12. N. S. Smirnova, S. K. Klimenko, M. N. Berezhnaya, T. V. Stolbova, and V. G. Kharchenko, Zh. Org. Khim., 11, 440 (1975).

REACTIONS OF AZIRINES WITH SULFUR NUCLEOPHILES.

4.* TREATMENT OF 2H-AZIRINE WITH MERCAPTOSUBSTITUTED ACIDS. REACTIONS OF AZIRIDINYL ALKYL SULFIDES WITH CARBOXYLIC ACIDS AND ACYL CHLORIDE DERIVATIVES

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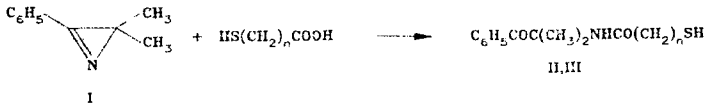
UDC 547.717'279.104

Treatment of 2H-azirines with mercaptosubstituted acids and their derivatives leads to β-ketoamides and 2-aziridinyl alkyl sulfides, respectively. 2-Aziridinyl alkyl sulfides, in turn, react with carboxylic acids to give β-ketoamides and substituted ethanethiol derivatives. Acylation of 2-aziridinyl alkyl sulfides with acyl halides generates a variety of products, depending on the reaction conditions; either products derived from cleavage and isomerization of the aziridinyl ring or (1-acylaziridinyl-2) alkyl sulfides are obtained.

Electrophilic addition of carboxylic acids to the C=N bond of 2H-azirines gives the corresponding β-ketoamides as a result of isomerization and 1,2-cleavage of the aziridine ring in the initially formed 2-acyloxyaziridine derivatives [2]. At the same time, 2,2-dimethyl-3-phenylazirine (I) reacts with β-substituted ethanethiols to give a new type of functional aziridine derivative, namely, aziridinyl alkyl sulfides [3].

It was of interest to us to study the reactions of azirine (I) with mercaptosubstituted acids, i.e., bifunctional reagents which should be capable of entering into both nucleophilic and electrophilic addition reactions to C=N bond of azirine (I). We have found that reaction of azirine I with mercaptoacetic and mercaptopropionic acids occurs at the carboxyl group to generate the corresponding α-(mercaptoacylamino)isobutyrophenones II and III:



I

II n = 1; III n = 2

The formation of products II and III from the reactions of azirine I with mercaptosubstituted acids should be anticipated based on a comparison of the ionization constants of these acids (pK_a 3.68; 10.40 and 4.32; 10.47, respectively) with those of unsubstituted carboxylic acids, which are known to react with 2H-azirines to give the corresponding β-ketoamides.

In cases where protonation of azirine ring and subsequent nucleophilic addition of a carboxylate anion are impossible, such as, for instance, during esterification or salt formation, the mercapto group of the carboxylic acid is the only reactive site, and as a result, nucleophilic addition of the mercapto group to the C=N bond of azirine I occurs, and the corresponding aziridinyl alkyl sulfides are formed, in analogy with the results reported in [3]. For instance, treatment of azirine I with the ethyl ester of mercaptoacetic acid for the sodium salts of N-acetylcysteine or cysteine yields the aziridinyl alkyl sulfides IV-VI as the only reaction products (Table 1):

*For communication 3, see [1].

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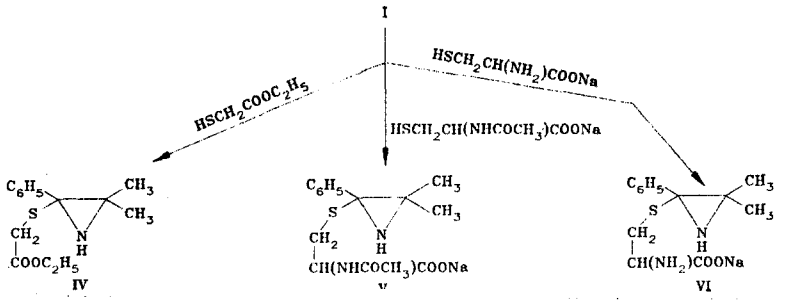
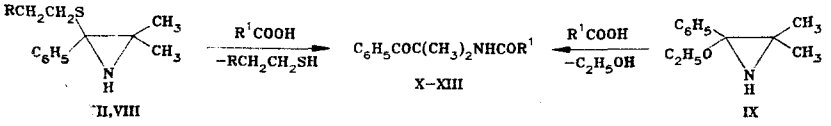
TABLE 1. Physical Chemical Properties of Sulfides IV-VI, XV-XVII, XIX, and XXI

Compound	mp, (bp), °C	IR spectrum, cm^{-1}	Found, %				Molecular formula	Calculated, %				Yield, %
			C	H	N	S(Cl)		C	H	N	S(Cl)	
IV	[68—69 (2,6 hPa)]	1080, 1260, 1730, 3280	63,3	7,2	5,0	11,8	$C_{14}H_{19}NO_2S$	63,4	7,2	5,3	12,1	72
V	178—180	1410, 1560, 1650, 1690, 3250, 3300	54,3	5,6	8,7	9,4	$C_{15}H_{19}NaN_2O_3S$	54,5	5,8	8,5	9,7	57
VI	120—121	1600, 3200, 3260, 3350	54,1	5,7	9,9	10,9	$C_{13}H_{17}NaN_2O_2S$	54,2	5,9	9,7	11,1	51
XV	46—48	1640, 3300	63,1	7,1	5,5	11,9	$C_{14}H_{19}NO_2S$	63,4	7,2	5,3	12,1	61
XVI	119—120	1650, 3350	69,6	6,1	4,5	9,6	$C_{19}H_{21}NO_2S$	69,7	6,4	4,3	9,8	58
XVII	15—18	900, 980, 1430, 1650, 3330	65,2	6,6	5,3	11,3	$C_{15}H_{19}NO_2S$	65,0	6,9	5,1	11,6	37
XIX	37—39	1050, 1250, 1640, 1720	62,4	6,5	4,4	10,1	$C_{16}H_{21}NO_3S$	62,5	6,8	4,5	10,4	45
XXI	183—185	825, 1540, 1650, 2110, 2210, 3300	49,6	6,3	8,4	9,3 (20,9)	$C_{14}H_{21}ClN_2OS \cdot HCl$	49,9	6,5	8,3	9,5 (21,1)	64



The aziridinyl alkyl sulfides were of considerable research interest, inasmuch as their structural characteristics, namely, the presence of both aziridinyl and sulfide functional groups, would seem to imply a wide spectrum of chemical reactivity, encompassing the chemistry of the aziridine ring as well as that of sulfides. We have therefore studied the reactivity of these sulfides in reactions involving both retention and cleavage of the aziridine ring, which are characteristic of aziridines. It is known, for example, that heterolytic cleavage of the aziridine ring occurs upon treatment with organic acids to give the corresponding 2-acyloxyethylamines [4]. However, our experiments concerning the reactions of 2-hydroxyethyl- and 2-dimethylaminoethylaziridinyl sulfides VII and VIII [3] with either saturated or unsaturated carboxylic acids unexpectedly revealed some unusual product structures. Instead of generating the expected 2-acyloxyethylamines, treatment of sulfides VII and VIII with carboxylic acids led to the formation of the corresponding β-ketoamides X-XIII and a substituted ethanethiol derivative (Tables 2 and 3). 2-Alkoxyaziridines react in a similar manner to aziridinyl alkyl sulfides with carboxylic acids. For instance, treatment of 2-ethoxy-3,3-dimethyl-2-phenylaziridine (IX) [5] with carboxylic acids gave the same β-ketoamides as prepared above, and the compounds X-XIII were identical with respect to all physical chemical and spectral characteristics with these compounds. It should be noted, however, that the reactions of aziridine IX with carboxylic acids require both longer reaction times (6 h) and higher reaction temperatures (80°C) than the analogous reactions of sulfides VII and VIII (3 h, 50 °C):



VII R = OH; VIII R = $N(CH_3)_2$; X R^1 = C_6H_5; XI R^1 = $C_6H_5CH=CH$; R^1 = $C_6H_5C{-}C$; XIII R^1 = $CH_2=CH$

We cannot exclude the possibility that these reactions occur via intermediate 2-acyloxyethylamines, since the rearrangement of 2-acyloxyethylamines to 2-hydroxyethylamides is known [6]. One observation supporting this assumption is the fact that reaction of aziridine IX with carboxylic acids requires harsher conditions than the analogous reactions of aziridinyl alkyl sulfides; the sulfide group is, of course, a better leaving group than an alkoxy group.

It is known that acylation of aziridines with acyl halides to give N-acylaziridines occurs only in the case of acceptor acids [7]. Treatment of the aziridinyl alkyl sulfides VII

TABLE 2. Physicochemical Properties of β-Ketoamides X-XIII

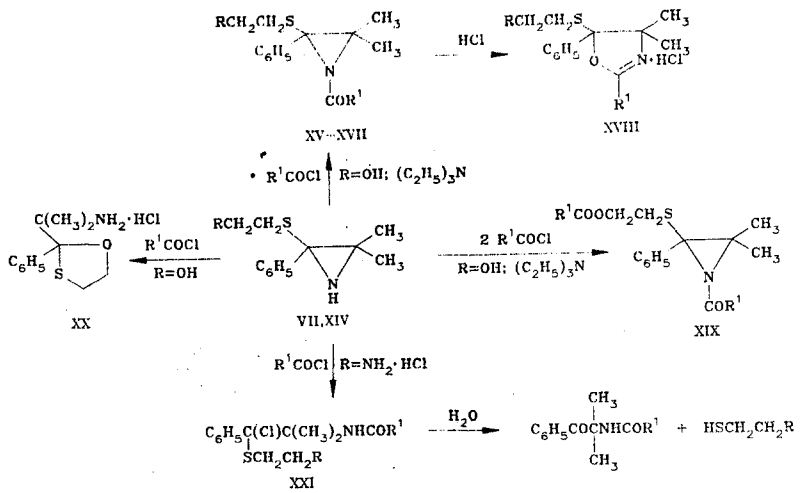
Compound	mp, °C	R_f ether	IR spectrum, cm^{-1}	Found, %			Molecular formula	Calc. %			Yield, %
				C	H	N		C	H	N	
X	153—155	0,71	1535, 1635, 1690, 3080, 3250	76,2	6,3	5,4	$C_{17}H_{17}NO_2$	76,4	6,4	5,2	78
XI	218—220	0,59	1540, 1620, 1655, 1680, 3280	77,7	6,3	4,9	$C_{19}H_{19}NO_2$	77,8	6,5	4,8	56
XII	118—120	0,75	1530, 1620, 1660, 1685, 2210, 3210, 3315	78,1	5,6	4,7	$C_{19}H_{17}NO_2$	78,4	5,8	4,8	78
XIII	158—160	0,44	1530, 1620, 1655, 1680, 3290, 3310	71,7	6,6	6,3	$C_{13}H_{15}NO_2$	71,9	6,9	6,4	53

TABLE 3. PMR Spectral Parameters of β-Ketoamides X-XII ($CDCl_3$)

Compound	δ, ppm			
	C_6H_5	CH_3	NH	H_{R^1} (J, Hz)
X	7,91 (H_o); 7,11—7,33 (H_m and H_p)	1,72	—*	7,58 (H_o), 7,11—7,33 (H_m and H_p)*
XI	7,93 (H_o); 7,4 (H_m and H_p)	1,78	6,56	7,4 (C_6H_5); 6,25 and 6,51 (CH=CH, 16)
XII	7,89 (H_o)†; 7,11—7,58 (H_m and H_p)†	1,71	7,02	7,11—7,58 (C_6H_5)†
XIII	7,91 (H_o); 7,42 (H_m and H_p)	1,76	6,67	5,58 (CH; 5,4; 6,6), 6,0 and 5,21 (=CH_2; 14,1; 5,4; 6,6)

*Multiplet, including both the aromatic ring proton signals and the NH group signal.
†Multiplet consisting of all of the aromatic ring proton signals.

and XIV [3] with acyl halides in the presence of triethylamine readily gave the corresponding N-acylaziridinyl alkyl sulfides XV-XVII (Tables 1 and 4):



VII R = OH; XIV R = $NH_2 \cdot HCl$, R^1 = CH_3, C_6H_5, CH_2 = CH

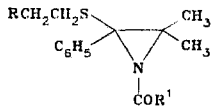
The rearrangement of N-acylaziridines in the presence of acid to give ring-enlarged products, namely, 2-oxazolines [8] is characteristic of N-acylaziridines; we have demonstrated this reaction using sulfide XV, which gave the hydrochloride salt of 2,4,4-trimethyl-5-phenyl-5-(2-hydroxyethylthio)-2-oxazoline XVIII.

When 1 mole of the aziridinyl alkyl sulfide VII was treated with 2 moles of acylating agent in the presence of base, the hydroxy group of the sulfide also underwent acylation, and the corresponding (1-acylaziridinyl-2-)-2-acylhydroxyethyl sulfide XIX was obtained.

In the absence of base the N-acylaziridines generated in these reactions undergo further conversions involving ring opening and formation of β-halosubstituted N-acylethylamines [9]. Our experiments have shown, however, that, depending on the nature of the substituent in the β-position to the sulfide group, a variety of products can be obtained from the reactions of the aziridinyl alkyl sulfides VII and XIV with acyl halides in the absence of base. For instance, treatment of sulfide VII with acetyl chloride in the absence of base gave an almost quantitative yield of a substituted 1,3-oxathiolane, which was isolated in the form of its hydrochloride salt XX [10]. Apparently, hydrogen chloride, which is generated in the beginning of the reaction, induces heterolytic cleavage of the aziridine ring, which leads to intramolecular rearrangement of sulfide VII to the 1,3-oxathiolane ring system, as has been demonstrated previously [10].

In contrast, workup of the hydrochloride salt of 2-aminoethyl aziridinyl sulfide XIV with acetyl chloride under analogous reaction conditions generates the sulfide XXI; the structure of the latter was verified by spectroscopic analysis, as well as by hydrolysis to give the known compounds [11] α-(acetylamino)isobutyrophenone and 2-aminoethanethiol hydrochloride.

TABLE 4. PMR Spectral Parameters of Sulfides XV-XVII, XIX ($CDCl_3$)



Compound	R	R′	δ, ppm					
			C_6H_5	CH_3	CH_2—S	CH_2—R	H_R	$H_{R'}$ (J, Hz)
XV	OH	CH_3	7,49 (H_o); 7,29 (H_m and H_p)	0,62 and 1,56	2,44	3,49	2,88	2,02
XVI	OH	C_6H_5	7,99 (H_o); 7,29—7,56 (H_m and H_p)*	0,78 and 1,73	2,58	3,56	2,13	7,62 (H_o); 7,29—7.56 (H_m and H_p)*
XVII	OH	CH_2=CH	7,33 (H_o); 7,56 (H_m and H_p)	0,71 and 1,64	2,51	3,40	2,51	5,78 (CH; 3,44; 8,1); 6,17 and 6,35 (=CH_2; 18,1; 8,1; 3,44)
XIX	CH_3COO	CH_3	7,92 (H_o); 7,48 (H_m and H_p)	0,76 and 1,77	3,06	4,44	2,18	2,03

*Multiplet corresponding to all of the protons of the aromatic ring.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 580B spectrophotometer using thin films. PMR spectra were obtained on a Bruker WH-90 spectrometer using 5% solutions and TMS as internal standard. Melting points of the compounds prepared in this paper were determined on a Boethius microheating apparatus.

2-(Mercaptoacetylamino)-2-methyl-1-phenylpropanone (II). A solution of 2.61 g (18 mmole) of azirine I [5] in 20 ml of acetone was treated dropwise with 1.66 g (18 mmole) of mercaptoacetic acid. The mixture was stirred 15 h at 70°C and the acetone was evaporated. The residue was recrystallized from 1:3 chloroform—hexane. Yield 2 g (47%), mp 183-185°C; R_f 0.18 (Silufol UV-254, ether). IR spectrum (nujol): 1550, 1645, 1690 (amide bands, C=O), 2500-2680 (SH), 3330 cm^{-1} (NH). PMR spectrum (DMSO-D_6): 8.57 (1H, s, NH), 7.92 (2H, m, H_o), 7.46 (3H, m, H_m, and H_p), 3.21 (2H, s, CH_2). 1.46 ppm (6H, s, CH_3). Found: C 60.4; H 6.0; N 5.7; S 13.4%. $C_{12}H_{15}NO_2S$. Calculated: C 60.7; H 6.3; N 5.9; S 13.5%.

2-(3-Mercaptopropionylamino)-2-methyl-1-phenyl-1-propanone (III). This was prepared in an analogous manner; mp 118-120°C. IR spectrum (nujol): 1545, 1650, 1685 (amide I and II bands, C=O), 2530-2600 (SH), 3300 cm^{-1} (NH). PMR spectrum (DMSO-D_6): 8.77 (1H, s, NH), 7.90 (2H, m, H_o), 7.46 (3H, m, H_m, and H_p), 2.89 (2H, m, 2-CH_2), 2.62 (3H, m, 3-CH_2 and SH), 1.46 ppm (6H, s, CH_3). Found: C 61.9; H 6.7; N 5.3; S 12.5%. $C_{13}H_{17}NO_2S$. Calculated: C 62.2; H 6.8; N 5.6; S 12.7%.

Ethyl (3,3-Dimethyl-2-phenylaziridinyl-2-thio)acetate (IV). A solution of 2.9 g (20 mmole) of azirine I in 10 ml of ethanol was treated dropwise with a solution of 2.5 g (20 mmole) of ethyl mercaptoacetate in 10 ml of ethanol. The reaction mixture was stirred 12 h at 50°C, the alcohol was evaporated, and the residue was distilled. Yield 3.8 g (72%); bp 68-69°C (2.6 hPa). PMR spectrum ($CDCl_3$): 7.94 (2H, m, H_o), 7.39 (3H, m, H_m and H_p), 4.21 (2H, q, O—CH_2), 3.58 (3H, s, S—CH_2 and NH), 1.29 (3H, t, CH_3), 0.89 and 1.69 ppm (3H and 3H, s, CH_3).

Sodium 2-Acetylamino-3-(3,3-dimethyl-2-phenylaziridinyl-2-thio)propanoate (V). This was prepared in a similar manner and was purified by washing twice with 20 ml of acetone. PMR spectrum (D_2O): 7.34 (5H, 2, C_6H_5), 4.33 (1H, t, J = 5 Hz, CH), 2.89 (2H, d, J = 5 Hz, CH_2), 2.03 (3H, s, CH_3CO), 0.87 and 1.59 ppm (3H and 3H, s, CH_3).

Sodium 2-Amino-3-(3,3-dimethyl-2-phenylaziridinyl-2-thio)propanoate (VI). This compound was also prepared analogously to the manner described for compound (IV) and was purified by recrystallization from a 1:3 chloroform—hexane mixture. PMR spectrum ($CDCl_3$): 7.22 (5H, m, C_6H_5), 3.26-2.71 (6H, m, S—CH_2, CH, NH_2 and NH), 0.83 and 1.53 ppm (3H and 3H, s, CH_3).

The physicochemical properties of compounds IV-VI are recorded in Table 1.

2-Benzoylamino-2-methyl-1-phenyl-1-propanone (X; Tables 2 and 3). A solution of 0.7 g (3 mmole) of sulfide VII or VIII [3] in 30 ml of acetone was treated dropwise with a solution of 0.37 g (3 mmole) of benzoic acid in 10 ml of acetone. The mixture was stirred 3 h at 50°C and the acetone was evaporated. The residue was recrystallized from 1:3 ethanol–ether. Yield 0.62 g (77.5%); mp 153-155°C.

Compounds XI-XIII were prepared in a similar manner (Tables 2 and 3).

1-(Acetyl-3,3-dimethyl-2-phenylaziridinyl-2)2- (hydroxyethyl) Sulfide (XV; Tables 1 and 4). A solution of 0.75 g (3.3 mmole) of sulfide VII and 0.34 g (3.3 mmole) of triethylamine in 20 ml of dry tetrahydrofuran was treated dropwise with a solution of 0.27 g (3.3 mmole) of acetyl chloride in 10 ml of dry tetrahydrofuran. The mixture was stirred 3 h at 20°C and the triethylammonium chloride precipitate was removed by filtration. The filtrate was concentrated and the residue was recrystallized from 1:3 ether–petroleum ether. Yield 0.53 g (60.9%); mp 46-48°C.

Sulfides XVI and XVII were obtained analogously (the latter was purified by recrystallization from hexane).

2,4,4-Trimethyl-5-phenyl-5-(2-hydroxyethylthio)-2-oxazoline Hydrochloride (XVIII). A solution of 0.53 g (3 mmoles) of sulfide XV in 10 ml of acetone was treated dropwise with a solution of 0.11 ml of concentrated hydrochloric acid in 5 ml of ethanol. The mixture was stirred 3 h at 20°C and the solvent was evaporated. The residue was recrystallized from 1:3 acetone–ether. Yield 0.76 g (84.4%); mp 118-120°C. IR spectrum (nujol): 1660 ($C{=}N^+$), 1810 (imine salt band), 2420 (ammonium band), 3300 cm^{-1} (OH). PMR spectrum (DMSO-D_6): 8.08 (2H, br s, NH^+ and OH), 7.46 (5H, m, C_6H_5), 3.33 (2H, t, $O{-}CH_2$), 2.39 (5H, m, $S{-}CH_2$ and 2-CH_3), 0.78 and 1.64 ppm (3H and 3H, s, 4.4-CH_3). Found: C 55.5; H 6.4; N 4.3; S 10.8%. $C_{14}H_{19}NO_2S \cdot HCl$. Calculated: C 55.7; H 6.6; N 4.6; S 10.6%.

(1-Acetyl-3,3-dimethyl-2-phenylaziridinyl-2) 2-Acetoxyethyl Sulfide (XIX). This compound was prepared similarly to compound XV. See Tables 1 and 4.

Hydrochloride Salt of (1-Chloro-2-acetylamino-2-methyl-1-phenylpropyl) 2-Aminoethyl Sulfide (XXI; Table 1). A solution of 0.52 g (2 mmole) of sulfide XIV [3] in 20 ml of ethanol was treated dropwise with a solution of 0.24 g (3 mmole) of acetyl chloride in 10 ml of ethanol. The mixture was stirred 10 h at 20°C, the alcohol was evaporated, and the residue was recrystallized from 1:3 alcohol–ether. Yield 0.43 g (64%); mp 183-185°C. PMR spectrum (DMSO-D_6): 9.77 (1H, br s, NH), 8.94 (3H, br s, NH_3^+), 7.96 (2H, m, H_o), 7.55 (3H, m, H_m and H_p), 3.56 (2H, t, $N{-}CH_2$), 3.29 (2H, t, $S{-}CH_2$), 2.03 (3H, s, CH_3CO), 1.76 ppm (6H, s, CH_3).

LITERATURE CITED

1. R. S. Él'kinson, A. V. Eremeev, Ya. Ya. Bleidelis, A. F. Mishnev, and S. V. Belyakov, Khim. Geterotsikl. Soedin., No. 12, 1633 (1985).
2. A. V. Eremeev and R. S. Él'kinson, Khim. Geterotsikl. Soedin., No. 6, 736 (1984).
3. R. S. Él'kinson, A. V. Eremeev, A. F. Mishnev, Ya. Ya. Bleidelis, and V. G. Semenikhina, Khim. Geterotsikl. Soedin., No. 1, 53 (1985).
4. J. Yukawa and S. Kimura, Patent No. 4,973 (Japan); Chem. Abst., 58, 1032 (1963).
5. R. F. Parcell, Chem. Ind., 33, 1396 (1963).
6. O. C. Dermer and G. E. Ham, Ethyleneimine and Other Aziridines, Academic Press, New York (1969).
7. H. C. Brown and A. Tsukamoto, J. Am. Chem. Soc., 83, 2016 (1961).
8. H. W. Heine, M. E. Fetter, and E. M. Nicholson, J. Am. Chem. Soc., 81, 2202 (1959).
9. H. Bestian, Ann., 566, 210 (1950).
10. R. S. Él'kinson, A. V. Eremeev, and É. É. Liepin'sh, Khim. Geterotsikl. Soedin., No. 5, 623 (1985).
11. A. Hassner, S. S. Burke, and I. Cheng-fan, J. Am. Chem. Soc., 97, 4692 (1975).