SYNTHESIS OF α-METHYLTHIOGLYCIDIC ACID AMIDES AND THEIR DISPROPORTIONATION PRODUCTS

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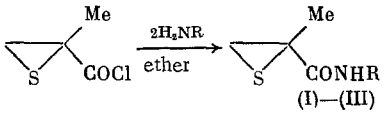
UDC 542.91:547.298.1:547.474.3

It is well known that thiiranes readily split out sulfur to give unsaturated compounds [1-4]. This is particularly characteristic for thioglycidic acids and their derivatives [2, 3, 5]; however, it has been found [3] that α-methylthioglycidic acid amides are least inclined to undergo desulfuration. The reactions of thioglycidic acids with electrophilic reagents have been previously investigated [1, 5-7]. In the present research we have studied the reactions of α-methylthioglycidic acid amides with secondary amines.

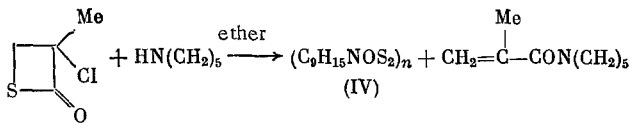
The α-methylthioglycidic acid amides were obtained by aminolysis of α-methylthioglycidyl chloride (method A) or α-chloro-α-methyl-β-thiolactone (method B). Amides I-III (Table 1) were obtained in high yields by the first method.



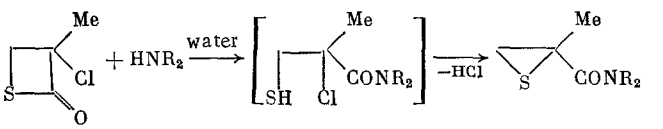
(A)

R = Ph (I); C_6H_4COOEt-*p* (II); CH_2COOH (III).

The available information regarding the aminolysis of α-chloro-α-methyl-β-thiolactone is contradictory. Thus, whereas the diethyl- and diisobutylamides of α-methylthioglycidic acid are obtained by aminolysis of the thiolactone under the influence of these amines in ether, unidentified product IV is the principal product in the case of piperidine [5]:



A similar reaction occurs with dimethylamine or morpholine [8]. Disproportionation products of the IV type are evidently obtained as a result of reaction of the intermediately formed α-methylthioglycidic acid amides with the amines, since the specially prepared piperidide of α-methylthioglycidic acid gives IV in the presence of piperidine (in ether) [5].



(B)

NR_2 = $NHCH_2COOH$ (III); NHC_6H_4COOH-*p* (V); N⟨⟩ (VI); NMe_2 (VII); NH—CHCOOH (VIII).
|
$CHMe_2$

In the present research we demonstrated that the chief reason for the unsuccessful experiments involving the aminolysis of α-chloro-α-methyl-β-thiolactone was the solvent: the same reaction (B) in water rather than in ether made it possible to obtain α-methylthioglycidic acid amides III and V-VIII in high yields both with piper-

*Deceased.

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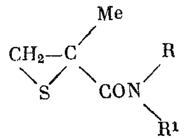
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 382-388, February, 1985. Original article submitted November 22, 1983.

 0568-5230/85/3402-0350$09.50

TABLE 1. α-Methylthioglycidic Acid Amides



(I)–(III), (V)–(VIII)

Compound	R	R¹	Synthetic method[a]	Yield, %	mp or bp (mm), °C	Found/calc., % C	Found/calc., % H	Found/calc., % N	Found/calc., % S	Empirical formula
(I)	H	Ph	A	90	70-71 hexane	61,95 / 62,18	5,80 / 5,70	7,20 / 7,25	16,40 / 16,58	$C_{10}H_{11}NOS$
(II)	H	$-C_6H_4-$COOEt	A	96	73–74 hexane	58,98 / 58,86	5,79 / 5,66	5,19 / 5,28	12,25 / 12,07	$C_{13}H_{15}NO_3S$
(III)	H	$-CH_2COOH$	A / B	72 / 86	84–86[b,c]	40,95 / 41,14	5,24 / 5,14	7,70 / 8,00	18,24 / 18,28	$C_6H_9NO_3S$
(V)	H	$-C_6H_4COOH$-*p*	B	99	202–204 (dec.) (MeCOOEt)[b,d]	55,10 / 55,73	4,62 / 4,64	5,81 / 5,91	13,96 / 13,50	$C_{11}H_{11}NO_3S$
(VI)		$-(CH_2)_5-$	B	70	112(5), n_D^{26} 1,5298[e]	–	–	–	–	–
(VII)	Me	Me	B	71,3	85(7–8), n_D^{22} 1,5139[g]	–	–	–	–	–
(VIII)	H	—CHCOOH (CHMe₂)	B	63	122–125 (benzene)[b,h] (in a sealed capsule)	50,85 / 49,80	7,13 / 6,91	6,36 / 6,45	14,88 / 14,75	$C_9H_{15}NO_3S$

[a]The letter "A" denotes aminolysis of α-methylthioglycidyl chloride, whereas "B" denotes aminolysis of α-chloro-α-methyl-β-thiolactone.

[b]Also purified by reprecipitation from aqueous $NaHCO_3$ solution by means of hydrochloric acid.

[c]Soluble in H_2O, EtOH, and Me_2CO but insoluble in Et_2O and $CHCl_3$.

[d]Soluble in MeOH, EtOH, MeCOOEt, and Me_2CO, insoluble in Et_2O, and only slightly soluble in H_2O.

[e]See [5].

[f]This is the yield of VII when the thiolactone was added to Me_2NH; VII was obtained in 40% yield when Me_2NH was added to the thiolactone.

[g]See [2]; soluble in H_2O and organic solvents.

[h]Soluble in EtOH, Me_2CO, Et_2O, and hot water.

TABLE 2. IR and PMR Spectra of the Compounds Obtained

Compound	ν, cm⁻¹					
	CON vs	Me m	$\delta_{def.}$, m	$\delta_{pulsat.}$	S—S	Other bands
(I)	1650	1450	670	1125 w	–	1542, 1600 (Ar), 3260 (NH)
(VII)	1645	1460	650	1125 s	–	–
(IX)	1620	1455			570, 585 m[a]	–

Compound	δ, ppm		
	Me	CH_2	Other signals
(I)[b]	1,85 s	2,52 s (H – A) 2,76 s (H – B)	5,15–5,75m (Ph), 6,55 s (NH)
(VII)[b]	1,79 s	2,37 s (H – A) 2,97 s (H–B)	3,08 s (Me_2N)
(VII) c	1,66 s	2,37 d (H – A) 2,83 d (H–B) J_{AB}=–1,7 Hz	3,04m (Me_2N)
(IX) c	1,54 s 1,63 s	3,11–3,24 m	3,03 (Me_2N)

[a]These bands are absent in the spectrum of starting amide VII.
[b]In CCl_4 with hexamethyldisiloxane as the internal standard.
[c]In CF_3COOH with tetramethylsilane as the external standard.

idine and dimethylamine and with a number of other amines (see Table 1). The basicities of aliphatic and heterocyclic amines in water are several orders of magnitude lower than in inert organic solvents [9-11]; therefore, the thiirane S atom probably is not attacked by amines in water, and the resulting thioglycidic acid amides III and V-VIII are not cleaved. In the case of piperidine and dimethylamine in the preparation of VI and VII the amine itself was the HCl acceptor; better yields of the amides were obtained in this case when the order of mixing the reagents was reversed. The starting amino acids (glycine, p-aminobenzoic acid, and L-valine) were used in the form of aqueous solutions of the sodium salts; cyclization of the intermediately formed chloro mercaptans was accomplished in the presence of $NaHCO_3$.

The IR spectra of α-methylthioglycidic acid amides I and VII contain bands that are characteristic for the thiirane ring; in the PMR spectra of these compounds in CCl_4 the protons of the ring CH_2 group show up in the form of singlets. The weak coupling of the geminal protons that is characteristic for thiiranes [1, 12, 13] can be detected only in CF_3COOH in the case of α-methylthioglycidic acid amides (Table 2).

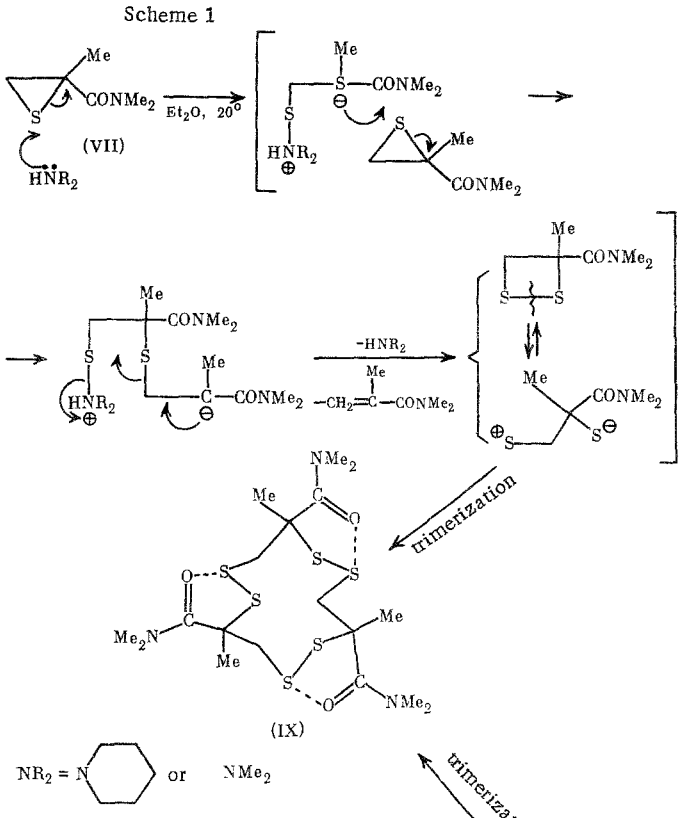
α-Methylthioglycidic acid amides are relatively stable compounds: they react with alcoholic alkali only upon refluxing. In the case of amino acids acylated by α-methylthioglycidic acid (III, V, and VIII) ring opening under the influence of a 0.7 N solution of NaOH/EtOH with heating proceeds most readily for glycine derivative III, less readily for L-valine derivative VIII: III > V > VIII (see Table 1).

α-Methylthioglycidic acid dimethylamide (VII) in the presence of small amounts of piperidine or dimethylamine in ether at ~20°C is converted to a mixture of methacrylic acid dimethylamide [identified by means of gas–liquid chromatography (GLC)] and crystalline product IX, the molecular weight of which corresponds to a trimer. A possible mechanism for the formation of IX is presented in Scheme 1. Structure IX was confirmed spectrally and by alternative synthesis – by the reaction of α-acetyldithio-β-chloroisobutyric acid dimethylamide (X) with diethylamine (Scheme 2). It follows from these results that IX is a trimer in which the individual links are connected "head to tail."

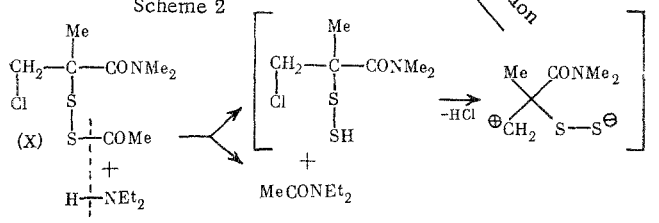
Trimer IX is insoluble in organic solvents (with the exception of CF_3COOH) and is only slightly soluble in $CHCl_3$, PhCl, C_5H_5N, and concentrated H_2SO_4 upon heating in these solvents. Piperidide IV, which evidently also has a trimeric structure similar to that of IX, also has a similar solubility. The low solubilities and unusual stabilities of these compounds (they are not decomposed even by hot concentrated acids) make it possible to propose for them the existence of a strong intramolecular interaction of the O and S atoms, as has been established for methyl 2,1-benzoxathiol-3-one-7-carboxylate (XI) [14, 15].

Schemes of the Formation of Trimer IX

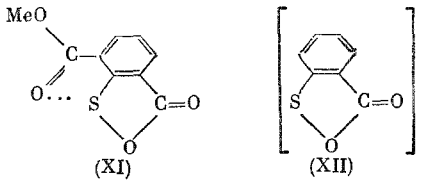
Scheme 1



Scheme 2

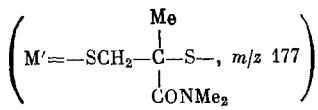


Compound XI is stable precisely due to the existence of an O...S interaction, in contrast to unstable XII, which does not contain a carboxy group in the aromatic ring [16]:



Intramolecular coordination of the carbonyl O atom with the S atom in IX is confirmed by the IR and PMR spectra. A consequence of this coordination is the significant (~30 cm^{-1}) lowering of the frequency of the stretching vibrations of the carbonyl group of IX to 1620 cm^{-1} as compared with starting thioglycidyl amide VII. Similar lowering of the frequency of the carbonyl group because of intramolecular coordination of the O atom with the S atom [14-15] or the H atom [17] is known. Interaction of the S atom with the carbonyl O atom in trimer IX in turn gives rise to a shift of the signal of the methylene group bonded to this S atom to weaker field (~0.57 ppm as compared with VII) (see Table 2).

A molecular ion is not observed in the mass spectra of trimer IX. Only a fragment with m/z 113 and its fragmentation products are recorded at low temperatures (≤65°C). Under electron impact at a higher temperature (150°C) trimer IX undergoes cleavage at the disulfide bonds to give a monomeric fragment



and a dimeric fragment (M'_2, m/z 354). Fragmentation of M' at the C–S, C–CO, and C–N bonds gives fragments with lower molecular weights (m/z 145, 113, and 72.69).

The α-methylthioglycidic acid amides synthesized in the present research (III, V, and VIII) have slight tuberculostatic activity.

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were obtained with a Perkin–Elmer R-12 spectrometer (60 MHz). The molecular weight of trimer IX was determined with an ÉP-3 ebulliometer with $CHCl_3$ as the solvent. The mass spectra of IX were recorded with a Varian CH-8 spectrometer.

The constants and results of elementary analysis of amides I-III and V-VIII are presented in Table 1, and data from the IR and PMR spectra of I, VII, and IX are given in Table 2.

Preparation of α-Methyl-α,β-thioglycidic Acid Amides I-III by Aminolysis of the Acid Chloride (Method A). Amides I and II. A 0.2-mole sample of aniline or ethyl aminobenzoate in 50 ml of dry ether was added at −40°C to 13.6 g (0.1 mole) of 2,3-epithioisobutyryl chloride (XII) [2] in 150 ml of dry ether, after which the temperature was allowed to rise to 20°C, and the precipitate was removed by filtration and washed with water. The ether solution was evaporated, and the residue was combined with the washed precipitate and recrystallized.

2,3-Epithioisobutyrylglycine (III) was similarly obtained from 3.45 g (0.025 mole) of XII and a solution of 3.52 g (0.025 mole) of glycine ethyl ester hydrochloride in $CHCl_3$ containing 6.1 g (0.05 mole) of Et_3N. The resulting 2,3-epithioisobutyrylglycine ethyl ester (5.2 g), which was obtained in the form of a viscous oil, was treated with the calculated amount of 1 N NaOH solution. The unchanged starting ester was washed away with ether, and the aqueous solution was acidified with concentrated HCl, saturated with NaCl, and extracted with ether. The extract was dried with $MgSO_4$ and evacuated to give 3.1 g of III.

Preparation of α-Methyl-α,β-thioglycidic Acid Amides III and V-VIII by Aminolysis of α-Chloro-α-methyl-β-thiolactone (XIII) in Water (Method B). Amides III, V, and VIII. A solution of 0.02 mole of glycine, p-aminobenzoic acid, or L-valine in 20 ml of 1 N NaOH containing 0.02 mole of $NaHCO_3$ was added dropwise with vigorous stirring to 0.02 mole of XIII, and the mixture was stirred at 20°C until a homogeneous neutral (pH ~ 7) solution formed (in the case of p-aminobenzoic acid the mixture was heated at 45°C for 0.5 h). The admixed unchanged XII was extracted with ether, and the aqueous solution was saturated with NaCl and acidified with 10% HCl. The resulting amides III, V, and VIII were extracted with ether, and the extracts were dried with $MgSO_4$ and evaporated to dryness in vacuo. Amino acid derivatives III, V, and VIII are best purified by reprecipitation from bicarbonate solution by means of an acid.

No melting-point depression was observed for a mixture of III with a sample from experiment A.

Amides VI and VII. An 8.19-g (0.06 mole) sample of XIII was added slowly with vigorous stirring at 5°C to 0.12 mole of piperidine in 30 ml of water or to 16.9 ml (0.12 mole) of a 32% aqueous solution of Me_2NH in 100 ml of water. After stirring for 2 h (at 20°C), the pH of the reaction mixture was checked (in the case of Me_2NH it was sometimes necessary to add a small amount of HCl for neutralization). The reaction mixture was filtered to remove the admixed polymer (if it was present), and the filtrate was saturated with NaCl and extracted with ether. The extract was dried with $MgSO_4$, the ether was removed, and the residue was distilled.

Reaction of α-Methylthioglycidic Acid Dimethylamide. A) With Piperidine. A 0.1-ml sample of piperidine was added to a solution of 1.45 g (0.01 mole) of VII in 50 ml of absolute ether, and the mixture was protected from sunlight. After 2-4 days (at 20°C) (or after refluxing for 3 h), the resulting white crystalline precipitate was removed by filtration and washed with ether to give 0.5 g (57%) of 4,8,12-trimethyl-4,8,12-tris(dimethylaminocarbonyl)-1,2,5,6,9,10-hexathiacyclododecane (IX) with mp 234°C (from $CHCl_3$). The filtrate contained methacrylic acid dimethylamide (according to GLC). In the case of IX thin-layer chromatography (TLC) [Silufol; $CHCl_3$–MeCOOH (95:5)] gave a spot with R_f 0.59 (with I_2 as the developer). Found: C 43.68; H 5.88; N 6.40; S 29.01%. $(C_6H_{11}NOS_2)_3$. Molecular weight (by ebullioscopy in $CHCl_3$) 540. Calculated: C 43.82; H 5.98; N 6.39; S 29.24%. Molecular weight 531. Mass spectrum, m/z (relative intensity, %): 354 $[M']_2^+$ (1.1); 290 $[M' - S]_2^+$ (1.7); 209 $[M' + S]^+$ (15); 177 $[M']^+$ (13.3); 145 $[M' - S]^+$ (43.3); 144 $[M' - HS]^+$ (45); 113 $[M' - S_2]^+$ (36.7); 112

$[M' - S - HS]^+$ (70); 98 (15); 84 (5); 72 $[CONMe_2]^+$ (100); 69 $[C_4H_5O]^+$ (45); 64 (11.7); 58 (21.7); 44 $[NMe_2]^+$ (45); 41 $[C_3H_5]^+$ (51.7); 39 (13.3); 34 (11.7); 32 $[S^+]$ (10); 28 $[CO]^+$ (33.3); 18 (83.3); 15 (16.7).

B) With Dimethylamine. Similarly, the reaction of 14.5 g (0.1 mole) of VII in 350 ml of absolute ether and 3 g of Me_2NH in 200 ml of absolute ether gave 6 g (68%) of IX with mp 200-205°C; crystallization from $CHCl_3$ gave a product with mp 230-232°C. No melting-point depression was observed for a mixture of a sample of this product with a sample from experiment A.

Independent Synthesis of IX. A solution of 1.46 g (0.02 mole) of Et_2NH in 20 ml of absolute ether was added with stirring at −30°C to 2.4 g (0.01 mole) of α-acetyldithio-β-chloroisobutyric acid dimethylamide (X)* in 80 ml of absolute ether. After 24 h (at 20°C), the resulting precipitate was removed by filtration, washed with ether, and then washed with water to remove the $Et_2NH \cdot HCl$ to give 1.2 g (68%) of IX with mp 230°C (from $CHCl_3$). No melting-point depressions were noted for mixtures of a sample of this product with samples from experiments A and B.

CONCLUSIONS

1. A cyclic trimer, viz., 4,8,12-trimethyl-4,8,12-tris(dimethylaminocarbonyl)-1,2,5,6,9,10-hexathiacyclododecane, was obtained as a result of the disproportionation of α-methylthioglycidic acid dimethylamide.

2. A number of new α-methylthioglycidic acid amides were obtained in high yields by the reaction of α-chloro-α-methyl-β-thiolactone with various amines and amino acids in water.

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*Obtained by cleavage of α-methyl-α,β-thioglycidic acid dimethylamide (VII) with acetylsulfenyl chloride [7].