STEREOCHEMISTRY OF HETEROCYCLES

XIII.* CONFIGURATIONS AND CONFORMATIONS OF SOME 4,5-DIALKYL-, 4,5,5-TRIALKYL-, 2,2,4-TRIMETHYL-5-ALKYL-, AND 2,2,4-TRIMETHYL-5,5-DIALKYL-1,3-DIOXANES

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Twenty-eight previously unreported compounds of the 4,5-dialkyl-, 4,5,5-trialkyl-, 2,2,4-trimethyl-5-alkyl, and 2,2,4-trimethyl-5,5-dialkyl-1,3-dioxane series, including 24 individual cis and trans isomers, obtained with a purity of the order of 85-99% by fractionation of the starting mixtures of stereoisomers with total condensation columns, were synthesized. The applicability of the Cram rule, modified for compounds with complex-forming groups, for the estimation of the possible configurations and conformations of the stereoisomers of the examined series was demonstrated. The cis configuration of the low-boiling stereoisomers and the trans configuration of the high-boiling stereoisomers were proved by NMR spectroscopy; the investigated compounds exist predominantly in the chair conformation. The 5-C-axial position is preferred over the 4-C-axial conformation in the examined series of compounds. The synthesis and hydrolysis of the examined 1,3-dioxanes proceed without involvement of the steric centers of the molecules, and the configurations of the corresponding diastereomeric 1,3-diols can be established on the basis of data on the configurations of the 1,3-dioxanes. The IR spectra of the stereoisomers of the examined series of compounds were studied, and the spectral characteristics of the trans and cis isomers, respectively, were found.

The stereochemical peculiarities of 2,5-substituted 1,3-dioxanes were investigated in [1, 2] and in our papers [3, 4]. The outcome of these studies was a set of concepts regarding the considerably higher conformational energy of a 2-C-alkyl substituent ($\geq$3.9 kcal/mole for CH_3) as compared with a 5-C-alkyl substituent (0.8 kcal/mole for CH_3). There is also information regarding the fact that a 4-C-axial substituent has higher conformational energy than a 5-C-axial substituent (about 2.9 kcal/mole for the CH_3 group). However, 4,5-substituted 1,3-dioxanes have been investigated to only a small extent, and there is very little information with respect to the problem of how preferable are the conformations with 5-C- or 4-C-axial substituents.

Considering this, we set out to study the stereochemistry of these sorts 4,5-substituted 1,3-dioxanes, whose configurations and predominant conformations might be estimated by conformational analysis. 4,5-Dialkyl- (A), 4,5,5-trialkyl- (B), 2,2,4-trimethyl-5-alkyl- (C), and 2,2,4-trimethyl-5,5-dialkyl-1,3-dioxanes (D) were selected for the investigation. These series of compounds provided an adequate number of models for the solution of the conformational problems. In addition, as in [5, 6], the proof of the configurations of the starting diastereoisomeric 1,3-diols could be provided by proving the configurations of these 1,3-dioxanes. A prerequisite for this is the fact that the 1,3-dioxanes of series A, B, C, and D cannot be epimerized, and their synthesis from 1,3-diols and their hydrolysis to 1,3-diols should proceed according to modern concepts regarding the mechanisms of these reactions without involvement of the steric centers and, consequently, without Walden inversion [7].

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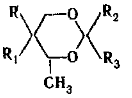
*See [30] for communication XII.

I. I. Mechnikov Odessa State University. A. E. Arbuzov Institute of Organic and Physical Chemistry, Academy of Sciences of the USSR, Kazan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 893-904, July, 1971. Original article submitted December 13, 1970.

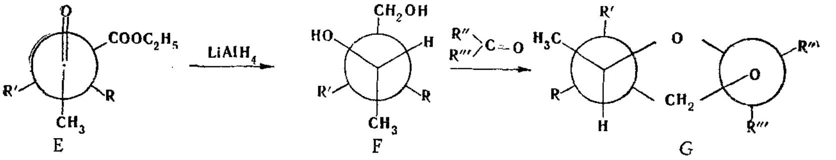
TABLE 1. Properties of 4,5-Substituted 1,3-Dioxanes



Comp.	R	R'	R²	R³	bp (mm)	d_4^{20}	n_D^{20}	MR_D		Isomer ratio, %		Yield, %
								found	calc.	low-boil. isomer	high-boil. isomer	
I	CH_3	H	H	H	134 (760)	0,9587	1,4239	30,89	30,99	65	35	46
II	C_2H_5	H	H	H	64 (29)	0,9542	1,4312	35,31	35,61	70	30	77
III	n-C_3H_7	H	H	H	81 (25)	0,9431	1,4351	39,89	40,23	70	30	88
IV	i-C_3H_7	H	H	H	73 (19)	0,9535	1,4386	39,74	40,23	75	25	86
V	CH_3	C_2H_5	H	H	55 (13)	0,9600	1,4373	39,90	40,23	70	30	88
VI	C_2H_5	C_2H_5	H	H	76 (13)	0,9585	1,4468	44,06	44,85	—	—	93
VII	CH_3	i-C_3H_7	H	H	88 (25)	0,9563	1,4463	44,24	44,85	85	15	77
VIII	C_2H_5	i-C_3H_7	H	H	66 (6)	0,9584	1,4538	48,92	49,47	85	15	99
IX	CH_3	H	CH_3	CH_3	52 (18)	0,9153	1,4260	40,35	40,23	65	35	60
X	C_2H_5	H	CH_3	CH_3	54—56 (10)	0,9159	1,4298	45,00	44,84	65	35	67
XI	n-C_3H_7	H	CH_3	CH_3	76 (13)	0,9051	1,4330	49,44	49,46	65	35	75
XII	i-C_3H_7	H	CH_3	CH_3	73 (13)	0,9132	1,4340	49,16	49,46	70	30	67
XIII	CH_3	C_2H_5	CH_3	CH_3	61 (6)	0,9173	1,4345	48,96	49,46	70	30	68
XIV	C_2H_5	C_2H_5	CH_3	CH_3	94 (13)	0,9218	1,4430	53,71	54,08	—	—	70
XV	CH_3	i-C_3H_7	CH_3	CH_3	87—89 (18)	0,9196	1,4414	53,40	54,08	85	15	67
XVI	C_2H_5	i-C_3H_7	CH_3	CH_3	73 (3)	0,9245	1,4480	58,03	58,70	85	15	79

The 1,3-dioxanes were synthesized by the condensation of 2-alkyl- and 2,2-dialkyl-1,3-butanediols with formaldehyde and acetone in the presence of acid catalysts [8]. The substituted 1,3-butanediols were in turn obtained by the reduction of mono- and dialkylacetoacetic esters with lithium aluminum hydride [9]. It is known that this reaction is stereospecific: it gives a mixture of erythro- and threo-1,3-diols containing a different ratio of diastereomers. The stereospecificity of the reduction is determined, in the case of acetoacetic esters, by the modified Cram rule [10] that is acceptable for compounds that have groupings capable of complexing with metals.

Following this rule, formula E can be assigned to the most favorable reactive conformation of substituted acetoacetic esters, and the entire successive course of the reactions in the synthesis of dioxanes of the A, B, C, and D types can be represented by the following scheme [where R = H or a smaller alkyl substituent, R' is alkyl when R = H (or the larger of two alkyl substituents), and R'' = R''' = H or CH_3]:



It is seen from this scheme that the starting substituted acetoacetic ester in conformation E is reduced to form erythro-1,3-diol F, which, on reaction with carbonyl compounds, forms the cis isomer of 1,3-dioxane G with an equatorial orientation of the 4-C-methyl group and a 5-C-axial orientation of the large substituent next to the 5-C atom. The alternative conformation of the substituted acetoacetic ester will lead to the threo-1,3-diol and the trans isomer of the 1,3-dioxane. Considering the degree of stereospecificity of the Cram rule [11], one might have expected that the percentage of the cis isomer in mixtures of the stereoisomeric 1,3-dioxanes of the A, B, C, and D series would be 60-70% compared with 30-40% for the trans isomer. Moreover, considering the conformational energies of the 5-C- and 4-C-substituents, one should have expected that the G ⇌ H and I ⇌ J equilibria would be ultimately shifted to favor the predominant G and I conformations, i.e., the 4-CH_3-axial group would "fix" the conformation:

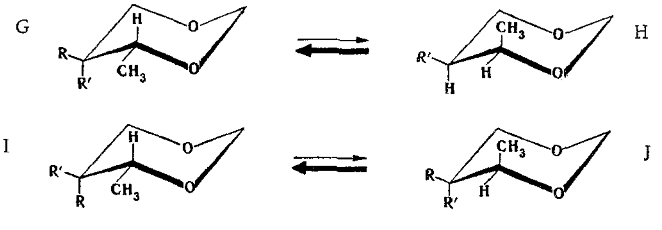
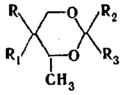


TABLE 2. Properties of the Stereoisomers of Substituted 1,3-Dioxanes



Comp.	R	R¹	R²	R³	bp (mm)	Δt	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Purity of isom., acc. to GLC, %	Charac. bands in IR spectra, cm^{-1}
Ib[a]	CH_3	H	H	H	132 (760)	6,7	0,9623	1,4241	30,79	30.99	80	609
					138,7 (760)		0,9567	1,4220	30,61		80	679
IIb[a]	C_2H_5	H	H	H	153,3 (760)	5,2	0,9585	1,4320	35,21	35,61	99	614
					158,5 (760)		0,9503	1,4290	35,32		98	676
IIIb[a]	n-C_3H_7	H	H	H	78 (20)	—	0,9453	1,4360	39,89	40,23	99	614
					78 (18)		0,9367	1,4325	39,94		98	686
IVb[a]	i-C_3H_7	H	H	H	175,9 (760)	2,3	0,9556	1,4396	40,06	40,23	99	624
					178,2 (760)		0,9320	1,4358	40,42		98	667
Vb[a]	CH_3	C_2H_5	H	H	71 (24)	—	0,9525	1,4370	39,65	40,23	99	578
					69 (20,5)		0,9529	1,4379	39,70		99	667
VIIb[a]	CH_3	i-C_3H_7	H	H	72 (13)	—	0,9570	1,4478	44,22	44,85	99	583
					73,5 (13)		0,9574	1,4463	44,11		90	661
IXb[a]	CH_3	H	CH_3	CH_3	146 (760)	5	0,9213	1,4240	39,92	40,23	95	577
					151 (760)		0,9121	1,4230	40,25		90	663
Xb[a]	C_2H_5	H	CH_3	CH_3	167,3 (760)	3,4	0,9175	1,4298	44,51	44,84	99	591
					170,7 (760)		0,9148	1,4287	44,54		99	657
XIb[a]	n-C_3H_7	H	CH_3	CH_3	75 (16)	—	0,9121	1,4325	49,01	49,46	99	588
					79 (16)		0,9100	1,4338	49,25		97	672
XIIb[a]	i-C_3H_7	H	CH_3	CH_3	184,7 (760)	0,6	0,9194	1,4355	48,90	49,46	99	599
					184,1 (760)		0,9166	1,4349	49,02		95	688
XIIIb[a]	CH_3	C_2H_5	CH_3	CH_3	86,2 (14)	—	0,9105	1,4348	49,32	49,46	99	577
					87 (13)		0,9170	1,4359	49,09		95	661
XVb[a]	CH_3	i-C_3H_7	CH_3	CH_3	76 (11)	—	0,9125	1,4430	53,72	54,08	95	578
					81 (12)		0,9190	1,4408	53,49			686

We have obtained 16 previously undescribed compounds of the A, B, C, and D series, the properties of which are described in Table 1. The data on the isomer ratios in the table, obtained by gas-liquid chromatography (GLC), correspond to the values proposed on the basis of the Cram rule. These results are in agreement with information regarding the ratio of the diastereomers of 1,3-diols, also obtained by GLC. Mixtures of the stereoisomeric 1,3-dioxanes were separated by rectification with efficient total condensation columns with glass and metal packings with HETP of 50 or 60. The course of the fractionation and the purity of the individual isomers were monitored chromatographically. The properties of 24 individual stereoisomers of the A, B, C, and D series are described in Table 2. It is apparent from Table 2 that, in this case, the linear dependence between the differences in the boiling points of the individual isomers (Δt), previously noted by us [12], is also observed in this case, within the limits of such steric series as those composed of isomers of I, II, and IV, as well as IX, X, and XII.

An analysis of the data presented in Table 2 confirms the inapplicability of the Auwers–Skita rule to compounds of the A, B, C, and D types, since there is no sharp correlation in the change in the boiling points, refractive indexes, and the densities in the stereoisomeric pairs. The configurations and predominant conformations of the examined substances were established by NMR spectroscopy. It was found that the PMR spectra for ν_0 = 60 MHz were virtually impossible to interpret; we therefore carried out the study at 100 MHz.

The PMR spectra of the stereoisomers of 4,5-dimethyl-1,3-dioxane (Ia and Ib) were recently described in [13]*; the spectra that we recorded for these compounds proved to be identical to those described in [13]. However, the most characteristic PMR spectra are those of the stereoisomers of 4-methyl-5-ethyl-1,3-dioxane (IIa and IIb) (Fig. 1). It can be seen that the methylene protons in the 2-C position (H_a and H_e) in the spectra of both isomers show considerable nonequivalent character ($\Delta\delta_{ae}$ = 0.29 ppm for IIa and 0.43 ppm for IIb.) In one of our publications [14] we presented a table of calculated (in the nondipole approximation) values of the relative changes in the nuclear magnetic shielding constants ($\Delta\sigma$) of the geminal protons and the gem-dimethyl groupings in different positions and for different conformations of 5,5-dimethyl-1,3-dioxane. The data in this table and the results of a study of the PMR spectra of 1,3-

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*These studies were carried out at almost the same time as ours, but the results were published earlier than ours.

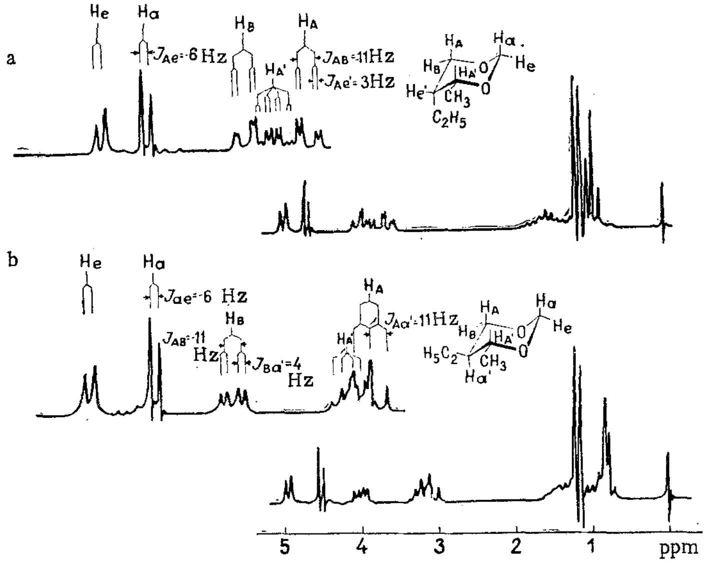

Fig. 1. PMR spectra of the stereoisomers of 4-methyl-5-ethyl-1,3-dioxane (II): a) low-boiling isomer; b) high-boiling isomer.

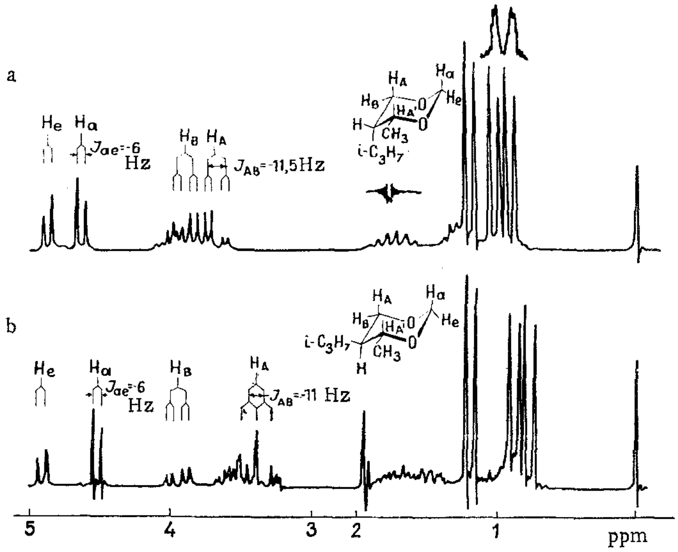

Fig. 2. PMR spectra of stereoisomers of 4-methyl-5-isopropyl-1,3-dioxane (IV): a) low-boiling isomer; b) high-boiling isomer.

dioxane systems [15-17] indicate that the considerable nonequivalent character of the H_a and H_e protons is typical for the predominent chair conformation, i.e., it can be assumed that the molecules of both stereoisomers of II have a predominant chair conformation. This conclusion is in agreement with a similar conclusion for the case of isomers Ia and Ib that was drawn both by us and Delmau and co-workers [13].

The position of the substitued (C_2H_5) attached to the 5-C atom can be determined from the character of the spin–spin splitting of the resonance lines of the protons of the 4-CH and 6-CH_2 groups. In Fig. 1 it is seen that, in the spectrum of isomer IIa, the proton attached to the 5-C atom interacts with the H_A and H_B protons with a vicinal constant of ${}^3J_{HH'} \approx 3$ Hz, while spin interactions with ${}^3J_{H_AH'} \sim 11$ Hz and ${}^3J_{H_BH'} \sim 4.5$ Hz are observed in the spectrum of the high-boiling isomer. According to the $\cos^2\Phi$ law [18], these values of the $J_{HH'}$ vicinal constants are possible if H_e occupies an equatorial position ($\Phi \approx 60°$) in the low-boiling isomer, and if $H_{a'}$ occupies an axial position ($\Phi \approx 180$ and $60°$) in the high-boiling isomer.

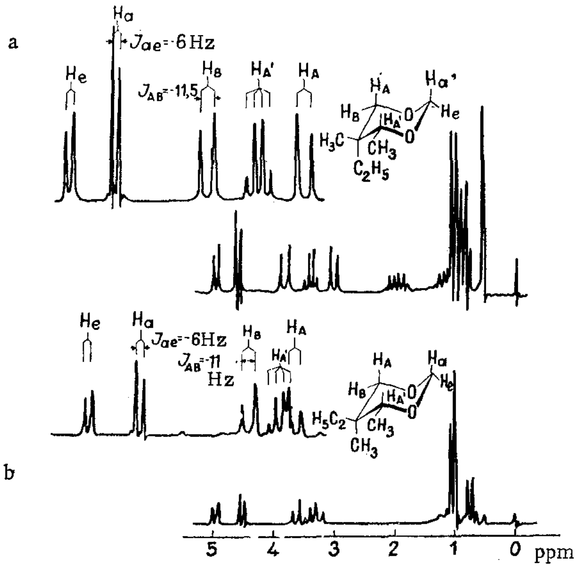

Fig. 3. PMR spectra of stereoisomers of 4,5-dimethyl-5-ethyl-1,3-dioxane (V): a) low-boiling isomer; b) high-boiling isomer.

From the spectrum of isomer IIb it can be seen that the signal of the H'_A proton has a complex multiplicity (a doublet consisting of two quartets), while the average chemical shift practically coincides with the chemical shift of the axial H_A proton attached to the 6-C atom. Consequently, the methyl group at 4-C is equatorial, and this means that isomer IIb is the trans isomer in the predominant chair conformation with a diequatorial orientation of the substituents. The H'_A resonance in the spectrum of isomer IIa is displayed as a quartet of doublets with an average chemical shift of 3.78 ppm. This sort of pattern of the spin interaction of H'_A and H'_e is possible only if the CH_3 group attached to 4-C is also equatorial. The shift in the resonance of the H_A and H'_A protons to lower fields is possibly explained by the effect of the anisotropy of the magnetic susceptibility of the axial 5-C−C bond. The conclusion that isomer IIa with a 5-C-axial orientation of the ethyl group has a cis configuration follows from this.

The PMR spectra (see Fig. 2) indicated that the spin−spin interaction peculiarities indicated above are retained completely when the ethyl group attached to the 5-C atom is replaced by an isopropyl group (IVa and IVb). One's attention should be directed to the character of the resonance signal of the methyl groups of the isopropyl radical in the spectra of both isomers. The observed nonequivalent character of these groups is readily explained by their diastereotopic character. Facts of this sort were previously observed in the case of some halo derivatives and other compounds of the aliphatic series [19].

All of the examined representatives of the 1,3-dioxanes of the A series consequently have similar configurations and conformations, and the relative differences in the densities, and refractive indexes of the stereoisomers are, therefore, completely regular.

In series B, the stereoisomeric 4,5-dimethyl-5-ethyl-1,3-dioxanes (Va and Vb) give the most distinct spectra. As seen in Fig. 3, the H_a and H_e protons in the spectra of both isomers (as in the case of all the other studied formulas of this series) resonate as an AB quartet with a relatively great nonequivalent character ($\Delta\delta_{ae}$), which again indicates the predominant chair conformation for both isomers.

Because of the absence of a hydrogen atom on the 5-C ring atom in compounds of the B type, it is impossible to establish the configurations and predominant conformations for these substances from the angular correlation of the vicinal $^3J_{HH'}$ constants. In this series we will therefore analyze the relative changes in the shielding constants ($\Delta\sigma$) for substituents attached to the 5-C atom. In [12] we presented a theoretical and experimental demonstration that the shielding constants (σ) for the protons and methyl groups attached to the 5-C ring atom undergo inversion (under the influence of the effect of the anisotropy of the magnetic susceptibility of the unshared pairs of electrons of the two oxygen atoms), i.e., the resonance of the equatorial protons (or CH_3 groups) is observed at higher fields than the resonance of the axial protons (or CH_3 groups). It is apparent from the spectrum of Va that the singlet line of the 5-CH_3 group has an anomalously low chemical shift (δ 0.55 ppm), which attests to its equatorial orientation, as we showed in [15-17] and Delmau and Barbier demonstrated in [20].

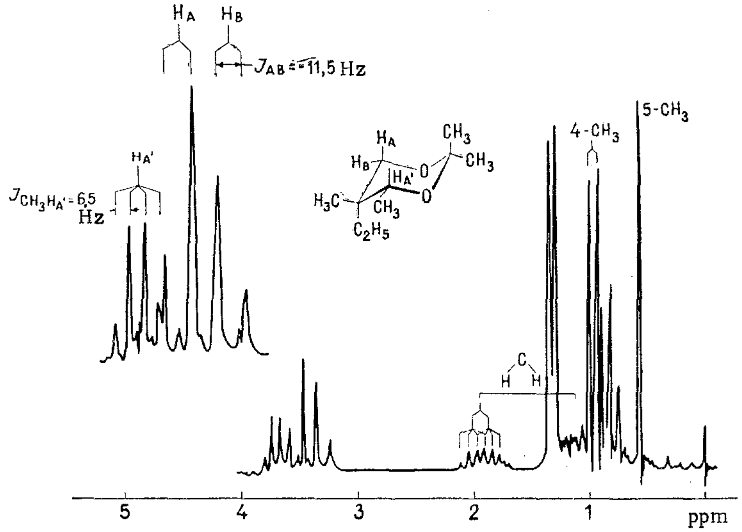

Fig. 4. PMR spectrum of the low-boiling isomer of 2,2,4,5-tetramethyl-5-ethyl-1,3-dioxane (XIIIa).

Another argument in favor of the axial orientation of the ethyl group (and, consequently, the equatorial character of the 5-C methyl group) can be provided by the magnitude of the chemical shift of the signal of the protons of the methylene group of the ethyl radical (1.60 ppm) and the character of its multiplet splitting. Instead of the expected spin quartet, the resonance band of this group is a sextet, which may be a consequence of the definite restriction of rotation of this substituent. Then, because of the effect of the anisotropy of the magnetic susceptibility of the substituent attached to the 4-C atom, there arises magnetic nonequivalence of the protons of the CH_2 group, which first of all undergo AB quartet splitting and, second, each component is split into a quartet under the influence of the adjacent CH_3 group.

The orientation of the CH_3 group attached to the 4-C atom can be determined from the angular correlation of the long-range spin interaction ($^4J_{HH'}$) [21], from which it follows that if the spin interaction between H and H' is realized in a planar zig-zag fragment of the $\diagdown\diagup\diagdown\diagup$ form ("tail-to-tail" or equatorial–equatorial), the value of the $^4J_{HH'}$ constants are larger than in fragments of the $|\diagup\diagdown|$ or $|\diagup\diagdown\diagup$ forms. Thus, if the H_A atom were in the equatorial position, the lines of the equatorial H_B atom attached to the 6-C atom would show an additional multiplicity (or line broadening) with $^4J_{HH'} \approx 0.8 \pm 1.5$ Hz [22]. In the spectra of isomers Va and Vb, presented in Fig. 3, this sort of multiplicity is absent. Relying on this fact and on a comparison with the spectra of "standard" 1,3-dioxanes [23], it can be asserted that the H'_A atom in both isomers is axial; consequently, the 4-C methyl group is equatorial. Both VIa and VIb have similar features in their PMR spectra.

Thus, as in the A series, the low-boiling isomers in the B series have the cis configuration, while the high-boiling isomers have the trans configuration. The predominant conformation of both isomers is the chair conformation and, in the case of the cis isomers, the largest alkyl substituent occupies the 5-C axial position. (The trans isomers are diequatorial.)

This conclusion is also valid for the acetonals of the C series. The signal of the gem-dimethyl group in the spectra of compounds of this series shows two distinctly separated singlet lines. For example, in the case of X, these lines have chemical shifts of 1.26 and 1.37 ppm. We think that the nonequivalency of the methyl protons of the gem-dimethyl grouping is an analytical indication of the predominant chair conformation. The nonequivalency of the H_a and H_e protons attached to the 6-C atom attests to this also, although the $\Delta\sigma_{ae}$ value is somewhat lower than that observed in series A and B. These facts attest to a certain distortion ("compression" [2, 24]) of the chair conformation because of the syn–axial interaction of the 2-C methyl group with the axial H_A and H'_A atoms. The configurations of the low-boiling and high-boiling isomers of the C series are comparatively simply established from the numerical values of the vicinal constants [$^3J_{HH'} = f(\Phi)$]. They are similar to those established in the A and B series.

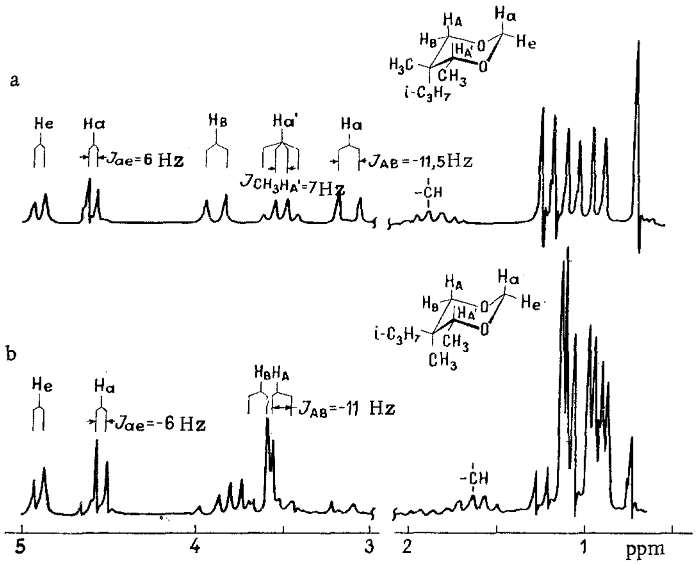

Fig. 5. PMR spectra of the stereoisomers of 4,5-dimethyl-5-isopropyl-1,3-dioxane (VII): a) low-boiling isomer; b) high-boiling isomer.

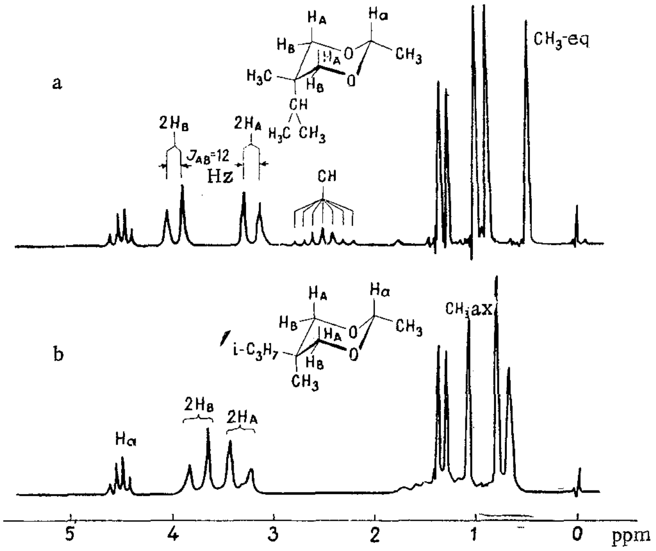

Fig. 6. PMR spectra of the stereoisomers of 2,5-dimethyl-5-isopropyl-1,3-dioxane (XX): a) low-boiling isomer; b) high-boiling isomer.

The same regularities as in the case of series C are observed in the case of the acetonals of the D series. The PMR spectrum of isomer XIIIa is presented in Fig. 4. All of the characteristic features of the chemical shifts and spin–spin multiplets peculiar to the spectra of compounds related to the A, B, and C series are also typical for this stereoisomer.

In connection with the conclusions set forth above, one might expect at least the following observations. First, is our proposed assignment of the configurations and predominent conformations of the isomers correct? Second, if the assignment is correct, why do the more stable and numerically predominant isomers in the 2,5-dialkyl- or 2,5,5-trialkyl-1,3-dioxane series have the trans configuration with 5-C equatorial orientation of the largest substituent, while the cis isomers with 5-C axial orientation of this substituent are present in larger amounts in the A, B, C, and D series?

The first possible observation is rejected on the basis of all that has been set forth above. A comparison of the NMR spectra of 2,5- and 4,5-substituted 1,3-dioxanes and the IR spectroscopic data may be an additional argument in favor of the correctness of our conclusions.

TABLE 3. Properties of Diol Isomers Obtained by the Methanolysis of Individual Stereoisomers of 4,5-Substituted 1,3-Dioxanes*

Comp.	R	bp (mm)	d_4^{20}	n_D^{20}	MR_D		Purity of isomers used for hydrolys; purity of diol isomers, %	Yield, %
					found	calc.		
XVIIb^a	C_2H_5	105 (6)	0,9736	1,4500	32,59	32,95	99	44
		108 (7)	0,9713	1,4457	32,42		88	35
XVIIIb^a	n-C_3H_7	117 (6)	0,9536	1,4486	37,15	37,57	95	71
		125 (11)	0,9495	1,4446	37,04		80	46
XIXb^a	i-C_3H_7	111 (6)	0,9612	1,4529	37,15	37,57	95	75
		113 (7)	0,9522	1,4470	37,08		85	24

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*Superscript a refers to isomers obtained from trans-1,3-dioxanes, i.e., the erythro isomers, while subscript b refers to isomers obtained from trans-1,3-dioxanes, i.e., the threo isomers.

The PMR spectra of, respectively, isomers VIIa and VIIb and of the low-boiling (XXa) and high-boiling (XXb) isomers of 2,5-dimethyl-5-isopropyl-1,3-dioxane are presented in Figs. 5 and 6. It is easy to see that the spectra of the isomers of the corresponding configurations are similar to one another. A singlet peak from the protons of the 5-C methyl group is observed at 0.55 ppm in the spectra of VIIa and XXa, while the resonance of these protons is observed at lower field (1.1 ppm) in the spectra of isomers VIIb and XXb. The position of the resonance band of the CH protons of the isopropyl group is similar in the spectra of isomers VIIa and XXa. In addition, a regular change in the resonance band of the AB quartet of the 4- and 6-CH_2 groups or 6-CH_2 group is observed on passing from isomers VIIa and XXa to isomers VIIb and XXb. In view of the fact that the peculiarities of the spectra of the compounds under consideration were commented upon in detail above, we will limit ourselves here to these observations, which clearly confirm the trans configuration of the high-boiling isomers and the cis configuration of the low-boiling isomers, and the predominant chair conformation for both isomers.

The IR spectroscopic data are presented in Table 2. It is known [17] that the characteristic bands of the individual stereoisomers of 1,3-dioxanes (the spectral indexes of the isomers) are the bands in the region of pulsation ring vibrations (500-680 cm^{-1}), and the trans isomers display absorption at higher wave numbers, while the cis isomers display absorption at lower wave numbers [25]. It is easy to see that this is also observed experimentally, attesting to the trans configuration of the high-boiling isomers and the cis configuration of the low-boiling isomers.

The second possible observation is eliminated by the fact of the stereospecificity of the reduction of substituted acetoacetic esters and by the fact that the synthesis of 1,3-dioxanes (like their hydrolysis) proceeds without Walden inversion. Hence, the configuration of 4,5-substituted 1,3-dioxanes and the ratio of their stereoisomers are determined by the configuration and isomer ratio of the starting 1,3-diols. Moreover, it is especially important to emphasize that epimerization is impossible for the compounds examined here.

The above is experimentally confirmed. Hydrolysis of the individual stereoisomers of 1,3-dioxanes gives diastereomers of 1,3-diols. It should be emphasized that the same diastereomeric 1,3-diol (XVIIIa) is formed from stereoisomers IIIa and XIa, while 1,3-diol XVIIIb is formed from isomers IIIb and XIb. The individual diastereomers of 1,3-diols in turn form the starting stereoisomers of 1,3-dioxanes on condensation with formaldehyde and acetone. The absence of isomer admixtures was monitored by gas-liquid chromatography. The properties of the 1,3-diol diastereomers are described in Table 3. The configuration of the 1,3-diol diastereomers is determined by the proved configuration of the corresponding 1,3-dioxanes. It is easy to comprehend that erythro isomers of 1,3-diols are obtained in the hydrolysis of isomers Ia-IVa, while threo isomers are the products of the hydrolysis of isomers Ib-IVb. All of this experimentally confirms the correctness of the modified Cram rule and all of the theoretical considerations presented in the first part of this paper.

In conclusion, it should be noted that the PMR spectra of the individual isomers of the 1,3-dioxanes of the A, B, C, and D series clearly attest to a shift in the equilibrium to favor one predominant conformation. It follows from [26] that in the 1,3-dioxane series there are no substantial energy differences between the skew conformation with a pseudodiequatorial orientation of the 2-C and 5-C substituents and the chair conformation with 2-C equatorial and 5-C axial orientation of the substituents. Hence the molecule assumes one or the other conformation as a function of the character of the 5-C substituent. In this connection, it is interesting to note that it is precisely in the case of the presence of large, branched substituents that molecules very definitely assume the chair conformation with 5-C axial orientation of even such groups as isopropyl [26] or tert-butyl [27]. It is not difficult to see that the data obtained in a study of 1,3-dioxanes of the A, B, C, and D series confirm these conclusions, since the PMR spectra clearly indicate that the statistical weight of the H and J conformations in the examined compounds is very low.

EXPERIMENTAL

The starting compounds for the 1,3-dioxanes of the A, B, C, and D series were 2-methyl-, 2-ethyl-, 2-propyl-, and 2-isopropyl-1,3-butanediols, whose physical constants were in agreement with those presented in [28], as well as 2-methyl-2-ethyl- [bp 100-102° (5 mm), d_4^{20} 0.9648, n_D^{20} 1.4522], 2,2-diethyl [bp 113° (5 mm), d_4^{20} 0.9632, n_D^{20} 1.4563], 2-methyl-2-isopropyl- [bp 110-112° (5 mm), d_4^{20} 0.9628, n_D^{20} 1.4580], and 2-ethyl-2-isopropyl- [bp 118-120° (5 mm), d_4^{20} 0.9643, n_D^{20} 1.4620] -1,3-butanediols, as well as purified and dried paraformaldehyde and acetone.

The substituted 1,3-butanediols were obtained from the corresponding alkyl- and dialkylacetoacetic esters by reduction with $LiAlH_4$ by the method in [9]. The method in [29] was used to obtain 2-methyl-1,3-butanediol.

The formals and acetonals of the A, B, C, and D series were synthesized by the method in [8] using the hydrogen form of KU-1 and KU-2 cation-exchange resins as catalysts. The stereoisomer ratios and the purity of the individual isomers were determined by gas-liquid chromatography (using an LKhM-8-M chromatograph with a 3-m long column, He as the gas carrier, 5% SKTFT-50 on Chromosorb W, a flow rate of 20-25 ml/min, and a column temperature of 60-115°).

The stereoisomers of I-V, VII, IX-XIII, and XV were separated with efficient total condensation columns with glass packing (column 1 with HETP 50) and with metal packing (column 2 with HETP 60). The fractionation conditions were: column 2 with a reflux ratio of 60-75 for mixtures of isomers of I, III-V, VII, IX, XI, and XV; column 1 with a reflux ratio of 65-77 for mixtures of isomers of II, X, XII, and XIII. All of the fractionations were carried out continuously for 24-60 h.

Several individual isomers of compounds of the A and C series were hydrolyzed by the following method to prove the stereospecificity of the hydrolysis and synthesis of 1,3-dioxanes: 0.025 mole of the cis or trans isomer of the 1,3-dioxane was heated for 10 h in methanol (0.125 mole) containing H_2SO_4 (0.38 g) on a water bath at 70°, and the volatile hydrolysis products were simultaneously removed by distillation with a high column. At the end of the reaction, the reaction mixture was neutralized with sodium carbonate, the methanol was removed by distillation, and the residue was treated with ether. The ether extracts were dried over Na_2SO_4, the ether was removed by distillation, and the diol was purified by vacuum fractionation.

The 1,3-dioxanes were synthesized from the thus obtained 1,3-diol diastereoisomers by the method in [8]. They proved to have the same constants as those described in Table 2, and their gas-liquid chromatograms confirmed the purity of the individual stereoisomers, which proves that neither Walden inversion nor epimerization occur.

The IR spectra of liquid films between KBr plates and of CCl_4 solutions were recorded with an IKS-14A spectrophotometer with a KBr prism. (The layer thickness was 0.249 mm, and the concentration was 0.2 M.)

The PMR spectra of 10-20% solutions in CCl_4 were recorded with an HA-100D spectrometer with an operating frequency of 100 MHz and with tetramethylsilane as the internal standard.

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