4,8,8-Tribromobicyclo[5.1.0]oct-4-en-3-ones from Dibromocarbene-Adducts of Cyclohexa-1,4-dienols

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Treatment of the bisdibromocarbene adducts (I) of substituted cyclohexa-1,4-dienols with pyridine or triethylamine gave α-bromo-αβ-unsaturated ketones (II) in good yields. The dihydroxy-diadduct (I; R^1 = H, R^2 = OH) gave the cyclo-octatrienone (IV), whereas the isomeric diadduct (I; R^1 = OH, R^2 = H) gave 3-bromo-4-hydroxybenzocyclobuten-1(2*H*)-one (VIII) in poor yield.

RECENTLY hydroxy-dihalogenocyclopropanes, formed as intermediates in the reduction by lithium aluminium hydride of dihalogenocarbene adducts from enol acetates,[1,2] were shown to rearrange to give αβ-unsaturated ketones. Also treatment of the hydroxy-bisdichlorocyclopropane (I; R^1 = H, R^2 = OMe, X = Cl) with methanolic alkali [3] has been shown to give the cyclo-octatrienone (III).

We now report that bisdibromocarbene adducts (I; X = Br) of cyclohexa-1,4-dienols, readily obtained from acidic hydrolysis of the corresponding methoxymethyl ethers, react with pyridine or triethylamine at room temperature giving high yields of α-bromo-αβ-unsaturated ketones (II; X = Br). However, the bisdichlorocarbene adduct (I; R^1 = OMe, R^2 = H, X = Cl) reacted much more slowly under the same conditions than the bromo-analogue (I; R^1 = OMe, R^2 = H, X = Br).

Treatment of compound (I; R^1 = H, R^2 = OH, X = Br) with pyridine gave the cyclo-octatrienone (IV), previously obtained from the corresponding dimethyl ether with silver salts in acidic medium.[4] In contrast, compound (I; R^1 = OH, R^2 = H, X = Br) with pyridine gave 3-bromo-4-hydroxybenzocyclobuten-1(2*H*)-one (VIII).

The mechanism of formation of the ketones (II), if

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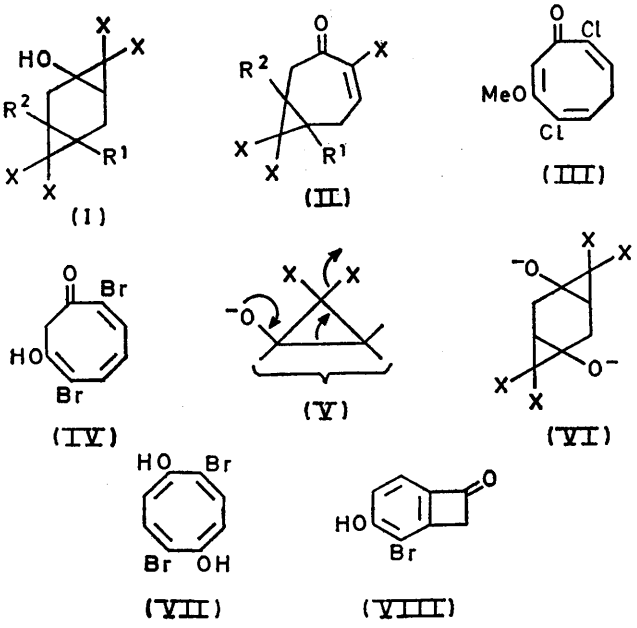
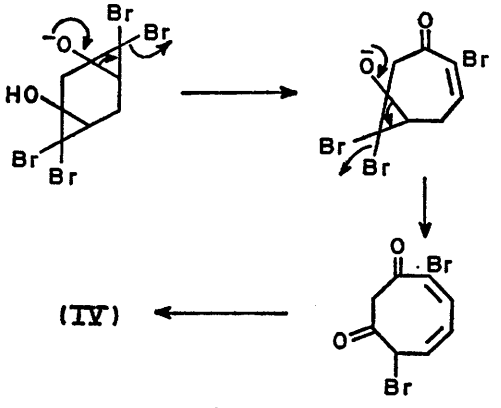
[1] R. C. De Selms, *Tetrahedron Letters*, 1966, 1965.
[2] R. C. De Selms, and T. W. Lin, *Tetrahedron*, 1967, **23**, 1479.
[3] A. J. Birch and R. Keeton, *Austral. J. Chem.*, 1971, **24**, 331.
[4] A. J. Birch, J. M. Brown, and F. Stansfield, *J. Chem. Soc.*, 1964, 5343.

analogous to that reported earlier,[1,2] might involve cyclopropane ring cleavage by way of the anion (V; X = halogen). The cyclo-octatrienone (IV) could presumably be obtained by similar consecutive opening of the two cyclopropane rings (Scheme). Formation of the



phenolic ketone (VIII) obtained from the diadduct (I; R^1 = OH, R^2 = H) might involve an eight-membered ring intermediate (VII) obtained from the dianion (VI).

Use of nitrogenous bases (especially pyridine) for these reactions minimises the risk of Favorskii rearrangement of the α-halogeno-αβ-unsaturated ketones, which can occur with alkoxides [5] or other bases.[1,2]



SCHEME

EXPERIMENTAL

I.r., u.v., and n.m.r. spectra were recorded with Unicam SP 1000, Unicam SP 800, and Varian A60 or Perkin-Elmer instruments.

Preparation of Methoxymethyl Phenyl Ethers.[6]—To a solution of the phenol (0·15 mol) in dry methanol (100 ml) was added cold methanolic sodium methoxide (100 ml) [from sodium (3·5 g)] under nitrogen and with exclusion of moisture. Chloromethyl methyl ether (0·15 mol) was added dropwise while the mixture was stirred and cooled in ice. The pH of the solution was kept ⩾8 by addition of more sodium methoxide solution. Addition of the methoxide solution followed by chloromethyl ether in the same amounts was repeated three times more, and finally the mixture was stirred overnight. The precipitated sodium chloride was filtered off and the filtrate evaporated *in vacuo*. Ether was added to the residue and the solution was shaken with aqueous alkali (10%). The ethereal extract was then dried (K_2CO_3) and evaporated, and the product distilled (see Table 1).

Reduction of Methoxymethyl Phenyl Ethers.—This was carried out in the usual way with sodium and ethanol in liquid ammonia.[7] The products (80—90%) were extracted with n-pentane, and the extract was dried (K_2CO_3) and used directly for the carbene addition.

4,4,8,8-Tetrabromo-1-methoxy-5-(methoxymethoxy)tricyclo-[5.1.0.$0^{3,5}$]*octane.*—A suspension of dry sodium t-butoxide [from sodium (3·5 g, 3 atom equiv.) in a solution of the enol ether (8·5 g, 0·05 mol)] in dry n-pentane (100 ml) was stirred and cooled in ice–salt while bromoform (38 g, 0·15 mol) in pentane (40 ml) was added dropwise (45 min). Stirring was continued for 2 h more at room temperature. Water (300 ml) was added and the mixture filtered. The crude product was washed with aqueous ethanol, dried (yield 10 g, 60%), and crystallised from ethanol to give *needles*, m.p. 132°, showing no i.r. peaks in the 1500—2000 cm^{-1} region (Found: C, 25·6; H, 2·7; Br, 62·0. $C_{11}H_{14}Br_4O_3$ requires C, 25·7; H, 2·7; Br, 62·2%).

In the same way were obtained the following 4,4,8,8-tetrabromotricyclo[5.1.0.$0^{3,5}$]octanes from the corresponding enol ethers: 1-methoxy-3-(methoxymethoxy)-, m.p. 119°; 1-methyl-5-(methoxymethoxy)-, m.p. 78°; 1-methyl-3-(methoxymethoxy)-, m.p. 117°; 1,5-bis(methoxymethoxy)-, m.p. 132°; 1,3-bis(methoxymethoxy)-, m.p. 130°; 1-(methoxymethoxy)-, m.p. 122°; none of these showed absorption between 1500 and 2000 cm^{-1}.

Conversion of the Methoxymethoxy-diadducts into Carbinols (I).—The methoxymethoxy-diadduct (*ca.* 2 g) was shaken with trifluoroacetic acid (3 ml) at room temperature; the solid dissolved (*ca.* ½ h) and immediately after dissolution a white crystalline precipitate of the carbinol was obtained. It was filtered off, dried, and crystallised from benzene (see Table 2).

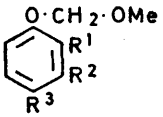
Reaction of the Carbinols (I) *with Pyridine.*—The carbinol (2 g) was dissolved in pyridine (3 ml) and left overnight at room temperature, during which time pyridine hydrobromide separated. Hydrochloric acid (5N) was then added in excess and the mixture was cooled in ice. The viscous oil which separated often solidified. The solid was filtered off, dried, and crystallised twice from light petroleum (b.p. 60—80°) to give needles (II) (see Table 3).

N.m.r. spectra: (II; R^1 = Me, R^2 = H, X = Br) τ ($CDCl_3$) 2·46 (1H, t, olefinic coupled with adjacent equivalent methylene protons at 7·32, *J* 7 Hz), 7·32 (2H, d, *J* 7 Hz), 8·50 (3H, s, Me), and 6·54—8·62 (3H, m, methylene and bridgehead protons); (II; R^1 = H, R^2 = Me, X = Br) τ ($CDCl_3$) 2·50 (1H, q, olefinic coupled with two vicinal non-equivalent methylene protons at C-6, *J* 4 Hz), 7·06—7·65 (5H, m, methylene and bridgehead protons), and 8·70 (3H, s, Me); (II; R^1 = H, R^2 = OMe, X = Br) τ ($CDCl_3$) 2·50

[5] G. M. Iskander and F. Stansfield, *J. Chem. Soc.*, 1969, 669.
[6] R. Stern, J. English, and H. G. Cassidy, *J. Amer. Chem. Soc.*, 1957, **79**, 5792.
[7] R. H. Moss and A. Mamantor, *Tetrahedron Letters*, 1968, 3425.

TABLE 1

Substituted (methoxymethoxy)benzenes



R¹	R²	R³	Yield (%)	B.p. (°C) [mm Hg]	Analysis (%) C	Analysis (%) H	n_D^{25}	$\nu_{max.}$/cm^{-1} (film)
H	H	H	68	38 [0·05]	69·3 (69·60)	7·4 [a] (7·30)	1·4995	1600vs, 1500, 1240, 1080, 1000
Me	H	H	52	52 [0·1]	70·45 (71·05)	8·2 [b] (7·90)	1·4900	1600vs, 1500, 1240, 1800, 1000
H	Me	H	60	44 [0·05]	70·8 (71·05)	8·0 [b] (7·90)	1·4977	1610vs, 1510, 1080, 1000
H	H	Me	67	40 [0·05]	70·9 (71·05)	8·1 [b] (7·90)	1·4961	1600vs, 1500, 1080, 1000
H	OMe	H	62	73 [0·1]	64·6 (64·70)	7·5 [c] (7·15)	1·5074	1600vs, 1500, 1080, 1020
H	H	OMe	60	114 [0·1]	64·6 (64·70)	7·2 [c] (7·15)	1·5051	1600vs, 1500, 1080, 1020
H	OCH_2OMe	H	64	98 [0·15]	60·7 (60·60)	7·15 [d] (7·10)	1·4996	1600vs, 1500, 1080, 1030
H	H	OCH_2OMe	60	75 [0·3]	60·85 (60·60)	7·2 [d,e] (7·10)	1·4965	1600vs, 1520, 1080, 1000

[a] $C_8H_{10}O_2$ requires C, 69·6; H, 7·3%. [b] $C_9H_{12}O_2$ requires C, 71·05; H, 7·9%. [c] $C_9H_{12}O_3$ requires C, 64·7; H, 7·15%. [d] $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%. [e] Lit.,[6] b.p. 75° at 0·3 mmHg, n_D^{25} 1·4972.

TABLE 2

Substituted 4,4,8,8-tetrabromotricyclo[5.1.0.0^{3,5}]octan-1-ols (I; X = Br)

R¹	R²	Yield (%)	M.p. (°C)	Formula	Analysis (%) [a] C	Analysis (%) [a] H	Analysis (%) [a] Br	$\nu_{max.}$/cm^{-1} (Nujol)
H	H	90	112	$C_8H_8Br_4O$	21·7 (21·8)	1·8 (1·8)	72·5 (72·7)	3400, 66s0
H	Me	90	110	$C_9H_{10}Br_4O$	23·75 (23·8)	2·15 (2·2)	70·5 (70·5)	3400, 660s
Me	H	96	103	$C_9H_{10}Br_4O$	23·7 (23·8)	2·1 (2·2)	70·1 (70·5)	3400, 660s
H	OMe	92	140	$C_9H_{10}Br_4O_2$	22·95 (23·0)	2·2 (2·1)	68·0 (68·1)	3400, 1180, 1120, 1080, 660s
OMe	H	90	110	$C_9H_{10}Br_4O_2$	22·9 (23·0)	2·1 (2·1)	68·1 (68·1)	3400, 1180, 1080, 660s
H	OH	94	115	$C_8H_8Br_4O_2$	21·0 (21·05)	1·75 (1·75)	70·0 (70·2)	3400, 660s
OH	H	92	109	$C_8H_8Br_4O_2$	21·0 (21·05)	1·75 (1·75)	70·1 (70·2)	3405, 660s

[a] Required values in parentheses.

TABLE 3

Substituted 4,8,8-tribromobicyclo[5.1.0]oct-4-en-3-ones (II; X = Br)

R¹	R²	Yield (%)	M.p. (°C)	Formula	Analysis (%) [a] C	Analysis (%) [a] H	Analysis (%) [a] Br	$\lambda_{max.}$(EtOH)/nm (ε)	$\nu_{max.}$/cm^{-1} (Nujol)
H	H	85	130 [b]	$C_8H_7Br_3O$	26·65 (26·7)	1·8 (1·95)	66·8 (66·85)	258 (5600)	1680vs, 1600
Me	H	92	111	$C_9H_9Br_3O$	29·0 (28·9)	2·5 (2·4)	64·25 (64·4)	258 (5650)	1680vs, 1600
H	Me	91	109	$C_9H_9Br_3O$	29·1 (28·9)	2·55 (2·4)	64·1 (64·4)	260 (5750)	1680vs, 1600
H	OMe	92	154 [c]	$C_9H_9Br_3O_2$	27·8 (27·7)	2·4 (2·4)	62·2 (61·8)	258 (6050)	1680vs, 1600, 1120
OMe	H	90	109 [d]	$C_9H_9Br_3O_2$	27·7 (27·7)	2·5 (2·4)	61·55 (61·8)	258 (6060)	1680vs, 1600, 1080

[a] Required values in parentheses. [b] Lit.,[4] 154—156°. [c] Lit.,[4] 132°. [d] Lit.,[4] 109—111°.

(1H, q, olefinic coupled with two vicinal non-equivalent methylene protons), 6·54 (3H, s, OMe), and 6·25—7·80 (5H, m, methylene and bridgehead protons); (II; R¹ = OMe, R² = H, X = Br) τ ($CDCl_3$) 2·52 (1H, q, olefinic coupled with two vicinal non-equivalent methylene protons), 6·56 (3H, s, OMe), and 6·50—8·30 (5H, m, methylene and bridgehead protons).

Reaction of 4,4,8,8-*Tetrabromotricyclo*[5.1.0.0^{3,5}]*octane*-1,5-*diol* (I; R¹ = OH, R² = H, X = Br) *with Pyridine*.—The carbinol (7·0 g) was dissolved in pyridine (10 ml) and the solution left at room temperature. Pyridine hydrobromide precipitated out. Hydrochloric acid (5N) was then added and the aqueous solution was extracted with ether. The extracts were dried and evaporated, and the residual oil was shaken with sodium hydroxide solution (10%). The alkaline solution was then acidified and the brown solid obtained was crystallised from water (charcoal) to give needles of 3-bromo-4-hydroxybenzocyclobuten-1(2*H*)-one (VIII) (1·2 g), m.p. 191° (lit.,[4] 195°) (Found: C, 44·75; H, 2·4; Br, 37·65. Calc. for $C_8H_5BrO_2$: C, 45·1; H, 2·35; Br, 37·55%), $\nu_{max.}$ (Nujol) 3200, 1730s, 1600, and 1570 cm^{-1}.

Reaction of 4,4,8,8-*Tetrabromotricyclo*[5.1.0.0^{3,5}]*octane*-1,3-*diol* (I; R¹ = H, R² = OH, X = Br) *with Pyridine*.—The above procedure was followed. Evaporation of the ethereal extract gave a yellow solid which crystallised from benzene as orange plates (1·2 g from 6·0 g of carbinol) of 2,6-dibromo-7-hydroxycyclo-octa-2,4,6-trienone (IV), m.p. 130° (lit.,[8] 130°), $\lambda_{max.}$ (EtOH) 206 (ε 27,600), 268 (14,200), and 470 nm (5400), $\nu_{max.}$ (Nujol) 3200, 2600, and 1620 cm^{-1}.

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[8] A. J. Birch, J. M. Brown, and F. Stansfield, *Chem. and Ind.*, 1964, 1917.