## 438. *Bisbenzylisoquinolines. Part II.*[1] *The Synthesis of 5-(2-Aminoethyl)-4′-carboxy-2 : 3-dimethoxydiphenyl Ether.*

By J. R. Crowder, M. F. Grundon, and J. R. Lewis.

The preparation of diphenyl ether derivatives from methyl 4-chloro-3 : 5-dinitrobenzoate, and from methyl 4-chloro-3-nitrobenzoate, and phenols has been examined. Both reactions lead to syntheses of the amino-acid (I) and its *N*-phthaloyl derivative.

The amino-acid (I) was required as an intermediate in a synthesis of bisbenzyl*iso*quinoline alkaloids of the tubocurarine type. A major difficulty in the preparation of these compounds lies in the formation of the diphenyl ether system, as was shown in the synthesis [1] of the related amino-acid (II). The latter compound was prepared by condensation of 4-chloro-3-methoxy-5-nitrobenzaldehyde with methyl 3-hydroxy-4-methoxyphenylacetate in pyridine, subsequent stages involving reduction, deamination, and conversion of the formyl group into a 2-aminoethyl side-chain.

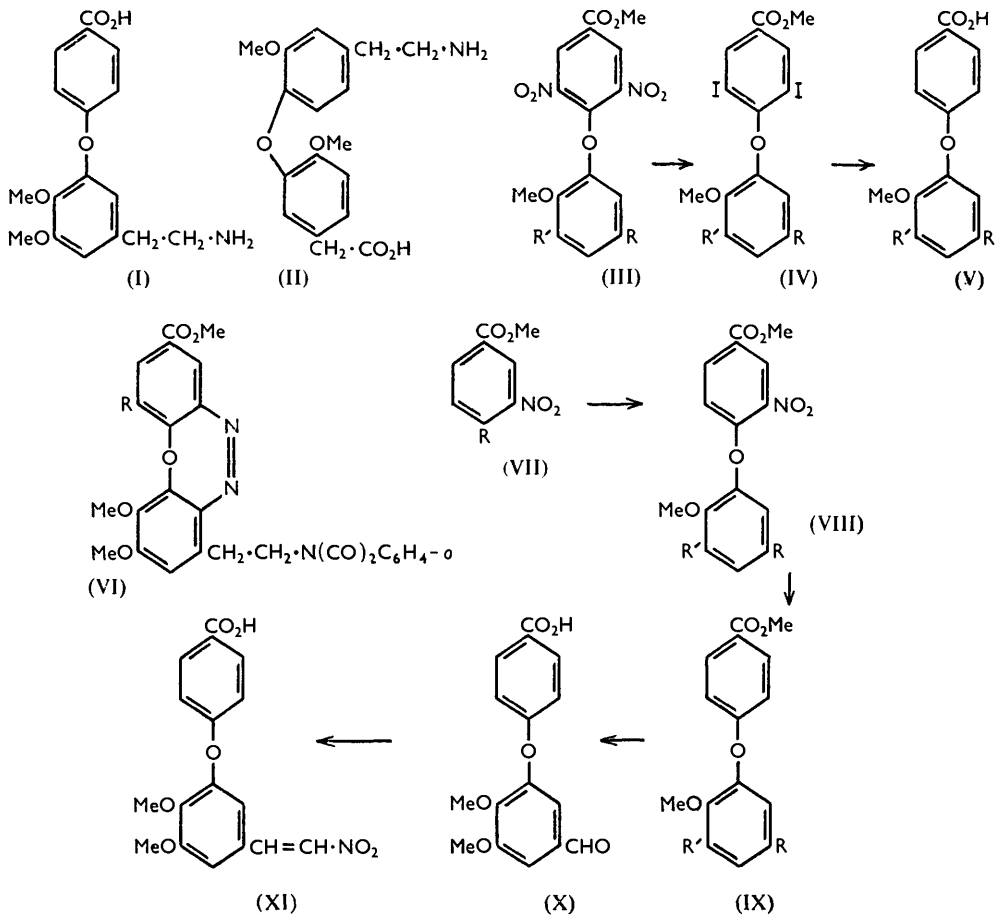
A similar scheme was envisaged for the amino-acid (I), but in this case the presence of an aromatic ring without methoxyl groups allows the use of a triply activated halogenobenzene in the condensation with a suitable phenol. Methyl 4-chloro-3 : 5-dinitrobenzoate has been shown [2] to give diaryl ethers readily, and, in a preliminary experiment, the chloro-compound and guaiacol in pyridine at room temperature afforded the diphenyl ether derivative (III; R = R′ = H) in 80% yield. Reduction to the corresponding diamine proceeded normally as shown by the isolation of a diacetyl derivative (95%), but tetrazotisation of the amine in aqueous solution or with nitrosylsulphuric acid, followed by treatment with hypophosphorous acid, gave no characterisable product. Hems and his co-workers [3] converted numerous dinitrodiphenyl ethers into the corresponding di-iodo-derivatives, and application of their method to our diamine gave the di-iodo-compound (IV; R = R′ = H) (21%). Catalytic reduction in the presence of diethylamine afforded methyl 4-*o*-methoxyphenoxybenzoate in high yield. The corresponding acid (V; R = R′ = H), obtained by hydrolysis, was prepared by Ungnade [4] by a different method.

The moderate success of this scheme encouraged its application to the synthesis of the amino-acid (I). 2 : 3-Dimethoxy-5-2′-phthalimidoethylphenol was chosen for the initial condensation. An essential intermediate in the synthesis of this phenol, namely, 3-hydroxy-4 : 5-dimethoxybenzaldehyde, was conveniently prepared by the McFadyen-Stephens method, as an alternative to other processes.[5,6] Späth and Roder [6] converted 3-ethoxycarbonyloxy-4 : 5-dimethoxybenzaldehyde into the nitrovinyl derivative, which, on reduction and hydrolysis, furnished 2 : 3-dimethoxy-5-2′-aminoethylphenol: we obtained 2 : 3-dimethoxy-5-2′-phthalimidoethylphenol from 3-hydroxy-4 : 5-dimethoxybenzaldehyde in 61% yield *via* the nitrovinyl derivative, without purification of the intermediate amine. Condensation with methyl 4-chloro-3 : 5-dinitrobenzoate then gave the diphenyl ether [III; R = $CH_2$·$CH_2$·$N(CO)_2C_6H_4$-*o*, R′ = OMe] (90%), which was reduced to an unstable diamine, characterised as its diacetate. Tetrazotisation of the crude diamine, followed by reaction with sodium iodide and iodine, gave a difficultly separable mixture of the colourless di-iododiphenyl ether [IV; R = $CH_2$·$CH_2$·$N(CO)_2C_6H_4$-*o*, R′ = OMe] (20—40%) and an orange compound (10—40%), $C_{26}H_{20}O_7N_3I$, considered to be the dibenzoxadiazepine (VI; R = I). The extended conjugation in the latter is shown

[1] Part I, Grundon and Perry, *J.*, 1954, 3531.
[2] Borrows, Clayton, Hems, and Long, *J.*, 1949, S190.
[3] Borrows, Clayton, and Hems, *J.*, 1949, S185; Chalmers, Dickson, Elk, and Hems, *J.*, 1949, 3424.
[4] Ungnade, *J. Amer. Chem. Soc.*, 1941, **63**, 2091.
[5] Mauthner, *Annalen*, 1926, **449**, 102.
[6] Späth and Roder, *Monatsh.*, 1922, **43**, 93.

by the ultraviolet spectrum ($\lambda_{max.}$ 360 mμ; log ε 3·8) which contrasts with that of the di-iodo-compound [IV; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OMe] (no intense absorption above 270 mμ). The iododibenzoxadiazepine, on catalytic reduction, gave the dibenzoxadiazepine (VI; R = H) ($\lambda_{max.}$ 360 mμ, log ε 3·7) quantitatively. The iododibenzoxadiazepine is formed apparently by an azo-coupling reaction, for which the intermediate tetrazonium salt is particularly suitable in that *m*-tetrazonium compounds are known to couple in strongly acid solution,[7] there is a free position *para* to a methoxyl group in the other aromatic ring, and the remaining substituents in this ring are situated favourably. Dibenz-1 : 4 : 5-oxadiazepines have not been recorded previously.

Catalytic reduction of the di-iodo-derivative [IV; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OMe] gave a product which did not crystallise and, without purification, was




hydrolysed with potassium hydrogen carbonate. As this process is liable to open the phthalimido-ring, the crude acid was heated at 150° to effect ring closure to the *N*-phthalimido-acid [V; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OMe] (27%).

The overall yield (6%, based on 3-hydroxy-4 : 5-dimethoxybenzaldehyde) in this synthesis is not satisfactory, and the deamination stage is not reliable. Consequently, a second route (VII—XI) to the amino-acid (I) and its *N*-phthaloyl derivative was explored, using the mononitro-esters (VII; R = Cl, F, or O·$SO_2{\cdot}C_6H_4$Me-*p*). Analogous

[7] Schoutissen, *Rec. Trav. chim.*, 1935, **54**, 381.

halogenobenzenes, such as 1-chloro-2 : 4-dinitrobenzene and 4-chloro-3-methoxy-5-nitrobenzaldehyde, require elevated temperatures for condensation with phenols in pyridine.[1,2] Borrows *et al.*[2] showed that excess of the phenolic component increased the yield of diphenyl ether, but in all our studies we used equimolecular quantities of phenol and halogenobenzene, because the phenol is often difficult of access. Methyl 4-chloro-3-nitrobenzoate and guaiacol gave the diphenyl ether derivative (VIII; R = R′ = H) (51%), but 2 : 3-dimethoxy-5-2′-phthalimidoethylphenol gave no diphenyl ether although none of the phenol was recovered. Thus, the *N*-phthaloyl group appears to be unstable to boiling pyridine, and phenolic aldehydes were employed in subsequent studies.

*iso*Vanillin and methyl 4-chloro-3-nitrobenzoate afforded the diphenyl ether derivative (VIII; R = CHO, R′ = H) (50—60%) with pyridine or with potassium carbonate, whereas use of the potassium derivative of *iso*vanillin in dimethylformamide or in diethylene glycol dimethyl ether gave the diphenyl ether in lower yield. The toluene-*p*-sulphonate (VII; R = O·$SO_2$·$C_6H_4$Me-*p*) and *iso*vanillin in pyridine gave the diphenyl ether (55%), but in dimethylformamide or in ethyl methyl ketone with potassium carbonate the only product isolated was *iso*vanillin toluene-*p*-sulphonate. Although there is some evidence that fluorine is more readily displaced than chlorine in nucleophilic

TABLE 1. *Preparation of the diphenyl ether derivatives* (VIII).

| Reactants * | Conditions | Reflux time (hr.) | Yield (%) of diphenyl ether |
|---|---|---|---|
| *iso*Vanillin + A | $COMeEt–K_2CO_3$ | 1·5 | 60 [a] |
| ,, + A | Pyridine | 1 | 55 [b] |
| K deriv. of *iso*vanillin + A | $NMe_2$·CHO | 2 | 25 [a] |
| ,, + A | $O(CH_2·CH_2·OMe)_2$ | 1 | 30 [b] |
| *iso*Vanillin + B | $COMeEt–K_2CO_3$ | 1·5 | 55 [a] |
| ,, + B | Pyridine | 1·5 | 60 [b] |
| ,, + C | Pyridine | 1 | 55 [b] |
| ,, + C | $NMe_2$·CHO | 0·5 | 0 |
| ,, + C | $O(CH_2·CH_2·OMe)_2$ | 2·5 | 0 |
| 3 : 4 : 5-$HO(MeO)_2C_6H_2$·CHO + A | Pyridine | (see Table 2) | |
| ,, + A | $COMeEt–K_2CO_3$ | 1 | 25 [b] |
| ,, + B | $COMeEt–K_2CO_3$ | 1 | 35 [b] |
| ,, + C | Pyridine | 1 | 30 [a] |
| K deriv. of 3-hydroxy-4 : 5-dimethoxybenzaldehyde + A | $O(CH_2·CH_2·OMe)_2$ | 1 | 30 [a] |

* A = Methyl 4-chloro-3-nitrobenzoate. B = Methyl 4-fluoro-3-nitrobenzoate. C = 4-Methoxycarbonyl-2-nitrophenyl toluene-*p*-sulphonate. [a] Isolated by crystallisation. [b] Isolated by chromatography.

TABLE 2. *Reaction of* 3-*hydroxy*-4 : 5-*dimethoxybenzaldehyde with methyl* 4-*chloro*-3-*nitrobenzoate in pyridine.*

| Temp. | Time (hr.) | Phenol recovered (%) | Diphenyl ether (%) | By-product (%) |
|---|---|---|---|---|
| 25° | 20 | 50 | 0 | 0 |
| 75 | 66 | 40 | 25 | — |
| 85 | 2·5 | 30 | 5 | 10 |
| 80 | 60 | 50 | 25 | 20 |
| 114 | 0·25 | 75 | 20 | 8 |
| 114 | 0·5 | 70 | 20 | 15 |
| 114 | 1 | 25 | 30 | 35 |

reactions with activated halogenobenzenes,[8] methyl 4-fluoro-3-nitrobenzoate showed reactivity similar to that of the chloro-compound when condensed with *iso*vanillin. Parallel reactions were carried out with 3-hydroxy-4 : 5-dimethoxybenzaldehyde, giving the diphenyl ether derivative (VIII; R = CHO, R′ = OMe) (25—33%), and the results

[8] Cf. Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 273.

for both phenols are incorporated in Table 1. The reaction of 3-hydroxy-4 : 5-dimethoxybenzaldehyde and methyl 4-chloro-3-nitrobenzoate in pyridine was studied in detail (Table 2). More vigorous conditions increased the yield of diphenyl ether, but the amount of phenol recovered was much less, apparently because of the increased production of a by-product which did not crystallise and was not investigated. The by-product was not detected in the preparation of the diphenyl ether (70%, based on phenol used) from methyl 4-chloro-3-nitrobenzoate and the potassium salt of the phenol in diethylene glycol dimethyl ether, and this method proved convenient for large-scale reactions.

The nitrodiphenyl ether (VIII; R = R′ = H) was reduced almost quantitatively to the amine, which on diazotisation and reduction of the diazonium salt with hypophosphorous acid afforded the diphenyl ether derivative (IX; R = R′ = H) (43%), identical with the compound prepared from the dinitrodiphenyl ether, as described above. Reduction and deamination of the nitrodiphenyl ether derivatives (VIII; R = CHO, R′ = H and OMe), after protection of the formyl groups by acetylation, furnished the diphenyl ethers (IX; R = CHO, R′ = H) (45%) and (IX; R = CHO, R′ = OMe) (70%), without purification of the intermediate amines. Isolation of the diazofluoroborates, followed by reduction by Roe and Graham's method,[9] was not advantageous.

The acid (X), obtained in good yield by hydrolysis of its methyl ester with potassium hydrogen carbonate, was converted into its nitrovinyl derivative (XI) (63%). Catalytic reduction afforded the required amino-acid (I), isolated more conveniently as its *N*-phthaloyl derivative (43%), identical with the compound prepared earlier. The overall yield (11%, from 3-hydroxy-4 : 5-dimethoxybenzaldehyde), and the convenience of the operations, compared favourably with the alternative route through the dinitrodiphenyl ether derivatives.

## Experimental

*Methyl* 4-o-*Methoxyphenoxy*-3 : 5-*dinitrobenzoate* (III; R = R′ = H).—Methyl 4-chloro-3 : 5-dinitrobenzoate (1·3 g.) was shaken with guaiacol (0·62 g.) in pyridine (8 c.c.) at room temperature for 30 hr. Addition of water gave the *diphenyl ether*, crystallising from ethanol (charcoal) in yellow needles (1·39 g., 80%), 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%).

*Methyl* 3 : 5-*Diacetamido*-4-o-*methoxyphenoxybenzoate*.—The dinitro-compound (0·56 g.) in ethyl acetate was hydrogenated at room temperature and atmospheric pressure with platinum. Removal of the catalyst and the solvent gave the diamine, m. p. 176—191°, which darkened rapidly. Acetylation with acetic anhydride and aqueous sodium hydroxide afforded the *diacetyl derivative*, separating from ethanol in needles (0·58 g., 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%).

*Methyl* 3 : 5-*Di-iodo*-4-o-*methoxyphenoxybenzoate* (IV; R = R′ = H).—Methyl 4-*o*-methoxyphenoxy-3 : 5-dinitrobenzoate (2 g.) in acetic acid (15 c.c.) was hydrogenated at room temperature and atmospheric pressure with platinum (0·2 g.) (6 mols. absorbed in 1 hr.). After removal of the catalyst, the solution was added during 40 min. to a stirred solution of nitrosylsulphuric acid [from sodium nitrite (1 g.) and concentrated sulphuric acid (20 c.c.)] in acetic acid (15 c.c.) at 0°. After 1 hr., the mixture was added in portions during 5 min. to a stirred mixture of sodium iodide (4 g.), iodine (3·4 g.), urea (0·5 g.), water (260 c.c.), and chloroform (50 c.c.). The solution was kept for 1½ hr., the chloroform was separated, and the aqueous solution and the tarry residue were washed with chloroform. The combined chloroform solution was washed with aqueous sodium sulphite saturated with sulphur dioxide, and with water, and then evaporated. The residue, in acetone, was added to an alumina column. Elution with acetone and evaporation of the solvent gave a solid residue. Crystallisation from ethanol afforded the *di-iodo-compound* as needles (0·67 g., 21%), m. p. 131—135° (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, 49·9%).

*Methyl* 4-o-*Methoxyphenoxybenzoate*.—(*a*) Methyl 3 : 5-di-iodo-4-*o*-methoxyphenoxybenzoate (0·5 g.) and diethylamine (0·2 g.) in ethyl acetate were hydrogenated at room temperature

[9] Roe and Graham, *J. Amer. Chem. Soc.*, 1952, **74**, 6297.

and atmospheric pressure in the presence of platinum. The filtered solution was washed with dilute hydrochloric acid, and with water, and evaporated. Distillation of the residue gave *methyl* 4-o-*methoxyphenoxybenzoate*, b. p. 154° (bath)/0·5 mm., separating from ethanol in prisms (0·22 g., 80%), m. p. 66—67° (Found: C, 69·8; H, 5·3. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%).

The corresponding acid, obtained by hydrolysis with potassium hydrogen carbonate in aqueous methanol, crystallised from light petroleum (b. p. 80—100°) in prisms, m. p. 156—157° (lit.,[4] 159°).

(*b*) Methyl 3-amino-4-*o*-methoxyphenoxybenzoate (see below) (0·5 g.) in 20% hydrochloric acid (15 c.c.) was diazotised at −5° with sodium nitrite (0·2 g.). After addition of 30% aqueous hypophosphorous acid (15 c.c.), the solution was kept at 0° for 12 hr. and extracted with ether. Evaporation of the ether and distillation of the residue gave methyl 4-*o*-methoxyphenoxybenzoate, b. p. 100° (bath)/0·01 mm. (0·21 g., 43%), m. p. or mixed m. p. 67°.

N-*Benzenesulphonyl*-N′-4 : 5-*dimethoxy*-3-*methoxycarbonyloxybenzoylhydrazine*.—4 : 5-Dimethoxy-3-methoxycarbonyloxybenzoyl chloride (4·2 g.) in benzene was added in portions to benzenesulphonhydrazide (2·9 g.) in pyridine (10 c.c.). The solution was stirred for 1 hr. and poured into dilute hydrochloric acid at 0°, and the precipitate collected and combined with a further quantity obtained by separation and concentration of the organic layer. Crystallisation from ethanol afforded the *diacylhydrazine* in prisms (4·3 g., 75%), m. p. 166—169° (Found: C, 49·5; H, 4·6. $C_{17}H_{18}O_8N_2S$ requires C, 49·7; H, 4·4%).

3-*Hydroxy*-4 : 5-*dimethoxybenzaldehyde*.—Anhydrous sodium carbonate (6·2 g.) was added in one portion to a solution of the diacylhydrazine (5 g.) in ethylene glycol (70 c.c.) at 160° (internal temp.). After 75 sec., water (500 c.c.) was added, and the solution was acidified with dilute sulphuric acid and extracted with ether (6 × 30 c.c.). The ether solution was washed with aqueous sodium hydrogen carbonate and with water, and evaporated. Distillation of the residue at 0·5 mm. gave the aldehyde (1·74 g., 70%), b. p. 150—155°, needles [from light petroleum (b. p. 60—80°)], m. p. 59—60° (lit.,[5] m. p. 60—61°) (Found: C, 59·1; H, 5·6. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5%). The 2 : 4-*dinitrophenylhydrazone* separated from 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*.—A mixture of 3-hydroxy-4 : 5-dimethoxybenzaldehyde (4·7 g.), nitromethane (5 c.c.), ammonium acetate (2 g.), and acetic acid (20 c.c.) was heated under reflux for 2 hr., and added to water. The precipitate, on crystallisation from ethanol, gave the *nitrostyrene derivative* (4·07 g., 69%), m. p. 160—170°, recrystallising in yellow needles, m. p. 168—170° (Found: C, 53·6; H, 5·1. $C_{10}H_{11}O_5N$ requires C, 53·4; H, 4·9%).

2 : 3-*Dimethoxy*-5-2′-*phthalimidoethylphenol*.—The nitrostyrene derivative (0·61 g.) in ethyl acetate was added to platinum oxide prereduced in 10% aqueous sulphuric acid (6 c.c.), and hydrogenated at room temperature and atmospheric pressure until 4 mol. of hydrogen had been absorbed (1 hr.). After removal of the catalyst the aqueous layer was separated, and the ethyl acetate solution washed with water. The combined aqueous solution was passed through an ion-exchange column (Amberlite IR-4B), and the eluate was evaporated. The residue in acetic acid was heated under reflux with phthalic anhydride (0·48 g.) for 30 min. Addition of water gave a precipitate of the *phthalimidophenol* (0·72 g., 91%), crystallising from ethanol in 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%).

*Methyl* 4-(2 : 3-*Dimethoxy*-5-2′-*phthalimidoethylphenoxy*)-3 : 5-*dinitrobenzoate* [III; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OMe].—2 : 3-Dimethoxy-5-2′-phthalimidoethylphenol (0·146 g.), methyl 4-chloro-3 : 5-dinitrobenzoate (0·176 g.), and pyridine (10 c.c.) were kept at room temperature for 36 hr., chloroform was added, and the solution washed with dilute hydrochloric acid, N-aqueous sodium hydroxide, and water. Evaporation and crystallisation of the residue from ethanol gave the *diphenyl ether* as yellow plates (0·22 g., 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%).

The corresponding *acid*, obtained by hydrolysis with potassium hydrogen carbonate in aqueous methanol, separated from ethanol in 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%).

*Methyl* 3 : 5-*Diacetamido*-4-(2 : 3-*dimethoxy*-5-2′-*phthalimidoethylphenoxy*)*benzoate*.—The dinitro-compound (0·175 g.) in acetic acid (5 c.c.) was hydrogenated at room temperature and atmospheric pressure with platinum. The catalyst was removed, 20% aqueous sodium

hydroxide (5 c.c.) and acetic anhydride (0·4 c.c.) were added, the mixture was shaken for 30 min., water added, and the solution was extracted with chloroform. Evaporation and crystallisation of the residue from ethanol gave the *diacetamido-derivative* in needles (0·141 g., 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%).

*Methyl* 4-(2 : 3-*Dimethoxy*-5-2′-*phthalimidoethylphenoxy*)-3 : 5-*di-iodobenzoate* [IV; R = $CH_2$·$CH_2$·$N(CO)_2C_6H_4$-*o*, R′ = OMe].—(*a*) The dinitrobenzoate (2 g.) was reduced as described in the previous experiment, and the solution of the diamine was added during 1 hr. to a stirred solution of sodium nitrite (0·8 g.) in concentrated sulphuric acid (35 c.c.) and glacial acetic acid (25 c.c.). After 1 hr. the solution was added to a mixture of sodium iodide (3·5 g.), iodine (3 g.), urea (0·4 g.), water (200 c.c.), and chloroform (70 c.c.). The chloroform layer was separated, washed with aqueous sodium sulphite, and evaporated. The residue in acetone was chromatographed on acid-washed alumina. Elution with acetone gave a red oil. Further chromatography achieved no purification. The combined fractions with ethanol gave a red solid (1·6 g.), m. p. 135—175°. By treating a portion (1·1 g.) with a little acetone the *di-iodo-compound* was obtained as a white solid (0·80 g., 46%), separating from acetone–methanol in needles, m. p. 164—165°, and crystallising above this m. p. in prisms, m. p. 179—183° (Found: C, 44·5; H, 2·9; I, 35·6; OMe, 12·6. $C_{26}H_{21}O_7NI_2$ requires C, 43·8; H, 3·0; I, 35·6; 3OMe, 12·8%).

The crude mixture (0·5 g.) was triturated with ether. The precipitate (0·1 g., 14%) of 1-*iodo*-9 : 10-*dimethoxy*-3-*methoxycarbonyl*-7-2′-*phthalimidoethyldibenz*-1 : 4 : 5-*oxadiazepine*, crystallised from ethanol in orange prisms, 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%).

(*b*) In some experiments in which less of the di-iodo-compound was present, purification by chromatography was successful. Thus, the crude product from the dinitrobenzoate (1·12 g.) in acetone was chromatographed on a long column of acid-washed alumina. Elution with acetone and crystallisation from ethanol gave the di-iodo-compound in needles (0·21 g., 15%), m. p. 150—160°, resolidifying in prisms, m. p. 180—184°, undepressed by mixing with a sample obtained as in (*a*).

Further elution with acetone gave a red oil, affording from ethanol orange prisms (0·48 g., 39%), m. p. and mixed m. p. with the iodo-oxadiazepine 192—194°.

p-(2 : 3-*Dimethoxy*-5-2′-*phthalimidoethylphenoxy*)*benzoic Acid* [V; R = $CH_2$·$CH_2$·$N(CO)_2C_6H_4$-*o*, R′ = OMe].—Methyl 4-(2 : 3-dimethoxy-5-2′-phthalimidoethylphenoxy)-3 : 5-di-iodobenzoate, (0·6 g.) in ethyl acetate (50 c.c.) containing diethylamine (0·2 g.) was reduced with hydrogen and platinum at room temperature and atmospheric pressure until 2 mol. of hydrogen had been absorbed (30 min.). After filtration, the solution, which rapidly became red, was washed with dilute hydrochloric acid and water, and was evaporated. The residual red oil was extracted with several portions of boiling light petroleum (b. p. 60—80°), and the petroleum-soluble oil was refluxed for 2 hr. with potassium hydrogen carbonate in aqueous methanol. The gum, obtained by removal of the methanol, acidification, and extraction with chloroform, was heated at 140—150° for 30 min. Crystallisation from methanol and trituration of the solid with benzene furnished the *acid* in crystals (0·10 g., 27%), m. p. 180—183°, separating from benzene–light petroleum in prisms, m. p. 182—184°, and, after cooling and resolidifying, m. p. 197—202° (Found: C, 67·4; H, 4·5. $C_{15}H_{21}O_7N$ requires C, 67·1; H, 4·7%).

9 : 10-*Dimethoxy*-3-*methoxycarbonyl*-7-2′-*phthalimidoethyldibenz*-1 : 4 : 5-*oxadiazepine* (VI; R = H).—The iodo-oxadiazepine (0·30 g.) was hydrogenated as described for the di-iododiphenyl ether derivative, until hydrogen absorption ceased. The *product* crystallised from ethanol in yellow needles (0·23 g., 97%), m. p. 217—214° (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%).

*Methyl* 4-o-*Methoxyphenoxy*-3-*nitrobenzoate* (VIII; R = R′ = H).—A solution of methyl 3-chloro-4-nitrobenzoate (2·5 g.) and guaiacol (1·44 g.) in pyridine was heated under reflux for 1½ hr., added to ice and water, and extracted with ether. The ether solution was washed with dilute hydrochloric acid and dilute sodium hydroxide, then evaporated. By crystallisation from ethanol *methyl* 4-o-*methoxyphenoxy*-3-*nitrobenzoate* was obtained as plates (1·81 g., 51%), 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%).

The *acid*, prepared by hydrolysis with potassium hydrogen carbonate, separated from ethyl acetate in prisms, m. p. 164° (Found: C, 58·2; H, 4·0. $C_{14}H_{11}O_6N$ requires C, 58·2; H, 3·8%).

4-*Methoxycarbonyl*-2-*nitrophenyl Toluene*-p-*sulphonate*.—Sodium carbonate (3 g.) was added in portions to a mixture of methyl 4-hydroxy-3-nitrobenzoate (3 g.), toluene-*p*-sulphonyl

chloride (3 g.), and water (30 c.c.) at 100°. After the addition of more toluene-*p*-sulphonyl chloride (0·5 g.) and sodium carbonate (0·5 g.), the solution was heated for a further 15 min. and cooled to 0°. The precipitate, after being washed with warm aqueous sodium carbonate and water, crystallised from ethanol, giving needles of the *toluene*-p-*sulphonate* (2·5 g., 50%), m. p. 95—96° (Found: C, 51·4; H, 3·7. $C_{15}H_{13}O_7NS$ requires C, 51·3; H, 3·8%).

iso*Vanillin Toluene*-p-*sulphonate*.—*iso*Vanillin (0·3 g.), toluene-*p*-sulphonyl chloride (0·6 g.), and diethylaniline (10 c.c.) were heated in a steam-bath for 2 hr. and added to dilute hydrochloric acid. The precipitated *ester* crystallised from ethanol as needles (0·5 g.), m. p. 144° (Found: C, 58·5; H, 4·7. $C_{15}H_{14}O_5S$ requires C, 58·8; H, 4·6%).

*Methyl* 4-(5-*Formyl*-2-*methoxyphenoxy*)-3-*nitrobenzoate* (VIII; R = CHO, R′ = H).—(*a*) A mixture of methyl 4-chloro-3-nitrobenzoate (0·5 g.), *iso*vanillin (0·5 g.), anhydrous potassium carbonate (1 g.), and ethyl methyl ketone (25 c.c.) was heated under reflux for 1·5 hr. After filtration and evaporation, the residue was washed in ether with aqueous sodium hydroxide and water. Evaporation of the ethereal layer and crystallisation of the residue from ethanol gave the *diphenyl ether* in needles (0·6 g., 60%), m. p. 118—121° (Found: C, 58·1; H, 4·1. $C_{16}H_{13}O_6N$ requires C, 58·0; H, 4·0%). The 2 : 4-*dinitrophenylhydrazone* separated from 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%).

(*b*) A solution of methyl 4-fluoro-3-nitrobenzoate (0·5 g.) and *iso*vanillin (0·5 g.) in pyridine (6·5 c.c.) was refluxed for 1½ hr., and added to dilute hydrochloric acid (50 c.c., 15%). Ether-extraction gave a brown oil (0·85 g.) which was chromatographed in benzene on alumina. Elution with light petroleum gave methyl 4-fluoro-3-nitrobenzoate (0·2 g.), and elution with benzene gave the diphenyl ether (0·6 g., 60%), m. p. and mixed m. p. 116—118°.

*Reaction of* 4-*Methoxycarbonyl*-2-*nitrophenyl Toluene*-p-*sulphonate with* iso*Vanillin*.—The toluene-*p*-sulphonate (1·0 g.), *iso*vanillin (0·5 g.), and potassium carbonate (1·5 g.) in dimethylformamide (30 c.c.) were heated under reflux for ½ hr. Addition of water and ether-extraction gave an oil which crystallised from ethanol in needles (0·9 g.), m. p. and mixed m. p. with *iso*vanillin toluene-*p*-sulphonate 140—142°.

*Methyl* 4-(5-*Formyl*-2 : 3-*dimethoxyphenoxy*)-3-*nitrobenzoate* (VIII; R = CHO, R′ = OMe).—(*a*) The potassium salt of 3-hydroxy-4 : 5-dimethoxybenzaldehyde [obtained from the aldehyde (4·9 g.) and potassium hydroxide in ethanol–ether as a brown oil] and methyl 4-chloro-3-nitrobenzoate (4·0 g.) were refluxed in diethylene glycol dimethyl ether (25 c.c.) for 1 hr. Water was added and the solution was extracted with ether. The ether was washed with aqueous sodium hydroxide and water and evaporated. The residue, on crystallisation from ethanol, afforded the *ether* (3·0 g., 31%), m. p. 88° (Found: C, 56·3; H, 4·0. $C_{17}H_{15}O_8N$ requires C, 56·5; H, 4·2%). Methyl 4-chloro-3-nitrobenzoate (2·5 g.), m. p. and mixed m. p. 74—76°, was recovered by concentration of the ethanol mother-liquor.

Acidification and ether-extraction of the alkaline washings gave 3-hydroxy-4 : 5-dimethoxybenzaldehyde (2·7 g., 55%), b. p. 125°/0·02 mm.

(*b*) 3-Hydroxy-4 : 5-dimethoxybenzaldehyde (0·5 g.) and methyl 4-chloro-3-nitrobenzoate (0·5 g.) were refluxed in pyridine (12 c.c.) for 1 hr., and the solution was added to dilute hydrochloric acid and extracted with ether. The ether solution was washed with aqueous sodium hydroxide and water and evaporated. The residue in light petroleum (b. p. 60—80°) was chromatographed on alumina. Elution with the same solvent gave methyl 4-chloro-3-nitrobenzoate (0·3 g.), m. p. and mixed m. p. 74—76°. Benzene elution gave the diphenyl ether (0·3 g., 35%), m. p. and mixed m. p. 80—84°. Further elution with benzene afforded a colourless by-product (0·25 g.), which did not crystallise.

The reaction was carried out under various conditions (Table 2).

*Methyl* 3-*Amino*-4-*o*-*methoxyphenoxybenzoate*.—Methyl 4-*o*-methoxyphenoxy-3-nitrobenzoate (0·73 g.) and 5% palladium–charcoal in ethyl acetate were hydrogenated at room temperature and atmospheric pressure. After filtration, the solution was evaporated. The residue, on trituration with light petroleum (b. p. 40—60°), gave the *amine*, separating from ethanol–light petroleum (b. p. 40—60°) in prisms (0·59 g., 90%), m. p. 70—71° (Found: C, 65·5; H, 5·5. $C_{15}H_{15}O_4N$ requires C, 65·5; H, 5·5%). The *acetyl derivative* crystallised from aqueous ethanol in 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-(5-*Formyl*-2-*methoxyphenoxy*)*benzoate* (IX; R = CHO, R′ = H).—Methyl 4-(5-formyl-2-methoxyphenoxy)-3-nitrobenzoate (2 g.) in acetic anhydride (10 c.c.) was treated with concentrated sulphuric acid (4 drops). After 15 min., water was added, and the precipitated

gum washed with ethanol (2 × 10 c.c.). The *diacetate* crystallised from ethanol in needles, 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%).

The crude product in ethyl acetate was hydrogenated with platinum at room temperature and atmospheric pressure. After filtration and evaporation the amine was treated in 15% hydrochloric acid (20 c.c.) at 0° during 20 min. with sodium nitrite (0·3 g.) in water. After 15 min. 30% hypophosphorous acid (30 c.c.) was added, the solution was kept at 0° for 12 hr., then extracted with ether, and the ether solution washed with dilute sodium hydroxide, dilute hydrochloric acid, and water. Evaporation and distillation of the residue gave the *aldehyde* (0·78 g., 45%), b. p. 200—220° (bath)/0·2 mm., separating from benzene–light petroleum (b. p. 40—60°) in 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%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in 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%).

*Methyl* 4-(5-*Formyl*-2 : 3-*dimethoxyphenoxy*)*benzoate* (IX; R = CHO, R′ = OMe).—Methyl 4-(5-formyl-2 : 3-dimethoxyphenoxy)-3-nitrobenzoate (3·2 g.) was acetylated, and the crude diacetate hydrogenated as in the preceding experiment. The amine in 15% hydrochloric acid (50 c.c.) at 0° was diazotised with sodium nitrite (0·5 g.) in water and, after 1 hr., 40% hypophosphorous acid (45 c.c.) and copper sulphate (10 mg.) were added. The solution was kept at 0° for 4 hr. and extracted with ether. After being washed with alkali and acid the ether solution was evaporated, and the residue (2·2 g.) in benzene chromatographed on alumina. *Methyl* 4-(5-*formyl*-2 : 3-*dimethoxyphenoxy*)*benzoate* was obtained by benzene elution, and separated from light petroleum (b. p. 40—60°) in needles (2·0 g., 70%), m. p. 111—113° (Found: C, 64·4; H, 5·1. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%).

4-(5-*Formyl*-2 : 3-*dimethoxyphenoxy*)*benzoic Acid* (X).—A solution of the ester (2·8 g.) and potassium hydrogen carbonate (15 g.) in methanol (100 c.c.) and water (40 c.c.) was heated under reflux for 2 hr. The methanol was removed, and the solution was acidified with dilute hydrochloric acid. The precipitated *acid* crystallised from benzene–light petroleum (b. p. 60—80°) in plates (2·1 g., 80%), m. p. 73—74°, and after being heated at 25°/0·001 mm. for 3 hr., 118—120° (Found: C, 63·4; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·7%).

4-(2 : 3-*Dimethoxy*-5-2′-*nitrovinylphenoxy*)*benzoic Acid* (XI).—5% Aqueous sodium hydroxide (3·5 c.c.) was added during 20 min. to a solution of 4-(5-formyl-2 : 3-dimethoxyphenoxy)benzoic acid (0·35 g.) at 0—10°. After 20 min., the solution was added to 15% hydrochloric acid (30 c.c.) Crystallisation of the precipitate from aqueous ethanol gave the *nitrovinyl-acid* as yellow needles (0·25 g., 63%), m. p. 164—167° (Found: C, 59·3; H, 4·7. $C_{17}H_{15}O_7N$ requires C, 59·1; H, 4·4%).

p-(2 : 3-*Dimethoxy*-5-2′-*phthalimidoethylphenoxy*)*benzoic Acid* [V; R = $CH_2$·$CH_2$·$N(CO)_2C_6H_4$-*o*, R′ = OMe].—The nitrovinyl-derivative (0·40 g.), acetic acid (35 c.c.), concentrated sulphuric acid (0·3 c.c.), and platinum oxide (200 mg.) were hydrogenated at room temperature and atmospheric pressure until hydrogen absorption ceased (1 hr.). After filtration, the solution was evaporated, and the residue in water passed through a column of ion-exchange resin (Amberlite IR-4B). The eluate, on evaporation, afforded p-(5-2′-*aminoethyl*-2 : 3-*dimethoxyphenoxy*)*benzoic acid* (0·35 g.), which, sublimed at 225—230° (bath)/0·0001 mm., had m. p. 260—264° (Found: C, 64·2; H, 6·0. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0%).

The crude amino-acid was heated at 140—160° for 2 hr. with phthalic anhydride (0·18 g.). The melt was extracted with chloroform, and the residue heated with a further quantity of phthalic anhydride and extracted with chloroform. Evaporation of the chloroform solution and crystallisation of the residue from methanol gave the phthalimido-acid (0·22 g., 43%), m. p. 180—190°. Recrystallisation from methanol gave cubes, m. p. 197—202°, identical (mixed m. p. and infrared spectrum) with a sample prepared by the alternative route.

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University of Glasgow,
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