STEREOCHEMISTRY OF HETEROCYCLES

XIV.* SYNTHESIS OF SOME 1,3-DIOXEPANS FROM SUBSTITUTED 1,4-DIOLS

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Methods were developed for the synthesis of 2-ethoxy-1,4-butanediol and 2-ethoxy-1,4-pentanediol. The latter was a mixture of diastereomers. These diols were used to synthesize 5-ethoxy-1,3-dioxepan and 2,2,4-trimethyl-6-ethoxy-1,3-dioxepan. Gas–liquid chromatography was used to demonstrate that 2,2,4-trimethyl-6-ethoxy-1,3-dioxepan is a mixture of cis and trans isomers; the ratio of these isomers is similar to the ratio of diastereomers in the starting 2-ethoxy-1,4-pentanediol. The configurations of the indicated isomers were evaluated by conformational analysis.

The stereochemistry of seven-membered cyclic acetals and ketals – 1,3-dioxepans – has received very little study. The previously unreported alkoxy-substituted 1,3-dioxepans are of extreme interest for stereochemical investigations. Considering that the chief method for the synthesis of 1,3-dioxepans is the reaction of 1,4-diols with carbonyl compounds (or their acetals) [2-4], we set out primarily to develop a route for the synthesis of alkoxy-substituted 1,4-diols.

There are two promising routes for the synthesis of these diols: the first involves the use of the transformations of alkoxysuccinic acid esters, and the second involves the use of 2-alkoxy-1,4-dihalo derivatives. Alkoxysuccinic acid esters can be obtained by the esterification of the corresponding acids and also from the esters of the corresponding unsaturated acids. Thus the alkoxides add fumaric acid at the ester double bond to form alkoxysuccinic acid esters [5]. In this case, it was observed that the reaction is realized only when sodium methoxide rather than sodium ethoxide is used with maleic acid esters [6]. By modifying the method in the case of the preparation of diethyl ethoxysuccinate (I), we were able to show the fundamental possibility of the synthesis of such substances by the reaction of sodium ethoxide with esters of both formic and maleic acids. Ester I is readily reduced with lithium aluminum hydride to form 2-ethoxy-1,4-butanediol (II).

The second route for the synthesis of 1,4-diols was based on the use of 1,4-dibromo-2-ethoxypentane (III), obtained by the reaction of α,β-dibromodiethyl ether with propylene in the presence of anhydrous zinc chloride. The direct substitution of the bromine atoms by hydroxyl groups in III is hindered, and ester III was therefore initially converted, by the action of potassium acetate in acetic anhydride, to 1,4-diacetoxy-2-ethoxypentane (IV), the saponification of which gave 2-ethoxy-1,4-pentanediol (V). Compound III is a mixture of diastereomers in a ratio of 23:77, as demonstrated by gas–liquid chromatography (GLC). There is a characteristic splitting of the band of the stretching vibrations of the C–O–C bond of the ether at 1080-1090 cm^{-1} in the IR spectrum of III. Compound IV is also a mixture of diastereomers with a similar isomer ratio, which possibly is evidence for the S_N2 character of the substitution of halogen by the acetoxy group. The isomer ratio of V coincides with that of IV, which again confirms the absence of Walden inversion during the hydrolysis of the esters due to acyl-oxygen rather than alkyl-oxygen bond cleavage.

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*See [1] for communication XIII.

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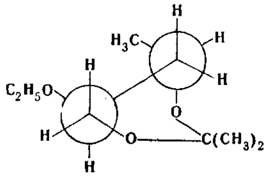
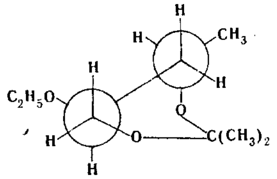
The structures of IV and V were proved by an examination of their IR spectra, which contain characteristic bands that confirm the structures of the indicated substances: carbonyl band at 1718 cm^{-1}, a band of the C—O—C bond of esters at 1226 cm^{-1}, and an ether band at 1090-1100 cm^{-1} for IV; hydroxyl group bands at 3200-3600 cm^{-1} and ether bands at 1080-1090 cm^{-1} for V [7]. A characteristic splitting of the band of the stretching vibrations of the C—O—C ether bond is observed in the spectra, which is again a confirmation of the presence of stereoisomers in the examined compounds

Side dehydration of the diols leading to the formation of tetrahydrofuran derivatives [8] is possible during the condensation of 1,4-diols with carbonyl compounds. Another side reaction may be polycondensation of the starting 1,4-diols, tetrahydrofurans, and 1,3-dioxepans [9]. The condensation of II with formaldehyde gives 5-ethoxy-1,3-dioxepan (VI), while similar condensation with acetone gives 3-ethoxytetrahydrofuran (VII). The condensation of V with formaldehyde gives a transparent resin; similar condensation with acetone makes it possible to obtain 2,2,4-trimethyl-6-ethoxy-1,3-dioxepan (VIII), but the yield is only 33%, and a considerable amount of resin is formed along with it. (In all cases, the condensation was carried out in the presence of the H form of KU-2 cation exchange resin.)

It is obvious that the hydroxyl groups should be as close as possible in the condensation of 1,4-diols with carbonyl compounds to give cyclic acetals (ketals). The cis isomer (A) of 1,4-dioxepan VIII should then be obtained from the erythro isomer of a 1,4-diol of the V type, and the trans isomer (B) of VIII should then be obtained from the threo isomer of V.



A



B

Since the asymmetrical centers of the diasteroemers of V are not involved in the condensation, the ratio of the stereoisomers of 1,3-dioxepan VIII should be similar to the ratio of the stereoisomers of diol V, i.e., 77:23, which is confirmed by GLC.

Bands at 1000, 1070, and 1118 cm^{-1}, which are characteristic [10] for the C—O—C—O—C fragments of the 1,3-dioxepan ring, are observed in the IR spectra of VI and VIII. It is interesting that the band at 1138 cm^{-1} that is typical for unsubstituted 1,3-dioxepan is absent in both spectra. The spectra of both substances contain a band at 1095 cm^{-1}, which can be assigned to the stretching vibrations of the C—O—C bond in the ethoxy fragment. In addition, there are bands at 832 and 1370 cm^{-1}, which are characteristic for gem-dimethyl groups, especially in cyclic ketals [11], in the spectrum of VIII.

The band at 1000 cm^{-1}, which is apparently most typical for the 1,3-dioxepan ring, is absent in the spectrum of VII. An examination of the PMR spectra of the synthesized 1,3-dioxepans gives even more distinct information.* The spectrum of VI contains a singlet from the protons of the OCH_2O group at δ 4.64 ppm (2 H), which is evidence of rapid ring inversion. In addition to the indicated band, the spectrum contains multiplet resonance bands of the signals of the methylene and methylidyne protons in the 4, 5, and 7 positions of the ring, as well as of the methylene protons of the ethoxy group (δ 3.64 ppm, 7H), protons of the methylene group in the 6-position (δ 1.77 ppm, 2H), and a typical methyl triplet at δ 1.14 ppm (3H). In the spectrum of VIII, the protons of the ester carbon atoms of the ring and the methylene protons of the ethoxy group (δ 3.91, 3.43 ppm), of the methylene group in the 5-position of the ring (δ 1.91 ppm), and of the methyl groups (δ 1.14 ppm) give poorly resolved complex multiplets with intensities of 6H, 2H, and 12H, respectively. The PMR spectra of VI and VIII constitute unambiguous proof of their structure; in addition, the multiplicity of essentially all of the signals in the spectrum of VIII indicates the presence of stereoisomers.

The spectrum of VII contains multiplet signals from the methylene and methylidyne protons in the 2, 3, and 5 positions of the tetrahydrofuran ring, as well as from the methylene protons of the ethoxy group

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*The PMR spectra were recorded in the N. D. Zelinskii Institute of Organic Chemistry Academy of Sciences of the USSR, by A. M. Moiseenkov, to whom the authors are sincerely grateful.

(δ 3.69, 3.35 ppm, 7H), from the methylene protons in the 4-position (δ 1.89 ppm, 2H), and a distinct triplet from the methyl protons of the ethoxy group (δ 1.14 ppm, 3H), which unambiguously proves the structure.

EXPERIMENTAL

The IR spectra of thin layers of the substances were recorded with an IKS-14A spectrometer, while the PMR spectra of CCl_4 solutions were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. Chromatographic analysis was performed with LKhM-8M and LKhM-7A chromatographs at 100-150°C. The liquid phases were 5% SKTFT-50 and 10% SKTSTV-803 on Chromosorb G. The column length was 2 m. Chromatographically pure substances (98-99%) were used in the syntheses.

Diethyl Ethoxysuccinate (I). Diethyl maleate [344 g (2 mole)] was added dropwise to a cooled solution of sodium ethoxide [from 46 g (2 g-atom) of sodium in 600 ml of absolute ethanol]. The mixture was cooled, and 120 g of glacial acetic acid was added. The precipitate was washed with ether, the ether and alcohol were removed by distillation, and the residue was vacuum distilled to give 261 g (60%) of product. The reaction of this product with diethyl fumarate gave 74% of I with bp 106° (5 mm), d_4^{20} 1.0369, and n_D^{20} 1.4230, in agreement with the literature data [12].

2-Ethoxy-1,4-butanediol (II). Ester I was reduced by the method in [13] to give 44% of II with bp 136° (10 mm), d_4^{20} 1.0422, and n_D^{20} 1.4501. Found: C 53.6; H 10.5%; H_{act} 1.96. $C_6H_{16}O_3$. Calculated: C 53.7; H 10.4%; H_{act} 2.00.

1,4-Dibromo-2-ethoxypentane (III). A stream of propylene, formed by the dehydration of propyl alcohol on activated aluminum oxide at 375° (space rate 2 h^{-1}), was passed through a mixture of 232 g (0.96 mole) of α, β-dibromoethyl ethyl ether [14], 50 ml of absolute ether, and 6.96 g of fused zinc chloride at 18-20° for 12 h. The reaction product was washed with 5% sodium carbonate solution and water, dried, and vacuum distilled under nitrogen to give 145 g (53%) of a product with bp 86° (4 mm), d_4^{20} 1.5511, and n_D^{20} 1.4970. Found: Br 58.3%. $C_7H_{14}Br_2O$. Calculated: Br 58.4%. The ratio of stereoisomers (by GLC) was 23:77.

1,4-Diacetoxypentane (IV). A mixture of 128 g (0.43 mole) of III and 135 g (1.38 mole) of anhydrous potassium acetate in 400 ml of acetic anhydride was refluxed for 27 h. The precipitate was removed by filtration and washed with ether. The ether and acetic anhydride were removed from the filtrate by distillation, and the residue was vacuum fractionated to give 71 g (66%) of a product with bp 91° (4 mm), d_4^{20} 1.0357, and n_D^{20} 1.4288. Found: C 56.8; H 8.7%. $C_{11}H_{20}O_5$. Calculated: C 56.9; H 8.6%. The ratio of stereoisomers (by GLC) was 77:23.

2-Ethoxy-1,4-pentanediol (V). A 58 g (0.25 mole) sample of IV was saponified with 30% aqueous alcoholic KOH via the method in [15] to give 30 g (80%) of a product with bp 122° (6 mm), d_4^{20} 1.0128, and n_D^{20} 1.4468. Found: C 56.8; H 10.7%. $C_7H_{16}O_3$. Calculated: C 56.8; H 10.8%.

5-Ethoxy-1,3-dioxepan (VI). A 33 g (0.26 mole) sample of II was condensed with 22.5 g (0.75 mole) of paraformaldehyde in absolute benzene in the presence of 3.75 g of the H form of KU-2 cation exchange resin via a method similar to that in [16] to give 11.5 g (32%) of a product with bp 76° (10 mm), d_4^{20} 1.0234, and n_D^{20} 1.4378. Found: C 57.3; H 9.7%. $C_7H_{14}O_3$. Calculated: C 57.5; H 9.6%. Compound VI gave a positive reaction with a hot hydrochloric acid solution of 2,4-dinitrophenylhydrazine [17].

3-Ethoxytetrahydrofuran (VII). This compound was obtained in 28% yield by the condensation of II with acetone via a method similar to that in [16] and had bp 44° (7 mm), d_4^{20} 0.9270, and n_D^{20} 1.4270. Found: C 62.3; H 10.5%. $C_6H_{12}O_2$. Calculated: C 62.1; H 10.3%. This compound did not give a positive reaction with a hot hydrochloric acid solution of 2,4-dinitrophenylhydrazine.

2,2,4-Trimethyl-6-ethoxy-1,3-dioxepan (VIII). A 17 g (0.115 mole) sample of V was condensed with 12 g (0.207 mole) of acetone in absolute benzene in the presence of 2.5 g of KU-2 cation exchange resin to give 7.1 g (33%) of a product with bp 71° (48 mm), d_4^{20} 0.9193, and n_D^{20} 1.4219. Found: C 63.7; H 10.8%. $C_{10}H_{20}O_3$. Calculated: C 63.8; H 10.6%. This compound gave a positive reaction with a hot hydrochloric acid solution of 2,4-dinitrophenylhydrazine. The ratio of the stereoisomers (by GLC) was 77 : 23.

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