*Bisbenzyl*isoquinolines. *Part I. The Synthesis of* 4-(2-*Aminoethyl*)-5′-*carboxymethyl*-2 : 2′-*dimethoxydiphenyl Ether and Phenoxy*isoquinolines.

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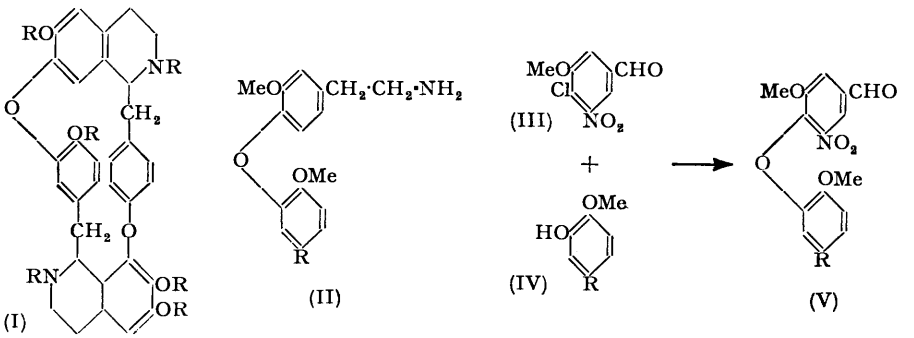
Formyldiphenyl ethers of type (V) have been prepared from 4-chloro-3-methoxy-5-nitrobenzaldehyde and the appropriate phenols, and converted into the 2-phenylethylamines (II). The amine (II; R = H) gave high yields of phenoxy*iso*quinoline derivatives.

IN spite of the medicinal importance of tubocurarine, a member of the cyclic bisbenzyl-*iso*quinoline group of alkaloids, the synthesis of this type of compound has attracted little interest. Kondo, Katoaka, and Nakagawa (*Ann. Rept. ITSUU Lab.*, 1952, **3**, 49) synthesised cepharanthine, but there is no record of any attempt to prepare bisbenzyl-*iso*quinolines of the general type (I) represented by the alkaloids curine, bebeerine, and the quaternary derivative tubocurarine. We have prepared the amino-acid (II; R = CH_2·CO_2H) and phenoxy*iso*quinoline derivatives which are possible intermediates in such a synthesis, for example, of *OO*′-dimethylcurine (I; R = Me).

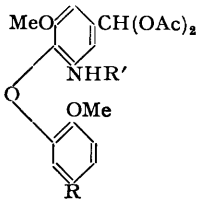
Whaley, Starker, and Meadow (*J. Org. Chem.*, 1953, **18**, 833), during a discussion of a possible synthesis of *iso*tetrandrine, commented on the difficulty of preparing suitable diphenyl ethers by the normal Ullmann procedure, but Borrows, Clayton, Hems, and Long (*J.*, 1949, S 190) showed that chloro-2 : 4-dinitrobenzenes and 2 : 4-dinitrophenyl toluene-*p*-sulphonates readily condense with phenols in pyridine. It now appears that the presence of two nitro-groups is not essential for the success of the method, provided there are present other groups which produce a similar activation. Thus, 4-chloro-3-methoxy-5-nitrobenzaldehyde (III) in pyridine condensed with guaiacol (IV; R = H) or with methyl *iso*vanillate (IV; R = CO_2Me) to give the diphenyl ether derivatives (V; R = H and CO_2Me) in yields of 47% and 63% respectively. 4-Chloro-3-methoxy-5-nitrobenzaldehyde was prepared by heating 5-nitrovanillin with phosphorus oxychloride, toluene,



and 1 mol. of diethylaniline. Borrows *et al.* (*loc. cit.*) observed that excess of diethylaniline caused no decrease in yield, but there was such a decrease in the present case. The use of toluene as solvent, instead of the customary large excess of phosphorus oxychloride, proved more convenient for large-scale preparations. The alternative synthesis, employing 5-nitrovanillin toluene-*p*-sulphonate and guaiacol, gave a lower yield (25%) of the diphenyl ether (V; R = H). A similar result was obtained when 5-nitrovanillin was heated in pyridine with toluene-*p*-sulphonyl chloride and guaiacol.

The availability of diphenyl ether derivatives of type (V) suggested a possible synthesis of (II) involving replacement of the nitro-group by hydrogen, and subsequent conversion of the aldehyde into a 2-phenylethylamine derivative. The nitro-aldehyde (V; R = H) was converted into the diacetate, in order to protect the formyl group during the subsequent catalytic reduction. The amine (VI; R = R′ = H) was unstable, but was

characterised as the triacetate (VI; R = H, R′ = Ac). The amine in acetic acid was diazotized and treated with hypophosphorous acid to give the aldehyde (VII; R = H) in 70% yield, based on the nitro-aldehyde. The β-nitrostyrene derivative (VIII; R = H), prepared from the aldehyde (VII; R = H) in high yield by nitromethane and aqueous alkali, was reduced to the amine (II; R = H) by lithium aluminium hydride (70% yield) or catalytic reduction (60% yield).



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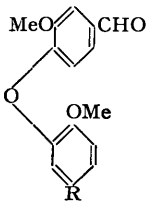

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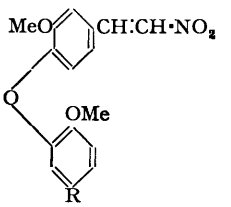

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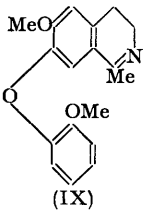
Preparations of 3-hydroxy-4-methoxyphenylacetic acid (IV; R = CH_2·CO_2H) from *iso*vanillin reported by Späth and Lang (*Monatsh.*, 1921, **42**, 273), Hahn and Schulz (*Ber.*, 1939, **72**, 1302) and Bersch (*Arch. Pharm.*, 1939, **277**, 271) gave only 18—40% yield but the rhodanine method (cf. Fischer and Hibbert, *J. Amer. Chem. Soc.*, 1947, **69**, 1208) afforded a 44% yield (H. J. H. Perry). With 4-chloro-3-methoxy-5-nitrobenzaldehyde this acid gave a 48% yield of the formyldiphenyl ether (V; R =CH_2·CO_2Me), the nitro-group in which was replaced as in the earlier case. The intermediate amine (VI; R = CH_2·CO_2Me, R′ = H) was characterised as the triacetate. Partial hydrolysis of the ester group during the reaction resulted in the isolation of some of the aldehydo-acid (VII; R = CH_2·CO_2H), which was conveniently prepared from the ester by hydrolysis with potassium hydrogen carbonate. The ester (VII; R = CH_2·CO_2Me) gave the β-nitrostyrene derivative (VIII; R = CH_2·CO_2Me) in high yield, but hydrolysis of the latter was not satisfactory. Consequently, the β-nitrostyrene acid (VIII; R = CH_2·CO_2H) was prepared directly from the aldehyde-acid (VII; R = CH_2·CO_2H) and then converted into the amino-acid (II; R = CH_2·CO_2H) by catalytic reduction. This compound was obtained as a hydrate, and, after being heated at 135° *in vacuo*, still retained ½ mol. of water of



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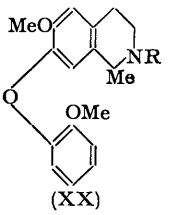

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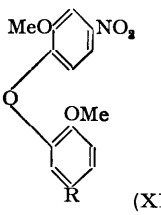

(XI)

crystallisation. The validity of the assigned structure (II; R = CH_2·CO_2H) was confirmed by preparation of the *N*-phthaloyl and the *N*-formyl derivative, and by reconversion of the latter into the amino-acid hydrate by acid hydrolysis. The five-stage synthesis of the amino-acid from 4-chloro-3-methoxy-5-nitrobenzaldehyde and methyl 3-hydroxy-4-methoxyphenyl acetate proceeded in an overall yield of 12%.

These 2-phenylethylamines seem suitable for the preparation of phenoxy*iso*quinoline derivatives. The 3 : 4-dihydro*iso*quinoline (IX) was prepared by standard methods from the amine (II; R = H) in 76% yield. Catalytic reduction gave the tetrahydro*iso*quinoline (X; R = H). The dimethyltetrahydro*iso*quinoline (X; R = Me) was obtained by a similar reduction of the 3 : 4-dihydro*iso*quinoline methochloride.

Earlier attempts to synthesise the amino-acid (II; R = CH_2·CO_2H) involved the preparation of diphenyl ethers of type (XI). Borrows *et al.* (*loc. cit.*) noted that mono-nitroaryl halides failed to condense with phenols in pyridine, and, in accordance with these findings, 2-bromo-5-nitroanisole failed to undergo this reaction. The diphenyl ether derivatives (XI; R = H, Me, and Ac) were prepared by fusing 2-bromo-5-nitroanisole with the potassium salts of the appropriate phenols, but the yields were poor.

Experimental

4-Chloro-3-methoxy-5-nitrobenzaldehyde.—Diethylaniline (7·5 g.) was added gradually to a suspension of 5-nitrovanillin (10 g.) in phosphorus oxychloride (20 c.c.) and toluene (20 c.c.), and the mixture was heated under reflux for 20 min. After being cooled, the solution was added to ice and water (300 c.c.), and the mixture extracted with ether (3 × 70 c.c.). The product, obtained by evaporation of the ether solution, was triturated with light petroleum (b. p. 40—60°). Crystallisation of the residue afforded *4-chloro-3-methoxy-5-nitrobenzaldehyde* (4·5 g.; m. p. 112—115°), obtained from aqueous ethanol as colourless needles, m. p. 118—119° (Found: C, 44·6; H, 2·7; N, 6·7. $C_8H_6O_4NCl$ requires C, 44·6; H, 2·7; N, 6·5%).

4-Formyl-2-methoxy-6-nitrophenyl Toluene-p-sulphonate.—A solution of 5-nitrovanillin (1 g.) in acetone (30 c.c.) and water (10 c.c.) containing aqueous sodium hydroxide (3 c.c.; 2N) was treated with toluene-*p*-sulphonyl chloride (1 g.) and kept at room temperature for 12 hr. After evaporation of the acetone and addition of excess of aqueous sodium hydroxide, the precipitate was collected and dissolved in benzene (20 c.c.). The benzene solution was washed with aqueous sodium carbonate, dried, and evaporated. Trituration of the oily residue with ethanol gave the colourless *toluene-p-sulphonate* (0·75 g., 34%), which crystallised from ethanol in plates, m. p. 144—145° (Found: C, 51·4; H, 3·7. $C_{15}H_{13}O_7NS$ requires C, 51·3; H, 3·7%).

4-Formyl-2 : 2′-dimethoxy-6-nitrodiphenyl Ether (V; R = H).—(*a*) A solution of 4-chloro-3-methoxy-5-nitrobenzaldehyde (4·5 g.) and guaiacol (3·5 g.) in pyridine (20 c.c.) was heated under reflux for 1·5 hr. The precipitate obtained by dilution with water (200 c.c.) was collected, and washed with a small quantity of ethanol. The *product* crystallised from ethanol in pale yellow needles (3·0 g., 47%), m. p. 135—138°, raised to 138—139° by recrystallisation from ethanol (Found: C, 59·4; H, 4·1; N, 4·8. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3; N, 4·6%). *2 : 2′-Dimethoxy-4-(2-nitrovinyl)diphenyl ether* was prepared therefrom with nitromethane and dilute potassium hydroxide solution, and crystallised from aqueous acetic acid in yellow rectangular plates, m. p. 194—195° (Found: C, 55·6; H, 4·4; N, 8·1. $C_{16}H_{14}O_7N_2$ requires C, 55·5; H, 4·1; N, 8·1%).

(*b*) 4-Formyl-2-methoxy-6-nitrophenyl toluene-*p*-sulphonate (0·75 g.), guaiacol (0·40 g.), and pyridine (5 c.c.) were heated under reflux for 1 hr. After the addition of water (50 c.c.), the diphenyl ether derivative was collected and crystallised from ethanol (charcoal) in yellow needles (0·15 g., 25%), m. p. 136—138°, alone or mixed with 4-formyl-2 : 2′-dimethoxy-6-nitrodiphenyl ether.

(*c*) 5-Nitrovanillin (1 g.), toluene-*p*-sulphonyl chloride (1 g.), guaiacol (1 g.), and pyridine (15 c.c.) were heated under reflux for 5 hr., and added to water (50 c.c.). The precipitate was filtered off. Crystallisation from ethanol (charcoal) yielded the diphenyl ether as yellow needles (0·25 g., 17%), m. p. and mixed m. p. 137—138°.

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonyl-6-nitrodiphenyl Ether (V; R = CO_2Me).—Treatment of 4-chloro-3-methoxy-5-nitrobenzaldehyde (0·50 g.) in pyridine with methyl *iso*vanillate (0·46 g.) (Faltis, Holzinger, Ita, and Schwarz, *Ber.*, 1941, **74**, 79) as described in the foregoing preparation, and crystallisation of the product from ethanol, gave the required *diphenyl ether* (0·42 g., 63%), forming cream-coloured plates, m. p. 127—128°, from ethanol (Found: C, 56·8; H, 4·3; N, 3·9. $C_{17}H_{15}O_8N$ requires C, 56·5; H, 4·2; N, 3·9%). The *oxime* crystallised from aqueous ethanol in prisms, m. p. 177—178° (Found: C, 54·5; H, 4·4; N, 7·2. $C_{17}H_{16}O_8N_2$ requires C, 54·3; H, 4·3; N, 7·5%).

3-Hydroxy-4-methoxybenzylidenerhodanine.—*iso*Vanillin (20 g.), rhodanine (20 g.), fused sodium acetate (37 g.), and acetic acid (100 c.c.) were heated under reflux for 10 min., and then transferred to a steam-bath. After 2 hr., the solution was cooled, diluted with water (400 c.c.), and kept at 0° for 4 hr. The orange solid (32·6 g., 91%) was collected and washed with water. The *rhodanine* derivative separated from acetone in yellow needles, m. p. 220—221° (Found: C, 49·5; H, 3·1; N, 5·1. $C_{11}H_9O_3NS_2$ requires C, 49·4; H, 3·4; N, 5·2%).

β-(*3-Hydroxy-4-methoxyphenyl*)-α-*thiopropionic Acid.*—The benzylidenerhodanine (32·6 g.) was heated on a steam-bath with aqueous sodium hydroxide (220 c.c.; 15%) for 1 hr. Hydrochloric acid (230 c.c.; 10%) was added to the ice-cold solution, and the buff precipitate of the *thio-acid* (25·9 g., 94%) was collected and washed with water. It crystallised from aqueous methanol in orange prisms, m. p. 158—160° (Found: C, 53·3; H, 4·5. $C_{10}H_{10}O_4S$ requires C, 53·1; H, 4·5%).

3-Acetoxy-4-methoxybenzyl Cyanide.—A solution of hydroxylamine, prepared from aqueous hydroxylamine hydrochloride (32·5 g. in 30 c.c. of water) and alcoholic sodium ethoxide, and

the above thio-acid (32·7 g.) was heated under reflux for 1 hr., then evaporated, and the residue was dissolved in aqueous sodium hydroxide (250 c.c.; 5%). The filtered solution was acidified at 0° with hydrochloric acid (225 c.c.; 10%), and extracted with ethyl acetate (3 × 100 c.c.). By evaporation, and trituration of the residue with light petroleum (b. p. 60—80°), the hydroxyamino-acid was obtained as a buff solid (30 g., 92%), m. p. 137—143°.

The crude product (4·5 g.) in acetic anhydride (12 c.c.) was heated at 50° until a clear solution was obtained, then on a steam-bath until effervescence ceased (5 min.), diluted with water (100 c.c.), and extracted with ether (3 × 30 c.c.). The ether solution was washed with aqueous sodium carbonate, and then with water. Evaporation gave the *cyanide* (2·2 g., 57%), b. p. 119—122°/0·15 mm., which crystallised. A sample separated from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 60—61° (Found: C, 64·6; H, 5·2; N, 7·0. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·8%).

Methyl 3-Hydroxy-4-methoxyphenylacetate.—The cyanide (8·5 g.) in ethanol (60 c.c.) was heated with aqueous potassium hydroxide (12·5 g. in 60 c.c. of water) under reflux for 10 hr. Removal of the ethanol, followed by acidification, yielded 3-hydroxy-4-methoxyphenylacetic acid (6·6 g.) as pale yellow plates, m. p. 126—129°. A further quantity (0·7 g.) was obtained by extraction of the aqueous solution with ether (total yield, 7·3 g., 97%).

Methanol (60 c.c.) containing sulphuric acid (6 c.c.) was added to a solution of the acid (7·3 g.) in methanol (60 c.c.). The solution was heated under reflux for 10 hr., concentrated at room temperature to 20 c.c., diluted with water (200 c.c.), and extracted with ether (4 × 30 c.c.). After the ether solution had been washed, first with water, then with aqueous sodium hydrogen carbonate, and finally with water, evaporation and distillation gave the required *ester* as a colourless oil (6·4 g., 82%), b. p. 102°/0·1 mm. (Found: C, 60·9; H, 6·4. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyl-6-nitrodiphenyl Ether (V; R = $CH_2{\cdot}CO_2Me$).—4-Chloro-3-methoxy-5-nitrobenzaldehyde (6·40 g.), methyl 3-hydroxy-4-methoxyphenylacetate (5·65 g.), and pyridine (50 c.c.) were heated at 120° for 1 hr. Addition of water (200 c.c.) precipitated the *diphenyl ether*, which crystallised from ethanol in plates (4·85 g.), m. p. 113—114°. The aqueous solution was extracted with ether (3 × 40 c.c.), and the ether solution washed successively with water, 10% hydrochloric acid, water, N-sodium hydroxide, and water. Evaporation of the ether solution, and trituration of the residue with ethanol, gave a further quantity of the diphenyl ether (0·18 g.), m. p. 108—111° (total yield, 5·03 g., 48%). A sample crystallised from ethanol in colourless plates, m. p. 114—115° (Found: C, 57·8; H, 4·5; N, 3·8. $C_{18}H_{17}O_8N$ requires C, 57·6; H, 4·6; N, 3·7%).

6-Amino-4-formyl-2 : 2′-dimethoxydiphenyl Ether Triacetate.—4-Formyl-2 : 2′-dimethoxy-6-nitrodiphenyl ether was converted in 94% yield by acetic anhydride containing sulphuric acid into the *diacetate*, plates, m. p. 103—104° (from ethanol) (Found: C, 56·2; H, 4·7; N, 3·5. $C_{19}H_{19}O_9N$ requires C, 56·3; H, 4·7; N, 3·5%).

The diacetate (0·38 g.) in ethyl acetate (20 c.c.) was hydrogenated at atmospheric pressure and at room temperature in the presence of 5% palladium–charcoal (0·5 g.) until 3 mols. of hydrogen were absorbed. The catalyst was removed and the solution evaporated at room temperature. The residue was acetylated with acetic anhydride in the presence of sulphuric acid. Water was added, and the *triacetate* was collected and crystallised from ethanol in colourless prisms (0·23 g.), m. p. 134—136°. It had m. p. 139—140° after recrystallisation from ethanol (Found: C, 60·3; H, 5·7; N, 3·6. $C_{21}H_{23}O_8N$ requires C, 60·4; H, 5·6; N, 3·4%).

4-Formyl-2 : 2′-dimethoxydiphenyl Ether (VII; R = H).—The foregoing diacetate (4·3 g.) was hydrogenated as described above. The crude amine in acetic acid (15 c.c.) was treated with hydrochloric acid (8 c.c.; 15%), and the solution at 0° was diazotised with sodium nitrite (0·85 g.) in water (2 c.c.). After 20 min., ice-cold aqueous hypophosphorous acid (20 c.c.; 30%) was added gradually with stirring. The solution was kept at 0° for 12 hr., diluted with water (200 c.c.), and extracted with ether (3 × 40 c.c.). The ether solution was washed with aqueous sodium hydroxide (2 × 30 c.c.; 10%), and then with water. Evaporation and distillation yielded *4-formyl-2 : 2′-dimethoxydiphenyl ether* as a pale yellow viscous oil (1·9 g., 70%), b. p. 169—173°/0·2 mm. (Found: C, 69·4; H, 5·8. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%). The *2 : 4-dinitrophenylhydrazone* crystallised from ethanol in red needles, m. p. 207—209° (Found: C, 57·5; H, 4·3; N, 12·7. $C_{21}H_{18}O_7N_4$ requires C, 57·2; H, 4·2; N, 12·8%).

2 : 2′-Dimethoxy-4-(2-nitrovinyl)diphenyl Ether (VIII; R = H).—A solution of the preceding aldehyde (4·1 g.) in ethanol (20 c.c.) containing nitromethane (2 g.) at 0° was treated gradually with a solution of potassium hydroxide (2·4 g. in 4 c.c. of water and 6 c.c. of methanol). After

10 min., the solution was added to hydrochloric acid (40 c.c.; 15%). The 2-*nitrovinyl* derivative was obtained as a yellow solid (4·5 g., 94%), m. p. 89—92°, and separated from ethanol in yellow needles, m. p. 97—98° (Found: C, 64·0; H, 5·1; N, 4·6. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

4-(2-*Aminoethyl*)-2 : 2′-*dimethoxydiphenyl Ether* (II; R = H).—(*a*) The nitrovinyl derivative (4·25 g.) in ether (250 c.c.) was added to a solution of lithium aluminium hydride (5 g.) in ether (250 c.c.), and the mixture was heated under reflux for 6 hr. Excess of the reagent was decomposed by moist ether, and the addition of aqueous potassium hydroxide (150 c.c., 40%) caused most of the inorganic precipitate to dissolve. The ether layer was separated, and the aqueous solution was extracted with ether (2 × 50 c.c.). Evaporation of the combined ether solutions and distillation yielded the *amine* as a colourless oil (2·65 g., 70%), b. p. 169—171°/0·2 mm. (Found: C, 69·8; H, 6·9; N, 4·9. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%). The *phthaloyl* derivative, prepared by heating the amine in acetic acid with phthalic anhydride, crystallised from ethanol in colourless plates, m. p. 156—157° (Found: C, 71·2; H, 5·3. $C_{24}H_{21}O_5N$ requires C, 71·5; H, 5·3%).

(*b*) The nitrovinyl derivative (0·75 g.) in acetic acid (50 c.c.), containing sulphuric acid (1 c.c.), was shaken in hydrogen in the presence of 5% palladium–charcoal (0·5 g.) until hydrogen absorption ceased (4 hr.). The solution was filtered, concentrated to 10 c.c. at 40°, diluted with water (150 c.c.), and extracted with ether (3 portions). The aqueous solution was made alkaline with 10% aqueous sodium hydroxide, and extracted with ether (5 × 30 c.c.). Evaporation of the ether solution yielded a pale yellow oil (0·41 g., 60%), shown to be identical with 4-(2-aminoethyl)-2 : 2′-dimethoxydiphenyl ether by conversion into the same dihydro*iso*quinoline derivative (see below).

3 : 4-*Dihydro*-6-*methoxy*-7-o-*methoxyphenoxy*-1-*methyl*iso*quinoline* (IX).—4-(2-Aminoethyl)-2 : 2′-dimethoxydiphenyl ether (1·10 g.) was treated with acetic anhydride (5 c.c.). After 30 min., water (100 c.c.) was added, and the mixture kept for 1 hr. before extraction with ether (4 × 30 c.c.). The ether solution was washed with aqueous sodium carbonate and water, dried, and distilled. The *N*-acetyl derivative was obtained as a pale yellow oil (1·15 g.).

The *N*-acetyl derivative (1·15 g.) in toluene (5 c.c.) was refluxed for 1 hr. with phosphorus oxychloride (3 c.c.). The solution was evaporated at 50°, and the gum which remained was triturated with light petroleum (b. p. 40—60°). Addition of ethanol (3 c.c.) and hydrochloric acid (0·5 c.c.) precipitated the *dihydro*iso*quinoline hydrochloride* (0·65 g.), m. p. 190—193°. A further quantity (0·44 g.) was obtained by dilution of the ethanol solution with ether. Recrystallisation from ethanol–ether gave the hydrochloride as colourless needles, m. p. 197—198° (decomp.) (Found: C, 61·6; H, 6·4; N, 4·1; After drying at 120° *in vacuo*: C, 64·6; H, 6·1. $C_{18}H_{20}O_3NCl,1H_2O$ requires C, 61·4; H, 6·3; N, 4·0. $C_{18}H_{20}O_3NCl$ requires C, 64·8; H, 6·0%).

The hydrochloride (1·09 g.) in warm water was treated with aqueous sodium hydroxide, and the mixture extracted with ether. Evaporation gave a colourless gum, which dissolved in light petroleum (b. p. 60—80°). The cold solution deposited the *dihydro*iso*quinoline* as colourless prisms [0·93 g., 76% based on 4-(2-aminoethyl)-2 : 2′-dimethoxydiphenyl ether], m. p. 90—92°. A sample, m. p. 91—92°, was prepared by recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 72·6; H, 6·2; N, 4·9. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%).

Tetrahydro-6-*methoxy*iso-7-o-*methoxyphenoxy*-1 : 2-*dimethylquinoline* (X; R = Me).—3 : 4-*Dihydro*-6-*methoxy*-7-o-*methoxyphenoxy*-1-*methyl*iso*quinoline methiodide*, prepared with methyl iodide in ethanol at room temperature, crystallised from ethanol in yellow prisms, m. p. 189—190° (Found: C, 51·7; H, 5·0. $C_{19}H_{22}O_3NI$ requires C, 51·9; H, 5·1%).

When passed through a column of ion-exchange resin (Amberlite IRA-400), a solution of the methiodide (0·3 g.) in water became cloudy. The precipitate probably consisted of the anhydro-base. The column was washed with ether (50 c.c.), and the ether solution was shaken with water (20 c.c.) containing hydrochloric acid (1 c.c.). The acid washings were added to the aqueous solution obtained from the column, and the clear acid solution was evaporated to dryness at 40°, leaving the methochloride as a colourless gum.

The crude methochloride in ethanol (20 c.c.), containing hydrochloric acid (0·5 c.c.), was shaken in hydrogen with platinum (0·2 g.), until hydrogen absorption ceased (30 min.). The catalyst was removed and the solution evaporated. A solution of the oily residue in water (20 c.c.) was made alkaline with sodium hydrogen carbonate and extracted with ether (3 × 10 c.c.). Evaporation of the ether left a colourless gum, which, on trituration with light petroleum (b. p. 40—60°), gave the colourless *tetrahydrodimethyl*iso*quinoline* as a colourless

solid (0·12 g., 55%). A sample crystallised from light petroleum (b. p. 40—60°) in large colourless prisms, m. p. 107—109° (Found: C, 72·9; H, 7·1. $C_{19}H_{23}O_3N$ requires C, 72·8; H, 7·4%). The *methiodide* separated from acetone–ether in colourless plates, m. p. 164—165° (Found: C, 52·7; H, 5·4. $C_{20}H_{26}O_3NI$ requires C, 52·8; H, 5·8%).

*Tetrahydro-6-methoxy-7-o-methoxyphenoxy-1-methyl*isoquinoline (X; R = H).—The dihydro-*iso*quinoline hydrochloride (1·05 g.) in ethanol (30 c.c.), containing hydrochloric acid (1 c.c.), was reduced at room temperature and atmospheric pressure in the presence of platinum (0·2 g.). 1 Mol. of hydrogen was absorbed in 45 min. After removal of the catalyst, the ethanol solution was evaporated, and water (50 c.c.) was added. The solution was made alkaline with aqueous sodium hydroxide and extracted with ether (3 × 20 c.c.). Evaporation of the ether gave the *tetrahydro*isoquinoline (0·44 g., 50%), m. p. 101—102°, crystallising from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 103—104° (Found: C, 72·5; H, 7·1. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1%).

6-Amino-4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl Ether Triacetate (VI; R = $CH_2{\cdot}CO_2Me$, R′ = Ac).—4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyl-6-nitrodiphenyl ether with acetic anhydride and sulphuric acid gave the *diacetate* (100% yield), prisms (from ethanol), m. p. 62—64° (Found: C, 55·4; H, 5·0. $C_{22}H_{23}O_{11}N$ requires C, 55·4; H, 4·9%).

The diacetate (0·25 g.) in ethyl acetate (30 c.c.) was shaken in hydrogen with palladised charcoal (0·5 g.; 5%), until hydrogen absorption ceased (3 hr.). Removal of the catalyst, followed by evaporation at room temperature, gave a yellow gum, which was acetylated with acetic anhydride and sulphuric acid. Addition of water to the acetylation mixture precipitated the *triacetate*, crystallising from ethanol in colourless plates (0·14 g.), m. p. 124—125°, raised by recrystallisation from ethanol to 128° (Found: C, 58·9; H, 5·7. $C_{24}H_{27}O_{10}N$ requires C, 58·9; H, 5·6%).

4-Formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl Ether (VII; R = $CH_2{\cdot}CO_2Me$). —The foregoing diacetate (4·17 g.) was reduced, as described in the previous experiment. The crude amine in acetic acid (12 c.c.) was diazotised in hydrochloric acid (12 c.c.; 15%) at 0° with sodium nitrite (0·7 g.) in water (3 c.c.). After 20 min., ice-cold hypophosphorous acid (20 c.c.; 30%) was added during 5 min., and the solution was kept at 0° for 12 hr. Addition of water (150 c.c.), extraction with ether (4 × 40 c.c.), washing with water, N-sodium hydroxide (4 × 10 c.c.), and water, evaporation, and distillation gave a pale yellow viscous oil, b. p. 190—195°(bath)/0·008 mm. By trituration with ethanol, *4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether* was obtained as a colourless solid (1·34 g.), separating from ethanol in prisms, m. p. 88—89° (Found: C, 65·3; H, 5·7. $C_{18}H_{18}O_6$ requires C, 65·5; H, 5·6%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetone–ethanol in red needles, m. p. 162—163° (Found: C, 56·3; H, 4·3; N, 11·3. $C_{24}H_{22}O_9N_4$ requires C, 56·5; H, 4·3; N, 11·0%).

The alkaline washings were acidified with hydrochloric acid and extracted with benzene (3 × 10 c.c.). The benzene solution was shaken with several portions of aqueous sodium hydrogen carbonate, and the combined alkaline solutions were acidified. Extraction with benzene and removal of the solvent gave *5′-carboxymethyl-4-formyl-2 : 2′-dimethoxydiphenyl ether*, obtained from aqueous ethanol as a cream-coloured solid (0·25 g.). The acid recrystallised from aqueous ethanol in rectangular plates, m. p. 125—127° (Found: C, 64·8; H, 5·4. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%). The total yield of ester and acid was 55%.

5′-Carboxymethyl-4-formyl-2 : 2′-dimethoxydiphenyl Ether (VII; R = $CH_2{\cdot}CO_2H$).—The corresponding ester (0·78 g.) in methanol (30·c.c.) was heated with potassium hydrogen carbonate (1·7 g.) in water (8 c.c.) under reflux for 2 hr. After removal of the methanol, the solution was acidified with hydrochloric acid, and the diphenyl ether acid was collected (0·72 g., 96%; m. p. and mixed m. p. 125—126° after recrystallisation from aqueous ethanol).

2 : 2′-Dimethoxy-5′-methoxycarbonylmethyl-4-(2-nitrovinyl)diphenyl Ether (VIII; R = $CH_2{\cdot}CO_2Me$).—By a method similar to that described for the preparation 2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl ether, the *2-nitrovinyl* derivative was obtained from 4-formyl-2 : 2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether (0·22 g.) as yellow plates (0·20 g., 80%), m. p. 108—109° after crystallisation from ethanol (Found: C, 60·9; H, 5·0. $C_{19}H_{19}O_7N$ requires C, 61·1; H, 5·1%).

5′-Carboxymethyl-2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl Ether (VIII; R = $CH_2{\cdot}CO_2H$).—(*a*) A solution of the above nitrovinyl derivative (0·2 g.) in aqueous N-sodium hydroxide (10 c.c.) and ethanol (5 c.c.) was kept at room temperature for 12 hr. The solution was added to hydrochloric acid (20 c.c.; 15%), and the precipitate was collected. Crystallisation from aqueous ethanol gave the *2-nitrovinyl diphenyl ether* (0·09 g.), in yellow plates, m. p. 189—191° (Found: C, 60·3; H, 4·8. $C_{18}H_{17}O_7N$ requires C, 60·2; H, 4·8%).

(*b*) A solution of 5′-carboxymethyl-2 : 2′-dimethoxy-4-formyldiphenyl ether (0·5 g.) in ethanol (4 c.c.) containing nitromethane (0·4 g.) was treated gradually with aqueous potassium hydroxide (4·5 c.c.; 10%). After 15 min. at 0°, the solution was added to hydrochloric acid (15 c.c.; 10%). The precipitate of the nitrovinyl derivative (0·52 g., 91%) was collected. It separated from aqueous ethanol in yellow plates, m. p. and mixed m. p. 187—189°.

4-(2-*Aminoethyl*)-5′-*carboxymethyl*-2 : 2′-*dimethoxydiphenyl Ether* (II; R = CH_2·CO_2H).—5′-Carboxymethyl-2 : 2′-dimethoxy-4-(2-nitrovinyl)diphenyl ether (0·4 g.), suspended in ethyl acetate (25 c.c.), was added to platinium oxide (0·2 g.), which had been pre-reduced in aqueous sulphuric acid (4 c.c.; 10%), and ethyl acetate (5 c.c.). 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 was separated. The ethyl acetate solution was washed with water (3 × 10 c.c.), 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 (5 c.c.), was kept at room temperature, and 4-(2-*aminoethyl*)-5′-*carboxymethyl*-2 : 2′-*dimethoxydiphenyl ether* slowly separated (0·21 g., 51%). By repeated crystallisation from 90% ethanol, the compound was obtained as a white powder, m. p. 177—178° (Found: C, 61·6; H, 6·3. Found, after heating at 135°/0·1 mm. for 12 hr.: C, 63·7; H, 6·2; N, 4·4. $C_{18}H_{21}O_5N$,lH_2O requires C, 61·9; H, 6·6. $C_{18}H_{21}O_5N$,$\frac{1}{2}H_2O$ requires C, 63·5; H, 6·4; N, 4·1%). The *phthaloyl* derivative, prepared by fusing the amino-acid with phthalic anhydride at 140—150° for 30 min., separated from methanol in colourless plates, m. p. 183—184° (Found: C, 67·6; H, 5·3; N, 3·1. $C_{26}H_{23}O_7N$ requires C, 67·7; H, 5·0; N, 3·0%).

5′-*Carboxymethyl*-4-(2-*formamidoethyl*)-2 : 2′-*dimethoxydiphenyl Ether*.—The amino-acid (50 mg.) in formic acid (1 c.c.) was kept in acetic anhydride (1 c.c.) at 40—50° for 30 min. The solvent was evaporated, and the oily residue treated with water. By extraction with ethyl acetate, a colourless oil was obtained, affording the N-*formyl* derivative (30 mg.), m. p. 130—136°, when triturated with ether. The compound crystallised from ethyl acetate–ether in prisms, m. p. 138—140° (Found: C, 63·3; H, 6·1. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9%).

Hydrolysis of the N-*Formyl Derivative*.—The derivative (40 mg.) in methanolic hydrogen chloride (5 c.c., 2%) was heated on a steam-bath for 30 min. Removal of the methanol and addition of water (2 c.c.) gave a clear solution, which was added to a column of ion-exchange resin (Amberlite IR-4B). Evaporation of the aqueous solution gave a yellow gum, which crystallised from ethanol as a white solid (25 mg.), m. p. 171—173°, alone or mixed with 4-(2-aminoethyl)-5′-carboxymethyl-2 : 2′-dimethoxydiphenyl ether (Found, after heating at 135°/0·1 mm. for 12 hr.: C, 63·7; H, 6·0. Calc. for $C_{18}H_{21}O_5N$,$\frac{1}{2}H_2O$: C, 63·5; H, 6·4%).

2 : 2′-*Dimethoxy*-4-*nitrodiphenyl Ether* (XI; R = H).—The potassium salt of guaiacol (0·35 g.) and 2-bromo-5-nitroanisole (0·5 g.) were heated at 140—150° for 2 hr., then treated with N-sodium hydroxide (20 c.c.), and extracted with ether (4 × 20 c.c.). The ether solution was dried and evaporated, and the residue was distilled in steam, which removed unchanged bromo-compound (0·17 g.). The solid residue crystallised from ethanol, affording the *diphenyl ether* in light brown prisms (0·22 g., 37%), m. p. 89—90° (Found: C, 61·1; H, 4·6; N, 5·3. $C_{14}H_{13}O_5N$ requires C, 60·9; H, 4·7; N, 5·1%).

2 : 2′-*Dimethoxy*-5′-*methyl*-4-*nitrodiphenyl Ether* (XI; R = Me).—Condensation of 2-bromo-5-nitroanisole (2·2 g.) with potassium 2-methoxy-5-methylphenoxide (1·7 g.) (Faltis *et al.*, *loc. cit.*) was carried out as in the previous experiment. The *diphenyl ether* separated from ethanol in yellow prisms (0·71 g., 30%), m. p. 92—93° (Found: C, 62·2; H, 5·4; N, 4·9. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%).

5′-*Acetyl*-2 : 2′-*dimethoxy*-4-*nitrodiphenyl Ether* (XI; R = Ac).—2-Bromo-5-nitroanisole (2·3 g.) was added to a mixture of 5-acetylguaiacol monohydrate (1·80 g.) (Coulthard, Marshall, and Pyman, *J.*, 1930, 280) and potassium hydroxide (0·55 g.) at 160°. Heating was continued for 3 hr. Water (50 c.c.) was added to the cooled melt, and the mixture was extracted with ether (5 × 30 c.c.). The ether extract was dried and evaporated, and the residue steam-distilled. The residue was extracted with ether, and evaporation of the ether solution yielded the required *diphenyl ether*, crystallising from ethanol in yellow prisms (0·73 g., 23%), m. p. 120—123°. A sample, m. p. 127—128°, was prepared by recrystallisation from ethanol (Found: C, 60·8; H, 4·7; N, 4·3. $C_{16}H_{15}O_6N$ requires C, 60·6; H, 4·7; N, 4·4%).

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