SIX-MEMBERED HETEROCYCLES

I. The Stereoisomerism of 2-Alkyl-5-hexyl-1,3-dioxanes

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2-Methyl-5-hexyl- and 2-isopropyl-5-hexyl-1,3-dioxanes have been synthesized for the first time by the condensation of 2-hexyl-1,3-propane-diol with acetaldehyde and isobutyraldehyde, and they have been separated into their stereoisomers by fractionation in efficient columns. It has been shown by a study of their PMR spectra that the low-boiling isomers have the cis- and the high-boiling isomers the trans-configuration. A study of the PMR spectra has enabled us to show not only the configuration but also the predominant conformations of the isomers; the cis-isomer exists predominantly in the unsymmetrical boat conformation with a diequatorial location of the substituents and the trans-isomer in the chair conformation, also with a diequatorial arrangement of the substituents.

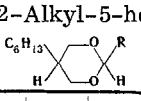
Developing the investigations that we are carrying out in the field of the stereochemistry of 1,3-dioxanes of [1], we have studied the stereoisomerism of 2-alkyl-5-hexyl-1,3-dioxanes (I), i.e., the simplest representatives of the 1,3-dioxane series, in comparison with the 2,5-dialkyl-5-α-alkoxyethyl-1,3-dioxanes that we have studied previously.

By the reaction of 2-hexyl-1,3-propane-diol with acetaldehyde and isobutyraldehyde in the presence of KU-1 sulfo cation-exchanger in the hydrogen form [2], we have synthesized the previously unreported 5-hexyl-2-methyl-1,3-dioxane (II) and 5-hexyl-2-isopropyl-1,3-dioxane (III). The presence of stereoisomers in these materials was shown by gas-liquid chromatographic analysis. The separation of the isomers was effected by fractionation in efficient rectifying columns. The results of the distillation showed that the low-boiling isomers of II and III have higher densities than the high-boiling isomers, i.e., they deviate from the rule known as the Auwers-Skita rule. This deviation has served as a basis for the assumption that the low-boiling isomer is the cis-form and the high-boiling isomer the trans-form.

The hypothesis put forward was confirmed by an analysis of the PMR spectra of the stereoisomers of I. Figure 1 gives the spectra of the stereoisomers of 5-hexyl-2-methyl-1,3-dioxane (II). As can be seen, the PMR spectrum of the high-boiling isomer of II clearly shows the absence of inversion of the ring, a symmetrical position of the 4-CH_2 and 6-CH_2 methylene groups, and a considerable nonequivalence of the axial H_a and the equatorial H_e protons of these methylene groups. This can be seen from the nature of the peaks located in the δ range from 2.90 to 4.10 ppm. The peak of the axial protons is located in a stronger field than the peak of the equatorial protons. In each methylene group, in the absence of inversion of the ring, the protons form a spin system of the AB type which must lead to a characteristic AB quadruplet with a J_{AB} constant, for symmetrically substituted 1,3-dioxanes [3, 4], of $(J_{AB}) = -11 \pm 0.5$ Hz. In the case under consideration, this constant is $(J_{ae}) = -11.2$ Hz. Since the 5-C carbon has a hydrogen, the spin interaction of the moment of the H_a proton with the methylene proton of the ring must lead to an additional multiplicity of the lines of the AB quadruplet. The spectrum shows that this spin interaction of the moment of the $H_{a'}$ proton with the axial H_a proton takes place with a constant $|{}^3J_{aa'}| = 9$ Hz and with a constant $|{}^3J_{ea'}| = 5$ Hz with the equatorial H_e proton. From the graph of the spin-spin coupling constants $J_{H-C-C-H}$ as a function of the dihedral angle that was drawn up by Conroy [5] and Karplus [6], it follows that such constants can only exist at a dihedral angle of 0 or 180° (${}^3J_{aa'} = 9$ Hz) and 38° (${}^3J_{ea'} = 5$ Hz). Excluding the first possibility, we see that the $H_{a'}$ hydrogen is axial, i.e., the hexyl radical occupies the equatorial position. These values of the constants are in good agreement with the results of work [4] giving the value $J_{5a-6a} = J_{5a-4a} = 9$ Hz for symmetrical 1,3-dioxanes and a value of 4.2 to 4.5 Hz, according to the nature of the substituent, for the axial-equatorial spin coupling constant of the type $J_{H-C-C-H}$.

The chemical shift of the methyl group in position 2 is $\delta = 1.16$ ppm which indicates its equatorial nature,

Stereoisomers of 2-Alkyl-5-hexyl-1,3-dioxanes



R	Isomer	Bp, °C (mm)	Δ T°	d_4^{20}	n_D^{20}	MR_D found	MR_D calculated	Ratio of isomers in the initial products, %
CH_3	Low-boiling	51 (0.5)	6.5	0.9042	1.437	53.97	54.08	30
CH_3	High-boiling	57.5 (0.5)		0.9008	1.436	54.02		70
i-C_3H_7	Low-boiling	71 (0.5)	2.5	0.8928	1.4385	63.02	63.32	34
i-C_3H_7	High-boiling	73.5 (0.5)		0.8918	1.440	63.34		66

*Calculated on the basis of the values of n_D^{20}.

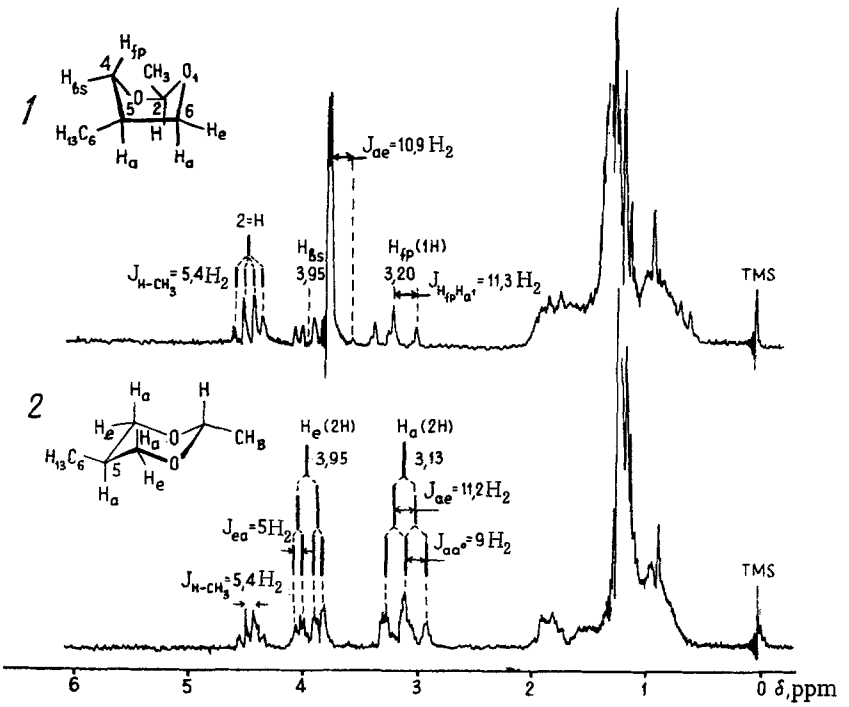


Fig. 1. Proton magnetic resonance spectra of 2-methyl-5-hexyl-1, 3-dioxane at 21° C and a frequency ν_0 of 60 MHz: 1) low-boiling **IIa**; 2) high-boiling **IIb**.

as we have shown previously. The chemical shift of the proton on the 2-C carbon is δ = 4.45 ppm. This shift, as has been shown previously [1, 7] is characteristic for an axial hydrogen. It may be concluded from this that in position 2 the methyl group occupies the equatorial position and the hydrogen atom the axial position. A comparison of these data with an analysis of the position of the substituents at C_5 leads us to the conclusion that this isomer is the trans-isomer if it exists predominantly in the chair conformation.

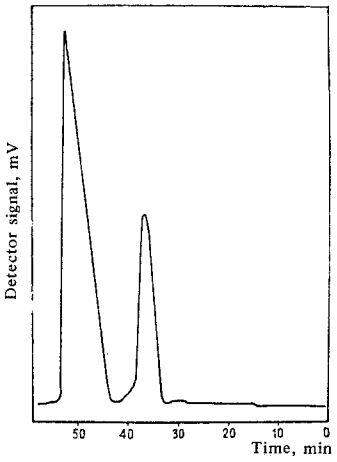


Fig. 2. Gas-liquid chromatogram of the stereoisomers of 2-methyl-5-hexyl-1,3-dioxane. Ratio of the isomers = 30 : 70.

The chair conformation can be deduced from theoretical evaluations of the nonequivalence of the axial and equatorial protons of the methylene groups of the ring [1, 7]. It is not difficult to see that the nonequivalence that exists $\Delta\delta = \delta_e - \delta_a$ = 0.82 ppm is in agreement with the calculated nonequivalence of the chair conformation $\Delta\delta_{calc}$ = 0.30 ppm obtained with allowance for the anisotropy of the magnetic susceptibility of the unshared pairs of electrons of the two oxygen atoms [2].

Thus, an analysis of the spectrum of the high-boiling isomer leads to the conclusion that this isomer has the trans-configuration and exists predominantly in the chair conformation.

In the spectrum of the low-boiling isomer of II (Fig. 1), the nonequivalence of the protons of the 4-CH_2 methylene group and the almost complete equivalence of the second methylene group of the ring (6-CH_2) are clearly shown, while the splitting of the bands of the first methylene group is similar to that of the bands of the methylene groups of the high-boiling isomer. This feature of the spectrum shows, in the first place, the absence of inversion of the ring and, in the second place, that the molecule of this isomer exits predominantly in the unsymmetrical boat conformation, as can be seen from the calculated figures given previously [1]. It is characteristic that the spin-spin coupling constants for this isomer are somewhat different, being: (J_{fp-a}) = 11.3 Hz, (J_{ae}) = 10.9 Hz, and $(J_{bs-a'})$ = = 4.8 Hz. It can be shown that the two groups of lines with centers at δ = 2.95 and 3.20 ppm, which we ascribe to the 4-CH_2 methylene group are due to the presence of the high-boiling isomer IIb as an impurity in the sample of IIa. This assumption is confirmed by a study of the integral intensities of the lines and also by the value of the chemical shift of the triplet with its center at δ = 3.20 ppm; in the high-boiling isomer the corresponding shift is δ = 3.13 ppm. The measurements of these values of the shifts were carried out extremely carefully.

The values of the $J_{HH'}$ constants and the form of splitting of the lines of the spectrum of the methylene protons are in some contradiction with the calculations mentioned above. Thus, according to the calculations in the unsymmetrical boat conformation the axial flagstaff H_{fp} and the equatorial bowsprit H_{bs} protons of the methylene group present at the apex of the boat (position 4) must have a nonequivalence of about 0.45 ppm. In this case, the equatorial proton must resonate in a stronger field than the axial one. However, the spectrum shows that although the total nonequivalence has the order of magnitude predicted by theoretical considerations, the axial proton resonates in a stronger field than the equatorial one.

Thus, the nature of the spectrum shows that the molecules of the low-boiling isomer IIa have the cis-configuration with a diequatorial position of the substituents in the predominant unsymmetrical boat conformation. The chair conformation must be rejected on the grounds that in the case of this conformation, in view of the similar chemical shifts of the C-2 protons in both isomers, the hexyl radical should occupy the axial position and the hydrogen at C-5 the equatorial position. However, for the equatorial proton the spin interaction constants would, according to the Conroy-Karplus graph [5], be completely different from those given above.

The PMR spectra of IIIa and IIIb show the same features with the exception that the doublet of the methylene proton of the isopropyl group on the C-2 hydrocarbon is superposed on one of the doublets of the equatorial proton of the methylene group of the ring in both isomers.

Taking all that has been said above into account, the low-boiling isomer of I must be ascribed the cis-configuration with a diequatorial position of the substituents in the unsymmetrical boat conformation and with the absence of inversion of the ring, and the high-boiling isomer of I must be assigned the trans-configuration with a diequatorial position of the substituents in the chair conformation, again with the absence of inversion of the ring.

Consequently, the reversal of the refractive indices and densities is connected with the formation of the configuration and depends on the number of carbon atoms in the dioxane molecule. It is obvious that such an inversion of the constants is characteristic only for 5-hexyl-substituted dioxanes. When smaller radicals are present in position 5, one must expect a different relationship between the isomers and different constants, and also that the low-boiling isomers will be not the cis- but the trans-isomers and the high-boiling ones, correspondingly the cis-isomers.

Here we should like to mention one more interesting fact about the compounds studied. We have observed that in the course of time the low-boiling stereoisomers IIa and IIIa undergo isomerization into the high-boiling isomers, which confirms their lability and the cis- conformation. It is very likely that their isomerization is initiated by the tetramethylsilane that was added to the samples as internal standard. This phenomenon is under further study.

EXPERIMENTAL

The starting material for the investigation was the hexylmalonic ester IV synthesized by the usual method [8] with bp 130° C (4 mm); d_4^{20} 0.9610; n_D^{20} 1.429.

2-Hexyl-1, 3-propane-diol (V). This compound was obtained by reducing IV with lithium aluminum hydride, prepared by Wiberg and Schmidt's method [9] from 38.5 g of lithium hydride and 267.0 g of aluminum bromide in 1500 ml of absolute ether. With cooling, 122 g (0.5 mole) of IV was carefully added to the aluminum hydride prepared from the amounts of LiH and $AlBr_3$ given. The reaction was carried out in the manner previously described [10]. The yield of compound V with the constants bp 128° (2 mm), d_4^{20} 0.9610, n_D^{20} 1.429. was 240 g (75%). Found, %: C 67.36; H 12.52. Calculated for $C_9H_{20}O_2$, %: C 67.50; H 12.50.

Synthesis of II and III. The synthesis was effected by a method similar to that which we have described previously [2] using 8.9 g (0.056 mole) of V, 11.7 g (0.27 mole) of acetaldehyde and 8.6 g (0.12 mole) of butyraldehyde in the presence of 0.8 g of KU-1 ion-exchange resin in the hydrogen form. The mixture was heated in 60 ml of absolute benzene until the separation of water in a Dean-Stark trap ceased, and the cation exchanger was then filtered off; after being washed with absolute benzene it could be used again as catalyst. The benzene was distilled off and the reaction product was fractionated in vacuum. The yield of II was 7.1 g (77%) and that of III 10.1 g (95%). Characteristics of II: bp 85° C (1 mm); d_4^{20} 0.9018, n_D^{20} 1.4367. Found, %: C 70.41; H 12.15. Calculated for $C_{11}H_{22}O_2$, %: C 70.96; H 11.83. Characteristics of III: bp 95° C (1 mm); d_4^{20} 0.8892, n_D^{20} 1.439. Found, %: C 71.77; H 12.24. Calculated for $C_{13}H_{26}O_2$, %: C 71.96; H 12.15.

Gas-liquid chromatographic analysis of II and III. The analysis was carried out on a LKhM-5 chromatograph of SKB IOKh AN SSSR [Special Design Bureau, Institute of Organic Chemistry, AS USSR] and a UKh-1 chromatograph under conditions similar to those that we have described previously [1, 2]. A chromatogram clearly showing the presence of isomers in the product II in a ratio of 30 : 70 is given in Fig. 2. The ratio of the isomers for compound III was 40 : 60.

Fractionation of the stereoisomers. The fractionation was carried out on a total condensation rectifying column with a efficiency of 37 theoretical plates day and night without interruption with reflux numbers of 60 for II and 180 for III. The distillation of 32 g of II yielded 12 fractions of which the second and the third (7.8 g) had identical constants and so did the eighth and ninth fractions (total weight 9.3g)

In the distillation of 32 g of III, fourteen fractions were collected of which the 3rd-6th (7.6 g) and the 12th-14th (6.3 g) had identical constants. The properties of the individual isomers of II and III are given in the table. The ratios of the isomers given in the table were obtained on the basis of calculations from the refractive indices, which agreed well with those found by GLC analysis.

The NMR spectra of compounds II and III were recorded on a RYa-2303 spectrometer at a frequency ν_0 of 60 MHz under the conditions that we have described previously [1, 7].

The purity of the stereoisomers of II and III was checked by analysis and by the NMR spectra, which showed that the low-boiling isomers had purities of the order of 88—94% and the high-boiling isomers 99.99%.

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