INDOLE DERIVATIVES

LXXXVI.* INDOLE-SUBSTITUTED AMINOALKANETHIOLS AND S-AMINOALKYL THIOSULFATES

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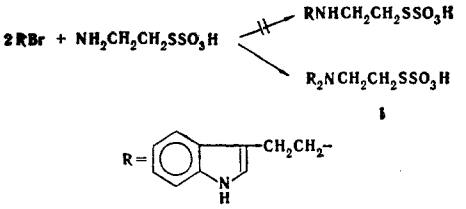
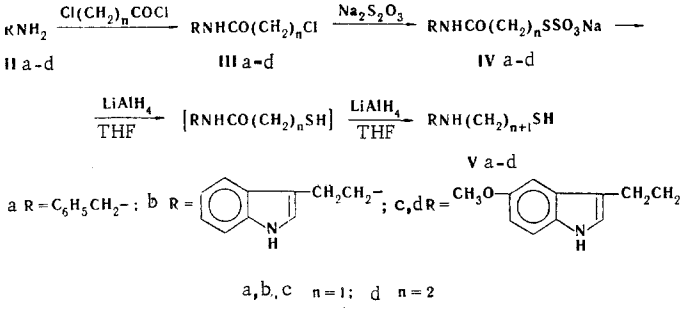
S-Carbamoylalkyl thiosulfates have been obtained from (indolylalkyl)amides of ω-chloroalkanecarboxylic acids, and these have been reduced to (indolylalkyl)aminoalkanethiols and then converted into S-[(indolylalkyl)aminoalkyl] thiosulfates.

The aminoalkanethiols $RNH(CH_2)_nSH$ and the S-aminoalkyl thiosulfates $RNH(CH_2)_nSSO_3H$ exhibit radioprotective properties. Recently, a search has been conducted for the most effective representatives of this series by means of a wide variation in R and in n [2-7]. In this connection, we have performed the synthesis of aminoalkanethiols and S-aminoalkyl thiosulfates containing indol-3-ylalkyl fragments, since tryptamines, especially serotonin and 5-methoxytryptamine are also effective radioprotectors.

The synthetic route usually used for compounds of this type [8] gave tertiary amines instead of secondary:



As a rule, the monohalogenoalkylation of primary amines is associated with the necessity for separating complex mixtures, so that indirect methods are used to achieve success [3]. We have succeeded in finding a method for synthesizing aminoalkanethiols from ω-halogenoalkanecarbonamides that led to individual products with fairly high yields.



With sodium thiosulfate, the ω-halogenoalkanecarbonamides (III) formed S-aminoalkyl thiosulfates (IV), which were then reduced with lithium tetrahydroaluminate to the aminoalkanethiols (V). The thio-

* For Communication LXXXV, see [1].

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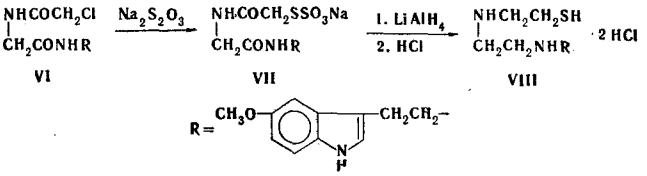
TABLE 1. Antiradiation Efficiency of Indole-Substituted S-Aminoalkyl Thiosulfates and Aminoalkanethiols

Substance	Dose, mmole/kg (intraperitoneally)	No. of animals (mice)	Survival rate, %	Mean life of the animals, days	Notes
$NH_2CH_2CH_2SSO_3H$	0,15	20	0*	12,5±1,42	
Vc	0,15	29	13,8±6,4	6,5±0,77	
Vd	0,15	20	0	6,0±0,55	
VIII	0,15	28	7,1±4,8	7,6±0,89	
IX	0,15	20	0	6,0±0,55	
Tryptamine	0,15	30	30,0±8,3	9,0±0,98	P<0,05
Control	—	44	6,8±3,8	7,9±0,53	

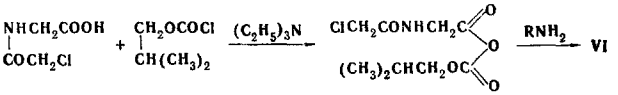
*The absence of a radioprotective effect of aminoethanethiosulfonic acid is due to the fact that in order to obtain comparable results it was used in a dose considerably smaller than usual.

sulfate group is first reduced to a thiol group, and then the amide group is converted into an amine group more slowly. No attempts were made to isolate the carbamoylalkanethiols, but their formation and subsequent transformation were traced chromatographically in a thin layer of silica gel.

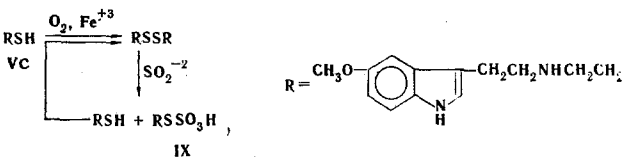
The method also proved suitable for the preparation of diaminoalkanethiols. Thus, from the halogen-substituted diamide (VI) we obtained the thiosulfate (VII), which was then reduced to the diaminoalkanethiol (VIII).



The synthesis of (VI) was performed by the mixed-anhydride method from chloroacetylglycine, isobutyl chloroformate, and 5-methoxytryptamine.

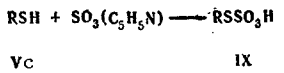


To convert a thiol into a thiosulfate, we made use of a known method [9].



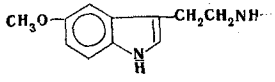
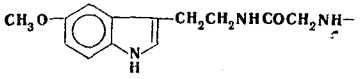
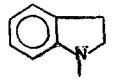
As follows from the scheme, the conversion of the thiol into the thiosulfate requires the repeated oxidation of the thiol to the disulfide and the sulfite cleavage of the disulfide. The time of synthesis was shortened considerably by the addition of catalytic amounts of iron. The presence of iron enables the end of the oxidation of the thiol to be recognized by the disappearance of the brown coloration of the iron mercaptide.

The same S-aminoalkyl thiosulfate acid (IX) is formed by the action of pyridine–sulfur trioxide on the thiol (Vc) [10].



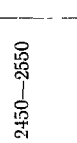
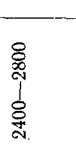
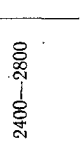
Experiments on animals showed (see Table 1) that the introduction of mercaptoalkyl and hydroxysulfonylthioalkyl residues into the amino group of 5-methoxytryptamine led to a fall in the radioprotective effect and to an increase in toxicity. The tertiary amine (I) also possesses an increased toxicity.

TABLE 2. The S-(Carbamoylalkyl) Thiosulfates $RNHCO(CH_2)_nS_2O_3Na$

Compound	R	n	mp, °C (solvent for crystallization)	R_f	Empirical formula	Found, %				Calc., %				IR spectrum, cm^{-1}			Yield, %
						C	H	N	S	C	H	N	S	NH, OH	amide	S_2O_3Na	
IVa	$C_6H_5CH_2NH$—	1	(Water)		$C_9H_{10}NNaO_4S_2 \cdot H_2O$	35,9	4,0	4,5	20,9	35,9	4,0	4,7	21,2	3330	1620	1250, 1240 1208, 1040 650	70,4
IVc		1	(Water)	0,65	$C_{13}H_{15}N_2NaO_5S_2 \cdot H_2O$	40,6	4,5	7,5	16,4	40,6	4,5	7,3	16,6	3455 3370	1632 1550	1255, 1230 1222, 1042	61,6
IVd	The same	2	126—127 (96% ethanol)	0,66	$C_{14}H_{17}N_2NaO_5S_2$	42,7	4,8	6,9	15,9	42,2	4,8	7,0	16,1	3440 3315	1635 1563	1243, 1200 1185, 1030 637	83
VII		1	159 (Water)	0,6	$C_{15}H_{18}N_3NaO_6S_2$	42,3	4,8	9,6	14,6	42,5	4,3	9,9	15,1	3300 (br.)	1670 1650 1550	1235, 1215 1170, 1032 643	79
		1	157,8 (Ethanol)	0,65	$C_{10}H_{10}NNaO_3S_2$	40,6	3,5	4,5	21,2	40,7	3,4	4,7	21,7	3120	1680	1250, 1220 1040	75,8
	NH_2†	1	(Water + ethanol)	0,25	$C_2H_4NNaO_4S_2$	12,9	2,2	7,1	31,2	12,5	2,1	7,2	31,2	3450 3350 3310	1690 1665 1570	1250, 1200 1177, 1040 640	73,2

*Obtained from chloroacetylindoline [19], mp 134-135°C; strongly irritates the skin, is not reduced by lithium tetrahydroaluminate. †After the end of the reaction, the solution was evaporated to dryness, and the amide was extracted with DMFA and was recrystallized from a small amount of water with the addition of ethanol. It was dried over phosphorus pentoxide. For the preparation of the unpurified compound, see [20]. The substance is insoluble in tetrahydrofuran and is not reduced to the aminoalkanethiol.

TABLE 3. The Aminoalkanethiol Hydrochlorides $RNH(CH_2)_nSH \cdot HCl$

Compound	R	n	mp, °C	R_f	Empirical formula	Found, % C	H	Cl	N	S	Calc., % C	H	Cl	N	S	IR spectrum, cm^{-1} NH	salt	Yield, %
Va	$C_6H_5CH_2-$	2	265*	0,6	$C_9H_{14}ClNS$	53,0	7,0	16,4	6,8	15,8	53,0	6,9	17,4	6,8	15,7		2400—2800	78
Vb		2	156—157	0,65	$C_{12}H_{17}ClN_2S$	56,3	6,9	13,9	10,7	12,5	56,1	6,7	13,8	10,9	12,5	3400	2400—2550	72
Vc		2	176—178	0,45	$C_{13}H_{19}ClN_2OS$	54,6	6,8	12,3	9,5	11,2	54,4	6,7	12,4	9,7	11,2	3300	2450—2550	85†
Vd		3	146—148	0,55	$C_{14}H_{21}ClN_2OS$	55,9	6,8	11,6	9,0	10,0	55,9	7,0	11,8	9,3	10,6	3240 (br.)	2400—2800	76†
VIII		2	177—178	0,6	$C_{15}H_{25}Cl_2N_3OS$	49,3	7,1	19,4	11,5	8,6	49,4	6,9	19,5	11,5	8,8	3360 (br.)	2400—2800	39

* From aqueous ethanol, according to the literature [21], mp 260-261°C.
†Yield of the base.

EXPERIMENTAL

Chromatography was performed on plates with a fixed layer of silica gel – Silufol UV-254 – with butanol–acetic acid–water (4:1:5) as the eluent, the spots being revealed with a solution of p-dimethylaminobenzaldehyde (indole ring), sodium nitroprusside (thiols), or phosphomolybdic acid. The IR spectra in paraffin oil were taken on a UR-10 instrument.

The testing of the antiradiation activity was performed on random-bred female white mice weighing 20-23 g. The animals were subjected to ^{60}Co γ radiation in a dose of 800-850 r at a dose rate of 48.7-56.2 r/min. The substances were dissolved in distilled water (in the case of the thiosulfates, the addition of an equivalent amount of caustic soda was necessary for dissolution), and were injected intraperitoneally 5-10 min before irradiation.

S-{Di[2-(indol-3-yl)ethyl]aminoethyl} Thiosulfate (I). A solution of 1 g (4.46 mmoles) of indol-3-ylethyl bromide (R_f 0.95, mp 102°C [11, 12]) in 10 ml of ethanol was added to a solution of 1.4 g (8.92 mmoles) of S-(aminoethyl) thiosulfate (R_f 0.32) and 0.357 g (8.92 mmoles) of caustic soda in 2.5 ml of water, the mixture was boiled for 4 h, the ethanol was distilled off in vacuum, and the residue was acidified with acetic acid to pH 4. The precipitate was washed with water to give 0.51 g (28%) of colorless crystals with R_f 0.55, mp 182-184°C (from 85% ethanol). ν_{max}, cm^{-1}: 3320 (NH of indole), 1260, 1195, 1185, 1020, 630 (SSO_3H)* Found: C 59.5; H 5.7; N 9.4; S 14.3%. $C_{14}H_{21}N_3O_3S_2$. Calculated: C 59.6; H 5.7; N 9.5; S 14.8%.

N-Benzylchloroacetamide (IIIa). With vigorous stirring at a temperature not exceeding 4°C, a solution of 33.9 g (0.3 mole) of chloroacetyl chloride in 50 ml of methylene chloride was added to solutions of 16.8 g (0.3 mole) of caustic potash in 50 ml of water and 32.1 g (0.3 mole) of benzylamine in 50 ml of methylene chloride. After 30 min, the methylene chloride was evaporated in vacuum and the residue was filtered off and was washed with benzene and ether to give 43.5 g (79.5%) of colorless crystals with mp 93-94°C (according to the literature [14], mp 93.5-94.5°C). ν_{max}, cm^{-1}: 3287, 1660, 1560 (amide).

N-Chloroacetyl-5-methoxytryptamine (IIIc). To a suspension of 25 g (0.1 mole) of 5-methoxytryptamine in 140 ml of dimethylformamide were added 21.7 g (0.215 mole) of triethylamine and, at 0-3°C, over 45 min, a solution of 12.42 g (0.11 mole) of chloroacetyl chloride in 30 ml of dimethylformamide, and then the mixture was stirred with cool-

* Bunte salts absorb in the 1190-1250, 1040-1050, and 640-660-cm^{-1} regions [13].

ing for 2 h 30 min, poured into 500 ml of water and ice, and HCl was added to pH 2.5-3. After 2 h, the precipitate was filtered off and was washed with acidified water and with pure water to give 20 g of colorless crystals. From the aqueous solution, methylene chloride extracted an additional 2.75 g of substance. The total yield was 22.75 g (85.5%), mp 128-129°C (according to the literature [15], mp 125-127°C), yield 55.4%. ν_{max}, cm^{-1}: 3390 (NH of indole), 3345, 1655, 1545 (amide).

N-(β-Chloropropionyl)-5-methoxytryptamine (IIId). This was obtained in a similar manner to (IIIc) from 5-methoxytryptamine hydrochloride and β-chloropropionyl chloride. Yield 80%, mp 109-110°C (from ethanol and water). ν_{max}, cm^{-1}: 3400 (NH of indole), 3310, 1645, 1573 (amide). Found: C 59.8; H 6.2; Cl 12.4; N 10.0%. $C_{14}H_{17}ClNO_2$. Calculated: C 59.8; H 6.1; Cl 12.6; N 10.0%.

Chloroacetylglycine.* At 2-5°C, 59.2 g (0.525 mole) of chloroacetyl chloride and 110 ml of a 4 N solution of caustic soda to maintain the pH at 11 were added simultaneously to a solution of 37.5 g (0.5 mole) of glycine in 125 ml of 4 N caustic soda. Then 200 ml of ethyl acetate was added and, with vigorous stirring, the mixture was acidified with 6 N sulfuric acid (~125 ml) to pH 1-2. The ethyl acetate layer was separated off and the aqueous layer was repeatedly extracted with ethyl acetate. The extracts were combined, washed with water, and dried with magnesium sulfate and evaporated in vacuum; the residue was washed with a small amount of ether to yield 45.18 g (59.5%) of bright-yellow crystals with mp 109-110°C (according to the literature [18], mp 105-106°C). ν_{max}, cm^{-1}: 3270 (broad), 1657, 1555 (amide), 1713 (COOH). Found: C 31.4; H 4.1; Cl 23.6; N 9.3%. $C_4H_6ClNO_3$. Calculated: C 59.8; H 4.0; Cl 23.4; N 9.3%.

N-[N-(Chloroacetyl)glycyl]-5-methoxytryptamine (VI). At −20°C, 12 g (88 mmoles) of isobutyl chloroformate was rapidly added to a solution of 10.9 g (72 mmoles) of chloroacetylglycine and 8.4 g (83 mmoles) of triethylamine in 180 ml of ethyl acetate, and immediately afterwards a suspension of 13.26 g (69.8 mmoles) of 5-methoxytryptamine (mp 120-125.5°C) in 75 ml of ethyl acetate was added and the mixture was stirred at −10°C for 30 min and +15°C for 1 h, and was cooled to −60°C, after which the precipitate was filtered off, washed with ethyl acetate, dried, and recrystallized from 1800 ml of water with carbon, giving 17.16 g (75.7%) of colorless crystals with mp 157-158°C. ν_{max}, cm^{-1}: 3412 (NH of indole), 3270, 1674, 1635, 1570 (amide). Found: C 55.5; H 5.5; Cl 10.7; N 12.9%. $C_{15}H_{18}ClN_3O_3$. Calculated: C 55.6; H 5.6; Cl 10.9; N 13.0%.

Sodium S-[β-(Indol-3-yl)ethylcarbamoylmethyl] Thiosulfate (IVb). A mixture of 11.8 g (0.05 mole) of N-[β-(indol-3-yl)ethyl]chloroacetamide (mp 93°C, from water; according to the literature [15], mp 90-91°C), 13 g (52.5 mmoles) of sodium thiosulfate, 100 ml of ethanol, and 75 ml of water was boiled for 3 h. The resulting solution was evaporated in vacuum, the residue was extracted with 100 ml of boiling absolute ethanol, the extract was treated with 4 ml of water, and, after cooling, colorless crystals were obtained with R_f 0.75. Found C 41.0; H 4.4; N 8.0; S 17.9%. $C_{12}H_{13}N_2NaO_4S_2 \cdot H_2O$. Calculated: C 40.7; H 4.3; N 7.9; S 18.1%. The hydrate was dried over phosphorus pentoxide, giving 13.5 g (80.4%) of the anhydrous salt. ν_{max}, cm^{-1}: 3430 (NH of an indole), 1660, 1550 (amide), 1260-1200, 1040, 645 (SSO_3Na). Information on the other S-(carbamoylmethyl) thiosulfates synthesized is given in Table 2.

N-(β-Mercaptoethyl)tryptamine Hydrochloride (Vb). A solution of 6.72 g (0.02 mole) of sodium S-[β-(indol-3-yl)ethylcarbamoylmethyl] thiosulfate in 150 ml of tetrahydrofuran was added to a suspension of 2.28 g (0.06 mole) of lithium tetrahydroaluminate in 50 ml of tetrahydrofuran at the boil, and the mixture was boiled for 10 h in a current of argon and was cooled, and at 5-10°C 43 ml (0.24 mole) of water was gradually added. The resulting precipitate was filtered off and was washed with tetrahydrofuran (2 × 50 ml), and then the solvent was evaporated off, and the residual oil (3.17 g, 72%) was dissolved in 10 ml of absolute ethanol, the solution was acidified with an ethanolic solution of hydrogen chloride, and 30 ml of ether was added, and, after two days, the colorless crystals that had deposited were filtered off. The characteristics of the product and of the other aminoalkanethiols, obtained similarly, are given in Table 3.

S-{β-[β-(5-Methoxyindol-3-yl)ethylamino]ethyl} Thiosulfate (IX). a) Air was passed through a solution of 3.54 g (12.4 mmoles) of N-(β-mercaptoethyl)-5-methoxytryptamine (Vc) in 100 ml of water and 100 ml of ethanol containing 3 mg of ferric chloride. After 30 min, the dark-brown color had disappeared, and a chromatogram showed the conversion of the thiol (R_f 0.50) into the disulfide (R_f 0.35). Then 6 mmoles of a solution of ammonium sulfite was added. After 40 min, the spot of the disulfide on a chromatogram had disappeared and spots of the thiol and of the thiosulfonic acid (R_f 0.65) had appeared. Air was passed for another 30 min, and another 3 mmoles of ammonium sulfite was added. After 30 min, the solution was evaporated to dryness in vacuum, and the residue was washed with water and recrystallized from 85% ethanol with carbon to give 2.68 g (65.5%) of colorless crystals with mp 187-189°C practically insoluble

* Prepared by analogy with the synthesis of chloroacetyltryptophan [16]; compare [17].

in water. Found: C 47.0; H 5.7; N 8.2; S 19.9%. $C_{13}H_{18}N_2O_4S_2$. Calculated: C 47.2; H 5.5; N 8.5; S 19.4%. ν_{max}, cm^{-1}: 3340 (NH of an indole), 1580, 1620, 1240, 1210, 1180, 1030, 645 (SSO_3H).

b) A mixture of 0.85 g (3.4 mmoles) of the free aminoalkanethiol (Vc) and 1.27 g (8 mmoles) of pyridine–sulfur trioxide was heated in a current of argon at 50°C for 3 h. Then it was cooled and 50 ml of water and acetic acid to pH 7 were added. After 2-3 h, the precipitate was filtered off and washed with water to give 0.8 g (71%) of light-yellow crystals identical in properties with the product obtained by method a).

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