SULFUR-CONTAINING CARBOXYLIC ACIDS.

COMMUNICATION 3.* SYNTHESIS OF β-(ACETYLTHIO)ALKANOIC ACIDS AMIDES

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In the preceding article we showed that β,β'-dithiodialkanoic acids and their derivatives are readily obtained by the reaction of β-(acetylthio)alkanoic acids, and their esters and acid chlorides with half-molar amounts of SO_2Cl_2 [1]

$$Ac\text{–}SCH_2CH_2COX \xrightarrow[-AcCl]{SO_2Cl_2} [ClSCH_2CH_2COX] \xrightarrow[-AcCl]{AcSCH_2CH_2COX} (SCH_2CH_2COX)_2$$

X = OH, OMe, Cl.

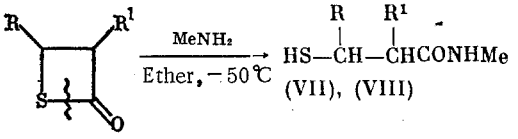
The extension of this method of synthesis of disulfides to the amides of β-(acetylthio)-alkanoic acids required the development of a synthesis route for these last compounds. The known method for the preparation of α-chloro-β-(acetylthio)butyramides by the addition of thioacetic acid to α-chlorocrotonamides [2] is limited by the reactivity of the initial unsaturated compounds. We synthesized β-(acetylthio)alkanoic acid amides (III)-(VI) by another method, i.e., the aminolysis of the corresponding acid chlorides

$$\underset{\text{(I), (II)}}{AcS\text{–}\overset{R}{\overset{|}{C}}H\text{–}\overset{R^1}{\overset{|}{C}}HCOCl} \xrightarrow[-R^2NH_2\cdot HCl]{2R^2NH_2(pK_b \geqslant 4,7)} \underset{\text{(III)–(VI)}}{AcS\text{–}\overset{R}{\overset{|}{C}}H\text{–}\overset{R^1}{\overset{|}{C}}HCONHR^2} \qquad (1)$$

R = H, R^1 = Me (I); R = Me, R^1 = H (II); R = H, R^1 = Me, R^2 = Ph (III); R = H, R^1 = Me, R^2 = CH_2Ph (IV); R = Me, R^1 = H, R^2 = Ph (V); R = Me, R^1 = H, R^2 = CH_2Ph (VI)

The corresponding anilides (III), (V) and benzylamides (IV), (VI) were obtained in high yields (see Table 1) by reacting β-(acetylthio)butyryl chloride (I) and β-(acetylthio)isobutyryl chloride (II) with aniline and benzylamine (Table 1).

However, in the case of more basic (than benzylamine) amines, reaction (1) becomes complicated by the parallel aminolysis of the S-acetyl group. Thus, the reaction of (I) or (II) with methylamine (pK_b = 3.4) led to a complex mixture of compounds containing products of splitting off the acetyl group, methylamides of β-mercaptoisobutyric (VII) or β-mercaptobutyric (VIII) acids. The last compounds were synthesized by an independent method, i.e., splitting of β-thiolactones by methylamine



R = H, R^1 = Me (VII); R = Me, R^1 = H (VIII).

In the IR and PMR spectra of (VII) and (VIII), the mercapto group appears in the region of values usual for thiols (ν = 2560 cm^{-1}, δ = 1.4-1.9 ppm, see Table 1), and hence, in contrast to hydrodisulfides [for $HSS\text{–}CH_2CH(CH_3)CONEt_2$ νSH = 2480 cm^{-1}, δSH = 7.63 ppm] [3], or thioenols [for HSC(Me)=CHCOOEt νSH = 2740 cm^{-1}, δSH = 6.95 ppm] [4], it does not participate in the formation of strong hydrogen bonds with the O atom of the carbonyl group.

In contrast to β-(acetylthio)isobutyryl chloride (I), the reaction of α-chloro-β-(acetylthio)propionyl chloride (IX) even with the strongly basic dimethylamine (pK_b 3.3) proceeds smoothly to give N,N-dimethyl α-chloro-β-(acetylthio)propionamide (X), which is identical

*For Communication 2, see [1].

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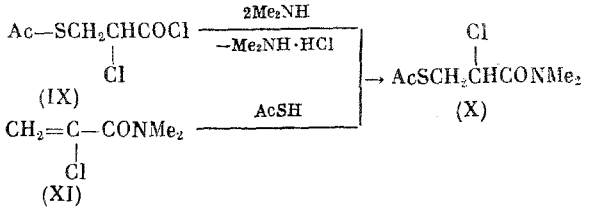
TABLE 1. Amides of β-(Acetylthio)-(III)-(VI) or β-Mercaptoalkanoic Acids (VII), (VIII)

Formula	Yield, %	mp, °C bp, °C (p, mm Hg)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm; J, Hz)	Found/calculated, %				Empirical formula
					C	H	S	N	
CH_3 CH_2–$CHCONHPh$ (III) $SCOCH_3$	96	108 (alcohol)	1557, 1602(Ar); 1660 (CON); 1692 (COS); 3260 (NH)	–	60,60 60,75	6,48 6,32	13,74 13,50	5,64 5,90	$C_{12}H_{15}NO_2S$
CH_3 CH_2–$CHCONHCH_2Ph$ (IV) $SCOCH_3$	88	60 (water)	1550 (Ar); 1645 (CON); 1690 (COS); 3318 (NH)	1,12 d (CH_3), J_{CH_3-CH}=7,33; 2,29 s (CH_3CO); 2,82–3,11 m (CH_2CH); 4,37 d (CH_2N); J_{NH-CH_2}=5,33; 7,28 s (C_6H_5); 7,36–7,67 m (NH)	62,38 62,15	6,79 6,77	12,80 12,74	5,61 5,58	$C_{13}H_{17}NO_2S$
CH_3 CH–$CH_2CONHPh$ (V) $SCOCH_3$	88	88–89 (alcohol or water)	1556, 1603(Ar); 1660 (CON); 1692 (COS); 3290 (NH)	–	60,78 60,75	5,96 6,32	13,67 13,50	5,64 5,90	$C_{12}H_{15}NO_2S$

TABLE 1 (continued)

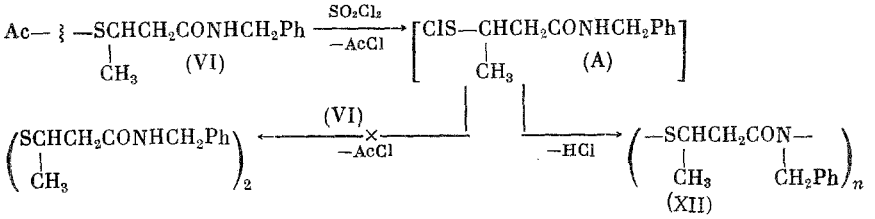
Formula	Yield, %	mp, °C bp, °C (p, mm Hg)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm; J, Hz)	Found/calculated, %				Empirical formula
					C	H	S	N	
CH_3 | $CH-CH_2CONHCH_2Ph$ (VI) | $SCOCH_3$	95	65–66 (aqueous alcohol)	1545 (Ar); 1650 (CON); 1690 (COS); 3290 (NH)	1,24 d (CH_3), J_{CH_3-CH}=7,33; 2,12 s (CH_3CO); 2,29–2,69 m (CH_2C); 3,67 m (CH); 4,25 d (CH_2N); J_{CH_2-NH}=5,34; 6,72–7,14 m (NH); 7,24 s (C_6H_5)	61,98 62,15	6,90 6,77	12,90 12,74	5,59 5,58	$C_{13}H_{17}NO_2S$
CH_3 | $CH_2-CHCONHCH_3$ (VII) | SH	78	48–50; 130 (5)	1415, (CH_3N); 1643, 1570 (CON); 2560 (SH) 3310 (NH)	1,28 d (CH_3), J_{CH_3-CH}=6,66; 1,4–1,6 m (SH); 2,93 d (CH_3N); J_{CH_3-NH}=4,4; 2,44–3,29 m ($CHCH_2$); 8,07 m (NH)	45,65 45,11	8,47 8,27	24,09 24,06	10,35 10,52	$C_5H_{11}NOS$
CH_3 | $CH-CH_2CONHCH_3$ (VIII) | SH	77	105 (2) n_D^{21} 1,5045	1415 (CH_3N); 1660, 1565 (CON); 2560 (SH); 3310 (NH)	1,5 d (CH_3), J_{CH_3-CH}=7,33; 1,9 d (SH); J_{SH-CH}=6,66; 2,65 dist. d (CH_2) J_{CH_2-CH}=6,0; 2,95 d (CH_3N), J_{CH_3-NH}=4,66; 3,1–3,7 m (CH); 8,07 m (NH)	45,30 45,11	8,13 8,27	–	10,14 10,52	$C_5H_{11}NOS$

to the dimethylamide obtained by the addition of thioacetic acid to N,N-dimethyl α-chloroacrylamide (XI)



It is possible that the presence of an electron-acceptor group (Cl in the α-position) in (IX) appreciably increases the stability of the S-acetyl group to aminolysis.

Further studies showed that alkylamides of β,β'-dithiodialkanoic acids cannot be synthesized by the above method [1]. Chlorolysis of N-benzyl β-(acetylthio)butyramide (VI) by a half-molar amount of SO_2Cl_2 is complicated by the competing dehydrochlorination reaction: the sulfenyl chloride (A) formed as an intermediate probably converts into a polymeric product (XII)



EXPERIMENTAL

The PMR spectra were obtained on a Perkin-Elmer R-12 spectrometer (60 MHz) in CCl_4, using TMS as external standard. The IR spectra were run in KBr tablets or in film. In all the experiments dry solvents were used.

Synthesis of β-(Acetylthio)alkanoic Acid Amides (III)-(VI). A 0.1-mole portion of the corresponding amine in 50-100 ml of ether was added at −40 to −60°C, with stirring, to a solution of 9 g (0.05 mole) of acid chloride (I) or (II) in 150 ml of ether. The mixture was left to stand at 20°C overnight, and the precipitate of amine hydrochloride was filtered and washed with ether. The mother liquor was evaporated to dryness, and the residue was crystallized.

Removal of ether in the case of (VI) gave an oily product, which was again dissolved in a small amount of ether. The ethereal solution was washed with dilute HCl, then with water, and dried over $MgSO_4$. After removal of ether in vacuo, compound (VI) was obtained in a solid state.

Anilide (III) is slightly soluble in water, and therefore it is partly precipitated together with aniline hydrochloride. This precipitate was combined with the residue after removal of ether from the mother liquor, and then the mixture was treated with water and the residue dried in air.

The yields, physical constants, IR and PMR spectra, and the analysis of amides (III)-(VI) are listed in Table 1.

Synthesis of Methylamides of β-(Mercapto)isobutyric (VII) and β-(Mercapto)butyric (VIII) Acids. A 2.48-g portion (0.08 mole) of methylamine was passed at −50°C, with stirring, through a solution of 4.08 g (0.04 mole) of α-methyl- or β-methyl-β-thiolactone in 200 ml of ether. The temperature was brought to 20°C, and ether and volatile impurities were removed in vacuo in a N_2 current. The compounds (VII) and (VIII) formed were purified from polymeric side products by distillation in vacuo. The purity of thiols (VII) and (VIII) obtained (see Table 1) was determined by iodometric titration.

N,N-Dimethyl α-Chloro-β-(acetylthio)propionamide (X). a) A 2.38-g portion (0.0528 mole) of dimethylamine was passed at −50°C through a solution of 5.3 g (0.0264 mole) of acid chloride (IX) [5] in 25 ml of absolute ether. The precipitate of dimethylamine hydrochloride (2.2 g) was filtered, the mother liquor was evaporated, and the residue was distilled. The yield of (X) was 4.05 g (74%), bp 129-130°C (3 mm), n_D^{20} 1.5209. Found: C 40.01; H 5.70; S 15.92; N 7.13%. $C_7H_{12}ClNO_2S$. Calculated: C 40.09; H 5.70; S 15.29; N 6.68%.

b) A 1.9-g portion (0.05 mole) of thiolacetic acid was added cautiously to 3 g (0.022 mole) of dimethylamide (XI); the reaction is exothermal. On the following day, the mixture was evaporated in vacuo, and the residue was distilled. The yield of (X) was 2.5 g (66%), bp 130°C (2 mm), n_D^{21} 1.5218.

Reaction of N-Benzyl β-(Acetylthio)butyramide (VI) with SO_2Cl_2. A 0.80-g portion (0.0059 mole) of SO_2Cl_2 in 3 ml of CH_2Cl_2 was added at −18°C to a solution of 2.51 g (0.01 mole) of benzylamide (VI) in 5 ml of CH_2Cl_2. The mixture was held at 20°C for ∿1.5 h, and the solvent was distilled in vacuo. According to the IR and PMR spectra, the residue obtained was probably a mixture (∿1:1) of polymer (XII) and the initial compound (VI).

IR spectrum (ν, cm^{-1}): 1550 (Ar, (VI + (XII)), 1635-1670 (CON, (VI) + (XII)), 1695 (COS, (VI)), 3270 (N-H, (VI)). PMR spectrum (in CH_2Cl_2, δ, ppm): 1.06-1.32 two d. (CH_3 (VI) + (XII), J_{CH_3-CH} = 7.33 Hz); 2.11 s (CH_3COS, (VI)); 2.54-3.84 hump (CH_2, (VI) + (XII)). 3.65-3.88 m (CH, (VI) + (XII)); 4.27-4.50 br. s (NCH_2, (VI) + (XII)); 6.70-7.38 (C_6H_5, (VI) + (XII); NH, (VI)).

CONCLUSIONS

Amides of β-mercapto- or β-(acetylthio)alkanoic acids were obtained by the reaction of β-thiolactones or β-(acetylthio)alkanoic acid chlorides with amines.

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INFLUENCE OF STRUCTURAL FACTORS ON STABILITY OF FLUORINE-CONTAINING METASTABLE ENOLS

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It has already been shown that perfluoro-2-propenol (I), obtained by heating 2-benzyloxyperfluoropropene with concentrated H_2SO_4 exists as an individual compound, and under the action of basic reagents is converted into a thermodynamically more favorable keto-form (pentafluoroacetone). For example, in the presence of water, this reaction is completed after 15-20 min of boiling, or after 1-2 days at room temperature [1, 2]

$$CF_2{=}C(OCH_2Ph){-}CF_3 \xrightarrow[t^\circ]{H_2SO_4} CF_2{=}C(OH){-}CF_3 \xrightarrow[20^\circ C,\ 2\ days]{H_2O} CF_2HC(O){-}CF_3$$

(I)

In the present work, we tried under similar conditions to obtain enols (II)-(IV) to determine the structural factors which impart the kinetic stability to the fluorine-containing enols

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