variety of esters but apparently no similar reaction has been reported for thiolesters. In the latter case the milder reaction conditions prevailing in hydrogenolysis over hydrolysis could be favorable to a better yield of mercaptan. This has been now demonstrated in the case of acyl derivatives of mercaptosterols.

From the hydrogenolysis of thioesters both the alcohol corresponding to the acyl group and the free mercaptan could be isolated and identified, accounting for 95–98% of the reaction products. Dioxane and ether are suitable solvents for the hydrogenolysis which can be carried out at room temperature or sped up by heating the reagents. When the reaction is carried out at semimicro level separation and purification of the mercaptans was best accomplished through the corresponding lead mercaptides.

Although esters are generally resistant to sodium borohydride,[3] phenyl thiobenzoate gave a 40% yield of thiophenol when the thioester was reduced with sodium borohydride in dioxane. In *n*-butyl ether the thioester was quantitatively recovered unchanged.

Cholestanyl thiobenzoate afforded 3-mercaptocholestane in 50% yield by hydrolysis with sodium ethoxide; resinous material which formed in the reaction made it difficult to crystallize the thiol. However a 65% yield and practically no resinous material was obtained by the use of lithium aluminum hydride.

The pertinent results are summarized in Table I.

TABLE I

REDUCTION OF THIO ESTERS BY $LiAlH_4$

Thio ester	Solvent	Thiol Formed	Yield of Thiol, %
n-Butyl thiobenzoate	$(C_2H_5)_2O$	*n*-Butyl mercaptan	45
2-CH_3-propanethiol benzoate	$(C_2H_5)_2O$	2-Methylpropanethiol	44
2-CH_3-2-propanethiol benzoate	$(C_2H_5)_2O$	2-Methyl-2-propanethiol	41
Phenyl thiobenzoate	Dioxane	Thiophenol	96
Benzyl thiobenzoate	$(C_2H_5)_2O$	Benzyl mercaptan	85
p-CH_3O-benzyl thiobenzoate	Dioxane	*p*-Methoxy benzyl mercaptan	96
7-Thioacetylcholesteryl benzoate	$(C_2H_5)_2O$	7-Mercaptocholesterol	83
Cholestanyl thiobenzoate	$(C_2H_5)_2O$	3-Mercaptocholestane	65

(1) This work is taken from part of a thesis directed by the late Prof. Heinrich Hauptmann and submitted by Paulo A. Bobbio to the Univ. of S. Paulo in partial fulfillment of the requirements for the Doctor of Science degree.

(2) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 1197 (1947).

(3) N. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, London, 1956, p. 500.

EXPERIMENTAL

All thioesters used were purified by fractional distillation or recrystallization. A typical example of the hydrogenolysis is as follows:

A solution of 14.0 g. of benzyl thiobenzoate in 50 ml. of ether was slowly added to a mechanically stirred suspension of 3.0 g. of lithium aluminum hydride in 250 ml. of ether. After 5 hr. the excess of lithium aluminum hydride was destroyed with hydrochloric acid. The ether layer was washed and dried and, after elimination of the solvent, the residue was fractionally distilled. Yield of benzyl mercaptan, b.p. 192–194°, 6.5 g.

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3-Mercapto-2,2-diethyl-1-propanol. Opening of Oxetane Rings by Sulfur-Containing Nucleophilic Reagents

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2,2-Disubstituted 3-mercapto-1-propanols were desired for conversion to 5,5-disubstituted 1,3-oxathianes by reaction with carbonyl compounds.[1] Mercaptopropanols $HSCH_2CR_2CH_2OH$ appear to be unknown. Several possible synthetic methods were investigated briefly. Displacement of the bromide atom in I by thiourea in ethanol, either at 80° or 150°, yielded only traces of the mercapto alcohol III, a result not unexpected from the known unreactivity of neopentyl-type halides.

$$BrCH_2CR_2CH_2OAc + HSC(=NH)NH_2 \longrightarrow$$

I. R = CH_3
II. R = C_2H_5

$$\left[H_2N(NH_2{=})CSCH_2CR_2CH_2OAc \right]^{+}\ Br^- \xrightarrow{\text{base}} HSCH_2CR_2CH_2OH$$

III. R = CH_3
IV. R = C_2H_5

Ring opening of 3,3-diethyloxetane by sulfur-containing nucleophiles was then examined. The oxetane ring is known to undergo displacement with nucleophiles much like the more familiar oxiranes, though less readily. For example, Searles[2] has explored the reaction of oxetane itself with mercaptans and with thiosulfate ion. Sodium sulfide, even in large excess, converted oxetane into the sulfide, not the mercaptan.[2] Substituted oxetanes are

(1) C. S. Rondestvedt, Jr., *J. Org. Chem.*, **26**, 2247 (1961).

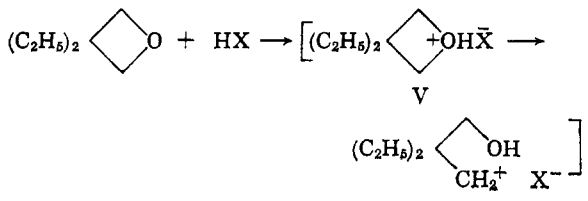
(2) S. Searles, *J. Am. Chem. Soc.*, **73**, 4515 (1951). The Bunte salt was not isolated.

cleaved by hydrogen halide or acetyl chloride.[3] We observed that when 3,3-diethyloxetane was added to aqueous hydrochloric acid saturated with hydrogen sulfide, the product was 80% of 3-chloro-2,2-diethyl-1-propanol (VI) and a little 2,2-diethyl-1,3-propanediol; no mercaptan was formed, as shown by the total absence of the intense garlic-like odor of authentic IV.

Thiourea proved to be a more effective nucleophile, and reasonable yields of IV were obtained when 3,3-diethyloxetane was exposed to this reagent in ethanol in the presence of a stoichiometric amount of hydrochloric acid. However, the product was accompanied by substantial amounts of the chlorohydrin VI, the ether-alcohol VII, and the diol VIII resulting from competition for V by chloride ion, ethanol, and water. The formation of VIII was suppressed by using anhydrous ethanol and dry hydrogen chloride, but the amounts of VI and VII were increased. Unfortunately, VI and VIII could not be separated efficiently from IV by distillation.

Replacement of hydrochloric acid by perchloric acid eliminated VI as a by-product; perchlorate anion is practically devoid of nucleophilic properties. After basic hydrolysis, the mercapto alcohol IV was obtained in 51% yield. About one fourth of the oxetane was converted into an undistillable material doubtless arising from acid-catalyzed polymerization.

It is surprising to find that the protonated oxetane V is so unselective among the nucleophilic reagents presented to it. Normally, sulfur nucleophiles like hydrogen sulfide and thiourea are much more reactive in displacement reactions than oxygen nucleophiles such as ethanol and water or chloride ion. However, most comparisons of nucleophilic character apply to basic or neutral solutions. There is evidently considerable "leveling" of nucleophilicity in acid medium. Perhaps V exists as an ion-pair in which a chloride ion is held close to the carbon atom undergoing displacement, or perhaps the reaction involves ionization to a carbonium ion.



V + $HSC(=NH)NH_2$ ⟶ $(C_2H_5)_2C(CH_2OH)CH_2SC(=\overset{+}{N}H_2)NH_2\ X^-$ —base⟶ IV

+ Cl^- ⟶ $ClCH_2C(C_2H_5)_2CH_2OH$ VI

+ C_2H_5OH ⟶ $C_2H_5OCH_2C(C_2H_5)_2CH_2OH$ VII

+ H_2O ⟶ $HOCH_2C(C_2H_5)_2CH_2OH$ VIII

(3) S. Searles, K. A. Pollart, and F. Block, *J. Am. Chem. Soc.*, 79, 952 (1957). Additional chemistry of oxetanes is considered in other papers of this series.

EXPERIMENTAL

3-Bromo-2,2-dimethyl-1-propyl acetate (I) was obtained from 2,2-dimethyl-1,3-propanediol with hydrogen bromide and acetic acid.[4] 3,3-Diethyloxetane, b.p. 135°, n_D^{25} 1.4230, was prepared by the action of hot concentrated potassium hydroxide on II.[4,5]

3-Chloro-2,2-diethyl-1-propanol (VI). *Reaction of 3,3-diethyloxetane with hydrogen sulfide and hydrochloric acid.* A mixture of 75 ml. of concd. hydrochloric acid and 150 ml. of water in a creased flask was cooled to 0–5° and saturated with hydrogen sulfide. While the flow of hydrogen sulfide continued, 34.2 g. (0.3 mole) of 3,3-diethyloxetane was added with vigorous stirring during 30 min. at 4°. After an additional 10 min., the mixture was allowed to warm to room temperature. The hydrogen sulfide flow was shut off and stirring was continued overnight. The upper layer was separated and washed with water. The combined aqueous layers were extracted with several small portions of carbon tetrachloride. The organic material was dried and distilled, b.p. 75–78°/3.5 mm., n_D^{25} 1.4624–1.4631, 35.7 g., 80% yield. Its infrared spectrum showed no SH absorption at 3.9 μ but a medium C-Cl band was visible at 13.15 μ. A portion of the distillate was crystallized from petroleum ether (b.p. 30–60°), m.p. 29.5–30.0°.

Anal. Calcd. for $C_7H_{15}ClO$: C, 55.81; H, 10.04; Cl, 23.54. Found: C, 56.2, 56.5; H, 10.2, 9.9; Cl, 23.6, 23.7; S, <0.1%.

3-Mercapto-2,2-diethyl-1-propanol. A mixture of 228 g. (2 moles) of 3,3-diethyloxetane, 500 ml. of ethanol, 100 ml. of water, and 200 g. (2.63 moles) of thiourea was stirred while 350 g. of 60% perchloric acid (2.1 moles of $HClO_4$) was added dropwise. After about one-fourth had been added, the thiourea had dissolved and the temperature had reached 50°. Cooling maintained the temperature near 30° for the balance of the addition, a total of 2.25 hr. The temperature was then raised to 50° for 2 hr., at the end of which the characteristic strong oxetane odor and its infrared band at 10.2 μ had vanished. The next day the *p*H of the mixture was adjusted to 5.0 with sodium hydroxide, and 500 ml. of solvent was removed at 60 mm., pot temperature 45°. The thiuronium perchlorate did not crystallize on treatment with methylene chloride or with benzene. The residue was boiled for 1 hr. after adding 100 g. (2.5 moles) of solid sodium hydroxide. The upper salmon-colored layer was separated, the water layer was extracted with benzene, and the organic phases were washed with water to remove ammonia and residual ethanol. The product was distilled quickly, leaving a dark viscous residue, 59.4 g. Fractionation of the distillate yielded a forerun, 47.5 g., b.p. 61–107°/13 mm., and product, b.p. 107–112°/13 mm., 150.5 g., 51% yield. A portion was crystallized from 30–60° petroleum ether, m.p. 31.5–32.0°.

Anal. Calcd. for $C_7H_{16}OS$: C, 56.70; H, 10.88; S, 21.63. Found: C, 56.1, 56.1; H, 10.8, 10.9; S, 20.9, 20.6.

Although the analysis does not agree as well as one might like, the two oxathianes[1] prepared from IV are derivatives of satisfactory purity. The infrared spectrum of IV shows the expected SH absorption at 3.9 μ; C—Cl bands are absent.

The yield can doubtless be improved by temperature control to minimize polymerization, by solvent variation (dioxane, glycol dimethyl ether, etc., and different proportions of water), and by use of other acids with weakly nucleophilic anions (RSO_3H, HBF_4, CF_3COOH).

In a similar experiment, using concentrated hydrochloric acid instead of perchloric acid, no polymer was formed but only 30% of impure IV was isolated; it was contaminated with VI. In dry ethanol with dry hydrogen chloride, the yield was 48% of IV contaminated with VI and VII. Attempted VPC analysis was foiled by the failure of the avail-

(4) Fonteyn and Ticket, *Natuurw. Tijdschr.* (*Belg.*), 25, 53 (1943).

(5) I am indebted to H. C. Walter and D. M. Lyons for this preparation.

able column packings to separate the peaks from IV and VI.

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Synthesis of Methylthiomethyl Isothiocyanate

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Considerable interest has been shown in methylthioalkyl isothiocyanates of the composition $CH_3S(CH_2)_nNCS$. These mustard oils contribute to the characteristic aroma of various *Cruciferae* species.[2] A number of these compounds (n = 2 to 9) were synthesized by Kjaer and Christensen,[2] but the first member of this series, methylthiomethyl isothiocyanate, has not been prepared. Recently, Bailey, *et al.*,[3] using gas chromatography and mass spectrometry for isolation and identification, have suggested that this isothiocyanate is an aroma component of fresh cabbage (*Brassica oleracea* var. *capitata alba*).

The synthesis of methylthiomethyl isothiocyanate was accomplished in good yields by refluxing chloromethyl methyl sulfide and potassium thiocyanate in petroleum ether, analogously to the preparation of methoxymethyl isothiocyanate.[4,5] The new mustard oil, which has a pleasing, pungent aroma, was characterized by conversion to the thiourea and isothiuronium picrate.[6]

Chloromethyl methyl sulfide was also found to react readily with thiourea to give the isothiuronium salt.

EXPERIMENTAL[7]

Chloromethyl methyl sulfide was prepared from dimethyl sulfide and sulfur chloride by the method of Richtzenhain and Alfredsson.[8]

Methylthiomethyl isothiocyanate. A mixture of 11.5 g. (0.12 mole) of dry, powdered potassium thiocyanate, 10 g. (0.10 mole) of chloromethyl methyl sulfide, and 40 ml. of petroleum ether (b.p. 35–75°) was stirred and refluxed for 6 hr. An additional 11 g. (0.11 mole) of powdered potassium thiocyanate was added during this period. After cooling overnight at 0–5°, the yellow oil that had separated as a lower layer was dissolved by adding methylene chloride. The solid present was filtered off, and the solvent was removed from the filtrate under reduced pressure. Distillation of the concentrate at 18 mm. yielded 9.88 g. (80%) of a light yellow liquid, b.p. 83–86°. Redistillation gave a mildly pungent, colorless liquid; b.p. 82–84° (17 mm.), n_D^{19} 1.5884.

Anal. Calcd. for $C_3H_5NS_2$: C, 30.23; H, 4.23; S, 53.79. Found: C, 30.40; H, 4.27; S, 54.16.

The infrared spectrum showed the typical strong isothiocyanate band at 4.97 μ.

N-(Methylthiomethyl)thiourea. A solution of 4 g. of methylthiomethyl isothiocyanate in 100 ml. of ammonia-saturated methanol was allowed to stand at room temperature for 16 hr. After removal of the methanol under reduced pressure, crystallization from hexane–ethyl acetate yielded 2.3 g. (50%) of white crystals, m.p. 96–101°. Several recrystallizations from hexane–ethyl acetate afforded glistening white leaflets, m.p. 102–104°. The absorption spectrum in ethanol showed a maximum at 247 mμ.

Anal. Calcd. for $C_3H_8N_2S_2$: C, 26.45; H, 5.92; N, 20.57. Found: C, 26.41; H, 5.96; N, 20.50.

S-Methyl-N-(methylthiomethyl)isothiuronium picrate was prepared by refluxing the thiourea in ethanol with a slight excess of methyl iodide and subsequent addition of ethanolic picric acid.[6] The picrate crystallized from ethanol as fine yellow leaflets, m.p. 153–155°.

Anal. Calcd. for $C_{10}H_{13}N_5O_7S_2$: C, 31.66; H, 3.45; S, 16.90. Found: C, 31.73; H, 3.56; S, 17.16.

S-(Methylthiomethyl)isothiouronium chloride. When a solution of 0.5 g. (0.0066 mole) of thiourea and 0.64 g. (0.0066 mole) of chloromethyl methyl sulfide in 17 ml. of acetone was allowed to stand at room temperature,[9] cloudiness began to appear in about 5 min. The mixture was cooled in ice after 1.5 hr. at room temperature, and the oil that had separated formed a white solid; 0.80 g. (70%), m.p. 126–129°. Two crystallizations from *n*-propyl alcohol gave colorless prismatic crystals, m.p. 131–133°.

Anal. Calcd. for $C_3H_9ClN_2S_2$: C, 20.86; H, 5.25; S, 37.13. Found: C, 21.10; H, 5.12; S, 37.40.

The picrate crystallized from ethanol as yellow needles, m.p. 158–160°.

Anal. Calcd. for $C_9H_{11}N_5O_7S_2$: C, 29.59; H, 3.04; S, 17.55. Found: C, 29.77; H, 3.22; S, 17.64.

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(2) A. Kjaer and B. Christensen, *Acta Chem. Scand.*, 11, 1298 (1957).

(3) S. D. Bailey, M. L. Bazinet, J. L. Driscoll, and A. I. McCarthy, *H. J. Food Sci.* 26, 163 (1961).

(4) T. B. Johnson and H. H. Guest, *Am. Chem. J.*, **41**, 337 (1909).

(5) E. Schmidt and W. Striewsky, *Ber.*, **73**, 286 (1940).

(6) L. Long, Jr., R. C. Clapp, F. H. Bissett, and T. Hasselstrom, *J. Org. Chem.*, **26**, 85 (1961).

(7) Melting points were determined in capillary tubes and are uncorrected.

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(9) J. M. Sprague and T. B. Johnson, *J. Am. Chem. Soc.*, **59**, 2439 (1937).

5-Sulfonamido-6-aminouracils

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As part of a study of 5-substituted 6-aminouracils[1] as diuretics, a series of 5-sulfonamido-6-

(1) M. Kalm, *J. Org. Chem.*, in press.