REACTIONS OF AZIRINES WITH SULFUR NUCLEOPHILES.

2.* REACTIONS OF 2H-AZIRINE WITH β,γ-DIHYDROXY THIOLS AND β-DITHIOLS. A NEW ROUTE TO THE SYNTHESIS OF CYCLIC SULFIDES

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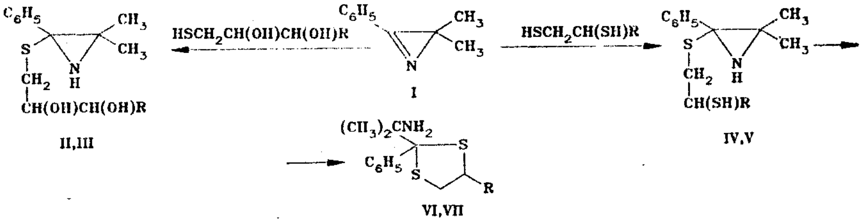
UDC 547.717'279.12:543.422.25

The reaction of 2H-azirine with a number of dihydroxy thiols and dithiols leads to aziridin-2-yl alkyl sulfides. The latter readily isomerize to cyclic sulfides the size of the ring of which is determined by the length of the alkyl sulfide chain.

Previously unknown aziridinyl alkyl sulfides have been obtained by the reaction of 2,2-dimethyl-3-phenylazirine (I) with β-functionally-substituted ethanethiols [1]. In view of the high reactivity of the C═N bond in the 2H-azirines in relation to sulfur-containing nucleophiles, it appeared of interest to continue investigations of the reactions of the azirine (I) with functionally substituted thiols in the β,γ-dihydroxy thiol and β-dithiol series. We have investigated the reactions of the azirine (I) with 2,3-dihydroxypropane-1-thiol, with 2,3-dihydroxybutane-1,4-dithiol, with ethane-1,2-thiol, and with 3-hydroxypropane-1,2-dithiol.

The reaction of the azirine (I) with β,γ-dihydroxy thiols formed the corresponding azirinyl alkyl sulfides (II) and (III) in a similar manner to the reaction of the azirine (I) with β-hydroxyethanethiol [1]:



II, IV, VI R=H; III R=CH_2SH; V, VII R=CH_2OH

The presence in the ^1H NMR spectra of compounds (II) and (III) of nonequivalent resonance signals at the gem-methyl groups at 0.89 and 1.65 ppm indicated a cyclic structure and confirmed the formation of aziridinyl alkyl sulfides in the reaction of the azirine (I) with β,γ-dihydroxy thiols.

At the same time, the properties of the products of the reactions of the azirine (I) with β-dithiols differed strongly from those of the expected corresponding aziridinyl alkyl sulfides. Thus, in the ^{13}C NMR spectra (Table 1) of compounds (VI) and (VII), obtained by the reaction of the azirine (I) with ethane-1,2-dithiol and with 3-hydroxypropane-1,2-dithiol, respectively, the singlet of a quaternary carbon atom in a C—S bond was observed at 83.2 ppm but there were no signals of quaternary carbon atoms at 44 and 55 ppm corresponding to the aziridine ring [1]. In their ^1H NMR spectra (Table 2), there were multiplets of the nonequivalent protons of the methylene group of a β-dithiol (2.9-3.3 ppm), which shows the cyclic structure of compounds (VI) and (VII). In view of the combination of spectral and analytical results, we came to the conclusion that the reaction of the azirine (I) with

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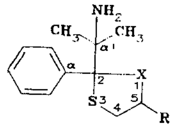
*For Communication 1, see [1].

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 623-627, May, 1985. Original article submitted June 4, 1984.

TABLE 1. ^{13}C Chemical Shifts of the Cyclic Sulfides (VIa), (VII), (VIIa), (IX), and (IXa)



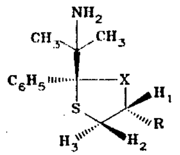
Compound	X	R	Solvent	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(\alpha')}$	CH_3	arom. C.	C_R
VIa	S	H	D_2O	83,2	41,0	41,0	62,4	25,4	142,0 (C_α); 131,2 (C_o); 129,5 (C_p); 128,8 (C_m)	—
VII	S	CH_2OH	DMSO-d_6	88,0	39,3	56,3	56,0	28,3; 28,0	143,7 (C_α); 129,6 (C_o); 126,4 (C_m & C_p)	62,9
VIIa	S	CH_2OH	D_2O	83,2	40,8	57,9	61,6	25,9; 25,5	141,3 (C_α); 129,8 (C_p); 131,5 (C_o); 128,9 (C_m)	63,9
IX	O	H	$CDCl_3$	107,3	34,0	71,2	56,4	26,9; 25,3	143,1 (C_α); 127,7 (C_o); 127,2 (C_m & C_p)	—
IXa	O	H	D_2O	103,2	34,5	72,6	61,4	24,6; 22,1	140,4 (C_α); 129,7 (C_p); 129,0 (C_o); 128,8 (C_m)	—

β-dithiols had formed the substituted 1,3-dithiolanes (VI) and (VII). It must be mentioned that in the ^1H and ^{13}C NMR spectra of the dithiolanes (VI) and (VII) the ^1H and ^{13}C chemical shifts are extremely close to those for 2,2-disubstituted 1,3-dithiolanes [2-4]. An analysis of the SSCCs between the protons in the ring permitted the assumption that the conformation of the compounds obtained were characteristic for 2-substituted 1,3-dithiolanes. The dihedral torsional angle between the $S(_3)-C(_4)-C(_5)$ and $C(_4)-C(_5)-S(_1)$ planes in compounds (VI) and (VII) calculated by the "R factor" method [5] is 50 ± 1°, which agrees well with the literature [2]. We obtained the 2-(1-amino-1-methylethyl)-1,3-dithiolanes (VI) and (VII) in the form of both the free bases and their hydrochlorides (VIa) and (VIIa) in order to compare the parameters of the ^1H and ^{13}C NMR spectra. However, the parameters of the NMR spectra of the 2-(1-amino-1-methylethyl)-1,3-dithiolanes scarcely changed when the nitrogen atom was protonated, i.e., the dihedral angle between the $S(_3)-C_{(4)}-C(_5)$ and $C(_4)-C(_5)-S(_1)$ planes did not change either (Tables 1 and 2).

Analysis of the ^1H and ^{13}C NMR spectra of the 1,3-dithiolane (VII) permitted the conclusion that it existed in the form of a single isomer in which the 5-hydroxymethyl group was apparently oriented pseudoequatorially.

The formation of substituted 1,3-dithiolanes in the reactions of the azirine (I) with β-dithiols can be represented as the result of intramolecular cyclization of the aziridinyl alkyl sulfides (IV) and (V) probably formed initially, accompanied by the cleavage of the 1,2-bond of the aziridine ring. We have confirmed this hypothesis experimentally. In actual fact, when the reaction mixture was analyzed 3 h after the beginning of the reaction of the azidirine (I) with ethane-1,2-dithiol, we established the presence in it of the aziridinyl alkyl sulfide (IV) and the 1,3-dithiolane (VI) in a ratio of 1:3, according to the results of the ^1H NMR spectrum. The vibrational spectrum of the mixture contained the bands of the vibrations of primary and secondary amino groups (3200, 3290, and 3370 cm^{-1}), and in the ^1H NMR spectrum, in addition to the signals of the nonequivalent gem-methyl groups of the aziridinyl alkyl sulfide (IV) (0.89 and 1.66 ppm), the signals of gem-methyl groups belonging to the 1,3-dithiolane (VI) were observed (1.21 and 1.24 ppm). The reaction of the azirine (I) with 3-hydroxypropane-1,2-dithiol took place similarly, with the formation, after 1.5 h, of a mixture of the aziridinyl alkyl sulfide (V) and the 1,3-dithiolane (VII) in a ratio of 2:3, according to the ^1H NMR spectra. An increase in the reaction time of the azirine (I) with β-dithiols to 24 h led to the formation of the corresponding 1,3-dithiolanes (VI) and (VII), alone. Consequently, the cyclic sulfides (VI) and (VII) were formed as the result of an intramolecular cyclization of the aziridinyl alkyl sulfides (IV) and (V), apparently as a consequence of the heterolytic opening of the aziridine ring by the sulfhydryl group of the alkyl chain. Under conditions preventing the heterolysis of the aziridine ring — for example, in the presence of bases — the reaction of the azirine (I) with 3-hydroxypropane-1,2-dithiol gave only the corresponding aziridinyl alkyl sulfide (V). In actual fact, when the above-described reaction of the azirine (I) with 2,3-dihydroxybutane-1,4-dithiol was carried out in the presence

TABLE 2. Parameters of the ^1H NMR Spectra of the Sulfides (VI), (VIa), (VII), (VIIa), (IX), and (IXa)



Compound	Solvent	Chemical shifts, δ, ppm							J, Hz			
		H_1	H_2	H_3	H_R	C_6H_5	CH_3	NH	1—2	1—3	2—3	Other
VI	$CDCl_3$	3,33	3,15	3,33	3,15	7,82 (H_o); 7,2—7,6 (H_m & H_p)	1,22; 1,25	2,4	5,1	6,7	−11,3	—
VIa	D_2O	3,34	3,13	3,34	3,13	7,68 (H_o); 7,1—7,2 (H_m & H_p)	2,10	—	4,9	6,9	−11,7	—
VII	DMSO-d_6	3,68	2,90	3,35	3,73; 3,55	7,90 (H_o); 7,2—7,3 (H_m & H_p)	1,15; 1,17	2,0; 4,9 (OH)	4,8	2,9	−12,0	−8,8 ($^2J_{OCH_2}$); 8,8 & 2,9 ($^3J_{CHCH_2O}$)
VIIa	D_2O	3,88	3,07	3,35	3,83; 3,69	7,98 (H_o); 7,4—7,5 (H_m & H_p)	1,39; 1,41	—	5,0	3,8	−12,6	−10,3 ($^2J_{OCH_2}$); 7,2 & 5,2 ($^3J_{CHCH_2O}$)
IX	$CDCl_3$	4,47	3,04	3,00	3,75	7,5—7,3	1,10; 1,14	2,4	5,7	2,0	−10,0	−9,0 (H_1—H_R); 10,5 (H_2—H_R); 5,8 (H_3—H_R)
IXa	DMSO-d_6	4,61	3,00	3,07	3,75	7,5—7,3	1,27; 1,44	8,2	6,1	1,3	−9,8	−9,0 (H_1—H_R); 10,0 (H_2—H_R); 5,2 (H_3—H_R)

TABLE 3. Physicochemical Characteristics of the Sulfides (II) and (III), (V-VII), and (IXa)

Compounds	mp*, °C	IR spectrum, ν, cm^{-1}	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
II	18—19	3210—3400	61,4	7,4	5,3	12,4	$C_{13}H_{19}NO_2S$	61,7	7,5	5,5	12,6	67
III	55—57	3220—3430	56,1	6,9	4,4	21,2	$C_{14}H_{21}NO_2S_2$	56,2	7,0	4,7	21,4	48
V	Viscous oil	3190—3380	57,8	7,1	5,0	23,5	$C_{13}H_{19}NOS_2$	58,0	7,1	5,2	23,8	59,5
VI	28—30	3280, 3370	60,1	6,8	5,6	26,6	$C_{12}H_{17}NS_2$	60,2	7,1	5,8	26,8	74
VII	115—117	3270, 3400	57,9	6,8	5,1	23,6	$C_{13}H_{19}NOS_2$	58,0	7,1	5,2	23,8	83
IXa	218—219	1490, 1570, 1600, 2580	55,3	6,7	5,1	12,1	$C_{12}H_{17}NOS \cdot HCl$	55,5	6,9	5,4	12,3	81

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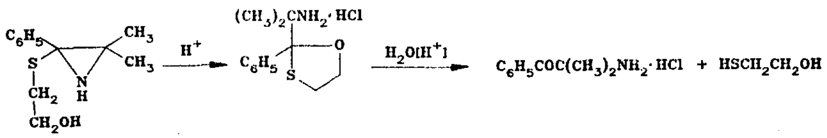
*The mp of compound (VIa) was 212-214°C; of (VIIa) 215-217°C; and of (IX) 31-32°C.

of sodium ethanolate, the yield of the aziridinyl alkyl sulfide (III) rose to 62% as compared with 47-48% without the use of a base.

There are also grounds for assuming that the corresponding cyclic sulfides analogous to (VI) and (VII) can be obtained under certain conditions in the reactions of the azirine (I) with β,γ-dihydroxy thiols.

In light of the results obtained, it appeared of interest to investigate the chemical behavior of the previously synthesized aziridinyl 2-hydroxyethyl sulfide (VIII) [1] under the conditions of the heterolytic cleavage of the aziridine ring. It was assumed that if the rearrangement of aziridinyl alkyl sulfides under these conditions had a general nature, it could be extended to the series of aziridinyl alkyl sulfides having functional substituents of nucleophilic nature in the β- or γ-positions in relation to the sulfide group. In actual fact, when a solution of the sulfide (VIII) in acetone was kept in the presence of an acid for 20 h, the 2,2-disubstituted 1,3-oxathiolane (IXa) was formed almost quantitatively:



VIII

IXa

The structure of compound (IX) and its hydrochloride (IXa) was confirmed by spectroscopy and by mass spectrometry. The ^1H and ^{13}C chemical shifts of compounds (IX) and (IXa) (Tables 1 and 2) were extremely close to those for the other 2,2-disubstituted 1,3-oxathiolanes [6-8]. We confirmed structures of the 1,3-oxathiolanes (IX) and (IXa) by their acid hydrolysis, which have α-aminoisobutyrophenone and the initial β-hydroxyethanethiol, and the physicochemical and chromatographic characteristics of which corresponded to those of authentic samples [1].

Thus the reactions of the azirine (I) with β-hydroxy thiols and β-dithiols form a new method for the synthesis of cyclic sulfides that is probably most effective in the case of β- or γ-substituted thiols, since the stability of the rings decreases with an increase in their size.

EXPERIMENTAL

The melting points of the substances obtained were determined on a micro heated stage in the Boëtius system. IR spectra were obtained on a Perkin-Elmer 580-B spectrophotometer (in Nujol), and ^1H NMR spectra on Bruker WH-90 and Bruker WH-360 spectrometers using 5% solutions (with TMS as internal standard). ^{13}C NMR spectra were taken on the Bruker WH-90 spectrometer at 22.63 MHz; the chemical shifts were measured relative to TMS. Mass spectra were recorded on a MS-905 spectrometer (70 eV).

The physicochemical characteristics of compounds (II), (III), (V-VII), and (IXa), are given in Table 3.

2,3-Dihydroxypropyl 3,3-Dimethyl-2-phenylaziridin-2-yl Sulfide (II). A solution of 4.74 g (0.03 mole) of the azirine (I) [9] in 30 ml of ethyl acetate was treated with 3.24 g (0.03

mole) of 2,3-dihydroxypropane-1-thiol. The mixture was stirred at 70°C for 3 h, and then the ethyl acetate was distilled off and the residue was recrystallized from chloroform. Yield 5.1 g (67%). PMR spectrum ($CDCl_3$), ppm: 7.33 (5 H, s, C_6H_5); 3.76 (1 H, m, CH); 3.51 (2 H, m, 3-CH_2); 2.89 (3 H, s, 2 OH and NH); 2.51 (2 H, m, 1-CH_2); 1.64 and 0.93 (3 H and 3 H, s, CH_3).

2,3-Dihydroxy-4-mercaptobutyl 3,3-dimethyl-2-phenylaziridin-2-yl sulfide (III) was obtained similarly, but it was recrystallized from a mixture of diethyl ether and petroleum ether (1:2). PMR spectrum ($CDCl_3$), ppm: 7.31 (5 H, s, C_6H_5); 3.55 (5 H, m, 2-CH, 3-CH, 2 OH, and NH); 2.98 (2 H, m, 1-CH_2); 2.44 (2 H and 1 H, m, 4-CH_2 and SH); 1.63 and 0.89 (3 H and 3 H, s, CH_3).

3,3-Dimethyl-2-phenylaziridin-2-yl 3-Hydroxy-2-mercaptopropyl Sulfide (V). A solution of 4.74 g (0.03 mole) of the azirine (I) in 30 ml of ethanol was treated with 3.72 g (0.03 mole) of 3-hydroxypropane-1,2-dithiol and 86 ml of a 4% solution of sodium methanolate in ethanol. The mixture was stirred at 20°C for 1 h, the ethanol was distilled off, and the residue was extracted with 50 ml of ether. The extract was evaporated and the residue was washed with 20 ml of petroleum ether and was crystallized from a mixture of ether and hexane (1:1). Yield 4.8 g (60%). PMR spectrum ($CDCl_3$), ppm: 7.35 (5 H, m, C_6H_5); 3.64 (2 H, m, 3-CH_2); 2.75 (6 H, m, CH, 1-CH_2, OH, NH, and SH); 1.64 and 0.91 (3 H and 3H, s, CH_3).

2-(1-Amino-1-methylethyl)-2-phenyl-1,3-dithiolane (VI). A mixture of 4.74 g (0.03 mole) of the azirine (I) and 2.83 g (0.03 mole) of ethane-1,2-dithiol was kept in a sealed tube at 70°C for 20 h, and the product was then washed twice with 20 ml of petroleum ether and crystallized from a mixture of diethyl ether and petroleum ether (1:1). Yield 5.3 g (74%).

2-(1-Amino-1-methylethyl)-5-hydroxymethyl-2-phenyl-1,3-dithiolane (VII). A solution of 4.74 g (0.03 mole) of the azirine (I) in 30 ml of ethanol was treated with 3.72 g (0.03 mole) of 3-hydroxypropane-1,2-diol. The mixture was stirred at 70°C for 22 h, and then the ethanol was distilled off. The residue was washed with 50 ml of petroleum ether and was dissolved in 30 ml of diethyl ether; on standing the solution deposited a precipitate. Yield 6.7 g (83%).

2-(1-Amino-1-methylethyl)-2-phenyl-1,3-oxathiolane Hydrochloride (IXa). A solution of 0.86 ml of concentrated HCl in 5 ml of ethanol was added dropwise to a solution of 2.23 g (0.01 mole) of 3,3-dimethyl-2-phenylaziridin-2-yl 2-hydroxyethyl sulfide (VIII) [1] in 30 ml of acetone. The mixture was heated at 70°C for 3 h and the resulting precipitate was filtered off and recrystallized from ethanol—ether (1:3). Yield 2.1 g (81%). $M^+ - HCl$: 223.

LITERATURE CITED

1. R. S. El'kinson, A. V. Eremeev, A. F. Mishnev, Ya. Ya. Bleidelis, and V. G. Semenikhina, Khim. Geterotsikl. Soedin., No. 1, 53 (1985).
2. L. A. Sternson, D. A. Coviello, and R. S. Egan, J. Am. Chem. Soc., 93, 6529 (1971).
3. K. Pihlaja, M. Eskonmaa, R. Keskinen, A. Nikkila, and T. Nurmi, Org. Magn. Reson., 17, 246 (1981).
4. Z. Kortylewicz and B. Burczyk, Pol. J. Chem., 56, 791 (1982).
5. H. R. Buys, Rec. Trav. Chim., 88, 1003 (1982).
6. G. E. Wilson, M. G. Huang, and F. A. Bovey, J. Am. Chem. Soc., 92, 5907 (1970).
7. D. E. Pasto, F. M. Klein, and T. W. Doyle, J. Am. Chem,, 89, 4368 (1967).
8. G. W. Gokel, H. M. Gerdes, and D. M. Dishong, J. Org. Chem., 45, 3634 (1980).
9. R. F. Parcell, Chem. Ind. (London), 33, 1396 (1963).