REACTIONS OF N-ACYLATED ETHYLENEIMINES WITH THIOACETIC ACID AND HYDROGEN SULFIDE

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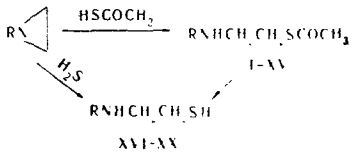
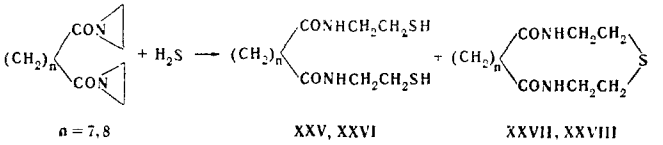
A series of β-(S-acetylmercapto)ethylamides of α-amino acids and α,β-unsaturated acids and bis[β-(S-acetylmercapto)ethyl]amides of dicarboxylic acids were obtained by cleavage of N-acylethyleneimines with thioacetic acid. The reaction of ethyleneimides of N-acylamino acids with hydrogen sulfide leads to the corresponding β-(N-acylamino)ethylmercaptans. Bis(ethyleneimides) of azelaic and sebacic acids react with hydrogen sulfide to form cyclic sulfides along with the corresponding bis[(β-mercaptoethyl)amides].

Ethyleneimides of carboxylic acids react vigorously with ring opening with both electrophilic and nucleophilic reagents [1]. We have shown that the ethyleneimides of N-acylated α-amino acids [2] and α,β-unsaturated acids [3] and the bis(ethyleneimides) of dicarboxylic acids [4] on reaction with thioacetic acid readily open the ethyleneimine rings and form the corresponding β-(S-acetylmercapto)ethylamides (I-XV) (Table 1).



The ethyleneimides of N-phthalylglycine, N-phthalylalanine, N-phthalylvaline, N-carbobenzoxyvaline, and N-acetylvaline were isolated in the reaction with hydrogen sulfide. The corresponding N-acyl-β-mercaptoethylamines (XVI-XX) are formed in yields up to 80%, judging from the amount of free mercapto groups. However, only N-(N-acetylvalyl)-β-mercaptoethylamine (XX, Table 2) could be isolated by repeated recrystallization of the reaction products. In this case, β-mercaptoethylamides XVI-XIX are gradually oxidized completely to the corresponding symmetrical disulfides (XXI-XXIV).

The reaction of bis(ethyleneimides) of azelaic and sebacic acids with a considerable excess of hydrogen sulfide leads to bis[(β-mercaptoethylamides)] XXV and XXVI (Table 2) and cyclic sulfides XXVII and XXVIII. Compounds XXVII and XXVIII are apparently products of intramolecular opening of the ethyleneimine ring by the mercapto group in the intermediate N,N-ethylene-N'-(β-mercaptoethyl)diamides of azelaic and sebacic acids. Cyclic sulfide XXVII are also synthesized from the bis(β-chloroethylamide) of azelaic acid (XIX) and sodium sulfide.



Alkali-resistant β-mercaptoethylamides XIX, XX, XXV, and XXVI were purified through their sodium thiolates (Table 2).

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TABLE 1. β-(S-Acetylmercapto)ethylamides $RNHCH_2CH_2SCOCH_3$ (I-XV)

Compound	R[a]	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % N	Found, % S	Calc., % C	Calc., % H	Calc., % N	Calc., % S	Yield, %
I	N-Phthalylglycyl	152—153[b]	$C_{12}H_{24}N_2O_4S$	54,6	4,8	9,1	10,7	54,9	4,6	9,1	10,5	61
II	N-Phthalyl-alanyl	Oil[c]	$C_{15}H_{16}N_2O_4S$	56,2	5,0	—	9,3	56,2	5,0	—	10,0	66
III	N-Phthalylvalyl	120—121[b]	$C_{17}H_{20}N_2O_4S$	58,9	6,0	—	9,2	58,6	5,8	—	9,3	78
IV	N-Phthalyl-phenylalanyl	128—129[d]	$C_{21}H_{20}N_2O_4S$	63,9	5,4	6,8	—	63,6	5,1	7,1	—	57
V	N-Carbobenz-oxyvalyl	111—112[e]	$C_{17}H_{24}N_2O_4S$	58,3	6,9	—	9,5	57,9	6,8	—	9,1	90
VI	N-Acetylvalyl	124—126[d]	$C_{11}H_{20}N_2O_3S$	51,5	8,0	11,4	12,0	50,7	7,7	10,8	12,3	86
VII	N-Benzoylleucyl	197—198[b]	$C_{17}H_{24}N_2O_3S$	61,0	7,1	8,8	8,9	60,7	7,2	8,3	9,5	62
VIII	Acrylolyl	[f]	$C_7H_{11}NO_2S$	—	—	7,8	18,2	—	—	8,1	18,5	50
IX	Methacryloyl	[g]	$C_8H_{13}NO_2S$	—	—	7,5	16,8	—	—	7,4	17,1	62
X	β,β-Dimethyl-acryloyl	44—45[h]	$C_9H_{15}NO_2S$	—	—	7,4	15,5	—	—	7,0	15,9	65
XI	Cinnamoyl	83—85[i]	$C_{13}H_{15}NO_2S$	—	—	5,8	12,4	—	—	5,6	12,9	68
XII	β-Carbometh-oxypropionyl	[j]	$C_9H_{15}NO_4S$	46,6	6,3	—	13,4	46,3	6,5	—	13,7	90
XIII	N-[β-(S-acetyl-mercapto)-ethyl]-adipyl	139—140[k]	$C_{14}H_{24}N_2O_4S_2$	48,5	7,1	—	18,2	48,3	6,9	—	18,4	75
XIV	N-[β-(S-acetyl-mercapto)-ethyl]-azelayl	109—111[k]	$C_{17}H_{30}N_2O_4S_2$	52,3	8,1	—	16,1	52,3	7,7	—	16,4	55
XV	N-[β-(S-acetyl-mercapto)-ethyl]-sebacyl	131—133[k]	$C_{18}H_{32}N_2O_4S_2$	53,6	8,0	—	15,5	53,4	8,0	—	15,8	73

[a] Amino acids of the D,L series. [b] From ethanol. [c] Purified by chromatography with a column filled with activity II aluminum oxide; the eluent was benzene–ether (1 : 1). [d] From benzene–petroleum ether. [e] From acetone–petroleum ether. [f] Bp 93-94° (3 mm), n_D^{20} 1.5104, d_4^{20} 1.1492. [g] Bp 152-153° (4 mm), n_D^{20} 1.5069, d_4^{20} 1.1305. [h] From ethyl acetate. [i] From petroleum ether. [j] Bp 172-174° (3 mm), n_D^{20} 1.5113, d_4^{20} 1.2132. [k] From acetone.

TABLE 2. N-Acylated β-Mercaptoethylamines $RNHCH_2CH_2SH$

Compound	R	mp, °C	Empirical formula	Found, % C	Found, % H	Found, % S	Calc., % C	Calc., % H	Calc., % S	Yield, %
XVII	N-Phthalylalanyl	124—125[a]	$C_{13}H_{14}N_2O_3S$	56,0	4,7	11,7	56,1	5,1	11,5	65
XVIII	N-Phthalylvalyl	122—123a	$C_{15}H_{18}N_2O_3S$	58,9	5,9	10,5	58,9	5,9	9,9	61
XIX	N-Carbobenzoxy-valyl	152—153a,b	$C_{15}H_{22}N_2O_3S$	58,1	7,0	9,7	58,0	7,1	10,3	70
XX	N-Acetylvalyl	151—153c,d	$C_9H_{18}N_2O_2S$	49,3	8,4	14,3	49,5	8,3	14,7	73
XXV	N-(β-Mercapto-ethyl)azelayl	131—132a,e	$C_{13}H_{26}N_2O_2S_2$	51,0	9,0	20,8	50,9	8,6	20,9	65
XXVI	N-(β-Mercapto-ethyl)sebacyl	141—143f,g	$C_{14}H_{28}N_2O_2S_2$	52,8	8,8	19,2	52,5	8,9	20,0	75

[a] From aqueous methanol. [b] 2,4-Dinitrophenyl thioether: mp 197-198° (from acetone). Found: C 53.1; H 5.5; S 6.3%. $C_{21}H_{24}N_4O_7S$. Calculated: C 52.9; H 5.1; S 6.7%. [c] From ether. [d] 2,4-Dinitrophenyl thioether: mp 215-216° (from methanol). Found: C 47.2; H 5.4; S 8.1%. $C_{15}H_{20}N_4O_6S$. Calculated: C 46.9; H 5.2; S 8.3%. [e] 2,4-Dinitrophenyl thioether: mp 126-128° (from methanol). Found: C 47.0; H 5.0; S 9.9%. $C_{25}H_{30}N_6O_{10}S_2$. Calculated: C 46.6; H 4.7; S 10.4%. [f] From benzene. [g] 2,4-Dinitrophenyl thioether: mp 141-142° (from methanol). Found: C 47.7; H 5.4; S 9.5%. $C_{26}H_{32}N_6O_{10}S_2$. Calculated: C 47.8; H 4.9; S 9.8%.

Since the synthesis of N-acylated β-mercaptoethylamines from ethyleneimides of acids and hydrogen sulfide proved to be complicated by difficulties involved in purification and side reactions, to prepare them S-acetylthioethers II, III, and V were subjected to alcoholysis under the influence of HCl, while VI, XIV, and XV were subjected to alkaline hydrolysis. The synthesized aminothiols (XVII-XX, XXV, and XXVI) (Table 2) required almost no further purification.

EXPERIMENTAL

The starting ethyleneimides of N-acylamino acids and α,β-unsaturated acids were obtained by the method in [2, 3]. The previously known ethyleneimides of succinic acid monoethyl ester [5] and phthalylglycine [6] were also obtained by the method in [2]. The bis(ethyleneimides) of dicarboxylic acids were obtained from dicarboxylic acid chlorides and ethyleneimine [4].

β,β-Dimethylacrylic Acid Ethyleneimide. This compound was obtained in 80% yield [mp 143-144° (from ethylacetate)] from 0.03 mole of β,β-dimethylacrylic acid, 0.03 mole of ethyleneimine, and 0.03 mole of 1,3-dicyclohexylcarbodiimide in chloroform by the method in [3]. Found: N 10.8%. $C_7H_{11}NO$. Calculated: N 11.2%.

Cinnamic Acid Ethyleneimide. This compound was similarly obtained as a mass, which was extracted with petroleum ether. Cooling of the extract gave 66% of ethyleneimide with mp 57-58° (from benzene–petroleum ether). Found: C 76.0; H 6.3%. $C_{11}H_{11}NO$. Calculated: C 76.3; H 6.4%.

β-(S-Acetylmercapto)ethylamides of N-Acylamino Acids (I-VII) and α,β-Unsaturated (VIII-XI) and Dicarboxylic (XII-XV) (Table 1) Acids. A 0.02-mole sample of the ethyleneimide of the appropriate monocarboxylic acid or 0.01 mole of the bis(ethyleneimide) of a dicarboxylic acid was added in portions with stirring at 5° to a solution of 0.02 mole of thioacetic acid in 15 ml of dry benzene or methanol; the reaction mixture was prevented from warming above 10°. The mixture was stirred for 15 min, after which the temperature was slowly brought up to room temperature (in the synthesis of VIII-XV) or to ~60° and stirred at this temperature for 1.5-3 h. Compounds VIII-XI were synthesized in a nitrogen atmosphere. The end of the reaction was monitored with respect to Congo red or by means of thin-layer chromatography (TLC). The solvent was then vacuum evaporated, and the S-acetylthioethers were recrystallized or vacuum distilled. Compound II was purified by chromatography with a column filled with activity II aluminum oxide with elution by chloroform. Thin-layer chromatography on activity II aluminum oxide in benzene–ether (1:1) was used to identify unsaturated S-acetylthioethers VIII-XI. IR spectra of amides VIII-XI: 3050-3070 (=CH–), 950-975 (=CH_2), 655 cm^{-1} (thiol sulfur); the IR spectra of I-XV have absorption bands at 1695-1700 (C=O in thiol esters) and 1660-1670 cm^{-1} (amide I).

Reaction of Ethyleneimides of N-acylamino Acids with Hydrogen Sulfide. A solution of 0.01 mole of N-acylamino acid ethyleneimide in 50 ml of dry methanol was added dropwise to 150 ml of dry methanol saturated at −10° with hydrogen sulfide (~2 g) by bubbling hydrogen sulfide into the mixture with vigorous stirring and cooling on an ice bath. The temperature of the mixture was raised slowly to room temperature, and the mixture was allowed to stand in a tightly sealed flask for 20 h. This procedure gave crude crystalline N-acylaminothiols XVI-XX, the percentage of free SH groups in which was 70-80% (determined iodometrically). Thin-layer chromatography on activity II aluminum oxide in benzene–ether–methanol (4:1:1) was used to identify and preparatively purify XVII and XVIII (Table 2). For purification, crude aminothiols XIX and XX were dissolved with shaking in 20 ml of 5% sodium hydroxide solution; the solutions were acidified with concentrated hydrochloric acid, saturated with NaCl, and the resulting aminothiol was separated. The filtrate was extracted several times with ether, the ether extracts were combined with the individual aminothiol, and the mixture was washed with water and dried with magnesium sulfate. The solvent was evaporated, and the residue was recrystallized one to two times to give 30-40% of pure products (Table 2). Repeated crystallization of crude N-acyl-β-aminothiols XVI-XIX from methanol gave bis(N-acyl-β-aminoethyl) disulfides XXI-XXIV (Table 3).

Reaction of Ethyleneimides of Azelaic and Sebacic Acids with Hydrogen Sulfide. This reaction was carried out similarly. The percentage of free SH groups in the crude products was ~40%. Bis(β-mercaptoethylamides) XXV and XXVI (Table 2) were also purified through the thiolates. Fractional crystallization of the crude reaction products gave XXVII and XXVIII. Azelaic acid N,N'-(3-thiapentamethylene)diamide (XXVII) was obtained in 42% yield and had mp 156-157° (from methanol). Found: C 56.8; H 9.3; S 12.3%. Mol. wt. (Rast method) 276. $C_{13}H_{24}N_2O_2S$. Calculated: C 57.2; H 8.9; S 11.8%. Mol. wt. 272. Sebacic acid N,N'-(3-thiapentamethylene)diamide (XXVIII) was obtained in 35% yield and had mp 131-132° (from ethanol). Found: C 58.4; H 9.0; S 11.5%. Mol. wt. 284. $C_{14}H_{26}N_2O_2S$. Calculated: C 58.7; H 9.2; S 11.2%. Mol. wt. 286.

TABLE 3. Bis(N-acyl-β-aminoethyl) Disulfides $(RNHCH_2CH_2S)_2$

Compound	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	S	C	H	S	
XXI	N-Phthalylglycyl	222—224[a]	$C_{24}H_{22}N_4O_6S_2$	54,4	4,3	12,3	54,7	4,2	12,2	40
XXII	N-Phthalylalanyl	218—219[b]	$C_{26}H_{26}N_4O_6S_2$	56,1	4,8	11,3	56,3	4,7	11,5	45
XXIII	N-Phthalylvalyl	130—131[c]	$C_{30}H_{34}N_4O_6S_2$	58,6	5,6	10,5	59,0	5,6	10,5	51
XXIV	N-Carbobenzoxy-valyl	188—189[b]	$C_{30}H_{42}N_4O_6S_2$	58,4	7,0	9,6	58,2	6,8	10,3	50

[a] From ethyl acetate (mp 137-138° [6]). [b] From methanol. [c] From aqueous methanol.

Compound XXVII was obtained by the method in [7] from bis(β-chloroethylamide) XXIX and Na_2S in the form of an oil (in 40% yield). It was purified by TLC on activity II aluminum oxide in benzene–ether–methanol (6 : 15 : 4) and had mp 155-156°. The compound obtained was chromatographically identical to the sample described above and did not depress its melting point.

N-Acetylvaline β-Mercaptoethylamide (XX) and Azelaic and Sebacic Acid Bis(β-mercaptoethylamides) (XXV and XXVI). A 0.01-mole sample of S-acetylthioether VI, XIV, or XV was shaken with 40 ml of 5% sodium hydroxide solution. The mixtures were then worked up as described above. The yields of amides XX, XXV, and XXVI were ~70% (Table 2).

N-Phthalylalanine, N-Phthalylvaline, and N-Carbobenzoxyvaline β-Mercaptoethylamides (XVII-XIX). A 0.01-mole sample of S-acetylthioether II, III, and V and 20 ml of a 1% HCl solution in absolute methanol were refluxed for 2 h. The solvent was evaporated to dryness, and the residue was washed with water and recrystallized. The yields were ~60% (Table 2).

Azelaic Acid Bis(β-chloroethylamide (XXIX). Ether saturated with the calculated amount of hydrogen chloride was added to a solution of 0.015 mole of azelaic acid bis(ethyleneimide) in 50 ml of absolute ether. Amide XXIX separated. The yield of product with mp 128-129° (from ethanol) was 85%. Found: C 50.6; H 7.5%. $C_{13}H_{24}Cl_2N_2O$. Calculated: C 50.4; H 7.7%.

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