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Chemistry of Cyclotriveratrylene (10,15-Dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a*,*d*,*g*]cyclononene). Part II.¹ Bromination

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Treatment of cyclotriveratrylene (I) with bromine-acetic acid gave three kinds of seco-compound, viz. a dibromocompound (III), a monobromo-alcohol (V), and the acetate of the latter.

ALTHOUGH the structure and conformation of cyclotriveratrylene (I)² are well established, its reactions, except for nitration ³ and oxidation, 2a, 2c, 4 have not been studied in detail. Nitration gives fission products with loss of carbon atoms (one and/or two veratrole units), e.g. (IIa).⁵ We have investigated its bromination, which shows another mode of fission.

Treatment of (I) with bromine-acetic acid at room temperature followed by chromatography afforded three products [(III), (IV), and (V)] in yields of 12.1,



⁷⁹Br and ⁸¹Br, and the n.m.r. spectra exhibited signals for aromatic protons of (III) as singlets at τ 3.56, 3.39, and 2.97 and CH_2OH protons of (V) as a sharp singlet at τ 5.45. Compound (V) was converted into (III) in bromine-acetic acid; acetylation of (V) with acetic anhydride-pyridine gave compound (IV).

On the basis of these data and elemental analyses, (III) and (V) were assigned the structures 1,2-bis-(2-bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene⁶ 1-(2-bromo-4,5-dimethoxybenzyl)-2-(2-hydroxyand methyl-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene, and (IV) was identified as the acetate of (V).

¹ Part I, B. Umezawa, O. Hoshino, H. Hara, K. Ohyama, S. Mitsubayashi, and J. Sakakibara, *Chem. and Pharm. Bull.* (Japan), 1969, **17**, 2240.

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The assignments of structures (III) and (V) were supported by the following interconversions. Lithium aluminium hydride reduction of (V) afforded the debromo-compound (VI) (31.2% yield) [τ 5.50 (s, $CH_{2}OH$]. When (V) was heated under reflux with zinc in 50% aqueous acetic acid, however, compound (I) was obtained in 57.4% yield. Catalytic reduction of (V) with 10% palladium-charcoal in acetic acid gave the methyl derivative (VII) (65.3%) [τ 7.85 (s, Me)]. When compound (III) was heated under reflux with zinc in 50% aqueous acetic acid, the debromo-compound (VIII)⁶ was obtained in 72.3% yield. Treatment of (VI) or (VIII) with 35% formalin in the presence of acid gave (I) (100 or $65 \cdot 1\%$, respectively).

Thus bromination of (I) causes cleavage of the ninemembered ring system with or without loss of one carbon atom. Since bromination of (VIII) or of bis-(4,5-dimethoxyphenyl)methane (IIb)³ with bromineacetic acid gives the corresponding dibromo-compound (III) or (IIa), with no further fission, the ready ring opening of (I) seems to be due to a specific property (probably strain) of the nine-membered ring system. The finding that bromination of (V) gave (III) appeared to imply that elimination of formaldehyde was aided by the presence of the p-methoxy-group. The analogous treatment of p-methoxybenzyl alcohol with bromineacetic acid affords p-bromoanisole and formaldehyde.⁷

EXPERIMENTAL

N.m.r. spectra were taken with a JNR-4-100 spectrometer for solutions (5-10%) in deuteriochloroform, with tetramethylsilane as internal standard. Mass spectra were measured with a Hitachi RMU-6E spectrometer. I.r. spectra were obtained with a Hitachi EPI-S₂ spectrometer. T.l.c. was performed on silica gel G (Merck), with benzene-methanol (20:1 or 10:1) as developing solvent. Organic extracts were dried over anhydrous magnesium sulphate, and products were recrystallized from benzenen-hexane unless otherwise noted.

Bromination of Cyclotriveratrylene (I).--To a stirred solution of (I) (451 mg., 1 mmole) in acetic acid (50 ml.), bromine (168 mg., 1.05 mmole) in acetic acid (3.5 ml.) was added dropwise at 15° during 10 min. After 30 min. at room temperature, the mixture was diluted with ice-water and the product was taken up in benzene. The benzene

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layer was washed with cold 3% sodium hydrogen carbonate solution and brine. Removal of the solvent left a brown oil (503 mg.), which was separated by chromatography in benzene and benzene-chloroform (10:1)-(3:1) on neutral alumina (6 g.; Woelm) into two fractions. Re-chromatography of the first fraction, a brown oil (200 mg.), in nhexane-ether (1:1) and ether on neutral alumina (10 g.) gave pale yellow crystals (118 mg.), and an oil, respectively. The former yielded colourless fine needles of 1,2-bis-(2bromo-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene (III) (72 mg., 12·1%), m.p. 133·5-134·5° (lit., 6 132-134°), τ 6.07 (4H, s, ArCH₂Ar \times 2) and 3.56, 3.39, and 2.97 (each 2H, s, aromatic), m/e 549, 551, and 553 (M^+ , M + 2, and M + 4; 1:2:1) (Found: C, 52.5; H, 4.75; Br, 26.75. Calc. for C₂₆H₂₈Br₂O₆: C, 52·35; H, 4·75; Br, 26·8%). The latter gave colourless prisms of 1-(2-acetoxymethyl 4,5-dimethoxybenzyl)-2-(2-bromo-4,5-dimethoxybenzyl)-

4,5-dimethoxybenzene (IV) (30 mg., 5·1%), m.p. 129–130°, τ 8·02 (3H, s, OAc), 4·96 (2H, s, Ar), ν_{max} (KBr) 1730 cm.⁻¹ (OAc) (Found: C, 59·75; H, 5·65; Br, 12·8. C₂₉H₃₃BrO₈ requires C, 59·1; H, 5·65; Br, 13·55%).

Pale yellow crystals (263 mg.) from the second fraction yielded colourless fine needles of 1-(2-bromo-4,5-dimethoxy-benzyl)-2-(2-hydroxymethyl-4,5-dimethoxybenzyl)-4,5-di-

methoxybenzene (V) (239 mg., 43.7%), m.p. 149—151°, $\tau 5.45$ (2H, s, Ar), m/e 546 and 548 (M^+ and M + 2; 1:1), $\nu_{\rm max.}$ (KBr) 3500 cm.⁻¹ (OH) (Found: C, 59.6; H, 5.7; Br, 14.55. C₂₇H₃₁BrO₇ requires C, 59.25; H, 5.7; Br, 14.6%).

Bromination of (V).—To a stirred solution of (V) (1.764 g., 3.22 mmoles) in acetic acid (30 ml.), bromine (550 mg., 3.44 mmoles) in acetic acid (20 ml.) was added dropwise at room temperature during 10 min. After 50 min., sodium acetate (2 g.) was added, and the solvent was removed below 50° under reduced pressure. Water was added to the residue, and the product was taken up in benzene. The benzene layer was washed with cold 10% sodium hydroxide solution, and brine. Removal of the solvent left a reddish brown oil (1.927 g.) which was chromatographed in n-hexane-chloroform (20:1)—(5:1) and chloroform on neutral alumina (64 g.) to give colourless fine needles of (III) (676 mg.), m.p. 128—130°, and unchanged (V) (395 mg.), m.p. 148—150°, identified by comparison of i.r. spectra, t.l.c., and by the mixed m.p.

Acetylation of (V).—A mixture of (V) (105 mg., 0.192 mmole) and acetic anhydride (0.1 ml.) in pyridine (2 ml.) was kept at room temperature for 12 hr. The mixture was diluted with water, and the product was taken up in benzene. The benzene layer was washed with water. Removal of the solvent left a pale yellow oil (110 mg.) which gave colourless prisms of (IV) (85 mg., 75%), m.p. 129—130°, characterized by comparison of i.r. and n.m.r. spectra, t.l.c., and mixed m.p.

Reduction of (V).—(a) With lithium aluminium hydride. A mixture of (V) (1.032 g., 1.88 mmole) and lithium aluminium hydride (100 mg.) in absolute tetrahydrofuran (50 ml.) and absolute ether (50 ml.) was stirred under reflux for 21 hr. After decomposition of the unchanged lithium aluminium hydride with wet ether, the mixture was diluted with 10% Rochelle salt solution, and the product was taken up in chloroform. The chloroform layer was washed with brine. Evaporation of the solvent afforded a pale brown oil (900 mg.), which was chromatographed in benzene-chloroform (10:1) and chloroform on neutral alumina (27 g.) to yield a pale yellow oil (548 mg.), rechromatography of which in benzene-chloroform (20:1) and chloroform on neutral alumina (15 g.) furnished crystals (324 mg.). Recrystallization from carbon tetrachloride-n-hexane gave colourless fine needles of 1-(4,5dimethoxybenzyl)-2-(2-hydroxymethyl-4,5-dimethoxybenzyl)-4,5-dimethoxybenzene (VI) (277 mg., $31\cdot2\%$), m.p. 115— 116.5°, τ 5.50 (2H, s, ArCH₂·OH) (Found: C, 69.5; H, 6.9.

C₂₇H₃₂O₇ requires C, 69.2; H, 6.9%).

(b) Catalytic reduction. Compound (V) (300 mg., 0.548 mmole) in acetic acid (60 ml.) was shaken with 10% palladium-charcoal (100 mg.) under hydrogen (uptake *ca.* 15 ml.). The filtered solution was evaporated under reduced pressure and a solution of the residue in benzene was washed with saturated sodium hydrogen carbonate solution and brine. Removal of the solvent left a pale yellow oil (272 mg.), which was chromatographed with benzene on neutral alumina (6 g.) to yield colourless prisms of 1-(2-bromo-4,5-dimethoxybenzyl)-2-(2-methyl-4,5-dimethoxy-

benzyl)-4,5-dimethoxybenzene (VII) (190 mg., 65·3%), m.p. 138·5—139·5°, τ 7·85 (3H, s, Me) (Found: C, 60·9; H, 5·95; Br, 14·4. C₂₇H₃₁BrO₆ requires C, 61·0; H, 5·9; Br, 15·05%).

(c) With zinc in 50% aqueous acetic acid. A mixture of (V) (1.092 g., 2 mmoles), granular zinc (12 g.), and zinc dust (12 g.) in 50% aqueous acetic acid (80 ml.) was stirred under reflux for 60 hr. The filtered solution was diluted with water and the product was taken up in benzene. The benzene layer was washed with 10% potassium carbonate solution and brine. Removal of the solvent left yellow crystals (744 mg.), which afforded colourless needles of (I) (420 mg.), m.p. 230.5—233°. Chromatography of the mother liquor in benzene and benzene-chloroform (10:1) on neutral alumina (4 g.) afforded a crystalline mass, which gave colourless needles of (I) (97 mg.), m.p. 231—234° [total yield 517 mg. (57.4%)], characterized by t.l.c. and mixed m.p.

Reduction of (III) with Zinc in 50% Aqueous Acetic Acid.—A mixture of (III) (537 mg., 0.90 mmole), granular zinc (10 g.), and zinc dust (5 g.) in 50% aqueous acetic acid (40 ml.) was stirred under reflux for 81 hr. The filtered solution was diluted with water and the product was taken up in chloroform. Work-up gave a brown oil (361 mg.), which furnished colourless crystals of (VIII) (260 mg.), m.p. 87—89°. Chromatography of the mother liquor in benzene-chloroform (20:1) on neutral alumina (5 g.) afforded a pale yellow oil (85 mg.), which gave colourless crystals of (VIII) (26 mg.), m.p. 84—87° [total yield 286 mg. (72·3%)] Further recrystallization, from carbon tetrachloride-n-hexane, furnished colourless needles of (VIII), m.p. 93—94° (lit.,⁶ 93—94°) (Found: C, 70·2; H, 6·95. Calc. for C₂₈H₃₀O₆0·5H₂O: C, 69·8; H, 7·0%).

Cyclization of (VI).—To a stirred solution of (VI) (200 mg., 0.426 mmole) in chloroform (100 ml.), 60% perchloric acid (20 ml.) was added at 3° in one portion, and the mixture was stirred at 3—5° for 10 min. The separated acidic solution was diluted with ice-water and the solution was washed with chloroform. Work-up of the combined layers gave a crystalline mass (196 mg.), which yielded colourless fine needles of (I) (192 mg., 100%), m.p. 234—236°.

Cyclization of (VIII).—To a stirred mixture of 35% formalin (1 ml.) and 60% perchloric acid (5 ml.) cooled in ice, (VIII) (99 mg., 0.226 mmole) was added, and the mixture was stirred at the same temperature for 30 min. Work-up gave pale yellow crystals (86 mg.), which were

fractionally recrystallized to give colourless needles of (I) (49 mg.), m.p. $230-232^{\circ}$, and colourless prisms of unchanged (VIII) (26 mg.), m.p. $90-92^{\circ}$.

Bromination of (VIII).—To a solution of (VIII) (98 mg., 0.22 mmole) in acetic acid (2 ml.), bromine (0.05 ml.) was added and the mixture was kept at room temperature for 10 min. Work-up gave a pale brown oil (128 mg.), which afforded colourless fine needles of (III) (92 mg., 70.3%), m.p. 131—133° (lit.,⁶ 132—134°), characterized by t.l.c. and mixed m.p.

Bromination of (IIb).—To a solution of (IIb) (576 mg., 2 mmoles), m.p. 69—71° (lit.,³⁶ 71°), in acetic acid (45 ml.), bromine (640 mg.) in acetic acid (20 ml.) was added at

room temperature during 15 min. After 10 min., work-up gave pale yellow crystals (763 mg.), which afforded colourless prisms of (IIa) (705 mg., 79%), m.p. $100-102^{\circ}$ (from methanol-water) (lit.,⁵ 97-98°).

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