"SYNTHETIC STUDIES IN THE ALKALOID FIELD"

Thesis submitted for the Degree of

Doctor of Philosophy

by

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Summary

The aim of the work has been to devise a method for synthesising 3-(4-carboxymethyl-phenoxy)-4:5-dimethoxy-phenylethylamine on a sufficiently large scale for use in a projected synthesis of cycleanine and of OO'-dimethyltubocurarine chloride.

Part I ACTIVE CHLORO-COMPOUNDS AS INTERMEDIATES

The principal difficulty in the work centres round the formation of the diphenyl ether link. Guaiacol, as a model, condensed with methyl 4-chloro-3:5-dinitro benzoate to give methyl-3:5-dinitro-4-(2-methoxy-phenoxy)-benzoate. The nitro-groups were replaced by iodo-groups, which were satisfactorily removed by reduction. 2:3-dimethoxy-5-(2-phthalimido-ethyl)phenol was prepared and gave methyl 3:5-dinitro-4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoate. Replacement of the nitro-groups with iodine gave by-products together with the di-iodo compound. Further treatment of this gave a small amount of 3-(4-carboxy-phenoxy)-4:5-dimethoxyphenyl-ethylamine.

Methyl 4-chloro-3-nitro-benzoate condensed with guaiacol and isovanillin as models, to give the corresponding diphenyl ethers. The nitro-groups

were satisfactorily removed by conversion to the diazo compounds and treatment with hypophosphorous acid. The same nitro-ester condensed with 3:4-dimethyl-gallaldehyde, to give methyl 3-nitro-4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate, the nitro-group was removed from this, and treatment of the product gave 3-(4-carboxy-phenoxy)-4:5-dimethoxy-phenyl-ethylamine. This last stage merits further investigation.

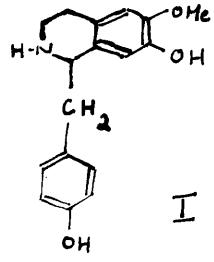
Part II DIPHENYLIODONIUM COMPOUNDS AS INTERMEDIATES

4:4'-Dimethoxycarbonylmethyl-diphenyliodonium salts were prepared and, on treatment with guaiacol gave methyl-4-(2-methoxy-phenoxy)-phenylacetate. Methyl 4-[2-methoxy-5-(2-phthalimidoethyl)-phenoxy]-phenylacetate was prepared similarly from the corresponding phenol, but no product could be obtained after treatment of the iodonium salt with 2:3-dimethoxy-5-(2-phthalimidoethyl)-phenol.

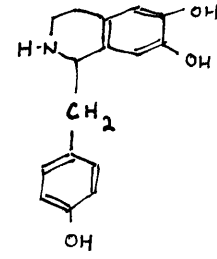
SYNTHETIC STUDIES IN THE ALKALOID FIELD

Introduction

The bisbenzyl*iso*quinoline group of alkaloids comprises some thirty known compounds which possess structures containing two benzyltetrahydro*iso*quinoline nuclei, joined by one, two or three diphenyl ether linkages. Faltis (1) pointed out that all the members of this class could be considered as offsprings of the known alkaloid, coclaurine (I) or of *nor*-coclaurine (II).

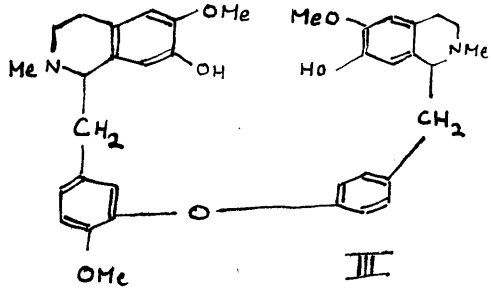


I

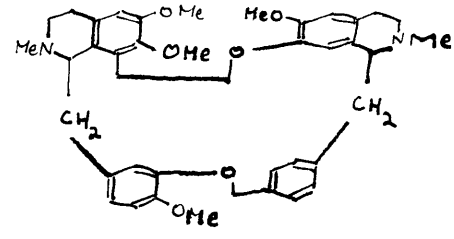


II

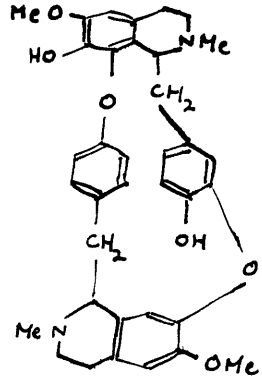
This is exemplified by magnoline (III), *iso*tetrandrine (IV), curine (V), and *iso*chondodendrine (VI). The



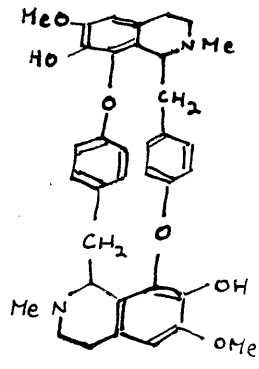
III



IV



V

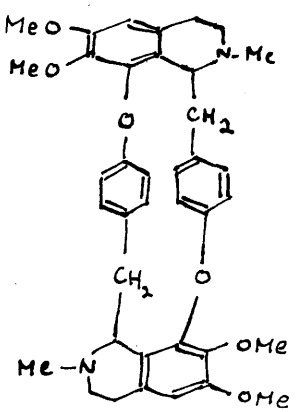


VI

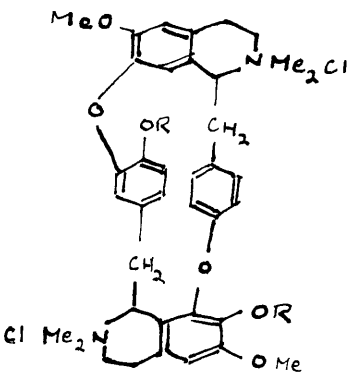
probable biogenetic route to these alkaloids, as Faltis suggested, is through enzymatic oxidative condensation of two molecules of nor-coclaurine, followed by methylation of some or all of the -OH and -NH groups. The structures of the alkaloids fall into two distinct classes: those, e.g. isotetrandrine (IV), in which one link connects the two benzene nuclei and, sometimes, another link joins the two tetrahydroisoquinoline nuclei; and those, e.g. isochondodendrine (VI), which is symmetrical, or curine (V) which is not, in which each of the two links joins a benzene to a tetrahydroisoquinoline nucleus. The compounds within these two classes also differ from one another in the state of methylation of the -OH groups, in the state of the nitrogen system, and in their stereo-chemistry, which is governed by the configurations of two asymmetric carbon atoms in the 1-positions of the isoquinoline nuclei of each of the compounds.

Synthetic work in this field has hitherto been mainly directed to the preparation of compounds of the first type, and there are few records of attempts to prepare compounds of the second type, in spite of the

medicinal importance of some of the members of this class. The aim of our group is to devise a general method of synthesis for compounds in the curine class. Our intention is, however, that the major ring-closure shall take place, not through the formation of the diphenyl ether links, as in the suggested biogenetic synthesis, but through the formation of amide links between the ends of two ω-amino acids. The eventual aim of the present work is the synthesis of two compounds with this type of structure. These are the alkaloid cycleanine (VII) and OO'-dimethyltubocurarine chloride (VIII ; R = Me) which is physiologically more potent than its naturally occurring parent substance, tubocurarine chloride (VIII ; R = H).



VII



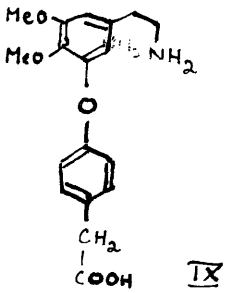
VIII

Cycleanine was isolated by Kondo and his colleagues (2), who applied the technique of chromatographic adsoprtion on alumina to the separation of the alkaloids of Cissampelos insularis and Stepahania cepharantha. By this means they isolated, in addition to alkaloids known to be present, a new crystalline alkaloid whose analysis agreed with that of a bisbenzylisoquinoline alkaloid. Through a comparison of its properties, and those of its derivatives, with samples of isochondodendrine dimethyl ether and derivatives, they established its structure as being fully methylated isochondodendrine. An attempt to synthesis this alkaloid was not successful (3).

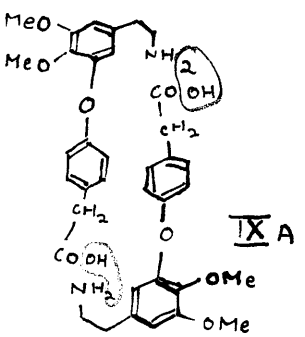
H. King first isolated, from the South American arrow poison, designated tube curare by Boehm (4), its main active constituent, which he named tubocurarine chloride. In 1935 King (5) established its structure, although the positions of one phenolic and one methoxy-group were not settled until 1948 (6). In that year, the formula (VIII ; R = H) was unequivocally established. It is of interest to note that the botanical source of tubocurarine chloride was first identified as

Chondodendrum tomentosum in 1946 (7), although the alkaloid had been under examination for forty years prior to this, d-Tubocurarine now has a wide use in clinical medicine, though principally in abdominal operations. It is claimed in a recent paper (8), which gives no experimental details, that a synthesis of racemic OO'-dimethyltubocurarine iodide has been successfully carried out.

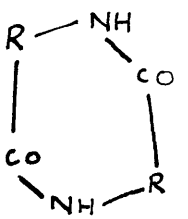
The work under consideration is directed primarily to the synthesis of the amino-acid (IX), which is a possible intermediate in the synthesis of the two compounds mentioned above. It is hoped that two molecules of this amino-acid may be condensed as



IX



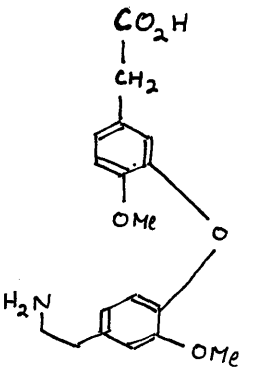
IXA



IXB

indicated (IXA) to give a cyclic di-amide of the form (IXB). Thereafter ring-closure would be effected by standard methods to the bisbenzyldihydroisoquinoline, and reduction, followed by methylation, carried out to give dl-cycleanine. It is hoped that, in a similar

manner, one molecule of the amino-acid (IX) may be condensed with one molecule of the amino-acid (X), which has already been synthesised (9), and the di-amide so obtained made to give, by similar treatment, dl-O<u>O</u>'-dimethyltubocurarine chloride. It will be necessary to separate the diastereo-isomers and for each to be resolved.



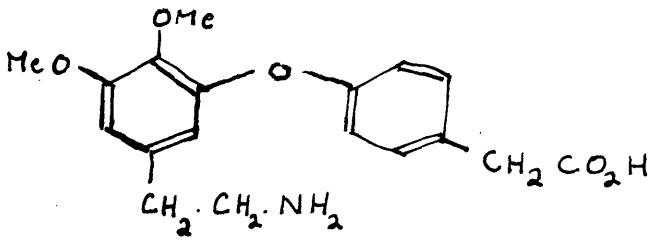
X

Part I

Active Chloro-Compounds as Intermediates

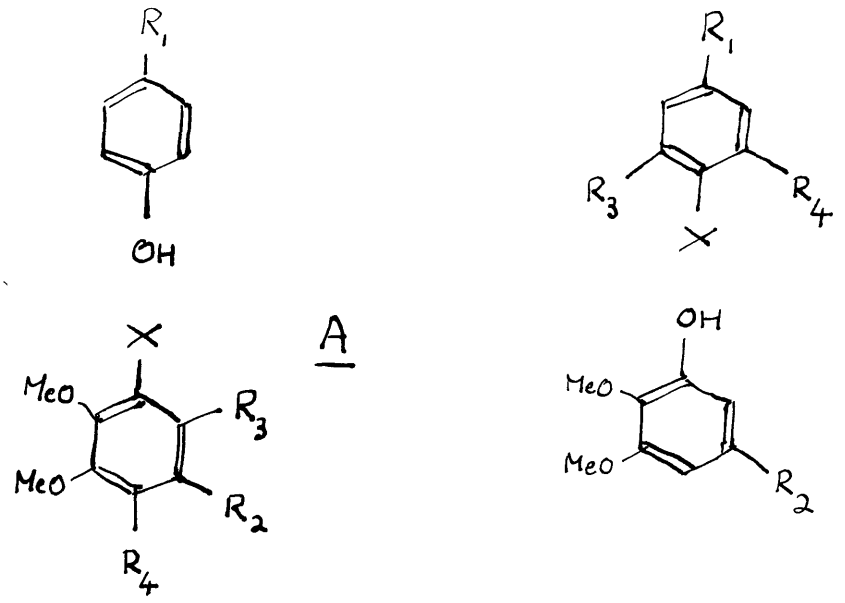
Discussion

The object of this work is to explore possible methods of synthesis of the amino-acid (IX) in order that it may be prepared on a sufficiently large scale for the further series of reactions, leading to the bisbenzyl*iso*quinolines, to be carried out. There are several possible routes to the amino-acid, but the main difficulty in all of them centres round the formation of the phenolic ether linkage.



IX

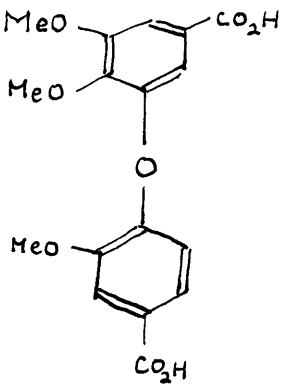
The standard methods available for the preparation of diphenyl ethers all involve, as one of the principal reagents, a phenol, which is condensed with a suitable aromatic compound, substituted with a group such as halide, which is eliminated. The condensation in the present work may be arranged in one of two possible ways, indicated by A and B (X = halide or other suitable



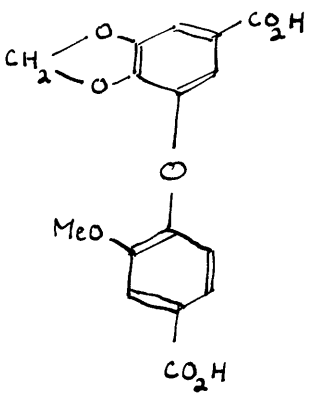
group; R_1 = $-CH_2COOH$, or a substituent which may be converted to it; R_2 = $-CH_2CH_2NH_2$, or a substituent which may be converted to it without interfering with R_1; R_3 and R_4 may be activating groups or hydrogen atoms). Synthesis of starting materials and subsequent removal of any activating groups would be simpler in method B, and accordingly this method of approach was used.

The Ullmann method for synthesis of diphenyl ethers, probably the most widely used method, has been found, in general, unsuitable for the preparation

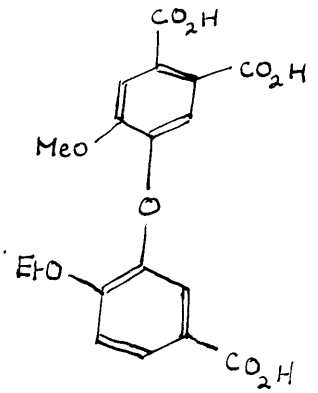
of complex ethers of the type required. Whaley and his colleagues (10) commented on this difficulty, and though they were able to obtain the ether (XII) in 27% yield, they indicated that the conditions under which the reaction had been carried out are not universally suitable. They pointed out the work of Kondo (11), who obtained the similar ether (XIII) in 10% yield, and that of King (12), who was able to prepare (XIV) in only 2% yield. The



XII



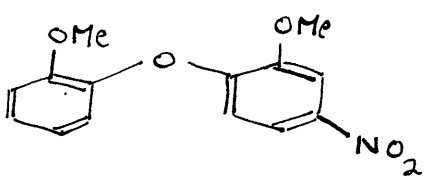
XIII



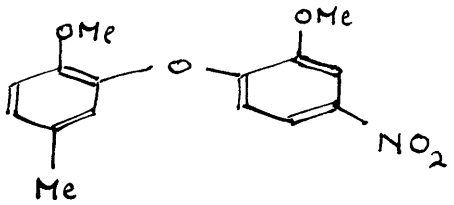
XIV

reaction is probably a nucleophilic substitution, as is indicated by the fact that the yield is improved when the position of attack is activated by electron-attracting groups in the ortho- and para- positions, e.g. nitro-groups. This is shown in work by Grundon (9), who was able to prepare the ethers

(XV) and (XVI) in yields of 37% and 30% respectively, by a method similar to the Ullmann method. These compounds, however, are comparatively uncomplicated,



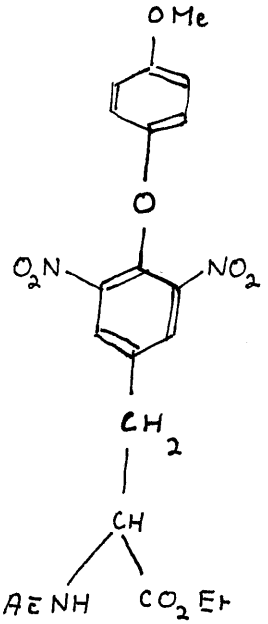
XV



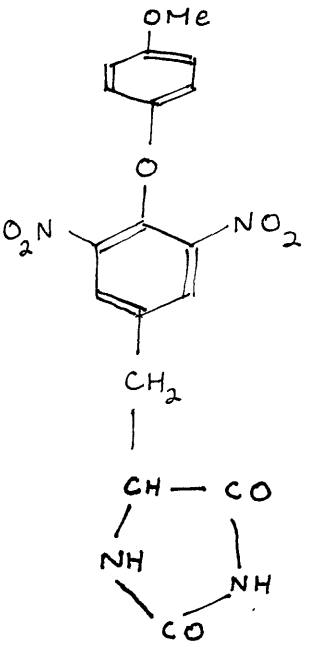
XVI

and fairly obviously, the more complex molecules liable to be used in this work, were less likely to give good yields. Also, since the reaction is carried out under comparatively drastic conditions, the variety of groups which may be present as substituents is severely limited.

A more recent method for preparation of diphenyl ethers, that of Borrows, Clayton and Hems (13), was shown by them to be more useful in the case of phenols with complex substituent groups. The method involves treatment of an active chloro-compound, in pyridine, with a phenol, and by this method they were able to prepare the ethers (XVII) and (XVIII) in



XVII

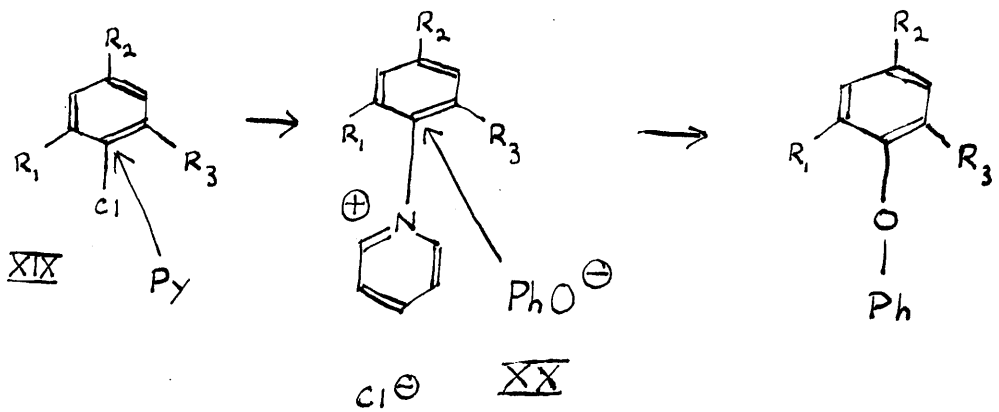


XVIII

yields of 68% and 77% respectively. Diphenyl ethers of this type were obtained by them in yields varying from 50 to 80%, by heating phenols with a dinitro-chloro-compound in pure pyridine. Grundon (9) has shown that a formyl group exerts an activating effect similar to that of a nitro-group in this reaction; and Loudon and Summers (14) showed that with two nitro-groups and a third activating group,

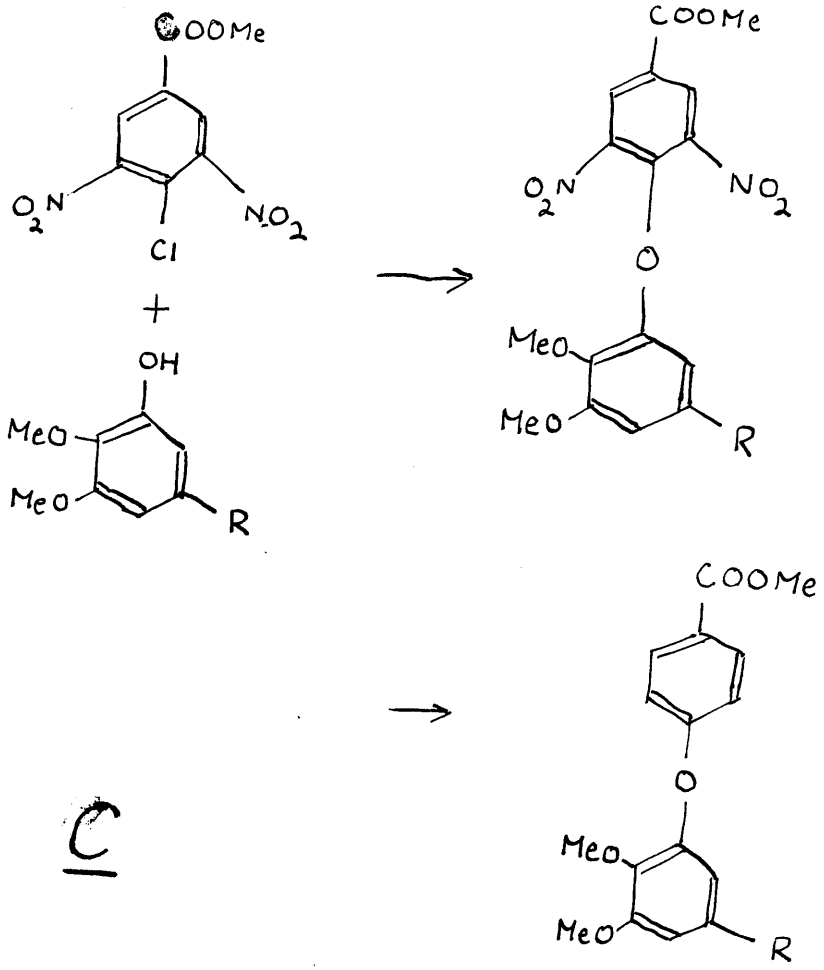
the condensation may be carried out at room-temperature.

The mechanism of the condensation was discussed by Hems (13), who showed it to involve a nucleophilic reaction. The chloro-compound (XIX; R_1, R_2, R_3 are activating groups) is first attacked by pyridine, which displaces the chloro-group, to give the pyridinium salt (XX). This is then attacked in the 1'-position by the ion of ($PhO^{\ominus}$) the phenol. At least two activating groups ortho- or para- to the position of attack were found to be necessary before reaction occurred.

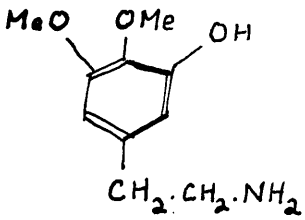


The chloro-compounds to be selected for use in the present work required two or three activating groups in the ortho- or para- positions, and since in the required amino-acid (IX), the para-position is filled by a $-CH_2COOH$ group, it was decided to use a

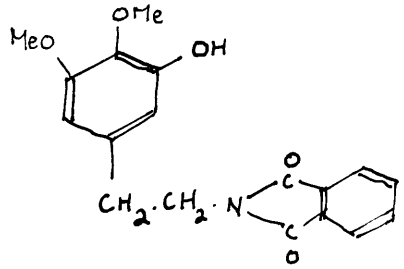
protected carboxy-group in this position. This should be readily convertible to its methyl homologue by an Arnd-Eistert reaction. The scheme first envisaged for the preparation is indicated in diagram C (R = $CH_2CH_2NH_2$ or some substituent which may be converted to it). Condensation would take place in pyridine, and the nitro-groups would then be removed.



The nature of the phenol to be used was of importance in consideration of the work. It seemed best, because of the difficulties which might be encountered in the condensation, that this stage of the scheme should be left until as late as possible. The aminophenol (XXI) appeared to be suitable for use, provided that the amino-group could be conveniently protected. A phthalimido-group has the advantages that it can be readily removed by treatment with hydrazine, and also that it gives compounds of high molecular weight, which are generally fairly easily crystallised. The phthalimido-phenol (XXII) was accordingly prepared and investigated.



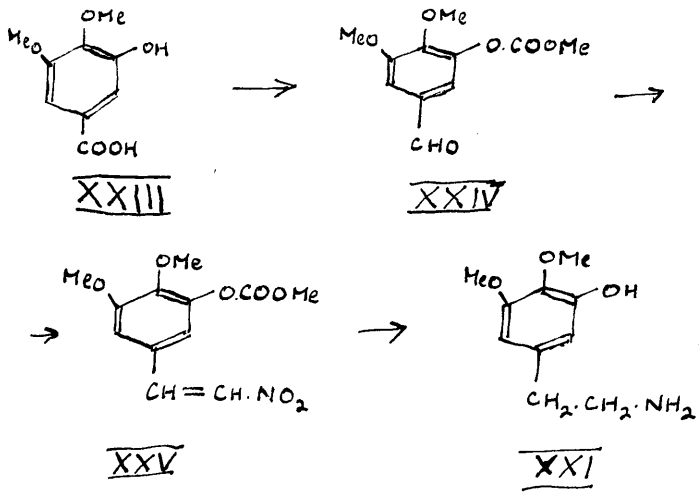
XXI



XXII

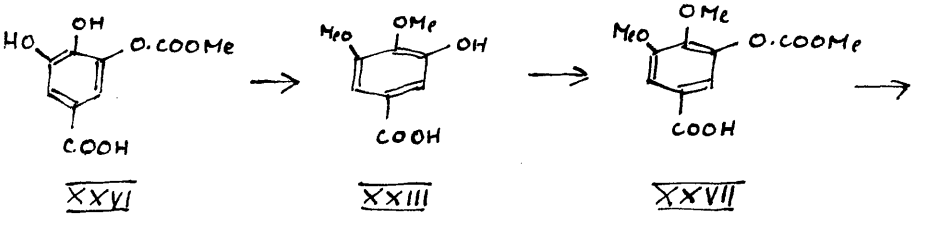
The aminophenol (XXI) had previously been prepared by Späth and Röder (15), and a modification of their method was used. Gallic acid had been

converted to the dimethoxy acid (XXIII) by the method of Fischer and Freudenberg (16), the hydroxyl group of this protected, and the acid chloride prepared. This was reduced, by the Rosenmund method, as described by Mauthner (17), to the aldehyde (XXIV), which condensed with nitromethane to give the nitrostyrene (XXV). Reduction and hydrolysis of this compound gave the required aminophenol (XXI), which was characterised as the hydrochloride.

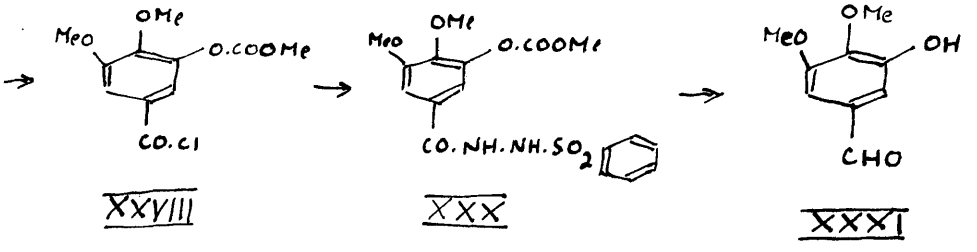


In the present work, gallic acid was converted to its 3-carbomethoxy derivative (XXVI), which was treated with diazomethane. Hydrolysis yielded 63% of 3:4-dimethyl-gallic acid (XXIII). The hydroxyl group was protected by conversion to the carbomethoxy acid (XXVII), and the chloride of this (XXVIII) was prepared in 76% yield. Mauthner (17)

had previously reduced this acid chloride to the corresponding aldehyde (XXIV) by the Rosenmund method. This method, which uses an adulerated catalyst, is notoriously unreliable and accordingly the McFadyen-Stevens method of preparing aldehyde (18) was applied. This method involves treatment of the benzenesulphonylhydrazide of the acid, in ethylene glycol, with sodium carbonate, and in general gives satisfactory results. The acid chloride (XXVIII) was treated with benzenesulphonyl hydrazide to give (XXX), which, on treatment with sodium carbonate, gave 3:4-dimethyl-gallaldehyde (XXXI) in 70% yield from the acid chloride. In a prior investigation of this



XXVI XXIII XXVII



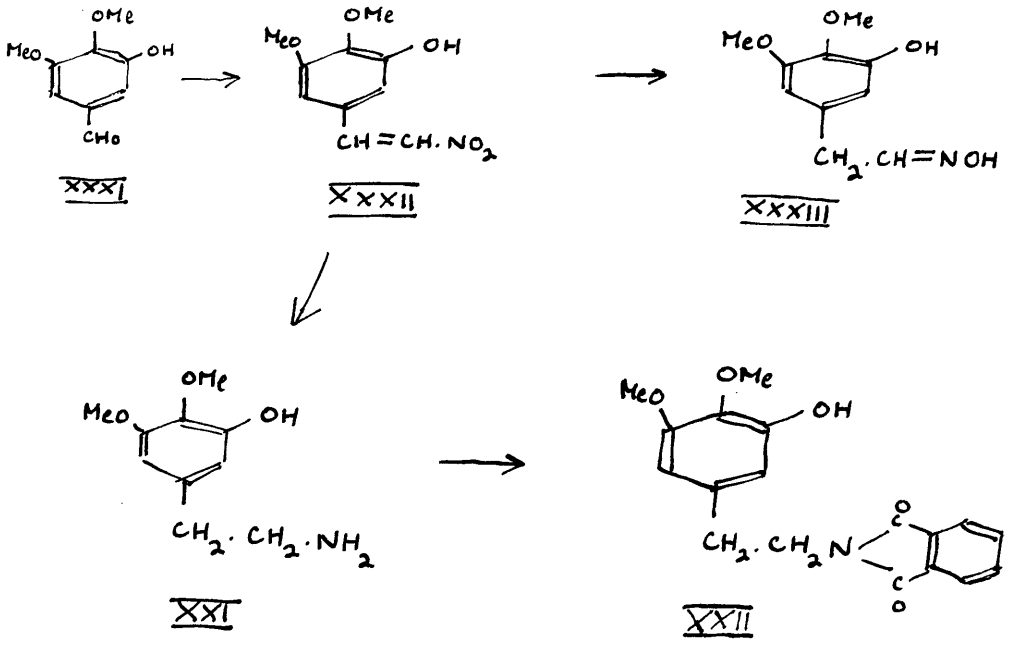
XXVIII XXX XXXI

method, McRae (19) had been unable to isolate the aldehyde by distillation, since the oily product

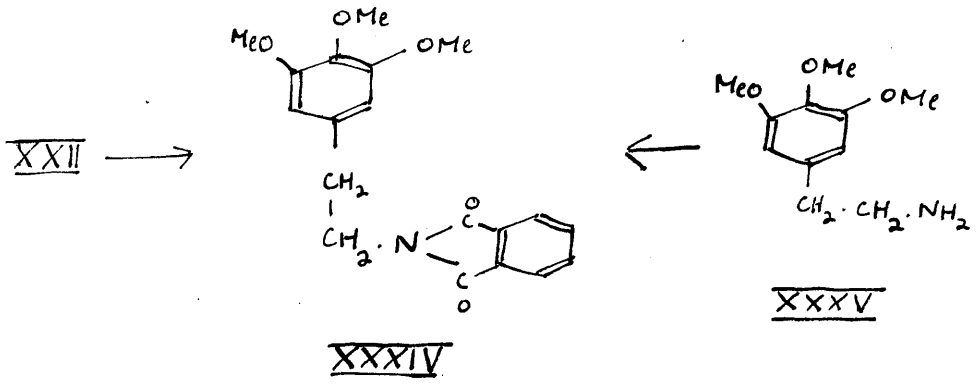
polymerised on heating. This was believed to be due to the presence of sulphinic acids formed as by-products in the reaction, and the difficulty was overcome by washing the ethereal extract of the aldehyde with sodium bicarbonate solution. This method was found to give reliable results, and the aldehyde was obtained from gallic acid in overall yield of 10%.

Späth and Röder (15) had treated the corresponding carboethoxy-aldehyde (XXIV) with nitromethane in alkaline solution to obtain the nitrostyrene (XXV), and reduced this by means of zinc in acetic acid. In the present work two methods of condensation of the aldehyde (XXXI) with nitromethane were investigated. The first method, in presence of alkali, in the cold (20), gave a moderate yield of fairly pure product (XXXII), and a quarter of the aldehyde was recovered in usable condition. The second method, in presence of ammonium acetate in boiling acetic acid (21), gave a rather better yield of a product which required considerably more purification. Eventually the former method was adopted, since impurities in the product from the latter interfered with the subsequent reduction. This reduction was first investigated using palladised

charcoal as catalyst, but only proceeded as far as the oxime (XXXIII), an intermediate stage. Reduction of the pure nitrostyrene proceeded smoothly in presence of platinum catalyst, to give the aminophenol (XXI), which was not isolated in a pure state, but was characterised as the phthaloyl derivative (XXII). The yield of this compound from the aldehyde was 61%.

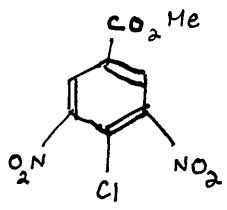


Support was obtained for the structure of the phthalimido-phenol by methylating it with diazomethane, and showing the resulting product (XXXIV) to be identical with the compound obtained from mescalin (XXXV), by treatment with phthalic anhydride in acetic acid.

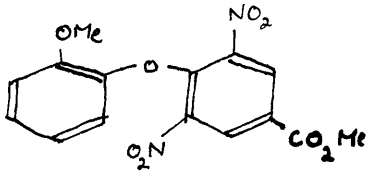


Methyl 4-chloro-3:5-dinitro-benzoate (XXXVI) was prepared, by nitration, followed by esterification, of 4-chloro-3-nitro-benzoic acid. The advantages of using this chloro-compound were that it gave easily crystallised products and that it readily condensed with phenols. It suffered from the disadvantage that removal of both nitro-groups after condensation was likely to give some trouble. The potentialities of this method were therefore first explored using guaiacol as a model. Shaking the chloro-compound with guaiacol in pyridine at room-temperature gave an 80% yield of the desired dinitro-diphenyl ether (XXXVII). Removal of the nitro-groups from this compound was investigated before any

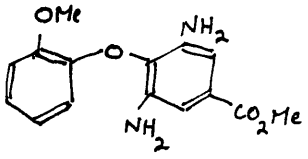
attempt was made to prepare the dinitro-phthalimido-ether.



XXXVI



XXXVII



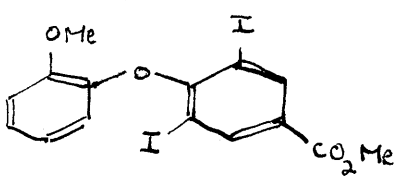
XXXVIII

Reduction of the dinitro-compound might be expected to proceed fairly smoothly, but tetrazotisation is, in general, rather difficult to carry out. (cf. Refs. (22) and (23)). Hems (13) carried out a series of tetrazotisations in a mixture of nitrosyl sulphuric and acetic acids, and found this method to be fairly successful, provided the temperature was carefully controlled. Catalytic reduction of the dinitro-ether (XXXVII) gave the diamine (XXVIII) as an unstable white solid, which was characterised as its di-acetyl derivative. Treatment of this diamine with an acetic/sulphuric acid mixture caused blackening, and the solution gave no identifiable product on tetrazotisation followed by treatment with hypophosphorous acid. The dinitro-compound was therefore reduced in acetic acid, and this time the

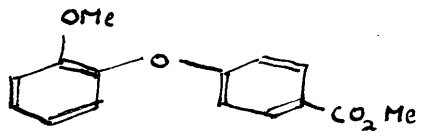
solution turned a clear brown colour on addition to nitrosyl sulphuric acid. From this it would appear that tetrazotisation was successful (cf. Ref. (13 b)), but again no product could be isolated after treatment of the solution with hypophosphorous acid. This apparently indicated that hypophosphorous acid is not a sufficiently strong reducing agent (cf. Ref. (24)) to replace both diazo-groups by hydrogen, i.e. one $-NH_2$ or $-N_2HSO_4$ group was probably still present in the product. An attempt to diazotise only one of the amino-groups by carrying out the reaction under the more usual aqueous conditions also failed to give any of the desired ether. As soon as the di-amine came into contact with mineral acid, blackening occurred, and neither neutral, nor basic products could be isolated after treatment of the diazotised solution with hypophosphorous acid.

Hems, in his work on the synthesis of thyroxine (13) had prepared diphenyl ethers similar to (XXXVII), with two nitro-groups adjacent to the ether-oxygen, and had been able to replace these nitro-groups by

iodine atoms. It was suggested that a similar replacement in the present case, followed by catalytic reduction to remove the iodine, might prove a possible route to the required diphenyl ether. The dinitro-ether (XXXVII) was reduced in acetic acid, tetrazotised in nitrosyl sulphuric acid, and treated with sodium iodide (cf. Ref. (13)). This yielded the di-iodo-ether (XXXIX) in 21% yield, and catalytic hydrogenation of this in presence of diethylamine (cf. Barltrop; reduction of methiodides; Ref. (25)) gave an 80% yield of the ether (XL). This was hydrolysed to the corresponding acid, which was shown to melt at the same temperature as that previously prepared by Ungnade (26) by another method.

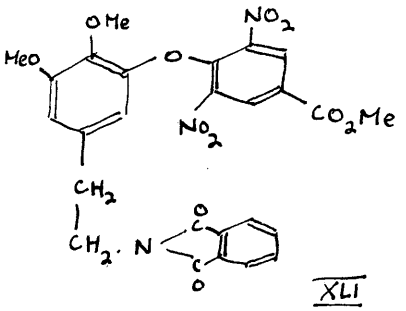


XXXIX

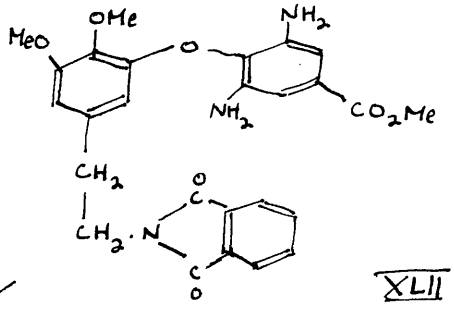


XL

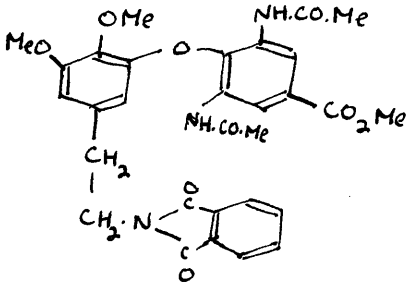
Since this approach had proved moderately successful in the simplified case, attempts were made to carry out the corresponding series of reactions using the phthalimido-phenol (XXII). This reacted with (XXXVI) under similar conditions to those applied to guaiacol, to give a 90% yield of the di-nitro ether (XLI). This was reduced catalytically to give an unstable product, characterised as the di-amine (XLII) by conversion to its di-acetyl derivative (XLIII). A small scale investigation of the more direct route to the ether (XLIV) by treatment of a tetrazotised solution of the diamine with hypophosphorous acid, was carried out, but proved to be fruitless.



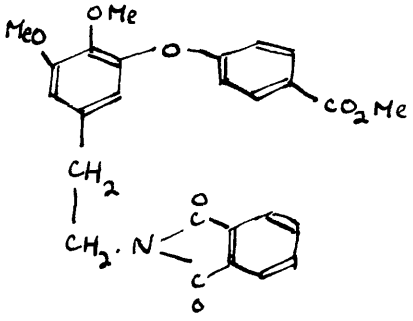
XLI



XLII

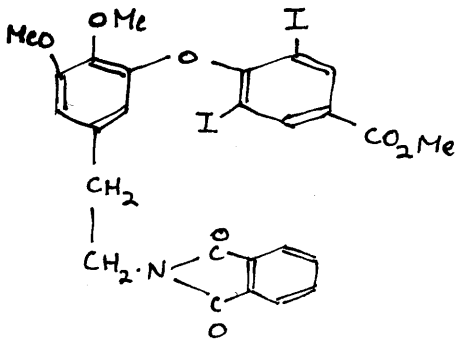


XLIII

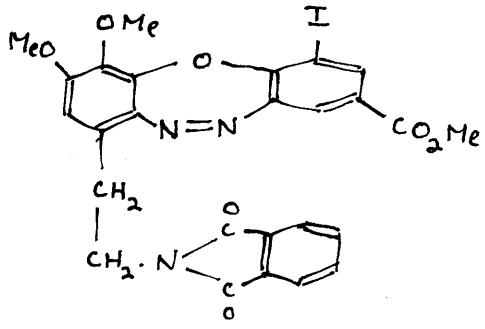


XLIV

Since the nitro-groups had been successfully removed from the model compound, by replacement with iodine and hydrogenation, the corresponding series of reactions was carried out on the dinitro-ether (XLI). This was hydrogenated in acetic acid, using platinum catalyst, and the solution tetrazotised in nitrosyl sulphuric acid. The tetrazonium solution was added to a sodium iodide solution, and a mixture of products was isolated from the reaction-mixture. Chromatography of the mixture afforded two products, the required di-iodo ether (XLV), and a second compound believed to be (XLVI).



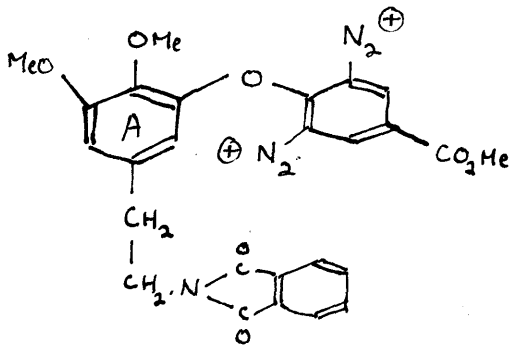
XLV



XLVI

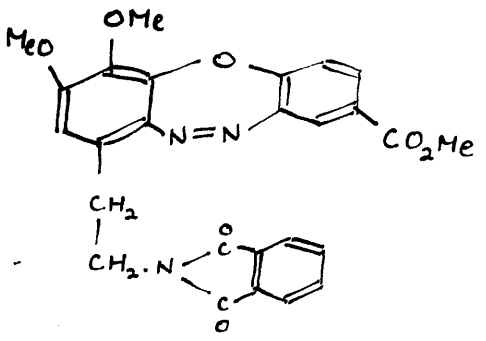
Formation of a compound such as (XLVI) might logically be expected in a reaction of this type. It is sterically favoured, and the reactive nature

of ring A (Diagram XLVII), due to the substituent methoxy-groups and the phthalimidoethyl-group, increases the likelihood of ring-formation, which is

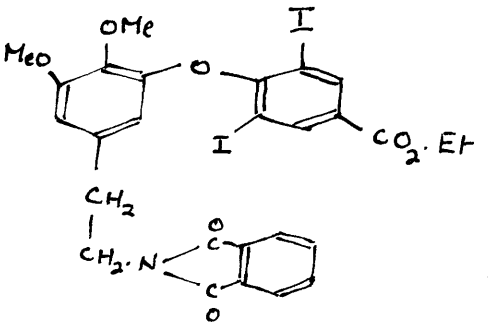


XLVII

known to occur in similar simpler cases (cf. Ref. (27)). The structure suggested for the product is supported by the analysis figures, by the bright orange colour, which might be expected in a compound with a conjugated system containing a -N=N- link, and by the infra-red absorption spectrum (IR-I). Support for the suggested structure was also obtained by reducing the compound on palladium black, in presence of di-ethylamine (cf. Ref. (25)). A bright yellow, readily crystallised product was obtained, and the analysis figures for this agree with the expected structure (XLVIII).



XLVIII



XLIX

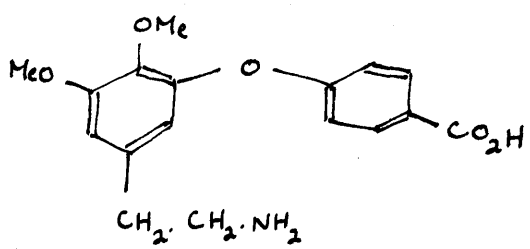
The reaction was repeated several times under the same conditions, but the crystalline mixture obtained could not be separated into the two components. On one occasion, a colourless crystalline product, differing in its melting-point from (XLV) was obtained in low yield. The analysis figures for this suggest that it has the structure (XLIX), the ester methyl-group having been replaced, under the conditions of reaction, by an ethyl-group. The infra-red absorption spectrum (IR-II) of the di-iodo compound (XLV) was compared with (IR-I) and with the infra-red spectrum of the mixture (IR-III). A semi-quantitative comparison of these three spectra indicated that the

mixture contained a higher proportion of the required di-iodo-compound (XLV) than of the by-product (XLVI). Support for this evidence was obtained from hydrogenation of the mixture in presence of diethylamine. The product was separated into a colourless oil and a quantity of the crystalline compound (XLVIII). The proportion of oily material in the product, approximately 80% of the total, indicated the predominance of the di-iodo-compound (XLV) in the unreduced mixture. The difficulty encountered in separation of the mixture was believed to depend on the relative proportions of the components, and also on the activity of the chromatographic alumina.

Removal of the nitro-groups from (XLI) by replacement with iodine may therefore be regarded as only moderately successful. Although most of the product isolated from the reaction-mixture was the required di-iodo-compound, in an estimated yield of 20%, the difficulty encountered in separation from the by-product, and the greater difficulty likely to be found in carrying out the separation on a larger scale, make it unsuitable as a preparative route to the required ether (IX).

In an attempt to proceed to this ether, the di-iodo-compound (XLV) was hydrogenated in presence of diethylamine, but the product could not be

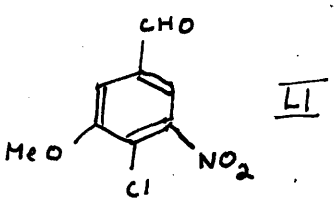
crystallised. The oil obtained was treated with dilute alkali, but, probably due to opening of the phthalimido ring, the hydrolysis product did not crystallise. The method of Sheehan (28) was used to remove the phthaloyl group. Treatment of the hydrolysis product with hydrazine gave a small quantity of crystalline product, whose analysis indicated the structure (L), and whose infra-red absorption spectrum (IR-IV) confirmed the amino-acid structure. The amount of this product, however,



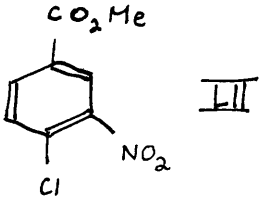
L

was insufficient to proceed with, by the Arnd-Eistert reaction, to the amino-acid (IX). The low yield (5%) was probably due to difficulty in isolation of the product rather than to failure of the reactions.

In view of the difficulty encountered in removing two nitro-groups from the diphenyl ethers, investigations were made of a reaction scheme similar to that already described, but involving the use of only one nitro-group together with a carbomethoxy-group to activate the chloro-compound. As has already been pointed out, the method of Hems (13), which employs two nitro-groups to achieve this activation, was discussed by Grundon (9), who showed that when one of the nitro-groups was replaced by a formyl group, a similar effect was obtained. Grundon showed that 4-chloro-3-methoxy-5-nitro-benzaldehyde (LI) condenses with phenols in boiling pyridine to give the corresponding diphenyl ethers in yields of from 45 to 65%.



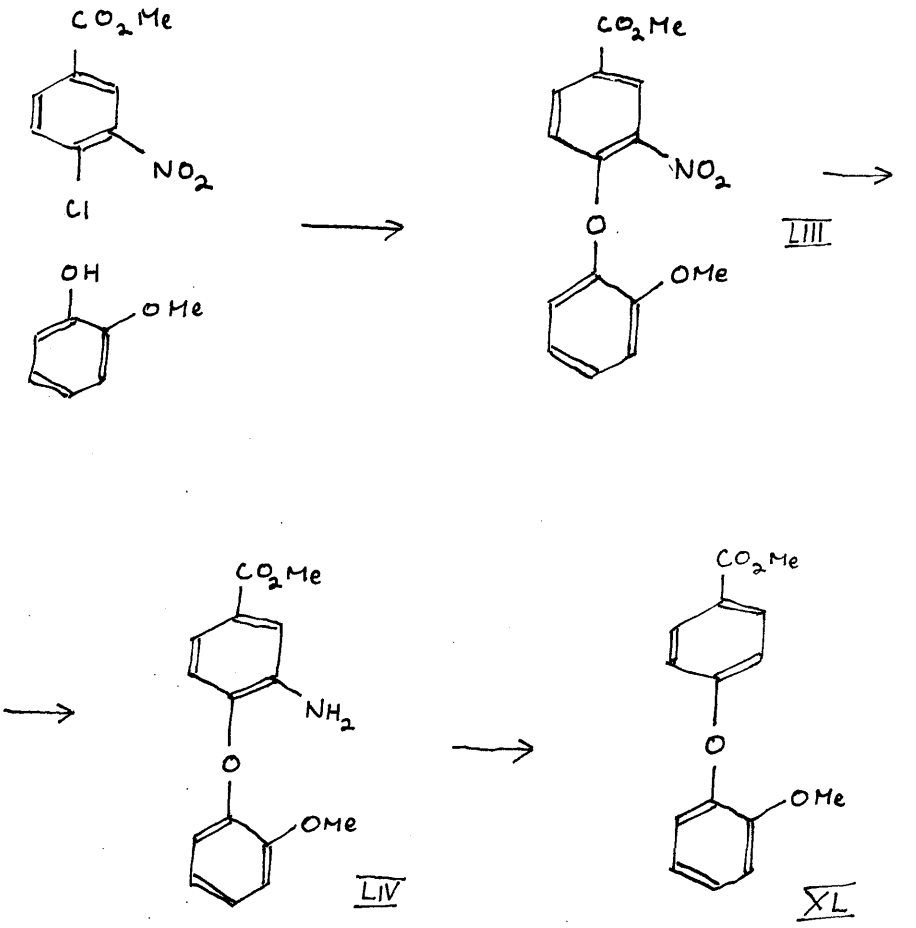
LI



LII

Accordingly methyl 4-chloro-3-nitro-benzoate (LII) was prepared by esterification of the corresponding acid and was found to condense with

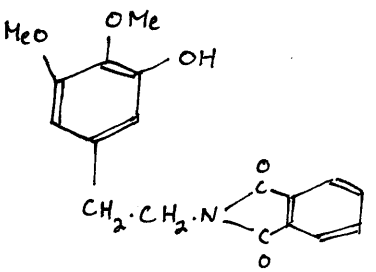
guaiacol to give the nitro-ether (LIII) in 51% yield. Although Hems (13) states that an excess of phenol raises the yields in this reaction, in the present work, the phenolic components are the more valuable, since they require more stages in preparation. Optimum yields of ethers were therefore obtained when equimolar quantities of the two reactants were used. The success of this condensation indicated that, provided that the nitro-group could be readily replaced by hydrogen, a similar method might prove successful with the phthalimido-phenol (XXII). The nitro-ether (LIII) was therefore catalytically reduced to the amine (LIV) in 90% yield, and this was characterised as its acetyl derivative. The amine, on diazotisation under aqueous conditions, followed by treatment with hypophosphorous acid, gave a 43% yield of the ether (XL), which was shown to be identical with that previously prepared by a different route (p. 23). The yield over this series of reactions (diagram D) was 20%.



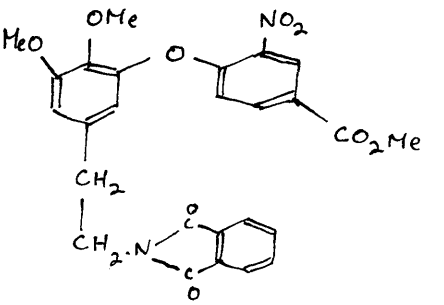
D

Since this scheme of reactions had proved successful in the simplified case, attempts were now made to condense the phenol (XXII) with methyl 4-chloro-3-nitro-benzoate, with a view to carrying out a similar scheme corresponding to D. The two reactants were heated together in pyridine, but none of the required product (LV) could be isolated.

Since in no case could any crystalline product or starting phenol be recovered from the reaction-mixture, it appears that the phthalimido-group is unstable to boiling pyridine.

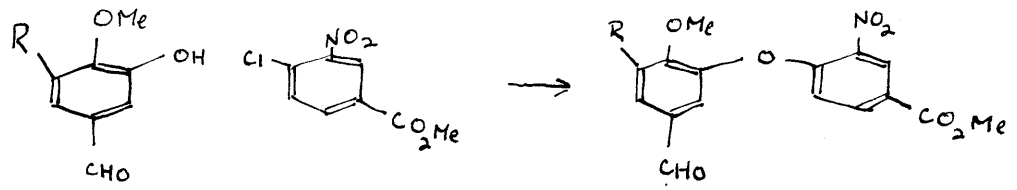


XXII

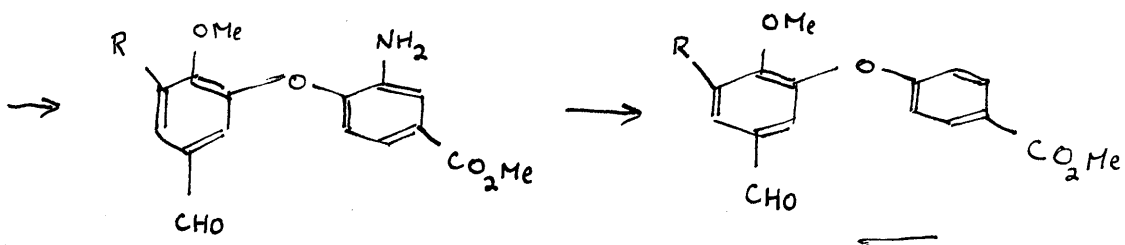


LV

Since this line of approach through the phthalimido-phenol did not appear to be very promising, consideration was given to a scheme (Diagram E; R = OMe) of preparing an ether with the phenolic aldehyde (XXXI). This method suffered from the disadvantage that, even if the ether (LVII; R = OMe) could be prepared, several more stages would be required to give the required amino-acid (IX).



LVI



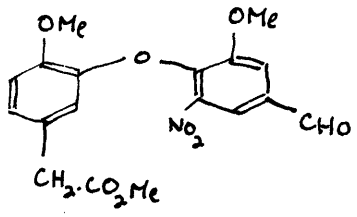
LVII

E

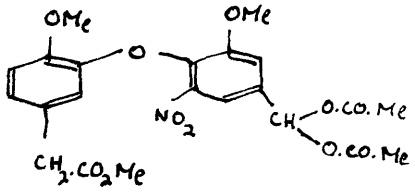
The scheme was first investigated using isovanillin as a model (Diagram E; R = H). Isovanillin condensed with methyl 4-chloro-3-nitro-benzoate to give a 51% yield of the ether (LVI; R = H), which was characterised as the 2:4-dinitrophenylhydrazone and the semicarbazone. It appeared that more of the required ether was

present in the mother liquors, but an attempt to recover this, by preparation and subsequent decomposition of the semicarbazone was not successful.

The nitro-group of this ether could not be hydrogenated directly, apparently due to inhibition by the formyl group. Grundon (9) had been able to reduce the nitro-group of the ether (LVIII) by converting it to the diacetate (LIX) before hydrogenation. Accordingly the nitro-formyl ether (LVI; R = H) was acetylated with acetic anhydride.



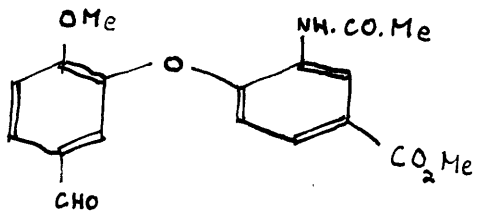
LVIII



LIX

The gummy product was hydrogenated after washing with water, but this method proved to be unreliable, since the acetylamino compound (LX) was sometimes obtained, probably due to the presence of unhydrolysed acetic anhydride. The structure of this by-product

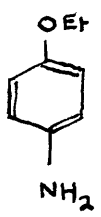
was confirmed by comparison with an authentic specimen prepared from the crystalline di-acetate (see below) and also by preparation of the dinitro-phenylhydrazone. Washing the gummy di-acetate with ethanol before hydrogenation was found to remove satisfactorily any excess of acetic anhydride, and though after this it was found possible to crystallise the product, the trouble involved was considerable, and in general, after washing with ethanol, the product was hydrogenated in its gummy state.



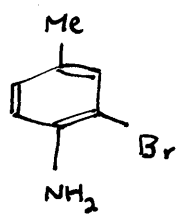
LX.

In previous work on the dinitro ether (XLI) (p. 25), attempted removal of the nitro-groups had resulted in ring-formation with the diazo-group, on tetrazotisation of the diamine obtained by reduction. This was apparently due to the activating effect of the methoxy groups, and since interference from a similar source might be expected in the present case,

some method of avoiding this difficulty was sought. Roe (29) had devised a method of removing amino-groups by diazotisation in presence of fluoboric acid, and subsequent reduction of the precipitated fluoborates. It seemed that, in the present case this immediate precipitation of the diazofluoborate might prevent ring formation. Roe had been able to remove the amino-groups from p-Phenetidine (LXI) in 54% yield and from 2-bromo-4-methyl-aniline (LXII) in 60% yield by this method, and accordingly



LXI



LXII

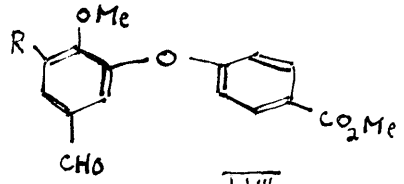
investigation of this method was carried out on the model compound. The gummy diacetate was reduced and diazotised in presence of sodium fluoborate and the precipitated gum was reduced with zinc in ethanol. The desired ether (LVII; R = H) was isolated in 19% yield and characterised as the 2:4-dinitrophenyl-hydrazone.

However, diazotisation in aqueous solution in absence of borofluoride, followed by treatment with hypophosphorous acid, was found to give a better yield (45%) of the same ether, and this method was therefore preferred. Diazotisation in nitrosyl sulphuric acid gave a 51% yield of the product, but this required considerable purification, and this method was not developed.

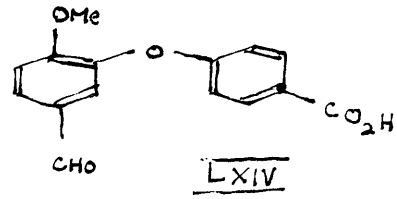
These experiments showed that the phenolic aldehyde could be satisfactorily converted to the corresponding ether (LVII; R = H) in the case of the model compound, in an overall yield of 23%, and an attempt was therefore made to proceed to the corresponding phenylethylamine (LXIII).

Hydrolysis of the ether (LVII; R = H) to the corresponding acid (LXIV) proceeded in 94% yield, and this condensed, in alkaline solution, with nitromethane to give the nitrovinyl derivative (LXV) in 86% yield. An attempt to condense the acid (LXIV) with nitromethane in presence of acetic acid and ammonium acetate failed to give any of the desired product. Hydrogenation of the nitrostyrene, however, gave only a 22% yield of very impure phenylethylamine (LXIII), which gave the phthalimido compound by a

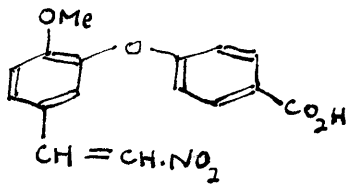
method similar to that described by Sheehan (30)



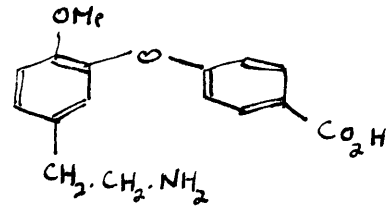
LVII



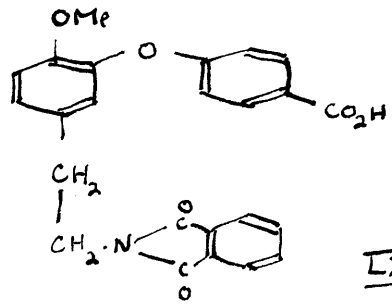
LXIV



LXV



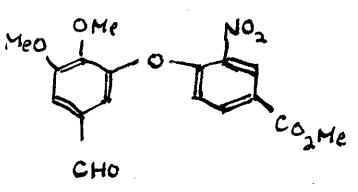
LXIII



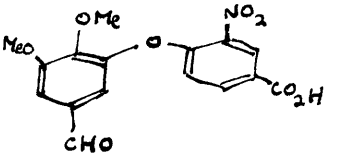
LXVI

in 29% yield. Although these experiments gave only a small yield (5% overall) of this last product, this was probably due to difficulty in isolation of the amino-acid (LXIII) and the yield is almost certainly capable of considerable improvement.

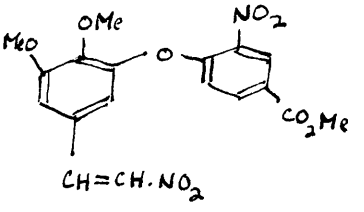
With this route now available to the ether, investigations were carried out using 3:4-dimethyl-gallaldehyde (XXXI) (See diagram E; R = -OMe). This condensed to give a 42% yield of the ether (LXVII), which proved very difficult to crystallise. The corresponding acid (LXVIII) was also isolated in 5% yield as a by-product, and was re-methylated with diazomethane to give (LXVII) in 85% yield. More of the required product was shown to be present by treating a portion of the mother liquors with 2:4-dinitrophenylhydrazine, but although this showed that much of the aldehyde was still present, no more could be isolated. The aldehyde condensed with nitromethane to give a product which was not the expected nitro-styrene (LXIX).



LXVII



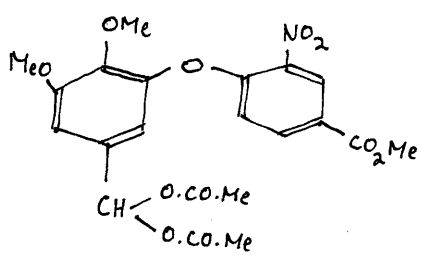
LXVIII



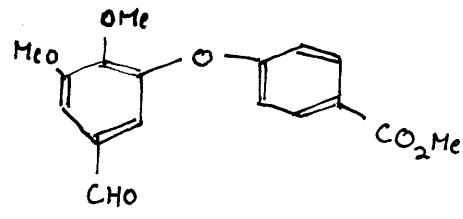
LXIX

In considering removal of the nitro-group, the

method found to be most successful in the case of the model compound was first investigated. The nitro-ether (LXVII) was diacetylated with acetic anhydride, and though the benzylidene diacetate (LXIXa) could not be isolated, the gummy product, after washing with ethanol, was hydrogenated with platinum catalyst. The reduced product was diazotised and treated with hypophosphorous acid. Distillation of the product gave the desired aldehyde (LXX). A small quantity of unchanged starting material was



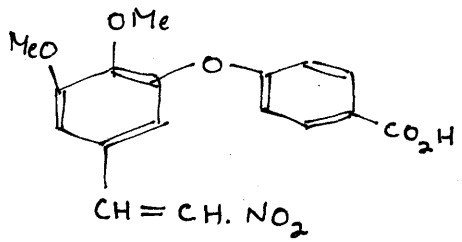
LXIXa



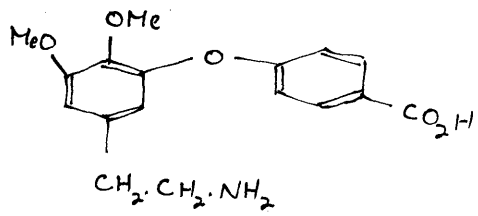
LXX

recovered, and allowing for this, the yield of the required ether was 68%. This yield is considerably higher than that obtained with the model compound, constituting an overall yield of 28% from the phenol. This may be regarded as a very satisfactory synthesis of the ether.

Some attempt was made to proceed to the amino-acid (LXXII). A small scale hydrolysis of the ether gave an acid which could not be crystallised, but which condensed in alkaline solution with nitro-methane, to give the nitrostyrene (LXXI). In a subsequent repetition of this experiment, the product could not be crystallised. The crude gum obtained

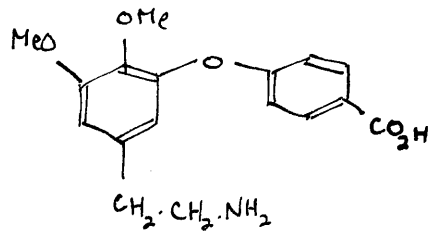


LXXI

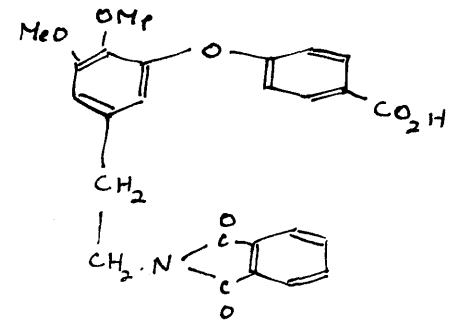


LXXII

was therefore hydrogenated, and a very small quantity of crystalline product obtained. The infra-red absorption spectrum of this was almost completely identical with that of the product from the di-nitro-ether (L) (IR-IV). The oil which did not crystallise after hydrogenation was converted by a method parallel to that of Sheehan (3) to the phthalimido-derivative, which analysed approximately for (LXXIII).

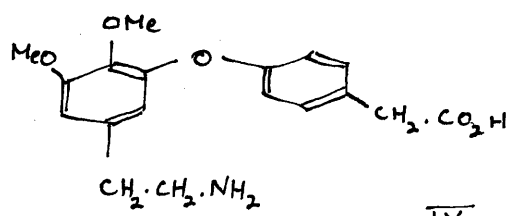


L



LXXIII

In view of the difficulties encountered in dealing with the di-nitro ethers, the method of preparing the required ether through the phenolic aldehyde and the mono-nitro ether is much more satisfactory. With a little further work on the formyl-ether (LXX), this should lead to a satisfactory synthesis of the required amino-acid (IX).



IX

Experimental

Original work only is described in detail. Yields and melting-points given in brackets are those quoted under the reference given. Melting-points are uncorrected.

3-Carbomethoxy-gallic acid (XXVI)

This was prepared by the method of Fischer and Freudenberg (16). Treatment of gallic acid (100g.), in alkaline solution, with methyl chloroformate gave 3-carbomethoxy gallic acid (40g.; 37%) in fairly pure white needles, m.p. 207-209° (36%; m.p. 204-207°).

3:4-Dimethyl-gallic acid (XXIII)

This was prepared by a modification of the method of Fischer and Freudenberg (16). 3-Carbomethoxy-gallic acid (10g.) on treatment with ethereal diazomethane, and removal of the ether, gave methyl-(3-carbomethoxy-4:5-dimethyl)-gallate (13g.) as an uncrystallisable brown oil. This was hydrolysed by stronger alkali than that used in Fischer's method (loc. cit.). It was heated under reflux for one hour with a little methanol and 20% aqueous caustic potash (130cc.). Acidification of the cooled solution precipitated the acid, which crystallised from aqueous methanol in colourless needles (6.8g.; 63%), m.p. 184-190°. (74%; m.p. 192-193°).

3-Carbomethoxy-4:5-dimethyl-gallic acid (XXVII)

This was prepared by Mauthner's method (17). 3:4-Dimethyl gallic acid (12.7g.) in alkaline solution, gave, on treatment with methyl chloroformate, colourless

needles of 3-carbomethoxy-4:5-dimethyl-gallic acid (12.9g.; 80%), m.p. 140-143° (92%; m.p. 146-147°).

3-Carbomethoxy-4:5-dimethyl-galloyl chloride (XXVIII)

This compound was prepared by Mauthner's method (17). Treatment of 3-carbomethoxy-4:5-dimethyl-gallic acid (5g.) with phosphorous pentachloride gave white prisms of the acid chloride (5.2g.; 95%), m.p. 60-65°, (100%; m.p. 65-66°).

3-Carbomethoxy-4:5-dimethyl-galloyl benzenesulphonyl hydrazide (XXX).

This was prepared by a modification of the method of McRae (19). 3-Carbomethoxy-4:5-dimethyl-galloyl chloride (4.2g.) was dissolved in the minimum quantity of benzene and added, portionwise with shaking, to benzenesulphonyl hydrazide (2.9g.) in pyridine (10cc.). The mixture was shaken for one hour at room temperature, poured into iced dilute acid, and the precipitate collected. Concentration of the organic layer of the solution gave a further quantity of solid. The combined solids crystallised from ethanol in white prisms of 3-carbomethoxy-4:5-dimethyl-galloyl benzenesulphonyl hydrazide (4.3g.; 75%), m.p. 166-169° (78%).

3:4-Dimethyl-gallaldehyde (XXXI)

3-Carbomethoxy-4:5-dimethyl-galloyl benzenesulphonyl

hydrazide (5g.) was dissolved in ethylene glycol (70cc.) and heated in a bath to 160°. Dry sodium carbonate (6.2g.; considerable excess) was added as rapidly as possible, with good shaking. Considerable effervescence occurred, and after 75 seconds, the reaction was stopped by addition of water (50cc.). The solution was acidified with dilute sulphuric acid and extracted with ether (6 x 30cc.). After the ether solution had been washed, first with sodium hydrogen carbonate solution and then with water, the solvent was evaporated, and the brown oil left was distilled, b.p. 150-155° (bath)/0.5mm. 3:4-Dimethylgallaldehyde (1.735g.; 70%) was obtained as a colourless oil. A sample crystallised from light petroleum (b.p. 60-80°) in colourless needles, m.p. 59-59.5° (60-61°; Ref. (17)). (Found: C, 59.1; H, 5.6. Calc. for $C_9H_{10}O_4$C, 59.3; H, 5.5%).

A sample was used to prepare the 2:4-dinitrophenylhydrazone, which crystallised from glacial acetic acid in red needles, m.p. 264-265°. (Found: C, 49.8; H, 4.1. $C_{15}H_{14}O_7N_4$ requires C, 49.8; H, 3.9%).

3-Hydroxy-4:5-dimethoxy-ω-nitrostyrene (XXXII)

a 3:4-dimethyl-gallaldehyde (1.728g.) was dissolved in methanol (10cc.) nitromethane (0.48g.) added, and the solution cooled to 0°. A cooled (0°) solution of sodium hydroxide (0.4g.) in ethanol (2cc.)/water (minimum quantity) was added dropwise, with good stirring, over 15 minutes. No precipitate was observed (cf. Ref. (20)). After stirring had been continued for a further 15 minutes, water (5 cc.) was added, and the solution poured slowly into a large excess of 30% hydrochloric acid, this being stirred by hand. The fine yellow precipitate was filtered with some difficulty, and crystallised from ethanol in yellow needles of the required nitrostyrene (1.07g.; 50%), m.p. 165-170°. A portion was recrystallised twice from ethanol for analysis, m.p. 168-170°. (Found: C, 53.6; H, 5.1. $C_{10}H_{11}O_5N$ requires C, 53.4; H, 4.9%). This product was sufficiently pure, after one crystallisation, for reduction in the next stage of the synthesis. The aqueous ethanolic filtrate from the precipitated nitrostyrene was extracted with ether, which was washed with sodium hydrogen carbonate solution and

evaporated. Distillation of the residue gave a yellow oil, consisting mainly of unchanged 3:4-dimethyl-gallaldehyde (0.43g.; 25% of the original material) in a sufficiently pure state for repetition of the preparation.

b 3:4-Dimethyl-gallaldehyde (4.7g.), glacial acetic acid (20cc.), nitromethane 5cc.) and ammonium acetate (2g.) were heated under reflux for 2 hours (cf. Ref. (21)). The solution, by now dark brown, was poured into water, and the yellowish-brown precipitate filtered with great difficulty. It crystallised from ethanol in yellow-brown needles, m.p. 150-170°, which required several recrystallisations before being sufficiently pure for the next stage of the series. Eventually yellow needles (4.07g.; 69%) were obtained, m.p. 160-170°; mixed m.p. with product from a showed no variation. No unchanged aldehyde could be recovered.

Reduction of 3-hydroxy-4:5-dimethoxy- - nitrostyrene

a The nitrostyrene (0.4g.) in ethyl acetate was added to palladium/charcoal and aqueous sulphuric acid (4cc.; 10%). The mixture was shaken with hydrogen at atmospheric pressure and room-temperature until

absorption ceased (2 hr.). The catalyst was removed, and the aqueous layer separated. The ethyl acetate was washed with water and the combined aqueous solutions passed through a column of ion-exchange resin (Amberlite IR-4B) and evaporated to dryness. Crystals were obtained on cooling, and these crystallised from water in colourless needles, of 3-hydroxy-4:5-dimethoxy-phenylacetaldehyde oxime (XXXIII), m.p. 200°. (Found: C, 56.5; H, 6.4. $C_{10}H_{13}O_4N$ requires C, 56.7; H, 6.2%).

b The nitrostyrene (0.61g.) was again hydrogenated, under the same conditions except that pre-reduced platinum oxide was used as catalyst instead of palladium/charcoal. The amount of hydrogen required (4 mol.) was absorbed in 1 hour, and the aqueous layer was treated as before. On evaporation, a gummy mass was obtained, and on standing with ethanol (5 cc.) a white solid separated (0.41g.; 77%). This crystallised from 90% ethanol to give a white powder, m.p. 123-159°. Repeated crystallisation did not improve the melting-point, and analysis gave no definite indication of the required phenylethylamine (XXI).

2:3-Dimethoxy-5-(2-phthalimidoethyl)-phenol (XXII)

The crude crystalline product (0.30g.), obtained as above from the reduction of the nitrostyrene, was heated under reflux with phthalic anhydride (0.24g.; 1.05 mol.) in acetic acid for ½ hour. The resultant solution was poured into cold water and the white precipitate was collected (0.45g.; 91%). It crystallised from ethanol in colourless prisms, m.p. 219-221°. (Found: C, 66.0; H, 5.5. $C_{18}H_{17}O_5N$ requires C, 66.0; H, 5.2%). On subsequent occasions the gum obtained from the aqueous solution after passing it through the ion-exchange column was treated directly with phthalic anhydride in acetic acid. A 91% yield of the phthalimidoethyl compound (based on the nitrostyrene) was obtained.

Methylation product of 2:3-dimethoxy-5-(2-phthalimidoethyl)-phenol

The phthalimidoethyl-phenol (0.3g.), in a mixture of methanol, moist ether and tetrahydrofuran, was treated with an excess of diazomethane, prepared in an ether/tetrahydrofuran mixture. After the solution had been allowed to stand for 48 hours, it was evaporated to dryness, and the white solid obtained

crystallised from ethanol in colourless needles (0.25g.; 80%). m.p. 168-169°. (Found: C, 66.8; H, 5.4. $C_{19}H_{19}O_5N$ requires C, 66.9; H, 5.6%). The compound did not depress the m.p. of N-phthaloyl mescalin.

N-Phthaloyl mescalin (XXXIV)

Mescalin sulphate (0.3g.) and phthalic anhydride (0.15g.) in glacial acetic acid were heated under reflux for 1 hour and the solution then poured into cold water. The precipitate crystallised from ethanol in colourless needles, (0.3g.; 85%), m.p. 167-169°. (Found: C, 66.8; H, 5.5. Calculated for $C_{19}H_{19}O_5N$: C, 66.9; H, 5.6%).

Methyl 4-chloro-3:5-dinitro-benzoate (XXXVI)

4-Chloro-3-nitro-benzoic acid (10g.) was dissolved in concentrated sulphuric acid, heated in a bath to 75°, and potassium nitrate (25g.) added (cf. Mauthner, Ref. (31)). The temperature of the solution was slowly raised to 140° and maintained there for 1½ hours. The solution was then cooled and water added to give a yellow precipitate of 4-chloro-3:5-dinitro-benzoic acid. This crystallised from benzene in yellow prisms (9.9g.; 81%), m.p. 156-159°. These crystals were

converted to the desired ester by the method of Ullmann and Bielecki (32). Treatment of the acid (9.9g.) with hydrogen chloride in methanol yielded pale yellow needles of methyl 4-chloro-3:5-dinitro-benzoate (8.7g.; 80%), m.p. 104-105°.

Methyl 3:5-dinitro-4-(2-methoxy-phenoxy)-benzoate (XXXVII)

Methyl 4-chloro-3:5-dinitro-benzoate (1.3g.), guaiacol (0.62g.; 1 mol.) and pyridine (8cc.) were shaken together at room temperature for 30 hours, and then added to water (40cc.). The gummy precipitate was collected and crystallised from ethanol (charcoal) in yellow needles (1.39g.; 80%), m.p. 134-140°. These crystals darkened on standing in daylight. A portion of the product was recrystallised from ethanol, m.p. 134-136°. (Found: C, 51.9; H, 3.6. $C_{15}H_{12}O_8N_2$ requires C, 51.7; H, 3.5%).

Di-acetyl derivative of methyl 3:5-diamino-4-(2-methoxy-phenoxy)-benzoate (XXXVIII)

Methyl 3:5-dinitro-4-(2-methoxy-phenoxy)-benzoare (0.56g.) in ethyl acetate was shaken in hydrogen with pre-reduced platinum oxide, at atmospheric pressure and at room-temperature. When 6 mols. of hydrogen had been absorbed, the catalyst was removed, and

the solution evaporated at room-temperature under reduced pressure. The diamino-compound was obtained as a white solid, m.p. 176-191°, which darkened on exposure to air. This was acetylated with acetic anhydride in the presence of dilute caustic soda solution. On allowing the solution to stand, a white flocculent precipitate of the diacetate was obtained, and this crystallised from ethanol in very fine white needles (0.58g.; 95%), m.p. 236-238°. (Found: C, 61.2; H, 5.4. $C_{19}H_{20}O_6N_2$ requires C, 61.3; H, 5.4%).

Attempted tetrazotisation of the diamine and reduction, by hypophosphorous acid, of the tetrazonium salt

a The dinitro-compound (0.5g.) in ethyl acetate, was reduced to the diamine, and the catalyst and solvent then removed. The solid obtained proved to be soluble in glacial acetic acid (10cc.) only with difficulty, and addition of concentrated sulphuric acid (5cc.) caused the solution to turn black. Tetrazotisation in glacial acetic (10cc.)/nitrosyl sulphuric acid (prepared with sodium nitrite (0.2g.) and concentrated sulphuric acid (10cc.)) at 0° was followed by treatment with excess of hypophosphorous acid (20cc.; 30%). The mixture was allowed to stand for 24 hours at 0°, and

extracted with ether. The extract was washed with dilute acid, alkali, and finally water, but, on evaporation, yielded only a trace of red oil.

b An attempt was made to diazotise only one of the amino-groups, by carrying out the reaction in dilute solution. The solid di-amine (0.4g.) was treated with dilute mineral acid, and again blackening occurred. The solution at 0° was diazotised with aqueous sodium nitrite (0.1g.) and after ½ hour, excess of hypophosphorous acid was added. The solution was left overnight in the refrigerator, and then extracted with ether. The extract was washed with dilute alkali and water, but no appreciable product could be obtained from it. The acid mother liquors were neutralised, but extraction gave only a brown oil, in insufficient quantity for identification.

c The dinitro-compound (1g.) was reduced in glacial acetic acid, and the solution, after removal of catalyst, added very slowly, with good stirring, to a glacial acetic/nitrosyl sulphuric acid mixture, the temperature being maintained at -2° -0°. The colourless solution became pale red, and was added after some time, to hypophosphorous acid (30% solution)

in excess. Once again no workable product was isolated from the mixture, after it had been allowed to stand overnight at 0°.

Methyl 3:5-di-iodo-4-(2-methoxy-phenoxy)-benzoate (XXXIX)

Methyl 3:5-dinitro-4-(2-methoxy-phenoxy)-benzoate (2g.) was shaken with glacial acetic acid (15cc.) and pre-reduced platinum oxide (0.2g.) in hydrogen at atmospheric pressure. When 6 mols. of hydrogen had been absorbed (1 hour), the catalyst was removed and the solution added dropwise over 40 minutes to a stirred and cooled (-2°-0°) solution prepared by cautious dilution with glacial acetic acid/(15cc.) at about 0°, of a solution of sodium nitrite (1g.) in concentrated sulphuric acid (20cc.). When the addition of the diamine solution was complete, the orange-coloured solution, semi-solid, owing to crystallisation of the acetic acid, was stirred for 1 hour at 0° and then added portionwise over 5 minutes, to a well stirred solution of sodium iodide (4g.), iodine (3.4g.), and urea (0.5g.) in water (260cc.) covering a layer of chloroform (50cc.). No attempt was made to cool the mixture, the temperature of which rose to about 35°. Stirring was continued for 1½ hours after the addition had been completed and,

after a black tarry precipitate had been removed by filtration, the chloroform layer was separated. The aqueous layer, together with precipitate, which contained a high proportion of undissolved iodine, was washed twice with chloroform and the combined chloroform solution washed with water. Free iodine was then removed from the chloroform solution by covering it with an aqueous solution of sodium sulphite and passing in sulphur dioxide. The solution was again washed with water, and evaporated to dryness to leave a brown gum. This was purified by being passed, in acetone, through an alumina column. Evaporation of the acetone left a solid residue, which crystallised from ethanol in pale brown needles of the di-iodo compound, m.p. 131-135° (0.67g.; 21%). (Found: C, 35.6; H, 2.6; I, 49.6. $C_{15}H_{12}O_4I_2$ requires C, 35.4; H, 2.4; I, 59.9%).

Methyl 4-(2-methoxy-phenoxy)-benzoate (XL)

Methyl 3:5-di-iodo-4-(2-methoxy-phenoxy)-benzoate (0.5g.) was hydrogenated at atmospheric pressure and room-temperature in ethyl acetate, using pre-reduced platinum oxide as catalyst, and in presence of di-ethylamine (0.2g.) (cf. Ref. (25)). The solution was filtered and washed with dilute acid, and the

solvent evaporated. The colourless oil obtained distilled at 154° (bath)/0.5mm. and the distillation product crystallised from ethanol in colourless prisms of the required ester, m.p. 66-67° (0.22g.; 80%) (Found: C, 69.8; H, 5.3. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%). The product was hydrolysed in aqueous methanol with potassium hydrogen carbonate, methanol was evaporated, and the solution acidified. The precipitate crystallised from light petroleum (b.p. 80-100°) in colourless prisms, m.p. 156-157°. 4-(2-methoxy-phenoxy)-benzoic acid had previously been prepared by a different method by Ungnade (26), who found it to have m.p. 159°.

Methyl 3:5-dinitro-4-[2:3-dimethoxy-5-(2-phthalimido-ethyl)-phenoxy]-benzoate (XLI)

2:3-dimethoxy-5-(2-phthalimidoethyl)-phenol (XXII) (0.146g.), methyl 4-chloro-3:5-dinitro-benzoate (0.176g.; 1 mol.) and pyridine (10cc.) were shaken together at room-temperature for 36 hours. The dark red solution was dissolved in chloroform, which was well-washed with dilute mineral acid and alkali. After the chloroform had been removed, an oil was left, and this crystallised from ethanol in pale yellow plates

of the dinitro-phenoxy-benzoate (0.220g.; 90%), m.p. 184-186°. (Found: C, 56.5; H, 3.6; N, 7.6. $C_{26}H_{21}O_{11}N_3$ requires C, 56.6; H, 3.8; N, 7.6%).

A portion of this ester was hydrolysed to the corresponding dinitro-acid. The ester was heated under reflux in methanolic aqueous potassium hydrogen carbonate. The precipitate obtained on acidification of the solution crystallised from ethanol in bright yellow needles, m.p. 201-204°. (Found: C, 56.0; H, 3.8; N, 7.7. $C_{25}H_{19}O_{11}N_3$ requires C, 55.9; H, 3.6; N, 7.8%).

Di-acetyl derivative (XLIII) of methyl 3:5-diamino-4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoate (XLII)

The dinitro-phenoxy-benzoate prepared above (0.175g.) was hydrogenated in glacial acetic acid (5cc.) using pre-reduced platinum oxide catalyst and under atmospheric conditions of temperature and pressure. When 6 mols. of hydrogen had been absorbed, the catalyst was removed and the solution treated with sodium hydroxide solution (5cc.; 20%) and acetic anhydride (0.4cc.). The mixture was shaken for ½ hour and then extracted with chloroform. The brown gum left on removal of the chloroform

crystallised from ethanol in white needles of the diacetyl compound (0.141g.; 77%), m.p. 190-192°. (Found: C, 62.3; H, 5.1. $C_{30}H_{29}O_9N_3$ requires C, 62.6; H, 5.2%).

Attempted removal of the nitro-groups from the di-nitro-ether

Methyl 3:5-dinitro-4-[2:3-dimethoxy-5-(2-phthalimido-ethyl)-phenoxy]-benzoate (0.72g.) in glacial acetic acid (20 cc.) was reduced at atmospheric temperature and pressure, using pre-reduced platinum oxide catalyst. When 6 mols. of hydrogen had been absorbed, the solution was filtered, and run, with good stirring, into a well-cooled (-2°-0°) mixture of glacial acetic acid (10cc.) and nitrosyl sulphuric acid (prepared from sodium nitrite (0.5g.) and concentrated sulphuric acid (20cc.). The addition took 1½ hours and the solution turned red. It was then added, dropwise over 20 minutes, to ice-cold hypophosphororous acid (75cc.; 30%). This was allowed to stand at 0° for 40 hours and then at room-temperature for 24 hours, before being extracted with chloroform. The extract was washed with alkali and acid, but on evaporation left only a minute quantity of a coloured oil. No products could be isolated from the neutralised acid and alkaline washings.

Methyl-3:5-di-iodo-4-[dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoate (XLV)

The 3:5-dinitro-benzoate (1.117g.) in glacial acetic acid (25cc.) was added to pre-reduced platinum oxide (0.15g.) and hydrogenated at atmospheric pressure and room-temperature. When the required quantity of hydrogen (6 mol.) had been absorbed (2 hrs.) the catalyst was removed, and the solution added dropwise, over 1 hours to a cooled (-2°-0°) stirred solution of sodium nitrite (0.5g.) in concentrated sulphuric acid (20cc.) and glacial acetic acid (10cc.). The red-brown solution was stirred for a further 1 hour and the run fairly rapidly, with good stirring, into a solution of sodium iodide (2g.), iodine 1.7g.) and urea (0.2g.) in water (130cc.) over chloroform (50cc.). No attempt was made to keep the mixture cool, and after the addition was complete, the mixture was stirred for a further 1½ hours. The organic layer was then separated and the aqueous layer washed with chloroform. The combined chloroform extracts were allowed to stand with sodium sulphite solution, and sulphur dioxide gas passed in to remove excess of iodine. The solution was washed with water, and the chloroform removed. The oily redidue was

dissolved in acetone and passed through a short column of acid-washed alumina to remove impurities. Since the residue on evaporation of acetone would not crystallise, it was redissolved in acetone and chromatographed on a long column of alkali-free alumina.

Elution with acetone gave a colourless fraction, which yielded a solid on evaporation. This crystallised from ethanol in colourless prisms (0.21g.; 15%) of the required di-iodo compound, m.p. 140-142°. (Found: C, 43.8; H, 3.7; I, 35.6. $C_{26}H_{21}O_7NI_{22}$ requires C, 43.8; H, 3.0; I, 35.6%).

Further elution with acetone gave a coloured fraction, yielding a red oil on evaporation. This crystallised from ethanol in orange prisms of 1-iodo-3-methoxycarbonyl-9:10-dimethoxy-7-(2-phthalimidoethyl)-dibenz(b,f)(1,4,5)-oxadiazepine (XLVI) (0.483g.; 39%), m.p. 192-195°. (Found: C, 50.8; H, 3.6; N, 6.9; I, 19.3. $C_{26}H_{20}O_7N_3I$ requires C, 50.9; H, 3.3; N, 6.9; I, 20.7%).

Attempted repetition of the previous preparation

The dinitro-benzoate (2g.) was hydrogenated in glacial acetic acid, the solution tetrazotised by adding dropwise over ½ hour to a stirred nitrosyl sulphuric

(sodium nitrite (0.3g.) in concentrated sulphuric acid (35cc.))/glacial acetic (25cc.) acid mixture. The solution was then added with stirring to sodium iodide (3.5g.), iodine (3g.) and urea (0.4g.) in water (200cc.) over chloroform (70cc.). The chloroform was separated, the aqueous layer washed with chloroform and excess of iodine in the combined chloroform solutions removed as before. The residue on evaporation was dissolved in acetone, and chromatographed on neutral alumina, but no separation of the products could be achieved. Acetone was evaporated, and the residual oil dissolved in dry benzene and again chromatographed on neutral alumina. Three fractions were taken and the residues on evaporation crystallised from ethanol. The first was pale red, m.p. 134-174°, the second a darker red, m.p. 132-175°, and the third dark red, m.p. 136-178°, but the infra-red spectra of all three fractions were identical in every respect. (IR-III). Comparison with the spectra of the pure di-iodo compound (IR-II) and of the pure iodo-oxadiazepine (IR-I), indicated a predominance, in the spectrum of the mixture, of the peaks shown in the spectrum of the di-iodo

compound. The three fractions were combined and recrystallised from ethanol in mixed red prisms, (1.6g.) m.p. 135-175°. (Found: I , 30.2%). By repeated crystallisation of this mixture from ethanol, one pure component, believed to be Ethyl-3:5-di-iodo--4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoate (XLIX) was obtained in colourless prisms, m.p. 170-172° (Found: C, 44.6; H, 3.3%. $C_{27}H_{23}O_7NI_2$ requires C, 44.6; H, 3.2%). No other pure fraction could be obtained from this mixture. Subsequent experiments yielded mixed products similar to these, and no more of either the required di-iodo compound or of the dibenzoxadiazepine was obtained in a pure state.

3-(4-carboxy-phenoxy)-4:5-dimethoxy-phenylethylamine (L)

The di-iodo compound (0.298g.) was dissolved in ethyl acetate with diethylamine (0.1cc.) (cf. Ref. (25)). The solution was hydrogenated at atmospheric pressure and room-temperature, and although it did not absorb any measurable amount of hydrogen, it was filtered, washed with dilute acid, and evaporated to dryness. An oil was obtained, and although several attempts to crystallise it were unsuccessful, it was separated from impurities which were less soluble in benzene.

Benzene was removed, and the oil (0.154g.) made up in 10% chloroform solution. The infra-red spectrum of this solution indicated the presence of phthalimido and ester groups, Chloroform was then removed, the oil dissolved in methanol, and hydrolysed by standing for 24 hours with an excess of sodium hydroxide solution (20cc.; 2 $\bar{N}$). Methanol was removed under reduced pressure, and the solution acidified. The gummy precipitate was extracted with chloroform, but on evaporation this yielded no crystalline material. The product was heated for 2 hours with alcoholic hydrazine hydrate (5cc.; 5$\bar{M}$) and evaporated to dryness under reduced pressure. The oily residue was warmed at 50° with hydrochloric acid (10cc.; 2$\bar{N}$) for 10 minutes and left for $\frac{1}{2}$ hour to cool. The aqueous layer was decanted, the flask washed several times with water, and the combined aqueous solutions passed through a column of ion-exchange resin (Amberlite IR-4B). The residue on evaporation of water crystallised with some difficulty from aqueous ethanol (90%), in white prisms (0.064g; 5%) of the required amino-acid, m.p. 220-231° (Found: C, 63.6; H, 6.2. $C_{17}H_{19}O_5N$ requires C, 64.3; H, 6.0%). The infra-red absorption spectrum of this compound was

measured in 'nujol' (IR-IV).

Reduction of the substituted iodo-dibenz-oxadiazepine

The compound (0.30g.) was hydrogenated at room-temperature and atmospheric pressure in ethyl acetate with diethylamine (0.1cc), using palladium black as catalyst. When absorption of hydrogen had ceased, the solution was filtered, washed with dilute acid and evaporated to dryness. The residue crystallised from ethanol in yellow needles of 3-methoxycarbonyl-9:10-dimethoxy-7-(2-phthalimidoethyl)-dibenz-(b,f)(1,4,5)-oxadiazepine (XLVIII)(0.23g.; 96.5%), m.p. 217-224° (Found: C, 64.3; H, 4.2; N, 8.2. $C_{26}H_{21}O_7N$ requires C, 64.3; H, 4.3; N, 8.6%).

Reduction of the mixture obtained by iodination

The red crystalline mixture obtained from an iodination (0.5g.) was dissolved in ethyl acetate, hydrogenated in presence of palladium black and diethylamine (0.2cc.) and after filtration and acid-washing of the solution, evaporated to dryness. The only product which could be obtained from the oil left on evaporation was a yellow crystalline solid, shown by m.p. and mixed m.p. to be the de-iodo oxadiazepine (0.08g.) obtained in the previous preparation.

Methyl 4-chloro-3-nitro-benzoate (LII)

This was prepared, in 85% yield, by Fischer-Speier esterification of 4-chloro-3-nitro-benzoic acid; m.p. 79-81° (83°).

Methyl 3-nitro-4-(2-methoxy-phenoxy)-benzoate (LIII)

Guaiacol (1.44g.) in pure pyridine was heated under reflux for 1½ hours with methyl 4-chloro-3-nitro-benzoate (2.5g.; 1 mol.) (cf. Ref. (13)). The solution, by now dark red in colour, was poured into iced water, but since the oil obtained did not crystallise, the mixture was extracted with ether. The extract was washed with dilute acid and alkali, and on evaporation yielded a brown oil, which crystallised from ethanol in colourless plates (1.81g.; 51%) of the required ether, m.p. 97° (Found: C, 59.3; H, 4.4; N, 4.7. $C_{15}H_{13}O_6N$ requires C, 59.4; H, 4.3; N, 4.8%).

A portion of this compound was hydrolysed to the corresponding acid. It was heated under reflux, in aqueous methanol, with an excess of potassium hydrogen carbonate, and when a drop of the solution caused no cloudiness on addition to cold water, the carbonate was neutralised with dilute acid. The

white solid which separated crystallised from ethyl acetate in colourless prisms of 3-nitro-4-(2-methoxy-phenoxy)-benzoic acid, m.p. 164°. (Found: C, 58.2; H, 4.0. $C_{14}H_{11}O_6N$ requires C, 58.2; H, 3.8%).

Methyl 3-amino-4-(2-methoxy-phenoxy)-benzoate (LIV)

The nitro ether (0.73g.) was hydrogenated in ethyl acetate, using palladised charcoal (5%) as catalyst. The filtered solution was evaporated to dryness under reduced pressure, and the oil obtained allowed to stand for some time with light petroleum (b.p. 40-60°) (5cc.). The solid which separated crystallised from ethanol/light petroleum (b.p. 40-60°) in colourless prisms (0.59g.; 90%) of the required amine, m.p. 70-71° (Found: C, 65.5; H, 5.5. $C_{15}H_{15}O_4N$ requires C, 65.5; H, 5.5%).

A portion of this amine was allowed to stand for some hours in presence of excess of acetic anhydride and dilute sodium hydroxide solution. The solution was then extracted with ether, which, on evaporation, yielded the acetyl derivative. This crystallised from aqueous ethanol (50%) in colourless needles, m.p. 121° (Found: C, 64.6; H, 5.2. $C_{17}H_{17}O_5N$ requires C, 64.8; H, 5.4%).

Methyl 4-(2-methoxy-phenoxy)-benzoate (VI)

Methyl 3-amino-4-(2-methoxy-phenoxy)-benzoate (0.5g.) was dissolved in hydrochloric acid (15cc.; 75%), the solution cooled to -5°, and a saturated aqueous solution of sodium nitrite (0.2g.) added dropwise with good stirring. Cooled (0°) hypophosphorous acid (15cc.; 30%) was added dropwise over 20 minutes (cf. Ref. (24)), stirring continued at -5° for 1 hour, and the solution allowed to stand overnight at 0°. It was then extracted with ether, and the extract on evaporation left a brown oil. This distilled (100°/0.01mm,) as a colourless oil, which crystallised from ethanol in colourless prisms of the required ether (0.21g.; 43%), m.p. 67° (Found: C, 69.8; H, 5.3. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%). Mixed m.p. with an authentic specimen of the ether (see p. 58) showed no depression.

This compound (0.2g.) was hydrolysed in aqueous methanol with potassium hydrogen carbonate. The product on acidification crystallised from light petroleum (b.p. 80-100°) in colourless prisms, m.p. 156-157°.

4-(2-methoxy-phenoxy)-benzoic acid had already been prepared by Ungnade (26), who found it to have m.p. 159°.

Attempted preparation of Methyl 3-nitro-4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoate (LV)

2:3-dimethoxy-5-(2-phthalimidoethyl)-phenol (0.204g.) and methyl 4-chloro-3-nitro-benzoate (0.134g.; 1 mol.) were heated under reflux in pure pyridine (10cc.) for 1½ hours. The solution was then poured into cold water and the oil obtained extracted with chloroform, which was well washed with acid and alkali. On evaporation of the chloroform, a trace of red oil was left, but this could not be induced to crystallise. No crystalline material could be obtained from the products on neutralisation of either the acid or alkaline washings.

Methyl 3-nitro-4-(2-methoxy-5-formyl-phenoxy)-benzoate (LVI; R = H)

This was prepared by a method similar to that used for methyl 3-nitro-4-2(methoxy-phenoxy)-benzoate. Iso-vanillin (5.0g.), 4-chloro-3-nitro-benzoate (7.5g.; 1 mol.) and pure pyridine (50cc.) were heated together under reflux for 1½ hours. The dark solution was poured into iced dilute acid and the mixture extracted with ether. The extract was well washed with dilute acid, alkali and water, and on evaporation

left a brown gum. This crystallised, with some difficulty, from ethanol (charcoal) in yellow needles (5.5g.; 51%) of the required ether. After several crystallisations, white needles were obtained, m.p. 118-121°. (Found: C, 58.1; H, 4.1. $C_{16}H_{13}O_9N$ requires C, 58.0; H, 4.0%). Treatment of a portion of the mother liquors with semicarbazide gave a fairly large amount of the semicarbazone, shown, by mixed m.p., to be the same as that prepared below, but no more of the product could be obtained in a crystalline state.

A portion of the unpurified solid was used to make the 2:4-dinitrophenyl-hydrazone. This crystallised from glacial acetic acid in red prisms, m.p. 274° (Found: C, 51.9; H, 3.2. $C_{22}H_{17}O_{10}N_5$ requires C, 51.7; H, 3.4%).

A portion was also treated with semicarbazide. The aldehyde (1.0g.) gave colourless needles of the semicarbazone (1.16g.; 95%), m.p. 209-211° (Found: C, 52.8; H, 4.3. $C_{17}H_{16}O_7N_4$ requires C, 52.6; H, 4.2%).

An attempt was made to purify the nitro-aldehyde through the semicarbazone. Isovanillin (1g.) was converted to the ether and the gum obtained after

charcoaling gave the semicarbazone (2.0g.; based on a 95% yield of the semicarbazone, this represents an 82% yield of the nitro-aldehyde), which was treated with sodium nitrite and hydrochloric acid, by a method similar to that used by Wolfrom (33). None of the aldehyde was obtained, and most of the semicarbazone was recovered unchanged.

Attempted reduction of the nitro-group of the above aldehyde

The aldehyde (2g.) was dissolved in ethyl acetate, and shaken in hydrogen at atmospheric pressure and room-temperature, with pre-reduced platinum oxide. Hydrogen (20cc.) was absorbed very slowly, and then absorption ceased. The aldehyde (1.8g.) was recovered unchanged.

Diacetyl derivative of the nitro-aldehyde as a preliminary to hydrogenation

i The aldehyde (2g.) was dissolved in acetic anhydride 10cc.), concentrated sulphuric acid (4 drops) added, and the solution shaken for 15 minutes. Water (100cc.) was added, the mixture shaken for 20 minutes, and the aqueous layer decanted. The gummy residue was washed with water and hydrogenated without further treatment. Hydrolysis of the diacetate was found

liable to occur in this preparation, but cooling of the solution to 0° before addition of water, also at 0°, prevented this. A large proportion of the diacetate was retained in the aqueous washings, but the gum retained much of the acetic anhydride, which interfered with subsequent reaction (See b below).

ii The aldehyde was treated with acetic anhydride and sulphuric acid as before, but this oil was dissolved in ether before washing with water. Less of the diacetyl derivative was lost, and no hydrolysis of the product occurred but more of the acetic anhydride was found to be present on concentration of the ethereal solution. Nothing was gained by using this method.

iii Acetylation of the aldehyde (2g.) was carried out as in i, but after the product had been cooled to 0° and twice washed with water, it was washed twice with ethanol (2 x 10cc.). This removed all excess of acetic anhydride, and though quite a lot of the diacetate was also retained in the washings, this was easily recovered as the aldehyde. This method was adopted as the most convenient for preparing the diacetate in a fairly pure state. A portion of

the product crystallised from ethanol in colourless needles of the diacetate, m.p. 109-111° (Found: C, 55.6; H, 4.3. $C_{20}H_{19}O_{10}N$ requires C, 55.4; H, 4.4%). This crystallisation was very laborious, and as a rule, the diacetate was reduced in its gummy state.

Removal of the nitro-group from the aldehyde

a The aldehyde (2g.) was converted to the diacetate as in i (see above) and after washing with water was dissolved in ethyl acetate and hydrogenated, using pre-reduced platinum oxide catalyst, at atmospheric pressure and room-temperature. When absorption of hydrogen ceased, ethyl acetate was removed from the filtered solution at room-temperature under reduced pressure. The residue dissolved only partially in hydrochloric acid (20cc.; 50%), sodium fluoborate (5g.) was added and the mixture was cooled to 0°. Sodium nitrite (1g.) was added dropwise in aqueous solution over 15 minutes with good stirring, and after stirring for a further 10 minutes, the aqueous layer was decanted from the gum which had been precipitated. The gum was washed with borofluoric acid (20cc.; 5%), then with methanol (8cc.), which

dissolved some of it, and finally with ether. It was dried in a vacuum desiccator and added portionwise to a mixture of ethanol (50cc.) and zinc dust (2.5g.). Some heating was observed, and the solution was heated under reflux for 1 hour. The colour changed from red to straw-yellow, and zinc was removed by filtration. The solution was evaporated to small bulk, and the oil obtained distilled at 190-220° (bath)/0.2mm. The product solidified, after standing for some time, in colourless crystals of methyl 4-(2-methoxy-5-formyl-phenoxy)-benzoate (LVII; R = H) (0.33g.; 19%). This crystallised from benzene/light petroleum (b.p. 40-60°) in colourless prisms, m.p. 71-73° (Found: C, 67.5; H, 4.9. $C_{16}H_{14}O_5$ requires C, 67.1; H, 3.9%).

A portion of the product was converted to the 2:4-dinitrophenylhydrazone, which crystallised from ethanol in dark red needles, m.p. 235° (Found: C, 56.5; H, 3.9. $C_{22}H_{18}O_8N_4$ requires C, 56.7; H, 3.9%).

b A repetition of this experiment with the nitro-aldehyde (2g.) under similar conditions appeared to proceed in the same manner, but on evaporation of

ethanol from the solution after boiling with zinc, a solid was obtained. This crystallised from ethanol in pale yellow needles (1.0g.; 48%) of methyl 3-acetylamino-4-(2-methoxy-5-formyl-phenoxy)-benzoate (LX), m.p. 209-212° (Found: C, 63.2; H, 5.0; N, 4.2. $C_{18}H_{17}O_6N$ requires C, 63.0; H, 5.0; N, 4.1%). A mixed m.p. of this product with a specimen prepared for comparison (See below) showed no depression. A portion of the product was converted to the 2:4-dinitrophenylhydrazone, which crystallised from glacial acetic acid in orange needles, m.p. 290-300° (Found: C, 54.8; H, 4.1. $C_{24}H_{21}O_9N_5$ requires C, 55.0; H, 4.0%). None of the required aldehyde was obtained in this preparation.

c The nitro-aldehyde (2g.) was converted to the di-acetate as in iii, and after washing with ethanol, dissolved in ethyl acetate, and hydrogenated as before, until absorption of hydrogen ceased. The gum left on evaporation of ethyl acetate at room-temperature under reduced pressure, dissolved in hydrochloric acid (20cc.; 40%). The solution was cooled to 0°, stirred, and sodium nitrite (0.3g.) added dropwise over 20 minutes. After the solution had been stirred for a further 10 minutes, cooled (0°) hypophosphorous

acid (30cc.; 30%) was added and the solution allowed to stand overnight at 0°. Extraction with ether, which was washed with alkali, acid and sodium bicarbonate, before being dried and evaporated, gave an oil, which distilled at 200-220°/0.2mm. to give the desired aldehyde (0.78g.; 45%), in a sufficiently pure state for the next stage of the scheme. A mixed m.p. of the hydrolysis product with that from the product of reaction a confirmed the identity of this product.

d The nitro-aldehyde (2g.) was acetylated as before, but reduction of the product was carried out in glacial acetic acid (20cc.). The solution was diazotised in an acetic acid (10cc.)/nitrosyl sulphuric acid (0.5g.) sodium nitrite/15cc. sulphuric acid) mixture, and the diazotised solution treated with hypophosphorous acid (30cc.; 30%). The desired aldehyde (0.88g.; 51%) was obtained by distillation of the product, but required a second distillation before being sufficiently pure for the next stage.

Methyl 3-acetylamino-4-(2-methoxy-5-formyl-phenoxy)-benzoate (LX)

The crystalline diacetate (see iii above) was hydrogenated in ethyl acetate, and the solution shaken with acetic anhydride (2cc.) and sodium

hydroxide solution (10cc.; 20%) for 1 hour. The product was isolated by extraction with chloroform and crystallised from ethanol in colourless needles (0.4g.; 77%) of the required product, m.p. 206-210° (Found: C, 62.8; H, 5.0. Calc. for $C_{18}H_{17}O_6N$: C, 63.0; H, 5.0%). This was used for comparison of the by-product in b (above).

4-(2-methoxy-5-formyl-phenoxy)-benzoic acid (LXIV)

Methyl 4-(2-methoxy-5-formyl-phenoxy)-benzoate (0.54g.) was heated under reflux with excess of aqueous methanolic potassium hydrogen carbonate for 3 hours. Methanol was removed by distillation, and the solution acidified. The precipitate obtained crystallised from benzene/light petroleum (b.p. 60-80°) in colourless prisms of the required acid, m.p. 155-160° (0.48g.; 94%) (Found: C, 66.2; H, 4.6. $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%).

4-[2-methoxy-5-(2-nitrovinyl)-phenoxy]-benzoic acid (LXV)

a 4-(2-methoxy-5-formyl-phenoxy)-benzoic acid (0.448g.) was dissolved in methanol (8cc.), nitromethane (2cc.) added and the solution cooled to 0°. Sodium hydroxide (2.8g.) in aqueous ethanol was added dropwise with good stirring over 40 minutes. A considerable bulk of pale yellow precipitate was produced, and more

methanol (10cc.) was added. The solution was stirred for a further 20 minutes with the cooling bath removed, sufficient water was added to dissolve the precipitate, and the solution was added fairly rapidly to well-stirred hydrochloric acid (100cc.; 33%). The yellow precipitate was allowed to settle and filtered. It crystallised from ethanol in yellow needles (0.448g.; 86%) of the required nitrostyrene, m.p. 214-222° (Found: C, 61.1; H, 4.0. $C_{16}H_{13}O_6N$ requires C, 61.0; H, 4.2%).

b 4-(2-methoxy-5-formyl-phenoxy)-benzoic acid (0.25g.) was heated under reflux for 2 hours with glacial acetic acid (5cc.), nitromethane (0.4cc.) and ammonium acetate (0.5g.). The solution was poured into water, but gave an oil from which no crystals could be obtained.

4-[2-methoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoic acid (LXVI)

4-[2-methoxy-5-(2-nitrovinyl)-phenoxy]-benzoic acid (0.48g.) was added in glacial acetic acid suspension (10cc.) to platinum oxide (0.2g.) which had been pre-reduced in aqueous sulphuric acid (4cc.; 10%). The mixture was shaken with hydrogen at atmospheric pressure and room-temperature until absorption ceased (2 hr.). The catalyst was removed and the aqueous

layer separated. The ethyl acetate solution was washed with water (3 x 10cc.) and the combined aqueous solutions were passed through a column of ion-exchange resin (Amberlite IR-4B) and evaporated to dryness. The brown gummy residue, dissolved in ethanol (5cc.), was kept at room-temperature, and a white precipitate (0.097g.; 22%) formed, m.p. 200-230°. This crystallised from 90% ethanol in colourless needles, m.p. 215-227°, but no further purification could be achieved. (Found: C, 61.5; H, 5.8%). The infra-red spectrum of this compound indicated a benzenoid amino-acid structure (IR-V). This product (0.077g.) was fused for ½ hour with phthalic anhydride (0.04g.) at 145-150°. The solid obtained on cooling crystallised from aqueous methanol in mixed plates and needles, m.p. 180-188°. These recrystallised from methanol in colourless needles of the required phthalimidoethyl compound (0.032g.; 29%), m.p. 186° (Found: C, 68.9; H, 4.7. $C_{24}H_{19}O_6N$ requires C, 69.1; H, 4.6%).

Methyl 3-nitro-4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate (LXVII)

3:4-dimethyl gallaldehyde (XXXI) (19.6g.), methyl 4-chloro-3-nitro-benzoate (23.2g.; 1 mol.) and

pure pyridine (130cc.) were heated together under reflux for 1½ hr. and the dark solution poured into ice-water (600cc.). After the mixture had been stirred and allowed to settle and the dark-coloured gum washed with water, the moist gum was dissolved in warm ethanol, which, on standing, yielded a solid (A) and an ethanolic solution (B). The aqueous washings were extracted with ether and the extract combined with (B) which had been evaporated almost to dryness. The extract, after being well washed with dilute acid and alkali, was evaporated, and the residual oil charcoaled in ethanol. The charcoal was removed, and on cooling, the ethanolic solution yielded a quantity of solid which was combined with solid (A) and crystallised from ethanol in yellow prisms, m.p. 80-88°, of the required ether (16.1g.; 42%). A portion recrystallised from ethanol in colourless prisms, m.p. 88°. (Found: C, 56.3; H, 4.0. $C_{17}H_{15}O_8N$ requires C, 56.5; H, 4.2%).

The ethanol mother liquors, on concentration, gave a dark oil (13.13g.). A portion of this (0.44g.) was treated with 2:4-dinitrophenylhydrazine and the product crystallised from ethanol in orange

prisms (0.55g.; 85% based on the oil), m.p. 200-213°. This product did not depress the m.p. of the product prepared as below. This indicates a total yield of the aldehyde of 27.4g. (71%), but no means was found of purifying the oily fraction of this.

A portion of the crystalline aldehyde was converted to the 2:4-dinitrophenylhydrazone, which crystallised from ethanol in orange prisms; m.p. 211-213° (Found: C, 50.9; H, 3.8. $C_{23}H_{19}O_{11}N_5$ requires C, 51.0; H, 3.5%).

The alkaline washings of the ethereal extract in the above preparation were neutralised with acid and extracted with ether. The oil obtained on evaporation of the ether crystallised from ethanol in colourless needles (1.7g.; 5%) of 3-nitro-4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoic acid (LXVIII) m.p. 217-223° (Found: C, 55.2; H, 3.6. $C_{16}H_{13}O_8N$ requires C, 55.3; H, 3.8%). This acid was reconverted to the methyl ester in 85% yield by treatment with diazomethane in ethereal solution. A mixed m.p. with the product obtained above showed no depression.

Condensation of the Aldehyde with nitromethane

Methyl 3-nitro-4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate (0.50g.) was dissolved in methanol,

nitromethane (0.2cc.) added and the solution cooled to 0°. A solution of potassium hydroxide (0.2g.) in aqueous methanol was added dropwise, with good stirring over 10 minutes. After a further 20 minutes stirring, the solution was poured into an excess of 30% hydrochloric acid. The precipitate was filtered and crystallised from ethanol in yellow needles (0.32g.), m.p. 86-87°. (Found: C, 55.8; H, 4.9%). A mixed m.p. showed that this was different from the starting material.

Methyl 4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate (LXX)

The nitro-formyl-ether (3.02g.) was dissolved in acetic anhydride (12cc.) with concentrated sulphuric acid (4 drops). The solution was shaken for 15 minutes, cooled to 0°, and treated with ice-water (30cc.). The mixture was well shaken, and after it had been allowed to settle, the aqueous layer was decanted. The gummy residue was washed with water, and then shaken twice with ethanol (2 x 10cc.) to remove any undecomposed acetic anhydride. The semi-solid residue was dissolved in ethyl acetate (80cc.) and the solution added to pre-reduced platinum oxide (0.35g.). It was shaken in hydrogen at atmospheric pressure and room-temperature for

2 hours (645cc. absorbed; equivalent is approximately 560cc.). The solution was then filtered and evaporated to dryness at room-temperature, under reduced pressure, and the gummy residue treated with hydrochloric acid (25cc.; 50%). Nearly all the material dissolved and the solution was stirred at -5°. Sodium nitrite (0.54g.) in aqueous solution was added dropwise over 15 minutes to the stirred solution, and after stirring for 15 minutes more, hypophosphorous acid (80cc.; 50% cooled to 0°) was added. The solution was allowed to stand overnight at 0°, extracted with ether and the extract washed with alkali, acid and sodium hydrogen carbonate solution. The material left on evaporation of ether distilled as a colourless oil (1.5157g.) at 180°/0.1mm. A specimen was redistilled and the distillate solidified on standing. It crystallised from light petroleum (b.p. 50-60°) in colourless needles of methyl 4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate, m.p. 111-113° (Found: C, 64.4; H, 5.1. $C_{17}H_{16}O_6$ requires C, 64.6; H, 5.1%).

The aqueous and ethanolic washings from the diacetylation were combined and extracted with chloroform, which was allowed to stand over dilute

caustic soda solution for one week before being evaporated. Unused nitro-ether (0.46g.), m.p. 80-88° was recovered. The weight of product (1.516g.) after allowing for the unused starting material, represents a yield of 68%.

Attempted preparation of the di-acetyl derivative (LXIX)

The nitro-formyl ether (0.25g.) was converted to the diacetyl derivative as before, and after this had been washed with water and ethanol, an attempt was made to crystallise the residue. Yellow-brown prisms (0.19g.) were obtained, m.p. 110-130°, but the purity of these could not be improved by further crystallisation.

4-[2:3-dimethoxy-5-(2-nitrovinyl)-phenoxy]-benzoic acid (LXXI)

Methyl 4-(2:3-dimethoxy-5-formyl-phenoxy)-benzoate (0.08g.) (oil) was heated under reflux with excess of methanolic aqueous potassium hydrogen carbonate. After 4 hours, methanol was removed by distillation, the solution acidified and the precipitate extracted with ether. Evaporation of the ether left a colourless oil, from which no crystals could be obtained.

This was dissolved in ethanol (5cc.), nitromethane (1cc.) added, and the solution cooled to -5°. A solution of potassium hydroxide (1.2g.) in aqueous methanol was added dropwise over 15 minutes with good stirring, and stirring continued, with the cooling-bath removed, until the solution attained room-temperature. It was then poured with stirring, into hydrochloric acid (30cc. 30%). On allowing the mixture to stand overnight, a yellow precipitate separated, and this crystallised slowly from aqueous ethanol. It recrystallised from ethanol in yellow needles of the required β-nitro-styrene (0.015g.; 17%), m.p. 158-162°. (Found: C, 59.3; H, 4.7. $C_{17}H_{15}O_7N$ requires C, 59.1; H, 4.4%).

Attempted preparation of 3-(4-carboxy-phenoxy)-4:5-dimethoxy-phenylethylamine (L)

The above preparation was repeated with the formyl-ether (1.5g.), but none of the desired nitrostyrene could be isolated in a crystalline condition. The gummy product was dissolved in ethyl acetate and added to platinum oxide (0.4g.), which had been pre-reduced in aqueous sulphuric acid (15cc.; 10%). The mixture was shaken with hydrogen at atmospheric

pressure and room-temperature until absorption ceased (3 hours). The catalyst was removed, and the aqueous layer separated. The ethyl acetate was washed with water (2 x 10cc.) and the combined aqueous solutions were passed through a column of ion-exchange resin (Amberlite IR-4B) and evaporated to dryness. The brown gummy residue was treated with ethanol (10cc.) and after standing for some time, a white solid separated. This crystallised from aqueous ethanol in colourless needles (4.0mg.) m.p. 210-250°. The infra-red spectrum of this compound was almost completely identical with that of the product from the dinitro-ether (IR-IV) (p. 65). The oil which had not crystallised from ethanol was evaporated to dryness, and heated at 145-150° with phthalic anhydride (0.3g.) for 30 minutes. The product crystallised from ethanol in colourless needles (0.10g.), m.p. 235-240°. (Found: C, 67.7; H, 3.8%). The compound was recrystallised from ethanol and dried for 10 hours, at 100°, under vacuum. (Found: C, 68.1; H, 4.2%). (4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-benzoic acid (LXIII) requires C, 67.1; H, 4.7%. ($C_{25}H_{21}O_7N$)).

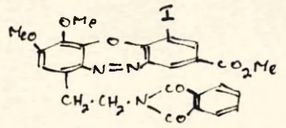
Infra-Red Absorption Spectra

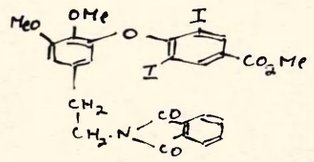
These were measured by means of a Model 13 Perkin-Elmer double-beam instrument, which records the intensity of absorption on a revolving cylinder. The speed of rotation of this cylinder changes at $\nu = 1300$ and again at $\nu = 2200$. These points are indicated by arrows on the charts.

IR – I

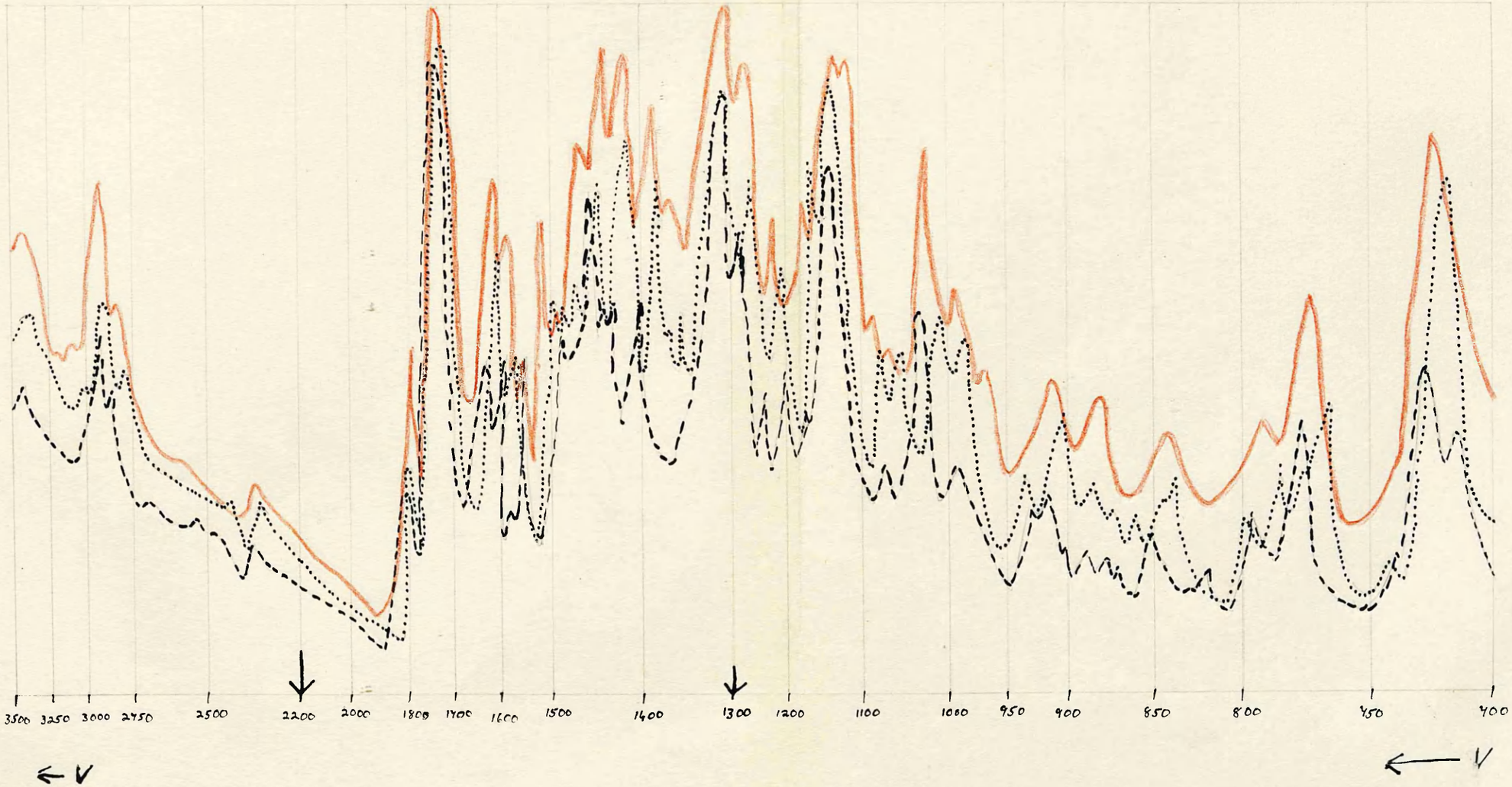
IR – II

IR – III

..... IR – I  2·5 mg. / KCl disc.

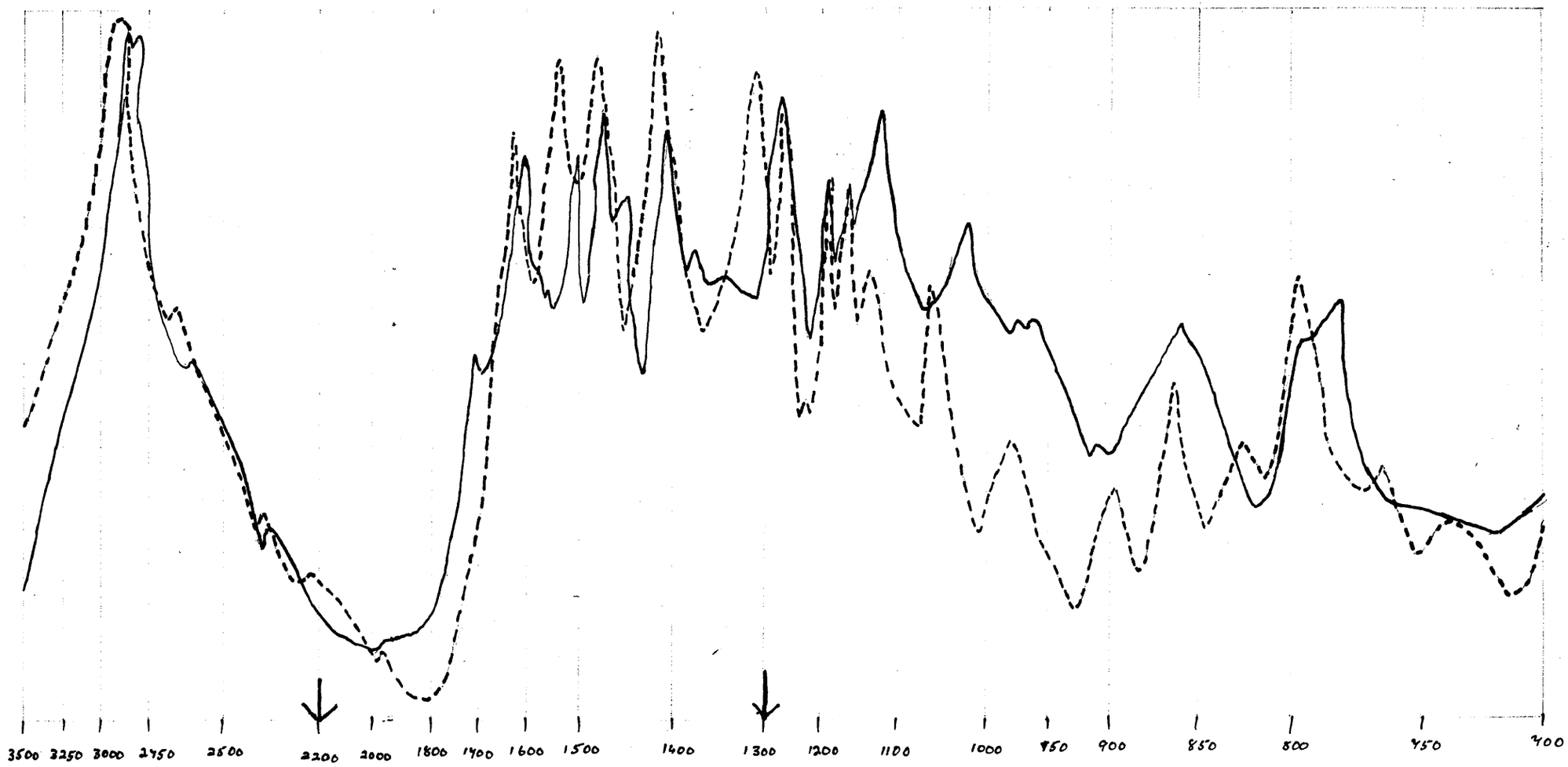
---------- IR – II  2·5 mg. / KCl disc

——— IR – III Mixture of the two compounds above 3·0 mg. / KCl disc



IR – IV 2·5 mg./Nujol

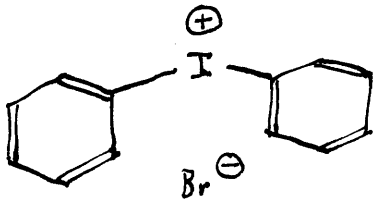
IR – V 2·5 mg./Nujol



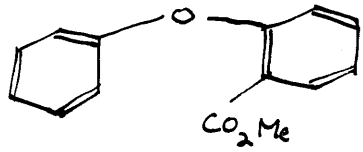
Part II

Diphenyl Iodonium Compounds as Intermediates

Beringer and his colleagues (34) have recently investigated the properties of diphenyl iodonium salts, and have shown their use as a means of phenylating organic bases. From diphenyl iodonium bromide (LXXIV) in reaction with the phenoxide ion, they obtained diphenyl ether in 70% yield, and under similar conditions applied to the ion of methyl salicylate, they prepared methyl o-phenoxy-benzoate (LXXV) in 44% yield.

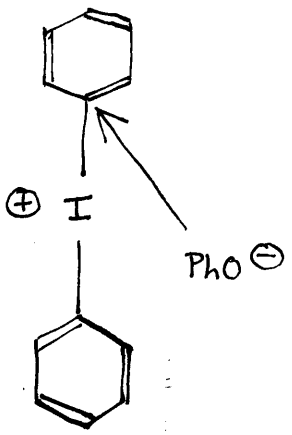


LXXIV

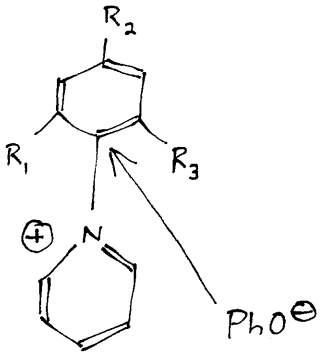


LXXV

From Beringer's paper on the mechanism of the reaction (35), it appears that the reaction involves a nucleophilic attack on the 1-position of the iodonium salt (See LXXVI), comparable to that involved in the method examined in Part I (LXXVII; R_1, R_2, R_3 are activating groups or hydrogen atoms). This is



LXXVI



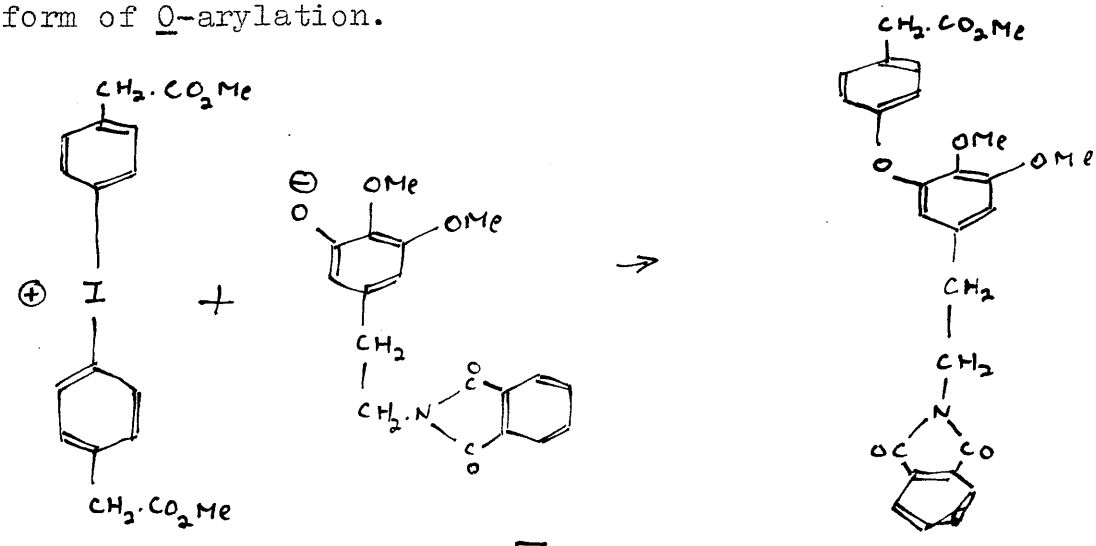
LXXVII

borne out by the work described in (34), in which it was shown that nitro-groups substituent to the iodonium salts improve the yields in the reaction. The fact that the reaction proceeds without any activating group indicates that iodonium salts are much more susceptible to nucleophilic attack than are pyridinium salts.

Beringer (34) has also devised a new method, resembling a Friedel-Crafts reaction, for the preparation of symmetrical di-aryl iodonium salts. The aromatic compound is treated, in an anhydrous acid solution, with potassium iodate, to give

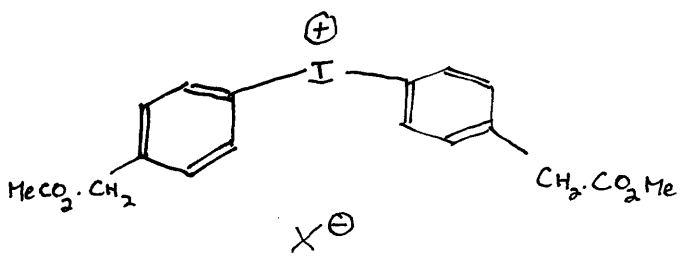
yields of up to 90% of the iodonium salt in this one-stage preparation. The previous best method of preparing these compounds, base-catalysed condensation of the iodoso-compound (ArIO) with the iodoxy-compound ($ArIO_2$), is a very laborious process, involving several stages, and yielding, at best, 40% of the product, calculated on the aromatic starting material.

The relatively mild reaction conditions and the accessibility of diphenyliodonium salts suggested that the process, whose potentialities as a synthetic method had not been extensively explored, might merit further examination. The prospect also emerged of reducing the number of steps in the present synthetic work (Diagram F) by this more direct form of O-arylation.



F

The substituted diphenyliodonium salt (LXXVIII) was accordingly prepared and identified. Methyl phenylacetate, in a solvent mixture of acetic acid, acetic anhydride and sulphuric acid, was treated with potassium iodate, and the salts required precipitated by the addition of a sodium bromide (LXXVIII; X = Br) or a saturated ammonium chloride (LXXVIII; X = Cl) solution. (cf. Refs. 34 and 35). To confirm that the reaction had taken place in the positions para- to the acetate side-chains, a specimen of the iodide (LXXVIII; X = I)



LXXVIII

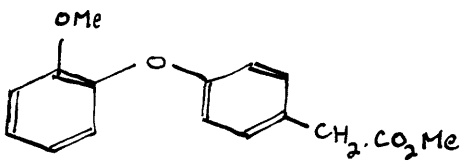
was precipitated from the reaction mixture by addition of potassium iodide solution, and thermally decomposed to give a methyl iodophenyl acetate. This, on hydrolysis, gave an acid shown to melt at the same temperature as p-iodophenylacetic acid (39) but at a higher temperature than the o-iodo acid(40). This confirms that reaction in the

preparation of the iodonium salts had taken place in the positions para- to the acetate side-chains.

The reaction was first investigated using certain phenols as models, and certain reaction conditions were chosen. The iodonium bromide (LXXVIII; X = Br) and the sodium salt of guaiacol were warmed in methanol, but the only tractable product obtained was a low-boiling oil, believed to be a mixture of methyl p-iodo- and p-bromo-phenyl-acetates. (These are formed both as by-products in this type of reaction and also from thermal decomposition of the iodonium salts). The reaction was therefore examined in warm aqueous solution, using the iodonium chloride (LXXVIII; X = Cl), both because Beringer (35) had obtained better results by using water as solvent rather than methanol, and because separation of the product was easier, since the reaction products precipitated as an oily mixture, while unchanged starting materials remained in solution.

A preliminary investigation, in which the sodium salt of guaiacol was treated, in aqueous solution, with 1 mol. of the iodonium chloride, for 24 hours gave

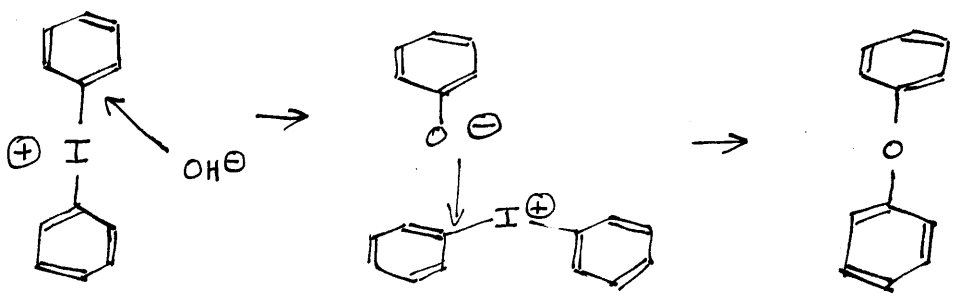
a 12% yield of the required ether (LXXXIX). This comparatively poor yield might be due either to incomplete reaction, or to side-reactions giving different products. The yield was improved to 15% by carrying out a preparation under the same conditions, but allowing reaction to proceed for a week. Since the yield still seemed capable of improvement, the reaction was carried out under varied conditions in an effort to find the most suitable method.



LXXIX

Under the reaction conditions used, there is probably competition with the phenoxide ion, for attack on the iodonium ion. In methanolic solution, this will come from methoxide ions, and in aqueous solution, from hydroxide ions. Since $-OH^{\ominus}$ appears to attack cations less readily than does $-OMe^{\ominus}$ (36) the reaction should have a better chance in aqueous

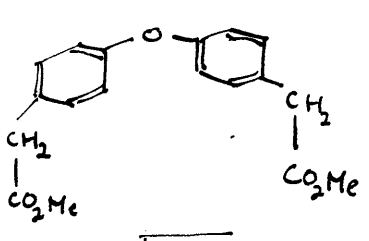
though the concentration of hydroxide ions in water is likely to be greater than that of methoxide ions in methanol. The presence of hydroxide ions may have a catalytic effect in promoting the yields, since reaction between sodium phenoxide and diphenyliodonium chloride gave only 76% of diphenyl ether, whereas diphenyliodonium chloride reacted with excess of caustic soda to give an 84% yield of diphenyl ether (Ref. 34), the reaction presumably proceeding as shown (G).



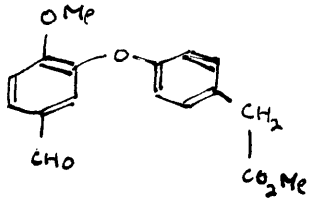
G

The reaction under consideration was investigated in presence of an excess of sodium hydroxide, but only a 5% yield of the desired ether (LXXIX) was obtained, together with a second product, which was not characterised, but was believed to be the symmetrical ether (LXXX). The combined yield of products isolated was smaller than in previous cases, indicating that the iodonium salt decomposed

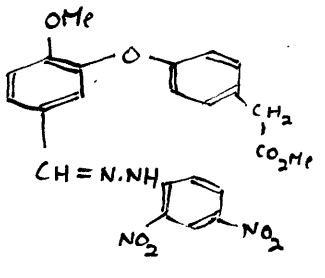
more readily in the presence of alkali. When an excess of phenoxide was used under similar conditions, the yield, based on the iodonium salt, was raised, but not sufficiently to allow the more valuable phenol to be used in this way. The results obtained from these experiments indicate that the method most likely to be applicable is that in which molar proportions of the reagents are used. The reaction was also examined in pyridine solution in absence of alkali, although Sandin and Brown (37) had carried out work which involved heating iodonium salts in pyridine, and their results indicated that decomposition only occurred when alkali was present.



LXXX



LXXXI

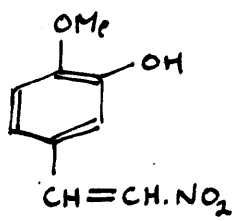


LXXXIa

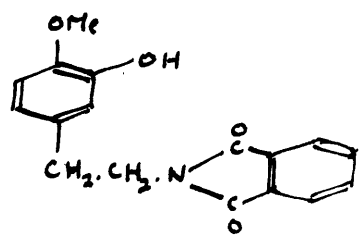
Preparation of the ether (LXXXI) from iso-vanillin was also attempted by a method parallel to that which had proved most successful in the

preparation using guaiacol. Only a small amount of fairly pure product could be isolated, however, and this was characterised only as the dinitrophenylhydrazone (LXXXIa). It appeared, from the range of higher boiling products obtained on distillation, that decomposition or polymerisation was causing a considerable reduction in the yield.

The phthalimidoethyl-phenol (LXXXIII) was prepared as a model, since it could be expected to show behaviour very similar to that of the phenol (XXII), to which this reaction was eventually to be applied. Isovanillin was converted to the nitrostyrene (LXXXII) by the method of Bersch (38), and this was catalytically reduced to the aminophenol, which was not isolated, but was treated with phthalic anhydride to give the phthalimidophenol. This compound was then treated with the iodonium compound

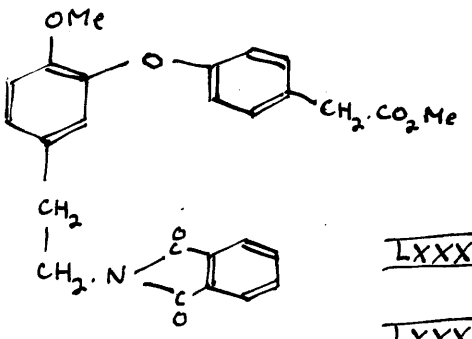


LXXXII



LXXXIII

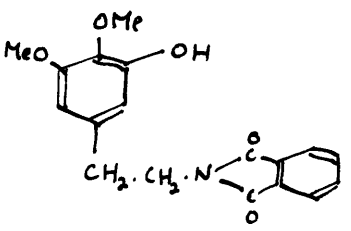
for a rather shorter period than that used in the previous examples, and the required product (LXXXIV) isolated in 5% yield. Since only a small proportion of the phenolic starting material could be recovered, it appears that the phthalimido-group is not very stable under the conditions used.



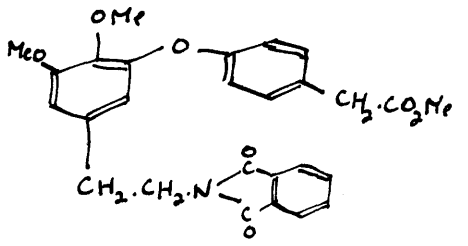
LXXXIV

LXXXIV

Finally, in an attempt to prepare the ether (LXXXV), the phenol (XXII) was treated, in neutralised aqueous solution, with the iodonium chloride, for a similar period to that used in the preparation of (LXXXIV), but neither a crystalline product, nor any unused starting material could be isolated from the reaction mixture.



XXII



LXXXV

It is apparent from the work described in this section that, although the attempt to prepare the ether (LXXXV) was not successful under the conditions used, further investigation along the lines followed might well give a satisfactory result. The general method is likely to be of value as a means of preparing certain types of diphenyl ethers, and with some refinements, such as the use of diphenyl iodonium compounds with substituent activating groups, will probably prove to be of fairly wide application as a synthetic method.

Experimental

Methyl Phenylacetate

This was prepared in 90% yield by Fischer-Speier esterification of phenylacetic acid: b.p. 212-215°.

4:4'-Dimethoxycarbonylmethyl-diphenyliodonium bromide (LXXVIII; X = Br)

A solution of methyl phenylacetate (19.0g.) in glacial acetic acid (80cc.), acetic anhydride (28cc.) and concentrated sulphuric acid (12cc.) was stirred at room temperature (maintained by a water-bath), and potassium iodate (12.8g.; 1 mol.) added over 2½ hours (cf. Ref. 34). The mixture was then stirred for a further 48 hours. Although a starch-iodide test indicated that the potassium iodate had not all reacted, the next stage in the preparation was carried out. Finely divided inorganic matter was removed by filtration through 'Celite 535,' ice-water (100cc.) was added, and excess potassium iodate decomposed with sodium sulphite solution. An aqueous solution of potassium bromide (30g.) was added, and the milky-white precipitate thus obtained filtered with difficulty and washed with water. Crystallisation from water gave a white solid (20g.; 64%) which recrystallised

from ethanol in colourless needles, m.p. 166-167°. (Found: C, 42.6; H, 3.8. 7.62 mg. gave 6.29 mg. silver halide. $C_{18}H_{18}O_4BrI$ requires C, 42.8. H, 3.6%, 7.62 mg. give 6.23 mg. silver halide).

4:4'-Dimethoxycarbonylmethyl-diphenyliodonium iodide (LXXVIII; X = I)

A small portion of the filtered reaction mixture in the previous preparation was removed before treatment with sodium bromide, and an aqueous solution of potassium iodide (excess) added. The yellow precipitate crystallised from ethanol in colourless needles, m.p. 150°. (Found: C, 39.1; H, 3.2. $C_{18}H_{18}O_4I_2$ requires 39.2; H, 3.3%).

Thermal decomposition of the preceding compound

The crystalline solid (2g.) obtained in the previous preparation was heated to 160° for 5 minutes and the brown oily product distilled under reduced pressure. Some iodine came over with the distillate, which was washed with sodium thiosulphate solution and redistilled as a colourless oil. (1.5g.; 75%), b.p. 110-120°/0.1mm. (Found: C, 39.3; H, 3.5. $C_9H_9O_2I$ requires C, 39.2; H, 3.3%.

A portion was hydrolysed in aqueous methanol with potassium hydrogen carbonate. The methanol was

removed by distillation, and acidification of the solution gave a white precipitate of o-iodophenylacetic acid, m.p. 123-137°. This crystallised from boiling water in colourless plates, m.p. 135° (lit. 135°).

4:4'-Dimethoxycarbonylmethyl-diphenyliodonium chloride (LXXVIII ; X = Cl) (cf. Ref. (35)).

A solution of methyl phenylacetate (95g.) in glacial acetic acid (400cc.), acetic anhydride (140cc.) and concentrated sulphuric acid (60cc.) was stirred at room temperature, and potassium iodate (64g.) added over 4 hours. After the mixture had been stirred for a further 48 hours, it was filtered as in the preparation of the bromide, and allowed to stand at room temperature for a week. By this time all of the potassium iodate had been consumed (starch-iodide test). Ice-water (400cc.) was added, the solution was extracted with ether (900cc.) and the ethereal extract washed twice with water (150cc. and 50cc.). The combined aqueous layers were treated with a hot saturated aqueous solution of ammonium chloride (70g.) and allowed to stand overnight at -10°. The precipitate was collected and crystallised from hot

ethanol, after filtration to remove inorganic salts, which had also precipitated. Colourless needles of the required iodonium chloride were obtained m.p. 188°, (43g.; 32%). (Found: C, 47.2; H, 4.0. $C_{18}H_{18}O_4ICl$ required C, 46.9; H, 3.9%).

Reaction of 4:4'-dimethoxycarbonylmethyl-diphenyl-iodonium halides with guaiacol

a With sodium methoxide

Guaiacol (2.0g.) was dissolved in a methanolic solution of sodium methoxide (prepared from 0.45g. sodium metal) and 4:4'-dimethoxycarbonylmethyl-diphenyliodonium bromide (2.0g.) added. The solution was stirred at 50° for 30 hours, and most of the methanol was then removed by raising the temperature to 80°. Dilute caustic soda solution was added to the residual oil and the mixture extracted with ether. The extract was washed with caustic soda solution until the washings gave only a trace of colour with diazotised aniline, and on evaporation left a yellow oil. Most of this distilled at 120-130° (bath)/0.2mm. as a colourless oil (1.5g.), consisting of mixed methyl p-iodo- and p-bromophenylacetates. The small amount of undistilled residue was combined with the residues

from other similar preparations and the gummy mixture distilled at 190°(bath)/0.001mm. A yellow oil was obtained in very small amount, and on treatment with a little ethanol yielded crystals. These recrystallised from ethanol in colourless needles, m.p. 220° (Found: C, 41.0; H, 3.3%).

b In pyridine

Guaiacol (2.0g.) and 4:4'-dimethoxycarbonylmethyl-diphenyliodonium bromide (8.0g.) in pure pyridine (50cc.) were warmed at 70° for 60 hours. The solution changed from colourless to dark red. It was extracted with chloroform, which was well washed with dilute acid and alkali, dried and evaporated. The gum obtained was dissolved in ether, which was allowed to stand over sodium hydroxide pellets for 5 minutes before being decanted and evaporated to give an oil. This was distilled in two fractions, the first, a colourless oil, boiling at 130-135°/0.5mm., and the second, a dark brown oil, at 150-165°/0.5mm. The second fraction of the distillate was redistilled, after washing with sodium thiosulphate, at 130-135°/0.5mm. Both fractions consisted of mixed methyl p-bromo- and p-iodo-phenylacetates, the higher boiling point

of the second being due to the decomposition of unchanged starting-material at that temperature. None of the desired product was obtained.

c In aqueous solution

Guaiacol (1.53g.) and 4:4'-dimethoxycarbonylmethyldiphenyliodonium chloride (5.9g.; 1 mol.) were treated with an aqueous solution (100cc.) of sodium hydroxide (0.5g.; slightly less than 1 mol.), and the solution warmed at 70° for 24 hours. The oil which had separated was then dissolved in ether, which was well washed with alkali, dried, and allowed to stand over caustic soda pellets for 5 minutes. The ether was evaporated, and the oil obtained distilled under reduced pressure. The first and larger fraction, a colourless oil, distilled at 130°/0.2mm., and consisted of mixed p-chloro- and p-iodophenylacetates. The second fraction consisted of methyl 4-(2-methoxyphenoxy)-phenylacetate (LXXIX) (0.402g.; 12%), and distilled at 175°/0.2mm., n_d^{18} = 1.567. (Found: C, 70.5; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).

d In aqueous solution for 1 week

The same conditions were used as in c, with the exception that the reaction period was one week.

Guaiacol (0.8g.) gave the required product (0.26g.) in 15% yield.

e In aqueous solution with excess of alkali

The same conditions were used as in d, with the exception that 3 mol. of sodium hydroxide solution were used. Guaiacol (2.0g.) with the iodonium chloride (1 mol.) and an aqueous solution of sodium hydroxide (2.1g.; 3 mol.) were heated together, and the mixture of oils obtained separated into fractions by distillation. The first fraction, b.p. 130-135°/0.5mm. consisted of decomposition products of the iodonium salt. A second fraction was obtained at 180-240°/0.1mm. and this was further separated. Fractional distillation gave methyl 4-(2-methoxy-phenoxy)-phenylacetate (LXXIX), b.p. 170-190°/0.1mm. (0.3g.; 5.5%), n_d^{18} = 1.568; and an oil (0.22g.) at 220-240°/0.1mm., n_d^{18} = 1.586, and presumed to be 4:4'-dimethoxycarbonylmethyl-diphenyl ether (LXXX), though not purified.

f In aqueous solution with excess of the sodium salt

Guaiacol (1.02g.), sodium hydroxide (1 mol.) and the iodonium chloride (1.25g.; 1/3 mol.) were warmed under the same conditions as in d. The desired

product (0.22g.; 30% on the iodonium salt) was isolated as before. Unchanged guaiacol was not recovered.

Methyl-4-(2-methoxy-5-formyl-phenoxy)-phenylacetate 2:4-dinitrophenyl-hydrazone (LXXXIa)

Isovanillin (2.0g.) was treated with aqueous caustic soda (0.52g.; 1 mol.), the solution diluted with water to 60cc. and 4:4'-dimethoxycarbonylmethyl-diphenyliodonium chloride (6.2g.; 1 mol.) added. The solution was stirred at 65-70° for 48 hours, and the precipitated oil extracted with ether. This was washed with alkali until no colour was obtained with diazotised aniline, then with acid, and finally with sodium hydrogen carbonate solution. The oily residue obtained on evaporation of ether was distilled under reduced pressure. A fraction of distillate was collected at 100-130°/0.2mm., and the remainder of the product distilled over a continuous range from 200-260°. This was arbitrarily separated into fractions: i a very small fraction at 200-214°/0.2mm., ii 214-220°/0.2mm. (0.3g.), iii 220-240°/0.2mm. (0.25g.), iv 240-260°/0.2mm. (0.12g.). None of these fractions could be crystallised, but 2:4-dinitrophenylhydrazones of all fractions were prepared. The only one which, after crystallisation,

gave a reasonably sharp melting-point was that obtained from the fraction boiling at 214-220°/0.2mm. This crystallised from glacial acetic acid/ethanol (1:3), in orange-red prisms, m.p. 175-177°. (Found: C, 57.9; H, 4.2. $C_{23}H_{20}O_8N_4$ requires C, 57.5; H, 4.2%). On the assumption that the aldehyde fraction from which this was prepared consisted mainly of (LXXXI), the yield of aldehyde was 7.5%. No further purification of the higher-boiling fractions, or of their D.N.P.'s could be achieved.

3-Hydroxy-4-methoxy-nitrostyrene (LXXXII)

a This was prepared by the method of Bersch (38). Isovanillin (20g.) in alkaline solution, on treatment with nitromethane, gave the required nitrostyrene (17g.; 66%). It was sufficiently pure (m.p. 154-156°), after one crystallisation, for subsequent reduction.

b Isovanillin (20g.) in glacial acetic acid (85cc.) was heated under reflux with notromethane (21cc.) and pure ammonium acetate (8.5g.) (cf. Ref. (21)). The solution was poured into water and the solid precipitate crystallised (charcoal) from ethanol in yellow needles (18g.; 70%), m.p. 150-156°; mixed m.p.

with product from a gave no depression. Impurities in this product interfered with catalytic reduction, unless the product was recrystallised several times.

2-Methoxy-5-(2-phthalimidoethyl)-phenol (LXXXIII)

The nitrostyrene (5g.) was added in ethyl acetate to platinum oxide catalyst, prereduced in sulphuric acid (15cc.; 10%) and hydrogenated at atmospheric pressure and room temperature. When 4 mol. had been absorbed, the catalyst was removed and the aqueous layer separated. The ethyl acetate was washed with water, the combined aqueous solutions passed through a column of ion-exchange resin (Amberlite IR-4B), and evaporated to dryness under reduced pressure.

The amine was not isolated (cf. Ref. (41)) but the brown gum obtained was heated for $\frac{3}{4}$ hour under reflux with phthalic anhydride (3g.) in glacial acetic acid. The solid which separated on pouring into cold water was filtered, and crystallised from ethanol in colourless needles (6.1g.; 80%), of the required phthalimido-phenol, m.p. 153-155°.
(Found: C, 68.9; H, 4.8. $C_{17}H_{15}O_4N$ requires C, 68.7; H, 5.1%).

Methyl 4-[2-methoxy-5-(2-phthalimidoethyl)-phenoxy]-phenylacetate (LXXXIV)

2-Methoxy-5-(2-phthalimidoethyl)-phenol (LXXXIII) (1.275g.) was added to a solution of caustic soda (0.17g.; 1 mol.) in water (40cc.). On warming to 65°, much of the phenol dissolved, and 4:4'-dimethoxycarbonylmethyl-diphenyliodonium chloride (2g.) was added. The mixture was stirred at 65-70° for 15 hours, a further quantity of the iodonium salt (1g.) was added, and the mixture stirred for 24 hours more. Some gum had now precipitated, and this was extracted with chloroform and washed several times with dilute sodium hydroxide. Evaporation of the chloroform left a gum which was treated with ether (20cc.). Most of the material went into solution readily, leaving a flocculent dirty precipitate, m.p. 180-185°. This could not be recovered after charcoaling in ethanol and is believed to have been unchanged iodonium salt. The ether-soluble fraction was distilled, giving a colourless oil at 120-130°/0.2mm., and leaving an undistilled gum. This, on trituration with ethanol, yielded a solid, which crystallised from ethanol (charcoal) in colourless needles of the required phthalimido-ether (0.095g.; 5.5%), m.p. 130-133°. (Found: C, 70.4; H, 5.4. $C_{26}H_{23}O_6N$

requires C, 70.1; H, 5.2%). Treatment of the alkaline washings of the chloroform gave unchanged phenol in small amount (0.05g.; 4%).

Attempted preparation of methyl 4-[2:3-dimethoxy-5-(2-phthalimidoethyl)-phenoxy]-phenylacetate (LXXV)

2:3-Dimethoxy-5-(2-phthalimidoethyl)-phenol (XXII) (0.442g.) was dissolved in a warm solution of caustic soda (0.054g.) in water (20cc.) with a little dioxan (5cc.). The iodonium chloride (0.62g.) was added, and the solution stirred at 70° for 30 hours. More iodonium chloride (0.3g.) was added, and stirring continued for a further 24 hours. The mixture was extracted with chloroform, which was washed with caustic soda and evaporated. The oil obtained was dissolved in ether, filtered to remove some impurities, and after drying, was allowed to stand over caustic soda pellets for 5 minutes. Ether was then evaporated, and mixed p-chloro- and p- iodo-phenylacetates removed by distillation under reduced pressure. The dark viscous residue was charcoaled in boiling ethanol, but on filtration and cooling, no crystals could be obtained. The ethanolic solution was allowed to stand overnight in presence of sodium hydroxide solution (10cc. $\bar{N}$). Acidification

of the solution gave an oil, and again no crystals could be obtained. Attempted recovery of unchanged phenol also gave an oil, from which no crystalline material could be isolated.

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