

## ALKOXY COMPOUNDS

XIX. The Stereoisomerism of Some 2, 5-Dialkyl-5- $\alpha$ -alkoxyethyl-1, 3-dioxanes\*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 2, pp. 195-203, 1967

UDC 547.841 : 541.67 : 543.544 : 542.952.1

Using PMR spectra and GL chromatograms, it is shown that 2, 5-dimethyl-, 2-isopropyl-5-ethyl-, 2, 5-diisopropyl-5- $\alpha$ -isopropoxyethyl-1, 3-dioxane are mixtures of isomers. Efficient columns are used to fractionate these mixtures into the individual isomers, purities being checked by GLC. From PMR spectra and dipole moments it was concluded that the low-boiling isomers of the stereoisomeric dioxanes are trans forms with chair configuration, while the high-boiling isomers are cis, and have the unsymmetrical boat-shaped configuration.

Previous papers gave information regarding the synthesis of some 2, 5-dialkyl-5- $\alpha$ -alkoxyethyl-1, 3-dioxanes, (I), and their separation into isomers [1-5]. Continuing the work, we have now separated the stereoisomers of some I compounds with an isopropyl group at position 2. The properties of these stereoisomers have been compared with those of the stereoisomers of the simplest compound 2, 5-dimethyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (II). From these results it was possible to draw definite conclusions regarding the configurations and conformations of the dioxanes I.

The properties of the following stereoisomers of I were investigated: 2-isopropyl-5-ethyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (III); 2, 5-diisopropyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (IV); and 2, 5-diisopropyl-5- $\alpha$ -isopropoxyethyl-1, 3-dioxane (V).

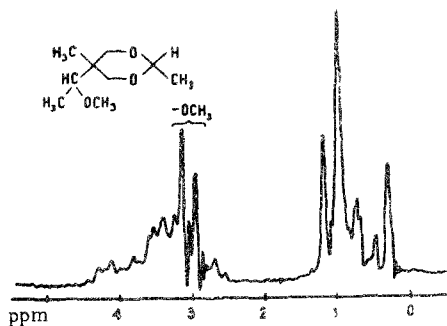


Fig. 1. PMR spectrum of 2, 5-dimethyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (mixture of isomers) at  $\nu_0 = 24.342$  Mc, YaMR-KGU-1 spectrometer.

There is quite extensive information regarding 1, 3-dioxanes regarded as hetero analogs of cyclohexane, but possessing a number of peculiarities

[6-8]. In particular 1, 3 interactions in these compounds are weakened, and in a number of cases, there can exist in addition to the stable chair configuration the equally stable boat shape [9]. Hence investigation of the stereoisomerism of systems such as I is quite interesting in connection with developing stereo-chemical concepts.

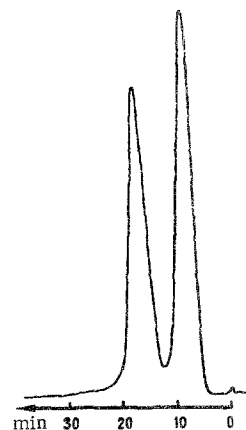


Fig. 2. Gas chromatogram of the mixture of stereoisomers of 2, 5-diisopropyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (IV). Ratio of isomers 57:43%.

Investigation of the PMR spectra of II-V showed that, as expected, they were not single compounds, but mixtures of stereoisomers. Thus investigation of the PMR spectrum of II showed it to contain two isomers, amounting to 66% and 34% of the whole (Fig. 1). This was inferred from the peculiarities characteristic of the spectrum of II.

The PMR spectra of the compounds which we have investigated also show that at room temperature there are no signs of inversion of the rings of I. In the spectrum of II the methoxyl group's resonance line is split into two components, while it is known from the literature, and from lists of PMR spectra [10], that methoxyl group peaks lack spin multiplicity. The splitting of the methoxyl group's line can only be explained by the specimen's containing two stereoisomers, and determination of the relative total intensities of the components of the line enables a conclusion to be reached regarding the ratio of the amounts of the isomers, as stated above.

Gas chromatography led to a similar conclusion regarding the synthesized compounds of the I series.

\*For Part XVIII see [14].

Table 1

Properties of Stereoisomeric 2, 5-Dialkyl-5- $\alpha$ -alkoxyethyl-1, 3-dioxanes

Compound no.	Stereo-isomer*	Bp, °C (pressure, mm)	$\Delta t$	$d_4^{20}$	$\Delta d$	$n_D^{20}$	$\Delta n$	MRD		$\Delta MRD$	Proportion of stereoisomer, %
								Found	Calculated		
II	a	74.5(15.5)	9.6	0.9800	0.0048	1.4330	0.0017	46.23	46.49	0.26	65.0
	b	84.1(15.5)		0.9848		1.4347		46.10	0.39	35.0	
III	a	56.5(0,1)	6.0	0.9578	0.0027	1.4431	0.0011	60.13	60.34	0.21	66.0
	b	62.5(0,1)		0.9605		1.4442		59.82	0.52	34.0	
IV	a	67.1(0,1)	3.2	0.9624	0.0034	1.4494	0.0021	64.36	64.77	0.41	57.0
	b	70.3(0,1)		0.9658		1.4515		64.21	0.56	43.0	
V	a	81.5(1,0)	5.0	0.9408	0.0028	1.4437	0.0025	73.34	74.20	0.86	60.0
	b	86.5(1,0)		0.9436		1.4462		73.25	0.95	40.0	

\*In every case a is the low-boiling isomer, b the high-boiling one.

Thus the chromatogram of IV also indicated that this particular dioxane was a mixture of two stereoisomers present in almost equimolecular amounts (Fig. 2).

In view of what has been stated above, an attempt was made to separate the mixed stereoisomers of I by fractionating through efficient total condensation columns. The literature describes some cases of separation of 1, 3-dioxanes into stereoisomers, but in all cases [11-13] separation was based on fractional crystallization either of the actual dioxanes, or of derivatives of these. 1, 3-Dioxanes have not previously been separated by fractionation through efficient columns.

The present paper gives data relating to separation of four mixtures of stereoisomeric 1, 3-dioxanes into the individual isomers. Table 1 gives the properties of the corresponding geometrical isomers. The purities of the isomers were checked by gas chromatography. Study of the chromatograms showed the isomers isolated to be 99-99.8% pure.

Various hypotheses can be given for demonstrating the configuration of each stereoisomer. According to the Auwers-Skita rule, if the orientation is to be related to the class of 1, 3-dioxanes, all the low-boiling isomers with lower constants (Table 1) are to be deemed trans isomers. All the high-boiling isomers are deemed cis isomers. However, it is generally known that the analogy method is not the best, and furthermore, that the Auwers-Skita rule has been shown to be wrong in very many cases. Also, such arguments do not solve the problem of configuration of the isomers. Actually in the case in question a number of additional problems arise: which is the cis and which the trans isomer, what is the position of the substituent which moves on passing from one isomer to the other, whether at position 2 or position 5 (in the stable configuration)? The problem of ring conformation is also unsolved. Prominent is the fact that the axial valence at position 5 in the chair-shaped configuration is not the usual axial valence. It is the only axial valence on one side of the ring. The substituent near this valence does not undergo

1, 3 interaction, its position may be more favorable than that of other axial substituents, as can be seen with Stuart-Brigleg models. We previously proposed calling this valence a "stem" one [14].

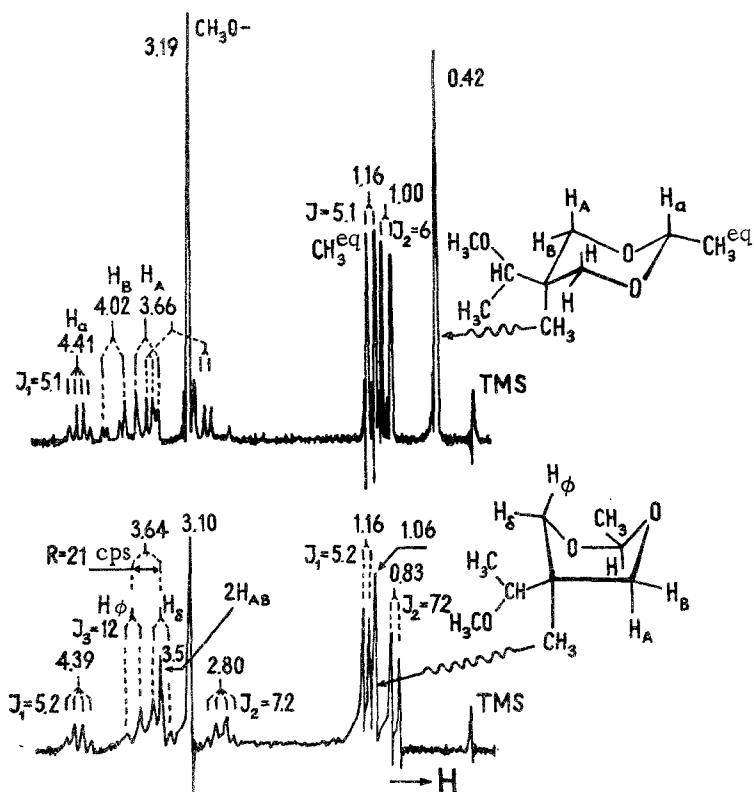
Study of the PMR spectra of the stereoisomeric Is gives quite definite arguments regarding this problem, and also regarding the most preferred conformation of each isomer. Figs. 3 and 4 show the spectra. Fig. 3 shows that the spectra of the stereoisomers are essentially different. It was natural to start analyzing the spectra of the individual isomers by analyzing the spectra of the simplest of them, II.

In a previous paper [15] one of the present authors showed that under conditions of fast ring inversion, protons of the group  $-(O)-CH-(O)-$  in 1, 3-dioxanes resonate at  $\delta = 4.65$  ppm ( $\tau = 5.35$  ppm). In the absence of inversion the equatorial protons resonate in a lower field than do axial ones.

Figs. 3 and 4 show that at room temperature, the rings show no signs of inversion, and that the chemical shift of the protons in the group  $-(O)-CH-(O)-$  is  $\delta = 4.40 \pm 0.02$  ppm (center of quadruplet) for both isomers.

The methyl group at position 2 has the same chemical shift in both isomers. Hence it can be concluded that the configurations of the substituents at position 2 in the two isomers are the same, with the hydrogen axial and the methyl group equatorial. Hence the stereoisomers differ with respect to the configuration of groups near C-5.

Fig. 3 shows that only the spectrum of the low-boiling isomer II has a singlet peak with an anomalously low value for the chemical shift,  $\delta = 0.42$  ppm, which we ascribe to axial methyl at position 5. That conclusion, and the next one, are based on theoretically predicted values for proton shifts in 5, 5-dimethyl-1, 3-dioxane, arising through magnetic anisotropy effects of chemical bonds (McConnell theory [16]) and through the electric field of molecular dipoles (Buckingham-Musher theory [17-18]) as well as on analysis of the Stuart-Brigleg model of molecule II, and study of dipole moments of stereoisomers.



Note: H<sub>A</sub> = H-axial in the positions 4 and 6; H<sub>B</sub> = H-equatorial in the same positions; H<sub>α</sub> = H-axial in position 2; H<sub>δ</sub> = H-bowsprit (boat); H<sub>φ</sub> = H-flagstaff (boat).

Fig. 3. PMR spectra of stereoisomeric 2,5-dimethyl-5- $\alpha$ -methoxyethyl-1,3-dioxanes. Top: low-boiling isomer IIa; bottom: high-boiling one IIb. For plotting conditions see text.

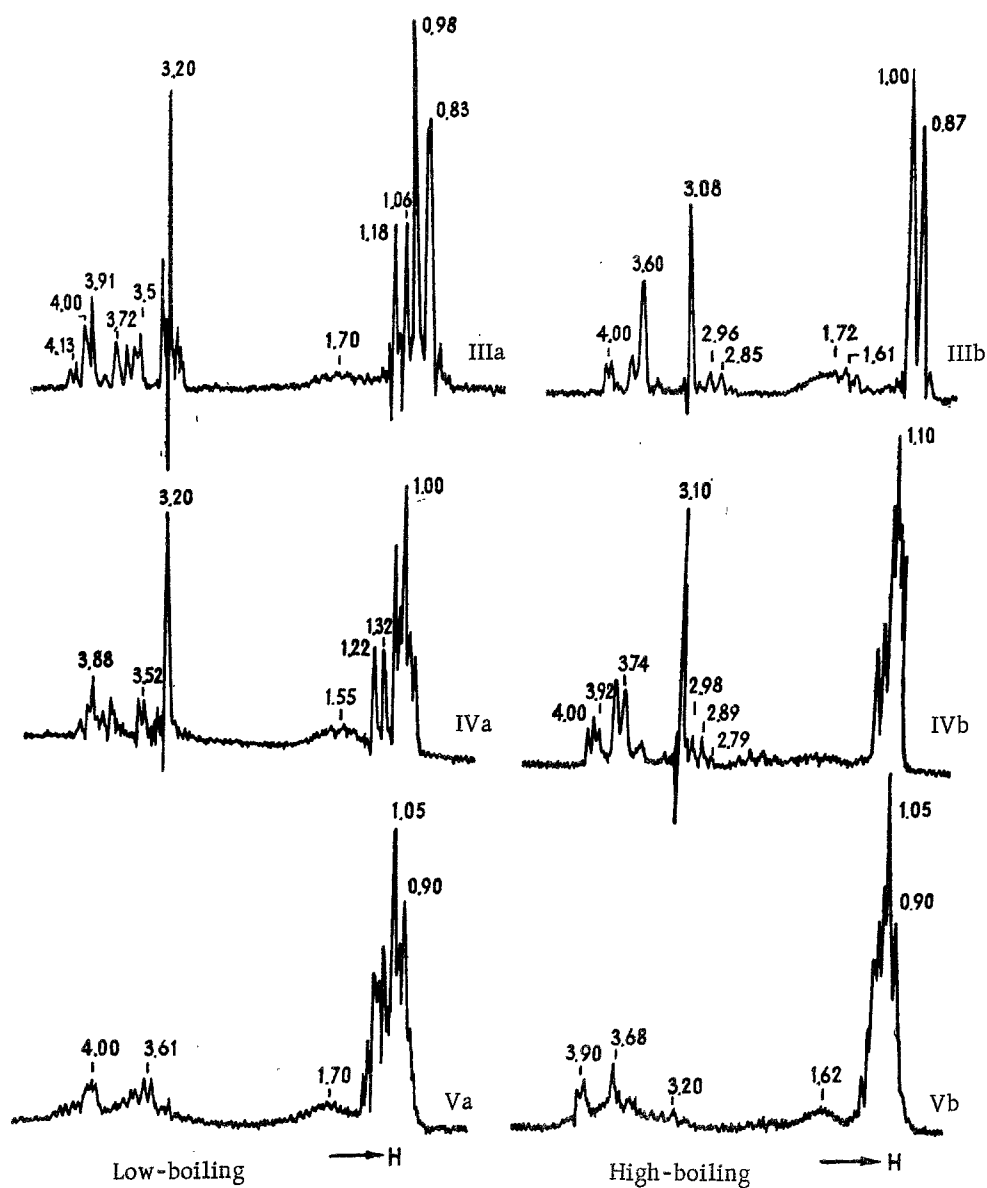


Fig. 4. PMR spectra of stereoisomeric compounds III-V. Left: low-boiling isomers IIIa-Va; right: high-boiling ones IIIb-Vb. For plotting conditions see text.

Table 2  
Changes in Chemical Shifts of Protons in 5, 5(2, 2)-  
dimethyl-1, 3-dioxane, ppm\*

Ring con- formation	Methylene protons 3', 4'				Total non- equivalence $\Delta\delta$		Methyl protons 2', 3'				Total non- equivalence $\Delta\delta$		
	Posi- tion of CH <sub>2</sub> group	H <sub>ax</sub> or H <sub>fb</sub>		H <sub>eq</sub> or H <sub>bs</sub>		Position of CH <sub>3</sub> group	(CH <sub>3</sub> -ax)(CH <sub>3</sub> -fb)(CH <sub>3</sub> -eq)(CH <sub>3</sub> -bs)		Total non- equivalence $\Delta\delta$		Total non- equivalence $\Delta\delta$		
		$\Delta\delta$ el	$\Delta\delta$ am	$\Delta\delta$ el	$\Delta\delta$ am		$\Delta\delta$ el	$\Delta\delta$ am	$\Delta\delta$ el	$\Delta\delta$ am			
	C-2	0.300	1.081	1.381	0.355	0.686	1.041	0.340	C-2	0.124	0.246	0.058	0.154
	C-4	0.206	0.659	0.865	0.116	0.450	0.566	0.300	C-5	-0.098	-0.346	-0.089	0.430
	C-6												
	C-5	-0.424	-0.169	-0.593	-0.269	-0.058	-0.327	0.266					
	C-2	+0.433	1.341	1.774	0.313	0.789	1.103	0.671	C-2				
	C-4	-0.065	0.140	0.075	+0.066	0.138	0.204	0.129	C-5	-0.067	0.216	-0.098	0.164
	C-6												
	C-5	-0.271	0.841	0.570	-0.307	0.106	-0.201	0.771					
	C-2	0.231	0.682	0.913	0.186	0.295	0.481	0.432	C-2	0.119	0.127	0.137	0.069
	C-4	0.141	-0.133	0.008	0.141	0.312	0.453	0.445	C-5	-0.082	+0.028	-0.105	0.114
C-6	0.144	0.550	0.694	0.123	0.407	0.530	0.164						

\*The following values of the molecular constants were used in the calculations:  $\angle C-C-C=109^\circ 28'$ ;  $\angle C-O-C=110^\circ$ ;  $\angle O-C-C=109^\circ 28'$ ;  $C-C=1.54 \text{ \AA}$ ;  $C-O=1.43 \text{ \AA}$ ;  $C-H=1.09 \text{ \AA}$ ;  $\mu_{C-O}=0.86 \text{ D}$ ;  $\mu_{C-H}=0.4 \text{ D}$ ;  $\Delta\chi_{C-O}=5.3 \cdot 10^{-6}$ ;  $\Delta\chi_{C-C}=5.4 \cdot 10^{-6}$ ;  $\Delta\chi_{C-H}=8.1 \cdot 10^{-6}$ ;  $\Delta\chi_{C-H} = 1.5 \cdot 10^{-6} \text{ cm}^3/\text{mole}$ .

2\* The table gives the average value of the methyl shift, as found from six positions of the protons.

3\* The center of gravity of the anisotropic group of electrons as well as of the electric dipole, is at the point of contact of the covariance spheres of the two atoms involved in the particular chemical bonding.

4\* A positive sign before  $\Delta\delta^{el}$  or  $\Delta\delta^{an}$  means that the expected resonance shift is towards higher fields, and a negative sign means that it is towards lower fields.

Table 2 gives results of calculations. There columns headed  $\Delta\delta$  give total non-equivalence of axial and equatorial ring protons. This is the first time in the literature that lone electrons pairs ( $2p_z^2$ ) of ring oxygen atoms have been taken into account. The data of Table 2 show that for the chair configuration, the non-equivalence of protons at C-4 and C-6 is about 0.3 ppm, i. e. large, that it is small for C-6 protons in the unsymmetrical boat-shaped configuration, but that it is relatively large at C-4 ( $\sim 0.4$  ppm). Looking at the PMR spectra of the individual stereoisomers (Figs. 3 and 4), it is seen that the methylene protons of low-boiling isomers give a wide absorption band. Consequently the low-boiling isomers have the chair configuration. Comparison of the dipole moment as calculated theoretically ( $\mu_{\text{calc}} = 1.16$  D, for the equatorial configuration of the 5- $\alpha$ -methoxyethyl group) with that found experimentally ( $\mu_{\text{exp}} = 1.15$  D) as a means of studying ring conformation of the low-boiling isomer II, leads to the same conclusion.\*

It is rather difficult to settle the question of the disposition of the substituents at position 5. The data of Table 2 show that the peak of the axial methyl group near carbon C-5 in 5,5-dimethyl-1,3-dioxane (VI) must substantially be displaced in the direction of a weaker field as compared with the usual resonance position for methyl protons. The peak of the equatorial methyl group must be displaced insignificantly in the same direction. Actually the spectrum of II has an anomalous peak  $\delta = 0.42$  ppm, present only in the spectrum of low-boiling isomer. Hence it is impossible to draw direct conclusions regarding the configuration of II from the data of Table 2 only. However it is not possible to transfer the data of Table 2 directly to a study of the configuration and conformation of II.

Actually VI has two identical methyl groups, while II has two non-identical groups, one containing an oxygen atom which cannot fail to have an additional effect on the chemical shifts. If, starting with the data of the table for the direction of the chemical shift, IIa is ascribed a cis configuration with an axial (stem) position for  $-\text{CH}(\text{OCH}_3)-\text{CH}_3$ , this is contradicted by analysis with Stuart-Brigleb models, dipole moments, and general stereochemical principles. Actually Stuart-Brigleb models show that the  $\alpha$ -methoxyethyl group attains relatively free rotation only when it is equatorial. Comparison of calculated and found dipole moments also leads to the conclusion that the  $\alpha$ -methoxyethyl group must be equatorial in IIa. It is not hard to see that this falls completely into line with the general rules of conformational analysis. Hence it is more probable that IIa has the trans configuration.

How then is the contradiction of the data of Table 2 to be explained? If similar calculations are made

without taking into account the lone electron pair of the oxygen atoms, the relationship found is the converse of that indicated by Table 2, i. e. calculation shows that the peak of an axial methyl should be shifted towards stronger fields by 0.268 ppm. Consequently with IIa there is some effect apparently neutralizing the anisotropic effect due to lone electron pairs of the oxygen atoms. Only the oxygen of the methoxyl group can exhibit such an effect. Study of Stuart-Brigleb models makes it possible to understand the effect of methoxyl oxygen. Detailed quantitative analysis is rendered difficult by the size of the calculations. Consideration of the problem using Stuart-Brigleb models, in conjunction with the spectrum leads to the conclusion that the assumption put forward above is correct.

Protons of  $\text{CH}_2$  groups at position 4 and 6 give peaks characterized by non-identical non-equivalence (see Fig. 3). This can be understood if it is admitted that the methoxyl oxygen has a greater effect on one  $\text{CH}_2$  than the other (Table 2 shows that this conclusion is also a deviation from analysis of the spectrum of VI). This means that the  $\alpha$ -methoxyethyl group is relatively rigidly bound in space, and lacks full opportunity to rotate freely. Obviously this is due to mutual repulsion between the ring and methoxyl oxygen atoms. Such fixing of the  $\alpha$ -methoxyethyl group can be reversed, and hence opposite in sign to the effect of axial methyl, thus neutralizing the shift due to the anisotropy of the magnetic susceptibility of the lone pair of electrons of the oxygen atom.

Using these arguments, the peak at  $\delta = 0.42$  ppm can be ascribed to an axial methyl group, so that it can be concluded that the configuration of IIa is trans, and that the conformation is primarily the chair one.

The following conclusions can be drawn regarding the configuration and main conformation of IIb. The configuration of IIb can be only the converse of IIa, i. e. it is the cis isomer. This is shown by the absence of a peak with an anomalously low chemical shift for the methyl group at position 5, and also by the compound's dipole moment ( $\mu_{\text{exp}} = 2.65$  D,  $\mu_{\text{calc}} = 2.60$  D for the unsymmetrical boat). Of all the possible conformations of IIb, it can be ascribed the quite definite configuration of the boat shape. This follows from analysis of its PMR spectrum, which shows clearly the inequality of the protons of the  $\text{CH}_2$  groups, at positions 4 and 6. As Table 2 shows, the non-equivalence of these protons is possible only if IIb has an unsymmetrical boat-shaped configuration.

Conclusions drawn from analyzing the spectra of IIa and IIb can be used to consider the spectra of III-V (a and b). Fig. 4 shows that in the spectra of the low-boiling isomers III-V (a) the chemical shift for the methoxyl groups is almost the same ( $\delta = 3.20$  ppm) as that of the analogous group in IIa. In all the spectra the methylene protons of the 2-*i*- $\text{C}_3\text{H}_7$  group give a wide multiplet band with an average shift of 1.55-1.72 ppm. Spin-spin interaction of this proton with the moment of the proton of the group  $-(\text{O})-\text{CH}-(\text{O})-$  takes place with constant  $J_{\text{H}-\text{C}-\text{H}} = 2.55$  cps, while with methyl protons it takes place

\*The author thanks L. K. Yuldasheva for determining and calculating the dipole moments of IIa and IIb.

with, on the average, a constant  $J_{\text{CH}_3-\text{H}} = 7$  cps. Hence resonance of the proton of the group  $-(\text{O})-\text{CH}-(\text{O})-$  gives a doublet where, as with II, with the low-boiling isomers this line is shifted towards lower fields as compared with the high-boiling ones. The character of the resonance of the methylene protons at C-4 and C-6 with the low-boiling isomers III-V (a) resembles the spectrum of IIa, while the spectra of the high-boiling isomers III-V (b) are like the spectrum of IIb.

Hence it can be concluded that all low-boiling isomers are trans isomers, existing primarily in the chair conformation, while the high-boiling isomers are cis isomers, existing mainly as the boat-shaped configuration.

#### EXPERIMENTAL

Previously synthesized [3, 4] compounds of the I series were used to investigate the stereochemical problems.

PMR spectra of II-V were observed at a frequency  $\nu_0 = 60$  Mc, using a RYa NMR spectrometer made by SKB, AS USSR. The conditions were those which we previously used [19], at room temperature  $\Delta H/\Delta t \sim 0.2$  mOe/sec. The peak positions were specified, in all cases, in relation to the tetramethylsilane (TMS) peak, chemical shift,  $\delta_{\text{TMS}} = 0$ . Peak positions were determined by the side-bands method and controlled to frequency  $\nu_0 = 24.342$  Mc using dual standards (TMS and  $\text{C}_6\text{H}_6$ ). The specimens were 40% solutions of the compounds in  $\text{CCl}_4$ .

Gas chromatography analysis\* was carried out with a LKhM-5 SKB IOKh AS USSR instrument using a current of helium and a catharometer detector. The liquid phase was polyethylene glycol (1.5%) supported on sodium chloride. The column was 4 m long, temperature  $100^\circ$ , column inlet pressure 0.4 atm.

Fractionation. Two total-condensation fractionating columns were used for sharp fractionation; No. 1 had 20 t.p. and No. 2 37 t.p. Both had ground glass joints.

**2, 5-Dimethyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (II).** The mixture (41.0 g) was distilled through No. 2 column, reflux ratio 60, and 10 cuts were taken. Fractions 2-4 (total weight 18.3 g) and fractions 7-8 (total weight 8.4 g) had the same constants which are shown in Table 1.

**2-Isopropyl-5-ethyl- $\alpha$ -methoxyethyl-1, 3-dioxane (III).** The mixture (47.0 g) was distilled continuously for 24 hrs through column No. 2, reflux ratio 55. Eleven cuts were taken, Nos. 3-6 (total weight 21.2 g) had the same constants, and so did nos. 9-11 (total weight 13.4 g, see Table 1).

**2, 5-Diisopropyl-5- $\alpha$ -methoxyethyl-1, 3-dioxane (IV).** The mixture (43.0 g) was distilled continuously for 24 hr, through column No. 2, at reflux ratio 60. Eleven cuts were taken, nos. 3-5 (total weight 13.7 g)

having the same constants. Table 1 gives properties of the isomers.

**2, 5-Diisopropyl-5- $\alpha$ -isopropylethyl-1, 3-dioxane (V).** The mixture (43.0 g.) was distilled continuously for 24 hr through column No. 2, using a reflux ratio of 60. 10 cuts were taken, nos. 1-3 (total weight 13.2 g) and nos. 7-9 also (total weight 16.0 g) had the same physical constants.

The authors wish to express their thanks to B. A. Kazanskii, B. A. Arbuzov, and A. L. Liberman, for help in carrying out the above work.

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28 June 1965

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\*The authors thank A. N. Preobrazhenskii for help in carrying out the GLC analytical work.