CLEAVAGE OF β-PROPIOTHIOLACTONES WITH METHANESULFENYL CHLORIDE AND ACETYL SULFUR CHLORIDE

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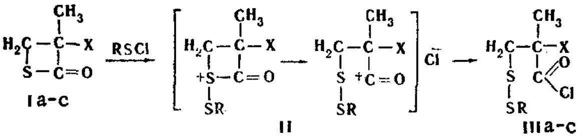
β-Propiothiolactones are cleaved at the S–CO bond by methanesulfenyl chloride and acetyl sulfur chloride to form mixed disulfides – derivatives of the acid chlorides of β-mercaptoisobutyric acid. The mixed disulfides readily disproportionate on heating under acid or base catalysis conditions to give the corresponding symmetrical disulfides. A convenient method was found for obtaining the previously hard-to-obtain symmetrical disulfides.

It has been demonstrated [1,2] that esters of thiolcarboxylic acids readily react with sulfenyl chlorides to form the corresponding disulfides [1,2]. In the present research, we studied the reaction of some β-propiothiolactones with methanesulfenyl chloride and acetyl sulfur chloride and demonstrated that, just as by the action of chlorine [3], β-propiothiolactones are cleaved by sulfenyl chlorides at the S–CO bond to give the corresponding unsymmetrical disulfides.

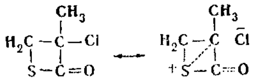
Thus α-methyl-β-propiothiolactone (Ia) is readily converted to β-(acetyldithio)isobutyryl chloride (IIIb) by the action of acetyl sulfur chloride.



I, IIIa X=H, R=CH$_3$; b X=H, R=COCH$_3$; c X=Cl, R=CH$_3$

The reactions of thioesters, sulfides, and disulfides with chlorine, sulfuryl chloride, and sulfenyl chlorides are usually considered to proceed through the formation of unstable adducts – sulfonium salts [4-6]. In the cleavage of β-thiolactone I, sulfenyl chloride also electrophilically attacks the sulfur atom to form adduct II, which is stabilized with rupture of the S–CO bond to give mixed disulfide III.

The nucleophilicity of the sulfur atom in α-chlorothiolactone Ic is reduced because of the possible contribution of a resonance structure, and, in contrast to α-methyl-β-propiothiolactone, α-chloro-α-methyl-β-propiothiolactone does not react with acetyl sulfur chloride even under severe conditions.



However, both thiolactones readily react with a stronger electrophile – methanesulfenyl chloride – under mild conditions to give the acid chlorides of mixed disulfides IIIa, c. It should be noted that symmetrical disulfides IV were obtained along with III, and the amount of unsymmetrical disulfide depended on the experimental conditions. In some cases, IV were the major reaction products. The formation of symmetrical disulfides IV was possible either as a consequence of disproportionation of III or as a result of side reactions. One cannot exclude the possibility that methanesulfenyl chloride could have simply

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TABLE 1. PMR Spectra

Compound	Chemical shift, δ, ppm (J, Hz)				
	CH (doublet)	C—CH₃	S—CH₃	O—CH₃	CH₂ (AB system)
$CH_3COSSCH_2CH(CH_3)COCl$ *	1,46 (6,7)				2,65—3,39 †
$CH_3SSCH_2CH(CH_3)COCl$ ‡	1,45 (6,7)		2,42; 2,45		2,63—3,47 †
$[—SCH_2CH(CH_3)COCl]_2$	1,44 (6,0)				
$CH_3SSCH_2CCl(CH_3)COCl$		1,95	2,46		3,31; 3,59 (14,7)
$[—SCH_2CCl(CH_3)COCl]_2$		1,95			3,45; 3,67 (14,7)
$CH_3SSCH_2CCl(CH_3)COOCH_3$		1,82	2,40	3,76	3,18; 3,54 (14,0)
$[—SCH_2CCl(CH_3)COOCH_3]_2$		1,82		3,78	3,27; 3,54 (14,0)
$CH_3SSCH_2CCl(CH_3)CONH_2$ **		1,86	2,49		3,33; 3,54 (14,7)

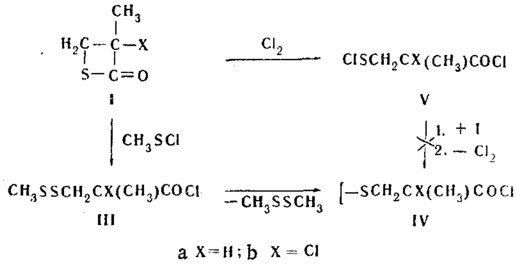
*A singlet at 2.44 ppm, which corresponds to the methyl group in $SCOCH_3$, is observed in the spectrum.

†Complex multiplet.

‡Two singlets, which correspond to the $S-CH_3$ group, are associated with the existence of two rotational isomers as a consequence of restricted rotation about the disulfide bond [5] (the character of the spectrum depends on the temperature).

**A doublet corresponding to the NH_2 group with δ 7.23 ppm and J = 44.0 Hz is observed in the spectrum.

chlorinated thiolactone I ($CH_3SCl \rightarrow CH_3SSCH_3 + Cl_2$) to sulfenyl chloride V, which could have been converted to disulfide IV either by subsequent reaction with excess thiolactone or by direct reduction.



Further investigation demonstrated that specially prepared sulfenyl chloride Vc does not react with thiolactone Ic under mild conditions and is not reduced to disulfide IVc even under severe conditions. Thus IVc was obtained as a result of the disproportionation of IIIc. A study* showed that the disproportionation depends on both the temperature and on acidic and basic impurities [7, 8]. More prolonged heating at higher temperatures (up to 150°) increases the percentage of symmetrical disulfide IV in the final products of the reaction. When crude methanesulfenyl chloride, obtained by chlorination of dimethyl sulfide with sulfuryl chloride, is used, the yield of symmetrical disulfide IV increases substantially. In a special experiment, pure mixed disulfide IIIc was readily converted to symmetrical disulfide IVc in SO_2-saturated carbon tetrachloride solution.

A symmetrical disulfide – α,α'-dichloro-β,β'-dithiodiisobutyryl chloride (IVc) – was previously obtained in several steps [9]. α-Chloro-β-(chlorothio)isobutyryl chloride (Vc) was reduced with aqueous KI and hydrolyzed to the corresponding acid, which was then reconverted to acid chloride IVc. Thus the method that we found for obtaining symmetrical disulfides by cleavage of β-thiolactones with methanesulfenyl chloride in the presence of SO_2 makes it possible to obtain quantitative yields of IV in one step.

The ready disproportionation of mixed disulfides hinders an investigation of their transformations. The following same derivatives of the corresponding symmetrical sulfides were obtained along with the methyl ester (VIa) and amide (VIb) of α-chloro-β-(methyldithio)isobutyric acid by the action of methanol or ammonia on acid chloride IIIc: the methyl ester (VIIa) and amide (VIIb) of α,α'-dichloro-β,β'-dithiodiisobutyric acid.

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*By means of PMR spectroscopy. The chemical shifts of all of the compounds are presented in Table 1.

$$\underset{\text{IIIc}}{CH_3SSCH_2CCl(CH_3)COCl} \xrightarrow{HR} \underset{\text{VIb}}{CH_3SSCH_2CCl(CH_3)COR} + \underset{\text{VIIa,b}}{[-SCH_2CCl(CH_3)COR]_2}$$

$$\text{a } R = OCH_3; \text{ b } R = NH_2$$

EXPERIMENTAL

The PMR spectra of CCl_4 solutions were recorded with a Perkin–Elmer R-12 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

β-(Acetyldithio)isobutyryl Chloride (IIIb). A 4.0-g (36 mmole) sample of CH_3COSCl was added dropwise with stirring at 0° to 3.7 g (36 mmole) of α-methyl-β-propiothiolactone. The mixture was allowed to stand at 20° for 24 h and was then vacuum-fractionated to give 85% of acid chloride IIIb with bp 110-112° (3 mm) and n_D^{20} 1.5380. Found: C 34.1; H 4.2%. $C_6H_9ClO_2S_2$. Calculated: C 33.9; H 4.2%.

β-(Methyldithio)isobutyryl Chloride (IIIa) and β,β'-Dithioisobutyryl Chloride (IVa). Acid chloride IIIa [bp 65-66° (3 mm), n_D^{20} 1.5310 . Found: C 32.7; H 4.9%. $C_5H_9ClO_2S_2$. Calculated: C 32.5; H 4.9%] and symmetrical acid chloride IVa [bp 142-143° (3 mm), n_D^{20} 1.5340. Found: C 35.0; H 4.4%. $C_8H_{12}Cl_2O_2S_2$. Calculated: C 34.9; H 4.3%] were obtained under the same conditions from 5.0 g (49 mmole) of α-methyl-β-propiothiolactone and 4.37 g (53 mmole) of undistilled CH_3SCl. The overall yield of IIIa and IVa was practically quantitative. The compounds were obtained in a ratio of 2 : 1.

α-Chloro-β-(methyldithio)isobutyryl Chloride (IIIc) and α,α'-Dichloro-β,β'-dithiodiisobutyryl Chloride (IVc). A 2.7-g (33 mmole) sample of freshly distilled CH_3SCl was added dropwise with stirring at −30° to 4.47 g (33 mmole) of α-chloro-α-methyl-β-propiothiolactone. The mixture was allowed to stand at 20° for 48 h and vacuum-fractionated to give IIIc [bp 73-75° (5 mm), n_D^{20} 1.5405. Found: C 27.1; H 3.7; Cl 33.1; S 29.3%. $C_5H_8ClOS_2$. Calculated: C 27.4; H 3.7; Cl 32.4; S 29.2%] and acid chloride IVc with bp 146-148° (3 mm) (bp 120-125° (0.02 mm) [9]); n_D^{20} 1.5510. Found: C 28.5; H 3.0; Cl 40.4; S 19.2%. $C_8H_{10}Cl_2O_2S_2$. Calculated: C 27.9; H 2.9; Cl 41.3; S 18.6%. The ratio of IIIc and IVc was 2.5 : 1. Under similar conditions but in a solution of 15 ml of dry CCl_4, the ratio of IIIc and IVc was 5.5 : 1. Under the same conditions but with crude, undistilled CH_3SCl, the ratio of IIIc and IVc was 1 : 1.

A solution of 7.75 g (94 mmole) of undistilled CH_3SCl in 15 ml of dry CCl_4 was added to 12.8 g (94 mmole) of Ic under the same conditions, and the mixture was heated at 70° for 7 h. The ratio of IIIc and IVc was 1 : 17.

A solution of 1.7 g (24 mmole) of chlorine in 30 ml of dry CCl_4 was added dropwise with stirring at −70° to a solution of 6.5 g (48 mmole) of Ic in 20 ml of dry CCl_4. The temperature of the reaction mixture was gradually brought up to 20°, and the mixture was then refluxed for 15 h. The solvent was removed, and the residue was vacuum fractionated to give, successively, unchanged Ic with bp 34-36° (3 mm), sulfenyl chloride Vc with bp 54-58° (3 mm) (bp 52-54° (2-3 mm) [3]), and, finally, acid chloride IVc with bp 146-148° (3 mm) in a ratio of 1 : 1 : 2.

A solution of 8.7 g (40 mmole) of IIIc in 50 ml of dry $CHCl_3$ saturated with SO_2 was held at 40° for 5 h. The solvent was removed, and the residue was vacuum-fractionated to give IIIc, symmetrical disulfide IVc, and CH_3SSCH_3 (in the trap) in a ratio of 1 : 6 : 6.

A solution of 2.5 g (11 mmole) of IIIc in 15 ml of dry SO_2-saturated $CHCl_3$ was held at 20° for 15 h to give IIIc, acid chloride IVc, and CH_3SSCH_3 in a ratio of 1 : 1 : 1.

Methyl α-Chloro-β-(methyldithio)isobutyrate (VIa) and Methyl α,α'-Dichloro-β,β'-dithiodiisobutyrate (VIIa). Absolute methanol (7 ml) was added to 2.19 g (10 mmole) of IIIc, and the mixture was refluxed for 1 h. The excess methanol was removed, and the residue was vacuum-fractionated to give 72% of VIa with bp 71-73° (2 mm) and n_D^{25} 1.5195. Found: C 33.4; H 5.1; S 29.9%. $C_6H_{11}ClO_2S_2$. Calculated: C 33.6; H 5.1; S 29.8%.

Symmetrical disulfide VIIa with bp 154-155° (2 mm) (bp 148° (0.04 mm) [9]), and n_D^{25} 1.5225 was also obtained in 15% yield.

α,α'-Dichloro-β,β'-dithiodiisobutyramide (VIIb). A solution of 0.5 g (29 mmole) of NH_3 in 10 ml of dry $CHCl_3$ was added dropwise with stirring at 0° to a solution of 1.72 g (5 mmole) of acid chloride IVc in 10 ml of dry $CHCl_3$. The NH_4Cl was removed by filtration, and the filtrate was partially evaporated. Petroleum ether was then added to the evaporated filtrate to give 96% of amide VIIb with mp 110-112°. Found: C 31.5; H 4.6; S 21.1%. $C_8H_{14}Cl_2N_2O_2S_2$. Calculated: C 31.5; H 4.6; S 21.0%.

α-Chloro-β-(methyldithio)isobutyramide (VIb). A solution of 0.34 g (20 mmole) of NH_3 in 20 ml of dry $CHCl_3$ was added dropwise at −30° to a solution of 2.19 g (10 mmole) of IIIc in 30 ml of dry $CHCl_3$, and the mixture was allowed to stand for 24 h. The NH_4Cl [0.53 g (98%)] was removed by filtration, and the residue (2.0 g) was dissolved in 5 ml of absolute ether. Petroleum ether was added to the ether solution to give 10% of symmetrical amide VIIb with mp 109-110°. A sample of this product did not depress the melting point of amide VIIb (see above). Evaporation of the mother liquor gave amide VIb as a viscous, undistillable oil in 85% yield. The structure of VIb was confirmed by the PMR spectrum (see Table 1).

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