Benzocyclobutenes. Part 5.[1] Synthesis of 4-Hydroxy-, 4,5-Dihydroxy-, and 3,6-Dihydroxy-benzocyclobutene-1,2-dione (Benzologues of Semisquaric and Squaric Acid)

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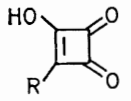
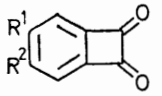
4-Methoxy- and 4,5-dimethoxy-benzocyclobutene-1,2-dione have been made by flash vacuum pyrolysis of the anthracene adducts of the corresponding phthalazine-1,4-diones which were prepared from the appropriate methoxyphthalic anhydrides. 3,6-Dimethoxybenzocyclobutene-1,2-dione has been prepared from 2-amino-3,6-dimethoxybenzoic acid *via* the addition of 3,6-dimethoxybenzyne to vinylidene chloride followed by hydrolysis of the resulting 1,1-dichloro-3,6-dimethoxybenzocyclobutene, bromination, and further hydrolysis. The three methoxy-diones and 4,5-dimethoxyphthalaldehyde have been demethylated by heating them with hydrobromic acid and the pK_a values of the four hydroxy-compounds have been measured. Preliminary experiments on the synthesis of 4,5-dimethoxybenzocyclobutene are recorded.

MONILFORMIN, the sodium and potassium salt of 3-hydroxycyclobutene-1,2-dione (1), has been isolated from the fungus *Fusarium monilforme*.[2] Its biological activity together with the high acidity of the parent acid (1) prompted us to extend our work [3] on dibenzologues of squaric acid (2) to monobenzologues of semisquaric acid (1) and squaric acid (2). This paper describes the synthesis of 4,5- and 3,6-dihydroxy- and 4-hydroxybenzocyclobutene-1,2-dione and some 1,2-disubstituted-4,5-dimethoxybenzenes, possible precursors of 4,5-dimethoxybenzocyclobutene.[4]

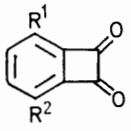
4,5-Dimethoxy- and 4-methoxy-benzocyclobutene-1,2-dione were prepared by the general method described in the preceding paper.[1] Thus 4,5-dimethoxyphthalic anhydride was converted into the corresponding cyclic hydrazide (12) which, on oxidation with lead tetra-acetate in the presence of anthracene, gave the adduct



(1) R = H
(2) R = OH

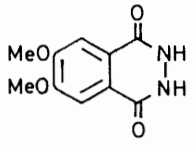


(3) R^1 = OH, R^2 = H
(4) R^1 = OMe, R^2 = H
(5) R^1 = R^2 = OH
(6) R^1 = R^2 = OMe



(7) R^1 = OH, R^2 = H
(8) R^1 = OMe, R^2 = H
(9) R^1 = OCH_2OMe, R^2 = H
(10) R^1 = R^2 = OH
(11) R^1 = R^2 = OMe

(13). The latter, when passed through a heated tube at 450 °C, gave the dimethoxy-dione (6) in 98% yield. When the analogous cyclopentadiene (14), indene (15), and 9-methylanthracene adducts were pyrolysed in the same way they gave the dimethoxy-dione (6) in 12, 0, and 0% respectively. The difference in behaviour of the adducts is probably caused by the greater volatility and higher decomposition temperature of the anthracene adduct compared with that of the other three adducts,



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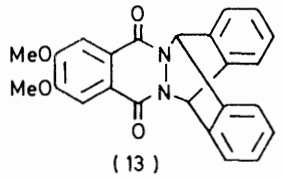

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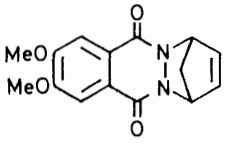

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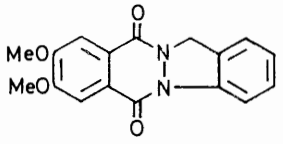
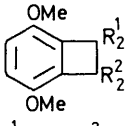


(15)

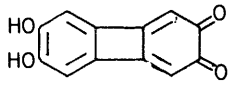
all of which decomposed extensively before much sublimation into the hot tube occurred. 4-Methoxybenzocyclobutenedione (4) has been made by us and the 3-isomer (8) by Jung [5] from the corresponding phthalic anhydrides and proceeding *via* the anthracene adducts. Jung also made the 3-methoxymethoxy-dione (9) by the same method. The 4,5-dimethoxy- and the 4-methoxy-diones were demethylated by heating them with 48% aqueous hydrobromic acid to give the 4,5-dihydroxy-dione (5) and the 4-hydroxy-dione (3). Jung hydrolysed the 3-methoxymethoxy-dione (9) with hydrochloric acid to prepare the 3-hydroxy-dione (7).

We prepared 3,6-dimethoxybenzocyclobutene-1,2-dione (11) by an entirely different method. 2-Amino-3,6-dimethoxybenzoic acid was treated with isopentyl nitrite and the resulting diazoniocarboxylate was heated in a mixture of 1,2-dichloroethane and vinylidene chloride so that the 3,6-dimethoxybenzyne thus generated underwent a [2 + 2] cycloaddition to the vinylidene chloride to give 1,1-dichloro-3,6-dimethoxybenzocyclo-

butene (16). This compound was readily hydrolysed to the ketone (17) which, on dibromination to (18) followed by hydrolysis, gave the 3,6-dimethoxy-dione (11). The dimethoxy-dione was then demethylated, by boiling it with aqueous hydrobromic acid, to give 3,6-dihydroxybenzocyclobutene-1,2-dione (10). An attempt to oxidise this quinol derivative to the corresponding *para*-quinone using lead tetra-acetate gave black, insoluble material, whereas similar oxidation of 1,4-



(16) R^1 = Cl, R^2 = H
(17) R_2^1 = O, R^2 = H
(18) R_2^1 = O, R_2^2 = Br



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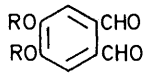
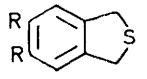


(20) R = H
(21) R = Me

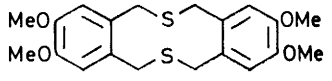
dihydroxy-9,10-anthraquinone is known to give the corresponding anthradiquinone.[6]

As expected, the three hydroxy-diones described in this paper are relatively strong acids. 4-Hydroxybenzocyclobutenedione (3), pK_a 5.35, is slightly stronger than the 3-isomer (7) (pK_a 5.8);[5] similarly, 4,5-dihydroxybenzocyclobutenedione (5), pK_1 4.48 and pK_2 8.05, is stronger than the 3,6-isomer (10), pK_1 5.3 and pK_2 9.3. It is interesting that both monobenzologues (5) and (10) of squaric acid are weaker acids than the dibenzologue, 6,7-dihydroxybiphenylene-1,2-quinone (pK_1 4.21 and pK_2 6.70),[3] which, itself, is weaker than squaric acid (2), pK_1 1.2 and pK_2 3.48.[7] There is also a larger difference between the first and second dissociation constants (*ca.* 4 pK units) of the monobenzologues than in the dibenzologue (*ca.* 2.5 pK units). This reflects the lower aromatic stabilisation gained in ionisation to the dianion and is probably due in part to the lower symmetry of the dianions of the monobenzologues (5) and (10) compared with those of the dibenzologue (19) and of squaric acid (2) which are centrosymmetrical. The acid-strengthening effect of the 4-membered ring is clear when the pK values of the benzologues above are compared with those of 4,5-dihydroxyphthalaldehyde (20), pK_1 6.56 and pK_2 10.92.

Attempted Syntheses of 4,5-Dimethoxybenzocyclobutene.—Before the general synthesis of benzocyclobutene-1,2-diones by the pyrolysis method described above and in Part 4 had been discovered we attempted to prepare 4,5-dimethoxybenzocyclobutene with the aim of converting it into the corresponding 1,2-dione *via* the 1,1,2,2-tetrabromo-derivative. Benzocyclobutene itself can be prepared in good overall yield by the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide which is prepared from 1,2-bisbromomethylbenzene *via* the cyclic sulphide (22).[8] We found that chloromethylation of 1,2-dimethoxybenzene gave 1,2-bischloromethyl-4,5-dimethoxybenzene in only 10% yield, also that reaction of the latter with sodium sulphide gave the cyclic sulphide (23) in 0—74% yield; in one experiment, the dithioether (24) (8%) was obtained. This route was not further investigated. Another entry into the benzocyclobutene series is provided by the action of sodium iodide on 1,2-bisdibromomethylbenzene which gives 1,2-dibromobenzocyclobutene *via* a transient *o*-quinodimethane intermediate.[9] Treatment of the 1,2-bischloromethyl compound (25) with one equivalent of bromine under u.v. irradiation gave a bromo-compound which underwent partial hydrolysis during isolation and yielded 2-chloromethyl-4,5-dimethoxybenzaldehyde (26); similarly reaction with two equivalents of bromine gave 4,5-dimethoxyphthalaldehyde (27). Reduction of the bischloromethyl compound (25) gave the dimethyl compound (28) which, on u.v.-catalysed bromination, underwent nuclear as well as side-chain bromination to give 3,6-dibromo-1,2-bisbromomethyl-4,5-dimethoxybenzene. Bromination of the dimethyl compound (28)



(22) R = H
(23) R = OMe



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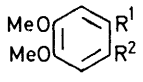
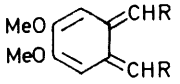


(25) R^1 = R^2 = CH_2Cl
(26) R^1 = CHO, R^2 = CH_2Cl
(27) R^1 = R^2 = CHO
(28) R^1 = R^2 = Me
(29) R^1 = R^2 = CH_2Br
(30) R^1 = R^2 = $CHBr_2$
(31) R^1 = R^2 = $CHCl_2$
(32) R^1 = R^2 = CH_2I



(33) R = Br
(34) R = H

with two equivalents of *N*-bromosuccinimide gave the bisbromomethyl compound (29), but further bromination with the same reagent gave a complex mixture. The desired bisdibromomethyl compound (30) was finally prepared (in 40% yield) by reaction of the dimethoxyphthalaldehyde (27) with phosphorus pentabromide, as previously reported.[10] 1,2-Bisdichloromethyl-4,5-dimethoxybenzene (31) was prepared similarly (in 37% yield) using phosphorus pentachloride in place of the pentabromide. Unfortunately, treatment of the bisdibromomethyl compound (30) with sodium iodide in dimethylformamide did not give 1,2-dibromo-4,5-dimethoxybenzocyclobutene; similar treatment of

the bisdichloromethyl compound (31) gave, after work-up, the phthalaldehyde (27). The former reaction generated the *o*-quinonoid intermediate (33) which could be trapped by carrying out the reaction in the presence of maleic anhydride and *N*-phenylmaleimide when the corresponding Diels–Alder (4 + 2) adducts were obtained in good yield.[10]

Reaction of the bischloromethyl compound (25) with sodium iodide in acetone gave the corresponding bisiodomethyl compound (32). Again, the reaction may have proceeded *via* an *o*-quinonoid intermediate (34) since this could be trapped by dienophiles when the reaction was carried out in dimethylformamide.[10]

EXPERIMENTAL

General directions are given in ref. 1.

4,5-Dimethoxyphthalic Anhydride.—(*a*) (With Dr. N. P. Hacker). 3,4-Dimethoxytoluene (30 g), 1,1-dichloromethyl methyl ether (56 ml), and 1,2-dichloroethane (200 ml) were stirred in an ice-bath for 30 min, and stannic chloride (200 ml) was added in one portion. The mixture was allowed to warm to room temperature and was stirred for 24 h. The mixture was poured into ice-cold 3N-hydrochloric acid (500 ml) and extracted with dichloromethane (3 × 200 ml). The extract yielded a brown solid which was sublimed at 120 °C and 0.01 mmHg to give 4,5-dimethoxy-2-methylbenzaldehyde (34.5 g, 97%). This aldehyde (12 g), water (50 ml), and potassium carbonate (12 g) were heated on a steam-bath and potassium permanganate (45 g) in water (400 ml) was added rapidly. The mixture was heated for a further 1 h, then acidified, filtered, concentrated to small volume, and extracted with ethyl acetate. Removal of the ethyl acetate gave the phthalic acid which was boiled for 30 min in acetic anhydride. Removal of the acetic anhydride and acetic acid followed by crystallisation from dichloromethane–light petroleum gave 4,5-dimethoxyphthalic anhydride (5.5 g, 40%), m.p. 165—171 °C (lit.,[11] 174—175 °C).

(*b*) A mixture of 4,5-bisacetoxymethylveratrole [12] (5 g) and 20% aqueous sodium hydroxide (100 ml) was heated under reflux and stirred until homogeneous (4.5 h). After cooling the solution to 80 °C, potassium permanganate was added in small portions, with stirring, until a pink colour persisted. The mixture was stirred at 80 °C for a further 30 min then worked up as in (*a*) above to give 4,5-dimethoxyphthalic acid (3.4 g, 70%) as needles, m.p. 173—174 °C (lit.,[11] 174—175 °C). It was converted into the anhydride as in (*a*) above.

6,7-Dimethoxy-2,3-dihydrophthalazine-1,4-dione (12).—A mixture of 4,5-dimethoxyphthalic anhydride (500 mg) and 64% aqueous hydrazine hydrate (0.2 ml) in ethanol (30 ml) was refluxed for 30 min, then cooled and filtered. The solid was collected and recrystallised from dimethylformamide to give the phthalazinedione (12) (496 mg, 93%) as prisms, m.p. 317—320° (decomp.) [lit.,[13] 333—335 °C (decomp.)].

Adducts of 6,7-Dimethoxyphthalazine-1,4-dione.—(a) *With anthracene* (13). A mixture of the dihydrophthalazine (12) (1.11 g) and anthracene (0.9 g) in dichloromethane (50 ml) was stirred at room temperature and lead tetra-acetate (2.5 g) was added in small portions during 3 h. The solution was filtered and evaporated then the residue was chromatographed on alumina with carbon tetrachloride as eluant until no more anthracene was eluted. Further elution of the column with dichloromethane gave the *adduct* (13) (824 mg, 41%) as needles, m.p. 303—304 °C: (decomp.) (from dichloromethane–light petroleum) (Found: C, 72.2; H, 4.6. $C_{22}H_{18}N_2O_4$ requires C, 72.4; H, 4.6%); τ 2.36 (ArH, s), 2.44 (2 ArH, q), 2.76 (2 ArH, q), 2.60 (N-CH, s), and 6.03 (OMe, s).

(b) *With cyclopentadiene* (14). A mixture of the dihydrophthalazine (12) (444 mg) and cyclopentadiene (0.3 ml) in dichloromethane (2 ml) was stirred at 0 °C while lead tetra-acetate (1 g) was added. Stirring was continued for 3 h at 0 °C and for a further 2 h at room temperature. The solution was filtered and the filtrate was washed with water and evaporated. The residue was recrystallised from dichloromethane–light petroleum to give the *adduct* (14) (298 mg, 52%) as prisms, m.p. 219—220 °C (decomp.), M^+, 286 (Found: C, 61.8; H, 5.0. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9%); τ 2.37 (ArH, s), 3.29 (=CH, t), 4.08 (N–CH, t), and 7.88 (CH_2, m).

(c) *With indene* (15). The dihydrophthalazine (12) (444 mg) and indene (0.2 ml) in dichloromethane (25 ml) were treated with lead tetra-acetate (1 g) as in (b) above and gave the *adduct* (15) as prisms (258 mg, 38%), m.p. 244—245 °C (decomp.) (Found: C, 67.0; H, 4.6. $C_{19}H_{16}N_2O_4$ requires C, 67.9; H, 4.8%).

(d) *With 9-methylanthracene.* This was made from the dihydrophthalazine (12) by the method used for the anthracene adduct. The *9-methylanthracene adduct* (35%) formed plates, m.p. 192—193 °C (decomp.) (from dichloromethane–light petroleum) (Found: C, 72.8; H, 4.8; N, 6.4. $C_{25}H_{20}N_2O_4$ requires C, 72.7; H, 4.9; N, 6.8%).

4,5-Dimethoxybenzocyclobutene-1,2-dione (6).—The anthracene adduct (13) (250 mg) was sublimed at 0.01 mmHg into a silica tube at 450 °C during 1.5 h. The pyrolysate was extracted with dichloromethane and chromatographed on a short column of silica gel. Elution with dichloromethane gave anthracene then a pale yellow eluate which, on concentration and recrystallisation from cyclohexane, gave the *dimethoxydione* (6) (117 mg, 98%) as almost colourless needles, m.p. 222—223 °C (Found: M^+, 192; C, 63.1; H, 4.2. $C_{10}H_8O_4$ requires C, 62.5; H, 4.2%); $\nu_{max.}$ (C=O) 1 780 and 1 750 cm^{-1}; $\lambda_{max.}$ (EtOH) 245, 258sh, 280, 313sh, 325, and 339 nm (log ε 4.47, 4.15, 3.63, 3.88, 4.08, and 4.03); τ 2.62 (ArH) and 5.94 (OMe). The dione gave a *mono-2,4-dinitrophenylhydrazone* as orange needles, m.p. 301—302 °C (decomp.) (Found: M^+, 372.071. $C_{16}H_{12}N_4O_7$ requires *M*, 372.071). When the dione was refluxed for 48 h in ethane-1,2-diol containing a trace of toluene-*p*-sulphonic acid while the water formed was removed azeotropically it gave the *bisethyleneacetal* as plates, m.p. 218—219 °C (Found: C, 59.8; H, 5.9. $C_{14}H_{16}O_6$ requires C, 60.0%; H, 5.8%).

Adduct of 6-Methoxyphthalazine-1,4-dione with Anthracene.—This was prepared from 6-methoxy-2,3-dihydrophthalazine-1,4-dione [14] as described above for the 6,7-dimethoxy-analogue (13). The *adduct* (55%) formed needles, m.p. 264—265 °C (decomp.) (from methanol) (Found: C, 74.9; H, 4.5; N, 7.6. $C_{23}H_{16}N_2O_3$ requires C, 75.0; H, 4.4; N, 7.6%).

4-Methoxybenzocyclobutene-1,2-dione (4).—The preceding anthracene adduct was pyrolysed as for the corresponding 4,5-dimethoxy-analogue. The *dione* (4) (83%) formed pale yellow needles, m.p. 101—103 °C (from cyclohexane) (Found: C, 66.3; H, 4.0. $C_9H_6O_3$ requires C, 66.7; H, 3.7%); $\nu_{max.}$ (C=O) 1 780 and 1 763 cm^{-1}; $\lambda_{max.}$ (EtOH) 246,

259sh, 273sh, 322, and 332 nm (log ε 4.37, 3.87, 3.76, 3.83, and 3.81); τ 2.08 (H-6, q, $J_{5,6}$ 6.4 Hz), 2.69 (H-3, H-5, m), and 6.04 (OMe, s).

1,1-*Dichloro*-3,6-*dimethoxybenzocyclobutene* (16).—A solution of 2-amino-3,6-dimethoxybenzoic acid [15] (13 g) in tetrahydrofuran (70 ml) containing trifluoroacetic acid (7 drops) was stirred at 0 °C. Isopentyl nitrite (15 ml) was added during 5 min and the mixture was allowed to warm to room temperature and was stirred for a further 2 h. The solution was then cooled to 10 °C and the diazonium carboxylate was collected on a plastic funnel. The solid was washed with cold tetrahydrofuran and then twice with 1,2-dichloroethane. The solvent-wet solid was transferred to a beaker containing 1,2-dichloroethane (75 ml) and vinylidene chloride (120 ml) and the slurry stirred at 50—55 °C for 3 h. The solution was filtered and the filtrate was distilled to give the *dichloride* (16) as a pale yellow liquid (4.9 g, 32%), b.p. 55—60 °C at 0.05 mmHg (Found: C, 51.8; H, 4.5; Cl, 30.1. $C_{10}H_{10}Cl_2O_2$ requires C, 51.5; H, 4.3; Cl, 30.4%). The dichloride is rapidly hydrolysed on exposure to moisture.

3,6-*Dimethoxybenzocyclobuten*-1(2H)-*one* (17).—A mixture of the above dichloride (16) (2.1 g) and silver nitrate (3.06 g) in 80% aqueous ethanol (60 ml) was warmed for 30 min. The mixture was cooled and filtered and the filtrate evaporated to dryness. The residue was dissolved in dichloromethane (30 ml), washed twice with water, then with a saturated solution of sodium chloride. The solution was dried and the solvent removed under reduced pressure to give the *ketone* (17) (1.3 g, 80%) as crystals, m.p. 107—108 °C (from light petroleum) (Found: C, 67.7; H, 5.9. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.6%), $\nu_{max.}$ (C=O) 1 760 cm^{-1}; τ 3.07 and 3.30 (2 ArH, ABq, J 9 Hz), 5.96 and 6.14 (2 × OMe), and 5.98 (CH_2).

2,2-*Dibromo*-3,6-*dimethoxybenzocyclobuten*-1(2H)-*one* (18).—A mixture of the ketone (17) (0.59 g), *N*-bromosuccinimide (3 g), benzoyl peroxide (0.06 g), and carbon tetrachloride (20 ml) was refluxed for 4 h. The mixture was cooled, diluted with light petroleum (b.p. 30—60 °C), then filtered. The filtrate, on evaporation, gave the *dibromo-ketone* (18) (0.67 g, 60%) as prisms, m.p. 128—130 °C (from petroleum) (Found: C, 35.8; H, 2.5; Br, 47.6. $C_{10}H_8Br_2O_3$ requires C, 35.8; H, 2.4; Br, 47.6%), $\nu_{max.}$ (C=O) 1 750 and 1 790 cm^{-1}; τ 2.84 and 3.02 (2 ArH, ABq), and 5.80 and 5.88 (2 × OMe).

3,6-*Dimethoxybenzocyclobutene*-1,2-*dione* (11).—A mixture of the dibromoketone (18) (0.4 g) and silver trifluoroacetate (0.53 g) in acetonitrile (15 ml) was refluxed, with stirring, for 4 h while the flask was wrapped in metal foil to protect the contents from light. The mixture was cooled and filtered, the precipitate being washed several times with acetonitrile. The filtrate and washings were evaporated and the residue was dissolved in dichloromethane (10 ml) and washed with water (2 × 7 ml) then with saturated aqueous sodium chloride. Evaporation of the solvent gave the *dimethoxydione* (11) (0.215 g, 94%) as yellow plates, m.p. 190—192 °C (from cyclohexane) (Found: M^+, 192.043; C, 62.1; H, 4.3%. $C_{10}H_8O_4$ requires M, 192.042; C, 62.5; H, 4.2%); $\nu_{max.}$ (C=O) 1 700 and 1 720 cm^{-1}; τ 2.94 (ArH) and 5.82 (OMe); *m/e* 192, 163, 134, and 76; $\lambda_{max.}$ (EtOH) 248, 254, and 338 nm (log ε 4.46, 4.40, and 3.49).

4,5-*Dihydroxybenzocylobutene*-1,2-*dione* (5).—The dimethoxydione (6) (150 mg) and 48% aqueous hydrobromic acid (5 ml) were refluxed for 6 h. The mixture was cooled and diluted with water (5 ml) then treated with charcoal and filtered. The yellow filtrate was evaporated and the solid was chromatographed on silica gel. Elution with ethyl acetate gave a yellow solid which after two recrystallisations from water gave the *dihydroxydione* (5) (56 mg, 44%) as pale yellow prisms, m.p. 243—245 °C (decomp.) (Found: C, 58.2; H, 2.6. $C_8H_4O_4$ requires C, 58.6; H, 2.5%); $\nu_{max.}$ 3 400, 3 180, 1 770, 1 730, 1 570, 1 318, 1 297, 1 218, 1 165, 882, and 815 cm^{-1}; $\lambda_{max.}$ (H_2O) (at pH 1) 244, 332, and 345sh nm (log ε 4.86, 4.40, and 4.32); (at pH 6) 235, 250, 275, 325sh, and 362 nm (log ε 4.59, 4.60, 4.43, 4.21, and 4.48); (at pH 10) 254, 300, 370, and 386 (log ε 4.67, 4.07, 4.63, and 4.66); τ (DMSO) 2.30 (ArH).

4-*Hydroxybenzocyclobutene*-1,2-*dione* (3).—The methoxydione (4) (150 mg) and 48% aqueous hydrobromic acid (7 ml) was refluxed for 4.5 h. The mixture was filtered and the filtrate evaporated to dryness. The brown solid was sublimed at 140 °C and 0.02 mmHg and gave the *hydroxydione* (3) (95 mg, 70%) as a pale yellow solid, m.p. 167—170 °C (Found: C, 65.2; H, 2.9. $C_8H_4O_3$ requires C, 64.9; H, 2.7%); $\nu_{max.}$ (C=O) 1 780, 1 760, 1 736, and 1 720 cm^{-1}; $\lambda_{max.}$ (H_2O) (at pH 1) 230sh, 244, 270, and 327 nm (log ε 4.17, 4.31, 3.76, and 3.69; (at pH 8.5) 260, 302, and 358 nm (log ε 4.30, 3.98, and 3.81); τ (CD_3CN) 1.1 (OH, removed by D_2O), 2.03 (H-6, d), and 2.64 (H-3, H-5, m).

3,6-*Dihydroxybenzocyclobutene*-1,2-*dione* (10).—The dimethoxydione (11) (150 mg) and 48% aqueous hydrobromic acid (5 ml) were refluxed for 3 h. The product, isolated and purified in the same way as for the 4,5-isomer above, gave the 3,6-*dihydroxydione* (10) (58 mg, 42%) as crystals, m.p. 225—228 °C (Found: M^+, 164.011. $C_8H_4O_4$ requires M, 164.011); $\nu_{max.}$ 3 340, 1 805, 1 760, and 1 740 cm^{-1}; $\lambda_{max.}$ (H_2O) (at pH 2.2) 248 and 330 nm (log ε 4.14 and 3.57); (at pH 6.3) 254 and *ca.* 350 nm (log ε 4.07 and 3.15); (at pH 11.3) 220, 274, and 338 nm (log ε 4.05, 3.63, and 4.16); τ [$(CD_3)_2CO$] −0.58 (OH) and 2.94 (ArH).

4,5-*Dihydroxyphthalaldehyde*.—A solution of 4,5-dimethoxyphthalaldehyde (500 mg) in dichloromethane (5 ml) was added to boron tribromide (1 g) in dichloromethane (5 ml) at −70 °C. The mixture was stirred and allowed to attain room temperature overnight. Water (10 ml) was added and the organic layer was collected. The aqueous layer was extracted with ether (5 × 20 ml) and the combined organic extracts were dried and evaporated. The residue, on crystallisation from aqueous ethanol, gave 4,5-*dihydroxyphthalaldehyde* (50 mg, 12%) as needles, m.p. 215—217 °C (decomp.) (Found: C, 57.9; H, 3.4. $C_8H_6O_4$ requires C, 57.8; H, 3.6%); $\nu_{max.}$ 3 370, 1 692, 1 595, and 1 312 cm^{-1}; $\lambda_{max.}$ (H_2O) (at pH 2) 256 and 304 nm (log ε 4.03 and 3.54); (at pH 8.6) 228 and 266 nm (log ε 3.76 and 4.17); (at pH 13) 241, 298, and 449 nm (log ε 3.58, 4.22, and 3.63).

Measurement of pK_a *Values*.—The pK values for 4,5-dihydroxybenzocyclobutene-1,2-dione and -phthalaldehyde were measured using a spectrophotometric titration technique at 20 °C and low ionic strength. The values found were pK_1 4.48 ± 0.05 and pK_2 8.05 ± 0.02 for the dione and pK_1 6.56 ± 0.05 and pK_2 10.92 ± 0.04 for the phthalaldehyde. These two compounds were stable for several hours in dilute aqueous sodium hydroxide whereas 4-hydroxybenzocyclobutene-1,2-dione was slowly hydrolysed and 3,6-dihydroxybenzocyclobutene-1,2-dione was fairly rapidly hydrolysed by dilute alkali. Their pK values were measured spectrophotometrically in buffer solutions over a range of pK values at 25 °C.[16] The 4-hydroxydione (3) had pK 5.34 ± 0.03 and the 3,6-dihydroxydione (10) had pK_1 5.3 ± 0.3 and pK_2 9.3 ± 0.2.

Reaction of 1,2-*Bischloromethyl*-4,5-*dimethoxybenzene with Sodium Sulphide*.—(*a*) A solution of 4,5-bischloromethyl-4,5-dimethoxybenzene [12] (500 mg) in acetone (10 ml) was added dropwise to a solution of sodium sulphide dihydrate (5 g) in acetone (50 ml) and the mixture was refluxed for a further 2 h. Water (50 ml) was added and the mixture left at 0 °C overnight. The crystals were collected and recrystallised from dichloromethane–light petroleum to give 5,6-*dimethoxy*-1,3-*dihydro*-2-*benzothiophen* (23) (0—74%) as needles, m.p. 113—114 °C (Found: C, 61.0; H, 6.3. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.1%); τ 3.28 (ArH), 5.80 (CH_2), and 6.16 (OMe).

(*b*) A mixture of the bischloromethyl compound (500 mg), sodium sulphide nonahydrate (5 g), and methanol (50 ml) was refluxed for 2 h. The methanol was removed and water (50 ml) added. Extraction with dichloromethane (3 × 50 ml) yielded a solid which on recrystallisation from dichloromethane–light petroleum gave 2,3,9,10-*tetramethoxy*-5,7,12,14-*tetrahydrodibenzo*[c,h][1,6]*dithiecin* (24) (35 mg, 8%) as plates, m.p. 283—285 °C, M^+, 392 (Found: C, 60.8; H, 6.2. $C_{20}H_{24}O_4S_2$ requires C, 61.2; H, 6.1%); τ 3.43 (ArH), 6.14 (OMe), and 6.20 (CH_2).

Bromination of 1,2-*Bischloromethyl*-4,5-*dimethoxybenzene*.—(*a*) A solution of the bischloromethyl compound (25) (940 mg) and bromine (640 mg) in carbon tetrachloride (50 ml) was heated by, and irradiated with, a 200 W tungsten-filament lamp for 18 h. The cooled solution was washed with 10% aqueous sodium hydrogensulphite, dried, and the solvent removed to leave a yellow oil which was chromatographed on alumina in dichloromethane. The product, after two recrystallisations from light petroleum, gave 2-chloromethyl-4,5-dimethoxybenzaldehyde (26) (225 mg, 39%) as needles, m.p. 75—76 °C (Found: C, 55.5; H, 5.2. $C_{10}H_{11}ClO_3$ requires C, 56.0; H, 5.1%); $\nu_{max.}$ (C=O) 1 670 cm^{-1}; τ (CCl_4) −0.17 (CHO), 2.70 (H-6), 3.00 (H-3), 5.03 (CH_2), and 6.03 and 6.07 (2 OMe).

(*b*) The above experiment was repeated using 2 mol of bromine (1.28 g) and with refluxing for 65 h. The product, isolated and purified as above, gave 4,5-dimethoxyphthalaldehyde (85 mg, 11%) as pale yellow needles, m.p. 163—164 °C (lit.,[17] m.p. 165 °C).

3,6-*Dibromo*-1,2-*bisbromomethyl*-4,5-*dimethoxybenzene*.—The bischloromethyl compound (25) was reduced with lithium aluminium hydride to give the dimethyl compound (28).[18] A solution of the latter (166 mg) and bromine (640 mg) in carbon tetrachloride (20 ml) was refluxed for 36 h while being irradiated with a 200 W tungsten-filament lamp. The cooled solution was washed with 10% aqueous sodium hydrogensulphite (10 ml), dried, and evaporated. The residue gave 3,6-*dibromo*-1,2-*bisbromomethyl*-4,5-*dimethoxybenzene* (156 mg, 33%) as needles, m.p. 171—172 °C (from ethanol) (Found: C, 25.4; H, 2.1. $C_{10}H_{10}Br_4O_2$ requires C, 24.9; H, 2.1%); τ 5.16 (CH_2) and 6.10 (OMe).

1,2-*Bisbromomethyl*-4,5-*dimethoxybenzene* (29).—(*a*) 4,5-Dimethoxyphthalyl alcohol [12] (320 mg) was stirred at room temperature with 48% hydrobromic acid (10 ml) for 17 h. The white precipitate was collected and recrystallised from light petroleum to give 1,2-bisbromomethyl-4,5-dimethoxybenzene (29) (394 mg, 80%) as prisms, m.p. 110—111 °C (lit.,[19] 107—109 °C); τ 3.26 (ArH), 5.46 (CH_2), and 6.19 (OMe).

(*b*) 1,2-Bisacetoxymethyl-4,5-dimethoxybenzene [12] (500 mg) was warmed with 48% hydrobromic acid (30 ml) until all the solid had dissolved. The solution was then stirred at room temperature for 18 h and gave the bisbromomethyl compound (29) (470 mg, 78%) as prisms, m.p. 109—110 °C (from light petroleum).

(*c*) The dimethyl compound (28) [18] (166 mg), *N*-bromosuccinimide (356 mg), and dibenzoyl peroxide (40 mg) in carbon tetrachloride (20 ml) were refluxed for 3 h. The cooled mixture, after being filtered, yielded the bisbromomethyl compound (29) (135 mg, 42%) as prisms, m.p. 108—110 °C (from light petroleum).

1,2-*Bisdichloromethyl*-4,5-*dimethoxybenzene* (31).—A mixture of the phthalaldehyde (27) (1 g) and phosphorus pentachloride (2.3 g) in carbon tetrachloride (100 ml) was stirred at room temperature for 18 h. The solution was added carefully to 1% aqueous potassium hydroxide (100 ml) and the mixture was stirred well for 15 min. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 50 ml). The combined organic layers were evaporated and the residue chromatographed on silica gel in benzene giving 1,2-*bisdichloromethyl*-4,5-*dimethoxybenzene* (31) as plates, m.p. 107 °C (Found: C, 40.0; H, 3.6. $C_{10}H_{10}Cl_4O_2$ requires C, 39.5; H, 3.3%); τ (CCl_4) 2.87 and 2.90 (ArH and CH), and 6.07 (OMe).

Reaction of 1,2-*Bisdichloromethyl*-4,5-*dimethoxybenzene with Sodium Iodide*.—The chloro-compound (31) (560 mg) and sodium iodide (700 mg) in dry dimethylformamide (20 ml) was kept at 60—70 °C for 5 h. The mixture was cooled, poured into water (100 ml), and 10% aqueous sodium hydrogensulphite added until the colour of iodine was discharged. The mixture was extracted with dichloromethane and yielded 4,5-*dimethoxyphthalaldehyde* (27) (137 mg, 38%) as crystals, m.p. 165—166° (from dichloromethane–hexane).

1,2-*Bisiodomethyl*-4,5-*dimethoxybenzene* (32).—The 4,5-bischloromethyl compound (25) (4 g) and sodium iodide (16 g) in acetone (10 ml) were refluxed for 30 min. The cooled mixture, after being filtered and evaporated, gave a solid which was dissolved in dichloromethane and washed with 10% aqueous sodium hydrogensulphite. The organic layer was then evaporated and gave the *bisiodomethyl compound* (32) (6.2 g, 88%) as yellow needles, m.p. 130 °C (decomp.) (from light petroleum) (Found: C, 28.8; H, 2.9. $C_{10}H_{12}I_2O_2$ requires C, 28.7; H, 2.7%); τ 3.34 (ArH), 5.54 (CH_2), and 6.20 (OMe).

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