Macrobicyclic Polyethers with Bridgehead Carbon Atoms

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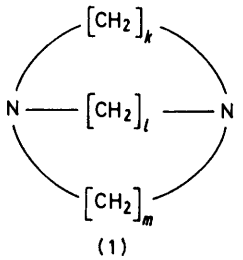
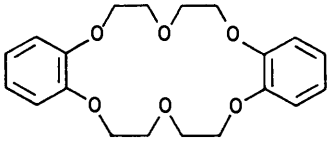
Syntheses of the carbon-bridgehead [2]cryptands (5)—(9) have been achieved in a number of different ways from the ditosylate (12) of diethylene glycol and either pentaerythritol (10) or 1,1,1-tris(hydroxymethyl)ethane (11). The [2]cryptands (5)—(9) all exist as their ' out,out ' isomers and form complexes in solution with alkali metal cations. Variable temperature ^{1}H n.m.r. spectroscopy indicates that the free energy of activation for the dissociation of the potassium ion complexes with the bisbenzyloxymethyl- (5) and dimethyl- (9) [2]cryptands in deuteriochloroform is *ca.* 12 kcal mol^{-1}. Stability constant measurements on the complexes of these [2] cryptands [*i.e.* (5) and (9)] and the bishydroxymethyl[2]cryptand (6) with sodium, potassium, rubidium, and caesium chlorides in methanolic solution indicate, surprisingly, that the complexes are extremely weak (*K' ca.* 100). All three [2]-cryptands [*i.e.* (5), (6), and (9)] exhibit a slight selectivity for binding postassium ions.

In 1968, Simmons and Park [1] reported the synthesis of a series of macrobicyclic diamines (1a—g) and drew attention to their topological and stereochemical properties.

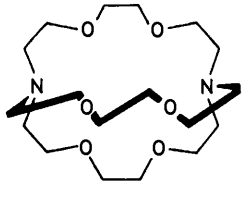


(1)

	k	*l*	*m*
a;	7	7	7
b;	8	8	8
c;	9	9	9
d;	10	10	10
e;	6	6	8
f;	6	8	10
g;	8	8	10



(2)



(3)

A year earlier, Pedersen had published his paper [2] on the syntheses and properties of a wide range of macrocyclic polyethers of which dibenzo-18-crown-6 (2) is probably the best known example. The crown ethers [3-10] have subsequently generated considerable interest because of their surprising ability to form complexes in solution, as well as in the solid state, with many metal, ammonium, and primary alkylammonium cations.

The association by Lehn and his collaborators [11] of the synthetic accomplishments of Simmons and Park [1] on the one hand and Pedersen [2] on the other led to the production of macrobicyclic polyethers containing bridgehead nitrogen atoms in 1969. Recently, Lehn has suggested [12] the use of the term ' cryptand ' to describe all types of cavity-containing ligands, and the bicyclic [2]cryptand (3) has been the most widely investigated of a large number of macrobicyclic polyether diamines. It, and other [2]cryptands, form extremely stable complexes ([2]cryptates) [5,11] with alkali and alkaline earth metal cations in which the cations are encapsulated by the

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ligands. Crystal structure determinations on the [2]-cryptand (3) [5,13] and on several derived [2]cryptates [5,13,14] show that in all cases the lone pairs of electrons on the nitrogen atoms are oriented inside the ligand cavity.

More recently, two isomers of the bicyclo[8.8.8]hexacosane (4) have been synthesised by Simmons and Park [15] in eleven steps from cyclo-octadecane-1,10-dione. In this constitutionally symmetrical three stranded hydrocarbon with bridgehead carbon atoms (Figure 1), three distinct structures can be recognised: (i) an ' in,out ' isomer (4a) in which the bridgehead carbon atoms have the same spatial sense with one of the two methine hydrogen atoms oriented towards the cavity while the other is oriented away, (ii) an ' in,in ' isomer (4b) in which the bridgehead carbon atoms have the opposite spatial sense with both methine hydrogen atoms oriented towards the cavity, and (iii) an ' out,out ' isomer (4c) in which the bridgehead carbon atoms again have the same spatial sense but this time both methine hydrogen atoms are oriented away from the cavity. The ' in,out ' isomer (4a) is configurationally related to both the ' in,in ' (4b) and the ' out,out ' (4c) isomers, which in turn are formally conformational isomers. Corey-Pauling-Koltun (CPK) space-filling molecular models show [15] that the degenerate inversion ' in,out ' $\rightleftharpoons$ ' out,-in ' and the conformational interconversion ' in,in ' $\rightleftharpoons$ ' out,out ' are not possible until the chains in bicyclic hydrocarbons contain at least ten methylene groups. The two isomers which were isolated have been assigned [15] the ' in,out ' (4a) and ' in,in ' (4b) structures on the basis of spectroscopic evidence and theoretical calculations.

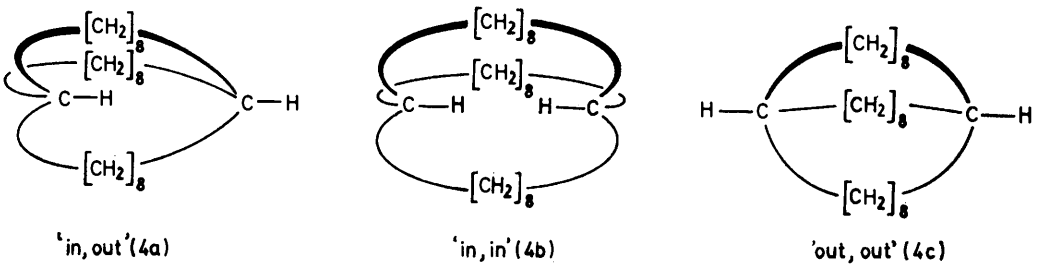
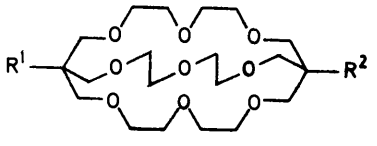


FIGURE 1 The ' in,out ' (4a), ' in,in ' (4b), and ' out,out ' (4c) isomers of bicyclo[8.8.8]hexacosane (4)



(5) $R^1 = R^2 = CH_2 \cdot O \cdot CH_2Ph$
(6) $R^1 = R^2 = CH_2 \cdot OH$
(7) $R^1 = R^2 = CH_2 \cdot OMs$
(8) $R^1 = Me, R^2 = CH_2 \cdot OH$
(9) $R^1 = R^2 = Me$

In 1972, we directed our attention towards the synthesis of macrobicyclic polyethers with bridgehead carbon atoms in the anticipation that, like their nitrogen analogues, they might prove extremely efficient in their complexation of metal cations. In addition we had high hopes that carbon-bridgehead [2]cryptands, in contrast with their nitrogen analogues, would be relatively rigid, on account of their inability to undergo inversion at the carbon atoms associated with their ring junctions, and therefore show pronounced selectivities towards different metal cations. In this paper, we describe synthetic routes to the [2]cryptands (5)—(9) and studies of their ability to form [2]cryptates with metal cations.[16]

EXPERIMENTAL

Apart from ^{13}C n.m.r spectroscopy the general methods used have been delineated elsewhere.[17] Broad-band decoupled ^{13}C n.m.r. spectra were recorded with a JEOL PS 100 spectrometer, with deuteriochloroform as ' lock ' and tetramethylsilane as internal standard.

2,4,8,10-Tetraoxaspiro[5.5]undecane (13).[18]—Pentaerythritol (10) (30.0 g) and paraformaldehyde (30.0 g) were mixed as fine powders and concentrated sulphuric acid (15.0 ml) was added. The mixture was kept at room temperature for 24 h. Extraction with chloroform yielded the spiroundecane (13) (24.1 g, 68%) as plates, m.p. 49° [from light petroleum (b.p. 60—80°)] (lit.,[18] 49°) [Found: C, 52.6; H, 7.27%; *M* (mass spec.), 160. Calc. for $C_7H_{12}O_4$: C, 52.4; H, 7.53%; *M*, 160], τ ($CDCl_3$) 5.23 (4 H, s, 2 × O·CH_2·O) and 6.27 (8 H, s, other CH_2).

1,3-Dioxan-5,5-diyldimethanol (14).[19]—(*a*) The diacetal (13) (19.0 g) dissolved in N-sulphuric acid (700 ml) was heated on a steam-bath for 5 h. On cooling, extraction with chloroform removed the unhydrolysed diacetal (13) (6.0 g, 32%). The acidic aqueous hydrolysate remaining was neutralised (barium hydroxide solution and finally barium carbonate). The suspension was filtered to remove barium sulphate and the filtrate was concentrated to yield an oily residue, which was extracted with chloroform. This extract afforded an oil, which crystallised to give the diol (14) (6.7 g, 38%), m.p. 60—61° [from chloroform–light petroleum (b.p. 60—80°)] (lit.,[19] 60°) [Found: *M* (mass spec.), 148. Calc. for $C_6H_{12}O_4$: *M*, 148], τ ($CDCl_3$) 5.20 (2 H, s, O·CH_2·O), 6.26 (8 H, s, other CH_2), and 6.84 (2 H, s, 2 × OH).

(*b*) The diacetal (13) (50.0 g), dissolved in water (500 ml), was heated under reflux wth Amberlite CG-120 resin (H^+

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form; 50.0 g) for 24 h with stirring. The resin was filtered off and the filtrate was extracted with chloroform to remove unhydrolysed diacetal (13) (12.8 g, 26%). The aqueous solution was evaporated under vacuum and the residue was extracted with chloroform to yield the diol (14) (19.0 g, 41%).

2-Benzoyloxymethyl-2-hydroxymethylpropane-1,3-diol (17). —Benzoyl chloride (12.1 g) was added dropwise with stirring over 1 h to pentaerythritol (10) (39.8 g) dissolved in dry pyridine (1.5 l) at 40 °C. The mixture was left for 1 h, then poured into ice–water, which was then extracted with chloroform to give an oil. Crystallisation from chloroform–light petroleum (b.p. 60—80°) gave crystals of the benzoate (17) (5.1 g, 24%), m.p. 77°, *m/e* 241 ($M + 1$), τ [$CDCl_3$–$(CD_3)_2CO$–D_2O] 1.96—2.06 and 2.44—2.64 (5 H, m, aromatic), 5.60 (2 H, s, CH_2·O·COPh), and 6.22 (6 H, s, 3 × CH_2·OH).

1,3-Dioxan-5,5-diylbis(methyl Benzoate) (16) *and 5-Hydroxymethyl-1,3-dioxan-5-ylmethyl Benzoate* (15).—Benzoyl chloride (29.1 g), dissolved in dry pyridine (25 ml), was added dropwise with stirring over 1 h to the diol (14) (36.7 g) dissolved in dry pyridine (250 ml). The mixture was set aside overnight and then poured into ice–water. The white precipitate gave crude *dibenzoate* (16) (5.8 g, 9%), m.p. 91—92° (from absolute ethanol) [Found: C, 67.3; H, 5.85%; *M* (mass spec.), 356. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.66%; *M*, 356], τ ($CDCl_3$) 1.98—2.09 and 2.42—2.78 (10 H, m, aromatic), 5.14 (2 H, s, O·CH_2·O), 5.52 (4 H, s, 2 × CH_2·O·COPh), and 6.06 (4 H, s, other CH_2). The filtrate was extracted with chloroform to yield crystals of the *benzoate* (15) (20.7 g, 41%), m.p. 113° [from chloroform–light petroleum (b.p. 60—80°)] [Found: C, 62.0; H, 6.43%; *M* (mass spec.), 252. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.39%; *M*, 252], τ ($CDCl_3$) 1.94—2.05 and 2.33—2.70 (5 H, m, aromatic), 5.11 and 5.23 (2 H, AB system, J_{AB} 6.0 Hz, O·CH_2·O), 5.50 (2 H, s, CH_2·O·COPh), 6.10 and 6.26 (4 H, 2 AB systems, J_{AB} 12.0 Hz, 4- and 6-H_2), 6.43br (2 H, s, CH_2·OH), and 7.37br (1 H, s, OH).

5-Hydroxymethyl-1,3-dioxan-5-ylmethyl Benzoate (15).—Monobenzoylpentaerythritol (17) (250 mg, 1.0 mmol) and *N*-bromosuccinimide (560 mg, 3.0 mmol) were stirred in dry dimethyl sulphoxide (20.0 ml) at 50 °C for 24 h. Saturated sodium hydrogen carbonate solution was added until the mixture was neutral, and it was then extracted with chloroform to yield crystals of the benzoate (15) (0.17 g, 65%).

5-(Methoxymethoxymethyl)-1,3-dioxan-5-ylmethyl Benzoate (19).—The monobenzoate (15) (200 mg) was heated under reflux in dimethoxymethane (70 ml) using a Soxhlet extraction apparatus containing anhydrous calcium chloride (2.0 g) for 36 h in the presence of concentrated sulphuric acid (1 drop). Sodium hydrogen carbonate (100 mg) was added and the solution was evaporated to yield a crude oil, characterised as the mixed acetal (19) (200 mg), *M* (mass spec.) 296, τ ($CDCl_3$) 1.92—2.06 and 2.40—2.64 (5 H, m, aromatic), 5.18 (2 H, s, cyclic O·CH_2·O), 5.42 (2 H, s, O·CH_2·OCH_3), 5.59 (2 H, s, CH_2·O·COPh), 6.14 (4 H, s, other ring CH_2), 6.38 (2 H, s, CH_2·O·CH_2·O·CH_3), and 6.52 (3 H, s, OCH_3).

5-(1-Methoxyethoxymethyl)-1,3-dioxan-5-ylmethyl Benzoate (20).—The monobenzoate (15) (100 mg), dissolved in 1,1-dimethoxyethane (30 ml) containing a trace of concentrated sulphuric acid (<5 mg), was left at room temperature for 16 h. Diethylamine (50 mg) was added with shaking and the volatile compounds were removed by evaporation to yield a crude oil, characterised as the mixed acetal (20) (110 mg), *M* (mass spec.) 310, τ ($CDCl_3$) 1.95—2.08 and 2.46—2.74 (5 H, m, aromatic), 5.19 (2 H, s, O·CH_2·O), 5.40 (1 H, q, *J* 5.0 Hz, C*H*·CH_3), 5.61 (2 H, s, CH_2·O·COPh), 6.15 (4 H, s, other ring CH_2), 6.77 (3 H, s, OCH_3), and 8.75 (3 H, d, *J* 6.0 Hz, CH·CH_3).

5-(1-Methoxy-1-methylethoxymethyl)-1,3-dioxan-5-ylmethyl Benzoate (21).—The monobenzoate (15) (0.80 g), dissolved in 2,2-dimethoxypropane (100 ml) containing a trace of concentrated sulphuric acid (<5 mg), was left at room temperature for 16 h. Diethylamine (50 mg) was added with shaking and the volatile materials were removed by evaporation to yield the crystalline mixed acetal (21) (0.91 g, 88%), m.p. 102° [from light petroleum (b.p. 60—80°)] [Found: C, 63.1; H, 7.2%; *M* (mass spec.), 324. $C_{17}H_{24}O_6$ requires C, 63.0; H, 7.45%; *M*, 324], τ ($CDCl_3$) 1.96—2.04 and 2.40—2.68 (5 H, m, aromatic), 5.17 (2 H, s, O·CH_2·O), 5.60 (2 H, s, CH_2·O·COPh), 6.15 (4 H, s, other ring CH_2), 6.51 (2 H, s, CH_2·O·CMe_2·O·CH_3), 6.89 (3 H, s, OCH_3), and 8.71 [6 H, s, CH_2·O·C(CH_3)$_2$·O·CH_3].

5,5′-Methylenebis(oxymethylene)bis-(1,3-dioxan-5-ylmethyl Benzoate) (18).—(*a*) Monobenzoylpentaerythritol (17) (4.8 g) and paraformaldehyde (4.8 g) were mixed as fine powders and concentrated sulphuric acid (3.0 ml) was added. The mixture was left at room temperature for 16 h. The extraction procedure, which was similar to that used in the preparation of the spiro-derivative (13), yielded a crude oil (2.7 g). The oil was subjected to column chromatography on silica gel [light petroleum (b.p. 60—80°)–ethyl acetate (9 : 1 v/v) as eluant] to give two major fractions. Fraction I afforded crystals of *5,5′-methylenebis(oxymethylene)bis-(1,3-dioxan-5-ylmethyl benzoate)* (18) (0.56 g, 11%), m.p. 93—94° (from methanol) [Found: C, 62.8; H, 6.09%; *M* (mass spec.), 516. $C_{27}H_{32}O_{10}$ requires C, 62.8; H, 6.24%; *M*, 516], τ ($CDCl_3$) 1.96—2.08 and 2.40—2.72 (10 H, m, aromatic), 5.20 and 5.28 (4 H, 2 AB systems, J_{AB} 6.0 Hz, cyclic O·CH_2·O), 5.36 (2 H, s, acyclic O·CH_2·O), 5.63 (4 H, s, 2 × CH_2·O·COPh), 6.19 (8 H, s, C-4, -4′, -6, and -6′ CH_2), and 6.41 (4 H, s, other CH_2). Fraction II afforded crystals of the diacetal (13) (1.51 g, 47%).

(*b*) The monobenzoate (15) (0.48 g, 1.9 mmol) and *N*-bromosuccinimide (0.70 g, 4.0 mmol) were stirred in dry dimethyl sulphoxide (25 ml) at 50 °C for 24 h. Sodium hydrogen carbonate solution was added until the mixture was neutral and then it was extracted with chloroform to give a yellow oil. Column chromatography on silica gel [light petroleum (b.p. 60—80°)–ethyl acetate (7 : 3 v/v) as eluant] afforded crystals of the acyclic methylene acetal (18) (0.24 g, 49%), m.p. 93—94° (from methanol).

(*c*) Monobenzoylpentaerythritol (17) (10 mg, 0.04 mmol) and *N*-bromosuccinimide (45 mg, 0.24 mmol) were stirred in dry dimethyl sulphoxide (2 ml) at 60 °C for 7 days. T.l.c. on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (3 : 2 v/v)] indicated the presence of a *ca.* 1 : 1 mixture of the monobenzoate (15) and the dibenzoate (18), as sole products.

5,5′-Methylenebis(oxymethylene)bis-(1,3-dioxan-5-ylmethanol) (22).—Sodium (0.10 g) was dissolved in dry methanol (100 ml) and the acyclic methylene acetal (18) (2.40 g) was added. After 24 h the methanol was removed and the residue was extracted with chloroform to yield crystals of the *diol* (22) (1.26 g, 90%), m.p. 87° [from chloroform–light petroleum (b.p. 60—80°)] (Found: C, 50.8; H, 7.7. $C_{13}H_{24}O_8$ requires C, 50.6; H, 7.85%), τ ($CDCl_3$) 5.12 and 5.26 (4 H, 2 AB systems, J_{AB} 6.0 Hz, cyclic O·CH_2·O), 5.31

(2 H, s, acyclic O·CH_2·O), 6.16 and 6.35 (8 H, 4 AB systems, J_{AB} 11.5 Hz, C-4, -4′, -6, and -6′ CH_2), 6.32 (4 H, s, 2 × CH_2·OH), 6.38 (4 H, s, other CH_2), and 7.10 (2 H, s, 2 × OH).

2,4,8,10,14,16,19,22,25-*Nonaoxadispiro*[5.5.5.9]*hexacosane* (23).—(*a*) The diol (22) (0.80 g) was dissolved in 1,2-dimethoxyethane (100 ml). Sodium hydride (0.50 g) was added and the mixture was stirred at 50 °C. Diethylene glycol ditosylate (12) [17,20] (1.18 g) dissolved in 1,2-dimethoxyethane (50 ml) was added dropwise over 5 h. Stirring was continued and the mixture was maintained at 50 °C overnight. The suspension was cooled in an ice-bath and the excess of sodium hydride was destroyed by addition of water. Extraction with chloroform yielded an oil, which was subjected to column chromatography on silica gel (ether as eluant) to afford crystals of the *dispiro-compound* (23) (0.38 g, 39%), m.p. 85° [from light petroleum (b.p. 60—80°)] (Found: C, 54.1; H, 8.05%; $M^{+\cdot}$ — 1, 377. $C_{17}H_{30}O_9$ requires C, 54.0; H, 8.0%; *M*, 378), τ ($CDCl_3$), 5.22 (4 H, s, C-3 and -15 O·CH_2), 5.34 (2 H, s, C-9 O·CH_2), 6.24 (8 H, s, C-1, -5, -13, and -17 CH_2), 6.40 (8 H, s, O·CH_2·CH_2·O·CH_2·CH_2·O), and 6.46 and 6.50 (8 H, 2 s, C-7, -11, -18, and -26 CH_2).

(*b*) The diol (22) (400 mg) was dissolved in dimethyl sulphoxide (40 ml). Sodium hydride (200 mg) was added and the mixture was stirred at 50 °C. Diethylene glycol ditosylate (12) (670 mg) in dimethyl sulphoxide (25 ml) was added dropwise over 5 h. Stirring was continued and the mixture was maintained at 50 °C overnight. The procedure described in (*a*) afforded the *dispiro*-compound (23) (117 mg, 25%).

5,5′-*Oxybis*(*ethyleneoxymethylene*)*bis*-(1,3-*dioxan*-5-*ylmethanol*) (24).—The dispiro-compound (23) (430 mg) was heated at 80 °C for 2 h in N-sulphuric acid (60 ml). The solution was neutralised with saturated sodium hydrogen carbonate solution and extracted with chloroform to give the *diol* (24) as an oil (342 mg, 82%), *M* (mass spec.) 366, τ ($CDCl_3$) 5.17 and 5.30 (4 H, 2 AB systems, J_{AB} 6.0 Hz, 2 × O·CH_2·O), 6.21 and 6.39 (8 H, 4 AB systems, J_{AB} 11.5 Hz, other cyclic CH_2), (12 H, s, 2 × O·CH_2·CH_2·O and 2 × CH_2·OH), 6.44 (4 H, s, other CH_2), and 6.54br (2 H, s, 2 × OH).

2,4,8,11,14,18,20,23,26,29-*Decaoxadispiro*[5.9.5.9]*triacontane* (25).—(*a*) The diol (24) (430 mg) and diethylene glycol ditosylate (12) (500 mg) were added to sodium hydride (500 mg) suspended in 1,2-dimethoxyethane (50 ml), and the mixture was stirred at 50 °C for 48 h. Water was then added to the cooled mixture. Extraction with chloroform gave an oil (340 mg), which was subjected to column chromatography on silica gel (ether as eluant) to afford the *dispiro-derivative* (25) (111 mg, 21%) [Found: *M* (mass spec.), 436.231 2. $C_{20}H_{36}O_{10}$ requires *M*, 436.230 8], τ ($CDCl_3$) 5.24 (4 H, s, 2 × O·CH_2·O), 6.27 (8 H, s, C-1, -5, -17, and -21 CH_2), 6.41 (16 H, s, 4 × O·CH_2·CH_2·O), and 6.50 (8 H, s, other CH_2).

(*b*) The diol (24) (25.6 g) and diethylene glycol ditosylate (12) (75.0 g) were added to sodium hydride suspended in dimethyl sulphoxide (300 ml), and the mixture was stirred at 50 °C for 72 h. Water was then added to the cooled mixture. Extraction with chloroform yielded an oil, which was subjected to vacuum distillation to give three major fractions: I (0.95 g), b.p. 180—200° at 0.04 mmHg; II (1.30 g), b.p. 200—220° at 0.04 mmHg; and III (5.71 g), b.p. 220—240° at 0.04 mmHg. Fraction II was subjected to column chromatography on silica gel (ether as eluant) to yield an oil characterised as the dispiro-derivative (25) (308 mg, 0.3%).

2-*Phenyl*-1,3-*dioxan*-5,5-*diyldimethanol* (28).[21]—Pentaerythritol (10) (180 g) was converted into the benzylidene derivative (28) (214 g, 72%), m.p. 133—134° (lit.,[21] 134—135°), *M* (mass spec.) 224, τ [$CDCl_3$–$(CD_3)_2CO$–D_2O] 2.47—2.85 (5 H, m, aromatic), 4.59 (1 H, s, PhC*H*), 5.86 and 6.24 (4 H, 2 AB systems, J_{AB} 11.5 Hz, C-4 and -6 CH_2), 5.97 (2 H, s, axial CH_2·OD), and 6.50 (2 H, s, equatorial CH_2OD) by a literature procedure.[21]

5,5-*Bisallyloxymethyl*-2-*phenyl*-1,3-*dioxan* (29), 5-*Allyloxymethyl*-c-2-*phenyl*-1,3-*dioxan*-r-5-*ylmethanol* (30), *and* 5-*Allyloxymethyl*-t-2-*phenyl*-1,3-*dioxan*-r-5-*ylmethanol* (31).—The benzylidene derivative (28) (3.73 g), allyl bromide (6.38 g), and powdered sodium hydroxide pellets (4.00 g) were stirred and heated under reflux in dry benzene (40 ml) for 4 h. The solution was filtered and the residue was washed with benzene. Benzene was removed by evaporation to yield an oil (2.60 g), which was subjected to column chromatography on silica gel [light petroleum (b.p. 60—80°)–ethyl acetate (2 : 1 v/v) as eluant] to give three major fractions. Fraction I was an oil, 5,5-*bisallyloxymethyl*-2-*phenyl*-1,3-*dioxan* (29) (0.85 g, 17%), *M* (mass spec.) 304, τ ($CDCl_3$) 2.46—2.80 (5 H, m, aromatic), 3.88—4.35 (2 H, m, CH_2·C*H*=CH_2), 4.60 (1 H, s, PhC*H*), 4.62—4.96 (4 H, m, 2 × CH_2·CH=CH_2), 5.66—6.24 (8 H, m and 2 AB systems, J_{AB} 12.0 Hz, 2 × CH_2·CH=CH_2 and C-4 and -6 CH_2), 6.24 (2 H, s, axial CH_2·O·CH_2·CH=CH_2), and 6.73 (2 H, s, equatorial CH_2·O·CH_2·CH=CH_2). Fraction II was an oil, 5-*allyloxymethyl*-c-2-*phenyl*-1,3-*dioxan*-r-5-*ylmethanol* (30) (0.82 g, 19%), *M* (mass spec.) 264, τ ($CDCl_3$) 2.44—2.74 (5 H, m, aromatic), 3.92—4.40 (1 H, m, CH_2·C*H*=CH_2), 4.60 (1 H, s, PhC*H*), 4.62—4.92 (2 H, m, CH_2·CH=CH_2), 5.76—6.34 (8 H, m, s, and 2 AB systems, J_{AB} 12.0 Hz, CH_2·CH=CH_2, CH_2·OH, and C-4 and -6 CH_2), 6.78 (2 H, s, CH_2·O·CH_2·CH=CH_2), and 7.40br (1 H, s, OH). Fraction III was an oil, 5-*allyloxymethyl*-t-2-*phenyl*-1,3-*dioxan*-r-5-*ylmethanol* (31) (0.50 g, 11%), 2.46—2.74 (5 H, m, aromatic), 3.88—4.32 (1 H, m, CH_2·C*H*=CH_2), 4.62 (1 H, s, PhC*H*), 4.62—4.90 (2 H, m, CH_2·CH=CH_2), 5.86 and 6.29 (4 H, 2 AB systems, J_{AB} 12.0 Hz, C-4 and -6 CH_2), 5.66—6.06 (2 H, m, CH_2·CH=CH_2), 6.12 (2 H, s, CH_2·O·CH_2·CH=CH_2), 6.53br (2 H, s, CH_2·OH), and 7.37br (1 H, s, OH).

In a second experiment the benzylidene derivative (28) (22.4 g), allyl bromide (48.4 g), benzene (250 ml), and powdered potassium hydroxide pellets (16.8 g) were stirred and refluxed for 48 h. By the procedure outlined above the diallyl ether (29) (19.1 g, 63%) was obtained in greater amounts.

5,5-*Bis*-(2-*hydroxyethoxymethyl*)-2-*phenyl*-1,3-*dioxan* (32).—The diallyl ether (29) (32.3 g), dissolved in dry methanol (150 ml), was subjected to ozonolysis at −78 °C until t.l.c. on silica gel (ethyl acetate as eluant) indicated that all the starting material had reacted. The vessel was flushed with nitrogen to remove the excess of ozone and then cooled in an ice–salt bath at −10 °C. A solution (150 ml) of sodium borohydride (10.3 g) in 1 : 1 aqueous ethanol was added with stirring to the mixture during 1 h. The mixture was stirred and allowed to warm to room temperature overnight. Neutralisation with dilute hydrochloric acid, followed by concentration gave a residue which was extracted with boiling chloroform to yield the *diol* (32) (31.5 g, 95%) [Found: C, 61.3; H, 7.7%; *M* (mass spec.), 312. $C_{16}H_{24}O_6$

[20] J. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, 1972, **26**, 1471.

[21] C. H. Issidorides and R. Gulen, *Org. Synth.*, Coll. Vol. IV, 1963, p. 679.

requires C, 61.5; H, 7.75%; *M*, 312], τ ($CDCl_3$) 2.40—2.90 (5 H, m, aromatic), 4.60 (1 H, s, PhC*H*), and 5.54—6.80 (18 H, m, other protons) as an oil.

5,5-*Bis*-(2-p-*tolylsulphonyloxyethoxymethyl*)-2-*phenyl*-1,3-*dioxan* (33) *and* 5-(2-*Hydroxyethoxymethyl*)-5-(2-p-*tolylsulphonyloxyethoxymethyl*)-2-*phenyl*-1,3-*dioxan* [(34) *and* (35)].—The diol (32) (12.5 g) was dissolved in dry pyridine (45 ml) and toluene-*p*-sulphonyl chloride (21.0 g) was added during 2 h as a powder to the stirred and cooled solution. Stirring was continued for a further 4 h at *ca.* 0 °C. The mixture was then set aside overnight at room temperature, poured onto ice (100 g), and diluted with water (50 ml). The aqueous solution was neutralised with 16% hydrochloric acid and then extracted with chloroform to give a viscous oil (14.1 g). T.l.c. on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (3 : 2 v/v) as eluant] indicated the presence of two major components. The viscous oil was subjected to column chromatography on silica gel [ethyl acetate–light petroleum (b.p. 60—80°) (1 : 3 v/v)] and two major fractions were obtained. Fraction I was a glass, the *ditosylate* (33) (4.8 g, 19%) [Found: C, 57.8; H, 5.85; S, 10.4%; *M* (mass spec.), 620. $C_{30}H_{36}O_{10}S_2$ requires C, 58.05; H, 5.85; S, 10.3%; *M*, 620], τ ($CDCl_3$) 2.12—2.30 and 2.44—2.80 (13 H, m, aromatic), 4.64 (1 H, s, PhC*H*), 5.66—6.50 (12 H, m, C-4 and -6 CH_2 and O·CH_2·CH_2·O), 6.31 (2 H, s, axial C*H*$_2$·O·CH_2·CH_2·OTs), 6.80 (2 H, s, equatorial C*H*$_2$·O·CH_2·CH_2·OTs), and 7.58 and 7.60 (6 H, 2 s, 2 × CH_3). Fraction II was an oil, shown by ^{1}H n.m.r. spectroscopy to contain the two diastereoisomers (ratio *ca.* 1 : 1) of the *monotosylate* [(34) and (35)] (5.11 g, 27.4%), *M* (mass spec.), 466.

1,4,7,11,14,17-*Hexaoxacycloeicosane*-9,9,19,19-*tetrayltetramethanol* (26).—(*a*) The dispiro-derivative (25) (110 mg) was heated in 5N-sulphuric acid (50 ml) at 80 °C for 17 h. Water (50 ml) was added to the hydrolysate, which was neutralised with barium carbonate. Barium sulphate was filtered off and the filtrate was extracted with chloroform to remove unhydrolysed dispiro-derivative (25) (5 mg, 4.5%). The aqueous solution was evaporated to dryness and the residue was extracted with chloroform to yield crystals of the *tetraol* (26) (80 mg, 76%), m.p. 77° [from ether–light petroleum (b.p. 60—80°)] [Found: C, 52.1; H, 8.55%; *M*, (mass spec.), 412. $C_{18}H_{36}O_{10}$ requires C, 52.4; H, 8.8%; *M* 412], τ ($CDCl_3$) 6.27—6.39 (32 H, m, CH_2) and 7.05br (4 H, s, 4 × OH).

(*b*) The dibenzylidene dispiro-derivative (27) (588 mg) was dissolved in ethanol (50 ml) and 10% palladium–carbon (50 mg) was added. The mixture was subjected to hydrogenolysis until 4.0 mol. equiv. of hydrogen had been absorbed, then filtered and concentrated to give crystals of the tetraol (26) (412 mg, 100%).

3,19-*Diphenyl*-2,4,8,11,14,18,20,23,26,29-*decaoxadispiro*-[5.9.5.9]*triacontane* (27), 3-*Phenyl*-2,4,8,11,14-*pentaoxaspiro*-[5.9]*pentadecane* (36), *and* 3,19,34-*Triphenyl*-2,4,8,11,14,18,-20,23,26,29,33,35,38,41,44-*pentadecaoxatrispiro*[5.9.5.9.5.9]-*pentatetracontane* (37).—(*a*) The tetraol (26) (0.85 g), benzaldehyde (0.90 ml), and concentrated hydrochloric acid (0.04 ml) were added to water (20 ml) and the mixture was stirred for 48 h. The solution was extracted with chloroform to give a crude oil (0.92 g). The oil was subjected to column chromatography on deactivated alumina (45 g) (ether as eluant) to afford crystals of the *dibenzylidene dispiro-derivative* (27) (0.69 g, 59%), m.p. 99° (from ether) [Found: C, 65.2; H, 7.55%; *M* (mass spec.), 588.291 3. $C_{32}H_{44}O_{10}$ requires C, 65.3; H, 7.55%; *M*, 588.293 4], τ ($CDCl_3$) 2.46—2.80 (10 H, m, aromatic), 4.60 (2 H, s, 2 × PhC*H*), 5.85 and 6.22 (8 H, 4 AB systems, J_{AB} 12.0 Hz, C-1, -5, -17, and -21 CH_2), 6.18 (4 H, s, axial C*H*$_2$·O·CH_2·CH_2·O), 6.35 and 6.40 (16 H, 2 s, 4 × O·CH_2·CH_2·O), and 6.66 (4 H, s, equatorial C*H*$_2$·O·CH_2·CH_2·O), δ_C ($CDCl_3$) 138.3, 128.1, and 126.0 (aromatic), 101.7 (PhCH), 71.1, 70.4, and 69.1 (secondary C), and 39.0 (quaternary C).

(*b*) The diol (32) (0.65 g) was dissolved in dry dimethyl sulphoxide (10 ml). Sodium hydride (0.30 g) was added and the mixture was stirred at room temperature for 30 min. The ditosylate (33) (1.28 g) dissolved in dry dimethyl sulphoxide (15 ml) was added dropwise over 30 min, and the mixture was then stirred at 50 °C for 48 h. The suspension was cooled in an ice-bath and the excess of sodium hydride was destroyed with water. Extraction with ether gave a crude oil (0.61 g), which was subjected to column chromatography on deactivated alumina (ether as eluant). The oil obtained yielded crystals of the dibenzylidene dispiro-derivative (27) (0.26 g, 21%).

(*c*) The benzylidene derivative (28) (7.6 g) and diethylene glycol ditosylate (12) (14.1 g) were added to sodium hydride (2.0 g) suspended in dimethyl sulphoxide (300 ml). The mixture was stirred at 50 °C for 72 h, then cooled and water was added. Extraction with ether yielded a crude oil (8.5 g), which was subjected to column chromatography on alumina (ether as eluant) to give three major fractions. Fraction I afforded crystals of the dibenzylidene dispiro-derivative (27) (1.50 g, 15%). Fraction II afforded an oil, 3-*phenyl*-2,4,8,-11,14-*pentaoxaspiro*[5.9]*pentadecane* (36) (0.63 g, 6.4%) [Found: *M* (mass spec.), 294.145 8. $C_{16}H_{22}O_5$ requires *M*, 294.146 7], τ ($CDCl_3$) 2.44—2.80 (5 H, m, aromatic), 4.62 (1 H, s, PhC*H*), 5.80 and 6.36 (4 H, 2 AB systems, J_{AB} 11.5 Hz, C-1 and -5 CH_2), 5.96 (2 H, s, axial C*H*$_2$·O·CH_2·CH_2·O), 6.29br (8 H, s, 2 × O·CH_2·CH_2·O), and 6.65 (2 H, s, equatorial C*H*$_2$·O·CH_2·CH_2·O). Fraction III afforded crystals of 3,19,34-*triphenyl*-2,4,8,11,14,18,20,23,26,29,33,35,38,41,44-*pentadecaoxatrispiro*[5.9.5.9.5.9]*pentatetracontane* (37) (0.51 g, 5.1%), m.p. 86—87° (from ether) [Found: C, 65.1; H, 7.65%; *M* (mass spec.), 882.439 9. $C_{48}H_{66}O_{15}$ requires C, 65.3; H, 7.55%; *M*, 882.440 2], τ ($CDCl_3$) 2.45—2.74 (15 H, m, aromatic), 4.59 (3 H, s, 3 × PhC*H*), 5.86 and 6.14 (12 H, 6 AB systems, J_{AB} 11.0 Hz, C-1, -5, -17, -21, -32, and -36 CH_2), 6.19 (6 H, s, axial C*H*$_2$·O·CH_2·CH_2·O), 6.35 and 6.41 (24 H, 2 s, 6 × O·CH_2·CH_2·O), and 6.67 (6 H, s, equatorial C*H*$_2$·O·CH_2·CH_2·O).

trans- (38) *and* cis- (39) 9,19-*Bisbenzyloxymethyl*-1,4,7,-11,14,17-*hexaoxacycloeicosane*-9,19-*diyldimethanol*.—A suspension of lithium aluminium hydride (1.0 g) in dry ether (60 ml) was added with stirring during 30 min to boron trifluoride–diethyl ether (13.00 g) at 0 to −10 °C. The dibenzylidene dispiro-derivative (27) (2.72 g) was then added as a solid during 10 min. The mixture was stirred at 0 to −10 °C for 4 h, and then under reflux for 2 h, cooled and decomposed by slow addition of 10% sulphuric acid (250 ml). The ethereal layer was separated and the aqueous layer was extracted with ether to give a crude oil (2.40 g). This oil was subjected to column chromatography on silica gel (ethyl acetate as eluant) to afford two major fractions. Fraction I was an oil, characterised * as the trans-*diol* (38) (0.86 g, 31%) [Found: *M* (mass spec.), 592.323 7. $C_{32}H_{48}O_{10}$ requires *M*, 592.324 7], τ ($CDCl_3$) 2.80br (10 H, s, aromatic),

* The configurational assignments were made on the basis of the attempted reaction of each isomer with diethylene glycol ditosylate (12) in 1,2-dimethoxyethane, with sodium hydride as base.

5.60 (4 H, s, 2 × PhCH_2), 6.20—6.60 (32 H, m, with intense s at 6.50, other CH_2), and 7.20br (2 H, s, 2 × OH). Fraction II was an oil, characterised * as the cis-*diol* (39) (0.86 g, 31%) [Found: *M* (mass spec.), 592.321 4. $C_{32}H_{48}O_{10}$ requires *M*, 592.324 7], τ ($CDCl_3$) 2.79br (10 H, s, aromatic), 5.59 (4 H, s, 2 × PhCH_2), 6.20—6.60 (32 H, m with intense s at 6.50, other CH_2), and 7.35br (2 H, s, 2 × OH).

Attempted Condensation of trans-9,19-*Bisbenzyloxymethyl*-1,4,7,11,14,17-*hexaoxacycloeicosane*-9,19-*diyldimethanol* (38) *with Diethylene Glycol Ditosylate* (12).—The *trans*-diol (38) (200 mg) was added to sodium hydride (200 mg) suspended in 1,2-dimethoxyethane (8 ml). Diethylene glycol ditosylate (12) (140 mg), dissolved in 1,2-dimethoxyethane (4 ml), was added over 1 h to the stirred mixture at 50 °C. The mixture was stirred at 50 °C for a further 20 h and then cooled. Water was added to destroy the excess of sodium hydride. Extraction with chloroform yielded an oil (161 mg), shown by t.l.c. on silica gel (ethyl acetate as eluant) to consist mainly of the diol (38) and the ditosylate (12).

1,11-*Bisbenzyloxymethyl*-3,6,9,13,16,19,22,25,28-*nonaoxabicyclo*[9.9.9]*nonacosane* (5).—The *cis*-diol (39) (0.86 g) was added to sodium hydride (0.40 g) suspended in 1,2-dimethoxyethane (25 ml). Diethylene glycol ditosylate (12) (0.60 g), dissolved in 1,2-dimethoxyethane (25 ml), was added over 4 h to the stirred mixture at 50 °C. The mixture was stirred at 50 °C for a further 20 h and then cooled. Water was added to destroy the excess of sodium hydride. Extraction with chloroform yielded an oil (1.00 g), which was subjected to column chromatography on silica gel (ether as eluant) to give the [2]*cryptand* (5) (0.28 g, 30%), m.p. 48—49° [from light petroleum (b.p. 60—80°)] [Found: C, 65.4; H, 8.1%; *M* (mass spec.), 662.368 5. $C_{36}H_{54}O_{11}$ requires C, 65.2; H, 8.2%; *M*, 662.366 6], τ ($CDCl_3$) 2.72 (10 H, s, aromatic), 5.52 (4 H, s, 2 × PhCH_2), 6.40 (36 H, s, 6 × CH_2·O·CH_2·CH_2·O), and 6.50 (4 H, s, 2 × PhCH_2·O·CH_2).

3,6,9,13,16,19,22,25,28-*Nonaoxabicyclo*[9.9.9]*nonacosane*-1,11-*diyldimethanol* (6).—The [2]cryptand (5) (70 mg) was dissolved in ethanol (30 ml) and 10% palladium–carbon (20 mg) was added. The mixture was subjected to hydrogenolysis until 2.0 mol. equiv. of hydrogen had been absorbed. The mixture was filtered and concentrated to give crystals of the *bicyclic diol* (6) (51 mg, 100%), m.p. 64—65° [from ether–light petroleum (b.p. 60—80°)] (Found: C, 54.8; H, 8.5%; $M^{+\cdot}$ + 1, 483. $C_{22}H_{42}O_{11}$ requires C, 54.8; H, 8.75%; *M*, 482), τ ($CDCl_3$) 6.36 and 6.40 (40 H, 2 s, CH_2) and 7.06br (2 H, s, 2 × OH).

1,11-*Bismethylsulphonyloxymethyl*-3,6,9,13,16,19,22,25,28-*nonaoxabicyclo*[9.9.9]*nonacosane* (7).—The bicyclic diol (6) (215 mg) was dissolved in dry pyridine (3 ml) and cooled to 0 °C. Methanesulphonyl chloride (0.5 ml) was added dropwise with stirring and the mixture was allowed to warm up overnight. Ice-cold water (15 ml) was added, and the solution was extracted with ether to give a yellow oil. Treatment of this oil with decolourising charcoal in hot methanol followed by filtration gave a colourless solution, which on concentration yielded crystals of the *bicyclic dimesylate* (7) (122 mg, 43%), m.p. 91° [Found: *M* (mass spec.), 638.227 4. $C_{24}H_{46}O_{15}S_2$ requires *M*, 638.227 8], τ ($CDCl_3$) 5.76 (4 H, s, 2 × MsO·CH_2), 6.40 (36 H, s, other CH_2), and 7.03 (6 H, s, 2 × CH_3).

Attempted Hydrogenolysis of the Dimesylate (7).—The bicyclic dimesylate (7) (122 mg) was refluxed in dry ether (10 ml) in the presence of lithium aluminium hydride (100 mg) for 72 h. The mixture was then cooled and ethyl acetate and subsequently water were added to destroy the excess of hydride. The suspension was filtered and the filtrate was concentrated to afford an oil (80 mg) which was subjected to column chromatography on silica gel (ethyl acetate as eluant); two major fractions were collected. Fraction I was an oil, 11-*methyl*-3,6,9,13,16,19,22,25,28-*nonaoxabicyclo*[9.9.9]*nonacosan*-1-*ylmethanol* (8) (10 mg, 11%) [Found: *M* (mass spec.), 466.278 9. $C_{22}H_{42}O_{10}$ requires *M*, 466.277 8], τ ($CDCl_3$) 6.24—6.50 (32 H, m, CH_2·OH, 6 × O·CH_2·CH_2·O, and HO·H_2·C·C·[CH_2]$_3$), 6.56 (6 H, s, CH_3·C·[CH_2]$_3$), 7.62br (1 H, s, OH), and 9.10 (3 H, s, CH_3). Fraction II crystallised and was characterised as the bicyclic diol (6) (40 mg, 45%).

5-*Methyl*-c-2-*phenyl*- (40) *and* 5-*Methyl*-t-2-*phenyl*-1,3-*dioxan*-r-5-*ylmethanol* (41).[22]—(*a*) A solution of 1,1,1-tris(hydroxymethyl)ethane (11) (12.0 g) in water (40 ml) and concentrated hydrochloric acid (0.6 ml) were heated to 75 °C. Benzaldehyde (10.6 g) was added and the mixture was shaken for 3 h. The white precipitate was filtered off and recrystallised from benzene–hexane to afford a crude product (12.5 g, 60%). ^{1}H N.m.r. spectroscopy indicated that this was a *ca.* 7 : 1 mixture of the *cis*- (40) and *trans*- (41) benzylidene alcohols. A portion was subjected to column chromatography on silica gel [light petroleum (b.p. 60—80°)–ethyl acetate (2 : 1 v/v) as eluant] to yield the pure isomers. Fraction I was the cis-*benzylidene alcohol* (40), m.p. 99—101° [from chloroform–light petroleum (b.p. 60—80°)] (Found: C, 69.1; H, 7.65%; $M^{+\cdot}$ − 1, 207. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.75%; *M*, 208), τ ($CDCl_3$) 2.44—2.80 (5 H, m, aromatic), 4.58 (1 H, s, PhC*H*), 5.95 and 6.37 (4 H, 2 AB systems, J_{AB} 11.0 Hz, C-4 and -6 CH_2), 6.13 (2 H, s, axial CH_2·OH), 8.07br (1 H, s, OH), and 9.23 (3 H, s, equatorial CH_3). Fraction II was the trans-*benzylidene alcohol* (41), m.p. 92—94° (from benzene–hexane) (Found: C, 69.0; H, 7.8%; $M^{+\cdot}$ − 1, 207), τ ($CDCl_3$) 2.42—2.80 (5 H, m, aromatic), 4.61 (1 H, s, PhC*H*), 6.17 (4 H, s, C-4 and -6 CH_2), 6.69 (2 H, s, equatorial CH_2·OH), 7.82 (1 H, s, OH), and 8.74 (3 H, s, axial CH_3).

(*b*) 1,1,1-Tris(hydroxymethyl)ethane (11) (10.0 g), fused powdered zinc chloride (10.0 g), and benzaldehyde (50 ml) were shaken for 12 h. Chloroform (200 ml) was added and the mixture was washed with water and then with sodium hydrogen carbonate solution. Excess of benzaldehyde was removed by evaporation under vacuum to yield crystals of the benzylidene alcohols [(40) and (41)] (14.1 g, 81%). From ^{1}H n.m.r. spectroscopy, the *cis* : *trans* ratio was estimated to be *ca.* 7 : 1.

2-*Benzyloxymethyl*-2-*methylpropane*-1,3-*diol* (42).—(*a*) A suspension of lithium aluminium hydride (2.0 g) in ether (100 ml) was added with stirring over 30 min to boron trifluoride–diethyl ether (26 ml) at 0 to −10 °C. The benzylidene alcohols [(40) and (41)] (10.4 g), dissolved in ether (100 ml), were then added dropwise with stirring during 10 min. The mixture was stirred at 0 to −10 °C for 4 h, and then under reflux for 2 h, cooled, and decomposed by slow addition of 10% sulphuric acid (500 ml). The ethereal layer was separated and the aqueous layer was extracted with ether to give an oil (8.0 g). The oil was subjected to column chromatography on deactivated alumina (320 g), initially with light petroleum (b.p. 60—80°) as eluant, gradually changing to dichloromethane and finally ether. This procedure afforded crystals of the *monobenzyl ether* (42)

* Same footnote as on page 771.

[22] R. F. Nassar and C. H. Issidorides, *J. Org. Chem.*, 1959, **24**, 1832.

(6.8 g, 65%), m.p. 48—49° [from chloroform–light petroleum (b.p. 60—80°)] [Found: C, 68.8; H, 8.85%; *M* (mass spec.), 210. $C_{12}H_{18}O_3$ requires C, 68.6; H, 8.65%; *M*, 210], τ ($CDCl_3$) 2.72 (5 H, s, aromatic), 5.52 (2 H, s, PhCH_2), 6.28—6.46 (4 H, m, 2 × CH_2·OH), 6.57 (2 H, s, CH_2·O·CH_2·Ph), 7.31br (2 H, s, 2 × OH), and 9.20 (3 H, s, CH_3).

(*b*) Sodium hydride (12.5 g) was added with stirring to dimethyl sulphoxide (250 ml), followed by 1,1,1-tris-(hydroxymethyl)ethane (11) (25.0 g). The mixture was cooled and benzyl chloride (47 ml) was added dropwise with stirring during 15 min. The mixture was then stirred at room temperature for 30 h, and, after cooling, water was added to destroy the excess of sodium hydride. Extraction with chloroform yielded a crude oil (50.1 g), which was subjected to column chromatography on alumina [ether–methanol (98 : 2 v/v) as eluant] to afford crystals of the *monobenzyl ether* (42) (3.0 g, 10%).

9-Benzyloxymethyl-9-methyl-1,4,7-trioxacyclodecane (43) *and* *9,19-Bisbenzyloxymethyl-9,19-dimethyl-1,4,7,11,14,17-hexaoxacycloeicosane* [(44) *and* (45)].—The monobenzyl ether (42) (3.0 g) and diethylene glycol ditosylate (12) (6.0 g) were added to sodium hydride (2.0 g) suspended in dimethyl sulphoxide (80 ml) and the mixture was stirred at 50 °C for 72 h. The mixture was cooled and water was added to destroy the excess of sodium hydride. Extraction with ether yielded an oil (3.3 g) which was subjected to column chromatography on silica gel [ether–light petroleum (b.p. 60—80°) (3 : 2 v/v) as eluant]. One major fraction was collected, which was shown by t.l.c. on silica gel [ether–light petroleum (b.p. 60—80°) (9 : 1 v/v)] to contain two components, R_F 0.80 and 0.75. From the nature of the compounds obtained on hydrolysis of this mixture, the product was assumed to contain compounds (43)—(45) (0.44 g), *m/e* 560 and 280, τ ($CDCl_3$) 2.74 (5 H, s, aromatic), 5.54 (2 H, s, PhCH_2), 6.30—6.82 (14 H, m, other CH_2), and 9.05 (3 H, s, CH_3).

2-Bromomethyl-2-hydroxymethylpropane-1,3-diol (55).[23]—Pentaerythritol (10) (200 g) was converted into monobromopentaerythritol (55) (145 g, 49%), m.p. 73—74° (from chloroform–ethyl acetate) (lit.,[23] 74—75°) (Found: C, 29.9; H, 5.45; Br, 40.2%. Calc. for $C_5H_{11}BrO_3$: C, 30.2; H, 5.55; Br, 40.1%) by a literature procedure.[23]

1-Oxacyclobutane-3,3-diyldimethanol (56).[24,25]—A solution of potassium hydroxide (13.0 g) in ethanol (190 ml) was added to a solution of monobromopentaerythritol (55) (39.8 g) in ethanol (160 ml). The mixture was stirred for 2 h, refluxed on a steam-bath for 5 min, cooled, filtered to remove potassium bromide, neutralised with acetic acid, and concentrated to yield a viscous residue. Fractionation through a Vigreux column yielded the oxetan-diol (56) (15.8 g, 70%), b.p. 120—130° at 0.5 mmHg (lit.,[25] 135—138° at 1—2 mmHg), τ [$(CD_3)_2CO$)] 5.63 (4 H, s, ring CH_2), 6.31 (4 H, s, 2 × CH_2·OH), and 6.16br (2 H, s, 2 × OH).

2,6,9,12-Tetraoxaspiro[3.9]tridecane (58) [26,27] *and* *2,6,9,12,-16,19,22,25-octaoxadispiro[3.9.3.9]hexacosane* (57).[27]—The oxetan-diol (56) (31.6 g) and diethylene glycol ditosylate (12) (111.0 g) were added to a suspension of sodium hydride (12.0 g) in dimethyl sulphoxide (800 ml) and the mixture was stirred at 50 °C for 72 h. The mixture was cooled and water was added to destroy the excess of sodium hydride. Extraction with chloroform yielded a crude oil (47.5 g), which was subjected to column chromatography on silica gel [ether–methanol (9 : 1 v/v) as eluant] to give two major fractions. Fraction I, an oil, was the *10-crown-3 derivative* (58) (1.6 g, 3%), *M* (mass spec.) 188, τ ($CDCl_3$) 5.67 (4 H, s, C-1 and -3 CH_2), 6.10 (4 H, s, C-5 and -13 CH_2), and 6.38 (8 H, s, other CH_2). Fraction II (crystalline) was the 20-crown-6 derivative (57) (4.6 g, 8%), m.p. 85—86° (from ether) (lit.,[27] 86—87°) [Found: C, 57.7; H, 8.3%; *M* (mass spec.), 376. Calc. for $C_{18}H_{32}O_8$: C, 57.4; H, 8.55%; *M*, 376], τ ($CDCl_3$) 5.57 (8 H, s, C-1, -3, -15, and -17 CH_2), 6.31 (8 H, s, C-5, -13, -18, and -26 CH_2), and 6.37 (16 H, s, other CH_2).

9-Methyl-1,4,7-trioxacyclodecan-9-ylmethanol (46) *and* cis- *and* trans- *9,19-Dimethyl-1,4,7,11,14,17-hexaoxacycloeicosane-9,19-diyldimethanol* [(47) *and* (48)].—The mixture of benzyl ethers (43)—(45) (0.44 g) was dissolved in methanol (50 ml) and 10% palladium–carbon (50 mg) was added. The mixture was subjected to hydrogenolysis until hydrogen absorption ceased, then filtered and concentrated to give an oil (0.33 g) which was subjected to column chromatography on silica gel [ether–methanol (95 : 5 v/v) as eluant]. Two major fractions were isolated. Fraction I was an oil (R_F 0.3 in ether on silica gel), characterised as *9-methyl-1,4,7-trioxacyclodecan-9-ylmethanol* (46) (0.10 g, 4%), *M* (mass spec.) 190, τ ($CDCl_3$) 6.28 and 6.47 (4 H, 2 AB systems, J_{AB} 11.0 Hz, C-8 and -10 CH_2), 6.32 (8 H, s, 2 × O·CH_2·CH_2·O), 6.56 (2 H, s, CH_2·OH), 7.00br (1 H, s, OH), and 9.21 (3 H, s, CH_3). Fraction II (R_F 0.1 in ether on silica gel) crystallised as a mixture of cis- and trans-*9,19-dimethyl-1,4,7,11,14,17-hexaoxacycloeicosane-9,19-diyldimethanol* [(47) and (48)] (0.22 g, 8%), m.p. 51—53° (from ether), *M* (mass spec.) 380, τ ($CDCl_3$) 6.39 and 6.48 (28 H, 2 s, CH_2), 6.90br (2 H, s, 2 × OH), and 9.17 (6 H, s, 2 × CH_3), δ_C ($CDCl_3$) 76.2 and 76.0 (2 × *cis*-CH_2·OH and 2 × *trans*-CH_2·OH), 72.2 and 71.6 (4 × O·CH_2·CH_2·O), 69.6 (C-8, -10, -18, and -20), 41.8 (C-9 and -19), and 18.5 (2 × CH_3).

cis- *and* trans-*9,19-Dimethyl-1,4,7,11,14,17-hexaoxacycloeicosane-9,19-diyldimethanol* [(47) *and* (48)].—The 20-crown-6 dispiro-derivative (57) (0.20 g) was dissolved in dry ether (25 ml) and lithium aluminium hydride (0.20 g) was added. The mixture was refluxed for 48 h and then cooled. Ethyl acetate and water were added to destroy the excess of hydride. The suspension was filtered and evaporated to yield an oil, which gave crystals of the *cis*- and *trans*-diols [(47) and (48)] (0.20 g, 99%), δ_C ($CDCl_3$) 76.2 and 76.0 (2 × *cis*-CH_2·OH and 2 × *trans*-CH_2·OH), 72.1 and 71.5 (4 × O·CH_2·CH_2·O), 69.6 (C-8, -10, -18, and -20), 41.6 (C-9 and -19), and 18.4 (2 × CH_3).

5,5′-Dimethyl-c-2,c′-2′-diphenyl-r-5,r′-5′-methylenebis(oxymethylene)di-1,3-dioxan (49).—The *cis*-benzylidene alcohol (40) (0.20 g) was added to a suspension of sodium hydride (0.20 g) in dimethyl sulphoxide (25 ml). Dichloromethane (0.3 ml) was added during 1 h and the mixture was stirred at 30 °C for 48 h. The suspension was cooled and water was added to destroy the excess of sodium hydride. Extraction with chloroform yielded an oil (0.21 g) which crystallised from ethanol to give the *acyclic methylene acetal* (49) (0.14 g, 65%), m.p. 81—82° (needles from ethanol) [Found: C, 70.1; H, 7.75%; *M* (mass spec.), 428. $C_{25}H_{32}O_6$ requires C, 70.1; H, 7.55%; *M*, 428], τ ($CDCl_3$) 2.46—2.80 (10 H, s, aromatic), 4.62 (2 H, s, 2 × PhC*H*), 5.24 (2 H, s, O·CH_2·O), 5.96 and

[23] S. Wawzonek, A. I. Matar, and C. H. Issidorides, *Org. Synth.*, Coll. Vol. IV, 1963, p. 681.
[24] F. Govaert and M. Beyaert, *Proc. Acad. Sci. Amsterdam*, 1939, **42**, 790.
[25] C. H. Issidorides and A. I. Matar, *J. Amer. Chem. Soc.*, 1955, **77**, 6382.
[26] J. W. Haskins, jun., *Du Pont Innovation*, 1974, vol. 5, no. 3, p. 10.
[27] C. G. Krespan, *J. Org. Chem.*, 1974, **39**, 2351.

6.43 (8 H, 4 AB systems, J_{AB} 11.0 Hz, C-4, -6, -4', and -6' CH_2), 6.22 (4 H, s, other CH_2), and 9.24 (6 H, s, 2 × CH_3).

5,5'-Dimethyl-2,2'-diphenyl-5,5'-methylenebis(oxymethylene)di-1,3-dioxan (49)—(51).—A mixture of the *cis*- and *trans*-benzylidene alcohols (40) and (41) (10.4 g) was added to a suspension of sodium hydride (3.5 g) in dimethyl sulphoxide (350 ml). Dichloromethane (17 ml) was added during 1 h and the mixture was stirred at 30 °C for 48 h. The mixture was then cooled and the excess of sodium hydride was destroyed with water. Extraction with chloroform yielded an oil, which was treated with decolourising charcoal in boiling ethanol to afford crystals of the acyclic methylene acetals (49)—(51) (6.2 g, 59%). ^{1}H N.m.r. spectroscopy ($CDCl_3$) indicated that this product was a mixture of three diastereoisomers.

2,8-Bishydroxymethyl-2,8-dimethyl-4,6-dioxanonane-1,9-diol (52).—A mixture of the acyclic methylene acetals (49)—(51) (1.50 g) was dissolved in ethanol (100 ml) and 10% palladium–carbon (150 mg) was added. The mixture was subjected to hydrogenolysis until 4.0 mol. equiv. of hydrogen had been absorbed, then filtered and concentrated to give crystals of the *tetraol* (52) (0.88 g, 100%), m.p. 87° [from ether–petroleum (b.p. 60—80°)] (Found: C, 52.5; H, 9.75%; $M^{+\cdot}$ + 1, 253. $C_{11}H_{24}O_6$ requires C, 52.4; H, 9.6%; *M*, 252), τ [$(CD_3)_2CO$–D_2O] 5.37 (2 H, s, O·CH_2·O), 6.30 (4 H, s, C-3 and -7 CH_2), 6.56 (8 H, s, other CH_2), and 9.15 (6 H, s, 2 × CH_3).

1,11-Dimethyl-3,6,9,13,16,19,22,24-octaoxabicyclo[9.9.5]pentacosane (53).—(*a*) The tetraol (52) (2.00 g) was added to a suspension of sodium hydride (3.00 g) in 1,2-dimethoxyethane–dimethyl sulphoxide (3 : 1 v/v; 200 ml), and diethylene glycol ditosylate (12) (6.60 g), dissolved in the same mixed solvent (160 ml), was added over 5 h to the stirred mixture at 50 °C. The mixture was stirred for a further 17 h at 50 °C and then cooled. Water was added to destroy the excess of sodium hydride. Extraction with ether yielded an oil (1.40 g), which was subjected to column chromatography on silica gel (ether as eluant) to give the *bicyclic methylene acetal* (53) (20 mg, 0.7%), m.p. 109—111°, *M* (mass spec.) 392, τ ($CDCl_3$) 5.44 (2 H, s, O·CH_2·O), 6.38 (16 H, s, 4 × O·CH_2·CH_2·O), 6.48, 6.50, and 6.56 (12 H, 3 s, other CH_2), and 9.07 (6 H, s, 2 × CH_3).

(*b*) A mixture of the *cis*- and *trans*-diols (47) and (48) (340 mg) and *N*-bromosuccinimide (320 mg) were stirred in dry dimethyl sulphoxide (30 ml) at 50 °C for 48 h. Saturated sodium hydrogen carbonate solution was added until the mixture was neutral. Extraction with chloroform yielded an oil (270 mg), which was subjected to column chromatography on silica gel (ether as eluant) to afford two major fractions. Fraction I contained crystals of the *bicyclic acetal* (53) (8 mg, 2%). The ^{1}H n.m.r. spectrum of this product in $CDCl_3$ was identical with that obtained previously for the bicyclic acetal (53). Fraction II was an oil corresponding to the *cis*- and *trans*-diols (47) and (48) (200 mg, 59%).

cis-*9,19-Dimethyl-1,4,7,11,14,17-hexaoxacycloeicosane-9,19-diyldimethanol* (47).—The bicyclic acetal (53) (8 mg) was dissolved in N-sulphuric acid (10 ml) and acetone (2 ml) and the mixture was refluxed for 45 min. The solution was neutralised with saturated sodium hydrogen carbonate solution. Extraction with chloroform yielded an oil, which was characterised as the cis-*diol* (47) (7 mg, 90%), *M* (mass spec.) 380, δ_C ($CDCl_3$) 76.2 (2 × *cis*-CH_2·OH), 72.0 and 71.6 (4 × O·CH_2·CH_2·O), 69.6 (C-8, -10, -18, and -20), 41.6 (C-9 and -19), and 18.6 (2 × CH_3).

1,11-Dimethyl-3,6,9,13,16,19,22,25,28-nonaoxabicyclo[9.9.9]nonacosane (9).—(*a*) The mixture of *cis*- and *trans*-diols (47) and (48) [obtained from reduction of the dibenzyl ethers (44) and (45)] (1.47 g) and diethylene glycol ditosylate (12) (1.60 g) were added to sodium hydride (1.50 g) suspended in 1,2-dimethoxyethane (250 ml), and the mixture was stirred for 48 h at 50 °C. It was then cooled, and water was added to destroy the excess of sodium hydride. Extraction with ether yielded an oil (1.07 g), which was subjected to column chromatography on silica gel (ether as eluant). Crystals were isolated and characterised as the *dimethyl[2]cryptand* (9) (0.15 g, 7%), m.p. 59—60° [from light petroleum (b.p. 60—80°)] [Found: C, 58.7; H, 9.25%; *M* (mass spec.), 450.283 9. $C_{22}H_{42}O_9$ requires C, 58.7; H, 9.4%; *M*, 450.282 9], τ ($CDCl_3$) 6.38 (24 H, s, 6 × O·CH_2·CH_2·O), 6.54 (12 H, s, other CH_2), and 9.09 (6 H, s, 2 × CH_3).

(*b*) The mixture of *cis*- and *trans*-diols (47) and (48) [obtained from reduction of the bisoxetan polyether (57)] (200 mg) and diethylene glycol ditosylate (12) (200 mg) were added to sodium hydride (300 mg) suspended in 1,2-dimethoxyethane (20 ml) and the mixture was stirred for 48 h at 50 °C. It was then cooled and water was added to destroy the excess of sodium hydride. Extraction with ether yielded an oil (157 mg), which was subjected to column chromatography on silica gel (ether as eluant) to give the dimethyl[2]cryptand (9) (43 mg, 17%), m.p. 59—60° [from light petroleum (b.p. 60—80°)].

RESULTS AND DISCUSSION

At the outset various synthetic routes were devised for the preparation of the [2]cryptands, (6) and (9), from pentaerythritol (10), 1,1,1-tris(hydroxymethyl)ethane (11), and diethylene glycol ditosylate (12).[20] The problem and its associated characteristics finds general expression in Figure 2. A requirement of any synthetic approach is the formation of six carbon–oxygen bonds. Exploratory experiments based on the chance that a template effect [2,4,9,28] involving the metal cation associated with the base might induce cryptand formation ruled out the ' shotgun ' approach.[9] It was also anticipated, with subsequent justification, that no advantage would be gained by resorting to the use of high dilution techniques because of the relatively slow formation of carbon–oxygen bonds (*cf.* carbon–nitrogen bond formation in the synthesis of [2]cryptands with bridgehead nitrogen atoms [5,11]). CPK models revealed that the ' in,in ' isomer of the [2]cryptands (5)—(9) is unlikely to be formed because of large steric interactions involving the bridgehead *C*-substituents. Although the ' in,out ' isomer is capable of existence, it should be readily differentiated from the ' out,out ' isomer by n.m.r. spectroscopy. In the ' out,out ' isomer, the potential of these ligands—with all nine ether oxygen atoms capable of lining the inside of an approximately spherical cavity—for binding metal cations with at least the ionic radius (1.49 Å) [5] of the rubidium cation is indicated. Furthermore, if the formation of [2]cryptates should occur, then, unlike their nitrogen analogues, they would be expected to be stable over a wide range of pH.

[28] R. N. Green, *Tetrahedron Letters*, 1972, 1793.

Finally, with regard to the [2]cryptands (6) and (9), whereas the hydroxymethyl groups in (6) are potential chemical 'handles', the methyl groups in (9) have attractions as ^{1}H n.m.r. probes.

Our first successful approach to the synthesis of the bishydroxymethyl[2]cryptand (6) employed the principle of forming an acyclic methylene acetal bridge between two appropriately substituted pentaerythritol residues. This line of attack is reminiscent of our stereospecific synthesis [17,29] of the *trans,anti,trans*- and *trans,syn,trans*-isomers of dicyclohexyl-18-crown-6 from the diastereoisomeric (±)- and *meso*-2,2′-methylenedioxydicyclohexanols [17,29-31] and involved stepwise condensation of three diethylene glycol ditosylate residues with suitably constructed diols at appropriate steps. Not only can acyclic methylene acetal bridges provide useful ^{1}H n.m.r. probes for stereochemical information,[17,29-31] but their introduction also represents, we believe, a more efficient means of bringing together two residues, each containing a non-phenolic hydroxy-group, than do base-promoted substitutions with, say, diethylene glycol ditosylate (12) (see later).

The reaction of pentaerythritol (10) with paraformaldehyde under conditions of acid catalysis afforded the dispiro-compound (13).[18] Partial acidic hydrolysis of this diacetal (13) in the presence of either N-sulphuric acid or Amberlite CG-120 resin (H^+ form) yielded a mixture of the unhydrolysed diacetal (13), the diol (14),[19] and pentaerythritol (10). A solvent extraction procedure afforded the diol (14) in 41% yield. Benzoylation with 0.8 mol. equiv. of benzoyl chloride gave the monobenzoate (15) as the major product together with a small amount of the dibenzoate (16).

Although initial attempts to prepare the dibenzoate (18) from pentaerythritol (10) *via* the intermediate monobenzoylpentaerythritol (17) were successful, the overall yield of the desired acyclic methylene acetal bridged product (18) was low. Benzoylation of pentaerythritol (10) afforded monobenzoylpentaerythritol (17) in 24% yield (based on the use of 0.3 mol. equiv. of benzoyl chloride). Treatment of the triol (17) with paraformaldehyde in the presence of concentrated sulphuric acid resulted in partial de-*O*-benzoylation and isolation of the diacetal (13) as the major product, with the dibenzoate (18) constituting only a minor component.

Attempts at acid-catalysed acetal exchange reactions between the monobenzoate (16) and dimethoxymethane, 1,1-dimethoxyethane, and 2,2-dimethoxypropane resulted in the mixed acetals (19)—(21), respectively. None of the fully exchanged acetals were formed, in keeping with previous observations [32] for acid-catalysed

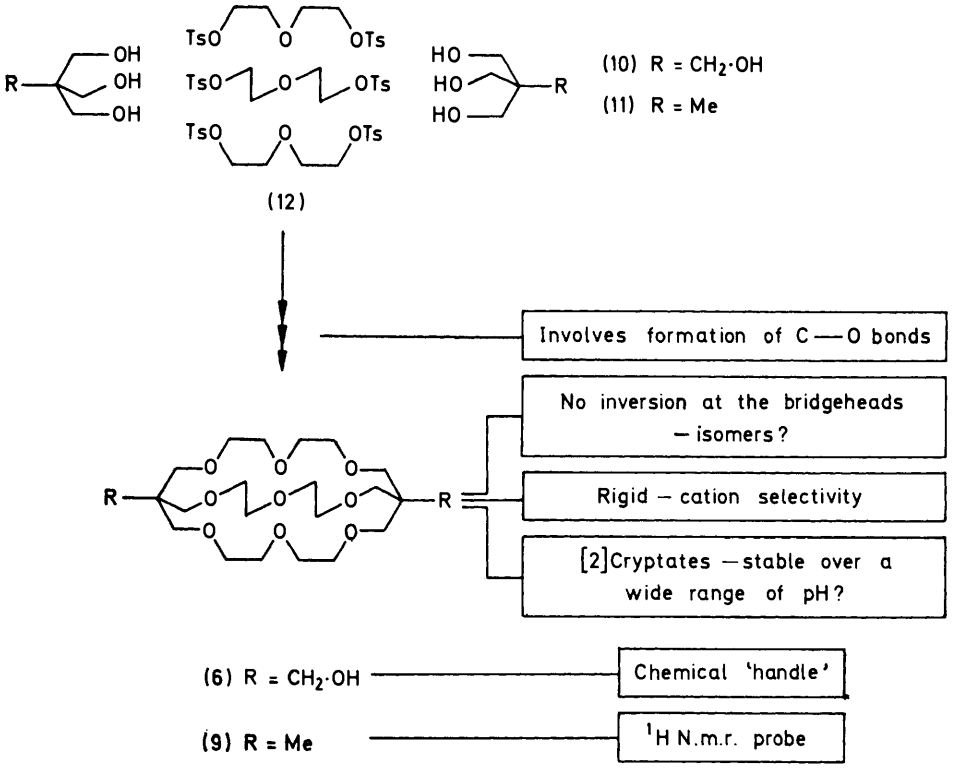
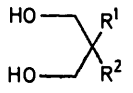


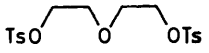
FIGURE 2 A schematic representation of the formation of the [2]cryptands (6) and (9) from pentaerythritol (10) and 1,1,1-tris(hydroxymethyl)ethane (11), respectively

[29] J. F. Stoddart and C. M. Wheatley, *J.C.S. Chem. Comm.*, 1974, 390.
[30] F. S. H. Head, *J. Chem. Soc.*, 1960, 1778.
[31] T. B. Grindley, J. F. Stoddart, and W. A. Szarek, *J. Amer. Chem. Soc.*, 1969, **91**, 4722.
[32] T. Maeda, *Bull. Chem. Soc. Japan*, 1967, **40**, 2122; T. Maeda, M. Kiyokawa, and K. Tokuyama, *ibid.*, 1969, **42**, 492.

acetal exchange reactions of dimethyl acetals with alcohols.

The dibenzoate (18) was prepared in good yield by methylenation of the monobenzoate (15) with dimethyl

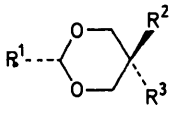




(12)

(10) $R^1 = R^2 = CH_2 \cdot OH$
(11) $R^1 = Me, R^2 = CH_2 \cdot OH$
(17) $R^1 = CH_2 \cdot OH, R^2 = CH_2 \cdot OBz$
(42) $R^1 = Me, R^2 = CH_2 \cdot O \cdot CH_2Ph$
(55) $R^1 = CH_2Br, R^2 = CH_2 \cdot OH$

(13)



(14) $R^1 = H, R^2 = R^3 = CH_2 \cdot OH$
(15) $R^1 = H, R^2 = CH_2 \cdot OBz, R^3 = CH_2 \cdot OH$
(16) $R^1 = H, R^2 = R^3 = CH_2 \cdot OBz$
(19) $R^1 = H, R^2 = CH_2 \cdot OBz, R^3 = CH_2 \cdot O \cdot CH_2 \cdot OMe$
(20) $R^1 = H, R^2 = CH_2 \cdot OBz, R^3 = CH_2 \cdot O \cdot CHMe \cdot OMe$
(21) $R^1 = H, R^2 = CH_2 \cdot OBz, R^3 = CH_2 \cdot O \cdot CMe_2 \cdot OMe$
(28) $R^1 = Ph, R^2 = R^3 = CH_2 \cdot OH$
(29) $R^1 = Ph, R^2 = R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH : CH_2$
(30) $R^1 = Ph, R^2 = CH_2 \cdot O \cdot CH_2 \cdot CH : CH_2, R^3 = CH_2OH$
(31) $R^1 = Ph, R^2 = CH_2 \cdot OH, R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH : CH_2$
(32) $R^1 = Ph, R^2 = R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
(33) $R^1 = Ph, R^2 = R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OTs$
(34) $R^1 = Ph, R^2 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH, R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OTs$
(35) $R^1 = Ph, R^2 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OTs, R^3 = CH_2 \cdot O \cdot CH_2 \cdot CH_2 \cdot OH$
(40) $R^1 = Ph, R^2 = Me, R^3 = CH_2 \cdot OH$
(41) $R^1 = Ph, R^2 = CH_2 \cdot OH, R^3 = Me$
(61) $R^1 = CHMe_2, R^2 = Me, R^3 = CH_2 \cdot OH$
(62) $R^1 = CHMe_2, R^2 = CH_2 \cdot OH, R^3 = Me$
(63) $R^1 = CHMe_2, R^2 = Me, R^3 = CH_2 \cdot OMe$
(64) $R^1 = CHMe_2, R^2 = CH_2 \cdot OMe, R^3 = Me$
(65) $R^1 = CHMe_2, R^2 = Me, R^3 = NO_2$
(66) $R^1 = CHMe_2, R^2 = NO_2, R^3 = Me$

sulphoxide in the presence of 2 mol. equiv. of *N*-bromosuccinimide.[33] When this methylenation procedure was applied to monobenzoylpentaerythritol (17), with 3 mol. equiv. of *N*-bromosuccinimide, a good yield of the monobenzoate (15) was obtained. Increasing the proportion of *N*-bromosuccinimide to 6 mol. equiv. resulted in equimolar amounts of the monobenzoate (15) and the dibenzoate (18). Practical difficulties encountered in the preparation of large quantities of monobenzoylpentaerythritol (17) render these direct approaches to the dibenzoate (18) less attractive than the indirect route already described.

De-*O*-benzoylation of the dibenzoate (18) with sodium methoxide in methanol afforded the diol (22) in high yield. The reaction between the diol (22) and diethylene glycol ditosylate (12) with sodium hydride as base in 1,2-dimethoxyethane yielded 39% of the dispiro-compound (23). In dimethyl sulphoxide with the same reagents the yield of the dispiro-compound (23) was 25%. However, yields were not optimised in either reaction. Selective acid-catalysed hydrolysis of the methylene acetal function in the largest ring of (23) afforded the diol (24) in high yield. Finally, the reaction of this diol (24) with diethylene glycol ditosylate (12) and sodium hydride in 1,2-dimethoxyethane gave a 21% yield of the 20-crown-6 derivative (25). This crown compound (25) was subsequently prepared directly in a four-molecule condensation by treatment of the diol (14) with sodium hydride and diethylene glycol ditosylate (12) in dimethyl sulphoxide. Acid-catalysed hydrolysis of the diacetal (25) afforded the tetraol (26), which, on treatment with benzaldehyde in the presence of an acid catalyst, gave the dibenzylidene dispiro-derivative (27) in 59% yield.

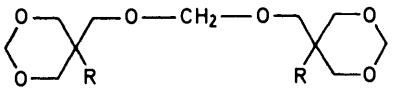
The dibenzylidene dispiro-derivative (27) was also obtained from pentaerythritol (10) in two other ways *via* the common intermediate, monobenzylidene pentaerythritol (28).[21] One approach was the four-molecule condensation of the diol (28) with diethylene glycol ditosylate;[16] the other was a two-molecule condensation of the ' half-crown ' diol (32) with its ditosylate (33).[34,35]

Pentaerythritol (10) was converted into its *O*-benzylidene derivative (28) with benzaldehyde under acid-catalysed conditions.[21] Treatment of the diol (28) with allyl bromide in benzene (potassium hydroxide as base) afforded the diallyl ether (29) in 63% yield. The diastereoisomeric monoallyl ethers, (30) and (31), were also isolated from this reaction and were characterised by ^1H n.m.r. spectroscopy (see Addendum). Ozonolysis of the diallyl ether (29) at −78 °C in methanol followed by reductive work-up with sodium borohydride in aqueous ethanolic solution at −10 °C afforded the extended diol (32) in excellent yield. Treatment of this ' half-crown ' diol (32) with tosyl chloride in pyridine at 0 °C followed by column chromatography on silica gel yielded a 19% yield of the ' half-crown ' ditosylate (33) and a *ca.* 1 : 1 mixture (from integration of a ^1H n.m.r. spectrum) of the diastereoisomeric monotosylates (34) and (35). Finally, the dibenzylidene dispiro-derivative (27) was obtained in 21% yield from the ' half-crown ' diol (32) and sodium hydride with the ' half-crown ' ditosylate (33) in dimethyl sulphoxide.

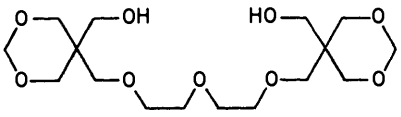
In the other approach to the dibenzylidene dispiro-derivative (27), the diol (28) was treated with diethylene glycol ditosylate (12) in dimethyl sulphoxide, with

[33] S. Hannessian, G. Yang-Chung, P. Lavallee, and A. G. Pernet, *J. Amer. Chem. Soc.*, 1972, **94**, 8929; S. Hannessian, P. Lavallée, and A. G. Pernet, *Carbohydrate Res.*, 1973, **26**, 258.
[34] G. H. Whitham, personal communication, November 1972.
[35] W. D. Curtis, D. A. Laidler, J. F. Stoddart, and G. H. Jones, *J.C.S. Chem. Comm.*, 1975, 833, 835; W. D. Curtis, R. M. King, J. F. Stoddart, and G. H. Jones, *ibid.*, 1976, 284; D. A. Laidler and J. F. Stoddart, *ibid.*, p. 979.

sodium hydride as base. Not only was the 20-crown-6 derivative (27) obtained from this mixture after column chromatography on alumina, but the 10-crown-3 (36) and 30-crown-9 (37) derivatives were also isolated in 6 and 5% yield, respectively. When this reaction was repeated under similar conditions, but with 1,2-dimethoxyethane as solvent, t.l.c. indicated that the proportions of the products were almost identical with those obtained when dimethyl sulphoxide was used.



(18) R = CH_2·OBz
(22) R = CH_2·OH



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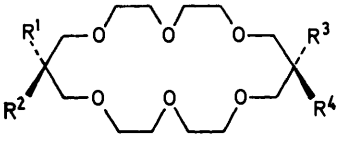
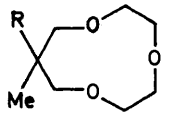
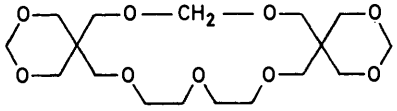


(26) $R^1 = R^2 = R^3 = R^4 = CH_2$·OH
(38) $R^1 = R^4 = CH_2$·O·CH_2Ph, $R^2 = R^3 = CH_2$·OH
(39) $R^1 = R^3 = CH_2$·O·CH_2Ph, $R^2 = R^4 = CH_2$·OH
(44) $R^1 = R^3 = CH_2$·O·CH_2Ph, $R^2 = R^4$ = Me
(45) $R^1 = R^4 = CH_2$·O·CH_2Ph, $R^2 = R^3$ = Me
(47) $R^1 = R^3 = CH_2$·OH, $R^2 = R^4$ = Me
(48) $R^1 = R^4 = CH_2$·OH, $R^2 = R^3$ = Me

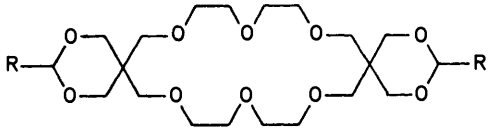


(43) R = CH_2·O·CH_2Ph
(46) R = CH_2·OH

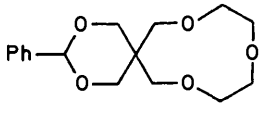
[2]cryptand (6) *via* the intermediate bisbenzyloxymethyl-[2]cryptand (5). Treatment of (27) with lithium aluminium hydride–boron trifluoride complex [36] effected partial hydrogenolysis of the benzylidene acetal rings and afforded two diastereoisomeric diols, (38) and (39), which could be separated by column chromatography on silica gel. The diol (39) underwent a further condensation with diethylene glycol ditosylate (12) in 1,2-dimethoxyethane in the presence of sodium hydride to give the



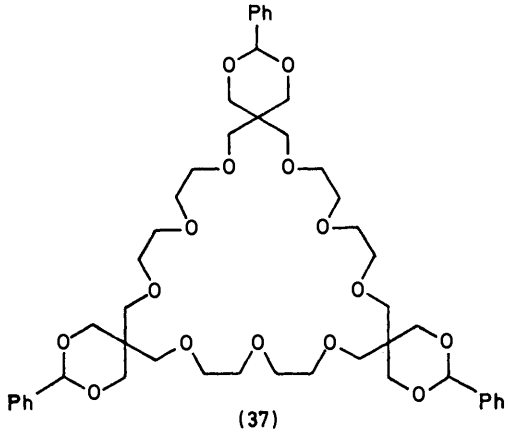
(23)



(25) R = H
(27) R = Ph



(36)



(37)

Although the 20-crown-6 derivative (27) is suspected to be a mixture of diastereoisomeric dispiro-compounds, it exhibits a sharp m.p., migrates as a homogeneous component on t.l.c., and provides ^1H and broad-band-decoupled ^{13}C n.m.r. spectra characteristic of one compound. The isomerism, which is associated with different relative orientations (*cis*- and *trans*-) of the phenyl groups attached to the acetal carbon atoms, is lost in subsequent reactions. Catalytic hydrogenolysis, for example, affords the tetraol (26) quantitatively.

The dibenzylidene dispiro-derivative (27) is a key compound in the synthesis of the bishydroxymethyl-bisbenzyloxymethyl[2]cryptand (5) in 30% yield. Under the same conditions, the diastereoisomeric diol (38) did not react. On the basis of these observations, and on the assumption (see later for the proof) that only the 'out,out' isomer of the bisbenzyloxymethyl[2]-cryptand (5) is formed, the diol (38) has been assigned the *trans*- and the diol (39) the *cis*-configuration. Catalytic hydrogenolysis of the dibenzyl ether afforded the bishydroxymethyl[2]cryptand (6) quantitatively. In the hope that it might be possible to effect hydrogenolysis

[36] A. R. Abdun-Nur and C. H. Issidorides, *J. Org. Chem.*, 1962, **27**, 67; E. L. Eliel and M. Rerick, *ibid.*, 1958, **23**, 1088.

of a suitable derivative of this diol (6) with lithium aluminium hydride, the dimesylate (7) was prepared. However, treatment of (7) with lithium aluminium hydride in ether under reflux yielded the bishydroxymethyl[2]cryptand (6) as the major product together with small amounts of the methyl-hydroxymethyl[2]-cryptand (8). This result was not unexpected since the reaction to form the dimethyl[2]cryptand (9) would involve displacement of mesylate ions by hydride ions at *two* neopentyl centres. Reactions of this type are known [37] to be unfavourable and other methods of reduction have usually been employed.[38] In the present situation, however, no other methods of reduction were explored because of the availability of only small quantities of the dimesylate (7).

More direct methods for the synthesis of the dimethyl-[2]cryptand (9) had to be developed and these will now be discussed. In fact, (9) has been synthesised by two independent routes, one from 1,1,1-tris(hydroxymethyl)-ethane (11) and the other from pentaerythritol (10). Both routes involve four-molecule condensations to give 20-crown-6 derivatives, which are then transformed into the dimethyl[2]cryptand (9).

1,1,1-Tris(hydroxymethyl)ethane (11) can be converted [22] under conditions of acid catalysis with benzaldehyde into a diastereoisomeric mixture of benzylidene acetals, (40) and (41), which were separated by column chromatography on silica gel. ^{1}H N.m.r. spectroscopy indicated that the ratio of the diastereoisomers in the crude reaction mixture was *ca.* 7 : 1 under the conditions employed. On the basis of chemical shift data (see Addendum), the major product was identified as the isomer (40) with the phenyl and hydroxymethyl groups *cis*, and the minor product as the isomer (41) with these groups *trans*. Better yields of these benzylidene derivatives, (40) and (41), were obtained by treating the triol (11) with benzaldehyde in the presence of zinc chloride as catalyst, although isolation of the product was more difficult in this case. Once again, the relative proportions of (40) and (41) were *ca.* 7 : 1 (^{1}H n.m.r. spectroscopy). This ratio probably corresponds to the proportions established under equilibration conditions (see Addendum). Although both diastereoisomers were separated and characterised, it was more convenient to use the diastereoisomeric mixture, (40) and (41), in the next step, treatment with lithium aluminium hydride–boron trifluoride [36] to give the monobenzyl ether (42). This method of preparation of the monobenzyl ether (42) proved more satisfactory than direct monobenzylation of 1,1,1-tris(hydroxymethyl)ethane (11). Treatment of the triol (11) with 2.5 mol. equiv. of benzyl chloride in dimethyl sulphoxide yielded only 10% of the ether (42). Treatment of the monobenzyl ether (42) with diethylene glycol ditosylate (12) in dimethyl sulphoxide in the presence of sodium hydride gave a mixture of the 10-crown-3 derivative (43) and the 20-crown-6 derivatives (44) and (45). This mixture was obtained from the crude product after column chromatography, without any purification with respect to any of the components. The mixture of the 10-crown-3 (43) and 20-crown-6 [(44) and (45)] derivatives was subjected to catalytic hydrogenolysis, and the product was chromatographed on silica gel to yield the pure alcohol (46) as an oil, together with crystals of the diastereoisomeric diols (47) and (48). The presence of two 20-crown-6 derivatives, (47) and (48), was indicated by the observation (Figure 3) of *seven* peaks in the broad-band decoupled ^{13}C n.m.r. spectrum. The pure *cis*-diol (47) obtained by stereospecific synthesis (see later) exhibited (Figure 3) only *six*

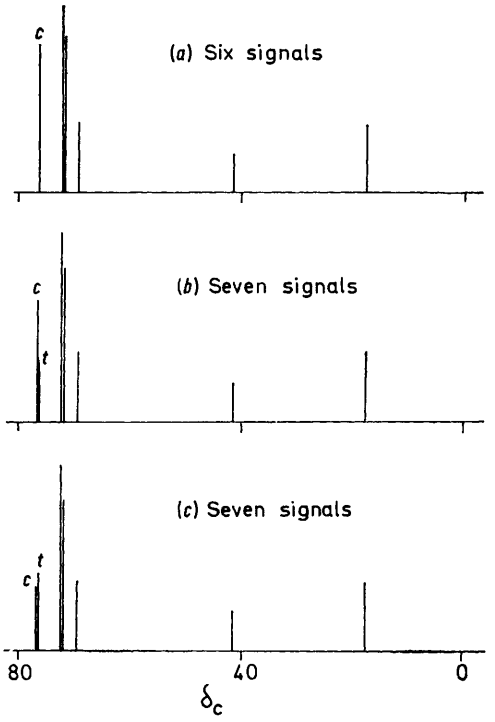


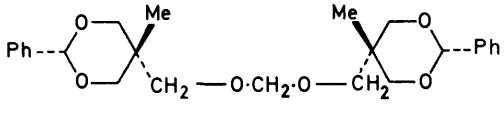
FIGURE 3 Line representations of the broad-band decoupled ^{13}C n.m.r. spectra of (*a*) the pure *cis*-diol (47) obtained stereospecifically from the bicyclic methylene acetal (53), (*b*) the *cis*- and *trans*-diols (47) and (48) obtained on catalytic hydrogenolysis of the dibenzyl ethers (44) and (45), and (*c*) the *cis*- and *trans*-diols (47) and (48) obtained on reductive ring opening of the bisoxetan (57)

peaks in the broad-band decoupled ^{13}C n.m.r. spectrum. The product from the hydrogenolysis of the dibenzyl ethers, (44) and (45), gave *two* peaks at low field (δ 76.2 and 76.0) in the ratio *ca.* 2 : 1, whereas the pure *cis*-diol (47) gave only *one* peak at low field (δ 76.2). Accordingly, the *cis* : *trans* ratio is *ca.* 2 : 1 in the mixture of the diastereoisomeric diols (47) and (48). We could not separate them, not even by high-pressure liquid chromatography. Thus, the final step in the synthesis had to be carried out on the mixture. Nonetheless, the reaction of the diastereoisomeric diols, (47) and (48), with diethylene glycol ditosylate (12) and sodium hydride in 1,2-dimethoxyethane yielded 7% of the dimethyl[2]cryptand (9).

[37] L. J. Dolby and D. R. Rosencrantz, *J. Org. Chem.*, 1963, **28**, 1888.

[38] S. Masamume, P. A. Rossy, and G. S. Bates, *J. Amer. Chem. Soc.*, 1973, **95**, 6452.

The *cis*-diol (47) was synthesised stereospecifically from the benzylidene acetal (40) as well as from the diastereoisomeric mixture of benzylidene acetals (40) and (41). The pure isomer (40) was converted into the acyclic methylene acetal (49) in good yield with sodium hydride and dichloromethane in dimethyl sulphoxide.[39] The diastereoisomeric mixture of benzylidene acetals, (40) and (41), reacted under similar conditions to give a diastereoisomeric mixture of acyclic methylene acetals (49)—(51). ^{1}H N.m.r. spectroscopy indicated that all



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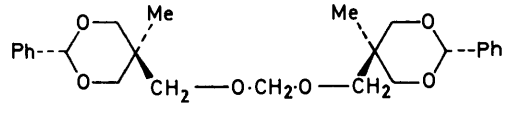

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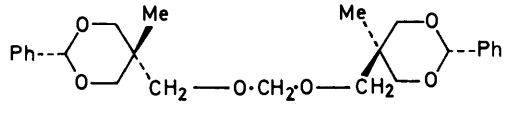
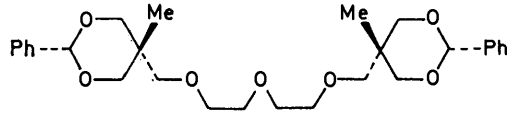


(51)



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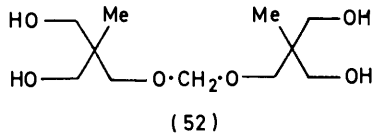

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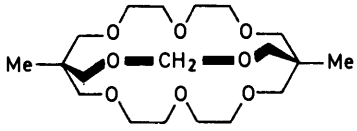

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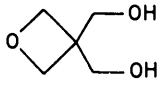

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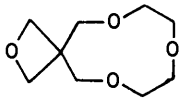

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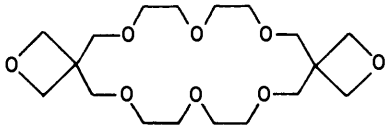


(57)

three isomers were present. Catalytic hydrogenolysis of both the diastereoisomeric mixture (49)—(51) and the pure isomer (49) afforded the tetraol (52) in quantitative yield. In the mixed solvent 1,2-dimethoxyethane–dimethyl sulphoxide, and in the presence of sodium hydride, the tetraol (52) reacted with diethylene glycol ditosylate (12) to afford the bicyclic methylene acetal (53) in 1% yield after column chromatography on silica gel. The bicyclic methylene acetal (53) was also prepared, in 2% yield, by methylenation of the diastereoisomeric diols, (47) and (48), with dimethyl sulphoxide in the presence of 2 mol. equiv. of *N*-bromosuccinimide.[33] CPK models revealed that the methylene acetal bridge can only span the face of the 20-crown-6 macrocyclic portion in the bicyclic methylene acetal (53), and cannot thread itself through the middle of the 20-crown-6 macrocyclic portion. Consequently, acid-catalysed hydrolysis of the bicyclic methylene acetal (53) yielded the *cis*-diol (47) stereospecifically. It had been hoped that the bicyclic methylene acetal (53) would be a useful intermediate from which the dimethyl[2]cryptand (9) could be synthesised, but this hope was not justified by the low yields associated with both routes to (53).

Attempts to prepare the oxybis(ethyleneoxy)-bridged analogue (54) of the acyclic methylene acetal (49) by base-promoted condensation of the benzylidene acetal (40) with diethylene glycol ditosylate (12) were unsuccessful.

Finally, the dimethyl[2]cryptand (9) was also synthesised from pentaerythritol (10). Treatment of the tetraol (10) with hydrobromic acid afforded [23] monobromopentaerythritol (55), which gave [24,25] the oxetan-diol (56) on treatment with ethanolic potassium hydroxide. The reaction of the oxetan-diol (56) with sodium hydride and diethylene glycol ditosylate (12) in dimethyl sulphoxide afforded the dispiro-20-crown-6 derivative (57) [26,27] and the spiro-10-crown-3 derivative (58) [27] in 8 and 3% yield, respectively. Reductive ring opening of the oxetan rings of the dispiro-compound (57) with lithium aluminium hydride yielded the diastereoisomeric diols,

[39] W. Bonthrone and J. W. Cornforth, *J. Chem. Soc.* (*C*), 1969, 1202.

(47) and (48). The presence of two diols was indicated by the observation (Figure 3) of *seven* peaks in the broad-band decoupled ^{13}C n.m.r. spectrum. The relative intensities of the low field signals at δ 76.2 and 76.0 indicated that the *cis* : *trans* ratio was *ca.* 1 : 1. The dimethyl[2]cryptand (9) was obtained in 17% yield after column chromatography on silica gel of the crude product from the reaction of the diols, (47) and (48), with sodium hydride and diethylene glycol ditosylate (12) in 1,2-dimethoxyethane.

Topology of the [2]*Cryptands* (5)—(9).—The ^1H n.m.r. spectra of the [2]cryptands (5), (7), and (9) are characteristic of compounds in which the bridgehead carbon atoms have the opposite spatial sense. The fact that isochronous signals are observed for constitutionally related protons in all these [2]cryptands is consistent with a topology where the two ends of the molecules are related by symmetry. Since the 'in,in' isomers cannot be formed, it is concluded that all three [2]-cryptands exist as their 'out,out' isomers. On account of their synthetic derivations, the other two [2]cryptands [(6) and (8)] must also exist as the 'out,out' isomers. In the case of the bishydroxymethyl[2]cryptand (6) this conclusion is vindicated by its *X*-ray crystal structure.[40]

Complex Formation between [2]*Cryptands with Bridgehead Carbon Atoms and Metal Cations.*—Preliminary experiments indicated that the [2]cryptands (5), (6), and (9) solubilised lithium, sodium, potassium, rubidium, and caesium *ortho*-nitrophenolates in chloroform. In addition, the 20-crown-6 derivatives (25)—(27), (38), (39), [(47) and (48)], and (57) all solubilize potassium *ortho*-nitrophenolate in chloroform. Potassium permanganate is sparingly soluble in benzene (*cf.* ref. 41) containing the [2]cryptands (5) and (9). These [2]cryptands [(5) and (9)] also solubilise both sodium and potassium iodides, and potassium thiocyanate, in chloroform.

The ^1H n.m.r. chemical shifts of the [2]cryptands (5) and (9) undergo appreciable changes on addition * of molar proportions of alkali metal salts. In the spectrum of the bisbenzyloxymethyl[2]cryptand (5) in deuteriochloroform, the benzylic methylene protons, the methylene protons within the bicyclic system, and the benzyloxymethylene protons attached to the bridgehead carbon atoms gave rise to three singlets of relative intensities 1 : 9 : 1 at τ 5.52, 6.40, and 6.50, respectively. When 0.5 mol. equiv. of sodium iodide was added,* the respective protons resonated at τ 5.55, 6.37, and 6.65 and the high-field signal had broadened considerably. When a total of 1.0 mol. equiv. of sodium iodide had been added,† the respective protons resonated at τ 5.57, 6.34, and 6.78 and the high-field signal was once again sharp. These changes in chemical shift may be attributed to complex formation, and the line broadening exhibited by the high-field signal could arise from slow exchange of sodium ions between the complex and the cryptand when these two species are present in about the same concentrations (*i.e.* the situation corresponding to the addition of 0.5 mol. equiv. of sodium iodide). The averaging of the chemical shifts as compared with those observed for the fully complexed and the free ligand supports the idea of a dynamic complex. Decreasing the temperature of the solution containing approximately equimolar amounts of the complex and the cryptand down to −50 °C resulted in broadening of all three singlets. The temperature-dependent behaviour was more striking in the case of the potassium iodide complex. When 0.5 mol. equiv. of potassium iodide was added * to a solution of the bisbenzyloxymethyl[2]cryptand (5) in deuteriochloroform, three singlets were observed at τ 5.54, 6.37, and 6.66 (1 : 9 : 1). On cooling the solution to −50° C all three signals were broadened considerably and the low-field singlet eventually gave rise to two singlets separated by 5.2 Hz ($\nu_A - \nu_B$). Although the temperature dependence of the high-field signal was less easy to discern on account of the neighbouring high intensity signal at τ *ca.* 6.37, it was evident nonetheless. The general equation for complex ([2]CM^+) formation by a [2]cryptand ([2]C) and solvated (*n* = number of such solvent molecules) monovalent metal cations (M^+) is given [5] by equation (i), where k_a is the association rate

$$[2]C + M^+, n \text{ solvent} \underset{k_d}{\overset{k_a}{\rightleftharpoons}} [2]CM^+ + n \text{ solvent} \quad \text{(i)}$$

constant and k_d is the dissociation rate constant. In the case of the benzyloxymethyl[2]cryptand (5) the temperature-dependent behaviour of the low field signal described above can be associated with exchange of potassium ions between the complex and the cryptand where the rate-limiting step is the dissociation of the complex, *i.e.* $k_d < k_a$ (*cf.* refs. 5 and 42). A rate constant ($k_c = 12\ s^{-1}$), which was equated with k_d, was calculated at the coalescence temperature (T_c −45° C) by using the approximate expression [43] $k_c = \pi\ (\nu_A - \nu_B)/2^{\frac{1}{2}}$ for exchange of nuclei between two equally populated sites, A and B, with no mutual coupling. A value for the free energy of dissociation, $\Delta G_d^{\ddagger}$, of 12.1 ±0.3 kcal mol^{-1} was obtained from the Eyring equation in the usual manner.

^1H N.m.r. spectroscopy also indicates [16] that the dimethyl[2]cryptand (9) and potassium thiocyanate form a strong complex in solution in deuteriochloroform–carbon disulphide (2 : 1). At room temperature, a sharp singlet was observed at τ 9.12 for the methyl protons in the free ligand. On addition * of an equimolar amount of potassium thiocyanate, a new well-resolved singlet was observed at τ 9.23 for the methyl protons. When 0.5 mol. equiv. of potassium thiocyanate was added * to the free ligand, such that in solution there existed equimolar amounts of the free ligand and the complexed ligand, the

* In order to solubilise these salts, a few drops of tetradeuteriomethanol were added to the deuteriochloroform solution of the [2]cryptand. Both solvents were then evaporated off under reduced pressure and the non-crystalline residues were found to be completely soluble in deuteriochloroform (*cf.* ref. 2).

[40] N. A. Bailey and S. Chidlow, personal communication.
[41] D. J. Sam and H. E. Simmons, *J. Amer. Chem. Soc.*, 1972, **94**, 4024.
[42] J. M. Lehn, J. P. Sauvage, and B. Dietrich, *ibid.*, 1970, **92**, 2916.
[43] H. S. Gutowsky and C. H. Hohn, *J. Chem. Phys.*, 1956, **25**, 1228.

methyl protons resonated as a well resolved singlet at τ 9.18. This averaged chemical shift suggested that the potassium ion was undergoing fast exchange between free and complexed ligands at room temperature. This belief was confirmed by cooling the solution to −60 °C and observing (Figure 4) two sharp singlets at τ 9.05 and

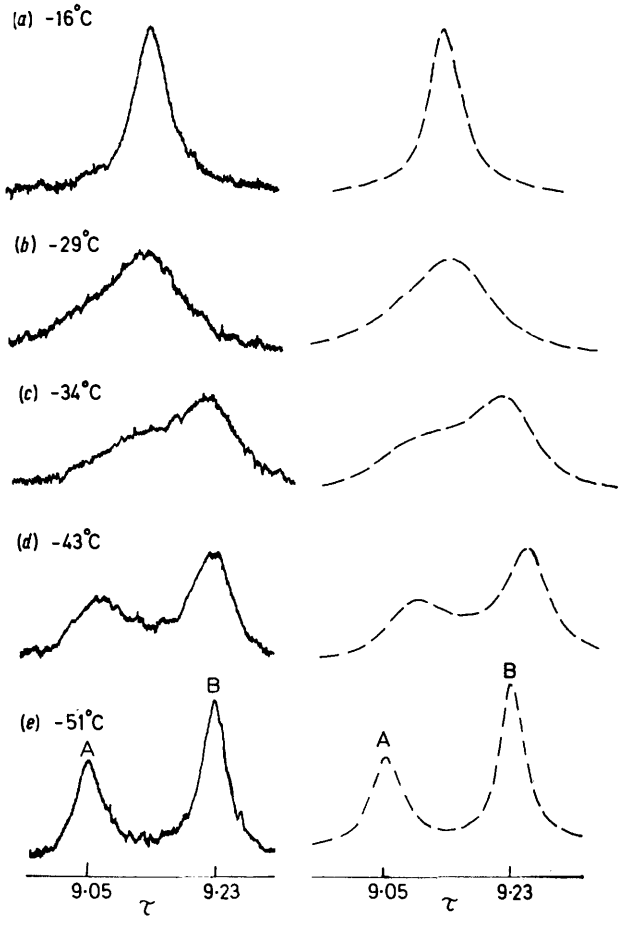


FIGURE 4 Observed (full line) and computed (broken line) spectra for the exchange of K^+ ions between the complex and the dimethyl[2]cryptand (9) at various temperatures; $p_A = p_B = 0.5$ at all temperatures

9.23 for the methyl protons in the free and complexed ligands, respectively. On raising the temperature, the two singlets were broadened and eventually coalesced to give one singlet at −27 °C. Rate constants (k_d) were obtained at several different temperatures between −16 and −51 °C by carrying out line-shape analyses (Figure 4) with a computer program [44] suitable for simulating n.m.r. line shapes resulting from exchange of nuclei between two sites with no mutual coupling. The corresponding free energies of activation, obtained from the Eyring equation in the usual manner, are listed in Table 1 and give rise to an average value for $\Delta G_d^{\ddagger}$ of 12.3 ±0.3 kcal mol^{-1}.

Thus it appears that the [2]cryptands (5) and (9) form strong complexes with potassium ions in aprotic solvents. Whether or not complexation is associated with cryptate formation is uncertain. However, the complexes are not nearly as strong as those formed between metal cations and the [2]cryptand (3) with bridgehead nitrogen atoms, where the free energy of activation for the dissociation process is higher than 12 kcal mol^{-1} in all cases, even in water as solvent.[5,42] This conclusion is borne out by the

TABLE 1

Rate constants (k_d) and free energies of activation ($\Delta G_d^{\ddagger}$) for exchange of potassium ions between the free and complexed ligands derived when 0.5 mol. equiv. of potassium thiocyanate is added to the dimethyl[2]-cryptand (9)

T/°C	k_d	$\Delta G_d^{\ddagger}$/kcal mol^{-1}
−16	346	12.0
−29	55.0	12.2
−34	31.1	12.3
−43	16.2	12.2
−51	1.78	12.6

formation of relatively weak complexes by the [2]cryptands (5) and (9) in methanol. The concentration stability constants for the formation of 1 : 1 complexes of (5) and (9) with Na^+, K^+, Rb^+, and Cs^+ in methanolic solution were measured potentiometrically with ion-selective electrodes. The stability constants, which are defined by the equilibrium constants ($k_a/k_d = K'$ in l mol^{-1}) for complex formation according to equation (i), were obtained essentially by the method described by Frensdorff,[45] assuming only 1 : 1 complex formation.[17] Values of the stability constants (log K') for the complexation of alkali metal cations with the [2]cryptands (5), (6), and (9), the diastereoisomeric diols (47) and (48), and the bisoxetan-20-crown-6 (57) are recorded in Table 2. Since Krespan [27] has reported stability constants for the complexation of K^+ ions with the bisoxetan-20-crown-6 (57) and the oxetan-19-crown-6 (59), these values are also included in Table 2. Finally, values [45] of log K' for 18-crown-6 (60) are listed in Table 2 since this compound serves as a ' standard ' for comparison.

A number of features and trends in Table 2 deserve special mention. (i) The stabilities of the complexes between the 20-crown-6 derivatives [(47) and (48)] and (57) and Na^+, K^+, Rb^+, and Cs^+ are a factor of 10^3—10^4 lower (in K') than the values for 18-crown-6 (60). This result was not unexpected since Pedersen [46] has noted that the introduction of $O{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}O$ units in place of $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$ units into crown ethers substantially decreases their complexing ability. Both 20-crown-6 derivatives [(47) and (48)] and (57) contain *two* $O{\cdot}CH_2{\cdot}CR_2{\cdot}CH_2{\cdot}O$ units. (ii) Comparison of the stability constants associated with the K^+ ion complexes of the bisoxetan-20-crown-6 (57) [log K' = 1.8 (1.67 from ref. 27)], the oxetan-19-crown-6 (59) (log K' = 3.81),[27] and 18-crown-6 (60) [log K' = 6.08 (6.10 from ref. 45)] leads to the conclusion that the introduction of each additional

[44] I. O. Sutherland, *Ann. Reports N.M.R. Spectroscopy*, 1971, **4**, 71.

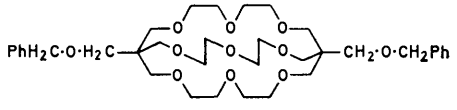
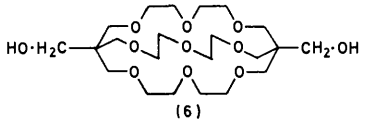
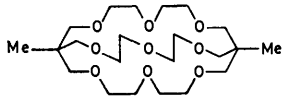
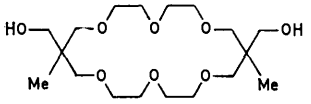
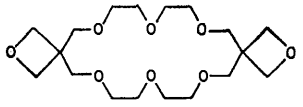
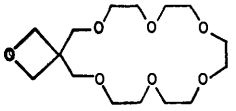
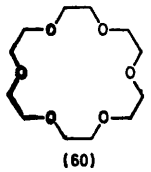
[45] H. K. Frensdorff, *J. Amer. Chem. Soc.*, 1971, **93**, 600.

[46] C. J. Pedersen, *J. Amer. Chem. Soc.*, 1970, **90**, 391.

carbon atom reduces K' by a factor of about 10^2. (iii) Although it might be expected that the presence of unfavourable $O{\cdot}CH_2{\cdot}CR_2{\cdot}CH_2{\cdot}O$ units in the 20-crown-6 derivatives [(47) and (48)] and (57) would be more than compensated for by the inclusion of another bridge to reduces the stabilities of all the alkali metal cationic complexes. (iv) The [2]cryptands (5) and (9) display the same modest selectivities as the 20-crown-6 derivatives [(47) and (48)] and (57), *i.e.* $K^+ > Rb^+ > Cs^+ > Na^+$ ions.

TABLE 2

Stability constants for 1 : 1 ligand–cation complexes based on K' in l mol^{-1}

Ligand	log K'^a (T/°C)			
	Na^+	K^+	Rb^+	Cs^+
 (5)	1.0 [b](23)	2.4(20)	2.1(22)	1.4 [b](19)
 (6)	<1.2(22)			1.4 [b](19)
 (9)	1.1 [b](22)	2.2(24)	1.9(24)	1.6(22)
 (47), (48)	1.6(23)	2.6(25)	2.3(25)	1.9(26)
 (57)	<0.8(22)	1.8(23) 1.65 [c](25)	1.4(25)	0.8(25)
 (59)		3.81 [c](25)		
 (60)	4.34(22) 4.32 [d](25)	6.08(25) 6.10 [d](25)	5.35(25)	4.70(22) 4.62 [d](25)

[a] log $K' \pm 0.1$ unless otherwise stated for the chlorides. [b] Error of ± 0.2. [c] Ref. 27. [d] Ref. 45.

form [2]cryptands, the results in Table 2 for the [2]-cryptands (5), (6), and (9) do not corroborate this optimism. For example, comparison of the stability constants obtained for the 20-crown-6 derivatives [(47) and (48)] and the dimethyl[2]cryptand (9) indicates, in fact, that the introduction of a third bridge marginally

The data in Table 2 highlight features concerned with the constitutional design of [2]cryptands which must be avoided if they are to stand a chance of forming strong complexes with metal cations. CPK models indicate that when the conformations of the bridges in the [2]-cryptands (5), (6), and (9) are arranged such that all nine

bicyclic oxygen atoms are oriented inwards, as would be expected during complex formation, the cavities are ellipsoidal rather than spherical in shape. Since complexes between metal cations and cryptands undoubtedly receive their stabilisation from electrostatic interactions [4] between the oxygen dipoles and the metal cations, a symmetrical cavity [5] with all the dipoles 'focusing' towards a central point is expected to provide the ideal environment in which a metal cation can be complexed. In the case of [1]cryptands, these requirements are fulfilled by 18-crown-6 (60). The dipoles can be drawn schematically such that they are all oriented towards the centre of the cavity (see Figure 5). The crystal structure [47] of the potassium thiocyanate complex of 18-crown-6 (60) is in accord with this structural representation of

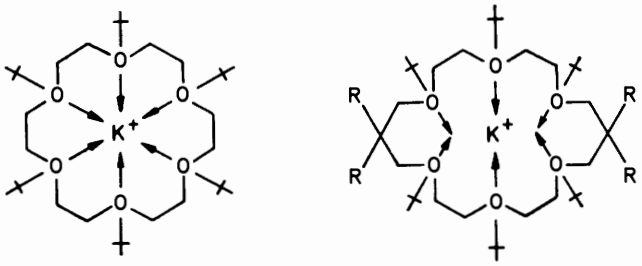
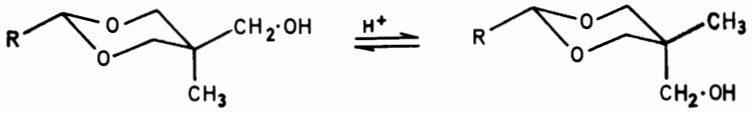


FIGURE 5 Schematic representations of the orientations of the oxygen dipoles in K^+ ion complexes of 18-crown-6 (60) and a 20-crown-6 derivative

the complex. In the 20-crown-6 derivatives [(47) and (48)] and (57), the constitutional symmetry of the [1]-cryptand is perturbed by the introduction of two $O{\cdot}CH_2{\cdot}CR_2{\cdot}CH_2{\cdot}O$ units as shown in Figure 5. The consequence of this is that the oxygen atoms are no longer in a circular array but rather an oval one in which the oxygen dipoles are prevented from intersecting at the centre, which could, in principle, be occupied by a metal cation. Hence 20-crown-6 derivatives are not expected to provide such a suitable complexing site for K^+ ions as 18-crown-6 derivatives. In the case of [2]cryptands, the same feature is evident in comparing the nitrogen bridgehead derivative (3) with the carbon bridgehead derivatives (5), (6), and (9). A spherical cavity contrasts with an ellipsoidal cavity in this comparison. Other features could contribute to the relative instability of the complexes formed by the [2]cryptands (5), (6), and (9) as compared with the extremely stable nitrogen bridgehead [2]cryptates. There is torsional strain associated with *gauche*-conformations in the $O{\cdot}CH_2{\cdot}CR_2{\cdot}CH_2{\cdot}O$ units which may help to destabilise complexes. There is also the relative rigidity of the carbon bridgehead derivatives which could mitigate against strong complex formation. The synthesis of macrobicyclic polyethers with bridgehead carbon atoms based on the 18-crown-6 constitution is now essential in order to achieve a better understanding of the relative importance of the structural features which contribute towards stabilisation and destabilisation of their metal cationic complexes.

ADDENDUM

Chemical Shifts of the 5-C-*Methyl and* 5-C-*Methylene Protons in the* ^1H *N.m.r. Spectra of Some* 5,5-*Disubstituted* 2-*Phenyl*-1,3-*dioxan Fragments; Stereochemical Consequences and Configurational Assignments.*—In 2-substituted 1,3-dioxans, the configurational equilibrium (see Figure 6) involves chair conformations as by far the major contributors and lies very much on the side of the equatorial conformation.[48-50] The conformational free energy for a phenyl group [49-53] on C-2 is 3.1 kcal mol^{-1}. The most favourable conformations for the 5,5-disubstituted 2-phenyl-1,3-dioxan derivatives (27)—(31), (33), (36), (37), (40), (41), and (49) (see Table 3 for formulae) are therefore expected to be chair conformations in which the 2-phenyl group occupies an equatorial position.



(41) R = Ph
(62) R = Pr^i

(40) R = Ph
(61) R = Pr^i

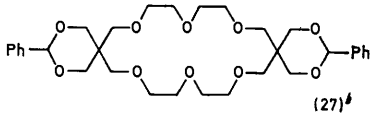
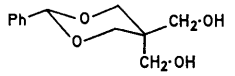
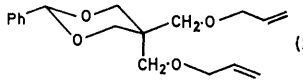
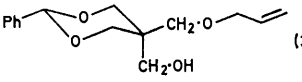
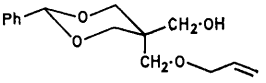
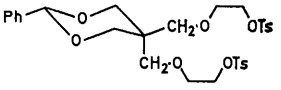
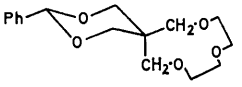
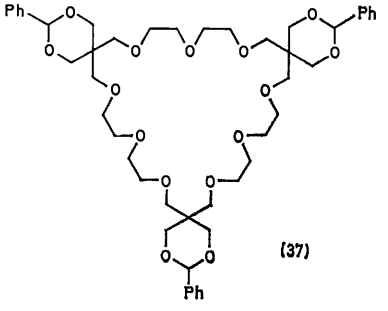
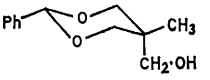
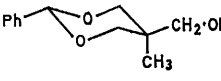
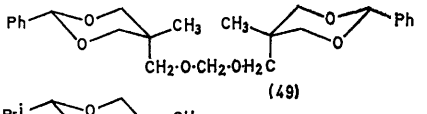
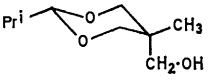
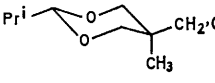
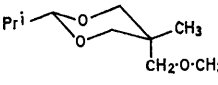
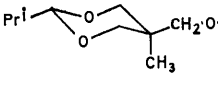
FIGURE 6 The acid-catalysed equilibration of the *cis*- and *trans*-isomers of the 2-phenyl-[(40) and (41)] and the 2-isopropyl- [(61) and (62)] 5-hydroxymethyl-5-methyl-1,3-dioxans

Configurations were assigned [53] to *cis*- (61) and *trans*- (62) 5-hydroxymethyl-2-isopropyl- and *cis*- (63) and *trans*- (64) 2-isopropyl-5-methoxymethyl-5-methyl-1,3-dioxans on the basis of chemical correlations with *cis*- (65) and *trans*- (66) 2-isopropyl-5-methyl-5-nitro-1,3-dioxans where configurational assignments were made on the basis of dipole moment measurements. The isopropyl group, with a conformational free energy [49-53] of 4.15 kcal mol^{-1}, is an even better biasing group [49,50] than the phenyl group at C-2 on a 1,3-dioxan ring. Table 3 shows that, in contrast with the situation in methylcyclohexanes, in 2-substituted 1,3-dioxans equatorial methyl groups on C-5 resonate in ^1H n.m.r. spectra at higher fields (0.5—0.6 p.p.m.) than axial methyl groups on C-5. The methylene protons of hydroxymethyl and methoxymethyl groups at C-5 also absorb at higher field if the group is equatorial than if it is axial.[52,53] By extrapolating these observations, chemical shifts were ascribed (see Table 3) to the appropriate equatorial and axial methylene protons in

[47] P. Seiler, M. Dobler, and J. Dunitz, *Acta Cryst.*, 1974, **B30**, 2744.
[48] E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 393.
[49] E. L. Eliel, *Pure Appl. Chem.*, 1971, **25**, 509.
[50] E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1972, **11**, 739.
[51] F. W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, 1970, **92**, 3050.
[52] E. L. Eliel and H. D. Banks, *J. Amer. Chem. Soc.*, 1972, **94**, 171.
[53] E. L. Eliel and R. M. Enanoza, *J. Amer. Chem. Soc.*, 1972, **94**, 8072.

TABLE 3

^{1}H N.m.r. chemical shift data [a] for 5,5-disubstituted 2-phenyl-1,3-dioxan derivatives

Compound	Chemical shift (τ)	
	Equatorial group	Axial group
 (27) [b]	6.66 (2 × CH_2O)	6.18 (2 × CH_2O)
 (28) [c]	6.50 (CH_2·OH)	5.97 (CH_2·OH)
 (29)	6.73 (CH_2O)	6.24 (CH_2O)
 (30)	6.78 (CH_2·O) 6.10 (O·CH_2·CH=CH_2)	6.06 (CH_2·OH)
 (31)	6.53 (CH_2·OH)	6.12 (CH_2O) 5.92 (O·CH_2·CH=CH_2)
 (33)	6.80 (CH_2O)	6.31 (CH_2O)
 (36)	6.65 (CH_2O)	5.96 (CH_2O)
 (37)	6.67 (3 × CH_2O)	6.19 (3 × CH_2O)
 (40)	9.23 (CH_3)	6.13 (CH_2·OH)
 (41)	6.69 (CH_2OH)	8.74 (CH_3)
 (49)	9.24 (2 × CH_3)	6.22 (2 × CH_2O)
 (61) [d]	9.27 (CH_3)	6.25 (CH_2·OH)
 (62) [d]	6.34 (CH_2·OH)	8.82 (CH_3)
 (63) [d]	9.29 (CH_3)	6.51 (CH_2O) 6.64 (CH_2·O·CH_3)
 (64) [d]	7.00 (CH_2O) 6.75 (CH_2·O·CH_3)	8.82 (CH_3)

[a] In $CDCl_3$ unless otherwise stated. [b] As a mixture of diastereoisomers. [c] In $CDCl_3$–$(CD_3)_2CO$. [d] Data from ref. 53.

(27)—(31), (33), (36), and (37). The configurations of the monoallyl ethers (30) and (31) were deduced initially from the fact that the singlets for the methylene protons of the hydroxymethyl groups resonated at τ 6.06 (axial CH_2·OH) and 6.53 (equatorial CH_2·OH), respectively. These configurational assignments were confirmed by the fact that both these signals were broad, on account of some coupling to the hydroxy-protons in deuteriochloroform solution. Also, the oxymethylene protons of the allyloxymethyl groups of (30) and (31) resonate at τ 6.10 (equatorial CH_2·O·CH_2·CH=CH_2) and 5.92 (axial CH_2·O·CH_2·CH=CH_2), respectively. This observation is in accord with the relative chemical shifts of the methoxy-protons in *cis*- (63) and *trans*- (64) 2-isopropyl-5-methoxymethyl-5-methyl-1,3-dioxans (see Table 3). Configurational assignments were made to the 5-hydroxymethyl-5-methyl-2-phenyl-1,3-dioxans (40) and (41) on the basis of the relative chemical shifts of the singlets for the methyl protons and the singlets for the methylene protons of the hydroxymethyl groups in the two isomers. The configuration of the bridged methylene acetal (49) is known since it was synthesised directly from the *cis*-isomer (40). The chemical shift data for both the methyl protons and the methylene protons of the hydroxymethyl groups are in accord with the configurational assignment.

Eliel and Enanoza [53] have shown that under conditions of acid-catalysed equilibration, the *cis*-isomer (61) with the hydroxymethyl group axial predominates over the *trans*-isomer (62) where the hydroxymethyl group is equatorial. The free energy difference for the equilibrium (62) $\rightleftharpoons$ (61) shown in Figure 6 varies between -0.62 and -1.03 kcal mol^{-1} at 25 °C, depending on the nature of the solvent. The *trans* : *cis* ratio [*i.e.* (41) : (40)] of the benzylidene acetals was found by ^{1}H n.m.r. spectroscopy (integration of the methyl proton signals) to be *ca.* 1 : 7 from both the acid-catalysed benzylidenation at 75 °C and the room temperature benzylidenation in the presence of zinc chloride. Thus, it was assumed that equilibrium had been attained in each reaction and that the free energy difference for the equilibrium (41) $\rightleftharpoons$ (40) shown in Figure 6 is *ca.* -1.25 kcal mol^{-1}.

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