786. *Aspects of Stereochemistry. Part XII.*[1] *Synthesis and Some Properties of* trans-*2-Alkyl Derivatives of 5-Hydroxy-1,3-dioxan.*

By N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Webber.

Hitherto unknown *trans*-2-methyl, -2-ethyl, and -2-isopropyl derivatives of 5-hydroxy-1,3-dioxan have been obtained by reaction of the corresponding *cis*-5-methanesulphonates with sodium benzoate in dimethylformamide, followed by hydrolysis of the resultant *trans*-benzoates. The infrared absorption patterns for free and bonded hydroxyl groups for the *trans*-2-alkyl-5-hydroxy-1,3-dioxans are similar. The implications of these results are considered.

In seeking further facts about the influence of bulk and orientation of substituents on the extent of intramolecular hydrogen bonding in derivatives of 5-hydroxy-1,3-dioxan (1,3-*O*-methyleneglycerol) attention was turned to the 2-alkyl derivatives. Hibbert and his co-workers found that benzoylation of the equilibrium mixtures of cyclic acetals formed by the acid-catalysed reaction of glycerol, severally, with acetaldehyde,[2] propanal,[3] and 2-methylpropanal [3] gave, in each case, a single crystalline benzoate which was subsequently identified as a 5-benzoyloxy-1,3-dioxan derivative. The *cis*-configuration has been tentatively assigned to each of these esters.[4] We now report a synthesis of the *trans*-isomers and confirmation of the structural assignments.

In certain cases, carbohydrate secondary sulphonates may be converted into the corresponding benzoates with inversion of configuration by reaction with sodium benzoate in dimethylformamide.[5] The feasibility of this approach to the *trans*-2-alkyl-5-hydroxy-1,3-dioxan series was established by using as model compounds *cis*- and *trans*-5-hydroxy-2-phenyl-1,3-dioxan (1,3-*O*-benzylideneglycerol), the structures of which have been determined.[6] Both isomers gave crystalline methanesulphonates, but only the *cis*-alcohol gave a crystalline toluene-*p*-sulphonate. Treatment of *cis*-5-methanesulphonyloxy-2-phenyl-1,3-dioxan with sodium benzoate in boiling dimethylformamide for 6 hr. gave the *trans*-5-benzoate in moderate yield (40%). Likewise the *trans*-methanesulphonate was converted into the *cis*-benzoate (39%). Considerable decomposition occurred in these reactions but no starting material could be recovered and the benzoates isolated were pure isomers. The similar ease of exchange of the *cis*- and *trans*-methanesulphonates is probably due to the remoteness of the phenyl group from the methanesulphonyloxy-residue, resulting in minimal steric hindrance and no great resistance to the assumption by the 1,3-dioxan ring of conformations with the methanesulphonyloxy-groups suitably oriented for nucleophilic displacement. The presence of a substituent vicinal and *trans* to the sulphonyloxy-group may prevent exchange; thus, 1,3 : 4,6-di-*O*-methylene-2,5-di-*O*-toluene-*p*-sulphonyl-D-mannitol, and 1,3-*O*-benzylidene-4-deoxy-2-*O*-methanesulphonyl-L-erythritol were largely unaffected by sodium benzoate in boiling dimethylformamide.

All the *cis*-2-alkyl-5-hydroxy-1,3-dioxans gave crystalline methanesulphonates and each of the latter derivatives was converted into the respective *trans*-benzoate by sodium benzoate in dimethylformamide. The *trans*-alcohols were obtained by hydrolysis of the benzoates and all the *cis*- and *trans*-2-alkyl-5-hydroxy-1,3-dioxans were characterised as the *p*-phenylazobenzoates; Table 2 contains details of physical properties for these 1,3-dioxan derivatives.

In solutions of alcohols in carbon tetrachloride which are $\not> 0{\cdot}005$M, intermolecular

---

[1] Part XI, Bukhari, Foster, Lehmann, Webber, and Westwood, *J.*, 1963, 2291.

[2] Hill, Hill, and Hibbert, *J. Amer. Chem. Soc.*, 1928, **50**, 2243.

[3] Hibbert and Trister, *Canad. J. Res.*, 1936, **14**, *B*, 415.

[4] Baggett and Foster, unpublished observations quoted in Barker, Brimacombe, Foster, Whiffen, and Zweifel, *Tetrahedron*, 1959, **7**, 10.

[5] Reist, Spencer, and Baker, *J. Org. Chem.*, 1959, **24**, 1618; see also Parts X and XI of this series.

[6] Dobinson and Foster, *J.*, 1961, 2338.

hydrogen bonding is negligible and absorptions in the hydroxyl stretching region of the infrared spectra may be assigned to free and intramolecularly bonded hydroxyl groups.[7] Further, the relative extinction coefficients for these absorptions may be used[8] as an approximate index of the proportion of free and bonded hydroxyl groups. The absorptions for the 2-alkyl-5-hydroxy-1,3-dioxans and related compounds are shown in Table 1. 5-Hydroxy-1,3-dioxan has absorptions for free and bonded hydroxyl groups at 3636 (ε 21) and 3593 cm.$^{-1}$ (ε 100) which have been interpreted[4] as indicating the conformational equilibrium (I) $\rightleftharpoons$ (II) with the latter predominant. The introduction of a substituent into the 1,3-dioxan ring apparently displaces the equilibrium. Thus, *cis*-5-hydroxy-2-phenyl-1,3-dioxan has absorption for bonded hydroxyl groups only suggesting stabilisation of conformation (III) by the equatorial phenyl group.[4] On the other hand, *trans*-5-hydroxy-2-phenyl-1,3-dioxan has absorptions at 3633 (ε 79) and 3601 cm.$^{-1}$ (ε 26) for free and bonded hydroxyl groups, indicating either a conformational equilibrium with the predominant contributor containing free hydroxyl groups or a single conformation with an incompletely bonded hydroxyl group. Thus, by analogy, the *cis*-configuration may be assigned to the 2-alkyl-5-hydroxy-1,3-dioxans which have absorption for bonded hydroxyl groups only and the *trans*-configuration to the isomeric compounds. These assignments have been further confirmed by proton magnetic resonance spectroscopy of the benzoates.[9]

TABLE 1.

Infrared spectral data for some derivatives of 5-hydroxy-1,3-dioxan in carbon tetrachloride (0·005M).

		$\nu_{max.}$ (cm.$^{-1}$)					$\nu_{max.}$ (cm.$^{-1}$)		
Derivative	Confign.	Free OH	Bonded OH	$\frac{\log_{10}(I_0/I_B)}{\log_{10}(I_0/I_F)}$ *	Derivative	Confign.	Free OH	Bonded OH	$\frac{\log_{10}(I_0/I_B)}{\log_{10}(I_0/I_F)}$ *
(Parent)	—	3636	3593	5·70	2-Pr^i	*cis*	—	3592	—
2-Me	*cis*	—	3592	—	2-Pr^i	*trans*	3634	3602	0·26
2-Me	*trans*	3633	3604	0·40	2-Ph	*cis*	—	3590	—
2-Et	*cis*	—	3592	—	2-Ph	*trans*	3633	3601	0·32
2-Et	*trans*	3634	3602	0·29					

* Values of I_0, I_B, and I_F, taken directly from the spectra, had average magnitudes of 22, 16, and 6 cm.

The proportions of free and bonded hydroxyl groups for each 5-hydroxy-1,3-dioxan derivative in Table 1 can also be described approximately in terms of the ratio $\log_{10}(I_0/I_B)/\log_{10}(I_0/I_F)$, where I_B and I_F refer to bonded and free hydroxyl absorptions, respectively. The ratio of 5·70 for 5-hydroxy-1,3-dioxan reflects (as also do the ε values) the interpretation that most of the hydroxyl groups are hydrogen-bonded. The infrared spectra in the hydroxyl stretching region for the *trans*-substituted 5-hydroxy-1,3-dioxans in Table 1 were very similar. The absorption ratios less than unity indicate that, in each case, most of the hydroxyl groups were free. Moreover, the ratios are not significantly different when the 2-substituent is Et, Pr^i, or Ph. It is difficult to reconcile these observations with the conformational equilibrium of the type (IV) $\rightleftharpoons$ (V) previously shown arbitrarily[10] for *trans*-5-hydroxy-2-phenyl-1,3-dioxan and in which bonding is shown to occur in conformation (V). If such were the case then, because of adverse non-bonded interactions associated with the axial 2-group in conformation (V), progressive destabilisation of the conformation would be expected to occur as its bulk increased along the series Me, Et, and Pr^i with a consequent increase in the proportion of free hydroxyl groups.

---

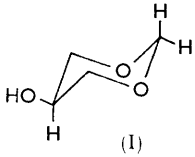
[7] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492; 1954, **76**, 4323.

[8] Cole and Jefferies, *J.*, 1956, 4391.

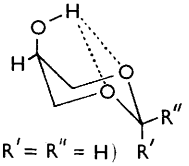
[9] Bukhari, Foster, Homer, Lehmann, Thomas, and Webber, unpublished results, cf. Baggett, Dobinson, Foster, Homer, and Thomas, *Chem. and Ind.*, 1961, 106.

[10] Baggett, Brimacombe, Foster, Stacey, and Whiffen, *J.*, 1960, 2574.

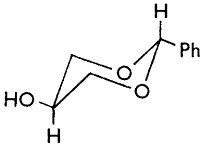
The slightly larger value of the ratio for *trans*-5-hydroxy-2-methyl-1,3-dioxan, if significant at all, must mean that the maximum steric effect is not achieved by the methyl group but is achieved by ethyl and larger groups. Reservations about the use of conformation (V) as that in which hydrogen bonding occurs in *trans*-5-hydroxy-2-phenyl-1,3-dioxan have been expressed,[10] and it was recognised that adverse non-bonded interactions associated with the axial phenyl group might cause deformation of the chair conformation to an extent that could not, however, be assessed.



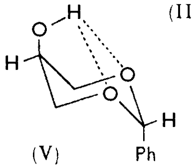
(I)



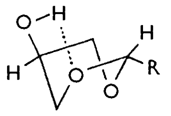
(II: R′ = R″ = H)
(III: R′ = H, R″ = Ph)



(IV)



(V)



(VI)

Examination of molecular models suggests that there may be conformations other than the chair forms of each *trans*-2-alkyl-5-hydroxy-1,3-dioxan in which intramolecular hydrogen bonding of the hydroxyl group with a ring-oxygen atom can occur and in which the bulk of the alkyl group might not be critically important. An example is the boat conformation (VI) which contains two noteworthy structural features. First, the alkyl group is eclipsed with a lone pair of electrons on the neighbouring ring oxygen atom; and, secondly, the inward pointing hydrogen atom at the " bow " position is directed toward a lone pair of electrons on the oxygen atom at the other " bow " position. The size of the resultant non-bonded interactions will depend on the steric requirement of the lone pairs of electrons, which is uncertain but may be less than that of a hydrogen atom in a methylene group.[11] If this is so, then boat conformations of certain 1,3-dioxan derivatives such as (VI) may be less unpreferred than in the analogous cyclohexane compounds. Other workers [12] have concluded that, in certain sugar derivatives, steric effects may cause deformation of the chair conformations normally preferred by tetrahydropyran rings.

EXPERIMENTAL

Preparation of Methanesulphonates.—Ice-cold solutions of *cis*-5-hydroxy-2-phenyl-1,3-dioxan (0·5 g.) in pyridine and methanesulphonyl chloride (1 ml.) in pyridine (4 ml.) were mixed and stored at room temperature for 5 hr. The mixture was then poured into ice–water (*ca.* 50 ml.), and the precipitate was collected, washed with water, and recrystallised from ethanol to give the methanesulphonate (0·52 g., 73%). The methanesulphonates in Table 2 were prepared by essentially the above method.

Benzoate Exchange Experiments.—A solution of *cis*-5-methanesulphonyloxy-2-phenyl-1,3-dioxan (10·4 g.) in dimethylformamide (370 ml.) was boiled under reflux for 6 hr. in the presence of sodium benzoate (29·7 g.). Water was then added to the cooled solution until precipitation was complete and, after 30 min., the precipitate was collected, washed with water, and recrystallised from ethanol. *trans*-5-Benzoyloxy-2-phenyl-1,3-dioxan (4·62 g., 40%) was obtained with m. p. 103—104° alone or in admixture with the authentic compound.[6] Likewise *trans*-5-methanesulphonyloxy-2-phenyl-1,3-dioxan gave *cis*-5-benzoyloxy-2-phenyl-1,3-dioxan (39%) with m. p. 103—104°, and the *trans*-benzoates in Table 2 were obtained from the corresponding *cis*-methanesulphonates.

---

[11] Roberts and Shoppee, *J.*, 1954, 3418; McCoubrey and Ubbelohde, *Quart. Rev.*, 1951, **5**, 364.

[12] Bentley, *J. Amer. Chem. Soc.*, 1959, **81**, 1952; Spedding, *J.*, 1961, 3617.

Saponification of the 5-*Benzoyloxy*-1,3-*dioxan Derivatives*.—A mixture of the benzoate (0·01 mole), 10% aqueous sodium hydroxide (30 ml.), and tetrahydrofuran (*ca.* 1·0 ml.) was heated at 95—100° for 4 hr. The cooled solution was neutralised with carbon dioxide and then continuously extracted with ether for 24 hr. The extract was dried ($MgSO_4$), and concentrated, and the residue distilled, to yield the *trans*-2-alkyl-5-hydroxy-1,3-dioxan derivative. Analytical data and other information are recorded in Table 2 for the alcohols and for the *p*-phenylazobenzoates which were prepared by a standard procedure.[13]

Infrared Spectra.—Spectra in the hydroxyl stretching region were obtained from CCl_4 solutions of the alcohols in 2- or 3-cm. layers (fused quartz cells) by means of a Unicam S.P. 100 spectrometer equipped with a grating (3000 lines per in.). Frequencies were checked against water vapour and ammonia bands. The concentration of the alcohols was always $<0{\cdot}005$M in order to eliminate intermolecular hydrogen bonding; the extinction coefficients (ε) are maximum values and are equal to $(1/cl)\log_{10}(I_0/I)$, with l in cm. and c in moles/l.

TABLE 2.

Analytical and other data for certain derivatives of 1,3-dioxan.

No.	1,3-Dioxan derivative	Confign.	Yield (%)	M. p. or b. p.
1	5-Methanesulphonyloxy-2-phenyl	*cis*	73	134—135°
2	5-Methanesulphonyloxy-2-phenyl	*trans*	74	106—107
3	5-Methanesulphonyloxy-2-methyl	*cis*	62	79—80
4	5-Benzoyloxy-2-methyl	*trans*	39	30—31
5	5-Hydroxy-2-methyl	*trans*	47	96—98°/~12 mm.
6	2-Methyl-5-*p*-phenylazobenzoyloxy	*trans*	41	141—143
7	2-Methyl-5-*p*-phenylazobenzoyloxy	*cis*	95	184—185
8	2-Ethyl-5-methanesulphonyloxy	*cis*	83	77—77·5
9	5-Benzoyloxy-2-ethyl	*trans*	41	48—49
10	2-Ethyl-5-hydroxy	*trans*	45	100°/~12 mm.
11	2-Ethyl-5-*p*-phenylazobenzoyloxy	*trans*	33	138—139
12	2-Ethyl-5-*p*-phenylazobenzoyloxy	*cis*	70	170—171
13	2-Isopropyl-5-methanesulphonyloxy	*cis*	83	99—100
14	5-Benzoyloxy-2-isopropyl	*trans*	47	49—50
15	5-Hydroxy-2-isopropyl	*trans*	55	106—112°/~12 mm.
16	2-Isopropyl-5-*p*-phenylazobenzoyloxy	*trans*	47	145—146
17	2-Isopropyl-5-*p*-phenylazobenzoyloxy	*cis*	46	177—178

	Found (%)					Required (%)			
No.	C	H	N	S	Formula	C	H	N	S
1	51·4	5·4		12·6	$C_{11}H_{14}O_5S$	51·2	5·4		12·4
2	50·85	5·3		12·1	$C_{11}H_{14}O_5S$	51·2	5·4		12·4
3	36·75	6·1		16·4	$C_6H_{12}O_5S$	36·7	6·1		16·3
4	64·7	6·05			$C_{12}H_{14}O_4$	64·9	6·3		
5	51·0	8·4			$C_5H_{10}O_3$	50·85	8·5		
6	65·7	5·6	8·5		$C_{18}H_{18}N_2O_4$	66·3	5·6	8·6	
7	67·0	5·3	8·45		$C_{18}H_{18}N_2O_4$	66·3	5·6	8·6	
8	40·05	6·8		15·15	$C_7H_{14}O_5S$	40·0	6·7		15·2
9	66·4	7·1			$C_{13}H_{16}O_4$	66·1	6·8		
10	53·9	9·1			$C_6H_{12}O_3$	54·5	9·1		
11	66·6	6·0	8·5		$C_{19}H_{20}N_2O_4$	67·05	5·9	8·2	
12	66·8	6·0	8·2		$C_{19}H_{20}N_2O_4$	67·05	5·9	8·2	
13	43·0	7·2		14·15	$C_8H_{16}O_5S$	42·9	7·1		14·3
14	66·9	7·2			$C_{14}H_{18}O_4$	67·2	7·2		
15	57·4	9·6			$C_7H_{14}O_3$	57·5	9·6		
16	67·7	6·3	8·0		$C_{20}N_{22}N_2O_4$	67·9	6·0	8·0	
17	67·9	6·1	8·2		$C_{20}H_{22}N_2O_4$	67·9	6·0	8·0	

The authors thank Professor M. Stacey, F.R.S., for his interest and for the provision of facilities. The Man-made Fibres Research Association is thanked for the use of the Unicam S.P. 100 spectrometer and Dr. H. Spedding for assistance with the instrument.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

[*Received, January* 18*th*, 1963.]

---

[13] Baggett, Haines, Foster, and Stacey, *J.*, 1960, 3528.