STEREOCHEMISTRY OF HETEROCYCLES

XVII.* CONFIGURATION AND CONFORMATION OF SOME STEREOISOMERIC 4,5-SUBSTITUTED 2,2-DIMETHYL-1,3-DIOXANES

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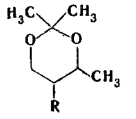
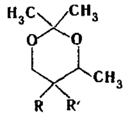
The configurations and preferred conformations in series of 4,5-dialkyl- and 4,5,5-trialkyl-substituted 2,2-dimethyl-1,3-dioxanes were studied. It was proved by PMR spectroscopy that the low-boiling isomers have the cis configuration, while the high-boiling isomers have the trans configuration; moreover, all of the isomers are found in the preferred chair conformation. This conformation experiences a certain amount of distortion, the degree of which depends on the number and character of the substituents in the 5 position.

We have previously [2-5] studied the conformations of 5-substituted 2,2-dimethyl-1,3-dioxanes and, using PMR and dipole moment methods, we have shown that their preferred conformation is a flexible form, the analytical indexes of which are the presence of a gem-dimethyl group singlet ($\delta \sim 1.30$ ppm) and a very small nonequivalence (or almost complete equivalence) of the signal of the methylene protons in the 4 and 6 positions. The configuration of 4,5-dialkyl-1,3-dioxanes, which do not have a substituent in the 2 position, can be predicted by the methods of conformational analysis, based on the rule of asymmetric induction and allowing for the fact that 4,5-substituted 1,3-dioxanes cannot undergo epimerization [6]. In [6] we only briefly indicated the routes to the solution of the problem of the configuration of 4,5-dialkyl-2,2-dimethyl-1,3-dioxanes, but we did not discuss this problem.

The present communication is devoted to a study of the configurations and the proof of the preferred conformations of stereoisomeric 2,2,4-trimethyl-5-alkyl- (A) and 2,2,4-trimethyl-5,5-dialkyl-1,3-dioxanes (B). The synthesis of compounds of the A and B types and their separation into stereoisomers have been previously described [6]. We [6-8] and others [9-12] have proved that their synthesis proceeds stereo-

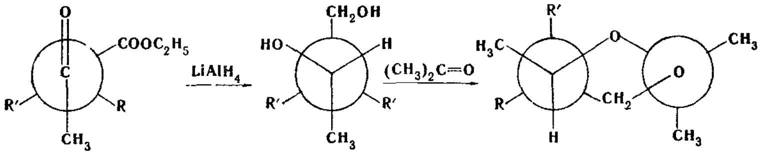


A
I-IV



B
V-IX

I $R=CH_3$; II $R=C_2H_5$; III $R=i\text{-}C_3H_7$; IV $R=n\text{-}C_3H_7$; V $R=CH_3$, $R'=C_2H_5$; VI $R=CH_3$, $R'=i\text{-}C_3H_7$; VII $R=C_2H_5$, $R'=i\text{-}C_3H_7$; VIII $R=R'=H$; IX $R=R'=CH_3$



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*See [1] for communication XVI.

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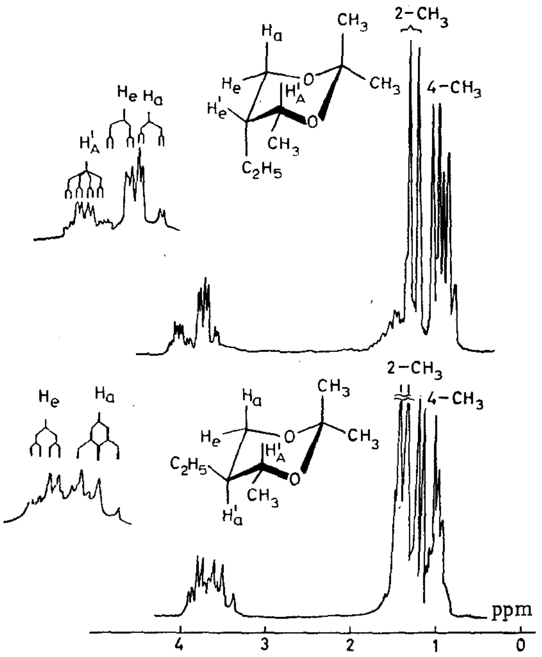

Fig. 1. PMR spectra of the low-boiling (IIa) and high-boiling (IIb) stereoisomers of 2,2,4-trimethyl-5-ethyl-1,3-dioxane.

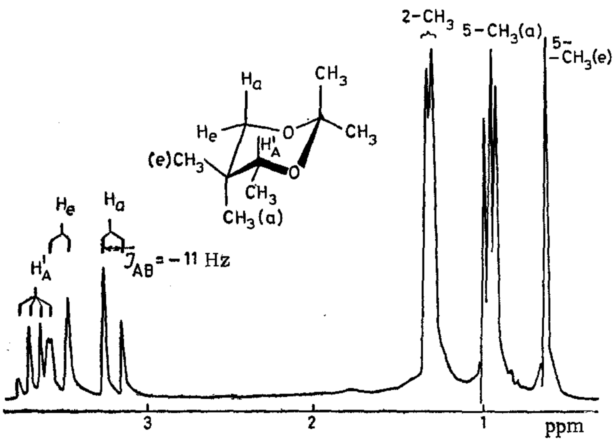

Fig. 2. PMR spectrum of 2,2,4,5,5-pentamethyl-1,3-dioxane.

specifically, and the configuration of the principally formed isomer is determined by one of the modifications of the Cram rule [13, 14]; the erythro isomer of the 1,3-diol (D) is obtained in preponderance from the substituted acetoacetic ester (C), while D gives predominantly the cis isomer of the 1,3-dioxane (E).

The ratio of stereoisomers in series A and B is determined by the degree of stereospecificity of the asymmetric induction during the conversion of compounds C to diols D. This ratio was found to be 65-85% 35-15%, depending on the substituents (R and R') [6]. The configurations and preferred conformations of dioxanes A and B were established by PMR spectroscopy.

2,2,4-Trimethyl-1,3-dioxane (VIII) was the standard for the study of the stereoisomers. In its PMR spectrum, each of the methyl groups in the 2 position gives a singlet (δ 1.35 ppm for the equatorial methyl group and 1.25 ppm for the axial methyl group). The signal of the 4-CH_3 group is a typical methyl doublet with a chemical shift of 1.07 ppm. It is observed at the same chemical shift values that are characteristic for a 4-CH_3 equatorial group [6]. Thus the character of the resonance of the methyl protons is typical for the preferred chair conformation with an equatorial 4-CH_3 group.

The PMR spectra of the low-boiling (IIa) and high-boiling (IIb) isomers of 2,2,4-trimethyl-5-ethyl-1,3-dioxane are presented in Fig. 1. Each of the two methyl groups of the gem-dimethyl grouping resonates at 1.36 ppm (equatorial methyl group) and 1.30 ppm (axial methyl group), respectively, in the spectrum of each of the isomers. The 4-H and 6-H ring protons also display the nonequivalence typical for the chair conformation.

The doublet of the methyl group in the 4 position has a chemical shift of 1.10 ppm in the spectra of both isomers; this, as noted above, is evidence for its equatorial orientation. The methylene protons in the 6 position form a typical AB quartet with a geminal $^2J_{HH'}$ constant of –12 Hz in the spectrum of IIb, the lines of which experience additional multiplicity with $^3J_{ae'}$ = 5.0 Hz and $^3J_{aa'}$ = 12 Hz. These data indicate the equatorial orientation of the 5-C_2H_5 group in isomer IIb. In the spectrum of isomer IIa, the signal of the methylene protons in the 6 position is characterized by a geminal $^2J_{HH'}$ constant of –12.0 Hz and vicinal constants $^3J_{ae'}$ = 3.0 Hz and $^3J_{ee'}$ = 2.0 Hz, respectively; this corresponds to an axial orientation of the 5-C_2H_5 group in isomer IIa.

It follows from the well-known Karplus correlation [15], taken with allowance for the effect of the electronegativity of the acetal oxygen, that dihedral angles $\Phi_{ae'}$ and $\Phi_{aa'}$ in the spectrum of isomer IIb are ~40 and ~180°, respectively; similarly, $\Phi_{ae'}$ ~ 55° and $\Phi_{ee'}$ ~ 60° in the spectrum of isomer IIa. Thus the preferred chair conformation with a slight deviation from parallelism of the axial valences in the 6, 4, and 2 positions is typical for the stereoisomers under consideration.

The orientation of the 5-C_2H_5 group can also be judged from the chemical shift of the signal of the protons of the methylene group of the ethyl group. In the low-boiling isomer (IIa), this group resonates at 1.45 ppm, but its signal is shifted to higher field in the high-boiling isomer (IIb).

Since the protons of the methyl groups and other substituents in the 5 position of the 1,3-dioxane ring experience a reversal of the chemical shifts under the influence of the anisotropy of the magnetic susceptibility of the unshared pairs of electrons of the two ring oxygen atoms [3], the C_2H_5 group is in the axial position in isomer IIa and in the equatorial position in isomer IIb.

This information is also confirmed by a study of the PMR spectra of isomers of 2,2,4,5-tetramethyl-1,3-dioxane. The 5-CH_3 group gives a doublet resonance signal at δ 1.03 ppm in the spectrum of isomer Ia; according to [3], this corresponds to an axial methyl group. This doublet is found at 0.68 ppm in the spectrum of isomer Ib, and this corresponds to an equatorial methyl group.

It follows from all of the above that isomer IIa is the cis isomer, while isomer IIb is the trans isomer.

The spectra of stereoisomers Ia and Ib and IIIa and IIIb are similar to the examined spectra of IIa and IIb. The PMR spectrum of the nonstereoisomeric 2,2,4,5,5-pentamethyl-1,3-dioxane (IX) (Fig. 2) is extremely close to the spectra considered above. The singlet peak of an equatorial methyl group in the 5 position (δ 0.64 ppm) and the singlet peak of an axial 5-CH_3 group (0.96 ppm) are distinctly displayed in this spectrum. The doublet of the methyl group in the 4 position has a chemical shift of 1.00 ppm, which indicates that it is equatorially oriented. An additional confirmation of the correctness of this sort of assignment is the absence of an additional multiplet signal of the equatorial 6-H proton; this attests to a very small long-range spin–spin coupling constant ($^4J_{HH'}$) and, consequently, to the axial character of the 4-H proton. The methyl groups in the 2 position resonate at 1.31 ppm (axial) and 1.34 ppm (equatorial), while the methylene protons in the 6 position form an AB quartet with $^2J_{HH'}$ = 11.0 Hz; this is characteristic for the chair conformation.

TABLE 1. Chemical Shifts and Spin–Spin Coupling Constants of 4,5-Substituted 2,2-Dimethyl-1,3-dioxanes

Comp.	$\delta_{2\text{-}CH_3}$, ax	$\delta_{2\text{-}CH_3}$, eq.	$\Delta\delta_{gem}$, Hz	$\delta_{4\text{-}CH_3}$, ppm	$\delta_{Ha'}$, ppm	$\delta_{He'}$, ppm	$^2J_{HH}$*, Hz	$\delta_{ae'}$, ppm	$J_{ae'}$, Hz	$J_{ee'}$, Hz	$J_{ea'}$, Hz	$J_{aa'}$, Hz	$\delta_{5\text{-}CH_3}$ (eq.), ppm	$\delta_{5\text{-}CH_3}$ (ax), ppm	$\delta_{H_X'}$, ppm
Ia	1,36	1,30	6	1,03							—	—	—	1,03	
b	1,36	1,30	6	1,11	3,36	3,58	–11,5	0,22	—	—	6,0	11,0	0,68		3,43
IIa	1,37	1,26	11	1,06	3,71	3,89	–12,0	0,17	2,0	3,0	—	—	—	—	4,82
b	1,33	1,24	9	1,10	3,43	3,75	–12,0	0,32	—	—	5,0	12,0	—	—	3,60
IIIa	1,34	1,22	12	1,08	3,84	3,87					—	—	—	—	4,17
b	1,32	1,24	8	1,10	3,59	3,66							—	—	3,85
IX	1,34	1,31	3	0,97	3,19	3,50	–11,0	0,37	—	—	—	—	0,64	0,96	3,63
Va	1,36	1,32	4	0,97	3,52	3,30	–11,5	0,22	—	—	—	—	0,58	—	3,71
VIa	1,35	1,30	5	1,14	3,31	3,72	–12,0	0,41	—	—	—	—	0,60	—	3,76

To a considerable extent, the spectra of stereoisomers Va and Vb and VIa and VIb remind one of the spectrum of IX, since doublets of the 4-CH_3 groups at 1.00-1.11 ppm, unequivalent singlets of a gem dimethyl group at 1.22-1.36 ppm, typical AB quartets of a methylene group in the 6 position, and different (for each type of substitution) signals of alkyl groups in the 5 position are observed in the spectra of all of these compounds. The overall pattern of the observed chemical shifts and spin–spin coupling constants is presented in Table 1. In the series under discussion, the low-boiling isomers are cis isomers and the high-boiling isomers are trans isomers.

It is extremely interesting to note that the $\Delta\delta$ value, which characterizes the nonequivalence of the methyl groups in the 2 position, depends substantially on the type of substitution in the ring. Thus, in the VIII : Ia : Ix series (see Table 1), the nonequivalence of the gem dimethyl groups decreases from 10.0 to 3.0 Hz, while it increases from 3.0 to 5.0 Hz in the order IX : V : VI. The same is also observed in the order VIII : IIa : IIIa [and larger nonequivalence values of the gem-dimethyl protons (up to 12 Hz) show up here] and, for the trans isomers, in the order Ib : IIb : IIIb, where the nonequivalence ranges from 6 to 9 Hz.

While the singlet character of the signal of the gem dimethyl group in the 2 position was one of the analytical indexes of the flexible conformation, the decrease in the equivalence of these protons can be acknowledged as an indication of the degree of distorted character of the chair conformation in the flexible form. Adopting this assumption as an explanation of the observed phenomenon, we arrive at the conclusion that the chair is most distorted in the region of the atoms of the 1, 2, and 3 positions of the ring in IX and that the introduction of large substituents into the 5 position promotes lesser distortion of the chair in this region. The latter may be a consequence of the fact that large substituents cause deformation of the ring in the region of the 4-5-6 atoms and thereby promote the most favorable arrangement of the alkyl substituents.

By following this explanation, we also arrive at the conclusion that the 1,3-dioxanes of series B experience more distortion of the chair conformation in the region of the 1-2-3 ring atoms than do the dioxanes of series A.

It is also apparent from Table 1 that a considerable shift of the signal of the 6-H and 4-H axial protons to lower field as compared with the spectra of the analogous trans isomers is observed in the spectra of the cis isomers in series A (in the case of Ia and IIIa, almost complete coincidence of the chemical shifts of the axial and equatorial protons is observed). This phenomenon is similar to that observed by Pihlaja and Äyräs [16] in the cyclohexane and 1,3-dioxane series, and it is explained by deshielding of the 4 and 6 axial positions by the axial substituent in the 5 position.

EXPERIMENTAL

The PMR spectra were recorded with a Varian HA-100D spectrometer at 100 MHz. The samples were 10% solutions of the compounds in CCl_4. Tetramethylsilane was used as the internal standard.

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