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Complex Dibenzofurans

XI.* A Study on the Mechanism of Acid-Catalysed Dehydration of 2,2′-Dihydroxybiphenyls

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The dehydration of 2,4,2′-trihydroxybiphenyl (II) and 2,5,2′-trihydroxybiphenyl (IV) with constant boiling hydrobromic acid has been investigated by labelling the 2′-hydroxyl group with oxygen-18. It was found that formation of the corresponding hydroxydibenzofuran involves elimination of the 2-hydroxyl group. Mechanisms for the reactions are proposed.

One of the most commonly used methods for the synthesis of substituted dibenzofurans is the demethylation and subsequent dehydration of 2,2′-dimethoxybiphenyls, the reaction being effected by refluxing with hydrobromic or hydroiodic acid. The method has been used extensively for the preparation of polyhydroxydibenzofurans and to some extent in the terphenyl series for the preparation of polyhydroxydioxidoterphenyls (*cf.* Ref. 1). The acid-catalysed dehydration of polyhydroxybiphenyls and polyhydroxyterphenyls with 2,2′-dihydroxyl groups has been found to proceed readily if hydroquinone or resorcinol groupings are present. However, catechol and monophenolic groupings do not facilitate ring closure.[1]

Results obtained previously on the acid-catalysed dehydration of 2,2′-dihydroxybiphenyls suggest that the two hydroxyl groups involved in dibenzofuran formation take part in different ways. One of the groups participates

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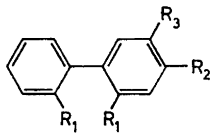
in formation of the oxygen bridge while the other is eliminated. A possible explanation of the differences outlined previously between resorcinol and catechol derivatives is that hydroxyl groups in resorcinol are more easily substituted than hydroxyl groups in catechol.

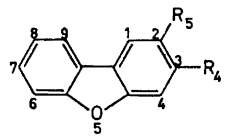
Resorcinol is known to be especially susceptible to acid-catalysed nucleophilic types of substitution. Treatment with methanol and potassium hydrogen sulphate results in formation of resorcinol monomethyl ether.[2] Phloroglucinol reacts in a similar way to give the dimethyl ether.[3] In acid solution, resorcinol, hydroquinone, phloroglucinol, and hydroxyhydroquinone undergo exchange of their hydroxyl groups with water-^{18}O whereas catechol and pyrogallol do not.[4]

The conversion of β-naphthol to its methyl ether, which can be effected in methanol with p-toluenesulphonic acid as catalyst, was studied by Wiberg and Saegebarth [5] by using methanol-^{18}O. It was found that the β-naphthol methyl ether formed contained heavy oxygen, the transfer being nearly quantitative.

It has been suggested by Stjernström that the acid-catalysed dehydration of 2,2′-dihydroxybiphenyls to dibenzofuran derivatives may be a similar type of reaction.[1] The proposed mechanism of conversion of 2,4,2′-trihydroxybiphenyl (II) to 3-hydroxydibenzofuran (V) is given in Fig. 1. The initial step is protonation of the dihydroxy-substituted aromatic ring. The subsequent or concerted ring closure may then be regarded as an intramolecular nucleophilic substitution. An analogous mechanism for the reaction of 2,5,2′-trihydroxybiphenyl (IV) is outlined in Fig. 2.

In order to test this hypothesis, experiments concerning the acid-catalysed demethylation and dehydration of 2,4,2′-trimethoxybiphenyl (I) and 2,5,2′-trimethoxybiphenyl (III) were performed.





I $R_1 = R_2 = OCH_3$, $R_3 = H$
II $R_1 = R_2 = OH$, $R_3 = H$
III $R_1 = R_3 = OCH_3$, $R_2 = H$
IV $R_1 = R_3 = OH$, $R_2 = H$

V $R_4 = OH$, $R_5 = H$
VI $R_4 = OCH_3$, $R_5 = H$
VII $R_4 = H$, $R_5 = OH$
VIII $R_4 = H$, $R_5 = OCH_3$

Note: The corresponding 2′-methoxy-^{18}O-labelled trimethoxybiphenyls and 5-^{18}O-labelled dibenzofurans are denoted by the suffix "a" after the Roman numeral.

It was first considered necessary to establish that the trihydroxybiphenyl is the precursor to the corresponding hydroxydibenzofuran in the demethylation and dehydration reaction. Thus, we have investigated by means of paper chromatography the course of the reactions of 2,4,2′-trimethoxybiphenyl (I)

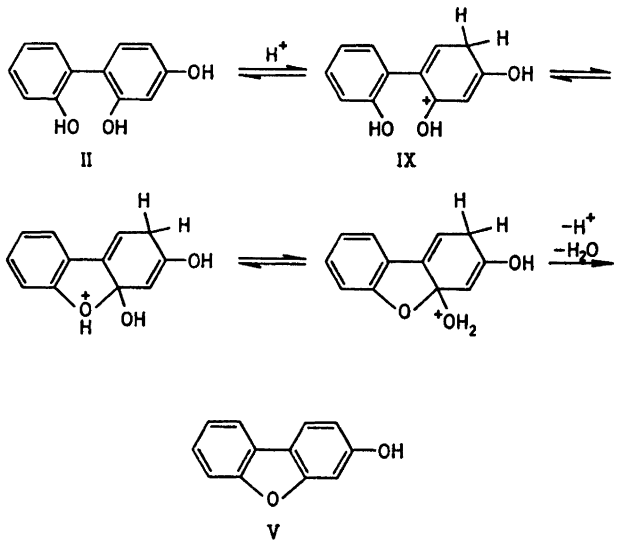


Fig. 1. Proposed mechanism for the acid-catalysed dehydration of 2,4,2′-trihydroxybiphenyl (II) to 3-hydroxydibenzofuran (V).

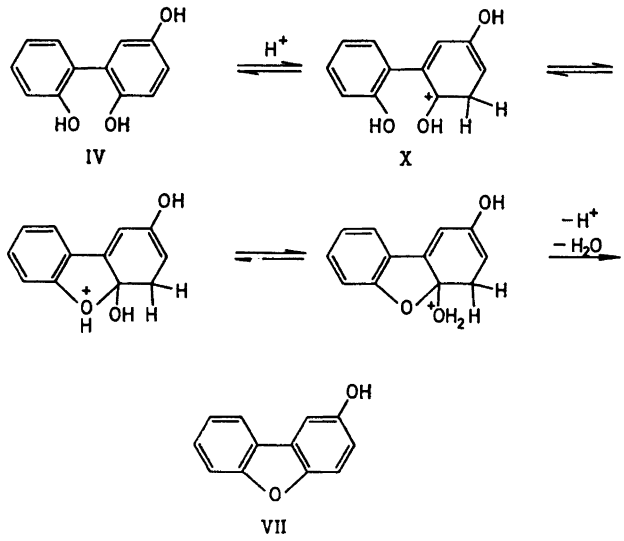


Fig. 2. Proposed mechanism for the acid-catalysed dehydration of 2,5,2′-trihydroxybiphenyl (IV)-to 2-hydroxydibenzofuran (VII).

and 2,4,2′-trihydroxybiphenyl (II) on the one hand and 2,5,2′-trimethoxybiphenyl (III) and 2,5,2′-trihydroxybiphenyl (IV) on the other with refluxing hydrobromic acid.

Of the trihydroxybiphenyls, only the 2,5,2′-compound had been prepared previously,[6] namely by reducing (2-hydroxyphenyl)-*p*-benzoquinone with zinc and acetic acid. We have prepared this compound by catalytic hydrogenation of the same quinone and by demethylation of the trimethyl ether with pyridine hydrochloride.

It was found that the dehydration step is considerably slower than the demethylation step. The reactions were complete within 24 h. 3-Hydroxydibenzofuran (V) was detected after 2—3 h during the reactions of both 2,4,2′-trimethoxybiphenyl (I) and 2,4,2′-trihydroxybiphenyl (II). 2-Hydroxydibenzofuran (VII) was detected after 30 min during the reactions of the 2,5,2′-compounds. Moreover, during demethylation of the trimethoxybiphenyls, the only distinct spots after 3 h were those due to the trihydroxybiphenyls and hydroxydibenzofurans. The possibility that methoxydibenzofurans are precursors to hydroxydibenzofurans seems unlikely. No spots corresponding to methoxydibenzofurans could be seen on irradiating the chromatograms with ultraviolet light. Hence, the experiments indicate that the trihydroxybiphenyls are precursors to the hydroxydibenzofurans under the described reaction conditions.

The 2′-methoxyl groups of 2,4,2′-trimethoxybiphenyl (I) and 2,5,2′-trimethoxybiphenyl (III) were now labelled with oxygen-18. Methyl 3-iodo-4-methoxy-^{18}O-benzoate was first prepared. 2-Iodo-4-carbomethoxybenzenediazonium fluoborate was hydrolysed by heating with water-^{18}O (30.1 atom % ^{18}O). A 40-fold excess of water was used and could be recovered after the reaction by distilling *in vacuo*. The dry residue consisted mainly of methyl 3-iodo-4-hydroxy-^{18}O-benzoate and methyl 3-iodo-4-fluorobenzoate together with the free acids. After removal of neutral compounds, the acidic and phenolic material was refluxed with methanolic hydrogen chloride in order to convert the free acids to methyl esters. Separation of the phenolic material could then be effected and after methylation with diazomethane, methyl 3-iodo-4-methoxy-^{18}O-benzoate was obtained in *ca.* 65 % yield from the diazonium fluoborate. The recovery of heavy isotope as water-^{18}O and methyl 3-iodo-4-methoxy-^{18}O-benzoate was *ca.* 99 %.

This method of obtaining ^{18}O-labelled phenols does not appear to have been used previously. Fusion of sodium arylsulphonates with sodium hydroxide-^{18}O has been used [7] and exchange of oxygen-18 between water-^{18}O and phenols in acid or alkaline solution may be employed where applicable.[4,8,9]

2,4,2′-Trimethoxy-(2′-^{18}O)-biphenyl (Ia) was synthesised from methyl 3-iodo-4-methoxy-^{18}O-benzoate by a method used previously with unlabelled materials.[10] A mixed Ullmann coupling between the ^{18}O-labelled compound and 4-iodoresorcinol dimethyl ether followed by saponification of the mixture of reaction products enabled the isolation of 6,2′,4′-trimethoxy-(6-^{18}O)-biphenyl-3-carboxylic acid. A 20-fold excess of 4-iodoresorcinol dimethyl ether was used to minimise formation of dimethyl 6,6′-dimethoxy-(6,6′-^{18}O)-biphenyl-3,3′-dicarboxylate. Decarboxylation of the monocarboxylic acid with a copper chromite catalyst in quinoline gave a good yield of 2,4,2′-trimethoxy-(2′-^{18}O)-biphenyl (Ia).

2,5,2′-Trimethoxy-(2′-^{18}O)-biphenyl (IIIa) was prepared similarly, the mixed Ullmann coupling being carried out between methyl 3-iodo-4-methoxy-

^{18}O-benzoate and idoohydroquinone dimethyl ether. A synthesis had been carried out on a larger scale with unlabelled material and the previously unknown 6,2′,5′-trimethoxybiphenyl-3-carboxylic acid and its methyl ester obtained.

The 2′-methoxy-^{18}O-labelled trimethoxybiphenyls were now refluxed with 48 % hydrobromic acid and glacial acetic acid for 40 h and the hydroxydibenzofurans isolated. The methoxydibenzofurans were also prepared. 3-Methoxydibenzofuran-5-^{18}O (VIa) was obtained by methylation of 3-hydroxydibenzofuran-5-^{18}O (Va) with diazomethane in ether. 2-Methoxydibenzofuran-5-^{18}O (VIIIa) had to be prepared by refluxing 2-hydroxydibenzofuran-5-^{18}O (VIIa) with dimethyl sulphate in dry acetone solution in the presence of potassium carbonate followed by separation of the required product by means of thin layer chromatography.

The ^{18}O-labelled trimethoxybiphenyls, hydroxydibenzofurans and methoxydibenzofurans were analysed by means of mass spectroscopy. Swain *et al.*[11] have stated that direct analysis by means of mass spectroscopy is of sufficient precision if the tracer enrichment is at least 5 %. In our experiments, the tracer enrichment of all the compounds proved to be *ca.* 30 %.

The methoxydibenzofurans were analysed due to the possibility of an isotope effect causing inaccuracies in the ratio $(M + 2)^+/M^+$ for the ^{18}O-labelled hydroxydibenzofurans. It is shown elsewhere [12] that the initial breakdown of the molecular ion of 3-methoxydibenzofuran (VI) and 2-methoxydibenzofuran (VIII) is by loss of a methyl radical and thus there is no possibility of error in $(M + 2)^+/M^+$ for the 5-^{18}O-labelled methoxydibenzofurans due to an isotope effect. However, such an effect may be apparent in the case of the 2′-methoxy-^{18}O-labelled trimethoxybiphenyls if the initial loss of a methyl radical is from the 2′-methoxyl group. The molecular ions of 3-hydroxydibenzo-

Table 1. Relative intensities of the M^+, $(M + 1)^+$, $(M + 2)^+$, and $(M + 3)^+$ ions in the mass spectra of the ^{18}O-labelled compounds and the corresponding unlabelled compounds.

	Compound											
m/e	I	Ia	V	Va	VI	VIa	III	IIIa	VII	VIIa	VIII	VIIIa
247		9.9						8.0				
246	2.4	52.7					2.5	52.7				
245	18.6	17.7					18.3	17.2				
244	100.0	100.0					100.0	100.0				
201						7.9						9.2
200					1.7	51.6					1.8	53.4
199					15.3	15.0					15.6	16.4
198					100.0	100.0					100.0	100.0
187				7.2						6.9		
186			1.4	51.7					1.7	51.4		
185			14.8	15.8					15.0	14.6		
184			100.0	100.0					100.0	100.0		

Table 2. $(M + 2)^+/M^+$ ratios for the ^{18}O-labelled compounds.

$(M + 2)^+/M^+$	^{18}O-labelled compound					
	Ia	Va	VIa	IIIa	VIIa	VIIIa
$(246)^+/(244)^+$	0.503			0.502		
$(200)^+/(198)^+$			0.499			0.516
$(186)^+/(184)^+$		0.503			0.497	

The ratios are corrected empirically by subtracting the ratio of $(M + 2)^+/M^+$ from the spectra of the unlabelled compounds from the ratios calculated from the spectra of the labelled compounds.

furan (V) and 2-hydroxydibenzofuran (VII) lose carbon monoxide mainly from the carbon-hydroxyl grouping, but also to an extent from the furan ring, so the possibility of an error in $(M + 2)^+/M^+$ for the 5-^{18}O-labelled compounds could not be overlooked. However, such an isotope effect could not be detected on studying the mass spectra.[12]

The relative intensities of the molecular ions are given in Table 1 and the values for $(M + 2)^+/M^+$ for the ^{18}O-labelled compounds are given in Table 2.

It was thus found that there is complete retention of heavy isotope in both reactions. This is in complete agreement with the ring closure reaction occurring by nucleophilic attack of the 2′-hydroxyl group on the 2-carbon atom of the protonated precursors (IX and X; *cf.* Figs. 1 and 2). Another protonated form of 2,4,2′-trihydroxybiphenyl (II) which may lead to ring closure is the intermediate protonated in the 3-position. The potential intermediate protonated in the 1-position is disfavoured because of the steric and electronic requirements of the 2-hydroxyphenyl group (*cf.* Oae and Kiritani's results on ^{18}O exchange between water-^{18}O and 2,4,6-trisubstituted phenols [8]). An investigation on exchange of resorcinol with heavy water in 0.01 N hydrochloric acid showed that the 4- and 6-hydrogens exchanged with deuterium six to seven times more rapidly than the 2-hydrogen, the 5-hydrogen not exchanging.[13] In analogy with these results, protonation of 2,4,2′-trihydroxybiphenyl (II) may be expected to occur chiefly at the 5-position.

The most favourable form of protonated 2,5,2′-trihydroxybiphenyl (IV) which can lead to ring closure is X (*cf.* Fig. 2). The intermediate protonated in the 1-position is disfavoured for the reasons given previously in connection with the resorcinol derivative. A further alternative protonated in the 5-position is improbable since the inductive effect of the 5-hydroxyl group will disfavour such a protonation.

Thus the reaction mechanisms for acid-catalysed dehydration of trihydroxybiphenyls outlined in Figs. 1 and 2 are the most probable and are supported by the labelling experiments.

EXPERIMENTAL

All melting points are uncorrected.

2,4,2′-Trihydroxybiphenyl (II). 2,4,2′-Trimethoxybiphenyl (I) [10] (490 mg) was heated with pyridine hydrochloride (10 g) at 165° for 3 h, air being excluded. The mixture was acidified with dilute hydrochloric acid and extracted with ether. After drying the ether extract over sodium sulphate and removal of the solvent, a brown syrupy residue remained which afforded 296 mg of a phenolic product on crystallisation from chlorobenzene, m.p. 149–150° (after sublimation *in vacuo*). Yield 73 %. (Found: C 71.27, 71.28; H 5.11, 4.93. Calc. for $C_{12}H_{10}O_3$: C 71.28; H 4.98). Methylation of the product with dimethyl sulphate and alkali gave 2,4,2′-trimethoxybiphenyl (I), m.p. 58–60° (lit.[10] m.p. 59–59.5°).

2,5,2′-Trihydroxybiphenyl (IV). Method 1. 2,5,2′-Trimethoxybiphenyl (III) [15] (780 mg) and pyridine hydrochloride (15 g) were reacted as described above. The product (495 mg) was a green-brown glass and attempts to crystallise it from various solvents were unsuccessful. On distillation (150°/0.001 mm Hg) an oil was obtained which gave a colourless glass on cooling (*cf.* Ref. 6). Paper chromatography of the glass on Whatman No. 1 filter paper using formamide-ether as the solvent system showed a large spot (R_F 0.24, yellow) and a faint spot (R_F 0.90, brown) on spraying with bis-diazotised benzidine followed by 10 % sodium carbonate solution. The faint spot had the same R_F value as 2-hydroxydibenzofuran (VII).

Method 2. (2-Hydroxyphenyl)-*p*-benzoquinone [14] (397 mg) was hydrogenated in ethanol in the presence of Adams' catalyst. The dark-red suspension took up 47.0 ml hydrogen giving a colourless solution which afforded 410 mg of a colourless glass after filtration and removal of the solvent. The yield was quantitative. Paper chromatography of the glass, carried out as described above, gave one spot (R_F 0.24, yellow).

Methylation of the glasses obtained by each method with dimethyl sulphate and alkali gave 2,5,2′-trimethoxybiphenyl (III) m.p. 90–90.5°. A mixed melting point with an authentic sample of 2,5,2′-trimethoxybiphenyl [15] (m.p. 93–94.5°) showed no depression (m.p. 91–93°).

3-Iodo-4-aminobenzoic acid. A solution of iodine monochloride (13.1 g, 0.08 mole) in a mixture of 14 ml concentrated hydrochloric acid and 50 ml water, cooled to 5° by addition of crushed ice, was added rapidly with stirring to a solution of 4-aminobenzoic acid (11.0 g, 0.08 mole) in 100 ml N hydrochloric acid which had been previously cooled to 20°. The mixture was stirred for 1 h and the resulting purple-brown precipitate was filtered, washed with three 10 ml portions of cold water and dried at 90–100°. The crude product (18.9 g, m.p. 210–220°) was stirred with 30 ml hot water and concentrated ammonia solution added until solution was complete and a slight excess of ammonia was present. The solution was kept at 60° and sufficient sodium dithionite added to bleach the solution which was then stirred with 1 g active charcoal and filtered while hot. On cooling the filtrate, a light precipitate was formed. This was removed and the remaining solution acidified with dilute hydrochloric acid. The heavy precipitate now obtained was removed by filtration, washed with water and dried. Yield of 3-iodo-4-aminobenzoic acid 11.6 g, 55 %, m.p. 201–203° (after sublimation *in vacuo*) (lit.[16] m.p. 203–204°).

Methyl 3-iodo-4-aminobenzoate. 3-Iodo-4-aminobenzoic acid (6.1 g) was dissolved in 40 ml methanol, the solution saturated with dry hydrogen chloride and refluxed for 3 h. After cooling, the precipitate (5.8 g) was collected and stirred with a slight excess of 10% sodium carbonate solution. The mixture was extracted with ether and the ether solution dried over magnesium sulphate. The solvent was evaporated and the residue was recrystallised from 50 % aqueous methanol. Yield 4.5 g, 73 %, m.p. 90.5–91.5° (after sublimation *in vacuo*). (Found: C 34.60, 34.50; H 2.79, 2.78; I 46.01; N 5.06. Calc. for $C_8H_8INO_2$: C 34.65; H 2.91; I 45.80; N 5.06).

2-Iodo-4-carbomethoxybenzenediazonium fluoborate. The preceding ester (20 g, 70 mmole) was stirred with 80 ml 4.5 N hydrochloric acid, the suspension cooled to 0–5° and diazotised by dropwise addition of a solution of sodium nitrite (5.25 g, 70 mmole) in a little water. The solution was filtered and a solution of sodium fluoborate (10.9 g, 100 mmole) in a minimum amount of water added to the filtrate. The mixture was allowed to stand at 5° for 1 h. The precipitate was removed by filtration and washed with a little cold water, ethanol and finally ether. The green-yellow crystals were dried *in vacuo*. Yield 17.2 g, 63 %, decomp. p. 130–131°. (Found: C 25.69; H 1.96; F 20.45; I 33.91; N 7.46. Calc. for $C_8H_6BF_4IN_2O_2$: C 25.54; H 1.61; F 20.22; I 33.77; N 7.45).

6,2',5'-Trimethoxybiphenyl-3-carboxylic acid. Methyl 3-iodo-4-methoxybenzoate [17] (4.7 g, 16 mmole), iodohydroquinone dimethyl ether [18] (16.9 g, 64 mmole), and copper bronze (50 g) were thoroughly mixed and heated to 220° whereupon a vigorous reaction took place and the temperature rose to *ca.* 270°. After 5 min, the 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. 140—210°/0.07 mm Hg, 8.34 g) was collected and saponified with ethanolic potassium hydroxide. Water was added and the mixture was extracted with ether to remove 2,5,2',5'-tetramethoxybiphenyl (3.94 g). The acids were precipitated from the alkaline solution with dilute hydrochloric acid. After drying, the precipitate (3.70 g) was triturated several times with boiling methanol. 6,2',5'-Trimethoxybiphenyl-3-carboxylic acid crystallised on cooling and was purified by recrystallisation from methanol. Yield 2.10 g, 46 %, m.p. 213—214° (after sublimation *in vaeuo*). (Found: C 66.56, 66.49; H 5.59, 5.49. Calc. for $C_{16}H_{16}O_5$: C 66.65; H 5.59). The trituration residue was 6,6'-dimethoxybiphenyl-3,3'-dicarboxylic acid (0.11 g), m.p. *ca.* 320° (lit.[19] m.p. 312°).

Methyl 6,2',5'-trimethoxybiphenyl-3-carboxylate. The corresponding acid (0.5 g) was treated with diazomethane in ether solution and the ester recrystallised from methanol. Yield 0.24 g, 47 %, m.p. 105—106°. (Found: C 67.67, 67.78; H 6.05, 6.08. Calc. for $C_{17}H_{18}O_5$: C 67.53; H 6.00).

Decarboxylation of 6,2',5'-trimethoxybiphenyl-3-carboxylic acid. The acid (200 mg) was stirred with a copper chromite catalyst [20] (60 mg) in 5 ml dry quinoline at 220—240° under argon. After 4 h, the reaction mixture was cooled, filtered, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed first with dilute sodium hydroxide solution, then with water, and finally dried over magnesium sulphate. The solvent was removed and the residue dissolved in a little chloroform. A ten-fold volume of light petroleum was added and the solution filtered through a short column of neutral alumina. After evaporation of the solvent, the residue was distilled *in vacuo* and the distillate recrystallised from methanol. Yield of 2,5,2'-trimethoxybiphenyl (III) 82 mg, 49 %, m.p. 91—91.5° (lit.[15] 93—94.5°).

Syntheses of ^{18}O-labelled compounds

Methyl 3-iodo-4-methoxy-^{18}O-benzoate. 2-Iodo-4-carbomethoxybenzenediazonium fluoborate (1.0 g, 2.7 mmole) was stirred with water-^{18}O (2.0 g, 107 mmole; 30.1 atom % ^{18}O) at 100° for 2 h in a flask to which a reflux condenser fitted with a blue gel guard tube was attached. When the reaction was complete, the guard tube was replaced by a U-tube which could be closed by taps. The other end of the U-tube was connected to a vacuum system (0.03 mm Hg). The tube was cooled to −78°, the entire apparatus evacuated and excess water-^{18}O distilled over. The recovery of water-^{18}O was 1.95 g. The dry residue in the flask was extracted with ether and the ether solution shaken with 10 % sodium hydroxide to remove phenolic and acidic material. The residual ether solution gave impure methyl 3-iodo-4-fluorobenzoate (350 mg) on evaporation. This ester was saponified to give 3-iodo-4-fluorobenzoic acid, 144 mg, m.p. 175—176° (after recrystallisation from first water, then isopropyl alcohol) (lit.[21] m.p. 175—176°). The alkaline extract was acidified and shaken with ether. The ether solution was dried over magnesium sulphate and the solvent removed. A residue remained which was refluxed with methanolic hydrogen chloride for 2 h. After this time, the mixture was poured into water, neutralised with 2 N sodium hydroxide solution and extracted with ether to remove non-phenolic material. The residual aqueous solution was then acidified with dilute hydrochloric acid and extracted with ether. After drying the ether solution over magnesium sulphate and removal of the solvent, 490 mg crude methyl 3-iodo-4-hydroxy-^{18}O-benzoate remained, m.p. 156—158° (after sublimation *in vacuo*) (lit.[22] m.p. 157—158°). The crude material was treated directly with diazomethane in ether and the solution filtered through a short column of active charcoal. The filtrate was evaporated to dryness to yield 520 mg slightly impure methyl 3-iodo-4-methoxy-^{18}O-benzoate, m.p. 91—95° (m.p. 94—95° after sublimation of a sample *in vacuo*) (lit.[17] m.p. 94—95°). Yield of slightly impure material 66 %.

Attempts to improve the yield of methyl 3-iodo-4-hydroxybenzoate by addition of catalytic amounts of 2,6-dimethylpyridine, 2,4,6-trimethyl-3,5-dicarboethoxypyridine or

potassium hydrogen sulphate to trial reaction mixtures of water and the diazonium fluoborate were unsuccessful.

6,2',4'-Trimethoxy-(6-^{18}O)-biphenyl-3-carboxylic acid. The slightly impure methyl 3-iodo-4-methoxy-^{18}O-benzoate (510 mg, 1.75 mmole), 4-iodoresorcinol dimethyl ether[23] (9.4 g, 35.6 mmole), and copper bronze (20 g) were reacted and the reaction mixture worked up to give a neutral substance, a monocarboxylic acid and a dicarboxylic acid as described previously.[10] In this way 2,4,2',4'-tetramethoxybiphenyl (3.55 g) and 6,2',4'-trimethoxy-(6-^{18}O)-biphenyl-3-carboxylic acid (168 mg, 34 %), m.p. 214—215° (after sublimation *in vacuo*) (lit.[10] m.p. 214.5—215.5°) were obtained. No dicarboxylic acid was isolated.

2,4,2'-Trimethoxy-(2'-^{18}O)-biphenyl (Ia). The ^{18}O-labelled monocarboxylic acid (150 mg) described above was decarboxylated with a copper chromite catalyst[20] (45 mg) in 2.5 ml quinoline in the usual manner.[10] Yield 82 mg, 65 %, m.p. 59—60° (lit.[10] 59—59.5°).

3-Hydroxydibenzofuran-5-^{18}O (Va). Substance Ia (39 mg) was refluxed with 4 ml 48 % hydrobromic acid and 4 ml glacial acetic acid for 40 h under argon. The product was worked up as described previously.[10] Yield 9.0 mg, 25 %, m.p. 141.5—142.5° (after sublimation *in vacuo*) (lit.[10] m.p. 141—141.5°).

3-Methoxydibenzofuran-5-^{18}O (VIa). Substance Va (3.4 mg) was methylated with a solution of diazomethane in ether. The product was purified by sublimation *in vacuo*. Yield 1.8 mg, 49 %, m.p. 95—97° (lit.[24] m.p. 97—97.5°).

6,2',5'-Trimethoxy-(6-^{18}O)-biphenyl-3-carboxylic acid. This compound was prepared in the manner described for the unlabelled compound. The Ullmann coupling was carried out with crude methyl 3-iodo-4-methoxy-^{18}O-benzoate (570 mg, 1.96 mmole), iodohydroquinone dimethyl ether (10.0 g, 37.7 mmole), and copper bronze (20 g). The products isolated where 2,5,2',5'-tetramethoxybiphenyl (3.22 g) and 6,2',5'-trimethoxy-(6-^{18}O)-biphenyl-3-carboxylic acid (333 mg, 52 %), m.p. 213—214° (after sublimation *in vacuo*). No dicarboxylic acid was isolated.

2,5,2'-Trimethoxy-(2'-^{18}O)-biphenyl (IIIa). Decarboxylation of the previous acid (259 mg) with a copper chromite catalyst[20] (70 mg) in 4 ml quinoline was carried out as described for the unlabelled compound. Yield 101 mg, 46 %, m.p. 91—91.5° (lit.[15] m.p. 93—94.5°).

2-Hydroxydibenzofuran-5-^{18}O (VIIa). The preceding compound (52 mg) was refluxed with a mixture of 5 ml 48 % hydrobromic acid and 5 ml glacial acetic acid under argon for 40 h. The product was worked up as described for compound Va and purified by recrystallisation from water and sublimation *in vacuo*. Yield 13 mg, 33 %, m.p. 134—135° (lit.[25] m.p. 136°).

2-Methoxydibenzofuran-5-^{18}O (VIIIa). The compound VIIa (3.3 mg, 0.018 mmole) was dissolved in 1 ml dry acetone and anhydrous potassium carbonate (10.0 mg, 0.072 mmole) added. After the addition of dimethyl sulphate (6.6 mg, 0.053 mmole), the mixture was stirred and refluxed in the absence of moisture for 5 h. Water was added and the mixture extracted with ether. The ether extract was dried over magnesium sulphate and the solvent removed. Thin layer chromatography of the residue on silica with isopropyl ether as the moving phase gave three spots which were observable in ultraviolet light. Separation was good and the middle spot had the same R_F value as 2-methoxydibenzofuran (VIII) (*ca.* 0.7). The other spots had R_F values of *ca.* 0.5 and *ca.* 0.8. The middle spot was extracted with ether, the solvent removed and the residue distilled *in vacuo*. The distillate gave one peak according to gas liquid chromatography (15 % 1,4-butanediol succinate on *Gas-Chrom P* column at 192°; Perkin-Elmer 801 chromatograph). The retention time was the same as that of an authentic sample of 2-methoxydibenzofuran (VIII) (13.5 min). Yield 0.2 mg, 6 %. The distillate did not crystallise at room temperature (lit.[26] m.p. 46—47°). The presence of small amounts of impurity as indicated by the mass spectrum is discussed elsewhere.[12]

Comparative demethylation and dehydration experiments followed by paper chomatography

General procedure. The comparative experiments described below were carried out by refluxing the biphenyl (16 mg) with a mixture of 48 % hydrobromic acid (1.5 ml) and glacial acetic acid (1.5 ml). Samples were withdrawn at certain intervals, extracted with ether and the extracts investigated by means of paper chromatography as described in a previous paper.[15] The solvent system formamide-ether was used throughout. The chromatograms were investigated in ultraviolet light before spraying with bis-diazotised benzidine followed by 10 % sodium carbonate solution.

Comparative demethylation and dehydration of 2,4,2'-trimethoxybiphenyl (I) and 2,4,2'-trihydroxybiphenyl (II). Compound I gave three spots after 1 min, eight spots being observed altogether. This is in agreement with previous findings.[15] Compound II (R_F 0.32, purple) was detected after 5 min and the end product, 3-hydroxydibenzofuran (V) (R_F 0.95, yellow-orange), after 2 h. These were the only distinct spots observable after 3 h. The reaction was complete within 24 h. No spot corresponding to 3-methoxydibenzofuran (VI) (R_F 0.98 in ultraviolet light) was observed.

Compound II gave a spot corresponding to 3-hydroxydibenzofuran after 2.5 h. Only a faint spot due to the trihydroxybiphenyl remained after 24 h. No other spots were detected.

Comparative demethylation and dehydration of 2,5,2'-trimethoxybiphenyl (III) and 2,5,2'-trihydroxybiphenyl (IV). Altogether seven phenols were detected on demethylation of compound III. (Pettersson and Stjernström [15] detected eight). Compound IV (R_F 0.24, yellow) was traced after 10 min and the end product, 2-hydroxydibenzofuran (VII) (R_F 0.90, brown), after 30 min. Only these two phenols could be detected after 3 h. The reaction was complete within 24 h. No spot corresponding to 2-methoxydibenzofuran (VIII) (R_F 0.98 in ultraviolet light) was detected.

Compound IV gave a spot corresponding to 2-hydroxydibenzofuran (VII) after 30 min. The reaction was complete within 24 h. No other spots were observed.

Mass spectrometric measurements

The full mass spectra of the compounds involved, both ^{18}O-labelled and unlabelled are given elsewhere.[12] The relevant data for calculation of $^{18}O/^{16}O$ ratios are given in Table 1 and the ratios of $(M + 2)^+/M^+$ for the various ^{18}O-labelled compounds are given in Table 2.

The mass spectra were obtained on a modified 180° mass spectrometer.[27] The electron energy was 70 eV the temperature of the inlet system was kept between 80° and 150°.

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