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Conformational Analysis

VIII. Separation and PMR Spectra of Some 4-Oxo-1,3-dioxans Derived from Diastereoisomeric 3-Hydroxy-2-methylbutyric Acids

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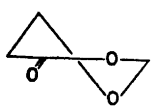
Isomeric 5,6-dimethyl-, 2,5,6-trimethyl-, and 2,2,5,6-tetramethyl-4-oxo-1,3-dioxans have been prepared and separated. The ring conformations were determined by means of chemical equilibration and PMR spectroscopy. The data reveal that most of the compounds adopt a half-chair conformation. 2,2-*cis*-5,6-Tetramethyl-4-oxo-1,3-dioxan, however, seems to assume a twist-boat conformation and *r*-2-*cis*-5-*trans*-6-trimethyl-4-oxo-1,3-dioxan seems to be a mixture of half-chair and 2,5-boat conformations.

Alkyl-substituted 4-oxo-1,3-dioxans have two favoured ring conformations.[1–3] The half-chair form (1) with a planar lactone grouping is the most usual, but a proper substitution, *e.g.* an axial substituent in the 6 position, forces the ring (at least partly) into a 2,5-boat form (2) which still has an approximately planar lactone grouping.[1] Geminal substitution in the 6 position seems to have a similar effect as was noted earlier for 2,6,6-trialkyl and 2,5,6,6-tetra-alkyl derivatives.[2,3] An axial 2 or 6 substituent can, however, also change



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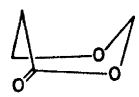

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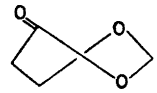

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the ring conformation towards a 2,5-twist-boat form (3) in which the lactone atoms are not wholly coplanar.[2–4] In this paper derivatives with a methyl substituent in the 5 and 6 positions and with 0 to 2 methyl substituents in the 2 position will be considered. These derivatives were prepared from a mixture of *erythro*- and *threo*-3-hydroxy-2-methylbutyric acids and so exist in diastereomeric forms as well.

EXPERIMENTAL

The synthesis of all oxalactones except that of the 2,2,5,6-tetramethyl-4-oxo-1,3-dioxans has been described earlier (Table 1).[5] The exception was prepared conventionally [1] and had a boiling point of 82 – 94°C/12 Torr (partly decomposed during distillation).

Table 1. 4-Oxo-1,3-dioxans derived from *erythro*- and *threo*-3-hydroxy-3-methylbutyric acids.

I	*trans*-5,6-Dimethyl-4-oxo-1,3-dioxan[a]
II	*cis*-5,6-Dimethyl-4-oxo-1,3-dioxan[b]
III	*r*-2-*trans*-5-*cis*-6-Trimethyl-4-oxo-1,3-dioxan[a]
IV	*r*-2-*cis*-5-*trans*-6-trimethyl-4-oxo-1,3-dioxan[a]
V	*r*-2-*cis*-5-*cis*-6-Trimethyl-4-oxo-1,3-dioxan[b]
VI	*r*-2-*trans*-5-*trans*-6-Trimethyl-4-oxo-1,3-dioxan[b]
VII	2,2-*trans*-5,6-Tetramethyl-4-oxo1,3-dioxan[a]
VIII	2,2-*cis*-5,6-Tetramethyl-4-oxo1,3-dioxan[b]

[a] From *threo* acid. [b] From *erythro* acid.

The diastereoisomers were separated on a preparative gas chromatograph.[1] The epimer pairs of the isomeric 2,5,6-trimethyl-4-oxo-1,3-dioxans were obtained directly from *erythro*- and *threo*-3-hydroxy-2-methylbutyric acids *via* their 5,6-dimethyl derivatives in the way described earlier.[6] The chemical equilibrations were performed as before (catalyst *p*-TOS).[1] The PMR spectra were recorded with a 60 MHz Perkin-Elmer R 10 instrument and a variable temperature probe was used for recording the spectrum of *cis*-5,6-dimethyl-4-oxo-1,3-dioxan at different temperatures. The samples contained 40 mg solute in 400 µl solvent. TMS was used as internal standard. A first order analysis was used to evaluate the spectral parameters.

RESULTS AND DISCUSSION

2,5,6-Trimethyl-4-oxo-1,3-dioxans. Epimeric *r*-2-*trans*-5-*cis*-6- (III) and *r*-2-*cis*-5-*trans*-6-trimethyl-4-oxo-1,3-dioxans (IV) were obtained from *threo*-3-hydroxy-2-methylbutyric acid (*cf.* Table 1). Chemical equilibration (eqn. 1) revealed that the tri-equatorial epimer (III) is favoured by enthalpy whereas

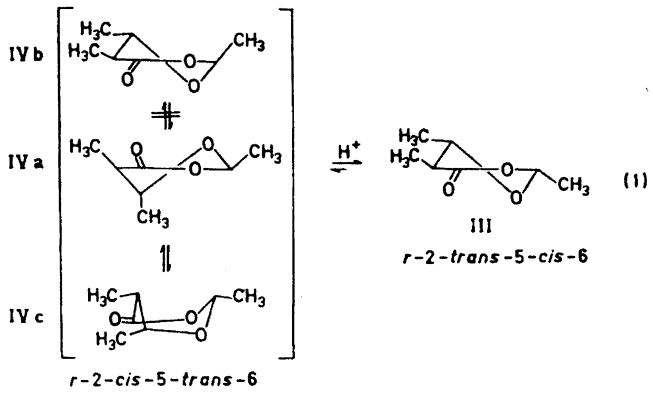


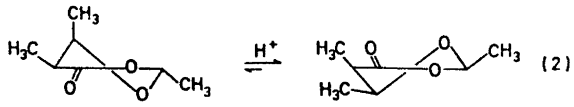
Table 2. The chemical equilibration of the epimer pairs of 2,5,6-trimethyl-4-oxo-1,3-dioxans.

°C	K III/IV[a]	$-\Delta G°$ kJ/mol	$-\Delta H°$ kJ/mol	$\Delta S°$ J mol^{-1} K^{-1}
65	3.28	3.34		
54	3.47	3.38		
45	4.10	3.75		
			4.98 ± 0.75[b]	-4.60 ± 2.38[b]
(25	5.02	4.00)		
11	4.61	3.61		
−9	5.51	3.75		
	V/VI[c]			
25	1.9	2.1		

[a] See eqn. 1. [b] Standard deviation. [c] See eqn. 2.

IV is favoured by entropy. The entropy difference (Table 2) is of opposite sign than for the 2,6-dialkyl-substituted derivatives.[1] In the latter the entropy was thought to arise from pseudo-libration of the half-chair conformation. In the present case the *gauche* interaction between the 5 and 6 substituents is thought to hinder pseudo-libration and hence the excess entropy of IV is mainly due to a conformational equilibrium between IVa and IVc (eqn. 1). We pointed out earlier[1] that an axial 6-substituent distorts the half-chair conformation towards a 2,5-boat form (IVc). In the half-chair form (IVa, IVb) the 5- and 6-substituents are (pseudo)-axial and the 2-methyl group pseudo-equatorial (IVa), or the 5- and 6-methyl groups are (pseudo)-equatorial and the 2-substituent pseudo-axial (IVb). The latter form makes a minor contribution as it includes a methyl-methyl *gauche* interaction and, moreover, the conformational free energy of an axial 2-methyl group is likely to be much greater than the sum of the conformational energies of the 5 and 6 axial methyl substituents (*cf.* 1,3-dioxans[7]).

Attempts were also made to equilibrate the other epimer pair (V and VI in Tables 1 – 2). Unfortunately, the compounds decomposed rapidly and only the free energy difference 2.1 kJ/mol at 25°C could be measured. This value is probably close to the energy difference between the conformations V and VI (eqn. 2). The other possible half-chair conformation on the right-hand side can be neglected, as in eqn. 1, because of a strong 1,3-interaction between the (pseudo)-axial 2 and 6 substituents. Similarly, 2,5-boat forms of V can be excluded on the basis of PMR data (see below) and those of VI because of



(2)

VI
r-2-*trans*-5-*trans*-6

V
r-2-*cis*-5-*cis*-6

Table 3. The chemical shifts (Hz from internal TMS in CCl_4) of 5,6-, 2,5,6-, and 2,2,5,6-substituted 4-oxo-1,3-dioxans.

	^{1}R(2)	^{2}R(2)	δ_{2H}	δ_{5H}	δ_{6H}	$\delta_{2\text{-}CH_3}$	$\delta_{5\text{-}CH_3}$	$\delta_{6\text{-}CH_3}$
I[a]	H	H	320.0 323.0	145.5	225.0		71.6	80.2
II[b]	H	H	325.0 319.0	169.5	257.0		70.7	72.1
III[a]	Me	H	328.0	136.5	222.5	86.2	70.6	78.4
IV[a]	Me	H	340.0	150.5	228.5	84.1	69.3	80.3
V[b]	Me	H	334.5	164.0	254.5	86.8	70.3	70.6
VI[b,c]	Me	H		144	223	87.0	71.5	77.9
VII[a]	Me	Me		131.5	238.5	91.9 91.9	69.5	76.5
VIII[b]	Me	Me		146.0	264.0	92.5 92.5	71.3	70.9

[a,b] See also eqns. 1 and 2. [a] From *threo* acid. [b] From *erythro* acid. [c] Impure.

Table 4. The coupling constants (Hz) of the compounds studied. Solvent CCl_4.

	^{1}R(2)	^{2}R(2)	$^2J_{2a2e}$	$^3J_{5,6}$	$^3J_{2H,CH_3}$	$^3J_{6H,CH_3}$	$^3J_{6H,CH_3}$
I[a]	H	H	−5.80	10.27		7.13	6.19
II[b]	H	H	−5.78	5.85		7.20	6.35
III[a]	Me	H		10.45	5.21	7.25	6.16
IV[a]	Me	H		9.51	5.18	6.81	6.21
V[b]	Me	H		5.50	5.06	7.30	6.66
VI[b,c]	Me	H			5.28	7.20	6.54
VII[a]	Me	Me		10.21		7.24	6.21
VIII[b]	Me	Me		3.10		7.55	6.43

[a,b,c] See Table 3.

Table 5. Solvent shifts ($\delta_{CCl_4} - \delta_{C_6H_6}$, Hz) of the 4-oxo-1,3-dioxans studied.

	^{1}R(2)	^{2}R(2)	$\Delta\delta_{2H}$	$\Delta\delta_{5H}$	$\Delta\delta_{6H}$	$\Delta\delta_{2\text{-}CH_3}$	$\Delta\delta_{5\text{-}CH_3}$	$\Delta\delta_{6\text{-}CH_3}$
I[a]	H	H	30.0 23.0	22.0	33.0		15.8	26.4
II[b]	H	H	25.5 25.5	28.0	40.0		14.6	24.2
III[a]	Me	H	27.0	17.5	33.5	12.7	13.4	24.5
IV[a]	Me	H	30.0	33.5	19.5	10.9	14.5	28.8
V[b]	Me	H	33.5	27.0	38.0	15.4	12.7	22.9
VI[b,c]	Me	H						
VII[a]	Me	Me		13.0	23.5	20.1 9.8	10.8	21.5
VIII[b]	Me	Me		13.0	31.5	20.2 12.1	8.7	22.6

[a,b,c] See Table 3.

Table 6. The temperature dependence of the coupling constants of *cis*-5,6-dimethyl-4-oxo-1,3-dioxan (II). Solvent CS_2.

T°C	$^3J_{5,6}$	$^3J_{5H,CH_3}$	$^3J_{6H,CH_3}$
−50	5.65	7.09	6.36
−35	5.43	7.40	6.42
−20	5.87	7.26	6.34
−10	5.84	7.12	6.40
10	5.84	7.12	6.37
25	5.27	7.08	6.40
50	5.77	7.12	6.38
75	5.85	7.08	6.30
100	5.46	7.14	6.43

trans-2,5-substitution. The alternative half-chair form of VI can also be neglected because of a pseudo-axial 2-methyl group, for reasons mentioned above.

The PMR parameters of the compounds studied. The PMR data (Tables 3 – 6) reveal that derivatives I, III, and VII (all from *threo* acid, see Table 1) have a similar conformation. The coupling constant $^3J_{5,6}$ is about the same as in *cis*-2,6-dialkyl-substituted derivatives [1] and evidently the 5 and 6 substituents are (pseudo)-equatorially orientated. J_{gem} of the 2 protons of I is −5.8 Hz, a typical value for a half-chair conformation.[3,4] Thus all these derivatives exist in a half-chair conformation like that of *r*-2-*trans*-5-*cis*-6-trimethyl-4-oxo-1,3-dioxan (III in eqn. 1). Compounds II and V (from *erythro* acid, Table 1) also have nearly equal parameters and most probably exist in a half-chair conformation with a pseudo-axial 5 substituent (V in eqn. 2). The solvent shifts of the 6 methyl protons of II and V (Table 5) are 24.2 and 22.9 Hz, respectively. This indicates a half-chair conformation since in a 2,5-boat the methyl group would occupy a pseudo-axial orientation and the solvent shift would be near to 10 Hz.[3,4] Moreover, the J_{gem} of 2 protons of the *cis*-5,6-dimethyl derivative (II) is −5.8 Hz, again a typical value for a half-chair conformation.[3,4] The spectrum of II was recorded at various temperatures (Table 6), but no significant changes were detected. Accordingly, the 5a6e conformation is clearly favoured in agreement with the close similarity of the PMR parameters of II and V.

The trimethyl derivative IV (see Table 1 and eqn. 1) seems to be a mixture of two conformations as mentioned above in discussing the equilibration results. $^3J_{5,6}$ 9.5 Hz, is close to the mean of the values for pure half-chair and 2,5-boat forms (IVa and IVc in eqn. 1),[1] an observation in accord with the entropy difference 4.6 kJ mol^{-1} K^{-1} between III and IV.

r-2-*trans*-5-*trans*-6-Trimethyl-4-oxo-1,3-dioxan (VI) contained too many impurities to allow a full analysis of its PMR spectra. $^3J_{5,6}$ for the tetramethyl derivative (VIII) is only 3.1 Hz, and the other PMR parameters clearly differ from the values for the other oxalactones derived from the *erythro* acid (II and V). Obviously, the *gem*-dimethyl grouping in the 2 position forces the ring

into a twist-boat conformation.[1,2] It is of interest that the other 2,2-disubstituted derivative (VII) has quite "normal" PMR parameters. This again demonstrates the fact that the conformation of the 4-oxo-1,3-dioxan ring is greatly dependent on substitution.

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