THESIS FOR THE DEGREE OF Ph.D.

SYNTHESIS OF POLYNUCLEAR BASES.

PART 1.

Synthesis of 6-methyl-3:4-benz-5-carboline and some of its derivatives.

PART 2.


by

James Fergus Smith, B.Sc., (Hons.).

(Under the joint supervision of Professor James Kendall, F.R.S., and Dr. Kermack.)

Research Laboratory of the Royal College of Physicians, Edinburgh.
PART I.

SYNTHESIS OF 6-METHYL-3:4-BENZ-5-CARBOLINE
AND SOME OF ITS DERIVATIVES.

It is only within the last decade or so, that attention has been drawn to a certain group of bases, consisting of a 3-ring system formed by the fusion of indole and pyridine nuclei, and to which the name of carbolines has been given from their relation to carbazole. This relationship can be seen by a study of the following structural representations of carbazole (I) and 4-carboline (II), the system of numbering adopted in the diagram being used throughout this thesis.

![Diagram of structures](I),(II)

It will be seen that there are four closely related isomeric carbolines containing the nitrogen in positions 3, 4, 5, and 6 respectively and of these, only one, namely, 6-carboline has not
been synthesised, although one of its derivatives, namely, "quindoline" has been known for a considerable time. It would seem from a perusal of the literature that the first to be prepared was 4-carboline, or norharman, as it was then called, (Kermack, Perkin, and Robinson, J.C.S. 1921, 119, 602).

These authors proved that it was the parent compound of a number of naturally occurring alkaloids principal amongst which were, harmine, (III) and harmaline, (IV).

Their method of synthesis involved the preparation of an indole derivative, having a straight chain chain attached to the 2-position; the subsequent ring-closure being effected by treatment with alcoholic hydrochloric acid as follows:-

1-methylindole-2-carboxyacetlylamide 3-oxo-1-methyl-4-3-dihydro-u-carboline
3-carboline and 5-carboline, however, were prepared by an entirely different method (Lawson, Perkin, Robinson, J.C.S., 1924, 125 625-57), (Robinson and Thornley, J.C.S., 1924, 125 2169-76).

Briefly, this method consisted in the condensation of chloropyridine with o-phenylene-diamine, subsequent diazotisation of the product in acid solution gave rise to a derivative of benztriazol which in turn, by rupture of the triazol ring, yielded 3-carboline or 5-carboline depending on whether 2-chloropyridine or 4-chloropyridine had been used, as follows:

Lawson, Perkin and Robinson found great difficulty in obtaining a satisfactory
yield of the desired product, and were only successful in obtaining 3-carboline by heating up the triazol derivative in very small quantities at a time, with zinc chloride. Robinson and Thornley, however, found that this difficulty could be overcome satisfactorily by the use of syrupy phosphoric acid.

If, instead of 2-chloropyridine, 2-chloroquinoline was used in the above synthesis, Lawson, Perkin and Robinson, found that the final product, which they named 4:5-benzé-carboline (V), to be identical with the "quinindoline" of Gabriel and Eschenbach, (Ber. 1897, 30, 3020), who had prepared it by the reduction of 2:2' dinitrocyanodibenzyl with ammonium sulphide:—

\[
\text{2:2'-dinitrocyanodibenzyl} \rightarrow \text{4:5-benz-6-carboline (VI)} + \text{NH}_3 + 2\text{H}_2\text{O}
\]

4:5-benz-6-carboline (VI) had been given the name "quindoline" by Fichter and Rohner (Ber., 1910, 43, 3489) who obtained it by the condensation of indoxyl with o-aminobenzaldehyde as follows:—
Of the other closely related benzcarbolines, only 5:6-benz-4-carboline has been synthesised. A derivative of this base (VII) was first prepared by Lawson, Perkin and Robinson (loc. cit) as a step in the synthesis of apoharmine.

The parent compound itself, however, has only recently been prepared (Kermack and Slater, J.C.S. 1928, 32-45). Their method was somewhat similar to that used in the synthesis of 4-carboline, i.e. it involved the preparation of a 3-o-aminophenyl derivative of indole, subsequent ring closure being effected by treatment of the formyl derivative with phosphoryl chloride in boiling toluene solution, thus yielding 5:6 benz-4-carboline (VIII) as outlined below:
It will be seen from the foregoing summary of the various syntheses of carbolines and benzcarbolines, that the objectives were reached, in general, by adopting either of two well-defined but totally dissimilar methods. Firstly, the method by which the desired carboline is obtained through the intermediate indole derivative, and secondly, the method involving the preparation of the corresponding benztriazol derivative.

In the following paper, the synthesis of 6-methyl-3:4-benz-5-carboline (IX) together with a few of its derivatives, is described. In the first scheme to be tried, the method was similar to that in which Kermack and Slater obtained 5:6-benz-4-carboline, and is here outlined step by step on the lines indicated in the following scheme:
Unfortunately, however, experimental difficulties soon began to present themselves. For example, the preparation of o-nitro acetophenone proved to be none too easy inasmuch as direct nitration of acetophenone appeared to yield a mixture of the ortho, meta, and para isomers, the respective percentages varying greatly according to temperature conditions.

Eventually it was decided to try and obtain o-nitroacetophenone by hydrolysis of ethyl o-nitrobenzoylacetoacetate, which could be prepared by the method of Needham and Perkin (J.C.S. 1904, 85, 148) as follows:

\[
\begin{align*}
\text{o-nitrobenzoic acid} & \quad \text{FCl}_3 \\
& \quad \text{o-nitrobenzylochloride} \\
& \quad \text{ethyl o-nitrobenzoylacetoacetate}
\end{align*}
\]

These authors obtained ethyl o-nitrobenzoylacetate from the above compound by hydrolysis of the acetyl group with a mixture of ammonia and ammonium chloride solution. When treated with concentrated sulphuric acid and left /
for two or three days, this ester yielded o-nitrobenzoylacetic acid, which on heating gently, decomposed with the loss of carbon dioxide and yielded o-nitroacetophenone. This method, however, proved to be somewhat lengthy, and moreover, gave a very poor yield of the desired product.

O-nitroacetophenone was obtained by Gevekoht (Annalen 1883, 221, 323), by refluxing ethyl o-nitrobenzoylacetoacetate with five times its volume of dilute sulphuric acid (1 part concentrated acid: two parts water), a small quantity of o-nitrobenzoylacetonc (X) being formed as a by-product.

\[
\text{X} \\
\begin{array}{c}
\text{NO}_2 \\
c\text{O}.\text{CH}_3\text{COCCH}_3
\end{array}
\]

In attempts to obtain o-nitroacetophenone by Gevekoht's method, 50%, 33%, and 29% (by weight) acid being used, the yields of o-nitroacetophenone and o-nitrobenzoylacetonc obtained were 27%, 22%, and 69%, 16% and 70% respectively of the theoretical.

It would seem from the above, that when ethyl o-nitrobenzoylacetoacetate is heated with dilute sulphuric acid, hydrolysis of the ester group, and elimination of carbon dioxide take place primarily; the acetyl group in the resulting o-nitrobenzoylacetonc not being readily susceptible to hydrolysis, o-nitroacetophenone is not obtained to any great extent.
It was obviously essential to remove the acetyl group before hydrolysis of the ester group took place. This was achieved by refluxing with alcoholic sulphuric acid.

The product, o-nitrobenzoylacetic-ester, was then hydrolysed with dilute aqueous sulphuric acid, yielding the desired o-nitroacetophenone in 80% yield. Results almost as good were obtained when the fission of the acetyl group was carried out by means of a 50% aqueous-alcoholic solution containing 10% of sulphuric acid. It is difficult to account for the fact that Gevekoht, using aqueous sulphuric acid, obtained o-nitroacetophenone as his main product. It is possible, however, that some alcohol may have been present.

The next step in the synthesis also proved rather troublesome, inasmuch as no solid compound could be isolated from the condensation of o-nitroacetophenone with phenylhydrazine. However, it was thought the difficulty could be overcome by the use of methylphenyl-hydrazine in view of the fact that the latter reacts more readily to form an indole derivative than does the former. The fact that this indole derivative would contain an m-methyl group, was in itself an advantage as the presence of such a group would preclude the possibility of subsequent ring-closure in the 1,2 positions, thus leaving the 3: position as the only one to which the chain could possibly attach itself to form a closed ring.
That such a possibility of alternative ring-closure does exist will be readily admitted when one refers back to the work of Kermack, Perkin and Robinson (loc. cit.) in which, during their efforts to synthesise norharman, they obtained a compound 5-keto-4:5-dihydroindole-diazine (1:4) (XI) from indole-2-carboxyacetamide (XII) by treatment with alcoholic hydrochloric acid as follows:

\[ \text{(XII)} \rightarrow \text{(XI)} \]

But when the N-methyl derivative of the indole was treated in the same way, they obtained 3-keto-1-methyl-4:3-dihydro-4-carboline (XIII)

Accordingly, o-nitroacetophenone was treated with methylphenylhydrazene. No solid compound, however, could be isolated, although the oil obtained by boiling with dilute hydrochloric acid, gave the indole colour test with Ehrlich's reagent, showing that the methylphenylhydrazone, had been formed to a certain extent at least. In the original scheme of this synthesis it had been intended to reduce the NO₂ group (see p. 7) after
after the indole ring had been closed, but in view of the difficulty experienced in isolating the methylphenylhydrazone, it was thought that perhaps this condensation would take place more readily with o-acetylamino-acetophenone. The reduction of o-nitroacetophenone was carried out quite smoothly by West's method (J.C.S. 1925, 127, 494), the resulting amino-compound being a dark red oil which when acetylated by treatment with acetic anhydride in the cold yielded o-acetylaminoacetophenone m.p. 74°. Heating was avoided since it was considered likely that the reaction would go further, i.e. ring-closure would occur with the elimination of water and the subsequent formation of a quinoline derivative as follows:—

\[ \begin{align*}
\text{OCH}_2\text{CH} & \quad \text{CH} \\
\text{CO.CH}_2 & \quad \text{CO.} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{NH} & \quad \text{CO} \\
\text{N} & \\
\text{OH} & \quad \text{OH}
\end{align*} \]

\text{2-methyl-o-hydroxyquinoline}

\text{2-hydroxy-4-methylquinoline}
O-acetylamino-acetophenone yielded a solid yellow methylphenylhydrazone (XIV) which gave an indole colour test with Ehrlich's reagent after warming with hydrochloric acid. The indole derivative so formed, however, could not be obtained in any other form than that of a dark red uncrystallisable oil.

![Structure of XIV]

It was thought that this oil might on further treatment with alcoholic hydrochloric acid yield the desired benzcarboline, but although a yellow solid was isolated, it did not give any fluorescence in acid or neutral solution as might have been expected.

However, 1:6-dimethyl-3:4-benz-β-carboline (XV) was eventually obtained directly from the methylphenylhydrazone of o-acetylamino-acetophenone, when the latter was treated with phosphoryl chloride in boiling toluene solution, the two stages of the reaction being represented as follows:
This yellow compound which was found to be fairly soluble in most organic solvents, the resulting solutions exhibiting a strong bluish fluorescence visible in daylight, was crystallised from ligroin in the form of peculiar petal-like crystals, m.p. 173°.

Attention was now directed to the second general method for the preparation of benz-carbolines, in the hope that 3:4-benz-5-carboline could be synthesised in this way. For the purpose in view, it was necessary to prepare 4-chloroquinoline or a suitable derivative of this compound.

From the literature, it was found that 2-methyl-4-hydroxyquinoline could be obtained very simply by the condensation of equimolecular quantities of aniline and ethyl acetoacetate (Conrad, Limpach, Ber. 1887, 20, 947), according to the following scheme:
2-methyl-4-chloroquinoline, which was obtained from the hydroxy derivative by treatment with phosphoryl chloride and phosphorus pentachloride, was found to condense quite readily with o-phenylene-diamine to yield, 2-methyl-4-O-aminophenylaminoquinoline m.p. 220° which, on diazotisation, with sodium nitrite in acid solution, readily formed the corresponding triazol derivative as outlined below:

Following the method of Thornley and Robinson (loc. cit.), 2-methyl-4-(benztriazolyl-3') quinoline, m.p. 149°, was converted into 6-methyl-3;4-benz-5-carboline, m.p. 298° by heating it with syrupy phosphoric acid.

Now theoretically, it is quite possible to obtain from the triazo-compound, by elimination of 2 nitrogen atoms from the triazol ring, an isomer of 6-methyl-3;4-benz-5-carboline which/
could be formulated as represented below by XVI, a reaction which would be somewhat analogous to the formation of apomorphine from 1-(O-aminobenzyl-)N-methyl-tetrahydroisoquinoline, (Gadamer, Oberlin and Schoeler, Arch. f. Pharm. 1925, 263, 82), in which the amino group is diazotised, and the diazonium salt of sulphuric acid is warmed in aqueous solution with copper powder, when the nitrogen is eliminated and a bond is formed joining the benzene ring to the quinoline nucleus as outlined below :-

\[ \text{1-(O-aminobenzyl-)N-methyl-tetrahydroisoquinoline} \rightarrow \text{apomorphine} \]

(XVI)
Now, the compound actually isolated exhibited a very strong bluish-violet fluorescence in all its solutions, both acid and neutral. This phenomenon of fluorescence is a general property of all benzcarbolines of this type. Moreover, it was observed from the literature that 3-carboline (loc.cit.) and its derivative 4:5-benz-3-carboline (loc.cit.) both exhibited a violet fluorescence in neutral solution; whilst 4-carboline (loc.cit.) and 5:6-benz-4-carboline (loc.cit.) both exhibited a brilliant blue fluorescence in acid solution. Therefore, from analogy, it would be expected that 5-carboline (loc.cit.) and the supposed 6-methyl-3:4-benz-5-carboline isolated as above, would exhibit the same colour of fluorescence. The fact, that 5-carboline in alcoholic hydrochloric acid solution does exhibit a bluish-violet fluorescence in the arc light similar to that observed in solutions of the supposed benzcarboline, would seem to lend some support to the claim that the latter was a derivative of 3:4-benz-5-carboline.

In order to further substantiate the above claim, it was thought desirable to prepare a derivative of the triazol compound already described, in which position 3, would be substituted by a methyl group, in order that the only possible method of ring-closure would lead to the formation of a derivative of XVI; the properties of this latter compound could then be compared with those of the supposed benzcarboline already prepared. An alternative method also /
suggested itself, namely, substitution in position 5, when only a benzcarboline could be formed from the corresponding triazol derivative by loss of nitrogen and subsequent ring-closure. It was found, however, that the substitution suggested in the first scheme, could be effected very conveniently by the condensation of p-anisidine with ethyl methylacetoacetate under similar conditions to those present in the preparation of 2-methyl-4-hydroxyquinoline, when 2:3-dimethyl-4-hydroxy-6-methoxyquinoline, m.p. 294° resulted, and this method was, therefore, adopted. 2:3-dimethyl-4-chloro-6-methoxyquinoline, m.p. 111° A white solid which was not nearly so volatile in steam as 2-methyl-4-chloroquinoline, and which differed also from the latter in not forming a hydrate, was obtained from the corresponding hydroxyquinoline by treatment with phosphorus oxychloride.

2:3-dimethyl-4-0-aminophenylamino-6-methoxyquinoline m.p. 193° which was obtained from the above chloro-derivative by condensation with 0-phenylenediamine, showed a striking resemblance to the phenylaminoquinoline previously isolated, and was converted into 2:3-dimethyl-4-(benztriazolyl-3')-6-methoxyquinoline m.p. 201°, by diazotisation, at low temperature, with sodium nitrite in acid solution. This compound on heating with syrupy phosphoric acid, did not seem to effervesce so freely and certainly not as so low a temperature as did 2-methyl-4-(benztriazolyl-3') quinoline, when similarly treated.
When it was thought that the reaction had been completed (judging by the cessation of effervescence) the resulting liquid was treated according to the method used in the isolation of 6-methyl-3:4-benz-5-carboline, i.e. the yellow solid which separated on making slightly alkaline with sodium hydroxide was extracted with boiling ammoniacal methyl alcohol.

Very little of the solid, however, went into solution, offering a striking contrast to the behaviour of the benzcarboline, which dissolved very readily in this solvent, leaving behind scarcely any insoluble material.

This yellow substance, which seemed to be sparingly soluble in most organic solvents and which could not be obtained in a crystalline condition from any of those tried, was, however, soluble in both dilute acids and sodium carbonate solution and even in water to a slight extent. Most of its solutions exhibited a greenish fluorescence in the arc light, the strength of which, however, contrasted unfavourably with that of the benzcarboline solutions. Furthermore, on treatment with acetic anhydride it yielded an acetyl derivative, a fact which, when taken in conjunction with its other properties, such as the reduction of ammoniacal silver nitrate and Fehling's solutions, would seem to indicate the presence of a phenolic group in the molecule.

From the above evidence it must be supposed that ring-closure does not occur in
position 5, under these conditions, even when that position is activated by the adjacent methoxy group, and that the substance actually formed is possibly 2:3-dimethyl-4-0-hydroxyphenylamino-6-methoxyquinoline. (XVII).

Since the influence of the methoxy group in the above triazo compound had not apparently been great enough to activate the hydrogen in position 5, so that ring-closure could occur in that position, it was resolved to try and synthesis the methoxy derivative of 6-methyl-3:4-benz-5-carboline.

Accordingly, 2-methyl-4-hydroxy-6-methoxyquinoline (Conrad and Limpach, loc.cit.) was prepared by the condensation of p-anisidine and ethyl acetoacetate according to the scheme already outlined in the analogous preparation of 2-methyl-4-hydroxyquinoline. 2-methyl-4-chloro-6-methoxyquinoline was then obtained in the usual manner from the corresponding hydroxyquinoline by treatment with phosphorus oxychloride and yielded 2-methyl-4-0-aminophenylamino-6-methoxyquinoline, m.p. 188° when condensed with /
o-phenylenediamine under reduced pressure.

This compound yielded on diazotisation with sodium nitrite, under the same conditions as before, 2-methyl-4-(benztriazolyl-3')-6-methoxyquinoline m.p. 144°. This latter base, which closely resembled those triazo bases already mentioned, effervesced when heated in syrupy phosphoric acid solution, yielding a yellow solid on neutralisation with dilute caustic soda, which however, only partly dissolved in ammoniacal methyl alcohol. The residue was comparatively sparingly soluble in ethyl alcohol and closely resembled the yellow substance, obtained exclusively from 2:3-dimethyl-4-(benztriazolyl-3')-6-methoxyquinoline in its inability to crystallise from alcohol and also in regard to the slight green fluorescence which it exhibited in this solvent. No further attention was paid, however, to it, as it was obviously not the required methoxy-benzcarboline.

The filtrate, however, yielded dark-colored crystals of 15-methoxy-6-methyl-3:4-benz-5-carboline, m.p. 236° on concentrating to small volume.

This compound was much more soluble in organic solvents than 6-methyl-3:4-benz-5-carboline, but on the other hand did not seem to be so readily soluble in dilute acids. It, however, exhibited a strong bluish-violet fluorescence in all its solutions, a phenomenon which had previously been noted in solutions of both 6-methyl-3:4-benz-5-carboline and 1:6-dimethyl-3:4-benz-5-carboline, and which appeared
to be characteristic of the derivatives of 5-carboline so far obtained.

According to the theory of anhydronium base formation (Kermack, Perkin and Robinson, J.C.S. 1922, 121, 1877), (Kermack and Slater, J.C.S. 1928, 789), the methosulphate of 6-methyl-3:4-benz-5-carboline should yield on treatment with caustic soda an anhydronium base (XVIII), the methosulphate of which should be identical with the methosulphate of 1:6-dimethyl-3:4-benz-5-carboline. The above theory can be followed more easily by a study of the diagrams below, illustrating the various compounds and reactions involved.
Thus if two methosulphates which were identical could be obtained from these two different benz-carbolines according to the above scheme, then the constitution of these supposed benzcarbolines which have been prepared as described in the preceding pages, would be proved beyond all reasonable doubt.

Now, although Kermack and Slater obtained an anhydronium base (XIX) from 5:6-benz-4-carboline methosulphate by treatment with dilute sodium hydroxide as depicted below:

![Diagram of chemical reaction]

(XIX)

Yet Armit and Robinson (J.C.S. 1922, 121, 827) were unable to convert the methosulphate of 4:5-benz-6-carboline (XX) into the corresponding anhydronium base (XXI) by similar treatment. More recently, (Robinson, J.C.S. 1929, 2948) it has been found that 2'-phenylpyrroloquinoline methosulphate (XXII) is decomposed by sodium hydroxide in aqueous solution with formation of a true anhydronium base (XXIII).
The above evidence would seem to show that the possibility of anhydronium base formation depends to a great extent on the distance (as measured by valency changes) separating the two nitrogen atoms. In view of the above, it seemed that the formation of the anhydronium base (XVIII) from 6-methyl-3:4-benz-5-carboline methosulphate by treatment with sodium hydroxide would be improbable since, in this case, as in that of 4:5-benz-6-carboline methosulphate the valency changes would have to traverse an extra benzene ring.

In practice, however, after experiencing many preliminary difficulties due to the presence of moisture when preparing the methosulphate, a yellow precipitate was obtained when an aqueous solution of the methosulphate of 6-methyl-3:4-benz-
either ammonium hydroxide or sodium hydroxide. This yellow compound which melted at 262° was probably the methohydroxide of the above 3:4-benz-5-carboline as it lost weight on heating at 110° equivalent to one molecule of water. The fact that the colour was not orange, as in the case of practically all these anhydronium bases, was not thought exceptional as Perkin and Robinson (loc.cit.) obtained harmine methohydroxide as a yellow precipitate from harmine methosulphate by treatment with sodium hydroxide, which in turn, yielded the colourless methyl harmine on heating at 100°; while more recently, Robinson and Thornley (loc.cit.) obtained 5-methyl-5-γ-carboline from an aqueous solution of the methosulphate of 5-carboline by treatment with ammonium hydroxide, in the form of yellow needles, which, like the above 3:4-benz-5-carboline did not change colour on heating at 110°.

This yellow compound yielded a colourless methosulphate in fairly good yield, which, after repeated recrystallisation from alcohol melted at 292°.

Even greater difficulty was experienced in obtaining the methosulphate of 1:6-dimethyl-3:4-benz-5-carboline, the various yields obtained at most of the stages in this synthesis being comparatively poor, with the result that only a fraction of a gram of impure methosulphate was obtained. It was found impossible with this small /
quantity, to obtain a pure sample of the compound by repeated recrystallisation. Sufficient was obtained, however, after being twice recrystallised from alcohol to give a melting point 281° this being 20° higher than that of the crude product first obtained. Although this melting point is still 11° below that of the supposed identical methosulphate 292°, the difference is probably due to the difficulty experienced in obtaining the former free from impurity, an explanation which is strengthened by the fact that a mixture of these two methosulphates melted at 285°. Aqueous solutions of both these methosulphates gave a canary-yellow precipitate with sodium hydroxide, but not with ammonium hydroxide, a fact which further strengthens the above view that these two methosulphates are identical. It is to be regretted that lack of material prevented any further comparative tests being carried out but from the evidence already advanced there would seem to be little doubt that 6-methyl-3:4-benz-5-carboline, 15-methoxy-6-methyl-3:4-benz-5-carboline, 5:6-dimethyl-3:4-benz-5-carboline, and 1:6-dimethyl-3:4-benz-5-carboline have been synthesised as described above.
EXPERIMENTAL

PART 1.

0-nitrobenzoyl chloride:

This compound was prepared from 0-nitrobenzoic acid (100 g.), by mixing it with phosphorus pentachloride (135 g.) and, as soon as the reaction, which commenced in the cold, had slackened, the whole was heated on the water-bath under an air condenser for 1-2 hours. The flask was then connected with the vacuum apparatus and the phosphorus oxychloride distilled off at the lowest possible temperature, leaving the 0-nitrobenzoyl chloride as a yellowish, strongly fuming liquid, which crystallised on cooling. (yield 85 g.).

Ethyl 0-nitrobenzoylacetoacetate:

Following the method of Needham and Perkin (J.C.S., 1904, 85, 148), this compound was obtained by the condensation of 0-nitrobenzoyl chloride and ethyl acetoacetate in the presence of sodium ethylate as follows:—

Sodium (31 g.) was dissolved in 500 c.cs. of ethyl alcohol and the solution allowed
to cool. 250 c.cs. of this solution were then mixed with ethyl acetoacetate (90 g.) and the whole cooled 0° by immersion in a freezing mixture.
O-nitrobenzoyl chloride (56 g.) was then gradually added by means of a dropping funnel, the liquid being kept constantly stirred, care being taken at the same time, that the temperature did not rise above 5°. After standing half an hour, 125 c.cs. of the sodium ethylate solution were added and 28 g. of the acid chloride run in as before.

When this latter operation had been completed, the whole was again allowed to stand for half an hour and subsequently treated with the remainder of the sodium ethylate and o-nitrobenzoylchloride under the same conditions as before. After remaining overnight at ordinary temperature, the thick yellow precipitate, which consisted of a mixture of sodium chloride and the sodium derivative of ethyl 0-nitrobenzoylacetoacetate, was filtered at the pump, and washed successively with alcohol and ether. It was then added to excess of dilute hydrochloric acid which had been cooled by the addition of ice, and the whole subsequently extracted with ether. This ethereal extract was treated with dilute sodium bicarbonate solution and then dried by means of anhydrous sodium sulphate. On distilling off the ether, a brownish-red oil was obtained, which consisted of nearly pure ethyl 0-nitrobenzoylacetoacetate. (yield 93 g.)
0-nitroacetophenone:

As mentioned in the theoretical part of this paper, this compound was obtained by the hydrolysis of ethyl 0-nitrobenzoylacetoacetate with alcoholic sulphuric acid (10% by weight) followed by aqueous sulphuric acid. According to Gewekoht (Annalen, 221, 323), the above ester (25 g.) was boiled under a reflux with five times its volume of a mixture of 1 part of concentrated sulphuric acid to 2 parts of water for 8-10 hours. The above phraseology is rather ambiguous inasmuch as the strength of the sulphuric acid would be different according as the parts were taken by weight or by volume. Because of this ambiguity three experiments were carried out in which three lots of ethyl 0-nitrobenzoylacetoacetate (12.5 g. each) were refluxed with three different strengths of dilute sulphuric acid, namely, (1) 47% by weight (i.e. 1:2 by volume), (2) 33% by weight (i.e. 1:2 by weight), and (3) 28% by weight for 9 hours. Each sample was then extracted with ether, and the ethereal extracts treated with 5% caustic soda, when any o-nitrobenzoylacetone was removed. The two layers were then separated and treated as follows:

The alkaline layer was neutralised with dilute hydrochloric acid when 0-nitrobenzoyl acetone separated as an oil which crystallised on standing and was subsequently filtered.
dried, and weighed. m.p. 54-5°. The ethereal layer was washed with water, dried over anhydrous sodium sulphate and evaporated, leaving o-nitroacetophenone as a dark brown oil which was subsequently distilled under reduced pressure to purify it. The corresponding yields of o-nitrobenzoylacetone and o-nitroacetophenone obtained from the above experiments are shown in the following table:

<table>
<thead>
<tr>
<th></th>
<th>No.1 (47%)</th>
<th>No.2 (33%)</th>
<th>No.3 (28%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-nitrobenzoylacetone</td>
<td>4.8 g. (52%)</td>
<td>6.4 g. (68%)</td>
<td>6.6 g. (70%)</td>
</tr>
<tr>
<td>o-nitroacetophenone</td>
<td>2.0 g. (27%)</td>
<td>1.6 g. (22%)</td>
<td>1.2 g. (16%)</td>
</tr>
</tbody>
</table>

From these figures it will be seen that the yield of o-nitroacetophenone is very poor, and that the main product of the hydrolysis under these conditions is undoubtedly o-nitrobenzoylacetone.

Eventually, however, the preparation of o-nitroacetophenone from ethyl o-nitrobenzoylacetoacetate was achieved in very good yield as follows:

The ester was refluxed with an alcoholic solution of sulphuric acid containing 10% by weight of acid, the acetyl group being removed as ethyl acetate. An amount of water equal to the volume of alcohol used, was then added, and the whole distilled until the liquid had been reduced to its original volume: the ethyl acetate and the bulk of alcohol were thus removed. The residue was refluxed for about an hour and cooled, and the o-nitroacetophenone
extracted with ether. Practically nothing was obtained from this ethereal solution on extraction with dilute alkali solution, showing that very little, if any, o-nitrobenzoylacetoacetone had been formed.

The extract was dried over anhydrous sodium sulphate, the ether removed, and the dark-brown residual oil distilled at 149°-152°/10mm. when o-nitroacetophenone was obtained in the receiver as a clear, pale yellow oil.

**O-aminoacetophenone:**

This compound was prepared from o-nitroacetophenone by the method of West (J.C.S. 1925, 127, 494) in which 5.5 g. (1/30 mol. wt.) of the oil were dissolved in 17 c.c.s. of absolute alcohol and 5 c.c.s. of concentrated hydrochloric acid added. This solution was heated on the water-bath under a reflux, and while boiling, 6 g. of iron filings were added in four portions, at intervals of five minutes. After 3-4 hours, the solution was made alkaline with dilute caustic soda and steam distilled when O-aminoacetophenone was obtained from the aqueous distillate by extraction with ether. The extract was dried over anhydrous sodium sulphate, and the ether distilled off, leaving the base as a clear, mobile, brown oil. (yield 60%).
O-acetylaminoacetophenone:

The oil obtained above, was treated with 3-4 times its own volume of acetic anhydride and the solution left to stand for two hours at room temperature. It was then warmed on the water-bath with excess water until all the acetic anhydride had been decomposed. On standing for some time, long, fine, silky, colourless needles of O-acetylaminoacetophenone separated, m.p. 74-5°.

O-acetylaminoacetophenone methylphenylhydrazone:

2 g. of O-acetylaminoacetophenone were dissolved in 20 c.c.s. of 50% acetic acid solution containing 1.5 g. of methylphenylhydrazone and the whole heated on the water-bath for half an hour. The solution which had darkened very considerably was allowed to stand, and the yellow crystals which subsequently separated, were filtered and dried. (yield 0.7 g.). When recrystallised from petroleum ether this compound separated in the form of tetragonal bipyramids, m.p. 131-2°.

(Found: C, 72.7%; H, 6.5% : \( \text{C}_{17} \text{H}_{19} \text{ON}_3 \) requires C, 72.6%; H, 6.8%).

This compound is very soluble in alcohol and benzene, moderately so in hot petroleum ether (b.p. 60-80°) but insoluble in water. It is
sparingly soluble in cold dilute mineral acids, but easily dissolves on warming to form yellow solutions. In dilute nitric acid it forms a reddish-purple coloured solution which disappears on warming or standing. That this colour is probably due to the presence of nitrous acid, would seem likely, since the same colour is observed on adding a drop of a dilute solution of sodium nitrite to a solution of the compound in dilute hydrochloric acid, and which again fades on heating or standing. The same colour develops in acetic acid solution on standing for 24 hours, but not in lactic acid. This colour, however, does not fade on heating or standing. With concentrated sulphuric acid it dissolves with difficulty in the cold to form a yellow solution which darkens on heating, and then exhibits a greenish fluorescence in the arc light. It is easily soluble in cold concentrated nitric acid to form a yellow solution, which undergoes no further colour changes on warming.

1,6-dimethyl-3,4-benz-5-carboline;

This compound was prepared by refluxing O-acetylaminoacetophenonemethylphenylhydrazone (2 g.) with phosphorus oxychloride (4 c.c.s.) in a solution of toluene (10 c.c.s.), (which had previously been distilled over phosphorus pentoxide) for two hours. The solution, which was originally clear brown, soon deposited a dark coloured, viscous oil,
which adhered to the sides of the flask. The toluene, was decanted off, and the sticky residue washed several times with light petroleum ether, in order to free it from toluene. The residue was then extracted with hot alcoholic potassium hydroxide (20%) and filtered; thus separating the base from the phosphoric acid which, of course, remained behind as the potassium salt. The dark coloured alcoholic filtrate was poured into a large excess of water, when a yellow solid separated in the form of a finely divided precipitate which, when an attempt was made to filter it, passed through the filter paper. The precipitate was, however, coagulated by the addition of a little sodium chloride solution, when it was filtered without difficulty and subsequently dried on the water-bath. Its solubility in alcohol was found to be rather too great for crystallisation purposes and benzene was found to be much more suitable. This base, which separated from the latter solvent, in a microcrystalline condition, was, however, best obtained from ligroin, separating in the form of yellow sharp pointed petals which curved outwards from a central nucleus. In later stages of development these petals joined together to form a flat circular surface the periphery of which was serrated (see diagram) (yield 0.5 g.).
This base, which melted at 173-4°, was much more soluble in organic solvents than 6-methyl-3:4-benz-5-carboline. It was sparingly soluble in dilute mineral acids to yield yellow coloured solutions which exhibited blue fluorescences, scarcely visible in daylight, but which were very strong in the arc light. It was moderately soluble in dilute acetic and lactic acids, yielding yellow solutions which exhibited an intense greenish fluorescence even in daylight. It was very soluble in alcohol, but moderately so in benzene, both solutions exhibiting a greenish fluorescence, the latter, however, being very weak, even in the arc light. When treated with concentrated sulphuric acid, the base yields a reddish-brown solution, exhibiting a light-blue fluorescence, which, when warmed, loses its reddish tinge, the colour of the fluorescence changing to violet. It is very soluble in concentrated nitric acid to yield a dark yellow solution, which, on warming, lightens considerably, and gives no fluorescence on dilution.

(Found: C, 81.8%; H, 5.7%; N, 11.4%)

C₁₇H₁₄N₂ requires C, 82.9%; H, 5.7%; N, 11.4%
1:6-dimethyl-3:4-benz-5-carboline methosulphate:

The amount of 1:6-dimethyl-3:4-benz-5-carboline available (0.3 g.) for conversion into the methosulphate was rather small for such a reaction, and it is little wonder that the yield of impure methosulphate obtained by refluxing the above quantity of benzcarboline with an equal weight of dimethyl sulphate in dry toluene solution for 1 hour, did not exceed 0.2 g. After two crystallisations from alcohol, the amount of methosulphate available, precluded the possibility of an accurate analysis and only sufficed for a melting point determination, and one or two reactions with the more common reagents. The melting point of the crude methosulphate first obtained was 20° lower than that finally obtained after recrystallisation from alcohol, namely, 281°. This compound, like the other, methosulphates to be described, is very soluble in water, but only moderately so in alcohol. In both of these solvents, it dissolves to form colourless solutions which exhibit a beautiful blue fluorescence easily visible in daylight. Its aqueous solution is unaffected by the presence of ammonium hydroxide, but on treatment with dilute sodium hydroxide a canary yellow precipitate separates, which is easily soluble on adding a very slight excess of dilute hydrochloric acid showing that this yellow solid was not 1:6-dimethyl-3:4-benz-5-carboline.
2-methyl-4-hydroxyquinoline:

This compound was prepared by the method of Conrad and Limpach (Berichter, 1887, 20, 947) in which equimolecular quantities of aniline (93 g.), and ethyl acetoacetate (130 g.) were kept in a well-stoppered conical flask for 4-5 days at 37°. The liquid became darker and the water which had separated was removed by transferring the contents to an evaporating basin and keeping in the vacuum dessicator for two days. The clear remaining oil was transferred to a distillation flask, and the contents rapidly heated to 250°, when a vigorous reaction commenced. When the frothing had begun to subside, but before the liquid had ceased to distil over, the flame was removed. The duration of heating was found to be very important, inasmuch as too little heating, like too much, tended to give a comparatively poor yield; with the same object, it was also found advisable to carry out the initial raising of the temperature, as quickly as possible.

The residue, which on cooling, solidified as a reddish-brown, brittle, glassy substance, was extracted repeatedly with boiling water, and filtered hot. The yellow-coloured filtrates, in general, yielded yellow crystals of 2-methyl-4-hydroxyquinoline on standing for a day or two.
It must be emphasised that the solution remains supersaturated, in some cases for many days, and the rate of crystallisation, even after it has begun, is still very slow. In spite of these disadvantages, this method of isolating the compound, by extraction with water, is to be preferred to that in which dilute hydrochloric acid is used, as the extract obtained in this latter case, yields only a very dirty sticky oil, when neutralised with alkali, which on standing for a week or so, may, or may not, yield sticky crystals.

By the first method, a yield of 27% of the compound was obtained in a very pure condition, m.p. 231°. This compound is fairly soluble in dilute mineral, acetic and lactic acids and in alcohol. It is insoluble in benzene and in petroleum ether. It yields no distinctive colour reactions with concentrated sulphuric and nitric acids but exhibits a faint greenish fluorescence in the former solvent when viewed by the rays of an arc lamp.
2-methyl-4-chloroquinoline :

This compound was prepared according to the method of Conrad and Limpach (loc. cit.), in which 2-methyl-4-hydroxyquinoline (10g.) was refluxed with phosphorus oxychloride (10g.), and phosphorus pentachloride (12g.) for 1 hour in an oilbath at 130°. When cool, the contents of the flask were carefully diluted with water and the whole, after making alkaline with caustic soda, steam distilled, when the desired product which was moderately volatile in steam was obtained as a white solid which tended to solidify in the condenser. (yield 90%). On attempting to dry the product in a vacuum dessicator, it was observed that the anhydrous compound when taken out, almost immediately began to melt and the liquid so formed, slowly crystallised when left in contact with the air. These latter crystals lost 8.9% of their weight when dried in the vacuum dessicator, corresponding to the loss of one molecule of water of hydration (9.2%). Apparently 2-methyl-4-chloroquinoline is only stable under ordinary conditions as the mono-hydrate m.p. 41°. This compound is moderately soluble in dilute mineral, acetic and lactic acids. It is very soluble in alcohol and benzene in which latter solvents it exhibits a faint greenish fluorescence in the rays of an arc lamp. A similar fluorescence is observed when it is dissolved in concentrated sulphuric acid but not in nitric acid.
No colour changes are observed when these latter two solutions are heated.

2-methyl-4-o-aminophenylaminquinoline:

Following the method of Lawson, Perkin and Robinson, (J.C.S. 1924, 125, 626-57), 2-methyl-4-chloroquinoline (10g.) and o-phenylenediamine (6g.) were heated together at 140° under a pressure of 20-30 mm. for two hours. The yellow solid which separated was extracted with boiling dilute hydrochloric acid (10%) and filtered. The filtrates on cooling deposited a greyish-green mass of prismatic crystals of the di-hydrochloride m.p. 301° (yield 13 gms.).

(Found: Cl- 22.3% C_{16}H_{15}N_3*2HCl requires 22.1%)

The base was obtained as a white precipitate from an aqueous solution of the hydrochloride, by making alkaline with caustic soda. It was recrystallised from benzene, separating in clumps of white prismatic needles, m.p. 220°.

(Found: C-77.6% H-6.3% ; C_{16}H_{15}N_3 requires C-77.2% H-6.0%).

This compound can also be crystallised from hot aqueous-alcohol but from this solvent the product obtained is not so pure owing probably to slight oxidation. This base is soluble in dilute hydrochloric acid and other mineral acids, and dissolves readily in benzene, alcohol, and chloroform, but is insoluble in either petroleum ether or water.
Its solution in concentrated sulphuric acid exhibits a faint greenish fluorescence in the arc light. Its yellow solution in concentrated nitric acid rapidly changes to reddish-brown on warming.

2-methyl-4-(benztriazoly1-3')-quinoline:

Following the method of Lawson, Perkin and Robinson, (loc. cit.), this compound was obtained by the gradual addition of sodium nitrite solution (1.6g. in 20 ccs. water), to a well-cooled solution of 2-methyl-4-o-aminophenylaminoquinoline, (6.4g.) in dilute hydrochloric acid (3%) with constant stirring until a slight excess of sodium nitrite was present (as shown by the potassium iodide-starch test paper). The voluminous white precipitate of the hydrochloride which separated, was filtered at the pump, washed with water, and redissolved in an aliquot volume of boiling water. The base was obtained from this hot solution as a white bulky precipitate, by treatment with caustic soda. The colour of the precipitate gradually darkens if left long in contact with the hot alkaline solution, and it was found advisable to cool the solution immediately after the precipitation had been completed in order to obtain the base in a pure form. It was filtered, dried, and recrystallised from hot aqueous-alcohol, from which solvent it separated in the form of slender colourless needles, m.p. 149° (yield 4 g.)
This base forms a monohydrochloride which is insoluble in cold water but which crystallizes from hot water in the form of fine needles m.p. 210°.

These crystals on drying at 110° lost 11.1% of their weight corresponding to the loss of two molecules of water of hydration (10.8%).

The base is soluble in dilute nitric, sulphuric, acetic, phosphoric and lactic acids; it is moderately soluble in benzene, very soluble in alcohol, but insoluble in either petroleum ether or water. It dissolves very readily in cold concentrated sulphuric acid to give a clear solution, which exhibits a light blue fluorescence in the arc light. On heating the solution, brisk effervescence takes place and the resulting brown solution exhibits a strong bluish-violet fluorescence, presumably due to the formation of 6-methyl-3;4-benz-5-carboline. No colour reactions take place when its solution in concentrated nitric acid is heated.

6-methyl-3;4-benz-5-carboline:

Following the analogous method for the preparation of 5-carboline (Robinson and Thornley J.C.S., 1924, 125, 2169) 5 g. of anhydrous 2-methyl-4- (benztriazoly1-3')-quinoline were heated with syrupy phosphoric acid (50 c.cs.) until the /
effervescence caused by the evolution of escaping nitrogen had ceased. When the dark coloured solution had cooled, it was neutralised with dilute caustic soda and the yellow precipitate which separated, was filtered and dried. Some difficulty was experienced at first in finding a suitable solvent from which to crystallise the benzcarboline owing to its slight solubility in most organic solvents. Eventually, however, it was obtained from hot methyl alcohol in the form of light brown needles m.p. 293°C.

(Found: C=32.6% H=5.3%; C_{16}H_{12}N_2 requires C=32.8% H=5.2%)

This compound is insoluble in water and petroleum ether, sparingly soluble in benzene and in ether, moderately soluble in ethyl alcohol and very soluble in methyl alcohol.

The hydrochloride of the base is sparingly soluble in water, but the base itself forms soluble salts with phosphoric, acetic, and lactic acids. In all its solutions, both neutral and acid, 6-methyl-3:4-benz-5-carboline exhibits a strong bluish-violet fluorescence. Its clear solution in concentrated sulphuric acid assumes a bluish colour on heating. It is sparingly soluble in cold concentrated nitric acid, but easily dissolves on warming to yield a pale yellow solution which when cool deposits a yellow solid.
6-methyl-3:4-benz-5-carboline methosulphate:

A suspension of 6-methyl-3:4-benz-5-carboline (1.5g.) in 50 c.c.s. dry benzene (freshly distilled over phosphorus pentoxide) was boiled with a slight excess of dimethyl sulphate (1.5g.) under a reflux for two hours. It was difficult to see when the reaction had been completed as at no time was there a clear solution, owing to the comparative insolubility of the benzcarboline in this solvent. The hot solution was filtered at the pump and the light-coloured residue treated with water when all the methosulphate easily dissolved and was thus separated from any unchanged benzcarboline. The aqueous solution was evaporated to dryness and the residue extracted with boiling alcohol. On cooling, fine white needles of the methosulphate separated from the strongly fluorescing solution. These were recrystallised once more from alcohol when they melted at 277° (decomp.)

\[
\text{Found: N, 8.2\% } \quad \text{C}_6\text{H}_{12}\text{N}_2\text{CH}_3\text{CH}_3\text{SO}_4 \text{ requires N, 7.8\%}
\]

This compound exhibited a very strong blue fluorescence in all its solutions. It is very soluble in water, sparingly soluble in cold alcohol and also in hot benzene. It dissolves readily in cold concentrated sulphuric acid to give a clear solution, exhibiting the usual strong blue fluorescence, but which on warming, rapidly changes
to a bluish solution, thus resembling the behaviour of the parent base when similarly treated. It is insoluble in cold concentrated nitric acid but easily dissolves on warming, and is reprecipitated on cooling or on dilution with water.

5:6-dimethyl-3:4-benz-5-φ-carboline:

This compound was precipitated as a pale yellow solid when an aqueous solution of the methosulphate of 6-methyl-3:4-benz-5-carboline was made alkaline with ammonium hydroxide. It was filtered, dried, and recrystallised from aqueous-alcohol, separating in the form of fine yellow needles, m.p. 262°.

These crystals on heating at 110° until constant, lost 6.5% of their weight, corresponding to the loss of one molecule of water of crystallisation (6.8%). Analysis of the yellow anhydrous compound gave the following results:

(Found: N, 11.4%; C, 82.1%; H, 5.9%)

C17H14N2 requires N, 11.4% C, 82.9% H, 5.7%

This base is soluble in dilute hydrochloric acid and sulphuric acid but insoluble in dilute nitric acid. It is more soluble however, in dilute acetic and lactic acids in which latter solvents it gives a much stronger blue fluorescence than in the former. It is moderately soluble in alcohol, and in benzene, each solution /
exhibiting a green fluorescence in the arc light, but is only slightly soluble in hot petroleum ether. It is sparingly soluble in water, the solution exhibiting a faint bluish fluorescence.

With concentrated sulphuric acid it easily dissolves in the cold to form a clear solution which exhibits a strong light blue fluorescence but which, on warming, yields at first a violet coloured solution which later changes to prussian blue. It is soluble in concentrated nitric acid to form a light yellow solution which on warming changes to reddish-brown, but which on continued heating acquires its original colour. On dilution a white solid is precipitated.

5:6-dimethyl-3:4-benz-5,9-carboline methosulphate:

The above compound was obtained in the usual way by refluxing a solution of 5:6-dimethyl-3:4-benz-5,9-carboline in toluene with a slight excess of anhydrous dimethyl sulphate for 1-2 hours when the light-coloured solid which had separated was filtered off, dissolved in water, evaporated to dryness, and the residue redissolved in alcohol, from which solvent, the methosulphate was obtained after one or two recrystallisations, in the form of fine white needles, m.p. 292°

(found: N, 7.7% C_{17}H_{14}N_{2}CH_{2}CH_{3}SO_{4} requires N, 7.5%)

This compound is very soluble
in water, the solution exhibiting a very strong blue fluorescence, and sparingly soluble in cold alcohol and in hot benzene, in which solvents it exhibits a bluish-violet fluorescence in the arc light.

It is very soluble in cold concentrated sulphuric acid to yield a yellow solution which on warming, changes to royal blue and finally prussian blue. With concentrated nitric acid, the methosulphate behaves exactly the same as in the case of the parent base, the yellow solution on heating changing to reddish-brown and then back again to yellow. On dilution a white solid is precipitated.

Its aqueous solution is unaffected by ammonium hydroxide, but with dilute sodium hydroxide solution, a canary-yellow precipitate is obtained which easily dissolves on adding a slight excess of dilute hydrochloric acid, this behaviour differing greatly from that of 6-methyl-3:4-benz-5-carboline methosulphate on similar treatment.

2-methyl-4-hydroxy-6-methoxyquinoline:

The method employed in this preparation was very similar to that used in the case of 2-methyl-4-hydroxyquinoline.

Equimolecular quantities of p-anisidine (123 g.) and ethyl acetoacetate (130 g.) were warmed together on the water bath until the
former had completely dissolved, and the mixture was kept for 3-4 days at 37°.

The water which separated was removed as before, in a vacuum desiccator, leaving behind a dark coloured-liquid which solidified after a short time. The resultant solid was quickly heated up to 250° in a distillation flask, care being taken, as before, to avoid heating the mixture for too long or too short a time. On completion of the reaction, the contents of the flask were allowed to cool when they solidified to a brown crystalline mass. In this case the solid appeared to be almost insoluble in hot water, but, fortunately, extraction with hydrochloric acid (5%) followed by neutralisation with ammonium hydroxide, yielded a dark coloured oily product which on standing overnight, set to a crystalline mass (yield 58%). When pure this compound is light yellow in colour and melts at 296°. It is fairly soluble in dilute mineral acids especially on warming, and is moderately soluble in alcohol, but sparingly soluble in hot benzene. It is much less soluble in hot water than 2-methyl-4-hydroxyquinoline. Its solution in concentrated sulphuric acid which exhibits a greenish-blue fluorescence similar to that of its alcoholic solution, in the arc light, darkens to dull brown on warming. It is easily soluble in concentrated nitric acid to yield a reddish-brown solution which loses its reddish tinge on warming.
2-methyl-4-chloro-6-methoxyquinoline:

This compound was prepared by treating 2-methyl-4-hydroxy-6-methoxyquinoline (20 g.) with phosphorus oxychloride (40 g.) for 1-2 hours at 120°-130° under a reflux. As before, the resultant chloro-compound was purified by steam-distillation after making alkaline with caustic soda. The white product obtained, however, in this case, was not so volatile as 2-methyl-4-chloroquinoline but, like the latter, was obtained as the hydrate, m.p. 98° (yield 80%).

The latter on drying on the water bath or in the vacuum dessicator, yielded the anhydrous base, m.p. 102° which, unlike 2-methyl-4-chloroquinoline, is stable under ordinary conditions. It can be recrystallised from aqueous-alcohol, separating in the form of fine silky needles.

This base is moderately soluble in dilute mineral acids, dilute lactic and acetic acids, all of which solutions exhibit a very strong blue fluorescence in the arc light. It is moderately soluble in alcohol, sparingly soluble in hot benzene, and insoluble in petroleum ether and water. Strong bluefluorescences are also exhibited by its solutions in cold concentrated sulphuric and nitric acids which solutions show practically no colour changes on heating.
2-methyl-4-o-aminophenylamino-6-methoxyquinoline:

This compound was prepared by an exactly similar method to that used in the preparation of 2-methyl-4-o-aminophenylaminoquinoline. 2-methyl-4-chloro-6-methoxyquinoline (6.9 g.) and 0-phenylene-diamine (4 g.) were condensed together at 140° under reduced pressure (12 mm.) until the contents had gone solid (1-2 hours). The yellow product was extracted with boiling water and filtered hot, when the monochloride separated from the filtrate on cooling in the form of light yellow needles, m.p. 294°. (yield 90%).

(Found: Cl, 10.2%; C_{17}H_{17}ON_3.HCl.2H_2O requires Cl, 10.3%)

The base was obtained from an aqueous solution of the hydrochloride, as a white precipitate on making alkaline with caustic soda, and was subsequently recrystallised from hot aqueous-alcohol, from which it was obtained in the form of pink, slender, rectangular prisms, m.p. 188°.

(Found: N, 15.1%; C_{17}H_{17}ON_3 requires N, 15.1%).

This base is fairly soluble in dilute mineral acids, but much more so in dilute acetic and lactic acids. It is moderately soluble in alcohol, sparingly soluble in hot benzene, insoluble in petroleum ether and water.

Its solution in cold concentrated sulphuric acid, in which solvent it dissolves with
difficulty, exhibits no fluorescence, but on heating the clear solution becomes yellow-brown. It dissolves very readily in concentrated nitric acid to yield a yellow solution which becomes crimson on heating.

2-methyl-4(benztriazolyl-3')6-methoxyquinoline:

This compound was prepared in an analogous manner to that of 2-methyl-4:(benztriazolyl-3')-quinoline by the diazotisation of the corresponding 0-aminophenylaminoquinoline, the temperature being kept below 10°.

Thus when 2-methyl-4-0-aminophenylamino-6-methoxyquinoline (8g.) in dilute hydrochloric acid solution was treated with sodium nitrite (2 g.) as before, the white gelatinous precipitate of the hydrochloride of the base separated, and was filtered and dried. It was recrystallised from hot water, separating in the form of white needles, m.p. 221°

(Found: Cl, 8.8%: C_{17}H_{14}ON_{2}HCl.4H_{2}O requires 8.9%)

The base itself was obtained from a hot aqueous solution of the hydrochloride, as a light-coloured voluminous precipitate on making alkaline with caustic soda and was subsequently recrystallised from hot aqueous-alcohol, from which solvent it separated in the form of large pink rhombohedrons, m.p. 144° (yield 4.7g.)
(Found: C, 70.6% H, 4.9%; C_{17}H_{14}ON_{4} requires C, 70.3% H, 4.8%)

This base forms very sparingly soluble salts with mineral acids and even with acetic and lactic acids the corresponding salts are only moderately soluble in the hot, and sparingly soluble in the cold: these latter solutions exhibit a light blue fluorescence in the arc light. It dissolves in cold concentrated sulphuric acid with difficulty, and the clear solution so formed, which gives a faint greenish fluorescence, darkens and effervesces slightly on warming and at the same time exhibits a very strong violet fluorescence. (c.f. behaviour of 2-methyl-4:(benztriazolyl-3' )-quinoline).

It also dissolves with difficulty in cold concentrated nitric acid to yield a yellow solution, which, however, does not undergo any colour change on heating, but which, subsequently on cooling, deposits a yellow crystalline solid.

15-methoxy-6-methyl-3:4-benz-5-carbol ine:

This compound was obtained in an exactly similar manner to that in which 6-methyl-3:4-benz-5-carbol in e (already described) was prepared, namely, by heating the corresponding triazol derivative (1 g.), in this case, 2-methyl-4-(benztriazolyl-3')-6-methoxyquinoline, with syrupy phosphoric acid (10 c.c.s.) until all effervescence had ceased. The dark-coloured/
liquid was subsequently poured into excess of water and neutralised with sodium hydroxide when the yellow solid which separated was filtered at the pump and dried on the water bath. This solid was extracted with about 30 c.c.s. of ammoniacal alcohol and filtered from the residual yellow substance which appeared to be comparatively sparingly soluble in this solvent, and the filtrate concentrated on the water-bath until its volume had been reduced by half. No definite crystals were obtained from the resulting solution (which had been kept alkaline by the addition of one or two drops of ammonium hydroxide), on cooling, but a little of the yellow amorphous substance which had separated, was filtered off and the filtrate again concentrated until its volume had been reduced to 5 c.c.s. when the hot solution, which was now very dark in colour, was treated with two drops of ammonium hydroxide, corked up in a small Erlenmeyer flask and left for a day or two.

At the end of this period fairly big dark-brown crystals had separated, m.p. 236°. These crystals when examined under the microscope were observed to belong to the rhombic system. As will be seen from a study of the accompanying diagrams they are in the hemimorphic class.
2:3-dimethyl-4-hydroxy-6-methoxyquinoline:

Equimolecular quantities of p-anisidine (123 g.) and ethyl methylacetoacetate (144 g.), were warmed together on the water-bath until the former had completely dissolved. A layer of water separated on standing for 3-4 days at 37°C, and was subsequently removed in the vacuum desiccator, leaving behind a solid crystalline mass. As in the preparation of the other hydroxyquinolines already described, the residue was quickly heated up to 250°C in a distillation flask, when the usual vigorous reaction took place. The product was soluble in boiling water and the filtrate soon deposited light yellow crystals of the monohydrate, m.p. 294°C (Found: 1oss of H₂O, 8.0%; C₁₂H₁₅O₂N·H₂O requires 8.1%).

It was found, however, more advantageous to use dilute hydrochloric acid (3%) as the extracting medium, as the latter yielded on neutralisation with ammonium hydroxide, a solid crystalline product which was entirely free from tarry material, (Yield 55%), in this way effecting a considerable saving in time as compared with the former method. The base when recrystallised from
hot aqueous-alcohol, separates as the monohydrate (see above) in the form of nearly colourless needles which when dried at 110° lose their water of crystallisation. (Found on the anhydrous base, N, 6.8%; requires N, 6.9%)

The base is moderately soluble in hot dilute mineral acids, cold dilute acetic and lactic acids, and alcohol, but is insoluble in benzene and in petroleum ether. Its solution in concentrated sulphuric acid which exhibits a faint blue fluorescence in the arc light, darkens very considerably on warming. It readily dissolves in concentrated nitric acid to yield a reddish solution which undergoes no further colour change on heating.

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2:3-dimethyl-4-chloro-6-methoxyquinoline:

This compound, which was prepared in the usual way from the corresponding hydroxyquinoline, in this case, 2:3-dimethyl-4-hydroxy-6-methoxyquinoline (16 g.), by treatment with phosphorus oxychloride (32 g.) at 130°-140° for 1-2 hours, (yield 10.5 g.), was found to be very much less volatile in steam than the chloroquinolines already described, and purification by this method was somewhat time-consuming.

This base which does not appear to form a hydrate, crystallised from hot alcohol in the form of long colourless needles, m.p. 111°.
It is soluble in dilute mineral acids, in which solvents it exhibits a strong blue fluorescence in the arc light. It is fairly soluble in alcohol, benzene and in petroleum ether, but is sparingly soluble in dilute lactic acid. With concentrated sulphuric and nitric acids it yields solutions which exhibit a very strong blue fluorescence in the arc light, but which do not undergo any colour changes on warming.

2:3-dimethyl-4-O-aminophenylamino-6-methoxyquinoline

This compound was prepared in a similar manner to the corresponding quinoline bases already described, by the condensation of 3-phenylenediamine (4 g.) with 2:3-dimethyl-4-chloro-6-methoxyquinoline (7.4 g.) at 140° for 2-3 hours under reduced pressure (12 mm.). The solid product was extracted with boiling water and filtered, when bronze-coloured needles of the monohydrochloride m.p. 125° separated from the filtrate on cooling.

(Found: Cl, 9.9%; \( \text{C}_{12}\text{H}_{12}\text{ONCl} \) requires 9.7%)
L'ound: C1, 17.9%: C_{18}H_{19}ON_{3}\cdot 2HCl \cdot 2H_{2}O requires 17.7%

The base itself, was obtained from an aqueous solution of either of the hydrochlorides as a light yellow precipitate on neutralisation with caustic soda. When recrystallised from hot aqueous-alcohol, it separated in the form of yellow-brown cubes and short rectangular prisms, m.p. 193°

(Found: N, 14.5%: C_{18}H_{19}ON requires N, 14.3%)

This substance is moderately soluble in hot dilute mineral acids, very soluble in dilute acetic and lactic acids, moderately in alcohol and hot benzene, but insoluble in petroleum ether and water. It is sparingly soluble in concentrated sulphuric acid to yield a reddish-brown solution which loses its reddish tinge on heating, and darkens slightly. It is, however, very soluble in concentrated nitric acid and yields a dark red solution which darkens still more on heating.

2:3-dimethyl-4:(benztriazolyl-3')-6-methoxyquinoline:

This compound was prepared in a similar manner to that of the two triazo-compounds already described, by diazotisation of the corresponding 0-aminophenylaminocquinoline in acid solution with a slight excess of sodium nitrite. In this case, however, no permanent precipitate of the hydrochloride of the triazo-base separated, it, apparently, being soluble in the excess of acid present.
The base, however, was obtained as a white precipitate on making alkaline with caustic soda. After drying, it was recrystallised from alcohol, separating in the form of beautiful white hexagonal prisms, m.p. 201°

(Found: N, 18.7%; $C_{18}H_{16}ON_4$ requires N, 18.4%)

This base forms sparingly soluble salts with mineral acids and the resulting solutions exhibit a faint violet fluorescence in the arc light, not nearly so strong, however, as the blue fluorescence exhibited by the base in dilute acetic and lactic acid solutions, in which solvents it is sparingly soluble, even in the hot. It is soluble with difficulty in cold concentrated sulphuric acid and nitric acid to yield yellow solutions, both of which exhibit a very faint bluish-green fluorescence in the arc light. No change takes place on heating the latter solutions, but the former develops a dark green colour on warming for some time, without, however, effervescing in the slightest. (cf. 2-methyl-4 (benztriazolyl-3')quinoline and 2-methyl-4(benztriazolyl-3')-6-methoxyquinoline.
PART II

Synthesis of some Piperidino- and Piperazino-derivatives of Quinoline.

In this research, attempts were made to synthesise basic derivatives of quinoline, which, it was thought, would be likely to possess some antimalarial action.

It is well known, that so far, efforts in this direction have been comparatively fruitless, and this despite the great number of compounds which have been prepared and tested. In fact, up to date, only one such substance has been synthesised which is definitely of the same order of efficiency as quinine, and which has been used in practice, namely, "plasmoquin"; but even this compound has its disadvantages, the most important being its comparatively high toxicity. It is said, that, so far, best results in the treatment of malaria have been obtained by the use of a mixture of quinine and "plasmoquin"; and although it is too early as yet, to dogmatise on the suitability of such a mixture for general use, it would seem from the results so
far obtained that the ideal "antimalarial" has still to be found

\[
\begin{align*}
\text{(I)}
\end{align*}
\]

From a study of the accompanying diagrammatic representation of quinine (I) it will be seen that it consists essentially of a rather complex piperidine group linked through a carbinol group to the 4-position of a quinoline nucleus. It was thought, therefore, that similarly constituted compounds might also possess some antimalarial action and accordingly it was decided to try and prepare quinoline derivatives containing aliphatic basic groups such as piperazine and piperidine in the 4-position. For this purpose, quantities of 4-chloroquinaldine and 4-chloro-6-methoxyquinaldine were prepared by the method described in Part I of this research.

When equimolecular quantities of piperidine and 2-methyl-4-chloroquinoline were heated together for 3-4 hours at 140°, the latter compound
was recovered unchanged, but when the temperature was raised to 180°, condensation took place with the formation of 2-methyl-4-piperidinoquinoline (II) a yellow viscous oil, b.p. 207°/12 mm. This compound yielded a yellow picrate, m.p. 182° and a red aurichloride, m.p. 174°.

Similarly, when piperidine and 2-methyl-4-chloro-6-methoxyquinoline were heated together in equimolecular proportions at 180°, 2-methyl-4-piperidino-6-methoxyquinoline (III), a yellow viscous oil, b.p. 220°/12 mm. was obtained, from which a yellow picrate, m.p. 191° and a red aurichloride, m.p. 156° were easily isolated.

When 2-methyl-4-chloroquinoline was heated at 140° with a considerable excess of piperazine hexahydrate for 2-3 hours, a white solid separated from which 2-methyl-4-piperazinoquinoline, m.p. 103° (IV) was isolated, besides a small quantity of an insoluble compound which later proved to be the hydrochloride of the diquinolyl piperazine.
When relatively less piperazine was used, a correspondingly larger quantity of \( \text{N:N'-di(2-methyl-4-quinoline-)} \text{piperazine (V)} \) was formed. The difference in solubility of these two compounds in almost any solvent was most marked, especially in hot water, where the former was very soluble and the latter altogether insoluble. Great difficulty was experienced in finding a suitable solvent from which to crystallise this base; finally, however, pyridine was found to be very suitable, big crystals being obtained from a hot solution of this solvent, melting at a temperature greater than 300°, a fact which agreed with the high molecular dimensions of such a compound.
Under similar conditions, 2-methyl-4-chloro-6-methoxyquinoline condensed with piperazine with the formation of 2-methyl-4-piperazino-6-methoxyquinoline, m.p. 113° (VII) and N,N'-di(2-methyl-6-methoxy-4-quinolino-)piperazine, m.p. 286° (VIII).

When treated with acetic anhydride, 2-methyl-4-piperazinoquinoline and 2-methyl-4-piperazino-6-methoxyquinoline yielded acetyl derivatives, m.p. 122° (VI) and 154° (IX) respectively.

![Chemical structures](VII), (IX), (VIII)

The preparation of mono-N-substituted derivatives of piperazine, usually presents considerable difficulty, and with the simpler reactive halides, the di-substituted compound is usually obtained exclusively, or in preponderating amount, (cf. Moore, Boyle and Thorn, J.C.S., 1929, p. 39).
0-chloronitrobenzene is said to yield the mono-substituted derivative readily; and it is therefore of some interest that 2-methyl-4-chloroquinoline and its derivatives can, without difficulty, be made to react with piperazine, so as to yield mono-substituted derivatives.

Practically all the compounds isolated as above have now been tested in respect of their antimalarial reaction, and it is interesting to note that not one of them is even slightly active. When tested for bacteriocidal activity, negative results were obtained, a fact which is just a little surprising.

It was found, however, that 2-methyl-4-piperazino-6-methoxyquinoline had a definite antipyretic action, although, unfortunately, it was rather toxic.

The temperature of a rabbit which had been raised to 104°, was brought down to 102.2° in ten minutes by injection of 0.2 mgms. of this compound. In an endeavour to reduce the toxicity, the acetyl derivative was tried out in a similar manner, with the result that the compound lost its toxicity, and with it, its antipyretic action. The acetyl derivative, when injected in comparatively large quantities effected little or no change in the temperature and condition of the rabbit.

This example of the specificity of a compound for a certain type of reaction, furnishes
a good idea of the difficulty which is being experienced in the search for the ideal "antimalarial" (a compound which is sure to be very specific) and further emphasises the need for more systematic research and closer co-operation between the individual research workers in this field, so that every favourable avenue may be fully explored, and no stone left unturned until the final object has been achieved.
EXPERIMENTAL

PART II.

2-methyl-4-piperidinoquinoline:

Equimolecular quantities of piperidine (2.5 g.) and 2-methyl-4-chloroquinoline (5.3 g.) were heated together at 180° under a reflux for 3-4 hours. The purple-coloured solid which separated, was extracted with dilute hydrochloric acid (3%), and the solution made alkaline with caustic soda.

The dark red oil which separated, was subjected to steam distillation to remove any excess piperidine or chloroquinaldine. The residue was dissolved in ether, and the crimson coloured extract dried over potassium carbonate. The ether was removed, and the residual dark coloured oil purified by distillation in a vacuum, when it was obtained as a somewhat viscous, light yellow oil, b.p. 207°/12 mm. which could not be induced to crystallise. For analysis, the crystalline picrate and aurichloride were prepared. The /
picrate was obtained by treating the benzene solution with a cold saturated solution of picric acid in benzene, the salt separating as a yellow solid on agitation. After washing well with benzene, the picrate was recrystallised from alcohol, separating in the form of yellow needles, m.p. 182°.

(Found: N, 15.4%: \( \text{C}_{15}\text{H}_{16}\text{N}_2\cdot\text{C}_6\text{H}_3\text{O}_7\text{N}_3 \) requires N, 15.4%).

The aurichloride was obtained by mixing a solution of the hydrochloride containing an excess of hydrochloric acid with an aqueous solution of gold chloride, when it separated as a yellow-brown precipitate, insoluble in hot water, but easily soluble in alcohol, from which it was recrystallised, separating in the form of dark-red rhombic plates (the acute angle being almost a right angle) m.p. 74°.

(Found: Cl, 24.9%: \( \text{C}_{15}\text{H}_{19}\text{N}_2\text{AuCl}_4 \) requires Cl, 25.1%).

2-methyl-4-piperidinoquinoline is fairly soluble in acids, although concentrated nitric acid when added to a solution of the hydrochloride, precipitates yellow needles, m.p. 192° (decomp.), presumably the nitrate, which is sparingly soluble in cold and rather more soluble in hot water. The hydrochloride could not be obtained as a solid by passing dry hydrochloric acid gas into a benzene solution of the base. The base is somewhat soluble in most of the organic solvents, but is sparingly soluble in cold water. Its solution is concentrated sulphuric acid exhibits a very faint bluish fluorescence when illuminated by the arc lamp. Very little
darkening of the solution is observed on warming (cf. behaviour of the methoxy derivative).

2-methyl-4-piperidino-6-methoxyquinoline:

When equimolecular quantities of 2-methyl-4-chloro-6-methoxyquinoline (6.2 g.) and piperidine (2.5 g.) were heated together under the conditions adopted in the preparation of 2-methyl-4-piperidinoquinoline, and the purple-coloured solid formed, subsequently extracted, and purified as above, a clear yellow, viscous oil was finally obtained which distilled at 220° / 12 mm. The base which could not be induced to crystallise, exhibited a strong greenish fluorescence, and in its properties closely resembled 2-methyl-4-piperidinoquinoline. With concentrated sulphuric acid, however, it gave a strong blue fluorescence which disappeared on dilution. On warming, the solution in concentrated acid developed an orange-brown colour, the blue fluorescence becoming less marked. The picrate was obtained as before and recrystallised from alcohol in clusters of long yellow prisms m.p. 191°.

(Found: N, 14.3%; C₁₆H₂₀O₃N₂.C₆H₃O₇N₃ requires N, 14.4%).

The aurichloride obtained as above, recrystallised from alcohol, in which it was readily soluble, as red rhombic plates, m.p. 156°.

(Found: Cl, 24.1%; C₁₆H₂₇O₃AuCl₄ requires Cl, 23.3%).
2-methyl-4-piperazinoquinoline:

2-methyl-4-chloroquinoline and a large excess of piperazine hexahydrate (15 g.) were heated for 3-4 hours in an oil bath at 140° under a reflux. The white solid which separated, was extracted with dilute hydrochloric acid (3%) and filtered, leaving behind a small amount of the white hydrochloride of the corresponding diquinolinopiperazine. The filtrate on making alkaline with caustic soda, deposited a yellow oil, which crystallised on standing. These crystals were purified by recrystallisation from hot water (in which solvent there is a marked tendency to supersaturation) when large yellow-brown rhombic plates of the hydrate were obtained, m.p. 60°. These, on drying in the dessicator lost 24.4% of their weight, corresponding to four molecules of water of crystallisation,(24.1%), and yielded the anhydrous base m.p. 103°.

(Found: C, 74.2%; H, 7.5%; N, 18.3%; \( \text{C}_{14}\text{H}_{17}\text{N}_3 \) requires C, 74.0%; H, 7.5%; N, 18.5%).

This compound is very soluble in alcohol, in dilute mineral and acetic acids, soluble in ether, but very slightly soluble in benzene and in cold water, dissolving quite readily, however, in hot water. When treated with concentrated sulphuric acid in the cold, this base dissolved only with difficulty, yielding a clear solution which exhibits
a very faint blue fluorescence in the arc lamp and which disappears on dilution. Neither the solution in concentrated sulphuric acid, nor that in concentrated nitric acid exhibits any characteristic colour changes on warming. (cf. methoxy derivative).

2-methyl-4-piperazino-6-methoxyquinoline:

2-methyl-4-chloro-6-methoxyquinoline (5 g.) was treated with piperazine hydrate (15 g.) under the same conditions as recorded in the preparation of 2-methyl-4-piperazinoquinoline. In this case, none of the corresponding diquinolinopiperazine was formed, the product being obtained in a very pure form, by diluting the condensation product with 3-4 times its volume of water, and allowing the hot solution to stand, when crystals of the hydrate soon separated as pink pyramids, which, when recrystallised from hot water, melted at 55°. These crystals when dried in the dessicator, lost 17.9% of their weight, corresponding to three molecules of water of crystallisation (17.4%) and yielded the anhydrous base, m.p. 113°.

(Found: C, 69.7%; H, 7.5%; N, 16.0%; C\textsubscript{15}H\textsubscript{19}ON\textsubscript{3} requires C, 70.0%; H, 7.4%; N, 16.3%).

This compound possessed in its solubilities very similar properties to those of 2-methyl-4-piperazinoquinoline. Its solution in cold concentrated sulphuric acid, however, exhibits
a very strong greenish blue fluorescence which disappears on dilution. When the concentrated acid solution is warmed, a reddish-brown colour develops, and the fluorescence, although less marked, is retained. When treated with hot concentrated nitric acid, this compound develops a red colour.

2-methyl-4-(N-acetyl piperazine) quinoline:

Anhydrous 2-methyl-4-piperazine-quinoline was warmed with acetic anhydride for 2-3 hours on the water-bath. After diluting with water and warming, to hydrolyse excess of acetic anhydride, the solution was made alkaline with caustic soda, when the base separated as an oil, which crystallised on standing. It was recrystallised from hot water, separating in the form of large brown rhombic plates of the hydrate, m.p. 70°. When dried in the desiccator, these crystals lost 16.9% of their weight, equivalent to three molecules of water of hydration (16.7%) and yielded the anhydrous base, m.p. 122°.

This acetyl derivative has very similar properties to that of the parent base, both in its solubility in various solvents, and in its exhibiting a very faint bluish fluorescence in concentrated sulphuric acid, by the arc light. In addition, its alcoholic solution exhibits a slight greenish fluorescence.
2-methyl-4-(N-acetyl-piperazino)-6-methoxyquinoline:

This compound was prepared in a similar manner to 2-methyl-4-(N-acetyl-piperazino) quinoline (see above).

The hydrate was obtained from hot water in the form of light brown needles, m.p. 86° which when dried in the dessicator lost 10.9% of their weight, equivalent to two molecules of water of crystallisation (10.7%), and yielded the anhydrous base, m.p. 154°.

Here again, the properties of this acetyl derivative, resemble closely those possessed by the parent base. The distinctive colour reactions shown by 2-methyl-piperazino-6-methoxyquinoline when warmed with concentrated nitric or sulphuric acids as well as the fluorescences exhibited, were slightly more marked in this case. In addition, its solution in alcohol exhibits a slight greenish fluorescence.

N,N'-di-(2-methyl-4-quinolino-)piperazine:

2-methyl-4-chloroquinoline (3.5 g.) was condensed with piperazine hydrate (2 g.) under the same conditions as those adopted in the preparation of the monoquinolinopiperazines. In 2-3 hours, the
white solid which had separated, was treated with cold hydrochloric acid (3%) and filtered so as to separate any unchanged reactant from the solid hydrochloride of the base. This latter was soluble in a large amount of boiling water, from which solution, the base itself was obtained as a white voluminous precipitate, by making alkaline with caustic soda. This compound was found to be practically insoluble in most organic solvents, but eventually it was obtained from hot pyridine in the form of white rhombohedrons, m.p. 314°. (Found: C, 78.1%; H, 6.7%; C₂₄H₂₄N₄ requires C, 78.3%; H, 6.5%).

This compound is fairly soluble in acetic acid and lactic acid, but forms sparingly soluble salts with dilute hydrochloric, nitric and sulphuric acids. It dissolves, however, in concentrated nitric acid to give a light yellow solution, which darkens only slightly on warming, (cf. methoxy derivative). With concentrated sulphuric acid it yields a clear solution which exhibits a very faint violet fluorescence in the arc light. When warmed, this solution rapidly turns green, changing to a greenish-brown and finally dirty brown.

N:N-di-(2-methyl-6-methoxy-4-quinolino)piperazine:

This compound was obtained when 2-methyl-4-piperazino-6-methoxyquinoline (2.5 g.) and 2-methyl-4-chloro-6-methoxyquinoline (2 g.) were
heated together at 140° for 2-3 hours, or when 2-methyl-4-chloro-6-methoxyquinoline (4 g.) and piperazine hydrate (2 g.) were heated under the same conditions as in the preparation of the last compound. In either case, the base was obtained as a white solid when a hot aqueous solution of the buff-coloured hydrochloride was made alkaline with caustic soda, the hydrochloride being readily isolated from the reaction mixture on account of its insolubility. It was recrystallised from hot pyridine, separating in the form of pink rhombohedrons, m.p. 286°.

(Found: C, 72.5%; H, 6.5%; C₂₆H₂₈O₂N₄ requires C, 72.9%; H, 6.5%).

In its sparing solubility in most solvents it resembles very closely N : N' -di- (2-methyl-4-quinolino-)piperazine, already described. On warming its solution in concentrated nitric acid, however, a dark red colouration quickly develops. Its pale yellow solution in concentrated sulphuric acid exhibits a strong green fluorescence which disappears on warming, the solution becoming successively pale violet, dark violet and finally reddish-purple.