Synthesis of 4,6-Dihydroxyisophthalaldehyde and the 5-Methyl and 5-Methoxy-derivatives

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4,6-Dibromoresorcinol dimethyl ether has been converted into 4,6-dihydroxyisophthalaldehyde (11) by lithium–bromine interchange, formylation, and demethylation. Similarly the 5-methyl and 5-methoxy-derivatives were prepared, all in good overall yields. Three dioxa-anthracenediones have been prepared from the isophthalaldehydes. Low-temperature lithium–bromine interchange, formylation, and selective demethylation provided a route to 5-bromo-3,4-dimethoxysalicylaldehyde (14), which has potential as an intermediate for the synthesis of oxygen heterocycles.

We have prepared 4,6-dihydroxyisophthalaldehyde (11), and its 5-methyl and 5-methoxy-derivatives, compounds which have potential as synthetic intermediates.*

Treatment of 1,5-dibromo-2,4-dimethoxybenzene [2] (1) with an excess of butyl-lithium and then *N*-methylformanilide gave 4,6-dimethoxyisophthalaldehyde (4) (72%) and 2,4-dimethoxybenzaldehyde (11%). Demethylation of (4) with aluminium bromide in nitrobenzene was accompanied by nuclear bromination to give (9) (76%). Aluminium chloride in 1,2-dichloroethane gave partial demethylation to afford (10) (5%), but in nitrobenzene dihydroxyisophthalaldehyde (11) (87%) was formed.

To examine the scope of this reaction the 5-methyl and 5-methoxy-derivatives of (11) were prepared. Bromination of 2,6-dimethoxytoluene gave (2) (78%) which was treated with an excess of butyl-lithium followed by *NN*-dimethylformamide to give (5) (74%). Demethylation of this with aluminium chloride in nitrobenzene proceeded smoothly to give (12) (89%).

The trimethoxyisophthalaldehyde (6) was prepared similarly (55%) from 4,6-dibromopyrogallol trimethyl ether [3] (3); on demethylation it gave 4,6-dihydroxy-5-methoxyisophthalaldehyde (13) (67%).

The use of these intermediates in the synthesis of symmetrical oxygen heterocycles was exemplified by condensing 4,6-dihydroxyisophthalaldehyde (11) with acetic anhydride under Perkin conditions to give the

* The use of (11) in a study of cobalt(III) chelates has been reported,[1] but its source could not be ascertained (M. Colvin, personal communication).

[1] R. H. Bailes and M. Calvin, *J. Amer. Chem. Soc.*, 1947, **69**, 1886.

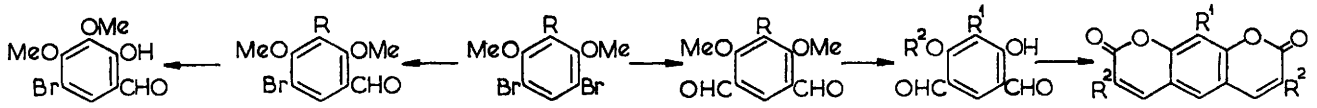
[2] H. Hönig, *Ber.*, 1878, **11**, 1039.

[3] M. Kohn and S. Grun, *Monatsh.*, 1925, **46**, 75 (*Chem. Abs.*, 1926, **20**, 1609).

dione (15). Condensation of isophthalaldehydes (11) and (12) with diethyl malonate furnished the two diones (16) and (17) respectively.

If, instead of introducing both formyl groups simultaneously, it were possible to introduce one at a time, then the dibromodimethoxybenzenes could be useful intermediates for the synthesis of unsymmetrical oxygen heterocycles (*e.g.*, furocoumarins). We found that when the lithium–halogen exchange is conducted at −75°, only one bromine atom is replaced apparently because of the low solubility of the aryl-lithium product. Treatment of dibromodimethoxytoluene (2) with butyl-lithium at −75° and then with *NN*-dimethylformamide gave the benzaldehyde (7) (68%), while similar treatment of (3) gave the methoxy-derivative (8) (64%).

Selective cleavage with boron trichloride of the *ortho*-methoxy-group in 5-bromo-2,3,4-trimethoxybenzaldehyde (8) gave 5-bromo-3,4-dimethoxysalicylaldehyde (14) in 74% yield.[4]



(14) (7) R = Me, (8) R = OMe (1) R = H, (2) R = Me, (3) R = OMe (4) R = H, (5) R = Me, (6) R = OMe (9) R^1 = Br, R^2 = H; (10) R^1 = H, R^2 = Me; (11) R^1 = R^2 = H; (12) R^1 = Me, R^2 = H; (13) R^1 = OMe, R^2 = H (15) R^1 = R^2 = H; (16) R^1 = H, R^2 = CO_2Et; (17) R^1 = Me, R^2 = CO Et

EXPERIMENTAL

M.p.s (capillary) are uncorrected. Photocopies of the i.r., u.v., and (in some cases) n.m.r. spectra of most of the compounds described below are available on request.

4,6-Dimethoxyisophthalaldehyde (4).—1,3-Dimethoxybenzene [b.p. 65—74°/2 mm. (lit.,[5] 214°)] was prepared in 74% yield by alkylation of resorcinol with methyl iodide. This ether (0·2 mole) was brominated in glacial acetic acid; the product was precipitated with ice–water, and crystallized from ethanol to give white needles of (1) (51·1 g., 86%), m.p. 145° (lit.,[2] 143—145°).

With a syringe 1·40N-butyl-lithium in hexane * (4·0 ml., 5·6 mmoles) was added at room temperature to a magnetically stirred solution of (1) (0·596 g., 2·01 mmoles) in sodium-dried ether (30 ml.) under nitrogen. The solution was stirred for 1 min. and then freshly distilled *N*-methylformanilide (0·90 g., 6·7 mmoles) was added at the rate of *ca.* 1 drop/sec. The precipitate was stirred for 5 min. and then 10% hydrochloric acid (10 ml.) was added; the stirring was continued for a further 5 min. after which the precipitate was worked with water and then ether. Upon sublimation (165°/0·25 mm.) it afforded needles (0·253 g., 65%) of (4), m.p. 217·5—223° (lit.,[7] 204°); $\lambda_{max.}$ (95% ethanol) 252 (log ε 4·55), 287 (4·27), and 324 nm. (3·84); τ (CF_3CO_2H) −0·12 (s, 2H, C*H*O), 1·40 (s, 1H, C2-*H*), 3·21 (s, 1H, C5-*H*), and 5·80 (s, 6H, OCH_3).

In a larger scale preparation the dibromide (1) (19·1 g.) gave the crude isophthalaldehyde in 72% yield (9·1 g.); this was used without further purification. On crystallization from ethyl acetate its m.p. was 211·5—218·5° (Found: C, 62·15; H, 5·55. Calc. for $C_{10}H_{10}O_4$: C, 61·85; H, 5·2%). Distillation of the diethyl ether layer that remained after filtration of the crude isophthalaldehyde gave crude 2,4-dimethoxybenzaldehyde (1·18 g., 11%), m.p. 65·5—67·5° [from light petroleum (b.p. 63—75°)] (lit.,[8] 69—70°) and τ ($CDCl_3$) −0·33 (s, 1H, C*H*O), 2·16 (d, 1, *J* 8·3 Hz, 6-*H*), 3·42 (q, 1H, $J_{3,5}$ 2·4 Hz, $J_{5,6}$ 8·3 Hz, 5-*H*), 3·52 (d, 1H, *J* 2·4 Hz, 3-*H*), and 6·10 and 6·13 (2s, 6H, OCH_3).

5-Bromo-4,6-dihydroxyisophthalaldehyde (9).—Powdered aluminium bromide (*ca.* 10 g., *ca.* 37 mmoles) was dissolved in nitrobenzene (100 ml.) (freshly distilled over anhydrous $MgSO_4$) with warming and swirling; the mixture was protected from moisture with a guard-tube. 4,6-Dimethoxyisophthalaldehyde (4) (1·00 g., 5·2 mmoles) was added to the warm solution, which was then heated at 100° on a steam-bath for 9·5 hr.; it was then poured into 10% hydrochloric acid and extracted with ether. The organic phase was extracted with aqueous sodium hydroxide; the alkaline extract was then acidified and extracted with ether to give an orange-brown residue which was sublimed at 150°/0·25 mm. The cream coloured sublimate (0·960 g., 76%), m.p. 173·5—174·2° (needles from water of unchanged m.p.) (Found: C, 39·5; H, 2·25; Br, 33·0. Calc. for $C_8H_5BrO_4$: C, 39·2; H, 2·05; Br, 33·6%); τ ($(CD_3)_2SO$ 0·02 (s, 2H, C*H*O) and 1·67 (s, 1H, 2-*H*).

4-Hydroxy-6-methoxyisophthalaldehyde (10).—A mixture of 4,6-dimethoxyisophthalaldehyde (4) (2·0 g., 10·3 mmoles), aluminium chloride (5·5 g., 41·2 mmoles), and 1,2-dichloroethane (250 ml.) was heated under reflux for 1·5 hr. and then worked up to provide a tan, amorphous material (0·9 g.), m.p. 120—135°, which recrystallized twice from ethyl acetate to give the partially demethylated product (10) (90 mg., 4·9%) as needles, m.p. 183—184° (Found: C, 60·0; H, 4·25; OCH_3, 17·16. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·5; OCH_3, 18·45%).

4,6-Dihydroxyisophthalaldehyde (11).—Anhydrous aluminium chloride (27·9 g., 0·209 mole) was stirred and heated at 120—125° in nitrobenzene (250 ml.) (freshly distilled over anhydrous $MgSO_4$) until solution was effected. 4,6-Dimethoxyisophthalaldehyde (4) (4·40 g., 22·7 mmoles) was added, and the solution was stirred at the same temperature for 35 min.; it was then poured into 10% hydrochloric acid (350 ml.), and extracted with ether. The organic phase was extracted with aqueous sodium hydroxide, and

* The normality was by the double-titration procedure.[6]

[4] F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Letters*, 1966, 4153.

[5] F. Tiemann and A. Parrisius, *Ber.*, 1880, **13**, 2354.

[6] H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515.

[7] J. H. Wood, C. C. Tung, M. A. Perry, and R. E. Gibson, *J. Amer. Chem. Soc.*, 1950, **72**, 2992.

[8] N. A. Lange, ed., 'Handbook of Chemistry,' Handbook Publishers, Sandusky, Ohio, 1956, 9th edn., p. 512.

the alkaline extract was acidified and extracted with chloroform. Evaporation (reduced pressure) of the extract and crystallization of the residue from carbon tetrachloride (3 crops) furnished 4,6-dihydroxyisophthalaldehyde (3·29 g., 87%) as cream-coloured needles, m.p. (capillary) 184—185·5° (corrected), m.p. (block) of a recrystallized sample, 191° (Found: C, 58·1; H, 3·9. Calc. for $C_8H_6O_4$: C, 57·85; H, 3·65%); τ ($CD_3)_2SO$ −0·12 (s, 2H, C*H*O), 1·88 (s, 1H, C2-*H*), and 3·47 (s, 1H, C5-*H*).

3,5-*Dibromo*-2,6-*dimethoxytoluene* (2).—2,6-Dimethoxytoluene (5·00 g., 0·0328 mole) was treated with bromine (10·5 g., 0·0657 mole) for ½ hr. in carbon tetrachloride. The reaction mixture was worked up to give a white solid (10·06 g., 99%) which crystallized from methanol as white needles (5·62 g., 55%), m.p. 42—43·5°, and a second crop (2·36 g., 23%), m.p. 38—41·5°; further crystallization raised the m.p. to 43° (Found: C, 35·0; H, 3·2; Br, 51·35. Calc. for $C_9H_{10}Br_2O_2$: C, 34·85; H, 3·25; Br, 51·55%).

4,6-*Dimethoxy*-5-*methylisophthalaldehyde* (5).—Under the conditions described for the preparation of 2,4-dimethoxyisophthalaldehyde (4) 1·25N-butyl-lithium (3·2 ml., 4·0 mmoles) was added to 3,5-dibromo-2,6-dimethoxytoluene (2) (500 mg., 1·61 mmoles) in ether (30 ml.); the mixture was stirred for 1 min. Freshly distilled *NN*-dimethylformamide (0·6 ml., 8 mmoles) was added to the stirred mixture. After 5 min. the mixture was diluted with water and extracted with ether. The organic extract was extracted with 5% aqueous sodium hydroxide followed by 10% hydrochloric acid, dried ($MgSO_4$), and evaporated to give a crystalline residue (354 mg.); chromatography of a portion (100 mg.) on Florisil (10 g.) (elution with 2% acetone in hexane) afforded the isophthalaldehyde (5) (70 mg., 74%) of m.p. 120—121·5° (lit.,[9] 123—124·5°)

4,6-*Dihydroxy*-5-*methylisophthalaldehyde* (12).—To a solution of aluminium chloride (2·79 g., 21 mmoles) in nitrobenzene (25 ml.) at 117° was added 4,6-dimethoxy-5-methylisophthalaldehyde (5) (538 mg., 2·6 mmoles). After 15 min. at 117° the reaction mixture was poured into 10% hydrochloric acid (40 ml.) and extracted with chloroform. The crude product (496 mg.) was isolated by extraction with base of the chloroform layer, acidification of the extract, and re-extraction with chloroform. Crystallization of a sample (251 mg.) from methanol gave the isophthalaldehyde (5) (209 mg., 89%), m.p. 181·5—183° (lit.,[9] 185—185·5°); $\lambda_{max.}$ (ethanol) 257 nm. (log ε 4·71).

4,5,6-*Trimethyoxyisophthalaldehyde* (6).—Methylation of pyrogallol with dimethyl sulphate gave the trimethyl ether which was converted into the dibromo-derivative (3) (92%), b.p. 157—161°/12 mm. [lit.,[2] 294—296°/748 mm.)].

To a stirred solution of the dibromo-derivative (3) (1·33 g., 4·08 mmoles) in ether (60 ml.) under nitrogen was added, with a syringe, 1·81N-butyl-lithium in hexane (7·0 ml., 12·7 mmoles). The solution was stirred for 1 min., and then anhydrous *NN*-dimethylformamide (1·0 ml., 13 mmoles) was injected into it. The reaction mixture was stirred for 5 min., quenched with water, diluted with ether, and extracted with 5% aqueous sodium hydroxide, followed by 5% hydrochloric acid. The extract was dried ($MgSO_4$) and evaporated to give the product (0·887 g.); this was washed in *ca.* 3 ml. of cold ether and rinsed with *ca.* 7 ml. of the same solvent to give 0·505 g. (55%) of material, m.p. 103·9—104·9° (corr.) (lit.,[10] 98·5°) (Found: C, 59·2; H, 5·6. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%); $\lambda_{max.}$ (95% ethanol) 253 nm (log ε 4·40); τ ($CDCl_3$) −0·31 (s, 2H, 1-*H* and C*H*O), 1·92 (s, 1H, C2-*H*), 5·86 (s, 6H, 4- and 6-OCH_3), and 6·07 (s, 3H, C5-OCH_3).

4,6-*Dihydroxy*-5-*methoxyisophthalaldehyde* (13).—To a solution of aluminium chloride (1·2 g., 9·0 mmoles) in nitrobenzene (25 ml.) at 60° was added 4,5,6-trimethoxyisophthalaldehyde (6) (100 mg., 0·45 mmole). After 50 min. the reaction mixture was poured into a mixture of 10% hydrochloric acid and chloroform. The chloroform layer was extracted with 5% sodium hydroxide. The extract was acidified, and then extracted with fresh chloroform to yield upon evaporation a nitrobenzene-containing residue. This was added to water (40 ml.) which was then reduced to a volume of *ca.* 25 ml. Re-isolation of the extract with chloroform gave a nitrobenzene-free product (59 mg., 67%), m.p. 141—142° from light petroleum (b.p. 100—120°) * (Found: C, 55·15; H, 4·4. Calc. for $C_9H_8O_5$: C, 55·1; H, 4·1%).

1,8-*Dioxa-anthracene*-2,7-*dione* (15).—A mixture of 4,6-dihydroxyisophthalaldehyde (11) (332 mg., 2·00 mmoles), anhydrous potassium acetate (392 mg. 4·00 mmoles), and acetic anhydride (1·15 ml., 12·2 mmoles) was heated under reflux for 5 hr.; it was then cooled and stirred overnight with chloroform, water, and a further small quantity of potassium acetate. The organic phase was washed with aqueous base and then evaporated to dryness (reduced pressure). The dark yellow residue sublimed at 220—230°/0·08—0·07 mm. to give the dione (15) (230 mg., 54%) as an off-white solid. Crystallization from ethanol gave white needles (136 mg., 32%), m.p. 337—339° (lit.,[12] 342° *in vacuo*); τ (CF_3CO_2H) 1·82 (d, 2H, *J* 9·8 Hz, 4-*H* and 6-*H*), 1·96 (s, 1H, 5-*H*), 2·41 (s, 1, 10-*H*), and 3·22 (d, 2H, *J* 9·8 Hz, 3-*H* and 7-*H*).

Diethyl 2,7-*Dioxo*-1,8-*dioxa-anthracene*-3,6-*dicarboxylate* (16).—To a warm solution of 4,6-dihydroxyisophthalaldehyde (11) (166 mg., 1·00 mmoles) in ethanol (2·0 ml.) was added diethyl malonate (0·36 ml., 2·4 mmoles) and one drop of piperidine. The solution was heated under reflux for 3·6 hr., cooled, taken up in chloroform–water, and extracted with base. The organic phase was dried ($MgSO_4$) and evaporated (reduced pressure) to yield the dicarboxylate (16) (60 mg., 17%) as a dark yellow solid. Crystallization from chloroform–carbon tetrachloride gave the product (20 mg.), m.p. 282° (Found: C, 60·0; H, 4·15. Calc. for $C_{18}H_{14}O_8$: C, 60·35; H, 3·95%); $\lambda_{max.}$ ($CHCl_3$) 290 (log ε 3·99), 362 (3·83), and 378 nm. (3·81).

Diethyl 9-*Methyl*-2,7-*Dioxo*-1,8-*dioxa-anthracene*-3,6-*dicarboxyate* (17).—A mixture of 4,6-dihydroxy-5-methylisophthalaldehyde (12) (98 mg., 0·55 mmole), piperidine (3 drops), and diethyl malonate (7 drops, 1—2 mmoles) was heated under reflux for 20 min. in ethanol (5 ml.); it was then cooled and filtered to give crystals (49 mg.) of the pure ester (17). Evaporation of the solvent from the filtrate left a red solid (209 mg.); a sample (50 mg.) was chromatographed on Florisil and then crystallized from benzene

* Manske *et al.* isolated unidentified diformylpyrogallol monoethyl ether, m.p. 142°, upon Duff formylation of impure 2-hydroxy-3,4-dimethoxybenzaldehyde.[11] The agreement between the m.p. of this material and ours suggests that we have identified their by-product.

[9] L. R. Worden, A. W. Burgstahler, K. D. Kaufman, J. A. Weis, and T. K. Schaf, *J. Heterocyclic Chem.*, 1969, **6**, 191.

[10] F. Dallacker, E. Meunier, J. Limpens, and M. Lipp, *Monatsh.*, 1960, **91**, 1077.

[11] R. H. F. Manske, A. E. Ledingham, and H. L. Holmes, *Canad. J. Res.* (*B*), 1945, **23**, 100.

[12] E. Späth and P. H. Löwy, *Monatsh.*, 1938, **71**, 365 (*Chem. Abs.*, 1938, **32**, 8419).

to give 30 mg. (86% based on 49 mg. +60% recovery of pure material from the 209-mg. residue) of a white solid, m.p. 292·5—294°. Recrystallization raised the m.p. to 292·5—294·5° (Found: C, 61·35; H, 4·35. Calc. for $C_{19}H_{16}O_8$: C, 61·3; H, 4·35%); $\lambda_{max.}$ (ethanol) 226sh (log ε 4·05), 294 (4·59), 361 (4·22), and 373 nm. (4·20; τ (perdeuterio-*NN*-dimethylformamide) 1·30 (s, 4-*H* and 6-*H*), 1·72 (s, 5-*H*), 5·66 (q, *J* 7·0 Hz, CH_2–CH_3), 7·57 (s, 10-CH_3), and 8·65 (t, *J* 7·0 Hz, CH_2–CH_3).

5-Bromo-2,4-dimethoxy-3-methylbenzaldehyde (7).—The compound was prepared in the same way as 4,6-dimethoxy-5-methylisophthalaldehyde (5) except that the reaction was run in an acetone–solid carbon dioxide bath. The reaction mixture was allowed to warm to room temperature during 5 min. after the addition of *NN*-dimethylformamide and was treated as before to give a residue. This was crystallized from aqueous methanol to give the benzaldehyde (7) (282 mg. 68%) as white crystals, m.p. 55·1—55·9° (Found: C, 46·45; H, 4·3; Br, 30·75. Calc. for $C_{10}H_{11}BrO_3$: C, 46·35; H, 4·3; Br, 30·85%); τ ($CDCl_3$) −0·25 (s, 1H, C*H*O), 2·04 (s, 1H, C6-*H*), 6·10 (s, 6H, OCH_3), and 7·69 (s, 3H, C3-CH_3).

5-Bromo-2,3,4-trimethoxybenzaldehyde (8).—To a solution of the dibromo-compound (3) (1·11 g., 3·40 mmoles) in anhydrous ether (50 ml.) at −76° (acetone–solid carbon dioxide bath) under nitrogen was added, with a syringe, 1·4M-butyl-lithium in hexane (2·4 ml., 3·4 mmoles). After 1 min. freshly distilled *NN*-dimethylformamide (0·4 ml., 5 mmoles) was injected into the mixture. The bath was removed, stirring was continued for 5 min., and the reaction was quenched with water. The crude product (0·953 g.) was chromatographed on silica gel (15 g.) (elution with benzene) and then distilled to give the product (0·600 g., 64%), b.p. 172—178°/10 mm.; $\lambda_{max.}$ (95% ethanol) 221 (log ε 4·29), 270 (3·91), and 312 nm. (3·40). The *semicarbazone* had m.p. 179·5—181° (from aqueous ethanol) (Found: C, 39·85; H, 4·25; Br, 24·05; N, 12·55. Calc. for $C_{11}H_{13}BrN_3O_4$: C, 39·75; H, 4·25; Br, 24·05; N, 12·65%).

5-Bromo-3,4-dimethoxysalicylaldehyde (14).—Freshly distilled boron trichloride (*ca.* 10 ml., 0·12 mole) was added to a solution of the benzaldehyde (8) (11·0 g., 40·0 mmoles) in methylene chloride (100 ml.); it was swirled, and then set aside at room temperature for 2 min. and finally poured into ice–water, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated (reduced pressure) to give a brown solid (10·4 g.). Crystallization of a sample (1·26 g.) (from methanol) (×2) gave the product (0·33 g., 26%), m.p. 57·5—59·0° (Found: C, 41·5; H, 3·65; Br, 30·6. Calc. for $C_9H_9BrO_4$: C, 41·4; H, 3·45; Br, 30·6); $\lambda_{max.}$ (95% ethanol) 225 (log ε 4·40), 275 (4·02), and 333 nm. (3·52); τ ($CDCl_3$) −1·19 (s, 1H, O*H*) 0·05 (s, 1H, C*H*O), 2·47 (s, 1H, C6-*H*), and 5·93 and 6·05 (s, 6, 3- and 4-OCH_3). From the mother liquors was isolated a second crop of product (0·61 g., 48%), m.p. 51·5—55·5°. The *semicarbazone*, m.p. 221·5—223° (from methanol) (Found: C, 37·9; H, 3·75; N, 13·15. Calc. for $C_{10}H_{12}BrN_3O_4$: C, 37·75; H, 3·8; N, 13·2%); $\lambda_{max.}$ (95% ethanol) 226 (log ε 4·29), 285 (4·30), and 325 nm (4·02).

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