ALKOXY COMPOUNDS

XXII. Synthesis and PMR Spectra of Some 2-Substituted 5-Alkyl-5-α-alkoxyethyl-1, 3-dioxanes*

Yu. Yu. Samitov, N. L. Garkovik, A. V. Bogatskii, and S. A. Zolotareva

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 4, pp. 608–613, 1968

UDC 547.841.07.541.67

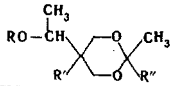
Six 2, 2, 5-trialkyl-5-α-alkoxyethyl-1, 3-dioxanes have been synthesized for the first time by the condensation of 2-alkyl-2-α-alkoxyethyl-1, 3-propane diols with ketones, and it has been shown by a study of their PMR spectra that they exist in the unsymmetrical boat conformation. The PMR spectra of a number of previously-synthesized 2-alkyl(aryl)-5-alkyl-5-α-alkoxyethyl-1, 3-dioxanes have been considered and it has been shown that from an analysis of the spectra it is possible to estimate the contents of geometrical isomers in a mixture. The stereochemistry of these compounds has been discussed.

In papers published previously [1-3], we have described the synthesis of some 2-alkyl(aryl)-5-alkyl-5-α-alkoxyethyl-1, 3-dioxanes (I) by the reaction of 2-alkyl-2-α-alkoxyethyl-1, 3-propanediols (II) with aldehydes in the presence of p-toluenesulfonic acid or KU-1 and KU-2 ion-exchangers in the hydrogen form. We have separated series I into geometrical isomers, and by a study of their PMR spectra and dipole moments it has been shown that the low-boiling isomers of I are the trans-isomers, which exist predominantly in the chair conformation, and the high-boiling isomers are the cis-isomers, existing predominantly in the unsymmetrical boat conformation. There were no clear indications of an inversion of the conformations. We have established that the splitting of the peak of the methoxy group in the spectra of mixtures of the stereoisomers is a sign of the existence of cis-trans-isomers, and a study of the relative integral intensities of the components of the doublet of the methoxy groups gives information on their quantitative ratio. It was also shown that in the spectra of the trans-isomers of I with a methyl radical on the 5-C carbon there is a peak with an anomalously low chemical shift (0.4-0.5 ppm) which is a consequence of the resonance of the methyl group mentioned located in the axial position. Obviously, a study of the relative integral intensity of this anomalous peak in the spectra of mixtures of the isomers of I can give information on the ratio of the stereoisomers in the mixture and furthermore, on the amount of the isomer with the axial arrangement of the methyl group in position 5.

In the present communication we give data on the synthesis of some new compounds I and on a study of their stereochemistry and the stereochemistry of a number of compounds I synthesized previously by considering their PMR spectra. We carried out the synthesis of I by the reaction of II with ketones by Salmi's method [4] with some modifications. The properties of the 2,2,5-trialkyl-5-α-alkoxyethyl-1, 3-dioxanes (III) not previously described are given in the table.

It is known from general stereochemical laws that in spite of the high stability of the six-membered cyclic acetals as compared with the five-membered compounds, the reverse situation applies to ketals. The cause of the instability of the six-membered ketals is, in Eliel's opinion [5], axial interactions which lower the stability of the systems. It is just this which explains the fact that the acetone derivatives of the sugars are 1,2- and not 1,3-ketals. This point of view is confirmed by other authors. Thus, Friebolin [6] came to the conclusion that ketals exist in a distorted chair conformation on the basis of the fact that in the PMR spectrum of 2,2-dimethyl-1, 3-dioxane, even on cooling to -88° C, the peaks of the methyl protons undergo no splitting. Friebolin assumes that this is a consequence of the fact that the introduction of geminal methyl groups into position 2 of the dioxane ring changes the capacity of this ring

2, 2, 5-Trialkyl-5-α-alkoxyethyl-1, 3-dioxanes



R	R′	R″	Bp, °C (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %		Calculated, %		Yield, %
						found	calculated		C	H	C	H	
CH_3	CH_3	CH_3	76 (8)	0.9603	1.4340	51.00	51.11	$C_{10}H_{20}O_3$	63.66	10.58	63.88	10.72	77
CH_3	C_2H_5	CH_3	74—75 (0.5)	0.9769	1.4430	55.87	55.72	$C_{11}H_{22}O_3$	64.90	11.43	65.20	11.59	80
CH_3	i-C_3H_7	CH_3	84—86 (4)	0.9709	1.4452	59.50	60.35	$C_{12}H_{24}O_3$	66.41	11.40	66.62	11.88	80
i-C_3H_7	CH_3	CH_3	89 (7)	0.9395	1.4320	59.60	60.35	$C_{12}H_{24}O_3$	66.70	11.32	66.62	11.18	79
i-C_3H_7	i-C_3H_7	CH_3	92 (4)	0.9477	1.4437	68.50	69.58	$C_{14}H_{28}O_3$	68.67	11.39	68.80	11.54	82
CH_3	i-C_3H_7	C_2H_5	99 (5)	0.9586	1.4509	64.59	64.95	$C_{13}H_{26}O_3$	67.60	11.15	67.88	11.39	65

---

*For part XXI, see [10].

for inversion. According to Friebolin, in 2,2-dimethyl-1,3-dioxane, because of strong 1,3-interactions (the distance between the axial protons at 4-C and 6-C and the hydrogen atoms of the axial methyl at 2-C is $\sim$0.4 A less than the sum of the van der Waals radii) there is a distortion of the chair conformation to such an extent that the gem-methyl groups very readily exchange with one another. Thus, according to the authors mentioned, a distortion of the ring leads to its high lability. An analysis of the PMR spectra of III leads to extremely interesting conclusions which supplement those of Eliel and Friebolin and, as we assume, have independent value for a study of the stereochemistry of cyclic ketals of the type considered.

We have studied the spectra of 2,2,5-trimethyl- (IV) and 2,2-dimethyl-5-ethyl- (V) -5-α-methoxyethyl-1,3-dioxanes and also of 2,2-dimethyl-5-isopropoxyethyl-1,3-dioxane (VI). Of course, IV-VI cannot have geometrical isomers. The spectrum of IV is given in Fig. 1 and that of V in Fig. 2. As can be seen from these figures, a characteristic feature in the spectra of the ketals IV and V is a singlet peak in the δ 1.31 and 1.39 ppm region, respectively (6 H). If the analysis of the stereoisomeric compounds I that we have considered previously and numerical data on the nonequivalence of the protons of the methyl groups present in the axial and equatorial positions at the 2-C carbon [2, 3] are taken into account, the predominant conformation of III may be deduced. Thus, the nonequivalence of the protons of the geminal methyl groups in position 2 must be 0.16 ppm in the chair conformation and 0.069 ppm in the unsymmetrical boat conformation. Experiment gives a singlet peak. It is not the result of the rapid inversion of two chair conformations into one another, even if their distortion is assumed. In actual fact, in this case the other features of the spectra of IV and VI, namely the presence in the spectrum of IV of an anomalous peak of an axial methyl group in position 5 with a shift of δ 0.78 ppm (3 H) and the characteristic peak for the protons of the methylene group at the 4-C and 6-C atoms (two quadruplets with centers at 3.33 and 3.55 ppm) would not appear, and the same applies to the similar bands in the spectrum of V. Excluding inversion, therefore, it must be assumed, taking the calculations given above into account, that the dioxanes IV-VI exist predominantly in the unsymmetrical boat conformation (A).

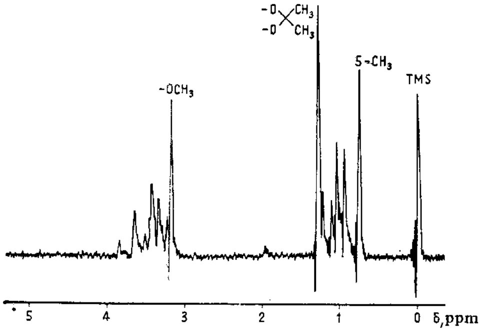


Fig. 1. PMR spectrum of 2,2,5-trimethyl-5-α-methoxyethyl-1,3-dioxane (IV).

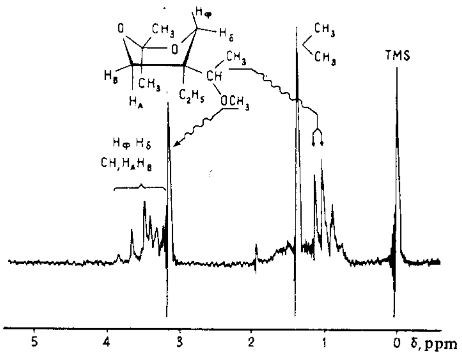
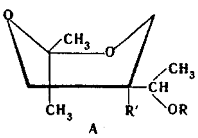


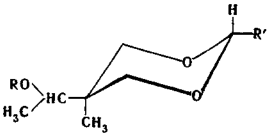
Fig. 2. PMR spectrum of 2,2-dimethyl-5-ethyl-5-α-methoxyethyl-1,3-dioxane (V).

This statement also agrees with results on the chemical shifts of the methyl groups at the 2-C carbon atom in the high-boiling isomers of I, which exist in the unsymmetrical boat conformation. As can be seen from previous papers [2, 3] this shift must be 1.16-1.37 ppm. Experiment gives a value of δ of 1.31 ppm for IV and of 1.32 and 1.34 ppm for V and VI.

It is interesting that the treatment of the spectra given and the ideas on the predominant unsymmetrical boat conformation for ketals of type III following from it agree with an analysis of Stuart-Briegleb models. With these models it can be seen clearly that in conformation A the boat-axial interaction of the geminal methyl groups is far less than in the chair conformation. In both conformations, the geminal methyl groups in position 2 are capable of free rotation.



A



B

Under these conditions, the alkoxy radical of the alkoxyethyl group occupies the remotest position from the oxygen atoms of the dioxane ring, which undoubtedly stabilizes this conformation.

All these results are also confirmed by a study of the dipole moment of IV. The dipole moment of IV, μ_{exp} = 1.64-1.66 D. Calculation of the dipole moment for the unsymmetrical boat conformation leads to similar values μ_{cal} = 1.52-2.20 D, depending on the conformation of the methoxy group in the alkoxyethyl radical. Consequently, a study of the dipole moment confirms the idea of conformation A for compound IV.

On the basis of these results it may be concluded that the greater stability of the six-membered ketals (at least of type III) as compared with the five-membered compounds is connected not with the axial interaction of the geminal methyl groups in the chair conformation (according to Eliel) but with the fact that because of the possibility of the interaction mentioned the molecules of the ketals assume the unsymmetrical boat conformation. Of course, the oxygen at the apex of such a boat is more accessible to hydrolyzing agents than in a five-membered ring where both oxygen atoms of the ring must be screened to an equal extent. It may also be assumed that Friebolin's failure to observe splitting of the geminal methyl group type in the ketals on deep cooling was not because the ring possesses an exceptionally large capacity for inversion due to distortion of the chair conformation but because these ketals exists in the unsymmetrical boat conformation where the nonequivalence of the protons of the geminal methyl groups at 2-C is exceptionally small.

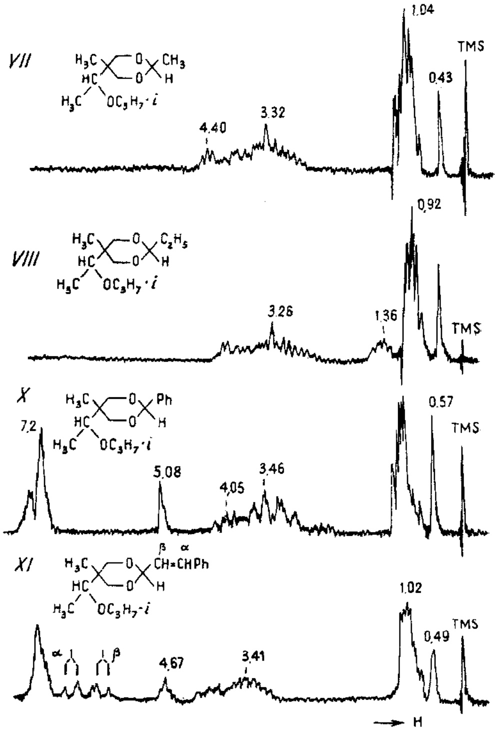


Fig. 3. PMR spectra of 2-alkyl(aryl)-5-α-isopropoxyethyl-1,3-dioxanes.

We have also considered a series of spectra of acetals of type I that we had synthesized previously [1,7] but had not studied from the stereochemical point of view. Figure 3 shows the PMR spectra of compounds I which, on the basis of general stereochemical ideas, must be mixtures of geometrical isomers and which have in common the presence of a methyl group on the 5-C carbon. We have considered the following spectra of compounds I from this series: 2,5-dimethyl-5-α-isopropoxyethyl-(VIII), 2-ethyl-5-methyl-5-α-isopropoxyethyl- (VIII), 2-isopropyl-5-methyl-5-α-isopropoxyethyl- (IX), 2-phenyl-5-methyl-5-α-isopropoxyethyl- (X), and 2-(2'-phenylvinyl)-5-methyl-5-α-isopropoxyethyl- (XI) -1,3-dioxane.

In spite of the fact that these substances do not contain a methoxy group, from an analysis of their spectra it is possible to formulate definite ideas concerning the presence and the ratio of the stereoisomers in the mixtures VII-XI. In actual fact, the spectra of all the compounds I have a line with an anomalously low value of the chemical shift, δ = 0.43-0.58 ppm. As follows from previous work [2,3], this line is due to the resonance of the protons of the methyl group on the 5-C carbon of the trans-isomers. Consequently, by studying the relative integral intensities of these peaks and carrying out simple calculations* it is possible to obtain an idea of their relative amounts. This ratio is 62 : 38 for VII, 70 : 30 for VIII, 74 : 26 for IX, 73 : 27 for X, and 59 : 41 for XI. Since the mixtures of VII and VIII were separated into their isomers by gas-liquid chromatography (ratio 57 : 43 for VII) and also by preparative fractionation (ratio 58 : 42 for VII 63 : 37 VIII) and these results are close to those obtained on the basis of an analysis of the PMR spectra, it can be stated, taking the error of the integral measurements as ±10%, that the other results are likewise reliable. Thus, on the basis of an analysis of the PMR spectra it can be stated that the mixtures contain the following percentages of the trans-configuration mainly with the chair conformation and the arrangement of the substituents given in the Figure (B): 70 for VIII, 74 for IX, 73 for X, and 59 for XI.

In the PMR spectrum of 2-(2'-phenylvinyl)-5-α-isopropoxyethyl-1,3-dioxane (XI), the resonance of the vinyl protons gives a typical AB quadruplet with a spin coupling constant $[J_{\alpha\beta}]$ = 15 Hz. This value of the constant shows the trans-arrangement of the hydrogen atoms about the double bond.

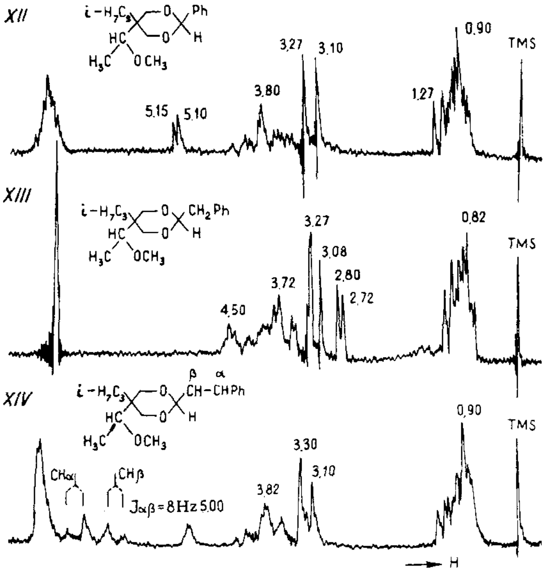


Fig. 4. PMR spectra of 2-alkyl(aryl)-5-isopropyl-5-α-methoxyethyl-1,3-dioxanes.

---

*The calculation was carried out from the formula X = (B • n)/n'(a + b), where (a + b) is the total integral intensity of the line of the methyl groups in the spectra of VII-XI, including the "anomalous peak", b is the integral intensity of the anomalous peak, n is the total number of methyl protons in the compound, n' is the number of protons of the group giving the "anomalous" peak in the PMR spectrum, and X is the relative amount (in %) of that isomer (trans-) that gives the "anomalous" peak.

Figure 4 gives the spectra of compounds I having in common the presence of a methoxy group and aromatic or alkylaromatic substituents in position 2. On the basis of general theoretical considerations, they must also be mixtures of stereoisomers. The spectra of 2-phenyl-5-isopropyl-5-α-methoxyethyl- (**XII**), 2-benzyl-5-isopropyl-5-α-methoxyethyl- (**XIII**) and 2-(2'-phenylvinyl)-5-isopropyl-5-α-methoxyethyl- (**XIV**) -1,3-dioxanes are given. In all these spectra, the doublet nature of the peak of the methoxy group is clearly visible, showing the presence of stereoisomers. In some cases the spectrum has a still more complex nature. Thus, the spectrum of **XII** has a doublet of a proton in position 2, δ = 5.10 and 5.15 ppm, which also shows the presence of stereoisomers. We have previously shown that the line of the methoxy group of trans-isomers is displaced in the direction of lower fields in comparison with the corresponding line of a cis-isomer [2]. Taking this fact into account and analyzing the integral intensities of the peaks of the methoxy groups, it can be stated that in the compounds considered the following ratios of the geometrical isomers exist (trans- : cis-): 59:41 (**XII**), 65:35 (**XIII**), 59:41 (**XIV**).

EXPERIMENTAL

Synthesis of ketals of type III. The starting materials for the synthesis of the type III ketals were: 2-methyl-2-α-methoxyethyl-1,3-propanediol, 2-ethyl-2-α-methoxyethyl-1,3-propanediol, 2-isopropyl-2-α-methoxyethyl-1,3-propanediol, 2-methyl-2-α-isopropoxyethyl-1,3-propanediol, and 2-isopropyl-2-α-isopropoxyethyl-1,3-propanediol, which we have synthesized previously [8, 9], and also "Soyuzreaktiv" acetone and methyl ethyl ketone previously purified by redistillation.

We performed the synthesis of ketals of type III by the reaction of the alkoxy diols listed above with acetone and methyl ethyl ketone in the presence of KU-1 ion-exchanger in the hydrogen form in absolute benzene with the azeotropic distillation of water in a similar manner to the synthesis of the 1,3-dioxanes of the acetal type that we have described [1].

PMR Spectra. The samples were pure liquids. Tetramethylsilane (TMS) was added to the samples as internal standard. The positions of the peaks on the spectrum were determined by the usual method of side frequencies. The PMR spectra were recorded at a proton resonance frequency of 60 MHz on a spectrometer of type RYa-2303 designed by SKB AP AN SSSR [Special Design Bureau, AS USSR]. The time of recording a spectrum was 500 sec.

REFERENCES

1. A. V. Bogatskii and N. L. Garkovik, ZhOKh collection: Problems of Organic Synthesis [in Russian] p. 42, 1965.
2. A. V. Bogatskii, Yu. Yu. Samitov, and N. L. Garkovik, KhGS [Chemistry of Heterocyclic Compounds], 2, 1335, 1966.
3. A. V. Bogatskii, Yu. Yu. Samitov, N. L. Garkovik, and S. A. Andronati, KhGS [Chemistry of Heterocyclic Compounds], 3, 195, 1967.
4. E. Salmi, Ber., 71, 1803, 1938.
5. E. Eliel, Stereochemistry of Carbon Compounds [Russian translation], Moscow, 195, 1965.
6. H. Friebolin, S. Kabuss, W. Meier, and A. Luttringhaus, Tetrah., 683, 1962.
7. N. L. Garkovik, A. V. Bogatskii, S. A. Andronati, and L. V. Basalaeva, KhGS [Chemistry of Heterocyclic Compounds], 2, 674, 1966.
8. G. V. P'yankova, A. A. Kolesnik, and A. V. Bogatskii, ZhOKh, 34, 1200, 1964.
9. A. V. Bogatskii, O. S. Stepanova, A. A. Kolesnik, N. L. Garkovik, and E. A. Yatsenko, Ukr. khim. zh., 30, 1326, 1964.
10. G. I. Goryashina, A. V. Bogatskii, Yu. Yu. Samitov, O. S. Stepanova, and N. I. Karelina, KhGs [Chemistry of Heterocyclic Compounds], 4, 391, 1968.

11 July 1966

Mechnikov Odessa State
University

Ul'yanova-Lenin Kazan
State University