

Complex Dibenzofurans

III*. The Synthesis of Unsymmetrical Biphenyl Derivatives by Mixed Ullmann Coupling

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The synthesis of unsymmetrical polymethoxybiphenyls from iodophenol methyl ethers by mixed Ullmann coupling suffers from the disadvantage that, sometimes, the reaction products are difficult to separate. If, however, one of the components is an iodinated carboxylic ester and the reaction products are subjected to alkaline hydrolysis a neutral product, a mono- and a dicarboxylic acid are obtained. The acids are easily separated and decarboxylation of the monocarboxylic acid gives the unsymmetrical biphenyl. In this way 2,4,2'-trimethoxybiphenyl has been conveniently prepared.

When treated with strong acids certain derivatives of 2,2'-dihydroxybiphenyl easily undergo dehydration with formation of dibenzofurans while others do not react or only react with considerable difficulty. We have been interested in the structural features necessary for facile ring closure as well as in the reaction mechanism involved.

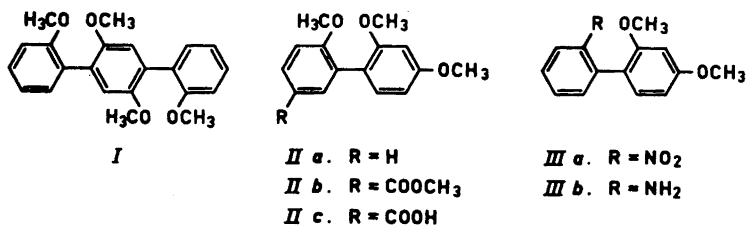
In an earlier investigation¹ it was observed that polymethoxy-*p*-terphenyls (all being methoxylated derivatives of I) possessing methoxyl groups in 4,4'', 5,5''- or 6,6''-positions (derivatives of *m*- and *p*-dihydroxybenzene) showed a pronounced tendency to give dioxidoterphenyls on demethylation with constant boiling hydrobromic acid.

A more suitable series of compounds, for a study of the structural requirements for ring closure, would however be substituted anisols containing in the *ortho* position a 2-methoxy-, a 2,3-dimethoxy- or a 2,4-dimethoxyphenyl group, *etc.*

Such unsymmetrical polymethoxybiphenyls can be prepared directly by mixed Ullmann couplings. Späth and Gibian² prepared 2,4,3',4'-tetramethoxybiphenyl and Riedl³ 2,4,6,3',5'-pentamethoxybiphenyl in this way. The reaction products obtained could be separated by fractional crystallisation² and by chromatography on silica gel³.

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During attempts to prepare 2,4,2'-trimethoxybiphenyl(IIa) from 2-iodoanisole and 4-iodoresorcinol dimethyl ether by a mixed Ullmann coupling, it was found, however, that the separation of the reaction products was laborious. A general method involving less complicated separation problems was therefore devised.



Mixed Ullmann coupling of an iodophenol methyl ether with an iodinated methyl methoxybenzoate gives, after hydrolysis, a mixture of a neutral methyl ether, a mono- and a dicarboxylic acid. These can be easily separated. Decarboxylation of the monoacid gives the required unsymmetrical polymethoxybiphenyl.

Methyl 3-iodo-4-methoxybenzoate and 4-iodoresorcinol dimethyl ether were subjected to a mixed Ullmann coupling in a ratio of 1:2 giving a mixture of mainly 2,4,2',4'-tetramethoxybiphenyl, dimethyl 6,6'-dimethoxybiphenyl-3,3'-dicarboxylate and methyl 6,2',4'-trimethoxybiphenyl-3-carboxylate (IIb). This mixture was saponified with alkali and the neutral tetramethoxybiphenyl was removed by extraction with ether. The mono- and dicarboxylic acids were precipitated with hydrochloric acid and separated by fractional crystallisation from methanol. The yield of the monocarboxylic acid IIc was *ca.* 40 % based on the iodo-ester. Decarboxylation of the acid IIc, with a copper chromite catalyst in quinoline, gave 2,4,2'-trimethoxybiphenyl (IIa) in good yield.

The biphenyl IIa on prolonged heating with hydrobromic acid gave 3-hydroxydibenzofuran which was also obtained directly from the acid IIc by similar treatment.

Although the following route failed to give the desired compound (IIa), certain results of interest were obtained which are recorded. Equivalent amounts of 2-bromonitrobenzene and 4-iodoresorcinol dimethyl ether were subjected to a mixed Ullmann coupling in boiling nitrobenzene. The reaction products were separated by chromatography on alumina and fractional crystallisation. The yield of the unsymmetrical product, 2-nitro-2',4'-dimethoxybiphenyl (IIIa) was *ca.* 65 %, only minor amounts of 2,4,2',4'-tetramethoxybiphenyl were isolated and no 2,2'-dinitrobiphenyl. Such good yields of unsymmetrical biphenyls in mixed Ullmann couplings are not common, but do occur in the preparation of 2- and especially 2,6-substituted nitrobiphenyls⁴.

2-Nitro-2',4'-dimethoxybiphenyl (IIIa) was converted to the corresponding amine (IIIb) by catalytic hydrogenation. Demethylation of this compound with boiling hydrobromic acid gave 2-amino-2',4'-dihydroxybiphenyl in excellent yield. Demethylation with pyridine hydrochloride, however, gave a *ca.* 75 % yield of 2-hydroxycarbazole. This synthesis of a carbazole derivative is closely

analogous to the formation of dibenzofurans from substituted 2,2'-dihydroxybiphenyls. That the demethylation with hydrobromic acid occurred without ring closure is probably due to the fact that under these strongly acidic conditions the nitrogen is present exclusively as ammonium ion.

Attempts to replace the amino group in IIIb by hydroxyl *via* diazotisation invariably failed, 3-methoxydibenzofuran being formed in *ca.* 80 % yield. This is in full accordance with the findings of Mascarelli *et al.*⁵ on the reactions of the diazonium salt of 2-amino-2'-methoxybiphenyl which gives dibenzofuran.

Syntheses of other unsymmetrical methoxybiphenyls are in progress as well as studies on the mechanism of the formation of dibenzofurans from 2,2'-dihydroxybiphenyls.

EXPERIMENTAL

All melting points are uncorrected.

6,2',4'-Trimethoxybiphenyl-3-carboxylic acid (IIc). Methyl 3-iodo-4-methoxybenzoate* (18 g), 4-iodoresorcinol dimethyl ether¹ (33 g) and copper bronze (*ca.* 120 g) were thoroughly mixed and heated to about 220° when a vigorous reaction started, which raised the temperature to about 280°. After some minutes the reaction mixture was allowed to cool and the organic products extracted with chloroform. After evaporation of the solvent the residue was distilled *in vacuo*. A fraction (b.p. 150–225°, 1 mm) was collected and saponified with ethanolic sodium hydroxide. Water was added and 2,4,2',4'-tetramethoxybiphenyl (9.2 g) removed by extracting with ether. The acids were then precipitated with dilute hydrochloric acid. The precipitate was dried and triturated with boiling methanol several times. 6,2',4'-Trimethoxybiphenyl-3-carboxylic acid (IIc) crystallised on cooling and was purified by recrystallisation from methanol. Yield 7.4 g, m.p. 214.5–215.5°. (Found: C 66.3; H 5.5; equiv.wt. 283. Calc. for C₁₆H₁₆O₅: C 66.7; H 5.6; equiv.wt. 288.) The less soluble acid was 6,6'-dimethoxybiphenyl-3,3'-dicarboxylic acid (4.5 g), m.p. *ca.* 310° (lit.⁷ m.p. 312°).

Methyl 6,2',4'-trimethoxybiphenyl-3-carboxylate (IIb). The acid IIc was quantitatively converted to the methyl ester with diazomethane. Crystals from methanol, m.p. 81–81.5°. (Found: C 67.6; H 6.3. Calc. for C₁₇H₁₈O₅: C 67.5; H 6.0.)

2,4,2'-Trimethoxybiphenyl (IIa). The acid IIc (1.0 g) in quinoline (15 ml) was heated for 3 h at 200° in an atmosphere of nitrogen in the presence of a copper chromite catalyst (300 mg). The filtered reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The extract was thoroughly washed with first dilute sodium hydroxide and then water. The solution was dried over magnesium sulphate, the solvent was evaporated and the residue dissolved in a small amount of chloroform. A tenfold volume of light petroleum was added and the solution filtered through a short column of neutral alumina. After evaporation of the solvent the product was collected and recrystallised from methanol. Yield 0.7 g, m.p. 59–59.5°. (Found: C 73.3; H 6.5; OCH₃ 37.0. Calc. for C₁₅H₁₆O₃: C 73.7; H 6.6; OCH₃ 38.1.)

3-Hydroxydibenzofuran and the corresponding methyl ether. The acid IIc (2.0 g) was refluxed for 36 h with hydrobromic acid (48 %, 50 ml) in an atmosphere of nitrogen. The reaction mixture was poured into water and extracted with ether. The extract was washed first with small amounts of dilute sodium bicarbonate and then with water. After drying over anhydrous calcium sulphate and evaporation of the solvent the residual dibenzofuran was recrystallised from water. Yield 0.8 g, m.p. 141–141.5° (lit.⁸ m.p. 138–138.5°). 3-Methoxydibenzofuran was obtained by methylation with dimethyl sulphate and alkali. M.p. 95–95.5° (lit.⁸ m.p. 97–97.5°).

The biphenyl IIa, treated with hydrobromic acid as described above, gave 3-hydroxydibenzofuran in *ca.* 75 % yield.

2-Nitro-2',4'-dimethoxybiphenyl (IIIa). A mixture of 4-iodoresorcinol dimethyl ether (20 g), 2-bromonitrobenzene (15.3 g), copper bronze (96 g) and nitrobenzene (150 ml) was boiled for 3 h with vigorous stirring (reflux). The reaction mixture was filtered and the solid washed with chloroform. The chloroform and nitrobenzene were removed by steam distillation and the residue extracted with chloroform. The extract was

dried over magnesium sulphate and concentrated to a small volume. Light petroleum (2 volumes) was added and the solution was chromatographed on neutral alumina (200 g, column constructed in a chloroform-light petroleum mixture, 1:2). The main component was eluted with the same solvent mixture. After evaporation of the solvent a dark syrup was obtained, which crystallised on scratching with light petroleum. This product was recrystallised from methanol. Yield 26 g, m.p. 101.5–102°. (Found: C 64.7; H 5.1; N 5.6. Calc. for $C_{14}H_{13}NO_4$: C 64.9; H 5.1; N 5.4.)

2,4,2',4'-Tetramethoxybiphenyl (1.5 g) was isolated from the methanolic mother liquor.

2-Amino-2',4'-dimethoxybiphenyl (IIIb). The nitro compound IIIa, in ethanol, was hydrogenated with a palladium charcoal catalyst (10 % Pd) at room temperature and atmospheric pressure. The calculated amount of hydrogen was rapidly absorbed. The amine IIIb, m.p. 68.5–69°, easily formed a picrate. Crystals from ethanol, m.p. 199–200°. (Found: C 51.8; H 4.1; N 12.3. Calc. for $C_{20}H_{18}N_4O_6$: C 52.4; H 4.0; N 12.2.)

2-Amino-2',4'-dihydroxybiphenyl. A mixture of the hydrobromide of compound IIIb (1.5 g, obtained by saturating an ether solution of the amine with dry hydrogen bromide, m.p. 155–160°) and hydrobromic acid (48 %, 30 ml) was boiled in an atmosphere of nitrogen for 24 h (reflux). During the first hours the reaction mixture was intensely green but gradually became brownish towards the end. On cooling crystals were deposited. They were dissolved in water and the free amine was precipitated with saturated sodium bicarbonate solution. Crystals from water. Yield 0.8 g, m.p. 149–149.5°. (Found: C 71.6; H 5.6; N 6.9. Calc. for $C_{12}H_{11}NO_2$: C 71.6; H 5.5; N 7.0.)

2-Hydroxycarbazole. The hydrobromide of compound IIIb (630 mg) was heated with pyridine hydrochloride (4.5 g) and pyridine (0.2 ml) at ca. 180° in an atmosphere of nitrogen for 3 h. The reaction mixture was poured into water and the crude product collected and dried. The substance was decolourised by shaking an ethanol-chloroform solution with charcoal and sublimed *in vacuo*. Yield 370 mg, m.p. ca. 260°, decomp. (lit.⁹ m.p. 277°, to a black liquid with previous darkening). (Found: C 79.0; H 5.2; N 7.5. Calc. for $C_{12}H_9NO$: C 78.7; H 5.0; N 7.7.)

2-Acetoxy-carbazole. The preceding phenol was acetylated with acetic anhydride and pyridine. Crystals from methanol, m.p. 183–184° (lit.¹⁰ m.p. 188°). (Found: C 75.0; H 4.9; N 6.2. Calc. for $C_{14}H_{11}NO_3$: C 74.7; H 4.9; N 6.2.)

Attempted replacement of the amino group in compound IIIb by hydroxyl. A mixture of the amine IIIb (2.8 g) and dilute sulphuric acid (15 %, 100 ml) was treated with a solution of sodium nitrite (1.5 g) in water (20 ml) at 0–5° with stirring. Excess of nitrite was destroyed with urea and the mixture heated at 70° until nitrogen evolution ceased. The reaction mixture was then extracted with chloroform. The extract was washed with water, dried over magnesium sulphate and filtered through a short column of neutral alumina. The solvent was evaporated and the residue recrystallised from methanol. Yield 2.0 g, m.p. 95–95.5°. A mixed melting point with 3-methoxydibenzofuran (prepared from the biphenyl IIa, m.p. 95–95.5°) showed no depression (m.p. 95–95.5°). The ultraviolet spectra of the two samples were identical.

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