

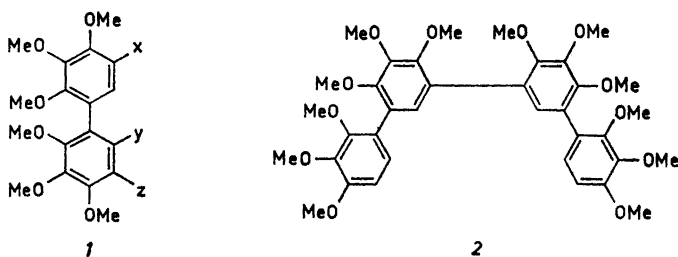
The Halogenation of 2,3,4,2',3',4'-Hexamethoxybiphenyl and 4-Ethylpyrogallol Trimethyl Ether and the Synthesis of Some Dodecahydroxytetraphenyl Derivatives

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Contrary to statements in the literature 2,3,4,2',3',4'-hexamethoxybiphenyl is first halogenated in position 5 and then in position 5'. Ullmann coupling of 5-iodo-2,3,4,2',3',4'-hexamethoxybiphenyl gave the dodecamethoxytetraphenyl 2.

Some twenty years ago two of us (H.E. and A.T.) iodinated 2,3,4,2',3',4'-hexamethoxybiphenyl (1, $x=y=z=H$) with iodine and mercuric oxide and obtained a monoiodo derivative (A), m.p. 94–95°, and a diiodo derivative (B), m.p. 115°. Subjected to the Ullmann reaction A gave a dodecamethoxytetraphenyl which was demethylated to the corresponding dodecahydroxytetraphenyl. Since pyrogallol trimethyl ether is halogenated in position 4

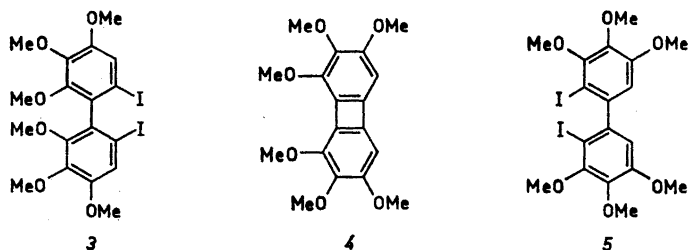


we considered it probable that 2,3,4,2',3',4'-hexamethoxybiphenyl would be iodinated in the positions 5 and 5'. Compound A would then be 1 ($x=I$, $y=z=H$), compound B would be 1 ($x=z=I$, $y=H$), and the dodecahydroxytetraphenyl would be 2 with Me replaced by hydrogen.

We have now also brominated 2,3,4,2',3',4'-hexamethoxybiphenyl to the mono- and dibromo derivatives and have transformed the monoiodo and monobromo compounds into identical monocarboxylic acids and also the diiodo and dibromo compounds into identical dicarboxylic acids.

During the early stages of this research we studied the oxygen consumption of pyrogallol, 2,3,4,2',3',4'-hexahydroxybiphenyl and the dodecahydroxytetraphenyl in alkaline solutions of different pH. This was done in the hope of getting some insight into the reactions occurring when pyrogallol is oxidized under these conditions. As expected the amount of oxygen consumed per pyrogallol unit decreased fairly regularly with increasing number of nuclei present in the molecules. This work was not published owing to the uncertain structure of the monoiodo derivative A and hence that of the dodecahydroxytetraphenyl.

In 1963 Baker *et al.*¹ iodinated 2,3,4,2',3',4'-hexamethoxybiphenyl with iodine and iodic acid and reported that they had obtained a monoiodo derivative melting at 142–143° and a diiodo derivative melting at the same temperature (115.5–116°) as our diiodo derivative B. It was stated that the monoiodo derivative could be converted *via* the corresponding iodoso compound and a cyclic iodonium iodide into a diiodo derivative melting at 170–171°. The structure of this diiodo compound was assumed to be 6,6'-diiodo-2,3,4,2',3',4'-hexamethoxybiphenyl (3) because, allegedly, it had been possible to transform it into the same hexamethoxybiphenylene (4) as that obtained



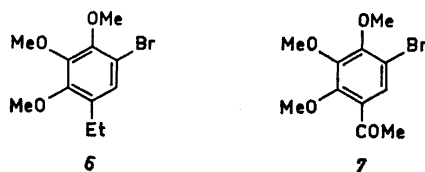
from the isomeric 2,2'-diiodo-3,4,5,3',4',5'-hexamethoxybiphenyl (5). The diiodohexamethoxybiphenyl, m.p. 115.5–116°, failed to give any biphenylene. From these results Baker *et al.* concluded that the monoiodohexamethoxybiphenyl, m.p. 142–143°, was 6-iodo-2,3,4,2',3',4'-hexamethoxybiphenyl (1, $x=z=H$, $y=I$) and that the diiodohexamethoxybiphenyl (m.p. 115.5–116°) was 5,6'-diiodo-2,3,4,2',3',4'-hexamethoxybiphenyl (1, $x=y=I$, $z=H$).

It appeared strange to us that the iodination of 2,3,4,2',3',4'-hexamethoxybiphenyl with iodine and mercuric oxide and with iodine and iodic acid would produce different monoiodo derivatives and that the melting point of one of these monoiodohexamethoxybiphenyls would be higher than that of one of the diiodo derivatives. For this reason we repeated the iodination experiments of Baker *et al.* A monoiodo derivative, m.p. 94–95°, and a diiodo derivative, m.p. 115°, were obtained which were identical with the iodo derivatives A and B, respectively. Professor McOmie has also kindly repeated their

iodination experiments and he concludes (private communication) that the m.p. 142–143° is in error.

During investigation of the alleged abnormal halogenation of 2,3,4,2',3',4'-hexamethoxybiphenyl it was of interest to study the halogenation of a simple analogue, 1-ethyl-2,3,4-trimethoxybenzene. This compound gave a monobromo derivative (6), the structure of which was proved as follows.

Gallacetophenone trimethyl ether has been brominated to an X-bromo derivative² (C). (We have found that methylation of X-bromogallacetophenone³ gives the same compound). *C*-Acetylation of 1-bromo-2,3,4-trimethoxybenzene (of established structure⁴) gave a compound identical with



C which consequently must have the structure 7. On Clemmensen reduction 7 gave a compound identical with the product of bromination of 1-ethyl-2,3,4-trimethoxybenzene, which thus has the structure 6. Hence 1-ethyl-2,3,4-trimethoxybenzene is brominated in the "normal" position.

NMR spectra of dichloro- and dibromo-2,3,4,2',3',4'-hexamethoxybiphenyl and of the diiodo-2,3,4,2',3',4'-hexamethoxybiphenyl, m.p. 115°, showed that these compounds are all symmetrical (only one signal integrating for two aromatic protons at δ 7.0, 7.2, and 7.4, respectively, as compared with 6.76 and 6.62 for 3,4,5,3',4',5'-hexamethoxybiphenyl and its diiodo derivative). As expected the monobromo and monoiodo derivatives exhibited more complex signal patterns in the aromatic region. Monobromo derivative: δ 7.18 singlet, one proton; AB quartet (J_{AB} 8.5 cps centered at δ 6.8). Monoiodo derivative: δ 7.42 singlet, one proton; AB quartet (J_{AB} 8.5 cps centered at δ 6.8).

It follows that 2,3,4,2',3',4'-hexamethoxybiphenyl is halogenated normally in positions 5 and 5' and that the dodecamethoxytetraphenyl has structure 2. It remains to investigate the true nature of the alleged 6,6'-diiodo-2,3,4,2',3',4'-hexamethoxybiphenyl, m.p. 171°, and its "conversion" into a biphenylene derivative.

EXPERIMENTAL

5-Iodo-2,3,4,2',3',4'-hexamethoxybiphenyl (1, $x=I$, $y=z=H$). To a refluxing solution of 2,3,4,2',3',4'-hexamethoxybiphenyl (10 g) in carbon tetrachloride (50 ml), iodine (7.6 g) and mercuric oxide (7.6 g) were added in portions. After filtration the organic phase was shaken repeatedly with a 10 % potassium iodide solution and then evaporated. The product crystallized upon addition of methanol and after recrystallization from ethanol and ligroin had m.p. 94–95°. (Found: OCH_3 40.5. Calc. for $C_{18}H_{14}(OCH_3)_6I$: OCH_3 40.4). With excess iodine the 5,5'-diiodo derivative, m.p. 115°, was obtained.

5,5'-Bis(2,3,4-trimethoxyphenyl)-2,3,4,2',3',4'-hexamethoxybiphenyl (2). 5-Iodo-2,3,4,2',3',4'-hexamethoxybiphenyl (10 g) was heated with copper bronze (10 g) to 240° (2 h). Extraction with chloroform, filtration through aluminium oxide and evaporation

gave a residue which crystallized on trituration with methanol. Recrystallization from methanol gave 2, m.p. 115–116.5°. (Found: OCH₃, 55.65. Calc. for C₂₄H₈(OCH₃)₁₂: OCH₃, 55.8). λ_{\max} (EtOH) 244–245 nm, log ϵ = 4.65. (Cf. λ_{\max} (EtOH) 250 nm, log ϵ = 4.11 for 2,3,4,2',3',4'-hexamethoxybiphenyl).

5,5'-Bis(2,3,4-triacetoxyphenyl)-2,3,4,2',3',4'-hexaacetoxybiphenyl. The above dodecamethoxytetraphenyl (2 g) was boiled with hydrogen bromide (66 %, 30 ml, 1 h) under reflux under carbon dioxide. On cooling crystals of the dodecahydroxytetraphenyl separated. They were collected and washed with a little water containing sulphur dioxide, and dried. Acetylation with acetic anhydride and pyridine followed by recrystallization from acetic acid gave the *dodecaacetate*, m.p. 225–228°. (Found: CH₃CO 52.5; OCH₃ 0.0. Calc. for C₂₄H₈(OCOCH₃)₁₂: CH₃CO 51.5).

5-Bromo-2,3,4,2',3',4'-hexamethoxybiphenyl. To a 2 % solution of 2,3,4,2',3',4'-hexamethoxybiphenyl in chloroform the calculated amount of bromine (as a 2 % chloroform solution) was added. The product was recrystallized from methanol and from ligroin alternately until crystals, m.p. 87°, were obtained which gave only one spot on TLC. The analytical sample, m.p. 88–89°, was distilled in a vacuum. (Found: Br 19.6. Calc. for C₁₈H₁₀O₆Br: Br 19.3). The mother liquors contained 5,5'-dibromo compound and unchanged starting material (TLC).

5,5'-Dibromo-2,3,4,2',3',4'-hexamethoxybiphenyl. Recrystallization from methanol gave crystals, m.p. 115°. (Lit.⁵ 110–111°).

5,5'-Dichloro-2,3,4,2',3',4'-hexamethoxybiphenyl. This was prepared from 2,3,4,2',3',4'-hexamethoxybiphenyl in chloroform and the calculated amount of chlorine, and had m.p. 94–95° after recrystallization from acetic acid. (Found: Cl 17.7. Calc. for C₁₈H₁₀O₆Cl₂: Cl 17.6).

2,3,4,2',3',4'-Hexamethoxybiphenyl-5-carboxylic acid. 5-Bromo-hexamethoxybiphenyl and the 5-iodo analogue (3 g) were lithiated with butyl lithium and the mixtures treated with solid carbon dioxide. The products were identical (IR), and after recrystallization from dilute acetic acid had m.p. 117–118°. (Found: C 60.4; H 5.8. Calc. for C₁₉H₁₂O₇: C 60.3; H 5.8).

2,3,4,2',3',4'-Hexamethoxybiphenyl-5,5'-dicarboxylic acid. 5,5'-Dibromo-2,3,4,2',3',4'-hexamethoxybiphenyl and the 5,5'-diiodo analogue were similarly transformed into the corresponding, identical, dicarboxylic acids, m.p. 169–170° after recrystallization from methanol-water. (Found: C 57.2; H 5.3. Calc. for C₂₀H₁₂O₁₀: C 56.9; H 5.2).

2,3,4,2',3',4'-Hexamethoxybiphenyl-5,5'-dicarboxylic acid dimethyl ester. Both dicarboxylic acid samples were treated with diazomethane in ether, and the products recrystallized from methanol-water. (M.p. and mix. m.p. 94–95°, identical IR). (Found: C 59.0; H 5.9. Calc. for C₂₂H₂₀O₁₀: C 58.7; H 5.8).

5-Bromo-2,3,4-trimethoxyacetophenone (5). a) X-Bromogallacetophenone³ was methylated with dimethyl sulphate and sodium hydroxide. b) 4-Bromopyrogallol trimethyl ether⁴ (3.1 g), acetyl chloride (1.3 g), aluminium chloride (1.7 g), and carbon disulphide (10 ml) were reacted under normal Friedel-Crafts' conditions to give a partly demethylated, crude product which was methylated with dimethyl sulphate and sodium hydroxide. The oily products obtained from experiments a and b, b.p. 134–135°/0.3 mm (lit.² 174–176°/13 mm), were identical (IR) and gave identical 2,4-dinitrophenylhydrazones. (M.p. and mix. m.p. 137–139°, identical IR). (Found: C 43.6; H 3.8; Br 17.2; N 11.9. Calc. for C₁₇H₁₁O₇N₄Br: C 43.5; H 3.6; Br 17.0; N 11.9).

5-Bromo-1-ethyl-2,3,4-trimethoxybenzene. a) A solution of 5-bromo-2,3,4-trimethoxyacetophenone (4.6 g) in alcohol (36 ml) was added dropwise (4 h) to a boiling mixture of dilute hydrochloric acid (16 ml H₂O + 34 ml conc. HCl) and amalgamated zinc under reflux. Every one hour conc. hydrochloric acid (10 ml) was added. The reaction product was isolated in the ordinary way with ether. The product distilled at 89–92°/0.3 mm Hg. (Found: C 47.7; H 5.6; Br 29.8. Calc. for C₁₁H₁₅O₃Br: C 48.0; H 5.45; Br 29.1). b) 4-Ethylpyrogallol⁶ was methylated with dimethyl sulphate and sodium hydroxide to yield 4-ethylpyrogallol trimethyl ether as an oil, b.p. 112°/6 mm Hg. (Found: OCH₃, 47.55. Calc. for C₉H₇(OCH₃)₃: OCH₃, 47.4). The compound (7.84 g) in chloroform (50 ml) was brominated with bromine (6.9 g) in chloroform (100 ml). The product, b.p. 88–92°/0.3 mm Hg, was identical (IR) with that prepared as above.

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