THE SYNTHESIS OF HETEROCYCLIC BASES OF POSSIBLE ANTIMALARIAL ACTIVITY.

by

Alice Patterson Weatherhead, A.I.C.

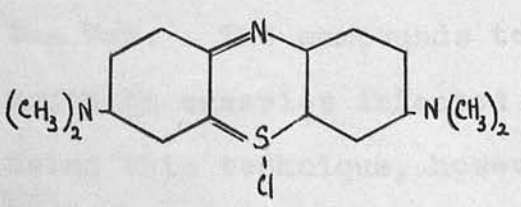
Thesis presented for the Degree of Ph.D.,
University of Edinburgh.

May 1939.

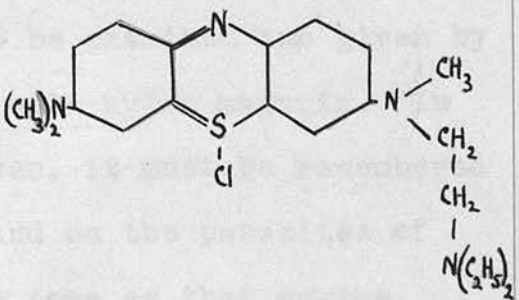
I. INTRODUCTION and GENERAL SURVEY OF THE LITERATURE.

INTRODUCTION and GENERAL SURVEY OF THE LITERATURE

From 1856 to 1914 attempts were made to synthesise quinine but always without success. It was only when the idea was rejected that an anti-malarial drug must contain (1) a quinoline nucleus and (2) a basic component similar to that of quinine, that an advance was able to be made. This advance was begun by the discovery by Schulemann (Proc. Roy. Soc. Med., 25, 897) that methylene blue (I), had some effect on the quartan parasite and that by the replacement of one of the NMe_2 groups by the chain $NMe.CH_2.CH_2.N(C_2H_5)_2$ (II), its anti-malarial properties were increased.



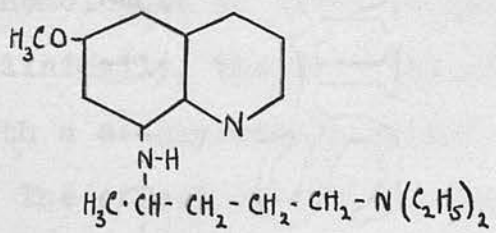
I.



II.

On/

On the basis of this result it was decided to apply the same modification to the quinoline nucleus. Thus from 8-amino-quinoline was produced plasmoquine (III), or 8-[δ -diethylamino-α-methylbutylamino] 6-methoxy quinoline.



III.

The method of testing these anti-malarial drugs is that devised by Roehl at Elberfield during the War. The compounds to be examined are given by mouth to canaries infected with avian malaria. In using this technique, however, it must be remembered that the effect of a compound on the parasites of bird malaria may not be the same as that on the parasites of human malaria.

Plasmoquine is effective in human malarial infections/

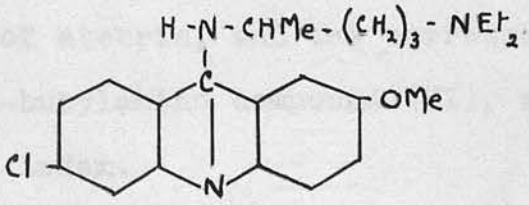
infections due to benign tertian and quartan parasites, since it acts especially on the gametocytes of both species and on the schizonts of Plasmodium malariae and to a rather less extent on those of Plasmodium vivax. Soon, however, it was found that although plasmoquine acted on the gametocytes of malignant tertian, it had little or no action on the schizonts of that parasite.

Of the homologues of plasmoquine which have been tested clinically, the majority are 6-methoxy quinolines with a dialkylaminoalkylamino chain in position 8. The effect of varying the length and nature of the two side chains in positions 6 and 8 has been studied by Fourneau, Trefouel and Benoit in France and by Magidson, Grigorowsky, Rubtzov and others in Russia. Fourneau and his co-workers, as a result of observations on these compounds, believe that the methoxy group in position 6 in the quinoline nucleus is not essential for anti-malarial activity. On the other hand, the substitution of $-OCH_3$ by $-OC_2H_5$ appears always to exert an unfavorable action as does the group $-C.CH_2.O.R-$ placed in the alkylamino chain.

Fourneau 710 or the methylene disalycilic acid salt of 6-methoxy-8- [α-diethylamino propylamino] quinoline, known generally as Rhodoquine, is chemically identical with the compound marketed extensively/

extensively in Russia as Plasmocide. Its action in bird malaria on the sporozoites of Plasmodium relictum is said to be similar to that of plasmoquine. It appears to have the defects of plasmoquine and to be somewhat less effective on benign tertian and quartan parasites.

With the object of getting rid of toxic properties said to be associated with the quinoline nucleus, recourse was made to a triple ring system. The ring system which was finally used was that of acridine and 3-methoxy-8-chloro-5-[δ -diethylamino-α-methyl butylamino] acridine was produced and has since been extensively used under the name of Atebrin (IV).



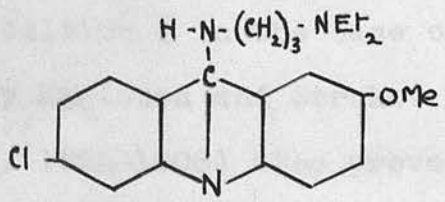
IV.

When tests were made on canaries infected with Plasmodium praecox, atebrin destroyed the schizonts but differed from plasmoquine in not being

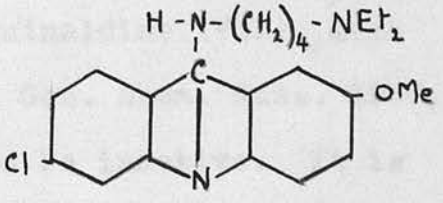
a/

a gametocide. Tests also showed that it had a similar action in man, since it resembles quinine in destroying all forms of benign tertian and quartan parasites and also the schizonts of malignant tertian, although the gametocytes are untouched.

In 1933 the first of a series of Russian papers was published by Magidson and Grigorowsky on "Anti-Malarial Derivatives of Acridine " (Chemico-Pharmaceutical Ind., (Russian) No. 1, 1933). From the results of their work they concluded that in the treatment of bird malaria, chemotherapeutic value increases with the number of carbon atoms in the alkylamino chain, being a maximum at C = 4. The outstanding result of this work was the production of 3-methoxy-8-chloro-5-[γ -diethylamino-n-propylamino] acridine (V), which has a chemotherapeutic index equal to that of atebrin, and the corresponding δ - diethylamino-n-butylamino compound (VI), which has an even higher index.



V.



VI.

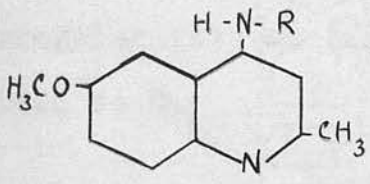
Since then Magidson and his co-workers have published many papers in which active anti-malarial compounds have been described. For the most part these are derivatives of 8-amino-quinoline having an alkoxy group in position 6. (J. Gen. Chem. Russ. 1934, 4, 1047-1056; Arch. Pharm. 1935, 273, 320-333; Arch. Pharm. 1934, 272, 74-84).

The compounds of this series act as a rule upon the gametocytes, with the exception of those with a long chain in position 8. There are indications that these latter possess also a schizonticidal action.

Magidson and Rubtzov (J. Gen. Chem. Russ. 1937, 7, 1896-1908) have also introduced the diethyl-amino alkylamine into 6-methoxy-quinoline in position 4, and have found that these compounds have specific action upon the malaria parasite. Analogous substitutes of 2-amino-6-methoxy-quinoline are completely inactive.

Compounds with diethylamino alkylamine in position 4 in the case of quinaldine (VII), made by Magidson and Strukov (J. Gen. Chem. Russ. 1937, 7, 1896-1908) also proved to be inactive. It is suggested that the quinaldine derivative becomes oxidised/

oxidised to the corresponding quinaldinic acid, and that the appearance of carboxyl destroys the activity.



VII.

R = (1) $(C_2H_5)_2$- N-CH_2-CH_2-CH_2-CH_2-

(2) $(C_2H_5)_2$- N-CH_2-CH(OH)-CH_2-

(3) $(C_2H_5)_2$- N-CH_2-CH_2-CH_2-

A curious alternation in the parasiticidal activity of members of a homologous series was first noted by Magidson (Terapeutichesky Arkhiv. XV, 1937, 693) in testing the anti-malarial activity in infected siskins of a series of 6-methoxy-quinolines substituted in position 8 by the chain -NH- CH_2 —.NEt_2, the chemotherapeutic indices (i) for different values of n being:-

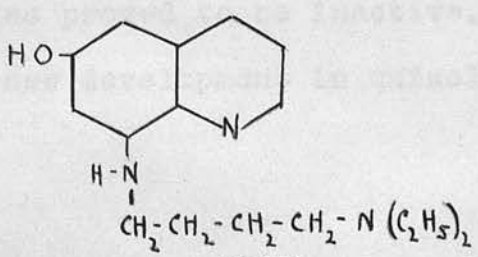
n	2	3	4	5	6	7	8	9	10	11
i	6		13		13.3				10	
i		27		25		33.3		40		5

Alternation however is not always observed in such tests with homologous series, for Magidson and Strukov in the same paper report that when the chain in position 8 was kept constant at $-NH-CH_2.CH_2.N(C_2H_5)_2$ and the group in position 6 varied from OH to $C_5H_{11}O$, there was a continuous but irregular fall in the chemotherapeutic index from 13.3 to 0.

OH	OCH_3	OC_2H_5	OC_3H_7	OC_4H_9	OC_5H_{11}
13.3	6	4	1	1	0

Similar results have been found by Fourneau and co-workers in a paper previously referred to.

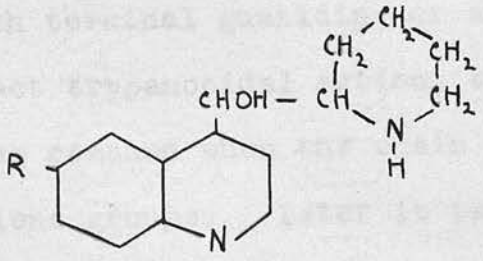
It is interesting to note that recently preparations have been put on the market under the names of "Certuna (Kikuth, Klin. Woch. 1938, 17,524) and "Cilional" (Chopra, Gupta and Sen, Ind. Med. Gazette, 1938, 73, 667) both of which are described as dialkylamino-butylamino-hydroxy quinolines. It seems probable that they have structures such as the following (VIII).



VIII.

These compounds are claimed to have high gametocidal activity.

Until last year when a paper was published by Ainley and King (Proc. Roy. Soc. 1938, 125, 60) no compound having anti-malarial activity had been synthesised on the pattern of the quinine molecule. Ainley and King prepared 4-quinolyl-α-piperidyl carbinol (IX) (R = H) and 4-(6-methoxy quinolyl)-α-piperidyl carbinol (IX) (R = OMe) and their N-alkyl derivatives, as hydrochlorides.



IX.

No quinolyl derivative without the 6-methoxy group had any activity. The two stereoisomeric 4-(6-methoxy quinolyl)-α-piperidyl carbinols, however, were both active in bird malaria, although their N-alkyl derivatives proved to be inactive.

Another new development in quinoline and acridine/

acridine anti-malarials has recently been published by Knunianz and Benevolenskaya (J. Gen. Chem. Russ. 1937, 7 , 2930-2933). By condensing 8-amino-6-methoxy quinoline with chlorolupinan they obtained 8-lupinylamino-6-methoxy quinoline, and by condensing 5:7-dichloro-3-methoxy acridine with amino lupinan, 7-chloro-5-lupinyl amino-3-methoxy acridine was obtained. Both of these compounds are claimed to be powerful anti-malarials.

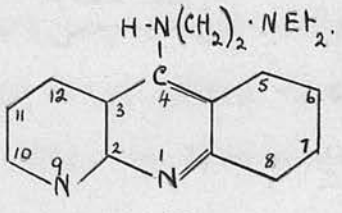
The discovery was made last year by King, Yorke and Lourie that a series of long-chain aliphatic compounds with terminal guanidine or amidine groupings had direct trypanocidal action, the optimal activity being reached when the chain contained eleven methylene groups. Later it was found that undecamethylenediamidine caused the disappearance of malaria parasites from the blood of birds, monkeys and man. So far compounds of this type have not been used as anti-malarial drugs so that a new field of possibilities is now open to exploration in the hope of finding a curative substance.

II./

II. GENERAL OBJECTS OF RESEARCH.

The object of the present research was to synthesise compounds analogous to quinine, plasmoquine and atebrin, but containing different heterocyclic nuclei, so that these might be tested in respect of their possible anti-malarial activity.

In the choice of ring systems one is to some extent guided by the ease with which they are synthesised, but in general the object has been to obtain systems containing two pyridine rings and one benzene ring in place of the two benzene rings and one pyridine ring such as are present in compounds of the atebrin type. Various attempts were made to synthesise compounds having the following structure: I.

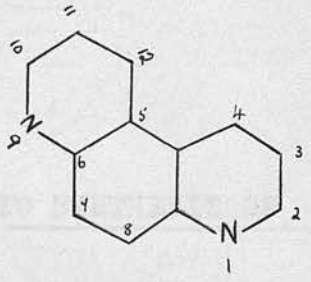


I.

but for technical reasons which will be explained later, this synthesis has not so far been successfully completed.

Attention was then directed to ring systems of/

of the phenanthroline type. (II).

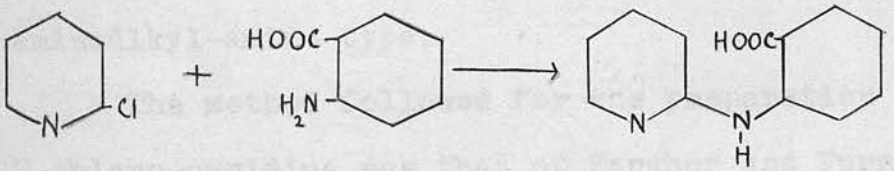


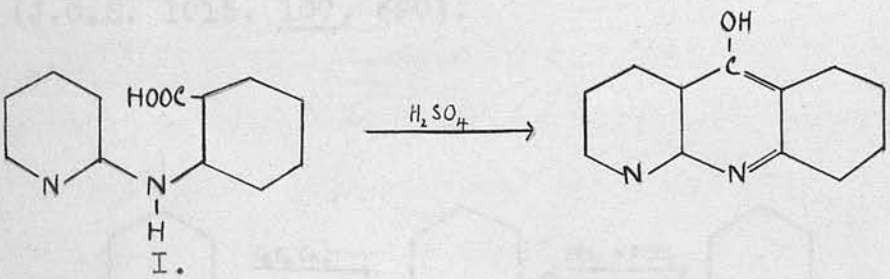
II.

Two series of compounds derived from this heterocyclic nucleus have been prepared, in which the side chains are in position 2 and position 4 respectively, the side chains being of the dialkyl-aminoalkylamino type. In connection with this work a secondary problem arose as to the position of entry of the nitro group when 4-hydroxy quinaldine was nitrated. This is discussed in Section V.

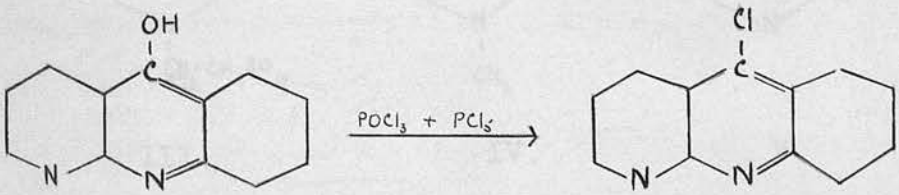
III. ATTEMPTED SYNTHESIS OF 2:3-PYRIDO-QUINOLINE DERIVATIVES.

In order to obtain compounds of the type containing two pyridine rings and one benzene ring, a scheme of synthesis was drawn up and is formulated below:

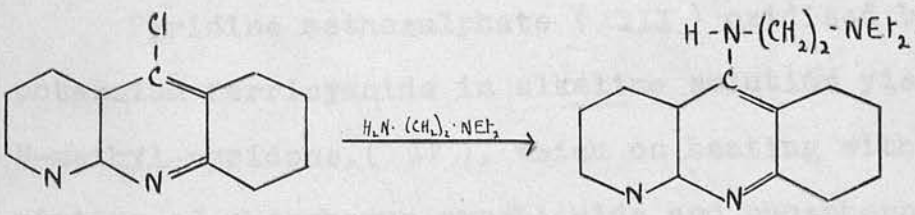




I.

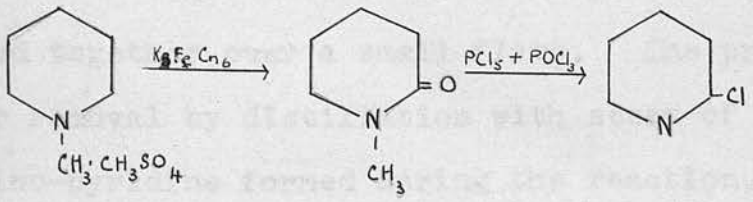


II.



It was proposed to condense 2-chloro-pyridine with anthranilic acid in order to obtain 2:3-pyrido-4-hydroxy quinoline (II). Replacement of the hydroxyl group by chlorine would then yield a compound with a chlorine atom in position 4 replaceable by a basic side-chain of the dialkyl-aminoalkyl-amino type.

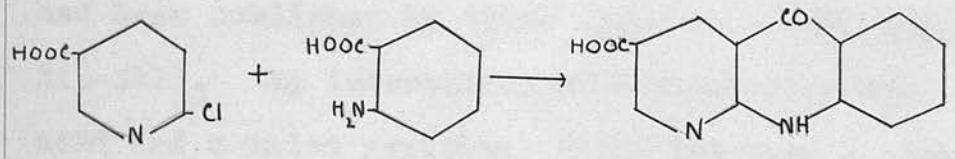
The method followed for the preparation of 2-chloro-pyridine was that of Fargher and Furness (J.C.S. 1915. 107, 690).

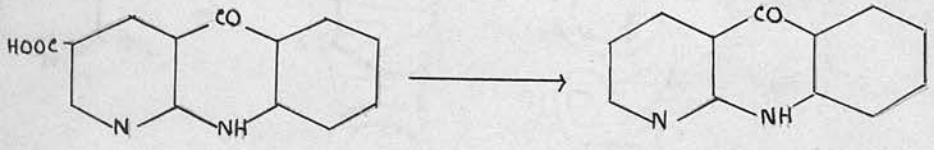


III. IV. V.

Pyridine methosulphate (III) oxidised by potassium ferricyanide in alkaline solution yields N-methyl-pyridone, (IV), which on heating with a mixture of phosphorus oxychloride and phosphorus pentachloride undergoes demethylation followed by enolisation and replacement of the hydroxyl group by/

by chlorine to give 2-chloro-pyridine (V) in almost theoretical yield. Attempts were then made to condense 2-chloro-pyridine with anthranilic acid in order to obtain the intermediate acid, pyridino-anthranilic acid (I). Heating the two reactants in glacial acetic acid solution and in amyl alcohol solution with copper bronze as catalyst yielded only the original materials, and it was decided to carry out the condensation according to the method of Bose and Sen (J.C.S. 1931, 2840) which claimed to produce the 2:3-pyrido-4-hydroxy-quinoline (II) directly. Accordingly equimolecular quantities of the components were heated together over a small flame. The product, after removal by distillation with steam of 2-anilino-pyridine formed during the reaction, re-crystallised from alcohol as yellow prisms, m.p. 210°, which dissolved in dilute mineral acid with a violet-blue fluorescence. The same compound was obtained by Reissert (Ber. 1895, 28, 119) by decarboxylating the condensation product of α - chloro-nicotinic acid and anthranilic acid. Reissert interpreted the course of the reaction as follows:

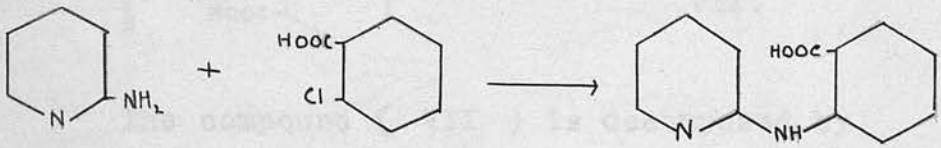


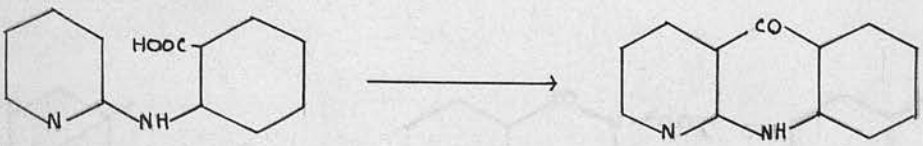


The product obtained by the condensation of chloro-pyridine and anthranilic acid, although clearly identical in all respects with that obtained by Reissert, had very different properties from those expected of a compound having such a structure. All attempts to make it react with phosphorus oxy-chloride and phosphorus pentachloride failed. On the other hand it dissolved easily in sodium hydroxide solution. These properties awakened the doubt as to the correctness of the Reissert, and Bose and Sen structure.

While/

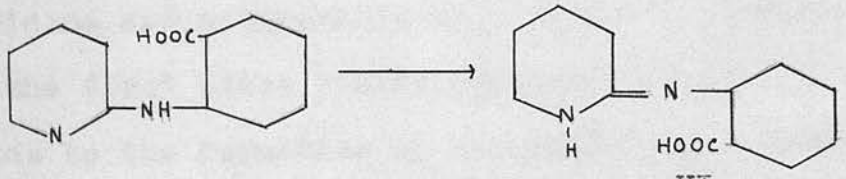
While this question was being investigated it was found that a paper bearing on the subject had been published by Seide (Annalen, 1924, 440, 311-321). By interaction of o-chloro-benzoic acid and α-amino pyridine, Seide obtained a compound, m.p. 210°, evidently identical with that of Reissert.



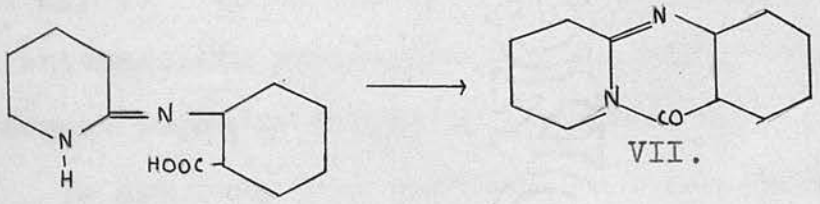


The unusual properties of the compound, namely its easy formation, its easy solubility in caustic soda and resistance against phosphorus halides, led Seide to suggest that ring closure to the nitrogen/

nitrogen of the pyridine nucleus takes place according to the scheme below:-

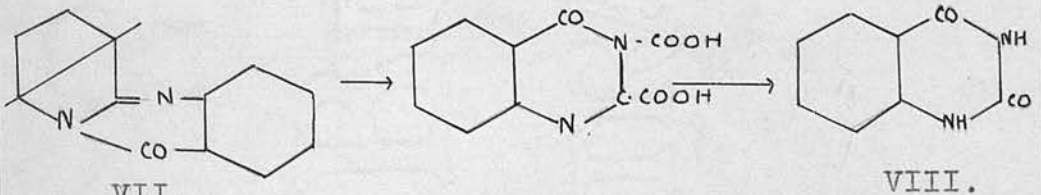


VI.



VII.

The compound (VII) is decomposed by potassium permanganate to the stable 2-4-dioxy-quinazoline (VIII), and is therefore, 2-3-di-hydrobenz-quinazolone-4.

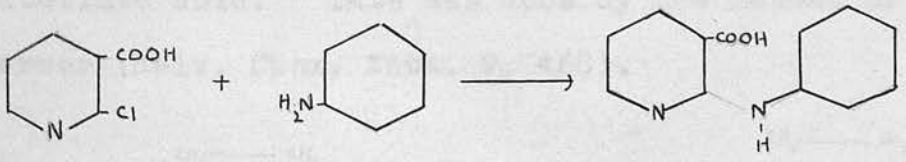


VII. VIII.

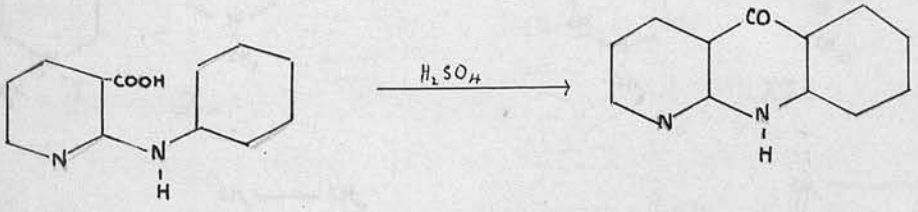
Now there is little doubt that the compound obtained by Seide is identical with that obtained by/

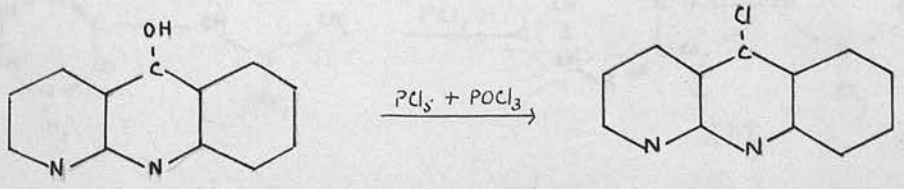
by Reissert, and by Bose and Sen. It follows, therefore, that the condensation of 2-chloro-pyridine and anthranilic acid, which presumably in the first place yields pyridino anthranilic acid, leads to the formation of 2-3-dihydrobenzquinazolone-4, (VII). As in the case of Seide's compound, the intermediate pyrido-anthranilic acid presumably undergoes isomeric change to structure VI.

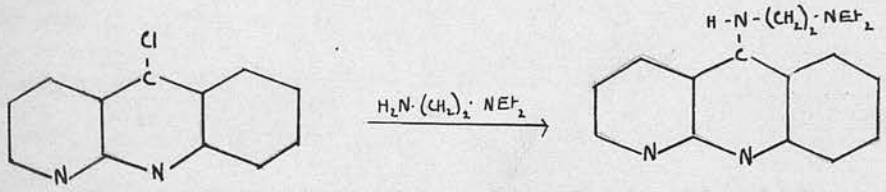
To get over this difficulty another method of synthesis was attempted. This scheme is shown below:-



IX.

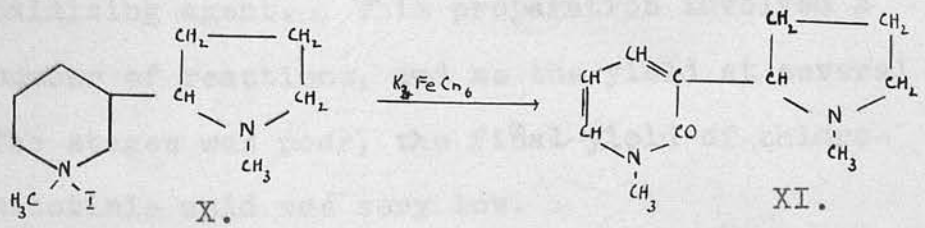




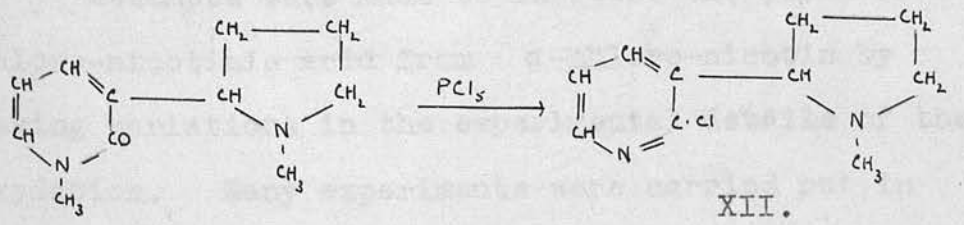


It was proposed to condense 2-chloro-nicotinic acid with aniline in order to obtain 2-anilino-nicotinic acid which on ring closure followed by chlorination would yield the desired 4-chloro-2:3-pyrido quinoline.

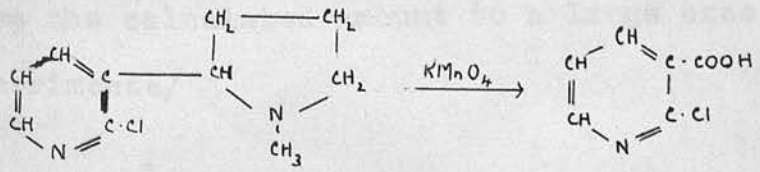
It was necessary first to prepare 2-chloro-nicotinic acid. This was done by the method of Karrer (Helv. Chem. Acta. 9, 458).



X. XI.



XII.



IX.

The hydriodic acid salt of nicotin iodo-methylate (X), was prepared. On oxidation with potassium ferricyanide in alkaline solution there was obtained N-methyl-nicotone (XI) which on heating with phosphorus pentachloride underwent demethylation followed by enolisation and replacement of the hydroxyl group by chlorine to give α-chloro-nicotin (XII). Oxidation of this compound to chloro-nicotinic acid (IX) was carried out using potassium permanganate as oxidising agent. This preparation involved a number of reactions, and as the yield at several of the stages was poor, the final yield of chloro-nicotinic acid was very low.

Attempts were made to increase the yield of chloro-nicotinic acid from α-chloro-nicotin by making variations in the experimental details of the oxydation. Many experiments were carried out in which the amounts of oxidising agent were varied, from the calculated amount to a large excess.

Experiments/

Experiments were also carried out at varying temperatures. Nitric acid used in place of potassium permanganate did not give good results. The best yield was obtained by following a modification of Tschitschibabin and Kirasanow's method (Ber. 57, 1168).

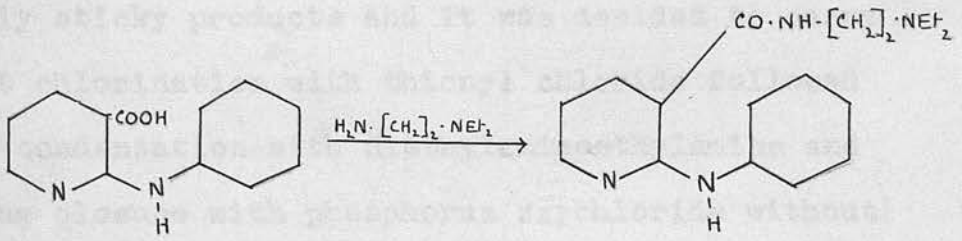
A very slight excess of the calculated amount of potassium permanganate solution was added, slowly, to the chloro-nicotin suspended in water. During the addition the flask was cooled in ice. After standing overnight the solution was gently warmed on the water bath for twenty minutes. The manganese dioxide was then filtered off and the filtrate evaporated down to small bulk. On acidifying the solution with hydrochloric acid the chloro-nicotinic acid separated and was recrystallised from hot water. In this way a 50-60% yield could be obtained.

When the chloronicotinic acid was obtained in sufficient quantity it was condensed with aniline by heating the two components together directly to 160-170° under reflux for one hour. A purple crystalline mass was obtained which, after removal of excess aniline by distillation with steam, was recrystallised from alcohol. Analysis showed it to be/

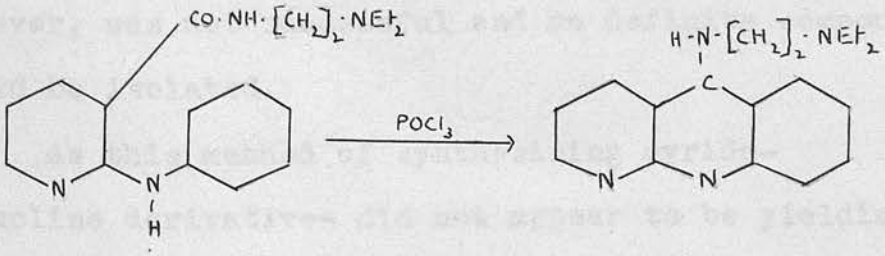
be the required 2-anilino-nicotinic acid m.p. 263°.

Attempts were then made to cyclise this compound, first by means of phosphorus oxychloride alone and then by a mixture of phosphorus oxychloride and pentachloride. It was hoped that cyclisation and chlorination might take place simultaneously (Magidson and Grigorowsky, Ber. 1933, 66, 866; Kermack and Goodall, J.C.S. 1936, II, 1163). Many experiments were carried out in which the time of heating and the quantities of phosphorus oxychloride and phosphorus pentachloride were varied, but in all cases the original material was recovered unchanged.

It was then decided to try to condense the acid with diethylamino-ethylamine first, and then to cyclise the resulting amide (XIII) (Kermack and Goodall, J.C.S. 1936, II, 1547), but it was found impossible to isolate a crystalline compound.



XIII



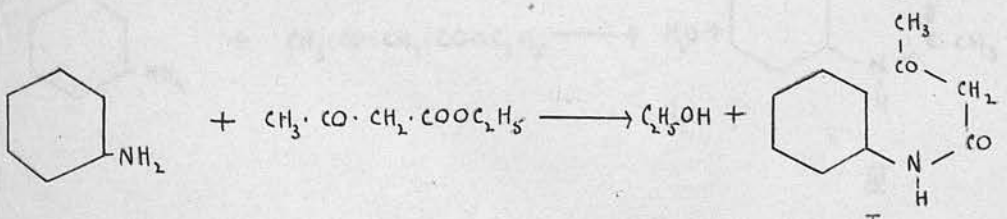
Further experiments were carried out using p-anisidine in place of aniline in order to observe if the presence of the methoxy group in the 6-position/

position would facilitate ring closure. Chloro-nicotinic acid condensed readily with p-anisidine to yield 2-p-anisidino-nicotinic acid, m.p. 295°. Chlorination with thionyl chloride followed by condensation with diethylaminoethylamine yielded only sticky products and it was decided to carry out chlorination with thionyl chloride followed by condensation with diethylaminoethylamine and ring closure with phosphorus oxychloride without attempting to isolate the intermediate compounds in the hope that the final ring-closed compound might crystallise in a pure form. This treatment, however, was not successful and no definite compound could be isolated.

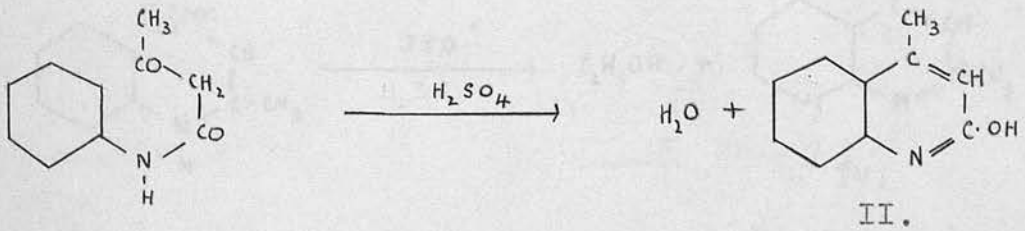
As this method of synthesising pyrido-quinoline derivatives did not appear to be yielding any satisfactory results, and as the starting material itself was difficult to obtain in quantity, attention was directed to the synthesis of phenanthroline derivatives, that is to say, compounds containing the heterocyclic ring system.(II)

IV. THE SYNTHESIS OF 5:6-PYRIDO-QUINOLINE (PHENANTHROLINE) DERIVATIVES, CONTAINING THE BASIC SIDE CHAIN IN POSITION 2.

Conrad and Limpach (Ber. 1931, 64, 970) have shown that aniline and ethylacetoacetate react together in two different ways according to the conditions employed. If the aniline is slowly added to the ester which has previously been heated to 160°, alcohol is split off and anilline acetoacetanilide (I), is formed. When this anilide is slowly added to concentrated sulphuric acid, ring closure takes place with elimination of water and the resulting product is 4-methyl-2-hydroxy quinoline (II).



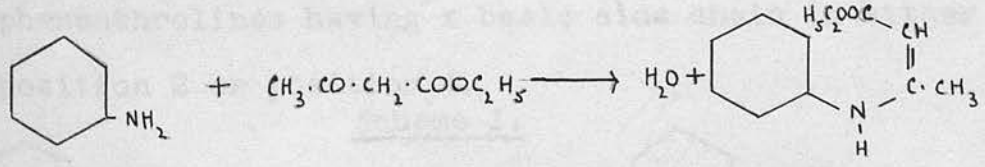
I.



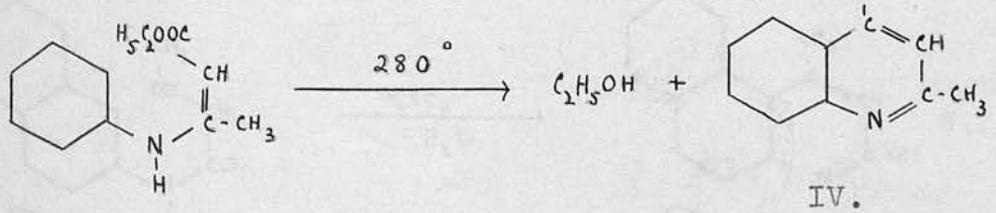
II.

If, however, the aniline and ester are merely mixed together and left for several days in an evacuated desiccator, water gradually separates and a crotonic acid ester (III) is formed.

Ring closure in this case is effected by dropping the ester into paraffin oil heated to 280°, when alcohol is split off and 2-methyl-4-hydroxy-quinoline (IV) separates from the oil on cooling.



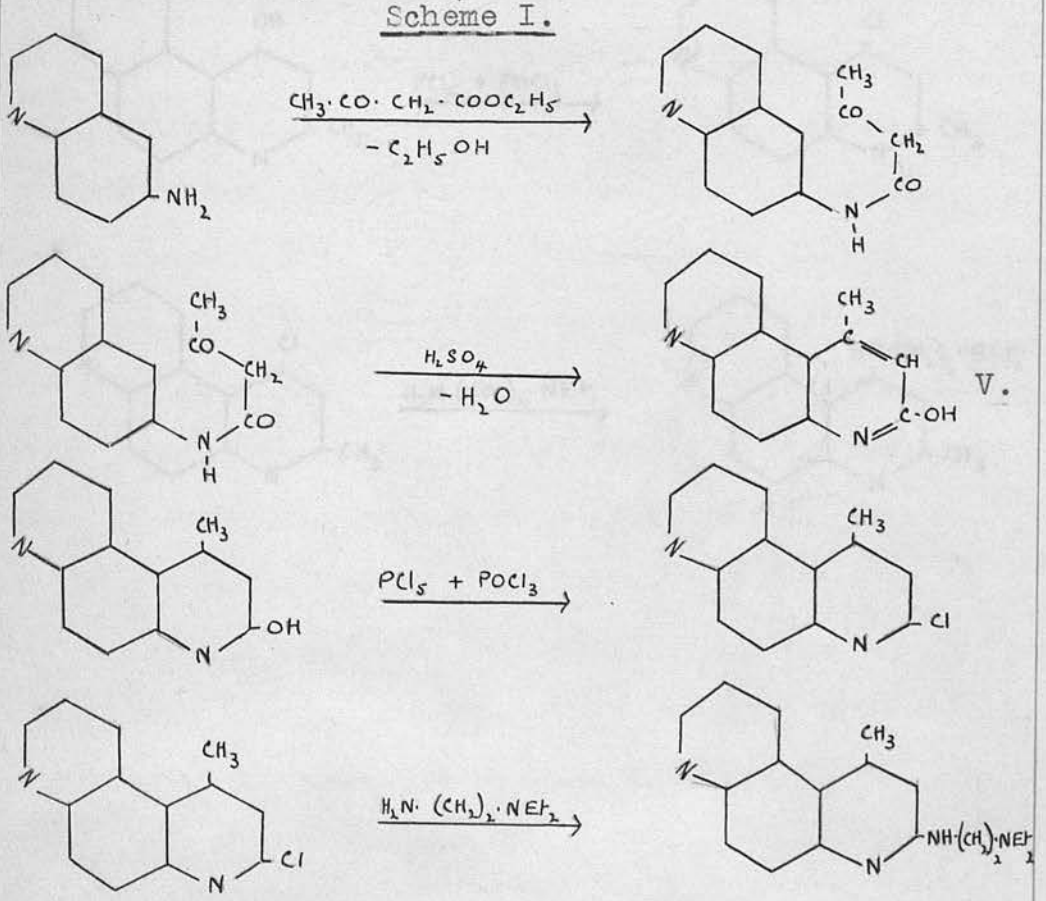
III



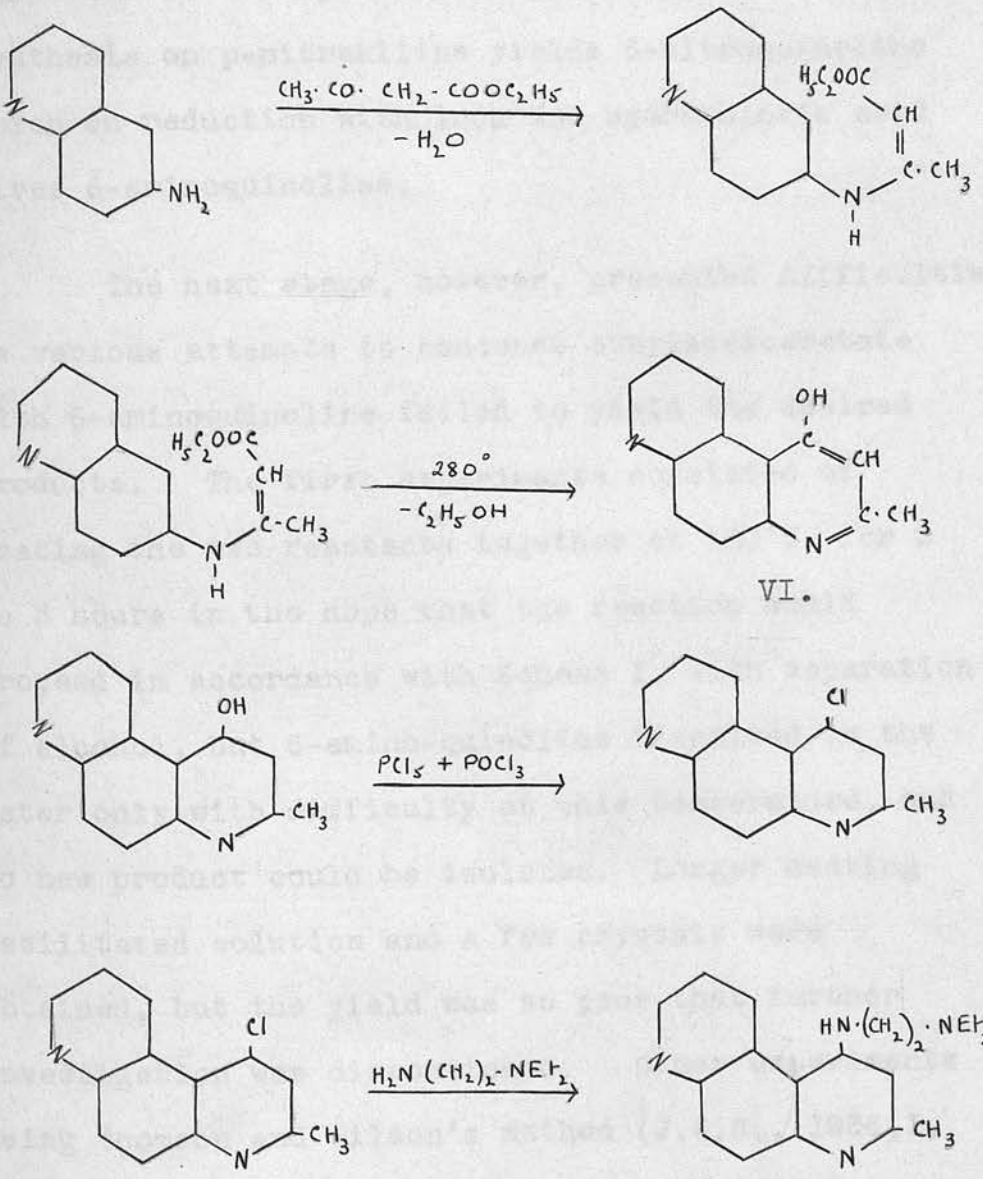
IV.

In the scheme of synthesis first suggested, it was proposed to replace aniline in the above synthesis by 6-aminoquinoline. If the reactions proceeded in a manner analogous to that shown above, the final products would be 2-hydroxy-4-methyl-5:6-pyrido-quinoline (V), and 2-methyl-4-hydroxy-5:6-pyrido-quinoline (VI). The hydroxyl groups in these compounds could then be replaced by chlorine and the chloro compounds, so obtained, condensed with long chain amines to give phenanthrolines having a basic side chain in either position 2 or position 4.

Scheme I.



Scheme II.


NH2
CH3·CO·CH2·COOC2H5
-H2O
H5C2OOC
CH
C·CH3
N
H
280°
-C2H5OH
OH
VI.
PCl5 + POCl3
Cl
CH3
HN·(CH2)2·NEt2

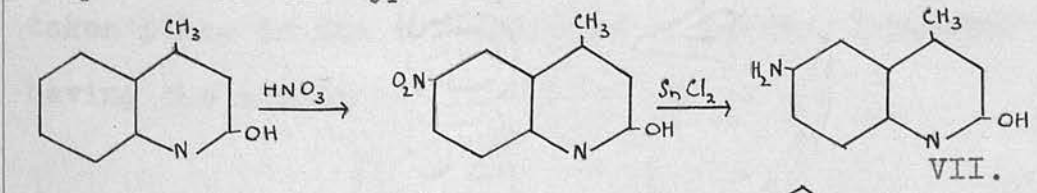
The conversion of p-nitraniline into 6-amino-quinoline is accomplished very easily. A Skraup synthesis on p-nitraniline yields 6-nitroquinoline which on reduction with iron and hydrochloric acid gives 6-amino-quinoline.

The next stage, however, presented difficulties as various attempts to condense ethylacetoacetate with 6-amino-quinoline failed to yield the desired products. The first experiments consisted of heating the two reactants together at 100°C. for 2 to 3 hours in the hope that the reaction would proceed in accordance with Scheme I, with separation of alcohol, but 6-amino-quinoline dissolved in the ester only with difficulty at this temperature, and no new product could be isolated. Longer heating facilitated solution and a few crystals were obtained, but the yield was so poor that further investigation was discontinued. Other experiments using Thomson and Wilson's method (J.C.S., 1936,I, 856) of employing iodine as a catalyst, did not yield any satisfactory result.

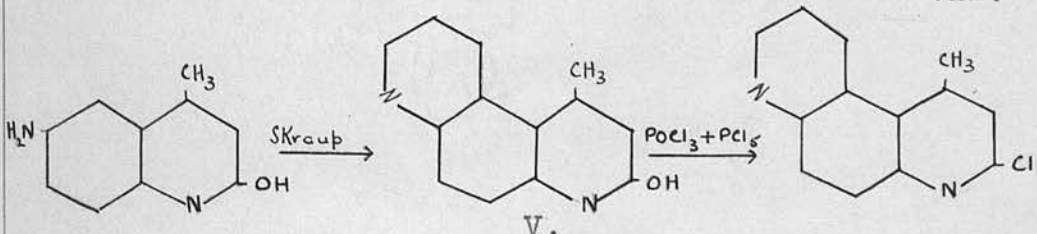
It was then decided to carry out the experiment at higher temperatures so that the reaction might possibly proceed as shown in Scheme II/

II. Accordingly the reactants were refluxed together in the oil bath for three hours. This experiment yielded a small quantity of brown crystals which melted at over 300°. The identity of this compound will be referred to later.

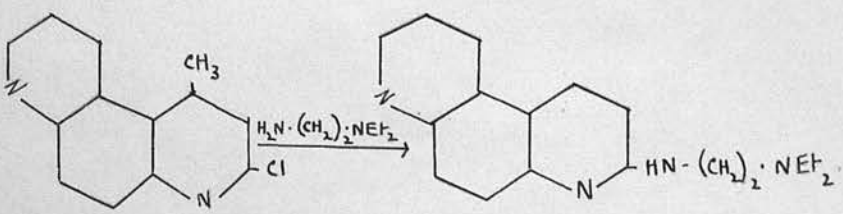
As these experiments were not satisfactory, the products being ill-defined and the yields poor, it was decided to try a new means of approach. 2-Hydroxy-4-methyl quinoline, prepared as described above, on nitration followed by reduction (Balaban, J.C.S., 1930, II, 2349) yields 6-amino-2-hydroxy-4-methyl quinoline (VII). A Skraup synthesis carried out on this compound should then yield the required phenanthroline or 2-hydroxy-4-methyl-5:6-pyrido quinoline (V.), which could then be chlorinated and condensed with various bases to give compounds of the type desired.



VII.

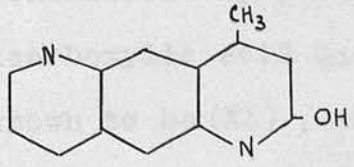


V.



This series of reactions proceeded smoothly and the product of the Skraup synthesis was a pale yellow solid which was shown by analysis to be 2-hydroxy-4-methyl-5:6-pyrido quinoline. It melted at 330° and gave no depression of the melting point with the compound obtained by refluxing 6-amino-quinoline and ethylacetoacetate together for three hours, thus proving that the two compounds were identical. It thus appears that the compound obtained by heating ethylacetoacetate and 6-amino-quinoline together directly is 2-hydroxy-4-methyl-5:6-pyrido-quinoline.

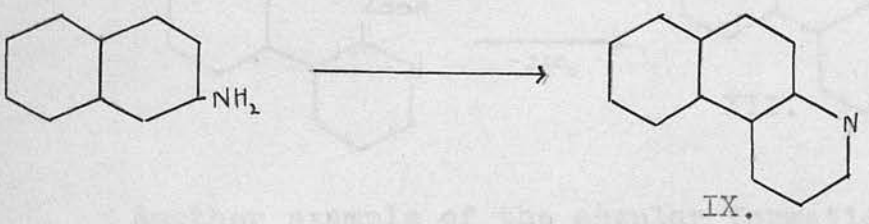
Up to this point it has been assumed that, in the Skraup reaction, ring addition has taken place so as to form the 5:6-pyrido-quinoline derivative, although the method of synthesis does not exclude the possibility of ring addition having taken place in the 6:7-position to yield a compound having the structure: (VIII)



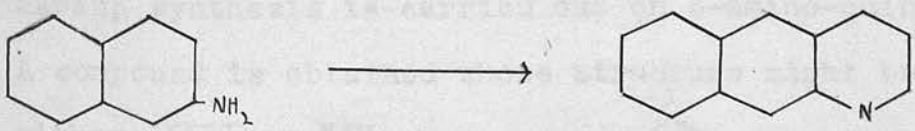
VIII.

This possibility was ruled out in view of the large amount of evidence which demonstrates the preferential formation of the angular rather than the linear type of compound during a Skraup synthesis. The following two examples illustrate this fact.

The benzo quinoline derived by the Skraup reaction from β-naphthylamine might have either of the two structures (IX) or (X):



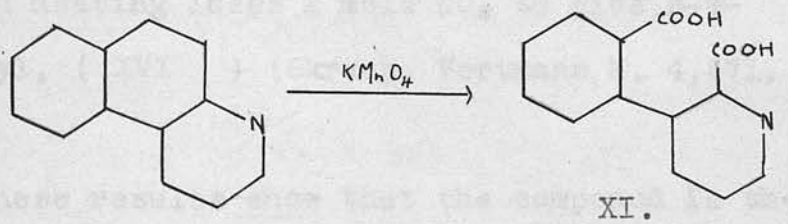
IX.



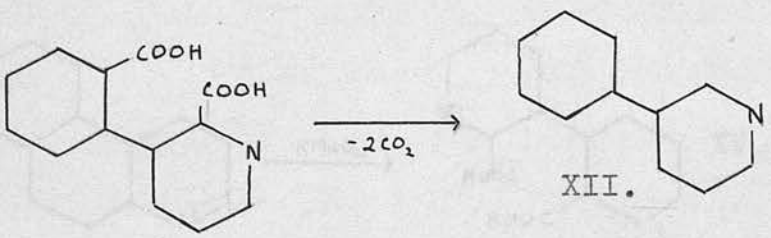
X.

The angular structure of the compound is shown by the fact that it is oxidisable by potassium permanganate to a dicarboxylic acid $C_{13}H_9O_4N$, whose structure is known to be (XI), and which on/

on heating loses 2 mols CO_2 to yield β-phenyl-pyridine (XII) (Skraup M.4. 456, 1883).

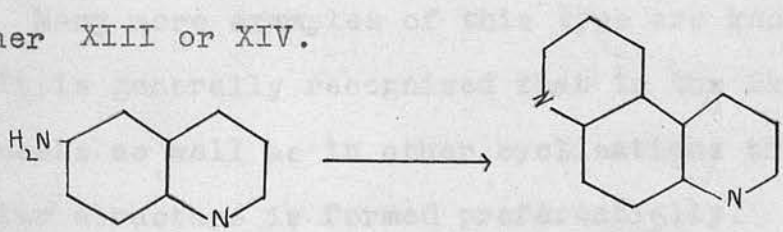


XI.

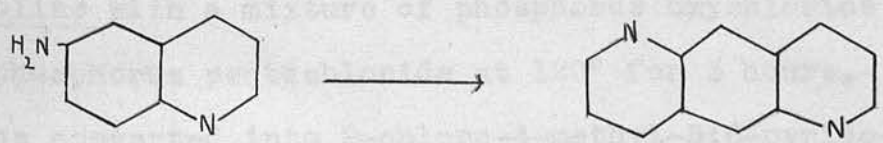


XII.

Another example of the angular formation is given by the reaction which takes place when the Skraup synthesis is carried out on 6-amino-quinoline. A compound is obtained whose structure might be either XIII or XIV.



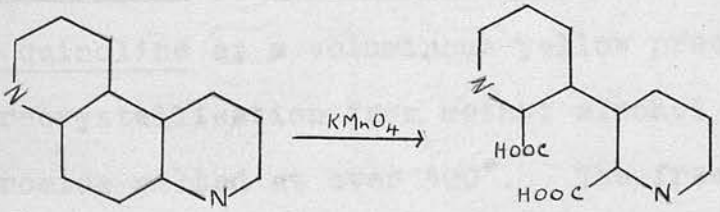
XIII.



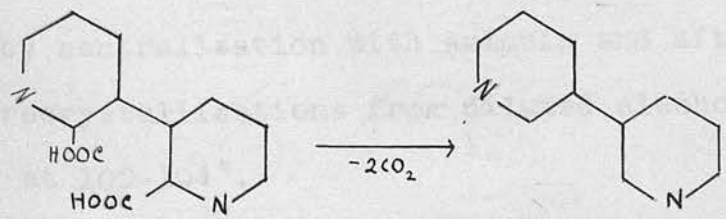
XIV.

The constitution is again proved by oxidation. On treatment with potassium permanganate it yields a dipyridyldicarboxylic acid, $C_{12}H_8N_2O_4$ (XV) which on heating loses 2 mols CO_2 to give β-β-dipyridyl, (XVI) (Skraup, Vortmann, M. 4,571, 1883).

These results show that the compound is the phenanthroline derivative and excludes the alternative structure.



XV.



XVI.

Many more examples of this type are known, and it is generally recognised that in the Skraup synthesis as well as in other cyclisations the angular structure is formed preferentially.

By refluxing 2-hydroxy-4-methyl-5:6-pyrido quinoline with a mixture of phosphorus oxychloride and phosphorus pentachloride at 120° for 5 hours, it was converted into 2-chloro-4-methyl-5:6-pyrido-quinoline which recrystallised from alcohol as white needles, m.p. 204°.

The/

The final stage in the synthesis was the condensation of 2-chloro-4-methyl-5:6-pyrido quinoline with various bases. As a preliminary experiment the first base to be used was piperidine. The condensation proceeded easily, and after two hours heating on the water bath, the liquid showed the presence of chlorine ions. Alcoholic hydrobromic acid added to the solution precipitated the hydrobromide of 2-piperidino-4-methyl-5:6-pyrido quinoline as a voluminous yellow precipitate. After recrystallisation from methyl alcohol the hydrobromide melted at over 400°. The free base was liberated from the hydrobromide as a white solid by neutralisation with ammonia and after three recrystallisations from diluted alcohol melted at 102-104°.

The condensation with diethylaminoethylamine when carried out in the same way yielded only unchanged products and more vigorous treatment had to be employed. When heating was continued up to 150° for two hours, the solution gave a marked reaction when tested for chlorine, showing that condensation had taken place. This base also

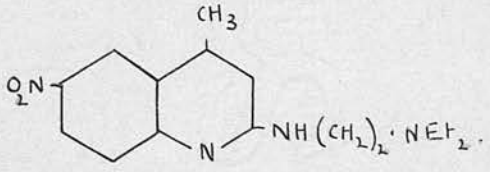
was isolated first as the hydrobromide, m.p. 225-229°. which liberated 2-(β-diethylaminoethylamino-)4-methyl-5:6-pyrido quinoline as a yellow oil on addition of ammonia. The oil solidified to a white solid which after recrystallisation three times from aqueous alcohol melted at 121-123°.

The condensation with diethylaminopropylamine required still more vigorous conditions and the presence of chlorine ions was not observed until heating had been continued for two hours at 160°. The hydrobromide of 2-diethylaminopropylamino-4-methyl-5:6-pyrido quinoline was recrystallised from ethyl alcohol and melted at 265-270°, but the base itself was obtained as an oil which did not solidify.

2-Chloro-4-methyl-5:6-pyrido quinoline also condensed readily with piperazine hexahydrate. The product was a yellow-brown solid which recrystallised from boiling water as pure white needles, m.p. 105-110° containing 2 mols of water of crystallisation. After driving off the water of crystallisation by heating the compound in vacuo at 100° it melted at 125°.

As 2-hydroxy-4-methyl-6-nitro quinoline could be easily prepared in quantity, it was thought of interest to prepare its chloro derivative, from which there could be obtained compounds having a basic side/

side chain in position 2 and a nitro group in position 6 (XVII). A comparison of these compounds could then be made with the 2-aklylamino-alkylamino 6-methoxy quinolines prepared by Magidson which were found to be inactive against malaria.



XVII.

Accordingly, the chlorination of 2-hydroxy-4-methyl-6-nitro quinoline was carried out as described by Balaban (J.C.S. 1930, II, 2350). Many experiments were performed but the yields in all cases were poor and sometimes a great deal of tarring took place. The 2-chloro-4-methyl-6-nitro quinoline gave, however, a very well defined condensation product when heated with piperidine at 110-120° in presence of a trace of copper bronze as catalyst. The dark brown solid which was/

was obtained, recrystallised from aqueous alcohol as brilliant golden leaflets, m.p. 168°.

With diethylaminoethylamine the condensation product was a dark brown oil which gave no hydrobromide and no metallic salt. The hydrochloride which was finally obtained melted at 165° and the picrate, which recrystallised from boiling water as flat plates, malted at 210°.

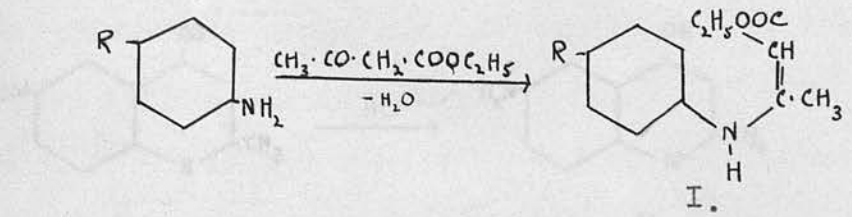
V. THE NITRATION OF 2-METHYL-4-HYDROXY-QUINOLINE

For the work to be described in the next section it was necessary to obtain 2-methyl-4-hydroxy-6-amino quinoline. It seemed likely that the simplest way of preparing this would be by nitration of 2-methyl-4-hydroxy quinoline followed by reduction. As described in Section III, 2-methyl-4-hydroxy quinoline is readily obtained from aniline and ethylaceto-acetate by condensing the two components to form the crotonic acid ester and cyclising the latter by dropping it into paraffin oil heated to 280°.

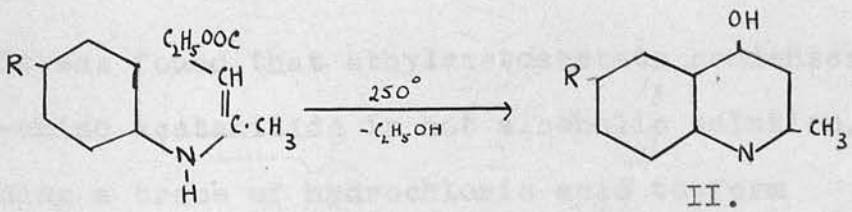
The nitration of 4-hydroxy-2-methyl quinoline, carried out in the same way as the nitration of the isomeric 4-methyl-2-hydroxy compound, (Balaban, J.C.S. 1930, II, 2349), yielded a mono-nitro derivative, m.p. over 400°, and it seemed probable that the nitro group had entered the 6-position in the quinoline nucleus. On reduction with stannous chloride the corresponding amino derivative was obtained, as colourless crystals which recrystallised from boiling water as shining rectangular plates, m.p. 345°. The alcoholic solution of this compound showed a strong blue-green fluorescence.

Attempts/

Attempts were made to establish the position of the amino group in this compound by converting it into the corresponding chloro- or bromo- derivatives by the Sandmeyer reaction, so as to be able to compare these with samples of 6-chloro and 6-bromo-2-methyl-4-hydroxy-quinoline (II), prepared by cyclising ethyl-β-p-chloro and bromo-phenyl-amino crotonates (I), formed from p-chloro- and p-bromo-aniline and ethylacetoacetate by Thomson and Wilson's modification of Conrad and Limpach's method (J.C.S. 1936, I, 856).



I.



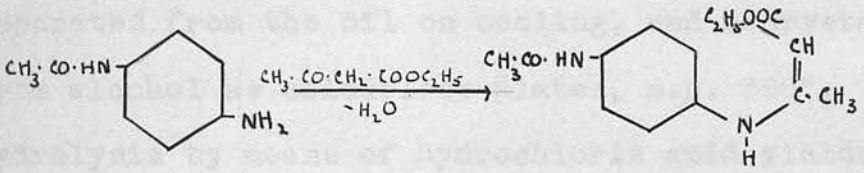
II.

R = Cl or Br.

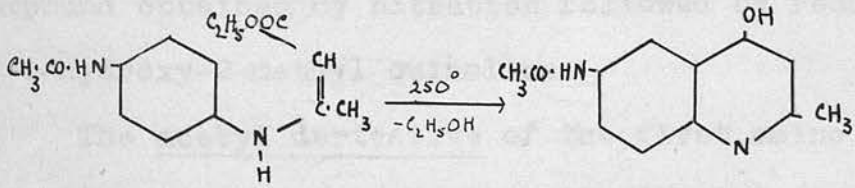
It was not found possible, however, to isolate the desired compounds in a crystalline condition from the products of the Sandmeyer reaction.

The identity of the amino-4-hydroxy-2-methyl quinoline as the 6-amino derivative was finally established/

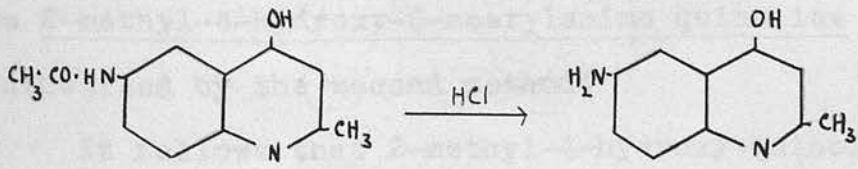
established by its synthesis by the following alternative method.



III.



IV.



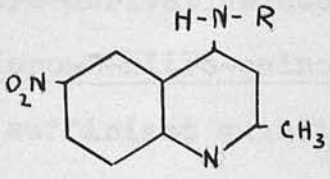
V.

It was found that ethylacetoacetate condenses with p-amino acetanilide in hot alcoholic solution, containing a trace of hydrochloric acid to form ethyl-β-p-acetylaminophenylamino crotonate (III). This compound separated from the alcoholic solution on addition of water, as a white crystalline solid which recrystallised from benzene as colourless needles, m.p. 180°. When added to paraffin oil heated/

heated to 250°, ring closure took place and 2-methyl-4-hydroxy-6-acetylamino quinoline (IV), separated from the oil on cooling, and recrystallised from alcohol as colourless plates, m.p. 368°. Hydrolysis by means of hydrochloric acid yielded 2-methyl-4-hydroxy-6-amino quinoline (V), which proved to be identical in all respects with the amino compound obtained by nitration followed by reduction of 4-hydroxy-2-methyl quinoline.

The acetyl derivative of the first amino quinoline, obtained by heating it with a large excess of acetic anhydride, also proved to be identical with the 2-methyl-4-hydroxy-6-acetylamino quinoline synthesised by the second method.

It follows that 2-methyl-4-hydroxy quinoline nitrates in the 6-position.



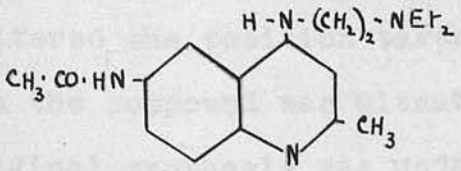
VI.

In order to obtain a series of compounds (VI) isomeric with the 2-alkylaminoalkylamino-4-methyl-6-nitro quinolines described in Section IV, the replacement of the hydroxyl group in 2-methyl-4-hydroxy-6-nitro quinoline by chlorine was undertaken, but in spite of many experiments in which the temperature and time of heating and also the quantities of the reagents were varied, the precise conditions promoting the formation of the 4-chloro derivative could not be definitely ascertained. Sometimes the reaction went smoothly and the solution acquired the deep purple colour which appeared to be an indication that the hydroxyl group had been replaced by chlorine. On basifying the solution with sodium hydroxide, the chloro compound separated as a white solid, which recrystallised from alcohol as colourless needles, m.p. 142°. But in other experiments only brown amorphous products were obtained and the chloro-derivative could not be isolated. 2-Methyl-4-chloro-6-nitro-quinoline was, however, obtained in sufficient quantity for its condensation with various bases to be carried out. When warmed with piperidine on the water bath, an orange-coloured solution was formed which showed the presence of chlorine/

chlorine ions after one hour. On cooling, crystals of the base, 2-methyl-4-piperidino-6-nitro quinoline (VI, $R = C_5H_{10}$) were deposited. It recrystallised from aqueous alcohol as golden leaflets, m.p. 145°.

Condensation with β-diethylaminoethylamine also took place readily, although heating had to be continued for three hours at 140°, before the solution showed the presence of chlorine ions. On cooling, 2-methyl-4-β-diethylaminoethylamino-6-nitro-quinoline (VI, $R = [CH_2]_2 \cdot NEt_2$) separated as a bright yellow solid which recrystallised from aqueous alcohol with 2 mols. of water of crystallisation. m.p. 99-102°.

As 2-methyl-4-hydroxy-6-acetylamino-quinoline (IV), could also be readily obtained from p-amino-acetanilide and ethylacetoacetate, it was decided to attempt to replace its hydroxyl group by chlorine so that derivatives containing a basic side chain in position 4 and an acetylamino group in position 6 might be obtained. (VI)



VII.

Replacement of the hydroxyl group was carried out using a mixture of phosphorus oxychloride and pentachloride. The reaction proceeded smoothly and 2-methyl-4-chloro-6-acetylamino-quinoline was obtained in good yield as a white solid which recrystallised from benzene and melted at 210°.

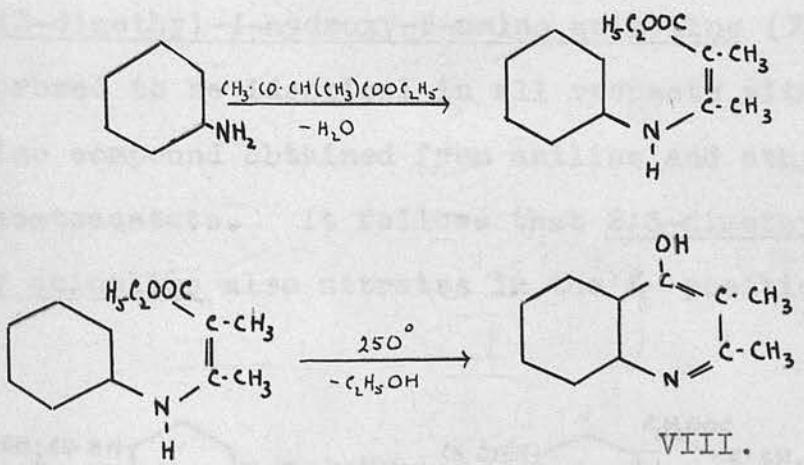
The series of compounds was completed by condensing 2-methyl-4-chloro-6-acetylamino-quinoline with piperidine and with diethylaminoethylamine. In both cases condensation took place without difficulty. 2-Methyl-4-piperidino-6-acetylamino-quinoline was isolated as a white solid, m.p. 87°, which recrystallised from aqueous alcohol with 1 mol. of water of crystallisation, while 2-methyl-4-β-diethylaminoethylamino-6-acetylamino-quinoline was isolated as its hydrochloride, which recrystallised from a mixture of alcohol and acetone as ball-shaped clusters of needles, m.p. 272°.

In order to discover if the presence of two methyl groups in positions 2 and 3 in the quinoline nucleus altered the position taken up by the nitro group when the compound was nitrated, an extension of the original synthesis was undertaken using ethylmethylacetoacetate in place of ethylacetoacetate.

2:3/

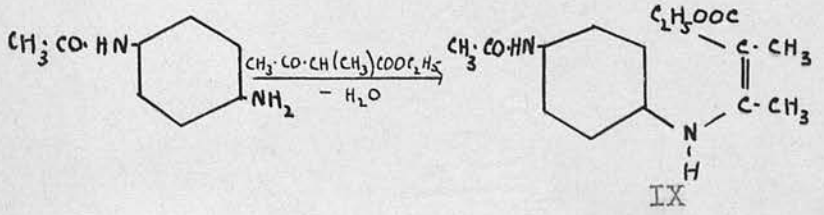
(VIII)

2:3-dimethyl-4-hydroxy-quinoline was prepared in a manner analogous to that described above, from aniline and ethylmethylacetoacetate. It formed a white crystalline solid which after recrystallisation from boiling alcohol melted at 330°. On nitration it yielded a mono-nitro derivative which recrystallised from nitro-benzene as small, greenish-yellow needles, m.p. 380°, and which on reduction gave a very pure crystalline amino derivative. It recrystallised from boiling water, as did the amino derivative of 4-hydroxy-2-methyl-quinoline and melted at 326°.

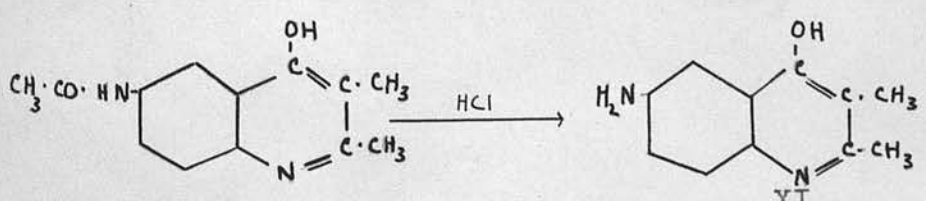


VIII.

The synthesis of 2:3-dimethyl-4-hydroxy-6-amino-quinoline was carried out in the same way as that of 2-methyl-4-hydroxy-6-amino-quinoline. Ethyl-methyl-acetoacetate and p-amino-acetanilide heated together in alcoholic solution yielded ethyl-α-methyl-β-p-acetylamino-phenylamino-crotonate (IX), which recrystallised from aqueous alcohol as small colourless plates, m.p. 169°. On ring-closure, this compound yielded 2:3-dimethyl-4-hydroxy-6-acetylamino-quinoline (X), m.p. 385°, the properties of which were very similar to those of 2-methyl-4-hydroxy-6-acetylamino quinoline. Hydrolysis in the usual way with hydrochloric acid gave 2:3-dimethyl-4-hydroxy-6-amino quinoline (XI) which proved to be identical in all respects with the amino compound obtained from aniline and ethyl-methylacetoacetate. It follows that 2:3-dimethyl-4-hydroxy quinoline also nitrates in the 6- position.



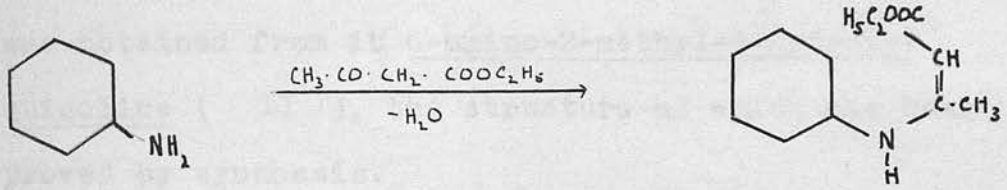
IX

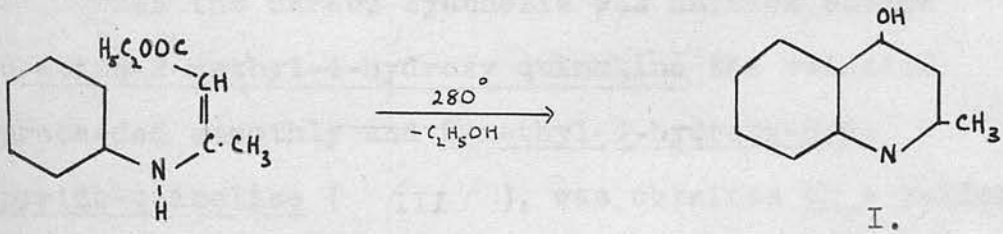


X. XI.

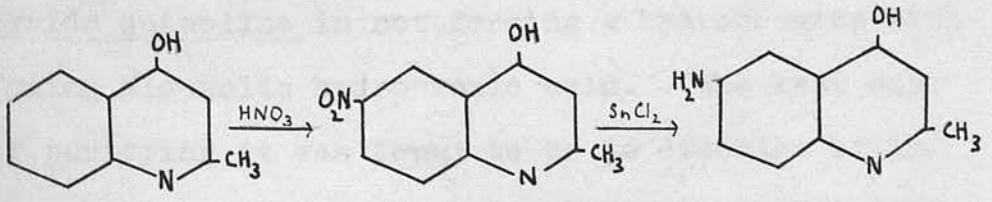
VI. SYNTHESIS OF PYRIDO-QUINOLINE DERIVATIVES CONTAINING THE SIDE-CHAIN IN POSITION 4.

The object of the synthesis to be described in this Section was to prepare a series of compounds isomeric with those of Section IV but having the positions of the CH_3 and OH groups interchanged. The series of reactions involved in this synthesis is shown below.

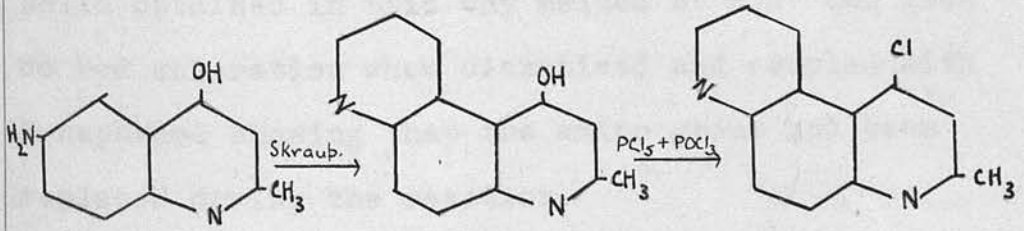




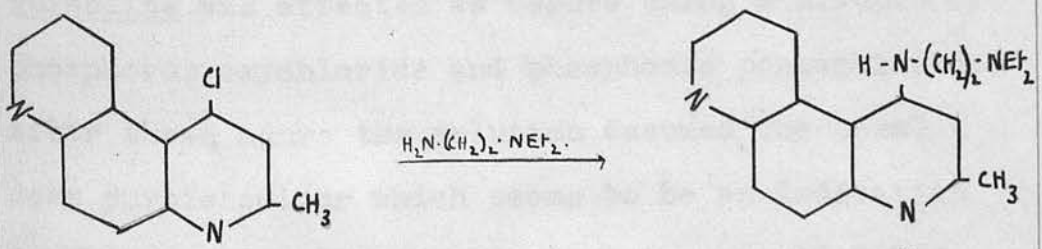
I.



II.



III. IV.



V.

It has been shown in previous sections how 2-methyl-4-hydroxy-quinoline (I) was prepared and how on nitration followed by reduction there was obtained from it 6-amino-2-methyl-4-hydroxy-quinoline (II), the structure of which has been proved by synthesis.

When the Skraup synthesis was carried out on 6-amino-2-methyl-4-hydroxy quinoline the reaction proceeded smoothly and 2-methyl-4-hydroxy-5:6-pyrido-quinoline (III), was obtained as a yellow solid. It differed from 2-hydroxy-4-methyl-5:6-pyrido quinoline in not forming a hydrobromide with fuming alcoholic hydrobromic acid. The best way of purifying it was found to be to dissolve it in hot alcohol, filter the hot solution and then add water until precipitation began. The pale yellow solid obtained in this way melted at 358° and gave no red coloration when diazotised and coupled with β-naphthol showing that the amino group had been replaced during the reaction.

The conversion to 2-methyl-4-chloro-5:6-pyrido-quinoline was effected as before using a mixture of phosphorus oxychloride and phosphorus pentachloride. After three hours the solution assumed the usual deep purple colour which seems to be an indication in this series of compounds that the reaction has

proceeded/

proceeded satisfactorily. 2-Methyl-4-chloro-5:6-pyrido-quinoline (IV) separated as a pink flocculent precipitate when the solution was basified with sodium carbonate solution. After recrystallisation from aqueous alcohol it melted at 149°.

2-Methyl-4-chloro-5:6-pyrido-quinoline when warmed on the water bath under reflux with piperidine formed a dark brown solution which gradually solidified to a crystalline mass of the base 2-methyl-4-piperidino-5:6-pyrido-quinoline which, after recrystallisation several times from aqueous alcohol, melted at 163°.

This base did not form a salt with salicylic acid, tartaric acid, or hydrobromic acid, but on addition of picric acid a greenish picrate separated which was recrystallised from boiling water. It melted at 225°, and analysis showed that it was a mono-picrate of the composition $C_{18}H_{20}N_3.C_6H_2(NO_2)_3OH$.

Condensation of 2-methyl-4-chloro-5:6-pyrido-quinoline with β-diethylaminoethylamine took place after heating had been continued for three hours at 140°. The base, 2-methyl-4-(β-diethylaminoethyl-amino)-5:6-pyrido-quinoline(V) , which separated on addition of sodium hydroxide as an oil gradually/

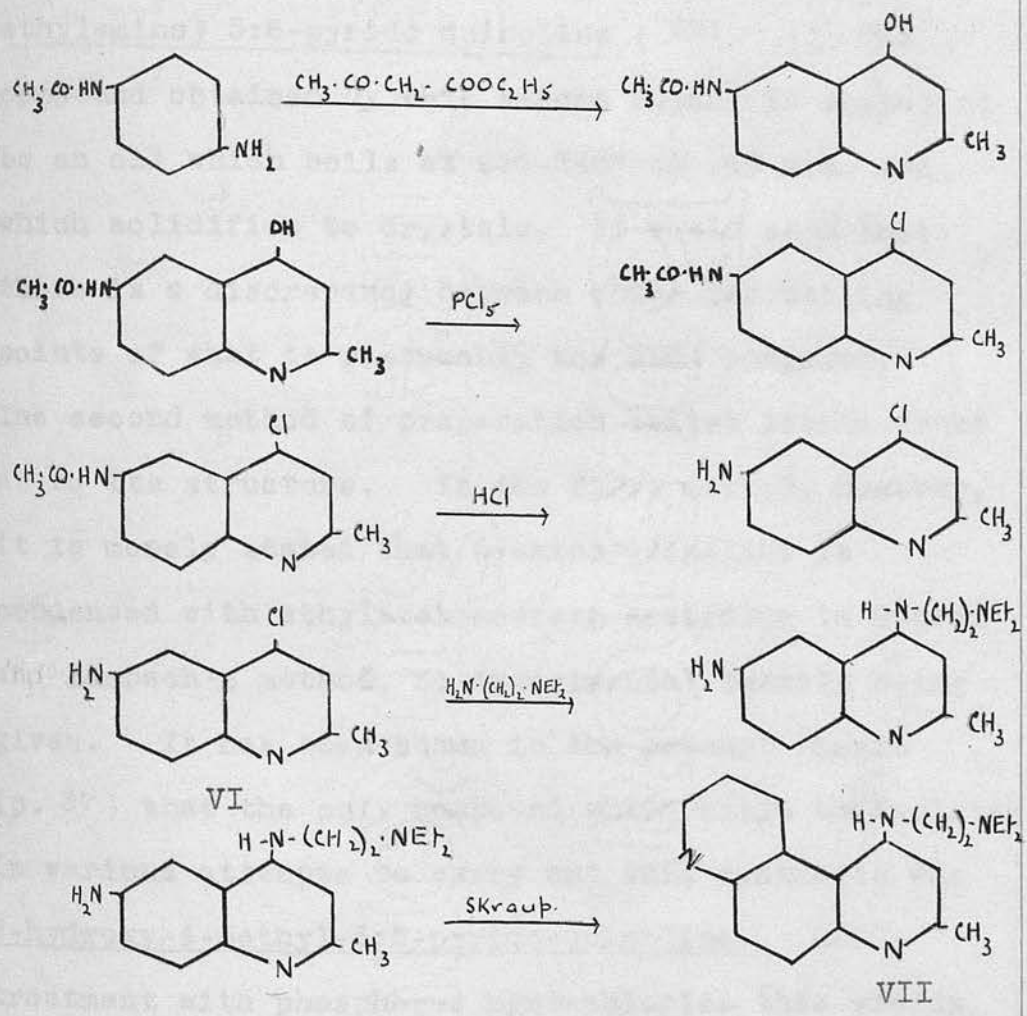
gradually solidified and recrystallised from petroleum ether as long rectangular plates, m.p. 68°.

While this work was in progress an I.G. Patent (B.P.481/874/1936) was published which reported the discovery that pyrido-amino quinoline derivatives having a basic radicle in the amino group were distinguished by their action against blood parasites, in particular, malaria parasites. The basic radicle in such compounds was of the aminoalkyl or alkylaminoalkyl type.

In this patent, the preparation of 2-methyl-4-chloro-5:6-pyrido-quinoline is described from 6-amino-quinoline and ethylacetoacetate according to Conrad and Limpach's method followed by replacement of the hydroxyl group by chlorine. The melting point of this chloro compound is given as 195°. By condensing it with diethylaminoethylamine it is reported that 2-methyl-4-(β-diethylaminoethylamino) 5:6-pyrido quinoline is obtained as a viscous oil boiling at 210-215° C. at 1 m.m.

The patent also describes a second method of preparation of the same compound 2-methyl-4-(β-diethyl/

diethylaminoethylamino) 5:6-pyrido quinoline.



VI

VII

In this case it is made from p-amino-acetanilide and ethylacetoacetate according to Conrad and Limpach's method followed by replacement of the hydroxyl group by chlorine, saponification of the acetylamino group and reaction of the 4-chloro-6-amino-2-methyl quinoline (VI)thus formed with 1-diethylamino-2-amino-ethane. A Skraup synthesis carried out on this/

this compound yields 2-methyl-4-(β-diethylamino-ethylamino) 5:6-pyrido quinoline (VII). The compound obtained by this second method is stated to be an oil which boils at 235-240° at .45 m.m. and which solidifies to crystals. It would seem that there is a discrepancy between these two boiling points of what is presumably the same compound. The second method of preparation leaves little doubt as to its structure. In the first method, however, it is merely stated that 6-amino-quinoline is condensed with ethylacetoacetate according to Conrad and Limpach's method, no experimental details being given. It has been shown in the present thesis (p. 37) that the only compound which could be isolated in various attempts to carry out this synthesis was 2-hydroxy-4-methyl-5:6-pyrido-quinoline. On treatment with phosphorus pentachloride this yields 2-chloro-4-methyl-5:6-pyrido-quinoline, m.p. 204°, and it is possible that the compound, m.p. 195°, mentioned in the patent, is really 2-chloro-4-methyl-5:6-pyrido quinoline in somewhat impure condition. (It will be recalled that 2-methyl-4-chloro-5:6-pyrido-quinoline prepared according to the method described on p. 58 melted at 149°). In this case the/

the base synthesised by the first method would be 2-(β-diethylaminoethylamino) 4-methyl-5:6-pyrido-quinoline, presumably identical with the compound described on p. 42 , and not the isomeric 4-(β-diethyl-aminoethylamino) 2-methyl-5:6-pyrido quinoline.

This suggestion accounts for the apparent inconsistency of the two recorded boiling points, and also for the discrepancy between the melting points of the 2-methyl-4-chloro-5:6-pyrido quinoline recorded in this thesis and that given in the patent for the same compound.

EXPERIMENTAL.

β-diethylaminoethylamine hydrochloride.

(Gough and King. J.C.S. 1928. 2436.)

β-diethylaminoethanol (59 gm.) dissolved in chloroform (100 c.c.) was added slowly, with stirring to a mixture of thionyl chloride (120 gm.) and chloroform (500 c.c.) cooled to -5°. The temperature during the addition should not exceed 0°. After standing for 1 hour at room temperature, most of the chloroform was removed on the water bath, and the last traces of thionyl chloride eliminated by twice evaporating the residue under reduced pressure with alcohol (100 c.c.). The remaining white crystalline solid was dissolved in a minimum of hot alcohol (about 50 c.c.). On cooling β-diethylaminoethyl chloride hydrochloride separated as colourless needles which were filtered off and dried. A further quantity was obtained by diluting the mother liquor with ether. The combined yields usually amount to about 60 gm. m.p. 209-210°.

β-diethylaminoethylamine.

(Ristenpart. Ber. 1896. 29, 2526)

β-diethylaminoethylchloride hydrochloride (8 gm.) was slowly added, with shaking, to a mixture of ammonia (25 c.c. of S.G. .880) and alcohol (25 c.c.), and the mixture/

mixture gently heated under reflux for 2 hours. The alcohol was distilled off on the water bath, the residue made strongly alkaline with sodium hydroxide and the β-diethylaminoethylamine separated by several extractions with ether. The ether extract was dried over anhydrous potassium carbonate, filtered, and the ether distilled off. The residue was distilled and the fraction distilling at 145-155° was retained. Yield 1.5 gm.

β-Diethylaminoethylamine.

(Ing and Manske. J.C.S. 1926. 2348)

β-diethylaminoethylchloride hydrochloride (20.6 gm.) was made alkaline with sodium hydroxide solution and the resulting oil extracted with ether and dried over potassium carbonate. The dry ethereal extract was placed in a 250 c.c. flask and the ether removed. Potassium phthalimide (18.5 gm.) was added, the flask fitted with an air condenser and placed in an oil bath at 120°. A reaction took place almost immediately. When this had diminished, the oil bath was heated to 130° and left for 1 hour. The product was cooled, taken up with alcohol and filtered, the residual potassium chloride being well washed with alcohol. The filtrate, consisting of diethylaminopthalimide in about 40 c.c. alcohol, was refluxed/

refluxed on the water bath, and 12 gm. hydrazine hydrate added. A slight precipitate formed and after about ten minutes the solution was made strongly acid with 17 c.c. concentrated hydrochloric acid. The thick paste formed was diluted with alcohol till quite mobile and heating continued for 15 minutes. The phthalyl hydrazide was filtered off and washed with alcohol. After concentrating the filtrate and cooling, more phthalyl hydrazide was filtered off and washed with a little water. The filtrate was made strongly alkaline and extracted four times with ether. The ether extract was dried over potassium carbonate, the ether distilled off and the residue fractionated. The fraction boiling at 145-147° consisted of pure β-diethylamino-ethylamine. Yield 2.7 gm.

γ-Diethylamino-n-propyl chloride.

γ-diethylamino-n-propanol (23.4 gm.) dissolved in chloroform (35 c.c.) was added slowly with stirring to a mixture of thionyl chloride (47.2 gm.) and chloroform (165 c,c.), cooled to -5°, the temperature during addition never exceeding 0°. The product was worked up in the same manner as described for β-diethylaminoethylchloride hydrochloride. As γ-diethyl/

diethylamino-n-propyl chloride hydrochloride could not be obtained crystalline from alcohol, even after allowing the solution to stand for several days, the alcohol was removed in vacuo, and the residue dissolved in water. The solution was made strongly alkaline and extracted three times with ether. The extract was dried over potassium carbonate, filtered, the ether removed, and the γ-diethylamino-n-propyl chloride remained as a yellow oil. Yield 11 gm.

γ-Diethylamino-n-propylamine.

Method I.

γ-Diethylamino-n-propyl chloride (11 gm.) and potassium phthalimide (13.4 gm.) were well mixed in a flask which was fitted with an air condenser, and placed in an oil bath at 175° for one and a half hours. The product was worked up in the same manner as described for the preparation of β-diethylaminoethylamine (Method II). On distillation the fraction boiling at 170-180° was retained. Yield 2.1 gm.

Method II.

For the preparation of γ-bromopropylphthalimide, phthalimide (15 gm.), anhydrous potassium carbonate (7.5 gm.) and α: γ-dibromopropane (50 gm.) were mixed and heated under reflux in an oil bath at 150° for five hours. After cooling, the unchanged α-γ dibromo/

dibromopropane was distilled off in a rapid current of steam. The grey residue was crystallised from alcohol (20 c.c.) and to remove any α: γ-diphthalyl propane, the crystalline product was extracted in a Soxhlet apparatus with ether for 6 hours. Only the γ-bromopropylphthalimide dissolved, and, after cooling, it was filtered off from the ether in the form of light green plates. Yield 15.1 gm. m.p.72°.

γ-Bromopropylphthalimide (15.1 gm.), dissolved in diethylamine (22 gm.) was gently refluxed on the water bath for three hours. The diethylamine hydrobromide formed was filtered off, and the excess of diethylamine distilled off under reduced pressure. The last traces of diethylamine were removed by keeping the residue in vacuo at 30° for two hours. The residual oil was dissolved in alcohol (15 c,c.) and hydrazine hydrate (7.5 c.c. 50% alcoholic solution) added. The solution was gently refluxed on the water bath for half an hour, and made strongly acid with 15 c.c. concentrated hydrochloric acid, when a white precipitate of phthalyl hydrazide was formed. The suspension was warmed for fifteen minutes, the phthalyl hydrazide filtered off and washed with alcohol. The combined filtrate and washings were concentrated to about 15 c.c.,cooled, filtered/

filtered, and the residue washed with a little water. The filtrate was made strongly alkaline with 45% caustic soda, and extracted four times with ether. The ethereal extract was dried over potassium carbonate, the ether removed, and the residue fractionated, the fraction boiling at 170-180° being retained. Yield 1.3 gm.

In the hope of obtaining a further quantity of the desired amine, the aqueous layer left from the last ether extraction was extracted three times with ethyl acetate, which, after drying and fractionating, gave a further 0.3 gm. During the collection of this fraction, the temperature rose to 140°, but on account of the small quantity it is probable that the real boiling point was somewhat higher.

β-diethylamino-n-propylamine.

(Magidson. Ber. 1936. 69, 402)

To γ-bromopropylphthalimide (55 gm.) 150 c.c. xylol were added and 20 c.c. distilled off. Diethylamine (50 c.c.) was added, and the whole gently refluxed under water condenser in an oil bath for ten hours. After cooling and filtering off the diethylamine hydrobromide, which was washed with a little xylol, the filtrate and washings were evaporated/

evaporated in vacuo. The residue was transferred to a round bottomed flask, the last traces being washed in with part of the 90 c.c. fuming hydrochloric acid which were now added. Gentle refluxing under a water condenser was carried out for eight hours. After cooling, the phthalic acid was filtered off and well washed with water. The collected filtrate and washings were evaporated in vacuo to about 20 c.c. and strongly basified by addition of about 25 c.c. of 45% caustic soda. The amine was extracted four times with benzene, dried over potassium hydroxide and distilled. The fraction boiling at 162-167° was retained.

Pyridine-methosulphate.

Dimethyl sulphate (9.8 c.c.) was slowly added, with stirring, to pyridine (7.8 c.c.). The reaction was completed by heating the flask for about fifteen minutes on the water bath. The pyridine methosulphate formed a pale yellow oil, which was used directly for the preparation of N-methyl-pyridone.

N-methyl-α-pyridone.

(cf. Fargher and Furness. J.C.S. 1915. 107,690)

A solution of potassium ferricyanide (65.6 gm.) in water (150 c.c.) was placed in a round-bottomed flask/

flask and benzene (100 c.c.) added. The flask, which was cooled in ice, was fitted with a two-holed rubber stopper carrying two dropping funnels from which were added separately potassium hydroxide (20 gm.) in water (20 c.c.) and pyridine methosulphate (20.5 gm.) diluted to 20 c.c. with water. The mixture was mechanically stirred while the potassium hydroxide and pyridine methosulphate were added, and for about half an hour after the addition was complete. As the pyridone was formed during the addition it was extracted by the benzene present in the solution. The potassium ferrocyanide which crystallised out was filtered off and washed several times with benzene. The filtrate was saturated with potassium hydroxide and extracted repeatedly with warm benzene. The benzene extract was dried over sodium sulphate and distilled, when N-methyl-α-pyridone was obtained as a yellow oil, b.p. 240-250°.

2-Chloro-Pyridine.

(loc. cit.)

N-methyl-α-pyridone (26 gm.) was heated with a mixture of phosphorus oxychloride (40 gm.) and phosphorus pentachloride (60 gm.) for 9 hours at 150-160° in a flask fitted with an air condenser. The/

The excess phosphorus oxychloride was distilled off under diminished pressure and the residue was carefully decomposed with water, made strongly alkaline with sodium hydroxide and steam-distilled. 2-Chloropyridine was extracted from the distillate with ether, dried over potassium hydroxide and distilled. b.p. 170°. Yield almost theoretical.

Condensation of 2-Chloro-pyridine and Anthranilic Acid.

(Bose and Sen. J.C.S. 1931, II, 2843).

Equimolecular quantities of the components were heated together over a small flame till a vigorous reaction set in and the mass swelled up. The horny product was heated on a water bath with water and then treated with ammonia. From the crystalline solid obtained, 2-anilino-pyridine (m.p. 108°) was removed by distillation in steam. The residue recrystallised from alcohol as yellow prisms, m.p. 210°. The compound was soluble in sodium hydroxide and acetone and in dilute mineral acids with a violet-blue fluorescence.

As explained in the theoretical section, this compound was identical with that obtained by Seide (Annalen. 1924, 440, 311-321) by condensing o-chloro-benzoic acid with α-amino-pyridine. It follows/

follows, therefore, that it is 2.3-dihydro-benzquinazolone-4.

Nicotin Dihydrodide.

(Pictet and Genequand. Ber. 1897, 30, 2120).

Nicotin (26.6 gm.) in water (50 c.c.) and hydriodic acid (50 c.c. sp.g. 1.7) were evaporated almost to dryness on the water bath. The dark yellow crystalline residue was filtered off and well pressed. The product recrystallised from alcohol as very pale yellow crystals, m.p. 195°.

The hydriodide of nicotin-methiodide.

(loc. cit.)

Nicotin dihydriode, 1 mol (25 gm.) was dissolved in boiling alcohol and nicotin, 1 mol. (9.75 gm.) added. To the alcoholic solution of the monohydriodide thus formed, methyl iodide (16.8 gm.) was added and the solution boiled for two hours under reflux. On cooling, the product solidified to a crystalline mass, which was drained on a filter. It recrystallised from alcohol as small colourless or pale yellow plates, m.p. 209°. Yield 84%.

N-Methyl-nicotone.

(Karrer. Helv. Chem. Acta. 8, 367)

100 Gm. of the hydriodic acid salt of nicotin/

nicotin-methiodide were dissolved in water (250 c.c.) The solution was cooled in ice and to it was added slowly, with stirring, a solution of potassium ferricyanide (150 gm.) in water (500 c.c.). The liquid was then saturated with solid potassium carbonate and extracted four or five times with benzene. The combined benzene extracts on evaporation left behind a thick brown oil which was purified by vacuum distillation. At 8 mm. the N-methyl-nicotone distilled over at 143-145°. After cooling and scratching, the distillate crystallised almost completely. It was then recrystallised from low-boiling petroleum ether from which it separated as long white needles, m.p. 80°.

α-Chloro-nicotin.

(Karrer. Helv. Chem. Acta. 9, 458)

N-methyl-nicotone (3 gm.) was heated under reflux condenser to 150° in an oil-bath for 4-5 hours with phosphorus pentachloride (3.5 gm.). After cooling, the solid mass was dissolved in hot alcohol, basified with potassium hydroxide and extracted with ether. The ether extract was dried over sodium sulphate and distilled. The α-chloro-nicotin was obtained as a colourless oil, b.p. 108-112° at 0.5 mm. Yield 1 gm.

α-Chloro-nicotinic acid.

(Tschitschibabin and Kirssanow. Ber. 57, 1168)

To α-chloro-nicotin (2.1 gm.) suspended in water (50 c.c.) 500 c.c. of a 4% solution of potassium permanganate were added in small amounts, the solution being cooled in ice. After addition was complete the solution was left to stand overnight. It was then warmed on the water bath for 20 minutes and decolourised by adding alcohol. The precipitate of manganese dioxide was filtered off and thoroughly washed with boiling water. The filtrate and washings were then neutralised with sulphuric acid and evaporated down to small volume. After cooling, the small amount of potassium sulphate which crystallised out, was filtered off and the filtrate acidified with hydrochloric acid. The α-chloro-nicotinic acid which separated was filtered off and well washed with cold water. After one recrystallisation from boiling water, it was free from inorganic chlorides and melted at 192°. The melting point was not raised by further recrystallisations. Yield 0.8 gm.

2-/

2-Anilino-nicotinic acid.

Chloro-nicotinic acid (0.1 gm.) and aniline (0.5 c.c.) were heated together under reflux in the oil bath for 1 hour at 160-170°. On cooling the product solidified to a purple crystalline mass which was boiled up several times with water to remove excess aniline. The purple solid was then filtered off and dried. After one re-crystallisation from alcohol it melted at 263-265°. (Found: N, 13.01. $C_{12}H_{10}O_2N_2$ requires N, 13.08%).

The acid is soluble in dilute sodium hydroxide, sodium carbonate and ammonia. It also dissolved in dilute mineral acids.

Attempts to cyclise 2-anilino-nicotinic acid.

1. 2-Anilino-nicotinic acid (0.5 gm.) was heated with concentrated sulphuric acid (2 c.c.) on the water bath for one hour. The solution was then poured into water and neutralised with sodium hydroxide. The grey precipitate was filtered off and washed with water. It gave no depression of the melting point when mixed with 2-anilino-nicotinic acid, showing that the two compounds were identical.

2. /

2. 2-Anilino-nicotinic acid (0.5 gm.) and phosphorus oxychloride (0.5 c.c.) were refluxed together in an oil-bath for 30 minutes, the temperature being kept at 110-120°. After cooling, the solution was poured into water and carefully neutralised with ammonia. The precipitate which was obtained was filtered off and washed with water. It melted at 250-260° and its identity with 2-anilino-nicotinic acid was proved by the fact that it gave no depression of the melting point when mixed with it.

3. 2-Anilino-nicotinic acid (0.2 gm.), phosphorus oxychloride (1 c.c.) and phosphorus pentachloride (0.1 gm.) were refluxed together at 120° for 7 hours. After cooling the excess phosphorus oxychloride was removed in vacuo. To the product water was added when a semi-solid mass was obtained which gradually became crystalline. This was filtered off and dried. The compound contained no chlorine and gave no depression of the melting point when mixed with the original material. It was therefore unchanged 2-anilino nicotinic acid.

2-Anisidino/

2-Anisidino-nicotinic acid.

Chloro-nicotinic acid (0.2 gm.) and p-anisidine (1 gm.) were heated together at 150° for one hour. A dark yellow solution was just formed which gradually solidified to a purple crystalline mass. After removal of the excess p-anisidine by steam distillation, the solid was filtered off and washed with hot water. After two recrystallisations from alcohol it melted at 295°. Yield 0.26 gm.

(Found: N, 11.41. $C_{13}H_{12}N_2O_3$ requires N, 11.48%)

The acid is soluble in dilute mineral acids. It is also soluble in dilute sodium hydroxide solution and in aqueous ammonia. It dissolves in warm dilute sodium carbonate solution and is sparingly soluble in benzene and acetone.

Attempt /

Attempt to condense 2-anisidino nicotinic acid with β-diethylaminoethylamine and to cyclise the product.

2-Anisidino nicotinic acid (0.2 gm.) was refluxed with thionyl chloride (0.5 c.c.) for 2 hours. The excess thionyl chloride was distilled off in vacuo on the water bath. A very black crystalline mass was obtained. To this a solution of β-diethylaminoethylamine (0.2 gm.) in dry benzene (1 c.c.) was added, in small quantities. A dark reddish-brown sticky product was formed. To this phosphorus oxychloride (1 c.c.) was added, and the mixture refluxed in the oil-bath for 1 hour. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The product, after dilution with ice-water, gave a very black substance which dissolved in dilute acid and on addition of ammonia gave a dark brown precipitate which, on filtering, immediately became tarry. It was not found possible to isolate any crystalline compound from this tar.

Ethyl Acetoacetanilide

(cf. Limpach. Ber. 1931. 64, 970)

Acetoacetic ester (260 gm.) was placed in a Claisen/

Claisen flask, one limb of which carried a dropping funnel containing aniline (46.5 gm.). To the side limb of the flask was attached a filter tube to collect the alcohol formed during the reaction. The flask was heated in an oil bath to 160° and a few drops of aniline were then slowly added. After a few minutes alcohol was seen distilling over into the filter tube. When the distillation ceased, more aniline was added and the process continued until all the aniline had been used up. The contents of the flask were then kept at 160° for 20-30 minutes. The excess aceto-acetic ester was distilled off in vacuo on the water bath and the remaining yellow liquid poured into a beaker. On cooling it solidified to a pale yellow crystalline mass which was drained on a filter and washed with ligroin or petroleum ether. A very pale yellow crystalline product was obtained. m.p. 76-78°.

It recrystallised from benzene or ligroin in pure white needles. m.p. 85°.

2-Hydroxy-4-methyl-quinoline.

(Roos. Ber. 1888. 21, 625; Limpach. Ber. 1931, 64, 970)

Ethyl-Acetoacetanilide (1 gm.) was added very slowly with stirring, to concentrated sulphuric acid (1 c.c.). The anilide went into solution giving

a/

a pale yellow liquid. The solution was allowed to stand for one hour and then warmed on the water bath for ten minutes. The resulting solution was poured into cold water when a white product was precipitated. This was filtered off, washed with water and dried at 100°. m.p. 220°.

6-Nitro-2-hydroxy-4-methyl quinoline.

(Balaban. J.C.S. 1930, II, 2349).

To a solution of 2-hydroxy-4-methyl quinoline (10.6 gm.) in concentrated sulphuric acid (50 c.c.) at 0° was added with mechanical stirring, a mixture of nitric acid (4.9 c.c. of sp.gr. 1.42) and 5 c.c. concentrated sulphuric acid. After standing for two hours at room temperature the mixture was poured into ice-water. The nitro compound was precipitated as a pale yellow mass which was filtered off and washed repeatedly with water until free of sulphuric acid. It recrystallised from glacial acetic acid as minute colourless rods, m.p. 340°.

2-Chloro/

made alkaline with sodium carbonate. The base was obtained as pale yellow needles. m.p. 313° (decomp.). Yield 3.5 gm.

2-Hydroxy-4-methyl-5:6-pyridoquinoline.

6-Amino-2-hydroxy-4-methyl quinoline (1.41 gm.), arsenic acid (1.16 gm.), concentrated sulphuric acid (2.20 gm.) and glycerin (2.40 gm.) were placed in a boiling tube fitted with an air condenser. The tube was cautiously heated on the sand bath until reaction had begun, and was then left to boil for two and a half to three hours. The solution, on cooling, was diluted with water and sodium hydroxide added. A brownish green precipitate was obtained which tended to dissolve in an excess of the sodium hydroxide.

I. A portion of the precipitate was dissolved in hot alcohol and a few drops of alcoholic hydrobromic acid added. A yellow precipitate of the hydrobromide separated out immediately and was filtered off. This hydrobromide had m.p. over 400°. It was dissolved in hot water and ammonia added. The base was precipitated as a pale yellow solid which was filtered off and washed with water. m.p. 330°. Yield 1.4 gm.

II./

II. A second portion was dissolved in hot alcohol and allowed to crystallise. Small flower-shaped crystals were obtained of a greenish-yellow colour. m.p. 325°.

As crystallisation was difficult and the yield small, purification of the base was carried out through its hydrobromide as in I. above. The final product gave no red coloration when diazotised and coupled with β-naphthol.

(Found: N, 13.46. $C_{13}H_{10}ON_2$ requires N, 13.33%).

2-Hydroxy-4-methyl-5:6-pyrido-quinoline

is sparingly soluble in alcohol, and acetone, but insoluble in ligroin, chloroform and benzene.

2-Chloro-4-methyl-5:6-pyridoquinoline.

To 2-hydroxy-4-methyl-5:6-pyridoquinoline (0.5 gm.) was added phosphorus pentachloride (0.5 gm.) and phosphorus oxychloride (4 c.c.). The compound did not go into solution. The mixture of reagents was heated in a test tube drawn out to act as a reflux condenser, to 120-130° in the oil-bath for 5 hours. The product was a dark brown liquid at the foot of the tube with a suspension of solid above it. This was poured on to ice when a brownish/

brownish product was obtained which dissolved in water as the ice melted. It was filtered from dirt and the clear, brownish coloured solution neutralised with sodium carbonate. A white solid was precipitated. This was filtered off, washed with a small quantity of water and dried. It contained chlorine and melted at 204°. It was insoluble in caustic soda, but soluble in hydrochloric acid. It also dissolved fairly readily in hot alcohol from which it crystallised in long, white needles. m.p. 204°. Yield 0.30 gm. (Found: N, 12.06. $C_{13}H_9N_2Cl$ requires N, 12.25%).

2-Chloro-4-methyl-5:6-pyridoquinoline is soluble in alcohol, ligroin, benzene and acetone, and is very soluble in chloroform. It dissolves only with difficulty in ether.

2-Piperidino-4-methyl-5:6-pyridoquinoline dihydrobromide.

2-Chloro-4-methyl-5:6-pyridoquinoline (0.3 gm.) and piperidine (0.5 gm.) were heated together on the water bath under reflux air condenser for 2 hours. The product, a dark brown liquid, was dissolved in alcohol and alcoholic hydrobromic acid added. After a few moments a yellow precipitate appeared and on addition of more acid more of the hydrobromide was obtained/

obtained. A large excess of the hydrobromic acid was required before precipitation was complete. The voluminous yellow precipitate was filtered off, and washed with alcohol and acetone. It was recrystallised from methyl alcohol. m.p. over 400°. Yield 0.6 gm.

(Found: N, 9.58. $C_{18}H_{19}N_3.2HBr$ requires N, 9.57%)

This hydrobromide is very soluble in water. It also dissolves readily in methyl alcohol. It is only sparingly soluble in alcohol and chloroform and is insoluble in ligroin and in benzene.

2-Piperidino-4-methyl-5:6-pyridoquinoline.

2-Piperidino-4-methyl-5:6-pyrido quinoline dihydrobromide was dissolved in cold water in which it was very soluble, and a few drops of ammonia added. After standing for a few hours and scratching the tube with a glass rod the base settled out as an oil which after continued scratching, crystallised to a white solid. It was recrystallised three times from aqueous alcohol. m.p. 103-105°.

(Found: C, 77.86; H, 6.38. $C_{18}H_{19}N_3$ requires C, 77.96, H, 6.86%).

The base is insoluble in water but dissolves readily in benzene, alcohol, ether and chloroform.

2-β-Diethylaminoethylamino-4-methyl-5:6-pyridoquinoline trihydrobromide.

The experiment was carried out in exactly the same way as the preceding one but heating was continued up to 150° in the oil bath for one and a half hours. The brown liquid then gave a marked reaction when tested for chlorine. To the brown solution hydrobromic acid was added when a creamy coloured precipitate was obtained after a few minutes. A very large amount of acid was required for complete precipitation. The precipitate was filtered off and washed with acetone. m.p. 225-229°. Yield 0.5 gm. It recrystallised from alcohol as pale yellow needles.

(Found: N, 10.16. $C_{19}H_{24}N_4.3HBr$ requires N, 10.02%)

The tri-hydrobromide is very soluble in water. It dissolves sparingly in methyl alcohol and alcohol, and is insoluble in ligroin, chloroform and acetone.

2-β-diethylaminoethylamino-4-methyl-5:6-pyridoquinoline.

The trihydrobromide from the previous experiment was dissolved in cold water and a few drops of ammonia added. The base was precipitated as/

as a yellow oil which on prolonged scratching solidified to a white solid. This was filtered and washed with water. After recrystallisation three times from diluted alcohol it melted at 121-123°.
(Found: C, 74.39; H, 7.769. $C_{19}H_{24}N_4$ requires C, 74.03; H, 7.79%).

The new base is very soluble in chloroform. It also dissolves easily in ligroin, ether and alcohol. It is slightly soluble in acetone and insoluble in water.

2-β-diethylaminopropylamino-4-methyl-5:6-pyridoquinoline trihydrobromide.

2-Chloro-4-methyl-5:6-pyridoquinoline (0.3 gm.) and β-diethylaminopropylamine (1 c.c.) were heated together in a test tube fitted with an air condenser, to 160° for one and a half hours. The resulting dark brown solution was treated with hydrobromic acid as in the previous experiment. The hydrobromide in this case did not settle out so quickly and was paler yellow in colour. It was filtered off and washed with acetone. It recrystallised from ethyl alcohol. m.p. shrinks and/

and partly melts 240°, completely melts 260-270°. (Found: C, 39.92; H, 5.69, N, 9.15; Br, 39.14. $C_{20}H_{26}N_4.3HBr.2H_2O$ requires C, 39.93; H, 5.49; N, 9.3 Br, 40.43%.

It is very soluble in water and dissolves without difficulty in alcohol and methyl alcohol. It is insoluble in chloroform, ligroin and acetone.

2-Piperazino-4-methyl-5:6-pyridoquinoline.

2-Chloro-4-methyl-5:6-pyridoquinoline, 1 mol. (0.46 gm.) and piperazine hexahydrate, 3 mols. (1 gm.) were heated together to 140° for 5 hours. (cf. Kermack and Smith, J.C.S. 1931, II, 3096). The product was a yellow brown solid which was drained on a filter and washed with water. It was then dissolved in dilute hydrochloric acid and reprecipitated with ammonia. The product was filtered off and washed with water. It was recrystallised three times from boiling water from which it separated as pure white needles containing 2 mols. of water of crystallisation. m.p. 105-110°. (Found: N, 17.77; H_2O, 11.39. $C_{17}H_{18}N_4.2H_2O$ requires N, 17.83; H_2O, 11.4%).

The water of crystallisation was driven off by heating the compound in vacuo at 100°. The melting point of the dehydrated compound was 125°.

2-Piperidino-4-methyl-6-nitro quinoline.

2-Chloro-4-methyl-6-nitro quinoline (0.3 gm.) and piperidine (0.5 c.c.) together with a trace of copper bronze were heated in a test tube in the oil bath to 110-120° for 4 hours. On cooling, the dark brown solution solidified to a dark brown mass which dissolved readily in dilute hydrochloric acid, and was reprecipitated by sodium carbonate as a bright yellow crystalline solid. This was filtered off and recrystallised twice from aqueous alcohol. It crystallised as brilliant golden leaflets. m.p. 167-168°. Yield 0.35 gm. (Found: N, 15.68. $C_{15}H_{17}O_2N_3$ requires N, 15.498%)

The base is readily soluble in alcohol, benzene, acetone, chloroform and ligroin, but is sparingly soluble in ether.

2-β-diethylaminoethylamino-4-methyl-6-nitro quinoline hydrochloride.

The experiment was carried out in the same way as the previous one but the oil bath was heated to 140°. The resulting very dark brown oily mass gave no hydrobromide when treated with fuming alcoholic hydrobromic acid. It was dissolved in a very small quantity of dilute hydrochloric acid and the acid solution made exactly neutral to litmus with/

with sodium bicarbonate, keeping the volume as small as possible. Yellow, needle shaped crystals appeared. After standing for an hour they were filtered off. They were extremely soluble in water, contained chlorine and melted at 120-130° . They were recrystallised from methyl alcohol in which they were fairly readily soluble and the minimum amount had to be used. m.p. 165°. Shrinks 120-130°.
(Found: N, 16.32; $C_{16}H_{22}N_4O_2 \cdot HCl$ requires N, 16.54%).

The mono picrate of 2-β-diethylaminoethylamino-4-methyl-6-nitro quinoline.

To the mother liquors from the hydrochloride of the previous experiment a saturated solution of picric acid was added. A bright yellow voluminous precipitate of the picrate was obtained. After recrystallisation three times from boiling water, it melted at 210°.
(Found: N, 18.25; C, 50.22; H, 4.79.
$C_{22}H_{25}O_9N_7$ requires N, 18.45; C, 49.7; H, 4.71%)

γ-Oxy-quinaldine.

(Limpach. Ber. 1931. 64, 969.

Equimolecular proportions of aniline and aceto-acetic ester were mixed together in a beaker, and the beaker placed in a vacuum desiccator over sulphuric/

sulphuric acid and left for several days.

The ester was then run into four times its quantity of paraffin oil heated to 260-280°. After addition the whole was heated to 240-260° for 15-20 minutes. After the splitting off of alcohol was complete, the mass was left to cool. The crystalline product was separated from the paraffin by centrifuging or filtration and recrystallised from boiling water. Yield, 90-95% theory. The m.p. after loss of 1 mol. of water of crystallisation was 228°.

Nitration of 2-methyl-4-hydroxy quinoline.

To a solution of 2-methyl-4-hydroxy quinoline (10.6 gm.) in concentrated sulphuric acid (50 c.c.) at 0°, was added with stirring, a mixture of nitric acid (1.42:4.9 c.c.) and 5 c.c. concentrated sulphuric acid. After standing for 2 hours at room temperature, the dark brown solution was poured into ice water. The nitro compound was slowly precipitated out as a pale yellow crystalline solid. It was filtered off and washed well with water. It was sparingly soluble in glacial acetic acid from which it crystallised as yellow rods. m.p. over 400°. Shrinks 340-350°. Yield 8.5 gm.

The/

The nitro compound is soluble in boiling dilute mineral acids. It also dissolves in cold dilute sodium hydroxide and sodium carbonate solutions and in aqueous ammonia, forming deep yellow solutions. It is very slightly soluble in hot alcohol and slightly soluble in hot methyl alcohol, ligroin and benzene.

6-Amino-2-methyl-4-hydroxy quinoline.

The nitro derivative (6.12 gm.) was slowly added to a hot solution of stannous chloride (20.34 gm.) in concentrated hydrochlorid acid (60 c.c.). The heating on the water bath was continued for 5 hours. On cooling, a pale yellow crystalline solid separated out which was filtered off. It dissolved readily in water. The hot solution was saturated with H_2S and the tin sulphide filtered off and washed well with boiling water. The solution was evaporated down to very small bulk when clusters of small crystals separated out. After cooling, these crystals of the hydrochloride of the required base were filtered off and dried. They were very soluble in water and the solution gave a marked red coloration when diazotised and coupled with β-naphthol. m.p. 300-305°.

To/

To a saturated solution of the hydrochloride in water a few drops of ammonia were added. After scratching, cream coloured crystals separated out. They were filtered off and washed well with water. They gave no test for chlorine. A deep red coloration appeared when the compound was diazotised and coupled with β-naphthol. This was presumably the free base. m.p. 345° with previous blackening at 320°. Yield 3.8 gm.

(Found: N, 16.43; $C_{10}H_{10}N_2O$ requires N, 16.28%).

The base dissolves in boiling alcohol. It is very soluble in ligroin, chloroform, acetone and benzene, and insoluble in ether. It crystallised from boiling water in colourless, shimmering rectangular plates. The mother liquor from the crystals had a blue fluorescence as also had the solution of the crystals in alcohol.

2-Methyl-4-hydroxy-5:6-pyrido quinoline.

6-Amino-2-methyl-4-hydroxy quinoline (2.82 gm.), arsenic acid (2.32 gm.), glycerine (4.8 gm.) and concentrated sulphuric acid (4.40 gm.) were cautiously heated on the sand bath in a flask fitted with reflux air condenser, and then left to boil for 5 hours. After cooling, the dark brown mass/

mass was added to cold water in which it dissolved to form a brown solution. The solution was neutralised with sodium hydroxide when a yellow solid separated. It was filtered off and washed well with water.

It was found that the most convenient way of purifying this compound was to dissolve it in alcohol, filter the solution and then add water until precipitation just began. The pale yellow solid obtained in this way gave no red coloration when diazotised and coupled with β-naphthol. m.p. 358°. Yield 3 gm.

(Found: C, 73.7; H, 4.83. $C_{13}H_{10}N_2O$ requires C, 74.28; H, 4.76%).

It dissolved in dilute acids, and in warm dilute alkalies. It is also readily soluble in hot alcohol and slightly soluble in hot ligroin. It does not dissolve in acetone.

2-Methyl-4-chloro-5:6-pyrido quinoline.

2-Methyl-4-hydroxy-5:6-pyrido quinoline (0.5 gm.) was mixed with phosphorus pentachloride (0.5 gm.) and phosphorus oxychloride (4 c.c.) in a test tube. The tube was drawn out to a capillary to act as a reflux condenser and heated in the oil bath to 120°.

After/

After about three hours the solution became deep indigo blue in colour. On cooling it was poured into ice water in which it formed a deep blue solution. The solution was neutralised by addition of sodium carbonate solution. A pink coloured solution was formed which on scratching yielded a pink flocculent precipitate. This was filtered off and washed with water. The product contained chlorine.

It recrystallised from diluted alcohol in small, colourless needles. m.p. 149°. Yield 0.34 gm. (Found: C, 67.83; H, 3.71. $C_{13}H_9N_2Cl$ requires C, 68.27; H, 3.94%).

It is soluble in dilute acids, but insoluble in alkali. It dissolves readily in alcohol and methyl alcohol and is slightly soluble in benzene and ligroin, but insoluble in acetone.

4-Piperidino-2-methyl-5:6-pyrido quinoline picrate

2-Methyl-4-chloro-5:6-pyrido quinoline (0.2 gm.) and piperidine (1 c.c.) were warmed together on the water bath under reflux air condenser for 4 hours. Adark brown solution was formed which gave a marked chlorine reaction. After 4 hours the solution solidified/

solidified to a crystalline mass.

The crystals of the base were extremely soluble in alcohol, ether, ligroin.

The base gave no salt with salicylic acid, hydrobromic acid or tartaric acid, but with picric acid a greenish picrate was produced. This was filtered off and recrystallised from boiling water. m.p. 225°.

(Found: C, 56.92; H, 4.35. $C_{24}H_{22}O_7N_6$ requires C, 57.67; H, 4.55%).

4-Piperidino-2-methyl-5:6-pyrido quinoline.

The crystals of the base were dissolved in dilute hydrochloric acid and ammonia added. An oiliness was produced, which on scratching solidified to a brownish solid. This was filtered off. It recrystallised from diluted alcohol as pure white needles, m.p. 163°.

(Found: N, 13.94. $C_{18}H_{19}N_3.1H_2O$ requires N, 14.24%)

The base was insoluble in water, but very soluble in alcohol, ether, ligroin and benzene.

4/

4-β-diethylaminoethylamino-2-methyl-5:6-pyrido quinoline.

4-Chloro-2-methyl-5:6-pyrido quinoline (0.3 gm.) and β-diethylaminoethylamine (0.6 c.c.) were heated together under reflux on the oil bath at 140° for three hours. The resulting dark brown oil gave a marked reaction when tested for chlorine ions.

The oil was dissolved in dilute hydrochloric acid and was reprecipitated on addition of sodium hydroxide as a cloudiness which on scratching gradually settled out as a white solid, which was filtered off and recrystallised from petroleum ether as long rectangular plates. m.p. 68°.
(Found: N, 17.23. $C_{19}H_{24}N_4.1H_2O$ requires N, 17.18%).

The base is soluble in acids, but insoluble in alkalies. It dissolves readily in petroleum ether, hot benzene and hot ligroin. It is also very easily soluble in alcohol and in methyl alcohol.

6-Acetylamino-2-methyl-4-hydroxy quinoline.

6-Amino-4-hydroxy-2-methyl quinoline (0.5 gm.) and a large excess of acetic anhydride (3 c.c.) were warmed together on the water bath under reflux/

reflux condenser for four hours. The white solid which separated was filtered off and washed well with water. It gave no red coloration when diazotised and coupled with β-naphthol. It dissolved in dilute acid and also in dilute sodium hydroxide and sodium carbonate. It recrystallised from boiling water as small colourless needles. m.p. 365° with previous blackening at 330°. Yield 0.35 gm.

(Found: N, 12.17; $C_{12}H_{12}N_2O_2.1H_2O$ requires N, 12.00%)

This compound is soluble in boiling water. It dissolves sparingly in alcohol and benzene and is insoluble in ligroin and in chloroform.

Ethyl-β-(p-chlorophenylaminocrotonate.

p-Chloro-aniline (0.5 gm.) and ethylaceto-acetate (0.5 gm.) were mixed together in a beaker, and a trace of hydrochloric acid added. After about 3 minutes the solution became milky, showing the splitting off of water. After standing over the week-end at room temperature in a vacuum desiccator, the milkiness had disappeared, and a yellow brown solution had been formed.

2-Methyl/

2-Methyl-4-hydroxy-6-chloroquinoline.

The solution was added very slowly to paraffin oil heated to 250°. After a few minutes a white solid separated from the oil. The heating was continued for another 5 minutes and then the contents of the flask were allowed to cool. The solid was filtered off from the oil and washed well with petroleum ether. A very pure white shimmering crystalline product was obtained. m.p. 320-322°. Yield 0.56 gm.

(Found: N, 7.32. $C_{10}H_8NOCl$ requires N, 7.24%)

2-Methyl-4-hydroxy-6-chloro quinoline is soluble in boiling dilute hydrochloric acid, and in hot dilute sodium hydroxide solution, but is soluble in sodium carbonate solution. It is insoluble in alcohol, benzene and ligroin, but soluble in methyl alcohol.

Ethyl-β-p-bromophenylaminocrotonate.

p-Bromoaniline (5 gm.) was added slowly to aceto acetic ester (3.8 gm.) . After the addition a trace of hydrochloric acid was added. In about 3 minutes the splitting off of water was observed, as the solution became cloudy. It was left in a vacuum/

vacuum desiccator overnight, when the liquid crystallised to colourless needles.

The ester recrystallised from petroleum ether as feathery needles. m.p. 54°. Yield 6.2 gm. (Found: N, 5.09. $C_{12}H_{14}NO_2Br$ requires N, 4.93%)

It is soluble in warm dilute hydrochloric acid, insoluble in sodium hydroxide solution, and in sodium carbonate solution. It dissolves easily in petroleum ether, benzene, alcohol and methyl alcohol.

2-Methyl-4-hydroxy-6-bromoquinoline.

Ethyl-β-p-bromophenylamino crotonate (5 gm.) was added very slowly to liquid paraffin heated to 250°. After addition was complete the temperature was kept at 220-230° for 15 minutes. A silvery white solid separated out and, after cooling, was filtered off. It was washed free of the oil with ether and appeared in a remarkably pure crystalline form. It recrystallised from diluted alcohol in sheaves of colourless needles. m.p. 338°. Yield 3.7 gm. (Found: N, 5.99. $C_{10}H_8ONBr$ requires N, 5.89%)

It dissolves in hot dilute hydrochloric acid and sodium hydroxide . It is slightly soluble in hot dilute sodium carbonate, soluble in alcohol, insoluble in methyl alcohol, ligroin and acetone.

Ethyl-β-p-acetylaminophenylaminocrotonate.

p-Amino-acetanilide (7.5 gm.) was dissolved in the smallest possible amount of boiling alcohol. Aceto acetic ester (6.5 gm.) was added and then a trace of hydrochloric acid and the heating on the water bath continued for 15 minutes. Water was then added to the solution when the ester was precipitated.

It recrystallised from benzene as colourless needles. m.p. 180°. Yield 11.8 gm.
(Found: N, 11.00. $C_{14}H_{18}O_3N_2$ requires N, 10.69%).

The crotonate is soluble in hot dilute hydrochloric acid but insoluble in dilute sodium hydroxide and sodium carbonate solutions. It dissolves readily in hot benzene, and alcohol, is difficultly soluble in ligroin and insoluble in petroleum ether.

2-Methyl-4-hydroxy-6-acetylamino quinoline.

Ethyl-β-p-acetylaminophenylamino crotonate (1 gm.) was slowly added to paraffin oil heated to 260°. Immediately the solid was added a cloudiness appeared which gradually settled out to a yellow-white solid. This was filtered off and washed well with/

with petroleum ether.

It recrystallised from boiling alcohol as colourless plates. m.p. 368° with previous blackening at 330°. Yield 0.7 gm. (Found: N, 13.15. $C_{12}H_{12}O_2N_2$ requires N, 12.96%)

It is insoluble in acids but dissolves readily in warm dilute sodium hydroxide solution, and in warm dilute ammonia. It dissolves with difficulty in warm dilute sodium carbonate solution. It is very soluble in methyl alcohol, soluble in alcohol, difficultly soluble in benzene and chloroform and insoluble in ligroin and acetone.

2-Methyl-4-hydroxy-6-amino quinoline.

2-Methyl-4-hydroxy-6-acetylamino quinoline (1 gm.) was placed in a flask fitted with reflux condenser. A solution of 5 c.c. concentrated hydrochloric acid in 5 c.c. water were added, and the solution boiled for 2 hours. On cooling, needle-shaped crystals separated and were filtered off and washed with acetone. They gave a marked red coloration when diazotised and coupled with β-naphthol. m.p. 295-305°.

They gave no depression of the melting point with the hydrochloride of the amino-4-hydroxy-2-methyl/

methyl quinoline prepared by the previous method. (see page 93)

The hydrochloride was dissolved in a very small amount of water and a few drops of ammonia added. After scratching, cream-coloured crystals separated out which were filtered off and washed well with water. m.p. 345°. Yield 0.5 gm.

They gave no depression of the melting point with the amino-4-hydroxy-2-methyl quinoline prepared by the previous method (see page 94)

2-Methyl-4-chloro-6-bromo-quinoline.

2-Methyl-4-hydroxy-6-bromo quinoline (0.34 gm.) phosphorus pentachloride (0.5 gm.) and phosphorus oxychloride (4 c.c.) were refluxed together on the oil bath for 4 hours at 120°. A dark brown solution was formed. This was poured on to ice and the aqueous solution so formed was neutralised with sodium hydroxide. A white precipitate separated, and was filtered off and washed well with water. It recrystallised from aqueous alcohol as long colourless needles. m.p. 75°. Yield 0.35 gm.

(Found: N, 5.33. $C_{10}H_7NBrCl$ requires N, 5.46%)

2-Methyl-4-chloro-6-bromoquinoline is

soluble/

soluble in dilute hydrochloric acid but insoluble in sodium hydroxide solution and sodium carbonate solution. It dissolves in alcohol, methyl alcohol, benzene and hot ligroin and is very soluble in acetone and in chloroform.

2:3-Dimethyl-4-hydroxyquinoline.

Ethylmethylacetoacetate (72 gm.) and aniline (46.5 gm.) were mixed together in a beaker and a trace of concentrated hydrochloric acid added. The solution was allowed to stand in a vacuum desiccator over sulphuric acid for several days. Crystals separated out.

The crystals were added slowly to liquid paraffin heated to 260°. After addition the whole was heated to 240° for 15-20 minutes. Alcohol was evolved and a white crystalline solid separated out. After cooling, the solid was filtered off and re-crystallised from boiling alcohol. m.p. 330°. Yield 52 gm.

Nitration/

Nitration of 4-hydroxy-2:3-dimethyl quinoline.

2:3-Dimethyl-4-hydroxy quinoline (11.6 gm.) was dissolved in concentrated sulphuric acid (50 c.c.). The solution was cooled to 0° and to it was added with stirring a mixture of nitric acid (1.42:4.5 c.c.) and concentrated sulphuric acid (5 c.c.). After standing for 2 hours at room temperature, the dark brown solution was poured into ice water. The nitro compound was immediately precipitated as a bright yellow solid.

It was recrystallised as small greenish yellow needles from nitrobenzene and well washed with petroleum ether. m.p. 380°. Yield 7.8 gm. (Found: N, 13.00. $C_{11}H_{10}O_3N_2$ requires N, 12.84%).

It is soluble in warm dilute hydrochloric acid and in dilute sodium hydroxide solution and sodium carbonate solution. It dissolves in alcohol, acetone, benzene and boiling nitrobenzene, but is insoluble in petroleum ether.

4-Hydroxy-2:3 dimethyl-6-amino quinoline.

4-Hydroxy-2:3-dimethyl-6-nitro quinoline (1 gm.) was added slowly to a boiling solution of stannous chloride (3.11 gm.) in concentrated hydrochloric acid (10 c.c.). The nitro compound dissolved, forming/

forming a yellow solution. On cooling, a crystalline tin salt separated out and was filtered off. It was dissolved in water and hydrogen sulphide passed into the hot solution, until precipitation of the tin was complete. The tin sulphide was then filtered off, and washed very thoroughly with boiling water. The combined filtrates were then evaporated down almost to dryness, when the hydrochloride of the new base crystallised out as colourless long prisms. m.p. 335°.

The hydrochloride was dissolved in smallest possible quantity of water and neutralised with sodium carbonate solution. After scratching, the base separated out as colourless crystals, which gave a deep red coloration when diazotised and coupled with β-naphthol.

It recrystallised as ball shaped clusters of needles from boiling water. m.p. 326°. Yield 0.64 gm. (Found: N, 15.15. $C_{11}H_{12}ON_2$ requires N, 14.89%).

Ethyl-α-methyl-β-p-acetylamino-phenylaminocrotonate.

p-Aminoacetanilide (1.5 gm.) was dissolved in the minimum amount of boiling ethyl alcohol. Ethyl methylacetoacetate (1.44 gm.) and a trace of hydrochloric acid were added and the solution heated on the/

the water bath for 15 minutes. Water was then added to the hot solution when the ester was precipitated.

It recrystallised from diluted alcohol as colourless small plates. m.p. 169°. Yield 2.4 gm. (Found: N, 10.33. $C_{15}H_{20}O_3N_2$ requires N, 10.14%).

The crotonate is soluble in hot dilute hydrochloric acid but insoluble in dilute sodium hydroxide and sodium carbonate solutions. It dissolves readily in alcohol, benzene and acetone and is sparingly soluble in ligroin.

2:3-Dimethyl-4-hydroxy-6-acetylamino quinoline.

The crotonate obtained in the previous experiment (1 gm.) was slowly dropped into paraffin oil heated to 250°. Immediately the solid was added a cloudiness appeared, which gradually settled out to a white solid. This was filtered off and washed well with petroleum ether. It recrystallised from alcohol as colourless small plates. m.p.385°. Blackens 350°. Yield 0.63 gm.
(Found: N, 12.03. $C_{13}H_{14}N_2O_2$ requires N, 12.17%).

It is insoluble in dilute acids, but soluble in warm dilute sodium hydroxide, ammonia and sodium carbonate. It is soluble in boiling alcohol, but insoluble/

insoluble in petroleum ether.

2:3-Dimethyl-4-hydroxy-6-amino quinoline.

2:3-dimethyl-4-hydroxy-6-acetylamino quinoline (0.5 gm.) was dissolved in a solution of 5 c.c. concentrated hydrochloric acid and 5 c.c. water. The solution was refluxed for 2 hours. After standing overnight, the solution deposited clusters of needle-shaped crystals. There were filtered off and washed with acetone. m.p. 335°.

They gave no depression of the melting point with the hydrochloride obtained by the previous method (p. 104.).

The hydrochloride was dissolved in the minimum amount of water and a few drops of ammonia added. After scratching, a white precipitate of the base settled out. This was filtered off and washed well with water. m.p. 326°. Yield 0.3 gm.

It gave no depression of the melting point with the amino, 4-hydroxy-2:3-dimethyl quinoline prepared by the previous method (p. 104.)

2/

2-Methyl-4-chloro-6-acetylamino quinoline.

2-Methyl-4-hydroxy-6-acetylamino quinoline (0.5 gm.), phosphorus pentachloride (0.5 gm.) and phosphorus oxychloride (4 c.c.) were refluxed together on the oil bath at 120° for one hour. A dark brown solution was formed, which, after cooling, was poured into water. Oily drops appeared which gradually went into solution. The pale yellow solution so formed was neutralised with sodium hydroxide. A white solid was precipitated and was filtered off and well washed with water. It contained chlorine.

It was recrystallised from benzene. m.p. 210°. Yield 0.48 gm.

(Found: N, 11.78. $C_{12}H_{11}N_2OCl$ requires N, 11.94%).

2-Methyl-4-chloro-6-acetylamino quinoline is soluble in dilute acids but insoluble in dilute alkalies. It is very soluble in alcohol, methyl alcohol, and in benzene, and is slightly soluble in ligroin.

2-Methyl/

2-Methyl-4-chloro-6-amino quinoline.

2-Methyl-4-chloro-6-acetylamino quinoline (0.3 gm.) was placed in a flask and a solution of 1 c.c. of concentrated hydrochloric acid in 4 c.c. water added. The compound went into solution and then solidified to a pale yellow crystalline mass. This solid gave no red coloration when diazotised and coupled with β-naphthol, and was presumably the hydrochloride of 2-methyl-4-chloro-6-acetylamino quinoline. The flask was gently heated, first on the water bath and then under reflux over a flame. A deep yellow solution was formed which, after 10 minutes, gave a marked diazo reaction. Boiling was continued for another 5 minutes. The solution was then cooled, and as no hydrochloride separated out, it was neutralised with sodium hydroxide. A bright yellow solid was immediately precipitated. It was filtered off, and well washed with water. It gave a deep red coloration when diazotised and coupled with β-naphthol, and contained chlorine. m.p. 145°, softens 130°. Yield 0.18 gm.
(Found: N, 14.32. $C_{10}H_9N_2Cl$ requires N, 14.55%).

2-Methyl-4-chloro-6-amino quinoline is soluble in dilute hydrochloric acid but insoluble in dilute sodium hydroxide, sodium carbonate and ammonia. It is /

is very soluble in ethyl alcohol and methyl alcohol but dissolves sparingly in ligroin and benzene. It is insoluble in water.

2-Methyl-4-piperidino-6-acetylamino quinoline.

2-Methyl-4-chloro-6-acetylamino quinoline (0.2 gm.) and piperidine (1 c.c.) were heated on the oil bath under reflux for 2 hours at 130°. The resulting orange coloured solution gave a very marked chlorine reaction. Water was added, after cooling, when a cloudiness appeared which gradually settled out to a white solid. This was filtered off, and washed with water.

It was found that the best way to purify this compound was to dissolve it in alcohol, filter the hot solution and precipitate the base with water. m.p. after three recrystallisations, 87°.

(Found: N, 14.24; H_2O, 5.86. $C_{17}H_{21}N_3O.1H_2O$ requires N, 13.95; H_2O, 5.98%).

The base is soluble in dilute acids, but insoluble in alkalies. It dissolves in boiling water, is very soluble in alcohol, but sparingly soluble in methyl alcohol.

2-Methyl-4-β-diethylaminoethylamino-6-acetylamino quinoline hydrochloride.

2-Methyl-4-chloro-6-acetylamino quinoline (0.2 gm.) and β-diethylaminoethylamine (1 c.c.) were heated together under reflux on the oil bath at 140-150° for 4 hours. The resulting brown solution gave a marked chlorine reaction. The excess diethylaminoethylamine was removed in vacuo on the water bath, when a sticky brown oil remained behind. This was made to solidify by rubbing it up with acetone. A yellow solid was produced which was filtered off and washed with acetone. It was very soluble in water and was presumably the hydrochloride of the desired base. The alcoholic solution showed a blue green fluorescence. It was recrystallised, as ball shaped clusters of needles, by dissolving it in the minimum amount of alcohol and reprecipitating it with acetone. m.p. 272°. (Found: N, 15.57. $C_{18}H_{26}N_4O.HCl$ requires N, 15.98%).

The hydrochloride is very soluble in water and in alcohol. It dissolves sparingly in ether and is insoluble in ligroin and benzene.

6-Nitro/

6-Nitro-4-chloro-2-methyl quinoline.

6-Nitro-2-methyl-4-hydroxyquinoline (6 gm.) was refluxed with phosphorus pentachloride (16.2 gm.) and phosphorus oxychloride (8 c.c.) for one hour at 160°. The solution became coloured deep purple. After cooling, it was poured on to ice and then filtered and washed through the filter with water. The resulting solution was purple coloured and a small amount of tar remained on the filter.paper. The solution was basified with sodium hydroxide when a white solid precipitate separated. This was filtered off and washed with water. It contained chlorine.

After two recrystallisations from alcohol it formed colourless needles. m.p. 142°. Yield 4.2 gm. (Found: N, 12.47. $C_{10}H_7O_2N_2Cl$ requires N, 12.58%).

6-Nitro-4-chloro-2-methyl quinoline is soluble in dilute acids but insoluble in alkalies. It dissolves readily in benzene, acetone and ether and is sparingly soluble in alcohol, methyl alcohol and ligroin.

2-Methyl/

2-Methyl-4-piperidino-6-nitro quinoline.

2-Methyl-4-chloro-6-nitro quinoline (0.3 gm.) and piperidine (0.5 c.c.) were warmed together on the water bath in a test tube fitted with reflux condenser, for one hour. The orange-coloured solution deposited crystals on cooling. The supernatant liquid gave a marked test for chlorine ions.

The crystals were filtered off and washed well with water. They recrystallised from diluted alcohol as golden leaflets. m.p. 145°. Yield 0.28 gm. (Found: N, 15.49. $C_{15}H_{17}O_2N_3$ requires N, 15.55%).

The new base is soluble in hydrochloric acid, but insoluble in sodium hydroxide solution, sodium carbonate solution and water. It dissolves readily in alcohol, methyl alcohol, benzene, ligroin and acetone.

2-Methyl-4-β-diethylaminoethylamino-6-nitro quinoline.

2-Methyl-4-chloro-6-nitro quinoline (0.3 gm.) and β-diethylaminoethylamine (0.5 c.c.) were heated together under reflux air condenser on the oil bath at 140° for 3 hours. The dark brown solution gave/

gave a marked reaction when tested for chlorine. On addition of water a bright yellow solid separated out. It was filtered off and recrystallised from diluted alcohol. m.p. after three recrystallisations 100-102°. Yield 0.23 gm.

(Found: N, 16.67. $C_{16}H_{22}O_2N_4.2H_2O$ requires N, 16.57%).

The base is soluble in warm alcohol, methyl alcohol, hot benzene and hot ligroin and is very soluble in chloroform.

SUMMARY.

SUMMARY.

I. A survey of the literature dealing with anti-malarial compounds is given, with special reference to the relationship between activity and chemical constitution.

II. Various unsuccessful attempts to synthesise derivatives of 2:3-pyrido-4-hydroxy quinoline are described, and the constitution of the compound obtained from 2-chloro-pyridine and anthranilic acid is discussed.

III. 2-Hydroxy-4-methyl-5:6-pyrido quinoline and 2-methyl-4-hydroxy-5:6-pyrido quinoline have been synthesised. The hydroxyl groups in these compounds have been replaced by piperidino, diethylaminoethyl-amino and diethylaminopropylamino side chains.

IV. The nitration of 2-methyl-4-hydroxy quinoline and of 2:3-dimethyl-4-hydroxy quinoline has been accomplished and the constitutions of the resulting compounds have been established by synthesis as 6-nitro-2-methyl-4-hydroxy quinoline and 6-nitro-2:3-dimethyl-4-hydroxy quinoline.

V./

V. Various derivatives of 2-methyl-6-nitro quinoline having a basic side chain in position 4 and of 4-methyl-6-nitro quinoline having a basic side chain in position 2 have been prepared. The hydroxyl group in 2-methyl-4-hydroxy-6-acetylamino quinoline has also been replaced by piperidino and diethylaminoethylamino side chains.