LITERATURE CITED

1. R. M. Carlson and S. J. Lee, Tetrahedron Lett., 55, 4001 (1969).
2. S. S. Symons, J. Org. Chem., 38, 414 (1973).
3. T. A. Foglia and D. Swern, J. Org. Chem., 33, 866 (1968).
4. T. A. Foglia and D. Swern, J. Org. Chem., 34, 1680 (1969).

SYNTHESIS AND STEREOCHEMISTRY OF 3-HYDROXY-4-ALKYLTHIOSULFOLANES

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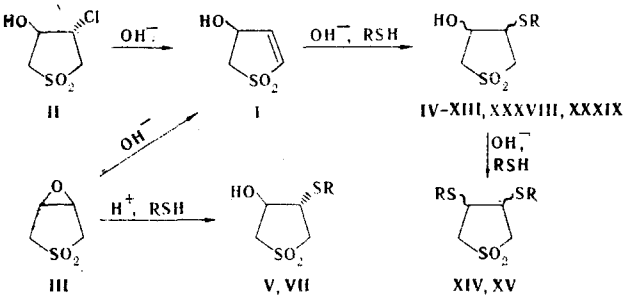
4-Hydroxy-2-sulfolene, 3-hydroxy-4-chlorosulfolane, and 3,4-epoxysulfolane react with thiols in alkaline media to give mixtures of cis,trans-3-hydroxy-4-alkylthisulfolanes in a ratio of 2:3.

In order to synthesize new 3,4-disubstituted sulfolanes, which are of interest both as biologically active compounds [1, 2] and as extractants for aromatic hydrocarbons [3], we carried out the reactions of 4-hydroxy-2-sulfolene (I), 3-hydroxy-4-chlorosulfolane (II), and 3,4-epoxysulfolane (III) with a number of thiols and studied the stereochemistry of these reactions.

The addition of thiols to sulfolene I proceeds readily and quantitatively in alkaline media [4]. Compounds II and III also react readily and quantitatively with thiols under the same conditions.



IV, V R = C_2H_5; VI, VII R = C_5H_{11}; VIII, IX, XIV, XV R = C_6H_{13}; X, XI R = $C_{10}H_{21}$; XII, XIII R = $C_{12}H_{25}$; XXXVIII, XXXIX R = CH_2CH_2OH

3-Hydroxy-4-alkylthiosulfolanes (Table 1) are formed as a result of the reaction. The ratio of the cis and trans isomers remains constant (2:3), regardless of the reaction time, the temperature, and the starting compound (I-III). This confirms the previously obtained data [5-7] that II and III are converted to sulfolene I in alkaline media. The explanation [8] of the formation of cis-3-hydroxy-4-RX-sulfolanes (X = O, S) from trans-2-hydroxy-4-chlorosulfolane by replacement of the chlorine atom is incorrect, since the inertness of the chlorine atom in the sulfolane ring has been confirmed by kinetic studies [9]. The inertness of chlorosulfolanes to nucleophilic substitution reactions [9, 10] is in contrast to the ease of elimination of HCl. Thus, for example, chlorohydrin II is readily titrated at room temperature [7].

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TABLE 1. Characteristics of the Compounds Obtained

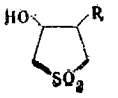
Compound	R^1	R^2	Isomer	mp, °C*	Found, %			Empirical formula	Calc., %			Yield, % (method)
					C	H	S		C	H	S	
IV, V	SC_2H_5	OH	Mixture	Oil	36,7	6,1	32,5	$C_6H_{12}O_3S_2$	36,7	6,1	32,7	96 (A—C)
V	SC_2H_5	OH	trans	Oil	36,6	6,1	32,4	$C_6H_{12}O_3S_2$	36,7	6,1	32,7	40 (D)
IV	SC_2H_5	OH	cis	Oil	36,6	6,1	32,5	$C_6H_{12}O_3S_2$	36,7	6,1	32,7	(E)
IV	SC_2H_5	OAc	cis	99—100	40,3	5,9	26,8	$C_8H_{14}O_4S_2$	40,3	5,9	26,9	98
XVII	SOC_2H_5	OH	trans	95—96	34,0	5,7	30,4	$C_6H_{12}O_4S_2$	34,0	5,7	30,2	95
XVI	SOC_2H_5	OH	cis	144—146	33,9	5,7	30,3	$C_6H_{12}O_4S_2$	34,0	5,7	30,2	95
XXVI, XXVII	$SO_2C_2H_5$	OH	Mixture	190—193	31,6	5,3	28,0	$C_6H_{12}O_5S_2$	31,6	5,3	28,1	90
XXVI	$SO_2C_2H_5$	OH	cis	145—146	31,6	5,3	28,2	$C_6H_{12}O_5S_2$	31,6	5,3	28,1	92
XXVI	$SO_2C_2H_5$	OAc	cis	156—157	35,4	5,3	23,7	$C_8H_{14}O_6S_2$	35,6	5,2	23,7	98
VI, VII	SC_5H_{11}	OH	Mixture	Oil	45,1	7,6	26,4	$C_9H_{18}O_3S_2$	45,3	7,6	26,9	92 (A—C)
VII	SC_5H_{11}	OH	trans	Oil	45,3	7,6	26,6	$C_9H_{18}O_3S_2$	45,3	7,6	26,9	40 (D)
XIX	SOC_5H_{11}	OH	trans	106—108	42,1	7,1	25,0	$C_9H_{18}O_4S_2$	42,2	7,1	25,2	90
XVIII	SOC_5H_{11}	OH	cis	Oil	42,4	7,2	25,4	$C_9H_{18}O_4S_2$	42,2	7,1	25,2	91
XXIX	$SO_2C_5H_{11}$	OH	trans	114—116	39,7	6,7	23,7	$C_9H_{18}O_5S_2$	39,9	6,7	23,7	90
XXVIII, XXIX	$SO_2C_5H_{11}$	OH	Mixture	113—116	39,8	6,7	23,5	$C_9H_{18}O_5S_2$	39,9	6,7	23,7	90
IX	SC_6H_{13}	OH	trans	Oil	47,2	7,9	25,4	$C_{10}H_{20}O_3S_2$	47,5	7,9	25,4	92 (A—C, F)
VIII	SC_6H_{13}	OH	cis	57—58	47,3	7,8	25,4	$C_{10}H_{20}O_3S_2$	47,5	7,9	25,4	96 (A—C, F)
XXI	SOC_6H_{13}	OH	trans	Oil	44,5	7,3	23,7	$C_{10}H_{20}O_4S_2$	44,7	7,4	23,8	89
XX	SOC_6H_{13}	OH	cis	108—110	44,6	7,3	23,5	$C_{10}H_{20}O_4S_2$	44,7	7,4	23,8	93
XXXI	$SO_2C_6H_{13}$	OH	trans	109—110	42,0	7,1	22,5	$C_{10}H_{20}O_5S_2$	42,2	7,0	22,3	90
XXX	$SO_2C_6H_{13}$	OH	cis	104—106	42,1	6,9	22,2	$C_{10}H_{20}O_5S_2$	42,2	7,0	22,3	91
X, XI	$SC_{10}H_{21}$	OH	Mixture	Oil	54,2	9,0	20,4	$C_{14}H_{28}O_3S_2$	54,5	9,1	20,8	93 (A,C)
XXII, XXIII	$SOC_{10}H_{21}$	OH	Mixture	89—90	51,3	8,6	19,3	$C_{14}H_{28}O_4S_2$	51,5	8,6	19,7	90
XXXII, XXXIII	$SO_2C_{10}H_{21}$	OH	Mixture	112—113	49,1	8,2	18,4	$C_{14}H_{28}O_5S_2$	49,3	8,2	18,8	92
XII, XIII	$SC_{12}H_{25}$	OH	Mixture	47—50	57,1	9,6	18,9	$C_{16}H_{32}O_2S_2$	57,1	9,5	19,1	98 (A,B)
XIIa, XIII	$SC_{12}H_{25}$	OAc	Mixture	50—52	57,1	9,1	17,0	$C_{18}H_{34}O_4S_2$	57,1	9,0	16,9	99
XXIV, XXV	$SOC_{12}H_{25}$	OH	Mixture	96—99	54,4	9,2	18,6	$C_{16}H_{32}O_3S_2$	54,6	9,1	18,2	92
XXXIV, XXXV	$SO_2C_{12}H_{25}$	OH	Mixture	110—113	51,9	8,8	17,5	$C_{16}H_{32}O_4S_2$	52,2	8,7	17,4	91
XIV	SC_6H_{13}	SC_6H	cis	55—56	54,5	9,2	27,0	$C_{16}H_{32}O_2S_3$	54,6	9,1	27,3	
XXXVII				Oil	33,4	5,2	35,4	$C_{10}H_{18}O_6S_4$	33,1	5,4	35,7	(A, B)
XXXVIII, XXXIX	SCH_2CH_2OH	OH	Mixture	Oil	33,8	5,8	30,5	$C_6H_{12}O_4S_2$	33,9	5,7	30,2	98 (A,B)
XLI	$SOCH_2CH_2OH$	OH	trans	94—96	31,7	5,4	28,0	$C_6H_{12}O_5S_2$	31,6	5,3	28,1	
XLII, XLIII	$SO_2CH_2CH_2OH$	OH	Mixture	Oil	29,0	4,7	25,9	$C_6H_{12}O_6S_2$	29,1	4,9	26,2	91

*The compounds were crystallized: IVa, VIII, XIIa, XIIIa, XIV, XVI, XVII, XXII-XXVII, XXVIa, XXXII-XXXV, and XLI from methanol, XII and XIII from acetone, and XIX, XX, and XXVIII-XXXI from benzene. Individual XVIII and XLI were isolated by crystallization of mixtures of the isomers. Liquid V, VII, IX-XI, XVIII, XXXVII-XXXIX, XLII, and XLIII decomposed during distillation.

The mixtures of isomers were analyzed quantitatively from the areas of the signals of the protons of the acetate groups in the spectra of the acetates of the hydroxy thioethers. It was first established that the protons of the OAc groups of the trans isomers resonate at stronger field than the corresponding protons of the cis isomers (Table 2). Individual compounds of the trans series were obtained from 3,4-epoxysulfolane (the catalyst was concentrated H_2SO_4) and also by separation of some mixtures by fractional crystallization or by preparative thin-layer chromatography (TLC). The assignment of the isomers to the cis or trans series was also confirmed by the data from the IR spectra. The position of the OH group (Table 2) of the hydroxy sulfides makes qualitative identification possible; this was previously noted for dihydroxy and hydroxy methoxy derivatives [7, 11]. The spectra of cis-3-hydroxy-4-alkylthiosulfolanes contain absorption bands of OH groups in the shorter-wave region (3400-3410 cm^{-1}) than the trans isomers (3450-3470 cm^{-1}). Both the cis- and trans-sulfoxides (XVI-XXV) readily form an SO···HO intramolecular hydrogen bond (IHB), and the position of this band is the same for both isomers (3210-3230 cm^{-1}). Evidence for the strength of the IHB is provided by the significant shift of the IHB band to the shortwave region, which is also confirmed by the significant shift of the band of the associated SO group (1008-1012 cm^{-1}) [12, 13].

Two types of IHB [11, 14], viz., OH···O_2S and OH···substituent heteroatom, are formed in dilute solutions in CCl_4 (c 10^{-4} mole/liter) of both cis- and trans-3-hydroxy-4-alkylthiosulfolanes. Primarily an OH···heteroatom IHB is characteristic for the cis isomers (e.g.,

TABLE 2. Spectral Characteristics of the Sulfolanes



Compound	R	Isomer	ν_{OH} (SO), cm^{-1}	δ, ppm ($CDCl_3$)	
				Ac	CHOAc
V, Va*	SC_2H_5	trans	3450—3470	2,08	5,32
VII, VIIa	SC_5H_{11}	trans	3450—3470	1,94	5,26
IX, IXa	SC_6H_{13}	trans	3460—3470	1,91	5,23
XIa	$SC_{10}H_{21}$	trans		1,88	5,21
XIII, XIIIa	$SC_{12}H_{25}$	trans	3480	1,87	5,21
IV, IVa	SC_2H_5	cis	3450—3470†	2,10	5,60
VIa	SC_5H_{11}	cis		1,98	5,60
VIII, VIIIa	SC_6H_{13}	cis	3410	1,94	5,58
Xa	$SC_{10}H_{21}$	cis		1,94	5,56
XII—XIIa	$SC_{12}H_{25}$	cis	3400	1,93	5,54
XVII	SOC_2H_5	trans	3210—3230 (1008)		
XVI	SOC_2H_5	cis	3210—3230 (1012)		
XIX	SOC_5H_{11}	trans	3210—3230 (1007)		
XX	SOC_6H_{13}	cis	3210—3230 (1011)		
XXIX, XXIXa	$SO_2C_5H_{11}$	trans	3455	2,13	5,70
XXVIII, XXVIIIa	$SO_2C_5H_{11}$	cis	3420	2,15	6,00

*The number with the letter "a" pertains to compounds that have an OAc group instead of an OH group.
†Compound IV is an oil, and it therefore gives a broad absorption band.

for IV the principal band of an associated OH group at 3497 cm^{-1}), whereas a band related to an IHB between OH and SO_2 appears at 3575 cm^{-1} in the spectrum of IV. On the other hand, primarily an $OH\cdots O_2S$ IHB is realized in the trans isomers e.g., 3525 cm^{-1} for V), whereas the band corresponding to an IHB between the substituents is a shoulder on the principal band (for V at 3560 cm^{-1}).

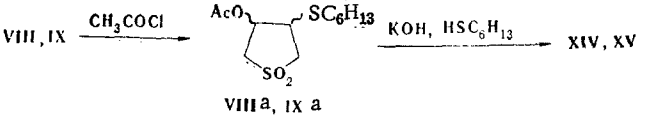
Thus, the assignment of the isomers by means of the IR spectra is in agreement with the assignment from the PMR spectra.

To establish the reaction time more precisely we carried out experiments involving the addition of thiols to sulfolene I. It was found that the latter reacts completely with thiols at room temperature almost instantaneously (according to TLC and PMR spectroscopy: the signals of the protons of the double bond vanish).

The use of excess thiol leads to the formation of isomeric dithioethers XIV and XV, which were separated from the hydroxy thioethers by means of preparative TLC and were also obtained by alternative synthesis.

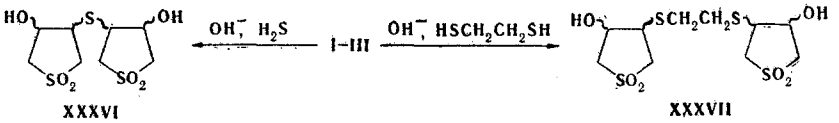
The pure monothioethers are obtained when the reaction is carried out in dioxane, alcohol, or water with an equimolar amount of the thiol.

The thioethers, which are obtained in high yields, are oxidized readily and selectively to sulfoxides (H_2O_2 in acetone) and sulfones (H_2O_2 and H_2SO_4) by the method in [15].



VIIIa, IXa

The addition of hydrogen sulfide and ethanedithiol to sulfolene I [4] and their reaction with sulfolanes II and III lead to sulfides XXXVI and XXXVII. It is characteristic that XXXVI cannot be obtained either by hydrolysis of the adduct of 3-sulfolene with SCl_2 [9] or by reaction of sulfolane II with Na_2S or thiourea. In the first two cases HCl is not split out, while in the latter case substitution does not take place even under severe conditions. According to the data in [8], sulfide XXXVI could not be obtained by the action of sodium hydrosulfide on sulfolene I.



XXXVI XXXVII

EXPERIMENTAL

The IR spectra of thin layers or mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of $CDCl_3$ solutions were recorded with a BS-487B spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The course of the reaction was followed by means of thin-layer chromatography (TLC) on activity II Al_2O_3 [elution with benzene–ethanol (9:1)].

Acetylation was carried out with acetyl chloride at 20°C by the method in [7].

Typical Methods for the Preparation of 3-Hydroxy-4-alkylthiosulfolanes. A) A solution of 30 mmole of sulfolene I in 20 ml of dioxane was added gradually to a solution of 30 mmole of the thiol and 4 mmole of KOH in 100 ml of aqueous dioxane (1:1), and the mixture was stirred at 20°C for 10-15 min. It was then neutralized with hydrochloric acid and evaporated to dryness, and the residue was extracted with acetone. The acetone was evaporated to give the product.

B) A solution of 33 mmole of KOH in 10 ml of H_2O was added dropwise at 40°C to a solution of 30 mmole of sulfolane II [7] and 30 mmole of the thiol in 100 ml of aqueous dioxane (1:1) at such a rate that the medium remained constantly weakly alkaline (pH < 7.5). The reaction was monitored from the color of an indicator [a mixture of a 0.1% solution of methylene red and a 0.2% solution of methylene blue (1:1), transition pH 7] added to the reaction medium. The mixture was stirred for 10-15 min and worked up as in method A.

C) A solution of 20 mmole of epoxysulfolane III [16], 20 mmole of the thiol, and 2 mmole of KOH in 50 ml of aqueous dioxane (1:1) was stirred at 20°C for 3 h and worked up as in method A.

D) A mixture of 20 mmole of epoxysulfolane III, 200 mmole of the thiol, and 1 ml of concentrated H_2SO_4 was heated at 160-170°C for 5-6 h, after which it was diluted with water, neutralized, and worked up as in method A.

E) A mixture of isomeric 3-hydroxy-4-alkylthiosulfolanes was treated with CH_3COCl by the method in [7]. Crystallization from methanol gave cis-3-acetoxy-4-(1-alkylthio)sulfolane. Hydrolysis of the acetate with 10% hydrochloric acid gave the individual hydroxy sulfide.

F) Isomeric mixtures of the hydroxy sulfides were allowed to stand, during which they underwent partial crystallization. The individual cis- and trans-3-hydroxy-4-(1-alkylthio)-sulfolanes were obtained after repeated separation of the crystalline portions by freezing out and filtration.

cis,trans-3,4-Di(1-hexylthio)sulfolanes (XIV, XV). A mixture of hydroxy thioethers VIII and IX was treated with acetyl chloride by the method in [7], and the mixture was worked up to give a mixture of cis,trans-3-acetoxy-4-(1-hexylthio)sulfolanes (VIIIa, IXa). A solution of 17 mmole of KOH in 10 ml of H_2O was added gradually at 20°C to a solution of 15 mmole of a mixture of VIIIa and IXa and 30 mmole of hexanethiol in 80 ml of aqueous dioxane, and the resulting solution was stirred for 1 h. It was then neutralized and evaporated to dryness, and the residue was extracted with acetone. The acetone was evaporated, and the residue was crystallized from methanol to give crystalline dithioether XIV.

Bis(3-hydroxysulfolan-4-yl) Sulfide (XXXVI). A) A solution of 220 mmole of sulfolene I in 700 ml of ethanol was saturated with hydrogen sulfide, 22 mmole of KOH in 20 ml of H_2O was added, and hydrogen sulfide was passed into the mixture for 2 h. The mixture was then worked up in the usual way. The residue contained 80% sulfide XXXVI in the form of a vitreous mass. IR spectrum: 1135, 1295, 1315 (SO_2), 3450-3480 cm^{-1} (OH). PMR spectrum (C_5D_5N), δ: 3.25-4.12 (m, $CH_2SO_2CH_2$, CHSCH) and 4.53-5.00 ppm (m, CHOH). Found: C 31.4 H 4.8 S 31.2%. $C_8H_{14}O_6S_3$. Calculated: C 31.8; H 4.6; S 31.8%. PMR spectrum of the diacetate ($CDCl_3$), δ: 1.94 (s, CH_3) and 2.03 ppm (s, CH_3). The ratio of the areas of the signals of the protons of the acetate groups of the trans and cis isomers was 3:2. Found: C 36.8; H 4.7; S 24.5%. $C_{12}H_{18}O_8S_3$. Calculated: C 37.3; H 4.7; S 24.9%.

B) Hydrogen sulfide was passed through a solution of 50 mmole of sulfolane II in 100 ml of water at 40°C with the simultaneous dropwise addition of 55.4 ml of 1 N aqueous KOH, after which the mixture was stirred at 20°C for 3-4 h and worked up as in method A to give sulfide XXXVI in 96% yield.

LITERATURE CITED

1. G. A. Tolstikov, N. N. Novitskaya, B. V. Flekhter, D. N. Lazareva, V. A. Davydova, and É. G. Kamalova, Khim.-Farm. Zh., No. 12, 33 (1978).
2. É. G. Kamalova, V. A. Davydova, D. N. Lazareva, G. A. Tolstikov, N. N. Novitskaya, and B. V. Flekhter, Farmakol. Toksikol., 42, 261 (1979).
3. N. N. Novitskaya, R. Kh. Khazipov, A. Z. Bikullov, B. V. Flekhter, and G. A. Tolstikov, USSR Inventor's Certificate No. 535308 (1976); Byul. Izobr., No. 42, 62 (1976).
4. G. A. Tolstikov, G. P. Gladyshev, N. N. Novitskaya, S. I. Lomakina, and L. E. Zhuravleva, USSR Inventor's Certificate No. 322327 (1971); Byul. Izobr., No. 36, 35 (1971).
5. B. V. Flekhter, N. N. Novitskaya, and G. A. Tolstikov, Summaries of Papers Presented at the Third All-Union Conference on Stereochemistry and Conformational Analysis in Organic and Petrochemical Synthesis [in Russian], Baku–Sumgait (1976), p. 96.
6. N. N. Novitskaya, B. V. Flekhter, and G. A. Tolstikov, Summaries of Papers Presented at the Fourteenth Scientific Session on the Chemistry and Technology of Organic Sulfur Compounds and Sulfurous Petroleum Oils [in Russian], Batumi (1976), p. 171.
7. N. N. Novitskaya, B. V. Flekhter, and G. A. Tolstikov, Khim. Geterotsikl. Soedin., No. 8, 1051 (1977).
8. T. É. Bezmenova, Author's Abstract of Doctoral Dissertation, Kiev (1977), p. 22.
9. S. N. Lewis and W. D. Emmons, J. Org. Chem., 31, 3572 (1966).
10. V. I. Dronov and V. A. Snegotskaya, Khim. Geterotsikl. Soedin., No. 3, 5 (1971).
11. B. V. Flekhter, N. N. Novitskaya, E. E. Zaev, L. V. Spirikhin, I. M. Dubrovkin, and G. A. Tolstikov, Summaries of Papers Presented at the Third All-Union Conference on Stereochemistry and Conformational Analysis in Organic and Petrochemical Synthesis [in Russian], Baku–Sumgait (1976), p. 82.
12. T. M. Ivanova, L. I. Denisova, and V. A. Batyanina, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 435 (1971).
13. E. V. Konovalov, Yu. P. Egorov, R. V. Belinskaya, V. N. Baiko, and L. M. Yagupol'skii, Zh. Prikl. Spektrosk., 14, 487 (1972).
14. B. V. Flekhter and I. M. Dubrovkin, Summaries of Papers Presented at the Conference of Young Scientists [in Russian], Ufa (1975), p. 20.
15. N. N. Novitskaya and S. I. Chernikova, Neftekhimiya, 10, 429 (1970).
16. W. Dittmann and F. Sturzenhofecker, Ann., 699, 177 (1966).