STEREOCHEMISTRY OF HETEROCYCLES.

XL.* STEREOCHEMISTRY OF THE SYNTHESIS OF 2,3-DIALKYLOXETANES

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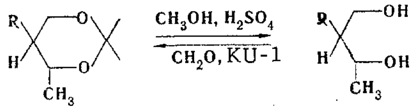
It is shown that trans-2,3-dialkyloxetanes are formed from the erythro isomers of 2-alkyl-1,3-butanediols, whereas cis-2,3-dialkyloxetanes are formed from the threo isomers.

Continuing our investigation [1] of the configuration and primary conformations of 2,3-dialkyloxetanes, we attempted to examine the entire chain of reactions leading to their preparation starting from the individual stereoisomers of 2-alkyl-1,3-butanedioles (I, II). Only one paper linking the three-dimensional structure of the starting β-diols with the configuration of the 3,3-difluoro-2,4-dialkyloxetanes formed is known [2].

The 2-alkyl-1,3-butanedioles (I, II) were obtained by reduction of the corresponding alkylacetoacetic esters with lithium aluminum hydride. This reaction proceeds stereospecifically following Cram's rule [3] and gives a mixture of diastereoisomers (enriched in the erythro isomer), which, after separation, was converted to the corresponding 4,5-dialkyl-1,3-dioxanes (III, IV). The reaction proceeds stereospecifically and gives a mixture of isomers with predominance of the cis forms of III and IV. The individual stereoisomers are isolated easily and with a high degree of purity by means of rectification. Their configurations were determined by analysis of their NMR spectra [3].

The individual erythro and threo isomers of I and II were obtained by hydrolysis of the cis and trans isomers of III and IV.



cis or trans isomer
III $R=C_2H_5$
IV $R=i\text{-}C_3H_7$

erythro or threo isomer
I $R=C_2H_5$
II $R=i\text{-}C_3H_7$

The 2-alkyl-1,3-butanediols were converted to 2,3-dialkyloxetanes (V-VII) through a step involving the formation of the acetates of the chloro-substituted alcohols. It is known [1, 4] that the reaction of diols I and II with acetyl chloride gives a mixture of 1-chloro-2-alkyl-3-acetoxybutanes (VIII, IX) and their structural isomers 3-chloro-2-alkyl-1-acetoxybutanes (X, XI). Compounds of the VIII and IX type are converted under the cyclization conditions to 2,3-dialkyloxetanes, whereas X and XI form primarily unsaturated alcohols. The ratio of the diastereoisomers of compounds such as VIII and IX determines the ratio of the resulting cis and trans isomers of 2,3-dialkyloxetanes [1].

There is no unified opinion in the literature regarding the mechanism of the reaction of 1,3-butanedioles with acetyl chloride. According to the data in [5], the reaction proceeds through a four-membered oxonium cation, whereas according to the data in [4] it proceeds through a cyclic carbonium ion.

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*See [1] for communication XXXIX.

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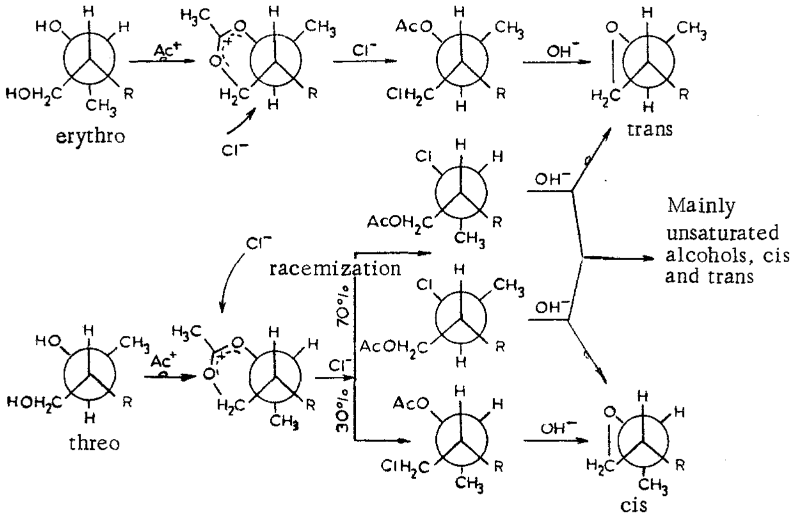
TABLE 1. Ratio of the Reaction Products during Transformations of erythro and threo Isomers of Diols I and II to Oxetanes V-VII

Configuration	Compound	1-Chloro-2-alkyl-3-acetoxybutane	3-Chloro-2-alkyl-1-acetoxybutane	Other products	Products of the action of alkali on VIII- XI		
					oxetanes		2-alkyl-2-buten-1-ols XII and XIII
					trans	cis	
		VIII, IX	X, XI		V–VII	V–VII	
Mixture of erythro and threo	XV	85					
		15					
The same	I	80	14	6	98	2	—
		18	78	4	2,2	27,8	70,2
The same	II	79	16	5	99,2	0,8	—
		22	74	4	3,5	27,0	69,5

The problem of the stereochemistry of the formation of a carbonium ion and the stereochemical specificity of the subsequent attack of the chloride ion on this cation has not been examined. From general stereochemical considerations it follows that inversion of the configuration at the C_3 atom occurs in the step involving conversion of the diol to acetoxy chlorides (through a four-membered oxonium cation or directly during the formation of the carbonium ion). Inasmuch as the electron density distributions in the indicated cyclic cations, formed from the stereoisomeric diols, should, to a first approximation, be identical, the direction of attack on the cation by the chloride ion is determined by steric factors.



erythro-Diols I and II are converted, with Walden inversion, primarily to threo-acetoxy chlorides VIII and IX. The amount of simultaneously formed erythro-acetoxy chlorides X and XI does not exceed 2% (see Table 1). The threo isomers of diols I and II are converted, with inversion of configuration, to the corresponding erythro- and threo-acetoxy chlorides X and XI mixed with erythro-acetoxy chlorides VIII and IX (primarily the former isomers are formed).

Cyclization of VIII and IX leads to primarily the trans-oxetanes (V, VI). Under these conditions acetoxy chlorides X and XI are converted primarily to 2-alkyl-2-buten-1-ols (XII and XIII), and the mixture also contains cis- and trans-oxetanes V and VI (no more than 30%).

The experimental data obtained in this study make it possible to assume that the direction of attack of the cation formed from the threo isomers of diols I and II by the chloride ion at the C_1 atom is more hindered than in the cation formed from erythro-diols I and II. The greater hindrance to attack on the carbonium ion formed from the threo isomer is due to the fact that the carbon atom undergoing attack here is shielded by the adjacent methyl group.

Thus, primarily the trans isomers of oxetanes V and VI are formed from erythro isomers I and II, whereas primarily unsaturated alcohols XII and XIII as well as the cis and trans isomers of V and VI are formed from the threo isomers of I and II.

TABLE 2. Properties of the Synthesized Compounds

Configuration	Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calc., %			Yield, %
					found	calc.		C	H	Cl	C	H	Cl	
cis	III	68(35)	0,9523	1,4318	35,5	35,6	$C_7H_{14}O_2$	64,5	10,9	—	64,6	10,8	—	78
trans		72(35)	0,9435	1,4290	35,5			64,5	10,8	—				
cis	IV	82(25)	0,9560	1,4397	39,5	40,2	$C_8H_{16}O_2$	66,6	11,2	—	66,6	11,2		61
trans		84,5(25)	0,9328	1,4354	40,4			66,6	11,2	—				
erythro	I	100(3)	0,9791	1,4510	32,5	33,0	$C_6H_{14}O_2$	60,8	11,9	—	61,0	12,0		51
threo		102(3)	0,9710	1,4453	32,4			60,9	11,9	—				30
erythro	II	108(2)	0,9615	1,4530	37,2	37,6	$C_7H_{16}O_2$	63,4	12,0	—	63,6	12,2	—	62
threo		109(2)	0,9526	1,4478	37,1			63,6	12,2	—				28
erythro	VIII, X	95—96(2)	1,0339	1,4391	45,4	45,5	$C_8H_{15}O_2Cl$	—	—	19,7	—	—	19,9	73
threo		96—98(2)	1,0219	1,4382	45,9			—	—	19,8				53
erythro	IX, XI	92—94(10)	1,0144	1,4420	50,3	50,2	$C_9H_{17}O_2Cl$	—	—	18,3	—	—	18,4	68
threo		93—95(10)	1,0034	1,4390	50,2			—	—	18,0				39

TABLE 3. Properties of the Synthesized Oxetanes (V-VII)

Configuration	Compound	R	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %		Calc., %		Isomer cont. in the mix, %	ppm of the proton attached to ring C_2
						found	calc.		C	H	C	H		
cis	VII	CH_3	80	0,8203	1,3980	25,11	25,27	$C_5H_{10}O$	69,6	11,7	69,7	11,6	15	4,25
trans			89	0,8469	1,4040	24,87							85	4,65
cis	V	C_2H_5	107	0,8310	1,4060	29,55	29,92	$C_6H_{12}O$	71,9	12,5	72,0	12,1	30	4,25
trans			114	0,8431	1,4112	29,46							70	4,65
cis	VI	C_3H_7	125	0,8112	1,4104	34,90	34,61	$C_7H_{14}0$	73,7	12,5	73,7	12,3	25	4,30
trans			131	0,8297	1,4132	34,32							75	4,65

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*A shift of the band to higher field constitutes evidence for a pseudoequatorial position of the hydrogen atom attached to C_2, whereas a shift to weak field attests to a pseudoaxial orientation; this proves the configuration, inasmuch as a pseudoequatorial orientation of the alkyl group attached to the C_3 atom is confirmed by comparison with the spectrum of the "standard" 3-methyl oxetane and does not raise any doubts because the signals of the proton and of the protons of the alkyl groups attached to the C_3 are identical in the spectra of the cis and trans isomers of the cis- and trans-V-VII types.

An additional confirmation of the correctness of the reasoning presented above regarding the stereochemistry of the formation of substituted oxetanes was provided by the synthesis of a 2,3-dimethyloxetane (VII) from 4-chloro-3-methyl-2-butanone (XIV). Reduction of XIV with lithium aluminum hydride gave 4-chloro-3-methyl-2-butanol (XV), which on acetylation is converted to 4-chloro-2-methyl-3-acetoxybutane (XVI). In view of the fact that according to Cram [6], the conformation of XIV in which the methyl group is shielded by a chloromethyl group is preferable in nucleophilic substitution reactions, its reduction leads primarily to the threo isomer XV. The latter is converted, without inversion of configuration, to threo-acetoxy chloride XVI, which gives 2,3-dimethyl oxetane VII under the cyclization conditions.

EXPERIMENTAL

2-Alkyl-1,3-butanedioles (I, II). These compounds were obtained as in [3].

4-Methyl-5-alkyl-1,3-dioxanes (III, IV) (Mixture of Stereoisomers). A mixture of the stereoisomers was synthesized by the method described in [7-10]. The mixture was separated into individual isomers by rectification with columns filled with a metal packing (60 theoretical plates). The rectification was monitored by gas–liquid chromatography (GLC).

Solvolysis of cis- and trans-4-Methyl-5-ethyl- and 4-Methyl-5-isopropyl-1,3-dioxanes (III, IV [15]). A solution of 3.2 g (0.025 mole) of the cis or trans isomers of 1,3-dioxane (III) in 4 ml (0.125 mole) of methanol was heated at 70° for 10 h with 0.38 g of concentrated H_2SO_4 (specific gravity 1.84) with simultaneous removal of the volatile hydrolysis products by distillation. At the end of the reaction, the mixture was neutralized, the methanol was removed by distillation, and the residue was extracted with ether. The ether extracts were dried with calcined sodium sulfate, the ether was removed by distillation, and the residue was vacuum distilled.

The properties of the erythro- and threo-2-alkyl-1,3-butanediols are described in Table 2.

1,3-Chlorohydrin Acetates (VIII, IX). These compounds were obtained by reaction of the individual isomers of 2-alkyl-1,3-butanedioles with acetyl chloride by the method in [12]. The composition of the reaction mixture was established by GLC. The peaks on the chromatograms of the reaction mixture were identified by comparison with chromatograms of substances obtained by alternative syntheses. Data on VIII-XI are presented in Table 2.

2-Methyl-3-alkyloxetanes (V-VII). These compounds were obtained by cyclization of the individual isomers of 1,3-chlorohydrin acetates by the method in [13]. The cyclization products were identified on the basis of analysis of the chromatograms of the geometrical isomers of oxetanes isolated by rectification. The structure of V-VII was established by NMR and IR spectroscopy and the results of elementary analysis (Table 3).

4-Chloro-3-methyl-2-butanone (XIV). A mixture of 84 g (1 mole) of methyl isopropenyl ketone, obtained by the method in [14], and 200 ml of dry chloroform was cooled to 0-5° and saturated with hydrogen chloride gas, after which it was allowed to stand for 3 days. The excess HCl and chloroform were then removed by heating the mixture to 70-100°, and the residue was vacuum distilled to give 68.8 g (57%) of XIV with bp 40-47° (35 mm), d_4^{20} 1.0140 and n_D^{20} 1.4330. Found, %: Cl 28.7. C_5H_9OCl. Calculated, %: Cl 29.4. The product darkened in light.

4-Chloro-3-methyl-2-butanol (XV). A suspension of 18 g of lithium aluminum hydride in 250 ml of dry ether was refluxed for 1 h, after which it was added dropwise to a cooled (to −5°) solution of 120.6 g (1 mole) of XIV in 350 ml of dry ether. After all of the suspension had been added, the mixture was stirred for 30 min and hydrolyzed with 10% sulfuric acid. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried with magnesium sulfate, the ether was removed by distillation, and the residue was vacuum distilled to give 88.3 g (72%) of XV with bp 67-70° (10 mm), d_4^{20} 1.0248, and n_D^{20} 1.4500. Found, %: Cl 20.0. $C_5H_{11}OCl$. Calculated, %: Cl 20.7.

1-Chloro-2-methyl-3-acetoxybutane (XVI). This compound was obtained by the method in [4]. The physical constants of the product were in agreement with the data in [1].

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PREPARATION OF 1,3-DIOXANIUM PERCHLORATES

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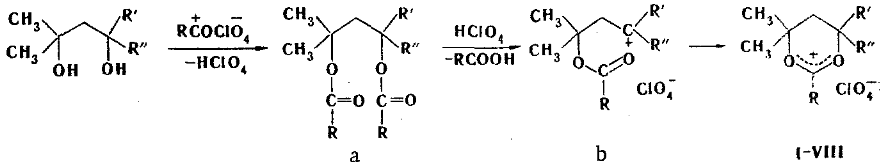
2,4,4,6,6-Substituted 1,3-dioxanium perchlorates were obtained by acylation of ditertiary 1,3-diols with carboxylic acid anhydrides in the presence of 70% perchloric acid.

1,3-Dioxanium salts contain a stabilized $-O-\overset{+}{C}-O-$ carboxonium ion, and this makes them extremely reactive and makes it possible to obtain valuable organic compounds from them.

We have previously reported [1] a method for the synthesis of 1,3-dioxanium salts by cyclization of primary 1,3-diols by means of an acylating mixture of acetic anhydride and perchloric acid.

However, the possibility of the extensive study and, especially, the application in organic synthesis of 1,3-dioxanium salts have been limited by the low yields of final products.

It is well known [2] that the stability of salts containing the $-O-\overset{+}{C}-O-$ fragment is determined by the presence in the ring of a substituent with donor character. We therefore used primary—tertiary and ditertiary 1,3-diols, synthesized by the method in [3], as starting compounds in the present research. In selecting the optimum reaction conditions we varied the component ratios, the temperature conditions, and the conditions used to isolate the products. The best yields (see Table 1) were obtained when the reaction was carried out by slow addition of 70% perchloric acid to a cooled (to 0 to −5°) mixture of the acid anhydride and 1,3-diol. The ratio of the starting materials was 1:5:1, respectively (method A). The evolution of a large amount of heat is observed during the reaction.



a b I-VIII

In refining the reaction scheme [1] we established that intermediate diacylate a is preferably formed in the first step and in acidic media splits out an acid molecule to give

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