870. *Bisbenzylisoquinolines. Part IV.*[1] *The Preparation of Diaryl Ethers from Diaryliodonium Salts.*

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The reaction of phenoxides with symmetrically substituted diaryliodonium salts provides a general route to substituted diaryl ethers. This procedure and other methods were used to synthesise the phthalimido-ester [VI; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*] and the corresponding amino-acid (VII).

Diaryliodonium salts are readily attacked at position 1 by nucleophiles,[2] and thus show promise as general electrophilic phenylating agents. The reaction with phenoxides proceeds, apparently, by a variation of the S_N2 mechanism,[3,4] and gives diphenyl ethers:

$$Ar_2I^+X^- + Ar'O^- \longrightarrow Ar{-}O{-}Ar' + ArI + X^-$$

We have studied the reaction further because of our interest in diphenyl ethers as intermediates in the synthesis of bisbenzylisoquinoline alkaloids. Since only a few examples have been reported,[2,4,5] the reactions of simple iodonium salts were examined first, in order to establish a suitable procedure and to determine the scope of the method. The

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[1] Part III, Grundon, *J.*, 1959, 3010.

[2] Beringer, Brierley, Drexler, Gindler, and Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75**, 2708.

[3] Beringer and Gindler, *J. Amer. Chem. Soc.*, 1955, **77**, 3203.

[4] Caserio, Glusker, and Roberts, *J. Amer. Chem. Soc.*, 1959, **81**, 336.

[5] Hillman, *Z. Naturforsch.*, 1956, **11**b, 419; Dibbo, Stevenson, Walker, and Warberton, *J.*, 1961, 2645.

investigation was confined to symmetrically substituted iodonium salts (I), which are prepared conveniently by oxidative iodination of aryl derivatives.[6]

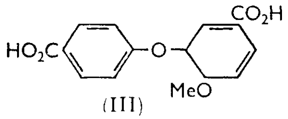
The reaction of diphenyliodonium bromide, chloride, or perchlorate with sodium phenoxide in water, methanol, butanol, or 2,2′-dimethoxydiethyl ether, afforded diphenyl ether in 41—72% yield (Table 1). In these experiments, equimolecular quantities of the components were employed; with an excess of phenoxide (5 mol.), Beringer and his colleagues obtained diphenyl ether from diphenyliodonium bromide in 76% yield.[2] If the associated anion (Br^- or Cl^-) competes with the phenoxide ion, the use of an iodonium salt containing a very weakly nucleophilic anion, for example a perchlorate ion, should be advantageous. The observation that diphenyliodonium perchlorate (I; X = ClO_4) does not give a higher yield of diphenyl ether (Table 1) suggests that the associated anions do not participate in the reaction. The highest yield of diphenyl ether was obtained from the iodonium bromide in water, and this procedure was applied to the preparation of substituted diphenyl ethers. Thus, diphenyliodonium bromide (I; R = H, X = Br) or di-*p*-tolyliodonium bromide (I; R = Me, X = Br) with the sodium salts of phenol, guaiacol, vanillin, or isovanillin furnished the corresponding diphenyl ethers (II) in 63—86% yield (Table 2). The preparation of the acid (III) by Grundon and McGarvey[7] illustrates the utility of the method; the acid was obtained by oxidation of 5-formyl-2-methoxy-4′-methyldiphenyl ether (II; R^1 = Me, R^2 = OMe, R^3 = CHO, R^4 = H), which was prepared from di-*p*-tolyliodonium bromide and isovanillin in 65% yield.

TABLE 1.

Formation of diphenyl ether from diphenyliodonium salts and sodium phenoxide.

Iodonium salt	Yield (%) in H_2O at 100°	Yield (%) in MeOH at 65°	Yield (%) in butan-1-ol at 116°	Yield (%) in $(MeO{\cdot}C_2H_4)_2O$ at 80°
Bromide	72	53	—	66
Chloride	66	41	—	—
Perchlorate	65	57	56	—

(I) (II)



(III)

TABLE 2.

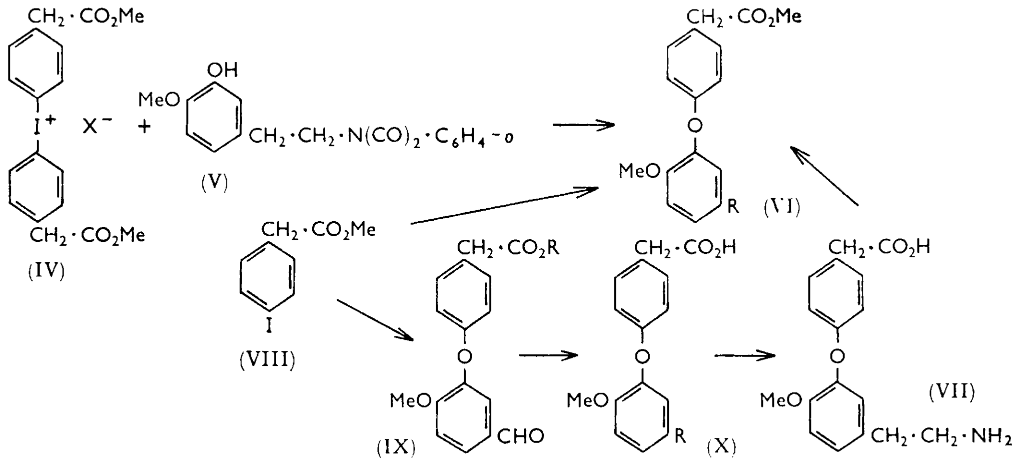
Preparation of diaryl ethers from diaryliodonium bromides, phenols (1 mol.), and sodium hydroxide (1 mol.) in water at 100°.

		Product (II)				
Iodonium salt	Phenol	R^1	R^2	R^3	R^4	Yield (%)
(I; R = H, X = Br)	Isovanillin	H	OMe	CHO	H	84
(I; R = Me, X = Br)	Phenol	Me	H	H	H	86
(I; R = Me, X = Br)	Guaiacol	Me	OMe	H	H	64
(I; R = Me, X = Br)	Vanillin	Me	OMe	H	CHO	63
(I; R = Me, X = Br)	Isovanillin	Me	OMe	CHO	H	65

The amino-acid (VII) is required in the synthesis of bisbenzylisoquinolines, and one scheme devised for its preparation involved the reaction of the phthalimido-phenol (V) with the 4,4′-di(methoxycarbonylmethyl)diphenyliodonium salt (IV) and hydrolysis of the product [VI; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*]. Oxidative iodination of methyl phenylacetate followed by addition of the appropriate inorganic salt gave the diaryliodonium bromide, chloride, or iodide (IV). Heating the iodide at 160° or refluxing its solution in

[6] Beringer, Drexler, Gindler, and Lumpkin, *J. Amer. Chem. Soc.*, 1953, **75**, 2705.
[7] Grundon and McGarvey, *J.*, 1960, 2739.

acetic acid furnished methyl *p*-iodophenylacetate (VIII). This product was homogeneous, since vapour-phase chromatography gave a single peak. The ester was identified by hydrolysis to *p*-iodophenylacetic acid, and by comparison of the ester and of the acid with samples prepared from *p*-aminophenylacetic acid. The identification of this ester as the sole decomposition product confirms the structure of the iodide. Beringer *et al.*[8] showed that in the iodination other aryl compounds containing electron-releasing groups were also substituted exclusively in the *para*-position. The phthalimido-phenol (V), which is the second component for the projected synthesis, was prepared from 3-benzyloxy-4-methoxy-ω-nitrostyrene; modification of the previous method[9] (see Experimental section) resulted in a greatly improved yield (67%).



The utility of the iodonium chloride (IV; R = Cl) for the preparation of diphenyl ethers was explored by studying the reaction of the compound with guaiacol (the bromide was insufficiently soluble in water). The chloride and 3 mol. of the sodium salt of guaiacol gave the ether (VI; R = H) in 30% yield. With equimolecular quantities of the reactants, the best yield (15%) was obtained when the reaction was conducted in water at 70°. Under these conditions, the chloride (IV; R = Cl) and the sodium salt of the phthalimido-phenol (V) furnished the ether [VI; R = $CH_2·CH_2·N(CO)_2C_6H_4$-*o*] (6%). The structure of the product was confirmed by its infrared absorption at 1775, 1710, and 724 $cm.^{-1}$ (*N*-phthaloyl group) and 1730 $cm.^{-1}$ (CO_2Me), and by two independent syntheses (see below). The presence of hydrolysable groups in both reactants is probably partly responsible for the low yield obtained in the reaction. 4,4′-Biscyanomethyldiphenyliodonium bromide (I; R = $CH_2·CN$, X = Br) was prepared in the usual way from benzyl cyanide, but reaction with sodium phenoxide did not yield a diphenyl ether derivative.

Bacon and Hill[10] reported recently that halogen in unactivated aryl halides is replaced readily in polar solvents with the aid of cuprous compounds. Iodobenzene, for example, with phenol and cuprous oxide in boiling 2,4,6-trimethylpyridine gave diphenyl ether in high yield. A strong base is not required, and the method should be particularly suitable, therefore, for the preparation of diphenyl ethers containing hydrolysable substituents. Application of the procedure to methyl *p*-iodophenylacetate and guaiacol furnished the

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[8] Beringer, Falk, Karniol, Lillien, Masullo, Mausner, and Sommer, *J. Amer. Chem. Soc.*, 1959, **81**, 342.

[9] Kulka and Manske, *J. Amer. Chem. Soc.*, 1953, **75**, 1322.

[10] Bacon and Hill, *Proc. Chem. Soc.*, 1962, 113, and unpublished results.

diphenyl ether (VI; R = H) (40%), which was characterised by conversion into the corresponding acid. Methyl *p*-iodophenylacetate, the phthalimido-phenol (V), and cuprous oxide gave the phthalimidodiphenyl ether [VI; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*] (7%, isolated by chromatography). Since the yield of this compound was only slightly higher than that obtained by the iodonium salt method, a new approach to the amino-acid (VII) was examined.

Methyl *p*-iodophenylacetate, isovanillin, and cuprous oxide in boiling lutidine afforded the formyldiphenyl ether ester (IX; R = Me) (22%). The corresponding acid (IX; R = H), obtained by hydrolysis, was converted into the nitrile (X; R = $CH_2{\cdot}CN$) by the rhodanine procedure, and into the nitrostyrene (X; R = $CH{:}CH{\cdot}NO_2$) by reaction with nitromethane. Reduction of either of these products with hydrogen and platinum afforded the amino-acid (VII). The nitrostyrene route is superior to the nitrile procedure, because the overall yield of the amino-acid is higher and because the intermediate is purified more easily. The amino-acid exists as a zwitterion, since it shows strong infrared adsorption at 1560 cm.$^{-1}$ (CO_2^-), but not in the carbonyl region of the spectrum. Phthalic anhydride yielded the phthalimido-derivative [$\nu_{max.}$ 1770, 1715, 723 (*N*-phthaloyl-group), and 1700 cm.$^{-1}$ (CO_2H)], which with diazomethane was converted into the phthalimido-ester [VI; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*] described above.

EXPERIMENTAL

Diphenyliodonium Perchlorate.—The preparation was carried out as for diphenyliodonium bromide [6] except that aqueous perchloric acid replaced aqueous sodium bromide. The *perchlorate* separated from ethanol in needles, m. p. 174—175° (Found: C, 38·1; H, 2·7. $C_{12}H_{10}ClIO_4$ requires C, 37·9; H, 2·7%).

4,4′-*Di*(*methoxycarbonylmethyl*)*diphenyliodonium Halides.*—Potassium iodate (12·8 g.) was added during 2·5 hr. to a solution of methyl phenylacetate (19 g.) in acetic acid (80 c.c.), acetic anhydride (28 c.c.), and concentrated sulphuric acid (12 c.c.). The mixture was stirred for 48 hr. and iced water (100 c.c.) was added. After filtration, the solution was saturated with sulphur dioxide. Addition of potassium bromide (30 g.) and crystallisation of the resultant precipitate from water gave the *bromide* (20 g., 64%). A sample separated from ethanol in needles, m. p. 166—167° (Found: C, 42·6; H, 3·8. $C_{18}H_{18}BrIO_4$ requires C, 42·8; H, 3·6%).

Addition of potassium iodide instead of potassium bromide gave the *iodide*, crystallising from ethanol in needles, m. p. 150° (Found: C, 39·1; H, 3·2. $C_{18}H_{18}I_2O_4$ requires C, 39·2; H, 3·3%).

The experiment was repeated with methyl phenylacetate (95 g.). After the potassium iodate had been consumed, iced water (400 c.c.) was added and the solution was extracted with ether (900 c.c.). The ether solution was washed with water, and the combined aqueous solutions were treated with a saturated solution of ammonium chloride (70 g.) in water and then kept as 0° for 12 hr. The precipitate was heated with ethanol. After filtration and concentration of the ethanol solution, the *iodonium chloride* separated in needles (43 g., 32%), m. p. 188° (Found: C, 47·2; H, 4·0. $C_{18}H_{18}ClIO_4$ requires C, 46·9; H, 3·9%).

4,4′-*Biscyanomethyldiphenyliodonium Bromide and Iodide.*—Potassium iodate (64 g.) was added during 2 hr. to a solution of benzyl cyanide (100 g.) in acetic acid (400 c.c.), acetic anhydride (140 c.c.), and concentrated sulphuric acid (60 c.c.). The mixture was stirred for 12 hr., added to ice and water, and extracted with ether. Saturation of the aqueous solution with sulphur dioxide gave a precipitate of the *iodide*, which separated from water in needles (3·3 g.), m. p. 158—160° (Found: C, 40·1; H, 2·6. $C_{16}H_{12}N_2I_2$ requires C, 39·6; H, 2·5%).

After removal of the iodide, the filtrate was saturated with sodium bromide. The precipitated *bromide* crystallised from water in needles (9·1 g.), m. p. 201—202° (Found: C, 43·7; H, 2·8. $C_{16}H_{12}BrIN_2$ requires C, 43·8; H, 2·8%).

Diphenyl Ether.—In each of the following experiments, diphenyl ether was identified by comparison of its infrared spectrum with that of an authentic sample.

(*a*) A mixture of diphenyliodonium bromide [6] (9 g.), phenol (2·3 g., 1 equiv.), sodium hydroxide (1 g., 1 equiv.), and water (200 c.c.) was stirred and heated under reflux for 24 hr.

and then extracted with ether. The ether solution was washed with aqueous sodium hydroxide and evaporated. Distillation of the residue gave diphenyl ether (3·05 g., 72%), b. p. 114—116°/8 mm. By the same procedure, diphenyliodonium chloride[11] (5·5 g.) gave diphenyl ether (1·97 g., 66%).

In a similar way, diphenyliodonium perchlorate (19 g.) was refluxed with 1 equiv. of aqueous sodium phenoxide for 40 hr. After being shaken with ether the mixture was filtered to give unchanged perchlorate (2·5 g.). Diphenyl ether (4·77 g.), b. p. 115—118°/9 mm., was obtained in the usual way. The yield was 65% based on the weight of perchlorate consumed.

(*b*) Diphenyliodonium bromide (18 g.) and phenol (4·7 g., 1 equiv.) were added to a solution from sodium (1·15 g., 1 equiv.) in dry methanol (300 c.c.). The mixture was stirred and heated under reflux for 24 hr., most of the methanol was removed by evaporation, water was added, and diphenyl ether (4·49 g., 53%), b. p. 116—118°/9 mm., was obtained with ether.

In the same way, diphenyliodonium chloride (15·8 g.) gave diphenyl ether (3·48 g., 41%).

Diphenyliodonium perchlorate (19 g.) gave diphenyl ether (3·8 g.), and unchanged perchlorate (4 g.). The yield of diphenyl ether was 57%, based on perchlorate consumed. When the experiment was carried out in boiling butan-1-ol instead of methanol, diphenyliodonium perchlorate (19 g.) gave diphenyl ether (4·75 g., 56%).

(*c*) Sodium (1·15 g.) was added to 2,2′-dimethoxydiethyl ether (250 c.c.) containing phenol (4·7 g.). After the addition of diphenyliodonium bromide (18 g.), the mixture was stirred and heated at 80° for 24 hr. Most of the solvent was removed by distillation under reduced pressure, and the residue was worked up in the usual way to give diphenyl ether (5·61 g., 66%), b. p. 117—118°/10 mm.

5-*Formyl*-2-*methoxydiphenyl Ether*.—A mixture of diphenyliodonium bromide (18 g.), isovanillin (7·6 g.), sodium hydroxide (2 g.), and water (300 c.c.) was refluxed for 24 hr. and worked up in the usual way. Distillation of the product gave 5-*formyl*-2-*methoxydiphenyl ether* (9·5 g., 84%), b. p. 160°/0·1 mm., which solidified. Crystallisation from ethanol gave prisms, m. p. 48—49° (Found: C, 73·2; H, 5·3. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%). The poor analysis is probably due to the difficulty in removing solvent. The 2,4-*dinitrophenylhydrazone* separated from acetic acid in red needles, m. p. 226—227° (Found: C, 58·7; H, 3·8. $C_{20}H_{16}N_4O_6$ requires C, 58·8; H, 4·0%).

4-*Methyldiphenyl Ether*.—A mixture of di-*p*-tolyliodonium bromide (20 g.), phenol (5 g.), sodium hydroxide (2 g.), and water (300 c.c.) was refluxed for 24 hr. and worked up in the usual way. Distillation gave 4-methyldiphenyl ether (8·46 g., 86%), b. p. 129°/8 mm. (lit.,[12] b. p. 138—140°/11 mm.) (Found: C, 84·5; H, 6·5. Calc. for $C_{13}H_{12}O$: C, 84·7; H, 6·5%).

2-*Methoxy*-4′-*methyldiphenyl Ether*.—By the method used for the preceding compound, di-*p*-tolyliodonium bromide (20 g.) and guaiacol (6·5 g.) gave 2-*methoxy*-4′-*methyldiphenyl ether* (7·07 g., 64%), b. p. 158—160°/8 mm., which solidified. Crystallisation from light petroleum (b. p. 60—80°) gave needles, m. p. 51—52° (Found: C, 78·5; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%).

4-*Formyl*-2-*methoxy*-4′-*methyldiphenyl Ether*.—By the procedure used for the preparation of 4-methyldiphenyl ether, di-*p*-tolyliodinium bromide (29 g.) and vanillin (11·3 g.) gave 4-*formyl*-2-*methoxy*-4′-*methyldiphenyl ether* oil (11·37 g., 63%), b. p. 144—146°/0·1 mm. (Found: C, 74·6; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%). The 2,4-*dinitrophenylhydrazone* separated from acetic acid in red prisms, m. p. 202—204° (decomp.) (Found: C, 59·8; H, 4·2. $C_{21}H_{18}N_4O_6$ requires C, 59·7; H, 4·3%).

5-*Formyl*-2-*methoxy*-4′-*methyldiphenyl Ether*.—A mixture of di-*p*-tolyliodonium bromide (30·5 g.), isovanillin (11·9 g.), sodium hydroxide (3·14 g.), and water (400 c.c.) was refluxed for 24 hr. and worked up in the usual way. Crystallisation of the crude product from light petroleum (b. p. 60—80°) gave the *formyldiphenyl ether* in needles (12·24 g., 65%), m. p. 108° (Found: C, 74·1; H, 5·6. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%).

Methyl p-*Iodophenylacetate*.—(*a*) 4,4′-Bismethoxycarbonylmethyldiphenyliodonium iodide (2 g.) was heated at 160° for 5 min. and distilled under reduced pressure. The brown distillate was washed with aqueous sodium thiosulphate. Redistillation gave *methyl* p-*iodophenylacetate* (1·5 g., 75%), b. p. 110—120°/0·1 mm. (Found: C, 39·3; H, 3·5. $C_9H_9IO_2$ requires C, 39·2; H, 3·3%).

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[11] Beringer, Geering, Kuntz, and Mausner, *J. Phys. Chem.*, 1956, **60**, 141.

[12] Dilthey, Bach, Grütering, and Hausdörfer, *J. prakt. Chem.*, 1927, **117**, 337.

(*b*) A mixture of crude 4,4′-bismethoxycarbonylmethyldiphenyliodonium iodide [obtained from methyl phenylacetate (300 g.)] and acetic acid (2 l.) was refluxed for 30 min., added to water (6 l.), and extracted with benzene (3 × 800 c.c.). The benzene solution was washed with 3% aqueous sodium thiosulphate and with 5% aqueous sodium hydrogen carbonate, and evaporated. Distillation of the residue gave methyl *p*-iodophenylacetate (190 g.), b. p. 98—104°/0·04 mm. Acidification of the alkaline washings precipitated *p*-iodophenylacetic acid (116 g.), m. p. 125—135°, which was converted into the methyl ester (108 g.), b. p. 90—96°/0·02 mm. The total yield was 298 g. (54%). Vapour-phase chromatography (Silicone E. 301 on Celite at 147°) gave a single peak.

Hydrolysis of ester with sodium hydroxide in aqueous methanol at 20° afforded *p*-iodophenylacetic acid, m. p. 133—138°, separating from water in plates, m. p. 138—140° with sublimation at *ca.* 132° (lit.,[13] m. p. 135—136°). Even after repeated crystallisation from water, aqueous ethanol, or benzene, sintering occurred, beginning at 132—136° depending on the rate of heating. The infrared spectrum was identical with that of an authentic sample prepared as in (*c*).

(*c*) *p*-Aminophenylacetic acid, m. p. 194—199°, was converted [13] into *p*-iodophenylacetic acid obtained (from water) as plates, m. p. 135—140°. Esterification gave the methyl ester, b. p. 100—102°/0·6 mm., shown by vapour-phase chromatography and a comparison of infrared spectra to be identical with a sample prepared as in (*b*). Hydrolysis of the ester gave *p*-iodophenylacetic acid separating from benzene in plates, m. p. 138—140° with earlier sublimation and sintering.

2-*Methoxy*-4′-*methoxycarbonylmethyldiphenyl Ether* (VI; R = H).—(*a*) A mixture of 4,4′-di(methoxycarbonylmethyl)diphenyliodonium chloride (5·9 g.), guaiacol (1·53 g., 1 equiv.), sodium hydroxide (0·5 g., 1 equiv.), and water (100 c.c.) was heated at 70° for 24 hr. and extracted with ether. The ether solution was washed with aqueous sodium hydroxide and with water and evaporated. Distillation of the residue gave a fraction, b. p. 130°/0·2 mm., and then 2-*methoxy*-4′-*methoxycarbonylmethyldiphenyl ether* (0·4 g., 12%), b. p. 175°/0·2 mm., 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%).

When the reaction period was one week, the same product was obtained in 15% yield.

(*b*) Heating the iodonium chloride (1·25 g.), guaiacol (1·02 g., 3 equiv.), and sodium hydroxide (0·33 g., 3 equiv.) as described in (*a*) gave the diphenyl ether (0·22 g., 30%).

(*c*) A mixture of methyl *p*-iodophenylacetate (19·3 g.), guaiacol (8·7 g.), cuprous oxide (5·0 g.), and 2,4,6-trimethylpyridine (300 c.c.) was stirred and refluxed under nitrogen for 48 hr. Filtration of the mixture and evaporation of the solution gave a residue, which was shaken with a mixture of benzene (300 c.c.), ether (300 c.c.), and 3N-hydrochloric acid (500 c.c.), and then filtered. The organic layer was washed with 3N-hydrochloric acid (twice) and with 2N-sodium hydroxide (2 × 250 c.c.) and evaporated. Distillation of the residue gave the diphenyl ether derivative (7·7 g., 40%), b. p. 148—152°/0·01 mm., n_D^{21} 1·5661.

Hydrolysis with aqueous potassium hydroxide furnished the corresponding acid, separating from light petroleum (b. p. 100—120°) in needles, m. p. 110—112° (lit.,[14] m. p. 108—110°).

5-*Formyl*-2-*methoxy*-4′-*methoxycarbonylmethyldiphenyl Ether* (IX; R = Me).—A mixture of methyl *p*-iodophenylacetate (83·1 g.), isovanillin (45·6 g.), cuprous oxide (21·1 g.), and lutidine (1 l.) (b. p. 154—158°) was stirred and refluxed under nitrogen for 12 hr., and the solvent was removed under reduced pressure. The residue was shaken with benzene (1500 c.c.), and the mixture was filtered. The benzene solution was mixed with 4N-hydrochloric acid (450 c.c.), kept for 2 hr., and then filtered. The organic layer was separated, washed with 4N-hydrochloric acid (450 c.c.) and with 2N-aqueous sodium hydroxide (2 × 400 c.c.), and evaporated. Distillation of the residue gave methyl *p*-iodophenylacetate (28·9 g.), b. p. 85—95°/0·003 mm., and then 5-*formyl*-2-*methoxy*-4′-*methoxycarbonylmethyldiphenyl ether* (12·7 g.), b. p. 200—220°/0·002 mm. (Found: C, 68·3; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). The yield was 22%, based on the weight of iodo-ester consumed. The 2,4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid in needles, m. p. 182—185° (Found: C, 57·4; H, 4·2; N, 12·0. $C_{23}H_{20}N_4O_8$ requires C, 57·5; H, 4·2; N, 11·7%).

4′-*Carboxymethyl*-5-*formyl*-2-*methoxydiphenyl Ether* (IX; R = H).—The corresponding ester (1·05 g.) in ethanol (30 c.c.) was heated with potassium hydrogen carbonate (1·0 g.) in water (10 c.c.) under reflux for 4 hr. After removal of the methanol, water (30 c.c.) was added and

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[13] Giannini and Fedi, *Boll. chim. farm.*, 1958, **97**, 602.

[14] Kimoto, Asaki, Kikuchi, and Kishi, *J. Pharm. Soc. Japan*, 1953, **75**, 734.

the solution was shaken with ether. The aqueous layer was acidified with hydrochloric acid. The precipitate of the *diphenyl ether acid* separated from benzene in prisms (0·72 g., 72%), m. p. 144—147°, raised by recrystallisation from benzene or aqueous ethanol to 149—150° (Found: C, 67·1, 66·7; H, 5·3, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%). Consistent analytical figures were not obtained, but the compound is adequately characterised by its nitrovinyl derivative and by other transformation products (see below).

4'-Carboxymethyl-2-methoxy-5-(2-nitrovinyl)diphenyl Ether (X; R = $CH{=}CH{\cdot}NO_2$).—10% Aqueous potassium hydroxide (5 c.c.) was added during 10 min. to a solution of 4'-carboxymethyl-5-formyl-2-methoxydiphenyl ether (0·57 g.) and nitromethane (0·56 g.) in ethanol (20 c.c.) at 0°. The solution was kept for 1 hr. at 0° and then added to ice and water (100 c.c.) containing concentrated hydrochloric acid (6 c.c.). The precipitated gum solidified and crystallisation from aqueous ethanol afforded the *nitrovinyl derivative* (0·46 g., 71%), m. p. 137—143°, which was obtained as yellow plates (from benzene), m. p. 148—149° (Found: C, 62·0; H, 4·5; N, 4·3. $C_{17}H_{15}NO_6$ requires C, 62·0; H, 4·6; N, 4·3%).

4'-Carboxymethyl-5-cyanomethyl-2-methoxydiphenyl Ether (X; R = $CH_2{\cdot}CN$).—A solution of 4'-carboxymethyl-5-formyl-2-methoxydiphenyl ether (26·0 g.), rhodanine (14·5 g.), and anhydrous sodium acetate (29 g.) in acetic acid (150 c.c.) was heated under reflux for 2 hr. and kept overnight. After the addition of 30% aqueous acetic acid, the precipitate of the rhodanine derivative (30·0 g.) was removed by filtration.

The rhodanine derivative and 15% aqueous sodium hydroxide (250 c.c.) were heated at 100° for 2 hr., diluted with water (250 c.c.), and filtered. The filtrate was acidified with hydrochloric acid, and extracted with ether. Evaporation of the ether gave the crude thioketo-acid (23·5 g.).

The thioketo-acid in ethanol (500 c.c.) containing an excess of hydroxylamine (prepared from hydroxylamine hydrochloride and sodium ethoxide) was refluxed for 1 hr. and evaporated, and the residue was treated with hydrochloric acid. Extraction with chloroform furnished the hydroxyimino-acid (21·5 g.).

The hydroxyimino-acid and acetic anhydride (125 c.c.) were heated at 100° for 1 hr. After the addition of water (200 c.c.), the mixture was kept for 12 hr. and extracted with chloroform. The residue obtained by evaporation of the chloroform solution was treated with aqueous sodium carbonate. After filtration, the solution was extracted with ether. The aqueous solution was acidified with hydrochloric acid and extracted with chloroform. Evaporation, and trituration of the residue with ethanol, afforded the *nitrile* (4·75 g., 18%), m. p. 147—150°, crystallising from carbon tetrachloride in needles, m. p. 152—154°, $\nu_{max.}$ 2250 (CN) and 1690 cm.$^{-1}$ (CO_2H) (Found: C, 68·6; H, 4·9; N, 4·7. $C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·1; N, 4·7%).

5-(2-Aminoethyl)-4'-carboxymethyl-2-methoxydiphenyl Ether (VII).—A solution of 4'-carboxymethyl-5-cyanomethyl-2-methoxydiphenyl ether (1·59 g.) in acetic acid (90 c.c.) containing platinum oxide (0·44 g.) was shaken with hydrogen at room temperature and atmospheric pressure until hydrogen absorption ceased (17 hr.). After filtration and addition of more catalyst, hydrogenation was continued for a further 1 hr. Filtration, evaporation, and trituration of the residue with ethanol gave the *amino-acid* (0·74 g., 46%), m. p. 186—190°, separating from ethanol–water (1 : 5) in prisms, m. p. 192—193° (Found: C, 63·8; H, 6·6; N, 4·4. $C_{17}H_{19}NO_4,H_2O$ requires C, 63·9; H, 6·6; N, 4·4%).

(*b*) A mixture of 4'-carboxymethyl-2-methoxy-5-(2-nitrovinyl)diphenyl ether (0·98 g.), platinum oxide (0·39 g.), ethyl acetate (75 c.c.), and 10% aqueous sulphuric acid (17 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure for 2·5 hr. The catalyst was removed and the aqueous layer was separated. The ethyl acetate solution was washed with water, and the combined aqueous solutions were stirred with a large excess of ion-exchange resin (Amberlite IR-4B), and evaporated. Trituration of the residue with ethanol gave the amino-acid (0·31 g., 34%), m. p. 189—192°, identical (mixed m. p. and infrared) with the compound obtained as in (*a*).

4'-Carboxymethyl-2-methoxy-5-(2-phthalimidoethyl)diphenyl Ether.—A mixture of 5-(2-aminoethyl)-4'-carboxymethyl-2-methoxydiphenyl ether (0·2 g.) and an excess of phthalic anhydride was heated at 160° for 3 hr. and then extracted with chloroform. The chloroform was evaporated, and phthalic anhydride was removed by sublimation. Crystallisation of the residue from ethanol afforded the *phthalimido-acid* (0·19 g., 66%), which was obtained as needles, m. p. 174—176°, by recrystallisation from the same solvent (Found: C, 69·3; H, 5·2; N, 3·4. $C_{25}H_{21}NO_6$ requires C, 69·6; H, 5·0; N, 3·3%).

2-*Methoxy*-5-2′-*phthalimidoethylphenol* (V).—3-Benzyloxy-4-methoxy-ω-nitrostyrene[15] (2·74 g.) was reduced with lithium aluminium hydride (1·5 g.) by the procedure described by Kulka and Manske.[9] A solution of the crude amine in acetic acid (20 c.c.) containing phthalic anhydride (1·42 g.) was refluxed for 1 hr., and water was added. Crystallisation of the precipitate from isopropyl ether gave 2-methoxy-5-2′-phthalimidoethylphenyl benzyl ether in needles (3·1 g., 82%), m. p. 128—129° (lit.,[9] 126—127°).

The benzyl ether (200 mg.) in acetic acid (30 c.c.) was hydrogenated at room temperature and atmospheric pressure in the presence of 5% palladium–charcoal (150 mg.) until hydrogen uptake ceased. 2-Methoxy-5-2′-phthalimidoethylphenol, obtained by filtration, and then evaporation of the solvent, separated from isopropyl ether in needles (126 mg., 82%), m. p. 155—157°) (lit.,[9] 155—157°) (Found: C, 68·8; H, 5·3. Calc. for $C_{17}H_{15}NO_4$: C, 68·7; H, 5·1%).

2-*Methoxy*-4′-*methoxycarbonylmethyl*-5-(2-*phthalimidoethyl*)*diphenyl Ether* [VI; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*].—(*a*) An excess of diazomethane in ether was added to a suspension of 4′-carboxymethyl-2-methoxy-5-(2-phthalimidoethyl)diphenyl ether (100 mg.) in ether (40 c.c.) and methanol (10 c.c.) and the mixture was kept for 1 hr. Evaporation and crystallisation of the residue from methanol gave the *methyl ester* (70 mg.), m. p. 132—133° (Found: C, 69·8; H, 5·3; N, 3·2. $C_{26}H_{23}NO_6$ requires C, 70·1; H, 5·2; N, 3·1%).

(*b*) 4,4′-Di(methoxycarbonylmethyl)diphenyliodonium chloride (2 g.) was added to a solution of 2-methoxy-5-2′-phthalimidoethylphenol (1·275 g.), and sodium hydroxide (0·17 g.) in water (40 c.c.), and the mixture was stirred and heated at 65—75° for 15 hr. and then, after the addition of iodonium salt (1 g.), for a further 24 hr. The mixture was extracted with chloroform, and the chloroform solution was washed with aqueous sodium hydroxide and with water and evaporated. The residue was extracted with ether (20 c.c.). Evaporation of the ether solution and distillation of the residue gave an oil, b. p. 120—130° (bath)/0·2 mm. Crystallisation of the involatile fraction from ethanol gave the diphenyl ether derivative in needles (0·095 g., 6%), m. p. and mixed m. p. 130—133°.

(*c*) A mixture of methyl *p*-iodophenylacetate (1·55 g.), 2-methoxy-5-2′-phthalimidoethylphenol (1·55 g.), cuprous oxide (0·4 g.), and 2,4,6-trimethylpyridine (30 c.c.) was stirred and refluxed under nitrogen for 48 hr. After filtration, the solution was evaporated, and the residue in chloroform (200 c.c.) was shaken with 3N-hydrochloric acid (100 c.c.) and then filtered. The chloroform layer was separated, washed with 3N-hydrochloric acid and with 5% aqueous potassium carbonate (3 times), and evaporated. The residue in benzene was chromatographed on acid-washed alumina. Elution with benzene gave a gum, which was triturated with ethanol. Crystallisation of the resultant solid from methanol afforded the diphenyl ether derivative (0·15 g., 7%), m. p. and mixed m. p. 131—133°.

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[15] Robinson and Sugasawa, *J.*, 1931, 3163.