PREPARATION OF STEREOISOMERIC FUNCTIONALLY SUBSTITUTED 2,6-DIETHOXYTETRAHYDROPYRANS

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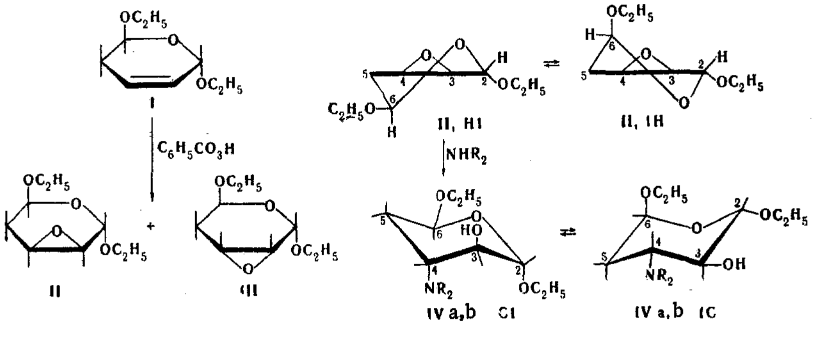
The oxidation of trans-2,6-diethoxy-Δ^3-dihydropyran with perbenzoic acid gave a mixture of stereoisomeric epoxides, from which one individual isomer was isolated. The configuration and conformation of the epoxide obtained was established by PMR spectroscopy. 2,6-Diethoxy-3-hydroxy-4-dialkylaminotetrahydropyrans were obtained by the reaction of 2,6-diethoxy-3,4-epoxytetrahydropyran with dimethylamine and piperidine; the structural direction of the opening of the epoxide ring was studied by mass spectrometry.

As we have previously shown [1], 2,6-dialkoxy-Δ^3-dihydropyrans obtained as a result of chemical or electrochemical bromoalkoxylation of 2-alkoxy-Δ^5-dihydropyrans and subsequent alkaline dehydrobromination are the individual trans isomers. The stereospecificity of the epoxidation of Δ^3-dihydropyrans depends to a considerable degree on the presence, character, and relative orientation of substituents in the 2 and 6 positions of the tetrahydropyran ring [2-4]. The behavior of 2,6-dialkoxy derivatives of pyran in this reaction has not been previously investigated. In the present research we have studied the stereospecificity of the oxidation of trans-2,6-diethoxy-Δ^3-dihydropyran (I) and opening of the resulting epoxide ring by secondary amines. The resulting stereoisomeric functionally substituted 2,6-dialkoxytetrahydropyrans can serve as intermediates for conversion to the corresponding functionally substituted compounds of the aliphatic series (dialdehydes [5,6], alkoxy alcohols [7], etc.).

A mixture consisting [according to gas-liquid chromatography (GLC)] of three products in a ratio of 20 : 54 : 26 is obtained in the epoxidation of I with perbenzoic acid. After freezing out and subsequent recrystallization from hexane, this mixture yielded the individual 2,6-diethoxy-3,4-epoxytetrahydropyran (II), which gives one peak on the chromatogram [this corresponds to the second peak of the mixture (54%)]. An absorption band at 1265 cm^{-1}, which is characteristic for the epoxy group, is present in the IR spectrum of II. The configuration and conformation of epoxide II were established by means of the PMR spectrum (Table 1).



a $R = CH_3$, b $R_2 = -(CH_2)_5-$

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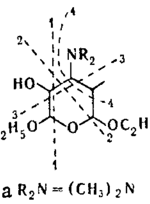
TABLE 1. PMR Spectrum of Epoxide II

Protons	Signal	Chemical shift δ, ppm	Sum of spin–spin coupling constants (ΣJ) of the vicinal protons, Hz
2-H	**Singlet**	4,9	0
6-H	**Quartet**	4,46	13,3
3-H	**Doublet**	2,63	3,6
4-H	**Multiplet**	2,9	
5-H	**Multiplet**	1,6	

TABLE 2. Mass Spectra m/e Values (relative intensities in percent of the maximum)



IV a $R_2N = (CH_3)_2N$
b $R_2N = C_5H_{10}N$

Compound	*M*	*M*-OC_2H_5	1–1			2–2		3–3	4–4
			$\underset{OH}{CH}{=}\underset{OC_2H_5}{CH}$	$\underset{\overset{\|}{{}^+NR_2}}{CH}-CH_2-\overset{OH}{\underset{OC_2H_5}{CH}}$	$\underset{\overset{\|}{{}^+NR_2}}{CH}-CH_2-CHO$	$\diagup\underset{OH}{CH}-\underset{OC_2H_5}{CH}-O-$	$\underset{\overset{\|}{{}^+NR_2}}{CH}-CH_2-\overset{\diagdown}{\underset{OC_2H_5}{CH}}$	$\underset{OH}{CH}{=}\underset{NR_2}{CH}$	$\underset{NR_2}{CH}{=}CH_2$
IVa	233 (18)	188 (7)	88(62)	146 (10)	100 (100)	60(33)	129 (19) +1 130 (16)	87 (73) +1 88 (62)	71 (96) +1 72 (76)
IVb	273 (4)	228 (8)	88(31)	186 (14)	140 (100)	58(24)	169 (12) +1 170 (12)	127 (60)	111 (81) +1 112 (75)

The signal of the anomeric 6-H proton at δ 4.46 ppm is a quartet with a half-width of 13.3 Hz, which reflects the sum of the constants of its spin–spin coupling with the vicinal protons of the 5-CH_2 methylene group of the tetrahydropyran ring of epoxide II. It follows from the magnitude of $\Sigma J_{6,5}$ that the 6-H proton is axially oriented and interacts axially-axially and axially-equatorially with the vicinal protons in the 5 position, since only this sort of combination of splittings can lead to the broad 6-H signal with a half-width of 13.3 Hz [8]. The signal of the anomeric 2-H proton at 4.9 ppm is a narrow singlet. The magnitude of the shift of this signal attests to the quasiequatorial orientation of the 2-H proton (the equatorial protons are less shielded and have larger chemical shifts than the axial protons). The absence of spin–spin splitting of the 2-H signal indicates its trans orientation with respect to 3-H [2-4]. Thus configuration II should be assigned to the isomeric epoxide formed from I in larger amounts, and, of the two conformers possible for it, conformation H1 should be selected.

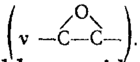
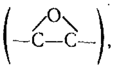
After isolation of the individual 2,6-diethoxy-3,4-epoxytetrahydropyran isomer (II), we obtained an uncrystallizable mixture consisting of three components in a ratio of 21 : 20 : 59 (the second component corresponds to the characterized oxide), which cannot be separated by distillation. According to elementary analysis, this mixture corresponds to an epoxide. However, its IR spectrum contains, in addition to an absorption band at 1265 cm^{-1} (ν of an epoxy group), an intense band at 1735 cm^{-1}, which characterizes the carbonyl group. The PMR spectrum of this mixture is basically identical to the spectrum of the individual oxide, but a new doublet appears at 5.00 ppm. Since the signal of the 6-H proton does not change and only the character of the signal of the 2-H proton (doublet) changes, we concluded that an isomeric oxide corresponding to structure III with cis orientation of the 2-ethoxy and 3,4-epoxy groups is present in this mixture.

The oxidation of trans-2,6-diethoxy-Δ^3-dihydropyran with perbenzoic acid is consequently devoid of stereospecificity and gives two isomeric oxides. The third peak of the mixture is apparently related to the ketone formed as a result of isomerization, although it remains unclear why the carbonyl compound is formed in such significant amounts (20%) in this case.

We investigated the reaction of the individual epoxide (II) obtained with secondary amines. Individual 2,6-diethoxy-3-hydroxy-4-dialkylaminotetrahydropyrans (IVa,b) were isolated when the epoxide was heated with a threefold excess of aqueous dimethylamine and piperidine. Considering that opening of the epoxides by amines proceeds trans axially via an S_N2 mechanism (the Fürst–Plattner rule) [9], it can be assumed that nucleophilic attack by amine of epoxide II, which is in the H1 conformation, should be directed predominantly to the 4 position of the tetrahydropyran ring. In fact, the mass spectra of the amino alcohols (IV) obtained (Table 2) confirm the orientation of the amino groups in the 4 position of the tetrahydropyran ring. These mass spectra demonstrate the presence of fragments that could have formed on disintegration of the molecule in the 1-1, 2-2, 3-3, and 4-4 directions characteristic for this class of compounds [10]. It should be noted that a constant difference in masses ($\Delta m/e$ 40), which corresponds to the difference in the molecular weights of the dimethylamino and piperidino groups, is observed for the fragments that contain the amino group. Thus opening of epoxide II by secondary amines proceeds stereospecifically. Amino alcohols IV are probably initially formed in the C1 conformation and then, as a result of conversion, assume the energetically more favorable 1C conformation. The favorability of the latter is determined by three factors: a) the three groups are equatorially oriented; b) the anomeric effect is retained; c) the 1C conformation is stabilized by an intramolecular OH . . . N hydrogen bond, the presence of which is demonstrated by the IR spectra of 0.005 M solutions of IVa,b (ν 3480 cm^{-1}). The intramolecular OH . . . N bond in conformation C1 is impossible in view of the trans diaxial orientation of the OH and NR_2 groups.

EXPERIMENTAL

Analysis by the GLC method was performed with an LKhM-7a chromatograph with a 2-m by 6-mm column packed with polyethylene glycol on Cellite with helium as the carrier gas, a flow rate of 60 ml/min, and a column temperature of 160°. The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were measured with a Varian spectrometer with an operating frequency of 60 MHz. The mass spectra were recorded with an SN-6 spectrometer at 150°.

2,6-Diethoxy-3,4-epoxytetrahydropyran (II). A 12.6-g (73.5 mmole) sample of 2,6-diethoxy-Δ^3-dihydropyran (I) was added to a solution of 25.3 g (184 mmole) of freshly prepared perbenzoic acid in chloroform, and the mixture was stirred and allowed to stand at room temperature in the dark. After 3 days, 70% of the perbenzoic acid had reacted. To decompose the residual perbenzoic acid, the solution was refluxed for 6 h, after which the mixture was shaken twice with potassium carbonate, vacuum-evaporated to 70 ml, washed with dilute potassium hydroxide solution and water, dried with potassium carbonate, and distilled to give 8.1 g (58%) of a product with bp 75-80° (1 mm), which gave three peaks on the gas-liquid chromatogram in a ratio of 20 : 54 : 26 [the retention times (τ) were, respectively, 3 min 20 sec, 4 min 35 sec, and 5 min 40 sec]. Freezing out yielded the crystalline epoxide with mp 52-52.5° (after two recrystallizations from n-hexane). Epoxide II gave one peak (τ 4 min 30 sec) on the chromatogram. IR spectrum: 1265 cm^{-1}  $\left(\nu\ \overset{O}{-C-C-}\right)$. Found: C 57.0, 57.1; H 8.4, 8.3%. $C_9H_{16}O_4$. Calculated: C 57.3; H 8.5%. The uncrystallizable epoxidation product was, according to GLC, a mixture of three components in a ratio of 21 : 20 : 59 (τ 3 min 10 sec, 4 min 35 sec, and 5 min 40 sec). IR spectrum: 1265 cm^{-1}  $\left(\overset{O}{-C-C-}\right)$, and 1735 cm^{-1} (C=O). Found: C 57.6, 57.6; H 8.8, 8.7%. $C_9H_{14}O_4$. Calculated: C 57.3; H 8.5%.

2,6-Diethoxy-3-hydroxy-4-dimethylaminotetrahydropyran (IVa). A mixture of 0.5 g (2.7 mmole) of epoxytetrahydropyran II and 1.2 g (8 mmole) of 33% aqueous dimethylamine solution was heated at 100° in a sealed ampule for 40 h. It was then poured into 3 ml of cold (−10°) concentrated hydrochloric acid and washed with chloroform. The aqueous solution was cooled and neutralized with solid potassium hydroxide and extracted with chloroform. The extract was dried with potassium carbonate, and the chloroform was removed by vacuum distillation to give 0.5 g (79%) of amino alcohol IVa with mp 37-37.5° (after two recrystallizations from n-hexane). IR spectrum (0.005 M solution in CCl_4): 3610, 3480 cm^{-1}. Found: C 56.4, 56.2; H 10.1, 10.6; N 6.2%. $C_{11}H_{23}NO_4$. Calculated: C 56.6; H 9.9; N 6.0%. The methiodide had mp 154-155°. Found: I 34.5%. $C_{12}H_{26}INO_4$. Calculated: I 33.6%.

2,6-Diethoxy-3-hydroxy-4-piperidinotetrahydropyran (IVb) with mp 58-59° was similarly obtained in 75% yield from epoxide II and piperidine. IR spectrum (0.005 M solution in CCl_4): 3610 and 3475 cm^{-1}. Found: C 61.3, 61.5; H 9.5, 9.7; N 5.1, 5.0%. $C_{14}H_{26}NO_4$. Calculated: C 61.8; H 9.6; N 5.4%.

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