Stereochemistry of Cyclic Ether Formation. Part I. Stereoselective Intramolecular Cyclisation of Aliphatic Disecondary 1,4-Diols and their Sulphonate Esters to Tetrahydrofurans

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Several methods of eliminative cyclisations of diastereoisomeric disecondary 1,4-diols and their 1,4-disulphonate esters, leading to the formation of tetrahydrofurans, have been studied, and it was found that they all proceed stereoselectively by S_N2-type mechanisms, with inversion of configuration at one (1,4-diols) or both (1,4-disulphonates) chiral centres, so that *meso* (*i.e. erythro*) 1,4-diols and ± (*i.e. threo*) 1,4-dimesylates afford only *trans*-2,5-dialkyl-tetrahydrofurans, while the respective diastereoisomeric substrates are converted exclusively into *cis*-2,5-dialkyltetrahydrofurans.

Two different approaches to tetrahydrofuran ring closure are known which can be used for syntheses of saturated five-membered cyclic ethers from acyclic substrates. The first (Scheme 1) (formally an eliminative cyclisation) has been achieved in different ways, *e.g.* by cyclodehydration of 1,4-diols (Scheme 1, *a*) with acids,[1-3] salts, [3,4] alumina,[1,5,6] or dimethyl sulphoxide; [7]

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[1] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 1953, 389.

[2] S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, 1954, **19**, 1449; I. L. Kotlyarevskii, M. S. Shvartsberg, and Z. P. Trotsenko, *Zhur. obshchei Khim.*, 1960, **30**, 440.

[3] W. Reppe, *Annalen*, 1955, **596**, 84, 111.

[4] J. Colonge, R. Falcotet, and R. Gaumont, *Bull. Soc. chim. France*, 1958, 211.

[5] R. C. Olberg, H. Pines, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, 1944, **66**, 1096.

[6] E. L. Wittbecker, H. K. Hall, jun., and T. W. Campbell, *J. Amer. Chem. Soc.*, 1960, **82**, 1218.

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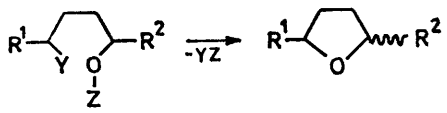
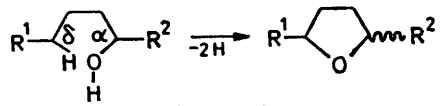
by internal dehydrohalogenation of 1,4-halogenohydrins (Scheme 1, *b*) with bases;[8] by elimination of sulphonic acid from 1,4-diol monosulphonates (Scheme 1, *c*);[9,10] by hydrolytic decomposition of 1,4-diol disulphonates (Scheme 1, *d*);[1,11] by intramolecular eliminations of 1,4-hydroxy-ethers (Scheme 1, *e*)[12] or their sulphonate esters (Scheme 1, *f*).[13]



SCHEME 1

(*a*) Y = OH, Z = H; (*b*) Y = halogen, Z = H; (*c*) Y = OSO_2R^3, Z = H; (*d*) Y = OSO_2R^3, Z = $OSOR^3$; (*e*) Y = OH, Z = alkyl; (*f*) Y = OSO_2R^3, Z = alkyl

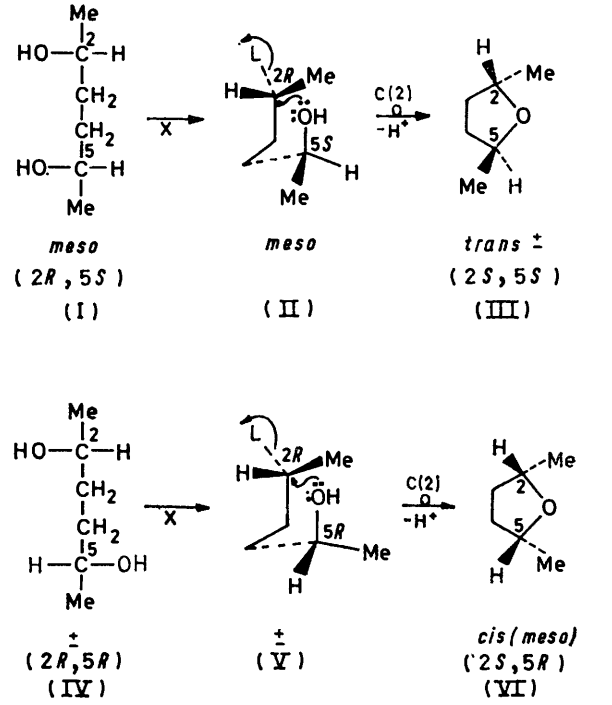
The second approach (Scheme 2) involves functionalisation of a non-activated δ-carbon atom by way of intramolecular oxidative cyclisation of monohydric alcohols with lead tetra-acetate,[14-17] lead tetra-acetate–iodine,[17,18] or silver or mercury(II) oxide or acetate–halogen (bromine or iodine).[18-20]



SCHEME 2

Whereas oxidative ring closure of secondary aliphatic alcohols (Scheme 2) is non-stereoselective, affording a mixture of *cis*- and *trans*-2,5-dialkyltetrahydrofurans,[14-16,20] little is known about the stereochemistry of formation of five-membered cyclic ethers from di-secondary acyclic 1,4-diols and their derivatives (Scheme 1). We have reinvestigated some of these procedures and, by using as model substrates the symmetrical diastereoisomeric hexane-2,5-diols (I) and (IV), we have found (Scheme 3) that under a variety of experimental conditions [such as cyclodehydration with concentrated sulphuric or phosphoric acid or dilute (15—25%) aqueous sulphuric acid (Scheme 3, *A*), with dimethyl sulphoxide (Scheme 3, *B*), or with alumina (Scheme 3, *C*), or intramolecular elimination of acid from the corresponding monomethanesulphonates (prepared *in situ* and decomposed thermally in pyridine[9]) (Scheme 3, *D*)] cyclisation is stereoselective; in all cases the *meso*-diol (I) affords only *trans*-2,5-dimethyltetrahydrofuran (III) and the ±-diol (IV) is converted exclusively into *cis*-2,5-dimethyltetrahydrofuran (VI).

The results obtained suggest that all these stereoselective cyclisations do not involve an S_N1 type mechanism with carbonium ions [*e.g.* at C(2), Scheme 3] as intermediates, but proceed by an intramolecular S_N2 substitution process with inversion of configuration at *one* chiral centre, *i.e.* at the asymmetric carbon [*e.g.* C(2), Scheme 3] containing the leaving group (L). The cyclic transition states with an appropriate arrangement of attacking and leaving group [at C(5) and C(2), respectively] should be easily attainable, because the conformations required for such an intramolecular



SCHEME 3

displacement are relatively favourable, as represented in Scheme 3 by (II) and (V) for the *meso*- and ±-diastereoisomer, respectively.

When cyclodehydration of the diol (I) or (IV) is

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[10] K. Alder and W. Roth, *Chem. Ber.*, 1955, **88**, 407.

[11] A. R. Jones, *Chem. Comm.*, 1971, 1042.

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[16] M. Lj. Mihailović and Ž. Čeković, *Synthesis*, 1970, 209.

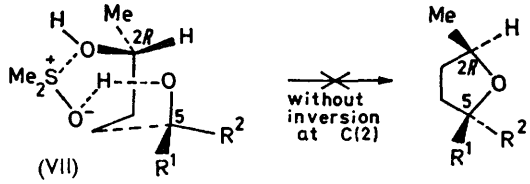
[17] K. Heusler and J. Kalvoda, *Angew. Chem.*, 1964, **76**, 518; *Angew. Chem. Internat. Edn.*, 1964, **3**, 525.

[18] K. Heusler and J. Kalvoda, *Synthesis*, 1971, 501.

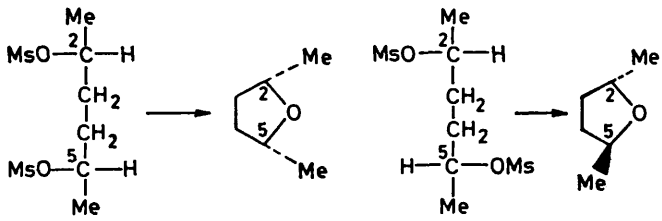
[19] R. H. Hesse, *Adv. Free-Radical Chem.*, 1969, **3**, 83.

[20] M. Lj. Mihailović, Ž. Čeković, and J. Stanković, *Chem. Comm.*, 1969, 981.

performed in dimethyl sulphoxide (Scheme 3, *B*), it is probable that the reagent, by some sort of association with one hydroxy-group, increases polarisation and therefore eases the breaking of one C–O bond [*i.e.*, the C–L bond in (II) and (V)] at the carbon undergoing S_N2 substitution with inversion of configuration, as shown for transition states (II, *B*) and (V, *B*). A similar situation might be involved possibly in the dehydrative cyclisation of diols (I) and (IV) by means of alumina [Scheme 3 (II, *C*) and (V, *C*)]. For tetrahydrofuran formation by dehydration of 1,4-diols with dimethyl sulphoxide, Gillis and Beck [7] have suggested a cyclic transition state in which one molecule of the reagent is associated with both hydroxy-groups (VII). However, since the proton of one (the attacking) hydroxy-group and the oxygen atom of the other (leaving) hydroxy-group must be relatively close to each other, the conformations adopted in the transition state (VII) for the 5*S*- (R^1 = Me, R^2 = H) and 5*R*-diastereoisomers (R^1 = H, R^2 = Me), corresponding to such a requirement, would allow intramolecular substitution at the carbon attacked [*e.g.* (2*R*)] *without* inversion of configuration, resulting in the wrong stereochemistry of ether ring closure.



On the other hand, an opposite stereochemical course is observed (Scheme 4) in the eliminative cyclisation of the dimesylates of the diastereoisomeric hexane-2,5-diols (VIII) and (IX), as also observed recently by Jones.[11] These hydrolytic reactions, carried out thermally in alkaline or neutral aqueous media (in dilute sulphuric acid the reaction occurs, but at a slower rate), are again stereoselective, but here the *meso*-diester (VIII) is

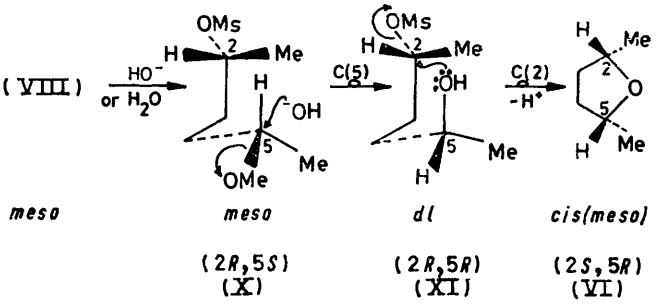


Ms = $MeSO_2$; reagent: HO^- or H_2O

SCHEME 4

converted exclusively to the *cis*-ether (VI), while the ±-isomer (IX) affords only the *trans*-ether (III).

These results suggest that tetrahydrofuran ring closure in the diastereoisomeric dimesylates (VIII) and (IX) does not proceed by an S_N1 mechanism but follows, as shown in Scheme 5 for the conversion of the *meso*-diester (VIII) into the *cis*-ether (VI), a double S_N2-type displacement process, involving two successive substitutions [one (X) intermolecular and the other (XI) intramolecular], with inversion of configuration at each chiral centre [C(5) and C(2)].



Ms = $MeSO_2$

SCHEME 5

All the procedures for cyclisation of hexane-2,5-diol (except dehydration with alumina) and its dimesylate (except hydrolysis in dilute sulphuric acid) afforded 2,5-dimethyltetrahydrofuran in very good yield (70—*ca.* 90%, see Experimental section, Tables 1 and 2).

With unsymmetrical disecondary 1,4-diols (Scheme 1, *a*; $R^1 \neq R^2$) and their disulphonate esters (Scheme 1, *d*, $R^1 \neq R^2$) as substrates, it was found that these ring closure reactions to five-membered cyclic ethers follow the same stereochemical course, *i.e.* *trans*-2,5-dialkyltetrahydrofurans are formed stereoselectively from *erythro*-1,4-diols and *threo*-1,4-diol disulphonates, while *threo*-1,4-diols and *erythro*-1,4-diol disulphonates are converted exclusively into *cis*-2,5-dialkyltetrahydrofurans.*

The results described here should find two useful applications: (*a*) as a synthetic tool, which provides the possibility to prepare separately both the *trans*- and the *cis*-isomers of a 2,5-disubstituted tetrahydrofuran from only one, no matter which, diastereoisomer of a disecondary 1,4-diol; and (*b*) as a convenient means for determining the diastereoisomeric composition and relative ratio of an acyclic disecondary 1,4-diol (of known or unknown configuration), since the separation of, and the assignment of the *cis*–*trans*-stereochemistry to, isomers of a 2,5-dialkyltetrahydrofuran are readily achievable on the basis of differences in gas-chromatographic retention times on suitable columns (the *cis*-isomer having a shorter retention time [15,16,21]) and differences in the signal positions of the α-protons [on C(2) and C(5)] in n.m.r. spectra (the chemical shift of these protons in the *trans*-isomer being displaced downfield [15,16,21,22]).

* Details of the cyclisations of unsymmetrical disecondary 1,4-diols and their esters will be published separately.

[21] Unpublished results.

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EXPERIMENTAL

Gas chromatography: a Varian Aerograph instrument series 1200 (flame-ionisation detector) was used for analytical work, and a Varian Aerograph instrument model A-700 (thermistor detector) for preparative purposes, with columns of Carbowax 20M or 1,2,3-tris-(2-cyanoethoxy)-propane adsorbed on Chromosorb P; carrier gas H_2; temperature 40—60°. N.m.r. spectra were recorded on a Varian A-60A spectrometer (CCl_4 was used as solvent and tetramethylsilane as internal standard) and i.r. spectra on a Perkin-Elmer Infracord instrument model 337.

Cyclisations of the Diastereoisomeric Hexane-2,5-diols to trans- *and* cis-*2,5-Dimethyltetrahydrofuran.*—Commercial (Fluka) hexane-2,5-diol, which is a mixture of diastereoisomers,* was esterified with phthalic anhydride, and the resulting diesters were separated [23] into *meso*-hexane-2,5-diol bis(hydrogen phthalate), m.p. 160—162°, and its ±-diastereoisomer, m.p. 184—185°.[23] Saponification, followed by chromatography on alumina and/or distillation,[23] afforded *meso*-hexane-2,5-diol (I), m.p. 40—41°, and ±-hexane-2,5-diol (IV), m.p. 23—24·5°.[24]

The cyclisations of the diols (see Table 1) were carried out in a small flask fitted with a short but efficient fractionating column, which was connected at the top to a condenser set for distillation. The *meso*- (I) or ±-diol (IV) (0·01 mol) and the reagent were placed in the flask, and the mixture was stirred magnetically and heated in an oil-bath as long as the *trans*- (III) or *cis*-2,5-dimethyltetrahydrofuran (VI) distilled over (up to 94°; usually in a temperature range of 60—90°). The distillate was dried (K_2CO_3), the products analysed and separated by g.l.c.,[15,16] and characterised by their n.m.r. spectra.[15,21] When a larger amount of diol was used, the distillate, prior to drying, was washed with a small volume of saturated aqueous sodium hydrogen carbonate which was then extracted with diethyl ether, and the products were purified by distillation; *cis*-2,5-dimethyltetrahydrofuran (VI), b.p. 90—92°, *trans*-(III), b.p. 92—94°.[15] [With higher 1,4-diols, either symmetric or unsymmetric and depending on the boiling point of the cyclic ether product, some or all the reactions listed in Table 1 should be performed under reflux (without direct distillation of the products), the mixture in the flask extracted with diethyl ether, and worked-up as usual.] When cyclodehydration was effected with dimethyl sulphoxide, the yields of cyclic ethers were somewhat lower (Table 1, *B*). From preliminary observations it appears that in this case the reagent attacks at higher temperature both isomeric ethers, but faster *trans*-2,5-dimethyltetrahydrofuran (III).†

* When this mixture of diastereoisomeric hexane-2,5-diols was converted into 2,5-dimethyltetrahydrofuran by procedure (A_3) and (*D*) in Table 1, it was found (by g.l.c.) that in both cases the ratio of *cis*-ether (VI) (shorter retention time) to *trans*-ether (III) was 62 : 38. Therefore (on the basis of the stereochemistry of these reactions given on Scheme 3), commercial hexane-2,5-diol (used in this work) contained 62% of ±-diol (IV) and 38% of *meso*-diastereomer (I) (which could not be separated by g.l.c.).

TABLE 1

Eliminative cyclisations of *meso*- (I) and ±-hexane-2,5-diol (IV) to *trans*- (III) and *cis*-2,5-dimethyltetrahydrofuran (VI)

Procedure		Substrate	Product (%)	
	Bath temp.	Diastereoisomer of hexane-2,5-diol	2,5-Dimethyltetrahydrofuran	
Reagent (amount)	(°C)	(0·01 mol)	*trans* (III)	*cis* (VI)
(A_1) H_3PO_4, 86% (0·3 ml) [3]	170—185	*meso* (I)	84	
		± (IV)		85
(A_2) Conc. H_2SO_4 (0·3 ml),[1] anh. $CaSO_4$ (1·5 g), and acetone (15 ml)	20 [a]	*meso* (I)	50	
		± (IV)		44
(A_3) 25% H_2SO_4 (10 ml) [2,3]	110—120	*meso* (I)	82	
		± (IV)		80
(*B*) Me_2SO (0·12 mol) [7]	180 [b]	*meso* (I)	64	
		± (IV)		72
(C) Basic Al_2O_3 (0·3 g) [1,6, c]	220	*meso* (I)	35 [d]	
		± (IV)		32 [d]
(*D*) $PhSO_2Cl$ (0·01 mol) [9] and anh. pyridine (0·04 mol)	110—125	*meso* (I)	88	
		± (IV)		85

[a] For 48 h. The mixture was worked-up as described previously.[1] [b] For 8—10 h. [c] With 25% aqueous sodium hydroxide at 100°, the diastereoisomeric hexane-2,5-diols did not undergo dehydrative cyclisation. [d] Other products (besides recovered starting material) were hexa-2,4-diene [3] (8%) and hex-4-en-2-ol (17%) (C. Prévost, *Bull. Soc. chim. France*, 1944, 218).

TABLE 2

Hydrolytic cyclisations of *meso*- (VIII) and ±-hexane-2,5-diol dimesylate (IX) to *cis*- (VI) and *trans*-2,5-dimethyltetrahydrofuran (III)

Procedure	Substrate	Product (%)	
	Diastereoisomer of hexane-2,5-diol dimesylate	2,5-Dimethyltetrahydrofuran	
Reagent (amount) [a,b]	(0·005 mol)	*trans* (III)	*cis* (VI)
2N-NaOH (15 ml) [1,11]	*meso* (VIII)		82
	± (IX)	80	
H_2O (3 ml) and dioxan (7 ml)	*meso* (VIII)		72
	± (IX)	76	
H_2O (10 ml)	*meso* (VIII)		70
	± (IX)	71	
25% H_2SO_4 (15 ml)	*meso* (VIII)		51
	± (IX)	46	

[a] In all cases the mixture was first heated for 1—2 h at 70—75° (bath temp.), and then the temp. was slowly raised (100—120°) so that the cyclic ether could distil over. [b] Similar results are obtained in 50% aqueous acetone (at reflux temp.), and in water (at 38°).[11]

† Thus, upon heating a 45 : 55 *trans* : *cis* mixture (0·4 g) of ethers with dimethyl sulphoxide (3 ml) and water (two drops) in a sealed tube at 180—185° for 8 h, the *trans* : *cis* ratio of recovered ethers changed to 35 : 65. (Under these conditions the *trans*-ether is not converted into the *cis*-isomer. Moreover, the *trans* : *cis* ratio does not change when the mixture of diastereoisomeric ethers is heated alone, or in the presence of a little water, at 180—185° for 8—10 h in a sealed tube.)

[23] R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, 1968, **33**, 3966.

[24] K. Serck-Hanssen, S. Ställberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, 1953, **5**, 203.

Cyclisations of the Diastereoisomeric Hexane-2,5-diol Dimesylates to trans- *and* cis-*2,5-Dimethyltetrahydrofuran.*—To a stirred and cooled (at 0°) solution of one diastereoisomer of the diol (3·6 g, 0·03 mol) in anhydrous pyridine (30 ml), methanesulphonyl chloride (8·3 g, 0·072 mol) was slowly added. The resulting mixture was stirred for another 4 h at 0°, and then treated with ice (50 g) and ice-cold water (100 ml). The precipitate was filtered off, washed thoroughly with ice-cold water, air-dried, and crystallised from benzene or methanol. In this way, the *meso*-diol (I) afforded the *meso*-dimesylate (VIII), m.p. 101—103° (from benzene),[11,25] and the ±-diol (IV) was converted into the ±-dimesylate (IX), m.p. 35—36° (from methanol).[11,26]

The hydrolytic reactions of the dimesylates (see Table 2) were carried out with 0·005 mol of substrate, as described above (for the cyclisations of the diols). No cyclic ether was obtained upon heating the dimesylates in glacial acetic acid or in anhydrous pyridine under reflux.

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[25] G. M. Timmis, R. F. Hudson, R. D. Marshall, and H. R. Bierman, U.S.P. 3,041,241/1962 (*Chem. Abs.*, 1962, **57**, 13,898); G. Ferrari and E. Marcon, *Boll. chim. farm.*, 1957, **96**, 429 (*Chem. Abs.*, 1958, **52**, 5282).

[26] S. S. Brown, J. L. Everett, and G. M. Timmis, B.P. 861,818/1961 (*Chem. Abs.*, 1961, **55**, 23,347).