MECHANISM OF THE REACTION OF 3,4-EPOXYSULFOLANES WITH AMMONIA AND AMINES

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The corresponding hydroxyaminosulfolanes were isolated from the reaction of 3,4-epoxysulfolane and 3-methyl-3,4-epoxysulfolane with ammonia and amines. The mechanism of the reaction was studied by thermography. The reaction proceeds through the intermediate formation of the corresponding unsaturated alcohols and subsequent addition of the nucleophile to the double bond. The reaction of 3,4-dimethyl-3,4-epoxysulfolane with the same reagents terminates with isomerization of the oxide.

We have previously shown that alcohols react with epoxysulfolanes in alkaline media to give monoethers of sulfolanediols through the intermediate formation of the corresponding unsaturated alcohols [1].

The aim of the present research was to investigate the reaction of epoxysulfolanes with other nucleophilic reagents such as ammonia and amines. It is known from the literature [2, 3] that sulfolene epoxide I reacts with ammonia to give a hydroxyaminosulfolane with a trans structure [3]. We studied the reactions of 3-sulfolene epoxide (I), 3-methyl-3-sulfolene epoxide (II), and 3,4-dimethyl-3-sulfolene epoxide (III) with ammonia, methylamine, ethylamine, piperidine, and morpholine. The characteristics of the compounds obtained are presented in Table 1.

The IR spectra of the amino derivatives of sulfolane obtained contain narrow intense bands at 3300-3400 cm⁻¹ due to the stretching vibrations of the N-H bond. At the same time, broad intense absorption at 2500-3500 cm⁻¹, which we assigned to the stretching vibrations of an associated OH group, is observed, and the hydroxyl group shows up in the form of a free band only in the case of XI, XIII, and XV.

The mechanism of the reaction was investigated by differential thermal analysis. It was established that the reactions of the epoxides take place in two steps; this is expressed on the thermograms by two exothermic effects (Fig. 1), the first of which corresponds to isomerization of the corresponding epoxides, the second of

| Com- pound | R' | R ² | x | mp, °C (from ethanol) | Found,% | | | | Empirical | Calc., % | | | | 0 <u>, 9</u> 0 |
|---------------|-----|----------------|--------------------------|-----------------------------|---------|------|------|-------|---------------------------|----------|------|------|-------|----------------|
| | | | | | с | Н | N | s | formula | С | н | N | s | Yiel |
| VII* | н | Н | Amino | 189 | 31,68 | 5,93 | 9,00 | 21,46 | C₄H₅NO₃S | 31,81 | 5,92 | 9,28 | 21,20 | 44 |
| VШ | Н | Η | Methyl- amino | 140,5 | 36.38 | 6,79 | 8,39 | 19,49 | C₅H₁₁NO₃S | 36,35 | 6,70 | 8,47 | 19,40 | 50 |
| 1X | Н | Н | Ethyl- | 137- | ŧ0,71 | 7,17 | 7,43 | | $C_6H_{13}NO_3S$ | 40.21 | 7,30 | 7,81 | 17,88 | 45 |
| x | н | Н | amino Piperid- ino | 138,5 173 | 49,00 | 7.64 | 6,31 | 14.67 | $C_9H_{17}NO_3S$ | 49,3 | 7,80 | 6,38 | 14,62 | 55 |
| XI | Н | Н | Morphol- ino | 157 | 13,62 | 6,82 | 5,99 | 14,57 | $\mathrm{C_8H_{15}NO_4S}$ | 43,42 | 6,83 | 6,33 | 14,49 | 71 |
| XII | CH₃ | Н | Amino | 170 | 36,20 | 6,42 | 8,53 | 18,80 | $C_5H_{11}NO_3S$ | 36,35 | 7,70 | 8,47 | 19,40 | 54 |
| хш | CH₂ | Н | Methyl- amino | 172 137 | 40,17 | 7,27 | 8,25 | 17,74 | $C_6H_{13}NO_3S$ | 40,21 | 7,30 | 7,81 | 17,88 | 71 |
| XIV | Н | CH_3 | Ethyl- | 169 | 43,42 | 7,98 | 6,71 | 16,53 | $C_7H_{15}NO_3S$ | 43,50 | 7,82 | 7,24 | 16,58 | 17 |
| xv | СН₂ | Н | amino Piperid- ino | 170 108,5— 110 | 51,11 | 8,14 | 5,89 | · | $C_{10}H_{19}NO_{3}S$ | 51,80 | 8,18 | 6,00 | 13,74 | 54 |

TABLE 1. Characteristics of the Compounds Obtained

*This compound has mp 198-199°C [2].

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Fig. 1. Thermographic curves of the reaction of 3,4-epoxysulfolanes with ammonia and amines (0.0007 mole of the epoxide and a threefold to fourfold excess of ammonia and the amines): 1), 4), and 6) I, II, and III with methylamine; 2) I with ammonia; 3) II with ammonia; 5) II with piperidine.

which corresponds to reaction of the isomerized products with the reagents. Epoxide I reacts most actively with methylamine (Fig. 1, curve 1). In the experiment with ammonia (Fig. 1, curve 2) the thermogram is somewhat more complex. It is possible that a certain amount of dimer XVI [4] (the shoulder with a maximum at 60°C on the thermographic curve) is formed in this case. The second exothermic effect on the thermograms of epoxide II with ammonia and methylamine (curves 3 and 4) is expressed less distinctly and lies in the higher-temperature region; however, this effect is completely absent in the case of piperidine (curve 5). We explain this by less active reaction of the isomerized product with these reagents. The isomerization of epoxide III (curve 6) takes place over the same range of temperatures, but a polymer is formed during subsequent heating.

Interruption of the recording of the thermographic curves at the maximum of the hypothetical isomerization peak and subsequent analysis by gas-liquid chromatorgraphy (GLC) of the reaction mixture showed that the 3-sulfolene epoxides undergo isomerization under the influence of bases to the corresponding unsaturated alcohols: epoxide I to 4-hydroxy-2-sulfolene (IV), epoxide II to a mixture of 3-methyl-4-hydroxy-2-sulfolene (Va) and 4-methyl-4-hydroxy-2-sulfolene (Vb) in a ratio of 1: 4-5, and, finally, epoxide III to 3,4-dimethyl-4hydroxy-2-sulfolene (VI). A resonance signal of the protons of the methyl group attached to $C_{(3)}$ [δ 1.96 ppm, ${}^{4}J_{(CH_{3})H_{2}} \approx 1.5$ Hz], which is shifted to weak field as compared with the resonance signal of the protons of the methyl group attached to $C_{(4)}$ (1.63 ppm), is observed in the PMR spectrum of VI. The spectrum of a mixture of alcohols V contains signals at 1.96 and 1.63 ppm with an integral intensity ratio of 1: 5. In conformity with the chemical shifts of the resonance signals of the methyl groups in VI, we assigned the components of the mixture to structural isomers Va and Vb.

When both isomers Va and Vb, which are formed under the reaction conditions from epoxide II, are present, the primary amines add to both possible isomers. Ammonia and piperidine add to isomer Vb, as demonstrated by analysis by GLC.

The reaction of epoxide III with ammonia and amines terminates with isomerization to alcohol VI. All attempts to add amines to alcohol VI were unsuccessful.

The ease of formation of the products depends not only on the structures of the sulfolene epoxides but also on the nature of the amines. Ammonia and primary amines add readily to epoxides I and II. The same products were obtained by the action of these reagents on alcohols IV and V. Secondary cyclic amines (piperidine and morpholine) react slowly with epoxides I and II. Thus in the case of the reaction of piperidine with epoxide II we were able to isolate intermediate unsaturated alcohol V after 10 days, and adduct XV was formed only after 40 days.

Diethylamine does not add to sulfolene epoxides but only brings about their isomerization to unsaturated alcohols or, in the case of epoxide I, forms dimer XVI, which was identified from its IR spectrum and a mixed-melting-point determination with a previously obtained sample [1, 4].

The formation of a mixture of two addition products of the composition $C_{9}H_{17}NO_{3}S$ with mp 104-105°C, from which individual product X was isolated by fractional recrystallization, was observed in the reaction of epoxide I with piperidine according to the results of thin-layer chromatography (TLC). The spectrum contains a multiplet resonance signal at 3.30-4.20 ppm which, according to the chemical shifts of the methylene protons attached to $C_{(2)}$ (δ 3.00 ppm) and $C_{(3)}$ (2.23 ppm) in sulfolane [5], we assigned to the protons of the methylene groups attached to $C_{(2)}$ and $C_{(5)}$. Consequently, piperidine adds to the $C_{(3)}$ atom of alcohol IV. This fact was confirmed by the observation that the magnitude of the $J_{H_{(4)}H_{(3)}}$ spin-spin coupling constant (2.6 Hz) corre-

sponds to a vicinal orientation of the $H_{(3)}$ and $H_{(4)}$ protons. We were unable to isolate the second isomer in pure form. It is difficult to assume the formation of a structural isomer due to the addition of piperidine to the $C_{(2)}$ atom on the basis of the polarity of the double bond of alcohol IV. A mixture of cis and trans isomers is most likely formed in this case.

The reaction of methylamine with epoxide II also gave a mixture of two isomers with the composition $C_{6}H_{13}NO_{3}S$ and mp 121-123°C; this was confirmed by the presence in the IR spectrum of two bands at 3320 and 3340 cm⁻¹ due to stretching vibrations of the N-H bond, whereas only one ν_{N-H} band at 3340 cm⁻¹ was present in the IR spectrum of individual product XIII isolated after separation on aluminum oxide. The PMR spectrum of this mixture contains a triplet at δ 4.50 ppm, which is related to the proton attached to $C_{(4)}$. Since this signal is not observed in the spectrum of individual XIII, it may be assumed that structural isomers are present in the mixture. Their ratio, determined from the integral intensities of the resonance signals of the methyl and methylamino protons, is 1:3 with predominance of the XIII isomer. It should be noted that the chemical shifts of the methyl protons of isomer XIII [$\delta_{C_{(4)}-CH_3}$ 1.63 and δ_{N-CH_3} 2.44 ppm] are close to the chemical

shifts of the analogous methyl groups in VI and VIII; this confirms the correctness of the structure assigned to it. However, only XIII is formed in the reaction of methylamine with alcohol V, obtained by isomerization of epoxide II in triethylamine and containing 83% isomer Vb.

The formation of a mixture of products with the composition $C_7H_{15}NO_3S$ and mp 92-130°C (in 90% yield) was also observed in the reaction of ethylamine with epoxide II. The PMR spectrum of the mixture contains resonance signals of methyl protons at δ 1.43 ppm $[C_{(3)}-CH_3]$ and 1.6 ppm $[C_{(4)}-CH_3]$ in a ratio of 1:4 (ν_{N-H}

3280 and 3300 cm⁻¹). We were able to isolate benzene-insoluble individual XIV ($\nu_{\rm N-H}$ 3280 cm⁻¹) by refluxing the mixture in benzene. The triplet at δ 4.50 ppm and the singlet at δ 1.40 ppm in the PMR spectrum of this product can be assigned to the proton attached to C₍₄₎ and to the methyl protons attached to C₍₃₎, respectively.

Thus it may be assumed that the reactions of sulfolene epoxides I-III with ammonia and amines are realized via a scheme involving detachment of an α -methylene proton under the influence of bases and subsequent addition of the nucleophile (if addition is not sterically hindered) to the double bond of the corresponding unsaturated alcohol to give the final addition products – hydroxyaminosulfolanes.

We also studied the relative capacities of epoxides I-III for isomerization in pyridine and triethylamine.



The amines, being weaker bases than sodium alkoxides, isomerize the epoxides with considerably greater difficulty. Whereas pyridine converts epoxide I to 4-hydroxy-2-sulfolene after heating for 12 h, all attempts to similarly isomerize epoxides II and III were unsuccessful, and the starting compounds were isolated. Triethylamine, which is a stronger base, not only isomerizes epoxide I to alcohol IV but also converts it to dimer XVI. Epoxides II and III undergo isomerization to unsaturated alcohols identical to V and VI described above.

On the basis of the above information it may be concluded that the abilities of the epoxides to undergo isomerization differ and depend both on their structures and on the character of the base.

EXPERIMENTAL

The thermograms were recorded with a PDS-021 two-coordinate potentiometer with Chromel-Alumel thermocouples under linear heating conditions at a rate of 2.5 deg/min. The reaction temperature was assumed to be the maximum peak on the differential curve. A Stepanov vessel with one inlet tube for introduction of the reagents was used for the experiments. The exothermic peaks were interpreted by interruption of the re-cording at the maximum peak or after the curve had passed through a maximum and investigation of the composition of the reaction mixture by GLC. Chromatography with a column filled with activity ΠAl_2O_3 (elution with benzene) and TLC on Silufol plates [elution with ethanol-benzene (10:1)] with development by iodine vapors were used for the separation and identification of the products.

Analysis by GLC was carried out with Khrom-4 chromatograph with a 250×0.3 cm column filled with 15% polymethylsiloxane oil on Chromaton N-AW-DMCS (0.200-0.250 mm) at 200°C and flame-ionization detection. The IR spectra of suspensions of the compounds between KBr plates were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard.

Starting epoxides I and II were obtained previously in [1]. Epoxide III was obtained by the action of peracetic acid on 3,4-dimethylsulfolene by the method in [6] and had mp 138-140°C (mp 83-85°C [7]). The diacetate, with mp 136-138°C ($\nu_{\rm C} = 0.1730 \,{\rm cm}^{-1}$) (mp 136-138°C [7]), was isolated by heating epoxide III with acetic anhydride.

Hydroxyaminosulfolanes VII-XV. A) Epoxides I and II were mixed with ammonia or the appropriate amine (a threefold or fourfold excess). The ammonia and methylamine were used in the form of 25-30% aqueous solutions, and the ethylamine was in the form of a 50% aqueous solution. The reaction mixtures were allowed to stand at room temperature for from 5 to 40 days, after which the amine was removed in vacuo, and the residue was recrystallized from ethanol to give the corresponding addition products (Table 1).

B) 3-Amino-4-hydroxy- (VIII), 3-Methylamino-4-hydroxy- (VIII), 3-Piperidino-4-hydroxy- (X), 3-Amino-4-methyl-4-hydroxy- (XII), and 3-Methylamino-4-methyl-4-hydroxysulfolane (XIII). A 1-g (0.007 mole) sample of IV or V (17% Va, 83% Vb) was dissolved in 5-10 ml of the appropriate amine, and the solution was allowed to stand for 24 h. The excess reagent was then removed by distillation, and the residue was recrystallized from ethanol. The products (in up to 50% yields) were identified by TLC and mixed-melting-point determinations with VII, VIII, X, XII, and XIII obtained by method A.

Isomerization of 3,4-Epoxysulfolanes in Pyridine. A 4-g (0.03 mole) sample of epoxide I, 4-g (0.034 mole) sample of epoxide II, or 4-g (0.022 mole) sample of epoxide III was refluxed in 60 ml of pyridine for 12 h. In the case of epoxide I, the residue after removal of the amine was distilled in vacuo to give 3.35 g (84%) of 4-hydroxy-2-sulfolene IV with bp 166°C (0.1 mm) and n_D^{20} 1.5240. Found: C 35.51; H 4.61; S 23.50%. C₄H₆O₃S. Calculated: C 35.81; H 4.51; S 23.91%. In the case of epoxides II and III, residues with mp 89-90 and 137-138°C, respectively, were obtained; they were identified as the starting epoxides from mixed-melting-point determinations.

Isomerization of 3,4-Epoxysulfolanes in Triethylamine. A 5-g (0.03 mole) sample of epoxide I, II, or III was refluxed for 5-6 h in excess triethylamine (25-50 ml) containing 1 ml of water, after which the mixture was cooled, and the resulting precipitate was removed by filtration or the solvent was removed and the residue was distilled in vacuo. Epoxide I yielded 5 g of dimer XVI with mp 260°C. Found: C 36.21; H 4.49; S 23.95%. $C_8H_{12}O_6S_2$. Calculated: C 35.81; H 4.51; S 23.90%. Epoxide II yielded 3.5 g (70%) of V (17% Va, 83% Vb) with bp 122-130° (0.03 mm) and n_D^{20} 1.5068, which was identical to the compound described in [1]. Epoxide III yielded 2 g (40%) of VI with mp 89-90°C. Found: C 44.45; H 66.86; S 19.84%. $C_6H_{10}O_3S$. Calculated: C 44.11; H 6.74; S 19.65%.

<u>Reaction of 3,4-Epoxy- (I) and 3-Methyl-3,4-epoxysulfolane (II) with Diethylamine.</u> A 0.037-mole sample of epoxide I or II was dissolved in 20 ml of diethylamine containing 1 ml of water, and the mixture was allowed to stand at room temperature for 1 week, after which the excess diethylamine was removed by distillation. A precipitate (in up to 57% yield) with mp 261°C, which was identical to dimer XVI described above, was isolated in the reaction with epoxide I. In the reaction with epoxide II the residue was distilled in vacuo to give a mixture of V with bp 140°C (0.03 mm) (in 55% yield) and n_D^{20} 1.5065.

Reaction of Epoxide III and Alcohol VI with Ammonia and Piperidine. A mixture of 0.012 mole of epoxide III or alcohol VI and 25-40 ml of amine was allowed to stand at room temperature for 1-1.5 months, after which

the excess reagent was removed, and a precipitate (in 50-90% yield) with mp 85-90°C, which was identified as alcohol VI ($\nu_{C=C}$ 1620 cm⁻¹) was isolated.

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FOR MATION OF SPIRO-SUBSTITUTED 1,3-DITHIOLANES AND THIRANES IN THE REACTION OF 3-AMINOINDENE-1-THIONES WITH ALIPHATIC DIAZO COMPOUNDS*

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3-A minoindene-1-thiones react readily with diazomethane to give the corresponding 4,4;5,5dispiro-substituted 1,3-dithiolanes. The production of both 2,2-spiro-substituted thiiranes and products of desulfuration of the latter is possible in the reaction of 3-aminoindene-1-thiones with substituted diazomethanes. The thermolysis, hydrolysis, and salt-forming reactions of the compounds obtained were investigated.

The reactions of thiocarbonyl compounds with diazoalkanes have been investigated in greatest detail in the case of thioketones [2-9]: thiadiazoles [2, 3], dithiolanes [4-6], thiiranes [4, 7], and other sulfur compounds [8, 9] were obtained. It is assumed that the direction of the reaction does not depend on the reagent ratio but is determined by the specific structures of the thioketone and the diazo compound and the reaction conditions [4]. No data on the cycloaddition of diazoalkanes to the C = S bond of thioamides are available, but individual representatives of thioamides are capable of methylation by diazomethane at the sulfur atom [10]. The reactions of vinylogs of thioamides with diazoalkanes have not been studied.

3-Aminoindene-1-thiones (I) react with diazomethane in ether, benzene, or acetone at -60 to 20° C to give 4,4;5,5-dispiroindene-substituted 1,3-dithiolanes (II) in high yields. The PMR (Table 1) and IR spectra (see the experimental section) confirm the structure of dithiolanes II. The protons of the $-S-CH_2-S-$ group resonate in the form of a singlet, which indicates their equivalence and, consequently, the trans orientation of the indene rings. The described reactions of unsymmetrically substituted thiocarbonyl compounds with diazomethane lead to a mixture of dithiolanes with cis and trans orientations of the substituents [5, 8]. The stereoselectivity of the I→II transformation is evidently due to steric hindrance that develops in the case of cis orientation of the indene rings in the transition state. A complex multiplet is observed instead of the usual triplet signal for the protons of the $-CH_2NCH_2$ fragment of the piperidine ring in the PMR spectra of IIe,h. This is due to restrained

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