A Thesis for the Degree of Doctor of Philosophy

by

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Part One: Ortho-HYDROXYLATION OF PHENOLS

Part Two: DIBENZ (b, f) OXEPINS

with an addendum on dibenz (b, f) thiepins.

Glasgow University September, 1955

Acknowledgments

The author wishes to express his sincere thanks to Dr. J.D. Loudon for his invaluable help, guidance and encouragement during this work, and to Mr. J.M.L. Cameron and Miss Christie for microanalyses.

The author is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.

Summary

Part One: Ortho-Hydroxylation of Phenols

Phenol and its homologues are condensed with 2-chloro-3,5-dinitrobenzophenone giving 2-aryloxy-3,5-dinitrobenzophenones. These are hydroxylated in concentrated sulphuric acid by treatment with acetic acid and hydrogen peroxide affording 2-(2"-hydroxyaryloxy)-3,5-dinitrobenzophenones which, by renewed hydroxylation yield 2-(2",6"-dihydroxyaryloxy)-3,5-dinitrobenzophenones. Scission of the mono-hydroxylated products leads to catechol and its homologues; scission of the di-hydroxylated products yields pyrogallol and its homologues. The requisite cleavage is more reliably effected by phenylhydrazine than by piperidine.

Part Two: Dibenz (b,f) oxepins

5-Nitro-2-phenoxybenzaldehyde, prepared from phenol in reaction with 2-chloro-5-nitrobenzaldehyde, is converted by standard methods into 5-nitro-2-phenoxyphenyl-pyruvic and -acetic acids. Each of these acids is cyclised by polyphosphoric acid to the appropriate derivative of 2-nitrodibenz (b,f) oxepin. Hence, or from modified intermediates, there are prepared the parent compound,

namely dibenz (b,f) oxepin and its 2-nitro-derivative. Incidentally, some aspects of the chemistry of this class of compound have been examined and the study has been extended to include members which incorporate certain structural features found in the alkaloid, cularine.

In an addendum the similar synthesis of dibenz (b,f)-thiepin derivatives from 5-nitro-2-(p-tolylthio)benzaldehyde is described and some of their transformations are discussed.

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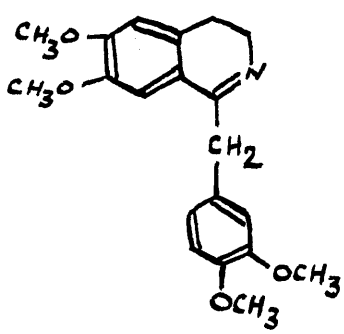
Part One: Ortho-HYDROXYLATION OF PHENOLS

Contents

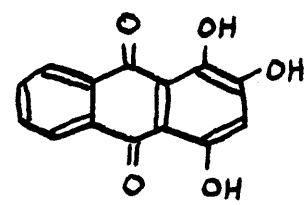
Ortho-Hydroxylation of Phenols

Introduction

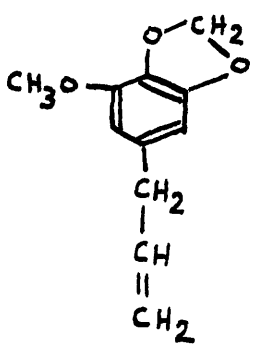
Aromatic compounds with two or three vicinal hydroxyl substituents occur in a wide variety of natural products, including alkaloids (I), pigments (II), essential oils (III), lichens (IV), coumarins (V), tannins (VI) and hormones (VII), either in the free state or as condensates. Frequently, as shown below, the hydroxyl groups are not present as such but as the methyl or methylenedioxy derivatives.



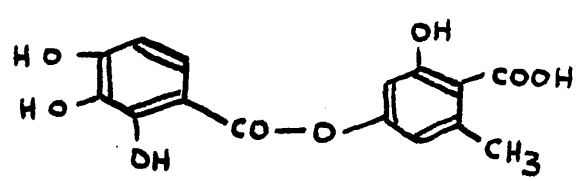
Papaverine (I)



Purpurin (II)



Myristicin (III)



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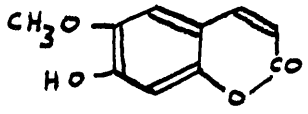
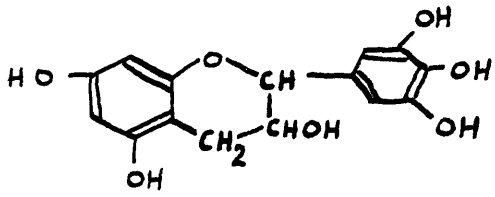
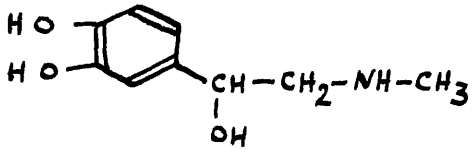


Scopoletin (V)



Gallocatechin (VI)

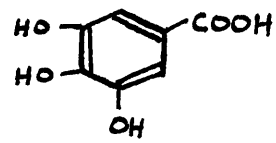


Adrenaline (VII)

Catechol, the simple 1,2-dihydroxybenzene, is present in coals, wood-tars, plants and vegetables, sometimes in the parent form (e.g. in onion scales), but more often in combination as in tannins, from which it was first obtained by dry distillation. Industrially it is produced by the action of alkali under suitable conditions on ortho-chlorophenol or phenol sulphonic acids. Because of its ease of oxidation, catechol is used in photographic developing. Its monoalkyl ethers, of which guaiacol (the mono-methyl ether present in beech-wood tar) is the most important, are made use of in medicine, particularly in the treatment of congestion of respiratory passages.

Alkyl catechols, prepared technically by the interaction of catechol with alkyl halides, olefins or alcohols, act as therapeutic agents, insecticides, antioxidants for fats and soaps, and as agents for stopping polymerisation and preventing gum-formation in petrols.

Pyrogallol, 1,2,3-trihydroxybenzene, occurs in combined form in creosotes. Its chief source, however, is gallic acid (VIII), which is widely distributed in



(VIII)

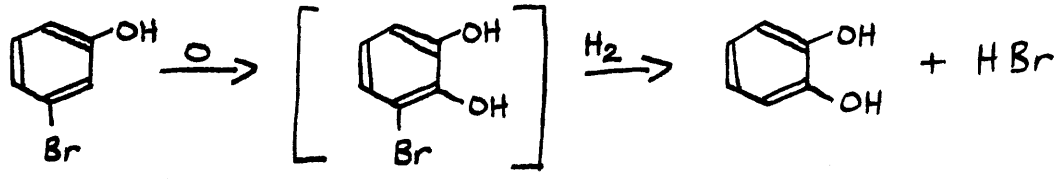
many plants rich in tannins. The decarboxylation process is carried out in industry by treating gallic acid with water at high temperature under pressure or by distillation from a mixture with pumice in an atmosphere of carbon-dioxide. Pyrogallol is useful as an absorbent for oxygen in alkaline solution, photographic developer, antioxidant, catalyst for certain oxidation processes and in medicine for the treatment of skin diseases. Alkyl pyrogallols are insecticides but are generally less powerful than the corresponding alkyl dihydroxy compounds.

It is thought desirable at this stage to review

briefly some of the methods which have been adopted to introduce hydroxyl groups into the ortho position of phenols.

Fittig and Mager[1] and other workers[2-9] studied the effect of alkali fusion on the three isomeric bromo (or chloro) phenols. In general, the ortho and meta isomers gave mixtures of resorcinol and catechol. From the para compound, resorcinol was the predominant product, along with varying quantities of hydroquinone. The iodophenols[4,10,11,12,13], however, by similar treatment produced the corresponding isomeric dihydroxybenzenes (e.g. catechol from ortho-iodophenol). Nolting and Stricker[4] explained the formation of catechol from meta-bromophenol on the basis of an oxidation-reduction system, thus:-

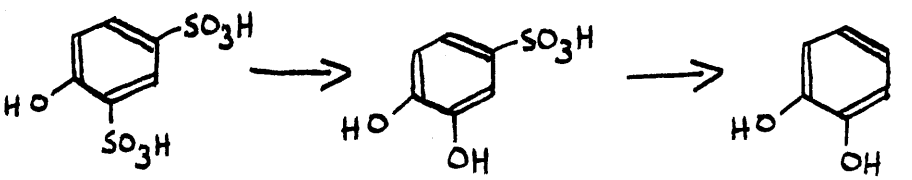
$$2\,KOH = K_2O + H_2 + O$$



With the iodophenols, the larger size of the iodine atom favours the straightforward elimination of the halogen. The yields of the dihydroxybenzenes are for the most part

poor due to the extreme conditions and the instability of polyhydric phenols towards strong alkali. Kipriyanov and Suich[14], however, obtained catechol in good yield from ortho-chlorophenol by hydrolysis with aqueous caustic soda, in forcing conditions, in presence of copper sulphate as catalyst and this method has been developed on an industrial scale. It may be noted also, that Freidlin and Fridman[15] have reported the formation of catechol by passing ortho-chlorophenol at high temperature over silica, promoted by cupric chloride.

Phenol sulphonic acids have been used as starting materials for the synthesis of dihydroxybenzenes, notably by Barth and coworkers[16,17]. Fusion of phenol-2-sulphonic acid with alkali gives only a small yield of catechol. The 2,4-disulphonic acid, similarly, forms benzene-1,2-dihydroxy-4-sulphonic acid as the main product. Merck[18] showed that hydrolysis of the remaining sulphonic acid group could be achieved under rigorous conditions with mineral acid to give catechol. This method, with modifications, has been developed as a technical process.



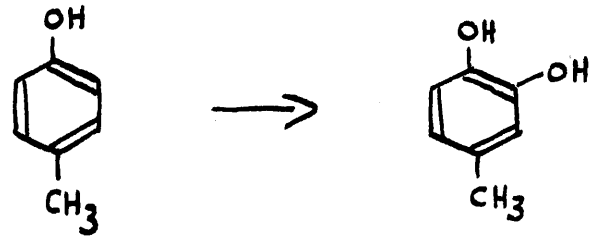
According to Petersen and Baehr-Predari[5], para-chlorophenol-2-sulphonic acid treated in a similar way gave pyrogallol, by incorporating the two fusion methods above.

Catechol has been prepared from ortho-aminophenol by treatment with mineral acid[19] or from its diazonium salt[20] but a more convenient laboratory approach is by Dakin's method[21,22]. This involves the oxidation of ortho-hydroxybenzaldehydes with hydrogen peroxide in alkali. Dakin observed that the reaction could be extended to

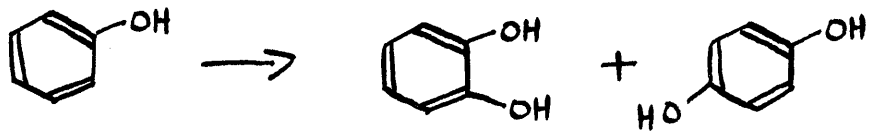
hydroxyacetophenones but the yield of dihydroxybenzenes was poor. Baker, Jukes and Subrahmanyam[23], however, have shown that it is readily possible to oxidise such compounds successfully, and since hydroxyacetophenones are generally accessible it is evident that this provides a valuable synthetic method. Moreover, although difficulty sometimes arises through the formation of rather insoluble, co-ordinated alkali salts of the ortho-hydroxyacetophenones, this may be circumvented by the use of ammonium hydroxides,

such as tetramethylammonium hydroxide or benzyltrimethyl-ammonium hydroxide[56].

The oxidation of monohydric phenols to dihydric phenols by the use of potassium persulphate in alkaline solution was introduced by Elbs[24] and has since been the subject for numerous publications. Baker and Brown[25] (who give a brief review of the method) found that if the para position to the phenol were vacant, then hydroquinone derivatives were formed, but in the event of the para position being occupied a derivative of catechol was obtained, generally in smaller yield. Forrest and Petrow[26]

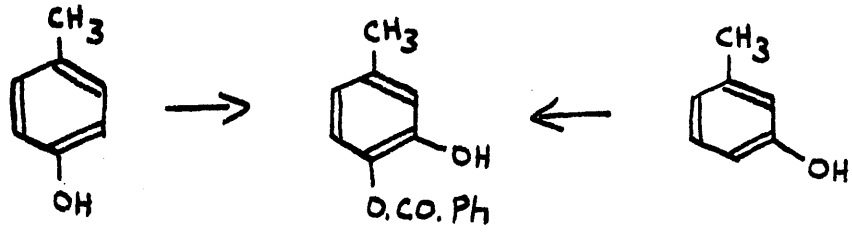


have shown, however, that appreciable quantities of catechols in addition to the quinols can be isolated even when the para position is unoccupied.



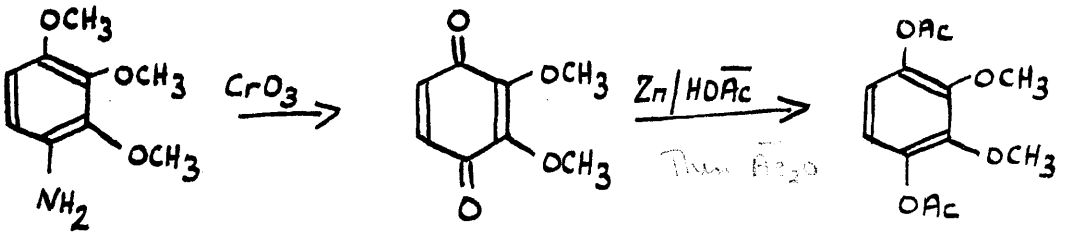
The use of free hydroxyl radicals (obtained from hydrogen peroxide in the presence of a ferrous salt) in the oxidation of phenols has been studied by many workers, notably Cross, Bevan and Heiberg[27] and Goldhammer[28]. It is quite evident that ortho-hydroxylation of the aromatic nucleus does occur, since catechol can be isolated more easily than the other reaction products, which include hydroquinone, pyrogallol and purpurogallin. Waters, et al[29,30] have confirmed the complex nature of the oxidation of phenol and shown that the direct oxidation of aromatic ring systems by free hydroxyl radicals is a process of no preparative value.

Of more practical application, however, is the method due to Cosgrove and Waters[31,32]. Monohydric phenols were shown to react with benzoyl peroxide in boiling chloroform to give monobenzoates of catechol derivatives. Para-and meta-cresol, for example, gave the same products. It is considered that the substitution of the para derivative



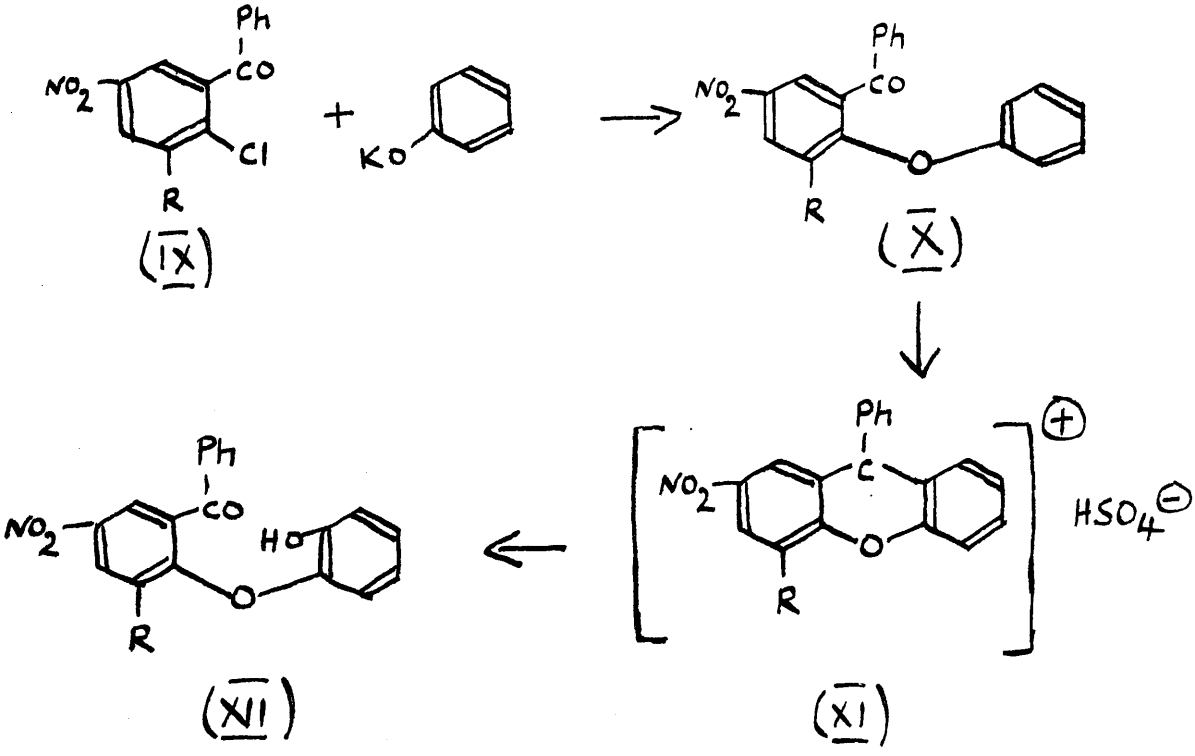
involves the molecular rearrangement of a benzoyl group. From the ortho isomer, the main product consisted of resinous material, the only simple reaction product isolated being 2-benzyloxy-m-cresol in poor yield. From phenol itself, derivatives of both catechol and, to a lesser extent, hydroquinone were obtained.

A variety of reactions involving ortho-hydroxylation have been devised by Baker, et al[33-37,23] in the preparation of derivatives of tetrahydroxybenzene. For example,

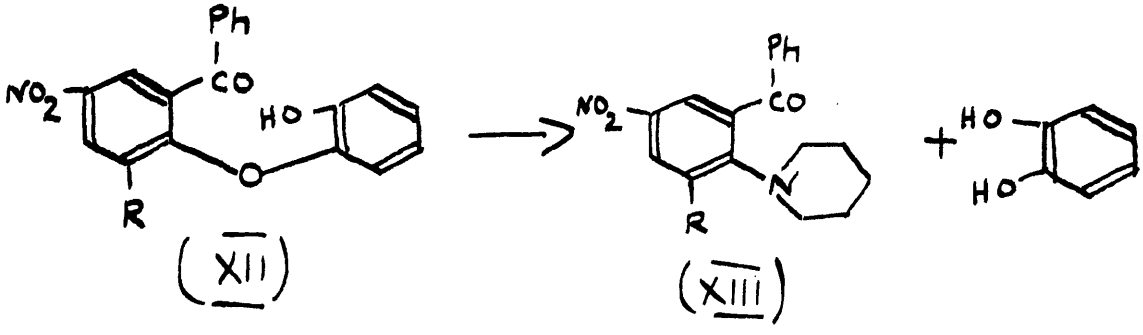


Stevens[42] has reported the synthesis of pyrogallol from 4-tert.-butylphenol, and it may also be noted that Stein and Weiss[43] have formed catechol in minute quantities by the action of neutron γ—rays on benzene.

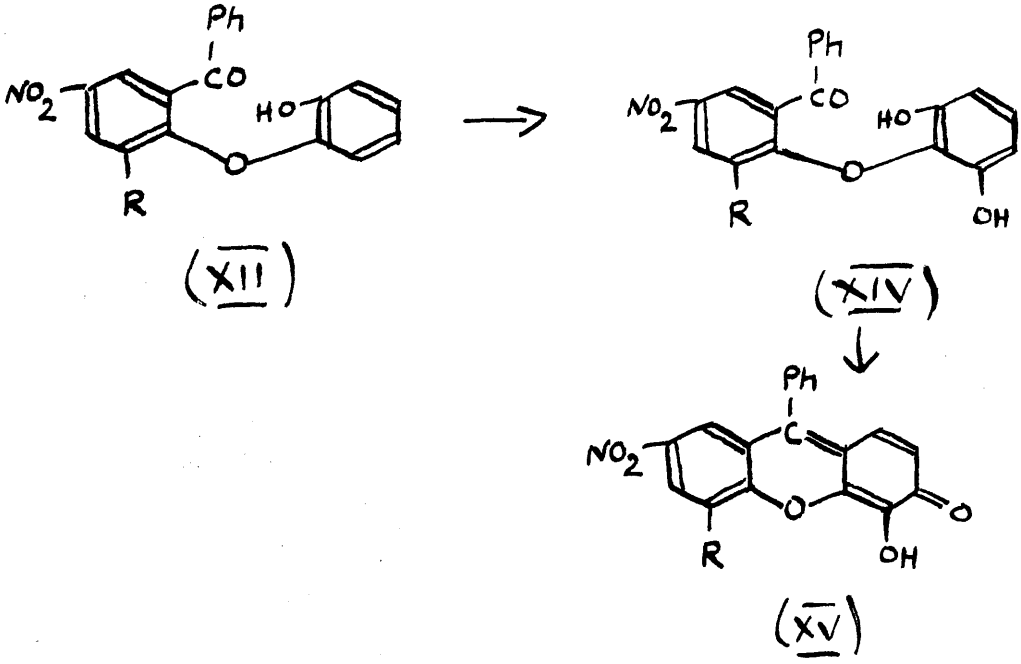
Loudon, et al[38,39,40] observed that potassium salts of phenols condensed with 2-chloro-5-nitrobenzophenone (IX; R = H) to form 2-aryloxy-5-nitrobenzophenones (X; R = H) which with concentrated sulphuric acid afforded solutions of the corresponding 9-phenylxanthylium sulphates (XI; R = H).



Subsequent treatment of these solutions with acetic acid and hydrogen peroxide gave 2-(2"-hydroxyaryloxy)-5-nitrobenzophenones (XII; R = H), which reacted with hot piperidine to give catechol derivatives and 5-nitro-2-piperidinobenzophenone (XIII; R = H). Compound (XII; R = H), similarly, on renewed hydroxylation yielded



2-(2",6"-dihydroxyaryloxy)-5-nitrobenzophenones (XIV; R = H). The latter compounds on heating with piperidine in general underwent rearrangement and cyclisation to form fluorone derivatives (XV; R = H) rather than the normal scission to pyrogallol derivatives.



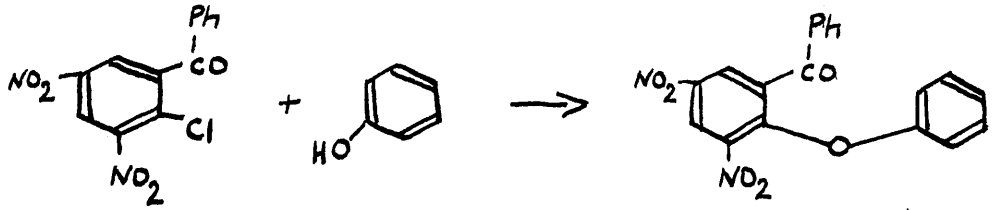
Scott[41], however, noted the ease with which 2-chloro-3,5-dinitrobenzophenone (IX; R = NO_2) (where the chlorine atom is further activated by the second nitro group in the appropriate position) condensed with phenols in cold pyridine to give the desired product (X; R = NO_2). Preliminary investigation suggested that oxidation of

(X; R = NO_2) proceeded smoothly to (XII; R = NO_2) and the latter product reacted with piperidine in mild conditions. This tended to confirm the expectation that scission of these compounds would be appreciably easier that in the mono-nitro series, and if this were indeed the case, the possibility of isolating sensitive polyhydroxy compounds would be greatly increased.

In the work about to be described the reaction scheme IX ⟶ XV (R = NO_2 in all cases) has been studied and extended and its application to a number of phenol homologues investigated.

Discussion

2-Aryloxy-3,5-dinitrobenzophenones



(XVI)

These compounds were prepared by adding the phenol in slight excess to a solution of 2-chloro-3,5-dinitrobenzophenone in pure pyridine (dried over KOH). After standing about 15 hours, the reaction mixtures were poured into dilute mineral acid. The desired products (XVI - XXI) precipitated and were crystallised from mixtures of benzene with methanol or light petroleum. The yields obtained were high (75-85%). If, however, impure pyridine is employed, the yields are considerably reduced due to the formation of intractable black tars. In this way, the following derivatives of phenol and its homologues were prepared:-

2-phenoxy-3,5-dinitrobenzophenone (XVI)

(previously prepared by Scott[41]) from phenol.

2-(3"-methylphenoxy)-3,5-dinitrobenzophenone (XVII)

from meta-cresol.

2-(4"-methylphenoxy)-3,5-dinitrobenzophenone (XVIII)
from para-cresol

2-(2",5"-dimethylphenoxy)-3,5-dinitrobenzophenone (XIX)
from 2,5-dimethylphenol.

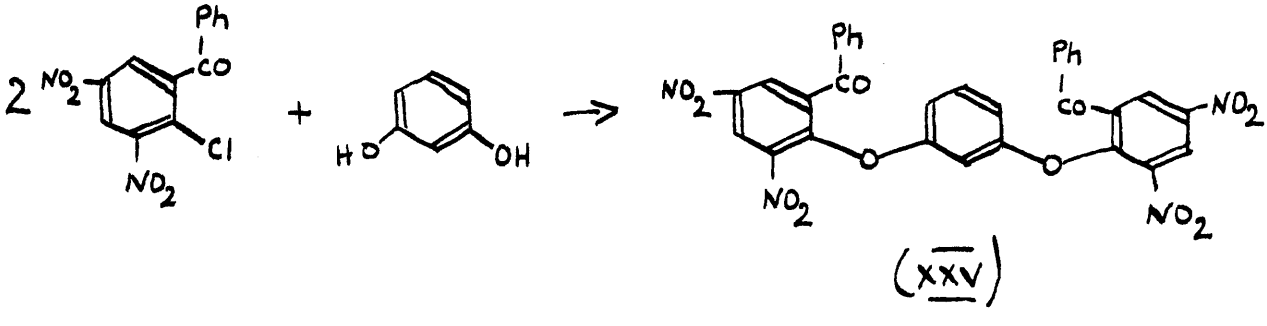
2-(3",4"-dimethylphenoxy)-3,5-dinitrobenzophenone (XX)
from 3,4-dimethylphenol.

2-(3",5"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXI)
from 3,5-dimethylphenol.

More sensitive phenols react similarly. For example, Scott[41] has prepared the corresponding derivatives from α-naphthol, β-naphthol, 1-phenanthrol and 7-hydroxy-coumarin.

It was found that from dihydric phenols also, the mono-ethers could be formed smoothly, provided a large excess of the phenol were present. 2-(2"-Hydroxyphenoxy)-3,5-dinitrobenzophenone (XXII) and 2-(3"-hydroxyphenoxy)-3,5-dinitrobenzophenone (XXIII) were thus prepared from catechol and resorcinol respectively.

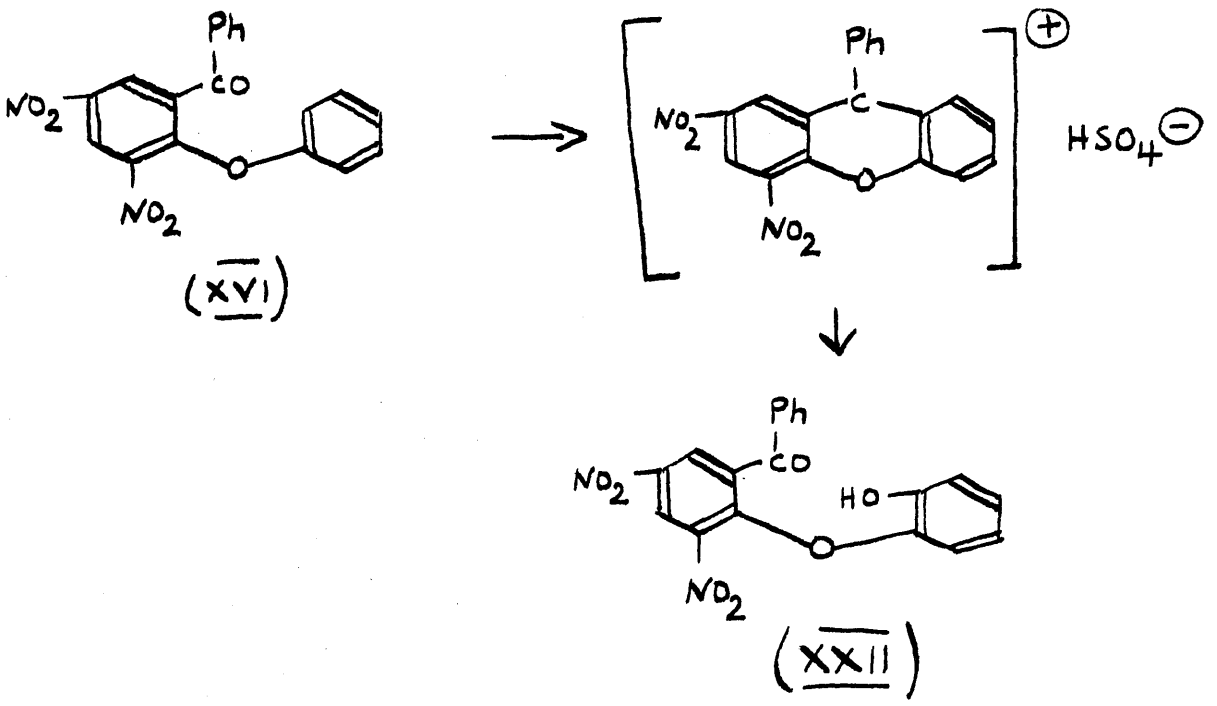
In the presence of rather more than 2 mols. of 2-chloro-3,5-dinitrobenzophenone the corresponding



(XXV)

diethers, catechol bis-(2-benzoyl-4,6-dinitrophenyl) ether (XXIV) and resorcinol bis-(2-benzoyl-4,6-dinitrophenyl) ether (XXV) were formed. These compounds crystallised readily from acetic acid. However, (XXV) retained the solvent tenaciously and correct analytical figures were only obtainable after fusion in vacuo.

2-(2"-Hydroxyaryloxy)-3,5-dinitrobenzophenones



The 2-aryloxy-3,5-dinitrobenzophenones (XVI - XXI) on treatment with warm concentrated sulphuric acid cyclised giving red solutions. On cooling, glacial acetic acid was added and the solutions were titrated with hydrogen peroxide until excess oxidising agent was present. The colour of the reaction mixtures became amber and in some cases the products crystallised out. After standing about half-an-hour, the entire mixture was added to crushed ice and the following hydroxylated compounds (XXII, XXVI - XXX) were obtained:-

2-(2"-hydroxyphenoxy)-3,5-dinitrobenzophenone (XXII) (identical with the mono-ether obtained from catechol, p. 14) from (XVI).

2-(2"-hydroxy-5"-methylphenoxy)-3,5-dinitrobenzophenone (XXVI) from (XVII)

2-(2"-hydroxy-4"-methylphenoxy)-3,5-dinitrobenzophenone (XXVII) from (XVIII)

2-(2"-hydroxy-3",6"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXVIII) from (XIX).

2-(2"-hydroxy-4",5"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXIX) from (XX).

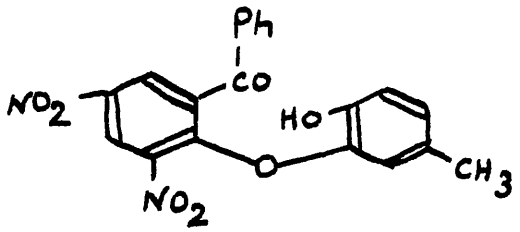
2-(2"-hydroxy-3",5"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXX) from (XXI).

These compounds crystallise easily but, as had been observed by Loudon and Scott[39] with the corresponding type of compound in the mono-nitro series, those which are obtained from hydrocarbon solvents (XXVI, XXVII) retain the solvent which can be removed by heating in vacuo to 125°.

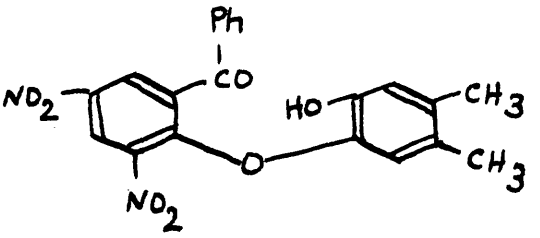
The reaction is subject to similar limiting conditions as in the mono-nitro series[38,39] and a number of experiments were carried out initially with the more accessible 2-phenoxy-3,5-dinitrobenzophenone (XVI) to determine the most suitable proportions of concentrated sulphuric acid

and glacial acetic acid. To obtain good yields of the products it is obviously desirable for the volumes of these reagents to be kept as low as possible and yet sufficient sulphuric acid must always be present to dissolve (XVI). As indicated by Table A (p. 44) even a slight variation in the ratio of concentrated sulphuric acid to acetic acid produces unwanted results. If the ultimate concentration of the mineral acid is too high, red by-products are formed and the desired products are then obtained crystalline only with difficulty and in poor yield. If it is too low, organic peroxides precipitate and to prevent their local formation the hydrogen peroxide was diluted with acetic acid and added gradually from a burette. The criterion of the ideal reaction was taken to be fading of the colour in the reaction solution to a clear amber when a calculated excess of hydrogen peroxide had been added. The conditions which were found to be most suitable for (XVI) were also applicable to the other 2-aryloxy-3,5-dinitrobenzophenones (XVII - XXI). When these ideal conditions were employed, the reaction could be carried out swiftly and efficiently and in high yields (80%) of the hydroxylated products (XXII, XXVI - XXX) obtained.

The hydroxylation of (XVII) and (XX) can obviously take place in two directions. The product from (XVII) has been shown to have in fact the structure (XXVI) by methylation and scission experiments (see p. 35)



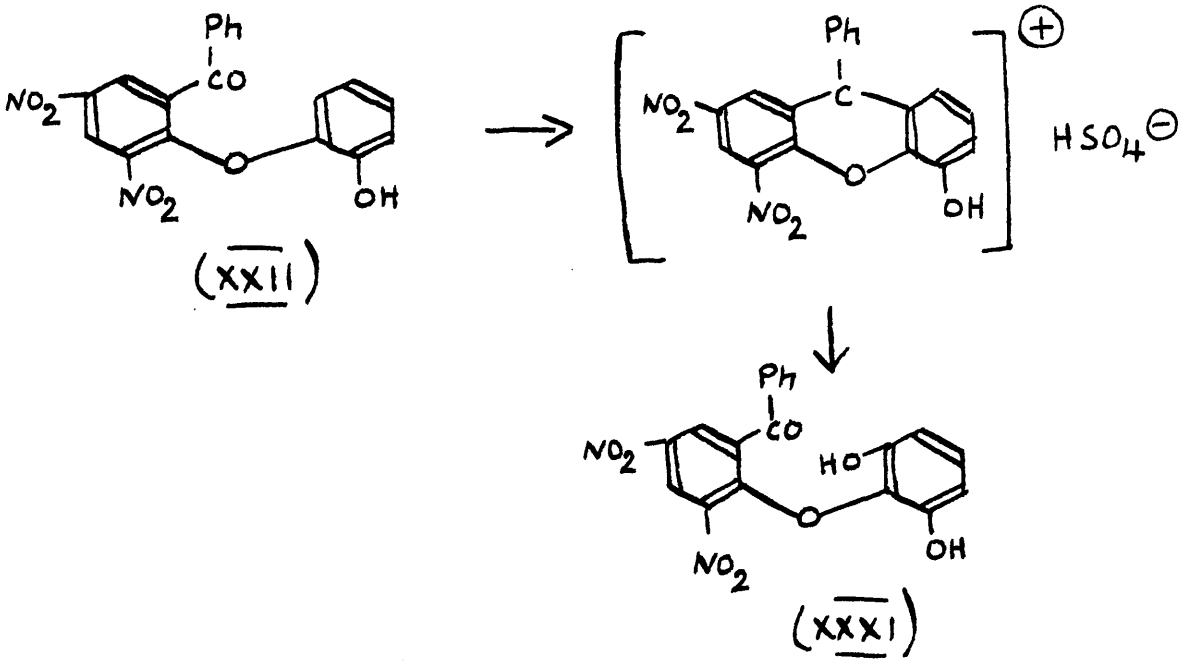
(XXVI)



(XXIX)

The product from (XX), however, remains ambiguous although it seems more likely to have the structure (XXIX).

2-(2",6"-Dihydroxyaryloxy)-3,5-dinitrobenzophenones



The 2-(2"-hydroxyaryloxy)-3,5-dinitrobenzophenones listed on p. 17 , with the exception of (XXVIII), which lacks the requisite free ortho-position, dissolved in warm concentrated sulphuric acid to give red-brown solutions of the corresponding xanthylium salts. On cooling, the addition of acetic acid produced no change of colour with (XXII), (XXVII), but gave green solutions with (XXVI), (XXIX), (XXX). On treatment with a slight excess of hydrogen peroxide the colours changed in a few minutes to clear amber. The solutions were then rapidly transferred to crushed ice, whereupon the following products were precipitated:-

2-(2",6"-dihydroxyphenoxy)-3,5-dinitrobenzophenone (XXXI) from (XXII)

2-(2",6"-dihydroxy-3"-methylphenoxy)-3,5-dinitrobenzophenone (XXXII) from (XXVI)

2-(2",6"-dihydroxy-4"-methylphenoxy)-3,5-dinitrobenzophenone (XXXIII) from (XXVII)

2-(2",6"-dihydroxy-3",4"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXXIV) from (XXIX)

2-(2",6"-dihydroxy-3",5"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXXV) from (XXX)

The compounds (XXXI - XXXIV) crystallised only with difficulty, and (XXXIII) obtained pure from benzene retained the solvent. The hydroxylation product of (XXX) could not be induced to crystallise although it was subsequently shown to be essentially the desired product (XXXV) by scission to 4,6-dimethylpyrogallol (p. 31).

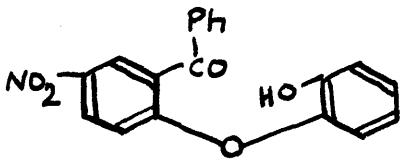
The preliminary investigation of the reaction was carried out with the appropriate derivative of phenol, 2-(2"-hydroxyphenoxy)-3,5-dinitrobenzophenone (XXII). It was observed that strict control of the ultimate concentrations of the critical reagents (concentrated sulphuric acid and acetic acid) was again necessary to prevent the formation of red by-products and peroxides (see Table B, p. 45). The most suitable conditions for

hydroxylation of (XXII) were found to be equally applicable to (XXVI), (XXVII) and (XXIX). Compound (XXX) however, required rather different proportions of acetic acid and concentrated sulphuric acid.

The 2-(2",6"-dihydroxyaryloxy)-3,5-dinitrobenzophenones are much less easily handled than the corresponding monohydroxy compounds. When the reaction solution is left in contact with excess oxidising agent the original amber colour rapidly darkens. They decompose quickly on storage and on heating in organic solvents. Since they crystallise with difficulty, they are seldom obtained pure in yields greater than 40-50% even when the conditions are most favourable.

Reactions with Piperidine

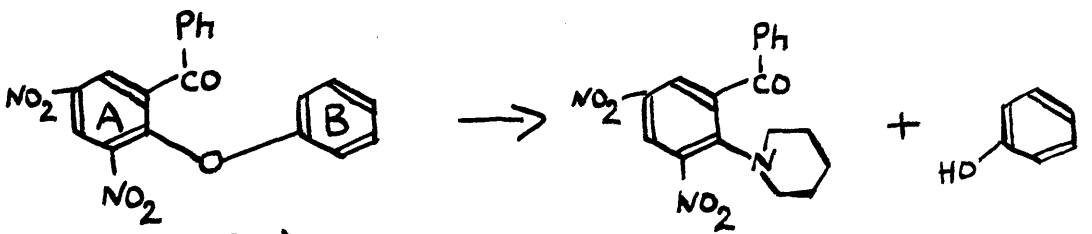
The scission of ortho and/or para nitrated diaryl ethers by means of piperidine was introduced by Turner, et al[57,58] Loudon, et al[38,39,40] extended this to a variety of compounds of the general type (XII), which



(XII)

by treatment with hot piperidine split to give catechol and 5-nitro-2-piperidinobenzophenone.

In the present work, this reaction was studied in the first instance with 2-phenoxy-3,5-dinitrobenzophenone (XVI).



(XVI) (XXXVI)

The activating influence of the two nitro groups ortho and para to position 2 of ring A, enabled breaking of the ether linkage with piperidine to occur under more moderate conditions than was the case with (XII) above.

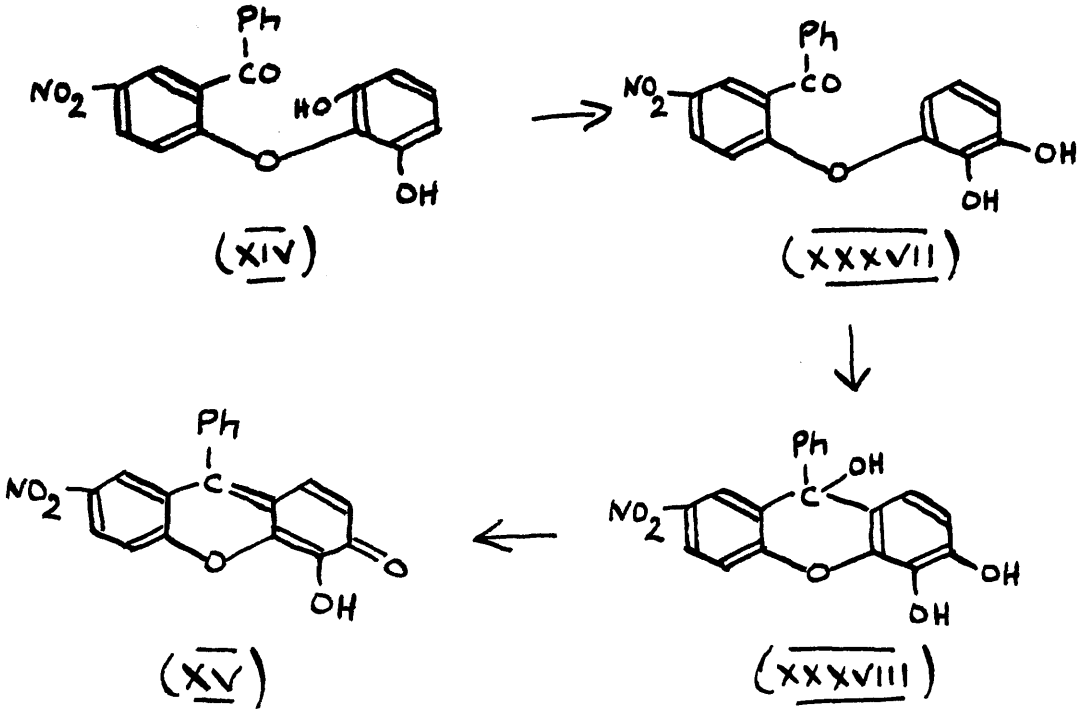
Thus, piperidine alone reacted vigorously with (XVI) and more slowly in the diluent benzene even at room temperature and in the presence of sufficient acetic acid to neutralise the quantity of amine used. The phenol was isolated from the benzene solutions of the products by acidification of the aqueous alkaline extracts and was estimated as tribromophenol. The other product, 3,5-dinitro-2-piperidinobenzophenone (XXXVI) was recovered from the residual benzene solutions.

Table C (p. **46**) summarises the experiments, which, although not intended to be quantitative, did indicate that the yield of phenol (determined by comparison with a test solution of phenol in piperidine and benzene) produced in all cases was high, and that the reaction was as profitably conducted in benzene solution at room temperature as in more vigorous conditions.

Extension of the reaction to the hydroxylated derivative of (XVI), 2-(2"-hydroxyphenoxy)-3,5-dinitro benzophenone (XXII) gave similar results, catechol and (XXXVI) being produced in all of the corresponding experiments. The dihydric phenol, however, has a higher solubility in water and is more readily oxidised in alkaline solution than phenol itself. Consequently it is difficult to develop a completely satisfactory process for

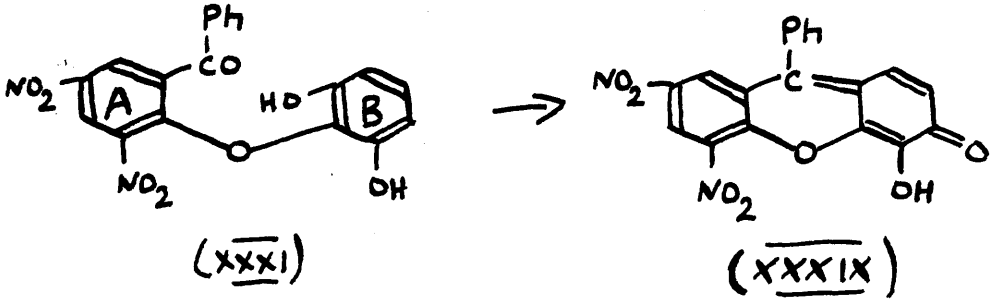
its isolation (cf. Scott[41]). The procedure eventually adopted involved alkaline extraction of the benzene reaction mixtures. The aqueous layers were then immediately run into dilute mineral acid, which was saturated with ammonium sulphate and exhausted with ether. The materials recovered from the ethereal solutions were sublimed under reduced pressure and catechol obtained in fair yield (c. 50%).

Loudon and Scott[40] by treating the dihydroxylated compounds of type (XIV) with hot piperidine found that normal scission to pyrogallols did not occur. The product isolated was 4-hydroxy-7-nitro-9-phenyl-fluorone (XV).



They had previously shown[38,39] that certain hydroxyaryloxynitrobenzophenones rearranged in alkali with the benzoylated nitrophenyl radical migrating to the adjacent oxygen atom. It was assumed that in this case a similar rearrangement was effected by the basic piperidine, (XIV) going to (XXXVII). Subsequent cyclisation involving the reactive position <u>para</u> to a phenolic ion gave (XXXVIII), which on dehydration formed (XV).

In the present work, 2-(2",6"-dihydroxyphenoxy)-3,5-dinitrobenzophenone (XXXI) on treatment with piperidine



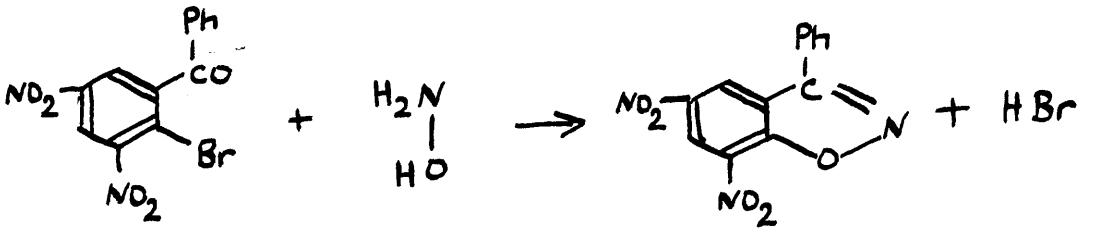
in benzene solution in moderate conditions, similar to those employed with the mono-hydroxylated (XXII) and the non-hydroxylated (XVI) compounds, also produced the corresponding fluorone, 4-hydroxy-5,7-dinitro-9-phenyl-fluorone (XXXIX). Evidently the presence of the second activating nitro group in ring A is insufficient to

promote scission of the other linkage in preference to cyclisation. In addition, when the reaction was carried out with sufficient acetic acid present to neutralise the amine (and indeed even in the presence of a slight excess of the acid) rearrangement still occurred, followed by cyclisation and dehydration. It must be noted, however, that on one occasion a large excess of piperidine was used (with no acid present) and although no pyrogallol was detected, the other scission product, 3,5-dinitro-2-piperidinobenzophenone (XXXVI) was isolated and identified by melting point of admixture with an authentic specimen. This observation remains unexplained.

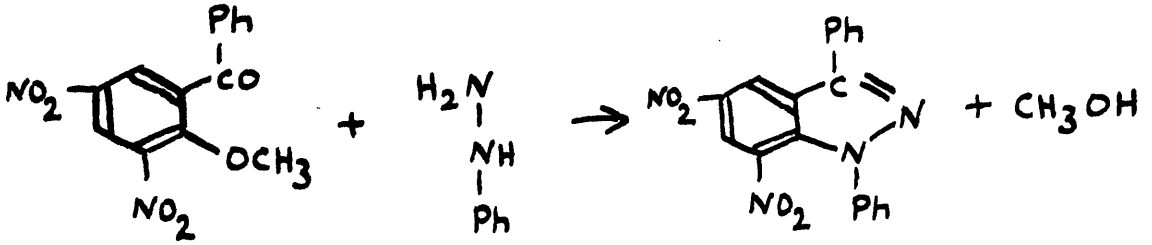
The fluorone (XXXIX) is purified readily from anisole. The stout black crystals retained the non-volatile solvent and were ground up in methanol before correct analytical figures could be obtained.

Scissions with Phenylhydrazine and Hydroxylamine

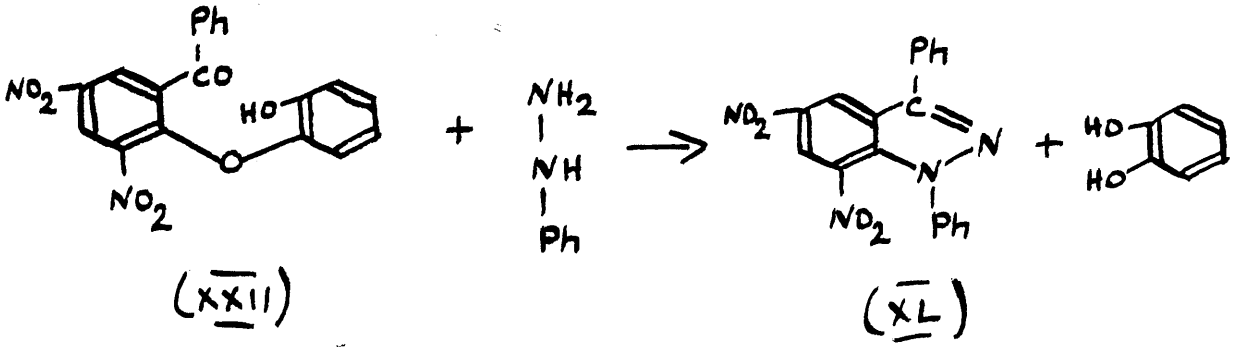
Meisenheimer, Zimmermann and Kummer[44] noted the ease with which 2-bromo-3,5-dinitrobenzophenone reacted with hydroxylamine to form the ring structure, 5,7-dinitro-3-phenylbenzisoxazole. Borche and Scriba[45] later extended



this to hydrazine and some of its derivatives. For example, 5,7-dinitro-1,3-diphenylindazole was readily produced from phenylhydrazine and 2-methoxy-3,5-dinitrobenzophenone



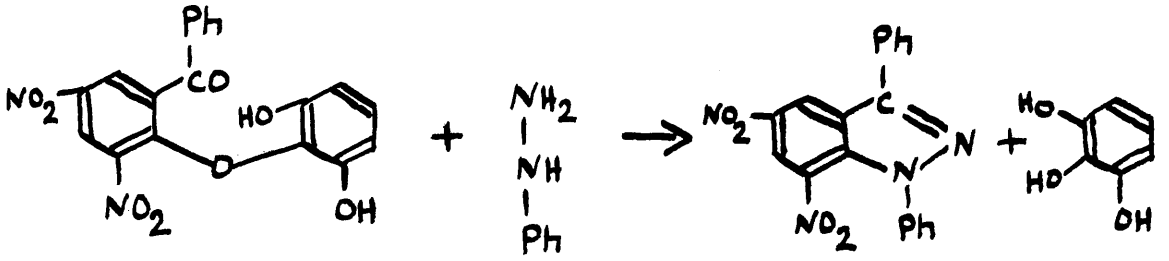
Application of this reaction to 2-(2"-hydroxyphenoxy)-3,5-dinitrobenzophenone (XXII) gave encouraging results.



(XXII) (XL)

A solution of (XXII) in benzene was allowed to stand overnight in contact with a slight excess of phenylhydrazine. On extraction with dilute sodium hydroxide, the aqueous layer was immediately run into dilute mineral acid, which was then saturated with ammonium sulphate and extracted with ether. The dried ethereal layer was evaporated to dryness and the residue sublimed under reduced pressure. Catechol was obtained. From the residual benzene solution after the excess amine had been removed by washing with aqueous acetic acid, 5,7-dinitro-1,3-diphenylindazole (XL) was recovered (identical with a sample prepared from 2-chloro-3,5-dinitrobenzophenone). 2-(2"-Hydroxy-3",6"-dimethylphenoxy)-3,5-dinitrobenzophenone (XXVIII) similarly treated gave 3,6-dimethylcatechol. Scission of the other 2-(2"-hydroxyaryloxy)-3,5-dinitrobenzophenones listed on p. 17 was not attempted.

The reaction proceeded smoothly also with the 2-(2",6"-dihydroxyaryloxy)-3,5-dinitrobenzophenones (p. 21)



(XXXI) (XL)

The two reactive centres in phenylhydrazine (unlike piperidine which contains only one such group) are capable of rapid simultaneous interaction with the carbonyl group and reactive position 2 of the dinitrobenzoylated benzene ring of (XXXI). This enables scission of the ether linkage to be accomplished unhindered by the rearrangement and cyclisation encountered in the reaction of (XXXI) with piperidine.

The following pyrogallols (which were extracted and isolated in an identical way to catechol above) were thus prepared:-

pyrogallol from (XXXI)

4-methylpyrogallol from (XXXII)

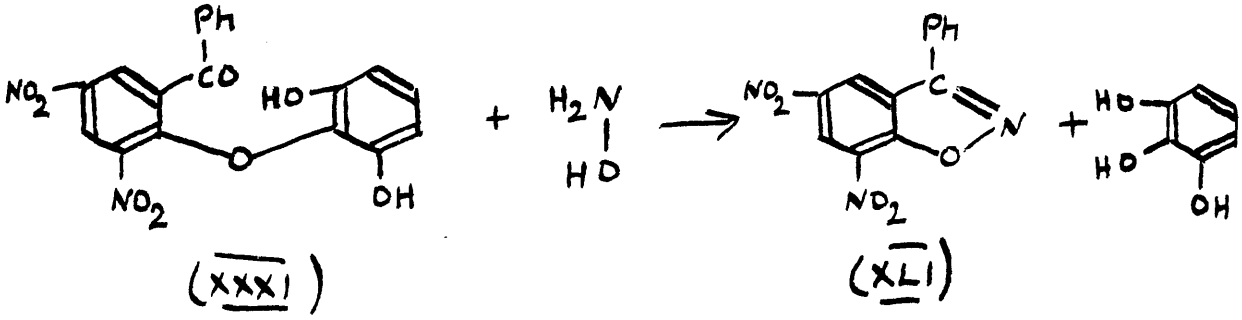
5-methylpyrogallol from (XXXIII)

4,5-dimethylpyrogallol from (XXXIV)

4,6-dimethylpyrogallol from the non-crystalline solid hydroxylation product (XXXV) obtained from (XXX).

The sublimed polyhydric phenols crystallised readily from pure benzene or from mixtures with light petroleum. The pyrogallols oxidised rapidly in alkaline solution, and were appreciably soluble in cold water. To prevent further oxidation and polymerisation, it is recommended that the sublimation be carried out quickly. In most cases, however, the pyrogallols were isolated in yields up to 50%, provided the dihydroxyaryloxydinitrobenzophenones used were pure. From the impure (XXXV) the yield of 4,6-dimethylpyrogallol was considerably lower.

Hydroxylamine and 2-(2",6"-dihydroxyphenoxy)-3,5-dinitrobenzophenone (XXXI) were shown to act together in a similar way by standing for a few hours in methanol solution. 5,7-Dinitro-3-phenylisoxazole (XLI) and pyrogallol were



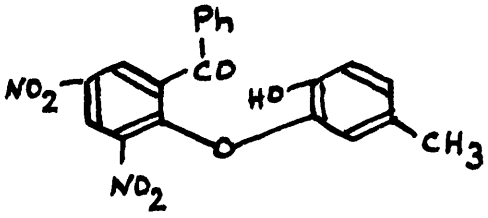
(XXXI) (XLI)

both isolated although the polyhydric phenol was only obtained in poor yield.

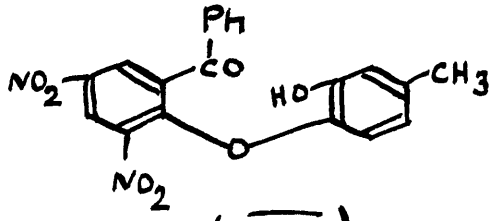
It is apparent from the work described that the synthesis of pyrogallols by this method is perfectly practicable. It has the disadvantage, however, of being of use only on a small scale due to the difficulty in preparing 2-chloro-3,5-dinitrobenzophenone in large quantities. In addition, the other products of the final scission, (XL) or (XLI) are unreactive materials, and preliminary attempts to regenerate the original benzophenone or one of its simple derivatives met with no success. Nonetheless, the reaction is likely to be of value and its possible development to include simultaneous double ortho-hydroxylation of compounds of type (XXIV) and (XXV) (p. 15) has interesting potentialities.

Methylation of 2-(2"-Hydroxy-5"-methylphenoxy)-and 2-(2"-Hydroxy-4"-methylphenoxy)-3,5-dinitrobenzophenones

It was observed that the mono-hydroxylated compounds (XXVI) and (XXVII) had identical melting points (139°) when obtained pure from a mixture of benzene and light petroleum. This value was not depressed by admixture of the two

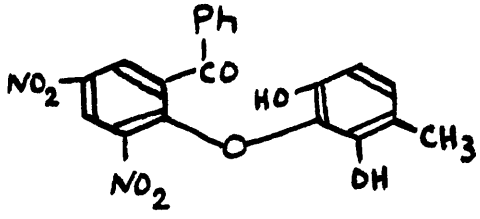


(XXVI)

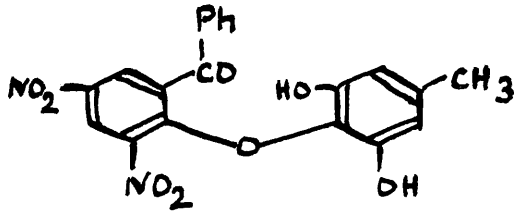


(XXVII)

specimens. Nonetheless, they are quite distinct since they give rise to different products, (XXXII) and (XXXIII) on further hydroxylation.



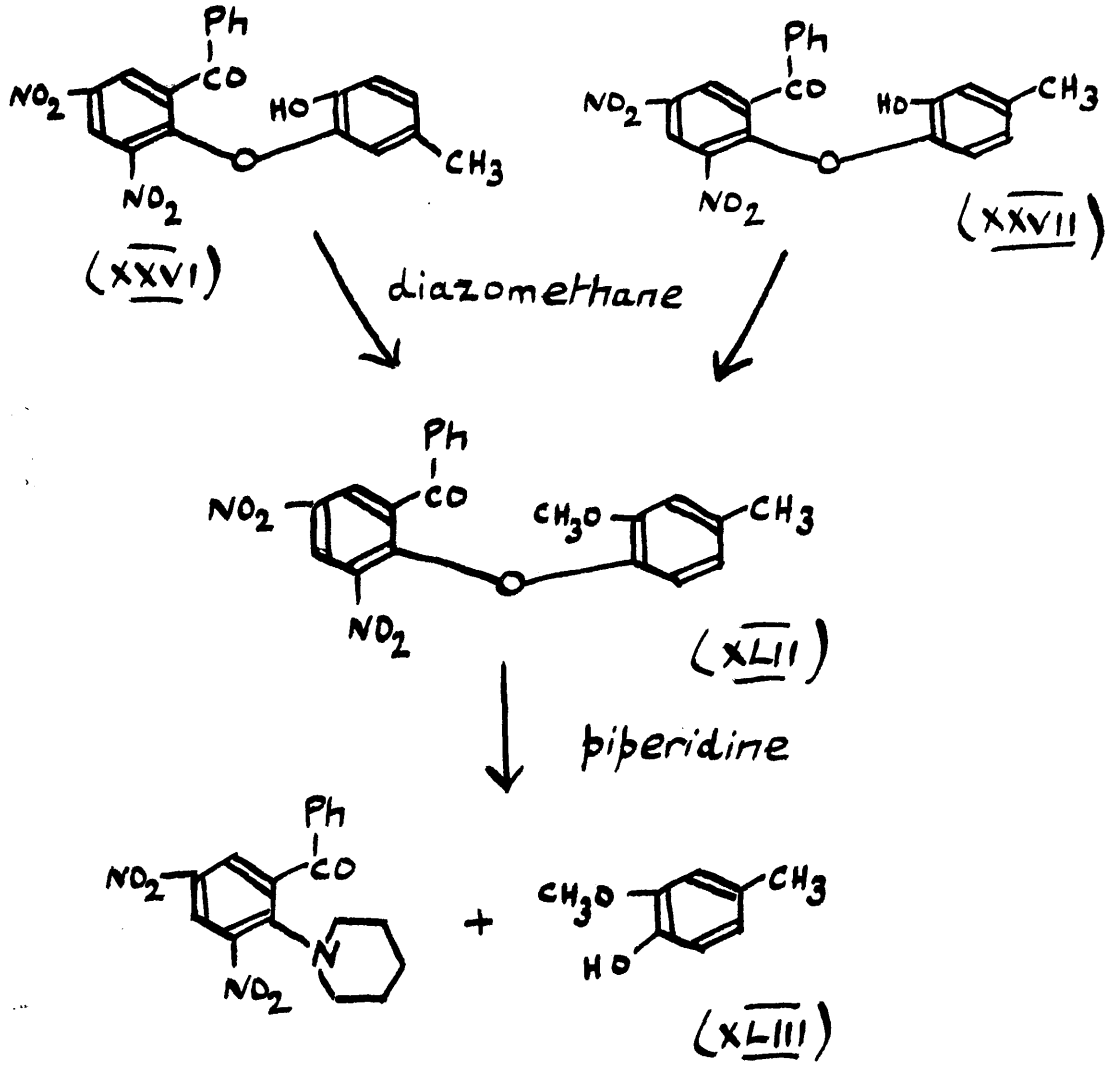
(XXXII)



(XXXIII)

However, on methylation of (XXVI) and (XXVII) with diazomethane an identical product, 2(2"-methoxy-4"-methylphenoxy)-3,5-dinitrobenzophenone (XLII) was obtained.

The structure of (XLII) was proved in each case by scission with piperidine and isolation of the oil, 4-hydroxy-3-methoxytoluene (XLIII), which was identified

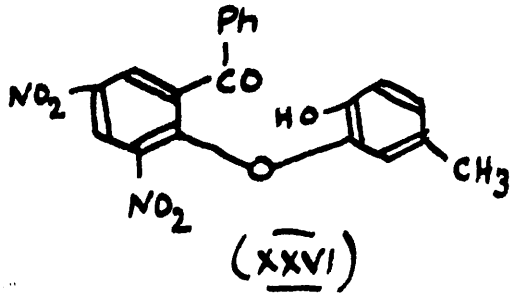


as its picrate, (micro) m.p. 104° (recorded m.p.'s range from 96°-112°) and benzoate, m.p. 72°. (Cosgrove and Waters[31] give m.p. 73°). Compound (XLII) is consequently

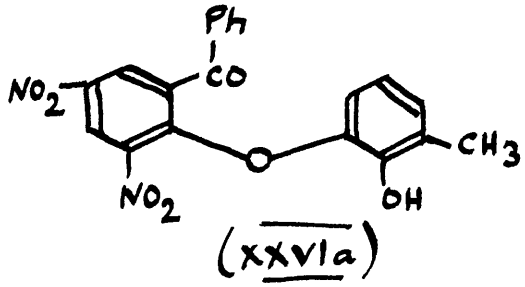
a derivative of 4-hydroxy-3-methoxytoluene. The other possible scission product, 3-hydroxy-4-methoxy-toluene has a picrate melting at 87.5° (De Vries[50]) and benzoate at 81° (Robinson, et al[51]).

During the course of methylation (XXVI) has undergone rearrangement to (XXVII). It has previously been shown by Loudon, et al[38,39] with the corresponding monohydroxylated compounds of the mono-nitro series that rearrangement readily occurs under the influence of alkali. This is the first instance, however, of its having occurred during methylation with diazomethane although Perkin and Storey[46] have reported similar behaviour in alizarin chemistry.

The above experiments also confirm that the structure of the hydroxylation product of (XVII) is indeed (XXVI) and not (XXVIa). Compound (XXVI) is a derivative of



(XXVI)



(XXVIa)

3,4-dihydroxytoluene and the scission product isolated above was 4-hydroxy-3-methoxytoluene. On the other hand, (XXVIa) is a mono-ether of 2,3-dihydroxytoluene and could not give rise to a derivative of 3,4-dihydroxytoluene even by such rearrangements as did occur above.

Experimental

Petroleum as solvent refers to light petroleum, b.p. 60°-80°. 2-Chloro-3,5-dinitrobenzophenone was prepared from 2-cnloro-3,5-dinitrobenzoic acid (produced as described by Ullmann[47]) by the method of Ullmann and Broido[48].

2-Aryloxy-3,5-dinitrobenzophenones: (Table D, p. **47**). These were prepared by dissolving the appropriate phenol (1-1.2 mols.) and 2-chloro-3,5-dinitrobenzophenone (1 mol.) in pure dry pyridine, leaving overnight at room temperature and pouring into dilute hydrochloric acid. The resultant solids, (XVI), (XVII), (XVIII), (XX), (XXI) were crystallised from benzene-methanol; (XIX) was obtained pure from benzene-petroleum. The compounds (XXII) and (XXIII) were obtained similarly from catechol and resorcinol respectively, by using 6 mols. of the dihydric phenol and were crystallised from methanol. Catechol bis-(2-benzoyl-4,6-dinitrophenyl)-ether m.p. 160° (from acetic acid) (Found: C, 59.3; H, 3.0. $C_{32}H_{18}O_{12}N_4$ requires C, 59.1; H, 2.8%) and resorcinol bis-(2-benzoyl-4,6-dinitrophenyl)-ether, m.p. 115° (from acetic acid) (Found, after fusion in vacuo; C, 58.9; H, 2.7%) were readily formed when rather less than 0.5 molar proportions of the phenols were used.

2-(2"-Hydroxyaryloxy)-3,5-dinitrobenzophenones: (Table E, p. **48**). The finely ground 2-aryloxy-3,5-dinitrobenzophenone (0.00027 mole) was dissolved in

concentrated sulphuric acid (0.5 c.c.) with shaking and gentle warming. After cooling, acetic acid (2.5 c.c.) was added and the mixture was titrated with a solution of 30% hydrogen peroxide in acetic acid (1:2 by volume) until a slight excess of the oxidising agent was present. The original red solution faded to amber and in some cases the products crystallised out. After 15-30 minutes the entire reaction mixture was poured into crushed ice and the precipitate obtained was washed with water and dried. Compounds (XXVI) and (XXVII) were crystallised from benzene-petroleum, the solvent being removed by heating in vacuo to 125°. Compounds (XXVIII), (XXIX) and (XXX) were crystallised from methanol, ethanol, and aqueous ethanol respectively.

2-(2",6"-Dihydroxyaryloxy)-3,5-dinitrobenzophenones (Table F, p 49). Compounds (XXII), (XXVI), (XXVII), (XXIX) were further hydroxylated in the following way. The 2-(2"-hydroxyaryloxy)-3,5-dinitrobenzophenone (0.00026 mole) was dissolved in concentrated sulphuric acid (0.5 c.c.) giving a red-brown solution. Acetic acid (3.5 c.c.) was added. No change of colour occurred from (XXII) and (XXVII), but from (XXVI) and (XXIX) green solutions were obtained. In all cases, on the addition of a slight excess of the hydrogen peroxide-acetic acid solution, the

colour changed to amber within a few minutes, and the whole was at once added to ice. The precipitate which was obtained was washed with water and dried. Compound (XXXI) was crystallised from acetic acid-petroleum; (XXXII) from chloroform; (XXXIII) from benzene (with subsequent heating in vacuo to 125°); (XXXIV) from methanol. The hydroxylation of (XXX) was best carried out by using increased quantities of concentrated sulphuric acid (3 c.c.) and acetic acid (10 c.c.), whereupon a dark green solution was obtained. The product (XXXV), m.p. 150-160° (dec.), which was isolated after treatment with the oxidising agent, could not be induced to crystallise.

Reactions with Piperidine

a) 2-phenoxy-3,5-dinitrobenzophenone

2-Phenoxy-3,5-dinitrobenzophenone was treated with piperidine under a variety of conditions (See Table C, p. 46). In all cases, a benzene solution of the reactants was extracted with bench caustic soda. The aqueous layer was acidified with dilute sulphuric acid and a standard bromine solution added. The resultant precipitate of tribromophenol was filtered on a sintered crucible, washed, dried and weighed. The residual benzene solution, when acid-washed, dried and concentrated, afforded 3,5-dinitro-2-piperidino-benzophenone. (Found: C, 60.9; H, 5.0.

$C_{18}H_{17}O_5N_3$ requires C, 60.8; H, 4.8%) on treatment with petroleum. It crystallised from ethanol, m.p. 125° and was also prepared from the interaction of 2-chloro-3,5-dinitrobenzophenone (1 mol.) and piperidine (2-3 mols.) in benzene at 18° by allowing the solution to stand 3-4 hours.

b) 2-(2"-Hydroxyphenoxy)-3,5-dinitrobenzophenone

2-(2"-Hydroxyphenoxy)-3,5-dinitrobenzophenone was reacted with piperidine in conditions corresponding to those already described for 2-phenoxy-3,5-dinitrobenzophenone (Table C p. 46). In every case, the benzene solution of the reaction mixture was extracted with dilute alkali, and the aqueous layer immediately run into excess dilute sulphuric acid. The acidified solution was saturated with ammonium sulphate and exhaustively extracted with ether. The dried ethereal layer was evaporated to dryness and the recovered material sublimed at 20 m.m. pressure. Catechol was obtained, m.p. 104° (from benzene-petroleum). The residual benzene solution afforded the other scission product, 3,5-dinitro-2-piperidinobenzophenone.

c) 2-(2",6"-Dihydroxyphenoxy)-3,5-dinitrobenzophenone

2-(2",6"-Dihydroxyphenoxy)-3,5-dinitrobenzophenone (1 mol.) and piperidine (4 mols.) were dissolved in benzene and allowed to stand at 18° for 24 hours. In two other similar experiments, acetic acid (4 mols.) and (5 mols.) was also present. In all three cases, the benzene solution was

extracted with dilute alkali, and the aqueous layer immediately acidified with dilute sulphuric acid. A maroon precipitate of 4-hydroxy-5,7-dinitro-9-phenylfluorone, m.p. 335° (decomposition) (from anisole; the stout black crystals were ground up in methanol before analysis) (Found: C, 60.45; H, 2.9. $C_{19}H_{10}O_7N_2$ requires C, 60.3; H, 2.65%) was obtained. When a large excess of piperidine (56 mols.) was used (with no acetic acid present) neither the fluorone nor pyrogallol could be isolated from the alkaline extract, but the residual solution afforded 3,5-dinitro-2-piperidinobenzophenone.

Scissions with Phenylhydrazine

The reaction was applied to the mono-hydroxylated compounds (XXII), (XXVIII), the dihydroxylated compounds listed in Table F (p. 49) and (XXXV), the impure hydroxylation product of (XXX).

A solution of the compound (1 mol.) and phenylhydrazine (5 mols.) in benzene was allowed to stand 15 hours at 18°. It was then extracted with dilute caustic soda and the aqueous layer immediately acidified with dilute sulphuric acid. The acid solution was saturated with ammonium sulphate and extracted with ether. The dried ethereal layer was evaporated down and the recovered material sublimed under reduced pressure (20 m.m.). The phenolic sublimate was further purified as required. The

following were prepared:-

catechol (from benzene-petroleum), m.p. and mixed m.p. 105° from (XXII)

3,6-dimethylcatechol (from benzene-petroleum), m.p. 102°, undepressed by admixture with sample prepared as by Loudon and Scott[39], from (XXVIII); pyrogallol, (from benzene) m.p. and mixed m.p. 132° from (XXXI)

4-methylpyrogallol, (from benzene-petroleum) m.p. 142°. (Found: C, 60.1; H, 5.8. Calc. for $C_7H_8O_3$: C, 60.0; H, 5.7%) from (XXXII). Majima and Okasaki[49] give m.p. 140-141°

5-methylpyrogallol, (from benzene) m.p. 120° from (XXXIII). (Found: C, 60.2; H, 5.9%). Recorded m.p.'s range from 119°-129°.

4,5-dimethylpyrogallol, (from benzene) m.p. 148° from (XXXIV). (Found: C, 62.6; H, 6.6. $C_8H_{10}O_3$ requires C62.3, H, 6.5%)

4,6-dimethylpyrogallol, (from benzene-petroleum) m.p. 122-123°, undepressed by admixture with sample prepared by Loudon and Scott[40], from (XXXV).

The residual benzene solution was thoroughly washed with aqueous acetic acid (to remove excess phenylhydrazine) and dried. On partial evaporation of solvent and cooling it afforded, 5,7-dinitro-1,3-diphenylindazole, m.p. 218°,

from ethanol (bright yellow plates), undepressed by mixture with sample prepared similarly from 2-chloro-3,5-dinitrobenzophenone. (Found: C, 63.3; H, 3.5. Calc. for $C_{19}H_{12}O_4N_4$: C, 63.3; H, 3.3%) (Borche and Scriba[45] give m.p. 221-222°).

Scission with Hydroxylamine

2-(2",6"-Dihydroxyphenoxy)-3,5-dinitrobenzophenone (1 mol.) and hydroxylamine (1-1.2 mols.; obtained from the hydrochloride and sodium acetate) were allowed to stand in methanol solution for 3 hours. An orange precipitate of 5,7-dinitro-3-phenylbenzisoxazole was obtained, m.p. 244° (from benzene, undepressed by admixture with sample prepared from 2-chloro-3,5-dinitrobenzophenone as described by Meisenheimer, Zimmermann and Kummer[44]) and was filtered off. The filtrate was diluted with ether and the solution washed with aqueous sodium carbonate, dilute acid and water. The dried ethereal solution was concentrated and the residue on sublimation at 20 m.m. afforded pyrogallol, m.p. 126° raised to 128-130° by admixture with authentic specimen.

Methylation of 2-(2"-Hydroxy-4"-methylphenoxy)- and 2-(2"-Hydroxy-5"-methylphenoxy)-3,5-dinitro-benzophenones and Scission of Product with Piperidine

2-(2"-Hydroxy-4"-methylphenoxy)-3,5-dinitrobenzophenone (1 mol.) in ether was treated with diazomethane (c. 10 mols.)

in ether and allowed to stand 48 hours at 18°. Removal of solvent gave 2-(2"-methoxy-4"-methylphenoxy)-3,5-dinitrobenzophenone, m.p. 186° (from benzene-petroleum) (Found, after heating in vacuo to 140°: C, 62.0; H, 4.0. $C_{21}H_{16}O_7N_2$ requires C, 61.8; H, 3.9%). The same product, m.p. and mixed m.p. 186°-187°, was similarly produced from 2-(2"-hydroxy-5"-methylphenoxy)-3,5-dinitrobenzophenone. A specimenof the product (1 mol.) from each source was dissolved in benzene and piperidine (3 mols.) added. After 15 hours, the solution was extracted with dilute sodium hydroxide and the aqueous layer acidified with dilute sulphuric acid. The acid solution was then saturated with ammonium sulphate, exhausted with ether and the dried ethereal layer evaporated to dryness. The residual oil, 4-hydroxy-3-methoxytoluene was identified in each case by its picrate (formed in ether solution and crystallised from water in bright yellow needles), (micro) m.p. 104°, (recorded m.p.'s range from 96°-112°) and its benzoate (from treatment with benzoyl chloride in aqueous alkaline solution), m.p. 72° (from petroleum) (Cosgrove and Waters[31] give m.p. 73°).

TABLE A

Reaction of 2-Phenoxy-3,5-dinitrobenzophenone in Sulphuric acid - Acetic acid Solution with slight Excess Hydrogen Peroxide

Weight of 2-phenoxy-3,5-dinitrobenzophenone in each experiment = 0.10g.

Volume of 30% H_2O_2/HOAc (1:2 by volume) added = 0.30c.c.

Volume of glacial acetic acid (c.c.)	Volume of concentrated sulphuric acid (c.c.)	Observation
1	0.30	Red/turbidity (A)
2	0.30	Yellow/turbidity (B)
3	0.30	" (B)
1	0.40	Brown/turbidity (A)
2	0.40	Red/turbidity (A)
3	0.40	Yellow/turbidity (B)
1	0.50	Dark red ppte. (C)
1.5	0.50	" (C)
2	0.50	Red/slight ppte. (C)
2.5	0.50	Amber solution (D)
3	0.50	Amber/turbidity (B)

Conclusions: (A) Total volume of reagents is low.

(B) Proportion of conc. sulphuric acid is low.

(C) Proportion of conc. sulphuric acid is high.

(D) Ideal conditions.

TABLE B

Reaction of 2-(2"-Hydroxyphenoxy)-3,5-dinitrobenzophenone in Sulphuric acid - Acetic acid solution with Slight Excess Hydrogen Peroxide

Weight of 2-(2"-hydroxyphenoxy)-3,5-dinitrobenzophenone in each experiment = 0.10g.

Volume of 30% H_2O_2/HOAc (1:2 by volume) added = 0.30c.c.

Volume of glacial acetic acid (c.c.)	Volume of concentrated sulphuric acid (c.c.)	Observation
1	0.30	Red solution (A)
2	0.30	Yellow/turbidity (B)
2.5	0.30	" (B)
1	0.40	Red solution (A)
1.5	0.40	" (A)
2	0.40	" (A)
2.5	0.40	" (A)
3.0	0.40	Amber/turbidity (B)
3.5	0.40	Yellow/turbidity (B)
1	0.50	Red solution (A)
1.5	0.50	" (A)
2.0	0.50	" (A)
2.5	0.50	Light red soln. (A)
3.0	0.50	" (A)
3.5	0.50	Amber solution (C)

Conclusions: (A) Proportion of conc. sulphuric acid is high.
(B) Proportion of conc. sulphuric acid is low.
(C) Ideal conditions.

TABLE C

Reaction of 2-Phenoxy-3,5-dinitrobenzophenone with Piperidine

Weight of 2-phenoxy-3,5-dinitrobenzophenone used in each experiment = 0.5g.

Volume of alkali for extraction = 8 c.c.; Volume of mineral acid = 4 c.c.;

Volume of bromine water = 6 c.c.

Conditions	Weight of phenol (g.)	Vol.of piperidine (c.c.)	Vol.of benzene solvent (c.c.)	Vol.of benzene for extn. (c.c.)	Vol.of glacial acetic acid (c.c.)	Wt. of tribromophenol (g.)
Blank experiment	0.1	0.25	8	–	–	0.15
Refluxed one hour	–	1.5	–	8	–	0.13
18° for 24 hours	–	1.5	–	8	–	0.14
18° for 4 hours	–	1.5	–	8	–	0.13
Refluxed one hour	–	0.25	8	–	–	0.14
18° for 24 hours	–	0.25	8	–	–	0.14
18° for 4 hours	–	0.25	8	–	–	0.14
18° for 24 hours	–	0.15	8	–	–	0.13
18° for 24 hours	–	0.20	8	–	–	0.13
18° for 24 hours	–	0.30	8	–	–	0.14
18° for 24 hours	–	0.35	8	–	–	0.14
18° for 24 hours	–	0.25	8	–	0.068	0.12
18° for 24 hours	–	0.25	8	–	0.135	0.12

TABLE D

2-Aryloxy-3,5-dinitrobenzophenones

No.	Subst.	Source	Formula	M.Pt.	Found C	Found H	Reqd. C	Reqd. H
XVI	-	phenol	$C_{19}H_{12}O_6N_2$	142°	62.6	3.2	62.6	3.3
XVII	3"-Me	m-cresol	$C_{20}H_{14}O_6N_2$	159°	63.55	3.9	63.5	3.7
XVIII	4"-Me	p-cresol	"	130°	63.8	3.5	"	"
XIX	2",5"-Me_2	2,5-dimethylphenol	$C_{21}H_{16}O_6N_2$	146°	64.5	3.8	64.3	4.1
XX	3",4"-Me_2	3,4-dimethylphenol	"	164°	64.5	4.3	"	"
XXI	3",5"-Me_2	3,5-dimethylphenol	"	217°	64.5	4.2	"	"
XXII	2"-OH	catechol	$C_{19}H_{12}O_7N_2$	160°	59.9	3.3	60.0	3.2
XXIII	3"-OH	resorcinol	"	160-163°	60.1	3.2	"	"

TABLE E

2-(2"-Hydroxyaryloxy)-3,5-dinitrobenzophenones

No.	Subst.	Source	Formula	M.Pt.	Found		Reqd.	
					C	H	C	H
XXII	-	XVI	$C_{19}H_{12}O_7N_2$	160°	See Table D			
XXVI	5"-Me+	XVII	$C_{20}H_{14}O_7N_2$	139°	60.85	3.6	60.9	3.55
XXVII	4"-Me	XVIII	"	139°	60.95	3.6	"	"
XXVIII	3",6"-Me_2	XIX	$C_{21}H_{16}O_7N_2$	171°	61.8	3.9	61.8	3.9
XXIX	4",5-Me_2	XX	"	175°	62.0	4.1	"	"
XXX	3",5"-Me_2	XXI	"	183°*	61.6	4.0	"	"

* Decomposition.

\+ On one occasion (XXVI) was obtained with m.p. 159° (from benzene-petroleum) changing to 146° on heating *in vacuo* (Found: C, 61.05; H, 3.8%).

TABLE F

2-(2",6"-Dihydroxyaryloxy)-3,5-dinitrobenzophenones

No.	Subst.	Source	Formula	M.Pt.	Found		Read.	
					C	H	C	H
XXXI	-	XXII	$C_{19}H_{12}O_8N_2$	148°*	57.6	3.3	57.6	3.0
XXXII	3"-Me	XXVI	$C_{20}H_{14}O_8N_2$	206°*	58.5	3.4	58.5	3.4
XXXIII	4"-Me	XXVII	"	164°*	58.7	3.6	"	"
XXXIV	3",4"-Me_2	XXIX	$C_{21}H_{16}O_8N_2$	203°*	59.7	3.7	59.4	3.8

* decomposition.

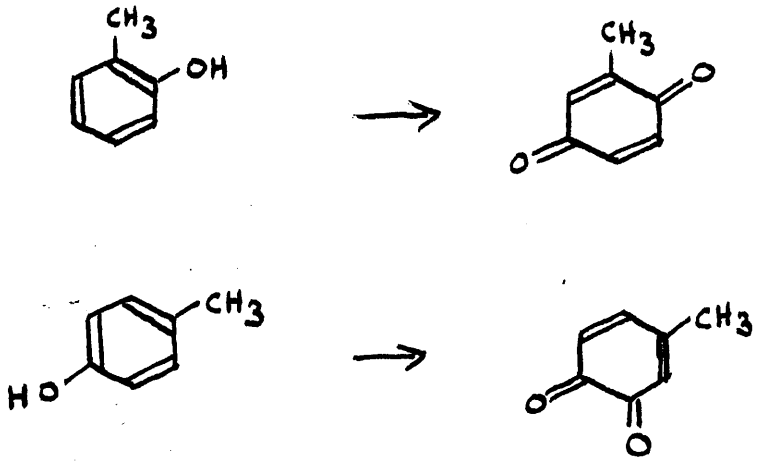
Note on Frémy's Salt

Frémy's salt is the potassium salt of nitrosodisulphonic acid, $ON(SO_3K)_2$. Raschig[52] developed a convenient method for its preparation by oxidation of the sodium salt of hydroxylaminedisulphonic acid with potassium permanganate in alkaline solution.

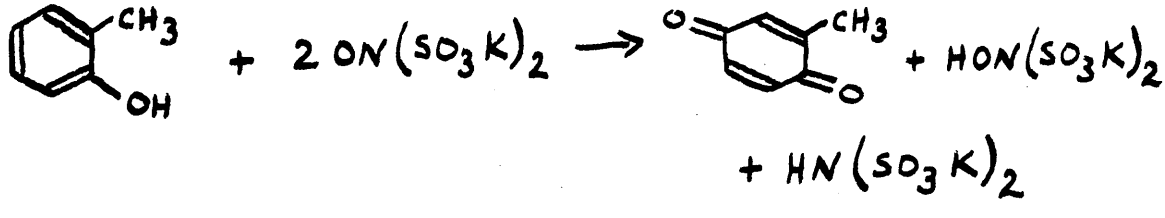
$$HON(SO_3Na)_2 \longrightarrow ON(SO_3K)_2$$

It was purified by crystallisation from aqueous caustic potash, the intense blue-violet solution producing dark yellow crystals. Asmussen[53] has suggested that, in an analogous way to nitrogen peroxide (N_2O_4 and NO_2), the solid yellow compound, which is diamagnetic, has the formula, $N_2O_4(SO_3K)_4$. In aqueous solution the blue colour is due to the paramagnetic $NO(SO_3K)_2$.

Because of its radical characteristics, Frémy's salt is readily reduced, and Raschig made use of this property in the conversion of aniline to nitrosobenzene. Recently, Teuber, et al[54,55] have improved the experimental details of the preparation of the salt and have developed its use in the oxidation of a variety of phenols to the corresponding quinones. When the para position to the hydroxyl group is vacant para-quinones are obtained, but if the para position is occupied, ortho-quinones are formed. The



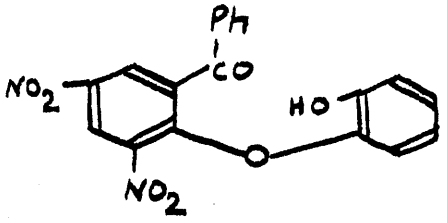
reaction was considered to take place in the following way:-



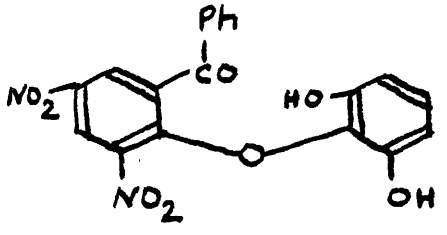
It was shown to be a convenient laboratory method of synthesising quinones, the reaction being generally completed in a few hours by allowing a methanol solution of the phenol to react at room temperature with an excess of Frémy's salt in water in the presence of sodium acetate (to prevent the formation of the unstable free nitrosodisulphonic acid).

In the present work, the salt was prepared as described by Raschig[52] and Teuber[54]. It was found to be a remarkable compound. The yellow crystalline solid gave a vivid violet aqueous solution, both colours being immediately discharged on the addition of dilute acid. It is fairly stable (cf. Teuber[54]) being stored for several weeks without deterioration in vacuo over caustic potash. In crystallisation, however, from dilute potassium hydroxide solution (1N strength) the violet colouration disappeared instantaneously when heated to about 60°.

The use of Frémy's salt as an agent for the oxidation of the mono-hydroxylated compounds of type (XXII) was investigated. The conditions adopted were similar to



(XXII)

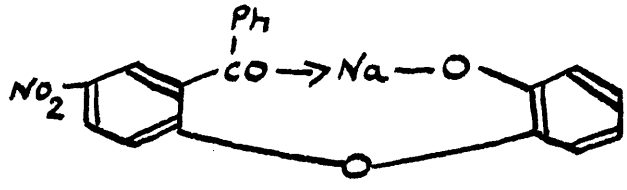


(XXXI)

those used by Teuber and Rau[55] for the oxidation of ortho-cresol. Even when the reaction mixture was gently heated, compound (XXII) remained unchanged. Similar results were obtained when (XXII) in ether was shaken with an aqueous solution of Frémy's salt. With the dihydroxylated compound

(XXXI), however, the violet colouration of the salt disappeared after several minutes. Unfortunately, the material recovered by ether extraction was resinous and tarry and all attempts at purification failed.

It is suggested that with (XXII), the hydroxyl group is connected by hydrogen bonding to the ketonic group and that this attraction is sufficiently strong to withstand attack on the phenolic group by Frémy's salt. (cf. Loudon, et al[38] who have shown that the sodium salts of the corresponding type of compound in the mono-nitro series are covalent in character and have suggested a strainless nine-membered ring structure (XLIV)).



(XLIV)

With (XXXI), this bonding may still persist but the presence of a second hydroxyl group (free from any such attachment) may enable the customary phenolic oxidation to proceed. Whilst it seems certain that oxidation of (XXXI) did, in fact, occur, the preliminary experiments did not indicate that the sensitive products would be readily isolated pure and no further investigation of the reaction of Frémy's salt on (XXXI) was attempted.

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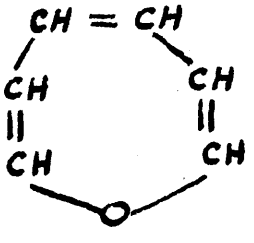
Part Two: DIBENZ (b,f) OXEPINS

Contents

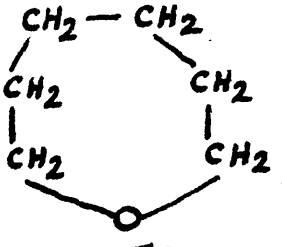
Dibenz (b,f) Oxepins

Introduction

The chemistry of the seven-membered heterocyclic ring system containing six carbon atoms and one oxygen atom has not as yet attracted much attention. For example, the parent compound, oxepin (I) does not appear to have been prepared, although the completely reduced hexamethylene oxide or oxepane (II) and a number of its derivatives



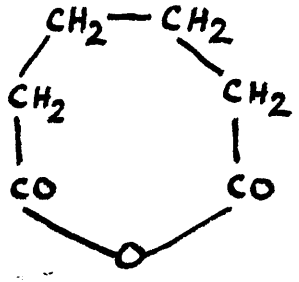
(I)



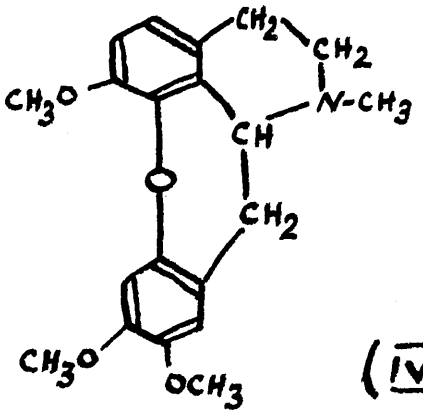
(II)

(e.g. monomeric adipic anhydride (III)) are fairly well known.

More interest has been aroused in this type of heterocyclic system by the recent work of Manske[1]. From certain fumariaceous plants, including Corydalis claviculata and Dicentra cucullaria (which are found mainly in the Netherlands and certain parts of North America) he

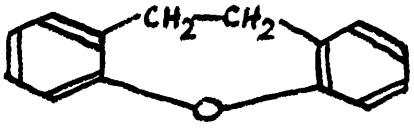


(III)

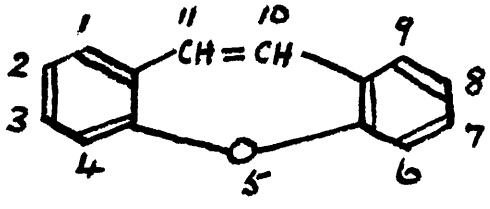


(IV)

obtained the alkaloid cularine which was shown to have the structure represented by formula (IV). A portion of the molecular structure of cularine comprises the 10,11-dihydro-dibenz (b,f) oxepin (V) nucleus, which is derived from the parent compound, dibenz (b,f) oxepin (VI).

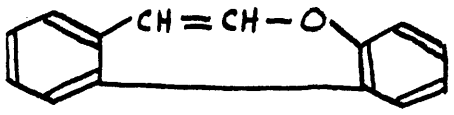


(V)



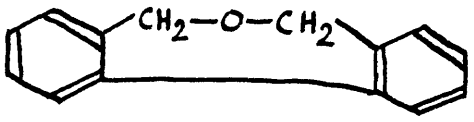
(VI)

It is of interest to note that three other possible dibenzoxepins (VII), (VIII), (IX) can be formulated. A



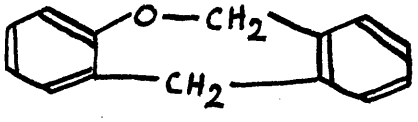
Dibenz (b,d) oxepin

(VII)



Dibenz (c,e) oxepin

(VIII)



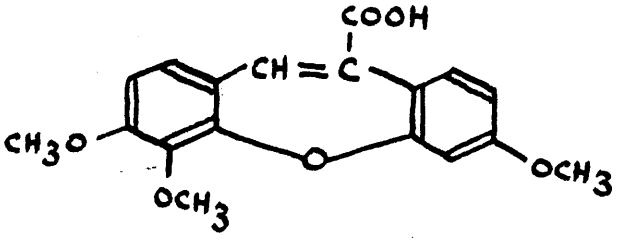
Dibenz(b,e) oxepin

(IX)

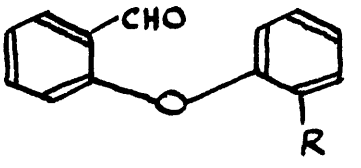
few derivatives of each of these dibenzoxepins are known. For example, dibenzohomopyran (Sieglitz and Koch[2]) is related to (VII), the well-known diphenic anhydride is derived from (VIII) and recently Baker,[3] et al and Berti[4] have prepared compounds which have (IX) as the basic structure. The present work, however, is concerned only with dibenz-(b,f) oxepin (VI) and its derivatives.

Prior to the isolation of cularine, it appears that only one compound analogous to (VI) has been prepared. Pschorr and Knoffler[5] obtained 10-carboxy-3,4,7-

trimethoxydibenz (b,f) oxepin (X) as a by-product in the synthesis of a substituted phenanthrene. Hanske

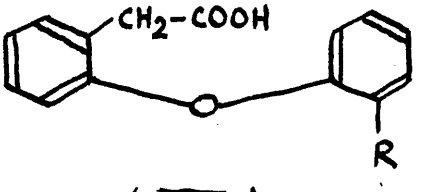


(X)

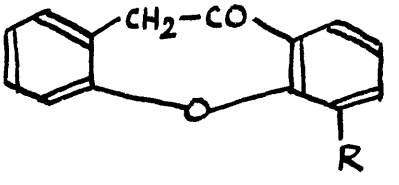


(XI)

and Ledingham[6], however, succeeded in preparing the parent compound, dibenz (b,f) oxepin (VI) by the following route. Ortho-phenoxybenzaldehyde (XI; R = H) (prepared in 25% yield from bromobenzene and the copper salt of salicylaldehyde) was converted to ortho-phenoxyphenylacetic acid (XII; R = H) via the azlactone and the ortho-phenoxy-



(XII)

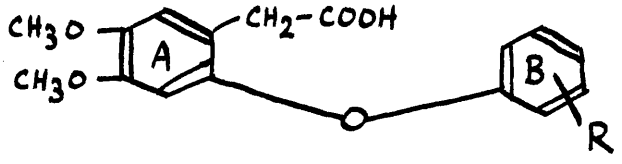


(XIII)

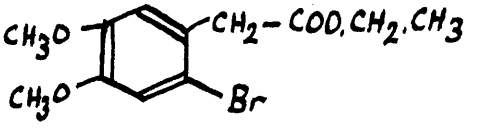
phenylpyruvic acid. The acid chloride of (XII; R = H), on treatment with aluminium chloride in nitrobenzene gave a good yield of (XIII; R = H), which was readily converted

to the carbinol by aluminium isopropoxide in isopropyl alcohol. Dehydration of the carbinol with para-toluene-sulphonic acid gave dibenz (b,f) oxepin (VI). A similar series of reactions was carried out from (XI; R = OCH_3) to (XII; R = OCH_3). The cyclodehydration of (XII; R = OCH_3) to (XIII; R = OCH_3), however, proceeded in poor yield (c. 10-20%), a large amount of resinous material being formed.

Kulka and Manske[7] continued the investigation of dibenz (b,f) oxepins and explored the possibility of synthesising cularine. With this end in view, the model compounds, 2-phenoxy-4,5-dimethoxyphenylacetic acid (XIV; R = H) and the three isomeric 2-(methoxyphenoxy)-4,5-dimethoxy-phenylacetic acids (XIV; R = OCH_3) were prepared by the Ullmann condensation of the appropriate phenol with ethyl 4,5-dimethoxy-2-bromophenylacetate (XV) followed by saponification. In all cases, the yield of compounds of type (XIV) was about 40-50%, with the

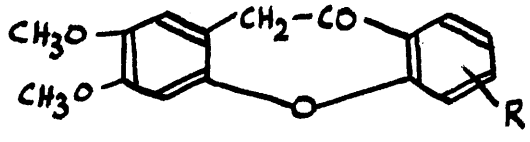


(XIV)

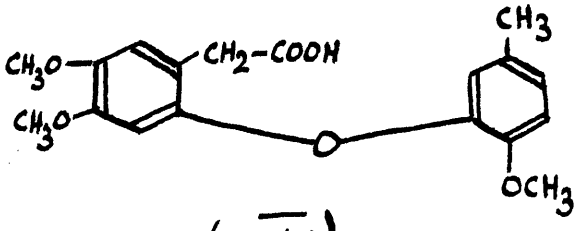


(XV)

exception of 2-(2'-methoxyphenoxy)-4,5-dimethoxyphenylacetic acid (XIV; R = OCH_3), which was obtained in low yield (subsequently it was more readily prepared by an alternative route). The cyclodehydration of compounds of type (XIV) to (XVI) was accomplished with hydrogen fluoride although 10,11-dihydro-2,3,6-trimethoxydibenz (b,f)oxepin-10-one (XVI; R = OCH_3) could be isolated only in poor



(XVI)

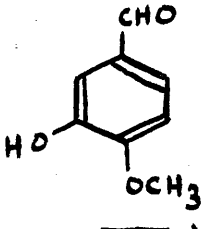


(XVII)

yield. Furthermore, when (XVII) (where a methyl group is placed ortho to the position of ring closure) was treated likewise with hydrogen fluoride cyclodehydration occurred only on about 3% of the material.

From these experiments, it was evident that while the synthesis of dibenz (b,f) oxepins by this method was perfectly practicable, considerable difficulties were encountered in at least two stages of the preparation. The initial Ullmann type condensation to form (XI) or (XIV)

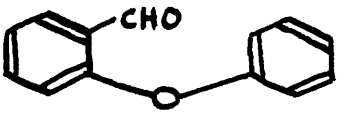
was generally accomplished only with moderate success and was more difficult still when the phenol used was substituted by a methoxyl group in the ortho position. Indeed, in preliminary attempts to synthesise cularine Kulka and Manske[7] found that the initial condensation of isovanillin (XVIII) with (XV) failed completely, none of the required diaryl ether being isolated, and subsequent similar attempts were equally unsuccessful. There remained, therefore, little hope for the synthesis of the alkaloid by this method. In



(XVIII)

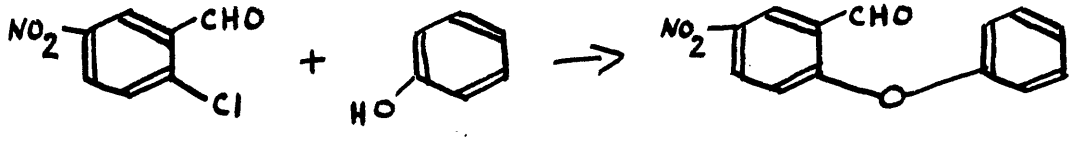
addition, as has already been stated, the cyclodehydration reaction from (XIV) to (XVI) was greatly hindered by the presence of a methoxyl group in position 2 of ring B (XIV; R = OCH_3), and was almost entirely prohibited when a methyl group as well was placed ortho to the point of ring closure.

The difficulties observed by Manske and his collaborators in preparing ortho-aryloxybenzaldehydes of general type (XI) have also been noted by other



(XI)

workers (Lock and Kempter[8], Ungnade and Orwoll[9]. See also Ungnade[10] who has reviewed the synthesis and reactions of diaryl ethers). However, patent literature[11] shows that in 2-chloro-5-nitrobenzaldehyde (XIX), the halogen atom is sufficiently activated by the nitro group in the <u>para</u> position to condense effectively with phenol in aqueous alkaline solution to produce 5-nitro-2-phenoxybenzaldehyde (XX). Recently, Grundon and Perry[12]



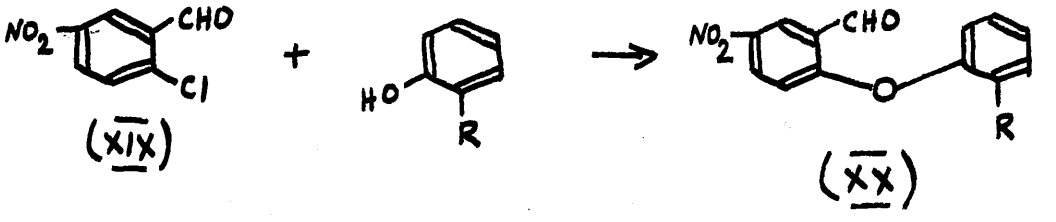
(XIX) (XX)

have applied a similar reaction to a 4-chloro-3-nitrobenzaldehyde where the halogen and nitro groupings are <u>ortho</u> to one another.

The object of the work about to be described was to investigate the reaction of (XIX) with phenol and guaiacol. With the products of type (XX) it was hoped to develop a convenient method of preparing derivatives of dibenz (b,f) oxepin (either with the nitro group still present or after its removal) and to elucidate some of the properties of this heterocyclic system.

Discussion

Preparation of 5-Nitro-2-phenoxy- and 2-(2'-Methoxyphenoxy)-5-nitro-benzaldehydes



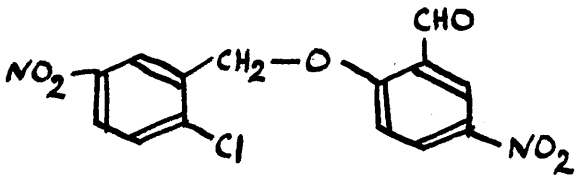
(XIX) (XX)

These compounds were prepared when 2-chloro-5-nitro-benzaldehyde (XIX) was refluxed for a few hours with an aqueous alkaline solution of the appropriate phenol in slight excess. (Patent literature[11] had previously prepared (XX; R = H) by a similar method). On cooling, crystals formed in the dark reaction mixture, the whole of which was extracted with ether (some material (XXI) remained insoluble and was filtered off). On evaporation of the dried ethereal layer, a semi-solid residue remained, which was exhaustively extracted with light petroleum. On concentrating and cooling, the white crystalline products, (XX; R = H) and (XX; R = OCH_3) were deposited. Although the yield of 5-nitro-2-phenoxybenzaldehyde was good (70%), 2-(2'-methoxyphenoxy)-5-nitrobenzaldehyde could not be obtained in a yield greater than 55%. Apparently, the

presence of the methoxyl group ortho to the phenolic group was again hindering condensation (cf. Introduction, p. 64). Nonetheless, the yields of both nitroaryloxybenzaldehydes were appreciably greater than those obtained by Manske and Ledingham[6] with the corresponding aryloxybenzaldehydes.

The attempted purification of (XX; R = H) by distillation in vacuo was found to be unreliable due to the frequent occurrence of minor explosions and the method above was subsequently adopted.

The ether insoluble residue (XXI) was produced in appreciable quantity during the preparation of (XX; R = OCH_3) (c. 5% yield calculated from (XIX)) and was identical with a little material obtained from the preparation of (XX; R = H). It was assigned the structure (XXI). This is in accord with analytical

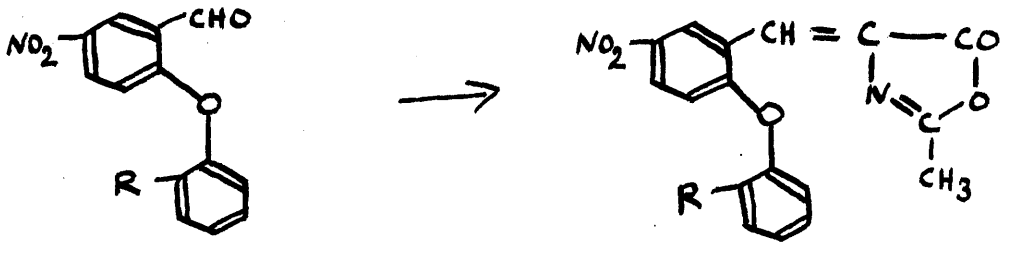


(XXI)

results and with the formation of a mono-oxime. Moreover, the same compound was obtained from 2-chloro-5-nitrobenzaldehyde in poor yield by treatment with hot aqueous alkali and in substantial yield by reaction with pre-formed 2-chloro-5-nitrobenzyl alcohol in the presence of solid potassium carbonate.

Preparation of 5-Nitro-2-phenoxy- and 2-(2'-Methoxyphenoxy)-5-nitro-phenylacetic acids

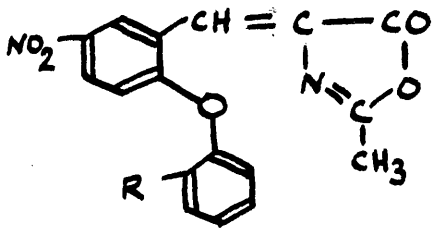
Compounds (XX; R = H) and (XX; R = OCH_3) were first converted to the corresponding azlactones, 2-methyl-4-(5'-nitro-2'-phenoxy)-benzylidene-5-oxazolone (XXII; R = H) and 4-[2'-(2"-methoxyphenoxy)-5-nitrobenzylidene]-2-methyl-5-oxazolone (XXII; R = OCH_3). When a method similar to



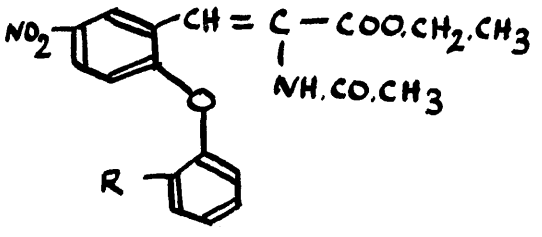
(XX) (XXII)

that given by Herbst and Shemin[13] was adopted the azlactones were obtained pure only in 55-60% yield. However, on using a modification of Galat's[14] improved procedure the yields were raised to 70-75%. The two azlactones were purified from benzene-petrol giving lemon-yellow crystals.

A preliminary investigation into the acid hydrolysis of these compounds showed that when (XXII; R = H) was treated with ethyl alcohol and concentrated sulphuric acid, the oxazolone ring was rapidly opened (cf. Carter[15]) and ethyl

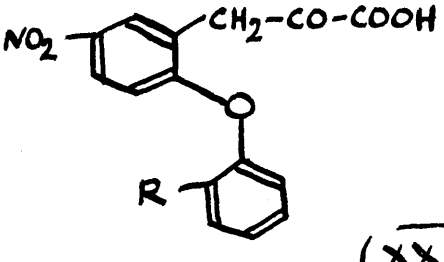


(XXII)



(XXIII)

α-acetamido-β-(5-nitro-2-phenoxyphenyl)-acrylate (XXIII; R = H) was produced. By heating for a few hours with a mixture of aqueous hydrochloric acid and acetic acid (XXIII; R = H) was smoothly converted in good yield to

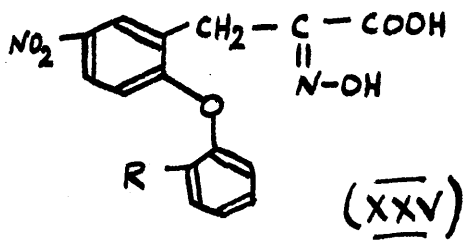


(XXIV)

5-nitro-2-phenoxyphenyl-pyruvic acid (XXIV; R = H).

When the azlactone (XXII; R = H) itself was similarly treated with acid, the hydrolysis proceeded directly to the keto acid, and it was, therefore, unnecessary to prepare the intermediate (XXIII; R = H). When (XXII; R = OCH_3) was thus hydrolysed, 2-(2'-methoxyphenoxy)-5-nitrophenyl-pyruvic acid (XXIV; R = OCH_3) was formed. Provided the

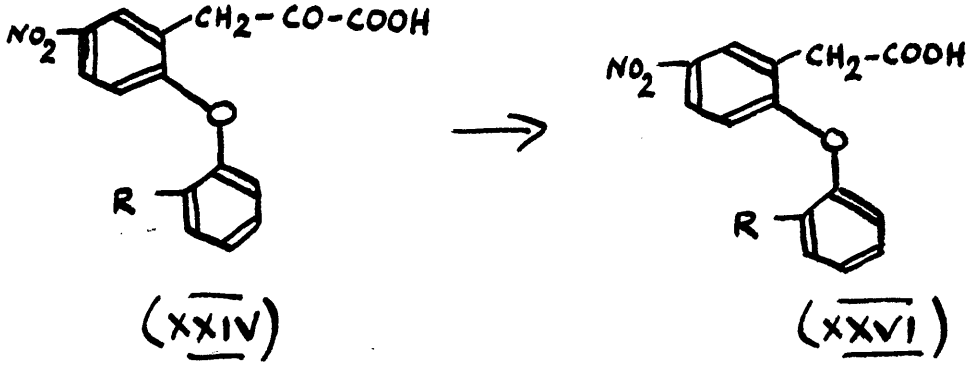
azlactones were pure, the pyruvic acids were isolated in very high yields (c. 95%). Both keto-acids were obtained as yellow crystals, which gave a dark red solution of the corresponding sodium salt in aqueous caustic soda. When this solution was treated with an excess of hydroxylamine hydrochloride, the dark colour rapidly cleared to yellow. On acidification, the oxime



(XXV)

precipitated. Compounds (XXV; R = H) and (XXV; R = OCH_3) were thus prepared from (XXIV; R = H) and (XXIV; R = OCH_3) respectively.

The oxidation of arylpyruvic acids to arylacetic acids with hydrogen peroxide in aqueous alkaline solution is well known. By a method similar to that used by Manske and Ledingham[6] (in preparation of ortho-phenoxyphenylacetic acid), (XXIV; R = H) and (XXIV; R = OCH_3) were conveniently converted to 5-nitro-2-phenoxyphenylacetic acid (XXVI; R = H) and 2-(2'-methoxyphenoxy)-5-nitrophenylacetic acid (XXVI; R = OCH_3) in high yield (90-95%). They were very



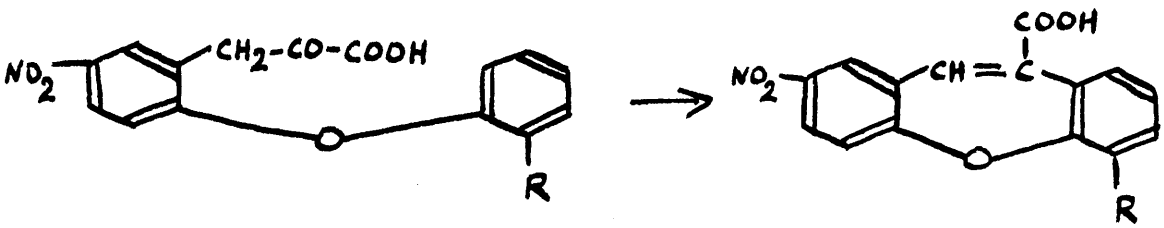
(XXIV) (XXVI)

easily handled and crystallised readily from benzene-light petroleum.

Cyclisations with Polyphosphoric Acid

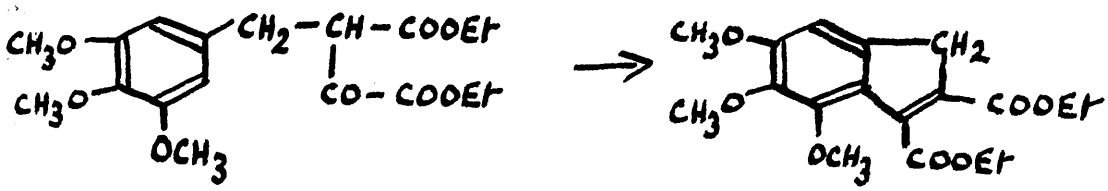
Since the use of polyphosphoric acid as a cyclising agent was first reported by Snyder and Werber[16], it has been shown to be successfully adaptable to the synthesis of a variety of ring structures, notably by Koo[17] (who gives other references). In general, it has advantages over other cyclodehydrating agents (such as sulphuric acid, hydrogen fluoride, and aluminium chloride) in that the experimental technique is more convenient and that the yields of cyclised products are usually higher due to the avoidance of side reactions (e.g. demethylation and sulphonation).

In preliminary investigations it was found that when 5-nitro-2-phenoxyphenylpyruvic acid (XXIV; R = H) was kept in contact with polyphosphoric acid for two hours at 100° no reaction occurred. If, however, the viscous mixture was warmed initially (to about 160°) for a few minutes (until a green-brown colour developed) and subsequently heated on a steam-bath for two hours the cyclised product, 10-carboxy-2-nitro-dibenz(b,f) oxepin (XXVII; R = H) was obtained. From (XXIV; R = OCH_3), 10-carboxy-6-methoxy-2-nitro-dibenz (b,f) oxepin (XXVII; R = OCH_3) was likewise isolated. A similar



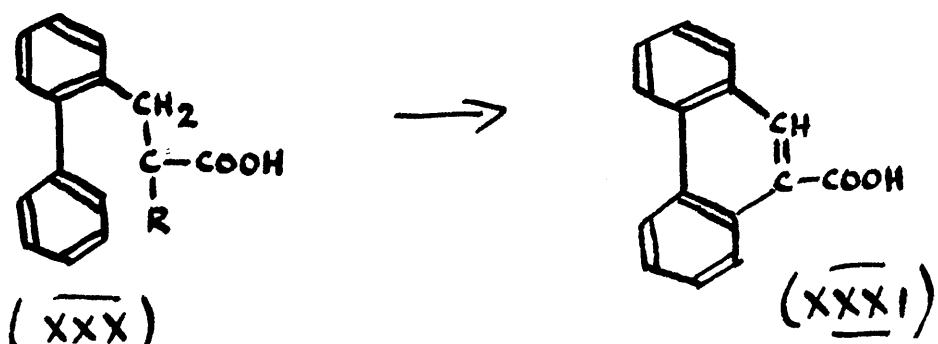
(XXIV) (XXVII)

type of ring closure with the ester (XXVIII) of an α-keto-acid has been reported by Koo[18], an indene derivative (XXIX) being formed.



(XXVIII) (XXIX)

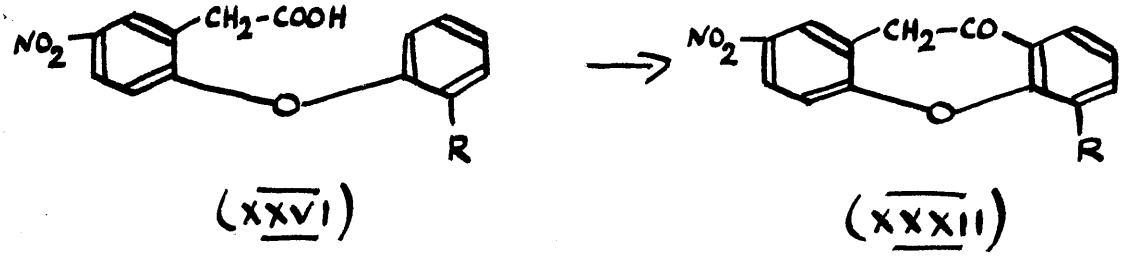
Also, Bradsher and Kittila[19] showed that (XXX; R = S) and (XXX; R = N - OH) both cyclised to 9-phenanthroic acid (XXXI), but in rather poor yield using acetic acid-hydrobromic acid as condensing agent.



(XXX) (XXXI)

Both nitro-dibenz (b,f) oxepin carboxylic acids were obtained in good yield, (XXVII; R = H) in 75%, (XXVII; R = OCH_3) in 70%.

The nitroarylacetic acids (XXVI; R = H) and (XXVI; R = OCH_3) when treated similarly with polyphosphoric acid gave the corresponding 10,11-dihydro-2-nitro-dibenz(b,f)-oxepin-10-one (XXXII; R = H) and 10,11-dihydro-6-methoxy-2-nitro-dibenz(b,f) oxepin-10-one (XXXII; R = OCH_3). Compound (XXVI; R = H) cyclised rather more readily (100° for two hours) than (XXVI; R = OCH_3) which required

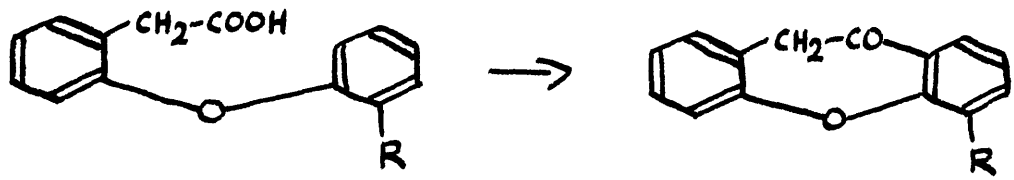


(XXVI) (XXXII)

the more vigorous conditions adopted in the cyclodehydration of the pyruvic acids above. Both (XXXII; R = H) and (XXXII; R = OCH_3), however, were produced in high yield (80%). They were purified from benzene-light petroleum and readily formed oximes in pyridine solution.

It will be remembered that Manske and his coworkers[6,7] (see Introduction, p. 64) had experienced difficulty in

inducing compounds of general type (XII; R = OCH_3) to cyclise to (XIII; R = OCH_3) with aluminium chloride or hydrogen fluoride as condensing agents. The cyclodehydration method with polyphosphoric acid, therefore, is obviously a considerable improvement.

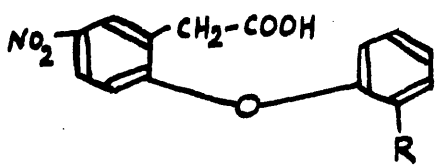


(XII) (XIII)

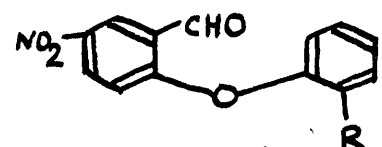
It remained now to determine the most suitable way of removing the undesirable nitro group still present in (XXXII), and this work is described in the following chapter.

Reductions and Deaminations

The nitroarylacetic acids (XXVI; R = H, OCH_3) having been successfully ring closed to derivatives of nitrodibenz (b,f) oxepin by polyphosphoric acid, it was necessary to obtain a satisfactory procedure for the removal of the undesirable nitro group, which had been essential for the successful formation of the diaryl ethers (XX; R = H, OCH_3) in the first stage of the synthesis.

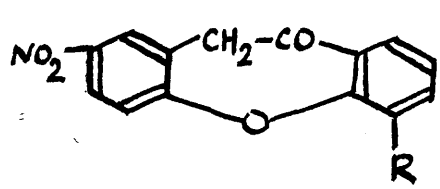


(XXVI)



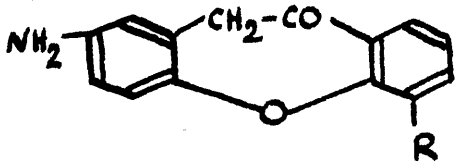
(XX)

The general method was considered to be probably the most suitable, namely the reduction of the nitro group to amino and subsequent replacement by hydrogen with hypophosphorous acid. However, initial experiments on the catalytic reduction of (XXXII; R = H) with palladium black did not give encouraging results. Compound (XXXII; R = H) was not sufficiently soluble in the more

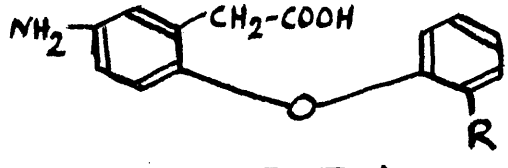


(XXXII)

usual hydrogenating solvents (acetic acid and alcohol) and when the reduction was carried out in distilled dioxan, the reaction solution (although absorbing the requisite volume of hydrogen) became very dark in colour on partial evaporation of the solvent <u>in vacuo</u>. The brown oil obtained on dilution with water could not be induced to solidify or form a solid hydrochloride. Treatment with ether and basification of the acid extract gave no more hopeful results. Although the desired amine (XXXIII; R = H) was in all probability formed, these tests indicated that it would not readily be isolated pure in good yield by this method.



(XXXIII)



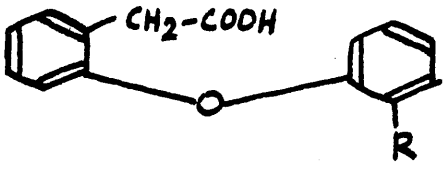
(XXXIV)

In view of these difficulties, the alternative procedure of reduction and deamination at the stage prior to cyclisation, (i.e. with (XXVI)) was investigated. It was found that while (XXVI; R = OCH_3) was reduced with ferrous sulphate in aqueous ammonia (by method similar to that adopted by Barton, Cook and Loudon[20]) to (XXXIV; R = OCH_3) on a test scale in a yield of 70%, when larger quantities

(above 5g.) were used the amino-acid was retained by the sludge of iron hydroxide with consequent detrimental effect on the yield.

However, (XXVI; R = H) and (XXVI; R = OCH_3) were more conveniently reduced by catalytic hydrogenation in aqueous potassium carbonate with palladised strontium carbonate as catalyst. On completion of hydrogenation, the solution of the amino acid rapidly turned a vivid blue colour which subsequently darkened. This deterioration was avoided by the introduction of a few crystals of sodium sulphite (to poison the palladium catalyst) immediately the reduction had ceased. On neutralisation, 5-amino-2-phenoxyphenylacetic acid (XXXIV; R = H) and 5-amino-2-(2'-methoxyphenoxy)-phenyl-acetic acid (XXXIV; R = OCH_3) were precipitated. (Yield 90%). Both amino-acids were colourless and they gave hydrochlorides readily on treatment with concentrated hydrochloric acid.

The deamination proceeded smoothly (cf. method of Kornblum[22]) by diazotisation of a solution of (XXXIV; R = H) in aqueous hydrochloric acid. A large excess of hypophosphorous acid was then added and after standing for fifteen hours at room temperature, the product, 2-phenoxyphenylacetic acid (XII; R = H) had precipitated.

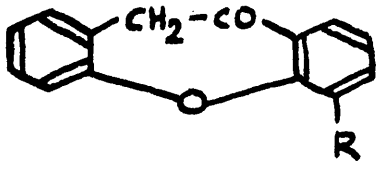


(XII)

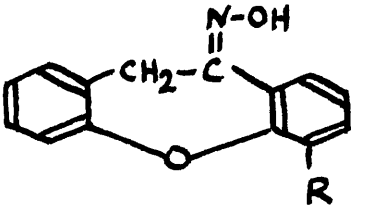
Compound (XXXIV; R = OCH_3) similarly gave 2-(2'-methoxy-phenoxy)-phenylacetic acid (XII; R = OCH_3). The phenylacetic acids were produced in good yield (70-75%) and were easily obtained crystalline as white needles from light petroleum (the melting points were in agreement with those reported by Manske and Ledingham[6]).

The cyclodehydration of the deaminated phenyl-acetic acids with polyphosphoric acid proceeded satisfactorily although not quite as readily as with the corresponding nitro compounds (XXVI; R = H) and (XXVI; R = OCH_3). Compounds (XII; R = H) and (XII; R = OCH_3) were thus heated (to about 160°) for a few minutes with polyphosphoric acid to initiate the cyclisation and then at 100° for two hours. On adding water to the cooled reaction mixture an oil separated. The whole was extracted with ether and the ethereal layer, after thorough washing with aqueous sodium carbonate, was dried. The residue obtained from

evaporation of the solvent afforded 10,11-dihydro-dibenz-(b,f) oxepin-10-one (XIII; R = H) and 10,11-dihydro-6-methoxy-dibenz (b,f) oxepin-10-one (XIII; R = OCH_3) as oils from (XII; R = H) and (XII; R = OCH_3) respectively.



(XIII)

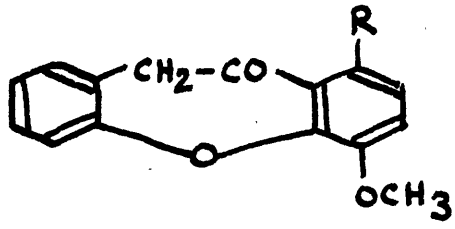


(XXXV)

Compound (XIII; R = H) was not further purified (it had previously been prepared by Manske and Ledingham[6]) but was directly converted to its oxime (XXXV; R = H), which was the required starting material for further investigations in mind (see later chapter). The yield of (XXXV; R = H) was good (70% calculated from (XII; R = H)). It was readily crystallised as white needles from benzene-light petroleum, and its melting point agreed with that of the sample prepared by Manske and Ledingham[6]. The oily (XIII; R = OCH_3) was, however, purified by extraction with hot light petroleum. White crystals of (XIII; R = OCH_3) (also previously prepared by Manske[6]) were deposited on cooling in about 70% yield. The oxime (XXXV; R = OCH_3) was also prepared.

From the results of the experiments in this and preceding chapters it has been shown that this method of preparing derivatives of dibenz (b,f) oxepin is practicable. Although the synthesis is rather longer than that adopted by Manske and Ledingham[6] (due to the necessity for removing the nitro group), the reactions in general, and the two critical stages in particular (namely the initial formation of the diaryl ethers and the cyclisation) occur more readily. Manske's observation that these two steps were more difficult when a methoxyl group is present in the ortho position to the hydroxyl group in the original phenol has been confirmed. In this case, as well, however, both reactions proceeded satisfactorily although not quite as conveniently as when the methoxyl group was absent.

The method is likely to be of value, especially if it can be successfully adapted to include the preparation of compounds of type (XXXVI; R = CH_3, CHO, etc.)



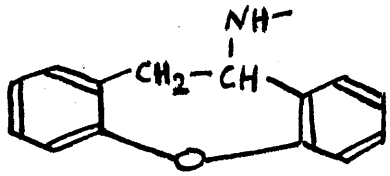
(XXXVI)

which were shown by Kulka and Manske[7] to be obtainable only with great difficulty. In addition, the conversion of the nitro group to methoxyl rather than hydrogen would be of value in future attempts at the synthesis of cularine.

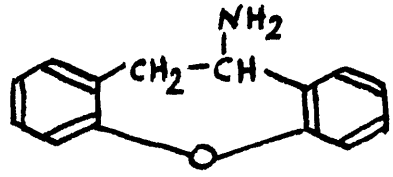
In the present work, however, these ideas were not developed. The following chapters are concerned with reactions and the preparation of a few more derivatives of dibenz (b,f) oxepin.

Preparation of 10-Amino-10,11-dihydrodibenz (b,f) oxepin

The presence of the system (XXXVII) in the alkaloid cularine (see Introduction, p. 59) suggested that it would

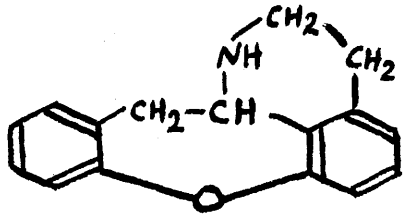


(XXXVII)

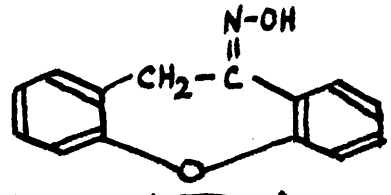


(XXXVIII)

be of interest to prepare the amine (XXXVIII), which in future work might be adaptable as starting material in an attempted synthesis of the fundamental structure of cularine (XXXIX). The oxime (XXXV) was therefore reduced catalytically with platinic oxide in acetic

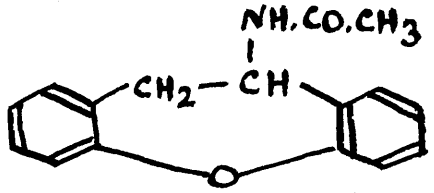


(XXXIX)



(XXXV)

anhydride as solvent to 10-acetamido-10,11-dihydrodibenz-(b,f) oxepin (XL). The hydrogenation proceeded smoothly

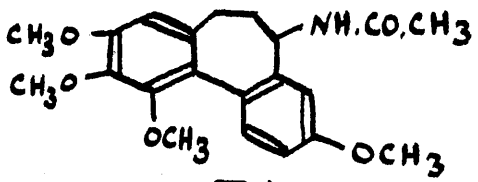


(XL)

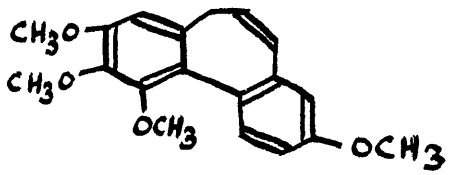
and the product was obtained pure and in high yield as white crystals from benzene-light petroleum. On hydrolysis of (XL) with dilute hydrochloric acid, the amine (XXXVIII) was isolated as its hydrochloride.

Preparation of Dibenz(b,f)oxepin

Cook, et al[23] discovered that N-acetyl-colchinol methyl ether (XLI) on treatment with phosphoric oxide in boiling xylene was converted to (XLII) with elimination of the elements of acetamide. Cook, Dickson and Loudon[24] have

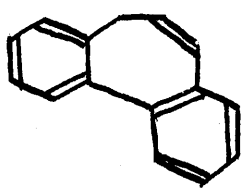


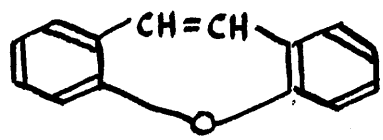
(XLI)



(XLII)

since prepared the pure 3,4,5,6-dibenzocyclohepta-1,3,5-triene (XLIII) by similar means from the corresponding acetamido compound.


(XLIII)



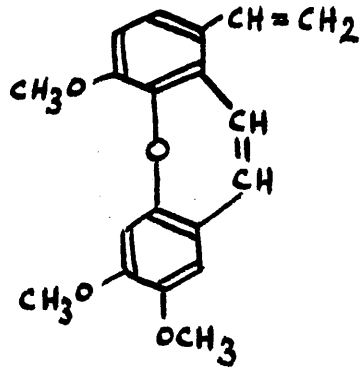
(VI)

When (XL) was likewise treated with phosphorus pentoxide in xylene, the parent compound, dibenz(b,f)oxepin (VI) was obtained readily as white plates (from methanol) in a yield of 85%. This represents an overall yield of

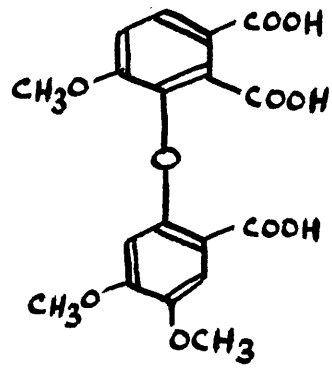
about 15% calculated from the original 2-chloro-5-nitro-benzaldehyde. The melting point agreed with that of the specimen prepared by Manske and Ledingham[6] from the dehydration of 10,11-dihydro-10-hydroxy-dibenz(b,f)-oxepin with <u>para</u>-toluene sulphonic acid.

Oxidation of 10-Carboxy-2-nitro-dibenz(b,f)oxepin

One of the degredation products (XLIV) of the alkaloid cularine was shown by Manske[1] to be oxidised with potassium permanganate in acetone to (XLV). A smaller quantity of (XLVI) was also isolated. Similar results[6] were obtained

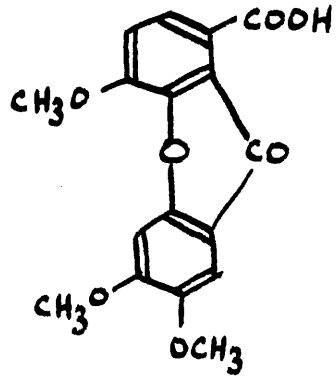


(XLIV)

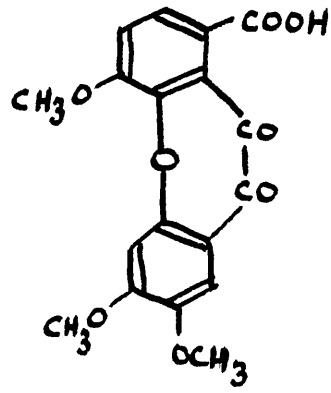


(XLV)

from dibenz (b,f) oxepin, the corresponding dicarboxylic acid (in 90% yield) and xanthone (6-7%) being formed. The

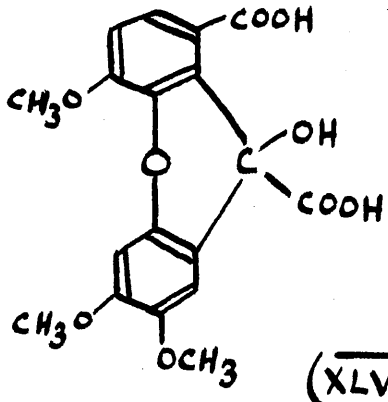


(XLVI)

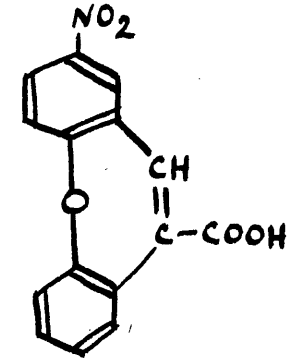


(XLVII)

production of the xanthone derivative (which is analogous to the oxidation of phenanthraquinone to fluorenone[25]) was explained by Manske by initial formation of (XLVII) which would be expected to present certain instability, and therefore, undergo the benzilic rearrangement to a xanthydrol-9-carboxylic acid (XLVIII). Decarboxylation and oxidation of (XLVIII) would then produce (XLVI).



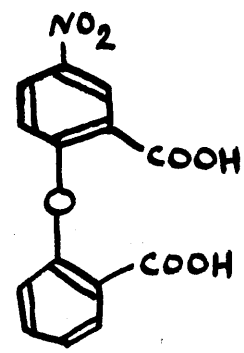
(XLVIII)



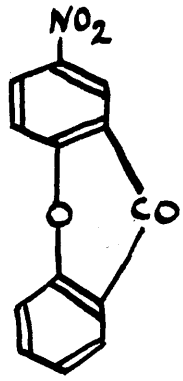
(XXVII)

The formation of xanthone derivatives also recalls the oxidation of dibenzocycloheptatriene (XLIII) to phenanthraquinone by sodium dichromate (Cook, Dickson and Loudon[24]) and the associated contrast to oxidation by potassium permanganate whereby compounds of type (XLIII) afford mainly homodiphenic acids (cf. Tarbell, Frank and Fanta[21]). The present work showed that this contrast was maintained in dibenz (b,f) oxepins, since, as main products, permanganate oxidation of (XXVII) yielded

2,2'-dicarboxy-4-nitro-diphenyl ether (XLIX) whereas dichromate oxidation gave 2-nitroxanthone (L)



(XLIX)

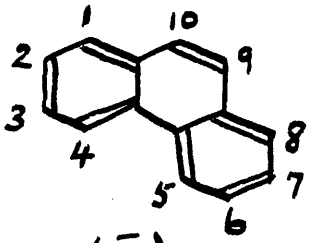


(L)

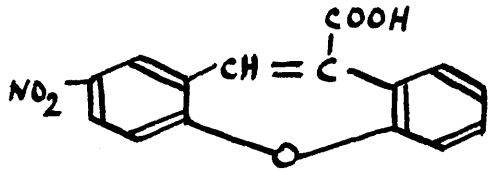
Hydrogenation of 10-Carboxy-2-nitro-dibenz(b,f)oxepin and Preparation of 10-Carboxy-10,11-dihydro-dibenz(b,f)oxepin

Preparation of 10-Carboxy-10,11-dihydro-dibenz(b,f)oxepin

It is known that the 9,10-double bond in phenanthrene (LI) is characteristically different from the other double bonds in the ring system, behaving in some respects like an olefinic bond. For example, it was reduced catalytically to 9,10-dihydrophenanthrene by Berger abd Mosettig[26]. It was thought that the 10,11-double bond in dibenz(b,f)oxepins was of a similar olefinic nature. This expectation was

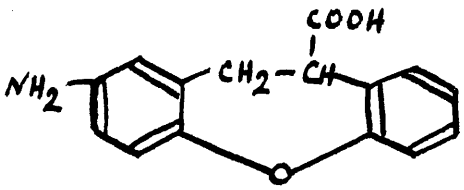


(LI)

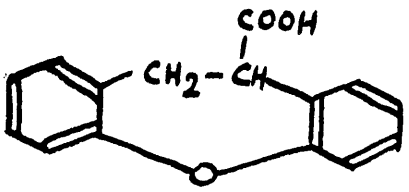


(XXVII)

fully realised on hydrogenation of (XXVII) with palladised strontium carbonate in aqueous potassium carbonate solution. The nitro group and the 10,11-double bond were both reduced and the product 2-amino-10-carboxy-10,11-dihydrodibenz(b,f)oxepin (LII) was obtained. Compound (LII) was crystallised from aqueous ethanol



(LII)

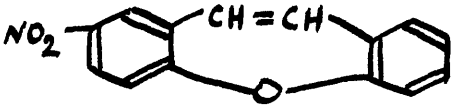


(LIII)

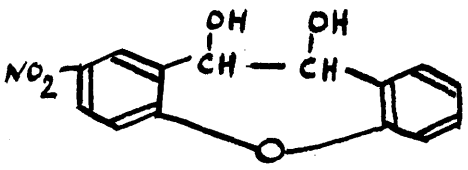
and on treatment with concentrated hydrochloric acid it gave a hydrochloride. Deamination of (LII) to 10-carboxy-10-11-dihydrodibenz(b,f) oxepin (LIII) proceeded smoothly.

Preparation of 2-Nitrodibenz(b,f)oxepin and cis-10,11-Dihydro-10,11-dihydroxy-2-nitrodibenz(b,f)oxepin

10-Carboxy-2-nitrodibenz(b,f) oxepin (XXVII) was decarboxylated by the general method with quinoline and copper bronze to 2-nitrodibenz (b,f) oxepin (LIV). It



(LIV)



(LV)

crystallised as pale yellow needles from methanol, but was only obtained in moderate yield (44%).

The olefinic nature of the 10,11-double bond was confirmed by the oxidation of (LIV) with osmium tetroxide in benzene solution in the presence of a little pyridine by the method adopted by Cook, et al[27] with 9-methylphenanthrene. The corresponding diol, cis-10,11-dihydro-10,11-dihydroxy-2-nitrodibenz (b,f) oxepin (LV) was thus formed, but in insufficient quantity to attempt further oxidation (e.g. with lead tetraacetate).

Experimental

Petrol as solvent refers to light petroleum, b.p. 60°-80°.

2-Chloro-5-nitrobenzaldehyde (XIX) was obtained from ortho-chlorobenzaldehyde by the method of Erdmann[28].

5-Nitro-2-phenoxybenzaldehyde (XX; R = H). 2-Chloro-5-nitrobenzaldehyde (40g.) and phenol (20g.) were refluxed for two hours with a solution of caustic soda (10g.) in water (400 c.c.). Crystals formed in the cold dark reaction mixture. The whole was extracted with ether and some material (XXI; see below) which remained undissolved was filtered off. The ethereal layer was repeatedly washed with dilute aqueous alkali, water and then dried. On evaporation of the solvent, a semi-solid residue remained, which, by exhaustive extraction with petrol, concentration of the solution and cooling, afforded 5-nitro-2-phenoxybenzaldehyde (36g.; 70% yield) as white crystals, which were further purified from benzene-petrol. Melting point obtained was 66° (Patent literature[11] gives m.p. 68°).

2-(2'-Methoxyphenoxy)-5-nitrobenzaldehyde (XX; R = OCH_3) was likewise obtained (55% yield) from 2-chloro-5-nitrobenzaldehyde and guaiacol, as white crystals, m.p. 111° (from benzene-petrol) (Found: C, 61.3; H, 3.9; N, 5.3. $C_{14}H_{11}NO_5$ requires C, 61.5; H, 4.0; N, 5.1%)

2-(2'-Chloro-5'-nitrobenzyloxy)-5-nitrobenzaldehyde (XXI) The ether insoluble residue obtained during the preparation of 5-nitro-2-phenoxybenzaldehyde was collected and dried. On crystallisation from benzene, 2-(2'-chloro-5'-nitrobenzyloxy)-5-nitrobenzaldehyde, m.p. 208°, (Found: C,50.2; H, 2.8; N, 8.6; Cl, 10.75. $C_{14}H_9ClN_2O_6$ requires C, 49.9; H, 2.7; N, 8.3; Cl, 10.55%) was obtained (Yield < 1% calculated from 2-chloro-5-nitrobenzaldehyde). Its oxime, m.p. 194° (white crystals from benzene-methanol) (Found: C, 47.8; H, 2.9; N, 11.9. $C_{14}H_{10}ClN_3O_6$ requires C, 47.8; H, 2.8; N, 11.9%) was prepared in pyridine solution.

Compound (XXI) was also formed:- a) during the preparation of 2-(2'-methoxyphenoxy)-5-nitrobenzaldehyde in 5% yield. b) when 2-chloro-5-nitrobenzaldehyde (0.5g.) was refluxed with water (12.5 c.c.) containing caustic soda (0.25g.) for 20 minutes. The product (after crystallisation from benzene) had m.p. 206°, undepressed by admixture with (XXI) obtained as by-product from preparation of 5-nitro-2-phenoxybenzaldehyde. (Yield 12%). c) when 2-chloro-5-nitrobenzyl alcohol (0.25g.) and 2-chloro-5-nitrobenzaldehyde (0.25g.) were heated to 100° with anhydrous potassium carbonate (0.25g.) for 15 minutes. On cooling, the solid, which had formed, was filtered and dried.

On crystallisation from benzene (XXI), m.p. 206°, and mixed m.p. (with samples prepared above) 206-8°, was obtained in 80% yield. The 2-chloro-5-nitrobenzyl alcohol, m.p. 78° (white needles from petrol) (Found: C, 44.8; H, 3.05. $C_7H_6ClNO_3$ requires C, 44.8; H, 3.2%) was prepared when 2-chloro-5-nitrobenzaldehyde (3g.) in methanol (50 c.c.) and sodium borohydride (1g.) in water (10 c.c.) were allowed to react at room temperature for 4 hours. The solution was made acid with dilute sulphuric acid and the methanol evaporated off. On cooling, the product was obtained as an oil which readily solidified.

Azlactones: A mixture of 5-nitro-2-phenoxybenzaldehyde (1 mol.), aceturic acid (1 mol.) and freshly fused sodium acetate (1 mol.) in acetic anhydride were gently warmed until in solution and then refluxed for one hour. From the dark coloured solution a crystalline mass was formed on standing overnight. The solid was filtered off, washed with a little acetic acid and dried. On purification from benzene (charcoal) and further recrystallisation from benzene-petrol, 2-methyl-4-(5'-nitro-2'-phenoxy)-benzylidene-5-oxazolone (XXII; R = H), m.p. 188°, was obtained as fine lemon needles. (Yield 58%). (Found: C, 62.9; H, 3.6. $C_{17}H_{12}N_2O_5$ requires C, 63.0; H, 3.7%). 2-(2'-Methoxy-

phenoxy)-5-nitrobenzaldehyde similarly afforded 4-[2'-(2"-methoxyphenoxy)-5'-nitrobenzylidene]-2-methyl-5-oxazolone (XXII; R = OCH_3), m.p. 197° d. (lemon needles from benzene-petrol) in 55% yield. (Found: C, 61.2; H, 4.1; N, 8.0. $C_{18}H_{14}N_2O_6$ requires C, 61.0; H, 3.95; N, 7.9%).

An improved method of preparing the azlactones based on Galat's[14] procedure was subsequently adopted. The aldehyde (1 mol.), aceturic acid (1 mol.) and pure potassium bicarbonate (1 mol.) in acetic anhydride were gently warmed until the yellow colour of the azlactone developed in the solution. Although heating was then ceased, the temperature of the reaction mixture continued to rise. The solution was then allowed to stand 24 hours at 18°, by which time the azlactone had crystallised out. It was filtered off, washed with hot water and dried. On recrystallisation from benzene-petrol, (XXII; R = H) and (XXII; R = OCH_3) were obtained in 70-75% yield.

Ethyl α-acetamido-β-(5-nitro-2-phenoxyphenyl)-acrylate (XXIII; R = H). A mixture of (XXII; R = H) (2 g.), ethanol (5 c.c.) and concentrated sulphuric acid (2 c.c.) was heated gently until in solution. The reaction mixture was then cooled and added to cold water, whereupon a pale yellow precipitate of ethyl α-acetamido-β-(5-nitro-2-

phenoxyphenyl)-acrylate, m.p. 195-6° (white crystals from ethanol) was obtained. (1.8g.; 80% yield). (Found: C, 61.8; H, 5.0. $C_{19}H_{18}N_2O_6$ requires C, 61.6; H, 4.9%)

5-Nitro-2-phenoxyphenylpyruvic acid (XXIV; R = H). Compound (XXII; R = H) (10 g.), dilute hydrochloric acid (100 c.c.; 1 part concentrated acid: 2 parts water, by volume) and glacial acetic acid (100 c.c.) were refluxed for five hours. (The reaction was equally successful when (XXIII; R = H) was employed as the starting material). The hot solution was filtered and allowed to stand 15 hours, by which time pale yellow crystals of the product had developed. A further crop was recovered by dilution of the mother liquors. (Yield 95%). The 5-nitro-2-phenoxyphenylpyruvic acid was recrystallised from benzene, m.p. 148-9°. (Found: C, 60.0; H, 3.8; N, 4.6. $C_{15}H_{11}NO_6$ requires C, 59.8; H, 3.65; N, 4.65%). When the dark red alkaline solution of the acid was treated with excess hydroxylamine hydrochloride and subsequently acidified, the oxime (XXV; R = H), m.p. 167° (white crystals from benzene) (Found: C, 56.7; H, 3.6. $C_{15}H_{12}N_2O_6$ requires C, 57.0; H, 3.8%) was precipitated.

2-(2'-Methoxyphenoxy)-5-nitrophenylpyruvic acid, (XXIV; R = OCH_3) m.p. 230° d., (yellow crystals from acetic acid) (Found: C, 57.8; H, 4.1; N 4.4. $C_{16}H_{13}NO_7$ requires C, 58.0; H, 3.9; N, 4.2%) was similarly prepared by the hydrolysis of (XXII; R = OCH_3). (Yield = 95%). The oxime (XXV; R = OCH_3) had m.p. 180° d. (white crystals from benzene with a trace of methanol) (Found: C, 55.6; H, 4.2; N, 8.4. $C_{16}H_{14}N_2O_7$ requires C, 55.5; H, 4.05; N, 8.1%).

5-Nitro-2-phenoxyphenylacetic acid (XXVI; R = H) 5-Nitro-2-phenoxyphenylpyruvic acid (6 g.) was dissolved in 10% aqueous caustic soda (100 c.c.), cooled to 0°, and maintained at this temperature while 10% hydrogen peroxide (25 c.c.) was added. The dark red solution of the sodium salt of the pyruvic acid rapidly lightened in colour. The mixture was then allowed to come to room temperature and after four hours it was acidified with dilute hydrochloric acid. The flocculent white precipitate of 5-nitro-2-phenoxyphenylacetic acid which was formed, crystallised readily from benzene-petrol as white needles m.p. 140° (Yield 4.9g.; 91%). (Found: C, 61.6; H, 4.0. $C_{14}H_{11}NO_5$ requires C, 61.5; H, 4.0%).

2-(2'-Methoxyphenoxy)-5-nitrophenylacetic acid (XXVI; R = OCH_3), m.p. 141°, (white crystals from benzene-petrol) (Found: C, 59.6; H, 4.5. $C_{15}H_{13}NO_6$ requires

C, 59.4; H, 4.25%) was likewise obtained from 2-(2'-methoxyphenoxy)-5-nitrophenylpyruvic acid. (Yield = 94%).

10-Carboxy-2-nitro-dibenz (b,f) oxepin (XXVII; R = H). 5-Nitro-2-phenoxyphenylpyruvic acid (2g.) was stirred into cooled polyphosphoric acid (from 14 c.c. of syrupy phosphoric acid and 21 g. of phosphoric oxide) and heated cautiously to about 160° for a few minutes until the colour of the mixture became green-brown. It was then kept at 100° for 2 hours, cooled and diluted with water. The resultant dark precipitate was filtered, repeatedly washed with water and dried. On successive purification from benzene (charcoal) and benzene-petrol it afforded 10-carboxy-2-nitro-dibenz (b,f) oxepin, m.p. 224°, as pale yellow crystals (1.4g.; 75%) (Found: C, 63.7; H, 3.45, N, 5.05. $C_{15}H_9NO_5$ requires C, 63.6; H, 3.2; N, 4.95%).

10-Carboxy-6-methoxy-2-nitro-dibenz (b,f) oxepin (XXVII; R = OCH_3), m.p. 250°d. (white crystals from benzene-petrol) (Found: C, 61.5; H, 3.8. $C_{16}H_{11}NO_6$ requires C, 61.3; H, 3.5%) was similarly prepared from 2-(2'-methoxyphenoxy)-5-nitro-phenylacetic acid. (Yield = 70%).

10,11-Dihydro-2-nitro-dibenz (b,f) oxepin-10-one (XXXII; R = H). 5-Nitro-2-phenoxyphenylacetic acid (2 g.) and polyphosphoric acid were heated at 100° for 2 hours. The mixture was then cooled and diluted with water, whereupon

a white solid precipitated. It was filtered, washed with aqueous sodium carbonate, water and dried. The 10,11-dihydro-2-nitro-dibenz (b,f) oxepin-10-one, m.p. 158°, (white crystals from benzene-petrol) (1.5 g.; 80% yield). (Found: C, 66.1; H, 3.55; N, 5.4. $C_{14}H_9NO_4$ requires C, 65.9; H, 3.5; N, 5.5%) readily formed an oxime, m.p. 184°, (white needles from benzene) (Found: C, 62.0; H, 3.8; N, 10.2. $C_{14}H_{10}N_2O_4$ requires C, 62.2; H, 3.7; N, 10.4%) when treated with excess hydroxylamine hydrochloride in pyridine solution.

10,11-Dihydro-6-methoxy-2-nitro-dibenz (b,f) oxepin-10-one (XXXII; R = OCH_3), m.p. 195° (colourless needles from benzene-petrol) (Found: C, 62.9; H, 4.0. $C_{15}H_{11}NO_5$ requires C, 63.15; H, 3.9%) was prepared likewise (78% yield) when 2-(2'-methoxyphenoxy)-5-nitrophenylacetic acid and polyphosphoric acid were heated initially to 160° for a few minutes and subsequently at 100° for 2 hours. Its oxime had m.p. 211° (white crystals from benzene-petrol) (Found: C, 60.2; H, 4.3. $C_{15}H_{12}N_2O_5$ requires C, 60.0; H, 4.0%).

5-Amino-2-phenoxyphenylacetic acid (XXXIV; R = H). 5-Nitro-2-phenoxyphenylacetic acid (5 g.) in potassium carbonate solution (2.3 g. in 500 c.c. water) was catalytically reduced with 2% palladised strontium carbonate (1.25 g.) until the requisite volume of hydrogen

(1300 c.c.) was absorbed. A few crystals of sodium sulphite were then added and the solution filtered. On neutralisation with dilute hydrochloric acid the product precipitated and the whole was allowed to stand overnight at 0°. The solid was filtered off and on purification from water, 5-amino-2-phenoxyphenylacetic acid, m.p. 148°, (Found: C, 68.95; H, 5.5. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.35) was obtained as white crystals (Yield: 3.9g.; 89%). The hydrochloride, m.p. c 230° d. (white needles from aqueous hydrochloric acid) (Found: C, 60.2; H, 5.25. $C_{14}H_{14}ClNO_3$ requires C, 60.1; H, 5.0%) was readily formed on treatment of the amino acid with concentrated hydrochloric acid.

5-Amino-2-(2'-methoxyphenoxy)-phenylacetic acid (XXXIV; R = OCH_3), m.p. 137°, (stout white crystals from aqueous methanol) (Found: C, 66.0; H, 5.6. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.5%) (Yield = 90%) and its hydrochloride, m.p. 134° (white crystals from benzene-ethanol, initially obtained from aqueous solution) (Found: C, 55.1; H, 5.8. $C_{15}H_{16}ClNO_4.H_2O$ requires C, 55.0; H, 5.5) were similarly prepared from 2-(2'-methoxyphenoxy)-5-nitrophenylacetic acid or alternatively when the nitro-acid (0.5 g.) in concentrated ammonia (3 c.c.) and water (10 c.c.) was added to a mixture of ferrous sulphate (5 g.), water

(13 c.c.) and concentrated ammonia (12 c.c.) and maintained with stirring at 70°. After 2 hours, the filtrate and washings from the sludge of iron hydroxide were neutralised and the amino-acid precipitated (70% yield). On an increased scale (nitro-acid (5 g.)), however, the yield was much lower. (c. 35-40%).

2-Phenoxyphenylacetic acid (XII; R = H) 5-Amino-2-phenoxyphenylacetic acid (3 g.) in concentrated hydrochloric acid (40 c.c.) and water (100 c.c.) was cooled to 0° and diazotised with an aqueous solution of sodium nitrite (1 g.). The mixture was gently warmed until the diazonium salt dissolved and then allowed to return to room temperature. Hypophosphorous acid (40 c.c.) was added and the solution kept at 18° overnight. The precipitate which was obtained, afforded 2-phenoxyphenylacetic acid, m.p. 89° (Manske and Ledingham[6] give m.p. 91°) (Found: C, 73.95; H, 5.4. Calc. for $C_{14}H_{12}O_3$; C, 73.7; H, 5.3%) as white needles when crystallised from petrol (Yield; 2.1 g.; 75%).

2-(2'-Methoxyphenoxy)-phenylacetic acid (XII; R = OCH_3), m.p. 90° (Manske and Ledingham[6] give m.p. 93°) (white needles from petrol) (Found: C, 69.8; H, 5.5. Calc. for $C_{15}H_{14}O_4$; C, 69.8; H, 5.4%) was prepared by the similar deamination of 5-amino-2-(2'-methoxyphenoxy)phenylacetic acid (Yield = 72%).

10,11-Dihydro-10-oximino-dibenz (b,f) oxepin (XXXV; R = H). 2-Phenoxyphenylacetic acid (1 g.) and polyphosphoric acid were heated to 160° for five minutes and then at 100° for 2 hours. The cooled reaction mixture was diluted with water and extracted with ether. The ethereal layer was washed with dilute alkali, water and dried. On evaporation of the solvent, 10,11-dihydro-dibenz (b,f) oxepin-10-one, (XIII; R = H) was recovered as a yellow oil, which was directly refluxed with excess hydroxylamine hydrochloride in pyridine solution for 2 hours. The cooled solution, on treatment with water, afforded 10,11-dihydro-10-oximino-dibenz (b,f) oxepin, m.p. 135° (white needles from benzene-petrol) (Found: C, 74.7; H, 5.1. Calc. for $C_{14}H_{11}NO_2$; C, 74.7; H, 4.9%) (Manske and Ledingham[6] give m.p. 137°) in a yield of 70%.

10,11-Dihydro-6-methoxy-dibenz(b,f) oxepin-10-one (XIII; R = OCH_3), m.p. 93° (white crystals from petrol) (Found: C, 74.9; H, 5.1. Calc. for $C_{15}H_{12}O_3$, C, 75.0; H, 5.0%) (Manske and Ledingham[6] give m.p. 85°) was similarly prepared from 2-(2'-methoxyphenoxy)-phenylacetic acid. The green oil which was recovered from evaporation of the ether extract was purified from petrol (charcoal). On cooling, the product crystallised out. (Yield = 70%). Its oxime, m.p. 198°, (from benzene-methanol) (Found:

C, 70.4; H, 5.1. Calc. for $C_{15}H_{13}NO_3$; C, 70.6; H, 5.1%) (Manske and Ledingham[6] give m.p. 196°) was prepared in pyridine solution.

10-Amino-10,11-dihydro-dibenz (b,f) oxepin (XXXVIII). 10,11-Dihydro-10-oximino-dibenz (b,f) oxepin (2 g.) in acetic anhydride (50 c.c.) was catalytically reduced with platinic oxide until the requisite volume of hydrogen (400 c.c.) had been absorbed. The solution was then filtered and the solvent partially evaporated at 20m.m. pressure. On dilution of the residue with water, a white oil formed which rapidly solidified. The solid, on crystallisation from benzene-petrol afforded 10-acetamido-10,11-dihydrodibenz(b,f) oxepin (XL), m.p. 139°, in 88% yield. (Found: C, 76.0; H, 6.0. $C_{16}H_{15}NO_2$ requires C, 75.9, H, 5.9%). On refluxing a sample of this product (0.1 g.) with aqueous hydrochloric acid for 4 hours, and cooling, 10-amino-10,11-dihydrodibenz(b,f) oxepin hydrochloride, m.p. c. 265°d. (white crystals from aqueous hydrochloric acid). (Found: C, 68.1; H, 5.8. $C_{14}H_{14}ClNO$ requires C, 67.9; H, 5.65%) was isolated.

Dibenz (b,f) oxepin (VI). 10-Acetamido-10,11-dihydro-dibenz (b,f) oxepin (0.1 g.) and phosphoric oxide (0.2 g.) in dry xylene (4 c.c.) was refluxed for 30 minutes. The hot solvent was then decanted from the phosphorus pentoxide

residue, which was extracted with xylene. The combined solutions were filtered and the filtrate evaporated to dryness in vacuo (20 m.m.). The recovered oil solidified on treatment with methanol and afforded dibenz (b,f) oxepin, m.p. 110° (Found: C, 86.4; H, 5.3. Calc. for $C_{14}H_{10}O$; C, 86.6; H, 5.15%) (Manske and Ledingham[6] give m.p. 111°) on further crystallisation from the same solvent. (Yield = 88%).

Oxidation of 10-Carboxy-2-nitro-dibenz (b,f) oxepin

a) With potassium permanganate

10-Carboxy-2-nitro-dibenz (b,f) oxepin (0.5 g.) in acetone solution was treated with finely powdered potassium permanganate in small portions until the pink colour was permanent. Water in small quantities and more oxidising agent were added until the colouration remained for several minutes. The solution was then treated with hot water, the acetone boiled off and the hot mixture filtered. (The precipitate of manganese dioxide was washed with fresh acetone. No material was recovered from the filtrate on evaporation to dryness and it was thus considered that no neutral product had been formed in the reaction). On acidification of the cooled aqueous filtrate with dilute hydrochloric acid, a white precipitate was obtained from which 2,2'-dicarboxy-4-nitro-diphenyl-ether (XLIX), m.p. 220° (white crystals from benzene-petrol with a trace

of methanol) (Found: C, 55.2; H, 3.2; N, 4.7. $C_{14}H_9NO_7$ requires C, 55.4; H, 3.0; N, 4.6%) was the only product recovered (Yield 90%).

b) With sodium dichromate

10-Carboxy-2-nitro-dibenz (b,f) oxepin (0.5 g.) and sodium dichromate (0.5 g.) in acetic acid (5 c.c.) were refluxed for one hour. The cooled solution was diluted with water, exhaustively extracted with chloroform, and the chloroform layer washed with dilute sodium carbonate. On extraction of the acidified aqueous layer with chloroform and evaporation to dryness, no material was recovered. From the original dried chloroform extract a white solid was obtained on removal of the solvent. On crystallisation from benzene the sole product isolated (Yield = 75%) was 2-nitroxanthone (L), m.p. 202° (Found: C, 65.0; H, 3.15; N, 5.8. Calc. for $C_{13}H_7NO_4$; C, 64.7; H, 2.9; N, 5.8) (Various reports give m.p. 200-204°).

2-Amino-10-carboxy-10,11-dihydrodibenz (b,f) oxepin (LII)

10-Carboxy-2-nitrodibenz (b,f) oxepin (0.5g.) in aqueous potassium carbonate solution was catalytically reduced with 2% palladised strontium carbonate. The volume of hydrogen absorbed (170 c.c.) indicated that 4 mols. of the gas had been used up. When the hydrogenation was completed, a few crystals of sodium sulphite were added

to poison the catalyst and on neutralisation of the solution with dilute hydrochloric acid, 2-amino-10-carboxy-10,11-dihydrodibenz (b,f) oxepin, m.p. 210° d. (pale yellow crystals from aqueous ethanol) (Found: C, 70.7; H, 4.9. $C_{15}H_{13}NO_3$ requires C, 70.6; H, 5.1%) was precipitated. (Yield = 86%). On treatment with concentrated hydrochloric acid and recrystallisation from the aqueous acid, the hydrochloride, m.p. 262° d. (Found: C, 61.9; H, 4.8. $C_{15}H_{14}ClNO_3$ requires C, 61.75; H, 4.8%) was obtained as colourless crystals.

10-Carboxy-10,11-dihydrodibenz (b,f) oxepin (LIII) 2-Amino-10-carboxy-10,11-dihydrodibenz (b,f) oxepin (0.2 g.) in aqueous hydrochloric acid was diazotised with sodium nitrite (0.1 g. in 3 c.c. water). The mixture was warmed until the solution was clear and then filtered. A large excess of hypophosphorous acid (2 c.c.) was added and after standing overnight, 10-carboxy-10,11-dihydrodibenz (b,f) oxepin had precipitated. It was purified from benzene as almost colourless crystals, m.p. 186°. (Found: C, 75.3; H, 4.8. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0).

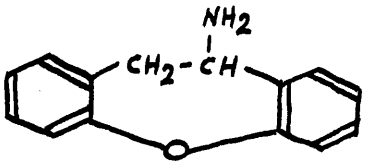
2-Nitro-dibenz (b,f) oxepin (LIV) 10-Carboxy-2-nitrodibenz (b,f) oxepin (2 g.), copper bronze (10 g.) and pure quinoline (50 c.c.) were refluxed for 4 hours. The cooled mixture was diluted with benzene (100 c.c.) and filtered from the copper bronze. The filtrate was repeatedly

washed with dilute sulphuric acid, water, aqueous sodium carbonate, water and dried. The solvent was partially evaporated and the residual solution filtered through charcoal. On dilution with petrol, the product was obtained and it was further crystallised from methanol, whereupon pale yellow needles of 2-nitrodibenz (b,f) oxepin, m.p. 130° (Found: C, 70.5; H, 3.9; N, 5.9. $C_{14}H_9NO_3$ requires C, 70.3; H, 3.8; N, 5.85) were formed. The yield was 44%.

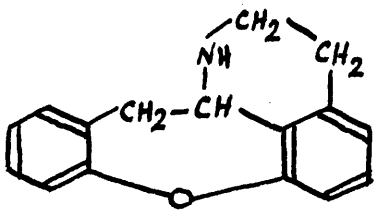
Cis-10,11-Dihydro-10,11-dihydroxy-2-nitrodibenz (b,f) oxepin (LV). Pyridine (3 c.c.) was added to a solution of 2-nitro-dibenz (b,f) oxepin (0.28 g.) and osmium tetroxide (0.45 g.) in thiophen-free dry benzene (15 c.c.). After 10 days, precipitation of the dark solid in the mixture was completed by the addition of petrol. The solid was collected, dissolved in chloroform and shaken for 4 hours with a solution of mannitol (3 g.) and potassium hydroxide (0.3 g.) in water (30 c.c.). The yellow chloroform layer was washed and dried and the solvent allowed to evaporate at room temperature, whereupon the white solid cis-10,11-dihydro-10,11-dihydroxy-2-nitrodibenz (b,f) oxepin was obtained. It crystallised readily from benzene-methanol as white needles, m.p. 196°. (Found: C, 61.3; H, 4.0. $C_{14}H_{11}NO_5$ requires C, 61.5; H, 4.0%).

Note on Attempted Synthesis of Isoquinoline Derivatives

10-Amino-10,11-dihydrodibenz(b,f) oxepin (XXXVIII) having been prepared (p. 84) a few tentative experiments were carried out in the hope of establishing a suitable method for the synthesis of the basic structure (XXXIX) of the alkaloid cularine, by lengthening the amine side-chain of (XXXVIII) by two carbon atoms and subsequent



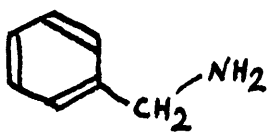
(XXXVIII)



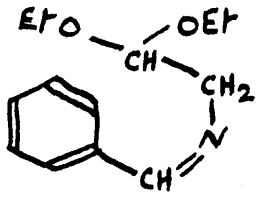
(XXXIX)

cyclisation to give the isoquinoline derivative (XXXIX).

The usual procedure for preparing isoquinolines from benzylamines (LVI) is a modification of the Pomeranz-Fritsch reaction involving condensation of the base with glyoxal hemi-acetal to give (LVII) followed by cyclodehydration. The method, however, has been found

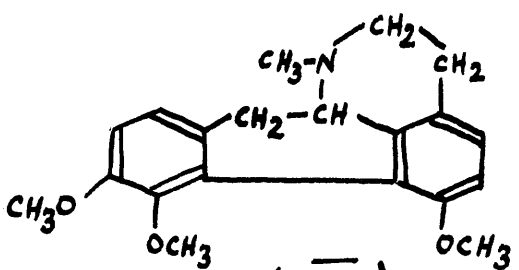


(LVI)

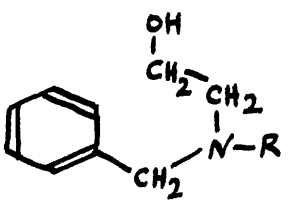


(LVII)

to be of only limited application (cf. Gensler[29]), as, for example, was borne out by the failure of an attempted synthesis of isothebainmethylether (LVIII) (an alkaloid closely related in structure to cularine) by Schlittler and Muller[30]. Consequently, attention was directed to attempts to prepare derivatives of isoquinoline from simple derivatives of benzylamine employing polyphosphoric acid, which has been shown, in the previous chapters, to be of considerable value as a cyclodehydration agent. Staub[31] and Clemo

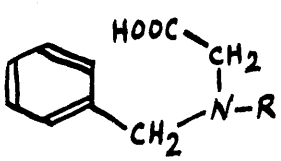


(LVIII)

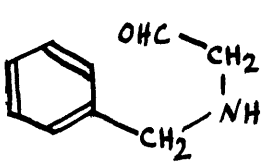


(LIX)

and Perkin[32] have reported uniform failure in all attempts to induce ring closure with a variety of compounds of general type (LIX; R = H or benzenesulphonyl) and (LX; R = p-tolylsulphonyl) with a number of cyclising

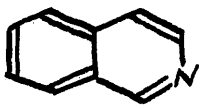


(LX)

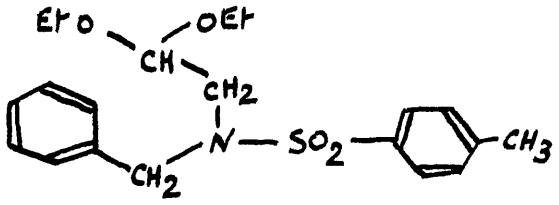


(LXI)

reagents (not including polyphosphoric acid), although a successful synthesis of this type was achieved by Emil Fischer[33] who obtained (LXII) from (LXI) employing sulphuric acid as the cyclodehydration agent.



(LXII)



(LXIII)

Similar failures attended the reactions of (LIX; R = H and p-tolylsulphonyl) and (LX; R = H and p-tolylsulphonyl) with polyphosphoric acid under a variety of conditions, the starting material being recovered unchanged or intractable gums being formed and preliminary attempts to prepare (LXIII) by the interaction of bromoacetal with N-benzyl-p-toluenesulphonamide were also unsuccessful.

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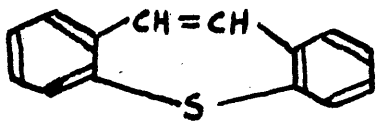
ADDENDUM ON DIBENZ (b,f) THIEPINS

Contents

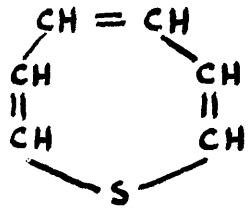
Addendum on Dibenz (b,f) thiepins.

Introduction

The synthesis of dibenz (b,f) oxepins described in the preceding chapters prompted investigation into the preparation (by a similar method) of derivatives of the corresponding thia -analogue, dibenz (b,f) thiepin (I). Neither (I) (nor, indeed any compound simply related to it)

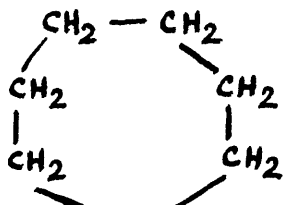


(I)



(II)

nor the parent seven-membered heterocyclic compound, thiepin (II) appear to be known. However, hexamethylene sulphide or thiepane (III) was obtained by Braun[1] and Grishkovich-Trokhimovski[2] as the monomer in addition to polymeric material (cf. Bost and Conn[3]) and within recent

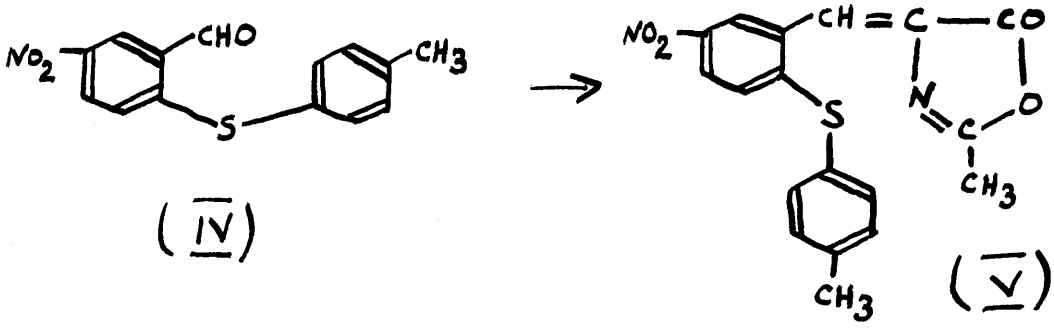


(III)

years compound (III) and a few of its simple derivatives have been prepared by Leonard and Figueras[4].

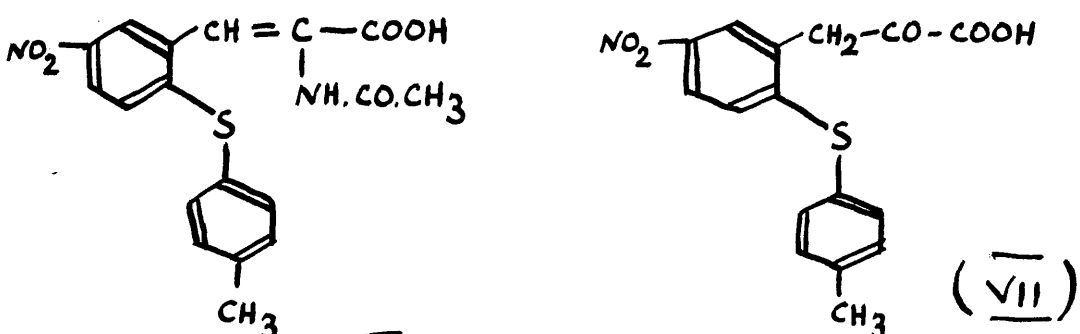
Discussion

Preparation of 5-Nitro-2-(p-tolylthio)-phenylpyruvic acid



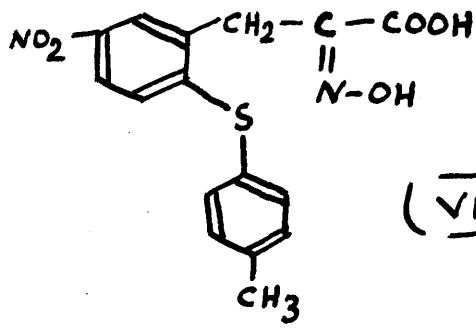
(IV) (V)

5-Nitro-2-(p-tolylthio)benzaldehyde (IV) (prepared as described by Loudon, et al[5]) was converted to the corresponding azlactone, 2-methyl-4-(5'-nitro-2'-p-tolylthio)-benzylidene-5-oxazolone (V) by the method of Herbst and Shemin[6] in moderate yield (55%). No improvement was observed on adopting Galat's[7] procedure (cf. p.69). Treatment of (V) in ethanol solution with concentrated sulphuric acid gave α-acetamido-β-(5-nitro-2-p-tolylthio)-phenylacrylic acid (VI) and hydrolysis of both (VI) and (V)



(VI) (VII)

in a mixture of acetic acid and aqueous hydrochloric acid proceeded smoothly and in high yield to 5-nitro-2-(p-tolylthio)-phenylpyruvic acid (VII). Compound (VII) was purified from benzene (with a trace of methanol) and the lemon crystals thus deposited, when dissolved in aqueous alkaline solution and treated with excess hydroxylamine hydrochloride gave the oxime (VIII) on acidification.

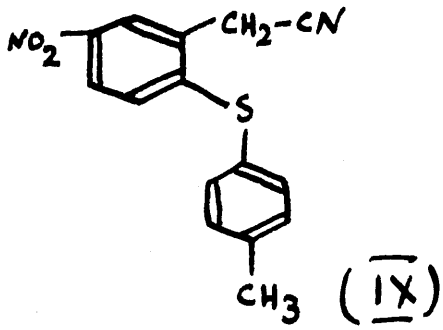


(VIII).

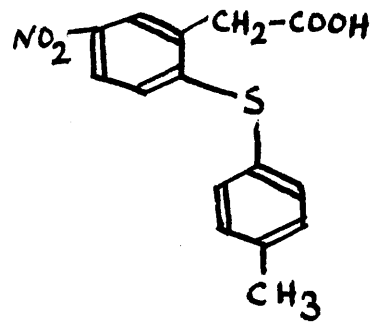
Preparation of 5-Nitro-2-(p-tolylthio)-phenylacetic acid

The method previously used (p. 71) for the conversion of a phenylpyruvic acid to the corresponding phenylacetic acid, by oxidation with hydrogen peroxide in aqueous caustic soda solution, was considered inapplicable in this case due to the readiness with which thio-ethers are known to oxidise to sulphoxides and sulphones. The following alternative procedure was thus adopted.

The oxime (VIII), when heated for a few hours with acetic anhydride, gave 5-nitro-2-(p-tolylthio)-benzyl cyanide (IX) in 60% yield. On acid hydrolysis (8-9 hours)



(IX)



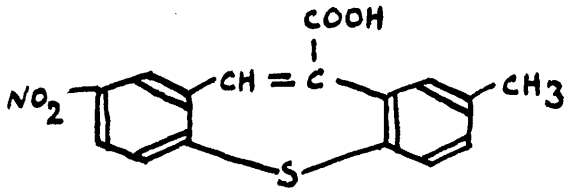
(X)

of (IX), the yellow gum, which was obtained on dilution of the cooled reaction mixture with water, was dissolved in ether. On acidification of the aqueous alkaline extract, 5-nitro-2-(p-tolylthio)-phenylacetic acid (X) was precipitated and purified from benzene-light petroleum. (Yield = 70%).

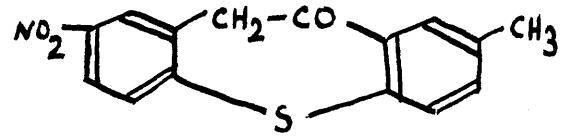
Cyclisations with Polyphosphoric acid

a) Preparation of 10-Carboxy-8-methyl-2-nitro-dibenz (b,f)-thiepin

The cyclisation of (VII) with polyphosphoric acid was carried out in essentially the same manner as in the previous cyclodehydration experiments (p. **73**). Initial heating for a few minutes (to about 160°) was required, whereupon the mixture became red-brown in colour, and after being kept for a further two hours (at 100°) the reaction was completed. On cooling and dilution with water, 10-carboxy-8-methyl-2-nitrodibenz (b,f) thiepin (XI) was precipitated. (Yield 70%).



(XI)



(XII)

b) Preparation of 10,11-Dihydro-8-methyl-2-nitrodibenz-(b,f) thiepin-10-one

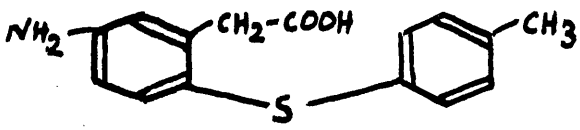
Compound (X) was more readily ring closed than the pyruvic acid (VII), the cyclisation being effectively accomplished in one and a half hours at 100°. The product 10,11-dihydro-8-methyl-2-nitrodibenz (b,f) thiepin-10-one (XII) was recovered from the chloroform extract of the diluted reaction mixture in 75% yield. It crystallised from methanol in bright yellow needles. When the purification was effected from benzene-light petroleum it was observed that the yellow crystals gave an almost colourless solution, from which identical coloured needles were recovered on cooling. The oxime of (XII) was conveniently prepared in pyridine solution.

Preparation of 2-(p-Tolylthio)phenylacetic acid

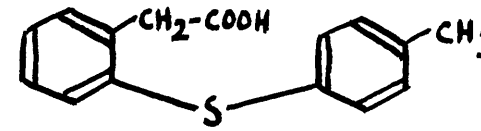
The removal of the undesirable nitro group in (X) by a similar procedure to that adopted in the synthesis of dibenz (b,f) oxepins was investigated. Although

the hydrogenation of (X) (with palladised strontium carbonate in aqueous potassium carbonate solution) proceeded smoothly on a test scale (0.5 g.), when a larger quantity was subsequently reacted, the reaction was completely unsuccessful. The hydrogen was absorbed only with the greatest reluctance (about half the volume required for complete hydrogenation was taken up in six hours) and the solution deteriorated in colour to such an extent that all attempts to recover the starting material or a pure product failed. The sluggishness with which the hydrogen was absorbed suggested that catalyst poisoning (presumably due to the presence of the sulphur atom in (X)) was the cause of the difficulties, for a similar attempt at reduction with fresh catalyst gave no better results. The failure of the hydrogenation on the larger scale was disappointing and insufficient material remained for the proposed preparation of dibenz (b,f) thiepin. Nonetheless, on neutralisation of the test reaction solution, 5-amino-2-(p-tolylthio)phenylacetic acid (XIII) was precipitated and purified from aqueous ethanol. Its hydrochloride formed white needles from aqueous hydrochloric acid. On treatment of the diazonium salt of (XIII) (in aqueous hydrochloric acid) with hypophosphorous acid, the deaminated product,

2-(p-tolylthio)phenylacetic acid (XIV) was isolated, but a subsequent attempt to induce cyclisation with polyphosphoric



(XIII)



(XIV)

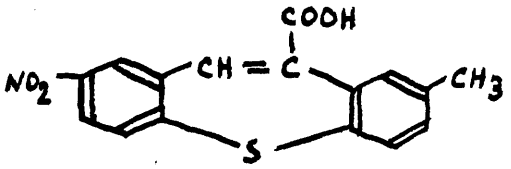
acid on the small quantity of (XIV) was unsuccessful when the conditions previously employed were adopted. Insufficient material was recovered for further investigation of the reaction.

The results of these experiments show that certain nitro-substituted derivatives of dibenz (b,f) thiepin can be readily made available for further study by this method. Although difficulties were encountered in the preparation of the corresponding denitrated compounds it seems reasonable to expect that closer examination of the two more difficult reaction stages (namely, the catalytic reduction of (X) and cyclodehydration of (XIV)) would give encouraging results.

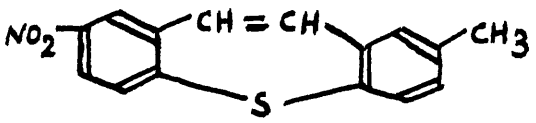
Decarboxylation of 10-Carboxy-8-methyl-2-nitrodibenz (b,f) thiepin

On treatment of (XI) with copper bronze in quinoline

solution, the product which was isolated (50% yield) was not the expected 8-methyl-2-nitrodibenz (b,f)-thiepin (XV). The analysis corresponded to $C_{15}H_{11}NO_2$ and a sodium fusion

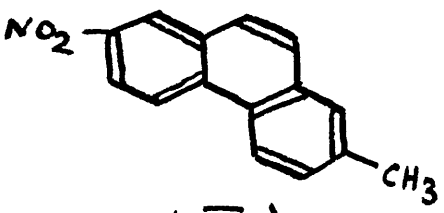


(XI)

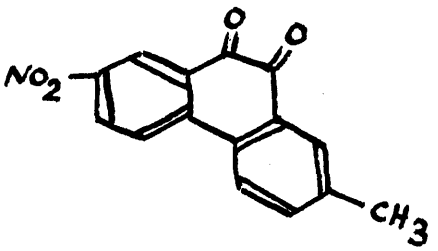


(XV)

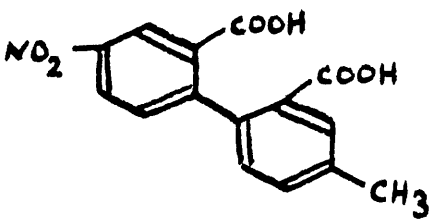
test confirmed the absence of sulphur in the molecule. The product was assigned the structure of 7-methyl-2-nitrophenanthrene (XVI). This was confirmed by the smooth oxidation to 7-methyl-2-nitrophenanthraquinone (XVII), which was further oxidised with hydrogen peroxide in aqueous alkali to 2,2'-dicarboxy-4'-methyl-4-nitrodiphenyl (XVIII).



(XVI)

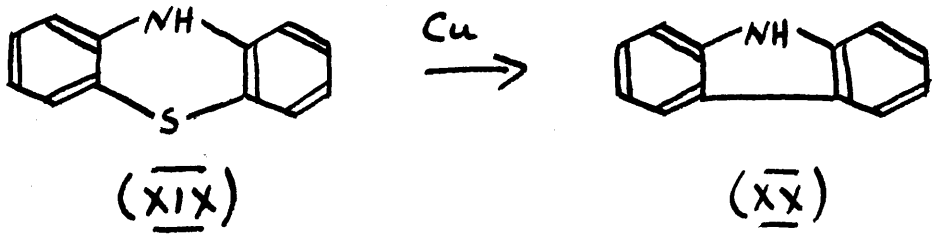


(XVII)

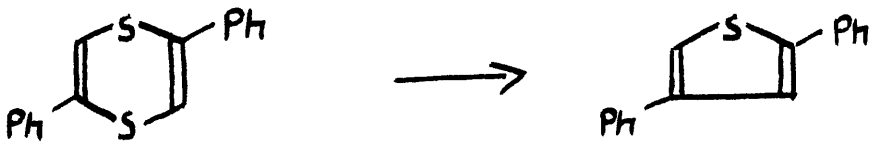


(XVIII)

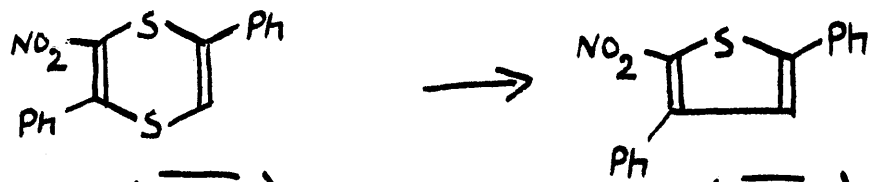
The removal of the sulphur atom recalls the similar elimination from phenthiazine (XIX) with copper to form carbazole (XX) (Goske[8]) and the recent work of Parham and Traynelis[9,10] who have converted (XXI) to (XXII) and (XXIII) to (XXIV) by thermal treatment.



(XIX) (XX)



(XXI) (XXII)



(XXIII) (XXIV)

Experimental

Petrol as solvent refers to light petroleum, b.p. 60°-80°.

5-Nitro-2-(p-tolylthio)benzaldehyde (IV) was obtained from 2-chloro-5-nitrobenzaldehyde and p-thiocresol by the method described by Loudon, et al[5]

2-Methyl-4-(5'-nitro-2'-p-tolylthio)benzylidene-5-oxazolone (V). 5-Nitro-2-(p-tolylthio)benzaldehyde (1 mol.), aceturic acid (1 mol.) and fused sodium acetate (1 mol.) in acetic anhydride were refluxed for one hour and the solution cooled. After 15 hours, the yellow crystals, which had formed, were filtered and washed with acetic acid. Recrystallisation from benzene-petrol afforded 2-methyl-4-(5'-nitro-2'-p-tolylthio)benzylidene-5-oxazolone, m.p. 188-9° as bright yellow crystals. (Found: C, 61.1; H, 4.0. $C_{18}H_{14}N_2O_4S$ requires C, 61.0; H, 3.95%) (Yield = 55%).

α-Acetamido-β-(5-nitro-2-p-tolylthio)phenylacrylic acid (VI). Compound (V) (0.5 g.), ethanol (1.25 c.c.) and concentrated sulphuric acid (0.5 c.c.) were heated until the suspension dissolved. The mixture was allowed to stand 5 minutes and on dilution with water a pale yellow solid precipitated. It was dried and on crystallisation from benzene-petrol, α-acetamido-β-(5-nitro-2-p-tolylthio) phenylacrylic acid was obtained as yellow needles, m.p. 215-6°. (Found: C, 58.2; H, 4.0. $C_{18}H_{16}N_2O_5S$ requires

C, 58.1; H, 4.3%).

5-Nitro-2-(p-tolylthio)phenylpyruvic acid (VII). Compound (VI) (0.3 g.) [or alternatively (V)], hydrochloric acid (7.5 c.c.; 1 part concentrated hydrochloric acid: 2 parts water, by volume), and glacial acetic acid (7.5 c.c.) were refluxed for 5 hours and the solution filtered. After 15 hours, lemon crystals of 5-nitro-2-(p-tolylthio)phenylpyruvic acid, m.p. 143° (from benzene-methanol) (Found: C, 57.8; H, 4.0; N, 4.2. $C_{16}H_{13}NO_5S$ requires C, 58.0; H, 3.9; N, 4.2%) had developed. (Yield 90%). The oxime (VIII), m.p. 169° d. (pale yellow crystals from benzene-methanol) was formed when an aqueous alkaline solution of the pyruvic acid was treated with hydroxylamine hydrochloride and the solution subsequently acidified. (Found: C, 55.6; H, 4.2. $C_{16}H_{14}N_2O_5S$ requires C, 55.5; H, 4.05%).

5-Nitro-2-(p-tolylthio)benzyl cyanide (IX) Compound (VIII) (30 g.) in acetic anhydride (600 c.c.) was refluxed for 2 hours. The solution was cooled, the solvent partially evaporated in vacuo (20 m.m.) and the residue diluted with water. On standing at 0° for 15 hours a yellow solid was obtained, and this was purified twice from benzene (charcoal). On recrystallisation from benzene-petrol, 5-nitro-2-(p-tolylthio)benzyl cyanide, m.p. 80°, (Found: C, 63.2; H, 4.4. $C_{15}H_{12}N_2O_2S$ requires C, 63.3; H, 4.2%) was

isolated as yellow crystals (Yield = 15 g.; 60%).

5-Nitro-2-(p-tolylthio)phenylacetic acid (X). Compound (IX) (10 g.) was hydrolysed by refluxing for 9 hours with aqueous hydrochloric acid (100 c.c.) and glacial acetic acid (100 c.c.). The cooled solution, on dilution with water, afforded a yellow gum, which was dissolved in ether. The aqueous alkaline extract on acidification afforded a precipitate of 5-nitro-2-(p-tolylthio)phenylacetic acid, m.p. 126° (pale yellow crystals from benzene-petrol) (Found: C, 59.5; H, 4.3. $C_{15}H_{13}NO_4S$ requires C, 59.4; H, 4.3%) in 70% yield.

10-Carboxy-8-methyl-2-nitrodibenz (b,f) thiepin (XI) Compound (VII) and polyphosphoric acid were heated with occasional stirring to 160° for 5 minutes and subsequently at 100° for 2 hours. The cooled mixture, on dilution with water, gave a dark-green precipitate which was well washed with water and dried. On purification from benzene-methanol (twice), 10-carboxy-8-methyl-2-nitrodibenz (b,f) thiepin, m.p. 264°, was obtained as colourless crystals. (Yield 70%). (Found: C, 61.1; H, 3.5. $C_{16}H_{11}NO_4S$ requires C, 61.3; H, 3.5%).

10,11-Dihydro-8-methyl-2-nitrodibenz(b,f)thiepin-10-one (XII). Compound (X) (0.5 g.) and polyphosphoric acid were heated 1½ hours at 100°. The diluted reaction mixture was

extracted with chloroform, washed with aqueous sodium carbonate, and dried. When the solvent was evaporated off, an oil was recovered, which was induced to solidify. The solid on dissolving in benzene (charcoal) gave a colourless solution which afforded 10,11-dihydro-8-methyl-2-nitrodibenz-(b,f) thiepin-10-one as yellow needles, m.p. 161° (from methanol for analysis) in 75% yield. (Found: C, 63.4; H, 4.1. $C_{15}H_{11}NO_3S$ requires C, 63.15; H, 3.9%). The oxime prepared in pyridine solution had m.p. 191° (white needles from benzene-petrol) (Found: C, 60.3; H, 4.0. $C_{15}H_{12}N_2O_3S$ requires C, 60.0; H, 4.0%).

5-Amino-2-(p-tolylthio)phenylacetic acid (XIII). Compound (X) (0.5 g.) in aqueous potassium carbonate (0.35 g. in 60 c.c. water) was catalytically hydrogenated with 2% palladised strontium carbonate. When the requisite volume of hydrogen (c. 100 c.c.) had been absorbed, a few crystals of sodium sulphite were added to the solution. The mixture was filtered and neutralised with aqueous hydrochloric acid, whereupon 5-amino-2-(p-tolylthio)phenylacetic acid, m.p. 127°, (cream crystals from aqueous ethanol) precipitated. (Found: C, 66.2; H, 5.4. $C_{15}H_{15}NO_2S$ requires C, 65.9; H, 5.5%). The hydrochloride formed white needles, m.p. 209° d., from aqueous hydrochloric acid. (Found: C, 58.0; H, 5.5. $C_{15}H_{16}ClNO_2S$ requires C, 58.1; H, 5.2%). When

the reduction was attempted on an increased scale (5 g. of the nitro-acid) neither a pure product nor the starting material could be recovered, due to considerable deterioration of the solution during hydrogenation.

2-(p-tolylthio)phenylacetic acid (XIV). Compound (XIII) (0.3 g.) in aqueous hydrochloric acid (10 c.c.) was diazotised with a solution of sodium nitrite. The mixture was gently warmed to dissolve the suspension and filtered. Hypophosphorous acid in excess was then added and after 20 hours, 2-(p-tolylthio)phenylacetic acid, m.p. 112° (straw yellow needles from benzene-petrol) (Found: C, 69.9; H, 5.4. $C_{15}H_{14}SO_2$ requires C, 69.8; H, 5.4%) had precipitated.

7-Methyl-2-nitrophenanthrene (XVI) 10-Carboxy-8-methyl-2-nitrodibenz (b,f) thiepin (2 g.), copper bronze (10 g.) and pure quinoline (50 c.c.) were refluxed for 4 hours. The cooled mixture was diluted with benzene and filtered. The filtrate was washed with dilute sulphuric acid, and the black precipitate of copper sulphide which was obtained was removed by filtration. The benzene layer was separated, and washed with water, aqueous sodium carbonate and water in turn. On removal of the solvent and dilution with methanol, 7-methyl-2-nitrophenanthrene, m.p. 187° (pale yellow crystals from methanol-benzene) was obtained.

(Yield 50%) (Found: C, 75.85; H, 4.6. $C_{15}H_{11}NO_2$ requires C, 75.95; H, 4.6%). When an aqueous solution of chromic acid (slight excess) was added gradually to a solution of (XVI) in hot glacial acetic acid, the resultant dark green solution, on dilution with water, afforded a yellow precipitate of 7-methyl-2-nitrophenanthraquinone (XVII), m.p. 230°d. (orange crystals from benzene-methanol). (Found: C, 67.5; H, 3.5. $C_{15}H_9NO_4$ requires C, 67.4; H, 3.4%). Compound (XVII) (0.2 g.) in methanol (4 c.c.) was treated with bench aqueous caustic soda (1 c.c.) containing hydrogen peroxide (0.5 c.c.; 30%) at 18°. After thorough shaking, a further portion of the oxidising agent (1 c.c.) was added and the whole was allowed to stand 15 hours. The methanol was boiled off and on acidification of the solution, a pale yellow solid precipitated. On crystallisation from benzene-methanol, 2,2'-dicarboxy-4'-methyl-4-nitro-diphenyl, m.p. 184-186°, was obtained as white crystals. (Found: C, 59.7; H, 4.0. $C_{15}H_{11}NO_6$ requires C, 59.8; H, 3.7%).

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