STEREOCHEMISTRY OF HETEROCYCLES

XXXIX.* STEREOCHEMISTRY OF 2-METHYL-5-ALKYL-5-PHENOXY-1,3-DIOXANES

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2-Methyl-and 2,5-dialkyl-5-phenoxy-1,3-dioxanes were synthesized and separated into their geometrical isomers by precision rectification. The configuration and conformations of these isomers were determined by PMR spectroscopy. It is shown that the low-boiling trans isomers exist primarily in the chair conformation with an equatorial phenoxy group, whereas the high-boiling cis isomers exist primarily in the chair conformation with an axial phenoxy group.

Considering the absence of sufficiently complete information regarding the effect of alkoxy and aryloxy groups on the conformation of the 1,3-dioxane ring [2-4], we undertook the present research. It is known that the chair conformation with axially oriented alkoxy groups is preferable in 2-alkoxy-1,3-dioxanes (the "anomeric effect," for example, see [5, 6]). The axial and equatorial orientations of the alkoxy substituent are practically equally probable for stereoisomeric 5-alkoxy-1,3-dioxanes ($-\Delta G^0 = 0.3 \pm 0.01$ kcal/mole) [2]. The expected multiplicity of the resonance signal of the protons of the 4,6-CH_2 groups is absent in the PMR spectra of the cis isomers of some 2,5-dialkyl-5-alkoxy-1,3-dioxanes, and their percentage in the stereoisomeric mixture does not exceed 30% [7]. This may indicate the existence of the cis isomers in a conformation other than the chair conformation. In order to obtain additional information regarding the effect of alkoxy groups in the 5 position on the primary conformation of substituted 1,3-dioxanes, we synthesized a number of 2,5-dialkyl-5-phenoxy-1,3-dioxanes (Table 1). The phenoxy group, which has a larger volume than the alkoxy group (CH_3O, C_2H_5O) in the previously investigated 2,5-dialkyl-5-alkoxy-1,3-dioxanes [7], should lead to a shift in the equilibrium to favor the trans isomer or to distortion of the chair conformation.

The substitutent in the 2 position (the methyl group) was the same in the investigated series of stereoisomeric 1,3-dioxanes. The selection of this substituent was due to the fact that the signal of the 2-CH_3 group is not superimposed on the resonance of the other protons during the study of the PMR spectra. Moreover, it has been previously proved [7] that the 2-CH_3 group preferably occupies the equatorial position and in this sense can be considered to be a "ring-fixing" substituent ($-\Delta G^0 \approx 4.0$ kcal/ mole).

The PMR spectra of the low-boiling (Ia) and high-boiling (Ib) isomers of 2-methyl-5-phenoxy-1,3-dioxane (I) are presented in Fig. 1. The resonance signal of the 2-CH_3 group appears as a doublet with a chemical shift of 1.27 ppm in the spectra of both isomers. The 2-H proton gives a quartet centered at 4.53 ppm. The identical character of the positions of the resonance signals of the indicated protons in the spectra of both isomers indicates identical conformations of the steric center in the 2 position, and a comparison of the chemical shifts of the H_a proton and the protons of 2-CH_3 groups with the data in [7] indicates the equatorial character of the latter. The H_a proton occupies the axial position. In addition, these data speak in favor of a chair conformation of the heteroring. The symmetrical character of the spectrum of

*See [1] for communication XXXVIII.

I. I. Mechnikov Odessa State University. V. I. Ul'yanov-Lenin Kazan State University. Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Odessa Branch. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1036-1041, August, 1975. Original article submitted June 25, 1974.

TABLE 1. Properties of Individual Isomers of 2-Methyl-5-alkyl-5-phenoxy-1,3-dioxanes

Compound	R	Isomer	bp, °C (mm)	d_4^{20}	n_D^{20}	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Percentage of the isomers in the mixture, %
I	H	trans	102 (1); mp 29—30°	—	—	$C_{11}H_{14}O_3$	67,9	7,4	68,0	7,3	92
		cis	110 (1); mp 98—99°	—	—		68,2	7,2			8
II	CH_3	trans	101 (1)	1,0904	1,5100	$C_{12}H_{16}O_3$	69,3	7,9	69,4	7,6	55
		cis	108 (1)	1,1005	1,5130		69,4	7,8			45
III	C_2H_5	trans	125 (4)	1,0843	1,5070	$C_{13}H_{18}O_3$	70,3	8,1	70,2	8,2	37
		cis	139 (5)	1,0900	1,5112		70,3	8,2			63
IV	C_3H_7	trans	137 (6)	1,0573	1,5035	$C_{14}H_{20}O_3$	71,2	8,6	71,1	8,6	62
		cis	147 (6)	1,0656	1,5076		71,3	8,6			38
V	i-C_3H_7	trans	121 (4)	1,0768	1,5126	$C_{14}H_{20}O_3$	71,2	8,5	71,1	8,6	37
		cis	127 (3)	1,0750	1,5109		71,0	8,5			63

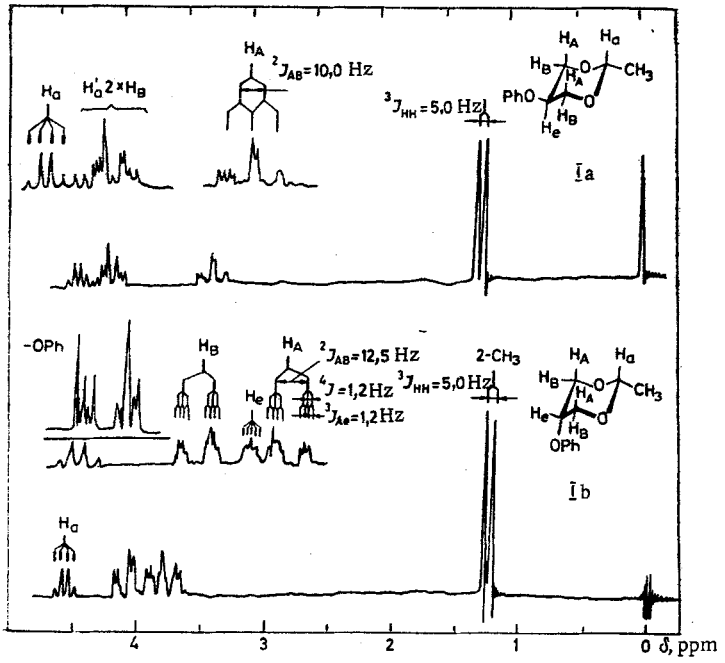


Fig. 1. PMR spectra of 2-methyl-5-phenoxy-1,3-dioxane (I): Ia) low-boiling isomer; Ib) high-boiling isomer.

the 4,6-methylene protons, the typical values of the geminal $^2J_{AB}$ constants, and the considerable magnetic nonequivalence of the axial and equatorial protons of these groups, which may serve as a criterion of the chair conformation [7], also constitute evidence in favor of the chair conformation. In view of the shift of the conformational equilibrium to favor one primary conformation, the protons of each of the 4,6-methylene groups form a spin system of the AB type with geminal spin—spin coupling constants (SSCC) of $^2J_{AB} = -10.0$ Hz for Ia and $^2J_{AB} = -12.5$ Hz for Ib. Subsequent splitting of the lines of the AB quartet with $^3J_{Aa} = 10.0$ Hz, which is due to the vicinal spin—spin coupling of the H_A proton with the 5-H proton, indicates its axial position in Ia. In the spectrum of stereoisomer Ib the 5-H proton, because of its coupling with the protons of the 4,6-methylene groups, resonates as a quintet with $^3J_{Ae} = {}^3J_{Be} = 1.2$ Hz and a chemical shift of δ 3.89 ppm, occupying the equatorial position. The additional multiplicity of the lines of the AB quartet in the spectrum of this isomer, with $^4J = 1.5$ Hz, is apparently due to long-range spin—spin coupling of the protons of the 4,6-CH_2 groups.

Thus the low-boiling isomer of dioxane Ia has the trans configuration and primarily the 2e5e-chair conformation. The H_a proton resonates in the region of the H_B proton. Low-boiling isomer Ib is the cis isomer with a preferred 2e5a-chair conformation.

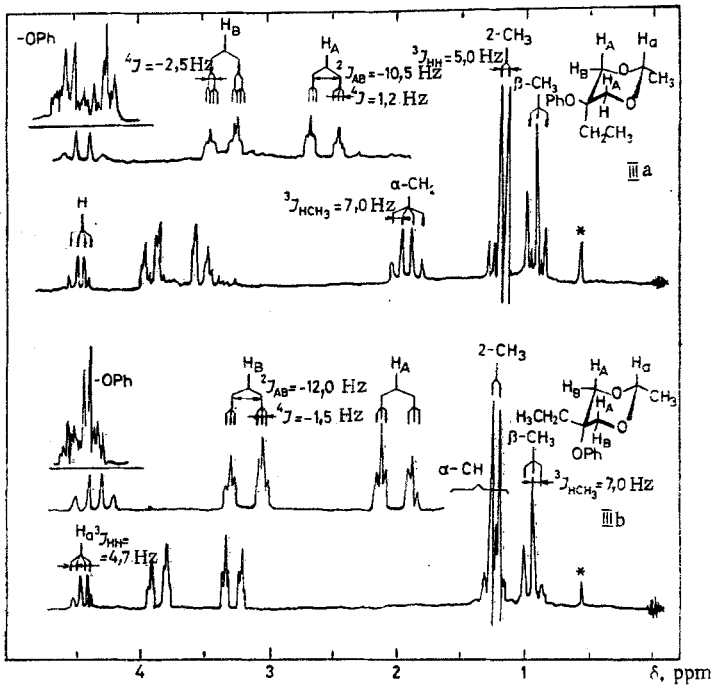


Fig. 2. PMR spectra of 2-methyl-5-ethyl-5-phenoxy-1,3-dioxane (III): IIIa) low-boiling isomer; IIIb) high-boiling isomer.

TABLE 2. PMR Spectra of 2-Methyl-5-alkyl-5-phenoxy-1,3-dioxanes

Compound	R	Isomer	Chemical shifts, δ, ppm*							SSCC, Hz		
			2-H_a	2-CH_3	4,6-H_A	4,6-H_E	5-R: α-CH_2 or CH	5-R: CH_3	Ph	$^2J_{AB}$	$^3J_{H_aCH_3}$	$^3J_{HCH}$ in 5-R
II	CH_3	IIa	4,57q	1,33d	3,32t	3,94t	—	1,43s		−10,4	5,0	
		IIb	4,60q	1,35d	3,66t	3,87t	—	0,89s		−12,4	5,0	
IV	C_3H_7	IVa	4,53q	1,23d	3,55t	3,93t	1,90	0,90t	7,06m	−12,2	5,0	7,0
		IVb	4,58q	1,26d	3,34t	3,90t	1,46	0,87t	7,05m	−12,2	5,0	7,0
V	i-C_3H_7	Va	4,53q	1,12d	3,42t	4,04t	2,35	1,05d	6,96m	−10,0	5,0	6,5
		Vb	4,54q	1,15d	3,53t	3,98t	1,69	0,94d	6,71m	−12,5	5,0	6,5

*Abbreviations: d is doublet, t is triplet, q is quartet, m is multiplet, and s is singlet.

The PMR spectra of the low-boiling (IIIa) and high-boiling (IIIb) isomers of 2-methyl-5-ethyl-5-phenoxy-1,3-dioxane (Fig. 2) have a typical AB quartet of methylene ring protons with centers of 3.50 and 3.89 ppm and $^2J_{AB} = -10.5$ Hz for isomer IIIa, and centers at 3.30 and 3.89 ppm and $^2J_{AB} = -12.0$ Hz for isomer IIIb. The indicated spectral data constitute evidence that both isomers exist in the preferred chair conformation at room temperature. The methyl group attached to the C-2 atom occupies the same position – equatorial (quartet centered at δ 4.41 ppm for IIIa and at 4.45 ppm for IIIb with $^3J_{HCH_3} = 5.0$ Hz; the protons of the methyl group attached to C-2 of both isomers give a doublet with a chemical shift of 1.26 ppm for IIIa and 1.18 ppm for IIIb) – in both isomers.

It is impossible to form a judgment regarding the spatial orientation of the substituents attached to C-5 in II-V by examining the vicinal SSCC, as in the case of I, because of the absence of a methylidyne proton attached to C-5 in the molecules of these compounds. In this case one can use the regularities in the changes in the chemical shifts of the protons attached to the α-carbon atom of the substituents bonded to the ring C-5 atom [7]. This is seen in the case of the PMR spectrum of 2-methyl-5-ethyl-5-phenoxy-1,3-dioxane (III). The ethyl substituent in low-boiling isomer IIIa is in the axial position, inasmuch as the quartet of the α-methylene protons of the ethyl group is shifted to lower fields as compared with the resonance signal of these same protons in the spectrum of high-boiling isomer IIIb. In this case the shift of the resonance band of the methylene protons to higher or lower field acts as a test criterion of the spatial orientation of the substituents attached to C-5 [8].

TABLE 3. Magnitude of the Difference in the Free Energies ($-\Delta G^0$) of the Configurational Isomerization of 2-Methyl-5-alkyl-5-phenoxy-1,3-dioxanes

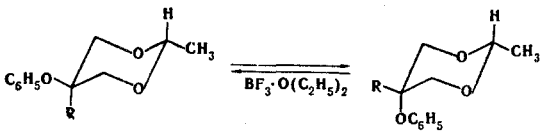
Compound	R	K_{av}	$-\Delta G^0$, kcal/mole
I	H	3,2 ±0,21	+0,77±0,07
II	CH_3	0,84±0,09	−0,11±0,07
III	C_2H_5	0,84±0,04	−0,11±0,04
IV	C_3H_7	0,84±0,04	−0,11±0,04
V	i-C_3H_7	0,53±0,03	−0,42±0,06

Summarizing the material set forth above, it can be asserted that stereoisomer IIIa has a trans configuration and a preferred 2e-methyl-5a-ethyl-5e-phenoxy chair conformation and IIIb has a cis configuration and a 2e-methyl-5e-ethyl-5a-phenoxy chair conformation.

A study of the PMR spectra of 1,3-dioxanes II-V (see Table 2) with allowance for the above-discussed features of the spectral characteristics makes it possible to assert that the low-boiling isomers are trans isomers with a 2e-methyl-5a-alkyl-5e phenoxy orientation of the substituents and exist in the preferred chair conformation, whereas the high-boiling isomers are cis isomers with a 2e-methyl-5e-alkyl-5a-phenoxy orientation of the substituents in the chair conformation.

The IR spectra of 1,3-dioxanes I-V contain absorption bands at 1000-1300 cm^{-1} which are characteristic for the 1,3-dioxane ring [9]. The same differences at 400-800 cm^{-1} as in the previously described compounds of the 1,3-dioxane series (for example, see [10]) are observed in the IR spectra of the individual stereoisomers of I-V.

An analysis of I-V by gas–liquid chromatography (GLC) shows that the trans isomer (92%) predominates in the stereoisomeric mixture of I. At the same time, the percentages of the two isomers in stereoisomeric mixtures II-V are either approximately equal (R = CH_3) or else the trans (R = C_3H_7) or cis (R = C_2H_5 and iso-C_3H_7) isomer predominates. Assuming that this mixed pattern of the ratio of the stereoisomers in their mixtures is due to the closeness of the conformational energies of the 5-alkyl (CH_3, iso-C_3H_7 = 1.0 kcal/mole, C_2H_5 = 0.76 kcal/mole [2, 4]) and 5-phenoxy substituents, we studied the epimerization of the pure stereoisomers of I-V:



It is seen from the data in Table 3 that the preferred character of the 5e position of the phenoxy group in I as compared with the 5a position is 0.77 kcal/mole. From a comparison of this value with the conformational energies of the alkyl groups attached to the ring C-5 atom, it can be seen that the axial orientations of the alkyl or phenoxy substituent are approximately equally probable (the axial orientation of the phenoxy substituent is preferred). Compound V, in which the axial orientation of the phenoxy group is considerably more advantageous (by 0.42 kcal/mole) than the axial orientation of the 5-isopropyl group constitutes an exception to this. Considering the data in [2, 11] and our results, it can be asserted that the ratio of stereoisomers of II-V is due to the difference in the conformational energies of the 5-alkyl groups and the phenoxy substituent. The shift in the conformational equilibrium to favor the trans isomer in the case of I can be explained by the different nature of the substituents attached to the ring C-5 atom and, in connection with this, by the change in the conformational energies of substituents determined for steric series of 1,3-dioxanes with substituents of the same nature.

EXPERIMENTAL METHOD

The PMR spectra of solutions (~10% by volume) of dioxanes I-V (Figs. 1 and 2, Table 2) were recorded with a Varian HA-100 spectrometer. The IR spectra of capillary layers of II-V and of a solution of I in carbon tetrachloride were recorded with a UR-10 spectrometer.

The epimerization of the individual isomers of I-V (Table 3) was carried out in the presence of boron trifluoride etherate ($3.5 \cdot 10^{-2}$ mole of the catalyst per mole of dioxane) at 60° by the method in [12].

The ratio of the isomers in the mixture was determined by GLC with an LKhM-8M chromatograph with a 2-m-long column filled with 15% E-301 on Chromosorb G with helium as the carrier gas and an operating temperature of 230-240°.

The $-\Delta G^0$ values were calculated by the method in [12].

2-Methyl-5-alkyl-5-phenoxy-1,3-dioxanes (I-V) (Table 1). These compounds were obtained by the method in [10]. The geometrical isomers were separated by rectification with total condensation columns with 37 theoretical plates.

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