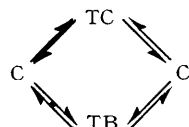


## Conformational Studies on 1,3-Dioxepans. Part II.<sup>1</sup> 1,3:2,5:4,6-Tri-*O*-ethylidene-*D*-mannitol and Some Related Compounds

By T. B. Grindley, J. F. Stoddart, and W. A. Szarek,\* Department of Chemistry, Queen's University, Kingston, Ontario, Canada

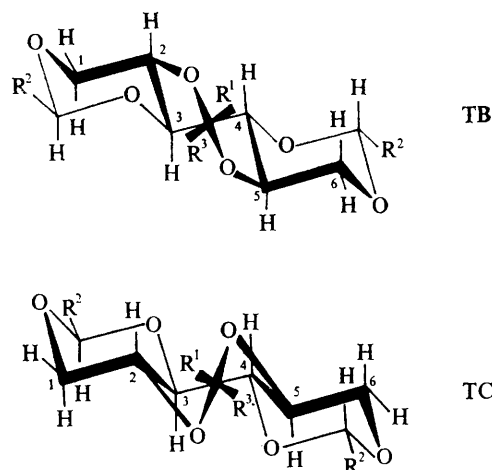
1,3:2,5:4,6-Tri-*O*-ethylidene-*D*-mannitol and 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol exist in one stable configuration. On the basis of n.m.r. studies and the comparative stabilities of the twist-chair (TC), twist-boat (TB), and chair (C) conformations for a seven-membered ring, it is suggested that the 1,3-dioxepan rings exist predominantly in the TC form. The chemical shift data for the *O*-ethylidene methine and methyl protons in the 1,3-dioxan and dioxepan rings of the above-mentioned derivatives and of 1,3:4,6-di-*O*-ethylidene-2,5-*O*-methylene-*D*-mannitol are compared.

RECENTLY,<sup>1</sup> n.m.r. studies on 1,3:2,5:4,6-tri-*O*-methylene-*D*-mannitol (1) and 1,3:4,6-di-*O*-benzylidene-2,5-*O*-methylene-*D*-mannitol (2) indicated that the 2,5-*O*-methylene protons are isochronous.† Molecular models showed that the 1,3-dioxepan ring may assume any of three discrete conformations, a twist-boat (TB), a chair (C), or a twist-chair (TC). By a process of ring-inversion, the seven-membered ring could conceivably undergo an interconversion of the type



where the two C forms are degenerate. As shown in Scheme 1, the TB and TC conformational types have a  $C_2$  axis of symmetry passing through their 2,5-*O*-methylene carbon atoms and the centres of their C(3)–C(4) bonds. As a consequence, the two *O*-methylene protons may be interchanged by a  $C_2$  symmetry operation and are therefore equivalent.† On the other hand, in the degenerate C conformational types shown in Scheme 2, the two *O*-methylene protons are diastereotopic.† The observation<sup>1</sup> that the protons are isochronous means that either the 1,3-dioxepan ring is undergoing a fast inversion process between two degenerate C forms or it exists in the stable TC or TB form. Arguments<sup>1</sup> employing the tenets of conformational analysis predict that the conformation containing the TC form is more stable than those containing the TB or C form. It has also been shown<sup>1</sup> that the methyl

groups of the isopropylidene group of 2,5-*O*-isopropylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (3) are iso-



- (1)  $R^1 = H, R^2 = H, R^3 = H$
- (2)  $R^1 = H, R^2 = Ph, R^3 = H$
- (3)  $R^1 = Me, R^2 = H, R^3 = Me$
- (4)  $R^1 = Me, R^2 = Me, R^3 = H$
- (5)  $R^1 = Me, R^2 = H, R^3 = H$
- (6)  $R = H, R^2 = Me, R^3 = H$

SCHEME 1 The TB and TC forms of 1,3:2,5:4,6-tri-*O*-methylene-*D*-mannitol (1), 1,3:4,6-di-*O*-benzylidene-2,5-*O*-methylene-*D*-mannitol (2), 2,5-*O*-isopropylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (3), 1,3:2,5:4,6-tri-*O*-ethylidene-*D*-mannitol (4), 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (5), and 1,3:4,6-di-*O*-ethylidene-2,5-*O*-methylene-*D*-mannitol (6)

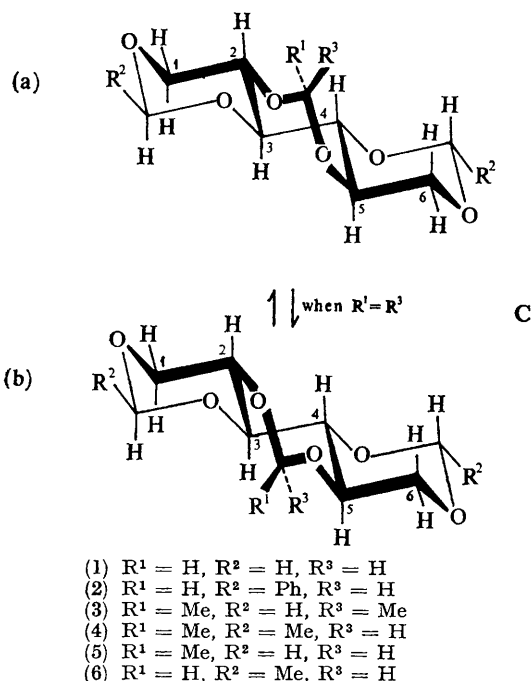
chronous, and it has been proposed that the TC form is the most stable for the 1,3-dioxepan ring of this novel

† The terms 'isochronous,' 'equivalent,' and 'diastereotopic' are used as described or defined by Mislow and Raban.<sup>2</sup>

<sup>1</sup> T. B. Grindley, J. F. Stoddart, and W. A. Szarek, *J. Chem. Soc. (B)*, 1969, 172.

<sup>2</sup> K. Mislow and M. Raban, 'Stereoisomeric Relationships of Groups in Molecules' in 'Topics in Stereochemistry,' ed N. L. Allinger and E. L. Eliel, Wiley, New York, 1967, p. 1.

seven-membered cyclic acetal. D-Mannitol also forms<sup>3</sup> 1,3:2,5:4,6-tri-*O*-ethylidene-D-mannitol (4). In this tri-*O*-ethylidene derivative, it has been claimed<sup>4</sup> that a new asymmetric centre is created in the seven-membered



SCHEME 2 The two degenerate C forms of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (1), 1,3:4,6-di-*O*-benzylidene-2,5-*O*-methylene-D-mannitol (2), 2,5-*O*-isopropylidene-1,3:4,6-di-*O*-methylene-D-mannitol (3), and 1,3:4,6-di-*O*-ethylidene-2,5-*O*-methylene-D-mannitol (6). 1,3:2,5:4,6-Tri-*O*-ethylidene-D-mannitol (4) and 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-D-mannitol (5) in two discrete C forms

ring and that a configurational assignment made previously by Mills<sup>5</sup> is erroneous. We suggest that this criticism is unjustified and that the tri-*O*-ethylidene derivative exists in one stable configuration, and probably predominantly in one stable conformation as well.

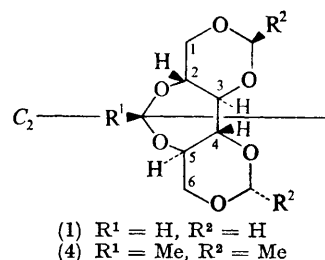
The structure in Scheme 3, proposed by Mills<sup>5</sup> for 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (1), has a  $C_2$  axis of symmetry. Thus, substitution of either of the equivalent *O*-methylene protons on the axis carbon atom by a methyl group will give identical structures. This statement is also true for the TC and TB conformations of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (1) (Scheme 1). In the case of one of the C conformations shown in Scheme 2, there is considerable  $CH_3-H$  repulsion between

\* Although the possibility of acetal ring migration during the acid-catalysed ethyldienation of 1,3:4,6-di- and 2,5-*O*-methylene-D-mannitol exists, the n.m.r. spectroscopic data for the products indicate that migration did not occur.

† As in the n.m.r. spectra<sup>1</sup> of 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (1) and 2,5-*O*-isopropylidene-1,3:4,6-di-*O*-methylene-D-mannitol (3), the A signals at low field for the equatorial protons of the *O*-methylene groups of the 1,3-dioxan rings are slightly broader than the B signals for the geminal axial protons. Long-range couplings through oxygen atoms over four bonds<sup>7</sup> in a W conformation<sup>8</sup> account for this observation.

the axial methyl group of the *O*-ethylidene group and the axial proton on C-4. In the other C conformation, the methyl group is equatorial and there is a less considerable H-H repulsion between the axial proton of the *O*-ethylidene group and the axial proton on C-3. Thus, only one of the C conformations is energetically viable.

2,5-*O*-Ethylidene-1,3:4,6-di-*O*-methylene-D-mannitol (5) was prepared\* by an acid-catalysed ethyldienation of 1,3:4,6-di-*O*-methylene-D-mannitol<sup>6</sup> with paraldehyde. The n.m.r. spectrum of the *O*-ethylidene derivative (5) showed a four-proton AB quartet<sup>†</sup> at  $\tau$  5.17, which was assigned to the 1,3- and 4,6-*O*-methylene protons, in addition to the one-proton quartet at  $\tau$  4.99



SCHEME 3 Mills' structures for 1,3:2,5:4,6-tri-*O*-methylene-D-mannitol (1) and 1,3:2,5:4,6-tri-*O*-ethylidene-D-mannitol (4). The tri-*O*-methylene derivative has a  $C_2$  axis of symmetry as shown

for the 2,5-*O*-ethylidene methine proton, which was coupled to the 2,5-*O*-ethylidene methyl protons, giving a three-proton doublet at  $\tau$  8.74. For the stereochemical reasons given in Part 1,<sup>1</sup> the TC conformation should be more stable than the TB or the C conformation. Experimental support for this statement from chemical shift data for *O*-ethylidene methine and methyl protons in 1,3-dioxan and -dioxepan rings will be presented later in this discussion. However, if the TC conformation is preferred, 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-D-mannitol (5) most likely exists in a distorted TC conformation because of the existence of non-bonded interactions between the ethylidene methyl group and the axial protons on the same side of the seven-membered ring larger than those between the ethylidene methine proton and the 'equivalent' axial protons on the other side of the ring.

<sup>3</sup> J. Meunier, *Compt. rend.*, 1889, **108**, 408; *Ann. chim. Phys.*, 1891, **22**, 412; *Bull. Soc. chim. France*, 1903, **29**, 735; M. Delépine, *ibid.*, 1901, **25**, 574; V. Ettel, *Coll. Czech. Chem. Comm.*, 1930, **2**, 457; E. J. Bourne and L. F. Wiggins, *J. Chem. Soc.*, 1948, 1933; E. J. Bourne, G. T. Bruce, and L. F. Wiggins, *ibid.*, 1951, 2708.

<sup>4</sup> R. U. Lemieux, 'Rearrangements and Isomerisations in Carbohydrate Chemistry,' in 'Molecular Rearrangements,' Part 2, ed. P. de Mayo, Wiley, New York, 1964, p. 709.

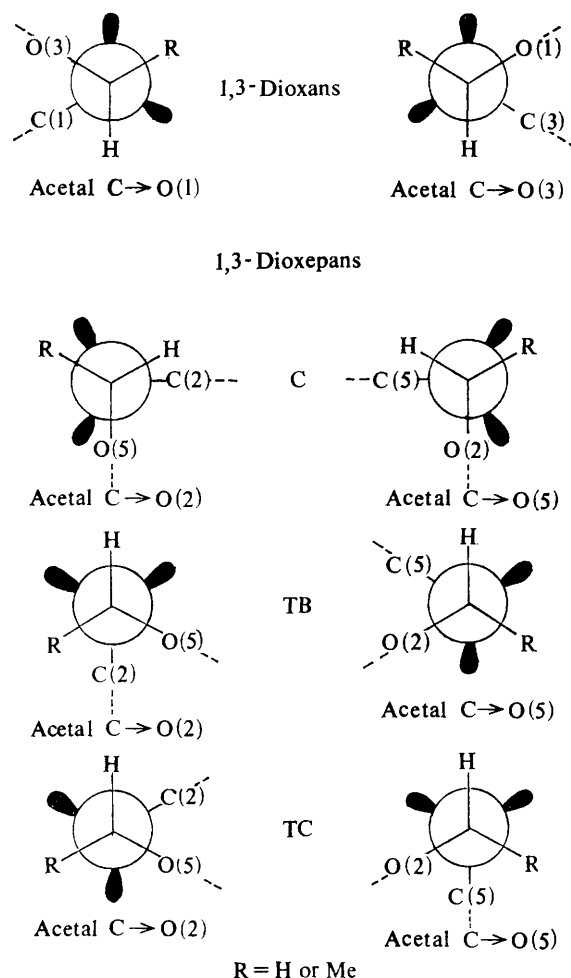
<sup>5</sup> J. A. Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.

<sup>6</sup> W. T. Haskins, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 67; R. Allerton and H. G. Fletcher, *ibid.*, 1954, **76**, 1957.

<sup>7</sup> R. U. Lemieux and J. Howard, *Canad. J. Chem.*, 1963, **41**, 393; J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, 1966, **62**, 39.

<sup>8</sup> A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Letters*, 1964, 233.

The n.m.r. data for 1,3:2,5:4,6-tri-*O*-ethylidene-*D*-mannitol (4) are also consistent with a distorted TC conformation. Comparison of this n.m.r. spectrum with that of 1,3:4,6-di-*O*-ethylidene-2,5-*O*-methylene-*D*-mannitol (6), obtained on acid-catalysed ethylenation of 2,5-*O*-methylene-*D*-mannitol<sup>9</sup> with paraldehyde, showed that in each case the six-proton doublets at  $\tau$  8.62 ( $J = 5.0$  Hz) are assignable to the 1,3- and 4,6-*O*-ethylidene methyl groups and the two-proton quartets at  $\tau$  5.29 ( $J = 5.0$  Hz) to the corresponding ethylidene methine protons. In the tri-*O*-ethylidene derivative (4), the three-proton doublet at higher field ( $\tau$  8.77) for the 2,5-*O*-ethylidene methyl group is coupled ( $J = 5.4$  Hz) to the one-proton quartet at lower field ( $\tau$  5.02) for the 2,5-*O*-ethylidene methine proton.



SCHEME 4 Newman projections along C-O bonds of the 1,3-dioxan and 1,3-dioxepan rings

If the lone-pair orbitals for the two electron pairs associated with each O atom are assumed to be orientated tetrahedrally,<sup>10</sup> a qualitative stereochemical picture of the orientation of acetal C substituents with respect to these orbitals may be presented with the aid of Newman

projections. Scheme 4 shows that in the 1,3-dioxan rings (C form), equatorial protons or methyl groups are in staggered positions between the two lone-pair orbitals on each adjacent O atom, whilst axial protons are staggered between one of the lone-pair orbitals and an O-C bond associated with position 1 or 3 (or 4 or 6) of the *D*-mannitol derivatives. N.m.r. spectra of 1,3:4,6-di-*O*-methylene derivatives,<sup>1</sup> including 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (5), indicate that equatorial protons are deshielded with respect to axial protons. In the 1,3-dioxepan rings, the orientation of acetal C substituents with respect to the lone-pair orbitals on neighbouring O atoms is dependent on the conformation of the seven-membered ring. In the C conformation, the orientation is qualitatively similar to that in 1,3-dioxans (C forms). However, in the TB and TC conformations, acetal C substituents, which are in staggered positions between the lone-pair orbitals of one adjacent O atom, are staggered between one lone-pair orbital on the other adjacent O atom and the O-C bond associated with either of the equivalent positions at C-2 and C-5. Thus, the chemical shift of the 2,5-*O*-methylene protons in 1,3:2,5:4,6-tri-*O*-methylene-*D*-mannitol (1) would be expected to be intermediate between those of the axial (at higher field) and equatorial (at lower field) protons of the 1,3- and 4,6-*O*-methylene groups. This has been observed.<sup>1</sup> Likewise, the 2,5-*O*-ethylidene methine proton of 1,3:2,5:4,6-tri-*O*-ethylidene-*D*-mannitol (4) should be deshielded with respect to the 1,3- and 4,6-*O*-ethylidene-methine protons, and the 2,5-*O*-ethylidene-methyl protons should be shielded with respect to the 1,3- and 4,6-*O*-ethylidene-methyl protons. The fact that this is the case supports the proposal that the 1,3-dioxepan ring of the tri-*O*-ethylidene derivative (4) of *D*-mannitol is predominantly in the TC conformation, albeit slightly distorted.

#### EXPERIMENTAL

General methods are described in Part 1.<sup>1</sup>

2,5-*O*-Ethylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (5).—1,3:4,6-Di-*O*-methylene-*D*-mannitol<sup>6</sup> [m.p. 208–212°,  $[\alpha]_D -88.7^\circ$  ( $c$  1.2 in water)] (600 mg.) in paraldehyde (50 ml.) was shaken overnight at room temperature with concentrated sulphuric acid (1 drop). The mixture was neutralised with potassium carbonate and filtered, and the filtrate was concentrated to a crystalline residue, which was recrystallised three times from ethanol to give long needles of 2,5-*O*-ethylidene-1,3:4,6-di-*O*-methylene-*D*-mannitol (5) (550 mg., 81%), m.p. 200–201°,  $[\alpha]_D -34.8^\circ$  ( $c$  1.0 in chloroform) (Found: C, 51.7; H, 6.85.  $C_{10}H_{16}O_6$  requires C, 51.7; H, 6.94%),  $\tau$  (CDCl<sub>3</sub>) 4.99 (1H, q,  $CH_3 \cdot CH<$ ,  $J = 5.4$  Hz), 5.17 (4H, ABq, 1,3:4,6- $O \cdot CH_2 \cdot O$ ,  $\Delta\nu_{AB}$  27.0 Hz,  $J_{AB}$  6.2 Hz), and 8.74 (3H, d, Me,  $J$  5.4 Hz).

1,3:2,5:4,6-Tri-*O*-ethylidene-*D*-mannitol (4).—The title compound (4) [m.p. 171.5–172.5°,  $[\alpha]_D -72.0^\circ$  ( $c$  2.3 in chloroform)] was prepared according to the procedure of Bourne and Wiggins;<sup>3</sup>  $\tau$  (CDCl<sub>3</sub>) 5.02 (1H, q, 2,5- $CH_3 \cdot CH<$ ,  $J$  5.4 Hz), 5.29 (2H, q, 1,3- and 4,6- $CH_2 \cdot CH<$ ,  $J$  5.0 Hz),

<sup>9</sup> A. T. Ness, R. M. Hann, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 2215.

<sup>10</sup> E. L. Eliel and Sr. M. C. Knoeber, *J. Amer. Chem. Soc.*, 1968, **90**, 3444; E. L. Eliel and C. A. Giza, *J. Org. Chem.*, 1968, **33**, 3754.

8.62 (6H, d, 1,3- and 4,6- $\text{CH}_3\cdot\text{CH}$ ,  $J$  5.0 Hz), and 8.77 (3H, d, 2,5- $\text{CH}_3\cdot\text{CH}$ ,  $J$  5.4 Hz).

1,3 : 4,6-Di-*O*-ethylidene-2,5-*O*-methylene-D-mannitol (6).—2,5-*O*-Methylene-D-mannitol<sup>9</sup> [m.p. 173—174°,  $[\alpha]_D -47.4^\circ$  ( $c$  1.2 in water)] (500 mg.) in paraldehyde (50 ml.) was shaken for 24 hr. at room temperature with concentrated sulphuric acid (1 drop). The mixture was neutralised with potassium carbonate and filtered, and the filtrate was concentrated to a dark crystalline residue, which was treated with decolourising carbon and then recrystallised from methanol-acetone and finally from acetone to give *needles*

of 1,3 : 4,6-di-*O*-ethylidene-2,5-*O*-methylene-D-mannitol (6) (320 mg., 54%), m.p. 208—209°,  $[\alpha]_D -109.1^\circ$  ( $c$  2.4 in chloroform) (Found: C, 54.0; H, 7.49.  $\text{C}_{11}\text{H}_{18}\text{O}_6$  requires C, 53.7; H, 7.37%),  $\tau$  ( $\text{CDCl}_3$ ) 5.22 (2H, s, 2,5- $\text{O}\cdot\text{CH}_2\cdot\text{O}$ ), 5.29 (2H, q, 1,3- and 4,6- $\text{CH}_3\cdot\text{CH}$ ,  $J$  5.0 Hz), and 8.62 (6H, d, 1,3- and 4,6- $\text{CH}_3\cdot\text{CH}$ ,  $J$  5.0 Hz).

We thank Prof. J. K. N. Jones for his interest and encouragement, and the National Research Council of Canada for a grant.

[8/1920 Received, December 30th, 1968]