STEREOCHEMISTRY OF HETEROCYCLES

XIX.* SYNTHESIS AND STEREOCHEMISTRY OF SOME 4,5-DIALKYL-5-α-METHOXYETHYL- AND 2,2,4-TRIMETHYL-5-ALKYL-5-α-METHOXYETHYL-1,3-DIOXANES

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A number of 4-methyl-5-alkyl-5-α-methoxyethyl- and 2,2,4-trimethyl-5-α-methoxyethyl-1,3-dioxanes were synthesized. Precision rectification was used to isolate the individual stereoisomers, the configurations and preferred conformations of which were confirmed by IR and PMR spectroscopy. The reduction of the alkyl-α-methoxyethylacetoacetic esters, which gives the starting compounds for the synthesis of 1,3-dioxanes of 2-alkyl-2-α-methoxyethylbutane-1,3-diols, proceeds stereospecifically.

In the course of a study of the stereochemistry of six-membered saturated heterocycles [2,3], we synthesized the previously undescribed 4,5-dialkyl-5-α-methoxyethyl- (A) and 2,2,4-trimethyl-5-alkyl-5-α-methoxyethyl-1,3-dioxanes (B) (Table 1). The synthesis of compounds of the A type was realized by reaction of 2-alkyl-2-α-methoxyethylbutane-1,3-diols (C) with paraformaldehyde, while dioxanes of the B type were synthesized by reaction of diols C with acetone.

The 1,3-diols of the C series were obtained by reduction of alkyl-α-methoxyethylacetoacetic esters (D) with lithium aluminum hydride. It is well known that this reduction should proceed stereospecifically via one of the modifications of the rule of asymmetric induction [4,5] to give the diastereomeric diols in a 60:40 ratio. In view of the complexity of the stereochemical picture in compounds of the D and C types [6], in contrast to 2-alkyl- or 2,2-dialkylbutane-1,3-diols [7], in this case the evaluation of the configurations of the 1,3-dioxanes on the basis of an evaluation of the configurations of the diols, obtained from conformational analysis of the course of the reduction of D, is difficult. However, as in the case in [7], the assertion, which flows out of the general principle in [8], that the conversion of diols C to dioxanes A and B proceeds without involvement of the steric centers, remains in force. The correctness of this assertion follows from Table 2, from which it is seen that the ratio of the stereoisomers of 1,3-dioxanes of the A and B series, obtained from the same diols (I and IV, II and V, and III and VI), is identical.

The presence and ratio of cis-trans isomers in the A and B series were proved by gas-liquid chromatography (GLC), after which the indicated stereoisomers were isolated in chromatographically pure form by fractionation of mixtures of the isomers with efficient total condensation rectification columns. The properties of the isolated stereoisomers are described in Table 2.

The structures of these compounds were proved and the configurations and preferred conformations were evaluated on the basis of a study of the IR spectra. The spectra contain a set of absorption bands that is characteristic, in the opinion of Ledwoch, Lagrange, and Mastaglie [9, 10], for the 1,3-dioxane ring, as well as the typical bands of methyl groups, C–O–C bonds [9], etc. One's attention is drawn to the presence of the typical (for acetonals) band at 843 cm^{-1}, which is the characteristic band of the pendulum vibrations of the $-OC(CH_3)_2O-$ fragment in a number of substituted six-membered cyclic acetonals [11, 12].

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*See [1] for communication XVIII.

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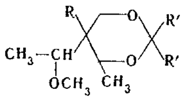
TABLE 1. 4-Methyl-5-alkyl-5-α-methoxyethyl- and 2,2,4-Trimethyl-5-alkyl-5-α-methoxyethyl-1,3-dioxanes



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, %
I	CH_3	H	59—60(4)	1,0064	1,4455	45,99	46,49	$C_9H_{18}O_3$	62,2	10,6	62,0	10,4	75
II	C_2H_5	H	67—69(4)	1,0144	1,4528	51,10	51,24	$C_{10}H_{20}O_3$	63,9	10,8	63,8	10,7	70
III	C_3H_7	H	84—86(4)	0,9950	1,4586	55,45	55,72	$C_{11}H_{22}O_3$	65,7	10,1	65,4	10,4	80
IV	CH_3	CH_3	62—63(4)	0,9653	1,4410	55,10	55,70	$C_{11}H_{22}O_3$	65,5	10,5	65,4	10,5	80
V	C_2H_5	CH_3	78—80(4)	0,9703	1,4480	59,01	60,35	$C_{12}H_{24}O_3$	66,9	11,4	66,6	11,2	91
VI	C_3H_7	CH_3	88—91(4)	0,9547	1,4530	65,03	64,96	$C_{13}H_{26}O_3$	68,1	11,7	67,7	11,4	93

TABLE 2. Stereoisomeric 4,5-Dialkyl-5-α-methoxyethyl-1,3-dioxanes

Compound		Isomer	bp, °C (mm)	d_4^{20}	n_D^{20}	Isomer ratio, %
I	a	trans	73 (9)	1,0024	1,4460	68
	b	cis	75 (9)	0,9947	1,4443	32
II	a	trans	49 (2)	1,0130	1,4532	63
	b	cis	52,5 (2)	1,0111	1,4522	37
III	a	trans	73 (2)	1,0084	1,4590	65
	b	cis	78 (2)	1,0109	1,4609	35
IV	a	trans	71 (7)	0,9688	1,4412	68
	b	cis	74 (7)	0,9604	1,4400	32
V	a	trans	70 (2)	0,9723	1,4472	65
	b	cis	74 (2)	0,9680	1,4480	35
VI	a	trans	69 (2)	0,9622	1,4521	62
	b	cis	74 (2)	0,9638	1,4528	38

TABLE 3. Characteristic Frequencies of the Absorption Bands of 4,5-Dimethyl-5-alkyl-5-α-methoxyethyl- and 2,2,4-Trimethyl-5-alkyl-5-α-methoxyethyl-1,3-dioxanes

Comp.		Isomer	Wave numbers, cm⁻¹ characteristic band of 1,3-dioxanes	ν_{C-O-CH_3}	$-OC(CH_3)_2O-$	bands of the ring skeletal vibrations
I	a	trans	1174, 1076, 1025	1106	—	520 —
	b	cis	1177, 1073, 1030	1102	—	684, 702, 552, 604
II	a	trans	1176, 1078, 1028	1106	—	672
	b	cis	1175, 1074, 1025	1102	—	563, 716
III	a	trans	1187, 1076, 1035	1112	—	679
	b	cis	1180, 1077, 1035	1110	—	583, 693, 718
IV	a	trans	1193, 1097, 1048	1104	843	565, 590, 680
	b	cis	1197, 1096, 1054	1104	843	478, 605, 709
V	a	trans	1197, 1098, 1042	1107	843	678 —
	b	cis	1197, 1096, 1043	1106	843	708 —
VI	a	trans	1196, 1097, 1044	1104	843	707, 862
	b	cis	1196, 1086, 1043	1102	843	665, 686, 832

The most interesting characteristic bands in the spectra under consideration are those that are typical for the cis and trans isomers at 450-720 cm^{-1}, i.e., in the region of the skeletal vibrations of the ring and the deformation vibrations of the individual C—H bonds. We have previously demonstrated [11,12] that in a series of 2,5-dialkyl-5-α-methoxyethyl-1,3-dioxanes the bands at 680 ± 5 cm^{-1} are characteristic for the trans isomers. Bands at 710 ± 10 cm^{-1} are characteristic for the cis isomers. It follows from Table 3 that the bands at 678 ± 6 cm^{-1} are characteristic for the low-boiling isomers in series A and B, while those at 710 ± 8 cm^{-1} are characteristic for the high-boiling isomers; this attests to the trans configuration of the low-boiling isomers and the cis configuration of the high-boiling isomers.

The PMR spectra confirm this information.* Thus the PMR spectrum of the low-boiling isomer of 4-methyl-5-isopropyl-5-α-methoxyethyl-1,3-dioxane (IIIa) contains a doublet of two methyl groups (6-H)

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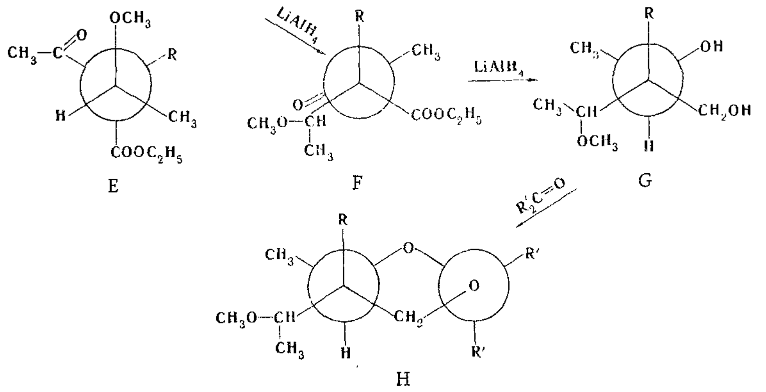
*The authors sincerely thank Yu. Yu. Samitov for recording the PMR spectra of the compounds under consideration.

at 0.78 ppm, a doublet of doublets of an isopropyl group at 1.12 ppm due to the manifestation of diastereotropism, a singlet of a methoxy group at 3.25 ppm, which attests to the purity of this isomer, and typical doublets of axial and equatorial protons in the 2 position. The doublets of the 6-H protons are observed at 4.12 ppm for the equatorial protons and at 3.45 ppm for the axial protons. The multiplet of the 4-H proton is observed at 3.68 ppm. The character of the spectrum, in conformity with the calculated data [13], leaves no doubt that this isomer corresponds to the preferred chair conformation; the concentration of the second conformer is very low at room temperature, and it is not determined by PMR spectroscopy. A comparison of the indicated spectrum with the spectrum of the low-boiling isomer of 4,5-dimethyl-5-isopropyl-1,3-dioxane makes it possible to prove the axial orientation of the isopropyl substituent. The resonance signal of the protons of the methyl groups in the spectrum of the low-boiling isomer of this compound is shifted to higher field (δ 1.05 ppm). The methylidyne proton of the isopropyl group resonates at a higher magnetic field strength (δ 1.85 ppm). This indicates that it is equatorially oriented. The character of the resonance of the 4-H proton and of the protons of the methylene group in the 6 position is similar to the resonance of these protons in the low-boiling isomer. The calculated data and the PMR spectra of the stereoisomeric 2-methyl-5-isopropyl-5-α-methoxyethyl-1,3-dioxanes [13] confirm this. Comparison with standard compounds [14], for which it was proved that the signal of the equatorial 4-CH_3 group should appear at 1.03 ± 0.05 ppm, and the angular correlation of the long-range spin interaction [15] both indicate the equatorial orientation of the 4-CH_3 group. It follows from the spectrum that the lines of the signal of the 6-H equatorial proton (H_C) do not show additional multiplicity; this is evidence in favor of the concepts of the axial character of the 4-H proton and, consequently, the equatorial character of the 4-CH_3 group.

On the basis of a study of the IR and PMR spectra, one can thus imagine the following stereochemical picture of the subsequent trend of the reduction of esters D to diols C and condensation of the latter with carbonyl compounds to give 1,3-dioxanes of the A and B series:



It is known that esters of the D type are diastereomers, in mixtures of which the erythro isomers, which are in the preferred E conformation, predominate. Hence, following the rule of asymmetric induction and considering the presence of the OCH_3 complexing grouping in D, it can be asserted that the starting reactive conformation of the erythro isomer will be conformation F, which leads to the preferred formation of stereoisomeric diol G, from which trans isomers H of the 1,3-dioxanes of series A and B are stereospecifically synthesized. The reduction of threo isomers of esters D leads, through the examined alternative steps, to the cis isomers of 1,3-dioxanes of the A and B series.

EXPERIMENTAL

4-Methyl-5-alkyl-5-α-methoxyethyl-1,3-dioxanes (A). A mixture of 0.22 mole of 2-alkyl-2-α-methoxyethylbutane-1,3-diol [6], 180 ml of absolute benzene, 20 g of paraformaldehyde, and 0.2 g of p-toluenesulfonic acid was heated in an apparatus equipped with a Dean–Stark trap until water separation had ceased. The mixture was then neutralized with 2-3 g of sodium carbonate. The unchanged paraformaldehyde and excess sodium carbonate were removed by filtration, the benzene was removed by distillation, and the residue was vacuum fractionated.

2,2,4-Trimethyl-5-alkyl-5-α-methoxyethyl-1,3-dioxanes (B). A 0.22-mole sample of 2-alkyl-2-α-methoxyethylbutane-1,3-diol was added to a mixture of 180 ml of absolute benzene, 0.65 mole of acetone, and 4.8 g of KU-1 ion exchange resin (in the H form). When water no longer separated as the mixture was heated, the mixture was separated from the KU-1, the benzene was removed by distillation, and the residue was subjected to fractional distillation in vacuo.

The presence of geometrical isomers in the mixtures and the purity of the individual isomers isolated by precision rectification with columns with 37 theoretical plates were monitored by chromatography with a Tswett-1 chromatograph with a flame ionization detector. A silicone elastomer of the SE-30 type (0.5%) applied to NaCl (0.13-0.25 mm) was used as the stationary phase. The carrier gas was nitrogen. The column was 3 m long, and the column temperature was 153°.

The IR spectra of a liquid film of the pure material between LiF and NaCl plates with LiF and NaCl prisms and of a 0.013-mm thick layer in a KBr cuvette with a KBr prism were recorded with an IKS-14A spectrometer.

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