STEREOCHEMISTRY OF HETEROCYCLES

XVIII.* CONFIGURATIONS AND PREFERRED CONFORMATIONS OF SOME 4,5-DIALKYL-5-METHOXYMETHYL- AND 2,2,4-TRIMETHYL-5-ALKYL-5-METHOXYMETHYL-1,3-DIOXANES

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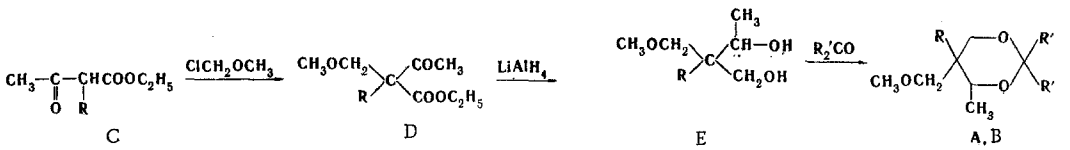
A group of previously undescribed methoxymethylalkylacetoacetic esters were obtained by the reaction of monochloromethyl ether with sodium salts of alkylacetoacetic esters. The reduction of the new esters with lithium aluminum hydride gave 2-alkyl-2-methoxymethylbutane-1,3-diols. In connection with the fact that the reduction is stereochemically regulated by the rule of asymmetric induction, the erythro isomers predominate in stereoisomeric mixtures of the 1, 3-diols. 4,5-Dialkyl-5-methoxymethyl- and 2,2,4-trimethyl-5-alkyl-5-methoxymethyl-1,3-dioxanes (mixtures of the stereoisomers with predominance of the trans isomers) were synthesized by the condensation of 2-alkyl-2-methoxymethylbutane-1,3-diols with formaldehyde and acetone. The stereoisomers were separated by precision rectification, and their configurations and preferred conformations were proved by PMR and IR spectroscopy. The low-boiling isomers of the 1,3-dioxanes under discussion are the trans isomers, while the high-boiling isomers are the cis isomers; the preferred conformation for these isomers is a somewhat distorted chair.

In the course of developing our research on the stereochemistry of 1,3-dioxanes [2-6], we have synthesized two new groups of compounds of this type – 4,5-dialkyl-5-methoxymethyl- (A) and 2,2,4-trimethyl-5-alkyl-5-methoxymethyl-1,3-dioxanes (B).



The reaction of alkylacetoacetic esters C with monochloromethyl ether occurs with predominant formation of a C-substitution product [7,8], as confirmed by a study of the IR spectra of D and reduction of them to 2-alkyl-2-methoxymethylbutane-1,3-diols (E). The properties of D and E are presented in Tables 1 and 2. We synthesized the previously undescribed 1,3-dioxanes of the A and B series (Table 3) by condensation of glycols E with formaldehyde and acetone via the method in [2]. As we [1-6] and others [9,10] have previously shown, the conversion of E to A and B proceeds without Walden inversion, and the ratio and type of predominantly formed stereoisomers of A and B are consequently determined in the step involving the conversion of D to E.

*See [1] for communication XVII.

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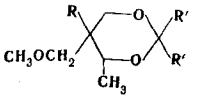
TABLE 1. Alkylmethoxymethylacetoacetic Esters (D)

Comp.	R	bp, °C, mm	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	Found, % C	Found, % H	Calc. % C	Calc. % H	Yield, %
I	CH_3	75—80 (4)	1,0145	1,4268	47,48	47,07	$C_9H_{16}O_4$	57,6	8,5	57,4	8,5	60
II	C_2H_5	80—84 (2)	1,0061	1,4311	51,42	51,68	$C_{10}H_{18}O_4$	59,3	9,0	59,4	8,9	58
III	C_3H_7	87—89 (2)	0,9988	1,4345	56,33	56,30	$C_{11}H_{20}O_4$	61,2	9,4	61,1	9,3	55
IV	i-C_3H_7	90—95 (2)	0,9987	1,4378	56,29	56,30	$C_{11}H_{20}O_4$	61,0	9,4	61,1	9,3	50

TABLE 2. 2-Alkyl-2-methoxymethylbutane-1,3-diols (E)

Comp.	R	bp, °C, mm	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empiric. formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, %
V	CH_3	107—109 (5)	1,0112	1,4518	39,02	39,25	$C_7H_{16}O_3$	56,6	11,1	56,7	11,0	63
VI	C_2H_5	97—98 (1)	1,0043	1,4546	43,73	43,87	$C_8H_{18}O_3$	58,3	11,0	58,6	11,0	71
VII	C_3H_7	122—126 (6)	0,9937	1,4554	48,09	48,49	$C_9H_{20}O_3$	59,8	11,3	60,0	11,2	78
VIII	i-C_3H_7	112—113 (1)	0,9948	1,4558	48,07	48,49	$C_9H_{20}O_3$	60,1	11,1	60,0	11,2	79

TABLE 3. 4-Methyl-5-alkyl-5-methoxymethyl- and 2,2,4-Trimethyl-5-alkyl-5-methoxymethyl-1,3-dioxanes (A, B)



Comp.	R	R'	bp, °C, mm	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, %	Isomer ratio trans	Isomer ratio cis
IX	CH_3	H	54 (1)	1,0101	1,4401	41,80	41,87	$C_8H_{16}O_3$	60,2	10,2	60,0	10,1	78	56	44
X	C_2H_5	H	89—90 (20)	1,0037	1,4448	46,13	46,49	$C_9H_{18}O_3$	61,9	10,7	62,0	10,4	82	49	51
XI	i-C_3H_7	H	71—72 (2)	1,0042	1,4522	50,63	51,10	$C_{10}H_{20}O_3$	63,9	10,5	63,8	10,6	70	42	58
XII	CH_3	CH_3	78—79 (7)	0,9680	1,4364	50,86	51,10	$C_{10}H_{20}O_3$	63,8	10,6	63,8	10,6	76	59	41
XIII	C_2H_5	CH_3	72—74 (4)	0,9631	1,4400	55,38	55,71	$C_{11}H_{22}O_3$	65,2	10,7	65,3	10,9	78	52	48
XIV	C_3H_7	CH_3	76—84 (4)	0,9506	1,4418	60,09	60,33	$C_{12}H_{24}O_3$	66,5	11,1	66,8	11,1	87	—	—
XV	i-C_3H_7	CH_3	76—77 (1)	0,9665	1,4461	60,07	60,33	$C_{12}H_{24}O_3$	66,2	11,0	66,8	11,1	76	44	56

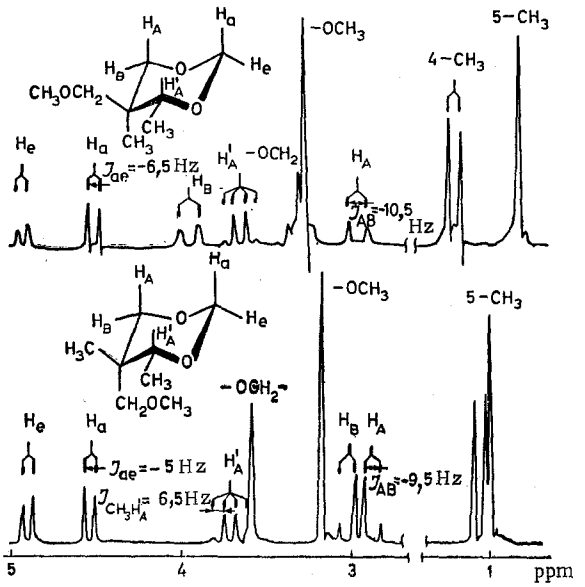


Fig. 1. PMR spectra of the low-boiling (IXa) and high-boiling (IXb) isomers of 4,5-dimethyl-5-methoxymethyl-1,3-dioxane.

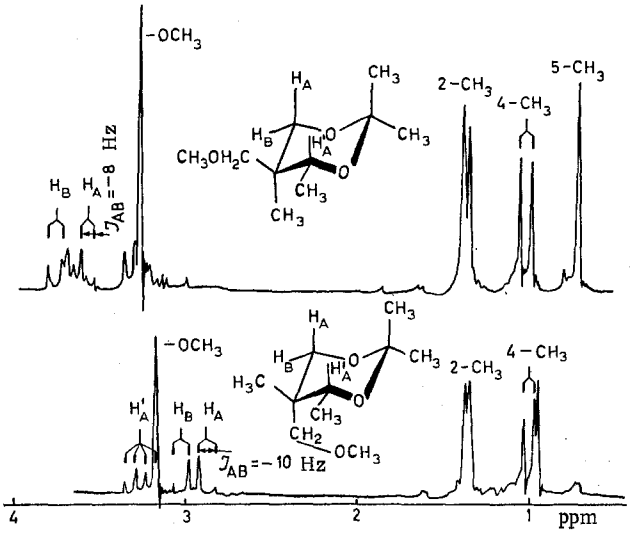
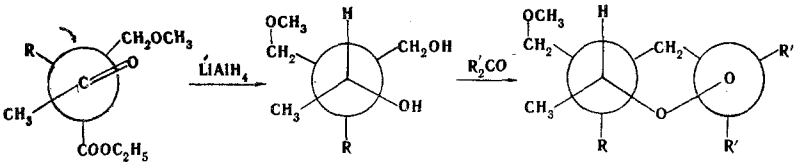


Fig. 2. PMR spectra of the low-boiling (XIIa) and high-boiling (XIIb) isomers of 2,2,4,5-tetramethyl-5-methoxymethyl-1,3-dioxane.

It is known that the stereochemistry of such reduction reactions is determined by the rule of asymmetric induction [11, 12], which is modified from its classical form [13] for substances that contain groups capable of complexing with metals. Moreover, it is known that the erythro isomer of the 1,3-diol is always the primary product in these sorts of reactions [14]. We [1,6] and others [9,10] have previously observed these sorts of transformations in several cases. However, the case examined in the present paper differs somewhat from those previously described. In contrast to the reduction of alkyl- and dialkylacetoacetic esters, the CH_2OCH_3 group can be a complexing group in the series of compounds under investigation; the erythro isomer of 1,3-diol E also differs from the erythro isomers of 2,2-dialkylbutane-1,3-diols in view of the fact that the methoxymethyl group, which is bulky and contains an oxygen atom, should of necessity be considered to be a large group. Considering these circumstances, the stereochemical picture of the production of the predominant isomers of 1,3-diols E and 1,3-dioxanes of the A and B groups can be represented in the following way:



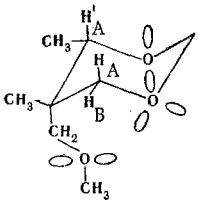
F G H

It is apparent from the scheme that the erythro isomers of 1,3-diols G, which are the starting materials for the preparation of trans isomers H of the 1,3-dioxanes of the A and B groups, are formed from the predominant reactive F conformation. Analysis of the PMR and IR spectra of the individual isomers of the A and B series and the data on the isomer ratio in mixtures of 1,3-dioxanes of the A and B groups confirm this scheme. Moreover, it should be noted that the introduction of a second substituent into the alkylacetoacetic ester molecule that is capable of complexing appreciably reduces the stereospecificity of the reduction, lowering it to zero in the case of X and XIII.

The 1,3-dioxanes of the A and B groups were separated into individual isomers by precision rectification with efficient total condensation columns with 60 theoretical plates. The purities of the individual stereoisomers, which were determined by gas-liquid chromatography (GLC), in all cases proved to be higher than 96% and were 99% for most of the substances.

The PMR spectra of cis- and trans-4,5-dimethyl-5-methoxymethyl-1,3-dioxanes (IXa and IXb) and cis- and trans-2,2,4,5-tetramethyl-5-methoxymethyl-1,3-dioxanes (XIIa and XIIb) are presented in Figs. 1 and 2, respectively. The signal of the 5-CH_3 protons in the spectra of the low-boiling isomers appears at high field (δ 0.70 ppm); this, as we have previously shown [3,4] in 5-α-alkoxyalkyl-substituted 1,3-dioxanes, attests to an axial orientation for the 5-CH_3 group. The signal of these protons is observed at 1.00 ppm in the spectra of the high-boiling isomers, i.e., the 5-CH_3 group is equatorial. The 4-CH_3 group gives a typical doublet at δ 1.02 ± 0.04 ppm; this indicates that it is equatorially oriented [1,6,15]. The low-boiling compounds are consequently the trans isomers, and the high-boiling compounds are the cis isomers.

An extremely characteristic feature of the spectra of the high-boiling isomers is the considerable shift of the signal of the equatorial 6-H proton to high field (to 3.00 and 3.37 ppm); this is not observed in the spectra of 5,5-dialkyl-substituted 1,3-dioxanes. This feature is an additional confirmation of the axial character of the methoxymethyl group in the cis isomers of the 1,3-dioxanes under discussion. Shielding of the equatorial 6-H proton by the orbital of the unshared pair of the oxygen atom of the alkoxyalkyl group can be observed only when the methoxymethyl substituent (structure I) is axially oriented. When the methoxymethyl substituent is equatorially oriented, this effect will of necessity be neutralized. It is easy to see that the pattern under consideration to some degree recalls the manifestation of the "rabbit ears" effect, the concepts of which were previously worked out in an examination of $-O-C-O-$ fragments [16].



The concepts of the shift of the equilibrium to favor one of the predominant isomers follow from everything mentioned above, and, in that the predominant conformation under consideration is the chair conformation, it urges spectral symmetry and the presence of an "internal" chemical shift for the gem-dimethyl protons in the spectra of XII-XV and nonequivalence of the signals of the methylene protons in the 6 position [2-6].

All of these data are confirmed by the IR spectra. The spectra of the low-boiling isomers of 1,3-dioxanes of the A and B series contain absorption bands at 575 and 673 cm^{-1} (as well as an absorption band at 683 cm^{-1} for 1,3-dioxanes of the B series), which, according to the data in [5,6], are typical for the trans isomers; the spectra of the high-boiling isomers contain absorption bands at 592 and 700 cm^{-1}, which are characteristic (according to the same data) for the cis isomers.

EXPERIMENTAL

The synthesized [from alkylacetoacetic esters (alkyl = CH_3, C_2H_5, C_3H_7, iso-C_3H_7) and monochloromethyl ether] alkylmethoxymethylacetoacetic esters [4,5] were reduced with lithium aluminum hydride in absolute ether to 2-alkyl-2-methoxymethylbutane-1,3-diols. The condensation of the latter with paraformaldehyde and acetone in the presence of KU-1 ion exchange resin [2] gave 4,5-dialkyl-5-methoxymethyl- and 2,2,4-trimethyl-5-alkyl-5-methoxymethyl-1,3-dioxanes. The individual stereoisomers were isolated by fractionation with total condensation rectification columns with a metal packing with 60 theoretical plates. The properties of the individual isomers of IX were as follows: the low-boiling isomer had bp 59° (6 mm), d_4^{20} 1.0118, and n_D^{20} 1.4390; the high-boiling isomer had bp 64° (6 mm), d_4^{20} 1.0102, and n_D^{20} 1.4399. The low-boiling isomer of X had bp 76° (6 mm), d_4^{20} 1.0031, and n_D^{20} 1.4449, while the high-boiling isomer had bp 80° (6 mm), d_4^{20} 1.0039, and n_D^{20} 1.4464. The low-boiling isomer of XII had bp 71° (8 mm), d_4^{20} 0.9668, and n_D^{20} 1.4361, while the high-boiling isomer had bp 74° (4 mm), d_4^{20} 0.9681, and n_D^{20} 1.4375.

The PMR spectra of 10% solutions of the compound in CCl_4 were recorded with a Varian HA-100D spectrometer with tetramethylsilane as the internal standard.

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