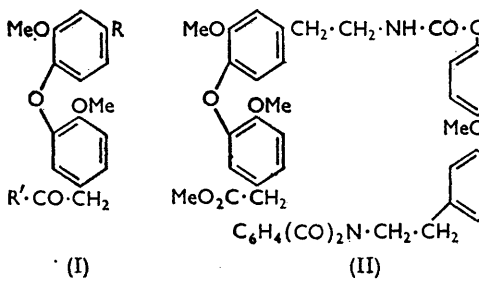
602. *Bisbenzylisoquinolines. Part III.*[1] *The Synthesis of Isoquinoline Intermediates.*

By M. F. GRUNDON.

The amide (II) was prepared by reaction of 5′-chlorocarbonylmethyl-2,2′-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether with 4-(2-aminoethyl)-2,2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether. Cyclisation gave the 3,4-dihydroisoquinoline [III; R = $CH_2{\cdot}N(CO)_2C_6H_4$-*o*], which was converted into the corresponding tetrahydro-2-methylisoquinoline (V).

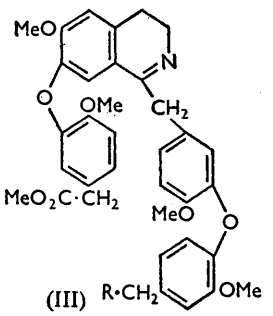
ONE approach to the synthesis of unsymmetrical cyclic bisbenzylisoquinoline alkaloids such as tubocurarine chloride involves condensation of amino-acids containing the diphenyl ether structure, followed by cyclisation. This method has been explored by using the amino-acid (I; R = $CH_2{\cdot}CH_2{\cdot}NH_2$, R′ = OH).[2]

The amino-ester (I; R = $CH_2{\cdot}CH_2{\cdot}NH_2$, R′ = OMe) was prepared by esterification of the acid, and characterised as its *N*-phthaloyl derivative, obtained for comparison by the reaction of the *N*-phthaloyl acid [I; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OH] with diazomethane. The phthalimido-acid chloride [I; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = Cl] and the amino-ester afforded the crystalline amide (II) in almost quantitative yield.

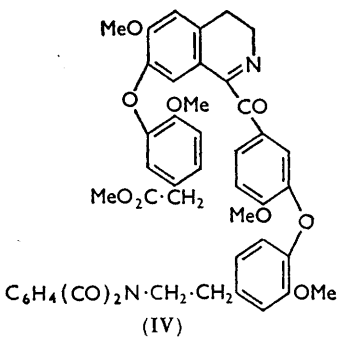


(I)

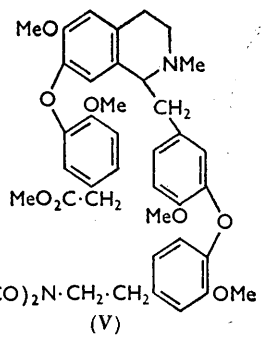
(II)



(III)



(IV)



(V)

Attempts to prepare amides from the amino-acid failed. Thus, the acid chloride and the amino-acid gave a product difficult to purify, which with diazomethane afforded the amide (II) in only poor yield.

The amino-acid did not react with the mixed anhydride derived from the phthalimido-acid and methyl chloroformate. The only product isolated was the methyl phthalimido-ester [I; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R′ = OMe], formed apparently by decomposition of the intermediate anhydride.

[1] Part II, Crowder, Grundon, and Lewis, *J.*, 1958, 2142.
[2] Grundon and Perry, *J.*, 1954, 3531.

When heated with phosphorus oxychloride, the amide (II) was converted into the 3,4-dihydroisoquinoline [III; R = CH_2·N$(CO)_2C_6H_4$-*o*], isolated as the picrate (75%). The amide and phosphorus pentachloride at room temperature gave a compound containing chlorine. Its structure has not been established, but it is apparently neither a hydrochloride nor an imino-chloride as it is unaffected by cold sodium hydroxide.

The 3,4-dihydroisoquinoline, like 1-benzyl-3,4-dihydroisoquinoline,[3] is autoxidised in ethanol to the 1-benzoyl-3,4-dihydroisoquinoline (IV).

The crude benzyldihydroisoquinoline, recovered rapidly from its picrate, gave a methiodide, which, although not crystalline, was shown by its infrared spectrum to resist atmospheric oxidation. Catalytic reduction of the methiodide in the presence of diethylamine afforded the 1,2,3,4-tetrahydro-2-methylisoquinoline (V), isolated as its picrate.

Reduction of the methiodide with sodium borohydride was unsatisfactory. The product was not characterised, but its infrared spectrum suggested that the alkaline conditions had caused partial hydrolysis of the phthaloyl group. Reaction of the phthalimido-ester [I; R = CH_2·CH_2·N$(CO)_2C_6H_4$-*o*, R′ = OMe] with sodium borohydride resulted in hydrolysis of the ester and *N*-phthaloyl groups: the product did not depress the melting point of the phthalimido-acid [I; R = CH_2·CH_2·N$(CO)_2C_6H_4$-*o*, R′ = OH], but the two compounds were not identical (infrared; Table); the product is apparently the phthalamic acid, which undergoes ring closure on heating. *N*-(3,4-Dimethoxyphenylethyl)phthalimide was unaffected by sodium borohydride: brief alkaline hydrolysis afforded the phthalamic acid.

An alternative synthesis was explored, using a nitrile group as a potential amino-group. 5′-Carboxymethyl-4-formyl-2,2′-dimethoxydiphenyl ether [2] was converted into the nitrile (I; R = CH_2·CN, R′ = OH) by the rhodanine method. Catalytic reduction of this nitrile is a more satisfactory method of preparing the amino-acid (I; R = CH_2·CH_2·NH_2, R′ = OH) than that recorded previously.[2] Without purification of intermediates, the nitrile was converted into its acid chloride and condensed with the amino-ester (I; R = CH_2·CH_2·NH_2, R′ = OMe), and the resultant amide cyclised with phosphorus oxychloride to the 3,4-dihydroisoquinoline (III; R = CH_2·CN), obtained as its picrate. The approach is not promising, as the yield is poor and reduction of the dihydroisoquinoline nitrile failed to give a characterisable product.

Assignment of infrared absorption bands (KBr *disc*) *in the region* 1800—1620 *cm.*$^{-1}$.

Substance *	*N*-Phthaloyl	CO_2Me	CO_2H	Amide	Others
(I; R = CH_2·CH_2·NH_2, R′ = OH)	—	—	—	—	1570 s (CO_2^-)
(I; R = CH_2·CH_2·NPT, R′ = OH)	1770 w, 1716 s	—	—	—	
(I; R = CH_2·CH_2·NPT, R′ = OMe)	1764 w, 1710 s	1736 m	—	—	
(II)	1768 w, 1705 s	1734 m	—	1673 m	
Hydrochloride of (III; R = CH_2·NPT)	1770 w, 1710 s	—	—	—	1650 m (–C=$\overset{+}{N}$H–)
(IV)	1765 w, 1708 s	1730 m	—	—	1667 m (–CO–C=N–)
Methiodide of (III; R = CH_2·NPT)	1770 w, 1715 s	—	—	—	
(V)	1757 w, 1700 s	1725 m	—	—	
Product from methiodide of (III; R = CH_2·NPT) + $NaBH_4$	—	1735 m	1700 m	1685 m	
Product from (I; R = CH_2·CH_2·NPT, R = OMe) + $NaBH_4$	—	—	1720 m, 1700 m	1667 s	
N-(2-3′,4′-Dimethoxyphenylethyl)phthalimide	1755 m, 1700 s	—	—	—	
Product from hydrolysis of preceding imide	—	—	1718 s	1625 s	

* PT = *o*-$C_6H_4(CO–)_2$

The compounds of high molecular weight reported in this paper are not always characterised uniquely by analytical results. Infrared evidence is summarised in the Table.

[3] See, for example, Buck, Haworth, and Perkin, *J.*, 1924, 2176; Clemo and Temple, *J.*, 1953, 678.

Experimental

5'-Chlorocarbonylmethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)diphenyl Ether [I; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R' = Cl].—5'-Carboxymethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)-diphenyl ether (0·45 g.), phosphorus pentachloride (0·45 g.), and benzene (10 c.c.) were heated under reflux for 15 min. The cold solution deposited the *acid chloride* (0·38 g.), crystallising from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 142—144° (Found: C, 65·6; H, 4·7. $C_{26}H_{22}O_6NCl$ requires C, 65·1; H, 4·6%).

N-[4-Methoxy-3-(2-methoxy-4-2'-phthalimidoethylphenoxy)phenyl]acetyl-2-[3-methoxy-4-(2-methoxy-5-methoxycarbonylmethyl)phenoxy]ethylamine (II).—(*a*) A solution of 5'-chlorocarbonylmethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether (0·4 g.) in chloroform (10 c.c.) was added during 30 min. to a solution of 4-(2-aminoethyl)-2,2'-dimethoxy-5'-methoxycarbonylmethyldiphenyl ether (0·29 g.) and tributylamine (0·25 g.) in chloroform (10 c.c.). After 12 hr. the solution was washed with N-hydrochloric acid, N-sodium hydroxide, and water. Evaporation gave a gum, which was triturated with N-hydrochloric acid and water. Crystallisation from methanol afforded the *amide* (0·6 g., 91%), m. p. 70—77°. A sample separated from methanol in aggregates of fine needles, m. p. 80—81° (Found: C, 68·2; H, 5·5. $C_{45}H_{44}O_{11}N_2$ requires C, 68·5; H, 5·6%).

(*b*) A solution of 5'-chlorocarbonylmethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether (0·35 g.) in aqueous dioxan was added during 45 min. to a solution of 4-(2-aminoethyl)-5'-carboxymethyl-2,2'-dimethoxydiphenyl ether (0·17 g.) in aqueous dioxan containing sodium carbonate (0·03 g.). The solution was kept alkaline by the periodic addition of aqueous sodium carbonate. After 1 hr. the solution was acidified with hydrochloric acid. Chloroform extraction gave a gum (0·35 g.), $\lambda_{max.}$ (in KCl) 1775 m, 1710 s, 720 s cm.$^{-1}$.

A portion of the gum, when esterified with diazomethane, gave the ester, separating from methanol in needles, m. p. 72—75°, not depressed by mixing with a sample prepared in (*a*).

2,2'-Dimethoxy-5'-methoxycarbonylmethyl-4-(2-phthalimidoethyl)diphenyl Ether [I; R = $CH_2{\cdot}CH_2{\cdot}N(CO)_2C_6H_4$-*o*, R' = OMe].—(*a*) A solution of 4-(2-aminoethyl)-5'-carboxymethyl-2,2'-dimethoxydiphenyl ether (0·17 g.) in water (3 c.c.) was added to a solution of 5'-carboxymethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether (0·17 g.) in dioxan (3 c.c.) containing methyl chloroformate (0·05 g.) and tributylamine (0·08 g.) at 0°. After 30 min. the solution was diluted with water and acidified with hydrochloric acid. The precipitate of the *ester* crystallised from ethanol in needles (0·13 g.), m. p. 146—150°, raised to 158—159° by recrystallisation (Found: C, 68·6; H, 5·4; N, 3·1. $C_{27}H_{25}O_7N$ requires C, 68·2; H, 5·3; N, 3·0%).

(*b*) 5-Carboxymethyl-2,2'-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether (0·1 g.) in acetone–methanol was treated with ethereal diazomethane. After 15 min. the solution was evaporated. The residue crystallised from methanol in needles (0·095 g.), m. p. and mixed m. p. 156—157°.

(*c*) A solution of 4-(2-aminoethyl)-5'-carboxymethyl-2,2'-dimethoxydiphenyl ether (50 mg.) and concentrated sulphuric acid (1 c.c.) in methanol (20 c.c.) was kept for 12 hr. The residue obtained by evaporation was dissolved in water, made alkaline with sodium carbonate, and extracted with chloroform. Evaporation of the chloroform gave an oil. Heating this with phthalic anhydride (30 mg.) at 140—150° for 1 hr. gave the methyl ester, needles (from methanol), m. p. and mixed m. p. 154—156°.

Picrate of 3,4-Dihydro-6-methoxy-7-(2-methoxy-5-methoxycarbonylmethylphenoxy)-1-[4-methoxy-3-(2-methoxy-4-2'-phthalimidoethylphenoxy)benzyl]isoquinoline [III; R = $CH_2{\cdot}N(CO)_2C_6H_4$-*o*].—The amide (II) (0·37 g.), toluene (20 c.c.), and phosphorus oxychloride (2 c.c.) were heated under reflux for 30 min. Evaporation, addition of water, and extraction with chloroform afforded a gum, which was triturated with toluene, to give the crude hydrochloride (for infrared spectrum see Table). A solution of the hydrochloride in warm ethanol (30 c.c.) was allowed to cool, filtered from insoluble material, and treated with excess of picric acid in ethanol. The *picrate* crystallised from methanol as a yellow solid (0·34 g., 75%). A sample separated from methanol in yellow prisms, m. p. 178—179° (Found: C, 61·3; H, 4·8; N, 7·1. $C_{51}H_{45}O_{17}N_5$ requires C, 61·2; H, 4·6; N, 7·0%).

3,4-Dihydro-6-methoxy-7-(2-methoxy-5-methoxycarbonylmethylphenoxy)-1-[4-methoxy-3-(2-methoxy-4-2'-phthalimidoethylphenoxy)benzoyl]isoquinoline (IV).—A solution of the above picrate (90 mg.) in chloroform was shaken with several portions of aqueous sodium carbonate and

evaporated. Crystallisation of the residue from ethanol gave the benzoyl compound in aggregates of needles (25 mg.), m. p. 101—103° (Found: C, 67·2; H, 5·4. $C_{45}H_{40}O_{11}N_2,1H_2O$ requires C, 67·3; H, 5·3%). A solution of the compound in acetic anhydride became blue-green when heated. The *picrate* had m. p. 110—114° (from ethanol) (Found: C, 59·8; H, 4·4; N, 6·8. $C_{51}H_{43}O_{18}N_5$ requires C, 60·4; H, 4·3; N, 6·9%).

Reaction of the Amide (II) *with Phosphorus Pentachloride.*—A solution of the amide (280 mg.) in chloroform (10 c.c.) was treated with phosphorus pentachloride (300 mg.) and kept for 3 days. The solution was shaken with water, and the chloroform evaporated. Crystallisation of the residue from methanol gave a white *product* (180 mg.), m. p. 100—102° (Found: C, 65·6; H, 5·5; Cl, 4·5. $C_{45}H_{43}O_{10}N_2Cl,1H_2O$ requires C, 65·7; H, 5·5; Cl, 4·3%).

Picrate of 1,2,3,4-Tetrahydro-6-methoxy-7-(2-methoxy-5-methoxycarbonylmethylphenoxy)-1-[4-methoxy-3-(2-methoxy-4-2′-phthalimidoethylphenoxy)benzyl]-2-methylisoquinoline (V).—The dihydroisoquinoline picrate (270 mg.) was converted into the base by shaking its chloroform solution with aqueous sodium carbonate. A solution of the base in methanol and methyl iodide was refluxed for 1½ hr. Evaporation gave the methiodide as a yellow powder, m. p. 110—114°.

The crude methiodide and diethylamine (0·5 c.c.) in ethanol (100 c.c.) were hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (0·5 g.). After removal of the catalyst, the solution was evaporated. A solution of the residue in chloroform was shaken with 2N-sodium hydroxide and water, and evaporated. Trituration of the residue with light petroleum (b. p. 40—60°) gave a colourless solid (160 mg.), converted, in ethanol, into the *picrate* (180 mg.), m. p. 103—105° (from ethanol) (Found: C, 60·3; H, 4·7; N, 7·4. $C_{52}H_{49}O_{17}N_5,1H_2O$ requires C, 60·4; H, 5·0; N, 6·8%).

Reaction of 2,2′-Dimethoxy-5′-methoxycarbonyl-4-(2-phthalimidoethyl)diphenyl Ether with Sodium Borohydride.—Sodium borohydride (50 mg.) was added in portions to a solution of the ester (50 mg.) in methanol (30 c.c.). After 10 min. most of the methanol was removed and water was added. Acidification with hydrochloric acid gave an oil which was obtained with chloroform and separated from ethanol in prisms (25 mg.), m. p. 179—180° alone or mixed with 5′-carboxymethyl-2,2′-dimethoxy-4-(2-phthalimidoethyl)diphenyl ether. The infrared spectrum of the product was not identical with that of the phthalimido-acid (Table).

2-(3,4-Dimethoxyphenyl)ethylphthalimide.—A solution of 2-(3,4-dimethoxyphenyl)ethylamine (1 g.) and phthalic anhydride (0·9 g.) in acetic acid (10 c.c.) was heated on a steam-bath for 2 hr. The solution was diluted with water; the precipitated *phthalimide* separated from methanol in plates, m. p. 173—174° (Found: C, 69·4; H, 5·6. $C_{18}H_{17}O_4N$ requires C, 69·4; H, 5·5%).

Hydrolysis by hot aqueous-ethanolic N-sodium hydroxide gave the *phthalamic acid*, rectangular plates (from ethanol), m. p. 159—161° (Found: C, 65·6; H, 5·8; N, 4·5. $C_{18}H_{19}O_5N$ requires C, 65·7; H, 5·8; N, 4·3%), and, after resolidifying, m. p. 171—172°, not depressed on admixture with the preceding phthalimide.

5′-Carboxymethyl-4-cyanomethyl-2,2′-dimethoxydiphenyl Ether (I; R = CH_2·CN, R′ = OH).—A solution of 5′-carboxymethyl-4-formyl-2,2′-dimethoxydiphenyl ether (9·65 g.), rhodanine (5·0 g.), and anhydrous sodium acetate (10·0 g.) in acetic acid (50 c.c.) was heated under reflux for 30 min. The precipitate of the rhodanine derivative was removed by filtration of the hot mixture. A further quantity was obtained by refluxing the filtrate for 1 hr.

The crude rhodanine derivative (13·1 g.) and aqueous 15% sodium hydroxide (80 c.c.) were heated on a steam-bath for 40 min. The solution at 0° was acidified with dilute hydrochloric acid, and the precipitated thioketo-acid was dried at room temperature.

A solution of the thioketo-acid in ethanol (100 c.c.) containing hydroxylamine [prepared from hydroxylamine hydrochloride (8·6 g.) and sodium (2·7 g.)] was refluxed for 40 min. After the ethanol had been removed, water (100 c.c.) was added, and the solution was acidified with hydrochloric acid. The solution was shaken with ether (40 c.c.), and the hydroxyimino-acid (10·5 g.), m. p. 155—159°, was removed by filtration. By separation of the ether solution and concentration to 5 c.c. a further quantity (0·5 g.) of the hydroxyimino-acid was obtained.

The crude product (11 g.) in acetic anhydride (50 c.c.) was warmed until a clear solution was obtained, then heated on a steam-bath for 20 min., diluted with water (250 c.c.), and set aside for 12 hr. The *nitrile* (6·5 g.), m. p. 154—158°, was obtained by trituration of the precipitate with ethanol. A further quantity (0·25 g.) was obtained from the aqueous solution with chloroform (total yield, 6·75 g., 68%). A sample crystallised from ethanol in rods, m. p. 158—160° (Found: C, 65·9; H, 5·1. $C_{18}H_{17}O_5N$ requires C, 66·1; H, 5·2%).

4-(2-*Aminoethyl*)-5′-*carboxymethyl*-2,2′-*dimethoxydiphenyl Ether* (I; R = $CH_2 \cdot CH_2 \cdot NH_2$, R′ = OH).—The nitrile (2·2 g.) in acetic acid (150 c.c.) containing platinum oxide (0·6 g.) was hydrogenated at room temperature and atmospheric pressure. When hydrogen absorption ceased (2·5 hr.), the catalyst was removed and the solution evaporated. Crystallisation of the residue from ethanol gave the amino-acid (1·98 g., 90%), m. p. and mixed m. p. 173—174°.

Picrate of 3,4-*Dihydro*-6-*methoxy*-1-[4-*methoxy*-3-(4-2′-*cyanoethyl*-2-*methoxyphenoxy*)-*benzyl*]-7-(2-*methoxy*-5-*methoxycarbonylmethylphenoxy*)*isoquinoline* (III; R = $CH_2 \cdot CN$).—A solution of 5′-carboxymethyl-4-cyanomethyl-2,2′-dimethoxydiphenyl ether (0·75 g.) in thionyl chloride (7 c.c.) was refluxed for 2 hr., and evaporated. The residue in chloroform (20 c.c.) was added during 30 min. to a solution of 4-(2-aminoethyl)-2,2′-dimethoxy-5′-methoxycarbonylmethyldiphenyl ether (0·75 g.) and tributylamine (0·45 g.) in chloroform (20 c.c.). The solution was kept overnight, then evaporated, and the residue was triturated with N-hydrochloric acid (2 × 20 c.c.) and dissolved in chloroform. The solution was shaken with aqueous sodium carbonate and evaporated, giving the amide as a gum (1·15 g.).

A mixture of the crude amide, toluene (20 c.c.), and phosphorus oxychloride (3 c.c.) was heated under reflux for 45 min. The solution was evaporated, and the residue was dissolved in boiling ethanol (60 c.c.) and allowed to cool. The clear solution, obtained by decantation, was treated with excess of picric acid in ethanol. The precipitate of crude *picrate* (0·91 g.), m. p. 89—92°, was extracted with boiling methanol (60 c.c.) and the methanol was removed. The residue separated from acetone–methanol in yellow needles (0·5 g., 25%), m. p. 118—120° and after recrystallisation, m. p. 119—120° (Found: C, 59·9; H, 4·5; N, 8·1. $C_{43}H_{39}O_{15}N_5$ requires C, 59·6; H, 4·5; N, 8·1%).

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