ALKOXY COMPOUNDS

XXIII. Synthesis, Properties, PMR Spectra, and Stereochemistry of 2-Alkyl-2-alkoxymethyl-1,3-propanediols and 2,2,5-Trialkyl-5-alkoxymethyl-1,3-dioxanes*

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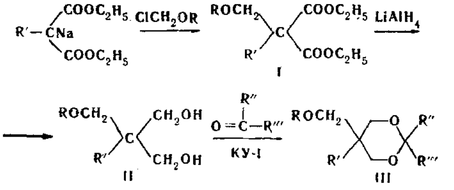
The reduction of alkoxymethylalkylmalonic esters with lithium aluminum hydride has given previously unknown 2-alkyl-2-alkoxymethyl-1,3-propanediols, and by the condensation of these with ketones six previously unreported 2,2,5-trialkyl-5-alkoxymethyl-1,3-dioxanes have been synthesized. The PMR spectra of these compounds have been studied and the unsymmetrical boat conformation has been shown for the 2,2,5-trialkyl-5-alkoxymethyl-1,3-dioxanes. The causes of the stereochemical features of the compounds mentioned are discussed.

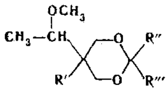
Developing our investigations in the field of the chemistry of alkoxy compounds [1,2] and, in particular, the study of the stereochemistry of alkoxyalkyl-substituted six-membered heterocyclic systems [3-5], we have synthesized a number of alkoxymethylalkylmalonic esters (I), by the reduction of which with lithium aluminium hydride we have obtained previously unknown 2-alkyl-2-alkoxymethyl-1,3-propanediols (II). By then condensing compounds II with ketones in the presence of KU-1 cation-exchanger in the hydrogen form we have obtained the previously undescribed 2,2,5-trialkyl-5-alkoxymethyl-1,3-dioxanes (III):



The structure of compounds I was shown by considering their PMR spectra. Figure 1 gives the PMR spectrum of methoxymethylmethylmalonic ester (IV). The spectrum contains the multiplet bands usual for this group of compounds [6]. The chemical shifts of the methoxy group and the methylene protons of the methoxymethyl radical of the ester I do not coincide and are, respectively, δ = 3.27 and 3.68 ppm.

The structure of compounds II was also confirmed by an analysis of their PMR spectra. Thus, a consideration of the PMR spectrum of 2-methyl-2-methoxymethyl-1,3-propanediol (V) shows that it contains the lines characteristic for such compounds [6]. As in the spectrum of compounds I, the resonance band of the methoxymethyl group in the spectrum of compounds II consists of two lines with δ 3.30 ppm ($-OCH_3$) and 3.50 ppm ($-O-CH_2$). The presence in the spectrum of a singlet line with δ 4.47 ppm (2 H) shows the existence in compound II of an intermolecular hydrogen bond which is identical for both hydroxy groups, in contrast to 2-alkyl-2-α-alkoxyethyl-1,3-propanediols that we studied previously, where one of the hydroxy groups possessed a hydrogen bond with a different energy [6].

The ketals of type III interested us because these compounds, although they belong to the type of 2-substituted 5-alkyl-5-alkoxyalkyl-1,3-dioxanes have certain differences from the 2,2,5-trialkyl-5-alkoxyethyl-1,3-dioxanes (VI) studied by us previously. In actual fact, the ketals III have substantial difference in the structure of the alkoxyalkyl group as compared with the ketals VI. In III, this group



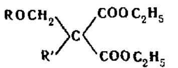
VI

has a smaller volume, not being branched, and all this can of course affect the stereochemical characteristics of III.

The characteristic feature of the spectrum of 2,2,5-trimethyl-5-methoxymethyl-1,3-dioxane (VII) (Fig. 2) is the presence of a singlet peak [δ 1.34 ppm (6 H)], which is due to the resonance of the two methyl groups at 2-C. We have considered a similar phenomenon previously [5]. Furthermore, in papers published previously we have shown that the methylene

Table 1

Alkoxymethylalkylmalonic Esters



R	R′	Bp, °C (pressure mm)	d_4^{20}	n_D^{20}	Empirical formula	Found, %		Calculated, %		Yield, %
						C	H	C	H	
CH_3	CH_3	82 (3)	1.0345	1.4220	$C_{10}H_{18}O_5$	54.85	8.61	55.03	8.31	58
CH_3	C_3H_7	104 (3)	1.0124	1.4278	$C_{12}H_{22}O_5$	—	—	—	—	66
CH_3	i-C_3H_7	101 (3)	1.0240	1.4302	$C_{12}H_{22}O_5$	—	—	—	—	48
i-C_3H_7	CH_3	91 (2)	0.9995	1.4200	$C_{12}H_{22}O_5$	58.40	9.08	58.51	9.00	55
i-C_3H_7	i-C_3H_7	112 (4)	0.9874	1.4275	$C_{14}H_{26}O_5$	60.94	9.84	61.29	9.55	54

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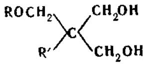
*For part XXII, see [5].

Table 2

2-Alkyl-2-alkoxymethyl-1,3-propanediols



R	R′	Bp, °C (pressure mm)	d_4^{20}	n_D^{20}	Empirical formula	Found, %		Calculated, %		Yield %
						C	H	C	H	
CH_3	CH_3	92(3)	1.0599	1.4523	$C_6H_{14}O_3$	53.65	10.79	53.71	10.52	78
CH_3	C_3H_7	109(3)	1.0139	1.4560	$C_8H_{18}O_3$	59.28	11.00	59.23	11.18	74
CH_3	i-C_3H_7	112(5)	1.0257	1.4553	$C_8H_{18}O_3$	59.13	11.19	59.23	11.18	70
i-C_3H_7	CH_3	103(3)	0.9870	1.4430	$C_8H_{18}O_3$	59.17	11.23	59.23	11.18	60
i-C_3H_7	i-C_3H_7	119(3)	0.9793	1.4510	$C_{10}H_{22}O_3$	62.85	11.74	63.11	11.65	89

protons of the 4-C and 6-C ring atoms are characterized in the chair conformation, in the absence of inversion, by considerable nonequivalence, while in the boat conformation they are almost equivalent. In the spectrum of VII, the nonequivalence of these protons is only 0.25 ppm (15 Hz). These two features of the spectrum of VII permit the conclusion that the molecules of the compound under consideration exist in the relatively rigid unsymmetrical boat conformation. The chair conformation is excluded for the reasons given above, and the symmetrical boat conformation because of general stereochemical laws. The absence of inversion of the "chair-chair" type is shown by the form of the resonance band of the methylene protons of the ring (quadruplet of a spin system of the AB type). The conclusion of the unsymmetrical boat conformation is also confirmed by the comparison of the dipole moments measured (μ_{found} = 1.84 D) and calculated for various conformations (for the unsymmetrical boat with different conformations of the alkoxymethyl group μ_{calc} = 1.82, 1.88, and 2.60 D).

The next feature of the PMR spectrum of VII is that the CH_3- and CH_2- protons of the methoxymethyl group make a contribution to the sharp singlet line with δ 3.26 ppm (5 H). The reason for the shift of the resonance line of the methylene protons of this group into the region of high fields in comparison with the values of the chemical shift of this group in acyclic compounds (I and II, Fig. 1) can be understood by considering a Stuart-Briegleb model of VII.

In the boat-equatorial position of the methoxymethyl group, its free rotation about the bond mentioned is limited in such a way that the ethereal oxygen of this group exists mainly in the 4-CH_2 region, while the axis of symmetry of the orbital of the unshared pair of electrons of the oxygen ($2p_z^2$) of the methoxy group is directed in such a way that it decreases the nonequivalence of the protons of this group. Such a conformation of this group is the most favorable one. At the same time, the methylene protons of the methoxymethyl group must exist mainly in the region of the diamagnetic influence of the σ-bond of the boat-axial methyl group. The influence of the latter group will be different from that calculated for 5,5-dimethyl-1,3-dioxane [5] in view of the fact that these calculations were carried out under the condition of the simultaneous free rotation of the equatorial and axial methyl groups. In the case of VII, the boat-equatorial position is occupied not by a methyl group but by a voluminous methoxymethyl group the rotation of which is restricted, as can be seen from models. This all leads to a shift in the resonance signal of the methylene protons of the —CH_2—O—CH_3 group in the direction of greater fields.

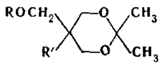
Thus, an analysis of the PMR spectra of the ketal VII leads to a proof of the unsymmetrical boat conformation for this compound with a boat-axial arrangement of the methyl radical and a boat-equatorial arrangement of the methoxymethyl radical. Consequently, the simplest of the ketals III is stereochemically analogous to the ketals VI.

A consideration of the PMR spectra of 2,2-dimethyl-5-propyl- (VIII) and 2,2-dimethyl-5-isopropyl- (IX) -5-methoxymethyl-1,3-dioxanes leads to somewhat different conclusions. A comparison of the spectrum of VIII with that of VII shows the almost complete equivalence of the methylene protons of the ring and the presence of a singlet peak of two methyl groups at 2-C (δ 1.32 ppm). This circumstance permits the statement that this ketal exists in a conformation which is flexible and is possibly pulsating between the unsymmetrical boat "twist forms".

In contrast to VII, in the spectrum of VIII the methylene protons of the methoxymethyl group resonate in a lower field (δ 3.32 ppm) than the protons of the methoxy group (δ 3.28 ppm). This fact may indicate a change in the order of arrangement of the

Table 3

2,2,5-Trialkyl-5-alkoxymethyl-1,3-dioxanes



R	R′	Bp, °C (pressure mm)	d_4^{20}	n_D^{20}	Empirical formula	Found, %		Calculated, %		Yield, %
						C	H	C	H	
CH_3	CH_3	64(3)	0.9770	1.4373	$C_9H_{18}O_3$	61.93	10.59	62.04	10.41	66
CH_3	C_3H_7	76(3)	0.9665	1.4378	$C_{11}H_{22}O_3$	65.23	10.80	65.31	10.96	75
CH_3	i-C_3H_7	74(3)	0.9724	1.4400	$C_{11}H_{22}O_3$	65.19	10.76	65.31	10.96	68
i-C_3H_7	CH_3	75(7)	0.9352	1.4260	$C_{11}H_{22}O_3$	65.26	11.20	65.31	10.96	69
i-C_3H_7	i-C_3H_7	83(3)	0.9386	1.4350	$C_{13}H_{26}O_3$	67.90	11.09	67.78	11.38	81

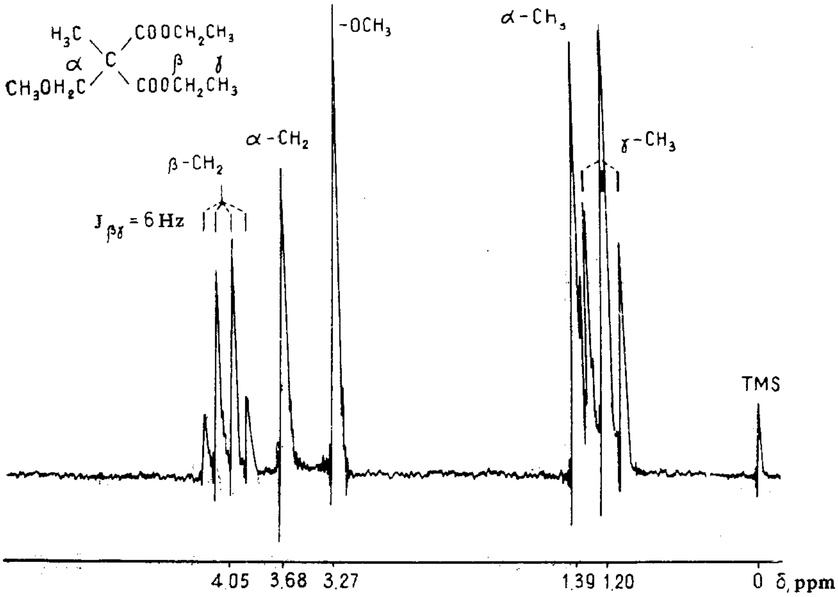


Fig. 1. PMR spectrum of methoxymethylmethylmalonic ester at $\nu_0 = 60$ MHz; internal standard—tetramethylsilane.

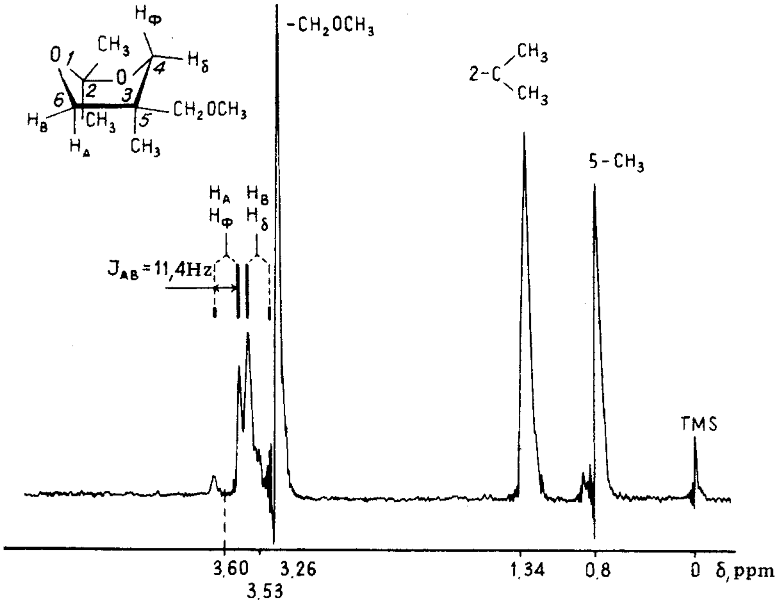


Fig. 2 PMR spectrum of 2,2,5-trimethyl-5-methoxymethyl-1,3-dioxane at 21° C; $\nu_0 = 60$ MHz.

substituents in VIII. In the molecule of VIII the methooxymethyl group probably occupies the boat-axial position. This assumption follows from a comparison of the PMR spectrum of the protons of VIII mentioned above, in the first place, with the results of a conformational analysis of the molecule of VIII according to which the alkyl substituent, more voluminous than the methoxymethyl group, should occupy the equatorial and not the axial position and, in the second place, with the results of the analysis of Stuart-Briegleb models of VIII, according to which the axial position of the methoxymethyl group leaves no possibility for its completely free rotation; this is limited and in these circumstances the hydrogen atoms of the methylene group apparently pass the bulk of the time in the field of the paramagnetic influence of the anisotropy of the magnetic susceptibility of the unshared pair of the 3-O ring atom.

Figure 3 gives the spectrum of IX, the general outlines of which are similar to the spectrum of VIII. The features mentioned above of the arrangement of the substituents in VIII can also be applied to IX, a confirmation of this being the septet band of the methine proton of the isopropyl group with a mean chemical shift of 1.80 ppm. In actual fact, according to calculations, the magnetic resonance of the boat-equatorial methine proton should undergo some shift ($\Delta\delta_{calc}$ 0.2 ppm) in the direction of lower fields in the case of the unsymmetrical boat conformation, as is actually observed in the spectrum.

In the case of IX, all the results of conformational analysis and of a consideration of Stuart-Briegleb models confirm the idea of the broad-equatorial position of the alkyl group and the boat-axial position of the methoxy methyl group to an even greater extent than in the analysis of VIII. It is interesting that this idea of the arrangement of the substituents correlates with data on the structure of stereoisomeric acetals of type III (R = H) that have been published previously.

The dipole moments of VII-IX confirm the unsymmetrical boat conformation with distortion into the "twist form" that we have assumed.

In actual fact, even in compound VII it is possible to achieve a definite distortion of the unsymmetrical boat conformation into the "twist form", which, as a Stuart-Briegleb model shows, leads to a further weakening of the conformational strain. Consequently, it may be assumed that the presence of a gem-dimethyl grouping leads to a distortion of the conformation of the unsymmetrical boat into the "twist form". This distortion cannot lead, in the first place, to a still greater decrease in the nonequivalence of the chemical shifts of the protons of the gem-dimethyl groups in comparison with calculation or, in the second place, to a decrease in the nonequivalence of the 4-C and 6-C protons, or, in the third place, to an approach of the conformation of the substituents at the 5-C ring atom to the configuration of the substituent in the low-boiling acetals. Just because of the influence of a methyl group, the peak of the protons of the axial methyl on the 5-C atom is displaced into the region of high fields as compared with the high-boiling acetals and into the region of low fields in comparison with the low-boiling acetals (0.8 ppm in VII and 1.15 and 0.6 ppm, respectively, in the acetals).

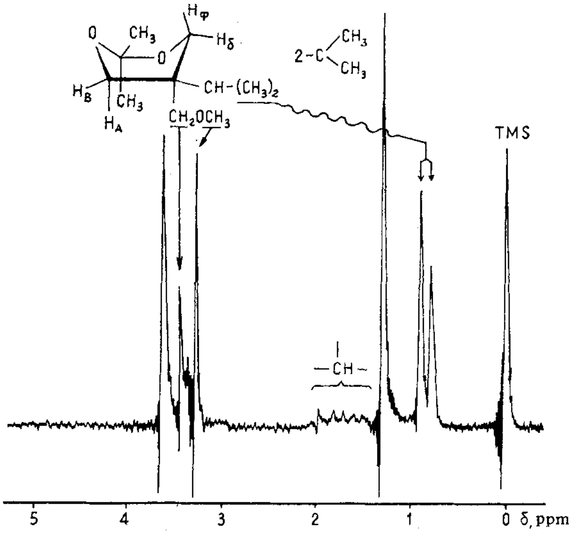


Fig. 3. PMR spectrum of 2,2-dimethyl-5-isopropyl-5-methoxymethyl-1,3-dioxane at 21° C, ν_0 = = 60 MHz.

In parallel with the substitution of the 5-C atom and, particularly, in the case of a change in the location of the alkoxyalkyl groups the distortion of the unsymmetrical boat into the "twist form" becomes greater. This appears clearly in the dipole moments. In fact, the dipole moment of VIII μ_{exp} = 1.63 D (for the unsymmetrical boat μ_{calc} = 1.82-2.60 D; for the "twist" conformation μ_{calc} = 1.20-2.03 D; the value found for the low-boiling acetals is μ = 1.15-1.20 D and for the high-boiling acetals μ = 2.50-2.60 D), i.e. judging from the dipole moment the boat is very slightly distorted into the "twist form"; the dipole moments of VIII and IX are, respectively, 1.37 and 1.28 D.

Thus, the ketals VIII-IX differ somewhat in their stereochemistry from the ketals of type VI. In actual fact, it was shown above that, because of the nonbranched nature of the methoxymethyl group, with sufficiently large alkyl radicals it may occupy not the boat-equatorial position (as in VI) but the boat-axial position.

At first sight it appears that the singlet nature of the absorption band of the protons of the 2-C methyl groups and, in particular, the methylene protons of 4-C and 6-C in the spectra of VIII and IX suggest an averaging of the chemical shifts of these protons because of rapid inversion of the "chair-chair" type, as stated by Friebolin [7] in a study of the PMR spectra of 2,2-dimethyl-1,3-dioxane at various temperatures. The appearance of such averaging of the shifts of the methylene protons of the dioxane ring has been reported previously [8] for the case of cis-5-acetoxy-2-phenyl-1,3-dioxane. In this isomer with any chair-like conformation of the ring either the acetoxy or the phenyl radical occupies the axial position, which creates an element of instability of the ring. As a result, internal conversion arises between the two chair conformations, leading to an averaging of the magnetic screening of the axial and equatorial protons. In the case considered, the possibility of inversion can be excluded because of the magnitude of the shift of the gem-dimethyl grouping, δ 1.31 ppm (in the ketal IX). The chemical shift of the equatorial methyl group at 2-C in 2-methyl-1, 3-dioxane [9] is 1.20 ppm. Evidently the chemical shift of the axial methyl must be still smaller, i.e. its line must be shifted in the direction of still higher fields. Thus, if the molecules of IX were present in a state of rapid inversion of the "chair-chair" type, the line of the gem-dimethyl group would have a chemical shift of about δ ~1.0 ppm, i.e. substantially smaller than that observed experimentally. We consider that Friebolin's conclusion that the molecule of 2, 2-dimethyl-1, 3-dioxane exists in the chair conformation is erroneous and requires further study.

EXPERIMENTAL

Chloromethyl ether (bp 57-59° C, n_D^{20} 1.3970) and chloromethyl isopropyl ether [bp 67-71°C(90 mm); d_4^{20} 0.9907; n_D^{20} 1,4056] were obtained by a published method [10]; the methylmalonic ester was synthesized by the usual method [11] and had the following constants: bp 63°C (4 mm); d_4^{20} 1.0241; n_D^{20} 1.4190; the propylmalonic and isopropylmalonic esters were synthesized by Conrad and Bishchoff's method [12] and had the following constants: bp 80°C (3.5mm); d_4^{20} 0.9878, n_D^{20} 1.4200; bp 79°C (4 mm); d_4^{20} 0.9890, n_D^{20} 1.4190, respectively.

Reaction of chloromethyl methyl and chloromethyl isopropyl ethers with the alkylmalonic acids. The reaction was carried out by the method that we have described previously [13, 14] and led to the alkoxymethylalkylmalonic esters the properties of which are given in Table 1.

The reduction of compound I with lithium aluminum hydride. The reduction was carried out by the method that we have described [15], giving the diols II (see Table 2). All these diols were synthesized by us for the first time. The 2-methoxymethyl-2-methyl-1, 3-propanediols can be isolated only be extracting the aqueous solution obtained by lithium hydride reduction with ether in a continuous extraction system for several hours. The other diols were isolated by the usual method.

Ketals of type III. The ketals were synthesized by the reaction of the alkoxydiols II with acetone in the presence of KU-1 cation-exchanger in the hydrogen form by the method that we have described previously [16]. The properties of compounds III are given in Table 3.

Determination of the dipole moments. The determination carried out in dilute benzene solutions at 25° C with an accuracy of ±0.1 D on the basis of the densities and refractive indices of benzene solutions of the dioxanes. The measurements and calculations of the dipole moments were performed by L. K. Yuldasheva and L. I. Spirina, to whom the authors express their hearty thanks.

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