

12.* REACTION OF 1-(CARBOMETHOXYALKYL)AZIRIDINES
WITH THIOLS AND MERCAPTO ACIDS

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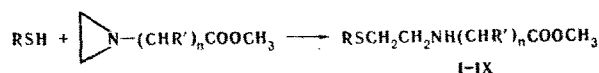
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The reaction of 1-(carbomethoxyalkyl)aziridines with thiols and mercapto acids, which leads to the formation of the corresponding sulfides and esters of S-substituted N-(2-mercaptoethyl)amino acids, was studied. The acid hydrolysis of o-[(N-carbomethoxyethyl)-2-aminoethylthio]benzoic acid and o-[(N-cyanoethyl)-2-aminoethylthio]benzoic acid leads to o-[N-(carboxyethyl)-2-aminoethylthio]benzoic acid hydrochloride. The cyclization of 1-[(N-carbomethoxyethyl)-2-aminoethylthio]benzoic acid in the presence of PCl₃ gives 5-oxo-4-(carbomethoxyethyl)-6,7-benzoperhydro-1,4-thiazepine.

2-Aminoethyl mercaptan derivatives are currently under extensive investigation as anti-radiation agents, antidotes, and substances with curarelike activity. Compounds that contain a 2-aminoethyl fragment have antibacterial, fungicidal, and herbicidal activity [2-4].

In order to obtain new types of physiologically active compounds we studied the reaction of 1-(carbomethoxyalkyl)aziridines with aliphatic and aromatic thiols, as well as with some mercapto acids.

1-(Carbomethoxyalkyl)aziridines react with thiols and mercapto acids with opening of the aziridine ring to give sulfides I-IX.



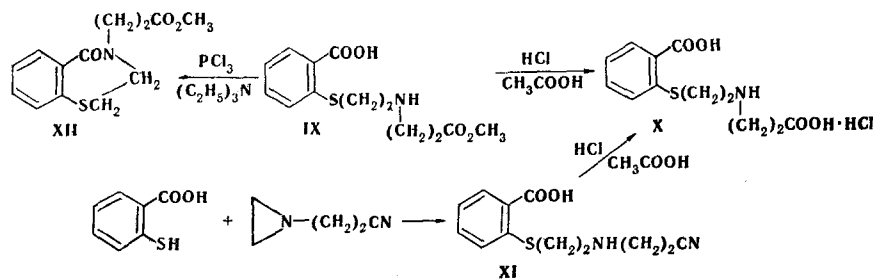
I R=CH₃, R'=H, n=2; II R=n-C₃H₇, R'=H, n=2; III R=n-C₄H₉, R'=H, n=2;
IV R=CH₂CH=CH₂, R'=H, n=1; V R=CH₂CH=CH₂, R'=H, n=2; VI R=C₆H₅, R'=H, n=2;
VII R=HOOCCH₂, R'=H, n=2; VIII R=o-C₆H₄COOH, R'=CH₃, n=1; IX R=o-C₆H₄COOH, R'=H, n=2

The reaction of 1-(carbomethoxyalkyl)aziridines with thiols takes place when mixtures of them are heated at 100-150°C for 8-10 h. The yields of sulfides I-VI range from 60 to 70%.

One might have expected that upon reaction with 1-(carbomethoxyalkyl)aziridines mercapto acids would react with opening of the aziridine ring through both the mercapto group via the scheme presented above and through the carboxy group to give 2-acyloxyethylamine derivatives [5-7]. It has been shown previously that aziridine reacts with thioglycolic and mercapto-benzoic acids to give mercaptoethylamine derivatives [8, 9]. The reaction of 1-(carbomethoxyalkyl)aziridines with mercapto acids that we investigated proceeds with the formation of [(N-carbomethoxyalkyl)-2-aminoethylthio]-substituted carboxylic acids (VII-IX) in 55-88% yields. The structure of amino acids VII-IX is proved by the fact that the acid hydrolysis of o-[(N-carbomethoxyethyl)-2-aminoethylthio]benzoic acid (IX) and o-[(N-cyanoethyl)-2-aminoethylthio]benzoic acid (XI) leads to the same hydrochloride X. o-[(N-cyanoethyl)-2-aminoethylthio]benzoic acid (XI) was obtained by the reaction of o-mercaptobenzoic acid with 1-(cyanoethyl)aziridine in 85% yield. Intramolecular cyclization of acid IX in the presence of PCl₃ leads to the formation of 5-oxo-4-(carbomethoxyethyl)-6,7-benzoperhydro-1,4-thiazepine (XII) in 70% yield.

*See [1] for communication 11.

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Absorption bands of ester and amino groups at 1732-1750 and 3315-3330 cm^{-1} , respectively, are present in the IR spectra of I-VI. The spectra of VII-IX and XI contain absorption bands of an NH_2^+ group at 3070, 1645, and 1550 cm^{-1} . The ionized carboxy group absorbs at 1570-1575 and 1365-1370 cm^{-1} . The absorption bands of aromatic CH and C=C bonds in the spectra of VIII, IX, and XI are found at 3030 and 1590 cm^{-1} . The ester group of VII-IX absorbs at 1740-1745 cm^{-1} , while the nitrile group of XI absorbs at 2260 cm^{-1} . Two absorption bands of a carboxy group (1720 and 1750 cm^{-1}) and a number of continuous absorption bands at 2500-3030 cm^{-1} are observed in the spectrum of hydrochloride X. The frequencies of the vibrations of the amide and ester groups of XII are found at 1660 and 1735 cm^{-1} , respectively.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 (I-VI) and CF_3COOH (IX) were recorded with a Tesla BS-487C spectrometer (80 MHz).

Methyl N-[2-(Methylthio)ethyl]-3-aminopropionate (I, Tables 1 and 2). A mixture of 10.8 g (0.08 mole) of 1-(carbomethoxyethyl)aziridine and 4.8 g (0.1 mole) of methanethiol was heated in a sealed ampul at 150°C for 10 h, after which it was distilled *in vacuo* to give 10.2 g (65%) of I. Compounds II-VI (Tables 1 and 2) were similarly obtained.

TABLE 1. S-Substituted N-(2-Mercaptoethyl)amino Acid Esters I-IX

Compound	bp, °C (mm)	n_D^{20}	Found, %				Empirical formula	Calc., %				Yield, %
			C	H	N	S		C	H	N	S	
I	120-123 (7)	1,4791	47,3	8,4	7,9	17,6	$\text{C}_7\text{H}_{15}\text{NO}_2\text{S}$	47,5	8,5	7,9	18,0	65
II	135-136 (3)	1,4825	—	—	7,0	15,1	$\text{C}_9\text{H}_{19}\text{NO}_2\text{S}$	52,7	9,3	6,8	15,6	65
III	152-153 (6)	1,4881	—	—	6,2	14,7	$\text{C}_{10}\text{H}_{21}\text{NO}_2\text{S}$	54,8	9,6	6,4	14,6	67
IV	119-120 (7)	1,5071	50,3	7,8	7,2	16,5	$\text{C}_8\text{H}_{15}\text{NO}_2\text{S}$	50,7	7,9	7,4	16,9	69
V	124-126 (3)	1,4920	53,6	8,3	6,2	15,7	$\text{C}_9\text{H}_{17}\text{NO}_2\text{S}$	53,2	8,3	6,8	15,8	70
VI	167-168 (3)	1,5450	59,6	7,1	5,4	12,8	$\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$	60,2	7,2	5,8	13,4	60
VII	— ^a	—	—	—	6,3	14,3	$\text{C}_8\text{H}_{15}\text{NO}_4\text{S}$	43,4	6,8	6,3	14,5	55
VIII	135-136 ^b	—	54,9	6,0	4,4	11,4	$\text{C}_{13}\text{H}_{17}\text{NO}_4\text{S}$	55,1	6,0	5,0	11,2	80
IX	200-201 ^b	—	55,0	6,6	5,3	11,3	$\text{C}_{13}\text{H}_{17}\text{NO}_4\text{S}$	55,1	6,0	5,0	11,2	88

^aOil. ^bThis is the melting point.

TABLE 2. Parameters of the PMR Spectra of $\text{RSCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{COOCH}_3$

Compound	R	δ , ppm			
		NH	NCH_2 , SCH_2 (m)	COOCH_3 (s)	SR
I	CH_3	1,55 (s)	2,43	3,62	2,05 (s)
II	$n\text{-C}_3\text{H}_7$	1,78 (s)	2,43	3,62	1,46 (m), 0,89 (t)
III	$n\text{-C}_4\text{H}_9$	2,10 (s)	2,43	3,61	1,57 (m), 0,97 (t)
V	$\text{CH}_2=\text{CHCH}_2$	1,55 (s)	2,43	3,60	5,66 (s), 5,06 (m)
VI	C_6H_5	1,45 (s)	2,43	3,58	7,23 (m)
IX	$o\text{-C}_6\text{H}_4\text{COOH}$	+ NH_2 7,80 (m)	3,10	3,45	7,23-7,69 (m)

o-[N-(Carbomethoxyethyl)-2-aminoethylthio]benzoic Acid (IX, Tables 1 and 2). A solution of 1.29 g (0.01 mole) of 1-(carbomethoxyethyl)aziridine in 5 ml of methanol was added with stirring to a solution of 1.54 g (0.01 mole) of o-mercaptobenzoic acid in 20 ml of methanol, after which the mixture was stirred at room temperature for 1 h. The resulting precipitate was recrystallized from 80% ethanol to give 2.8 g (88%) of the product. Compounds VII and VIII (Table 1) were similarly obtained.

o-[N-(Carboxyethyl)-2-aminoethylthio]benzoic Acid Hydrochloride (X). A 0.01-mole sample of IX or XI was dissolved in 30 ml of acetic acid, 7 ml of concentrated HCl was added, and the mixture was heated at 100°C for 2 h. The solvent was evaporated at reduced pressure, and the residue was recrystallized from methanol to give a product with mp 213-214°C in 90-92% yield. Found: Cl 11.4; S 11.3%. $C_{12}H_{15}NO_4S \cdot HCl$. Calculated: Cl 11.4; S 10.5%.

o-[N-(Cyanoethyl)-2-aminoethylthio]benzoic Acid (XI). This compound was obtained from 5.6 g (0.036 mole) of o-mercaptobenzoic acid and 3.5 g (0.036 mole) of 1-(cyanoethyl)-aziridine by the method used to prepare IX. Workup gave 7.7 g (85%) of a product with mp 208-209°C. Found: C 57.6; H 5.6; N 11.2; S 12.4%. $C_{12}H_{14}N_2O_2S$. Calculated: C 57.6; H 5.6; N 11.2; S 12.8%.

5-Oxo-4-(carbomethoxyethyl)-6,7-benzoperhydro-1,4-thiazepine (XII). A solution of 0.3 ml of PCl_3 in 10 ml of DMF was added at 0°C to a suspension of 1.0 g (3.5 mmole) of acid IX and 0.6 g of triethylamine in 40 ml of DMF. As the PCl_3 was added, the substance dissolved. The mixture was stirred for 2 h, after which it was allowed to stand overnight. The precipitate was removed by filtration, the solvent was evaporated, and the residue was dissolved in methanol and precipitated by the addition of ether to give 0.65 g (70%) of the product in the form of an oil. Found: C 58.4; H 5.6; N 5.4; S 11.8%. $C_{13}H_{15}NO_3S$. Calculated: C 58.8; H 6.0; N 5.7; S 12.1%.

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