SULFUR HETEROCYCLES.

COMMUNICATION 11.* A NOVEL REACTION OF β-THIOLACTONES

T. P. Vasil'eva, V. M. Bystrova,
O. V. Kil'disheva, and I. L. Knunyants

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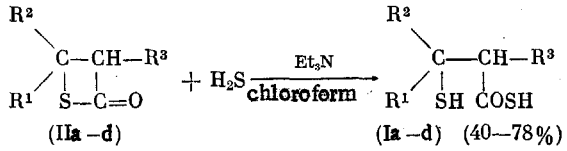
In a study of the preparation of β-mercaptothiolcarboxylic acids (I) by the reaction between acid chlorides and H_2S in the presence of triethylamine, the intermediate formation of β-thiolactones has been postulated [2]. Reactions of β-propiothiolactones with sulfur-containing nucleophilic reagents have not been studied. We here show that the reaction of β-thiolactones (IIa-d) with H_2S in the presence of Et_3N does indeed give β-mercaptothioalkanoic acids (Ia-d).

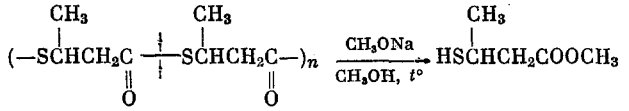


(IIa–d) (Ia–d) (40–78%)

$R^1 = R^2 = R^3 = H$ (a); $R^1 = R^2 = H$, $R^3 = Me$ (b); $R^1 = R^3 = H$, $R^2 = Me$ (c); $R^1 = R^2 = Me$, $R^3 = NHAc$ (d).

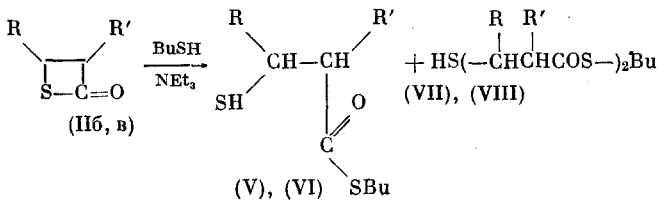
The structures of the thiol acids (Ia-d) were confirmed by spectroscopy (Table 1) and by iodometric and acidimetric titration (Table 2). Compounds (Ia-c) were obtained for the first time, but N-acetylthiolpenicillamine (Id) has been obtained previously in 20% yield by the reaction between 2-methyl-4-isopropylideneoxazolone and H_2S [3].

The reaction of β-thiolactones with H_2S is frequently complicated by polymerization, the structure of the polymeric product in the case of β-methyl-β-thiolactone (IIc) being established by depolymerization by treatment with MeONa, which resulted in the formation of methyl β-mercaptobutyrate:



For some properties of the thiol acids (Ia-c), see [2].

Cleavage of β-thiolactones with Na_2S or NH_4SH gives polymers only. It is, however, noteworthy that in the presence of sulfur-containing nucleophiles (Na_2S, NH_4SH, or sodium mercaptides) β-thiolactones (IIb-c) are extremely readily cleaved by methanol to give the esters $HSCH(R)CH(R')COOCH_3$ (R = H, R' = Me (III); R = Me, R' = H (IV)). This method can be used for the synthesis of β-mercaptocarboxylate esters cf. [4, 5]). In the presence of triethylamine, however, β-thiolactones (IIb, c) are readily cleaved by butyl mercaptan, and only under these conditions could the butyl β-mercaptothiolcaroboxylates (V) and (VI) be obtained, albeit in low yields, in addition to the dimers (VII) and (VIII).



(IIб, в) (VII), (VIII)

(V), (VI)

R = H, R′ = Me (V), (VII); R = Me, R′ = H (VI), (VIII).

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TABLE 1. Some IR (ν, cm^{-1}) and PMR (δ, ppm; J Hz) Spectral Parameters of Thiols (I) and (III)-(VIII)

Compound	PMR spectrum							IR spectrum		
	SH	COSH	CH_3	CH	CH_2	CH_2CH_2	other signals	C=O (v.s)	S—H(w)	CH_3 (m)
(Ia)	1,71t, J_{SH-CH_2}=8,0	4,69 s	–	–	–	2,6–3,2 m	–	1691, 1710	2568	–
(Ib)	1,78t, J_{SH-CH_2}=8,7	4,73 s	1,51 d, J_{CH_3-CH}=6,7	2,59–3,24 m		–	–	1691, 1708	2570	1454
(Ic)	1,92d, J_{SH-CH_2}=6,7	4,8 s	1,47d, J_{CH_3-CH}=6,7	3,19–3,69 oct	2,84–3,08m	–	–	1695, 1710	2570	1454
(Id) *	2,48s	2,61 s 1,73 s	1,47 s 1,73 s } $(CH_3)_2$ 2,28s (Ac)	3,61–3,87m	–	–	4,73d (NH), J_{NH-CH}=9,3	1693 (COS) 1545, 1660 (CON)	2540	1450, 1460
(III)	1,38t, J_{SH-CH_2}=8,0	–	1,21d J_{CH_3-CH}=6,7	2–27–3,02m		–	3,69 s (OCH_3)	–	–	–
(IV)	1,78d, J_{SH-CH}=6,7	–	1,37d, J_{CH_3-CH}=7,3	2,94–3,49 m	2,54 distorted d J_{CH_2-CH}=7,3	–	3,67 s (OCH_3)	1725–1740	2550–2565	–
(V)	†	–	1,25d, J_{CH_3-CH}=6,7	2,23–3,23m ($CH_2CHCOSCH_2$)		1,38–1,79 m	0,92 m [CH_3(Bu)]	1678, 1691	2575	1455
(VI)	1,73d, J_{SH-CH}=6,0	–	1,35d [CH_3–(CH)], J_{CH_3-CH}=6,7	3,28sext.	2,64–2,96 m (CH_2COSCH_2)	1,21–1,33 m	0,94 distorted t [CH_3(Bu)], $J_{CH_3-CH_2}$=6,7	1680, 1693	2575	1455
(VII)	†	–	1,27distorted d. J_{CH_3-CH}=6,7	2,33–3,28 sext, ($CH_2CHCOSCH_2CHCOSCH_2$)		1,38–1,77 m	0,96 distorted t [CH_3(Bu)], $J_{CH_3-CH_2}$=6,7	1680, 1690	2580	1455
(VIII)	1,74d, J_{SH-CH}=5,3	–	1,35d, J_{CH_3-CH}=6,7	3,09–3,58 m (CH^b), 3,58–4,1m (CH^a)	2,58–2,98m [$CH_2C(O)SCH_2$, $C(O)CH_2)CH^b$)]	1,31–1,63 m	0,9 distorted t [CH_3(Bu)], $J_{CH_3-CH_2}$=6,7	1680, 1692	2573	1455

*The PMR spectrum of (Id) was obtained in $CDCl_3$. In the IR spectrum, ν(NH) = 3270 cm^{-1}.
†The signal for the SH group was masked by the CH_2CH_2 multiplet of the BuS group at 1.4–1.8 ppm.

TABLE 2. Physicochemical Constants and Elemental Analyses and Titration of Thiols (I) and (III)-(VIII)

Compound prepared	Yield, %	bp, °C (p, mm Hg), or mp, °C	n_D (T., °C)	Found/calculated, %			Empirical formula	Equivalent, found/calculated	
				C	H	S		neutralization with NaOH	oxidimetric, I_2
$HSCH_2CH_2COSH$ (Ia)	42	70–73 (10)	1,5542 (23)	30,31 / 29,51	5,02 / 4,92	52,25 / 52,46	$C_3H_6OS_2$	121,9 / 122,0	57 / 61
$HSCH_2CH(CH_3)COSH$ (IB)	45	58 (3)	1,5378 (21,5)	36,04 / 35,29	5,55 / 5,88	47,05 / 47,06	$C_4H_8OS_2$	–	64 / 68
$HSCH(CH_3)CH_2COSH$ (Ic)	40	68 (6)	1,5335 (21,5)	35,40 / 35,29	5,85 / 5,88	47,84 / 47,06	$C_4H_8OS_2$	134 / 136	71 / 68
$HSC(CH_3)_2CH(NH-COCH_3)COSH$ (ID)	78	(95–98) a	–	40,83 / 40,58	6,32 / 6,28	30,71 / 30,92	$C_7H_{13}NO_2S_2$	211 / 207	105 b / 103,5
$HSCH_2CH(CH_3)COOCH_3$ (III)	40 c	65 (10)	1,4590 (22) d	–	–	–	–	–	–
$CH_3CH(SH)CH_2COOCH_3$ (IV)	29 e	65–67 (10)	1,4580 (23)	44,58 / 44,77	7,25 / 7,46	24,12 / 23,88	$C_5H_{10}O_2S$	–	138 / 134
$HSCH_2CH(CH_3)C(O)-SCH_2CH_2CH_2CH_3$ (V)	11	49 (0,02)	1,5100 (15)	49,92 / 50,00	8,20 / 8,33	33,33 / 33,33	$C_8H_{16}OS_2$	–	191 / 192
$HSCH(CH_3)CH_2C(O)-SCH_2CH_2CH_2CH_3$ (VI)	28	53–56 (0,03)	1,5005 (29)	49,75 / 50,00	8,49 / 8,33	33,45 / 33,33	$C_8H_{16}OS_2$	–	189 / 192
$HS[CH_2CH(CH_3)C(O)-S]_2CH_2CH_2CH_2CH_3$ (VII)	10,5	115–120 (0,02)	1,5250 (15)	49,13 / 48,98	7,70 / 7,70	33,05 / 32,65	$C_{12}H_{22}O_2S_3$	–	314 / 294
$HS[CH(CH_3)CH_2-C(O)S]_2CH_2CH_2CH_2CH_3$ (VIII)	22	103–105 (0,03)	1,5228 (18)	49,93 / 48,98	7,79 / 7,48	32,66 / 32,65	$C_{12}H_{22}O_2S_3$	–	285 / 294

[a] Recrystallized from benzene–hexane, mp 99°C [3].
[b] Titrated in 80% acetic acid.
[c] Yield from the reaction of (IIb) with Na_2S/MeOH; with n-BuSNa and MeOH the yield was 30%.
[d] bp 63.5-64°C (14 mm), n_D^{20} 1.4600 [4].
[e] Yield from the reaction of (IIc) with i-PrSNa/MeOH.

Monomers and dimers were thus obtained in ratios of ∿1:1, with polymers as by-products.

Some IR and PMR spectral parameters for mercaptans (III)-(VIII) are given in Table 1.

Biological tests on some of these compounds revealed that β-mercaptothiolbutyric acid (Ib) had fungicidal and insecticidal activity, and N-acetylthiopenicillamine (Id) was fungicidally and insectoacaricidally active. The activities of the compounds did not exceed 57%, but a search for novel pesticides in this type of compound holds promise.

EXPERIMENTAL

PMR spectra were obtained on a Perkin-Elmer R-12 spectrometer (60 MHz) in CCl_4 (unless another solvent is indicated), from an internal or external standard, HMDS or TMS, and IR spectra on a UR-20 spectrophotometer. Dry solvents were used in all the experiments. The molecular weights of the thiols (mono-, di-, and trimers) were determined by iodometry, by direct titration with 0.1 N iodine in alcohol [(Id) in 80% AcOH] until color persisted. The yields, constants, and the results of elemental analyses and titrations (with iodine or NaOH) of the compounds obtained (I) and (III)-(VIII) are given in Table 2, and IR and PMR spectral data in Table 1.

α-Acetylamino-β,β-dimethyl-β-thiolactone (IId). This thiolactone was obtained by a modification of the method given in [6]. To a suspension of 9.77 g (0.051 mole) of N-acetyl-D,L-penicillamine in 300 ml of CH_2Cl_2 was added at −10°C with stirring 5.17 g (0.051 mole) of Et_3N, followed by the dropwise addition of 5.54 g (0.051 mole) of ethyl chloroformate in 50 ml of CH_2Cl_2. After 1 h at − 10°C, the mixture was warmed to ∿20°C and poured into ∿0.5 liter of ether. The precipitated $Et_3N \cdot HCl$ (4.97 g, 71%) was filtered off and washed with ether. The mother liquors were evaporated to dryness under reduced pressure, and the residue triturated with ether, then with water (3 ml). The solid was then filtered off and washed on the filter with 4 ml of water to give 4.4 g (50%) of (IId), mp 122-125°C (chloroform-ether). The compound was insoluble in ether and benzene, but soluble in alcohol, CH_2Cl_2, chloroform, ethyl acetate, hot water, and dioxane. IR spectrum (ν, cm^{-1}): 1755-1760 (COS), 1560, 1658 (CON), 3245 (NH). PMR spectrum (in chloroform, from HMDS, δ, ppm): 1.73 s, 1.86 s (CH_3), 2.11 s (NAc), 3.13 d (CH); J_{CH-NH} = 7.3 Hz; 5.58-5.89 m (NH). Found: C 48.66; H 6.36; S 18.44; N 8.48%. $C_7H_{11}NO_2S$. Calculated: C 48.55; H 6.36; S 18.50; N 8.09%.

General Method for the Preparation of β-Mercaptothiolcarboxylic Acids (Ia-d). In a flask fitted with a bubbler and condenser cooled with a mixture of dry ice and acetone was placed 0.1 mole of (IIa-d) in 200 ml of chloroform. Hydrogen sulfide was passed into the solution for 0.5 h, then 10.1 g (0.1 mole) of Et_3N in 50 ml of chloroform was added, and passage of H_2S continued for 6-7 h. The mixture was warmed to ∿20°C and extracted with water (3 × 60 ml). The extract was acidified to pH ∿ 1-2, extracted with chloroform, and dried over $MgSO_4$. The solvent was removed under reduced pressure (under nitrogen), and the residue distilled in vacuo or crystallized. The thiols obtained (Ia-d) were sparingly soluble in water (pH ∿ 2-3). With sodium nitroprusside in alkaline solution they gave a raspberry coloration (qualitative test for the SH group).

Methyl β-Mercaptoisobutyrate (III). a) To a suspension of 19.2 g (0.08 mole) of $Na_2S \cdot 9H_2O$ in 200 ml of methanol at 0-5°C was added under nitrogen a solution of 8.16 g (0.08 mole) of (IIb) in 40 ml of methanol. After 2 h, the mixture was evaporated under reduced pressure, and the residue diluted with water and acidified with 10% HCl (to pH ∿ 2). The oil which separated was extracted with ether, dried over Na_2SO_4, and fractionated in vacuo under nitrogen to give 4.35 g of (III).

b) The preparation of the ester (III) by reacting α-methyl-β-thiolactone (IIb) with n-BuSNa in MeOH was carried out as for the reaction of (IIc) with i-PrSNa [see synthesis of (IV), below].

Methyl β-Mercaptobutyrate (IV). To a solution of 4.56 g (0.06 mole) of isopropanethiol in 20 ml of methanol was added under nitrogen 1.15 g of sodium, and the mixture was stirred until dissolution was complete. To the resulting mercaptide was added at −40°C 5.1 g (0.05 mole) of (IIc). The mixture was worked up as described above for (III). Fractionation gave 1.9 g of (IV).*

*The formation of (IV) in the reaction of $CH_3CH{=}CHCOOMe$ with NaSH has been reported previously [5], but no constants were given for the compound.

Reaction of (IIb) with n-Butanethiol. To a solution of 7.11 g (0.08 mole) of n-butanethiol in 50 ml of chloroform was added 6.97 g (0.07 mole) of Et_3N in 10 ml of chloroform, followed at 0°C by a solution of 7.05 g (0.07 mole) of (IIb) in 20 ml of chloroform. After 3 h at 20°C, the mixture was poured into 200 ml of ice-water, and the organic layer was separated, dried over $MgSO_4$, and fractionated to give 1.4 g of butyl β-mercaptothioloisobutyrate (V). Additionally, 1.1 g of n-butyl 4-thia-2,6-dimethyl-5-oxo-7-mercaptothiolheptanoate (VII) and 1.1 g (12.1%) of what was apparently the trimer $HS[CH_2CH(CH_3)C(O)S]_3Bu$ (n-butyl 4,8-dithia-2,6,10-trimethyl-5,9-dioxo-11-mercaptothiolundecanoate), bp 160-165°C (0.02 mm), n_D^{15} 1.5330 (iodometric mol. wt., found 411. $C_{16}H_{28}O_3S_4$ requires mol. wt. 396) were obtained.

Reaction of β-Methyl-β-thiolactone (IIc) with n-Butanethiol. The reaction of 5.1 g (0.05 mole) of (IIc) with 5.4 g (0.06 mole) of n-BuSH and 5.05 g (0.05 mole) of Et_3N was carried out as for (IIb) to give 2.7 g of n-butyl β-mercaptothiolobutyrate (VI) and 1.6 g of n-butyl 4-thia-3-methyl-5-oxo-7-mercaptothioloctanoate (VIII).

CONCLUSIONS

A method is proposed for the synthesis of β-mercaptothiolcarboxylic acids, by the reaction between β-thiolactones and hydrogen sulfide in the presence of triethylamine.

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SULFUR-CONTAINING CARBOXYLIC ACIDS.

COMMUNICATION 4. β-MERCAPTOTHIOLCARBOXYLIC ACIDS†

T. P. Vasil'eva, V. M. Bystrova, O. V. Kil'disheva, and I. L. Knunyants

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β-Mercaptothiolcarboxylic acids are important key compounds in the synthesis of 1,2-dithiolan-3-ones. Their preparation has, however, received little attention. Thiolcarboxylic acids are usually obtained by the reaction of carbonyl chlorides with H_2S in the presence of $AlCl_3$, chlorine in the α or β position of the acid chlorides not being replaced by SH [2-4]. β-Mercaptothiolcarboxylic acids are known only as the α-acylaminoderivatives, formed in low yields on reaction of 4-isopropylideneoxazolones with H_2S [5, 6].

We have now developed a general method for the preparation of the hitherto unknown β-mercaptothiolcarboxylic acids (Ia-c) from readily available β-halocarbonyl chlorides. Reaction of the latter with H_2S in the presence of triethylamine gives the thiolate anions (II) as intermediates, which then cyclize to the β-thiolactone (III), which is cleaved with H_2S without isolation to give the final products (Ia-c) as the triethylammonium salts. The intermediate β-thiolactones (III) were previously known, being obtained by cyclization of β-halothiolcarboxylic acids [7].

*Deceased.
†For communication 3, see [1].

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow.

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