STEREOCHEMISTRY OF HETEROCYCLES

XX.* SYNTHESIS, PROPERTIES, AND SOME QUESTIONS OF STEREOCHEMISTRY OF 2,2,5-SUBSTITUTED 1,3-DIOXANES

A. I. Gren', Nguyen Van Dyep,
A. V. Bogat-skii, and Yu. Yu. Samitov

UDC 547.841.07:541.67.634

Some 2,5-dialkyl-2-methyl-1,3-dioxanes and 5-alkyl-2-methyl-2-phenyl-1,3-dioxanes have been synthesized. All the compounds studied consist of epimeric mixtures of geometric isomers the equilibrium in the course of the formation of which is shifted in the direction of the isomers with the diequatorial position of the largest substituents. The predominant conformation of the molecules of both isomers is the chair conformation. The cis isomers of the substances investigated consist of mixtures of conformers.

The stereochemical problems of substituted 1,3-dioxanes have been studied by a number of workers [2-4]. However, the stereochemical features of 5-substituted 1,3-dioxanes having two substituents in position 2 one of which is a methyl and the other either an alkyl or an aryl group have not previously been discussed. The study of the predominant conformations of the molecules of such compounds is important for a further investigation of the features of the conformational interactions in various substituted 1,3-dioxane systems. Attempting to obtain this information, we have synthesized a series of 2,2,5-trialkyl- and 2,5-dialkyl-2-phenyl-1,3-dioxanes. The synthesis was performed by the usual methods [4], and the structure of the compounds obtained (Table 1) was confirmed by the usual analysis of IR and PMR spectra.

From the PMR spectra of the 2,2,5-trisubstituted 1,3-dioxanes it follows that they are mixtures of geometric isomers. Only in the dioxanes (XI-XIII) is one of the stereoisomers present in very small amounts (5-6%) in the epimeric mixture. As follows from the PMR spectra, the predominant conformation of the molecules of both isomers is the chair conformation, and the isomer existing in the epimeric mixture in larger amount has the trans configuration with the diequatorial position of the larger substituents.

Figure 1 gives the PMR spectra of the low-boiling isomer of compound (IX) isolated from the mixture of epimers by fractionation in total-condensation fractionating columns with an efficiency of 60 theoretical plates. The spectrum has the singlet signal of the protons of the 2-CH_3 group at 1.15 ppm, the doublet of the protons of the methyl groups of two isopropyl substituents at 0.87 ppm, and two septets of the methine protons of the isopropyl substituents with chemical shifts of 1.60 and 2.24 ppm. The doublets of the methyl protons of the two isopropyl groups in the spectrum of this isomer fuse.

The fact that the chair conformation is the predominant one is shown by the form of the signal of the methylene protons in positions 4 and 6 of the ring. Axial protons resonate further upfield (3.59 ppm) than equatorial protons (3.77 ppm). In the spectrum of each methylene group, because of the limiting shift of the conformational equilibrium in the direction of a definite predominant conformation, the protons form an AB spin system with a geminal constant $^2J_{AB} = -11.5$ Hz. According to the literature [4], such a constant is typical for 1,3-dioxanes in the chair conformation.

The interaction of the 5-H proton with the methylene protons of the ring leads to an additional multiplicity of the AB line of the quadruplet. The following values of the vicinal constants are observed:

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*For Communication XIX, see [1].

I. I. Mechnikov Odessa State University. V. I. Ul'yanova-Lenin Kazan' State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1240-1245, September, 1973. Original article submitted July 31, 1972.

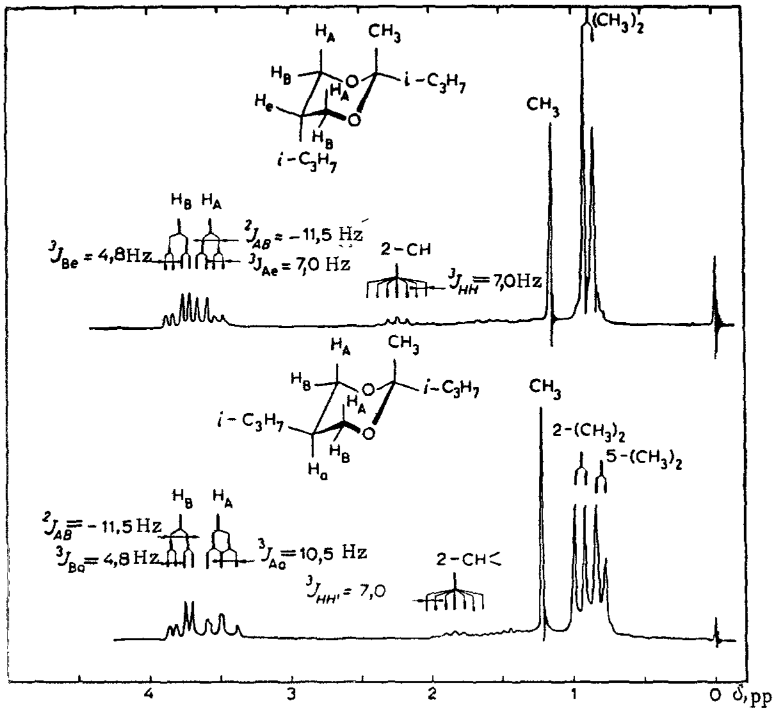


Fig. 1. PMR spectra of the low-boiling (top) and high-boiling (bottom) isomers of 2,5-diisopropyl-2-methyl-1,3-dioxane.

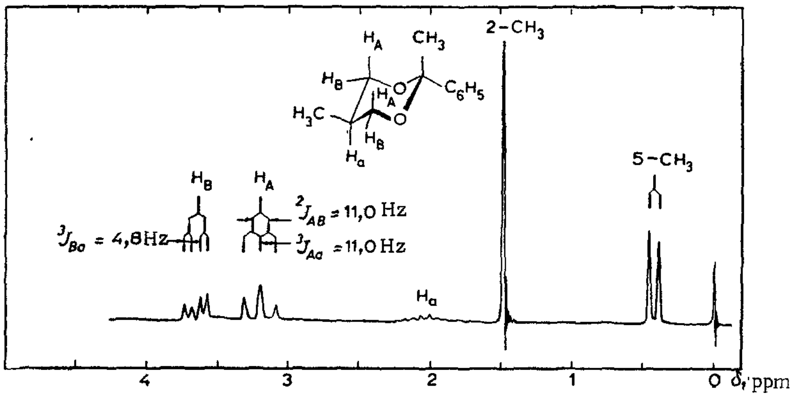
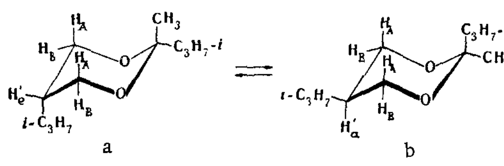


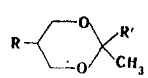
Fig. 2. PMR spectrum of 2,5-dimethyl-2-phenyl-1,3-dioxane.

$^3J_{H_AH'_e}$ = 7,0 Hz and $^3J_{H_BH'_e}$ = 4,8 Hz. However, it is known [2, 3, 5] that the values of these constants for the majority of the 2,5-dialkyl-1,3-dioxanes studied are 3-4.5 and 1.5-2.5 Hz, respectively. The higher vicinal constants observed in the spectrum of the low-boiling isomer of compound (IX) can be explained by assuming that the sample investigated was an equilibrium mixture of the conformers a and b with a predominance of the former (a : b ratio approximately 60 : 40).



The orientation of the isopropyl group in position 5 of the conformer a can be determined from the value of the chemical shift of the methine proton of this group (δ 2.24 ppm); in view of the presence of conformer b and the averaging of the chemical shift of this proton, and also previous results [6], it may be assumed that the isopropyl substituent is axial. This is also indicated by the nature of the resonance of the methylene protons of the 1,3-dioxane ring that has been discussed above.

TABLE 1



Compound	R	R′	bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %		Calc., %		Yield, %
						found	calc.		C	H	C	H	
I	CH_3	C_2H_5	39 (6)	0,9322	1,4290	40,52	40,23	$C_8H_{16}O_2$	66,6	11,1	66,9	11,0	61
II	C_2H_5	C_2H_5	65 (6)	0,9280	1,4350	44,77	44,84	$C_9H_{18}O_2$	68,0	11,1	68,4	11,4	83
III	n-C_3H_7	C_2H_5	77 (7)	0,9129	1,4369	49,76	49,46	$C_{10}H_{20}O_2$	69,8	11,6	69,8	11,6	83
IV	i-C_3H_7	C_2H_5	76 (6)	0,9109	1,4330	49,46	49,46	$C_{10}H_{20}O_2$	69,6	11,5	69,8	11,6	72
V	i-C_4H_9	C_2H_5	85 (6)	0,9018	1,4385	54,33	54,08	$C_{11}H_{22}O_2$	70,7	11,6	71,0	11,8	71
VI	CH_3	i-C_3H_7	72 (21)	0,9314	1,4340	44,64	44,84	$C_9H_{18}O_2$	68,4	11,2	68,4	11,4	78
VII	C_2H_5	i-C_3H_7	66 (5)	0,9259	1,4370	49,42	49,46	$C_{10}H_{20}O_2$	69,5	11,7	69,8	11,6	78
VIII	n-C_3H_7	i-C_3H_7	64 (3)	0,9159	1,4390	53,60	53,08	$C_{11}H_{22}O_2$	70,8	11,2	71,0	11,8	75
IX	i-C_3H_7	i-C_3H_7	76 (6)	0,9159	1,4390	53,65	54,08	$C_{11}H_{22}O_2$	70,8	11,6	71,0	11,8	74
X	i-C_4H_9	i-C_3H_7	73 (4)	0,9154	1,4410	58,35	58,69	$C_{12}H_{24}O_2$	71,4	11,4	71,9	12,0	73
XI	CH_3	C_6H_5	73—74*	—	—	59,00	—	$C_{12}H_{16}O_2$	74,9	8,3	74,9	8,3	58
XII	C_2H_5	C_6H_5	106—107 (5)	1,0215	1,4960	—	58,92	$C_{13}H_{18}O_2$	75,9	8,8	75,6	8,7	73
XIII	n-C_3H_7	C_6H_5	133 (10)	1,0267	1,4965	64,41	64,32	$C_{14}H_{20}O_2$	76,3	9,4	76,2	9,1	68
XIV	i-C_3H_7	C_6H_5	110—112 (4)	1,0149	1,5010	64,10	64,31	$C_{14}H_{20}O_2$	76,3	9,0	76,2	9,1	62
XV	i-C_4H_9	C_6H_5	130—131 (3)	1,0140	1,5020	68,60	68,64	$C_{15}H_{22}O_2$	76,8	9,3	76,9	9,4	67

*Melting point.

It is more difficult to determine the orientation of the substituents in position 2. It follows from the work of Pihlaja and Teinonen [7] that the resonance signal of an axial methyl group in this position is found in lower fields. In view of this, the resonance signal of the protons of the methyl group in the spectrum of the isomer considered (δ 1.15 ppm), taking the presence of the conformer b into account, indicates its axial position and, consequently, the isopropyl group is present at an equatorial valence. Thus, the low-boiling isomer has the cis configuration and its molecule exists in the predominant chair conformation, consisting of a mixture of the conformers a and b with a predominance of the former.

As follows from the geminal constant of the axial and equatorial protons in positions 4 and 6 ($^3J_{AB}$ = −11.5 Hz) and the multiplet nature of the resonance signal of the same protons ($^3J_{H_BH'_a}$ =4,8 Hz, $^3J_{H_AH'_a}$ = 10.5 Hz*), the high-boiling isomer of compound (IX) (Fig. 1) also exists in the chair conformation. The trans configuration of this isomer follows from the vicinal constant $^3J_{H_AH'_a}$ = 10,5 Hz and the chemical shifts of the protons of the 2-CH_3 group (δ 1.23 ppm) [7] and of the methine proton of the 5-isopropyl group (δ 1.60 ppm) [6].

Thus, the low-boiling isomer of compound (IX) is the cis isomer with the 2e5a and 2a5e positions of the larger substituents, and the high-boiling isomer the trans isomer with the 2e5e position of these substituents. The predominant conformation of the molecule of each of the stereoisomers is the chair conformation.

The PMR spectra of the other compounds that we obtained show similar features (Table 2). It can be seen from this table that the cis isomers of compounds (I-XIII) are characterized by a vicinal spin–spin coupling constant higher than expected $^3J_{H_AH'_e}$ = 6—7 Hz. As in the case of compound (IX), this indicates their conformational inhomogeneity. The amount of the less suitable conformer with the 2a5e position of the larger substituents is approximately the same for all the compounds.

In the series of compounds (XI-XV) including the 2-C_6H_5 group, the amount of trans isomer is considerably greater than for the case of substances (I-X). Figure 2 gives the PMR spectrum of compound (XI), from which its predominant chair conformation with an equatorial 5-CH_3 group (δ 0.43 ppm) can be clearly seen. The resonance of the protons of the 2-CH_3 group is observed at 1.49 ppm which, according to the literature [7], indicates its axial position. Consequently, compound (XI) has the trans configuration. The similar conformation of the high-boiling isomers of compounds (XII-XV) is confirmed by the figures of Table 2. The cis configuration of the low-boiling isomers of compounds (XII-XV) also follows from the figures of this table.

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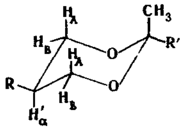
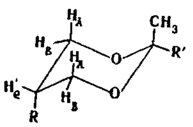
*It follows from the values of these constants that the concentration of the predominant conformer at room temperature amounts to about 95%.

TABLE 2. Parameters of the PMR Spectra and the Stereochemistry of the 2,2,5-Trialkyl-1,3-dioxanes





Comp.	R	R′	Chemical shifts, δ, ppm			Spin-spin coupling constants					Configuration	Orientation		
			4,6-H_A	4,6-H_B	2-CH_3	J_{AB}	J_{Aa}	J_{Ae}	J_{Ba}	J_{Be}		R	CH_3	R′
I	CH_3	C_2H_5	3,40	3,77	1,21	−11,5	11,5	—	4,6	—	trans	*e*	*a*	*e*
			3,42	3,78	1,17	−11,5	—	6,7	—	4,6	cis	*a*	*a*	*e*
II	C_2H_5	C_2H_5	3,43	3,81	1,27	−11,5	11,5	—	4,7	—	trans	*e*	*a*	*e*
			3,41	3,76	1,25	−11,0	—	7,1	—	4,5	cis	*a*	*a*	*e*
III	*n*-C_3H_7	C_2H_5	3,44	3,76	1,28	−11,0	11,0	—	4,5	—	trans	*e*	*a*	*e*
			3,42	3,76	1,26	−11,0	—	7,0	—	4,5	cis	*a*	*a*	*e*
IV	*i*-C_3H_7	C_2H_5	3,54	3,80	1,27	−11,0	11,0	—	4,5	—	trans	*e*	*a*	*e*
			3,56	3,78	1,24	−11,5	—	7,1	—	4,5	cis	*a*	*a*	*e*
V	*i*-C_4H_9	C_2H_5	3,40	3,73	1,28	−11,5	11,5	—	4,4	—	trans	*e*	*a*	*e*
			3,55	3,74	1,24	−11,0	—	7,2	—	4,3	cis	*a*	*a*	*e*
VI	CH_3	*i*-C_3H_7	3,40	3,78	1,23	−11,0	11,0	—	4,3	—	trans	*e*	*a*	*e*
			3,40	3,80	1,17	−11,0	—	7,0	—	4,3	cis	*a*	*a*	*e*
VII	C_2H_5	*i*-C_3H_7	3,43	3,76	1,22	−11,0	11,0	—	4,7	—	trans	*e*	*a*	*e*
			3,71	3,80	1,17	−10,7	—	7,1	—	4,3	cis	*a*	*a*	*e*
VIII	*n*-C_3H_7	*i*-C_3H_7	3,42	3,73	1,22	−11,0	11,0	—	4,7	—	trans	*e*	*a*	*e*
			3,45	3,78	1,19	−11,0	—	6,9	—	4,7	cis	*a*	*a*	*e*
IX	*i*-C_3H_7	*i*-C_3H_7	3,50	3,80	1,23	−11,0	11,0	—	4,8	—	trans	*e*	*a*	*e*
			3,59	3,77	1,15	−11,5	—	7,0	—	4,8	cis	*a*	*a*	*e*
X	*i*-C_4H_9	*i*-C_3H_7	3,50	3,77	1,11	−11,0	11,0	—	4,6	—	trans	*e*	*a*	*e*
			3,72	3,90	1,16	−11,0	—	7,1	—	—	cis	*a*	*a*	*e*
XI	CH_3	C_6H_5	3,21	3,68	1,49	−11,0	11,0	—	4,8	—	trans	*e*	*a*	*e*
XII	C_2H_5	C_6H_5	3,22	3,81	1,45	−11,0	11,0	—	4,5	—	trans	*e*	*a*	*e*
			3,70	3,81	1,43	−11,5	—	6,2	—	4,5	cis	*a*	*a*	*e*
XIII	*n*-C_3H_7	C_6H_5	3,25	3,82	1,46	−11,5	11,5	—	4,2	—	trans	*e*	*a*	*e*
			3,68	3,80	1,46	−11,5	—	7,1	—	4,2	cis	*a*	*a*	*e*
XIV	*i*-C_3H_7	C_6H_5	3,31	3,82	1,44	11,0	—	4,5	—		trans	*e*	*a*	*e*
			3,71	3,32	1,43	−11	—	6,9	—	4,1	cis	*a*	*a*	*e*
XV	*i*-C_4H_9	C_6H_5	3,22	3,33	1,45	−11,5	11,5	—	4,2	—	trans	*e*	*a*	*e*
			3,70	3,31	1,43	−11,0	—	7,3	—	4,2	cis	*a*	*a*	*e*

The IR spectra and the dipole moments of the isomers agree well with the conclusions concerning the cis and trans configurations of the compounds under consideration. Thus, the IR spectrum of the trans isomer of (IX) has a strong band at 675 cm^{-1} which is characteristic for trans isomers of the 1,3-dioxane series [8]. In the spectrum of the low-boiling isomer of this compound there is an absorption band at 695 cm^{-1}, which is characteristic for the cis isomer.

The dipole moments of the individual isomers of compound (IX) are 1.82 D for the cis isomer and 1.76 D for the trans isomer and confirm their chair conformation [9].

EXPERIMENTAL

The 2,2,5-trialkyl-1,3-dioxanes were synthesized by condensing the corresponding 2-alkylpropane-1,3-diols with methyl ethyl ketone, methyl isopropyl ketone, and acetophenone in the presence of KU-1 cation-exchange resin in the H form [4]. The presence of geometric isomers in samples of the compounds studied was established by GLC and PMR spectroscopy.

Gas–liquid chromatographic analysis was performed on an LKhM-8M chromatograph. SKTFT-50, Carbowax-20M, SKTFV-803, and PFMS-4 were used as stationary phases.

The PMR spectra were taken on a Varian H-100 instrument in the form of 10% solutions in CCl_4 with TMS as internal standard.

The epimerization of the individual isomers of compound (IX) in order to determine the preferential existence of one of them was performed in sealed tubes in the presence of BF_3 etherate as catalyst by heating at 30, 60, and 90°C until equilibrium had been achieved. The course of epimerization and the setting in of equilibrium were monitored by GLC.

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