (VIII, $R^9 = CH_3$) or the dimeric anhydrobase (X) are alkylated in the presence of anhydrous potassium carbonate, different products are obtained depending upon the reaction conditions. These products have been assigned the structure (XIII) and (XIV).



XIII, $R^2 = -\underset{\stackrel{|}{H}}{C}=O$

XIV, $R^2 = -\underset{\stackrel{|}{H}}{C}-(OR)_2$

Due to the presence of C = O in position 2, (XIII) shows ultraviolet absorption similar to that of 2-formyl indole, unaffected by pH. In (XIV), the conjugation of the indole chromophore with C = O is lost due to acetal formation and in alkaline solution the compound shows ultraviolet absorption similar to that of indole. In acidic

In (XVII) the indole nucleus is in conjugation with two unsaturated groups and ultraviolet absorption of such compounds should be at longer wavelengths than that of the compounds of the type (XVIII) in which the indole nucleus is conjugated with only one centre of unsaturation.

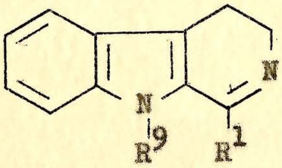
The ultraviolet absorption maxima of 3,4-dihydro-β-carbolines and their derivatives have been summarised in Table V.

TABLE V

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

3,4-Dihydro-β-Carbolines
(Figure 1)



R^1	R^9	0.1 N HCl	0.1 N NaOH
H	H	355 (4.2), 245 (4.0)	320 (4.0), 242 (4.0)
H	CH_3	360 (4.1), 248 (4.1)	322 (4.0), 252 (3.9)
CH_3	H	350 (4.2), 245 (3.9)	315 (4.2), 240 (4.1)
CH_3	CH_3	352 (4.2), 250 (4.0)	318 (4.0)

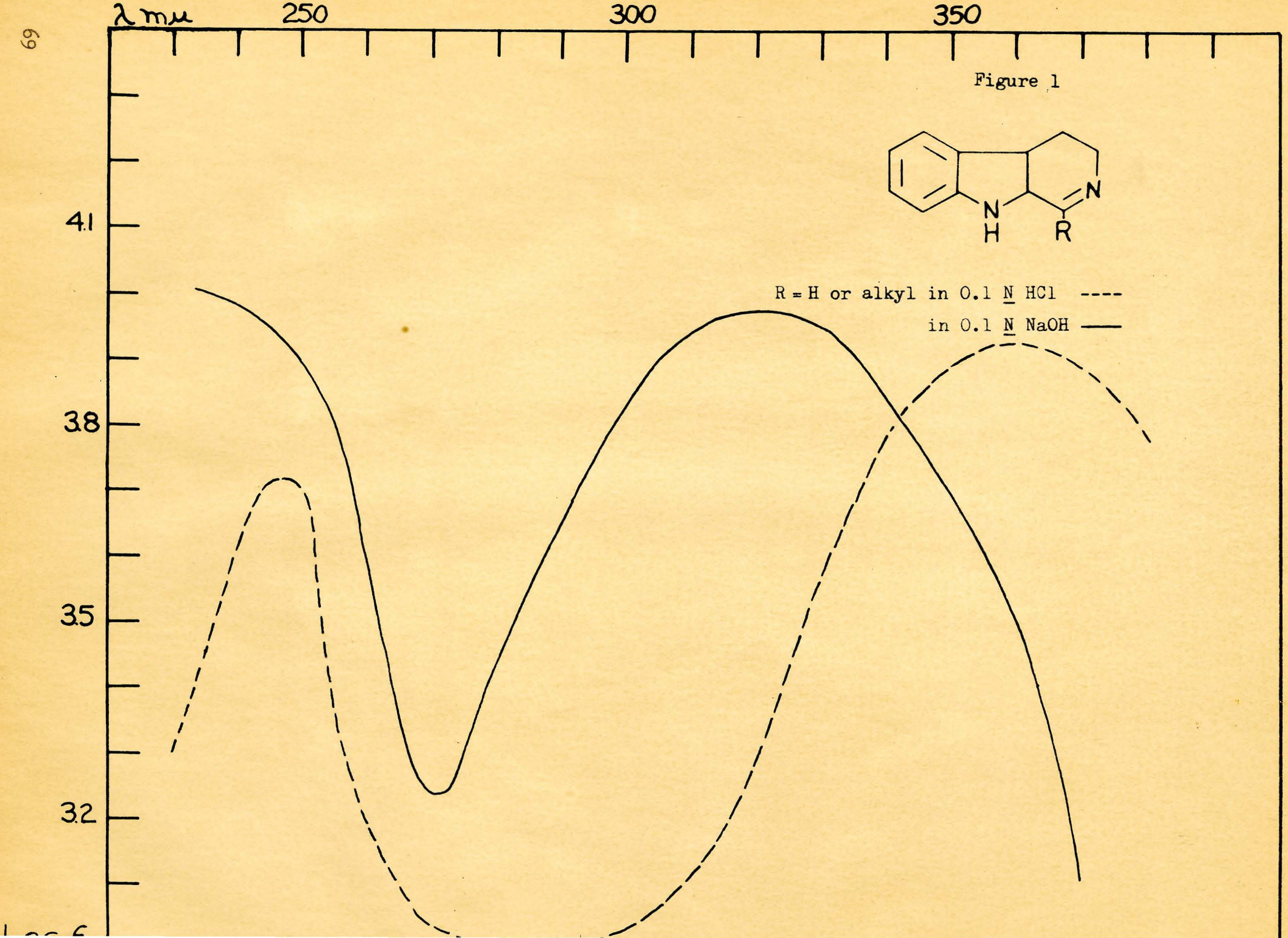


Figure 1

λ mμ
250
300
350
4.1
3.8
3.5
3.2
N
H
R
N
R = H or alkyl in 0.1 N HCl ----
in 0.1 N NaOH ——

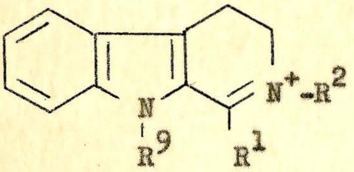
TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

3,4-Dihydro-β-Carboline Alkiodides

(Figure 2)



R^1	R^2	R^9	0.1 N HCl	0.1 N NaOH
H	CH_3	H	360 (4.3), 248 (4.0)	282 (3.7)
H	CH_3	CH_3	360 (4.4), 252 (4.1)	286 (3.8)
CH_3	CH_3	H	355 (4.3), 250 (4.1)	315 (4.2)
CH_3	n-C_3H_7	H	360 (4.4), 250 (4.1)	370 (4.0), 320 (4.2)
CH_3	CH_3	CH_3	355 (4.1), 250 (4.0)	300 - 308 (3.8)

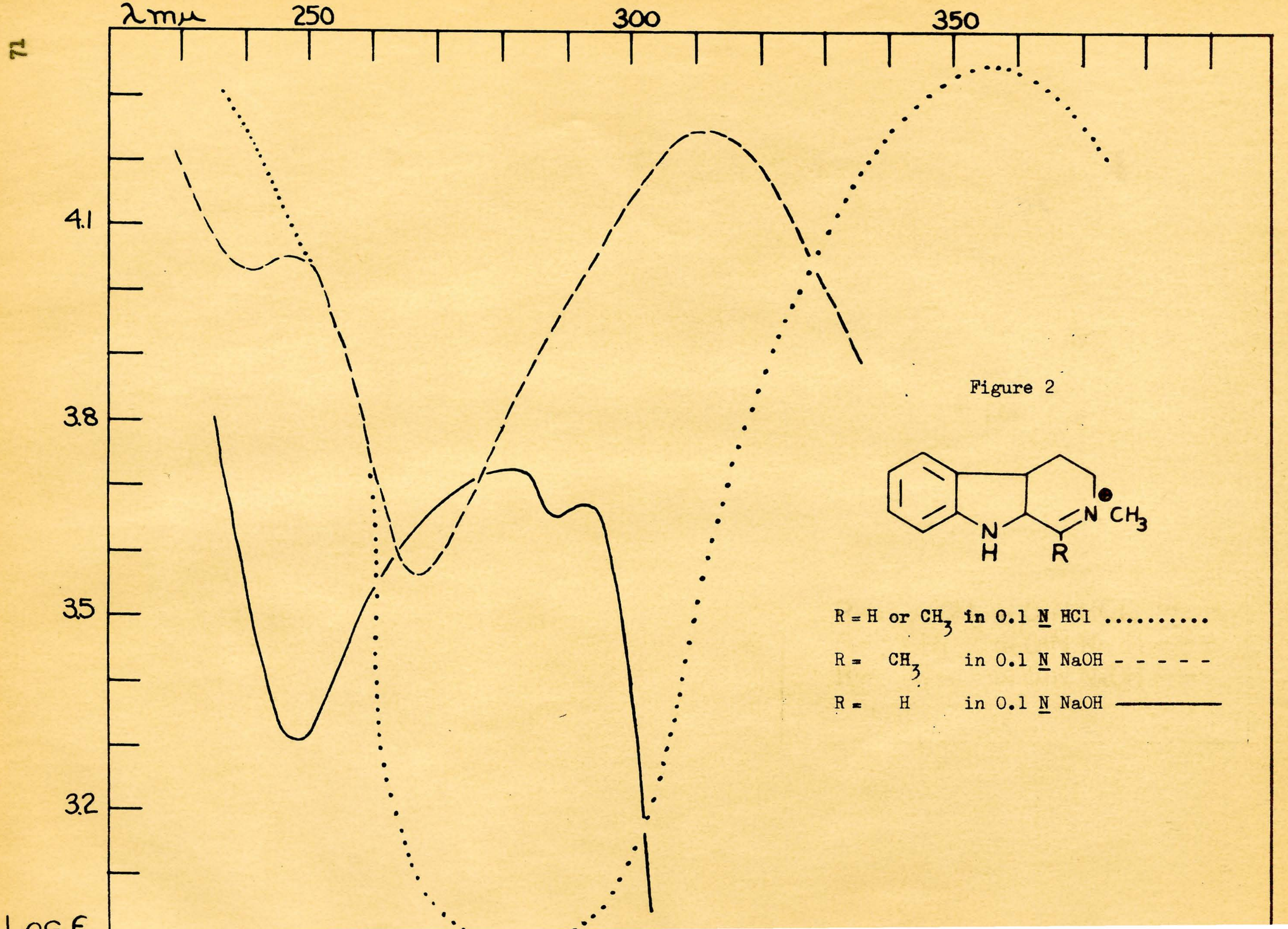

λ mμ
250
300
350
4.1
3.8
3.5
3.2
Log ε
N
H
R
N CH3
R = H or CH3 in 0.1 N HCl ....
R = CH3 in 0.1 N NaOH - - - - -
R = H in 0.1 N NaOH ————

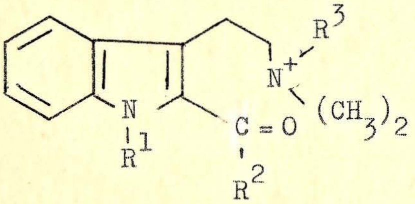
Figure 2

TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

2-Carbonyl-3-(β-Trialkylammoniumethyl) Indole Iodides



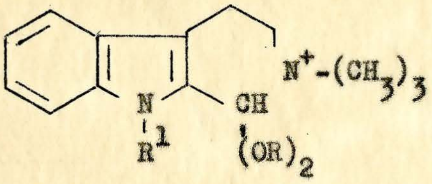
R^1	R^2	R^3	0.1 N HCl = 0.1 N NaOH
H	H	CH_3	315 (4.1), 237 (4.1)
CH_3	H	CH_3	318 (4.2), 240 (4.2)
H	CH_3	CH_3	315 (4.1), 242 (4.1)
H	CH_3	n-C_3H_7	315 (4.1)
CH_3	CH_3	CH_3	315 (4.1)

TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

Acetals of 2-Formyl-3-(β-Trialkylammoniumethyl) Indole Iodides



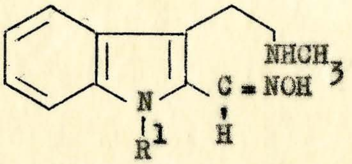
R	R^1	0.1 N HCl	0.1 N NaOH
CH_3	H	318 (3.9)	282 (3.7)
C_2H_5	H	318 (3.9)	282 (3.7)
CH_3	CH_3	318 (4.3), 242 (4.3)	282 (4.0)

TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

Oximes of 2-Formyl-3-(β-N-Methylethylamine) Indoles



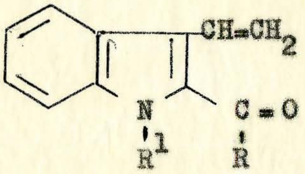
R^1	0.1 N HCl	0.1 N NaOH
H	310 (4.3), 240 (4.2)	315 (4.3)
CH_3	310 (4.3), 243 (4.3)	315 (4.3)

TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

2-Formyl-3-Vinyl Indoles



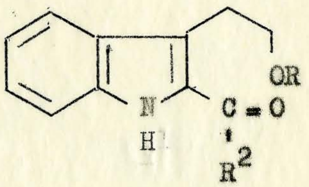
R	R^1	0.1 N HCl = 0.1 N NaOH
H	H	322 (4.2), 252 (4.1)
H	CH_3	322 (4.2), 253 (4.2)
CH_3	CH_3	318

TABLE V (CONTINUED)

Ultraviolet Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Their Degradation Products.

(λmax mμ (log E))

2-Formyl3-(β-Alkoxyethyl) Indoles



R	R^2	0.1 N HCl = 0.1 N NaOH
CH_3	H	317 (4.2), 238 (4.1)
CH_3	CH_3	315 (4.1)
C_2H_5	CH_3	315 (4.1)

Infrared Spectra of 3,4-Dihydro-β-Carboline and its Derivatives

Not only ultraviolet but also infrared absorption spectra proved of value in the present study. Since most of the compounds studied are quaternary salts and their spectra cannot be studied in solutions, nujol mulls were used in all cases for better comparison. The spectra were obtained with a Perkin Elmer 21 double beam spectrophotometer equipped with a rock salt prism.

In the following discussion, the spectra of eight groups of compounds, prepared in the course of this work, will be reviewed and the frequencies of important bands listed in Table VI.

1. 3,4-Dihydro-β-Carbolines

The spectra of these bases show bands which can be assigned to the NH group of indole nucleus and to the C = N function.

NH

Although weak NH absorption has been observed in harmaline (Marion and Ramsay, 1951) in chloroform, this NH absorption was not observed in 1-substituted 3,4-dihydro-β-carbolines (I c, I d) in nujol mulls. 3,4-Dihydro-β-carboline (I a) shows NH absorption of medium intensity at 3380 cm^{-1}, whereas the indole itself shows a band in the region 3480 cm^{-1}. This shift towards lower frequency is in accord with the general observation that substituents at the 2- or 3-positions of indole shift NH absorption to lower frequency. As expected, 9-substituted-3,4-dihydro-β-carbolines (I h and I e) do not show NH absorption.

C = N

In harmaline, a band at 1629 cm^{-1} was observed (Marion and Ramsay, 1951) which was attributed either to C = C or to C = N stretching vibrations. Isoquinoline itself shows three bands between 1600 - 1500 cm^{-1}. All the dihydro-β-carbolines (I a to I e) studied showed absorption bands of medium intensity between 1600 - 1620 cm^{-1} which is most likely due to C = N stretching vibrations. Since these are present also in 9-substituted-3,4-dihydro-β-carbolines, these bands cannot be attributed to NH bending vibrations.

2. 2-Alkyl-3,4-Dihydro-β-Carbolinium Salts

NH

In contrast to 3,4-dihydro-β-carbolines, all indole-N-unsubstituted dihydro-β-carbolinium salts show broad bands of medium intensity between 3100 - 3160 cm^{-1} in nujol mulls. This shift to lower frequency is attributed to the presence of C = N$^+$ in conjugation with the indole nucleus.

C = N$^+$

A band at 1661 cm^{-1} in cotarnine hydrochloride was attributed to the presence of C = N$^+$ (Witkop and Patrick, 1953). A similar band at 1672 cm^{-1} was found in hydrastinine hydrochloride. In all the carbolinium salts now studied, strong bands between 1600 - 1650 cm^{-1}, characteristic for $C = N^+$, have been observed. The absorption due to C = N is shifted to higher frequency (from 1600 - 1620 to 1600 - 1650 cm^{-1}), which is in general agreement with the behaviour of such compounds. This fact has been used as a diagnostic criterion for the presence of C = N (Witkop, 1954).

3. Dimeric 2-Methyl-3,4-Dihydro-β-Carboline Anhydrobase and 2,9-Dimethyl-3,4-Dihydro-β-Carboline Pseudobase

NH; OH

Neither of these compounds show NH or OH absorption. This lack of NH and OH in (IIIa) is consistent with the dimeric structure assigned to the compound. The lack of OH absorption in pseudobase (IIIb) does not disprove this structure since a similar complete absence, or very weak bands due to OH, has been reported in other pseudobases whose structure is otherwise well established (Schneider, 1961).

$C = N^+$

The absence of bands in the region 1500 - 1700 show that these compounds do not exist as quaternary hydroxides.

4. 1,2-Dialkyl-3,4-Dihydro-β-Carboline Anhydrobases

1-Methylene anhydrobases (IV a, IV b) show quite sharp NH bands of medium intensity, whereas the 1 ethylene derivative (IV c) shows only very weak, broad NH absorption.

C = C

All the anhydrobases show bands at 1625 - 1655 cm^{-1} of medium to strong intensity. Bands in this region indicate unsaturation in the molecule due to C = C or C = N stretching. Although on the basis of infrared spectra alone $C = N^+$, or C = N, cannot be excluded, other physical and chemical evidence would indicate that this absorption is due to C = C stretching.

5. 2-Carbonyl-3-(β-Trialkylammoniumethyl) Indole Iodides

NH

All 9-unsubstituted quaternary salts of this type show absorption bands due to NH between 3280 - 3380 cm^{-1}. Due to the presence of the electronegative group C = O at the 2-position, the indole NH absorption should shift to lower frequency, in the region of 3200 cm^{-1} (Becker and Millich, 1958). Since substituents at the 3-position of an indole nucleus have a much greater influence on the spectrum than substituents at 2-position, the presence of a substituted ethyl group at the 3-position partly cancels the effect of 2 substitution.

C = O

Absorption due to C = O is observed between 1640 - 1660 cm^{-1}. As usual, due to conjugation of indole nucleus with C = O, absorption due to latter group is shifted to lower frequency (Becker and Millich, 1958).

6. Acetals of 2-Formyl-3-(β-Trialkylammoniumethyl) Indole Iodides

NH

Due to acetal formation, the C = O group is lost and absorption due to NH is shifted to longer wavelengths as compared to the formyl compound itself.

OR

Characteristic acetal bands in the region 1000 - 1200 cm^{-1} are present (Bergman and Pinchas, 1952).

7. 2-Carbonyl-3-Vinyl Indoles

C = C

Apart from the strong bands in the region 1600 - 1650 cm^{-1} which are also due to C = O, characteristic bands due to the vinyl group are observed in the region 900 - 1000 cm^{-1}.

The hydrogen deformation frequencies of CH = C are observed at 992 cm^{-1} for 1-substituted indole compounds, whereas such bands are observed at 972 cm^{-1} in the case of 1-unsubstituted indoles. It seems that the presence of an indole NH modify this frequency.

8. 2-Carbonyl-3-(β-Alkoxyethyl) Indoles

OR

Characteristic bands due to OR absorption are present in the region 1000 - 1200 cm^{-1}.

TABLE VI

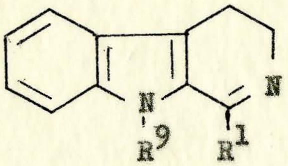
Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

---

1. 3,4-Dihydro-β-Carbolines



	R^1	R^9	NH	C = N
Ia	H	H	3380	1615 (M)
Ib	CH_3	H	x	1608 (M)
Ic	H	CH_3	not observed	1600 (M), 1620 (W)
Id	H	C_2H_5	not observed	1598 (M), 1615 (W)
Ie	CH_3	CH_3	x	1610 (M)
If	Harmaline ($CHCl_3$)		3470 (V.W.)	1629 (M)

(Marion and Ramsay, 1951)

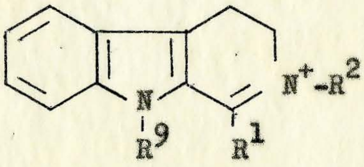
TABLE VI (CONTINUED)

Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Degradation Products

(Frequencies in cm-1)

(M = medium; S = strong; V = very; W = weak)

2. 3,4-Dihydro-β-Carboline Alkiodides



	R^1	R^2	R^9	NH	$C = N^+$
IIa	H	CH_3	H	3160 (M)	1640 (S)
IIb	H	CH_3	CH_3	x	1648 (S)
IIc	CH_3	CH_3	H	3130 (M)	1618 (S)
IId	CH_3	C_3H_7 (n)	H	3130 (M)	1615 (S)
IIe	C_2H_5	CH_3	H	3100 (M)	1615 (S)
IIf	CH_3	CH_3	CH_3	x	1620 (S)
IIg	Cotarnine (Witkop and Patrick, 1953)			x	1661 (M)
IIh	Hydrastinine (Schneider and Müller, 1958)			x	1672 (M)

TABLE VI (CONTINUED)

Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

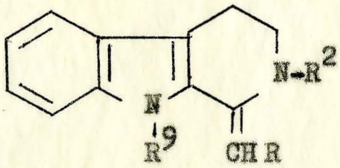
---

3. **Base**

		NH	OH	$C = N^+$
IIIa	Dimeric anhydrobase	absent	absent	absent
IIIb	2,9-Dimethyl-3,4-dihydro β-carboline pseudobase	x	absent	absent
IIIc	Hydrastinine	x	absent	absent

(Schneider, 1961)

4. **Anhydrobases**



	R	R^2	R^9	NH	C = C
IVa	H	CH_3	H	3410 (M)	1625 (M), 1605 (W)
IVb	H	C_2H_7	H	3410 (M)	1630 (M)
IVc	CH_3	CH_3	H	3270 (V.W.) Broad	1655 (S)
IVd	H	CH_3	CH_3	x	1640 (S)

TABLE VI (CONTINUED)

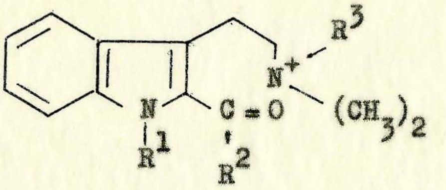
Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

---

5. 2-Carbonyl-3-β-(Trialkylammoniumethyl) Indole Iodides



	R^1	R^2	R^3	NH	C = O
Va	H	H	CH_3	3280 (M) Broad	1655 (V.S)
Vb	CH_3	H	CH_3	x	1652 (V.S)
Vc	H	CH_3	CH_3	2280 (M)	1660 (V.S)
Vd	H	CH_3	n-C_3H_7	3390 (M) Broad	1640 (V.S)
Ve	CH_3	CH_3	CH_3	x	1640 (V.S)
Vf	2-Formyl Indole			3185	1675

(Taylor, 1950)

TABLE VI (CONTINUED)

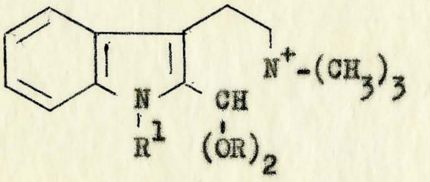
Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

---

6. Acetals of 2-Formyl-3-β-(Trialkylammoniumethyl) Indole Iodides



	R	R^1	NH	OR
VIa	CH_3	H	3380 (M)	1030 (M), 1090 (S)
VIb	C_2H_5	H	3380 (M)	1030 (M), 1090 (S)
VIc	CH_3	CH_3	x	1040 (M), 1095 (S)

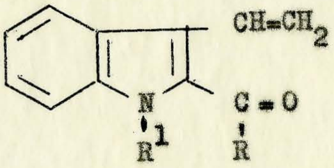
TABLE VI (CONTINUED)

Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

7. 2-Carbonyl-3-Vinyl Indoles



	R	R^1	NH	C = O C = O	Vinyl
VIIa	H	H	3280 (M)	1640 (V.S) 1615 (S, incomp)	918 (M), 972 (M)
VIIb	H	CH_3	x	1650 (V.S) 1605 (S, incomp)	928 (M), 992 (M)
VIIc	CH_3	CH_3	x	1650 (V.S) 1605 (S, incomp)	912 (M), 992 (M)

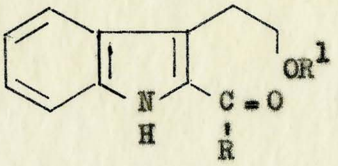
TABLE VI (CONTINUED)

Infrared Absorption Spectra of 3,4-Dihydro-β-Carbolines, Their Derivatives and Degradation Products

(Frequencies in cm^{-1})

(M = medium; S = strong; V = very; W = weak)

8. 2-Carbonyl-3-(β-Alkoxyethyl) Indoles



R	R^1	NH	C = O	OR
H	CH_3	3210 (M)	1650 (V.S)	1012 (M), 1070 (M), 1094 (S)
CH_3	CH_3	3250 (M)	1660 (V.S)	1028 (M), 1065 (M), 1090 (S)
CH_3	C_2H_5	3230 (M)	1646 (V.S)	1032 (M), 1065 (M), 1090 (S)

EXPERIMENTAL

3,4-Dihydro-β-Carbolines

3,4-Dihydro-β-carbolines were prepared by established methods and details are given only for modifications of accepted procedures.

3,4-Dihydro-β-Carboline (Norharmalan)

N_{β}-formyltryptamine (Schöpf and Steuer, 1947) (1.5 g) and polyphosphoric acid (10 g) were heated for forty minutes at 100 - 110° with constant stirring. The dark melt was added to cold water and the solution was diluted to about one litre and decolorised. The clear filtrate was extracted with ether to remove any non-basic impurities and made alkaline with 10% NaOH. The turbid solution was extracted with ether and the ether extract dried and evaporated. The residue could not be crystallised in any solvent nor could it be purified by partition chromatography. In every case a brown polymeric material was obtained.

Sublimation at 2.10^{-3} mm and 130 - 140° gave the product as a glassy solid (0.74 g, 52.1%) melting at 120 - 125° after sintering at 100°, pKa 7.8. It did not give a satisfactory analysis.

A sample was converted to the picrate, melting at 233 - 234°. Reported melting point 241 - 242° (Asahina and Kashiwaki, 1915) (Found: C, 51.1; H, 3.3; Calc. for $C_{17}H_{13}N_5O_7$: C, 51.1; H, 3.3%). Ultraviolet absorption (λmax, mu(log E)): in 0.1 N HCl: 355 (4.2), 245 (4.0); in 0.1 N NaOH: 320 (4.0), 242 (4.0).

Ind-N-Methyl-N_β-Formyltryptamine

Ind-N-methyltryptamine was prepared from N-methylindole (Snyder and Eliel, 1948) which was obtained by reducing N-methylindoxyl with $LiAlH_4$ (Julian and Printy, 1949).

Ind-N-methyltryptamine (3 g) was treated for 2 hours with freshly distilled dried ethyl formate (25 ml) in a sealed tube at 100°. The solution was diluted with ether, washed with dilute HCl and with water and dried. Ethyl formate and ether were evaporated and the residue was distilled at 5.10^{-3} mm and 165 - 170° to give the product as a colourless viscous oil (2.8 g, 80%). The infrared spectrum showed strong carbonyl absorption at 1640 cm^{-1} (Found: N, 13.8; $C_{12}H_{14}N_2O$ requires: N, 13.9%).

9-Methyl-3,4-Dihydro-β-Carboline

Ind-N-methyl-N_β-formyltryptamine (1.5 g) was treated with polyphosphoric acid (10 g) and the reaction mixture worked up as in the preparation of 3,4-dihydro-β-carboline. The crude base was sublimed at 5.10^{-3} mm and 120° when the product (0.75 g, 55%), melting at 120 - 130°, was obtained as a colourless solid. It did not give a satisfactory analysis. Ultraviolet absorption (λmax, mu(log E)): 0.1 N HCl: 360 (4.1), 248 (4.1); in 0.1 N NaOH: 322 (4.0), 252 (3.9).

1-Methyl-3,4-Dihydro-β-Carboline (Harmalan)

This was obtained by dehydration of 1-hydroxymethyl-1,2,3,4-tetrahydro-β-carboline (Spenser, 1959).

(dl)-9-Methyl-1-Hydroxymethyl-1,2,3,4-Tetrahydro-β-Carboline

A solution of 1-methyltryptamine (3.4 g) and glycolaldehyde (1.27 g) in 200 ml water containing 20 ml 2 N HCl was refluxed for 2 hours. The solution was decolorised, extracted with ether to remove non-basic impurities, and made alkaline with NaOH to yield a dark brown solid which was dissolved in ethanol, decolorised and crystallised from aqueous ethanol. It sublimed at 2.10^{-3} mm and 140 - 160° to give the product (3 g, 70%) as a colourless crystalline solid melting at 146° (Found: C, 72.4; H, 7.7; N, 13.1. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.4; N, 13.0%).

1,9-Dimethyl-3,4-Dihydro-β-Carboline

The above tetrahydro-β-carboline (2.5 g) was wetted with water, treated with 85% phosphoric acid (30 ml) and kept on the steam bath until the absorption band at 280 mu, characteristic of the indole chromophore of the starting material, had disappeared (4 hours). The dark brown solution was diluted with water, decolorised and made alkaline with 20% NaOH, and the product was extracted into ether. The extract was dried (Na_2SO_4), ether was removed and the solid residue was dissolved in methanol. The solution was decolorised and evaporated and the colourless residue was sublimed at 2.10^{-3} mm and 90 - 100° to yield the product (1.2 g, 58%), melting at 80 - 84°, as a colourless solid (Found: C, 78.8; H, 7.4; N, 14.2. Calc. for $C_{13}H_{14}N_2$: C, 78.8; H, 7.1; N, 14.1%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 *N* HCl: 352 (4.2), 250 (4.0); in 0.1 *N* NaOH: 318 (4.0).

N-Alkyl Derivatives of 3,4-Dihydro-β-Carbolines

3,4-Dihydro-β-Carboline Methiodide

Norharmalan (1 g) was dissolved in 50 ml dry benzene, the solution filtered and the residue rejected. The filtrate was diluted to 250 ml with dry benzene, methyl iodide (3 ml) was added and the mixture allowed to stand at room temperature for 48 hours. Yellow needles contaminated with a brown impurity deposited. The solid was dissolved in methanol, the solution treated with charcoal, concentrated and the residue crystallised from aqueous methanol when the product (1.4 g, 70%) was obtained as long needles of the monohydrate, melting at 223° after sintering at 215° (Found: H_2O, 4.9. $C_{12}H_{13}N_2IH_2O$ requires H_2O, 5.45%. After drying to constant weight, found: C, 46.2; H, 4.4; N, 8.9. $C_{12}H_{13}N_2I$ requires C, 46.1; H, 4.2; N, 8.0%).

Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl: 360 (4.3), 248 (4.0); in 0.1 N NaOH: 282 (3.7).

Dimeric 2-Methyl-3,4-Dihydro-β-Carboline Anhydrobase

Norharmalan methiodide (0.25 g) was dissolved in 20 ml H_2O and 10% sodium hydroxide was added with constant stirring. The yellowish precipitate which separated was washed with water, rubbed with methanol (5 ml), filtered and again washed with a little methanol to yield a colourless amorphous powder (0.18 g) melting at 185°. Crystallisation from dry chloroform did not raise the melting point. Molecular weight: Found: 346 ± 35 $(C_{12}H_{12}N_2)_2$ requires: 368. The carbon analysis was unsatisfactory but the product did not contain oxygen (Found: C, 77.3; H, 6.5; H, 15.0. $(C_{12}H_{12}N_2)_2$ requires: C, 78.3; H, 6.5; N, 15.1%).

The same product was obtained when more dilute NaOH or ammonia was used. Addition to a small sample of the anhydrobase of concentrated sulphuric acid containing a trace of ferric chloride gave an ultramarine colour which on standing changed to crimson.

Treatment of Dimeric 2-Methyl-3,4-Dihydro-β-Carboline Anhydrobase with Alkali

The anhydrobase (0.02 g) was suspended in 30% KOH in aqueous ethanol (5 ml) and refluxed on the steam bath for 4 hours. Alcohol was evaporated and the residue acidified with HCl. The solution was extracted with ether, the ether extract dried (Na_2SO_4) and concentrated.

The ether extract did not contain material absorbing in the ultraviolet region of the spectrum.

The aqueous solution was made alkaline with excess 10% NaOH when unchanged starting material was recovered.

Distillation of Dimeric 2-Methyl-3,4-Dihydro-β-Carboline Anhydrobase

The anhydrobase (0.1 g) was distilled at 10^{-2} mm and 140 - 150°. A mixture of a colourless and a yellow substance sublimed and a black residue remained. The sublimate was re-distilled at 10^{-2} mm below 100° when the colourless substance sublimed and the yellow substance remained as residue.

The colourless substance was 2-methyl-1,2,3,4-tetrahydro-β-carboline, melting at 216 - 217°, identical in melting point, mixed melting point, infrared and ultraviolet spectra with an authentic sample (Boekelheide and Ainsworth, 1950).

The yellow substance melting at 212 - 214° proved to be identical by similar criteria with an authentic sample of 2-methyl-β-carboline anhydrobase (Spenser, 1956).

1-Hydroxylamino-2-Methyl-1,2,3,4-Tetrahydro-β-Carboline

The dimeric anhydrobase (0.1 g) and hydroxylamine hydrochloride (0.05 g) in methanol (25 ml) were refluxed for 15 minutes. The solvent was distilled off and the residue was dissolved in water. Addition of ammonia gave a heavy precipitate which was dissolved in ether and filtered. The ether solution was dried (Na_2SO_4), solvent evaporated and the residue crystallised from methanol, yielding colourless crystals (0.08 g, 75%) melting at 182° (Found: C, 66.6; H, 7.5; N, 18.9. $C_{12}H_{15}ON_3$ requires: C, 66.3; H, 7.0; N, 19.3%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and 0.1 N NaOH: 310 (4.2), 240 (4.1).

9-Methyl-3,4-Dihydro-β-Carboline Methiodide

9-Methyl-3,4-dihydro-β-carboline (0.5 g) was dissolved in 75 ml benzene, the solution treated with methyliodide (2 ml) and kept at 37° for 24 hours. The yellow solid was re-crystallised from water to give pale yellow needles (0.7 g, 70%) melting at 228° (Found: C, 48.1; H, 4.9; N, 8.6; I, 38.9. $C_{13}H_{15}N_2I$ requires: C, 47.8; H, 4.6; N, 8.6; I, 39.0%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl: 360 (4.4), 252 (4.1); in 0.1 N NaOH: 286 (3.8).

2,9-Dimethyl-3,4-Dihydro-β-Carboline Pseudobase

The above methiodide (0.5 g) dissolved in a small amount of hot water was treated with 20% NaOH. The solution was cooled in ice, the product filtered and re-precipitated from water. It was isolated as a greenish solid, melting at 55° and was not analysed.

Treatment of Pseudobase with Alkali

9-Methyl-3,4-dihydro-β-carboline methiodide (0.5 g) was dissolved in water. The solution was treated with 20% NaOH, the pseudobase was extracted into ether and the solvent evaporated. The residue was refluxed 2 hours with 35% KOH (10 ml). On cooling, the solution was extracted with ether and the ether extract was successively washed with 1 N HCl and with water and dried. Ether was evaporated and the residue sublimed at 10^{-3} mm and 90° to give a colourless solid, melting at 68°. The ultraviolet spectrum ((λmax, mμ) in 0.1 N HCl and 0.1 N NaOH: 310) was similar to that of 2-formylindole and the infrared spectrum showed C = O absorption at 1640 cm^{-1}. The compound was not analysed.

The acid extract was made alkaline, extracted with ether, and the ether extract was dried (Na_2SO_4) and evaporated, yielding the starting material.

Distillation of the Pseudobase

Pseudobase obtained from 0.5 g methiodide was distilled at 3.10^{-3} mm and 110° to yield a dark yellow oil which was dissolved in ether, the solution washed with HCl, dried and evaporated. A very small amount of a colourless residue, melting at 68°, was obtained which proved to be identical with the neutral fragment obtained above.

The acid solution was made alkaline and extracted with ether. The ether extract was dried and evaporated when the starting material was recovered.

1-Hydroxylamino-2,9-Dimethyl-3,4-Dihydro-β-Carboline

9-Methyl-3,4-dihydro-β-carboline methiodide (0.5 g) was dissolved in hot water, 20% NaOH added, the solution cooled and extracted with ether. The ether extract was dried (Na_2SO_4) and the solvent evaporated. The residue was dissolved in methanol (30 ml) and hydroxylamine hydrochloride (0.125 g) and potassium carbonate (0.2 g) were added. The mixture was kept at 40° for 2 hours, the solvent then evaporated, the residue was washed with 2 portions (3 ml) of cold water and crystallised from methanol after treatment with charcoal. The product (0.23 g, 65%) was obtained as a colourless solid melting at 156° (Found: C, 67.2; H, 7.5; N, 18.1. $C_{13}H_{17}N_3O$ requires: C, 67.5; H, 7.4; N, 18.2%). Ultraviolet absorption in 0.1 N HCl and 0.1 N NaOH (λmax, mμ(log E)): 310 (4.2); 243 (4.2).

1-Methyl-3,4-Dihydro-β-Carboline Methiodide

Harmalan (0.5 g) was suspended in 5 ml nitrobenzene and 100 ml benzene was added when a clear yellow solution was obtained. Methyl iodide (2 ml) was added and the mixture was kept at 37° for 48 hours. A yellow precipitate was obtained which was crystallised from methanol after treatment with charcoal, yielding light yellow needles (0.8 g, 80%) melting at 280° (Found: C, 47.8; H, 4.7; N, 8.7. $C_{13}H_{15}N_2I$ requires: C, 47.8; H, 4.6; N, 8.6%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl: 355 (4.3); 250 (4.1); in 0.1 N NaOH: 315 (4.2).

1,2-Dimethyl-3,4-Dihydro-β-Carboline Anhydrobase

An aqueous solution of harmalan methiodide (0.5 g) was treated with 20% NaOH, when a yellow turbidity appeared. The solution was extracted with ether. The ether extract was dried (solid KOH), concentrated and the residue distilled at 2.10^{-3} mm and 110 - 120° to give the product, melting at 115° after sintering at 105°, as a colourless solid which turned yellow on standing (Found: C, 78.4; H, 7.2; N, 13.7. $C_{13}H_{14}N_2$ requires: C, 78.7; H, 7.0; N, 14.1%).

1-Methyl-3,4-Dihydro-β-Carboline-n-Propiodide

Harmalan (0.5 g) was suspended in 10 ml nitrobenzene and 100 ml benzene was added. 1-Iodo-propane (3 ml) was added and the solution kept at 37° for 72 hours. An orange precipitate was obtained which was crystallised from methanol after treatment with charcoal to yield 1-methyl-3,4-dihydro-β-carboline n-propiodide (0.73 g, 70%) melting at 269° (Found: C, 50.7; H, 5.5; N, 7.9. $C_{15}H_{19}N_2I$ requires: C, 50.8; H, 5.4; N, 7.9%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl: 360 (4.4); 250 (4.1); in 0.1 N NaOH: 370 (3.95); 320 (4.2).

1-Methyl-2-n-Propyl-3,4-Dihydro-β-Carboline Anhydrobase

Treatment of an aqueous solution of harmalan propiodide with 20% NaOH gave a brown solid, melting at 104 - 106°, which darkened on drying in air. Sublimation under reduced pressure gave a glassy solid which was not analysed.

1,9-Dimethyl-3,4-Dihydro-β-Carboline Methiodide

1,9-Dimethyl-3,4-dihydro-β-carboline (0.5 g) was treated with methyliodide (2 ml) in 100 ml benzene and allowed to stand for 24 hours at 39°. A yellow solid was obtained which was crystallised from water after treatment with charcoal, yielding the product as the monohydrate (0.8 g, 80%) in yellow needles, melting at 216° (Found: C, 47.7; H, 5.6; N, 7.9; I, 35.1. $C_{14}H_{19}N_2IO, H_2O$ requires: C, 47.2; H, 5.3; N, 7.8; I, 35.5%). Ultraviolet absorption (λmax, mµ(log E)): in 0.1 N HCl: 355 (4.1); 250 (4.0); in 0.1 N NaOH: 300 - 308 (3.8) broad.

1,2,9-Trimethyl-3,4-Dihydro-β-Carboline Anhydrobase

The above methiode (0.4 g) was dissolved in hot water and treated with 20% NaOH, when the anhydrobase separated as colourless solid which discoloured rapidly on standing. It was dissolved in ether, dried (Na_2SO_4) and the solvent evaporated. The residue did not crystallise and was not analysed.

A sample of the product was distilled at 2.10^{-3} mm. The major portion decomposed but a small amount of an oil was obtained, which showed ultraviolet absorption (λmax, mµ) in 0.1 N HCl and in 0.1 N NaOH: 310) similar to that of 2-formylindole. This substance was not characterised but was presumably 2,9-dimethyl-1-oxo-1,2,3,4-tetrahydro-β-carboline.

Further Alkylation of N_β-Alkyl-3,4-Dihydro-β-Carboline Anhydro and Pseudobases

Further Alkylation of Dimeric 2-Methyl-3,4-Dihydro-β-Carboline Anhydrobase

(a) 2-Formyl-3-(β-Trimethylammoniumethyl) Indole Iodide

Dimeric 2-methyl-3,4-dihydro-β-carboline anhydrobase (0.4 g) was suspended in 20 ml moist methanol. Potassium carbonate (0.2 g) and methyl iodide (5 ml) were added and the mixture was kept at 40° for 24 hours. The solvent was evaporated and the residue washed with cold water (3 ml) and crystallised from 50% aqueous methanol after treatment with charcoal, when colourless needles (0.42 g, 70%) melting at 270° were obtained (Found: C, 46.9; H, 5.3; N, 7.8; I, 35.8. $C_{14}H_{19}N_2OI$ requires: C, 46.9; H, 5.3; N, 7.6; I, 35.5%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 315 (4.1), 237 (4.1).

Hofmann Degradation of Quaternary Salt

The above quaternary salt (0.35 g) was treated with 5% methanolic KOH (20 ml). The solution was kept at 50° and swept with a current of nitrogen for 2 hours and the issuing gas passed through an alcoholic solution of picric acid, which on concentration and recrystallisation from methanol gave a yellow picrate (0.25 g) melting at 216°, which was identified as trimethylamine picrate by comparison with authentic sample (Found: C, 37.7; H, 4.3; N, 19.2. Calc. for $C_9H_{12}ON_4$: C, 37.5; H, 4.1; N, 19.4%).

The reaction mixture was evaporated under vacuum. Water (10 ml) was added to the residue and the solution extracted with ether. The ether extract was washed with water, dried and evaporated. The residue was dissolved in methanol, the solution treated with charcoal, filtered and again evaporated. The residue was distilled at 3.10^{-3} mm and 70° when two fractions were obtained.

The first fraction (0.035 g), a colourless solid melting at 110°, was 2-formyl-3-(β-methoxyethyl)indole (Found: C, 70.9; H, 6.6. $C_{12}H_{13}NO_2$ requires: C, 70.9; H, 6.5%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 317 (4.2), 238 (4.1).

The second fraction, a pale yellow substance (0.045 g) melting at 126° after softening at 115°, was 2-formyl-3-vinylindole (Found: C, 77.0; H, 5.4; N, 8.0. $C_{11}H_9NO$ requires: C, 77.2; H, 5.3; N, 8.2%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 322 (4.2), 252 (4.1).

(b) Dimethyl Acetal of 2-Formyl-3-(β-Trimethylammonium ethyl) Indole Iodide

Dimeric 2-methyl-3,4-dihydro-β-carboline anhydrobase (0.4 g) was suspended in 20 ml methanol. Anhydrous potassium carbonate (2.0 g) and methyl iodide (5 ml) were added and the reaction mixture was kept at 40° for 24 hours. The solvent was evaporated, the residue washed with cold water (2 - 3 ml) and crystallised from aqueous methanol after treatment with charcoal to give colourless needles (0.58 g, 66%) melting at 180° (Found: C, 47.4; H, 6.2; N, 7.0. $C_{16}H_{25}N_{2}O_{2}I$ requires: C, 47.5; H, 6.2; N, 6.9%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 _N_ HCl: 318 (3.9); in 0.1 _N_ NaOH: 282 (3.7).

(c) Diethyl Acetal of 2-Formyl-3-(β-Trimethylammonium ethyl) Indole Iodide

The above experiment was repeated using ethanol instead of methanol. The diethyl acetal was obtained as colourless needles melting at 230° (Found: C, 50.3; H, 6.8; N, 6.4. $C_{18}H_{29}N_{2}O_{2}I$ requires: C, 50.0; H, 6.7; N, 6.5%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 _N_ HCl: 318 (3.9); in 0.1 _N_ NaOH: 282 (3.7).

Hofmann Degradation of the Dimethyl Acetal

The acetal (0.20 g) was treated with 5% methanolic KOH (20 ml). The solution was kept at 60° and swept out with a current of nitrogen for 4 hours and the outcoming gas passed through an alcoholic solution of picric acid which on concentration and crystallisation from methanol gave trimethylamine picrate.

The reaction mixture was evaporated under vacuum, water was added to the residue and the solution extracted with ether. The ether extract was washed with water, dried and evaporated. The residue was dissolved in methanol, treated with charcoal, filtered and again evaporated.

The residue was distilled at 3.10^{-3} mm and 70° when a small amount of product which was probably dimethyl acetal of 2-formyl-3-vinylindole melting at 125° after sintering at 115° was obtained. Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl: 319 (4.1); in 0.1 N NaOH: 317 (3.9).

Further Alkylation of 2,9-Dimethyl-3,4-Dihydro-β-Carboline Pseudobase

(a) 1-Methyl-2-Formyl-3-β-(Trimethylammoniumethyl) Indole Iodide

9-Methyl-3,4-dihydro-β-carboline methiodide (0.5 g) was dissolved in hot water, 20% NaOH added, the solution cooled and extracted with ether. The ether extract was dried and evaporated and the residue dissolved in 20 ml of moist methanol. Potassium carbonate (0.2 g) and methyl iodide (5 ml) were added and the mixture kept at 40° for 24 hours. The solvent was evaporated, the residue washed with water and crystallised from 50% aqueous methanol after treatment with charcoal. Pale shining plates (0.38 g, 60%) of the monohydrate melting at 244° were obtained (Found: C, 46.3; H, 6.1; N, 6.8; I, 32.4. $C_{15}H_{21}N_2OI$, H_2O requires: C, 46.2; H, 5.9; N, 7.2; I, 32.6%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and 0.1 N NaOH: 318 (4.2), 240 (4.2).

Hofmann Degradation of the Above Quaternary Salt

The quaternary salt (0.25 g) was treated with 5% methanolic KOH (15 ml) under nitrogen and products isolated as earlier. The basic product was isolated as the picrate (0.17 g) melting at 216°, and identified as trimethylamine picrate by comparison with an authentic sample.

The neutral product was obtained as pale yellow crystals melting at 82°. The product was 1-methyl-2-formyl-3-vinylindole (Found: C, 77.9; H, 6.3; N, 7.6. $C_{12}H_{11}NO$ requires: C, 77.8; H, 6.0; N, 7.6%). Ultraviolet absorption (λmax, mu(log E)): in 0.1 *N* HCl and 0.1 *N* NaOH: 322 (4.2), 253 (4.2).

Oxime of 1-methyl-2-formyl-3-(β-Trimethylammonium ethyl) Indole Iodide

2-Formyl-3-(β-trimethylammoniumethyl) indole iodide (0.20 g) was dissolved in aqueous alcohol. Hydroxylaminehydrochloride (0.05 g) and potassium carbonate (0.05 g) were added. The reaction mixture was kept at 60° for half an hour. It was concentrated and cooled, and filtered. The oxime (0.15 g, 73%) melting at 256° was re-crystallised from aqueous alcohol (Found: C, 46.6; H, 6.0; N, 11.1. $C_{15}H_{22}N_3IO$ requires: C, 46.5; H, 5.7; N, 10.9%). Ultraviolet absorption (λmax, mu(log E)): in 0.1 *N* HCl: 310 (4.1); in 0.1 *N* NaOH: 315 (4.1), 254 (4.1).

(b) Dimethylacetal of 1-Methyl-2-Formyl-3-β-(Trimethylammonium ethyl) Indole Iodide

When the alkylation was carried out in the presence of large excess of anhydrous potassium carbonate, instead of the free aldehyde, the dimethyl acetal was obtained as colourless needles melting at 233° (Found: C, 48.7; H, 6.6. $C_{17}H_{27}N_2IO_2$ requires: C, 48.6; H, 6.5%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 *N* HCl: 318 (4.3); in 0.1 *N* NaOH: 282 (4.0).

Further Alkylation of 1,2-Dimethyl-3,4-Dihydro-β-Carboline Anhydrobase

2-Acetyl-3-β-(Trimethylammoniumethyl) Indole Iodide

Harmalan methiodide (1.0 g) was dissolved in hot water, 20% NaOH was added, the solution was cooled and extracted with ether. The ether extract was dried, solvent evaporated and the residue dissolved in 50 ml moist methanol. Potassium carbonate (0.4 g) and methyl iodide (5 ml) were added. The mixture was kept for 24 hours at 40° and worked up as before. Pale yellow plates (0.88 g, 70%) melting at 278°, were obtained (Found: C, 49.3; H, 5.9; N, 7.4. $C_{15}H_{21}N_2OI$ requires: C, 48.4; H, 5.7; N, 7.5%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 *N* HCl and 0.1 *N* NaOH: 315 (4.1), 252 (4.1).

Hofmann Degradation of the Above Quaternary Salt Using Methanolic KOH

The quaternary salt (0.70 g) was treated with 2% methanolic KOH (40 ml) and the experiment carried out as before. The basic fragment was isolated as the picrate (0.48 g) melting at 216°. It was identified as trimethylamine picrate by comparison with an authentic sample and by analysis (Found: C, 37.7; H, 4.1; N, 19.2. $C_9H_{12}O_7N_4$ requires: C, 37.5; H, 4.2; N, 19.4%).

The reaction mixture was evaporated, water was added to the residue, the solution was extracted with ether and the ether extract dried and evaporated. The residue was dissolved in benzene and passed through an alumina column. The column was eluted with benzene and the colourless eluate collected and evaporated, when 2-acetyl-3-(β-methoxyethyl) indole was obtained as a colourless residue (0.10 g) melting at 140° (Found: OCH_3, 14.1; C, 71.7; H, 7.3; N, 6.2. $C_{13}H_{15}O_2N$ requires: OCH_3, 14.3; C, 71.8; H, 6.9; N, 6.5). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 315 (4.1).

Hofmann Degradation Using Ethanolic KOH

The quaternary salt was degraded as before with ethanolic KOH. The basic fragment was isolated as trimethylamine picrate and the neutral fragment was 2-acetyl-3-(β-ethoxyethyl) indole, isolated as a colourless substance melting at 118° (Found: OC_2H_5, 18.4; C, 73.4; H, 7.9; N, 6.1. $C_{14}H_{17}O_2N$ requires: OC_2H_5, 19.4; C, 72.2; H, 7.4; N, 6.1%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 315 (4.1).

Further Alkylation of 1-Methyl-2-n-Propyl-3,4-Dihydro-β-Carboline Anhydrobase

2-Acetyl-3-(β-Dimethyl-n-Propylammoniumethyl) Indole

Harmalan propiodide (1.0 g) was dissolved in hot water, treated with NaOH, the anhydrobase extracted into ether and quaternised with methyl iodide as described earlier. The quaternary salt was isolated as pale yellow plates (0.87 g, 70%) melting at 170° (Found: C, 50.9; H, 6.7; N, 6.4; I, 31.9. $C_{17}H_{25}N_2OI$ requires: C, 51.0; H, 6.3; N, 7.0; I, 31.6%). Ultraviolet absorption (λmax, mu(log E)): in 0.1 N HCl and in 0.1 N NaOH: 315 (4.1).

Hofmann Degradation of the Quaternary Salt

Treatment of the quaternary salt with methanolic and ethanolic KOH in the usual manner and purification of the degradation products as before gave 2-acetyl-3-(β-methoxyethyl) indole and 2-acetyl-3-(β-ethoxyethyl) indole respectively, identical with those obtained by degradation of the corresponding trimethylammonium salt. The corresponding compounds had identical melting points and gave overlapping infrared spectra.

Isolation of n-Propyl-Dimethylamine Picrate

As before during degradation the gas was swept into an alcoholic solution of picric acid by means of a stream of nitrogen. After concentration of the solution n-propyldimethylamine picrate was obtained as lemon yellow plates melting at 108°, after re-crystallisation from ethylacetate. There was no depression in the melting point on admixture of an authentic sample of n-propyldimethylamine picrate (Found: C, 42.0; H, 5.3; N, 17.3. Calc. for $C_{11}H_{16}O_7N_4$: C, 41.8; H, 5.1; N, 17.7%).

Further Alkylation of 1,2,9-Trimethyl-3,4-Dihydro-β-Carboline Anhydrobase

1-Methyl-2-Acetyl-3-)β-Trimethylammoniumethyl) Indole Iodide

The anhydrobase was precipitated from 0.5 g of the methiodide and the moist precipitate dissolved in 25 ml methanol. Methyliodide (2 ml) and potassium carbonate (0.4 g) were added and the reaction mixture was kept at 40° for 24 hours. The quaternary salt (0.35 g, 62%), melting at 215°, was crystallised from aqueous methanol (Found: C, 48.0; H, 6.4; N, 7.2; I, 32.1. $C_{16}H_{23}N_2OI$, H_2O requires: C, 47.5; H, 6.2; N, 6.9; I, 31.4%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 315 (4.1).

Hofmann Degradation of the Quaternary Salt

The quaternary salt was treated with 3% methanolic KOH (20 ml) in the usual manner. The basic fragment was isolated and identified as trimethylamine picrate. The reaction mixture was evaporated, water added to the residue, the solution extracted with ether and the extract dried and evaporated. The residue was dissolved in methanol, decolorised with charcoal and again evaporated. The residue was sublimed at 3.10^{-3}

mm and 70° when pale yellow crystals of 1-methyl-2-acetyl-3-vinylindole melting at 54° were obtained (Found: C, 78.7; H, 6.9; N, 6.9. $C_{13}H_{13}NO$ requires: C, 78.4; H, 6.6; N, 7.0%). Ultraviolet absorption (λmax, mμ(log E)): in 0.1 N HCl and in 0.1 N NaOH: 318.

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