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STRUCTURE AND CONFORMATION OF HETEROCYCLES—VIII[1]

PERIPHERALLY SUBSTITUTED 1,4,5,8-TETRAOXADECALINS

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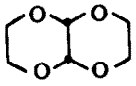
Abstract—The synthesis of the title compounds was examined and a mechanistic scheme was put forward, which accounts for their formation along with higher substituted by-products and with the corresponding bidioxolan-2-yl isomers.

Chemical correlation between two members of the series, *trans* - 2, 3 - dicarbomethoxy- and *trans* - 2, 3 - dimethyl - tetraoxadecalin, was performed.

All stereoisomeric 2, 3 - dicarbomethoxy - 1, 4, 5, 8 - tetraoxadecalins were prepared and chemically equilibrated. The free energy differences at 65° between them were thus obtained. This led to an evaluation of the conformational free energy of the carbomethoxy group in dioxanes, $\Delta G^{\circ}_{CO_2Me} = 0{\cdot}38$ kcal/mole.

Dynamic conformational analysis by variable temperature NMR measurements on *cis* - 2, 3 - dicarbomethoxy - *anti* - *cis* - 1, 4, 5, 8 - tetraoxadecalin led to a ring inversion barrier of $\Delta G^{\ddagger}_{193} = 10{\cdot}0$ kcal/mole.

Recent years have brought an upsurge in the study of conformational analysis of heterocyclic systems.[3] In this framework, the ketalization products of 1, 2 - diketones have been accorded special attention.[4-13] Some of the reasons for this notoriety may be the ease of obtainment of these systems by a variety of methods[4] and their practical, albeit unexplained, use in industrial processes.[14] It is, however, certain that these systems exhibit properties which can be traced back to a peculiar interplay of C—O bond dipoles leading to enhanced "anomeric" or as lately defined "rabbit-ear" or "gauche" effects.[3,15,16,10]



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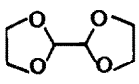


2

Early investigations including synthetic studies[4,5] and attempts for structural assignments[5] were followed by X-ray diffraction,[7,10b] PMR studies,[8-10a] mass spectrometric investigations[11-13] and finally DNMR[10] studies.

Strangely, notwithstanding the large amount of available synthetic and structural data, there are several aspects that are not known or not quite well understood in this field. These include: the complete elusiveness of the *trans* - 1, 4, 5, 8 - tetraoxadecalin system; the formation of the isomeric bidioxolan - 2 - yl compounds in reactions that do not involve the parent 1, 2 - dicarbonyl moiety; conformational energy differences between substituents; relative stabilities of epimeric compounds; the influence of the C—O bond lengths and angles as well as that of the anomeric effect on the conformation *in solution*. This paper presents some of the results obtained in attempts to tackle some of these problems.

The reaction of 2, 3 - dichloro - 1, 4 - dioxane **3** with ethylene glycol yields, besides the expected tetraoxadecalin **1**, the isomeric bidioxolan-2-yl **2**;[5] as does also, understandably, the acid-catalyzed condensation of ethylene glycol with glyoxal or the latter's hydrate ester derivatives.[4] Analogously, 2,3-dichloro - 1, 4 - dioxane with ethanedithiol gives exclusively bidithiolan - 2 - yl[18] *instead* of the expected 1, 4 - dithio - 5, 8 - dioxadecalin. The intermediacy of glyoxal has often been invoked for such reactions,[18,6] but with no firm evidence to support it. In fact, glyoxal does not form to any significant extent from dichlorodioxane under non-hydrolytic conditions (see also Ref 6c). Moreover, in no case was the *trans* isomer of **1** obtained.

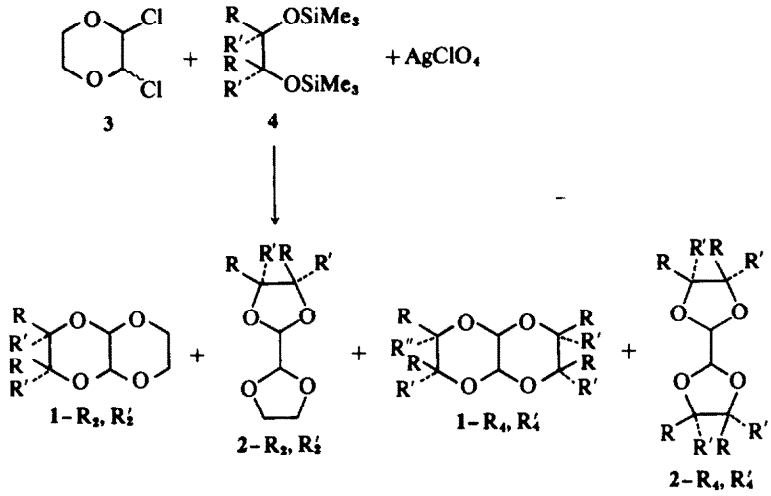
We decided to look more carefully into the conditions of the available synthetic procedures and to devise some new ones, with the idea in mind that a kinetically controlled process might provide a single, even if less stable, product.

To this end we prepared *bis*-trimethylsilyl ethers **4** of various ethyleneglycols and treated them with dichlorodioxane. Unfortunately, no reaction took place unless silver perchlorate was added.[19] The expected tetraoxadecalins were formed in modest yields, but in every analysable case, only the *cis* isomer could be identified. Interestingly, however, in addition to the displacement of the chlorines of dichlorodioxane by the ethylene glycol moiety, an

incorporation of the latter into the dioxane ring was observed. The proof for this assertion was provided *inter alia* by mass spectrometric measurements of the various products. Thus the reaction of 2, 3 - dichloro - 1, 4 - dioxane with the bis-trimethylsilyl ether of ethylene glycol-d_4 gave a mixture of *cis* - 1, 4, 5, 8 - tetraoxadecalin - d_8, -d_4 and -d_0. In some cases such as the reaction of **3** with the bis - trimethylsilyl ethers of *threo* and *erythro* butan - 2,3 - diol or pinacol, bidioxolan - 2 - yl products were also isolated, in the latter case, as the major product. The question whether or how much of the expected 2, 3- and/or 2, 3, 6, 7 - substituted 1, 4, 5, 8 - tetraoxadecalins and/or the isomeric substituted bidioxolan - 2 - yls will form apparently cannot be answered *a priori*. In any case, products of type **1** and sometimes **2** are usually formed in varying yields.

The above scheme also provides the explanation for the formation of 1, 4, 5, 8 - tetraazadecalin from ethylenediamine with dichlorodioxane[6b] as well as the decomposition of the latter in hot sulphuric acid to give 4, 4', 5, 5' - tetrachlorobidioxolan - 2 - yl.[20]

An alternative synthetic method was tried by treating *cis* - or *trans* - 2, 3 - dichlorodioxane with the lithium salt of ethylene glycol in the latter as solvent. Only *cis* - tetraoxadecalin in moderate yields was isolated; the yield improved with increasing concentration of the reagents and *no* bidioxolan - 2 - yl was detected. This result is, in fact, analogous to the results of Faas and Hilgert[17] who also obtained tetraoxadecalin as a sole product in the reaction of dichlorodioxane and ethylene glycol *in pyridine*. We repeated the latter procedure but with tetradeuterated ethylene glycol at room temperature and obtained only tetraoxadecalin-d_4.



A similar situation prevails in the reactions of **3** with ethylene glycols themselves. Specifically, the incorporation into the dioxane ring occurs to a comparable extent whereas bidioxolanyl formation occurs only at higher temperatures and not at all at room temperature.

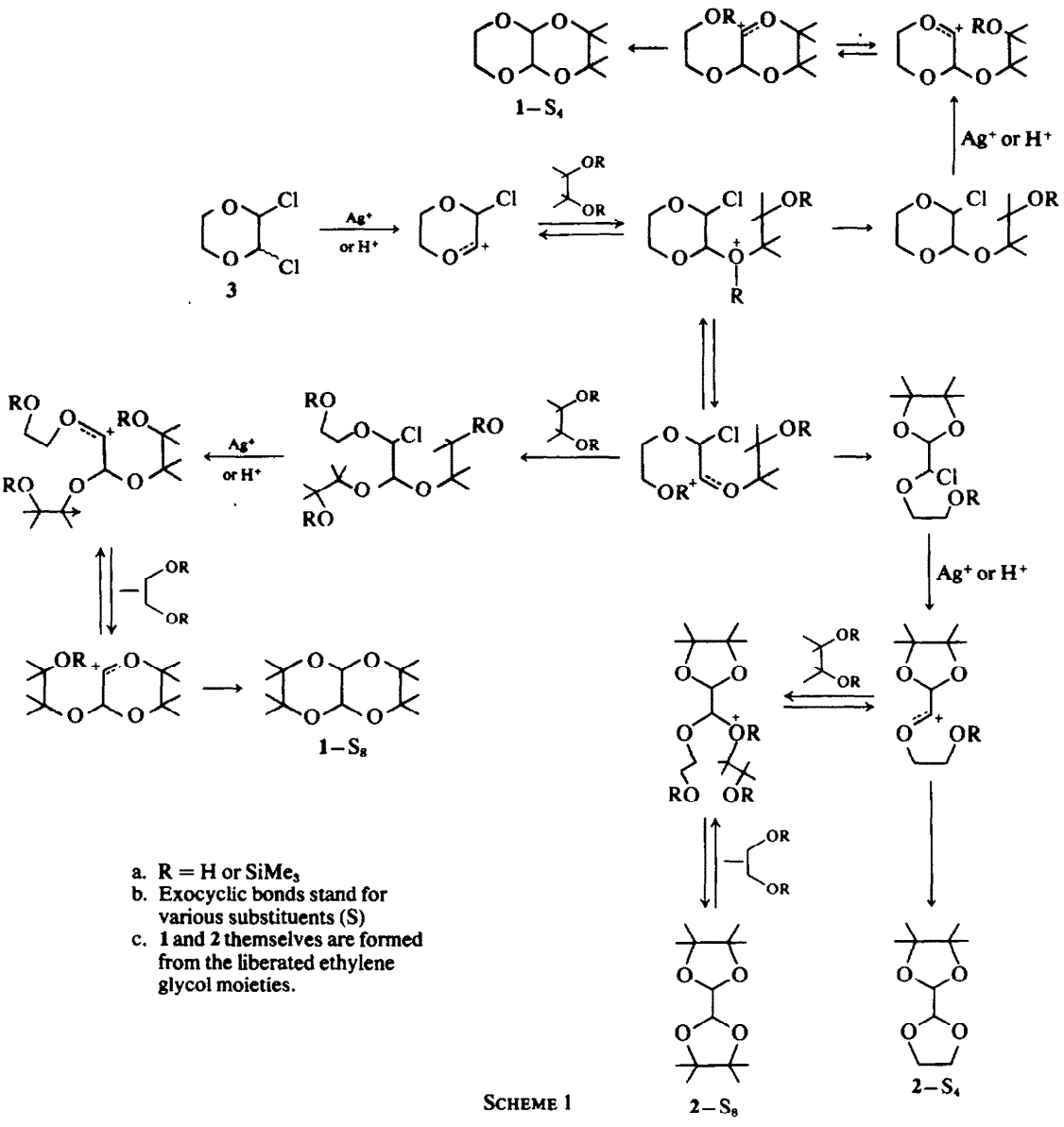
Following these observations we suggest a mechanism (Scheme 1) which accounts for this behavior, without invoking the actual formation of glyoxal. Understandably, the α-chloroether **3** readily reacts under these conditions via carbonium ions, or rather oxonium ions, to give a variety of intermediates in reversible processes. Apparently, the relative stabilities of the intermediates determine the outcome of the reaction. Furthermore, attempts to isomerize **1** to **2** or vice versa in refluxing benzene with acid catalysis were unsuccessful. Hence, under these conditions only the steps linking two cations are reversible in a practical sense. Also, it should be mentioned that in a control experiment, none of the products were isolated from dichlorodioxane and silver perchlorate alone.

It appears that in the two processes mentioned in this paragraph the basic media suppress the opening of the ring after initial displacement of the chlorine in mild conditions. However, pinacol or butane - 2, 3 - diol require higher activation energy to react and then rearranged products are obtained.

Finally, stereospecific synthesis of *trans* - 1, 4, 5, 8 - tetraoxadecalin was attempted following a method used by Sweet and Brown[21] for the preparation of *trans* - 1, 4, 5 - trioxadecalin (Scheme 2). A mixture of (21:79) *cis* - and *trans* - dioxane - 2, 3 - diol **5** (R = H) was condensed with 2-chloroethanol to give 2 - hydroxy - 3 - β - chloroethoxydioxane **6** which was cyclized by sodium hydride in glyme. A 75% yield of *cis* - 1, 4, 5, 8 - tetraoxadecalin **1** was obtained!

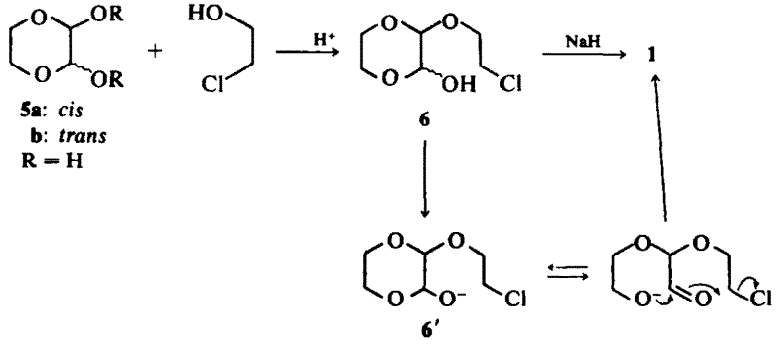
A tentative explanation for this result would be the ring opening and reclosure of the hemiketal-anion **6'** in a thermodynamically preferred *cis* geometry.

Our interest in the stereochemical and conformational features of the tetraoxadecalin system has



a. R = H or $SiMe_3$
b. Exocyclic bonds stand for various substituents (S)
c. 1 and 2 themselves are formed from the liberated ethylene glycol moieties.

SCHEME 1



SCHEME 2

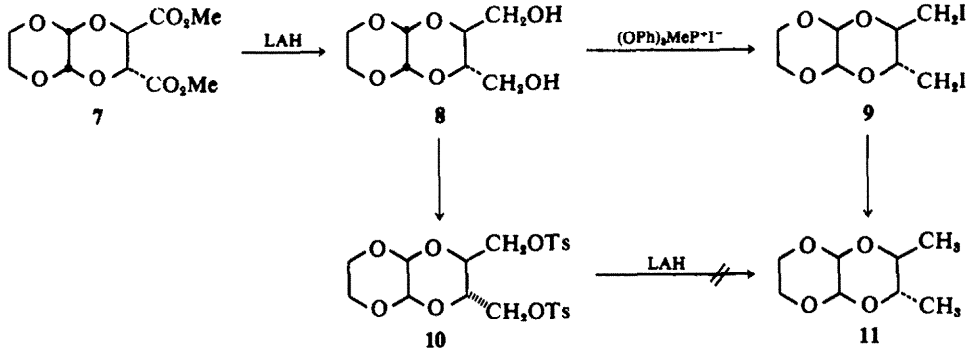
led us to investigate more closely some peripherally substituted derivatives. Thus we turned our attention to the 2, 3 - diesters. The *trans*-dicarboethoxy derivative had been synthesized[5] and its NMR spectrum analyzed[6a] to confirm its configuration. We had several objectives in mind: chemical correlation between different derivatives in order to probe into and to prove structural and configurational assignments; relative stabilities of isomers; conformational analysis, both static and dynamic.

To this end we decided to work with the dimethyl esters. Thus, (−) - *trans* - 2, 3 - dicarbomethoxy - 1, 4, 5, 8 - tetraoxacedalin **7** was readily obtained by treating 2, 3 - dichlorodioxane with D(+) - dimethyltartarate.[5,6a] In a sequence of reactions (Scheme 3), **7** was reduced by lithium aluminum hydride to the diol **8**, followed by tosylation to **10** which proved to be inert to LAH reduction. Therefore **8** was converted by $(OPh)_3CH_3P^+I^-$ into the diiodide **9** which upon Ra-Ni hydrogenolysis yielded (−) - *trans* - dimethyl - *cis* - 1, 4, 5, 8 - tetraoxadecalin **11**. The latter was chemically identical with a racemate obtained from the reaction of d, 1 - butanediol - *bis* - trimethylsilylether **4** ($R_1 = R_2' = Me$, $R_2 = R_1' = H$) with dichlorodioxane. An unequivocal structural and configurational correlation was thus achieved.

cis - 2, 3 - Dicarbomethoxy - *cis* - 1, 4, 5, 8 - tetraoxadecalin was unknown and we went about its synthesis by direct condensation of dichlorodioxane with *meso*-dimethyl tartarate as well as with the latter's trimethylsilyl ether and silver perchlorate. A single isomer was obtained and thermodynamic control having been assumed, the relatively stable *cis* - *anti* - *cis* configuration **12** was assigned. To prove the structural assignment, chemical equilibration was undertaken using sodium methoxide in methanol and starting from either optically active **7** or **12**. In both cases an identical inactive equilibrium mixture was achieved but the latter contained also a third and minor component which was assigned the less stable configuration *cis* - 2, 3 - dicarbomethoxy - *syn* - *cis* - 1, 4, 5, 8 - tetraoxadecalin **13**. The equilibrium process and composition is described in Scheme 4. In practice, the composition was proven by GLPC, whereby **12**, **13** and **7** left the column in this order.

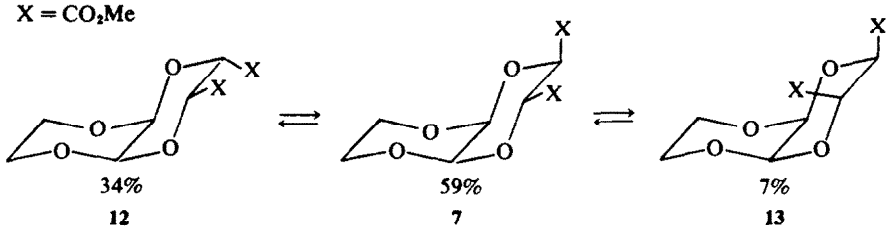
While **12** and **7** were readily identified using the authentic compounds, **13** was not amenable to isolation by preparative GLPC due to the fact that its retention time was close to that of the major component, **7**. A way out of this impasse was found by a GC-MS analysis of the mixture: in the analytical mode a very clean GLPC separation of all three components was achieved and the mass spectra proved the isomeric structures.

From the equilibrium constants $K_{12/7} = 0{\cdot}57$ and $K_{13/7} = 0{\cdot}11$, the free energy differences at 65°C were evaluated: $\Delta G^\circ_{12\to7} = -0{\cdot}38$ kcal/mole and $\Delta G^\circ_{13\to7} = -1{\cdot}48$ kcal/mole and from this: $\Delta G^\circ_{13\to12} = -1{\cdot}10$ kcal/mole. The first value, 0·38, constitutes, in fact, a good estimate for the conformational energy of the carbomethoxy group in 1, 4 - dioxanes and is considerably lower than the corresponding



7 8 9 10 11

SCHEME 3



12 7 13

SCHEME 4

parameter in cyclohexane (1·27 kcal/mole).[22] Since only one 1,3-diaxial interaction operates in the 1,4 - dioxane ring, pure steric arguments would predict this trend, albeit not to such an extent. It is possible that electrostatic interactions of the polar carbomethoxy group with the ring oxygens further contribute to the lowering of the ΔG° value.

Turning now to dynamic conformational analysis, both esters **7** and **12** were subjected to variable temperature PMR spectroscopy.[23] The *trans*-diester **7** exhibited an unchanged PMR spectrum between −80° and +150°, as expected, since the diequatorial conformation should strongly prevail in this temperature range over the diaxial one. Not so with the axial-equatorial *cis* - *anti* - *cis* isomer **12** where the interconversion of axial–equatorial carbomethoxy groups due to rapid ring inversion can be slowed down and eventually frozen out. Thus the carbomethoxy singlet at τ 6·35 broadens on cooling and eventually splits with $\Delta\nu$ = 6·0 Hz at −93° and up (60 MHz). Coalescence occurs at $T_c = -80°$ and the rate constant of exchange k_c is evaluated using the approximation for two non-interacting sites $k_c = \pi\Delta\nu/\sqrt{2}$.[23,24] Using the absolute reaction rate (Eyring) expression

$$k_c = \frac{\kappa f}{h} T_c \exp(-\Delta G^*/RT_c)$$

one obtains $\Delta G^*_{193} = 10{\cdot}0$ kcal/mole. Attempts to supplement this result by a scrutiny of the two interacting α-protons failed since their signals overlap with that of the angular protons.

The value of the inversion barrier of **14** is virtually the same as that of dioxane itself (9·7 kcal/mole)[25] and lower than that of the angularly disubstituted analogs 9, 10 - bis (bromomethyl) - 1, 4, 5, 8 - tetraoxadecalin (11·2 kcal/mole)[10] and 2, 5, 7, 10, 11, 14 - hexaoxapropellane (12·6 kcal/mole).[1a] This trend is interpreted to be due to a rise in ground state energy because of the axial carbomethoxy group. Furthermore, the absence of angular substituents evidently contributes to lowering the transition state energy on the potential surface for inversion (the reader might find it helpful to consult the discussion and energy profiles in Ref 10*b* for better understanding of this point). In fact, one must not exclude the possibility that twist-boat conformations are appreciably populated in solution.

The above-found inversion barrier for **12** is, moreover, conspicuously lower than the barriers in decalin and its substituted derivatives.[26] Again,[10] we tend to attribute this behavior to the lower torsional barriers of the C—O bonds coupled with a decrease in dipole–dipole interaction (i.e. anomeric or rabbit-ear effect[3]) in the transition state.

*A detailed mass spectrometric study will be published elsewhere. In this paper it is mainly used as one of the criteria for distinguishing between the tetraoxadecalin and the bidioxolanyl structures.[12]

EXPERIMENTAL

Procedures and equipment. M.ps were determined in capillaries using a calibrated thermometer. Reaction products were analyzed and, if necessary, isolated by GLPC (XE − 60 8%) and characterized by IR, PMR and mass spectrometry.* IR spectra were measured on a Perkin Elmer 337 spectrophotometer. Routine PMR spectra were taken at 60 MHz on $CDCl_3$ solns using a Jeol C-60-HL spectrometer. Mass spectra* were recorded on a Hitachi–Perkin Elmer RMU-6 mass spectrometer, courtesy of Bar Ilan University, Ramat Gan.

Condensations of glyoxal with α-diols.[4,27] 0·1 Mole glyoxal hydrate, 0·2 mole diol and a catalytic amount of *p*-toluenesulfonic acid in benzene were refluxed with continuous water removal using a Dean-Stark head. After no more water separated, the mixture was washed with K_2CO_3 soln and water, dried, and the solvent was removed.

Ethylene glycol[4,5] yielded a mixture of **1** and **2**. The 1-d_8 and 2-d_8 derivatives were secured by using ethylene glycol-d_4 (Merck) in the process.

Butane - 2, 3 - diol gave a complex mixture of stereoisomers of the two structures which were not separated.

Pinacol gave bi(tetramethyldioxolan - 2 - yl)[27] **2**-Me_8 accompanied by pinacolon.

Condensation of trans - 2, 3 - *dichlorodioxane*[28] **3** *with α-diols or their derivatives*

Ethylene glycol. The direct reaction of **3** with ethylene glycol in refluxing benzene gave, as previously described,[4,5b] a mixture of **1** and **2**, similar to that obtained by the former method. At room temp and neat, however, only **1** was obtained. When the same reaction was carried out with ethylene glycol-d_4 (0·8 g, 0·95 g **3**, stirring for 20 h at room temp; work up as usual; yield: 110 mg, m.p. 130°) a mixture of 1, 4, 5, 8 - tetraoxadecalin - d_0, -d_4 and -d_8 (3:21:4) was obtained. This was determined by mass spectrometry from the relative abundances of the respective molecular ions *m/e* 146, 150, 154.*

The reaction of ethylene glycol with **3** in pyridine[17] is known to yield only **1**. The same reaction but using ethylene glycol-d_4 afforded 1, 4, 5, 8 - tetraoxadecalin - d_4 (2, 2, 3, 3) with only traces of the d_8-derivative.

Similar results were obtained from the reaction of **3** with the lithium salt of ethylene glycol (or its d_4-derivative). 21 ml of a 25·25% soln of n-butyllithium in benzene was added with cooling and stirring to 130 ml dry ethylene glycol. The resulting solid redissolved readily. A THF soln of 10 g **3** was added dropwise and the soln was stirred overnight. The mixture was poured into ice-water and thoroughly extracted with ether. 200 mg of **1**, m.p. 134°, were obtained. The yield improved as the excess of ethylene glycol was decreased. When the reaction was attempted by taking equimolar quantities of the salt and **3** in aprotic solvents (pyridine, diglyme, hexamethylphosphoramide) only starting material **3** was recovered.

The following procedures involving ethylene glycol *bis*-trimethylsilyl ether were used for all* substituted TMS-derivatives described below.

Silylation procedure. To 12·4 g ethylene glycol (0·2 mole) and 32 g pyridine (0·4 mole) in 250 ml benzene (all dry!) were added dropwise 44 g trimethylchlorosilane (0·4 mole). The reaction was stirred at 60° overnight. The solid pyridinium hydrochloride was filtered off and the filtrate was evaporated. The residue was distilled at 83–84°/80 torr, yield: 90% **4** (R = R′ = H); PMR: τ 9·91

(18 H, s), 6·33 (4 H, s); mass spectrum (70 eV) *m/e* (rel. abundance): 206 (<1), 191 (23), 147 (100), 103 (10), 73 (100). Calc. for $C_8H_{22}O_2Si_2$: C, 46·56; H, 10·75. (Found: C, 46·59; H, 10·99).

The d_4 derivative was similarly obtained starting with ethylene glycol-d_4.

Reaction of bis-trimethylsilyl ethers with 2, 3 - *dichlorodioxane* 3. To a soln of 0·1 mole *trans* - 2, 3 - dichlorodioxane (*cis* or *trans*) and 0·1 mole ethylene glycol *bis*-trimethylsilyl ether in 200 ml dry benzene were added dropwise (safety screen!) and with stirring and ice-cooling, a benzene soln of 0·2 mole silver perchlorate. (The latter was obtained by suspending the commercial monohydrate in benzene and azeotropically removing the water whereby a homogeneous soln formed). After 2 h of stirring at room temp the AgCl was filtered off and the filtrate was washed with 10% K_2CO_3aq and water. After drying and removal of the solvent 510 mg of **1**, m.p. 133–134°, was obtained. No reaction occurred in the absence of silver perchlorate even during reflux.

When ethylene glycol-d_4 *bis*-trimethylsilyl ether was used, a mixture of **1**-d_0, -d_4 and -d_8 (4 : 14 : 5) was obtained.

Similar results were obtained when *cis* - 2, 3 - dichlorodioxane was used in all above described reactions.

1 was found in varying amounts in the analogous reactions of the TMS-derivatives of all glycols, described below.

The bis-trimethylsilyl ethers **4** of the following α-diols were prepared and treated analogously.

(1) d, 1, - *Butane* - 2, 3 - *diol** **4** (1 − R = 2 − R′ = Me; 1 − R′ = 2 − R = H); yield: 89%; b.p. 85°/68 torr; PMR τ 9·92 (18 H, s), 8·94 (6 H, d, J = 7 Hz), 4·56 (2 H, m); mass spectrum (70 eV) *m/e* (rel. abundance) 234 (<1), 147 (54), 117 (100), 73 (100). (Found: C, 51·38; H, 11·02. Calc. for $C_{10}H_{26}O_2Si_2$: C, 51·23; H, 11·18%).

The reaction of this TMS-derivative with **3** and silver perchlorate gave a complex mixture of type **1** and **2** compounds which was resolved by GLPC. One of the major components turned out to be identical in retention time, IR, PMR and mass spectra with an authentic sample of *trans* - 2, 3 - dimethyl - *cis* - 1, 4, 5, 8 - tetraoxadecalin (see below).

(2) meso - *Butane* - 2, 3 - *diol** **4** (R = Me, R′ = H); yield: 92%; b.p. 80–81°/40 torr; PMR: τ 9·87 (18 H, s), 8·86 (6 H, d, J = 5 Hz), 4·43 (2 H, m); mass spectrum (70 eV) *m/e* (rel. abundance) 234 (<1), 147 (39), 117 (100), 73 (100). (Found: C, 51·20; H, 11·19. Calc. for $C_10H_26O_2Si_2$: C, 51·23; H, 11·18%).

The reaction of this TMS-derivative with **3** and silver perchlorate gave a complex mixture of type **1** and **2** compounds, as shown by GLPC and mass spectrometry.

(3) *Pinacol*, **4** (R = R′ = Me); yield: 80%; b.p. 64–65°/2 torr; PMR: 9·85 (18 H, s), 8·85 (12 H, s); mass spectrum (70 eV) *m/e* (rel. abundance) 247 (10), 147 (35), 131 (100), 73 (70).

The reaction of this TMS-derivative with **3** and silver perchlorate gave as the major product bi (4, 4, 5, 5 - tetramethyldioxolan - 2 - yl) **2**-Me_8,[27] m.p. 89°, yield 15%, accompanied by minute amounts of three byproducts, two of which were tentatively assigned the isomeric structures 4, 4, 5, 5-tetramethylbidioxolan-2-yl **2**-Me_4 and 2, 2, 3, 3-tetramethyl - 1, 4, 5, 8 - tetraoxadecalin, on the basis of their PMR and mass spectra.

*Commercial butane - 2, 3 - diol was resolved via the 2, 2, 4, 5 - tetramethyldioxolanes, *cf*, A. C. Neish and F. S. MacDonald, *Canad. J. Chem.* **25B**, 70 (1947).

(4) *Dimethyl* - D(+) - *tartarate* **4** (1 − R = 2 − R′ = CO_2Me, 1 − R′ = 2 − R = H); yield: 95%; b.p. 101°/12 torr; PMR: τ 9·91 (18 H, s), 6·68 (6 H, s), 5·29 (2 H, s); mass spectrum (70 eV) *m/e* (rel. abundance) 322 (<1), 307 (25), 234 (27), 147 (100), 73 (95). (Found: C, 44·52; H, 8·14. Calc. for $C_{12}H_{26}O_6Si_2$: C, 44·70; H, 8·13%).

The reaction of this TMS-derivative with **3** and silver perchlorate gave a crude product from which, on addition of MeOH, the main product crystallized out and was shown to be **7**, yield 40%, m.p. 76–77°, $[\alpha]_D$ −64·9° and identical in all spectral properties with the compound obtained by direct condensation of dimethyl - D(+) - tartarate with **3**.[5a, 6a]

(5) *Dimethyl* - meso - *tartarate* **4** (R = CO_2Me, R′ = H); yield: 95%; b.p. 75–77°/0·15 torr; PMR: τ 9·85 (18 H, s), 6·59 (6 H, s), 5·27 (2 H, s); mass spectrum (70 eV) *m/e* (rel. abundance) 322 (<1), 307 (10), 161 (20), 147 (71), 73 (100). (Found: C, 44·90; H, 8·05. Calc. for $C_{12}H_{26}O_6Si_2$: C, 44·70; H, 8·13%).

The reaction of this TMS-derivative with **3** and silver perchlorate gave a 4% yield of **12** crystallized from MeOH, m.p. 93–94°; PMR; τ 6·24 (6 H, s), 6·19 (4 H, m, $w_{1/2}$ = 48 Hz)[12], 5·02 (4 H, s coincidental); mass spectrum (70 eV) *m/e* (rel. abundance) 262 (6, M^+). (Found: C, 46·01; H, 5·50. Calc. for $C_{10}H_{14}O_8$: C, 45·80; H, 5·38%).

12 was also obtained in low yields by direct condensation of dimethyl - *meso* - tartarate with **3** following Boeseken's general procedure.[5a]

(6) 1, 4 - *Dioxan* - 2, 3 - *diol* **5** (R = $SiMe_3$): (The starting diol was commercial-Eastman-Kodak.) The crude product was shown by GLPC to consist of three components and was fractionally distilled on a spinning band column at 75–82°/20 torr. 36 fractions were collected and analysed by GLPC (5% SE-30 on chromosorb- W at 103°). The forerun consisted mostly of ethylene glycol *bis*-trimethylsilyl ether. The extreme fractions were enriched by either one of the remaining two components up to 90%. Small samples were collected in preparative GLPC runs and configurations were tentatively assigned based on the PMR spectra.

cis - 1, 4 - Dioxan - 2, 3 - *bis* - trimethylsilyl ether, b.p. 75°/20 torr; PMR: τ 9·87 (18 H, s), 6·4 (4 H, m, $w_{1/2}$ = 21 Hz), 5·48 (2 H, s). Mass spectrum (70 eV) *m/e* (rel. abundance) 249 (4), 147 (38), 119 (38), 103 (79), 73 (100). (Found: C, 45·29; H, 9·19. Calc. for $C_{10}H_{24}O_4Si_2$: C, 45·42; H, 9·14%).

trans - 1, 4 - *Dioxan* - 2, 3 - *bis* - trimethylsilyl ether, b.p. 82°/20 torr; PMR: τ 9·82 (18 H, s), 6·48 (4 H, m, $w_{1/2}$ = 39 Hz), 5·71 (2 H, s). Mass spectrum (70 eV) *m/e* (rel. abundance) 264 (<1), 147 (23), 119 (49), 103 (90), 73 (100). (Found: C, 45·22; H, 8·82. Calc. for $C_{10}H_{24}O_4Si_2$: C, 45·42; H, 9·14%).

The ratio of the *cis* and *trans* isomers in the crude reaction product was 21 : 79 respectively, as determined by GLPC.

The reaction of any of these TMS-derivatives of **5** with **3** and silver perchlorate gave 1, 4, 5, 8, 9, 10 - hexaoxaperhydroanthracene, crystallized from ether/methylene chloride, m.p. 230–231°; yield 14%; PMR: τ 5·16 (8 H, m), 4·99 (4 H, s); mass spectrum (70 eV) *m/e* (rel. abundance) 204 (4, M^+).

(−) - trans - 2, 3 - *Dihydroxymethyl* - cis - 1, 4, 5, 8 - *tetraoxadecalin*, **8**. The D(+) - *trans* - diester **7** (12 g, 0·043 moles) and LAH (6 g) in 250 ml abs ether were stirred overnight. The large excess of LAH was destroyed using an ethereal soln of EtOAc. Water was added with stirring and after 15 min, the ethereal layer was de-

canted.[30] The aqueous mixture was evaporated to dryness and the residue was taken up in EtOH. The mixture was filtered and the solvent evaporated. This residue was taken up in methylene chloride and filtered again from inorganic material. The residue from this soln was crystallized from ether, yield 8 g (68%); m.p. 90–91°; $[\alpha]_D$ −86·2°; IR (KBr) 3480, 3425, 1170, 1088, 1070, 995, 910 cm^{-1}; PMR τ 8·07 (2 H, s, broad), 6·08 (10 H, m), 5·25 (2 H, s); mass spectrum (70 eV) *m/e* (rel. abundance) 206 (16, M^+). (Found: C, 46·45; H, 6·91. Calc. for $C_8H_{14}O_6$: C, 46·60; H, 6·84%).

The ditosylate **10** was prepared from **8** with *p*-toluenesulfonyl chloride in pyridine as usual, m.p. 188–189°; $[\alpha]_D$ −38·9°. (Found: C, 51·38; H, 4·95; S, 12·43. Calc. for $C_{22}H_{26}O_{10}S_2$: C, 51·35; H, 5·09; S, 12·46%).

Attempts to reduce **10** by LAH were unsuccessful.

(−) - trans - 2, 3 - *Diiodomethyl* - cis - 1, 4, 5, 8 - *tetraoxadecalin*[30b] **9**. A mixture of the diol **8** (460 mg, 0·0024 mole), triphenil phosphite methiodide (2·1 g, 0·0045 mole) and MeI (7 ml) was stirred for 1 h at 50° and then overnight at room temp. Ether was added and the soln was washed with 5% NaOHaq and water and dried. Evaporation of the solvent and recrystallization from ether gave 135 mg (13%) of **9**, m.p. 148°; $[\alpha]_D$ −88·3°; IR (KBr) 1275, 1170, 1090, 630 cm^{-1}; PMR τ 6·28 (10 H, m), 5·20 (2 H, m); mass spectrum (70 eV) *m/e* (rel. abundance) 425 (7). (Found: C, 22·48; H, 2·88; I, 59·13. Calc. for $C_8H_{12}I_2O_4$: C, 22·55; H, 2·85; I, 59·59%).

(−) - trans - 2, 3 - *Dimethyl* - cis - 1, 4, 5, 8 - *tetraoxadecalin*, **11**. A soln of **9** (250 mg, $5·4 \times 10^{-4}$ mole) in EtOH (60 ml) was stirred with Raney Nickel in a hydrogen atmosphere for 3 hr. After filtration and evaporation of the solvent, the residue was crystallized from ether, yield 70 mg. (75%); $[\alpha]_D$ −88·1°; IR ($CHCl_3$) 2980, 2900, 1460, 1385, 1280, 1185, 1150, 1120, 1110, 1090, 1040 cm^{-1}, PMR τ 8·92 (3 H, d, J = 6·5 Hz), 8·80 (3 H, d, J = 6·5 Hz), 5·9–6·8 (6 H, m), 5·35 (2 H, q, J_{AB} = 1·5 Hz); mass spectrum (70 eV) *m/e* (rel. abundance) 174 (22, M^+), 101 (9), 86 (33), 73 (30), 56 (100).

2 - *Hydroxy* - 2 - *β* - *chloroethoxy* - 1, 4 - *dioxane*, **6**. A mixture of **5** (R = H; mixture of *cis*- and *trans*- isomers as described above) (100 g, 0·84 mole), *β*-chloroethanol (67 g, 0·84 mole) and *p*-toluenesulphonic acid (1 g) in 300 ml dry benzene was refluxed for several hours with azeotropical removal of water (Dean-Stark head); *ca* 15 ml water separated. The mixture was cooled, washed with K_2CO_3aq and water, and dried; the solvent was removed to give 35 g of crude product. The latter contained, besides the main product, small amounts of **1** and **2** as shown by GLPC. Distillation at 117–120°/3×10^{-3} torr was accompanied by extensive polymerization and therefore, for preparative purposes, the crude reaction product may be used. Characterization of **6** was accomplished by acetylation with acetyl chloride in pyridine which gave the acetate, b.p. 125°/0·1 torr; IR (film) 1755, 1585, 1485, 1440, 1070, 1030, 990, 750, 705; PMR τ 7·85 (3 H, s), 5·7–6·7 (8 H, m), 5·4 (1 H, m), 4·25 (1 H, m); mass spectrum (70 eV) *m/e* (rel. abundance) 167 (3), 165 (9) $(M\text{-}OAc)^+$, 111 (5), 109 (14), 73 (100). (Found: C, 42·45; H, 5·92; Cl, 16·08. Calc. for $C_8H_{13}O_3Cl$: C, 42·77; H, 5·79; Cl, 15·79%).

Cyclization of **6**. A soln of **6** (5 g, 0·0275 mole) in dry glyme was added dropwise to a suspension of NaH (1 g) in the same solvent. Strong evolution of H_2 occurred but the temp did not rise above 27°. After addition and stirring for 90 h, the mixture was filtered and the solvent was removed *in vacuo*. The residue was taken up in chloroform, washed and dried, and the solvent was removed. The residue was crystallized from ether, yield: 3 g (75%); m.p. 133–134° and all spectroscopic data show that the product consists exclusively of **1**.

Equilibration of the dimethyl - cis - 1, 4, 5, 8 - *tetraoxadecalin* - 2, 3 - *dicarboxylates* **7**, **12** *and* **13**. The diester **7** or **12** (500 mg) was placed in a test tube equipped with a magnetic bar and a rubber septum. The tube was flushed with N_2 and fitted into a reactor with refluxing MeOH. A methanolic soln of 0·1 N NaOMe (1 ml) was injected and the mixture was brought to equilibrium. Multiple experiments showed that after 15 min equilibrium is reached, since the composition does not change. The reaction was quenched by injecting 1·1 equivalent of methanolic HCl. The mixture was then poured into ice water and this was extracted with dichloromethane. Washing and drying of the organic soln gave a near quantitative yield of a mixture of isomers **7**, **12**, **13** in the ratio 59:34:7 respectively, as analyzed by GLPC (8% XE-Go on chromosorb W-DMCS, 2 m × 1/4", 142°, 50 ml He/min).

The above GLPC resolved mixture was analyzed by mass spectrometry, using a Finnigan-1015 GC-MS setup,

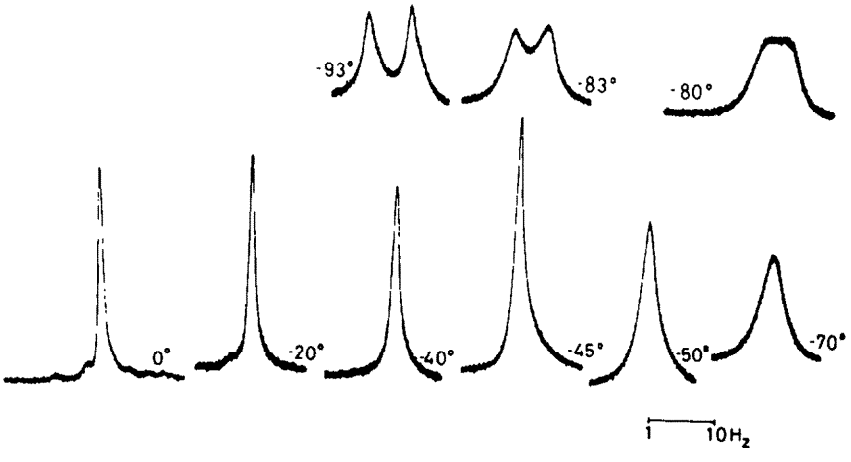


Fig 1. Variable temperature PMR (100 MHz) spectral measurements of *cis* - 2, 3 - dicarbomethoxy - *anti* - *cis* - 1, 4, 5, 8 - tetraoxadecalin. Only the methyl resonance is shown.

courtesy of the Weizmann Institute, Rehovot. Clean background spectra were obtained between each two isomers. The mass spectra of the three isomers were very similar and each showed the molecular ion m/e 162 in appreciable intensity.

Variable temperature PMR spectroscopy of **12**. This was performed on a *ca* 10% soln of **12** in acetone-d_6:pyridine (2:1) using a Varian-HR-100 instrument, equipped with variable temp probe and controller. The relevant spectral changes with temperature are given in Fig 1.

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