THESIS FOR THE DEGREE OF Ph. D.

Preparation of 2-β-aminoethyl-quinoline Derivatives of Possible Anti-Malarial Activity.

by

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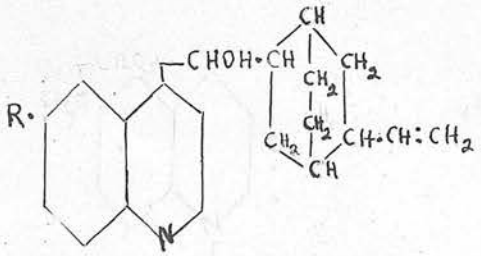
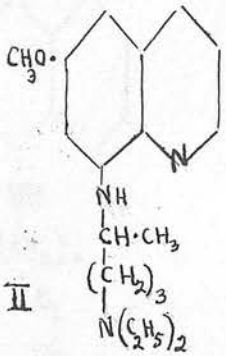
E D I N B U R G H.

It was shown by Roehl in 1926 that the antimalarial activity of chemical compounds could be conveniently tested by observing their effect on canaries infected with plasmodium relictum. The disease which this parasite produces in these birds bears a very close resemblance to human malaria. By the application of this technique the new synthetic antimalarial plasmoquin was discovered. In addition it afforded for the first time a standard method for the measurement and comparison of the antimalarial activity of all compounds likely to possess this property. It appears, however, that all compounds effective in the treatment of bird malaria are not necessarily so in their action towards human malaria. Demeplasmin, for example, is effective in the former whereas it is inactive in the latter. Nevertheless from wide experience Roehl's technique has proved generally applicable and may be considered the starting point of a thorough scientific investigation of the chemotherapy of malaria.

With this method as a basis Barger and Robinson (J.C.S. 1929, II. 2947), have outlined briefly the main lines along which chemical investigations are proceeding in an endeavour to produce more efficient antimalarials. The investigations are based upon the production of synthetic compounds with a close similarity in structure to the quinine group of alkaloids and the recently discovered synthetic compound plasmoquin.



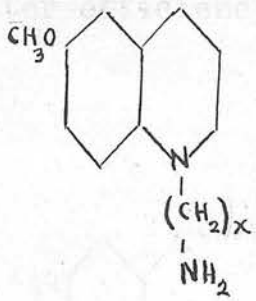
I



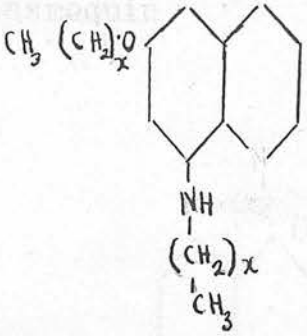
II

The principal alkaloid of the quinine group consist of two pairs of stereo-isomerides, quinine and quinidine, cinchonine and cinchonidine. The former pair is represented in formula I. where R = OCH_3 and the latter where R = H. Plasmoquin as shown in formula II although its constitution has not been officially disclosed is supposed to be 8-diethyl-amino-isopentyl-amino-6-methoxy-quinoline. Briefly the relationship of the quinine alkaloids to plasmoquin is expressed by the common possession of a quinoline nucleus, a basic side chain, and a methoxy group in the six position.

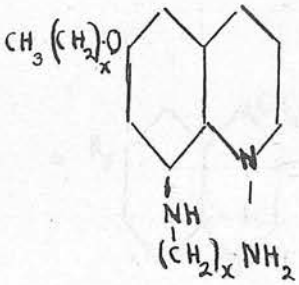
In accordance with Barger and Robinson's general scheme T. R. Seshadri (J.C.S. 1929 II., 2952), and A. W. Baldwin (J.C.S. 1929 II., 2959) have attacked the problem along the lines of the plasmoquin model.



III



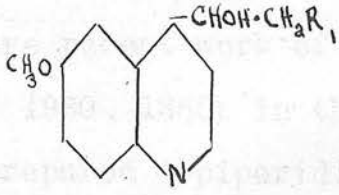
IV



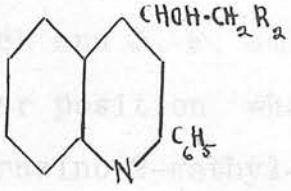
V

T. R. Seshadri by preparing compounds of the general type shown in formula III has investigated the effect of certain variations in the alkylated amino side chain in the one position of the quinoline nucleus. A. W. Baldwin, on the other hand, has prepared compounds of the type IV and V, and has observed the effect of certain variations in the alkylated-amino and amino-alkylated-amino-side chains in the eight position of the quinoline nucleus, and, in addition, has noted the effect of alkoxy groups other than the methoxy in the six position. The physiological results show that of these compounds those with the closest relationship to plasmoquin with three or four carbon atoms in the side chain /

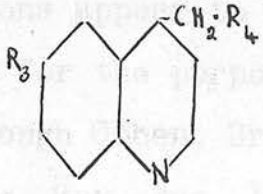
chain prove to be the most effective but do not display a greater efficiency than plasmoquin.



VI



VII



VIII

$R_1 = -NH_2$ = amino
" $= -NC_5H_{10}$ = piperidyl

$R_3 = -H$
" $= -OCH_3$ = methoxy

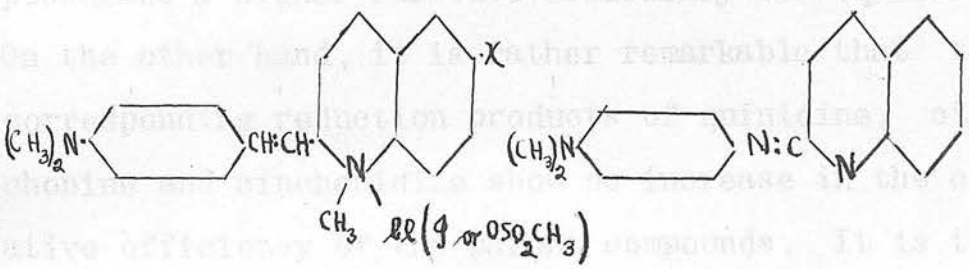
$R_2 = -NH_2$ = amino
" $= -N(CH_3)_2$ dimethyl-amino
" $= -NH\cdot C_6H_5$ phenyl-amino

$R_4 = -NC_5H_{10}$ = piperidyl
" $= -N\cdot C_4H_8\cdot NH$ = piperazino

A. Kaufmann (Ber. 1913, 46 1825) and R. Schweiz (from Chem Zentre 1922, IV, 950), have synthesised 6-methoxy and 2-phenyl-4-(β-amino-α-hydroxy) ethyl-quinoline derivatives as shown in formulae VI and VII with a view to examining the effect of quinoline compounds with a side chain in the four position. It would appear, however, that these compounds do not possess /

possess any specially useful physiological properties, although the relationship of this type to the quinine group of alkaloids is very close, the difference lying mainly in the extra carbon atom of the side chain. No more successful, from a physiological view point, is the more recent work of W. O. Kermack and J. F. Smith (J.C.S. 1930, 1356), in this particular position when they prepared 4-piperidino and piperazino-2-methyl-quinoline derivatives along with the 6 methoxy analogues as shown in formula VIII.

No investigations appear to have been carried out on the two position for the purpose of preparing new antimalarials, although Cohen, Browning, Ellinworth and Gulbransen, (Proc. Roy. Soc. 1926, B. 100, 293; 1929 B. 105, 99), have endeavoured with success to prepare new antiseptics. Recently certain of these compounds have been applied in the treatment of trypanosomiasis.



IX X

X = $-NH_2$ amino

" = $-NHOC\cdot CH_3$ = acetylamino

" = $-N(CH_3)_2$ = dimethyl-amino

The /

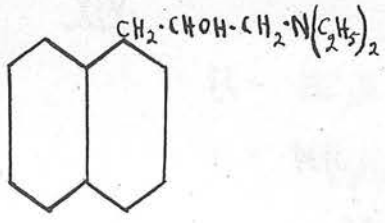
The compounds prepared were derivatives of styryl-quinoline IX and anil-quinoline X obtained by the condensation of quinaldine derivatives with ⌇ -dimethyl-amino-benzaldehyde and ⌇ -nitroso-dialkyl-aniline. There was found to be a close parallelism in the properties of the fundamental compounds 2-(p.-amino-styryl) and 2-(p.- amino-anil)-quinoline metho-chlorides. The trypanocidal activity is characteristic of the first series, and, as in the case of the active antimalarials, appears to be dependent upon the presence of a side chain containing a basic group.

At present there is no generally accepted theory concerning the curative activity of closely related compounds of a specific type. There is no doubt, however, according to recent investigations that this activity is related in a very complex way to the molecular structure of the compound. For example, by the reduction of the vinyl group in quinine dihydro-quinine is obtained which, when tested by Roehl's method, possesses a higher curative efficiency than quinine. On the other hand, it is rather remarkable that the corresponding reduction products of quinidine, cinchonine and cinchonidine show no increase in the curative efficiency of the parent compounds. It is this irregular effect of small changes in molecular structure that makes the formulation of an activity theory so difficult.

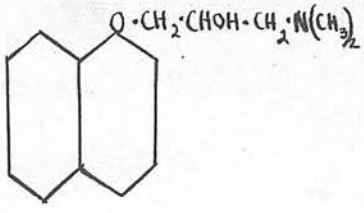
The researches of Goodson, Henry and Macfie, (J. Bio. Chem. 1930, 24, 874), however, on the alkyl-quitenines, which are obtained by the oxidation of the /

the vinyl group in the quinine alkaloids to the carboxyl and subsequent esterification showed a certain relationship between the activity and the length of the side chain. This research was instituted as a result of an observation made by Giesma, Weise and Tropp, (Arch. Schiff. Trop. Hyg. 1926, 30, 334) that these acids which are themselves inactive regain their activity on esterification. It was found that the activity gradually increases to a maximum value with increasing molecular weight of the esterifying alcohol and then commences to decrease. The maximum was reached in the case of quitenine with the butyl and amyl esters although at no point was it ever as great as that of quinine. The compounds prepared by Baldwin of the plasmoquin type previously described behave in an analogous manner where it is found, in a particular series, that compounds with a side chain of three or four carbon atoms possess maximum activity.

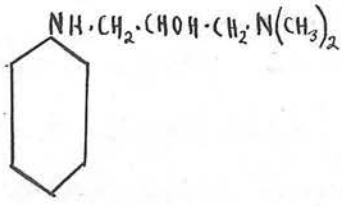
Geisma, Weise and Tropp have further pointed out that if the hydroxyl group in the chinchona alkaloids is in any way protected loss of activity results.



XI



XII

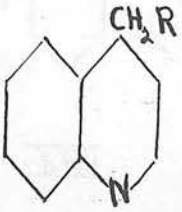


XIII

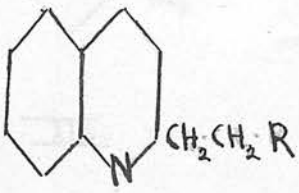
It /

It was no doubt this statement that led Fourneau and his co-workers (Ann. Inst. Pasteur 1930, 44, 503) to prepare certain amino alcohols of the types shown in formulae XI, XII and XIII. Some of these were active in the case of bird malaria but entirely ineffective on application to human malaria.

It was the object of this research to continue the investigations on the four position of the quinoline nucleus and at the same time to investigate the two position which up to the present appears to have been neglected for the attempted preparation of more efficient antimalarials. It was hoped to introduce into these positions a basic radicle such as piperidyl (NC_5H_{10}), diethyl-amino ($N(C_2H_5)_2$), methyl-phenyl-amino ($N<^{CH_3}_{C_6H_5}$) etc. separated from the quinoline nucleus by one or two carbon atoms.



XIV



XV

R = $-NC_5H_{10}$ = piperidyl.

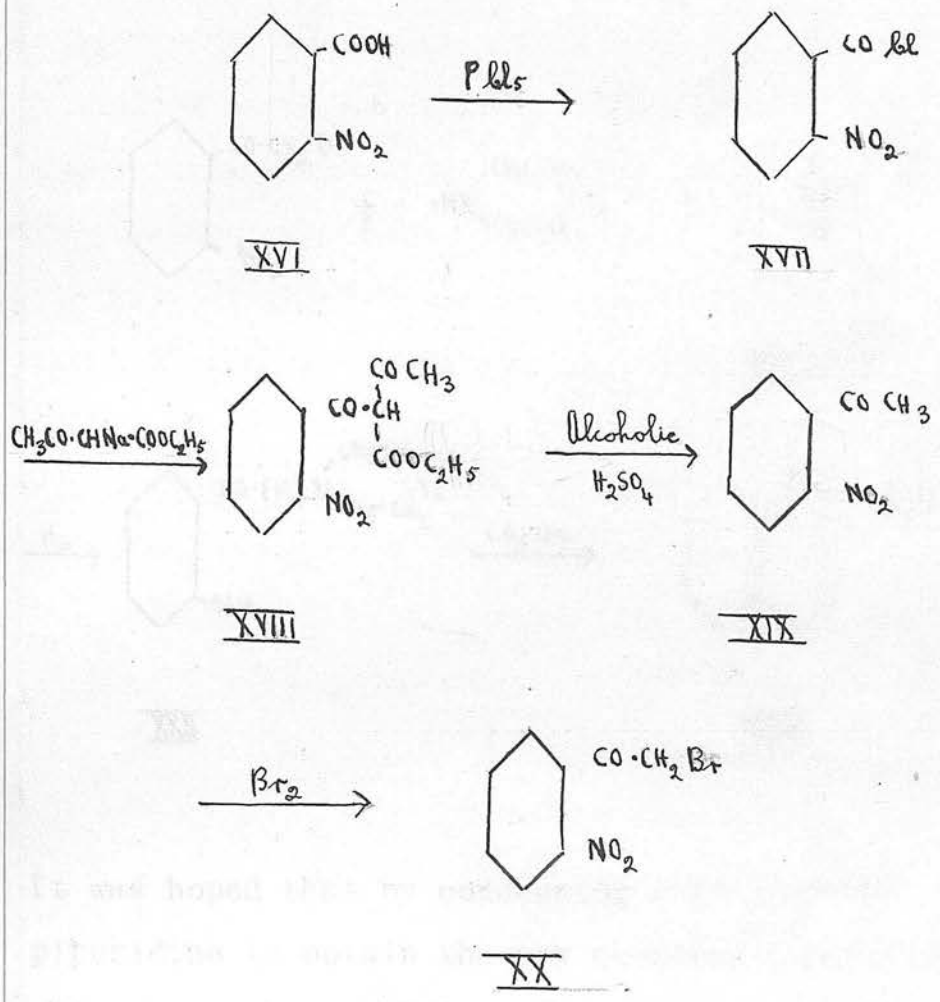
" = $-N(C_2H_5)_2$ = diethyl-amino.

" = $-N<^{CH_3}_{C_6H_5}$ = methyl-phenyl-amino.

The parent bases of these compounds would be 4-amino-methyl-quinoline XIV and 2-(β-amino)-ethyl-quinoline XV. In addition, by a method to be described later, an /

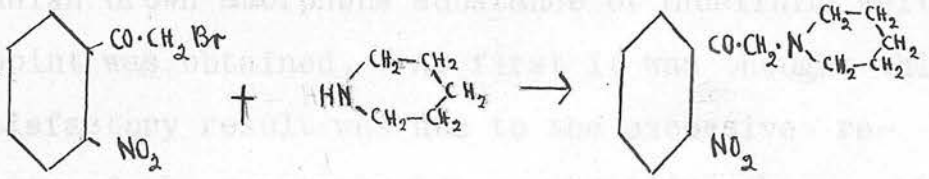
an alkyl radical is introduced into the α position of the side chain of type XV whereby the α carbon atom becomes assymetric and consequently the base should be capable of existing in two optically active enantiomorphic forms.

The attempted synthesis of 4-(N-piperidyl)-methylquinoline was carried out according to the following scheme.

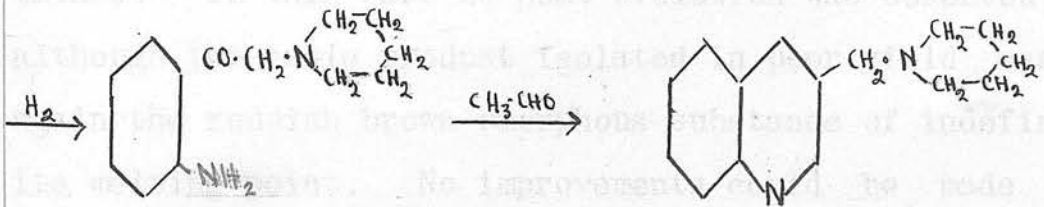


O-nitro-benzoic acid XVI was readily converted by treatment with phosphorus pentachloride into the corresponding /

corresponding o-nitro-benzoyl chloride XVII which was then condensed with sodium ethyl-aceto-acetate to form ethyl-o-nitro-benzoyl-aceto-acetate XVIII according to the method of Perkin and Needham (J.C.S. 1904, 85, 151). The latter compound was readily converted into o-nitro-acetophenone XIX by the method of Kermack and Smith (J.C.S. 1929, 814). The bromination of o-nitro-acetophenone was readily effected by the method of Gevekoht (A. 1883, 221, 327), to give w-bromo-o-nitro-acetophenone XX.



XXI

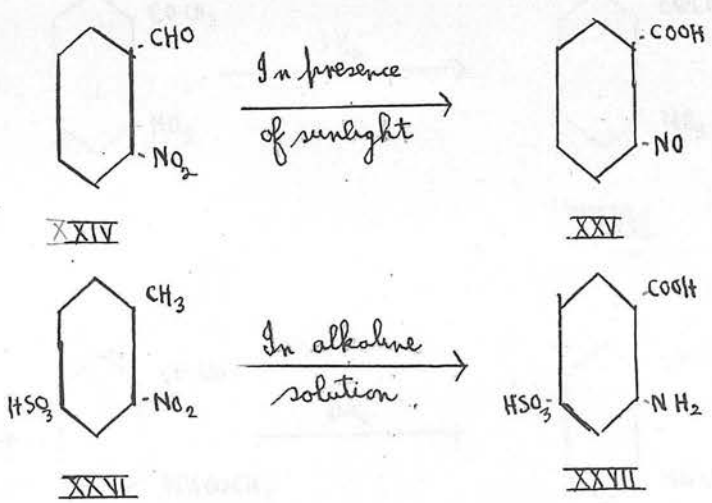


XXII XXIII

It was hoped that by condensing this compound with piperidine to obtain the new compound w-piperidyl-o-nitro-acetophenone XXI. The reduction of the latter to w-piperidyl-o-nitro-acetophenone XXII followed by ring closure with acetaldehyde according to the method of /

of Friedlander would give the desired new base 4-(N-piperidyl-methy)-quinoline XXIII.

The various attempts to condense piperidine and w-bromo-o-nitro-acetophenone did not lead to the isolation of w-piperidyl-o-nitro-acetophenone. The direct interaction of these two compounds in equi-molecular proportions produced a vigorous reaction accompanied with the evolution of much heat in which the product of the reaction completely tarred. By extraction of the tarry substance with dilute hydrochloric acid, followed by basification with dilute sodium hydroxide a reddish brown amorphous substance of indefinite melting point was obtained. At first it was thought this unsatisfactory result was due to the excessive reactivity of the reactants but on repeating the reaction using benzene as a diluent no better results were obtained. In this case no heat evolution was observed, although the basic product isolated in poor yield was again the reddish brown amorphous substance of indefinite melting point. No improvements could be made on this result by modifications of the foregoing method.



XXIV XXV

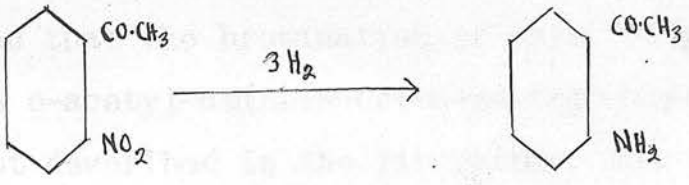
XXVI XXVII

It /

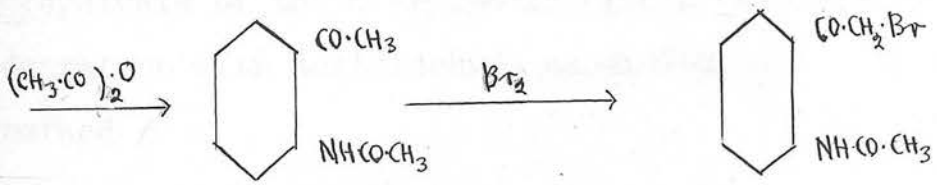
It is well known that o-nitro-benzaldehyde XXIV in the presence of sunlight as catalyst is converted into o-nitroso-benzoic acid XXV due to the reduction of the nitro and oxidation of the aldehyde groups respectively. By a mechanism of a similar type 2-nitro-toluene 4-sulphonic acid XXVI in a strong alkaline medium is converted into 3-amino-4-carboxy-benzene-sulphonic acid XXVII.

These are two examples which demonstrate the tendency of the nitro group to oxidise an adjacent group and itself simultaneously to undergo reduction. It is possible that, in the presence of piperidine, the oxidation of the bromo-acetyl side chain and the simultaneous reduction of the nitro group might lead to the formation of some such basic amorphous substance as was isolated.

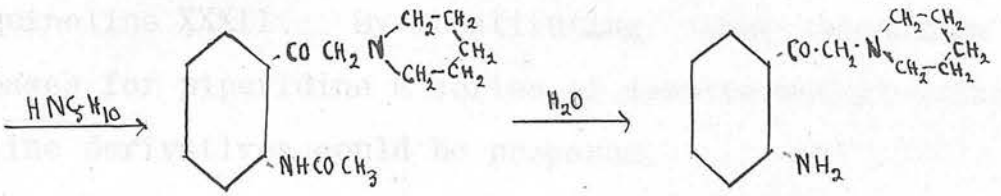
Since the condensation of w-bromo-o-nitro-acetophenone with piperidine did not proceed as desired the following modification of the above procedure was adopted.



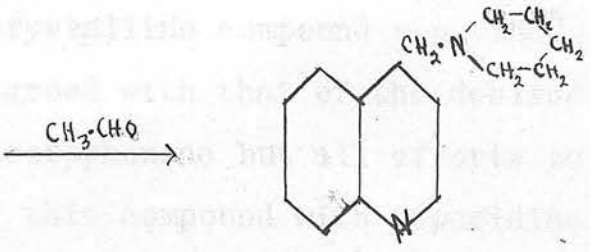
XXVIII



XXIX XXX



XXXI

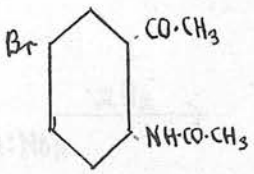


XXXII

O-nitro-acetophenone was reduced by means of iron filings and hydrochloric acid to the corresponding o-amino-acetophenone, XXVIII, according to the method of West (J.C.S. 1925, 127, 494). The latter compound was acetylated by dissolving in acetic anhydride and warming to obtain o-acetyl-amino-acetophenone, XXIX. It was hoped that the bromination of this compound would yield o-acetyl-amino-w-bromo-acetophenone, XXX, which is not described in the literature and that o-acetyl-amino-acetophenone, XXXI, would be obtained by condensation of the latter with piperidine. The hydrolysis of the acetyl-amino group followed by condensation with acetaldehyde according to Friedlander's method /

method would lead to the desired 4-piperidyl-methyl-quinoline XXXII. By substituting other secondary bases for piperidine a series of 4-amino-methyl-quinoline derivatives could be prepared.

The bromination of o-acetylamino-acetophenone carried out in glacial acetic acid yielded readily a white crystalline compound m.p. 155°, the analysis of which agreed with that of the desired o-acetylamino-bromo-acetophenone but all efforts to effect condensation of this compound with piperidine were unsuccessful. On examination of the literature it was found that this compound was identical with that prepared by A. Baeyer and F. Bloem (Ber. 1884, 17, 965), by the bromination of o-acetylamino-acetophenone namely methyl-5-bromo-2-acetyl-amino-phenyl-ketone XXXIII, m.p. 160°.



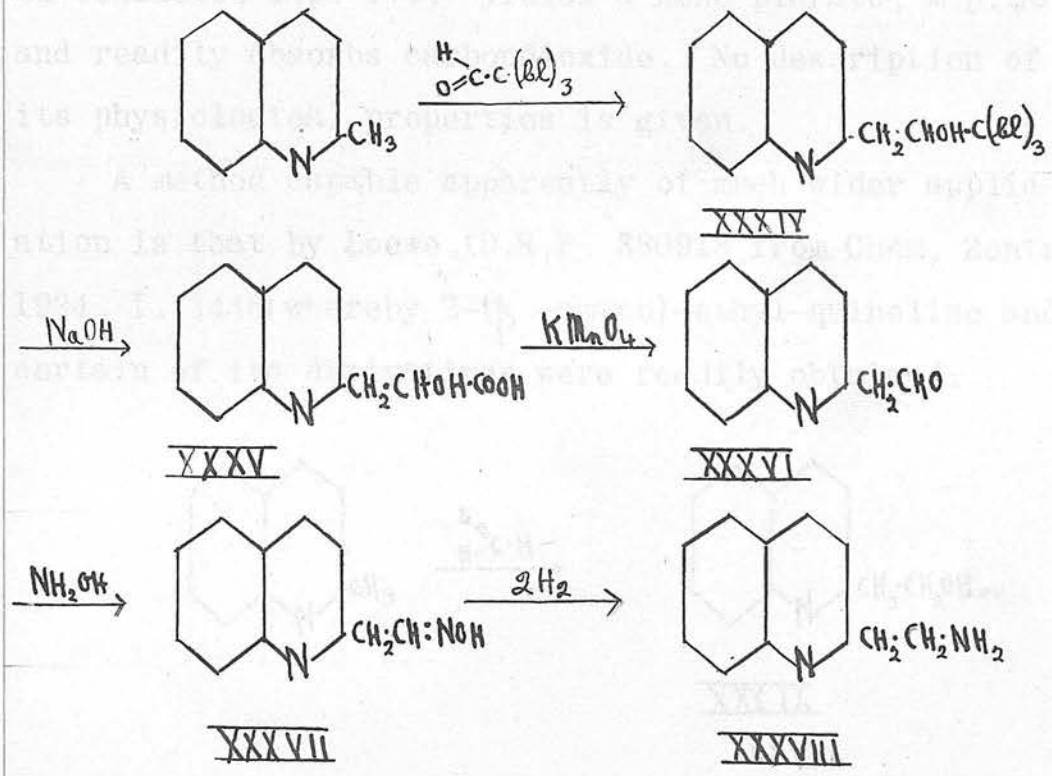
XXXIII

It would appear that by the method employed the bromination has resulted in the bromine atom entering the nucleus instead of the side chain. Consequently the failure to effect condensation with piperidine is explained and affords an additional proof to that given by A. Baeyer and F. Bloem of the bromine atom entering the nucleus preferentially to the side chain.

The /

The attempted preparation of 4-amino-methyl-quinoline derivatives was abandoned and attention concentrated on a method for the synthesis of 2-(β -amino)-ethyl-quinoline derivatives. Certain of these bases are described in the literature.

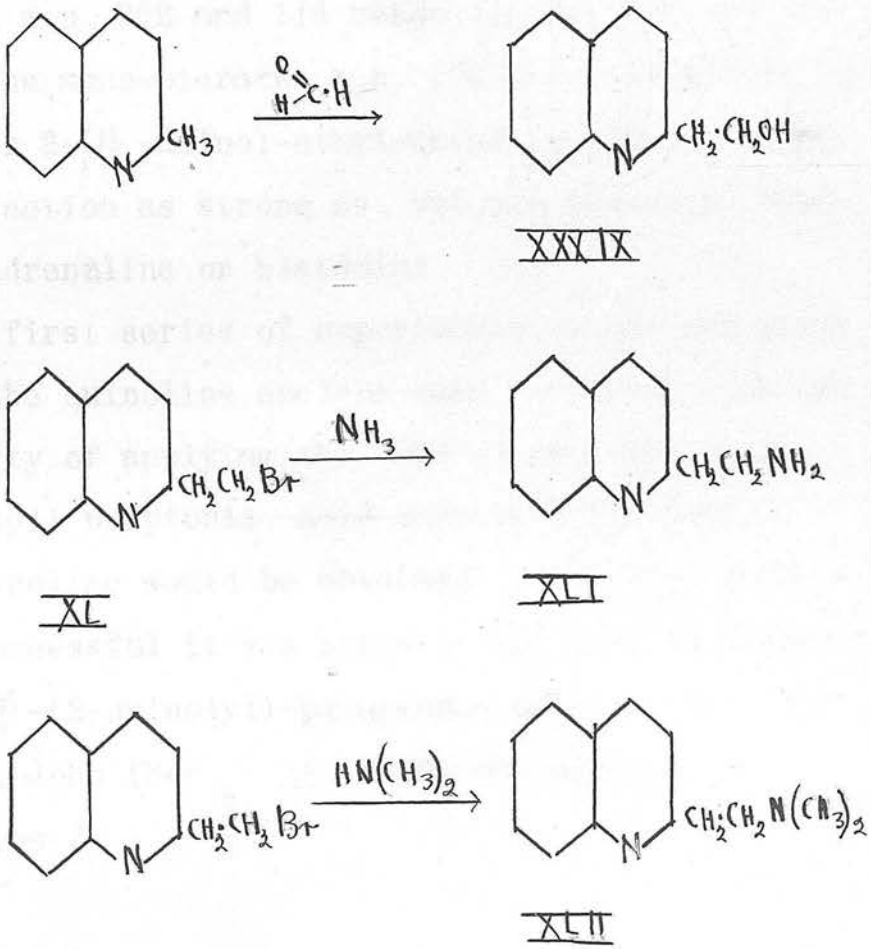
R. Hupe and A. Schramme (Ztschr. Physiol. Chem. 117, 315), have described a method for the preparation of the parent base 2-(β -amino)-ethyl-quinoline.

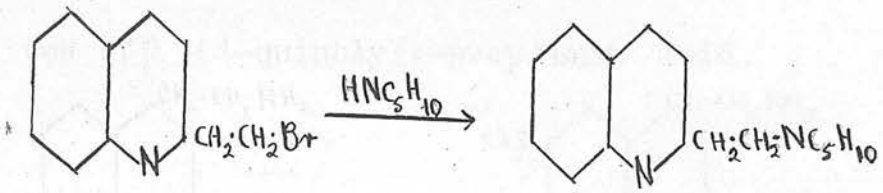


By the condensation of quinaldine and chloral hydrate α-(2-quinolyl)-β -hydroxy-γ -trichlor-propane XXXIV was obtained which on hydrolysis with dilute sodium hydroxide yielded β -(2-quinolyl)-lactic acid, XXXV. The oxidation of the latter with weak potassium permanganate gave 2-quinolyl acetaldehyde, XXXVI. This compound /

compound on condensation with hydroxylamine produced the corresponding oxime XXXVII, which on reduction with hydrogen and platinum black yielded the desired base 2-(β -amino)-ethyl-quinoline, XXXVIII. This method, however, did not produce the base in good yield and is therefore not suitable for general application to the preparation of its derivatives. The base 2-(β -amino)-ethyl-quinoline recrystallises from ammonia in coloured leaflets, m.p. 174°, yields a mono picrate, m.p.209°, and readily absorbs carbondioxide. No description of its physiological properties is given.

A method capable apparently of much wider application is that by Loewe, (D.R.P. 380918 from Chem. Zentre. 1924, I. 1446) whereby 2-(β -amino)-ethyl-quinoline and certain of its derivatives were readily obtained.



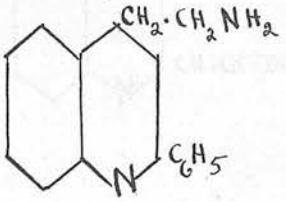


XLIII

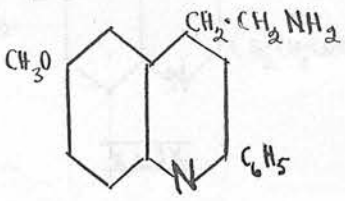
β -(2-quinolyl)-ethyl-alcohol, XXXIX, was obtained by condensing together quinaldine and a 40% aqueous solution of formaldehyde. On treatment of this alcohol with hydrobromic acid 2-(β -bromo)-ethyl-quinoline XL was produced. On condensing the latter compound with certain bases ammonia (NH_3), dimethyl-amine ($HN(CH_3)_2$) and piperidine (HNC_5H_{10}), the following compounds were isolated and described as their picrates 2-(β -amino)-ethyl-quinoline, XLI, 2-(β -dimethyl-amino)-ethyl-quinoline, XLII, and 2-(β -piperidyl)-ethyl-quinoline, XLIII. The first and the last were obtained as di-picrates, m.p. 202° and 145° respectively, and the second as the mono-picrate, m.p. 185°-188°. According to the author 2-(β -amino)-ethyl-quinoline shows a physiological action as strong as, but not identical with, that of adrenaline or histamine.

The first series of experiments on the two position of the quinoline nucleus were concerned with the possibility of applying the Curtius reaction to β -(2-quinolyl) propionic acid whereby 2-(β -amino)-ethyl-quinoline would be obtained. If this reaction proved successful it was hoped to apply it to derivatives of β -(2-quinolyl)-propionic acid in the same way as H. John (Ber. 58, 2779), has applied it to derivatives /

derivatives of β-(4-quinolyl)-propionic acid.



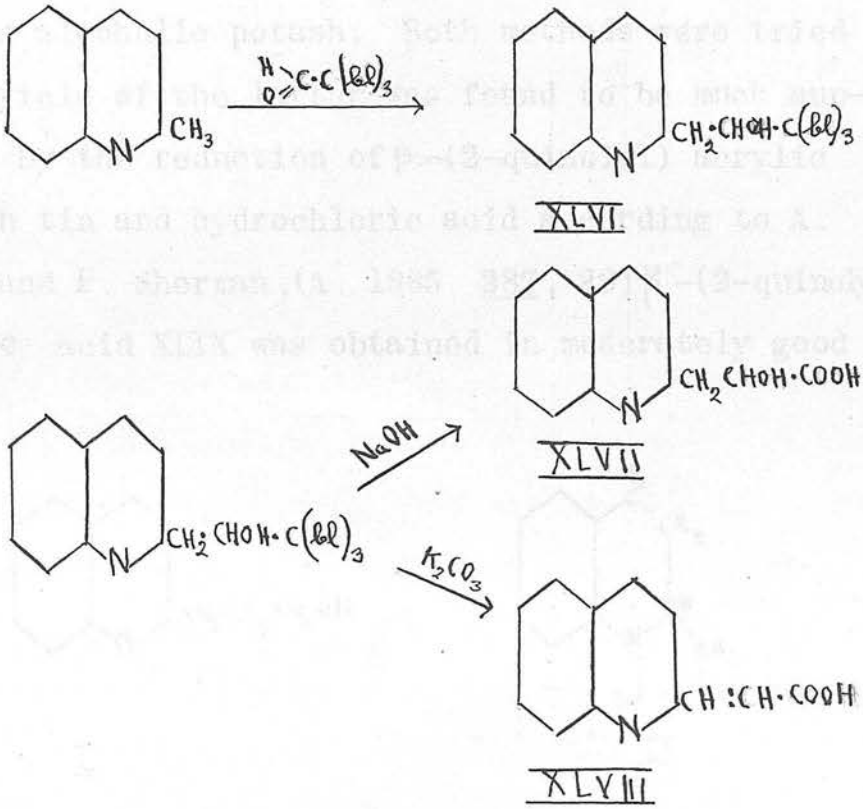
XLIV



XLV

This author has obtained [β-(2-phenyl-4-quinolyl) ethyl] amine XLIV, and [β-(2-phenyl-6-methoxy-4-quinolyl) ethyl] amine XLV. by a successful application of the Curtius reaction to β-(2-phenyl-4-quinolyl) propionic acid and β-(2-phenyl-6-methoxy-4-quinolyl) propionic acid respectively. The bases were prepared for chemotherapeutic purposes but no description is given of their physiological activity.

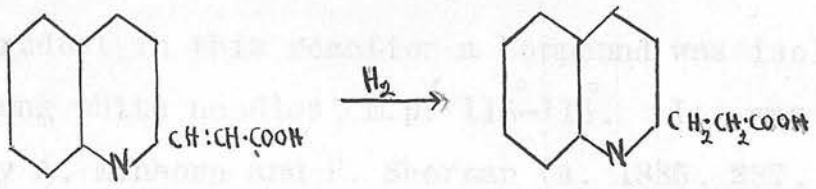
To obtain β-(2-quinolyl) propionic acid the following scheme was adopted.



XLVI

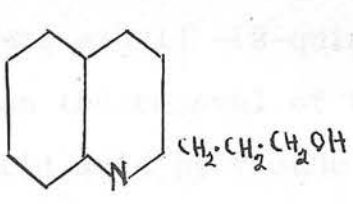
XLVII

XLVIII

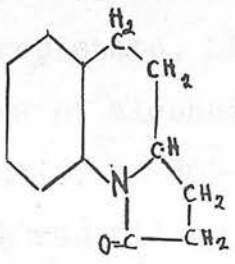


XLIX

By the condensation of quinaldine and chloral hydrate according to the method of Miller and Spady (Ber. 1885 18, 3402) α-(2-quinolyl)-β-hydroxy-γ-trichlor-propane XLVI was obtained in good yield. According to these authors the latter compound can be hydrolysed into two acids. With aqueous sodium hydroxide β-(2-quinolyl) lactic acid XLVII is obtained whilst with aqueous potassium carbonate β-(2-quinolyl) acrylic acid XLVIII. In a later paper by A. Einhorn and P. Sherman, (A. 1895 287, 27) β-(2-quinolyl) acrylic acid is formed in much better yield by using in place of aqueous potassium carbonate alcoholic potash. Both methods were tried and the yield of the latter was found to be much superior. By the reduction of β-(2-quinolyl) acrylic acid with tin and hydrochloric acid according to A. Einhorn and P. Sherman, (A. 1885 287, 29) β-(2-quinolyl) propionic acid XLIX was obtained in moderately good yield.



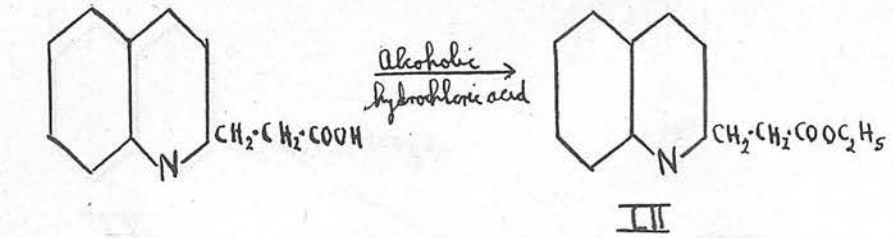
I



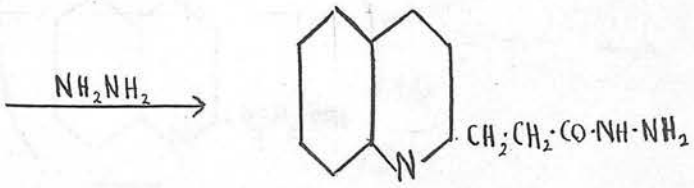
II

As /

As a by-product in this reaction a compound was isolated in long white needles, m.p. 115°-116°. It was thought by A. Einhorn and P. Sherman (A. 1885, 287, 29) to be β-(2-quinolyl) propyl alcohol, L, but it was proved by Konig, (B. 1900, 33, 218) to be the lactam of β-(tetra hydro-2-quinolyl) propionic acid, LI. Konig prepared the latter acid by reduction of β-(2-quinolyl) acrylic acid with sodium and alcohol. The acid liberated from its alkaline solution by the addition of acid rapidly changes into the lactam.



LII

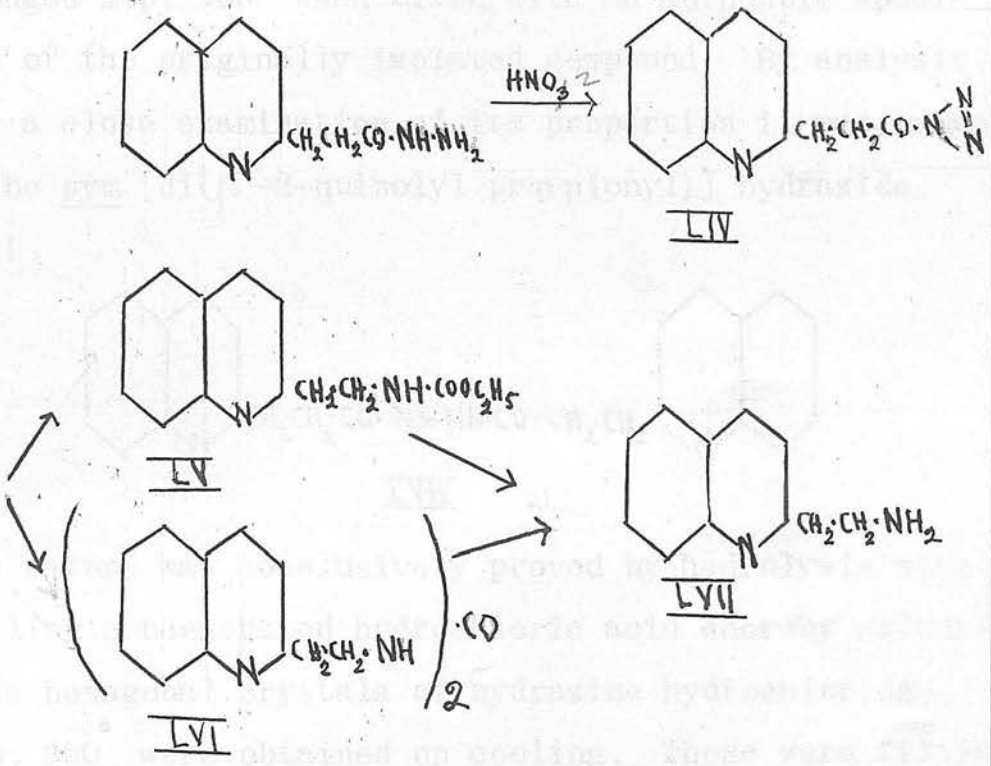


LIII

By refluxing β-(2-quinolyl) propionic acid with saturated alcoholic hydrochloric acid according to the Fisher esterification method, the hydrochloride of the new compound ethyl β-(2-quinolyl) propionate, LII, was obtained on the removal of the excess of alcoholic hydrochloric acid by vacuum distillation at 30° - 40°. The basic ester, obtained as a thick red oil by treatment of the hydrochloride with sodium hydroxide, was condensed without further purification with excess of

a /

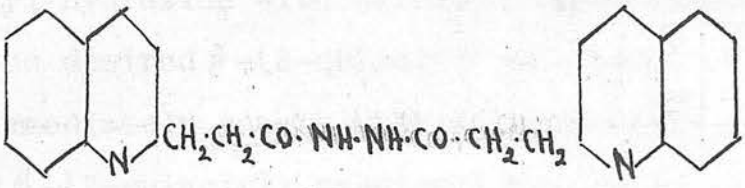
a 50% aqueous solution of hydrazine hydrate on the oil bath at 140°. On cooling β-(2-quinolyl) propionyl hydrazide LIII crystallised out in long white needles, which on recrystallising from ligroin in silvery leaflets gave m.p. 165°. It was obtained in almost quantitative yield.



By treatment of β-(2-quinolyl) propionyl hydrazide with sodium nitrite and hydrochloric acid it was hoped to obtain β-(2-quinolyl) propionyl azide LIV, which on decomposition would yield either β (2-quinolyl) propionyl urethane LV or [β-(2-quinolyl) ethyl)] urea, LVI. Either of these compounds on hydrolysis with concentrated hydrochloric acid would give the desired base 2-(β-amino) ethyl-quinoline, LVII.

However, on treatment of the hydrazide with nitrous /

nitrous acid a gas was evolved and a compound was isolated, m.p. 265°, which, at first, was thought to be the expected β-(2-quinolyl) propionyl azide, but on subsequent attempts to decompose it with boiling ethyl alcohol and then in boiling amyl alcohol the original compound was re-obtained. This was shown by its unchanged m.p. 265° when mixed with an authentic specimen of the originally isolated compound. By analysis and a close examination of its properties it was proved to be sym [di(β-2-quinolyl propionyl)] hydrazide, LVII.



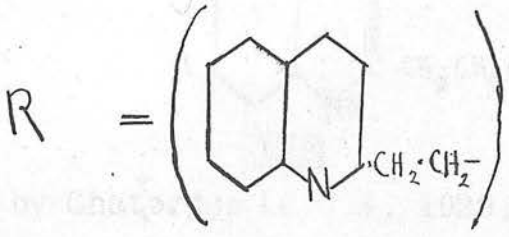
LVII

Its nature was conclusively proved by hydrolysis with boiling concentrated hydrochloric acid whereby colourless hexagonal crystals of hydrazine hydrochloride, m.p. 200° were obtained on cooling. These were filtered off and the acid filtrate taken down to dryness. The residue was taken up in a small amount of water and made definitely alkaline with ammonium hydroxide and again taken to dryness. By extraction of this residue with acetone β-(2-quinolyl) propionic acid m.p. 122° was isolated.

The reaction resulting in the formation of sym [di(β-2-quinolyl-propionyl)] hydrazide may take place according to the following scheme.

(1) $R\cdot CON_3 + R\cdot CO\cdot NH\cdot NH_2 + HNO_2 = R\cdot CO\cdot NH\cdot NH\cdot CO\cdot R + H_2O + N_2O + N_2$

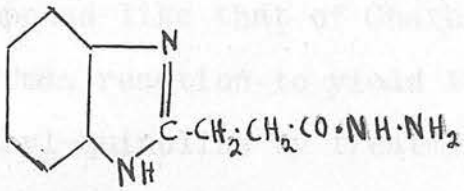
(2) $R\cdot CO\cdot N_3 + H_2O = R\cdot CO\cdot NH\cdot NH\cdot CO\cdot R + N_2O + N_2$



It may be assumed that the treatment of β-(2-quinolyl) propionyl hydrazide with nitrous acid actually produces the desired β-(2-quinolyl) propionyl azide which immediately reacts with a molecule of the unchanged β-(2-quinolyl) propionyl hydrazide in the presence of nitrous acid to give sym [di (β-2-quinolyl propionyl)] hydrazide, water, nitrous oxide and nitrogen as shown in equation (1). An alternative explanation as indicated in equation (2) is that the azide is immediately decomposed into the hydrazide derivative, nitrous oxide and nitrogen in the presence of water.

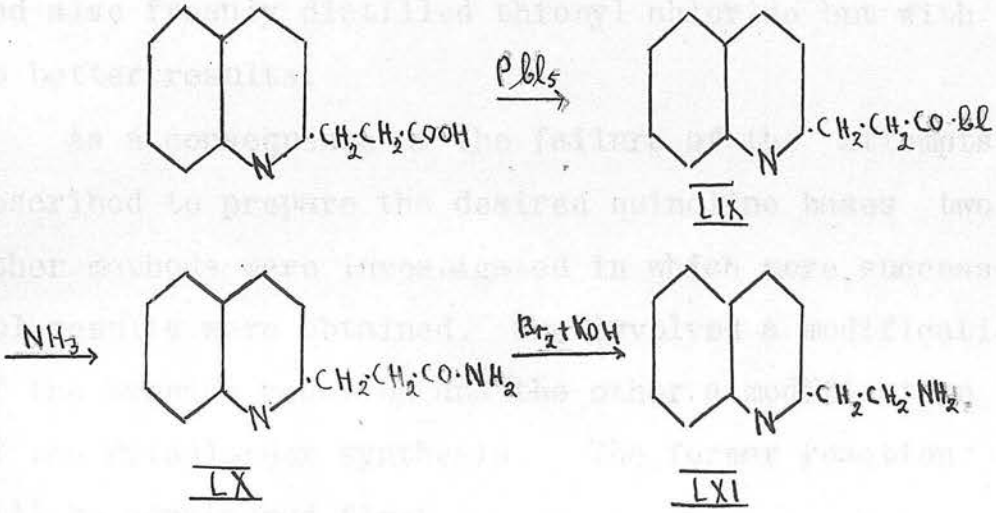
Further attempts to obtain β-(2-quinolyl) propionyl azide using amyl nitrite and alcoholic hydrochloric acid were unsuccessful. The reaction proceeded in the same way as in the case of sodium nitrite and hydrochloric acid to give sym [di(β-2-quinolyl-propionyl)] hydrazide although in much better yield. From the evidence of these experiments it appears that the Curtius reaction follows an abnormal course of which /

which no parallel is recorded in the available literature. Consequently it renders this method unsuitable for the preparation of 2-(β-amino)-ethyl-quinoline and its derivatives.



LVIII

In a paper by Chaterjee (J.C.S. 1929, II. 2965) there is described how attempts to apply the Curtius reaction to β-(2-benziminazolyl)-propionyl hydrazide LVIII, which in certain respects is not unlike β-(2-quinolyl)-propionyl hydrazide, failed completely. In all his attempts the hydrazide was re-obtained unchanged. In this case, however, the acid amide of β(2-benziminazolyl) propionic acid was obtained which underwent the Hoffman reaction to give the desired β-(2-benziminazolyl) ethyl-amine.



LX LXI

According to A. Einhorn and P. Sherman (A. 1885 287, 31) by treatment of β-(2-quinolyl) propionic acid with phosphorus /

phosphorus pentachloride using phosphorus oxychloride as a solvent, the corresponding acid chloride LIX is obtained which on condensation with ammonia gives β-(2-quinolyl) propionic acid amide LX. It was thought that this compound like that of Chaterjee's might undergo the Hoffman reaction to yield the desired 2-(β-amino)-ethyl-quinoline by treatment with bromine and potassium hydroxide.

In all the numerous attempts made, however, to convert the propionic acid with phosphorus pentachloride and phosphorus oxychloride under varying conditions into the corresponding acid chloride a dark tarry substance was obtained which when added to a well cooled concentrated solution of ammonia yielded a fine black carbonaceous sediment. Other methods were tried such as phosphorus pentachloride and acetyl chloride as the solvent according to the Method of Kermack, Perkin and Robinson, (J.C.S. 1921, 119, 1626) and also freshly distilled thionyl chloride but with no better results.

As a consequence of the failure of the attempts described to prepare the desired quinoline bases two other methods were investigated in which more successful results were obtained. One involved a modification of the Mannich reaction and the other a modification of the Friedlander synthesis. The former reaction will be considered first.

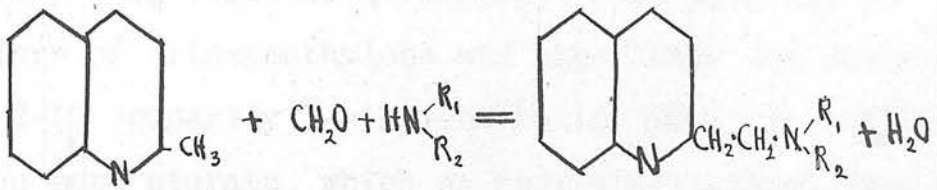
$$CH_3\cdot CO\cdot CH_2R + CH_2O + HN\begin{matrix}R_1\\R_2\end{matrix} = CH_3\cdot CO\cdot \underset{R}{CH}\cdot CH_2N\begin{matrix}R_1\\R_2\end{matrix} + H_2O$$

LXII LXIII LXIV

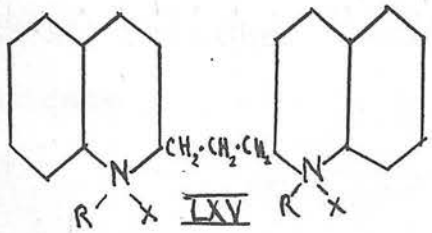
It /

It involves the condensation of a ketone of the general type, LXII, with formaldehyde and a secondary base of the general type, LXIII, resulting in the formation of basic acetone derivatives, LXIV. R, R_1 and R_2 represent like or unlike alkyl radicals. R may represent an alkyl radical or a hydrogen atom. The secondary base is present as the hydrochloride so that the reaction takes place in a neutral or possibly very faintly acid medium.

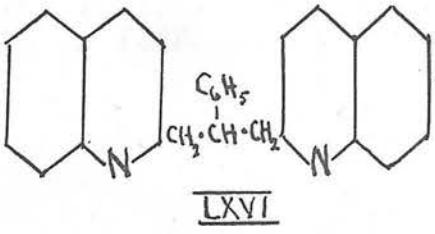
It is well known that the methyl group in quinaldine and certain of its derivatives is active and so it was thought that it might be possible to substitute this compound in place of the ketone in the Mannich reaction. In this way derivatives of 2-(β-amino)-ethyl-quinoline would be produced according to the following equation.



It has, of course, to be borne in mind that the base unlike the ketone is basic in action and that in consequence special care may be necessary to regulate this factor. A reaction which bears some resemblance to the one proposed is that carried out by F. M. Hamer (J.C.S. 1923, 123, 246) in the preparation of a number of methylene diquinaldine derivatives.



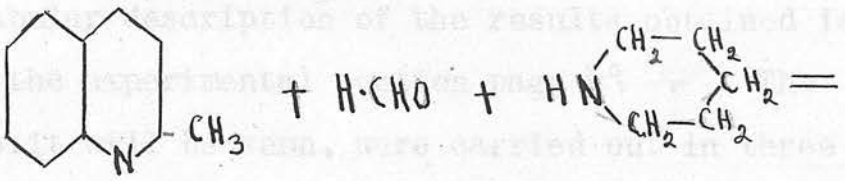
LXV

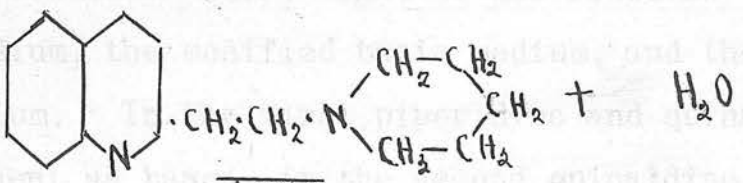


LXVI

Compounds /

Compounds of the type LXV were prepared by the condensation of one molecule formaldehyde with two molecules of quinaldine alkyl halide in the presence of piperidine as a catalyst whilst those of type LXVI by the condensation of one molecule of benzaldehyde with two molecules of quinaldine. The difference between this reaction and the one proposed lies in the substitution of a secondary base for a quinaldine molecule.





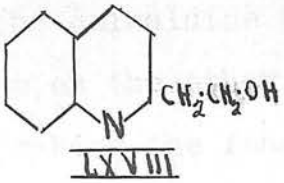
LXVII

By condensing together quinaldine, formaldehyde, in the form of trioxymethylene and piperidine the desired base 2-(β -piperidyl)-ethyl-quinoline LXVII was isolated as the mono picrate, which on recrystallisation from alcohol in long fine yellow needles gave m.p. 155°. The base is a pale yellow viscous oil which decomposes when distilled in vacuum. The hydrochloride was obtained as a white crystalline compound m.p. 184-185° by decomposing the picrate with dilute sodium hydroxide, and passing in dry hydrochloric acid gas into the benzene extract of the base. This base, as was stated previously in this paper, was isolated by Loewe (D.R.P. 380918 from Chem. Zentre. 1924, I, 1446), as the di picrate /

picrate m.p. 145°, but since it is described in a patent and no details of the analysis are given it is possible that this compound might be the mono-picrate in a slightly impure form.

This reaction was made the subject of careful investigation to determine the most suitable conditions which would yield the best results so that these might be applied to subsequent reactions.

A tabular description of the results obtained is given in the experimental section page 49 . The reactions, it will be seen, were carried out in three distinct mediums. These might be described as the basic medium, the modified basic medium, and the neutral medium. In the first, piperidine and quinaldine were present as bases, in the second, quinaldine as the hydrochloride and piperidine in the form of the base, whilst in the third both were present as hydrochlorides. In certain of the reactions formaldehyde was employed as trioxymethylene and in others as a 40% aqueous solution "formalin". It was found that by using equimolecular quantities of the reactants in the basic medium reaction the bulk of the isolated product was 2(β-hydroxy)-ethyl-quinoline LXVIII , m.p. 103°-104°.



LXVIII

The formaldehyde, in this case, has reacted preferentially with quinaldine to the exclusion of piperidine. This compound was recognised by analysis and picrate, m. /

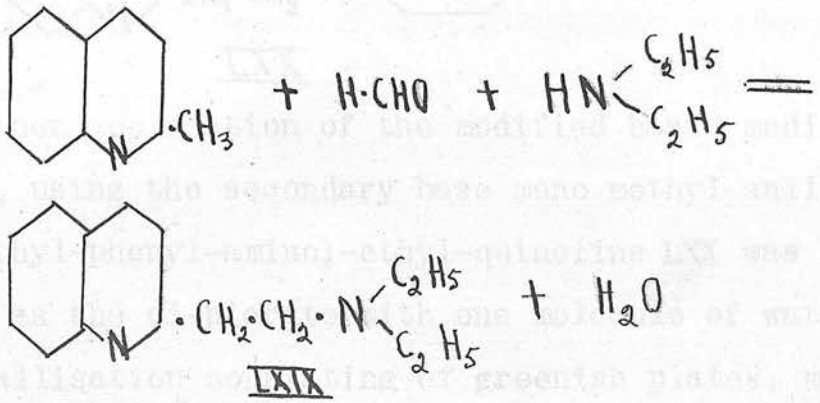
m.p. 165°, and has been prepared previously by Konig (Ber. 1899, 32, 224). To suppress the formation of this compound, piperidine and formaldehyde were allowed to interact before the addition of quinaldine and the molecular proportions of piperidine and formaldehyde to quinaldine were increased in the ratio of two to one respectively. The yield obtained by this basic medium reaction calculated on the isolated picrate was never greater than 16%, and this value could not be increased by varying the molecular proportions. It is to be noticed, however, that the use of formalin in place of trioxymethylene increased the yield from 11% to 16% when the conditions in both cases were the same, and in addition helped to decrease the amount of tar admixed with the crude condensation product. Consequently formalin was used in the remainder of the experiments.

The application of the modified basic medium reaction proved much more successful. By again using the same molecular proportions as applied in the basic medium reaction, namely two to one, the yield was increased to 72%. This may be due to the increased positive charge on the nitrogen atom in the quinaldyl ion as compared with the quinaldine molecule.

The neutral medium, on the other hand, yielded negative results. On making the reactants alkaline after condensation and steam distilling, a hard basic tar was left behind. It is most probable that this was caused by the excessive reactivity of the hydrochlorides of the bases with formaldehyde in which case higher /

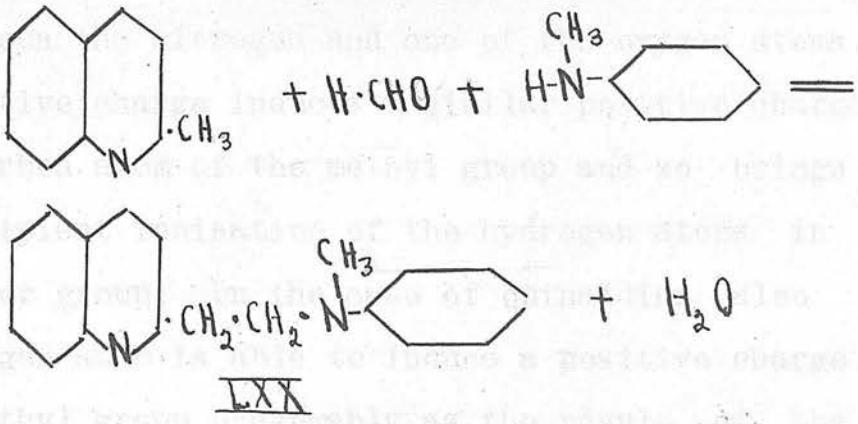
higher condensation products would be obtained.

It would appear, therefore, from the observations on this particular reaction that the modified basic medium seems the most suitable for the production of 2-(β-amino)-ethyl-quinoline derivatives.



LXIX

On substituting the secondary base diethylamine for piperidine, by a similar application of the reaction, the base 2(β-diethylamino)-ethyl-quinoline LXIX was isolated as the mono-picrate which recrystallised from alcohol in long fine yellow needles, m.p. 124°-125°. The base is a pale yellow viscous oil, which decomposes on vacuum distillation. The hydrochloride could not be isolated in a crystalline condition as it was extremely deliquescent. As a result it was always obtained as a thick sticky yellowish red oil. It appears that diethylamino derivatives frequently exhibit this property. Again it was found by use of the modified basic phase the yield was considerably greater than that obtained by the basic medium, namely 33% to 14%. The neutral medium as in the case of the corresponding piperidyl compound yielded a basic tar, and in consequence the use of this medium was discontinued.



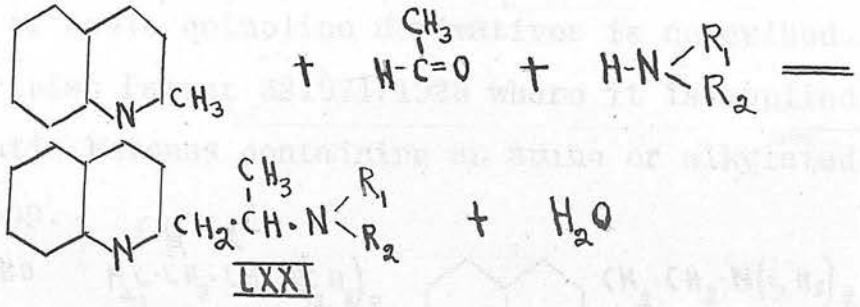
LXX

By a further application of the modified basic medium reaction, using the secondary base mono methyl-aniline, 2-(β -methyl-phenyl-amino)-ethyl-quinoline LXX was isolated as the di-picrate with one molecule of water of crystallisation consisting of greenish plates, m.p. 175° (decomp.). The yield of the picrate was exceedingly poor as it was difficult to isolate, and was only obtained pure after several recrystallisations from water. This may have been due to certain secondary reactions predominating. By means of the basic and neutral mediums the reactants were reobtained unchanged.

The successful application of this modified form of the Mannich reaction presumably depends upon the successful substitution of the active methyl group in quinaldine for the active methylene group adjacent to the keto group in the general ketone used in the original Mannich reaction. The activity of the methyl group in quinaldine may be compared with that of the methyl group in o-nitro toluene. In the latter case the nitrogen atom of the nitro group virtually has a positive charge in consequence of the semi polar double bond /

bond between the nitrogen and one of the oxygen atoms. This positive charge induces a similar positive charge on the carbon atom of the methyl group and so brings about insipient ionisation of the hydrogen atoms in this latter group. In the case of quinaldine also the nitrogen atom is able to induce a positive charge on the methyl group presumably as the result of the attachment of surrounding molecules to this atom, brought about by the presence on it of two lone electrons. If now the three mediums, the basic, modified basic, and neutral are considered it is clear that, in the last case, the quinaldine will exist chiefly as hydrochloride and so the nitrogen atom will tend to possess a relatively strong positive charge, hence the methyl group will be very reactive. In the case of the basic medium the quinaldine will exist largely as free base so that the charge on the nitrogen atom will be smaller, and the activity of the methyl group will be less marked. The modified basic medium would occupy an intermediate position. The considerations serve to explain the results obtained above, namely, the small yield in the basic medium, and the improved yield in the modified basic medium, whilst the tar which was obtained in the neutral medium is probably the result of the relatively strong activity of the methyl group under these conditions. In view of these considerations it appeared of interest to ascertain the effect of the substitution of quinaldine methosulphate in the place of quinaldine hydrochloride. In this

case piperidine was added as base so that the experiment was similar to that carried out in the modified basic medium. The experiments carried out on these lines were, however, unsuccessful as the reactants blackened and tarred even at the temperature of a freezing mixture. This unsatisfactory result may be the consequence of the relatively high activity of the methyl group in quinaldine methosulphate. In this case the nitrogen atom has a permanent positive charge as the result of the attachment to it of a methyl group. It is, therefore, not surprising that, even in the modified basic medium, the activity of the molecule is sufficiently great to bring about a degree of tarring more pronounced than that observed in the neutral medium where quinaldine hydrochloride was employed.



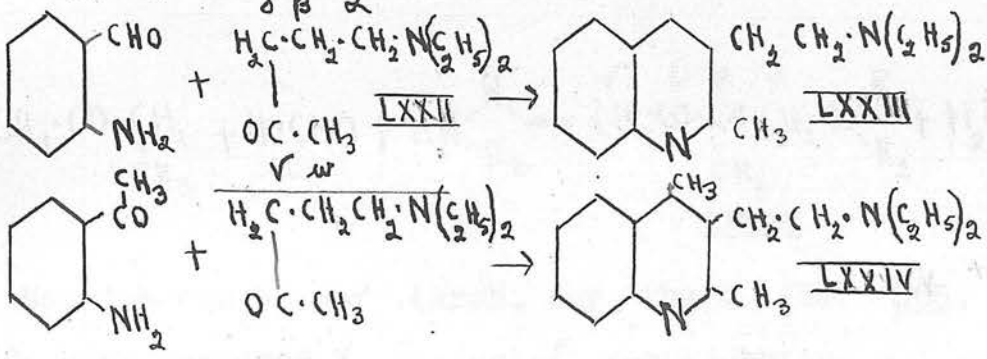
LXXI

A further extension was considered such as the substitution of acetaldehyde for formaldehyde in the reaction whereby 2-(β-amino-β-methyl)-ethyl quinoline derivatives LXXI might be prepared. Accordingly several attempts were made to obtain 2-(β-piperidyl-β-methyl)-ethyl-quinoline and 2-(β-diethylamino-β-methyl)-ethyl-quinoline by condensing together quinaldine hydrochloride, acetaldehyde and the secondary bases /

bases piperidine, and diethylamine respectively. In each case, however, the final product after steam distillation to remove the unchanged reactants, was a basic brittle black tar, from which no crystalline material could be isolated.

The second successful scheme, involving an application of the Friedlander synthesis was developed for the production of 2-(β -amino)-ethyl-quinoline derivatives in which an alkyl substituent is introduced into the α position of the side chain. In the Friedlander synthesis, o-amino benzaldehyde or its derivatives is condensed with various compounds containing the reactive $-CH_2\ CO-$ group such as aldehydes, ketones, aceto-acetic ester, malonic ester etc., so that various substituted quinoline derivatives are produced.

The use of the Friedlander synthesis in the preparation of basic quinoline derivatives is described in the British Patent 321974/1928 where it is applied to aliphatic ketones containing an amino or alkylated amino group.

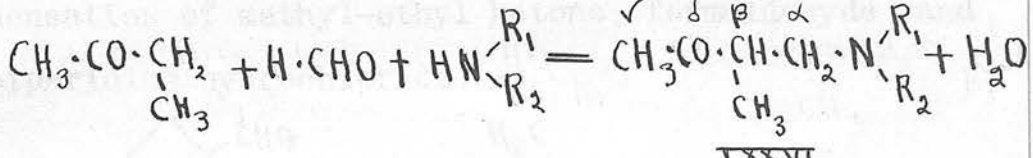


For example 2-methyl-3-(β -diethyl amino) ethyl-quinoline LXXIII and its 4-methyl homologue LXXIV were obtained from o-amino benzaldehyde and o-amino acetophenone by condensation with diethyl-amino-propyl ketone LXXII /

LXXII in the presence of alkali.

In this particular case, the alkylated amino side chain is introduced into the three position of the quinoline nucleus as might be expected by the methylene and keto groups in the δ and γ positions of the ketone molecule condensing with o-amino-benzaldehyde and o-amino-acetophenone in the manner as shown in the preceding equations.

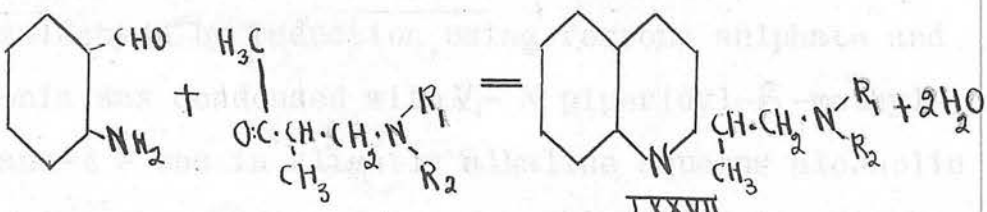
In accordance with the scheme of research pursued in the present investigations it was desired to apply a similar reaction to the preparation of quinoline derivatives substituted in the two position. It was, however, clearly necessary to prevent the reaction going in the direction indicated in the patent. The methylene group in the δ position of the basic ketone had therefore to be blocked in some way for example with an alkyl group so that the γ and ω positions would condense in place of the δ and γ. In this way the basic side chain would be introduced into the two position of the quinoline nucleus.



LXXVI

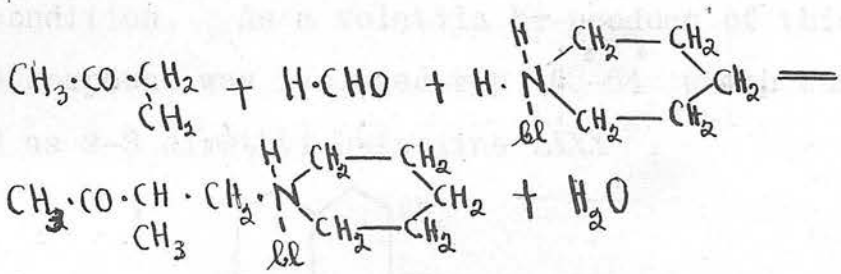
C. Mannich and W. Hof (Arch. der. Pharm. 1927 265, 589), have prepared α-(amino)-β-methyl-butane - δ - one. derivatives LXXVI in which the active methylene group is blocked with a methyl group by the condensation of /

of methyl ethyl ketone, formaldehyde, and the hydrochlorides of various secondary bases.



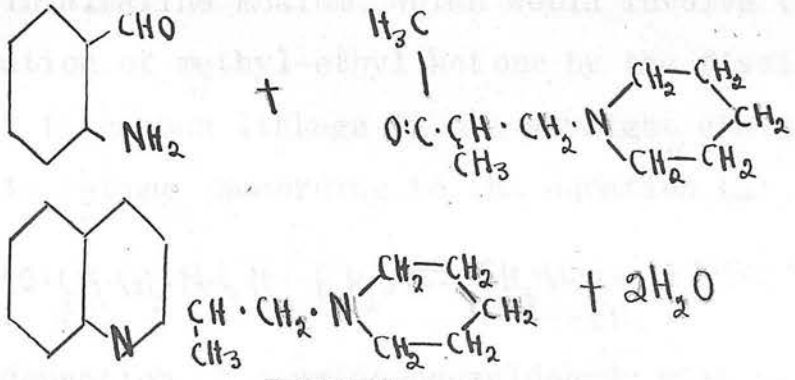
LXXVII

It was thought by condensation of basic ketones of this type with o-amino benzaldehyde 2-(β-amino-α-methyl)-ethyl-quinoline derivatives LXXVII would be obtained, because with the methyl group in the β position condensation can only take place at the δ and γ positions of the ketone according to the above equation.



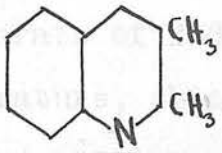
LXXVIII

γ- N-piperidyl-β-methyl butane-δ- one hydrochloride LXXVIII was prepared in good yield according to Mannich and Hof, (Arch. der Pharm., 1927, 265, 594) by the condensation of methyl-ethyl ketone, formaldehyde and piperidine hydrochloride.



LXXIX

O-amino-benzaldehyde, obtained by the method of Bamberger and Demuth (Ber. 1901, 34, 1330) from o-nitro benzaldehyde by reduction, using ferrous sulphate and ammonia, was condensed with α- N piperidyl-β-methyl-butane-δ - one in slightly alkaline aqueous alcoholic solution on standing for a few days at 37 C. The desired new base 2-(β-piperidyl-α-methyl)-ethyl-quinoline LXXIX was obtained as a non volatile yellow viscous oil and isolated as the mono picrate which on recrystallisation from benzene in yellow prisms gave m.p. 167°-168°. The hydrochloride, platini or auri chlorides of the base could not be isolated in a crystalline condition. As a volatile by-product of this reaction a compound was isolated m.p. 63°-64° which was identified as 2-3 dimethyl quinoline LXXX .



LXXX

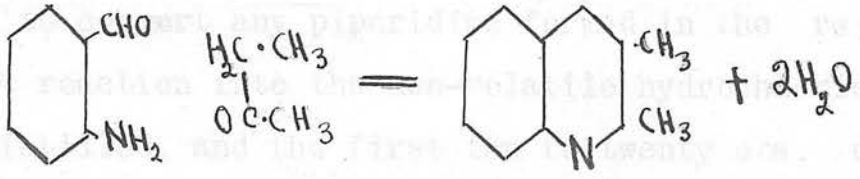
Two possible theories can be put forward as explanations concerning the formation of the latter compound by this reaction.

One demands the reversibility of the Mannich reaction in alkaline medium, which would involve the regeneration of methyl-ethyl ketone by the fission of a carbon to carbon linkage in the straight chained aliphatic ketone according to the equation (1).

I) $CH_3 \cdot CO \cdot \underset{CH_3}{CH} \cdot CH_2 \cdot N \cdot C_5H_{10} + H_2O \rightleftharpoons CH_3 \cdot CO \cdot \underset{CH_3}{CH_2} + H \cdot CHO + HNC_5H_{10}$

The condensation of o-amino-benzaldehyde with methyl-ethyl ketone would then be expected to lead to the formation /

formation of 2-3 dimethyl quinoline according to the equation (2).

2) 

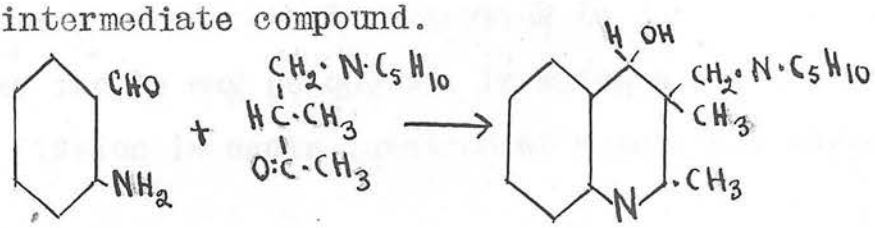
Certain investigations were carried out to test this theory. An experiment with methyl-ethyl ketone and o-amino benzaldehyde showed the readiness with which this condensation takes place in slightly alkaline aqueous alcoholic solution. The product on recrystallisation from petroleum ether was identical with the by-product. This was shown by the similar plate like crystalline structure, and the unchanged m.p. 63°-64° when mixed with a pure specimen of the by-product. Both gave picrates m.p. 224°-225° which were identical with the picrate of 2-3-dimethyl-quinoline mentioned in the literature, obtained by Rode (Ber. 1887, 20, 1911), on condensation of dimethyl-acrolein with aniline hydrochloride. In order to prove that the methyl-ethyl-ketone necessary for the formation of 2-3 dimethyl-quinoline according to this theory, may be obtained from the fission of α-N piperidyl-β-methyl-butane-δ-one, the following experiment was carried out.

α N piperidyl-β-methyl-butane-δ- one hydrochloride, the purity of which was proved by its melting point and chlorine content, was dissolved in water and the base obtained by adding a slight excess of alkali. Alcohol was run in until a homogeneous slightly alkaline aqueous alcoholic solution was formed. It was /

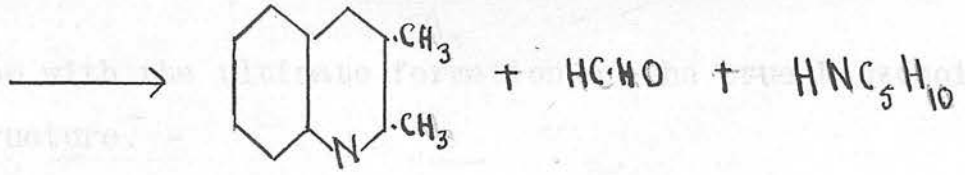
was allowed to stand at 37° C for a few days and then refluxed for one hour. The contents were made slightly acid to convert any piperidine formed in the reversible reaction into the non-volatile hydrochloride, steam distilled, and the first ten to twenty ccs. of the distillate collected. The acidification prevented contamination of the distillate with piperidine which might interfere with subsequent tests. The presence of a ketone in the distillate was shown by the sodium nitroprusside test. To the remainder of the distillate was therefore added o-amino-benzaldehyde and a drop of strong sodium hydroxide. The solution was kept for a few days at 37° C, refluxed for one hour, and then steam distilled. From the contents a crystalline compound was isolated which was identical in all respects with an authentic specimen of pure 2-3-dimethyl-quinoline.

It would seem, therefore, that experimental data supports its formation according to this theory. In addition it suggests the reversibility of the Mannich reaction in slightly alkaline solution with respect to α - N-piperidyl-β-methyl-butane-δ-one, an observation which, if investigated, might prove general among ketones of this type. No mention is made of this fact by Mannich and his co-workers in any of their published papers.

The second theory assumes the formation of an unstable intermediate compound.



LXXXI



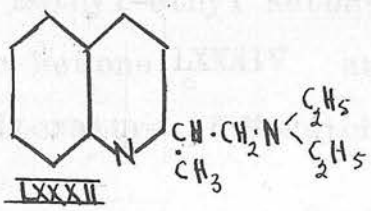
Although there is a methyl group present in the β position of the basic ketone it is still possible for the β and δ positions to react as well as the δ and γ with the formation of 2-3 dimethyl-3-(N piperidyl-methyl)-4-hydroxy-1-2-dihydro-quinoline LXXXI . By interaction of the closely situated hydroxyl group and the piperidyl-methyl side chain 2-3 dimethyl quinoline could be formed as shown in the above equation. This, of course, would involve a carbon to carbon split at the tertiary carbon atom in the three position, which, although a rather remarkable feature, has considerable support in the literature.

Gulland and Robinson (J.C.S. 1923, 123, 984) have pointed out the common occurrence of a carbon to carbon fission at a tertiary carbon atom in the degradation of the morphine alkaloids to non-basic phenanthrene derivatives. These authors put forward the view that the driving force of this reaction is the tendency of an aromatic ring to assume its original benzenoid structure, a statement which might equally apply to the foregoing decomposition.

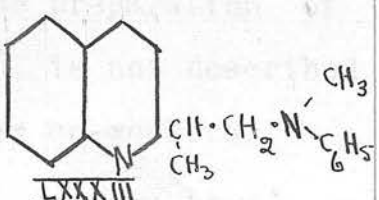
As further evidence of a similar nature, Stedman and Barger, (J.C.S. 1925, 127, 247), where the constitution of the alkaloid physostigmine is discussed the degradation of eserethole hydroxide to 1-3 dimethyl-5-ethoxy indole may be quoted, in which a carbon to carbon fission is again involved at a tertiary carbon atom /

atom with the ultimate formation of the true benzenoid structure.

It may, therefore, be concluded that in view of the positive evidence gained in support of the first theory it seems the more probable of the two, but, nevertheless, this second theory cannot be definitely excluded by the experimental evidence at present available, and, in addition, it appears consistent with certain analagous reactions mentioned in the literature.



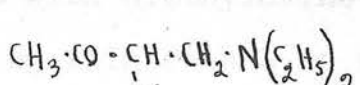
LXXXII



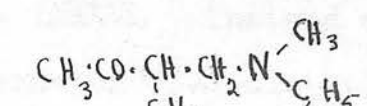
LXXXIII

In order to obtain a series of compounds analagous to those prepared by the first method an attempt was made to prepare 2-(β-diethylamino-α-methyl)-ethyl-quinoline LXXXII and 2-(β-methyl-phenyl-amino-α-methyl)-ethyl quinoline LXXXIII by a further application of the modified Friedlander synthesis.

The synthesis of these compounds required the intermediate preparation of α diethylamino-β-methyl-butane-δ-one LXXXIV and α(methyl-phenyl-amino)-β-methyl-butane-δ-one LXXXV .

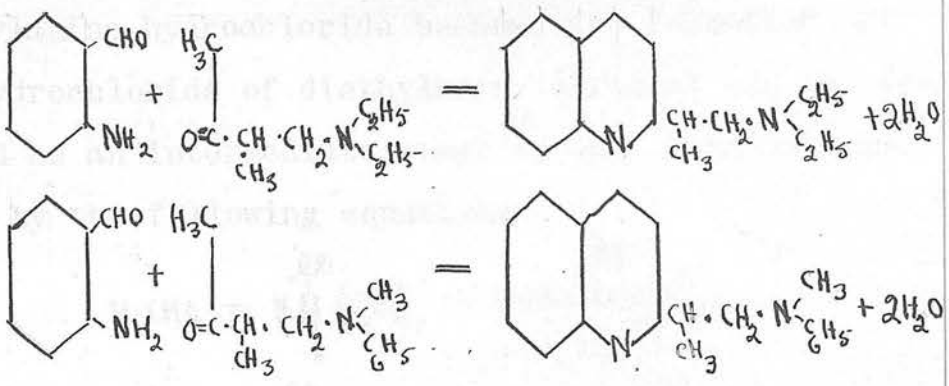


LXXXIV

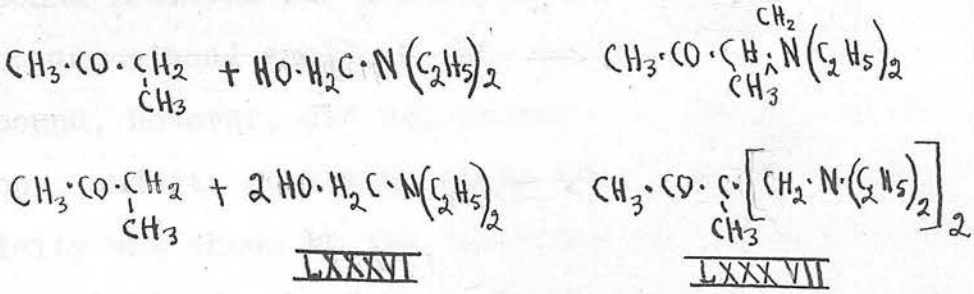


LXXXV

It was thought, by condensation of LXXXIV and LXXXV respectively with o-amino benzaldehyde, LXXXII and LXXXIII would be readily obtained, in a manner similar to the preparation of 2-(β-piperidyl-α-methyl--ethyl-quino: line according to the following equations.



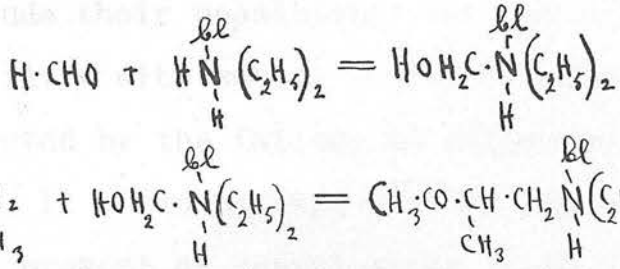
The application of the Mannich reaction to the hydrochlorides of the bases diethylamine and mono methyl aniline using formaldehyde in the form of trioxymethylene and methyl-ethyl ketone for the preparation of the basic ketone LXXXIV and LXXXV is not described in the literature of Mannich and his co-workers.



LXXXVI LXXXVII

However, according to Chem. Zentre. 1913, II, 1832, the desired ketone α-diethylamino-β-methyl-butane-δ-one B. Pt. 77-78/16 mm. along with β-β-acetyl-methyl-trimethylene-tetra-ethyl-diamine LXXXVII B.Pt. 105-110/7mm. were obtained by the condensation of methyl-ethyl-ketone with diethylamino carbinol LXXXVI. Instead of applying this method to the preparation of α-diethyl-amino-β-methyl-butane-δ-one which involves the separate preparation and isolation of diethylamino carbinol, an attempt was made to apply the Mannich reaction by the condensation of methyl-ethyl-ketone, formaldehyde in the form of trioxymethylene, and diethylamine /

diethylamine hydrochloride because the formation of the hydrochloride of diethylamine carbinol can be regarded as an intermediate stage in the reaction as shown by the following equations :-

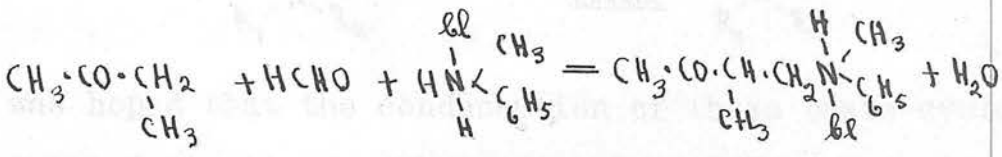


This reaction was carried out by a method in complete analogy to the preparation of the corresponding piperidyl ketone of Mannich and Hof, (Arch. der Pharm. 1927, 265, 594) using excess of methyl-ethyl ketone. The compound isolated was a colourless mobile oil with a faint ammoniacal smell, B. Pt. 68 /9-11 mm. This compound, however, did not prove to be the desired ketone, and its constitution is still in doubt. Its basicity was shown by its behaviour in acids and alkali, being soluble in the former and reprecipitated by the latter. It did not form a crystalline hydrochloride or yield a picrate. Since no hydrazone, oxime or semi carbazone could be prepared on treatment with phenyl hydrazine, hydroxylamine, or semi carbazide respectively no evidence could be obtained that it possessed a keto group. In an attempt to condense it with o-amino benzaldehyde in the presence of alkali and in one experiment in the presence of a drop of diethylamine to act as catalyst, o-amino benzaldehyde was recovered unchanged on steam distillation without the isolation of any new compound. It is possible that it may be a diethylamine carbinol formed by the condensation /

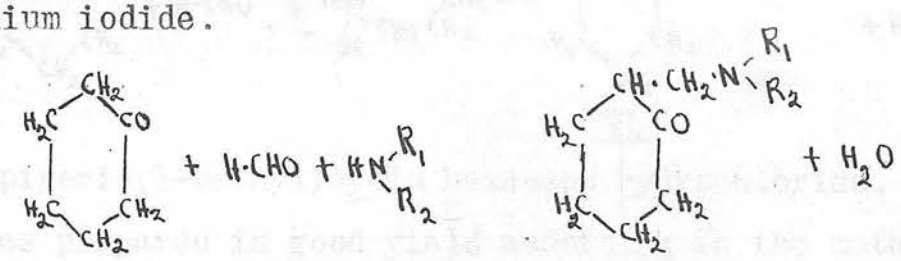
condensation of diethylamine hydrochloride and formaldehyde. Certain physical properties of these compounds described by H. Gault,(Chem. Zentre, 1908, I, 1676), exclude their possibility such as boiling point and miscibility with water. This conclusion is further supported by the failure to obtain an acetyl derivative. It would be expected that if an hydroxyl group were present an acetyl group would be readily introduced into the molecule. The only positive evidence concerning the nature of this base was obtained on treatment of it with bromine, when a white crystalline compound was isolated, m.p. 212-213° which was ultimately proved to be diethylamine hydrobromide by an examination of its properties, and a determination of its nitrogen and bromine content. The yield was exceedingly small, indicating that it was but the by-product of some major reaction, the main product of which could not be identified.

Summing up all the evidence gained from these various experiments, and taking into account the inconclusive results of the analysis it is not unlikely that the compound is β-β-acetyl-methyl-trimethylene-tetra-ethyl-amine although the boiling point obtained differs considerably from that given in the literature, namely 68° /9-11 mm. to 108-110° /7 mm. The inconclusiveness of the analysis might be due to the readiness with which these bases absorb carbon dioxide and moisture from the air, and the lack of ketonic properties to the stereo hindrance effect of the two closely situated diethyl-amino-methyl groups adjacent to the keto /

keto radicle. As a result of the failure to obtain the desired basic ketone the attempted preparation of 2-(β-diethyl-amino-∠-methyl) ethyl-quinoline was abandoned.

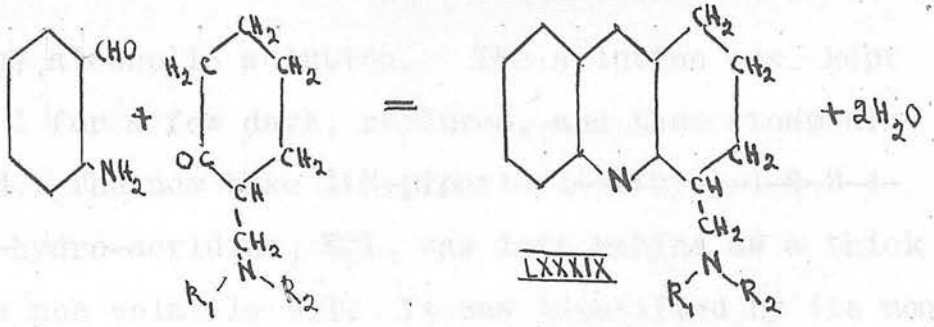


An attempt to condense mono methyl-aniline hydrochloride, formaldehyde and methyl-ethyl ketone according to the above equation also failed to yield the desired ketone. In each of several experiments mono-methyl aniline was recovered unchanged and no new compound could be isolated. Mono methyl-aniline was recognised by its picrate and methiodide derivative tri-methyl-phenyl-ammonium iodide.



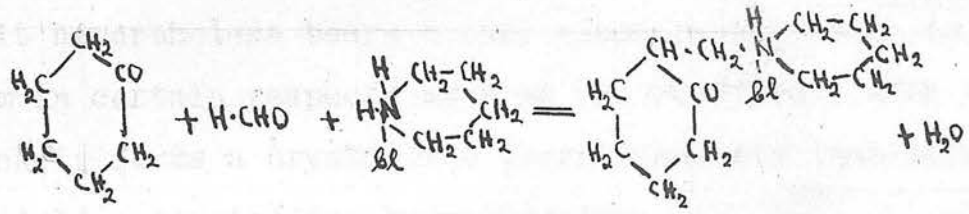
LXXXVII LXXXVIII

C. Mannich and F. Hönig, (Arch. der Pharm. 1927, 265, 598), have extended the Mannich reaction, using cyclo hexanone LXXXVII as the ketone, formaldehyde and several secondary bases of the general type shown in the above equation, to obtain 2-(amino-methyl)-cyclo hexanone derivatives LXXXVIII. In this reaction, as in the case of methyl-ethyl ketone, it is the methylene group adjacent to the keto group which is reactive.



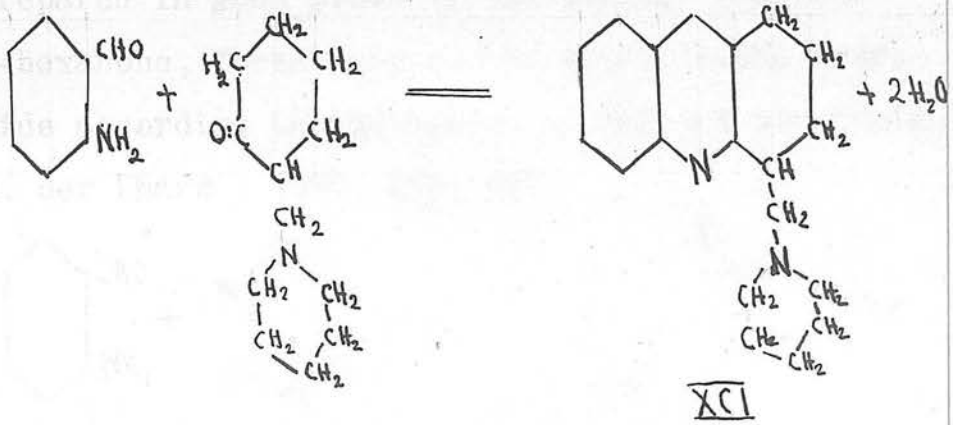
LXXXIX

It was hoped that the condensation of these basic cyclo hexanone derivatives with o-amino benzaldehyde would yield 1(amino-methyl)-1-2-3-4-tetra-hydro-acridine derivatives LXXXIX. These compounds would be more complex derivatives of 2-(β-amino)-ethyl quinoline in which the α-carbon atom of the side chain is substituted and forms part of a partly reduced benzene ring.



XC

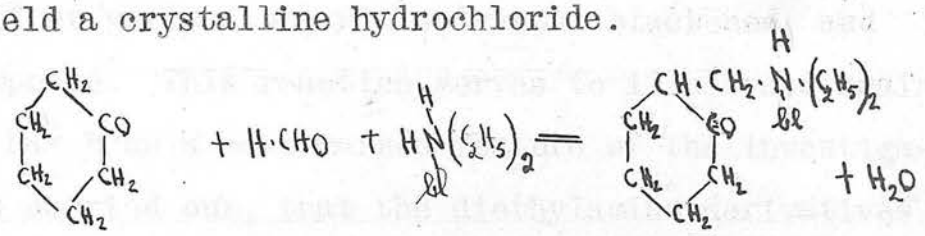
2-(N-piperidyl-methyl)cyclo hexanone hydrochloride, XC, was prepared in good yield according to the method of C. Mannich and F. Hönig,(Arch. der Pharm. 1927, 265, 602), by the interaction of cyclo hexanone, formaldehyde and piperidine hydrochloride.



XCI

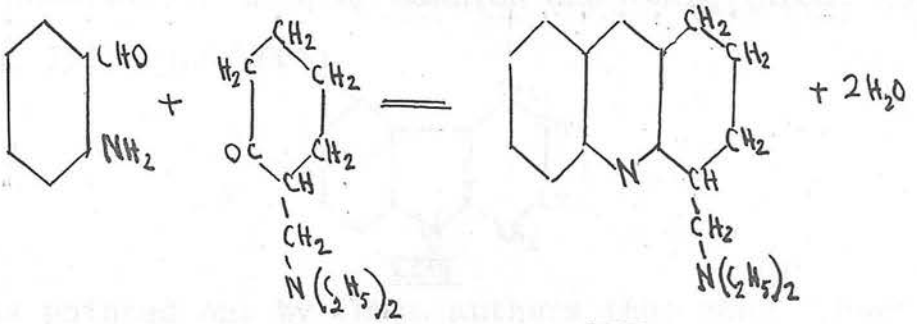
The base 2-(N-piperidyl-methyl)-cyclo hexanone was condensed with o-amino-benzaldehyde in slightly alkaline aqueous /

aqueous alcoholic solution. The solution was kept at 37 C for a few days, refluxed, and then steam distilled. The new base 1(N-piperidyl-methyl)-1-2-3-4-tetra-hydro-acridine, XCI, was left behind as a thick yellow non volatile oil. It was identified by its mono picrate which recrystallised from alcohol in fine long yellow needles, m.p. 205°. By passing in dry hydrochloric acid gas to an ethereal solution of the base, the hydrochloride was obtained as a sticky white deliquescent solid which could not be recrystallised from various organic solvents. Although this base is of a more complex nature than those previously prepared it nevertheless bears a very close resemblance to them in certain respects such as the readiness with which it forms a crystalline picrate and its inability to yield a crystalline hydrochloride.



XCII

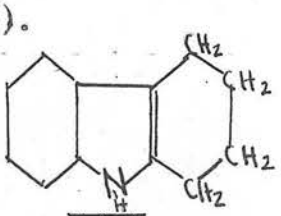
2-(diethylamino)methyl cyclo-hexanone hydrochloride, XCII, was prepared in good yield by condensing together cyclo-hexanone, formaldehyde, and diethylamine hydrochloride according to the method of Mannich and Hönig, (Arch. der Pharm., 1927, 265, 601).



XCIII

It was hoped on condensation of the basic ketone, obtained from the above hydrochloride, with o-aminobenzaldehyde by a method similar to that used in the preparation of the corresponding piperidyl derivative to prepare 1-(diethylamino-methyl)-1-2-3-4-tetrahydro-acridine XCIII. When this condensation was carried out, instead of the desired base being isolated a hard brownish glass was obtained which on several recrystallisations from ligroin yielded a pale yellow amorphous powder of indefinite m.p. 65°-75°. All the attempts made to obtain crystalline derivatives of this substance such as picrate, hydrochloride, platini and auri chlorides failed completely. The platini and auri chlorides were indefinite amorphous substances which, when attempts were made to recrystallise them from various organic solvents, blackened and decomposed. This reaction serves to illustrate again what has been a most marked feature of the investigations carried out, that the diethylamino derivatives as compared with the corresponding piperidyl derivatives have always been the most difficult to prepare.

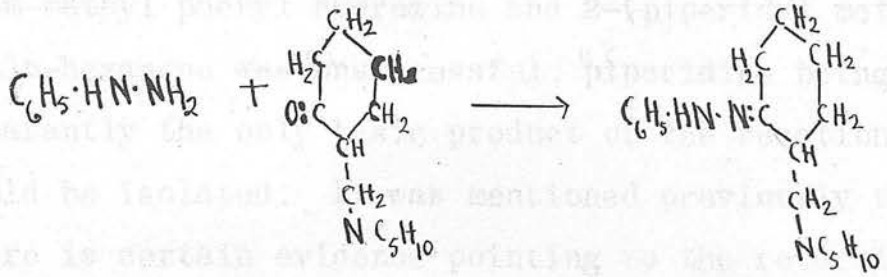
Before concluding it may be noted that the behaviour of 2-(piperidyl-methyl)-cyclo-hexanone with phenyl hydrazine was investigated as a consequence of a certain observation made by Mannich and Hönig, (Arch. der Pharm. 1927, 265, 605).



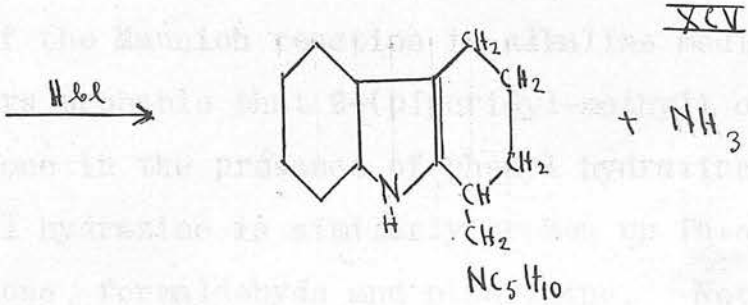
XCIV

It was pointed out by these authors that when they endeavoured /

endeavoured to obtain the hydrazone of 2-(piperidyl-methyl) cyclo-hexanone by condensing phenyl-hydrazine with 2-(piperidyl-methyl) cyclo hexanone, 1-2-3-4-tetra-hydro carbazole, XCIV, was isolated.

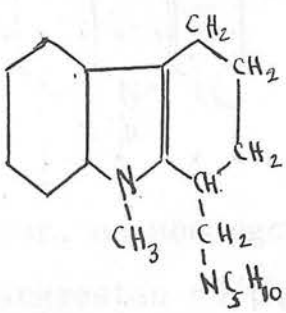


XCV



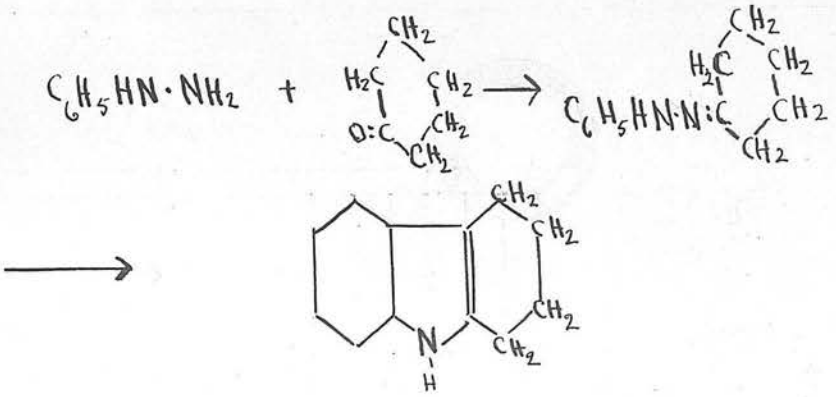
XCVI

Since a large excess of phenyl hydrazine was used it was thought that by employing equimolecular proportions of phenyl hydrazine and 2-(piperidyl-methyl) cyclo hexanone, the hydrazone, XCV, might be obtained and that this, on treatment with hydrochloric acid, might yield 1 (N-piperidyl-methyl) 1-2-3-4-tetra-hydro-carbazole, XCVI. The experiment was carried out, but instead of the latter compound being isolated piperidine hydrochloride was obtained.



XCVII

Methyl-phenyl-hydrazones usually undergo indole cyclisation more readily than the corresponding phenyl hydrazones, but an attempt to produce 1(piperidyl methyl-9-methyl) 1-2-3-4-tetra hydro-carbazole XCVII from methyl phenyl hydrazine and 2-(piperidyl methyl) cyclo-hexanone was unsuccessful, piperidine being apparently the only basic product of the reaction which could be isolated. It was mentioned previously that there is certain evidence pointing to the reversibility of the Mannich reaction in alkaline medium. It appears probable that 2-(piperidyl-methyl) cyclo-hexanone in the presence of phenyl hydrazine or methyl phenyl hydrazine is similarly broken up into cyclo hexanone, formaldehyde and piperidine. Not only would this account for the isolation of piperidine hydrochloride but it would also explain as the result of the intermediate formation of the hydrazone of cyclo hexanone, the isolation of 1-2-3-4 tetra hydro carbazole previously described by C. Mannich and P. Hönig according to the following scheme.



In both cases, however, an analogous explanation to the second possibility suggested on page 39 for the formation of 2-3 dimethyl quinoline may also be put forward /

forward here as the liberation of piperidine may take place simultaneously with cyclisation and formation of tetra-hydro-carbazole.

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EXPERIMENTAL.

O-nitro-benzoyl-chloride.

O-nitro-benzoic acid (100 g.) was mixed with phosphorus pentachloride (135 g.) and, as soon as the reaction, which commences in the cold, had slackened, the whole was heated on the water bath under an air condenser for 1-2 hours. The flask was then connected with the vacuum pump and the phosphorus oxychloride distilled off at the lowest possible temperature leaving the o-nitro-benzoyl-chloride as a yellowish strongly fuming liquid, which recrystallises on standing. Yield 85 g.

Ethyl-o-nitro-benzoyl-aceto-acetate.

According to the method of Needham and Perkin (J.C.S. 1904, 85, 148) sodium (31 g.) was dissolved in ethyl alcohol (500 ccs.) and the solution allowed to cool. 250 ccs. of this solution were then mixed with ethyl aceto-acetate (90 g.) and the whole cooled to 0°C. O-nitro-benzoyl-chloride (56 g.) was then gradually added, the liquid being kept constantly stirred, care being taken at the same time that the temperature did not rise above 5°C. After standing for half an hour, sodium ethoxide solution (125 ccs.) was then added and the acid chloride (28 g.) run in as before. The whole was again allowed to stand for half an hour and subsequently treated with the remainder of the sodium ethoxide solution /

solution and o-nitro benzoyl chloride under the same conditions as before. After remaining overnight at ordinary temperature, the thick yellow precipitate, which consisted of a mixture of sodium chloride and the sodium derivative of ethyl-o-nitro-benzoyl-aceto-acetate, was filtered at the pump and washed successively with alcohol and ether. It was then added to excess of dilute hydrochloric acid which had been cooled by the addition of ice, and the whole subsequently extracted with ether. This ethereal extract was washed with sodium bicarbonate solution, and then dried over anhydrous sodium sulphate. On distilling off the ether, a brownish red oil was obtained which consisted of nearly pure ethyl-o-nitro-benzoyl-aceto-acetate. Yield 85 g.

O-nitro-acetophenone.

Ethyl o-nitro-benzoyl-aceto-acetate (85 g.) was refluxed with an alcoholic solution of sulphuric acid containing 10% by weight of acid according to the method of Kermack and Smith (J.C.S. 1929, 814). An amount of water, equal to the amount of alcohol used, was then added, and the whole distilled until the liquid was reduced to original volume. The residual liquid was then refluxed for about an hour and cooled, and the o-nitro-acetophenone extracted with ether. The extract was dried over anhydrous sodium sulphate, the ether distilled off and the dark brown residual oil distilled at 149°-152°/10 mm. when o-nitro-acetophenone was obtained as a clear pale yellow oil.

W. /

W-bromo-o-nitro-acetophenone.

O-nitro acetophenone (8 g. = $1/20$ mol.) was dissolved in 30 ccs. glacial acetic acid, and bromine (8 g. = $1/20$ mol.) in 10 ccs. glacial acetic acid was added drop by drop according to the method of Gevekoht (A. 1883, 221, 327). After all the bromine had been added, the deep red solution was warmed slightly on the water bath until decolourisation took place and the solution became pale yellow in colour. The solution was then poured into 150 ccs. water, whereby a thick yellow oil separated, which, on standing, went crystalline. It was filtered off, washed with water, dried in the vacuum desiccator, and recrystallised from petroleum ether, m.p., 55^0 - 56^0. Yield 85% of theory.

The behaviour of W.-bromo-o-nitro-acetophenone with piperidine.

1st Method. From a small dropping funnel piperidine (·9 g. = $1/100$ mol) was added drop by drop to w-bromo-o-nitro-acetophenone (2·4 g. = $1/100$ mol.) During the careful addition of the piperidine a vigorous reaction took place, accompanied with the evolution of much heat and dense white fumes. The reactants darkened in colour and became tarry and resinous in appearance. After the reaction had subsided, the dark brown coloured mass was heated on the water bath for 3-4 hours under an air condenser during which period no further change was observed. It was then extracted three times, using for each extraction 10 ccs. dilute hydrochloric acid /

acid, and filtered to remove the insoluble tarry matter. The filtrate was a clear yellowish red solution, which on making alkaline with caustic soda solution gave a flocculent brownish red precipitate. This was filtered off and dried in the vacuum desiccator. On microscopic examination it proved to be a brownish red amorphous powder. It was soluble in dilute acids, hydrochloric, sulphuric and nitric, forming in each case a yellowish red solution, from which it was re-precipitated on making alkaline in the amorphous condition. It was freely soluble in alcohol, benzene acetone, and chloroform, forming in each case a reddish yellow solution. It was insoluble both in the hot and cold, in ligroin and petroleum ether. With pyridine it was insoluble in the cold but slightly soluble in the hot from which it came out in the same amorphous form. The melting point was indefinite being between 85°- 120°. Yield 1 gm.

2nd Method. W.-bromo-o-nitro-acetophenone (2.4 g. = $^1/_{100}$ mol.) and piperidine (1.8 g. = $^1/_{50}$ mol.) were each dissolved in 10 ccs. benzene carefully dried over phosphorus pentoxide. The piperidine solution was carefully added drop by drop from a dropping funnel to the solution of the bromo compound with constant agitation of the solution. No rise in temperature was observed. When approximately half the piperidine solution had been added, the solution changed in colour from pale yellow to reddish yellow, and a slight reddish gelatinous precipitate commenced to settle out. /

out. After all the piperidine had been added the solution was allowed to stand for 2-3 hours. The gelatinous precipitate was filtered off, dried in the vacuum desiccator, and found to be piperidine hydrobromide m.p. 235°. After drying, however, the amount was exceedingly small. It gave an unchanged m.p. with a pure specimen of piperidine hydrobromide. The benzene filtrate was then shaken up three times with 15 ccs. of dilute hydrochloric acid in a separating funnel, and the combined clear reddish yellow acid extracts made carefully alkaline with dilute sodium hydroxide. A flocculent reddish brown precipitate settled out, which was filtered off, washed with water and dried in the vacuum desiccator. It again proved to be the reddish brown amorphous powder with properties similar to those described in the previous experiment, and having the same indefinite m.p. 85° - 120°.
Yield ·75 g.

The red coloured benzene layer was dried over anhydrous sodium sulphate, filtered, and the benzene distilled off. A small quantity of a thick sticky viscous oil was left behind which on scratching thoroughly and leaving in the ice chest over-night did not crystallise. It was insoluble in acids and alkali. No crystalline material could be isolated from it by treatment with various organic solvents. It was soluble in alcohol, benzene, acetone, and chloroform, forming deep red coloured solutions, and insoluble in ligroin and petroleum ether both in the hot and cold.
3rd Method. Piperidine (10 g. = $^1/_{10}$ mol.) in 15 ccs. dry /

dry benzene was surrounded by a freezing mixture, and from a dropping funnel w-bromo-o-nitro-acetophenone (4·8g. = $^1/_{50}$ mol.) in 10 ccs. dry benzene was added, drop by drop. As in the previous experiment the solution developed a slight reddish tint accompanied with the slight settling out of the gelatinous precipitate of piperidine hydrobromide. The solution was allowed to stand in the freezing mixture for two hours, and then at room temperature for two hours. The benzene solution was then extracted three times with 20 ccs. dilute hydrochloric acid and the combined red coloured acid extracts made carefully alkaline with dilute ammonium hydroxide. Again the flocculent reddish brown amorphous precipitate was obtained which on filtering off and drying in the vacuum desiccator gave the same indefinite m.p. 85° - 120°. Again all attempts to recrystallise it or obtain crystalline material from it with various organic solvents failed. Yield 1·3 g. The benzene layer on drying and distilling off the benzene again yielded the non basic viscous red oil which could not be identified.

A fourth experiment was tried identical with that described in (2), the only difference being that the reactants in the benzene solution were refluxed on the water bath for half an hour. On cooling, the reddish coloured benzene solution was treated in the same way, and the only substance which could be isolated of a basic nature was again the indefinite reddish brown amorphous powder.

O-amino-acetophenone.

This compound was prepared from o-nitro-acetophenone by the method of West, (J.C.S., 1925, 127, 494), in which 5·5 g. ($\frac{1}{50}$ mol.) of the oil were dissolved in 17 ccs. absolute alcohol and 5 ccs. concentrated hydrochloric acid added. This solution was refluxed on the water bath, and, while boiling, 6 g. iron filings were added in four portions at intervals of five minutes. After three to four hours the solution was made alkaline with dilute sodium hydroxide, and steam distilled when o-amino-acetophenone was obtained from the aqueous distillate by extraction with ether. The extract was dried over anhydrous sodium sulphate, and the ether distilled off, leaving the base as a clear mobile brown oil. Yield 60% of theory.

O-acetyl-amino-acetophenone.

The oil obtained above was treated with three to four times its own volume of acetic anhydride and the solution left to stand at room temperature for two hours. It was then warmed on the water bath with excess of water until all the acetic anhydride had decomposed. On standing for some time long silky needles of o-acetyl-amino-acetophenone began to separate, m.p. 74° - 75°.

Attempted preparation of w-bromo-o-acetyl-amino-acetophenone.

O-acetyl-amino-acetophenone (3·5 g. = $\frac{1}{50}$ mol.) was dissolved in 5 ccs. glacial acetic acid and to this solution bromine (3·2 g. = $\frac{1}{50}$ mol.) in 5 ccs. glacial /

glacial acetic acid was slowly added. During the addition of the bromine a light red crystalline precipitate alowly commenced to settle out, which, on filtering off and drying in the vacuum desiccator gave the indefinite m. p. 95°- 100°. These crystals on contact with water immediately became white, and on filtering off and drying gave m.p. 155°. Apparently they were crystals of the hydrobromide of the brominated compound.

The filtrate from this hydrobromide was warmed on the water bath until complete decolourisation of the solution had taken place, and then poured into 50 ccs. water. A bulky white crystalline precipitate was obtained which was filtered off, washed with water, and dried in the vacuum desiccator. It recrystallised from water in long white needles, m.p. 155°. Yield 3 g.

It was mentioned in the theoretical discussion that this compound was thought to be the desired o-acetyl-amino-w-bromo-acetophenone because of the following analysis.

$C_{10}H_{10}NO_2Br$. Calculated: C = 46·9% ; H = 3·9%

Found: C = 46·9% ; H = 3.9%

However, since this bromo compound could not be condensed with piperidine as described in the following experiment, an examination of the literature showed it to be an isomeride of the desired compound, namely, 5-bromo-2-acetylamino-acetophenone previously prepared by Baeyer and Bloem,(Ber. 1884, 17, 965) by a method not unlike the one just described.

Behaviour /

Behaviour of 5-bromo-2-acetylamino-acetophenone with piperidine.

5-bromo-2-acetylamino-acetophenone (2·5 g.) in 15 ccs. benzene was refluxed steadily under a reflux condenser with excess of piperidine (2 g.) for two hours. During this period the colourless solution changed to a reddish colour. On cooling nothing separated and so the benzene solution was extracted three times with 15 ccs. dilute hydrochloric acid. On making the colourless combined acid extracts alkaline with dilute sodium hydroxide, no precipitate was obtained. The benzene layer was then dried over anhydrous sodium sulphate, filtered, and the benzene distilled off. On boiling up the reddish brown semi solid residue with water and filtering hot, the bulk of the bromo compound crystallised out unchanged, m.p. 155°.
Recovered 1·9 g.

α(2-quinolyl)-β-hydroxy-√-trichlor-propane.

Quinaldine (43 g. = $^3/_{10}$ mol.) and chloral hydrate (49·5 g. = $^3/_{10}$ mol.) were heated together on the water bath for ten hours according to the method of Miller and Spady, (Ber. 1885, 18, 3402). During this period the chloral hydrate went slowly into solution, which darkened in colour, and then went into a hard crystalline mass. The solid was powdered up and boiled under a reflux condenser with 250 ccs. of absolute alcohol. The reddish coloured alcoholic solution was filtered hot, and on cooling α-(2-quinolyl-β-hydroxy-√-trichlor-propane /

propane crystallised out, m.p. 144°- 145°. Yield 85g.

β-(2-quinolyl)-acrylic acid.

α-(2-quinolyl)-β-hydroxy-√-trichlor-propane (50 g.) was slowly introduced during a period of two hours into a 20% boiling alcoholic potash solution (250 g.) according to the method of Einhorn and Sherman, (A. 1895, 287, 27). After the addition of the condensation product the solution was boiled for another hour. The hot solution was then quickly filtered from the potassium chloride formed in the reaction, and, on cooling, the potassium salt of β-(2-quinolyl)-acrylic acid settled out. It was filtered off, dried, and then dissolved in the minimum amount of water. From the aqueous solution, by decomposing the potassium salt with concentrated hydrochloric acid, β-(2-quinolyl) acrylic acid was obtained as a pinkish coloured precipitate.

The potassium chloride from which the alcoholic solution was filtered was mixed with a large amount of the potassium salt of the acrylic acid, and so a further quantity of the acid was obtained by dissolving the mixture in the minimum amount of water, and decomposing with concentrated hydrochloric acid. The combined precipitates of the acrylic acid were filtered off, washed with water, dried, and then recrystallised from alcohol from which it was obtained in pinkish coloured leaves, m.p. 197°. Yield 60%.

By using aqueous potassium carbonate to hydrolyse the condensation product, according to the method of Miller /

Miller and Spady, (Ber. 1885, 18, 3402), the yield of the acrylic acid was 15%.

β -(2-quinolyl) propionic acid.

The reduction of 2-(β -quinolyl) acrylic acid was carried out according to the method of Einhorn and Sherman, (A. 1895, 287, 29). 2-(β -quinolyl) acrylic acid (20 g.) concentrated hydrochloric acid (200 ccs.) and granulated tin (60 g.) were gently heated together until the acrylic acid had dissolved. The pale yellow solution was then filtered from the undissolved tin, and taken to dryness under reduced pressure at (30-40)°C. The residue was dissolved up in hot water and sulphuretted hydrogen passed into the solution. From the warm solution the black precipitate of tin sulphide was filtered off, and from the pale yellow filtrate long white needles crystallised out. These were filtered off, dried, and on recrystallisation from water gave m.p. 115°-116°. This compound was proved by its properties to be the lactam of β-(tetra-hydro-2-quinolyl) propionic acid previously prepared by Honig, (Ber. 1900, 33, 218). Sulphuretted hydrogen was again passed into the filtrate to make sure that all the tin was precipitated as sulphide. The pale yellow filtrate was evaporated down to dryness on the water bath. The residue was taken up in a few ccs. of water and (30-40) ccs. of strong ammonia added, and again taken to dryness. This operation was repeated and the residue heated on the water bath for eight hours to make sure that the ammonium salt of β -(2-quinolyl) propionic acid /

acid was completely decomposed. The residue was extracted with 80 ccs. acetone in four successive portions of 20 ccs. each. The acetone was distilled off and the residue recrystallised from benzene gave β-(2-quinolyl) propionic acid and in large flaky crystals of greasy lustre, m.p. 122-123. Yield 55%.

Ethyl β-(2-quinolyl) propionate.

β-(2-quinolyl) propionic acid (13 g.) was dissolved in ethyl alcohol (200 ccs.). The pale yellow alcoholic solution was saturated with dry hydrochloric acid gas and the contents refluxed on the water bath for half an hour. The alcoholic solution was again saturated with dry hydrochloric acid gas and refluxed on the water bath for another half hour. The solution by this time had assumed a deep red colour. The excess of alcoholic hydrochloric acid was distilled off under reduced pressure on the water bath at a temperature between 30° C and 40° C. The hydrochloride of the ester was left behind as a thick red viscous oil which did not crystallise on standing. It was dissolved up in 100 ccs. water, and the slightly turbid solution filtered from the trace of impurities present. The clear reddish yellow solution of the hydrochloride was then made alkaline and the thick red oily base, which separated extracted with ether. The ethereal extract was dried over potassium carbonate, filtered and the ether distilled off, leaving behind a thick red oil which, on standing in the ice chest, did not crystallise. It was easily soluble in alcohol, benzene and acetone /

acetone forming reddish yellow solutions, and insoluble in petroleum ether and ligroin both in the hot and cold. Yield 80%.

The ester was used in the next experiment without further purification.

β-(2-quinolyl)-propionyl-hydrazide.

Ethyl-β-(2-quinolyl) propionate (12 g. = 1/20 mol.) was suspended in excess of a 50% solution by weight of hydrazine hydrate (50 ccs.) The reactants were heated in an oil bath under a reflux condenser to 140°. After three hours the ester completely dissolved forming a reddish coloured homogeneous solution. The hot solution was poured rapidly into a beaker, and, on cooling, white needle shaped crystals commenced to crystallise out. These were filtered off at the pump, washed with distilled water to remove traces of hydrazine hydrate, and dried in the vacuum desiccator. It recrystallised from ligroin in white silvery leaflets, m.p. 165. Yield 12 g.

$C_{12}H_{13}ON_3$ Calculated N = 19·5%

Found N = 19·6%

This compound is easily soluble in dilute hydrochloric, sulphuric and nitric acids, forming colourless solutions, from which it is precipitated on the addition of alkali. It is readily soluble in alcohol and benzene and less readily in acetone forming colourless solutions. With ligroin and petroleum ether it is sparingly soluble in the cold but soluble in the hot, from which it recrystallises in silvery leaflets. It readily /

readily reduces Fehling's solution on gentle warming, and gives a silver mirror with an ammoniacal solution of silver nitrate.

The Behaviour of β-(2-quinolyl)-propionyl-hydrazide with nitrous acid.

1st Method. β-(2-quinolyl) propionyl-hydrazide (1 g.= 1/200 mol.) was dissolved in normal hydrochloric acid (10 ccs.= 1/100 mol.) and to this solution sodium nitrite (·36g. in 5 ccs. water = 1/200 mol.) was added drop by drop from a pipette. A reaction took place with the slow evolution of ~~nitrogen~~ a gas. The pale yellow solution became slightly turbid, and on standing for two hours a pale green solid finally settled out. It was filtered off, washed with water, and dried in the vacuum desiccator. It appeared to blacken at 220° and melted between 240° and 250°. The aqueous filtrate was made alkaline with sodium hydroxide, and a white precipitate was obtained which on filtering of and drying in the vacuum desiccator behaved in the same way, namely, blackened at 220° and melted between 240° and 250°. It recrystallised from ligroin in silvery leaflets, m.p. 265°. Yield ·3 g.

According to the following analysis this compound is sym [di(β-2-quinolyl-propionyl)]-hydrazide.

$C_{24}H_{22}N_4O_2$ Calculated C = 72.3%; H = 5.5%; N = 14.1%

Found C = 71.6%; H = 5.5%; N = 14.3%

It is soluble in dilute hydrochloric, sulphuric, and nitric acids, forming clear colourless solutions from which the base is reprecipitated on making alkaline. It does not reduce Fehling's solution or an ammoniacal solution /

solution of silver nitrate. It is insoluble in alcohol and benzene in the cold, and sparingly soluble in the hot from which it crystallises in silvery leaflets. It is insoluble in ligroin in the cold, but moderately soluble in the hot forming a colourless solution from which it readily crystallises in silvery leaflets.

2nd Method. β-(2-quinolyl) propionyl hydrazide (4.3 g. = $\frac{1}{50}$ mol.) was dissolved in normal hydrochloric acid (40 ccs. = $\frac{1}{25}$ mol.), and the solution cooled by a freezing mixture. Sodium nitrite (1.4 g. in 16 ccs. water = $\frac{1}{50}$ mol.) was similarly cooled in a freezing mixture, and then added drop by drop to the hydrazide solution with constant shaking from a pipette over a period of one hour. During the addition of the sodium nitrite solution, slow evolution of ~~nitrogen~~ a gas took place and the yellowish coloured solution became turbid. After the addition of the sodium nitrite the whole was allowed to stand in the freezing mixture for two to three hours. A fine greenish coloured powder settled out, which was filtered off, washed, and dried in the vacuum desiccator. As in the previous experiment it blackened slightly at 220° and melted between 240° and 250°. The greenish yellow filtrate was made carefully alkaline with sodium hydroxide solution, and a white precipitate was obtained, which, on filtering off, washing with water, and drying in the vacuum desiccator, blacked at 220° and melted between 240° and 250°. It recrystallised from ligroin in silvery white leaflets, m.p. 265°. Yield 1.6 g.

Preparation /

Preparation of sym-[di-(β-2-quinolyl-propionyl)]-hydrazide using amyl nitrite and alcoholic hydrochloric acid.

β-(2-quinolyl) propionyl-hydrazide (4.4g. = $1/100$ mol.) was dissolved in 40 ccs. absolute alcohol, and to this solution, freshly distilled amyl nitrite (2.4 g. = $1/100$ mol.) was added. 4.5 N Alcoholic hydrochloric acid (4.4. ccs. = $1/100$ mol.) was then run in with constant shaking of the mixture. No reaction was observed. The pale yellow solution was then boiled under a reflux condenser for eight hours during which period a white solid commenced to settle out. On cooling it was filtered off, washed with absolute alcohol, and dried in the vacuum desiccator. On recrystallisation from ligroin in silvery leaflets it gave m.p. 265°. Yield 3.2 g.

Hydrolysis of sym-[di-(β-quinolyl)-propionyl)] hydrazide into hydrazine hydrochloride and β-(2-quinolyl) propionic acid.

Sym [di-[β-(2-quinolyl)-propionyl]] hydrazide (2.g.) was refluxed with 30 ccs. concentrated hydrochloric acid for eight hours. From the clear pale yellow solution a substance crystallised out on cooling in colourless cubic crystals, which on filtering off, washing with alcohol, and drying in the vacuum desiccator gave m.p. 200°. This compound was proved to be hydrazine hydrochloride by its unchanged m.p. 200°, when mixed with an authentic specimen of hydrazine hydrochloride, and also by its general reducing properties /

perties. It readily gave a silver mirror with an ammoniacal solution of silver nitrate, and reduced Fehling's solution in the cold.

The filtrate obtained after removal of the hydrazine hydrochloride was evaporated down to dryness, and the pale yellow residue left behind dissolved in the minimum amount of water. 20 ccs. of strong ammonia were then added, and the solution again evaporated down to dryness, and the residue left behind heated on the water bath for another eight hours. It was then extracted with acetone, and the acetone distilled off leaving behind β-(2-quinolyl) propionic acid which recrystallised from benzene in flaky crystals of greasy lustre m.p. 122°-123°. The melting point was unchanged when mixed with an authentic specimen of β-(2-quinolyl) propionic acid.

2-(β-piperidyl)-ethyl-quinoline (using the basic medium reaction).

A 40% aqueous solution of formaldehyde (6 ccs. = $^2/_{25}$ mol.) was slowly added to piperidine (6.8 g. = $^2/_{25}$ mol.) with constant shaking. After the evolution of heat, which accompanies the solution of these reactants had subsided, and a clear homogeneous solution had been formed, quinaldine (5.7 g. = $^1/_{25}$ mol.) was then added and the contents heated on the water bath under a reflux condenser for eighteen hours. During this period the solution changed in colour from a pale yellow to a dark red colour. On cooling a thick red oil separated. A trace of potassium carbonate was then /

then added to neutralise any formic acid formed during the reaction, and the contents steam distilled to remove excess of quinaldine, formaldehyde, and piperidine. The thick red oil which was left behind was dissolved in dilute hydrochloric acid, boiled with animal charcoal and filtered. The pale yellow solution was made alkaline, and the oil which separated extracted with ether, dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The base 2-(β -piperidyl)-ethyl-quinoline was left behind as a viscous pale yellow oil which did not crystallise on standing in the ice chest overnight. It was dissolved in a few ccs. of dry benzene and a bright yellow precipitate of the mono-picrate of the base obtained by the addition of excess of a saturated solution of picric acid in benzene. The picrate recrystallised from alcohol in long fine yellow needles, m.p. 155°.

Yield of the base calculated as picrate 16%.

Analysis

$C_{16}H_{20}N_2 \cdot C_6H_3O_7N_3$ Calculated C = 56.3%; H = 5.0%; N = 14.9%

Found C = 56.1%; H = 4.9%; N = 14.9%

The mono picrate was sparingly soluble in alcohol and benzene in the cold, but easily soluble in alcohol, and less readily in benzene in the hot, forming pale yellow solutions from which it recrystallised in long fine yellow needles. It is freely soluble in acetone, but insoluble in ligroin and petroleum ether both in the hot and cold.

2 g. of the picrate were decomposed on the water bath /

bath with 30 ccs. dilute sodium hydroxide by gentle warming. The base which collected on the surface as a separate layer was extracted with benzene. The benzene layer was washed two or three times with dilute sodium hydroxide and then distilled water to remove the last traces of picric acid and alkali, and then dried over anhydrous potassium carbonate. 2-(β-piperidyl)-ethyl-quinoline hydrochloride was obtained as a white crystalline compound, m.p. 184°-185° by passing in dry hydrochloric acid gas to the benzene extract. The hydrochloride readily absorbs moisture from the air.

The base 2-(β-piperidyl)-ethyl-quinoline is a pale yellow viscous oil which decomposes on attempted vacuum distillation. It is readily soluble in dilute hydrochloric, sulphuric, nitric and acetic acids, forming pale yellow solutions from which it is readily precipitated on the addition of alkali.

On the addition of a few drops of a solution of platinic chloride (3%) to a moderately strong solution of the hydrochloride a dense yellow precipitate of the platini chloride was obtained, which on close examination proved to be amorphous. Several attempts to recrystallise it from various organic solvents failed. In each case it readily blackened and decomposed in the hot. In the same way a dense brownish red precipitate of the auri chloride was obtained when a few drops of a gold chloride solution (10%) were added to the aqueous solution of the hydrochloride. This compound proved also

to /

to be amorphous and readily decomposed on attempted recrystallisation from various organic solvents.

2-(β-piperidyl)-ethyl-quinoline (modified basic medium reaction).

On the careful addition of piperidine (6.8 g. = $^2/_{25}$ mol.) to a 40% aqueous solution of formaldehyde (6 ccs. = $^2/_{25}$ mol.) a homogenous solution was formed with the evolution of an appreciable amount of heat. On cooling quinaldine hydrochloride (7.1 g. = $^1/_{25}$ mol.) was added which, with constant shaking and slight warming on the water bath, soon went into solution. The contents were then heated on the water bath for eighteen hours under a reflux condenser, during which period the solution developed a deep red colour. The contents were made alkaline with sodium hydroxide and a thick red oil separated, which was steam distilled to remove unchanged quinaldine, formaldehyde, and piperidine. The thick red oil which was left behind, mixed with a small amount of tar, was dissolved up in dilute hydrochloric acid, boiled with animal charcoal, filtered, and the pale yellow filtrate made alkaline. The base which separated as a thick yellow oil was extracted with ether, dried over anhydrous potassium carbonate, filtered and the ether distilled off. The pale yellow oil left behind was dissolved up in a few ccs. benzene and excess of a saturated solution of picric acid in benzene added. The dense yellow precipitate of picrate was filtered off, washed with benzene and dried. It recrystallised from alcohol in long fine yellow needles /

needles, m.p. 155°. Yield 72%.

2-(β-piperidyl)-ethyl-quinoline. (neutral medium reaction).

Piperidine hydrochloride (9.6 g. = $^2/_{25}$ mol.) was added to a 40% aqueous solution of formaldehyde (6 ccs. = $^2/_{25}$ mol.), and a homogeneous solution was formed after vigorous shaking without the evolution of heat in this case. Quinaldine hydrochloride (7.1g.= $^1/_{25}$mol.) was then added and the reactants heated on the water bath for eighteen hours. The solution became dark red accompanied by the partial separation of a thick dark coloured oil mixed with a certain amount of tar. On making the contents alkaline, and steam distilling complete tarring took place, and from the solid basic black tar left behind no crystalline substance could be isolated.

A summary of the other experiments on this particular reaction, along with those described, is given in a Table on page 49. It shows the results obtained using trioxymethylene in place of a 40% solution of formaldehyde and varying molecular proportions of the reactants.

2-(β-diethylamino)-ethyl-quinoline. (modified basic medium).

A 40% solution of formaldehyde (6 ccs. = $^2/_{25}$ mol.) was added to diethylamine (5.8 g. = $^2/_{25}$mol.) with constant shaking. A slightly turbid solution was formed with the evolution of a moderate amount of heat.

On /

On cooling quinaldine hydrochloride (7.1 g. = $^{1}/_{25}$ mol.) was added to the solution, and the contents heated on the water bath for eighteen hours. The solution changed from colourless to a deep red colour with the formation of a homogeneous solution. It was then made alkaline with sodium hydroxide and steam distilled to remove the unchanged, quinaldine, diethylamine and formaldehyde. A non volatile reddish brown oil mixed with a small amount of tar was left behind. It was dissolved in dilute hydrochloric acid, boiled with animal charcoal, filtered, and the pale yellow filtrate made alkaline with sodium hydroxide. The base which separated, was extracted with ether, dried over anhydrous potassium carbonate, filtered, and the ether distilled off, leaving behind a viscous pale yellow oil. It did not crystallise on standing in the ice chest overnight, and so it was dissolved up in a few ccs. benezene, and excess of a saturated solution of picric acid added. A thick yellow precipitate of the mono picrate of 2-(β-diethylamino)-ethyl-quinoline was obtained after vigorous scratching, which on filtering off, drying, recrystallised from alcohol in long fine yellow needles, m.p. 123°-124°. Yield 33% of theory.

Analysis

$C_{15}H_{18}N_2 \cdot C_6H_3O_7N_3$ Calculated C = 55.1%; H = 5.0%; N = 15.3%

Found C = 55.1%; H = 5.1%; N = 15.4%

The mono picrate is sparingly soluble in alcohol and benzene in the cold, but freely soluble in alcohol, and moderately /

moderately soluble in benzene in the hot, forming pale yellow solutions from which it recrystallises in long fine yellow needles. It is freely soluble in acetone whilst insoluble in ligroin and petroleum ether both in the hot and cold.

The base 2-(β -diethylamino)-ethyl-quinoline is very similar to 2-(β -piperidyl)-ethyl-quinoline in properties. It decomposes on vacuum distillation. With dilute hydrochloric, sulphuric, nitric and acetic acids it forms pale yellow solutions from which the base is reprecipitated on making alkaline. On the addition of a few drops of platinic chloride solution (3%) to a moderately strong solution of the hydrochloride of the base, a dense yellow amorphous precipitate of the platini chloride was obtained, which like the corresponding piperidyl compound decomposed on attempted recrystallisation from various organic solvents. The auri chloride was obtained as a deep red flocculent amorphous precipitate which similarly decomposed on treatment with various organic solvents.

The hydrochloride could not be isolated in a crystalline condition by passing in dry hydrochloric acid gas to an ethereal solution of the base obtained by decomposing the pure picrate with dilute sodium hydroxide solution. The resulting precipitate of the hydrochloride was of a white sticky oily nature. On exposure to air it rapidly absorbed moisture and darkened in colour. It could not be recrystallised from various organic solvents.

As /

As shown in the Table (page 49) the basic and neutral mediums were also tried in the preparation of 2-(β-diethylamino)-ethyl-quinoline. The former was successful but the yield 14% is much lower as in the case of the corresponding piperidino compound than that obtained by the modified basic medium just described, whilst the neutral medium tarred in the same way as the corresponding piperidino reaction on making the reactants alkaline and steam distilling.

2-(β-methyl-phenyl-amino)-ethyl-quinoline.

Freshly distilled mono-methyl-aniline (8.6 g. = $^2/_{25}$ mol.) was shaken up with a 40% aqueous solution of formaldehyde (6 ccs. = $^2/_{25}$ mol.) to form a yellowish coloured emulsion. Quinaldine hydrochloride (7.1 g. = $^1/_{25}$ mol.) was then added and soon dissolved after vigorous shaking. The reactants were kept at 37°C for twenty four hours and then allowed to stand at room temperature for two days. During this period, the contents were vigorously shaken from time to time, and the colour passed from pale yellow to a deep red with the separation of a thick red viscous oil. The supernatant liquid was poured off, and the thick red oil dissolved up in water containing a drop or two of strong hydrochloric acid, filtered from traces of an insoluble dark resinous material, and the deep red filtrate made alkaline with a saturated solution of sodium carbonate. During this process, prior to the neutral point being reached, a white sticky gummy material was thrown out of solution as a thick white flocculent /

flocculent precipitate which was filtered off. This on exposure to air or on standing in the vacuum desiccator changed to a deep red sticky oily material. After removal of the gummy substance the filtrate was made definitely alkaline with sodium carbonate solution resulting in the separation of a red mobile oil, which was steam distilled to remove the unchanged volatile reactants. The non volatile red oil which was left behind was extracted with ether, dried over potassium carbonate, filtered and the ether distilled off. The base left behind was taken up in a few ccs. of benzene and a dense greenish yellow precipitate of the picrate obtained by the addition of an excess of a saturated solution of picric acid in benzene. The picrate was filtered off, washed with benzene, and dried. Water was found to be the most suitable solvent for recrystallisation, but a large portion of it proved to be insoluble in the hot. The insoluble portion was, in the cold, a solid yellowish brown amorphous substance, whilst in the hot an insoluble dark coloured thick oil. From the soluble portion 2-(β -methyl-phenyl-amino)-ethyl-quinoline was isolated as the di-picrate with one molecule of water of crystallisation in large greenish yellow plates, m.p. 175° with decomposition. Yield 1 gm.

Analysis

$C_{18}H_{18}N_2 \cdot (C_6H_3O_7N_3)_2 \cdot H_2O$

Calculated C = 48.8%; H = 3.5%; N = 15.2%

Found C = 48.4%; H = 3.9%; N = 15.4%

The di-picrate is insoluble in cold alcohol and benzene, but is sparingly soluble in the hot, forming in each

case a greenish yellow solution from which it comes out on cooling as a greenish yellow amorphous powder. It is readily soluble in acetone but with ligroin and petroleum ether completely insoluble both in the hot and cold. The pure base, in this case, could not be obtained from the picrate because the latter blackened and decomposed when treated with dilute sodium hydroxide. Consequently the common properties of the base could not be determined.

The use of the basic and neutral reactions were not successful. In the case of the former where mono methyl-aniline, formaldehyde and quinaldine were heated together on the water bath for eighteen hours, the reactants were reobtained unchanged on steam distillation without the formation of a non volatile oil, whereas in the case of the latter, a certain amount of tarring took place during condensation, and on making alkaline and steam distilling more tarring occurred, whilst a large portion of the reactants were re-obtained unchanged.

Behaviour of Quinaldine metho-sulphate, formaldehyde and diethylamine.

Diethylamine (3 g. = $^1/_{25}$ mol.) was slowly added to a 40% solution of formaldehyde (3 ccs. = 1/25 mol.) with constant shaking. After the heat evolution, which took place, had subsided quinaldine metho-sulphate (5.4 g. = $^1/_{50}$ mol.) was gradually added in small portions. During the addition of the quinaldine metho-sulphate the solution was kept constantly stirred.

A /

A deep red colour soon developed accompanied with the settling out of a dark red tarry material. After all the quinaldine metho-sulphate had been added the contents were then heated on the water bath for two hours, during which period the deep red resinous material remained undissolved. The contents were then cooled and made alkaline. Nothing was observed to separate. The contents were steam distilled to remove the unchanged reactants. The distillate remained clear whilst the dark oily material left behind went into a hard black tar on cooling. The supernatant liquid was poured off and the tar washed two or three times with water. After drying in the desiccator, attempts were made to obtain some crystalline material from it by treatment with various organic solvents without success.

This experiment was repeated twice using the same quantities. In the one case the reactants after the addition of quinaldine metho-sulphate were allowed to stand at room temperature for one hour, and in the other the addition of quinaldine metho-sulphate to the diethylamine formaldehyde solution was carried out while the latter was immersed in a freezing mixture. In both cases, however, the settling out of tarry resinous material occurred during the addition of quinaldine metho-sulphate although in the latter case the tarring proceeded much more slowly.

Using piperidine in the place of diethylamine no better results were obtained.

Behaviour of Quinaldine hydrochloride, acetaldehyde, and /

and diethylamine.

Acetaldehyde (1.8 g. = $^1/_{25}$mol.) was slowly added to diethylamine (3 g. = $^1/_{25}$ mol.) with constant shaking. A moderate amount of heat was evolved and the solution appeared slightly turbid. After the heat evolution had subsided quinaldine hydrochloride (4.6 g. = $^1/_{50}$ mol.) was added and the solution vigorously shaken to dissolve the hydrochloride. The contents were then heated on the water bath under a reflux condenser for eighteen hours. During this period the colourless homogenous solution assumed a deep red colour. On cooling a small quantity of a white crystalline compound crystallised out, which on filtering off and drying in the vacuum desiccator proved to be diethylamine hydrochloride, m.p. 211°. This was confirmed by its chlorine content.

$C_4 H_{12} N Cl.$ Calculated Cl. = 32.4%

Found Cl. = 32.7%

The filtrate was then made alkaline and the thick red oil that separated steam distilled. The non volatile dark coloured oil left behind after steam distillation, solidified into a black brittle tar on cooling, whilst the distillate contained a small amount of unchanged quinaldine.

The tar was soluble in dilute hydrochloric, sulphuric and nitric acids, forming dark coloured solutions from which it was precipitated in the dark amorphous form on making alkaline. It was freely soluble in alcohol, benzene and acetone, whilst insoluble in petroleum ether and ligroin both in the hot /

hot and cold.

The above experiment was repeated using piperidine (3.4 g. = $^1/_{25}$ mol.) in place of diethylamine, but again the black brittle tar was obtained after steam distillation.

These experiments were repeated using powdered anhydrous zinc chloride as a condensing agent and the time of heating on the water bath was reduced to nine hours, but without success. The product, after steam distillation, was again the black brittle tar.

O-amino-benzaldehyde.

O-nitro-benzaldehyde (16 g.) was suspended in a solution of ferrous sulphate (280 g. in 480 ccs. of water) according to the method of Bamberger and Dermuth (Ber. 1901, 34, 1330). The solution was heated on the water bath to 90° under a reflux condenser, and 50 ccs. of concentrated ammonia rapidly run in with constant shaking of the liquid. Keeping the temperature constantly at 90° another three portions of ammonia were run in, 20 ccs. at a time with constant agitation of the liquid. At the end of this operation the solution had changed from a pale yellow to a permanent greenish yellow. The alkaline solution was then steam distilled, and the o-amino benzaldehyde obtained as a volatile oil which soon crystallised in large flat plates, m.p. 38°- 39°. Yield 10 g.

α-piperidyl-β-methyl-butane-δ-one hydrochloride.

Piperidine hydrochloride (6.1 g.), methyl-ethyl ketone (42 g.) and trioxymethylene (2.1 g.) were boiled /

boiled under a reflux condenser according to the method of Mannich and Hof, (Arch. der Pharm, 1927, 265, 594). 5 ccs. of absolute alcohol were gradually added until complete solution of the trioxymethylene had been effected. The excess of methyl-ethyl-ketone was then distilled off, and the hydrochloride of the base left behind as a pale yellow oil which on cooling soon crystallised. On recrystallisation from alcohol and acetone it was obtained as a white crystalline solid, m.p. 150°.

2- (β-piperidyl-α-methyl)-ethyl-quinoline.

α piperidyl-β-methyl-butane-δ- one hydrochloride (8.4 g. = $^1/_{25}$ mol.) dissolved in 20 ccs. of water was added to o-amino-benzaldehyde (4.8 g. = $^1/_{25}$ mol.) in 10 ccs. alcohol. 10N sodium hydroxide solution (4.8 ccs.) sufficient to liberate the base and provide a slight excess of alkali to catalyse the reaction, was slowly run in with constant shaking of the aqueous alcoholic solution. The slightly alkaline clear yellow solution was stoppered and kept at 37°C for three days. During this period a thick mobile yellow oil separated from the solution, which was then steam distilled. The distillate at first was clear consisting largely of alcohol, but after a few minutes it soon went turbid due to the presence of a pale yellow volatile oil which was collected separately. On standing in the ice chest for a few hours the oil crystallised in the form of large plates of rhombic structure. On filtering off and recrystallising from ligroin it gave m.p. 63°- 64°. Yield ·6 g.

Its /

Its properties agreed with those of 2-3 dimethyl quinoline and was identical with a specimen prepared from methyl ethyl ketone and o-amino-benzaldehyde. Its identity was confirmed by means of its picrate which recrystallised from alcohol in microscopic prisms, m.p. 225°. This picrate is identical with that prepared by Rode, (Ber. 1887, 20, 1911), from 2-3 dimethyl quinoline.

The pale yellow non volatile oil left behind after steam distillation was extracted with ether, dried over anhydrous potassium carbonate, filtered, and the base obtained by distilling off the ether. On standing in the ice chest overnight the oil did not crystallise. It was, therefore, dissolved in a few ccs. of benzene and excess of a saturated solution of picric acid in benzene added. The picrate was immediately thrown out of solution as a dense yellow precipitate, which was filtered off and washed with benzene. It recrystallised from alcohol in fine yellow rectangular prisms, m.p. 167° - 168°. Yield 55g.

Analysis

$C_{17}H_{22}N_2 \cdot C_6H_3O_7N_3$

Calculated C = 57.1%; H = 5.2%; N = 14.5%

Found C = 56.7%; H = 5.0%; N = 14.7%

The picrate is insoluble in alcohol and benzene in the cold but moderately soluble in the hot, forming pale yellow solutions from which it recrystallises in fine rectangular prisms. It is freely soluble in acetone, but insoluble in water, petroleum ether, and ligroin in /

in the cold, whilst sparingly soluble in water in the hot from which it recrystallises in microscopic prisms.

A second picrate was isolated in small quantity (.5 g.) from the crude picrate by means of its insolubility in hot alcohol. It recrystallised from hot water in long narrow rectangular prisms giving m.p. 201°. It is in all probability the dipicrate of the base although the results of the analysis shown below are not conclusive.

Analysis

$C_{17} H_{22} N_2 \cdot (C_6 H_3 O_7 N_3)_2$.

Calculated C = 49.0%; H = 3.9%; N = 15.7%

Found C = 50.0%; H = 4.4%; N = 15.5%

Owing to the small quantity of picrate isolated further investigations were not possible.

The base 2-(β -piperidyl-α - methyl)-ethyl-quinoline is a pale yellow, non volatile oil which decomposes on vacuum distillation. It is readily soluble in dilute hydrochloric, sulphuric, nitric, and acetic acids, forming pale yellow solutions from which it is reprecipitated on making alkaline. It is readily soluble in alcohol, benzene and acetone forming pale yellow solutions, whilst insoluble in ligroin and petroleum ether. The hydrochloride was obtained by passing in dry hydrochloric acid gas to an ethereal solution of the base. On filtering off, washing with ether, and drying in the vacuum desiccator, it was found to be a solid light coloured glass which on exposure to air slowly turned a deep red colour and became /

became sticky to the touch. Several attempts made to recrystallise it from various organic solvents gave no definite results. An aqueous solution of the hydrochloride gave with a few drops of a platinic chloride solution (3%) a dense buff coloured precipitate of the platini chloride, whilst with a few drops of a gold chloride solution (10%) a dense dark red precipitate of the auri chloride. Both these compounds, however, proved to be amorphous and all the efforts made to recrystallise them from various organic solvents in which they were practically insoluble resulted in decomposition.

The Behaviour of α-piperidyl-β-methyl-butane-δ-one in slightly alkaline solution.

α-piperidyl-β-methyl-butane-δ- one hydrochloride (2.1 g.) was dissolved in 10 ccs. water and 5 ccs. alcohol. 10 N sodium hydroxide solution (1.2 ccs.) was added and the slightly alkaline pale yellow solution kept at 37°C for four days. It was then refluxed for two hours on the water bath, made slightly acid with dilute hydrochloric acid, and then steam distilled. The first 20 ccs. of the aqueous alcoholic distillate were collected in order to test for the presence of methyl-ethyl ketone. The presence of a ketone in the distillate was shown by the sodium-nitroprusside test. 2 ccs. of the distillate were taken and added to solution of sodium nitroprusside, which on making alkaline with sodium hydroxide gave a distinct red colour. Therefore to the remainder of the distillate was added o-amino-benzaldehyde (.3 g.), a drop or two

of /

of strong sodium hydroxide, and just sufficient alcohol to dissolve the o-amino-benzaldehyde. The clear solution was kept at 37°C for four days, refluxed for half an hour, and then steam distilled. From the turbid distillate, on placing in the ice chest for a few hours, a compound was obtained in large plate-like crystals, which, on recrystalling from ligroin, gave m.p. 63°-64°. It was proved to be 2-3 dimethyl quinoline by its unchanged m.p. 63°-64° when mixed with an authentic specimen of 2-3 dimethyl quinoline, obtained from the condensation of methyl-ethyl ketone with o-amino benzaldehyde, and also by its picrate which, on recrystallising from alcohol in microscopic prisms, gave m.p. 225°.

Condensation of methyl-ethyl ketone, formaldehyde, and diethylamine hydrochloride.

Diethylamine hydrochloride (16.2 g.) methyl-ethyl ketone (126 g.) and trioxymethylene (6.3 g.) were boiled on the water bath under a reflux condenser with the gradual addition of 15 ccs. alcohol until complete solution of the trioxymethylene was effected. The clear solution was refluxed for another two hours, and then the excess of methyl ethyl ketone distilled off. The thick red oily hydrochloride left behind, which did not crystallise on standing in the ice chest overnight, was dissolved in (20-30) ccs. water and filtered to remove traces of insoluble impurities. The base was precipitated in a separating funnel as a red coloured oil with dilute sodium hydroxide and extracted with /

with ether, dried over potassium carbonate, filtered and the ether distilled off. On repeated vacuum distillation a colourless mobile oil with a faint ammoniacal smell was obtained with boiling point 68° (9-11) mm. Yield 14 g. This base is thought to be $\beta-\beta$-acetyl methyl-trimethylene-tetra-ethyl amine (I) (cf. page 44) although the results of the analysis given below are not conclusive.

A comparison is also given with the theoretical analysis of α-diethylamino-β-methyl-butane-δ-one (II) and diethylamino methyl carbinol (III) because these compounds were mentioned in the theoretical discussion as possibilities but were ultimately dismissed for certain reasons. The results of the analysis tend to support this conclusion.

	Found	C = 67.3%	H = 11.9%	N = 11.5%
For I.	Calculated	C = 69.4%	H = 12.4%	N = 11.6%
" II.	"	C = 68.8%	H = 12.1%	N = 8.9%
" III.	"	C = 61.5%	H = 12.8%	N = 12.0%

The oil is soluble in dilute hydrochloric, sulphuric, nitric and acetic acids, forming colourless solutions from which it is precipitated on making alkaline. It is freely soluble in alcohol benzene and acetone whilst insoluble in ligroin and petroleum ether.

To try and settle definitely the identity of the basic oil the following attempts were made to prepare crystalline derivatives.

Hydrochloride.

The base (2 g.) was dissolved in 10 ccs. dry benzene and dry hydrochloric acid gas passed into the solution /

solution. A thick oily precipitate was obtained which on scratching thoroughly, and leaving to stand for some time in the ice chest did not crystallise. The supernatant liquid was poured off, and the last trace of benzene removed at the vacuum pump. By treatment of the slightly reddish coloured oil with various organic solvents no crystalline substance could be isolated.

An aqueous solution of the hydrochloride obtained by dissolving the above hydrochloride (2 g.) in a few ccs. of water or by dissolving a few ccs. of the base in dilute hydrochloric acid, failed to yield a platini or auri chloride.

Behaviour of base with phenyl hydrazine.

The base (1.6 g.) was dissolved in glacial acetic acid (5 ccs.) and to this solution phenyl hydrazine (1.1 g.) in 2 ccs. glacial acetic acid was added. The yellowish coloured solution was heated on the water bath for half an hour, under an air condenser. It was then cooled and allowed to stand for a few hours but nothing separated. The solution was then diluted with a few ccs. of water and made carefully alkaline with dilute sodium hydroxide. A thick reddish coloured oil separated, which on thoroughly scratching and standing in the ice chest did not crystallise. A few drops of this oil were heated on the water bath for a few minutes with 3 ccs. concentrated hydrochloric acid, and a few drops of Erhlich's reagent were then added to the reddish coloured solution, but no colour change indicated the formation of an indole derivative. A

similar /

similar procedure in an endeavour to prepare the methyl phenyl hydrazone of the base was carried out with methyl phenyl hydrazine, but it also yielded negative results.

Behaviour of base with hydroxylamine hydrochloride.

The base (1.6 g.) was suspended in 3 ccs. water, and just sufficient dilute hydrochloric acid added to dissolve it. Hydroxylamine hydrochloride (.7 g.) was then added, and the clear colourless solution heated on the water bath for about an hour under an air condenser. The solution changed to a deep red colour and on cooling thoroughly nothing separated. The solution was again heated on the water bath for another hour, cooled, and then allowed to stand for a few hours, but again nothing separated. The solution was made faintly alkaline, and a red oil separated, which on scratching thoroughly and leaving to stand in the ice chest did not crystallise. It was extracted with ether, dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The mobile base left behind did not yield a picrate, a platini or auri chloride, and thus appeared to be the unchanged base.

Behaviour of base with semi carbazide hydrochloride.

Semi carbazide hydrochloride (.8 g.) was dissolved with sodium acetate (1.4 g.) in 10 ccs. of water and the base (1.6 g.) was then added, and the slightly turbid solution heated on the water bath for two hours. During this period an insoluble white crystalline compound separated, which on filtering off, drying, proved

to /

to be hydrazide dicarbonimide from its m.p. 266° and nitrogen content. From the clear filtrate after the removal of the above hydrazide derivative nothing settled on standing. On making the filtrate just alkaline, an oily turbidity was obtained and the oil which collected did not crystallise on standing. It was, therefore, extracted with ether, dried over anhydrous potassium carbonate and the ether distilled off. Since the mobile oil which was left behind did not form a picrate, platini or auri chloride, it appeared to be the unchanged base.

Attempted condensation of the base with o-amino-benzaldehyde.

O-amino-benzaldehyde (3.6 g.) and the base (4.8 g.) were dissolved in 10 ccs. alcohol and two drops of strong sodium hydroxide solution added. The clear pale yellow solution was kept at 37°C for four days, and then refluxed for two hours. The alcohol was distilled off, and a mobile yellow oil remained behind which was steam distilled. After steam distillation a very small amount of a non volatile red coloured oil was left behind, whilst the distillate contained the bulk of the o-amino-benzaldehyde unchanged, m.p. 37-38°. The non volatile oil was extracted with ether, dried over potassium carbonate, filtered, and the ether distilled off. The trace of oil left behind was dissolved in the minimum amount of benzene, and to the solution a saturated solution of picric acid in benzene added. A slight amorphous precipitate was obtained after vigorous scratching, and partial concentration /

concentration of the solution. After filtering off and drying, the brownish yellow amorphous powder recrystallised from alcohol in the same amorphous condition of indefinite m.p. 185°- 195°. The yield, however, was so poor that further treatment was impossible. The above condensation was repeated only in this case a few drops of diethylamine were added to catalyse the reaction. The results obtained, however, were of the same indefinite nature so that the attempted condensation was abandoned.

Bromination of the compound in an endeavour to prepare a crystalline derivative.

The base (2 g.) dissolved in 5 ccs. dry benzene was treated drop by drop with bromine (2 g.) dissolved in 10 ccs. dry benzene. Decolourisation of the bromine solution occurred until almost all the solution had been added when a permanent red colour persisted, accompanied by the slight separation of a dark red oil. The solution was heated on the water bath for about a quarter of an hour under an air condenser, during which period a further separation of oil occurred. The benzene solution was then distilled off under reduced pressure, leaving behind a thick dark red oil, which, on standing in the vacuum desiccator for a few days, crystallised in large plate like crystals, surrounded by a thick dark brown greasy material. Part of it recrystallised from acetone in silvery white leaflets, m.p. 212° - 213°. It was proved to be diethylamine hydrobromide by its properties /

properties and bromine content.

Analysis

$C_4 H_{12} N Br$. Calculated Br = 52%

Found Br = 51.9%.

An aqueous solution of the hydrobromide gave an acid reaction towards litmus and no precipitate with alkali, whilst with silver nitrate solution a precipitate of silver bromide was obtained. The acetone filtrate containing the remainder of the soluble material was evaporated down to dryness, but the dark brown oily like residue could not be recrystallised from the various organic solvents tried. It was freely soluble in alcohol, benzene and acetone, whilst insoluble in petroleum ether and ligroin. It appeared to be insoluble in acids and alkali both in the hot and cold.

From these negative results no final conclusion could be drawn as to the constitution of the base.

Attempted preparation of α-methyl-phenyl amino-β-methyl-butane-δ-one.

Methyl-ethyl ketone (42 g.), mono methyl aniline hydrochloride (5.5 g.) and trioxymethylene (2.1 g.) were boiled together on the water bath under a reflux condenser with the gradual addition of 10 ccs. alcohol. The solution became deep red in colour with the gradual formation of a thick dark oily layer at the bottom of the flask. It was refluxed for six hours, and then the excess of methyl-ethyl ketone distilled off, and the thick dark oily material left behind taken up in water and the base liberated with dilute sodium hydroxide /

hydroxide solution. The dark red coloured oil which separated, was extracted with ether dried over anhydrous potassium carbonate, filtered and the ether distilled off. The oil left behind was vacuum distilled, and a pale yellow oil distilled over at 69° (9-11) mm. which was found to be mono methyl aniline. It was identified by means of its readily formed picrate, m.p. 156°. Above 69° (9-11) mm. the contents of the Claisen flask blackened and decomposed, and the fraction which distilled was collected separately as it was thought this might be the desired ketone. This fraction, however, was also identified as mono-methyl aniline by dissolving a few ccs. of the pale yellow distillate in 5 ccs. of methyl iodide, and heating on the water bath for a few minutes. The excess of methyl iodide was distilled off and the residue, which recrystallised from alcohol in long colourless needles, gave m.p. 198°. Its melting point and nitrogen content proved it to be trimethyl-phenyl-ammonium iodide.

Analysis

$C_9 H_{14} N I$ Calculated N = 5.3%

Found N = 5.5%

2- (N-piperidyl-methyl)- cyclo-hexanone.

Piperidine hydrochloride (20 g.) dissolved in 10 ccs water, formaldehyde (13 ccs. of a 40% aqueous solution) and cyclo hexanone (66 g.) were heated on the water bath for two hours according to the method of Mannich and Hönig, (Arch. der Pharm, 1927, 265, 602) The cyclo hexanone which at first formed a separate layer /

layer soon dissolved forming a clear homogeneous solution. On cooling the solution again formed two layers. The aqueous one was separated off and taken to dryness in a vacuum at 50° - 60° on the water bath. The white crystalline residue was recrystallised from a mixture of acetone and alcohol from which 2-(N-piperidyl-methyl cyclo-hexanone hydrochloride separated in long shiny needles, m.p. 161°. This compound actually melts at 161°, but hardens again at 165° and then finally melts at 227°. This is due according to the authors to the molecule splitting up under the action of heat into methyl-cyclo-hexanone, formaldehyde and piperidine hydrochloride. Yield 26 g.

1-(N-piperidyl-methyl)1-2-3-4 tetrahydro-acridine.

O-amino-benzaldehyde (3 g. = $1/40$ mol.) dissolved in 15 ccs. alcohol was mixed with 2-(N-piperidyl-methyl) cyclo-hexanone hydrochloride (5.7 g. = $1/40$ mol.) dissolved in 5 ccs. water. To the clear homogenous solution 10 N sodium hydroxide solution (2.6 ccs.) was run in so that the solution was just alkaline. It was then stoppered and kept at 37° C for four days. No oil separated during this period, but the solution changed from colourless to a pale yellow. It was then refluxed for half an hour to complete the reaction and the alcohol distilled off. The oil which separated was steam distilled and the non volatile oil which was left behind extracted with ether, dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The pale yellow viscous oil which remained behind /

behind was left in the ice chest overnight, but did not crystallise. It was, therefore, taken up in a few ccs. of benzene and the mono picrate of 1-(N-piperidyl-methyl)-1-2-3-4-tetrahydro-acridine obtained as a thick yellow precipitate on the addition of excess of a saturated solution of picric acid in benzene. The precipitate was filtered off, washed with benzene, dried, and recrystallised from alcohol from which it was obtained in long fine silky yellow needles, m.p. 206°. (decomposition). Yield 5.5 g.

Analysis

$C_{19}H_{24}N_2 \cdot C_6H_3O_7N_3$ Calculated N = 13.8%

Found N = 13.9%

The picrate is a pale yellow crystalline solid which is sparingly soluble in alcohol and benzene in the cold, but in the hot readily soluble in the former, and less readily in the latter. From the hot pale yellow solutions of both it recrystallises in long pale yellow silky needles. In the hot and cold it is freely soluble in acetone, but insoluble in petroleum ether and ligroin.

The base 1-(N-piperidyl-methyl)-1-2-3-4 tetrahydro-acridine is a pale yellow viscous oil which is readily soluble in dilute hydrochloric, sulphuric, nitric and acetic acids forming pale yellow solutions from which it is reprecipitated on making alkaline with dilute sodium hydroxide. It is freely soluble in alcohol, benzene, acetone and chloroform, forming pale yellow solutions whilst it is insoluble in ligroin and petroleum /

petroleum ether.

A moderately strong solution of the hydrochloride gave a dense pale yellow amorphous precipitate when a few drops of a solution of platinic chloride (3%) were added. In the same way when a few drops of a gold chloride solution 10% were added to the aqueous solution of the hydrochloride, a dense deep red amorphous precipitate of the auri chloride was obtained. On several attempts being made to recrystallise the platini and auri chlorides from water and various organic solvents they readily blackened and decomposed. The isolation of the hydrochloride in a crystalline state was attempted. The base (4 ccs.) was dissolved in 15 ccs. dry benzene and dry hydrochloric acid gas passed into the pale yellow solution. A white sticky precipitate was obtained, which was quickly filtered off, washed with benzene, and dried in the vacuum desiccator. On standing in the desiccator it slowly changed to a reddish colour and still remained sticky to the touch. On exposure to air it rapidly absorbed moisture. Several attempts to recrystallise it from various organic solvents failed completely.

2-(Diethylamino-methyl)-cyclo-hexanone.

Diethylamine hydrochloride (11 g.), formaldehyde (8 g. of a 40% solution), and cyclo hexanone (50 g.) were heated on the water bath under a reflux condenser according to the method of Mannich and Hönig, (Arch. der Pharm., 1927, 265, 601.) The reactants soon formed a colourless homogeneous solution. On cooling the solution /

solution separated into two layers, and the water and excess of cyclo-hexanone were removed under reduced pressure on the water bath at 70° - 80°. The crude yellowish coloured hydrochloride of 2-(diethylamino-methyl) cyclo-hexanone left behind was recrystallised from acetone from which it was obtained in fine white needles, m.p. 105° - 107°. Yield 16 g.

Attempted preparation of 1-(diethylamino-methyl)-1-2-3-4 tetra-hydro-acridine.

O-amino benzaldehyde (3 g. = $1/40$ mol.) dissolved in 15 ccs. alcohol was mixed with 2-(diethylamino-methyl)-cyclo-hexanone (5.5 g. = $1/40$ mol.) dissolved in 5 ccs. of water. To the clear solution 10 N sodium hydroxide solution (2.6 ccs.) was run in so that the solution was just alkaline. The flask was then stoppered and kept at 37°C for four days. During this period no oil separated but the solution changed to a slightly red colour. It was refluxed on the water bath for half an hour, and steam distilled. After steam distillation a dark coloured oil was left behind which on cooling went into a brownish red coloured glass. It was filtered off, washed with water, dissolved in dilute hydrochloric acid by warming on the water bath, and filtered from some dark tarry insoluble material. The yellowish red coloured filtrate was made alkaline and a flocculent amorphous precipitate obtained, which was filtered off, washed with water, and dried in the vacuum desiccator. It was then

boiled /

boiled up with ligroin in the presence of animal charcoal and filtered hot. On cooling it separated from the clear yellow filtrate as an oil forming an emulsion with the ligroin, and then on further cooling it settled as a pale yellow amorphous powder. On filtering off, washing with ligroin, and drying it gave an indefinite m.p. 65°- 75°. The indefinite melting point could not be improved by several such recrystallisations from ligroin. Its analysis did not agree with that of the expected 1-(diethylamino-methyl)-1-2-3-4-tetrahydro-acridine, the nitrogen content being much too low as shown below.

Analysis

$C_{18}H_{24}N_2$	Calculated	N = 10.5%
	Found	N = 6.1%

This pale yellow powder is soluble in hydrochloric acid from which it is reprecipitated with alkali in the amorphous condition. It is freely soluble in alcohol, benzene, acetone and chloroform forming clear yellow solutions. With ligroin and petroleum ether it is insoluble in the cold, but in the hot moderately soluble in the former but less readily in the latter forming pale yellow solutions from which it comes out out on cooling as an oil forming an emulsion and then settles as a pale yellow amorphous powder. No picrate could be obtained when to a benzene solution of the pale yellow powder an excess of a saturated solution of picric acid in benzene was added. An aqueous solution of the hydrochloride of the base gave an amorphous /

amorphous brownish yellow precipitate of the platini chloride, and an amorphous reddish brown precipitate of the auri chloride when treated with the appropriate reagent. Both these precipitates on filtering off and drying proved to be insoluble in water and various organic solvents and blackened and decomposed on attempted recrystallisation.

Behaviour of 2-(N-piperidyl-methyl)-cyclo-hexanone with phenyl hydrazine.

2-(N-piperidyl-methyl) cyclo hexanone (2.1 g. = $^1/_{100}$ mol.) and phenyl hydrazine (1.1 g. = $^1/_{100}$ mol.) were dissolved in 10 ccs. alcohol, and the pale yellow solution heated on the water bath for five hours under a reflux condenser. On cooling from the faintly reddish coloured solution nothing separated. It was then saturated with dry hydrochloric acid gas, and a trace of a white crystalline compound was observed to separate from the alcoholic solution. The solution was again heated up on the water bath for about a quarter of an hour and the alcohol distilled off. The dark reddish coloured oily hydrochloride left behind did not crystallise on standing. It was boiled up with a mixture of acetone and alcohol, filtered, and from the solution long needles of piperidine hydrochloride crystallised out, m.p. 242°. Its identity was confirmed by a determination of its chlorine content $C_5H_{11}N \cdot HCl$ required Cl. = 29.2%, found Cl. = 29.4%. The yield of piperidine hydrochloride was very small (·3 g.)

Another experiment using the same procedure was tried /

tried with 2-(N-piperidyl-methyl) cyclo hexanone (2.1 g. = $^{1}/_{100}$ mol.) and methyl phenyl hydrazine (1.2 g. = $^{1}/_{100}$ mol.), but again the only base which could be isolated was piperidine identified as its hydrochloride, m.p. 242°.

Mol. proportions of reactants Q. F. P.	Variations in nature of reactants	Yield of base	Conditions	Remarks
111	Q and P as bases F as trioxymethylene	-	Reactants heated on the water bath for 18 hours	Bulk of yield mainly 2-β-hydroxyethylquinoline with a moderate amount of basic tar and unchanged Q.
121	Q and P as bases F as trioxymethylene	-	Heated at 140 for 18 hours	Bulk of yield 2-β-hydroxyethylquinoline, with increased amount of basic tar as compared with I and a moderate amount of unchanged Q.
122	Q and P as bases F as trioxymethylene	11%	Heated on the water bath for 18 hours	Moderate amount of basic tar and unchanged Q.
124	"	"	"	Result same as III.
122	Q and P as bases F as 40% formalin	16%	Heated on the water bath for 18 hours	Slightly improved yield, no basic tar but a moderate amount of unchanged Q. When P increased to 4 and temperature raised to 140 yield drops to 11% and tarring takes place.
122	Q as hydrochloride P as base F as 40% formalin	72%	Heated on the water bath for 18 hours	Yield considerably improved, slight amount of basic tar and a trace of unchanged Q.
122	Q as hydrochloride P as " F as 40% formalin	-	Heated on the water bath for 18 hours	Considerable amount of tarring during heating which was completed on making alkaline and steam distilling.

Q.F.D.				
122	Q as base D " " F as 40% formalin	14%	Heated on the water bath for 18 hours	Yield slightly better than in corresponding piperidine expt. No basic tar and a moderate amount of unchanged Q.
122	Q as hydrochloride D as base F as 40% formalin	33%	Heated on the water bath for 18 hours	Yield not so good as in corresponding piperidine expt. Trace of basic tar and unchanged Q.
122	Q as hydrochloride D " " F as 40% formalin	-	Heated on the water bath for 18 hours	Crude product of basic tar - and no unchanged Q.
Q.M.F.				
122	Q as base M " " F as 40% formalin	-	Heated on the water bath for 18 hours	Obtained unchanged Q and M. Repeated at 140 with same result.
122	Q as hydrochloride M as base F as 40% formalin		Conditions as described in expt. page 24.	The base could only be isolated as the di-picrate in very poor yield. Heating on the water bath caused complete tarring.
122	Q as hydrochloride M " " F as 40% formalin		Conditions approximately those of ~~XII~~ XI	Partial tarring and indefinite results.

Q - Quinaldine

D - Diethylamine

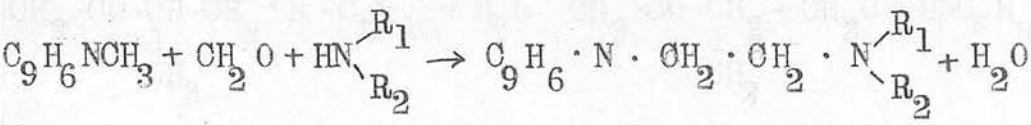
F - Formaldehyde

M - Mono-methylaniline

P - Piperidine

S U M M A R Y.

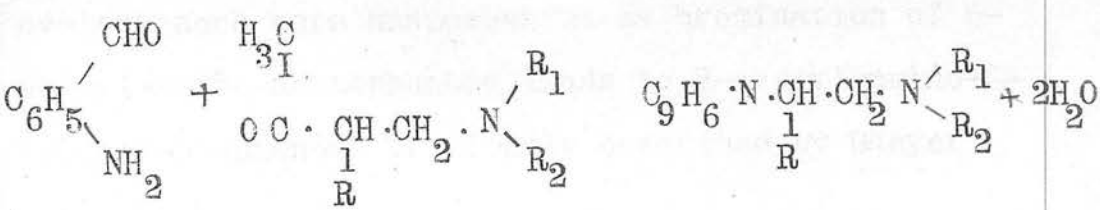
1. By the condensation of quinaldine, formaldehyde, and secondary bases, derivatives of 2-(β -amino) ethyl-quinoline have been obtained according to the following equation :-



The bases obtained are viscous non-volatile oils which could not be distilled in vacuum without decomposition. They yielded well defined crystalline picrates, and also gave hydrochlorides, the latter often being deliquescent.

2. Attempts to substitute aldehydes such as acetaldehyde in place of formaldehyde in the above reaction, or to replace quinaldine hydrochloride by quinaldine methosulphate or by o-nitro-toluene did not prove successful.

3. Derivatives of 2-(β -amino) ethyl-quinoline were also prepared by an application of the Friedlander synthesis when o-amino-benzaldehyde was condensed in dilute alkaline solution with amino ketones of the type $CH_3 \cdot CO \cdot \underset{\underset{R}{|}}{CH} \cdot CH_2 \diagup \begin{matrix} R_1 \\ \diagdown R_2 \end{matrix}$ according to the following equation :-



4. When α-N piperidyl-β-methyl-butane-δ-one was boiled in /

in slightly dilute alkaline solution methyl-ethyl ketone was formed, presumably as a result of the reversal of the Mannich reaction according to the equation :-

$$CH_3 \cdot CO \cdot \underset{\underset{CH_3}{|}}{CH} \cdot CH_2 \cdot N \cdot C_5H_{10} + H_2O \quad CH_3 \cdot CO \cdot \underset{\underset{CH_3}{|}}{CH_2} + CH_2O + HNC_5H_{10}$$

This observation may account for the formation of 2-3 dimethyl-quinoline as a bi-product when o-amino-benzaldehyde was condensed with α-N piperidyl-β-methyl-butane-δ-one by the Friedlander method described under 3.

5. An attempt to prepare 2-(β-amino) ethyl-quinoline by the Curtius method from β-(2-quinolyl)-proprionyl-hydrazide was unsuccessful. When this hydrazide was treated with nitrous acid under various conditions the azide could not be isolated but instead a gas was evolved and the compound $C_9H_6 \cdot N \cdot CH_2 \cdot CH_2 \cdot CO \cdot NH \cdot NH \cdot CO \cdot CH_2 \cdot CH_2 \cdot N \cdot C_9H_6$ was obtained.

6. The condensation of o-nitro-w-bromo-acetophenone with piperidine leads to the formation of resinous substances from which no crystalline compound could be isolated. Various attempts to obtain o-amino-w-piperidyl-acetophenone through o-acetyl-amino-w-bromo-acetophenone were unsuccessful as bromination of o-acetyl-amino-acetophenone leads to 2-acetyl-amino-5-bromo-acetophenone previously described by Baeyer.