330. *The Preparation of Novel Benzodioxan Derivatives by Chloromethylation of* p- *and* o-*Diacetoxybenzenes.*

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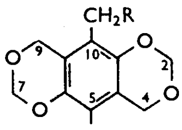
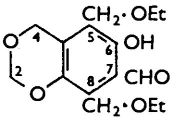
p-Diacetoxybenzene subjected to chloromethylation gave 5,10-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan (I; R = Cl). Similarly *o*-diacetoxybenzene gave 5,6,7-tri(chloromethyl)-8-hydroxy-1,3-benzodioxan (III) and 5,6-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[5,4,-*h*]-1,3-benzodioxan (IV). The structures of these compounds were confirmed, and aspects of their chemistry and stereochemistry are discussed.

THE high reactivity of phenols usually precludes their direct chloromethylation since polymers are readily formed.[1] Quinol and catechol are particularly intractable in this respect and chloromethylation has to be accomplished through their alkyl ethers.[2] With the aim of avoiding dealkylation the possibility of chloromethylation of the di(ethyl carbonate) or diacetate of quinol and of catechol diacetate has been examined.

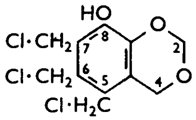
Quinol di(ethyl carbonate) was insufficiently reactive to permit chloromethylation, but treatment of the diacetate with formaldehyde–hydrochloric acid at 0° gave a crystalline product, shown to be 5,10-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan (I; R = Cl) on the basis of its analysis, chemical reactions, and spectroscopic characteristics, and by an alternative synthesis. The two chlorine atoms were readily replaced by ethoxy- or acetoxy-groups, and catalytic reduction gave the dimethyl compound (I; R = H). The dimethyl compound was also readily prepared by treating 1,4-diacetoxy-2,5-dimethylbenzene with formaldehyde–hydrochloric acid. Compound (I; R = Cl) gave a positive Feigl test [3] for a methylenedioxy-group. The ultraviolet and infrared absorption spectra confirmed the presence of the aromatic nucleus and of aryl and alkyl ether linkages, and the absence of carbonyl groups. For the alternative synthesis tetra(hydroxymethyl)-quinol [4] was treated with formaldehyde–hydrochloric acid. The same compound was produced in very low yield by treating di(methoxymethyl)quinol with chloromethyl methyl ether.



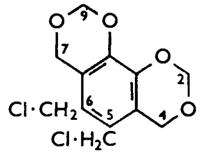
(I)



(II)



(III)



(IV)

The compound (I; R = OEt) was oxidised by chromium trioxide in acetic acid to an amorphous yellow compound, $C_{15}H_{20}O_6$, for which the structure (II) is consistent with the chemical evidence and the infrared absorption spectrum. The compound (I; R = Cl) was not readily cleaved by hydrogen chloride in hot acetic acid. Addition of water facilitated cleavage of the dioxan rings but the products were too reactive for characterisation.

The di(chloromethyl)compound (I; R = Cl) with potassium acetate in glacial acetic acid furnished low- (162°) and high-melting (196°) diacetates in approximately equal amount, the melting points being unchanged after the compounds had been heated at 196° so that they are not dimorphic modifications. Molecular models of the chloro- and acetoxy-compounds (I) show that four stereoisomers are possible, two arising from different

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[1] Fuson and McKeover, " Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. I, p. 65.

[2] Jaccini and Bacchetti, *Gazzetta*, 1950, **80**, 48.

[3] Feigl, " Spot Tests in Organic Analysis," Elsevier Publ. Co., Amsterdam, 1960, p. 207.

[4] Euler, Adler, and Gie, *Arkiv Kemi, Min., Geol.*, 1940, **14**, *B*, No. 9.

conformations of the dioxan rings and two from the restricted rotation of the chloromethyl groups. Differentiation between the two ring isomers is not possible on the information available, but interconversion is unlikely under the conditions used for replacing chlorine by acetoxyl. The two crystalline diacetates are therefore probably *cis*- and *trans*-forms, with the same conformation of the cyclic structure in the di(chloromethyl) and the two di(acetoxymethyl) compounds. The infrared absorption spectra of the solid diacetates exhibit differences (probably owing to differences in the crystal structure), but the solution spectra are very similar. If replacement of chlorine by acetoxyl involves a carbonium ion whose rotation is not sterically hindered, then the two diacetates are equally likely to be formed, and in approximately equal amount, as found experimentally.

Catechol diacetate and formaldehyde–hydrochloric acid gave oily mixtures from which two crystalline compounds were isolated in low yields. By analogy with the product from quinol diacetate, and on the basis of the chemical properties and spectroscopic characteristics, the two compounds were assigned the structures (III) and (IV). Refluxing compound (III) with formaldehyde–hydrochloric acid converted it into compound (IV), providing support for the proposed structures.

Although substituted phenols are known to give bicyclic benzodioxans when treated with formaldehyde [5,6] the compounds (I) and (IV) appear to be the first examples of similar tricyclic systems.

EXPERIMENTAL

Microanalyses were carried out by the Microanalytical Section of this Laboratory. Ultraviolet absorption spectra of solutions in dioxan were measured by means of a Unicam S.P.500 spectrophotometer. Infrared absorption spectra of solids, in potassium chloride discs, were measured either on a Hales double-beam grating spectrometer [7] (H) or on a Grubb–Parsons G.S.3 double-beam grating instrument (G); only strong and medium-strength bands are reported, these being correct to ± 3 cm.$^{-1}$, except where indicated.

Chloromethylation of Quinol Diacetate.—A mixture of 40% aqueous formaldehyde (130 ml.) and concentrated hydrochloric acid (200 ml.) was saturated with hydrogen chloride at 0°. Finely powdered quinol diacetate (15 g.) was added in two approximately equal portions to the stirred mixture at 0°, and stirring continued for 6 hr. After 45 min. hydrolysis of the acetate was complete and subsequently a white solid separated. The solid product (12 g.) was washed with ice-cold water and recrystallised from glacial acetic acid, to give colourless needles of 5,10-*di(chloromethyl)*-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan*, m. p. 250° (decomp.) (bath preheated at 240°) (Found: C, 49·6; H, 4·1; Cl, 24·2. $C_{12}H_{12}Cl_2O_4$ requires C, 49·5; H, 4·2; Cl, 24·4%), $\lambda_{max.}$ (in dioxan) 228, 242, 319 mμ (log ε 4·02, 3·98, 3·74, respectively), $\nu_{max.}$ (H), 1483, 1453, 1399, 1365, 1289, 1249, 1241, 1170, 1084, 1031, 967, 951, 925, 788, 729, 692, 636, and 599 cm.$^{-1}$.

5,10-*Dimethyl*-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan*.—(i) 2,5-Dimethyl-1,4-diacetoxybenzene (1·5 g.) was suspended in 40% formaldehyde solution (12 ml.) and concentrated hydrochloric acid (16 ml.) previously saturated with hydrogen chloride at 0° and held at that temperature for 3 hr. The mixture was then heated on the steam-bath for 30 min., then cooled and the solid product (~1·0 g.) was filtered off. Recrystallisation from ethanol gave 5,10-*dimethyl*-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan*, m. p. 189—190° (Found: C, 65·1; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·4%), $\nu_{max.}$ (H), 1488, 1466, 1428, 1399, 1378, 1358, 1263, 1166, 1079, 1058, 1012, 996, 964, 933, 800, 674, and 647 cm.$^{-1}$. (ii) 5,10-Di(chloromethyl)-4*H*,9*H*-*m*-dioxino-[4,5-*g*]-1,3-benzodioxan (1·0 g.) in dry ethyl acetate (210 ml.) was shaken with hydrogen in the presence of Adams catalyst (200 mg.) and anhydrous potassium carbonate (500 mg.) at room temperature until no further absorption occurred (3·5 hr.). The filtered solution was evaporated *in vacuo*, giving a crystalline product (700 mg.). After filtration through alumina of a solution in benzene, and recovery of the product, recrystallisation from ethanol gave 5,10-dimethyl-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan as needles, m. p. and mixed m. p. 189—190° [Found: C, 64·95; H, 6·4%; *M* (Rast), 219. $C_{12}H_{14}O_4$ requires *M*, 222], $\lambda_{max.}$ (in dioxan) 230, 295 mμ (log ε 3·71, 3·53, respectively).

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[5] Borsche and Berkhout, *Annalen*, 1904, **330**, 82.

[6] Buehler, Bass, Darling, and Lubs, *J. Amer. Chem. Soc.*, 1940, **62**, 890; Ioffe and Zal'manovich, *J. Gen. Chem. (U.S.S.R.)*, 1959, **29**, 2685.

[7] Hales, *J. Sci. Instr.*, 1959, **36**, 264.

5,10-*Di*(*acetoxymethyl*)-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan*.—5,10-Di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-g]-1,4-benzodioxan (1·0 g.) and freshly fused potassium acetate (3·0 g.) were refluxed for 60 min. in glacial acetic acid (75 ml.) containing acetic anhydride (5 ml.). After addition of dry benzene and removal of the acetic acid as an azeotrope under reduced pressure, the solid residue was extracted with dry benzene. Fractional crystallisation furnished 5,10-*di*(*acetoxymethyl*)-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan* as prisms, m. p. 195—196° (Found: C, 56·7, 56·8; H, 5·6, 5·7. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·4%), $\nu_{max.}$ (G) (solid) 1736, 1457, 1445, 1381, 1372, 1354, 1273, 1234, 1213, 1173, 1083, 1047, 1020, 985, 959, 941, 900, 806, 714, 673, 628, 609, 598, and 584 cm.$^{-1}$, $\nu_{max.}$ (G) (in CCl_4) 1273, 1243, 1218, 1172, 1097, 1051, 1008, 973, 960, 942, and 898 cm.$^{-1}$, and a low-melting *stereoisomer* as needles [from benzene–light petroleum (b. p. 80—100°)], m. p. 161·5—162° (Found: C, 56·8, 57·1; H, 5·6, 5·5%), $\nu_{max.}$ (G) (solid) 1736, 1474, 1448, 1444, 1406, 1378, 1360, 1263, 1253, 1222, 1169, 1104, 1063, 1035, 1013, 1004, 985, 963, 955, 925, 908, 844, 775, 751, 670, and 602 cm.$^{-1}$, $\nu_{max.}$ (G) (in CCl_4) 1273, 1234, 1218, 1170, 1110, 1064, 1018, 1000, 971, 970, 945, and 898 cm.$^{-1}$.

5,10-*Di*(*ethoxymethyl*)-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan*.—5,10-Di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan (500 mg.) was refluxed with ethanol (50 ml.) containing dissolved sodium (100 mg.) for 1·5 hr. Working up in the usual way gave 5,10-*di*(*ethoxymethyl*)-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan* (310 mg.), m. p. 160° (from ethanol) (Found: C, 61·8; H, 7·1. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·15%), $\nu_{max.}$ (G) 1479, 1467, 1457, 1440, 1394, 1369, 1341, 1263, 1240, 1165, 1114, 1080, 1042, 1012, 984, 967, 934, 885, 806, and 724 cm.$^{-1}$.

Oxidation of 5,10-*Di*(*ethoxymethyl*)-4H,9H-m-*dioxino*[4,5-g]-1,3-*benzodioxan by Chromium Trioxide*.—This compound (1·9 g.) was suspended in glacial acetic acid (60 ml.) at 0° and treated with chromium trioxide (1·8 g.) in acetic acid (20 ml.) and water (2 ml.), the temperature being kept at ≯25°. After 72 hr. at room temperature the mixture was worked up in the usual way and the yellow product (1·2 g.) recovered by ether-extraction. Material (540 mg.) soluble in hot light petroleum (b. p. 60—80°) was chromatographed on silica gel in that petroleum, the main fraction (yellow) being eluted with 1 : 9 ether–benzene. The yellow product was dissolved in light petroleum (b. p. 60—80°), the solution depositing, on cooling, a pale yellow amorphous powder m. p. *ca.* 125°. Reprecipitation did not improve the m. p. (Found: C, 61·0, 60·9; H, 7·0, 7·1. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). The compound is tentatively considered to be 5,8-*di*(*ethoxymethyl*)-7-*formyl*-6-*hydroxy*-1,3-*benzodioxan*. It was insoluble in water, soluble in aqueous sodium hydrogen carbonate without effervescence, and gave a greenish-yellow colour with ethanolic ferric chloride, a positive Feigl test,[3] and an orange 2,4-dinitrophenylhydrazone, m. p. 235° (decomp.); it had $\nu_{max.}$ (G) *ca.* 3374w, 2968, 2870, 2810w, 2692w, 1674, 1638w, 1475, 1435, 1410, 1386, 1367, 1340, 1282, 1263, 1165, 1115, 1080, 1044, 1010, 987, and 957 cm.$^{-1}$; the bands at 2810, 2692, 1674, 1638, and 1410 cm.$^{-1}$ are indicative of CHO, that at 3374 cm.$^{-1}$ of OH (cf. salicylaldehyde, D.M.S. series).

Reaction of Tetrahydroxymethylquinol with Formaldehyde–Hydrochloric Acid.—Recrystallised tetrahydroxymethylquinol[4] (4·0 g.) was added portionwise to 40% formaldehyde solution (30 ml.) and concentrated hydrochloric acid (40 ml.) previously saturated with hydrogen chloride at 0° for 2 hr. After a further 4 hours' stirring at 0° the sticky product was filtered off and washed with ice-cold water. Recrystallisation from acetic acid gave 5,10-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan (1·63 g.), m. p. and mixed m. p. 250° (decomp.), with the above infrared spectrum.

Chloromethylation of Quinol Di(*methoxymethyl*) *Ether*.—Quinol di(methoxymethyl) ether,[8] b. p. 75°/0·2 mm. (5 g.), and freshly redistilled chloromethyl ether (25 ml.) were left in acetic acid (50 ml.) at room temperature for 48 hr. Addition of anhydrous diethyl ether precipitated polymeric material (1 g.) which was filtered off. The filtrate was washed with saturated potassium carbonate solution, and the ethereal solution dried and reduced to small volume *in vacuo*. The crystalline product recrystallised from glacial acetic acid, to give 5,10-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[4,5-*g*]-1,3-benzodioxan (250 mg.), m. p. 250° (decomp.) (mixed m. p. and infrared spectrum).

Chloromethylation of Catechol Diacetate.—(i) The finely powdered diacetate (15 g.) was added to a stirred mixture of 40% aqueous formaldehyde (180 ml.) and concentrated hydrochloric acid (240 ml.) saturated with hydrogen chloride at 0°. After 3 hours' stirring at 0° the temperature was raised to 30° during 5 hr. After storage at 0° for 72 hr. the oily product had partly crystallised. The recovered solid recrystallised from benzene–light petroleum (b. p. 80—100°),

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[8] Stern, English, and Cassidy, *J. Amer. Chem. Soc.*, 1957, **79**, 5792.

to give 5,6,7-*tri*(*chloromethyl*)-8-*hydroxy*-1,3-*benzodioxan* (5 g.) as needles, m. p. 165—166° (Found: C, 44·3; H, 3·7; Cl, 36·1. $C_{11}H_{11}Cl_3O_3$ requires C, 44·4; H, 3·7; Cl, 35·8%), $\nu_{max.}$ (G) *ca.* 3360, 1611w, 1591w, 1490, 1467, 1352, 1310, 1287, 1248, 1178, 1108, 1088, 1058, 1003, 990, 972, 910, 884, 825, and 676 cm.$^{-1}$ The compound gave a positive reaction in the Feigl colour test.[3]

Refluxing the tri(chloromethyl)-hydroxy-benzodioxan with equal volumes of 40% aqueous formaldehyde and concentrated hydrochloric acid for 3 hr. and recrystallising the product from glacial acetic acid gave the 5,6-di(chloromethyl)-4*H*,9*H*-*m*-dioxino[5,4-*h*]-1,3-benzodioxan described below (m. p., mixed m. p., and infrared spectrum).

(ii) Finely powdered catechol diacetate (20 g.) was added to a stirred mixture of 40% aqueous formaldehyde (120 ml.) and concentrated hydrochloric acid (16 ml.) saturated with hydrogen chloride at 0°. After 6 hours' stirring the oily product was separated. Treatment with ether furnished a little solid which recrystallised from acetic acid, giving 5,6-*di*-(*chloromethyl*)-4H,9H-m-*dioxino*[5,4-h]-1,3-*benzodioxan* (1·5 g.), m. p. 217—218° (decomp.) (Found: C, 49·6; H, 4·3; Cl, 24·3. $C_{12}H_{12}Cl_2O_4$ requires C, 49·5; H, 4·1; Cl, 24·4%), $\nu_{max.}$ (G) 1571, 1498, 1481, 1468, 1361, 1341, 1301, 1282, 1243, 1178, 1170, 1108, 1064, 998, 976, 943, 906, and 678 cm.$^{-1}$. The absence of bands in the 3 and 6 μ regions and the presence of bands around 1470, 1350, 1250, and 1060—1110 indicate the dioxymethylene ring. The compound gave a positive Feigl colour test.[3]

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