PREPARATION OF ANTI-MALARIAL COMPOUNDS.

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For the preparation of anti-malarial compounds.

Abstract

The preparation of anti-malarial compounds.

Submitted by D. Lockhart, B.Sc., for the degree of Doctor of Philosophy.
The Preparation of anti-malarial compounds. - abstract.

The quinine molecule has been decomposed giving Pyridine and quinoline derivatives. Compounds having two discrete basic centres and a methoxy group show pharmacological activity. These considerations led to the choice of Lepidines and Quinaldines as likely starting points from which to prepare derivatives having drug action. Furthermore such molecules have a methyl group \( \text{CH}_3 \) which, situated as it is with respect to the nitrogen in the ring, should be reactive.

For the same reason substitution in the 2- and 4- positions should give reactive compounds with which to work. Quinoxalines and Pyrimidines are examples of such compounds; they were also investigated in order to produce additional evidence of this reactivity.

Lepidines.

It was hoped to prepare 4Styryl 2phenoxy Lepidine by Rabe's method (Ber., 1931, 64, 2492)

But the attempt proved unsuccessful.
An unsuccessful attempt was made to modify the synthesis. The diaryl ethers were prepared, but attempts to nitrate 2:3 diphenoxy 2:3 dihydroxy- and 2:3 dichlorquinoxaline failed.

This method of preparing ethoxy quinoxalines failed owing to the instability of the o-diamine.

Dichlorquinoxaline was condensed with primary bases giving:
- 2:3 Dianilino quinoxaline
- 2:3 Di m Toluidine
- 2:3 Di p
- 2:3 Di praidine

Pyrimidines.

Trichlorpyrimidine was prepared from barbituric acid, and the triarethers were prepared using phenol
- p-cresol
- p-methoxy phenol
- p-chlor phenol.

Quinaldines.

4 chlor 6 ethoxy quinaldine was prepared and its reaction to methyl iodide.
Hydrochloric Acid

nitrating agents

was studied.

The four aryl ethers were prepared.

The nitration of 4 (p-anisoxyl, 6 ethoxy quinoline) was studied.

A trinitro and a mononitro body (C) were obtained and their

constitutions investigated.

\[
\begin{align*}
\text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} \\
\text{NO}_2 & \quad \rightarrow & \quad \text{O} & \quad \rightarrow & \quad \text{OH} & \quad \rightarrow & \quad \text{EtO} \\
\end{align*}
\]

This synthesis of C failed but the following proof was affected.

\[
\begin{align*}
\text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} \\
\text{NO}_2 & \quad \rightarrow & \quad \text{O} & \quad \rightarrow & \quad \text{NH}_2 & \quad \rightarrow & \quad \text{Br} \\
\text{EtO} & \quad \rightarrow & \quad \text{EtO} & \quad \rightarrow & \quad \text{EtO} & \quad \rightarrow & \quad \text{EtO} \\
\text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{OMe} \\
\text{OH} & \quad \rightarrow & \quad \text{OMe} & \quad \rightarrow & \quad \text{Br} & \quad \rightarrow & \quad \text{F}_3 \\
\end{align*}
\]

S was identified with S'.

The base C gave a water soluble Hydrochloride and

seemed suitable to test for pharmacological action.
Phenyl Naphthalene.

This was an investigation into the possibilities of preparing these compounds cheaply. Adam's method for preparing 4 brom diphenyl was unsuccessfully applied. This method was modified by the preparation of the borofluoride for coupling with naphthalene. But this gave very little better results.
PREPARATION OF ANTI-MALARIAL COMPOUNDS.

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2) QUINOXALINES.

3) PYRIMIDINES.

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I. INTRODUCTION.

The use of cinchona bark as an antipyretic, especially in cases of Malarial fever, is over three hundred years old. Its active principle is Quinine, and many chemists have attempted to substitute for it a synthetic drug of equal or greater efficiency. In 1841 Gerhardt split the Quinine Molecule by fusion with potassium hydroxide, and later the decomposition products thus obtained were identified as pyridine and quinoline derivatives. This directed the attention of chemists to the study of the pharmacological properties of quinoline compounds. In the course of these investigations many valuable drugs have been discovered.

From consideration of the quinine molecule, and those of other substance of known pharmacological action, such as Plasmoquin, it would seem that anti-malarial properties are connected with the presence in the molecule of two discrete basic centres, and a methoxy group.
Such considerations suggested such substances as lepidines, quinaldines, etc. as likely starting points from which to build up a molecule analogous to that of quinine. Furthermore, such molecules have a methyl group $\text{CH}_3$ which, situated as it is with respect to the nitrogen in the ring, should be reactive; for the same reason substitution in the 2- and 4- positions should give reactive compounds with which to work. Characteristic reactivity such as this has long been recognised in methyl ketones - nitromethane, or in the methylene group in phenyl acetonitrile. (Henrich, Ber., 1899, 32; 688). This is now definitely compared with the reactivity of 2-methyl groups in heterocyclic bases. The methyl and methylene group is in each case attached to a multivalent element $Y$, which is doubly or trebly linked to an element $Z$ of strongly negative character $\text{CH}_2 - Y = Z$. Thus Henrich, and Vorländer also, suggest that the 2-methyl groups in heterocyclic compounds should be regarded as being $\text{CH}_3 - C = N$ - the $C = N$ having the same effect on the methyl group as the carbonyl group in $\text{CH}_3 - C = \text{CO}$ of the methyl ketones. This suggests two compounds: -

```latex
\begin{center}
\begin{tikzpicture}
  \node [draw, fill=red!30] (n) at (0,0) {$N$};
  \node [draw, fill=red!30] (mc) at (0:1) {$\text{CH}_3$};
  \node [draw, fill=red!30] (m) at (90:1) {$\text{CH}_3$};
  \node [draw, fill=red!30] (m2) at (180:1) {$\text{CH}_3$};
  \node [draw, fill=red!30] (m3) at (270:1) {$\text{CH}_3$};
  \node [draw, fill=red!30] (m4) at (360:1) {$\text{CH}_3$};
  \draw (-30:1) -- (0,0) -- (30:1);
  \draw (90:1) -- (180:1) -- (270:1) -- (360:1) -- (90:1);
  \draw (0,0) -- (m);
  \draw (0,0) -- (mc);
  \draw (0,0) -- (m2);
  \draw (0,0) -- (m3);
  \draw (0,0) -- (m4);
  \node [align=center] at (30:1.5) {more reactive};
  \node [align=center] at (270:1.5) {less reactive};
\end{tikzpicture}
\end{center}
```
Owing to the mobility of the system this could not be tested on pyridine, but the mobility of the system was reduced by fusing it to a benzene ring producing an isoquinoline nucleus.

The two rings each tend to retain their aromatic character with the result that the linkings are fixed in the positions assumed in the Erlémeyer Naphthalene formula. Marckwald (Annalen 1893, 274, 331; 1894, 279, 1) has shown much experimental evidence in support of this.

Mills & Smith (J.C.S. 1922, 2724) in support of this theory shewed that

\[
\text{\begin{tikzpicture}
\node at (0,0) {\text{CH}_3};
\node at (0.5,0.25) {\text{N}};
\node at (0.5,-0.25) {\text{S}};
\end{tikzpicture}} \quad \text{is much more reactive than} \quad \text{\begin{tikzpicture}
\node at (0,0) {\text{CH}_3};
\node at (0.5,0.25) {\text{N}};
\node at (0.5,-0.25) {\text{S}};
\end{tikzpicture}}
\]

They also fixed the links by replacing a \(-\text{CO}_2\text{H}_2-\) in the pyridine ring by an atom of sulphur - thus giving rise to a thiazole series. Again they shewed

\[
\text{\begin{tikzpicture}
\node at (0,0) {\text{CH}_3};
\node at (0.5,0.25) {\text{N}};
\node at (0.5,-0.25) {\text{S}};
\end{tikzpicture}} \quad \text{to be more reactive than} \quad \text{\begin{tikzpicture}
\node at (0,0) {\text{CH}_3};
\node at (0.5,0.25) {\text{N}};
\node at (0.5,-0.25) {\text{S}};
\end{tikzpicture}}
\]
They made perfectly clear the very definite difference between the reactivity of a substituent methyl group adjacent to the nitrogen atom according as it is situated on one side of the nitrogen atom or the other.

But Mills and Smith, following on Lapworth's work on acetone (T. 1904, 85, 30) and Dimroth (Ber., 1907; 40, 2404) and K. H. Meyer (Annalen 1911, 379 - 59; 380, 212, etc) on the relative reactivity of keto-enol desmotropes further pointed out that the distinctive reactivity in the methyl groups in compounds containing CH₃-CO is dependent on their capability of passing over in a greater or lesser degree into enolic modifications.

Probably the capacity of the actual methyl groups for condensing is comparatively slight. Thus quinaldine which condenses with aldehydes:

Meyer's work (Ber., 1921, 54, 2265-2268) harmonises with this, and the formation of these tautomericides is supported by other workers on pyridine and quinoline derivatives.

It is therefore possible to consider the reactivity of a methyl group in heterocyclic bases according to which side
of the nitrogen it lies, and not only from the point of view of the nitrogen-carbon linkages, but also from that of tautomeric change. On this view the reactivity of the methyl groups in quinaldine lepidine etc. is dependent on a power possessed by those bases of passing over to some extent into forms of the constitution.

It has furthermore been observed that it seems to be a general rule that, when in a methyl compound \( R-\text{CH}_3 \) the radicle is of such a nature that the reactivity of the methyl group is enhanced, then in the corresponding chloro compound the chlorine will also be unusually reactive. There is very satisfactory evidence to this effect. Schemes for preparation of compounds of possible antimalarial action were thought out bearing this theory in mind. This led to the choice of substances of the four classes:- lepidines, quinoxalines, pyrimidines, quinaldines.
LEPIDINES.

In this class the following synthesis had been worked out by Murray & Turner, (J.C.S. 1934, 856):

Aceto acetonilide was heated with strong sulphuric acid and glacial acetic acid and poured into a large volume of water when clouds of 2-hydroxy lepidine are formed. The next reaction goes very easily using an excess of phosphorus pentachloride and a little oxychloride. The chlor compound is treated with excess sodium phenoxide and heated.

The product of this reaction has never been prepared.

Rabe converted methoxy lepidine into 4-styryl-6-methoxy
lepidine by condensing the former with benzaldehyde in the presence of zinc chloride as condensing agent. (Ber., 1931, 64, 2493). This method was applied to the 2-phenoxy lepidine. The reaction mixture was worked up according to Rabe's method but the product was not soluble in ether as his base was. However, it was dissolved easily in alcohol. The solvent was evaporated to dryness and a black amorphous solid remained behind. This resisted all attempts to dissolve it in acid, and it was concluded that the styryl derivative had not been formed under these conditions.

The phenoxy lepidine was treated with zinc chloride alone - the result was a deep red liquid which smelled strongly of phenol, and from which no ether could be recovered unchanged. Thus it seemed that the zinc chloride simply destroyed the lepidyl ether, and that the benzaldehyde had no other part in the reaction but that of a diluent.

The reaction -

was attempted using exactly the same method. But the result was as negative as in the foregoing case.

On heating the chlor-lepidine alone with zinc chloride a
pink sticky mass was produced. Thus the action of the reagent seemed, once again, to be too drastic.

The exceptional ease with which 2:4 dinitrobenzaldehyde condenses with the reactive methyl groups of heterocyclic bases was pointed out by Bennett and Willis (J.C.S. 1928, 1962). Further investigations into this type of reaction were carried out by Bennett, Lawrence & Pratt, (J.C.S. 1929, II, 1465). They condensed 2.4 dimethyl quinoline with 2:4 dinitro-benzaldehyde in the presence of acetic anhydride. Some 2:4 dimethyl quinoline was tested for purity by preparing the methiodide and then the condensation with 2:4 dinitro-benzaldehyde was successfully repeated. This was done to gain experience in the technique and also some idea of the type of condensation product to expect. The method was then applied to the phenyl lepidyl ether. On working up the reaction mixture a crystalline product was obtained. Its melting point was taken, also mixed melting points with the two starting products. This evidence shewed that this crystalline product was but a mixture of the two starting products. This conclusion was further tested:-

The product was treated with concentrated hydrochloric acid in which the aldehyde is insoluble while the ether and the product required are soluble. Part of the product dissolved in the acid, and, on cooling, gave long white
needles. These were dissolved in water and basified but only a faint cloudiness resulted. It was judged to be a trace of phenoxy lepidine. The styryl compound was expected to be a shade of yellow owing to the presence of the two nitro groups. The crystalline product was therefore assumed to be a mixture of the starting products only.

Repetitions of these experiments with benzaldehyde and chlor-benzaldehyde gave equally negative results under the conditions employed. Finally the line of enquiry was abandoned owing to the difficulties involved/working up the reaction mixtures.

Hinsberg employed this method for II [Ber., 1896; 29, 784] which was originally used by Bidin [A. 237, 547]. It was necessary to heat under reflux for an hour at 180°. Experiments were made as to the best quantity of oxalic acid to use as Hinsberg was not explicit. The best yield of the purest product was found to be given with 1.5 molecules of acid to one molecule of the diacine. This gave a 75% yield. However o-phenylene diacine is an expensive starting product and so before proceeding with the synthesis, mapped out above, an attempt was made to
II. QUINOXALINES.

This class of compound has not been very widely investigated. However quinoxalines have two positions which should, according to the above arguments, be very reactive - i.e. the 2- and 3- positions. Furthermore, the reactivity should be especially noticeable in the 2:3 dichlor compound.

A very similar scheme to that employed to prepare lepidines was used to prepare quinoxalines:

Hinsberg employed this method for \( \text{II} \) (Ber., 1896; 29, 784) which was originally used by Bladin (A. 237, 347). It was necessary to heat under reflux for an hour at 160°. Experiments were made as to the best quantity of oxalic acid to use as Hinsberg was not explicit. The best yield of the purest product was found to be given with 1.5 molecules of acid to one molecule of the diamine. This gave a 75% yield. However o-phenylene diamine is an expensive starting product and so, before proceeding with the synthesis, mapped out above, an attempt was made to
dispense with its use.

Instead of \( \text{I} \rightarrow \text{II} \) it was proposed to substitute

\[
\begin{align*}
\text{NH}_2 & \quad \text{NO}_2 \\
\text{NH}_2 & \quad \text{NO}_2
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 - \text{CO} - \text{CO} - \text{NH} & \\
\text{NH}_2 - \text{CO} - \text{CO} - \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \\
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 - \text{CO} - \text{CO} - \text{NH} & \\
\text{NH}_2 - \text{CO} - \text{CO} - \text{NH}
\end{align*}
\]

It is quite simple to make (a) ethyl-o-nitro oxanilate by condensing ethyl oxalate with o-nitraniline. This is Pickard's method as quoted in Beilstein. However on examination of the reference no details of the method were given. The conditions in this condensation are important as a mono-(a) and a di-(b) condensation product are produced. The experiment was therefore repeated about 6-10 times in order to see which conditions were most favourable to the formation of the required
It seemed as though mono and di-compounds were equally easily formed. The results were very variable, but experience shewed that the best yields of mono-compound were obtained by heating till the first traces of the di compound appeared (about 1 1/2 hours). The di condensation product is easy to see as, having a melting point $> 300^\circ$. It separates out at once as a solid at the temperature of the experiment (b.p. of ethyl oxalate). The mono condensation product, on the other hand melts at 113$^\circ$ and so remains in solution. In an attempt to prepare the amino compound (c) the West and the Wet Iron methods of reduction were applied to samples of ethyl-o-nitro-oxanilate, but both proved to be utterly unsuccessful. This synthesis was therefore abandoned in favour of Phillips method of preparing \( \text{II} \) (J.C.S.1928,2393) This is really only a modification of Hinsberg and Bladin's method but it gives 100% pure yield and is very quick and simple. The method consists in boiling the o-phenylene diamine with ordinary oxalic acid crystals in the proportion of 1:1 (molecules) for ten minutes in the presence of a certain quantity of 4N hydrochloric acid. The product hardly requires purifying if pure diamine is used. Purification can however be easily effected by boiling the product up with alkali when it very readily dissolves to give the sodium salt. The solution is then
filtered and acidified when the pure 2:3 dihydroxy quinoxaline is precipitated.

II is easily converted into III by heating with phosphorus pentachloride and a little oxychloride. (O. Hinsberg, Ber., 1896, 784). Hinsberg used two molecules of the pentachloride to one of the quinoxaline and heated at 160° for two hours. It was found to be better to use a larger excess of reagent, and heat 160-180°. Experiments were also made to see if it were really necessary to heat for two hours. Samples were heated for ½ hour, 1 hour, 1 ½ hours, and 2 hours. The results expressed on a graph shewed that a heating period of 1 hour gave the best result.

The yield on this method is about 82% (crude). The dichlor compound recrystallised from alcohol in pale buff-yellow or colourless needles melting at 150°; it had a strongly dermatitic action and great care had to be exercised in handling it.

The two chlorine atoms have been replaced by amino groups, and

![Chemical structure diagram](image-url)
by hydroxyl groups by the action of weak caustic alkali:
and they also react with Grignard compounds

\[
\begin{align*}
\text{N} & \quad \text{Cl} \\
\text{N} & \quad \text{Cl} \\
\end{align*}
\]

The dichlorquinoxaline was treated with sodium phenoxide employing the method of preparation of phenoxy lepidine.
The reaction proceeded with much greater ease than in the case of phenoxy lepidine. The flask was heated to a much lower temperature, and for a shorter time. The product was insoluble in methyl alcohol but crystallised beautifully from ethyl alcohol giving a steady melting point of 160°. The yield was 74-80%.
Tests for chlorine in the molecule gave negative results and analysis definitely established the compound as 2:3 diphenoxy quinoxaline (IV).
A sample of IV was heated on the water bath for a day in a sealed tube with excess methyl iodide. When the contents of the tube were examined IV was recovered pure. Thus no methiodide was formed under these conditions.
Condensations using p-methoxyphenol, p-cresol, and p-chlorophenol gave respectively 2:3 di (p-methoxy) phenoxy quinoxaline, 2:3 di p-cresoxy quinoxaline, and 2:3
di (p-chlor) phenoxy quinoxaline.

The reaction in which both chlorine atoms in III were substituted proceeded so readily that an attempt was made to substitute one chlorine atom only by altering the conditions of the condensation.

The impurity of the caustic potash sticks used was estimated and all weights recorded of alkali used were based upon this estimation.

In the first experiment half the quantities of reagent were used and temperature only allowed to rise to 60°. An oil separated which on shaking and cooling became solid. Melting points and mixed melting points were taken of the recrystallised solid. This evidence showed the product to be a mixture and no pure substance. The proportion of phenoxide was then again reduced, the alkali being used as a 20% solution in which the phenol was readily soluble. The whole mixture was boiled under reflux for two hours.

The contents of the flask was then worked up for the six possible products, viz:-
only is soluble in hot water and 2 grams of this were obtained by extraction with hot water.

The residue dissolved in alcohol. Melting points taken of the various crops of crystals which separated, indicated a very intimate mixture of several or all of the five possibilities.

The caustic alkali was then strengthened to 45% solution and half the phenol (as before) was dissolved in it. The dichlor compound was added dissolved in the rest of the phenol (100%) and the whole was kept at 50-70° for ten minutes. The product obtained was shown to be merely recovered dichlor compound. The alkaline mother liquor
was acidified and gave a yield of the dihydroxy compound. The last experiment was repeated heating the reaction mixture under reflux at 130-140° for an hour. The acidified mother liquor gave a small yield of dihydroxy compound. The product was recrystallised and the melting points of the various crops of crystals were taken. This evidence indicated once more an intimate mixture of several substances.

These experiments led to the conclusion that 2:3 dichlor quinoxaline when heated with weak alkali and excess phenol mostly yields dihydroxy quinoxaline. If the phenoxide solution is sufficiently strong and in sufficient excess both chlorine atoms are replaced simultaneously by the phenoxy radicle. Both chlorine atoms are, therefore, so reactive that one cannot be replaced without the other, at least in any appreciable yield.

As both these atoms are in exactly analogous positions this result is really only to be expected. Thus further attempts to prepare the mono substituted compound were abandoned.

None of these phenyl quinoxalyl ethers dissolved in hydrochloric acid to give hydrochlorides. They were therefore themselves not suitable to test for therapeutic action. It was hoped however that, if they could be nitrated, and these nitro groups reduced, the resulting
compounds might be of interest therapeutically.

When quinoline is nitrated it does so most readily in the 8 or 5 position. Now in the case of quinoxaline the 8 and 5 positions are identical. It was therefore hoped that 2:3 dihydroxy quinoxaline might nitrate to give:

If this nitro group could be reduced, and some kind of side chain added at this point, a compound of the quinoxaline series would have been formed very similar to Plasmoquin.

It was hoped to complete the following synthesis:

\[ R = -C-(CH_2)_3-N^+\text{Et} \]

plasmoquin
A sample of the dihydroxy quinoxaline was treated with a large excess of fuming nitric acid. The temperature rose to 40°. The nitration mixture was heated to 100°. On dilution a yellow precipitate was obtained which crystallised from acetone. The melting point was 345°. This might be expected as the addition of a nitro group usually raises the melting point. On this assumption the melting point of this substance should be greater than 416°. It is therefore no criterion of the reaction. A second recrystallisation gave a melting point of 251° and a third gave a much higher value. These results were so uncertain that this set of conditions was abandoned.

An attempt was then made with potassium nitrate and concentrated sulphuric acid, at -5° to -10° as nitrating agent. On dilution a product was precipitated which gave a melting point of 320°, this product also gave evidence of being a mixture. It was hoped to convert it into the nitro 2:3 dichlorcompound by the foregoing method for substituting the hydroxyl group by chlorine atoms. As the dichlorcompound melts at 150° this nitro compound should have a melting point more easily ascertainable, and which would provide a valuable piece of evidence as to the course of the nitration reaction. But attempted nitration of the chlor compound met with no better success.
Similar attempts were made to nitrate 2:3 diphenoxy quinoxaline. This was expected to nitrate 4 4', i.e.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

It was nitrated with a 1:1 mixture of fuming nitric acid and glacial acetic acid at room temperature, and at 50°. Both these methods gave products of very uncertain melting point. In some crops from recrystallisation the melting point rose to 232-246° indicating that a nitro compound or compounds were formed, but that the conditions were not those to promote a straightforward reaction.

A 1:2 mixture of glacial acetic acid and fuming nitric acid was then tried at 50°. After a second recrystallisation of the product obtained a melting point fairly sharp at 245° was given.

An experiment using simple excess of fuming nitric acid gave unsatisfactory results and so a further attempt was made using five parts of a 1:2 mixture of fuming nitric acid and strong sulphuric acids at -5° to 1 part of
phenoxy compound. The product recrystallised from nitro benzene, came down in clusters of tiny pale yellow prisms of melting point 238-240°. This was also not satisfactory. This nitration was no further investigated.
It was hoped to prepare a series of ethoxy quinoxaline by the synthesis:

\[ \text{a} \rightarrow \text{b} \text{ proceeded easily by Wender's method. (Gazetta 1889, 19, 29).} \]

The hydrolysis proceeded equally well. (Turner & Carpenter, J.C.S. 1934, 869.)

Many methods were tried to reduce \( c \) to \( d \) but nothing gave a good yield under the conditions employed. The difficulty of preparation lies in the extreme instability of these
o-diamines in the presence of moisture. For this reason methods using tin and hydrochloric acid, or "wet iron" were of no use.

A great many nitro bodies can be reduced to the bases with sodium hydroëulphite. Morgan & Thorpeon (J.C.S. 1926, 2694, 2695) used it to reduce 2:7 di nitro fluorene to 2:7 diamino fluorene.

\[
\begin{align*}
\text{NO}_2 & \quad \text{CO} \quad \text{NO}_2 \\
\text{NH}_2 & \quad \text{NH}_2
\end{align*}
\]

But in this case sodium hydrosulphite formed a complex with the base which rendered working up extremely difficult. The same disadvantage applies to the use of zinc and alcoholic potash.

The same difficulty exactly was encountered in the attempt to reduce 3-nitro p-toluidine in order to give an o-tolylene diamine from which a series of methyl quinoxalines could be prepared. Beilstein (XII Bd S. 845) recommends tin and hydrochloric acid to effect this reduction giving the reference NoeltingfStoecklin (Ber., 1891, 24, 565). This reference does not state the yield of base obtained only the melting
point. Sufficient base was actually prepared by this method to take a melting point but not sufficient with which to carry out the remainder of the above synthesis.

The reduction has also been effected using zinc dust and alcoholic potash by Limpricht's method (Ber., 1885, 18, 1404) and (Ar of Pharmazie 228, 243). In neither case is the yield stated but in the latter case the corresponding quinoxaline was actually prepared from the diamine obtained. This method was repeated exactly substituting a distillation in a stream of carbon dioxide for one in a stream of hydrogen owing to the difficulty of disposing of the hydrogen which came off. But the results were not capable of repetition under the conditions used.

R. A. Ogg, Junr., and F. W. Bergstrom (J.A.C.S., 1931, 53, 1846) condensed 2:3 dichlor quinoxaline with diamines, but no attempts have been made to condense it with monoamines. 2:3 dichlorquinoxaline was therefore heated carefully with an appropriate excess of aniline; toluidine; ortho; meta; and para; piperidine; and a methyl aniline respectively.

With aniline, and ortho and meta toluidine highly coloured crystalline condensation products were formed, crystallising from glacial acetic acid, and having fairly high melting points.
Condensation with p-toluidine gave an amorphous deep orange powder, soluble in most solvents but crystallising from none. On being precipitated from a solvent by petroleum ether (in which it is insoluble) it came down as an oil. Condensation with piperidine gave a beautifully crystalline compound crystallising from alcohol. But the more often it was recrystallised the more nearly did its melting point approximate to that of 2:3 dichlorquinoxaline. On repetition of the experiment the compound was found to give a steady m.p. of 146°. Condensation with p-methyl aniline produced only a red sticky glue. The experiment was repeated but always with the same results.

Analysis established the three crystalline condensation products as:

Although quinoxaline itself is soluble in hydrochloric acid to give a hydrochloride easily soluble in water the 2:3 dianiline, die-toluidine, and dip-toluidine derivatives proved to be well nigh insoluble in
hydrochloric acid and gave only traces of a hydrochloride which was insoluble in water. They are therefore useless as media against malaria.
PYRIMIDINES.

The plan drawn below was successfully carried out.
The barbituric acid was prepared by the Claisen reaction after the method used by Gabriel and Colman (Ber., 1904, 37, 3657). Several attempts were made to prepare trichloropyrimidine without having recourse to the sealed tube (Ber., 1900, 33, 3666), but these attempts proved unsuccessful.

The four ethers were prepared for the first time by the ether-condensation method. They proved to be very easily formed, white, and beautifully crystalline; in fact in this case the liquid chloropyrimidine had to be added to the solution of the phenol in caustic potash with the greatest circumspection, the reaction was so violent, and instantaneous.

Nevertheless the synthesis of these pyrimidine derivatives was pursued no further as it was feared that nitration would produce only mixtures of inseparable character as in the case of the quinoxaline ethers.
QUINALDINES.

The following scheme was evolved for the preparation of 4-hydroxy-6-ethoxyquinaldine which was to form the starting product from which further derivatives might be prepared.

The phenacetin was first hydrolysed with strong caustic soda in the ratio 1:5 molecules. The average yield of such an experiment proved to be about 45%. This was not considered satisfactory, and another method was investigated. The phenacetin (100 g.) was boiled with concentrated sulphuric acid (200 g.) and water (200 g.) This gave at first a yield of 65%, which was finally
improved up to 96%. The p-phenetidine thus prepared was easily converted into \( \text{p-(p ethoxy phenyl) amino crotonic ester} \) by allowing it to stand for a day in contact with aceto acetic ester. (Limpach, Ber., 1931, 64, 969). This beautifully crystalline substance is converted into the hydroxyquininaldine by throwing it into paraffin oil at 280° - 290°. (Ber., 1931, 64, 970) and (Murray and Turner J.C.S., 1934, 856).

The chlor derivative had not been prepared before, but the hydroxyethoxyquininaldine reacted with phosphorus pentachloride in the presence of a trace of the trichloride in a manner exactly analoguous to hydroxylepideidine, and dihydroxyquinoxaline. The reaction mixture, after diluting and basifying, was steam distilled as it was anticipated that chlorquinaldine, like chlorlepideidine, would be steam-volatile. This proved to be the case - the crude product of steam distillation melting at 45-65°; on crystallising from light petroleum, in which solvent this substance is exceedingly soluble, it melted at 65°. Chlorethoxyquininaldine formed a hydrochloride readily soluble in water, and a methiodide.

Nitrification took place readily at 0° in fuming nitric acid. The presence of the ethoxy-group in the 6 position activates the adjacent 5 position, and therefore
it seems most likely that the nitro group enters this position. Moreover, 6 methoxy- and 6 ethoxyquinoline shew nitration in the 5 position, but never in the 7 or 8 position. (Thacker and Engles (Ber., 1909, 42, 1740) and Vis. J. Pr. chem. (2) 40, 27). Therefore the constitution A was assigned to this nitro body which gave evidence of auto-oxidation in the air, turning a greenish colour on the surface exposed. The colour when freshly prepared is a pale yellowish buff.
On treating A with methyl iodide in a sealed tube at 90-100° a methiodide was formed. This was soluble in hot water, and separated on cooling, but not satisfactorily and the crystals, which melted at 200°, had no special form. It proved very soluble in absolute alcohol but would not separate out again.

A nitro group is highly kationoid, i.e. electron accepting, while the basic nitrogen atom is electron donating in character. Thus, in a compound like A, there is a tendency for the electrons to move from one point to the other causing partial neutralisation of the activity of the groups concerned. This leads one to expect that A should form a methiode much less readily than 4chlor6ethoxy quinaldine - which has proved to be the case.

A was condensed quite easily with p-methoxy-phenol to give 5 nitro 4 (p anisoxy) 6 ethoxy 2methylquinoline (B). This mono-nitro ether manifested the same tendency to auto oxidation on exposure to the air as A; it went pinkish on the surface, the colour when freshly made being a pale yellowish green. It readily formed a methiodide however which crystallised in beautiful needles from hot water and absolute alcohol - though in rather poor yield.

B was nitrated at 0° with a 1:1 mixture of glacial acetic and fuming nitric acids. A very poor
yield was obtained of a substance which seemed, on further investigation, to be a mixture. This attempt to prepare a dinitro body was, therefore, not pursued.

Chlorethoxyquinaldine reacted also with potassium salts of phenols as is the case with chlorlepidine, dichlorquinoxaline, etc. By this means four white, and beautifully crystalline ethers were prepared, each of which readily formed a methiodide.

The phenols used were:

Phenol, p-cresol, p-methoxy phenol, and p-chlor phenol.
An attempt was made, in the first place, to nitrate 4 phenoxy 6 ethoxy quinaldine. A 1:2 mixture of fuming nitric and glacial acetic acids were used at 20°. The mixture was then warmed to 50°. A yellow body separated out on dilution and basification which crystallised well from alcohol. However the melting point proved to be uncertain and frequent crystallisations produced no improvement. These results suggested that a mixture had been obtained, and the product was not investigated further.

Work was taken up, instead, on the 4 (p anisoxo) 6 ethoxy quinaldine. It was hoped that reactions would occur more easily in this series because of the presence of the methoxy group, in the para position of the benzene ring; for this exerts an activating effect on the 3-position in that ring. The same method of nitration was applied, but again with much the same results. In this case, however, it was observed that, when the nitro-product separated from alcohol, the least soluble part crystallised in long needles, while the more soluble part separated in rounded clusters, the further structure of which could not be distinguished, even under the microscope.

It seemed therefore that this product was also a mixture; as such it had two possible constitutions viz:-
a mixture of the anisoxyl-ether and a nitro-body, or a mixture of two nitro-bodies.

With a view to obtaining more information upon this point the product of this nitration was re-nitrated by exactly the same method. The quantities employed were based on the assumption that the substance undergoing nitration was pure unchanged p-anisoxyl ether.

The product obtained from this experiment was deep yellow and crystallised in such a way that it could now be seen, by the aid of the microscope, that needles were the only form present. A sharp melting point was obtained, and analysis shewed that three nitro groups had been introduced.

This trinitro-body would form no methiodide, but was split about the ether linkage by the action of piperidine into an alkali soluble part and an acid-soluble part, of melting points 237° and 230° respectively.

The most probable constitution of this trinitrobody seems to be:-
in which case the action with piperidine would yield either Y and X, or X and Z as shown above.

Analysis of the acid soluble body obtained gives a result for two nitro groups, and it seems reasonable to assume that one of these is ortho to the methoxy group, as that position is activated in the presence of the methoxy group. The analysis shows the third nitro group to have entered the quinoline nucleus. The position of greatest vulnerability in this nucleus has already been considered in connection with A to which the constitution 4 chlor 5 nitro 6 ethoxy 2 methyl quinoline was assigned.
The same arguments applied in this case justified the assumption that the third nitro group had entered the 5 position of the quinoline nucleus.

Neither X, Y nor Z have previously been prepared, and analysis of the acid-soluble product obtained by reaction with piperidine did not give any evidence which would distinguish between Y and Z. The following scheme was therefore drawn up for the synthesis of Y.

\[
\begin{align*}
\text{OMe} & \quad \rightarrow \quad \text{OMe} \quad \rightarrow \quad \text{OMe} \\
\text{OMe} & \quad \rightarrow \quad \text{OMe} \\
\text{OMe} & \quad + \text{piperidine}
\end{align*}
\]

Reaction with piperidine does not proceed so well when nitro groups are in the 2:3 position.
Habermann (Ber., 1875, 11, 1034) prepares the dinitro compounds directly from hydroquinone dimethylether; but Nietāki (Ber., 1887, 22, 1216) recommends preparing the mononitro compound first. His method was employed yielding 62-63% of the mono-nitro compound. Habermann's method was then reverted to for the conversion of the mononitroboddy into the mixture of 2:3 and 2:5 dinitro-hydroquinone dimethyl ether. An attempt was made to separate these isomers by partial crystallisation from ethyl acetate. This proved to be both difficult and tedious. However, finally a small quantity of each isomer was isolated.

The 2:5 isomer was heated with excess piperidine in a sealed tube on the water bath, but the starting product was recovered unchanged.

The difficulties encountered in isolating the 2:5 isomer forbade repetition of this attempt to synthesise Y and hence to distinguish between constitutions I and II of the trinitrobody.

4 hydroxy 6 ethoxy quinaldine is well known and melts at 253°. It would be allowable to assume that its mono-nitro derivative would melt at a considerably higher temperature. This compound is identical with X - the alkali soluble body obtained from the reaction of piperidine or trinitro p-anisoyl 6 ethoxy
quinaldine. But the melting point of this body was found to be 257° only. However it is quite possible that, in this case, the melting point of X is lowered by the formation of a chelate.

![Chemical Structure](image)

The study of the nitration of 4 (p-anisoxyn) 6 ethoxy 2 methyl quinoline was now pursued in attempts to prepare a dinitro compound.

The ether was nitrated at 0° with a 1:1 mixture of glacial acetic, and fuming nitric acids, and then warmed to 30-40°. A product was obtained on dilution and basification which gave every sign of being a mixture, and it was therefore not further investigated. Potassium nitrate and concentrated sulphuric acid at -5° were used as nitrating agents, but this method produced only the trinitrobody. The ether was then once more nitrated, as at first, at 0°, and the temperature was carefully kept down. The nitration mixture was diluted by pouring onto ice, and was allowed to stand for some time. While still ice-cold it was basified. The product
crystallised well, and melted sharply. Analysis however shewed it to be, not a dinitro, but a mononitrobody (C). This compound is isomeric with the mononitro ether B, prepared by condensing 5 nitro 4 chlor 6 ethoxy quinaldine (A) with p-methoxy phenol.

C is quite distinct however, melting at 183-4°C, whereas the melting point of B is 152°C. It shews none of B's tendency to auto oxidation in the air, and it very readily forms a crystalline methiodide. B gave no satisfactory dinitrobody on nitration, and its isomer C was recovered unchanged after gentle nitration. The use of more drastic reagents produced the trinitro ether. 4 (p anisopy) 6 ethoxy quinaldine may thus be added to the list of substances which it seems impossible to nitrate in certain given ways.

For example: -

\[
\begin{align*}
\text{(NO}_2)\text{N} & \quad \text{N} \quad \text{CO} \quad \text{N} \quad \text{(NO}_2) \\
\end{align*}
\]

This substance will nitrate quantitatively in the 4 4' positions but no process of direct nitration will yield a mononitro derivative. In this case however such a
derivative has been prepared by synthesis.

Abandoning therefore the idea of preparing a dinitro anisooxy ethoxy quinaldine the problem of the constitution of C remained to be solved. C, it has been pointed out, is quite distinct from B where the nitro group is known to be in the quinoline nucleus. The nitro group in C is therefore in the benzene ring. If this nitro group had entered the benzene ring meta to the methoxy group this compound should be easily capable of scission about the ether linkage by means of piperidine.

An attempt was made to synthesise the piperidine compound W as before. A sample of mononitrodimethoxybenzene was heated at 90-100°C with piperidine in a sealed tube. In this also the starting material was recovered unchanged at the end of the experiment. From a consideration of its analogues nitromethoxyphenyl
piperidine should be easily formed, yet this was found not to be the case.

It was not considered necessary to repeat this attempt to synthesise W as the other reaction product - 4 hydroxy 6 ethoxy quinaldine is well known and thus easily identifiable.

C was treated with piperidine under exactly the same conditions as the trinitrobody, but it was recovered unchanged at the end of the experiment.

Many compounds have been known to remain stubborn at the temperature of the boiling water bath which reacts readily at temperatures of 160-170°. (Murray & Turner, J.C.S., 1934, 856). But in this case, it would be quite exceptional if the nitro group had entered the position meta to the methoxy group - the ortho position being activated by this group. Therefore repetition of the above experiment at a higher temperature was reserved as a last resort if more positive results did not accrue from other lines of investigation.

If the constitution of C is:-
treatment with .880 ammonia and absolute alcohol in a
sealed tube should bring about the following reaction:-

\[
\begin{align*}
\text{ON} & \quad \text{NO}_2 \\
\text{O} & \quad \text{Me}
\end{align*}
\]

This experiment was performed, the tube being heated at 180-200° for a day. On working up, the contents of the
tube presented a charred appearance, and only a tar was
isolated.

The experiment was repeated heating the tube at 140° for
four hours. From this almost the whole of the nitrobody
was recovered unchanged; it crystallised out from the
alcohol in the tube on cooling. These crystals were
filtered off and the mother liquor remaining was diazotised
and added to an alkaline solution of \( \text{p} \)-naphthol. A deep
red colour was obtained indicating the presence of traces
of the nitroamino body, which was, clearly, far more
soluble in alcohol than the original nitrobody G.

The experiment was repeated a third time upon the unchanged
nitrobody and the tube was heated for 6 hours at 160-170°.
This yielded hardly any better results than before. It
had been hoped that it would be possible to prepare the nitroamino body in such a quantity as to be able to reduce it - forming the o-diamine, and to condense this with some suitable substance such as benzal or phenanthraquinone, thus obtaining a quinoxaline. Such characteristic reactions would have established the constitution of the nitroamino body, and hence of C, beyond further doubt.
As the foregoing scheme proved incapable of realisation it was decided to attempt the synthesis of C. The obvious method of doing this is to condense 4 chlor 6 ethoxy quinaldine with the appropriate phenol, i.e. 3 nitro 4 methoxy phenol. This phenol is not very easily prepared and finally the following scheme was evolved as likely to provide a good yield of the compound.

Neither P nor Q have been prepared before. The condensation of p-methoxy phenol and 2:4 dinitro chlorbenzene proceeded very easily, and P was obtained in beautifully crystalline form from alcohol.

This 2:4 dinitro 4' methoxy diphenyl ether (P) was nitrated with a 1:1 mixture of fuming nitric and glacial acetic acids
at room temperature. A solid was obtained on dilution which recrystallised from alcohol, and which analysis confirmed to be trinitro methoxy diphenyl ether Q. Attempts were made to introduce a fourth nitro group into Q, but the starting product was always recovered. Nitrating reagents of all strengths were used excepting only potassium nitrate and concentrated sulphuric acid, as it was feared that some sulphonation might take place, thus complicating the reaction.

Q dissolved at once in piperidine and the reaction proceeded very easily on the water bath giving 3-nitro 4 methoxy phenol, and 2:4 dinitro phenyl piperidine. Both these substances are well known, and were therefore easily identified.

It now remained to effect the condensation of this phenol and chlorethoxy quinaldine. It has been established that this kind of reaction does not proceed so easily when nitro groups are introduced into the phenol. Murray and Turner (J.C.S. 1932, 856) effected some successful condensations using nitro-phenols, but they found it necessary to have a much greater quantity of water present.

Accordingly a quite considerable quantity of water was used, and the reaction mixture was heated under reflux at 140-160°. Nevertheless working up only isolated
unchanged chlorothoxy quinaldine.

In the second attempt the potassium salt of the phenol was first carefully prepared. This bright red, and beautifully crystalline salt was added to the molten chlor compound, and then heated to 200° in a vessel open to the air. This resulted in complete charring of the reaction mixture.

In fact various experiments showed that if the temperature were low no reaction took place, and unchanged chlor-compound was recovered; while if the temperature were raised, a sudden and violent reaction took place resulting in complete charring. Between these two extremes there seemed to be no mean. The direct synthesis of C was thus rendered impossible.

With the failure of the direct synthesis a more roundabout scheme was devised to establish the constitution of C. This scheme necessitated two pieces of work - firstly some derivative of C must be prepared in which the nitro group is converted into the group X. Secondly this X-derivative must be synthesised, and for this only the one method is possible, i.e. the condensation of (X) 4 methoxy phenol with 4 chlor 6 ethoxy quinaldine. If the products of these two syntheses can be shown to be identical the problem will be solved.
Halogen-substituted phenols (ex. p-chlor phenol) have been condensed successfully with chlor lepidine, chlor ethoxy quinaldine, etc. Moreover it seemed possible to convert the nitro compound C into a halogen substituted compound by reduction and diazotisation.

Thus it seemed suitable that X should be a halogen, and bromine was the halogen selected.

The first synthesis was readily effected. C readily reduced when treated with stannous chloride and concentrated hydrochloric acid yielding 3 (4 methoxy ? amino phenoxy) 6 ethoxy quinaldine, though not in very good yield.

This base readily formed a beautifully crystalline hydrochloride easily soluble in water.

The structure of the molecule of this base comprises two basic centres (viz: $\text{-NH}_2$ and $\text{N}$) and a methoxy group. This it was regarded as a very suitable substance to test for antimalarial properties.

The base was diazotised and from the clear diazo solution the brom derivative S was prepared by the Sandmeyer method.

After several recrystallisations a pure sample of S was prepared, colourless and crystalline, melting at 193-194°.
To synthesise 3 it was necessary in the second piece of work to prepare 3 brom 4 methoxy phenol.

This compound has been prepared by F. M. Irvine and J. C. Smith (J.C.S. 1927, 74.)

They showed that it was first necessary to benzoylate p-methoxyphenol. When this benzoyle derivative was brominated the brom group entered the 3 position.

3 brom 4 methoxy phenol was then obtained by hydrolysis.

If, on the other hand, p-methoxy phenol were brominated directly, the brom group entered the 2 position. This monobromination follows the usual course for the relative directing powers of hydroxy, methoxy, and benzoyloxy groups are in the order:

\[ \text{OH} > (\text{O Me}) > (\text{O-Bz}). \]
However an alternative method of preparation was devised which possessed the advantages of entailing an investigation of the bromination of the hitherto unknown compound, P, and also of utilising that product, already prepared in some quantity:
Accordingly attempts were made to brominate P.

In the first method the bromine was dissolved in glacial acetic acid, and after its addition the reaction mixture
was warmed to 40°. When the product was worked up it seemed as if some bromination had taken place but the reaction appeared to be by no means complete, and the result obtained - a mixture.

Anhydrous sodium acetate was added in the second attempt, and the reaction mixture was boiled under reflux for several hours. This modification produced no better result.

The bromine was then added neat in the presence of a crystal of iodine to the diphenyl ether. The mixture was heated on the water bath for several hours. The product of this reaction was a dark vitreous mass which separated from alcohol in shining clusters of silky needles of sharp melting point.

The brom compound thus prepared was treated with piperidine and on working up 2:4 dinitrophenyl piperidine, which is already known, was isolated, and also a phenol containing bromine. The latter compound separated from hot water in long white needles of m.p. 110°. Now Irvine and Smith's methoxy bromphenol melted at 77-78° so that the higher melting point of the compound just prepared seemed to indicate that more than one brom group had been introduced.

Analyses of the bromether and bromphenol confirmed this, shewing that dibromocompounds had been formed.
The behaviour of this phenol with chlorethoxy quinaldine was not now of any immediate relevance to the problem in hand. But as it was a new compound its action in this connection was investigated.

The behaviour of this dibrom 4 methoxy phenol with alkali shewed a distinct resemblance to that of 3 nitro 4 methoxy phenol. Great care had to be taken in adding the phenol to the molten alkali when performing an ether-condensation, or else too vigorous a reaction took place, and charring resulted.

The first attempt to condense the phenol with chlorethoxy quinaldine by the usual method proved unsuccessful, the chlorcompound being recovered intact on working up.

The experiment was repeated using a pinch of copper bronze as a catalyst and heating to 160-180° on the metal bath. This resulted in complete charring.

The reactants were once more mixed in the flask in the usual way, but at a fairly low temperature. The whole was then refluxed on the boiling water bath for a week. On working up this reaction mixture large quantities of the chlor compound and of the bromphenol were recovered. But, in addition, a tiny trace of a substance was isolated which melted at 156° while still in a comparatively impure state, and which manifested none of the
properties of the starting materials (for example - it was insoluble in boiling alkali in which the bromphenol is, of course, soluble; it was insoluble in light petroleum (b.p. 60-80°) in which the chlor compound is exceptionally soluble.)

The quantity of this substance obtained was, however, so small, and the time taken to obtain it comparatively so great, that further investigation of it was precluded.

The required 3 brom 4 methoxy phenol was then prepared by Irvine and Smith's method. The yields obtained from this synthesis were very low.
The bromphenol was purified by recrystallisation and a sample was then condensed with chlorethoxy quinaldine in the presence of molten caustic potash. This monobromphenol shewed no tendency to react violently with the molten alkali, and char, as was found to occur in the case of 3 nitro 4 methoxy phenol, and 2:5: dibrom 4 methoxy phenol. In fact here the phenol had to be added at a pretty high temperature. After addition of the chlor compound the reaction mixture was heated for 2-3 hours at 170-190°.

The yield of this reaction was extremely low - much tar being formed, especially if the temperature were allowed to rise above 190°.
The crude product S was obtained dark brown, and very gummy.
Several crystallisations from dilute, and finally from absolute alcohol affected purification and $S'$ separated from the solvent in colourless crystals melting at 193-194°.

Small samples of $S$ and $S'$ were melted together on a watch glass, and after cooling, the homogeneous mass thus formed was well ground to a fine powder. The melting point of this intimate mixture of $S$ and $S'$ was still quite unchanged, and undepressed. Analysis confirmed this evidence that $S$ and $S'$ were identical. In $S'$ the bromine is known to occupy the position ortho to the methoxy group in the benzene ring. Therefore it also occupies this position in samples of $S$. But the bromine group in $S$ occupies the same position as the nitro group in $G$. Hence the formula assigned to $G$ was:
Investigation of the Preparation of phenyl naphthalenes.

The object of these experiments was to find a method of preparing phenyl naphthalenes by a simple laboratory method, involving the use of inexpensive chemicals only.

The formation of biaryls by diazo reactions has been investigated before at various times. Such compounds are formed under the following conditions:-

(I) Reduction of the salt, which is only partial, accompanied by the liberation of nitrogen.

(a) \( R \text{N}X + H_2 \rightarrow R + N_2 + HX \)
(b) \( 2 \text{R}X + H_2 \rightarrow 2 \text{R} + 2 \text{N} + 2 HX \)

Alcohol, and sodium phenoxide, stannous chloride, alone, or with formic acid, finely divided copper and cuprous chloride are the agents usually used.

Only symmetrical biaryls can be prepared by this method, which is especially successful when the diazonium salt has negative substituents in the benzene nucleus.

(II) In some cases a diazonium salt has been known to couple directly with some other component to form an unsymmetrical biaryl.

Ex. \( C_6H_5N_2Cl + C_6H_5OH \rightarrow \) OH

(III) This involves a modification of the Friedel Craft's reaction using a dry diazonium salt. Phenyl naphthalene among other diaryls, has actually been prepared by this process - but it is not a really practical one as these solid diazonium salts are so highly explosive.
(IV) Kühling (Ber., 1871, 4, 523) (Ber., 1896, 29, 165) and 446) used a coupling reaction of isodiazo, isodiazo hydroxides, and of diazo oxides with benzene thiophene etc.

\[
p - \text{NO}_2-C_6-H_4-N_2-OCOR + C_6 H_6 \rightarrow p - \text{NO}_2-C_6H_4-C_6H_5 + N_2 + HOCOR
\]

Bamberger modified this method (Ber., 1895, 26, 403). He shewed that isodiazo hydroxides are equally effective for this reaction. He also developed a new method using what he called 'diazonium oxides' or 'diaz o anhydrides' viz:

\[
\text{NO}_2-C_6 H_4-N_2-C-N_2-C_6 H_4-\text{NO}_2 + 2 C_6 H_6 \rightarrow 2 \text{NO}_2-C_6H_4C_6H_5 + N_2 + H_2O
\]

These compounds were however highly explosive and work with them was extremely dangerous. Gomberg and Bachmann, therefore, modified the method still further. The diazonium salts are never isolated as such. They found that when diazonium salts in aqueous solution are neutralised, a slight excess of the alkali activates the diazo compound in such a manner that they can now couple with aromatic hydrocarbons and various derivatives therefrom. This method is quoted in Roger Adams 'organic Syntheses' vol: VIII, p.42 as giving a good yield of 4-brom diphenyl by diazotising p-brom aniline and coupling it with benzene in presence of alkali. It was thought possible to apply this to the preparation of phenyl naphthalenes.

The yield of 4-brom diphenyl quoted was actually prepared by this method, but the replacement of naphthalene for benzene presented some difficulties. Being a solid it required a
solvent; a large excess of reagent was used, and it was difficult to dissolve it all in a reasonable bulk of solvent; it was difficult to get rid of the excess of reagent after the experiment was finished. Moreover the yield proved to be microscopically small and was inextricably mixed with the excess reagent. Vacuum distillations, and re-crystallisations did nothing to improve the situation. A much smaller excess of naphthalene was used, but this only very slightly ameliorated the conditions.

Turner and Le Pèvre (J.C.S. 1930, 1, 1160) used diazonium borofluorides to prepare p-fluoroaniline. This borofluoride separates quantitatively on addition of borofluoric acid to the diazo solution; it is quite stable even when dry, and is immediately decomposed on addition of alkali. Comberg's modification of Bamberger's method depends on the volume of the diazo solution being kept at a minimum. But it cannot be kept below a certain minimum or highly-coloured condensation products precipitate. Thus it was thought advisable to substitute for Bamberger's diazonium chlorides, and Comberg's minimum volume diazo solution the dry borofluoride. This modification gave an improved yield of 4-brom diphenyl. The yields of phenyl naphthalene and 4-brom phenyl naphthalene were also slightly improved. By this method it was possible to separate a very small quantity of each pure. But the yield was even then too small to make the method of any real practical use.
SUMMARY:

A good deal of work has already been done on the lepidines; nevertheless it was hoped that 4 styryl 2 phenoxy lepidine might be prepared, and from it other derivatives suitable to test for drug action. As the introduction of the phenoxy group rendered the molecule too inactive for such a scheme to be successful the line was abandoned in favour of the quinoxalines. Diaryl ethers were prepared in this series but nitration of these only gave mixtures. Nitration of the dihydroxy- and dichlor-compounds did not give any better results. di-anilino, di-toluidino (m & p) and dipiperidino quinoxalines were prepared, but tests shewed them to be inactive pharmacologically. Attempts to prepare a series of ethoxy quinoxalines failed because of the difficulties encountered in preparing the requisite o-diamine. The pyrimidines were next investigated; attempts to prepare trichloropyrimidine without recourse to the sealed tube failed. The triaryl ethers were prepared - but no attempt was made to nitrate them as it was feared they would behave like the diarylethers of quinoxalines.

In the foregoing cases investigation was limited strictly to lines likely to produce compounds having drug action. Where these lines shewed signs of failing the investigation was abandoned. However in the case of the last type of compound
considered - the 6ethoxyquinaldines, only the hydroxy derivative had been previously prepared, and thus the field was so fresh that it was examined from a more general aspect.

The chlor compound was prepared and its methiodide and hydrochloride. Its nitration was studied; the anisoxyl ether of the nitro derivative was prepared, and also the aryl ethers of chlorethoxy quinaldine.

The nitration of 6-anisoxyl ethoxy quinaldine was studied. A tri- and a mono-nitro derivative were prepared, and their constitution examined. In the course of this examination three new diphenyl ethers were prepared, and a new phenol.
was prepared and it gave a water soluble hydrochloride. It seemed very suitable to test for drug action as it had two discrete basic centres and a methoxy group. Although only one such compound resulted from investigation of the quinaldines a certain amount of the general chemistry of this class of compound was established. A certain lack of positive results in places is attributable to the fact that the object of the work was the search for drugs. This directed the investigation in certain lines which proved among the least easy of realisation while other, and probably more fruitful, avenues were passed by.
EXPERIMENTAL.

1. 2-hydroxy-l-naphtaline.

Acetocetanilide 16 g.
sulphuric acid (conc.) 20 cc.

Acetocetanilide was added slowly to cold concentrated sulphuric acid which became brown, and warm and effervesced. When all the aniline had been added the solution was left to stand for 10 minutes.

It was then poured into 15 volumes of cold distilled water. The white precipitate was filtered off and washed with about two litres of water till the filtrate was clean of sulphate.

Dried on the water bath it gave yield of 9.5 gms.
(Theoretical yield 10 gms.) 95% yield and m.p. 319°.
EXPERIMENTAL.

1. Lepidines.

1. 2-hydroxy lepidine.

Acetoacetaldehyde 18 g.

Sulphuric acid (conc) 20 cc.

Acetoacetaldehyde was added slowly to cold concentrated sulphuric acid which became brown, and warm and effervesced. When all the anilide had been added the solution was heated on the water bath for 15 minutes. It was then poured into 12 volumes of cold distilled water. The white precipitate was filtered off and washed with about two litres of water till the filtrate was clean of sulphate. Dried on the water bath it gave yield of 9.5 gms.

(Theoretical yield 10 gms.) 95% yield and m.p. 219°C.
II. 2-chlor lepidine.

\[
\begin{align*}
\text{CH}_3 & \\
&
\end{align*}
\]

2-hydroxy lepidine 1 Mol.

\[
\begin{align*}
\text{P}_5\text{Cl}_5 & \\
&
\end{align*}
\]

1 "

Dry hydroxy lepidine was treated with phosphorus pentachloride in a large conical flask. A little phosphorus oxychloride was added, and the whole was mixed to a stiff paste. The flask was heated on the water bath till there was no further effervescence (about 2 hours.) The pasty mass was then poured into a little water. The liquid was basified using very strong alkali solution, and steam distilled. Chlor-lepidine comes over free from impurities. m.p. 58°.

Yield 66-67%.
III. 2-phenoxy lepidine.

Potassium hydroxide with a few drops of water was melted and cooled until crystallisation just set in. Phenol was added very slowly and cautiously and the whole heated till a clear melt was obtained. The phenoxide formed dissolves in the excess phenol present. Chlorlepidine was added and the whole was heated for 1-2 hours on a metal bath 200-210° under an air condenser. Dilute alkali was then added, and the flask was shaken when the ether separated out solid. It was recrystallised from alcohol in which it was extremely soluble. It gave shining white plates.

m.p. 51°.

Yield 84-85%.
IV. Attempted preparation of 2-phenoxy styryl lepidine

Phenoxylepidine 0.05 Mols.
benzaldehyde 0.5 
Zinc chloride 3 g.

Phenoxy lepidine and benzaldehyde freshly distilled and purified were heated together under reflux for 5-6 hours in the presence of zinc chloride. On cooling the syrupy liquid was added to a mixture of ether and 5N sulphuric acid. A yellow sticky precipitate was formed which was filtered off and treated with strong alkali to obtain the base, a brown oily substance separated which on cooling, solidified. This was not soluble in ether, but easily so in alcohol. Therefore it was taken up in alcohol and the solvent evaporated off. A black amorphous residue remained. This substance resisted all attempts to dissolve it to form a hydrochloride.
V. Effects of Zinc chloride on phenoxy lepidine.

The last experiment was repeated using only phenoxy lepidine and zinc chloride. The proportions were kept the same, and they were heated 5-6 hours as before. The liquid changed from colourless to deep red, and on cooling, set hard. It was treated with alkali in the hopes of obtaining unchanged phenoxy lepidine back again. The mass however yielded no unchanged ether. Phenol had been formed during the reaction for it could be detected by its smell. Thus the zinc chloride had decomposed the ether.
VI. Attempt to prepare 2-phenoxy (2-4 dinitro styryl lepidine.

\[
\text{Acetic anhydride} \quad 10 \text{ mols} \\
2:4 \text{ dinitrobenzaldehyde} \quad 2 " \\
\text{Phenoxy lepidine} \quad 1 " \\
\]

The acetic anhydride was introduced into a flask and 2:4 dinitro benzaldehyde was allowed to dissolve in it. Phenoxy lepidine was then added. The mixture was heated under reflux on a liquid paraffin bath for 5-6 hours. The temperature was that of boiling acetic anhydride. On cooling most of the acetic anhydride was removed by evaporation in vacuo. A little of the resulting liquid was treated with sodium carbonate to neutralise any acetic acid formed in the process of condensation. An oily substance separated which was washed with water and alcohol till it became solid. The remaining liquid being inoculated with these crystals set nearly solid.
The product was recrystallised from alcohol - filtered, dried.
m.p. 50-70°.
Mixed m.p. 2:4 dinitrobenzaldehyde 65°

m.p. of " " 71°
Thus the product appeared to be a mixture of the starting materials.

The product was treated with concentrated hydrochloric acid. Part of it remained insoluble and was found to be 2:4 dinitrobenzaldehyde. From the acid solution long white needles crystallised out. These were filtered off, dissolved in water, and the solution basified. A white cloudiness resulted, of no account on the filter.
2:4 dimethyl quinoline methiodide.

2:4 dimethyl quinoline (b.p. 265°, \( \frac{1}{4} \) test tube full) and methyl iodide (\( \frac{1}{2} \) test tube full) were heated under reflux for 20 minutes. The product - a yellow solid - was recrystallised several times from boiling alcohol. The pure product appeared as yellow-grey soft sparkling needles. m.p. 255°. (Richter 252-253°.)
VIII: 4-methyl-2(2:4 dinitrostyryl) quinoline.

![Chemical structure of 4-methyl-2(2:4 dinitrostyryl) quinoline]

- acetic anhydride 12.5 g.
- 2:4 dinitrobenzaldehyde 2.5 g.
- 2:4 dimethylquinoline 1.75 g.

2:4 dimethyl quinoline and 2:4 dinitrobenzaldehyde (2.5 gms) and acetic anhydride, i.e. the same molecular proportions as in Experiment VI, were boiled together under reflux for 1/2 - 1 hour.

The mixture was poured into a beaker and stirred and scratched till the product separated out.

This was filtered off, recrystallised from alcol. m.p. 163-164°. (Bennet J.C.S. 1929, 1466 - 163.5°)
IX. Attempted preparation of 2 chloro-styryl lepidine.

2 chlor lepidine .05 Mols.
benzaldehyde .5 "
zinc chloride 3 g.

2 chlor lepidine and benzaldehyde, freshly distilled and purified with zinc chloride (3 gms) were heated under reflux for 6-7 hours.

The benzaldehyde was kept gently boiling. On cooling most of the excess benzaldehyde was taken off by evaporation in vacuo. A crystalline product separated from the mixture left which when recrystallised from alcohol gave a melting point 55-60°. It was therefore judged to be again a mixture of starting materials.
X. Effect of zinc chloride on chlor-lepidine.

Small quantities of zinc chloride and chlor lepidine were heated together in a test tube. The chlor lepidine was at once decomposed to a sticky pink mass smelling strongly of phenol.

The reaction was boiled under reflux; when an air condenser was used the alcohol eliminated in the reaction could be detected as it escaped thus proving the required reaction to be proceeding. In this case the double condensation is affected as well as the single one.

\[
\begin{align*}
\text{NH}_2 & \text{CO}_2\text{H} \\
\text{Na}_2 & \to \\
\text{Na}_2 & \text{CO}_2\text{Na}_2
\end{align*}
\]

So that it is necessary to find conditions to eliminate the formation of II as much as possible.

The experiment was repeated 10 times using different times of boiling. The best yield of the noncontaminated product was obtained by boiling till the decomposition...
Preparation of ethyl-o-nitro oxanilate.

(This method is Pickard's. But no experimental details are given in the references.)

\[
\begin{align*}
\text{o-nitraniline} & \quad 20 \text{ g.} \\
\text{ethyloxalate} & \quad 28 \text{ g.}
\end{align*}
\]

The reactants were boiled under reflux; when an air condenser was used the alcohol eliminated in the reaction could be detected as it escaped thus proving the required reaction to be proceeding. In this case the double condensation is effected as well as the single one.

So that it is necessary to find conditions eliminate the formation of II as much as possible.

The experiment was repeated 10 times using different times of boiling. The best yield of the monocondensation product was obtained by boiling till the dicondensation
compound began to appear. This was easily seen as II appears solid having a melting point 300°, and it happened after about 1½ hours boiling. Any traces of alcohol formed during the reaction were distilled off and also about a third of the excess ethyl oxalate. The residue was thoroughly extracted with hot alcohol as I is soluble while II is insoluble. After several recrystallisations the oxanilate separated from alcohol in pale yellow needles of m.p. 113°. The residue of the extraction was recrystallised from aniline whence it separated in mustard coloured needles, m.p. 360°.
III. Attempt to prepare ethyl-o-amino oxanilate (West process).

\[
\begin{align*}
\text{NH}_2 & \\
\text{NH}_2\text{COOC}_2\text{H} & \\
\end{align*}
\]

Iron filings 20 g.
ethyl o-nitro oxanilate 20 g.
(rectified spirit (80% water 250 cc (20%) .

The ethyl o-nitro oxanilate was dissolved in alcohol. Water is necessary for the reduction. The solution was boiled under reflux on the water bath with iron filings and hydrochloric acid (2 cc) for three hours. The iron was added in about four lots during the first \( \frac{1}{4} \) hour, and the flask was continually shaken to prevent the iron sticking. A drop of 880 ammonia was added to render the solution alkaline and it was filtered hot through a sintered glass funnel. The clear alcoholic solution was evaporated to dryness. The residue when diazotised and coupled with \( \beta \)-naphthol gave the same result as when ethyl o-nitro oxanilate was used. The appearance of the residue was also the same as that of the starting product, so it was evident that no reduction had taken place.
IV. Attempt to prepare ethyl-o-amino oxanilate.

(Wet iron method).

ethyl-o-nitrooxanilate 20 g.
iron filings 20 g.

The fine iron filings were mixed to a paste which was kept hot on the water bath. A few drops (10) of glacial acetic acid were added, and the nitro compound was stirred in. The mixture effervesced and it was stirred vigorously till reaction had ceased (1/2 hour). The mixture was extracted with hot alcohol (250 cc) and filtered to remove the iron. The alcoholic solution was evaporated to dryness. The residue was extracted with hydrochloric acid but no hydrochloride of a base could be obtained from it. Thus this method also was unsuccessful.
V. 2:3 dihydroxy quinoxaline. (J.C.S.1926, 2393)

The o-phenylene diamine was boiled for 10 minutes with the oxalic acid crystals, and the hydrochloric acid. The contents of the flask were washed with water and dissolved in caustic alkali. The liquid was then acidified and the pure 2:3 dihydroxy quinoxaline was again precipitated. This was filtered off and dried. The yield is theoretical.
VI. 2:3 dichlor quinoxaline. (B. 29, 784.)

2:3 dihydroxy quinoxaline 1 Mol.
phosphorus pentachloride 2 Mols.

The dihydroxy quinoxaline and phosphorus pentachloride and a little phosphorus oxychloride were heated together under reflux for 2 hours on the oil bath at 160-180°. After cooling ice water was added, the solid product thoroughly washed, filtered and dried. It was then recrystallised from alcohol - very pale yellow to colourless needles separated at m.p. 150°.

Yield 82%.
VII. 2:3 diphenoxy quinoxaline.

2:3 dichlorquinoxaline 1 Mol. 8 g.
phenol 6 " 23 g.
caustic potash 3.5 " 9 g.

Caustic potash was melted with one drop of water. After cooling a little phenol was added and heated till a clear melt was formed. After further cooling the dichlorquinoxaline was gradually added, and the flask warmed till the reaction began. The flask was then kept on the metal bath at 100-120° for 20 minutes under an air condenser. The contents of the flask were then washed with water and alkali and filtered off. The crude product was insoluble in methyl alcohol but very soluble in acetone and ethyl alcohol. From the former it crystallised white and shining in star-shaped clusters of needles.

m.p. 160°.

Yield 75% pure.
88% crude.

.2177 gave 17.8 ccN₂ at 27°C & 751 mm.

whence \( \% N₂ = 8.99 \).

\( C_{20}H_{14}N_2O_2 \) requires \( \% N₂ = 8.75 \).
VIII. Attempt to prepare 2:3 diphenoxy quinoxaline methiodide.

The 2:3 diphenoxy quinoxaline with excess of methyl iodide was heated in a clean sealed tube in the water bath for a day. On cooling the contents of the tube became solid; they were insoluble in water, but soluble in alcohol and ether. From alcohol the solid was recrystallised and then dried. m.p. 160°.

It had also the appearance of the starting product. Therefore no reaction had taken place under these conditions.
Caustic potash was melted with one drop of water and p-methoxy phenol was gradually added with heating till a clear melt was obtained. 2:3 dichlorquinoxaline was added gradually with very gentle heating. Suddenly the reaction started and the mixture effervesced vigorously. Further heating after the effervescence had died down had no more effect, the product was insoluble in ethyl alcohol, but very soluble in chloroform. It crystallised well from acetone but best from glacial acetic acid. Very tiny white shining needles came down. m.p. 193.7°.
Yield 53-54%.

\(0.1358 \text{ gave } 10\text{ccN at } 27.5^\circ \text{C c } 763 \text{ mm.} \)

whence \(\% \text{ N}_2 = 7.490\).

\(\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_4 \text{ requires } \% \text{ N}_2 = 7.489.\)
2:3 di p-cresoxy quinoxaline.

A clear melt of phenoxide was made exactly as above using p-cresol (13 gms) instead of p-anisoyl phenol. After the addition of dichlorquinoxaline reaction proceeded as above. The product crystallised in white shining needles from ethyl alcohol.

m.p. 145.9°.

Yield 65-66%.

Analysis.

(0.1623 gave 12cc N at 28° Cc 759 mm)

\[ \text{whence } \% N_2 = 8.23. \]

\[ \text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_2 \text{ requires } \% N = 8.19. \]
The above method was used employing the appropriate amount of p-chlor phenol (16 gms). The product crystallised from ethyl alcohol.
m.p. 153.3°.
Yield 72-73%.

Analysis.

0.2269 gave 11.4cc of N₂ at 765 mm & 25.5° C.

whence % N₂ = 7.10

C₂₀H₁₄N₂O₂Cl₂ requires % N₂ = 7.27.
XII. Attempted monosubstitution of 2:3 dichlorquinoxaline.

(a) Estimation of caustic potash used -
Wt of KOH in 1 litre of $\text{H}_2\text{O} = 7.9460$ gms.
Strength of standard HCl Soln = 1.09 (5 N).
60 cc of KOH = 8.46 cc of HCl.
:. Normality of KOH = $\frac{8.4 \times 1.097}{60}$ N.
KOH used was 83.9% Pure.

(b) 2:3 dichlorquinaxaline (1 Mol. 8 g) was added to phenol (2 mols 7.5 g.) molten in a beaker. This was stirred to a paste and heated to 60-70°. While it was cooling caustic potash with a drop of water (1.75 Mols 4.8 g) was melted and phenol (7.5 g) was added to form the clear melt. This melt was added to the first mixture and the whole stirred at 50-60° for 10 minutes. This mixture was then worked up as before. On addition of water an oil separated which finally went solid. It was recrystallised from alcohol in which it was found to be easily soluble.
m.p. of product 90-100°.
Mixed "
This product thus seems to be a mixture and no new pure substance.

Caustic potash 2 Holes 23cc of 20% solution
  phenol  2 "  9.5 g.
  2:3 dichlor-
quinoxaline 1 "  10 g.

(a) Caustic potash was dissolved in water thus forming a 20% solution. Phenol was dissolved in this solution. 2:3 dichlorquinonaline was added and the whole mixture was heated under reflux for two hours. The product was filtered off and extracted with boiling water. Some 2:3 dihydroxy quinoxaline crystallised from the hot water. Acidification of the mother liquor gave a further small yield of this substance.

m.p. of this substance 73.09°.
Yield 2 gms.

The residue after extraction with water was dissolved in alcohol from which it crystallised out in crops.

Each crop was examined:

<table>
<thead>
<tr>
<th>From</th>
<th>W.P.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>96° - 100°</td>
<td>4.8 gms.</td>
</tr>
<tr>
<td>II.</td>
<td>94° - 100°</td>
<td>1.25 &quot;</td>
</tr>
<tr>
<td>III.</td>
<td>93° - 100°</td>
<td>1.8 &quot;</td>
</tr>
<tr>
<td>IV.</td>
<td>92° - 96°</td>
<td>1.75 &quot;</td>
</tr>
<tr>
<td>V.</td>
<td>97° - 98°</td>
<td>1.0 &quot;</td>
</tr>
</tbody>
</table>

Total crude yield before recrystallising = 11.3 gms.

A. 25% of 2:3 dichlorquinodaline  A mixture of other possible products
XIII. Effect of caustic potash solution varying strength on 2:3 dichlorquinoxaline.

Caustic potash 2 Mols 28cc of 20% solution.

phenol 2 " 9.5 g.

2:3 dichlorquinoxaline 1 " 10 g.

(a) Caustic potash was dissolved in water thus forming a 20% solution. phenol was dissolved in this solution. 2:3 dichlorquinoxaline was added and the whole mixture was heated under reflux for two hours. The product was filtered off and extracted with boiling water. Some 2:3 dihydroxy quinoxaline crystallised from the hot water. Acidification of the mother liquor gave a further small yield of this substance.

m.p. of this substance 73.00°.

Yield 2 gms.

The residue after extraction with water was dissolved in alcohol from which it crystallised out in crops.

Each crop was examined:

<table>
<thead>
<tr>
<th>Crop</th>
<th>m.p.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>98° - 106°</td>
<td>4.5 gms.</td>
</tr>
<tr>
<td>II</td>
<td>95° - 104°</td>
<td>1.25 &quot;</td>
</tr>
<tr>
<td>III</td>
<td>94° - 100°</td>
<td>1.0 &quot;</td>
</tr>
<tr>
<td>IV</td>
<td>90° - 96°</td>
<td>1.75 &quot;</td>
</tr>
<tr>
<td>V</td>
<td>97° - 98°</td>
<td>1.0 &quot;</td>
</tr>
</tbody>
</table>

Total crude yield before recrystallising = 11.5 gms.

.. .25 of 2:3 dichlorquinoxaline
.75 of 2:3 dihydroxyquinoxaline
(A mixture of other (possible products.
(b) 2:3 dichlorquinoxaline 11 g.

Caustic potash (7.342 g. (64% pure)
in 16-16.5 cc of water.
(i.e. 45% solution.

phenol 5 g. 5.5 g.

The caustic potash was dissolved in the water. Phenol was dissolved in this solution. 2:3 dichlorquinoxaline was added to molten phenol and the mixture was heated till it formed a running melt. (C. 100°). The phenoxide solution was added and the whole mixture kept at 50-70° for 10 minutes. The mixture was cooled and the product filtered off and recrystallised from alcohol.
m.p. of product 150°.
Yield 7 gms.

This product was therefore unchanged 2:3 dichlorquinoxaline. The mother liquor gave a precipitate on acidification.
m.p. 73.40°.
Yield 3.3 gms.

.: This is 2:3 dihydroxy quinoxaline.
The yields account completely for the weight of starting material used.
The above experiment was exactly repeated except that the reaction mixture was heated on the oil bath for one hour at 120-130°.

The product was worked up exactly as in (a).

Extraction with water, and acidification of the mother liquor gave a small yield of dihydroxyquinoxaline.

The residue of product after extraction dissolved in alcohol but with a variable rapidity.

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Crop</th>
<th>m.p.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most soluble</td>
<td>I.</td>
<td>155-160°</td>
<td>4 gms</td>
</tr>
<tr>
<td></td>
<td>II.</td>
<td>157-160°</td>
<td>3 gms</td>
</tr>
<tr>
<td>less</td>
<td>I.</td>
<td>97-98°</td>
<td>1.5 gms</td>
</tr>
<tr>
<td></td>
<td>II.</td>
<td>100° abt.</td>
<td>1 gms</td>
</tr>
<tr>
<td>least</td>
<td>I.</td>
<td>155-160°</td>
<td>.5 gms</td>
</tr>
</tbody>
</table>

On recrystallization the melting point went up indefinitely but became neither clear nor sharp.

The experiment was repeated using ten times the quantities.

Yield 16 gms. grade.

m.p. about 60°.

The product was recrystallized from alcohol.

<table>
<thead>
<tr>
<th>Crop</th>
<th>m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>63-74°</td>
</tr>
<tr>
<td>II.</td>
<td>155-165°</td>
</tr>
<tr>
<td>III.</td>
<td>180-185°</td>
</tr>
</tbody>
</table>

This evidence indicates a very intimate mixture—probably of a di- and a mono-nitro compound.
XIV. Attempt to nitrate 2:3 diphenoxy quinoxaline

2:3 diphenoxy quinoxaline 2 g.
fuming nitric acid 20cc.
glacial acetic acid 20cc.

(a). Fuming nitric acid and glacial acetic acid were mixed and allowed to attain room temperature. 2:3 diphenoxy quinoxaline was dusted into the mixture. During this process no rise in temperature could be detected. The temperature was then raised to 40° for ten minutes. On addition of much water a very pale yellow amorphous precipitate was formed which was filtered, washed and dried.

Yield 2.16 gms.
m.p. 132-133°.

On recrystallisation the melting point went up indefinitely but became neither clear nor sharp.

The experiment was repeated using ten times the quantities.

Yield 16 gms crude.
m.p. about 60°.

The product was recrystallised from alcohol.

<table>
<thead>
<tr>
<th>Crop</th>
<th>m.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>63 - 74°</td>
</tr>
<tr>
<td>II.</td>
<td>158 -165°</td>
</tr>
<tr>
<td>III.</td>
<td>180 -185°</td>
</tr>
</tbody>
</table>

This evidence indicates a very complicated mixture - probably of a di and a mono-nitro compound.
2:3 diphenoxy quinoxaline 2 g.
fuming nitric acid 20cc.

2:3 diphenoxy quinoxaline was dusted into fuming nitric acid at room temperature. During the addition the temperature rose sharply (64°). The mixture was allowed to stand for ten minutes. It was then poured on to crushed ice and the yellow precipitate was washed, dried, and recrystallised from alcohol.

Yield 2.2 gms.

m.p. 90-97° (crude)
" of first crystallisation = 140-152°.
" second " = 150-165°.
" third " = 190-195°.

This evidence seems to indicate that a more drastic nitrating agent should be used.
(c) 2:3 diphenoxy quinoxaline (2.5 gms) were dusted into a 1:1 mixture of fuming nitric acid and glacial acetic acid kept at 50°. The temperature was kept at 50° for 15 minutes after addition was completed. A yellow product separated from the nitration mixture. Nothing further separated on diluting or basifying. Crude yield 1.84 gms.

m.p. (crude) 94-98°.

The product recrystallised from glacial acetic acid in flower-like clusters of very pale yellow prisms. After the first recrystallisation a melting point was taken. The substance went deep yellow from 190-215° and seemed to shrink from 215-230°. m.p. 232°. After the second recrystallisation m.p. 232-246°. Not at all sharp.
(d) 2:3 diphenoxy quinoxaline (2 gms) was dusted into a 1:2 mixture of glacial acetic acid and fuming nitric acid at 50°. On diluting the nitration mixture a yellow precipitate was obtained. (Yield 2.65 gms). The melting point of the crude product was 68-82°. It crystallised in colourless plates from glacial acetic acid from which it was twice recrystallised. After the first recrystallisation the product went a deep yellow and softened as the temperature rose in taking the melting point.

m.p. 214-220°.

After second recrystallisation m.p. 238-242°.

This method was repeated using five times the amount of material (crude yield 7 gms.) When a melting point of the crude product was taken shrinking was observed from:

170-178°. m.p. 180-190°.

After first recrystallisation m.p. 215° (approx)

" second " m.p. 248°
(e) 2:3 diphenoxy quinoxaline was gradually added to five times the weight of a 1:2 mixture of fuming nitric acid and concentrated sulphuric acid at -5°. On dilution a deep yellow product was obtained. (crude yield 6.96 gms.) m.p. 67-70°.

This product was boiled up with water which was then basified. The remaining product was filtered off and dried. m.p. 32-36°.

This product proved insoluble in most solvents except nitrobenzene from which it would not crystallise. It was taken up in nitrobenzene and precipitated by adding petroleum ether (40-80%). Shrinking was observed from 170-190. m.p. 190-191°.

Some was also taken up in glacial acetic acid and precipitated with water. m.p. 80-90°.

Both these products were then recrystallised from nitrobenzene from which they then separated in clusters of tiny pale yellow prisms. Softening was observed 198-240°. m.p. 239-240°.

Thus not even the most drastic nitrating agents yielded a pure product.
XV. Attempts to nitrate 2:3 dihydroxy quinoxaline.

2:3 dihydroxyquinoxaline 4 g.
fuming nitric acid 10 g.

(a) 2:3 dihydroxy quinoxaline and fuming nitric acid were mixed, when the temperature rose (38-39°) and heated to 100°. On dilution a deep yellow product was obtained. Nothing further was obtained on dilution or basification.
Crude yield .92 gms.

goes deep yellow steadily darkening 250-340° and is then still unmelted.
A first recrystallisation from acetone gave softening and shrinking from 230°-250°. m.p. 251°.
A second recrystallisation from acetone gave m.p. 340°.
(b) Attempt to prepare 5-nitro 2:3 dichloro quinoxaline.

2:3 dihydroxy quinoxaline 5 g.
potassium nitrate 3.1 g.

2:3 dihydroxy quinoxaline was added to sulphuric acid and potassium nitrate at -5° to -10°.

A yellow product was obtained on adding crushed ice to this mixture. (crude yield 4 gms.)
m.p. 320°. Substance darkens.

On recrystallising from acetone substance still gave m.p. 320°.

When dry it proved to be soluble in most solvents but would crystallise from none of them.
m.p. of crude product 320°.

This coupled with its appearance led one to believe that no reaction had taken place - for 2:3 dichloro quinoxaline melts at 150° and thus the nitro product should have a melting point rather higher than that.
Attempt to prepare 5 nitro 2:3 dichlor quinoxaline.

Product of the previous experiment 5 g.
phosphorus pentachloride 24 g.

These substances were introduced into a flask together with a little phosphorus oxychloride, and heated under reflux for 1-1 ½ hours at 160-180°. After cooling ice-cold water was added and the product was filtered off, washed and dried. When dry it proved to be soluble in most solvents but would crystallise from none of them. m.p. of crude product 320°. This coupled with its appearance led one to believe that no reaction had taken place - for 2:3 dichlorquinoxaline melts at 150° and thus the nitro product should have a melting point rather higher than that.
XVI. 2:3 dianiline quinoxaline.

Aniline and dichlorquinoxaline were mixed and heated together cautiously under an air condenser. A thick deep yellow liquid was formed. Suddenly the liquid frothed up and rose in the flask. When this excitement had subsided the reaction seemed to be finished. On cooling a solution of sodium bicarbonate was added till the contents of the flask were faintly alkaline. The mixture was then steam distilled. Excess base and hydrogenchloride were thus removed and pure derivative left in the flask. The residue in the flask - an oil at the temperature of steam, set to a hard mass on cooling. It was ground to a powder which was found to be insoluble in acetone, alcohol, and petroleum ether. It recrystallised readily from glacial acetic acid in feathery shining clusters of deep yellow needles.

Wt. of crude yield 8.7 gms.
" pure " 6 gm

m.p. 223°.

.2050 g gave 32.5 cc N₂ at 753 mm at 17° C.

whence \( \% N₂ = 17.9 \)

\( C_{20}H_{16}N_4 \) requires \( \% N₂ = 17.83 \).
XVII. 2:3 di (o-toluidine) quinoxaline.

\[ \text{O-toluidine} \quad 5 \text{ mols.} \quad 11 \text{ g.} \]
\[ 2:3 \text{ dichlorquinoxaline} \quad 1 \text{ Mol.} \quad 4 \text{ g.} \]

O-toluidine and 2:3 dichlorquinoxaline were mixed and heated together. The experiment was conducted in exactly the same way as the previous one. The crude product was an orange powder (yield 6 gms). This substance dissolved readily in every solvent but would crystallise out from none. When it was attempted to precipitate it from solution with petroleum ether (in which it was insoluble) only an oil resulted.
XVIII. 2:3 di (meta toluidine) quinoxaline.

\[ \text{m-toluidine} \quad 5 \text{ Mols. } 13.5 \text{ g.} \]
\[ \text{2:3 dichlorquinoxaline} \quad 1" \quad 5 \text{ g.} \]

Exactly the same preparative method was employed as in the above experiments. m-toluidine (5 mols. 13.5 g) were heated with 2:3 dichlorquinoxaline (1 mol. 5 g).
The product crystallised from glacial acetic acid in shining pale yellow oblong plates.
Crude yield 9.2 g.
Pure " 8.5 g.
m.p. 225°.

.1707 gives 24 cc N\(_2\) at 753 mm and 17° C.

whence \( \% \text{ N}_2 = 16.1 \)
\[ \text{C}_{22}\text{H}_{20}\text{N}_4 \text{ requires} \quad \% \text{ N}_2 = 16.47 \]
The experiment was exactly identical with the last in every detail save that an equal weight of p-toluidine was substituted for that of m-toluidine. The product crystallised from glacial acetic acid in fine yellow needles.

Crude yield 9 g.
Pure " 7 g.
m.p. 254°.

1920 gave 28.2 cc N₂ at 755 mm and 21° C.
whence \( \% N₂ = 16.51 \).
C\(_{22}\)H\(_{20}\)N\(_4\) requires \( \% N₂ = 16.47 \).
methylaniline (13.5 g) freshly distilled was used in a repetition of the experiment above. The product was a deep red glue, very sticky, which was soluble in all solvents and could not be made to crystallise from any of them.
The preparative method was repeated using piperidine (5 mols. 10.75 g) and dichlorquinoxaline. A beautiful shining white crystalline product was obtained which crystallised very easily from alcohol in platelets of m.p. 146°. After repeated recrystallisations a steady melting point was obtained.

(N.B. In these experiments 5 mols of base were used because the reactions taking place are

\[
2 \text{HCl} + 2 \text{RNH}_2 \rightarrow 2 \text{RNH}_2 \cdot \text{HCl}
\]

\[
2 \text{RNH}_2 \cdot \text{HCl} + 2\text{NaHCO}_3 \rightarrow 2 \text{RNH}_2 + 2\text{NaCl} + 2\text{CO}_2 + 2\text{H}_2\text{O}
\]

Analysis.

0.1259 gives 20.6 cc N\text{\textsubscript{2}} at 750 mm and 20° C.

whence \( \% \) \( \text{N}_2 = 22.41 \)

\( \text{C}_{14}\text{H}_{26}\text{N}_4 \) requires \( \% \) \( \text{N}_2 = 22.41 \)
Attempt to prepare 2:3-di (3-dinitro 4-methoxy phenoxy) quinoxaline.

The ether was dusted into the mixture of acids at room temperature, during which addition the temperature rose 4-5°. The mixture was heated to 50-60° for 1/2 hour. It was then cooled, and poured into large excess of water. The orange precipitate so formed was filtered off, washed and dried.

It proved very soluble in acetone ether etc. and would not separate out again. Alcohol dissolved some of it, but always a residue was left.

It dissolved in chloroform, carbon tetrachloride, and nitrobenzene, and on cooling separated at once as a buff-coloured oil and no means were successful in making it solidify.
XXII. 3 nitro 4 acetamino phenetole

Phenacetin  
100 g.

nitric acid (d=1.275)  
430 cc.

(450 cc HNO₃ (d=1.42.)  
400 cc H₂O) at 15°C

Phenacetin was dissolved in glacial acetic acid and nitric acid was added, gradually, the temperature being kept at 20°C by means of a bath of ice-water. (better a freezing mixture). The solution became deep orange and a bright yellow product began to separate towards the end of the addition. Crushed ice was added until the precipitation was complete; when the ice melted the solid was filtered off, well washed with water, pressed, and dried on the water bath.

Yield 72% - 96%. Average 84%.
XXIII. 3 nitro 4 amino phenetol

Nitrophenacetin 90 g.
conc. hydrochloric acid 360 g.
water 90 g.

Nitrophenacetin, concentrated hydrochloric acid and water were mixed in a flask and boiled for 40 minutes on a gauze. The dark orange red solution so obtained was poured into a large excess of cold water and the suspension rendered ammoniacal with 8.80 ammonia. A bright red solid was obtained which was filtered off, washed and dried on the water bath.
Yield 82% - 100%. Average 95%.
XIX. Attempted preparation of 3:4 diamino phenetole

[Diagram]

Stannous chloride 60 g.
conc: hydrochloric acid 100 cc.
3 nitro 4 amino phenetole 10 g.

(a) "Stannous chloride and hydrochloric acid."

The stannous chloride was dissolved in concentrated hydrochloric acid and the 3 nitro 4 amino phenetole was gradually added. The mixture was heated on the water bath till no precipitate appeared on adding water. The liquid was diluted with 1 litre of water and strong caustic alkali was added to ensure that all the tin was in solution while the base was precipitated. When a large excess of alkali had been added the remaining precipitate was filtered off. This precipitate gave tests for o-diamines and for tin. It was found impossible to isolate the base from this complex.
(b) "Wet Iron".

Nitrobase 20 g.
Iron filings 20 g.

The nitro base was stirred into fine iron filings, stirred to a thin paste with water, to which a few drops of glacial acetic acid had been added. The mixture was kept very hot on the water bath and constant addition of boiling water kept the texture the same. After about 2 hours all reaction seemed to have ceased. The mixture was extracted with about 500 cc of boiling alcohol and the iron filtered off as quickly as possible. The alcohol was evaporated down in vacuo and a large excess of concentrated hydrochloric acid was added. Soon the hydrochloride of a base crystallised out but on examination was found to be that of the nitro base only.
(c) Sodium hydrosulphite method (Morgan & Thomson J.C.S. 1926, 2694-5.

Nitro base 20 g.

sodium hydrosulphite 70 g.

The nitro base was dissolved in alcohol and boiled under reflux with sodium hydrosulphite which was added down the condenser and washed in with a little more alcohol. \((\text{Na}_2\text{S}_2\text{O}_4\cdot\text{O} \cdot \text{Na}_2\text{SO}_3\cdot\text{SO}_2); \text{thus 3 mols. were used to reduce one nitro-group})\.

When the mixture lost its rich red brown colour the excess hydrosulphite was quickly filtered off and the excess alcohol then evaporated off in vacuo. Very soon a white substance began to separate. This on examination proved to be a complex of the hydrosulphite and the diamine from which it was not possible to separate the diamine.
Lempricht's method. (Ber., 1885, 18, 1404)

The nitro base (20 g.) was dissolved in 95% alcohol in a flask on the water bath. Dilute aqueous caustic in small portions was added till a large excess had been added. The mixture was then boiled under reflux till it became a greeny pale colour.

Most of the alcohol was distilled off but any base which separated from the remaining liquid proved to be the starting product only.

The filtrate was then distilled in a current of carbon dioxide to remove the alcohol and to prevent oxidation of the diamine in the oxygen of the air. The remaining dark coloured residue was treated with a little water, as the diamine did not separate the contents of the flask were extracted with ether. On evaporation of the ethereal solution a very tiny yield of the diamine was obtained, white and feathery. It was however a mere trace and not sufficient to make the method a practical one.
A lively reaction set in. When the reaction became less lively more alkali and zinc dust were added. When a large excess of these reagents had been added the whole mixture was boiled under reflux till it became pale green and nearly colourless. The mixture was then filtered the residue being extracted several times with alcohol which was added to the filtrate. The filtrate was then distilled in a current of carbon dioxide to remove the alcohol and to prevent oxidation of the diamine in the oxygen of the air. The remaining dark coloured residue was treated with a little water. As the diamine did not separate the contents of the flask were extracted with ether. On evaporation of the ethereal solution a very tiny yield of the diamine was obtained, white and feathery. It was however a mere trace and not sufficient to make the method a practical one.
XX. Attempted reduction of 3-nitro p-toluidine.

The five methods of reduction described above were also applied to 3-nitro p-toluidine but without any better success.

In method (e) a trace of tolylene diamine was obtained—just sufficient to take a melting point. This method was also modified by distilling off most of the alcohol in the stream of carbon dioxide, as before, and then adding to the residual solution a large excess of concentrated hydrochloric acid. A small yield of hydrochloride of a base was obtained, but the base proved to be not the diamine but the original nitro base.
Preparation of barbituric acid. (Gabriel & Colman Ber., 1904, 37, 3657).

Malonic ester 1 Mol. 88.5 g.
sodium 1 " 12.72g.
absolute alcohol 500cc. 277cc.
300cc. 165cc.
urea 1 33.2 g.

Yields.

About 550 cc. of alcohol (rectified spirit 99.97%) was refluxed for a day with a spoonful of calcium turnings under a double surface condenser fitted at the top with a drying tube. (Glass wool/ caustic potash/ calcium chloride/). The dry alcohol was then distilled off into a large distilling flask also fitted with a drying tube.

The requisite amount of the alcohol was transferred to a small dry flask which already contained the urea previously dried in the vacuum desiccator. The mixture was then boiled under a double surface condenser fitted with drying tube till the urea was in solution.

Meanwhile the sodium was cut and weighed under xylol, and added to the remainder of the dry alcohol in a strong round-bottomed flask fitted with a double surface.
solution the malonic ester was added, and the hot urea solution. The whole was boiled under reflux for 6-7 hours.

442 cc of distilled water were boiled and 47 cc of concentrated hydrochloric acid was added. This mixture was poured into the flask containing the reaction mixture; the whole was heated till a clear solution was formed. It was then left to stand over-night. The acid precipitated in a fine crystalline meal which was filtered off and dried on the water bath.

The experiment was repeated once just as above. In the third preparation the alcohol was not dried over calcium turnings. It was desirable to cut out this tedious process if possible, and this experiment was performed to see what difference it made to the yield, if any.

The fourth time the alcohol was dried, but the reaction mixture was left to stand all night before refluxing for the 6-7 hours, instead of being refluxed at once.
<table>
<thead>
<tr>
<th></th>
<th>I.</th>
<th>II.</th>
<th>III.</th>
<th>IV.</th>
</tr>
</thead>
<tbody>
<tr>
<td>malonic ester</td>
<td>88.5 g.</td>
<td>86.3 g.</td>
<td>52.3 g.</td>
<td>94 g.</td>
</tr>
<tr>
<td>sodium</td>
<td>12.72 g.</td>
<td>12.4 g.</td>
<td>7.52 g.</td>
<td>13.49 g.</td>
</tr>
<tr>
<td>urea</td>
<td>33.2 g.</td>
<td>45.5 g.</td>
<td>19. g.</td>
<td>35 g.</td>
</tr>
<tr>
<td>alcohol</td>
<td>277 165 cc.</td>
<td>270 227.5 cc</td>
<td>164 100 cc</td>
<td>295 177 cc</td>
</tr>
<tr>
<td>water</td>
<td>442 cc</td>
<td>440 cc</td>
<td>260 cc</td>
<td>470 cc</td>
</tr>
<tr>
<td>HCl</td>
<td>44.2 cc</td>
<td>40 cc</td>
<td>26 cc</td>
<td>47 cc</td>
</tr>
<tr>
<td>Yields</td>
<td>(60%)</td>
<td>(61%)</td>
<td>(39%)</td>
<td>(54%)</td>
</tr>
<tr>
<td></td>
<td>(40 g.)</td>
<td>(42.5 g)</td>
<td>(15.5 g)</td>
<td>(41 g.)</td>
</tr>
</tbody>
</table>

It is necessary to dry the alcohol and to complete the experiment all in one day in order to get the best yield.
Preparation of 2:4:6 trichlorpyrimidine.

The acid, together with the oxychloride were introduced into a round bottomed flask. The acid shewed no signs of dissolving. The pentachloride was cautiously added, but the addition produced no rise in temperature. The mixture was heated under reflux on a vigorously boiling water bath for about an hour. The flask was then cooled and immersed in a freezing mixture and 100 g. of crushed ice were added. A yellow flocculent precipitate formed and a heavy oil. The contents of the flask were extracted with ether; the yellow precipitate was insoluble.

The ethereal solution was dried over calcium chloride, and the ether distilled off. A small yellow residue was left. The yellow precipitate was filtered off. It was insoluble in hot water so it was not barbituric acid. It was soluble in bicarbonate solution, and was...
precipitated again on acidifying so it was not the required trichlor-compound.

A lassaigne test for chlorine gave a positive result. m.p. 73.10.

The substance was not further investigated.

paraffin oil that kept at 130-140° for about one hour.

The reaction mixture was worked up as in I. the yellow precipitate insoluble in ether. only very slightly b. was again obtained. m.p. 58.1°. therefore this method was also abandoned.
Sarbituric acid 5 g.
PcCl₃ 15 cc.
PcCl₅ 7.5g.
PcCl₅ 25 cc.

The substances were heated under reflux on a paraaffin oil bath kept at 130-140°C for about one hour.

The reaction mixture was worked up as in I.

The yellow precipitate insoluble in ether - or only very slightly so, was again obtained.

Therefore this method was also abandoned.
III. Method of Gabriel. (Ber., 1900, 23, 3666)
(Ber., 1904, 23, 3657)

Barbituric acid 8 g.
POCl₃ 25 cc.

The substances were placed in a tube which had been carefully cleaned. It was then sealed and heated in the furnace at 130-140° for 1½ hours. When cool the tube was opened carefully - the pressure within being still quite high. The contents of the tube were filtered through glass wool into a claisen flask; it was further washed through with carbon tetrachloride.

The mixture was vacuum distilled; at first the tetrachloride came over. When the temperature reached 100° the receiver was changed. Oxychloride with traces of the trichlorocompound came over until the temperature reached 148°.

The fraction coming over at 148-156° was nearly pure trichlorocompound.

Water was added to the flask containing this last fraction; the traces of oxychloride were thus destroyed and a heavy oil separated to the bottom. This was washed with water, by decantation; finally it was
placed in a freezing mixture when it solidified. It was filtered off and dried in vacuo. m.p. 19-20°. (Gabriel found m.p. 21°.)

<table>
<thead>
<tr>
<th>Tube No.</th>
<th>Yield in g.</th>
<th>%age yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6 g.</td>
<td>70%</td>
</tr>
<tr>
<td>1 - 4</td>
<td>43 g.</td>
<td>57-58%</td>
</tr>
<tr>
<td>5 - 8</td>
<td>35 g.</td>
<td>49%</td>
</tr>
</tbody>
</table>

Finally the total yield of 84 gms. was purified by redistilling in vacuo.
Final pure yield 53 g.

N.B. The %age yield fell when more than 8-10 g. of barbituric acid were placed in the tube. Preparations are best done in the small quantities.
2:4:6 triphenoxy pyrimidine.

2:4:6 trichlorpyrimidine 1 Mol. 5 g.
phenol 9 " 22 g.
KOH 5.25" 7.5g.

The caustic alkali was heated with 2 drops of water till it dissolved. The phenol was then added and the flask heated till a clear melt was formed. Trichlorpyrimidine was added very cautiously drop by drop. The addition caused development of great heat and loud hissing as the reaction took place instantaneously. The flask was heated in a metal bath for about 20 minutes the temperature of which was taken up to 210-220°; no further reaction took place. The flask was then cooled and the contents washed clean with strong alkali and water. Yield 100% pure.
The substance formed pure white, slender, long needles from (ethyl alcohol & acetone. of m.p. 156°.

Found % C = 74.6 % H. = 4.6
C₂₂H₁₈O₃N₂ requires % C = 74.57 % H. = 4.9
2:4:6 tri (paramethoxy-phenoxy) pyrimidine.

The method was exactly identical with that used in the foregoing experiment.

The substance forms long shining white needles from ethyl alcohol of m.p. 120°.

Yield 81%.

Analysis.

Found % C = 67.1. % H = 5.25.

C_{25}H_{24}O_{6}N_{2} requires % 67.6. % H = 5.8.
The method of the last two experiments was again employed exactly.
The substance forms long silky white needles from ethyl alcohol of m.p. 118°.
Yield 100%.

Analysis.

Found % C = 75.0. % H = 5.0.
C<sub>25</sub>H<sub>24</sub>O<sub>3</sub>H requires % C =75.7. % H = 5.2.
2:4:6 tri (p-chlorophenoxy) pyrimidine.

This substance was prepared by the same method as its analogues. It formed clusters of stout needles from ethyl alcohol of m.p. 107°.

Yield 75%.

Analysis.

\[ \text{C}_{21}\text{H}_{14}\text{O}_3\text{N}_2\text{Cl}_3 \text{ requires } \% \text{ N } 5.9 \quad \text{Found } 6.0 \% . \]

\[ \% \text{ Cl } 22.5. \quad " \ 22.8\% . \]
Attempt to prepare $2:4:6 \text{ tri (o-nitro phenoxy) pyrimidine.}$

trichloropyrimidine \hspace{1cm} 5 g.
o-nitro phenol \hspace{1cm} 35 g.
caustic potash \hspace{1cm} 7.5g.

The caustic potash was dissolved in a little water, and the nitro phenol was added. Water was then added till all the nitrophenol was dissolved in the boiling solution. The chlorcompound was added, and the mixture was boiled all day long under reflux.

When it was cool the solid formed was washed well with dilute alkali, and crystallised from alcohol. This product however melted indefinitely and not until a very high temperature, and ignition shewed it to contain an inorganic substance - i.e. potassium.

Therefore it was concluded to be but the potassium salt of the phenol and not the required ether.
I. Preparation of p-phenetidine.

\[
\begin{array}{ccc}
\text{I.} & \text{Phenacetin} & 1 \text{ Mol.} \\
& \text{NaOH} & 5 " \\
\end{array}
\]

(1) (2) 

\[
\begin{array}{ccc}
50 \text{ g.} & 67 \text{ g.} \\
150 \text{ g.} & 201 \text{ g.} \\
\end{array}
\]

The phenacetin was placed in a 1½ litre flask and the caustic soda, dissolved in sufficient water to half fill the flask was added. The mixture was boiled under reflux for about 2 hours. When cool the solution was extracted with ether; the ethereal solution was dried over sodium sulphate, and the ether distilled off leaving the dark coloured oil p-phenetidine behind.

This method produced imperfect hydrolysis and the yield was only 45% so it was abandoned in favour of II.
The phenacetin was boiled under reflux with acid and water for 6-7 hours. It was then allowed to cool and neutralised with a slight excess of caustic soda. The base appeared as an oil floating on the top of the solution. Some unchanged phenacetin was still mixed with it so the alkaline liquid was filtered and washed through with a little ether. The whole filtered liquid was then extracted with ether. The ethereal solution of the base was dried over sodium sulphate. The ether was distilled off and the remaining base was finally purified by vacuum distillation.

Yield (a) 300 g. phenacetin gave 218 g. pure base.
(b) 400 g.

b.p. 136° at 77 cm of Hg.
Preparation of $\beta$ - (p-ethoxy phenylamino crotonic ester).

The liquids were well mixed in a large beaker and left to stand for 24 hours. A solid mass of crystalline plates was formed.

This, the crotonic ester, formed plates from ethyl alcohol of m.p. 51-52° in which it was moderately soluble.

Yield 285 g.
Preparation of 4 hydroxy 6 ethoxy 2 methyl quinoline.

b-(p-ethoxy phenyl-imino) crotonic ester  285 g.
paraffin oil  940 g (approx)

The paraffin oil in a three litre pyrex beaker was slowly raised to 280-290°. The crotonic ester was then thrown in, and the temperature was kept at about 260° for a few minutes with stirring. The mixture was then allowed to cool - the product crystallising out.
The oil was filtered off through a sintered glass funnel. The quinaldine was first washed in the funnel with light petroleum (b.p. 40-60°) and then dried, and recrystallised from methyl alcohol.
The substances were heated together in a litre round bottomed flask in a metal bath kept at 146° (approx.) until no more hydrogen chloride was evolved (1 hour approx.) Ice-water was then added to destroy excess halides of phosphorus, and the acids thus formed were basified with caustic soda. This liquid was steam distilled. A brownish-white, low-melting solid came slowly over. This was filtered off and dried. (Yield 80-85% crude).

The substance forms cream-coloured clusters of prismatic needles of m.p. 65° from light petroleum (b.p. 60-80°) in which it is extremely soluble.

**Analysis.**

Found % Cl₂ = 16.15.

C₁₂H₁₂ONCl requires %Cl₂ = 16.05%.
Preparation of 4 chlor 5 nitro 6 ethoxy 2 methyl quinoline.

4 chlor 6 ethoxy 2 methyl quinoline 10g. 40g.
fuming nitric acid (d 1.5) 35cc 140cc.

The acid was cooled to 0°, and the base was slowly added, each addition causing a rise in temperature. The temperature was never allowed to rise above 10°, and it sank again to 0° before a fresh addition of base was made. The solution was filtered on to ice, and left to stand a little. While still ice-cold it was neutralised with 880 ammonia, and the buff-coloured precipitate formed was filtered off, washed, and dried on the water bath. The substance proved to be sparingly soluble in light petroleum from which it separated in crystals shewing various forms of the hexagonal prism system of m.p.125°. Yield (crude) 9.-92%.

Analysis.

Found % N₂ = 10.8 and % Cl₂ 12.8
Cl₂H₁₁O₂N₂Cl requires % N₂=10.5 % Cl₂ 13.3
Preparation of 5 nitro 4 (p anisoxo) 6 ethoxy 2 methyl quinoline.

4 chlor 5 nitro 6 ethoxy 2 methyl quinoline 1 Mol. 7 g 20 g
p methoxy phenol 2 " 6.5 g 19 g
KOH 1.33" 2 g 6 g

Yield 14 g.

The condensation was effected in the usual manner. When the chlorocompound was added the flask was heated until effervescence began; this was allowed to rise up and die away again before further addition of chlorocompound. The flask was then heated for 1 hour on the metal bath at 150-170°.

On cooling and adding dilute alkali an oil separated which finally went solid.

It proved soluble in light petroleum from which it separated in buff-coloured hexagonal prisms of m.p. 109°. It went greenish on the surface on exposure to air.

Analysis.

Found % N₂ = 8.3

C₁₈H₁₈O₅N₂ requires % N₂ = 7.9
Attempt to synthesise 4 (nitro p anisox) 5 nitro 6 ethoxy 2 methyl quinoline.

5 nitro 4 (p anisox) 6 ethoxy quinaldine 10 g.
nitric acid (d 1.5) 150 cc.
glacial acetic acid 150 cc.

The two acids were mixed, and cooled to 0° in a freezing mixture. The nitrobody was then added. Addition did not produce much rise in temperature. The nitrination mixture was then poured onto ice, and strongly diluted, and while still ice-cold, it was basified with .880 ammonia. A sticky precipitate was formed. This was allowed to stand for a while, and the precipitate solidified. It was filtered off, washed, and dried.

The product proved insoluble in light petroleum, but very soluble in ethyl alcohol, benzene, glacial acetic acid and carbon tetrachloride. It separated, and that but slightly, only from the two last solvents. On repeated recrystallisation from dilute glacial acetic the melting points were:- 1st recrystallisation 95° 2nd " 152° 3rd " 125°

These results indicated the formation of a mixture and not a pure compound and the method was not further investigated.
**Preparation of the methiodides of 4 chlorothoxy quinaldine, and its nitro-derivatives.**

The procedure was always the same. The compound and the methyl iodide were introduced into a tube which was then sealed. This tube was heated for two hours in the vigorously boiling water bath. After cooling the contents of the tube were washed out with ether, and recrystallised from water and absolute alcohol.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Quantities</th>
<th>Crystallisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Cl] 2 g.</td>
<td>1-2 g.</td>
<td>Tiny clusters of jade-green needles from water and ethyl alcohol of m.p. 218°.</td>
</tr>
<tr>
<td>![Cl] 5 cc CCl I.</td>
<td>6-7 cc of MeI.</td>
<td></td>
</tr>
<tr>
<td>![Cl] 2 g.</td>
<td>2 g.</td>
<td>Tiny dark green needles from water of m.p. 200° Very sparingly soluble in ethyl alcohol.</td>
</tr>
<tr>
<td>![Cl] 5 cc CH₃ I.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>![Cl] 2 g.</td>
<td>2 g.</td>
<td>From water separates in shining plum-red needles from absolute alcohol in old-gold needles of m.p. 172°.</td>
</tr>
<tr>
<td>![Cl] 5 cc CH₃ I.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4-phenoxy-6-ethoxy-2-methylquinoline.

4-chlor-6-ethoxy-2-methylquinoline 1 Mol. 6 g.
phenol 2 " 4.2 g.
KOH 1.33 " 1.6 g.

The condensation was carried out in the usual way, the mixture being heated in a metal bath kept at 180-190° for one hour. After cooling dilute alkali was added. The dark viscous mass formed in the reaction gradually solidified to an ochre-yellow solid. It was ground with strong alkali and filtered. It was ground fine again with water and filtered and dried in air.

Yield (pure) 82-83%.

The substance forms colourless star-like clusters of needles. m.p. 107-108° from light petroleum in which it is easily soluble.

Analysis.

Found % N₂ = 5.05.

C₁₇H₁₇O₂N requires % N₂ = 5.04%. 
The preparation of 4 phenoxy 6 ethoxy 2 methyl quinoline methiodide.

4 phenoxy 6 ethoxy 2 methyl quinoline 2 g. (about)
methyl iodide 6-7 cc "

The substances were heated together in a sealed tube on the boiling water bath for about three hours. The tube was cooled, opened, and the contents washed out with ether. The solid was filtered off and recrystallised from water in which it dissolved to give a violet-coloured solution. It separated from water in cooling in shining heliotrope needles of m.p. 210°. It was recrystallised from absolute alcohol, and though the crystals separating were of a considerably paler shade the melting point remained constant.

Analysis.

(.2155 gave .1167 g AgI.

whence % I₂ = 30.08.

C₁₇H₁₇O₂N'I requires % I₂ = 30.2.
The preparation of 4-(p-methoxy phenoxy) 6-ethoxy 2-methyl quinoline.

\[
\begin{align*}
\text{4 chlor 6 ethoxy 2 methylquinoline} & \quad 6 \text{ g.} \quad 1 \text{ Mol} \\
p\text{-methoxy phenol} & \quad 5.5 \text{ g.} \quad 2 " \\
\text{KOH} & \quad 1.6 \text{ g.} \quad 1.33"
\end{align*}
\]

The same method was employed as before. The substance forms hexagonal cream-coloured prisms of m.p.115° from light petroleum.

The yield was low.

**Analysis.**

Found % N₂ = 4.68.

C₁₉H₁₉O₃N requires % N = 4.56%
Preparation of 4-p-methoxy phenoxy 6 ethoxy 2 methyl quinoline methiodide.

The usual method was once more applied in this experiment. The substance formed separated from water and absolute alcohol in lilac leaflets of m.p. 216°.

Analysis:

0.2440 gave 0.1247g AgI.

whence \( \% I_2 = 27.92 \).

C_{19}H_{19}O_5I requires \( \% I_2 = 28.2 \).

In each of these four cases the methiodides sublimed on heating, and melted to give a dark purple blue liquid.
The method is exactly identical with that in the foregoing experiment.

The mixture is heated for 1 hour at 180-190°C.

The substance forms tiny colourless cubes from light petroleum (b.p. 60-80°C) of m.p. 134°C in which it is only moderately soluble.

Yield 62.3%.

Analysis.

Found \( \% \text{ N}_2 \) = 5.04.

\( \text{C}_{18}\text{H}_{19}\text{O}_2\text{N} \) requires \( \% \text{ N}_2 \) = 4.80%.
Preparation of 4 p-cresoxy 6 ethoxy 2 methyl quinoline methiodide.

The method of preparation followed was exactly identical with that in the previous preparation. The substance formed crystallised from water and absolute alcohol in small dark heliotrope needles of m.p. 213°.

Analysis.

0.2408 gave 0.1337 g AgI.

whence \( \% I_2 = 30.12 \).

C\(_{18}\)H\(_{19}\)O\(_2\)N I requires \( \% I_2 = 30.38 \).
44p chlorphenoxy)-6-ethoxy-2 methylquinoline.

4 chlor-6-ethoxy-2-methyl quinoline 6 g. 1 Mol.
p-chlorophenol 6 g. 2 "
KOH 1.6g. 1.33"

The same method as before was employed for the preparation of this substance.
It forms colourless rectangular prisms from light petroleum of m.p. 125° in which it is pretty soluble.
Yield 82%.

Analysis.

Found  % N₂ = 4.76 & % Cl₂ = 11.2
C₁₇H₁₆O₂NCl requires% N₂ = 4.487 % Cl₂ = 11.30.
Preparation of 4-p-chlorphenoxy 6 ethoxy 2 methyl quinoline methiodide

4 p-chlorphenoxy 6 ethoxy 2 methylquinoline 2 g. (abt)
methyl iodide 6-7 cc.

The same method was applied as in the two previous experiments.
The substance formed separated from water and absolute alcohol in long thin pale greyish mauve needles of m.p. 213-214°.

Analysis.

0.2014 gave 0.1027g AgI

whence % I₂ = 27.74

C₁₇H₁₆O₂NI requires % I₂ = 27.87
The nitration of 4 anisooxy 6 ethoxy 2 methyl quinoline.

I. 4 anisooxy 6 ethoxy 2 methylquinoine 23 g.
   glacial acetic acid 175 cc.
   fuming nitric acid (d=1.5) 350 cc.

The base was quickly added to the mixture of acids at 20°. The solution was warmed to 50° for 15 minutes. It was then poured into much water, and a yellow solid precipitated, which remained unchanged on further dilution, and on neutralisation of the solution with .880 ammonia.

The precipitate was filtered off, well washed, and recrystallised from alcohol; it seemed to separate from the solvent in two portions - viz: the least soluble portion in long needles, and the most soluble portion in round balls, the further structure of which could not be discerned, even under the microscope.

The melting points were unsatisfactory. Thus the conclusion was reached that this nitration product was a mixture either of the starting product and a nitro-body, or of two nitro-bodies.

Yield of nitration product 16 g.
II. Nitration product  16 g.
  glacial acetic acid  122 cc.
  fuming nitric acid (d 1.5)  244 cc.

In order to decide more nearly upon the identity of the product of Experiment, the product was taken and nitrated again using exactly the same proportions, and under identical conditions.

The product obtained crystallised from alcohol, and the balls could now be seen to be composed of tiny deep yellow needles - of m.p. 188-189°.

Light petroleum 100-120 proved to be an equally good solvent.

Analysis.

0.1792 gave 20.9 cc N₂ at 742 mm and 16.5°C.

whence % N₂ = 12.29

C₁₉H₁₇O₃N (NO₂) 2 requires 10% N.

C₁₉H₁₅O₃H (NO₃) 3 " 12% N.

Thus the substance was assumed to be a trinitrobody, and the nitration product of the first experiment to be a mixture probably of di and tri-nitrobodies.
The base was added quickly to the mixture of the two acids at 0°. Half the solution was poured onto ice. When it had stood awhile it was strongly diluted, and rendered neutral with .880 ammonia. The precipitate was then filtered off, washed, dried, and recrystallised from ethyl alcohol and light petroleum from which it separated in tiny pale-cream coloured needles of m.p. 183.5°. (m.p. of crude nitro-product 182°). The experiment was then repeated using ten times the amount of material.

Analysis.

0.2033 gave 14.0ccN₂ at 18.5° & 767 mm
whence $\%$ N₂ = 8.034.

C₁₉H₁₆O₃N₁ (NO₂) requires $\%$ N 7.9.

This method therefore gives a mononitrobody.
While in method III half the solution was poured onto ice at once, the other half was allowed to attain the temperature of the room. It was warmed for a few minutes to 30-40°. After standing awhile, it was strongly diluted, and rendered neutral with .880 ammonia.

The precipitate was filtered off, dried, and recrystallised from ethyl alcohol - from which it separated in dull yellow needles of m.p. (after first crystallisation) about 158 (softening at 138°)

m.p. (after second " ) " 145 (shrinking at 130°)

m.p. of crude product 140°-150° softening at 55°. These results were so uncertain that this product was concluded to be a mixture, and was no further investigated.
4 anisox 6 ethoxy 2 methyl quinoline 5 g. 1 part
potassium nitrate 1.6 g. 1 "
conc: sulphuric acid 4.2 cc. 5 "

The potassium nitrate was dissolved in the acid and
the mixture placed in a strong freezing mixture.
When the temperature was -5° the base was gradually
stirred in keeping the temperature always below 0°.
This reaction mixture was filtered into ice-cold
water and the yellow precipitate formed dried, and
was filtered off, washed and recrystallised from ethyl
alcohol. It separated in deep yellow prismatic
needles just like the trinitro body of m.p. 188°.
(m.p. of trinitro body 188.9°).
Therefore this method gives only the trinitro body.

The product was subjected to exactly the same process of
nitration again. The product of this also melted at
Attempt to nitrate 4 (mononitro p anisox) 6 ethoxy 2 methyl quinoline.

4 (mononitro p anisox) 6 ethoxy product
quinoline 8 g. 4 g.

2 methyl

The mononitrobody was quickly added to the mixture of the two acids kept at 0° in a freezing mixture. The nitration mixture was then poured onto ice, and left to stand for a little while. Whilst still ice-cold it was basified with .880 ammonia, and the precipitate was filtered off, washed, and dried on the water bath.

The product proved insoluble in light petroleum, sparingly soluble in ethyl alcohol from which it separated in platelets of m.p. 187°, and very soluble in benzene from which it separated in tiny needles of creamy-greenish tinge of m.p. 187°. Its solubilities and melting point indicate that the product is not the starting material.

Mixed m.p. trinitro compound 140-150°, i.e. m.p. is depressed. This would indicate that it is not the trinitro compound either.

The product was subjected to exactly the same process of nitration again. The product of this also melted at
187° and seemed to be no further changed.

% N in mononitro compound calculated 7.9% N found here
% N dinitro " " 10 8.6
% N trinitro " " 12.6

% N in a mixture of mono and dinitro compounds is 8.9.

.: It would seem that in this case some such a mixture was obtained.

This method was therefore no further investigated.
Attempt to prepare the methiodide of the trinitro 4-anisoxyl 6 ethoxy 2 methyl quinoline.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>trinitrobody</td>
<td>2 g. abt.</td>
</tr>
<tr>
<td>methyl iodide</td>
<td>6.7 cc.</td>
</tr>
</tbody>
</table>

The substances were heated together in a sealed tube on the boiling water bath for about three hours. The tube was then cooled, and opened and the contents washed out with ether. They were black and tarry in appearance and proved to be insoluble in water. They dissolved in alcohol, but would not separate out again.

The presence of the three nitro groups evidently made the substance too acid to form a methiodide.
Preparation of mononitro 4 anisoyl 6 ethoxy 2 methyl quinoline methiodide.

mononitrobody 2 g.
methyl iodide 6.7 cc.

The substances were heated together in a sealed tube on the boiling water bath for about two hours. After cooling the tube was opened, and the contents washed out with ether. They were recrystallised from absolute alcohol from which they separated in tiny deep-cream coloured needles of m.p. 224° (decomp.) Recrystallisation from water did not alter the m.p.

Analysis.

0.2954 gave 0.1463 AgI.

whence \( \frac{27.0}{2} \) requires % I\(_2\) 27.2
Effect of piperidine on trinitro 4-p-anisoxyl 6 ethoxy 2 methyl quinoline.

The two substances were heated together in a sealed tube on the water bath for 6-7 hours. When the tube was cooled and opened a solid had already separated out; on pouring the contents of the tube into alkali more solid separated. This was filtered, washed and dried. It was a red solid insoluble in water, light petroleum, benzene, etc. It dissolved in acetone, and alcohol but would not crystallise from them. It was purified by dissolving in acetone, filtering and precipitating with light petroleum 60-80. m.p. 257°. The alkaline filtrate was acidified with dilute acetic acid, and a yellow solid was obtained of m.p. 230°. It proved, however, difficult to crystallise, being quite insoluble in all ordinary solvents. The acidified solution was also ether extracted, and a dark orange solid of m.p. 100 (approx) was obtained on evaporating off the ether. As the melting point was so uncertain it was assumed to be a tarry by-product, and not a direct result of scission of the nitrobody.

\[
\text{2075 gave } 27.6 \text{ccN}_2 \text{ at } 755 \text{ mm and } 21^\circ \text{ C.}
\]

whence \( \% \text{ N}_2 = 15.0 \)

\( \text{C}_{13}\text{H}_{15}\text{O}_5\text{N}_3 \) requires \( \% \text{ N}_2 = 15.0 \)
Preparation of mononitrohydroquinone dimethyl ether.

Nietzki (Ber., 1878; 11; 1034)
Habermann (Ber., 1890, 22; 1216)

hydroquinonedimethylether30g.

The dimethyl ether, taken in lots of 10 g. was shaken in a separating funnel with water of 50-60°. About \( \frac{1}{8} \) litre was used per 10 g. The ether which did not go into solution formed oily droplets and the solution went milky.

\[ \text{Volume of water in nitric acid of usual concentration was added; after shaking strongly a moment a clear yellow liquid was formed which rapidly went cloudy owing to the formation of tiny crystalline needles of a pure yellow colour. This is the mononitrobody. After several hours standing it was purified by recrystallisation from 50\% alcohol in which it easily dissolved, and whence it separated in golden yellow silky shining needles of m.p. 70-71°.} \]

Yield 25 g. 62-63\%.
Preparation of 2:3 and 2:5-dinitro-hydroquinone dimethyl ether.

Nietzki, (Ber., 1890, 23: 1216.)
Habermann, (Ber., 1878, 11: 1037.)

Mononitrohydroquinonedimethylether 20g.
glacial acetic acid (100g. (i.e. 106 cc.)
nitric acid (cl 1.48) 106 cc.

Yield 22 g. (88%).

The mononitrobody was suspended in the glacial acetic acid, and the mixture was immersed in a freezing mixture. The nitric acid was then slowly added. When all the acid was added, the mixture was allowed to stand a little, and then was strongly diluted.

The bright yellow precipitate was filtered off, and well washed with cold water, and dried on the water bath.

Samples of the two isomers were obtained by careful partial crystallisation from ethyl acetate from whence the substance separates in needles.

of m.p. 177° (2:3 dinitro cpd.)
of m.p. 202° (2:5 " " )
Attempted synthesis of 2:5 dinitro 4 methoxy phenyl piperidine.

2:5 dinitro hydroquinone methyl ether 1.5 g.

piperidine excess.

The reactants were introduced into a glass tube which was then sealed. The tube was heated for 3-4 hours on the boiling water bath. A dark yellow solution was obtained. The contents of the tube were washed out with alkali, and the precipitate which formed was filtered off. It recrystallised from ethyl acetate giving a melting point 202° thus shewing that no reaction had taken place.
Effect of piperidine on mononitrohydroquinone dimethylether.

Piperidine 2.38 g.
mononitrohydroquinone dimethylether 4.95 g.

Some pure piperidine was introduced into the tube which had been previously weighed. Thus by weighing again the weight of piperidine used was accurately determined. The exact amount of nitrobody required was then weighed out from the weighing bottle and placed in the tube. After sealing the tube was heated 6-7 hours on the boiling water bath. A dark red solution was formed, from which long reddish needles separated on cooling. The contents of the tube were washed out with alkali, and the solid was filtered off and washed. It was recrystallised from 50% alcohol whence it separated in tiny yellow needles of m.p. 71°. Thus it was recognised as the starting product, almost the whole of which was recovered.
Effect of piperidine on mononitro 4 anisoxoy 6 ethoxy 2 methyl quinoline.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>mononitrobody</td>
<td>2 g.</td>
</tr>
<tr>
<td>piperidine</td>
<td>12-15 g.</td>
</tr>
</tbody>
</table>

These substances were heated together in a sealed tube on the boiling water bath for 6-7 hours. On cooling the tube contained a brownish-yellow solution with a bright yellow substance crystallising out at the bottom in long needles.

The contents of the tube were washed out with alkali, and the precipitate was filtered off, and washed. It was found to recrystallise from both methyl and ethyl alcohol in tiny dull yellowish coloured needles of m.p. 183°.

As this substance had the same appearance and m.p. as the starting product it was concluded that no reaction had occurred.

The alkaline filtrate, on acidification with dilute acetic acid gave no signs of a precipitate.
Effect of alcoholic .880 ammonia on mononitro 4-anisooxy 6 ethoxy 2 methyl quinoline.

These substances were introduced into a carius tube and it was sealed. It was heated on the electric water bath until the water boiled in an effort to get all the substance into solution; however, it did not all go up under these conditions. It was then transferred to the furnace and heated at 170-180° for four hours. After cooling the tube was unsealed and opened, and the contents washed out with alkali. They were then filtered off and taken up in dilute hydrochloric acid. After filtering the acid solution it was basified and a slight gelatinous brown precipitate was formed. This was filtered off, and a portion was diazotised and coupled with p-naphthol. No cherry-red colour or precipitate was formed however and so no information was given as to the position of the nitro group.
The tube was sealed and heated as before after the substances had been introduced. This time however the temperature was kept at $140^\circ$ and heating was continued for 4 hours.

When the tube was cooled large crystals had formed in the solution. These were filtered off and recrystallisation shewed them to be but the mono-nitrobody unchanged. The mother liquor was then diazotised and added to an alkaline solution of $\beta$-naphthol. A bright cherry red colour appeared, thus indicating that a trace of nitro-amino body had been formed, and that it was considerably more soluble in alcohol than the unchanged nitrobody.
Mononitrobody — that which was recovered from II.

ammonia

absolute alcohol as in II.

The experiment was repeated exactly as before — the only variation being that the tube was heated at 160-170° for 6 hours. When the tube was cooled it was found to contain a clear solution.

On scratching crystals were formed which were filtered off. This again was found to be the unchanged mononitrobody.

A portion of the mother liquor was tested as before and gave a very red colour. The rest of the mother liquor was then evaporated to dryness, but the residue was so small that it was impossible to investigate it further.
Preparation of 2:4 dinitro 4'-methoxy diphenyl ether.

2:4 dinitrochlorobenzene 1 Mol. 28g 56g 112g 82g 74g 74g
p-methoxy phenol 2 "  30g 60g 120g 88g 82g 82g
potassium hydroxide 1.33 "  9g 18g 36g 26.5 25g 25g

The clear melt of potassium salt of the phenol in the phenol was made in the usual way. This was allowed to cool till it was of a "gummy" consistency. The dinitro chlorobenzene was then cautiously added.

The reaction mixture was heated on the boiling water bath for 30 minutes.

The ether proved easily soluble in ethyl alcohol whence it separated on cooling in lemon-yellow prisms of m.p. 110°. Yield 75% (pure).

0.2228 gave 20cc N₂ at 737mm and 16.5° C.

whence \( \% N = 10.0 \)

\( \text{C}_12\text{H}_10\text{O}_6\text{N}_2 \) requires \( \% N = 9.7 \).
Nitration of 2:4 dinitro 4′methoxy diphenyl ether.

2:4 dinitro 4′methoxy diphenylether 4g 24g 60g 85g.

Fuming nitric acid (d 1.5) 50cc 300cc 750cc 1065cc.

Glacial acetic acid 50cc 300cc 750cc 1065cc.

The 1:1 mixture of acids was allowed to stand till it acquired room temperature. The ether was then quickly added, the temperature being kept down by immersing the nitration mixture in a bath of cold water. When all the ether was dissolved the mixture was much diluted, and the pale yellow solid which precipitated was filtered off, washed and dried.

It proved sparingly soluble in ethyl alcohol, and light petroleum, and very soluble in benzene, whence it separated in little clusters of hexagonal prisms of a very pale lemon yellow colour, and m.p. 143°.

Yield 75%.

\% N₂ found = 12.01

C₁₂H₉O₆N₃ requires \% N₂ = 12.51.
Attempt to nitrate 2,4,3'-trinitro 4'-methoxy diphenyl ether.

I. Trinitro methoxy diphenyl ether 1 part 10 g.
   fuming nitric acid 10 " 100 g.
   67 cc.

   The ether was added to the nitric acid at 0°. After 20 minutes this nitration mixture was poured into water. The precipitate was filtered off, washed, and dried on the water bath. It was recrystallised from glacial acetic acid from which it separated in perfect cream coloured shining rectangular plates of m.p. 143°.
   m.p. of trinitroether = 143°.
   Mixed m.p. of this product + trinitroether 145°.
   Yield of trinitroether recovered = 9 g.
II. trinitroether 10 g.  
nitric acid (d=1.5) 50 g.

The ether was added to the acid, and the mixture was heated for two hours on the vigorously boiling water-bath. The nitration mixture was then cooled, poured into water, and worked up as in I. The unchanged trinitro ether was once more recovered. This attempt at nitration was pushed no further as resort would now have to be made to such reagents as potassium nitrate and concentrated sulphuric acid, and it was feared that this would only lead to complications in the reaction.
Preparation of 3 nitro 4 methoxy phenol.

2:4 3' trinitro 4' methoxy diphenyl ether
1 Mol. 4g. 30g. 60g
piperidine 2 " 2g. 15g. 30g

These substances were warmed together on the water bath for 1 hour. Directly the ether was added a deep reddish colour was produced, and it dissolved in the piperidine.

When the reaction mixture had cooled it was taken up in ether, and washed with alkali. It was then acidified. As there were no signs of a precipitate it was extracted once more with ether. The ethereal solution was evaporated down, and an orange yellow solid remained. This was once more taken up in a minimum quantity of dilute alkali. When this solution was acidified a yellow precipitate was obtained. This was filtered off, and recrystallised from water, whence it separated in needles of m.p. 97-99°.

The alkali insoluble portion of the product was filtered off also, washed, and dried, and recrystallised from ethyl alcohol whence it separated in little yellow needles of m.p. 92°. This substance was therefore thus identified as dinitrophenyl piperidine.

Yield 97%:

(Phenol) Yield 92-93%.
Attempts to synthesise 4 (3 nitro p anisoxyl
6 ethoxy 2 methyl quinoline.

\[
\begin{align*}
\text{I.} & \\
4 \text{ chlor 6 ethoxy 2 methyl quinoline} & 1 \text{ Mol.} \ 10g. \\
3 \text{ nitro 4 methoxy phenol} & 2 " \ 15.5g. \\
\text{KOH} & 1.33 " \ 7 g. \ \text{in} \ 5 \text{ cc} \ H_2O.
\end{align*}
\]

The alkali was fused with the water, and when the liquid was pretty cool the phenol was added with two further lots of 5cc of water at suitable intervals. The chlorocompound was next added, and the reaction mixture was heated at 140-160° for three hours under reflux.

On cooling working up was carried on as usual, but the product so isolated proved to be unchanged chlorethoxy quinaldine which recrystallised from light petroleum and gave a m.p. 65°.

Mixed m.p. specimen of chlorethoxy quinaldine 65°.
II. 4 chlor 6 ethoxy quinaldine 1 Mol. 3.8 g.
3 nitro 4 methoxy phenol 2 " 5 g.
caustic potash 1.33" 2 g. in 5cc H₂O.

The phenol was dissolved in the caustic potash solution which was then carefully evaporated nearly to dryness, on the water bath. The potassium salt of the phenol crystallised out in long stout red needles; these were collected and dried. This salt was added slowly to the molten chlorcompound in a flask which was then heated, open to the air, for an hour at 200°. Dilute alkali was added, and a solid was filtered off. This however was quite clearly nearly tar and carbon—the experiment having resulted in complete charring of the substituents.
III. Materials - the same as in II.

Very cautiously the materials were introduced into a distilling flask in the usual way - the temperature however being kept very low. A moderate amount of water was added and the flask was then fitted with a condenser, and corked, and heated steadily with a low flame.

As chlorcompound and water were distilled over they were returned once more into the flask. This induced no reaction, though it was carried on for some time. Directly the temperature was raised a little a violent reaction took place, resulting in complete charring.
Bromination of 2:4 dinitro 4'-methoxy diphenyl ether.

I. 2:4 dinitro 4'-methoxy diphenyl ether  1 Mol.  20 g.
bromine Br₂  (1 mol)
= 160 g  4 cc.
= 54 cc

glacial acetic acid  1 Mol.  82 g  9 cc.

A solution of bromine in glacial acetic acid was made up as follows: The bromine was weighed out of a stoppered bottle and dissolved in the appropriate amount of acid. The volume of the solution was ascertained, and a burette was then filled with it. The volume of solution which contained the correct weight of bromine was calculated.
The diphenyl ether was dissolved in a little glacial acetic acid, and the solution was brought to room temperature. The bromine solution was measured from the burette into a dropping funnel and from this it was gradually added to the ether. After addition the mixture was allowed to stand for ten minutes and then it was cautiously warmed to 40° on the water bath. It was then cooled, and water was added drop by drop with stirring and scratching to bring the brom compound down crystalline. The precipitate thus
obtained was filtered off, washed, and dried. A lassaigne test for halogen gave a positive result but repeated crystallisations from alcohol gave very varied and ill-defined melting points so that it was concluded that by this method bromination was incomplete, and a mixture of starting material, and brom product was obtained.

Data.

Weight of stoppered bottle - 137.430 g.
" " " bromine = 247.455 g.
" " " = 110.025 g.

Volume of glacial acetic acid used to dissolve = 247.5 cc.
Volume of solution = 287 cc.
" " " required for experiment = \( \frac{160 \times 4 \times 287}{54} \) \( \frac{110}{110} \) = 27.23 cc.

Burette readings 2) 42.4
            ) 15.1

:. Volume of \( \text{Br}_2 \) solution used = 27.3 cc.
II. The quantities used were as in I

anhydrous sodium acetate \(1 \text{ Mol.} \) (\(\approx 82 \text{ g.} \ 6 \text{ g.}\))

The bromine solution was added as before to the diphenyl ether solution in the presence of the sodium acetate. The flask - which had a ground glass neck, was then fitted with a condenser, and the mixture was boiled for three hours under reflux. Decolourisation appeared to take place, and on cooling a white substance separated out. This was filtered off and well washed for it was supposed that it would contain sodium bromide. However, on further investigation the product gave much the same results as in I, and this method was therefore also abandoned.
The ether was introduced into a flask fitted with a condenser by means of a ground glass joint. The bromine and the iodine crystal were added down the condenser. Addition caused fuming, and a violent reaction appeared to take place although no heat was developed. When addition was complete the reaction mixture was heated under reflux for 4 hours on the boiling water bath. A clear greenish vitreous looking mass was produced which was poured out of the flask (while still quite warm) into a little water. On cooling this mass set hard. It was ground up, well washed, and dried. It dissolved easily in alcohol from which it separated in shining clusters of pale greenish yellow silky needles of m.p. 130°.

0.3227 gms gave 15.0 cc of nitrogen at 19° C and 758 mm pressure.

whence percentage of nitrogen is 6.5

C₁₂H₁₀O₂Br₂ requires 6.3
Preparation of 2:5 dibrom 4 methoxy phenol.

\[
\text{3' brom 2 4 dinitro 4' methoxy diphenyl ether} \quad 10 \text{ g. 1 Mol.}
\]
\[
\text{piperidine} \quad 14 \text{ g. 2 "}
\]

The piperidine was poured onto the brom compound in a conical flask, which was then heated on the water bath for an hour. The dark red solution formed was taken up in chloroform, to this strong alkali was added. The solution formed two layers which were separated, and the chloroform layer was well washed with alkali and water. It was then evaporated on the water bath, and the residue was recrystallised from alcohol. This substance separated in shining orange needles of melting point 91.2° and was thus identified as 2 4 dinitrophenylpiperidine which is already well known. A mixed melting point with a sample of 2 4 dinitrophenylpiperidine gave an unchanged melting point, which completed the identification.

Meanwhile the alkali solution was acidified with strong hydrochloric acid and extracted with ether. The ether was evaporated off and the residue was recrystallised from water from which it separated in shining white needles of m.p. 110°.

0.2094 gms of this compound 0.2782 gave AgBr.

\[
\text{whence } \% \text{ Br}_2 56.72.
\]

C\textsubscript{7}H\textsubscript{5}O\textsubscript{2}Br\textsubscript{2} requires \% Br\textsubscript{2} 56.74.
Attempts to prepare 4 (2:5 dibromo 4 methoxy phenoxy) 6 ethoxy quinaldine.

2:5 dibromo 4 methoxy phenol 5 g. 2 mols
4 chlor 6 ethoxy quinaldine 2 g. 1 "
caustic potash 1 g. 1.33"

The phenol was added to the molten potash after the latter had been considerably cooled. The rest of the condensation was carried out in the usual manner, the mixture being heated on the metal bath for two hours at 150-170°. On cooling and adding alkali a residue was filtered off, but this melted on the water bath, when it was recrystallised from light petroleum it was identified as unchanged chlorethoxyquinaldine.

II. Experiment was exactly repeated, only in this case a speck of copper bronze was added as a catalyst. The results were exactly the same as in I.

III. The experiment was repeated raising the temperature to 200-210° and heating for a day. This resulted in complete charring.
**IV.** Exactly the same quantities were used. The reactants when mixed were heated under reflux on the boiling water bath for 1 week.

Dilute alkali solution was added to the contents of the flask and the insoluble portion was filtered off. On acidifying the mother liquor a considerable amount of the unchanged phenol was recovered.

The precipitate was well extracted with light petroleum (b.p. 60-80°) and from this solution much unchanged chlorquinaldine separated out. However there remained still a tiny residue. This was soluble in most solvents but would not separate again. Finally it was dissolved in alcohol and precipitated by addition of a little water. This substance gave a melting point 156°. Thus it seemed to be a new substance but it was clearly far from pure, and was present in such minute quantities that no further attempts were made to investigate it.
Preparation of 4 (amino 4 methoxy phenoxy) 6 ethoxy quinaldine.

4 (nitro 4 methoxy phenoxy) 6 ethoxy quinaldine 10g in 20cc of G.A.A stannous chloride 19.5g.
concentrated hydrochloric acid 17 cc.

The nitro compound dissolved in the glacial acetic acid was kept simmering; to this the hydrochloric acid was added. The stannous chloride was cautiously added in little portions and the flask was kept heated until the reaction began to take place. This was over very quickly and the flask was heated for a further half hour on the water bath. When cool the contents of the flask were made strongly alkaline by addition of about three times the theoretical amount of caustic potash. By this means the tin was precipitated, and redissolved again, and the base was freed. The solution was extracted thoroughly with ether, and washed, and dried over potassium carbonate; it was then distilled off leaving a solid residue of base in the flask. This residue was dissolved out with a little dilute hydrochloric acid. The acid solution thus obtained was rendered faintly alkaline and the amino
compound was precipitated. It was filtered off, washed and dried. It proved to be very soluble in ethyl alcohol from which it separated in rectangular platelets, and sparingly soluble in ether from which it separated in rectangular prisms.

m.p. 139°.

Yield about 60%.

Analysis.

0.2648 gives 21.7 cc N₂ at 747 mm and 19°C.

whence % N₂ = 8.60.

C₁₉H₂₀O₃N₂ requires % N₂ = 8.64.

Meanwhile copper bromide was prepared by adding the potassium bromide solution to the copper sulphate solution and passing in sulphur dioxide till no more white crystalline copper bromide was precipitated. This precipitate was filtered off and well washed.

It was then dissolved in the hydrobromic acid solution and kept cold in a freezing mixture. To this solution
The preparation of 4 (brom 4 methoxy phenoxy) 6 ethoxy quinaldine.

Aminobody 10 g.
hydrochloric acid (conc) 7 cc in 4 cc of H₂O.
sodium nitrite 2.5 g.
xtalised copper sulphate 6 g. in 20 cc of H₂O.
potassium bromide 3 g. in 7 cc of H₂O.
hydrobromic acid 10 cc (S.gr. 1.49)

The amino body was dissolved in the hydrochloric acid and water and cooled down to 0° in a freezing mixture, stirring all the while so that the hydrochloride which separated out might be finely divided.
The sodium nitrite solution was slowly added keeping the temperature at 0°, and sufficient urea to destroy any excess nitrous acid.
Meanwhile cuprous bromide was prepared by adding the potassium bromide solution to the copper sulphate solution and passing in sulphur dioxide till no more white crystalline cuprous bromide was precipitated. This precipitate was filtered off and well washed.
It was then dissolved in the hydrobromic acid solution and kept cold in a freezing mixture. To this solution
the filtered diazo solution was added. A deep chocolate brown precipitate was formed and nitrogen was evolved. It was left to stand till all the nitrogen had been given off; then it was filtered off, washed, and recrystallised several times from alcohol. Each time it separated out highly coloured, but finally on boiling the hot alcoholic solution with blood charcoal for ten minutes the solution filtered through perfectly clean, and the bromderivative separated out on cooling in prismatic needles, m.p. 193-194°. Mixed m.p. with S'. 193-194°.

% Br₂ found 19.7.

C₁₉H₁₈O₂NBr requires % Br₂ = 20.62.
The preparation of 2 bromquinolmonomethylether.
Irvine & Smith (J.C.S. 1927, 74.)

quinol monomethylether 1 Mol. 6.2 g.
carbon disulphide 140 cc.
bromine 1 Mol. 12.5cc of 20% (Vol) in CS₂.

The ether was dissolved in 140 cc of cold carbon disulphide and 20% (Vol.) solution of bromine in carbon disulphide was added slowly, with constant stirring, in the appropriate quantity. When the yellow colour had disappeared the solvent was distilled off. After some scratching the residue went solid.
Benzoylation of p-methoxy phenol.

Schotten-Baumann.

\[ \text{p-methoxy phenol} \quad 20 \text{ g.} \quad 1 \text{ Mol.} \]
\[ \text{benzoyl chloride} \quad 30 \text{ g.} \quad 1\frac{1}{2} " \]
\[ = 175 \text{ g} \]
\[ 10\% \text{ sodium hydroxide solution} \quad 200 \text{ cc. (XS)} \]

The benzoyl chloride was added to the phenol in a well stoppered conical flask. The alkali was then added, and the flask was shaken till the benzoyl derivative formed went solid.

This was recrystallised from alcohol and ligroin when it was taken as pure.

Yield 19 g.
Bromination of 4 methoxyphenyl benzoate.

p-methoxyphenyl benzoate 1 Mol. (20 g.)
anhydrous formic acid (136 cc.
bromine. (5.5 cc.

The solid was dissolved in the formic acid and warmed on the steam bath.
The bromine with an equal volume of formic acid was run in dropwise, and the mixture was gently boiled for a few minutes until excess bromine was driven off. It was then poured into 880 cc. of water. The brown oil which formed solidified, and was recrystallised from alcohol.
Hydrolysis of 3-brom-4-methoxyphenyl benzoate.

Aqueous methyl alcoholic caustic soda 300 cc. of (18 gms. in 500 cc. salt.)

3-brom-4-methoxyphenyl benzoate 28 g.

The brombenzoate and the alkali were boiled together under reflux for two hours. The hot solution was then filtered to eliminate any undissolved impurity. The methylalcohol was distilled off from the solution and residual solution was acidified. This precipitated both the benzoic acid and the bromphenol. The precipitate was filtered off and taken up in a solution of sodium bicarbonate. The benzoic acid went into solution and the bromphenol remained insoluble and was filtered off, and recrystallised from alcohol.
Synthesis of 4 (3 brom 4 methoxy phenoxy) 6 ethoxy quinaldine (S').

4 chlor 6 ethoxy quinaldine 1 Mol. 2.7 g.
3 brom 4 methoxy phenol 2 " 5 g.
caustic potash 1.33 " 1 g.

The phenol was added to the molten alkali at a pretty high temperature; the mixture had to be heated a little more before a clear homogeneous melt was obtained.

The chlor ethoxy quinaldine was added and the reaction mixture was heated under reflux for 2 hours at 180-190°.

Dilute alkali was then added and a small quantity of a tarry oil separated which solidified on standing overnight. It was filtered off, washed, and extracted with light petroleum (b.p. 60-80°) in which it was mostly insoluble. By this means any unchanged chlor compound was removed. The residue proved soluble in most solvents but would separate from none.

It was taken up in alcohol and after the solution had been filtered it was precipitated by addition of water. This was repeated.
It was taken up in alcohol the third time and blood charcoal was added. The solution was thoroughly boiled and filtered. The filtrate came through clear and the ether separated out on cooling in prismatic needles of m.p. 193-194°.

Mixed m.p. (+S) 193-194°.

The yield was very small, much tar being formed.

Repetition of the experiment shewed that this yield was rendered even smaller if the temperature was allowed to rise above 190°.

Analysis.

Found % Br₂ 20.2
C₁₉H₁₈O₃NBr₂ requires % Br₂ 20.62.

Thus S' was proved identical with S.
EXPERIMENTAL.

(1) Preparation of 4-brom diphenyl.
(Method of Gomberg & Bamberger.)

\[ \begin{align*}
\text{p-bromaniline} & \quad .25 \text{ Mols. 43 g.} \\
\text{concentrated hydrochloric acid} & \quad \text{in 20cc of water} \\
\text{sodium nitrate} & \quad 50 \text{ cc.} \\
\text{benzene} & \quad 18 \text{ g in 36 cc of water.} \\
\text{sodium hydroxide} & \quad 300 \text{ cc.} \\
\text{58 cc of 20\% solution.} & 
\end{align*} \]

The bromaniline was melted under the water. The mixture was heated with mechanical stirring while the concentrated hydrochloric acid was added. When all the resulting hydrochloride had gone into solution it was cooled in a freezing mixture and diazotised at \(-5^\circ\) with the sodium nitrate solution. Urea was added to remove any excess of nitrous acid.
The diazo solution was filtered and added to the cold benzene in a wide-necked bottle. The mixture was kept at the temperature of melting benzene and vigorously mechanically stirred while the sodium hydroxide solution was added drop by drop. (1-2 hours).
The mixture was allowed to reach room temperature, 0, then
steam distilled the flask being kept immersed in a paraffin oil bath at 170° when once all the benzene was distilled off. When all the benzene had come off, the 4-brom diphenyl started to come over - a liquid which readily solidified in the condenser to an orange solid. This was recrystallised from 200 cc. of hot ethyl alcohol with 5 cc concentrated hydrochloric acid and 5 grams of zinc dust. It came down in white shining plates.

Crude yield 18 grams.

Pure " 14 "

m.p. 90°.
Attempted preparation of 4-brom phenyl naphthalene.

Exactly the same quantities of 4-brom aniline was diazotised just as before - a few pieces of ice being added during diazotisation.

The clear filtered diazo solution was added to 426 grams of naphthalene suspended in carbon tetrachloride as solvent in a wide-mouthed bottle.

The mixture was kept at the temperature of ice-water and stirred just as before while the same amount of alkali was added drop by drop over a period of 1-2 hours.

The mixture was allowed to attain the temperature of the room and steam distilled. After all the carbon tetrachloride had come over the water condenser was changed for an air-condenser, and a water-cooled receiver was used. The naphthalene came over pure at first and then coloured deep yellow to orange by the phenyl naphthalene. There was very little of this and it could not be separated from the naphthalene by distilling, vacuum distilling, or recrystallising.
Preparation of 4-brom diphenyl using borofluoric acid.

4-bromaniline was diazotised exactly as before, and in the same quantity. To the clear diazo solution borofluoric acid was added until no more white crystalline borofluoride was precipitated. The borofluoride was filtered off — pressed on the Buchner funnel, and dried in the vacuum desiccator. When dry it was introduced into the wide-mouthed bottle containing the 300 cc of benzene. The addition of alkali then proceeded just as before. From time to time a drop of the reaction mixture was tested with β-naphthol in caustic soda. At first a bright red precipitate appeared shewing the diazo solution to be present in the mixture. At the end of the addition of alkali the mixture was slightly alkaline and gave no red precipitate with the β-naphthol shewing that the diazo solution had all been used up in the reaction. The mixture was then allowed to attain room temperature and steam distilled as before.

Crude yield 20 grams.

Pure yield 18 grams.
(IV. Attempted preparation of phenyl naphthalene using the borofluoride method.

Aniline .25 Mols.
naphthalene 5 " 160 g. in 300 ether.

\[ \frac{1}{2} \text{molecule of aniline was diazotised and the borofluoride prepared as before.} \]

It was then introduced into the wide-mouthed bottle containing 160 gms of naphthalene in 300 cc of ether. (5 molecules of naphthalene to one of aniline). The alkali was added with cooling and stirring as before. During the stirring for 1-2 hours the ether tended to evaporate and had to be carefully kept up to a certain mark on the bottle by constant additions.

The steam distillation was done in exactly the same manner as the previous experiment with naphthalene. As before the naphthalene came over stained yellow to orange. When all this was over a pale yellow oil began to distil over and water was once more run through the condenser. When the distillate came over clear the flask was put into a paraffin bath and the temperature raised - distillation was continued till the distillate once more came over clear. This effected a moderately complete separation. (Chattaway, J.C.S. 63, 1185)

The product was a pale yellow oil solid below 45° with a
faint blue fluorescence.

Yield 2.5 grams.

The boro-fluorescence of the 4-bromocinnamylidene cinnamylidene compound was made exactly as in the preparation of 4-bromodiphenyl. It was added to 150 grams of naphthalene (2 Mols. of BBr₃ and 1 Mol. base) suspended in 300 cc of ether as in the foregoing experiment. During the addition of the bromine, the reaction mixture was tested for the diene compound and it was found to be present; when all the alkali was added however the test for the diene compound was negative.

The mixture was shaken distilled in exactly the same manner as in the foregoing experiment. As before the naphthalene at the last was deeply colored with the condensation product, and finally a thick amber brown oil distilled over which solidified in the receiver to a brown solid.

m.p. 76-77°.

Yield 1.5 grams.
(V) Attempted preparation of 4-brom phenyl naphthalene by the foregoing method.

The borofluoride of the 4-bromaniline diazonium compound was made exactly as in the preparation of 4-bromdiphenyl. It was added to 160 grams of naphthalene (5 Mols. of \overset{\frown}{\&} : 1 Mol. base) suspended in 300 cc of ether as in the foregoing experiment. During the addition of the alkali the reaction mixture was tested for the diazo compound and it was found to be present; when all the alkali was added however the test for the diazo compound was negative. The mixture was steam distilled in exactly the same manner as in the foregoing experiment. As before the naphthalene at the last was deeply coloured with the condensation product, and finally a thick syrupy brown oil distilled over which solidified in the receiver to a brown solid. m.p. 76-77°.

Yield 1.5 grams.
(VI). Attempt to couple Anthranilic acid with benzene by the Bamberger-Gomberg method.

Anthranilic acid was heated with water and concentrated hydrochloric acid (1 molecule of anthranilic acid to 1 molecule of hydrochlor acid) on a water bath till no more solid seemed to go into solution. The hydrochloride thus formed was diazotised using 1 molecule of sodium nitrate. The filtered diazo solution was introduced into a wide-mouthed bottle containing 343 cc of melting benzene and 2.5 molecules of the alkali were added as before in 20% solution drop by drop with stirring. The addition took three hours. The mixture was allowed to reach room temperature and the two layers separated in a funnel. The watery layer was boiled with blood charcoal but it was not decolourised. It was acidified and a copious dark brown precipitate appeared. This was taken up in alkali and reprecipitated by acid but it became no cleaner. It was filtered off and dried on the water bath where it separated into a black tar and a yellow watery solution. Evaporation of this solution to dryness gave only crystals of sodium chloride. This method therefore did not seem suitable, and gave no yield.