NEW METHOD FOR THE SYNTHESIS OF cis-2,5-DISUBSTITUTED SULFOLANE DERIVATIVES*

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A new method for the preparation of functional derivatives of sulfolane by ozonolysis of 13-thiabicyclo[8.2.1]-cis-5-tridecene and its derivatives was developed.

Sufficiently effective general methods for the preparation of di- and polyfunctional sulfolane derivatives have not yet been described. The essential inadequacies in the known methods include the low yields of the target compounds, the many steps involved in the syntheses, the difficulty in obtaining the starting materials, and the laborious separation of the stereoisomers [1].

The possibility for the synthesis of 2,9-dichloro-13-thiabicyclo[8.2.1]-cis-5-tridecene (I) by reaction of sulfur dichloride with trans,trans,cis-cyclododeca-1,5,9-triene was recently demonstrated [2]. We have established that I is formed in a steady yield of no less than 90% in the reaction of equimolar amounts of reagents in dilute dichloromethane solutions at −20°C. 13-Thiabicyclo[8.2.1]-cis-5-tridecene (II) is obtained in high yield by reduction of I by means of $LiAlH_4$. Its ozonolysis as a function of the conditions and solvents was studied. The ozonolysis was carried out in dilute (1:20) solutions.

Acetoxyhydroperoxyaldehyde III is formed in acetic acid at −20°. The structure of aldehyde III was confirmed by determination of the percentage of active oxygen, positive reaction with 2,4-dinitrophenylhydrazine, and IR spectral data.

Absorption bands of equal intensity at 1760 and 1260 cm^{-1} are related, respectively, to the stretching vibrations of the carbonyl group and the asymmetrical stretching vibrations of the C−O−C group of an ester grouping, while the absorption band at 1015 cm^{-1} is related to the symmetrical stretching vibrations of this same grouping. The aldehyde group is characterized by the frequency of the stretching vibrations of the carbonyl group at 1740 cm^{-1} and the stretching vibrations of the CH group at 2730 cm^{-1}. The absorption at 930 cm^{-1} is due to the stretching vibrations of the −O−O− peroxide grouping.

Frequencies in the region of the vibrations of an SO_2 group are absent in the IR spectrum of aldehyde III, but there are other frequencies in the region of the vibrations of the SO group (1050 cm^{-1}); the SO vibrations therefore cannot be isolated. However, inasmuch as macrocyclic saturated sulfide VI is oxidized only to sulfoxide VII under the ozonolysis conditions, it can be supposed that the degree of oxidation of the sulfur atom is also the same in III. In addition, we showed by special experiments that under these same conditions thiophan is oxidized to the sulfoxide, but thiophan sulfone is not formed even at 20°.

Oxidation of III with hydrogen peroxide in the presence of sulfuric acid gives cis-2,5-di(γ-carboxypropyl)sulfolane (IV) in 85-90% yield. The IR spectra of acid IV and its dimethyl and p-bromophenacyl esters contain bands at 1120, 1290, and 1310 cm^{-1}, which are characteristic for the symmetrical and asymmetrical stretching vibrations of the SO_2 group. As seen, the oxidation of SO to SO_2 proceeds during the

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decomposition of the ozonolysis product. The conformation of the substituents follows from the fact that the addition of SCl_2 to cyclic dienes always proceeds with the formation of cis-disubstituted heterocycles [3].

Ozonation in formic acid promotes the more rapid oxidative decomposition of the hydroperoxide and an increase in the yield of IV to practically quantitative levels. The structure of intermediately-formed formoxyhydroperoxyaldehyde V follows from the IR spectra, the results of iodometric titration of the active oxygen, and a positive reaction with 2,4-dinitrophenylhydrazine.

The yield of acid IV falls on passing from acids to alcohols and then to inert solvents (chloroform, hexane). Judging from the IR spectra of the products of ozonolysis of II, a mixture of monomeric and polymeric ozonides, the yields of which are ~ 60 and 40%, respectively, is formed in inert solvents. An increase in the ozonolysis temperature in any of the solvents leads to a decrease in the yield of IV.

The oxidation of the ozonolysis products is accelerated considerably by the use of seleniun dioxide. Thus the oxidation of identical amounts of the intermediate with 30% hydrogen peroxide in acetic acid containing sulfuric acid usually proceeds in 30-50 h, as compared with 20-30 h at 60° in formic acid containing sulfuric acid, while oxidation with hydrogen peroxide in the presence of a catalytic amount of selenium dioxide takes 12-15 h at room temperature. The amount of hydrogen peroxide consumed is reduced considerably.

The acetolysis of I gives 2,9-diacetoxy-13-thiabicyclo[8.2.1]-cis-5-tridecene (VIII), the saponification of which gives diol IX. Ozonolysis of IX in acetic acid with subsequent oxidation in the presence of sulfuric acid gives 2,5-di(γ-butanolid-γ-yl)sulfolane (XI) in high yield (91%), the IR spectrum of which contains an absorption band at 1780 cm^{-1}, which is characteristic for the stretching vibrations of the carbonyl group in a five-membered lactone. The IR spectrum of intermediate X, in which absorption bands of an aldehyde group are absent, the negative reaction of X with 2,4-dinitrophenylhydrazine, and the considerably smaller amount of hydrogen peroxide required for the formation of XI as compared with the hydrogen peroxide consumption in the preparation of acid IV indicate that lactonization proceeds immediately after the formation of the aldehyde through intermediate hemiacetal X, bypassing the step involving the formation of the hydroxy acid.

Bislactone XI was also obtained in quantitative yield during milder oxidation by means of selenium dioxide without heating.

Lactone XI is also formed in the ozonolysis of diacetate VIII but in lower yield (50%). Reaction of the intermediate with 2,4-dinitrophenylhydrazine is also negative in this case. Hydrolysis of the intermediate at room temperature in water also gives bislactone XI. Lactone XI reacts very readily with ammonia in water to give 2,5-di(α-hydroxy-γ-amidoxypropyl)sulfolane (XII); its structure was confirmed by its IR spectrum, which contains two bands at 1615 and 1680 cm^{-1}, characteristic for a free $CONH_2$ group, and a doublet at 3500, 3400 cm^{-1}.

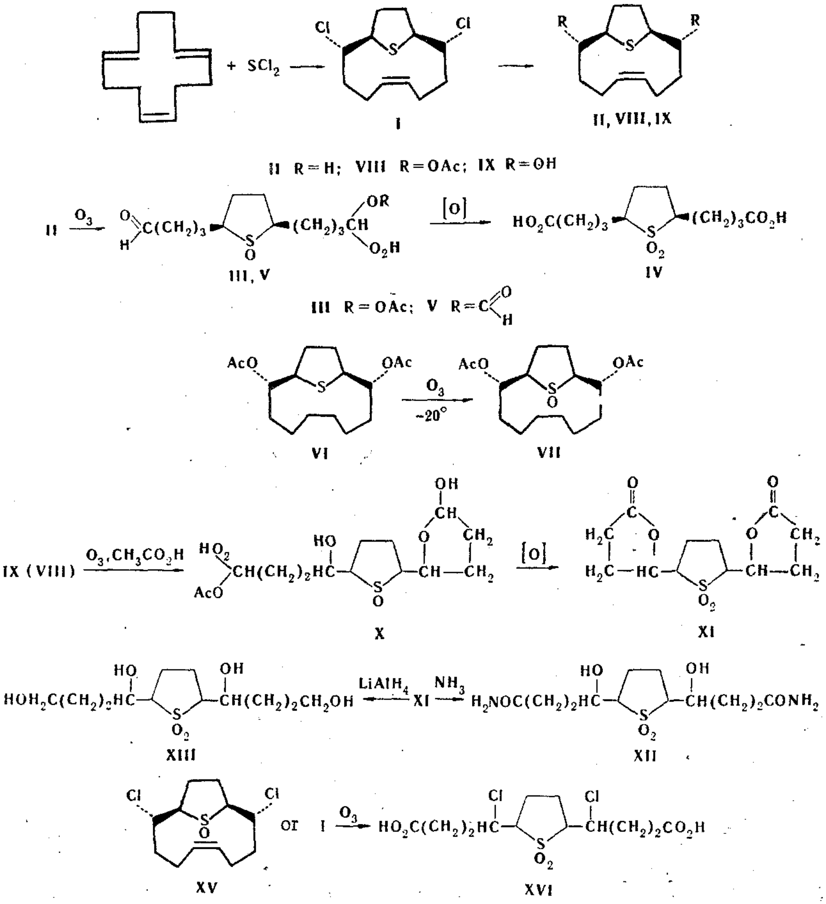
The reduction of lactone XI by $LiAlH_4$ in ether at 20° proceeds readily and gives, in high yield, 2,5-di(α,γ-dihydroxypropyl)sulfolane (XIII), which was characterized as the tetra(p-nitrobenzoate) (XIV).

The ozonation of dichloro sulfide I is complicated by side reactions as a consequence of the high lability of the chlorine atoms. Dichloro acid XVI therefore cannot be obtained in yields of more than 10-20%, but the yield can be raised to 30% in the ozonolysis of sulfoxide XV.

EXPERIMENTAL

The IR spectra of mineral oil suspensions, hexachlorobutadiene suspensions, liquid films, or CCl_4 solutions were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS487B spectrometer with an operating frequency of 80 MHz with hexamethyldisiloxane (HMDS) as the internal standard. Thin-layer chromatography (TLC) was carried out on activity III aluminum oxide.

2,9-Dichloro-13-thiabicyclo[8.2.1]-cis-5-tridecene (I). A solution of 35.8 g (0.34 mole) of SCl_2 in 200 ml of dry CH_2Cl_2 was added dropwise with stirring in the course of 5 h at −20° to a solution of 64.8 g (0.34 mole) of trans,trans,cis-cyclododeca-1,5,9-triene in 160 ml of dry CH_2Cl_2. The solvent was then removed by vacuum distillation, and the residue was washed on the filter with dimethylformamide (DMF) and ether. The solvents were evaporated, and the residue was worked up similarly to give 100 g (95%) of I with mp 128-129°. Found: C 54.1; H 6.8; Cl 27.0; S 12.0%. $C_{12}H_{18}Cl_2S$. Calculated: C 54.3; H 6.8; Cl 26.8; S 12.0%. IR spectrum, ν, cm^{-1}: 686 (C−Cl), 720 (cis-CH=CH). PMR spectrum, δ, ppm (in $CDCl_3$): 3.12 (2H, m Cl−C−H), 3.50 (2H, m S−C−H), 5.30 (2H, d, J=12 Hz, H−C), 1.87-2.07 (12H).



13-Thiabicyclo[8.2.1]-cis-5-tridecene (II). This compound was obtained in 85% yield by reduction of dichloride I with $LiAlH_4$ in ether and had bp 108-110° (2 mm) and n_D^{20} 1.5462. Found: C 73.7; H 10.5; S 15.5%. $C_{12}H_{20}S$. Calculated: C 73.4; H 10.2; S 16.1%.

2,9-Diacetoxy-13-thiabicyclo[8.2.1]-cis-5-tridecene (VIII). This compound was obtained in 80% yield by the action of sodium acetate on I in glacial acetic acid and had mp 143-144°. Found: C 61.4; H 7.8; S 10.5%. $C_{16}H_{24}O_4S$. Calculated: C 61.5; H 7.6; S 10.3%. IR spectrum, ν, cm^{-1}: 725 (cis-CH=CH), 1245, 1745 ($OCOCH_3$). PMR spectrum, δ, ppm (in CCl_4): 5.5 (–CH=CH–), 1.87 (s $OCOCH_3$).

2,9-Dihydroxy-13-thiabicyclo[8.2.1]-cis-5-tridecene (IX). This compound was obtained in 90% yield by saponification of VIII and had mp 176-178°. Found: C 63.1; H 9.0; S 14.0%. $C_{12}H_{20}O_2S$. Calculated: C 63.1; H 8.8; S 14.1%. IR spectrum, ν, cm^{-1}: 725 (cis-CH=CH–), 3300-3400 (OH).

cis-2,5-Di(γ-carboxypropyl)sulfolane (IV). A) Ozonized oxygen was passed through a solution of 2 g (0.01 mole) of II in 40 ml of glacial acetic acid and 60 ml of $CHCl_3$ at −20° until ozone began to appear in the outlet from the flask. The $CHCl_3$ was removed by vacuum distillation at 20°, 10 ml of 30% H_2O_2 and a drop of sulfuric acid were added, and the mixture was heated at 60° until the peroxide decomposed. The mixture was then vacuum evaporated to dryness at 40-50°, after which the oxidation was repeated until a crystalline residue had formed (30-50 h). This residue was crystallized from acetone to give a product with mp 164-165°. Found: C 52.9; H 7.7; S 9.9%. $C_{14}H_{24}O_6S$. Calculated: C 52.6; H 7.6; S 10.0%. IR spectrum, ν, cm^{-1}: 1120, 1290, 1310 (SO_2); 1713 (COOH).

B) A 2 g (0.01 mole) sample of II in a solution of 40 ml of formic acid and 15 ml of ethyl acetate was similarly ozonized. The ozonolysis product was oxidized as in method A (20-30 h, 10 ml of H_2O_2) to give 2.4 g (96%) of IV with mp 164-165° (from acetone).

C) A 2 g (0.01 mole) sample of II was ozonized under the conditions of method B. The ethyl acetate was removed by vacuum distillation, 3.5 ml of 30% H_2O_2 and 0.001 g of SeO_2 were added, and the mixture was allowed to stand overnight. It was then heated at 60-80° for 1-2 h to decompose the peroxide to give 2.5 g (98%) of IV with mp 165-165.5°.

Acetoxyhydroperoxyaldehyde III. A 2 g (0.01 mole) sample of II was ozonized under the conditions of method A. The solvents were removed by vacuum distillation at 0-20°, and the residue was dried thoroughly in vacuo to give 3 g of a hygroscopic oil. The material contained 4.8% active oxygen (the calculated value was 5.2%). The reaction with 2,4-dinitrophenylhydrazine was positive. IR spectrum, ν, cm^{-1}: 930 (−O−O−); 1260, 1760, 1015 ($OCOCH_3$); 1740, 2730 (−CHO).

Formyloxyhydroperoxyaldehyde V. This compound was similarly obtained under the conditions of method B. It contained 5.3% active oxygen (calculated value 5.4%). The reaction with 2,4-dinitrophenylhydrazine was positive. IR spectrum, ν, cm^{-1}: 930 (−O−O−); 1200, 1740 (OCOH); 1020 (−C−O−C−); 1780, 2730 (CHO).

2,5-Di(γ-butanolid-γ-yl)sulfolane (XI). A) A 2.3 g (0.01 mole) sample of IX was ozonized in 70 ml of glacial acetic acid and 100 ml of chloroform at −20°. The chloroform was then removed by vacuum distillation, 3.5-4 ml of H_2O_2 and a drop of sulfuric acid were added, and the mixture was heated at 60° until the peroxide had decomposed (10-15 h). When the oxidation was carried out with selenium dioxide, a catalytic amount of selenium dioxide was added to the residue after removal of the chloroform by distillation, and the mixture was allowed to stand at room temperature overnight. The residual peroxide was decomposed by heating at 60° for 1-2 h, after which the solvent was removed by evaporation, and the residue was crystallized from acetone to give 2.5 g (91%) of XI with mp 176-177°. Found: C 50.6; H 5.5; S 10.9%. $C_{12}H_{16}O_6S$. Calculated: C 50.4; H 5.6; S 11.2%. PMR spectrum (pyridine), δ, ppm: 3.5 (2H, S−C−H); 4.5 (2H, H−C−O−); 2.06 (m), 2.37 (m, 12H). IR spectrum, ν, cm^{-1}: 1100, 1300 (SO_2); 1780 (CO).

B) A 0.23 g (0.001 mole) sample of IX was ozonized in a mixture of 7 ml of acetic acid and 10 ml of chloroform. The solvents were then removed in vacuo, 10 ml of water was added to the residue, and the mixture was heated at 40-50° for 70 h. It was then cooled and filtered to give crystals with mp 169-172°. The IR spectrum was identical to the IR spectrum of sulfolane XI.

cis-2,5-Di(α-hydroxy-γ-amidoxypropyl)sulfolane (XII). Gaseous ammonia was bubbled at 15-20° through a saturated aqueous solution of 2 g (0.01 mole) of XI; after XI had disappeared on the thin-layer chromatogram [15-20 min, R_f 0.57, hexane−acetone (1 : 1)], ammonia was bubbled into the mixture for another 2 h. The resulting precipitate was removed by filtration and crystallized from alcohol to give XII with mp 158-160°. Found: C 45.1; H 7.2; N 8.5; S 9.8%. $C_{12}H_{22}N_2O_6S$. Calculated: C 44.8; H 6.8; N 8.7; S 9.9%. IR spectrum, ν, cm^{-1}: 1130, 1290 (SO_2); 1615, 1680 ($CONH_2$); 3200, 3300, 3420 (OH, $CONH_2$).

2,5-Di(α,γ-dihydroxypropyl)sulfolane (XIII). A solution of 1 g (3.4 mmole) of XI in 100 ml of dry tetrahydrofuran (THF) was added to a suspension of 0.34 g (0.009 mole) of $LiAlH_4$ in 20 ml of dry THF, after which the mixture was stirred for 15 min. It was then treated with moist THF and water, and the precipitate was removed by filtration and washed on the filter with water. The combined filtrates were evaporated, and the resulting orange oil was dried in vacuo. The salts were separated by dissolving the oil in dry acetone and filtering the solution. Workup gave 0.9 g of an oil. IR spectrum, ν, cm^{-1}: 1125, 1300 (SO_2); 3200-3445 (OH).

Treatment of the oil with p-nitrobenzoyl chloride gave tetra(p-nitrobenzoate) XIV with mp 204-205°. Found: C 53.6; H 3.8; N 6.2; S 3.7%. $C_{40}H_{32}N_4O_{18}S$. Calculated: C 54.1; H 3.6; N 6.3; S 3.6%. IR spectrum, ν, cm^{-1}: 1110, 1330 (SO_2); 1355, 1535 (NO_2); 1280, 1730 (OCOR); 1610 (Ph).

cis-2,5-Di(α-chloro-γ-carboxypropyl)sulfolane (XVI). This compound was obtained in 10-20% yield by ozonolysis of I by method B and in 30% yield via method B by ozonolysis of sulfoxide XV; the product had mp 147-150°. Found: C 39.9; H 4.9; Cl 22.0; S 9.0%. $C_{12}H_{18}Cl_2O_6S$. Calculated: C 39.9; H 5.0; Cl 19.6; S 8.9%. IR spectrum, ν, cm^{-1}: 1130, 1320 (SO_2); 1710 (COOH).

Dimethyl Ester of Acid IV. This compound was obtained by treatment of IV with diazomethane in ether and had bp 225° (2 mm) and n_D^{20} 1.4920. Found: C 52.5; H 7.6; S 10.0%. $C_{14}H_{24}O_6S$. Calculated: C 52.8; H 7.7; S 9.9%. IR spectrum, ν, cm^{-1}: 1120, 1280, 1285 (SO_2); 1210, 1740 ($OCOCH_3$). PMR spectrum, δ, ppm (CCl_4): 3.55 (OCH_3); 3.85 (2H, $HC-SO_2$); 1.6-2.6 (16H).

Dimethyl Ester of Acid XVI. This compound was similarly obtained from XVI and had n_D^{20} 1.5075. Found: C 36.0; H 5.6; Cl 18.3; S 8.2%. $C_{12}H_{22}Cl_2O_6S$. Calculated: C 36.9; H 5.6; Cl 17.3; S 8.3%. IR spectrum, ν, cm^{-1}: 1140, 1320 (SO_2); 1210, 1740 ($OCOCH_3$). PMR spectrum (CCl_4), δ, ppm: 3.55 (OCH_3), 3.5-4.0 (2H, $HC-SO_2$); 2.5-1.2 (16H).

p-Bromophenacyl Ester of Acid IV. This compound was obtained by the usual method and had mp 151-152°. Found: C 49.6; H 4.4; Br 22.2; S 4.7%. $C_{28}H_{39}Br_2O_8S$. Calculated: C 49.2; H 4.4; Br 23.4; S 4.7%. IR spectrum, ν, cm^{-1}: 1120, 1300 (SO_2); 1710 (COPh); 1745 (OCOR).

Sulfoxide XV was obtained by the method in [4] and had mp 138.5-140°. Found: C 51.2; H 6.5; Cl 25.8; S 10.9%. $C_{12}H_{18}Cl_2OS$. Calculated: C 51.2; H 6.4; Cl 25.0; S 11.4%. IR spectrum, ν, cm^{-1}: 680 (C–Cl); 720 (cis-C=C); 1045 (SO).

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