for the microanalyses, Dr. T. Williams for the nmr spectra, Mr. S. Traiman for the ir spectra, Dr. W. Benz for the mass spectra, and Dr. V. Toome for the uv spectra.

Registry No.—1a, 2888-64-4; 1d, 28506-53-8; 2a, 41075-53-0; 2b, 40973-75-9; 2c, 40973-76-0; 2d, 41075-54-1; 2e, 28199-30-6; 3f, 40973-78-2; *cis*-3g, 40973-79-3; *trans*-3g, 40973-80-6; 4, 40973-81-7; 5h, 40973-82-8; 5i, 40973-83-9; 5k, 40973-84-0; 5m, 40973-85-1; 6, 3294-96-0; 7, 40973-87-3; 8, 40973-88-4; 9, 20927-53-1; 10, 40973-90-8; 11, 40973-91-9; 12, 4964-49-2; 13a, 40973-93-1; 13b, 40973-94-2; 14, 40973-95-3; 15c, 40973-96-4; 15d, 40973-97-5; 15e, 40973-98-6; allyl bromide, 106-95-6; crotyl chloride, 625-35-4; 1-chloro-3-methyl-2-butene, 503-60-6.

Carboxyalkylthioacrylates[1]

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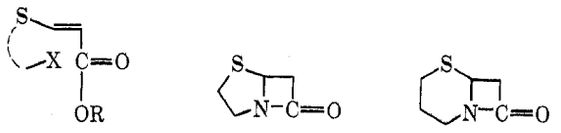
Base-catalyzed addition of mercaptoalkanoic acids and esters to propiolic acid and its esters gives, under mild conditions, carboxyalkylthioacrylic acids and their mono- and diesters. Reaction in protic polar solvents gives predominantly cis thioacrylates whereas aprotic solvents strongly favor the trans products.

It is well known that thioacrylates (I) are produced when thiols add to propiolic acid and its esters.[2]

$$RSH + HC{\equiv}CCOOR' \longrightarrow RSCH{=}CHCOOR'$$

Our interest in these compounds stemmed from the observation that the S—C=C—C=O moiety which they contain simulates a major structural feature of the penicillins (II) and cephalosporins (III). Thus,



I II III

suitably constructed thioacrylates might well be useful intermediates in the synthesis of such fused β-lactam antibiotics, the group X providing the nitrogen atom, and either X or the thioacrylate function the carbonyl group. Thioacrylates, moreover, are conveniently prepared in either the cis or the trans geometry, and preservation of this geometry during cyclization might permit a stereoselective penicillin–cephalosporin synthesis.

Alkyl, as opposed to aryl, thioacrylates seem to have been little studied. We report here upon one group of such compounds, the carboxyalkylthioacrylic acids (I, R = H, X = –COOH), their esters and half-esters, and other derivatives. The compounds (**1–15**) prepared are listed in Table I.

TABLE I

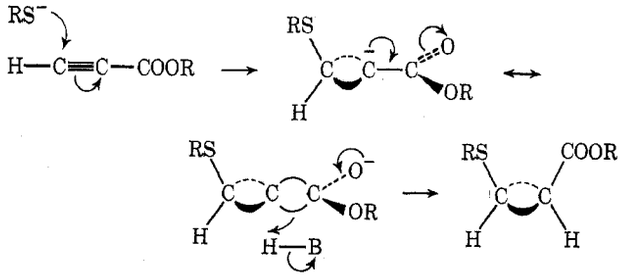
CARBOXYALKYLTHIOACRYLIC ACIDS AND ESTERS

A—CH_2CH_2—S—CH=CH—B

Compound		Group	
cis	trans	A	B
1	2	CO_2H	CO_2Et
3	4	CO_2H	CO_2H
5	6	CO_2Me	CO_2Et
7	8	CH_2CO_2H	CO_2H
9	10	CH_2CO_2H	CO_2Et
11		CO_2Me	CO_2H
12	13	COCl	COCl
14		$CONHC_6H_5$	CO_2Et
15		$CONHC_6H_5$	CO_2Et

The reaction of thiols with propiolates is very slow in the absence of catalysts but is accelerated remarkably by bases. Thus neutral alkanethiols such as benzyl mercaptan, methyl β-mercaptopropionate, and methyl γ-mercaptobutyrate react completely with propiolate esters in alcohol, aqueous alcohol, acetonitrile, or diethyl ether within 30–60 min after addition of catalytic amounts of pyridine or triethylamine at room temperature. Free mercaptoalkanoic acids neutralized to pH ~8 with rather more than 1 mol of aqueous base react equally readily, the pH of the reaction mixture rising to 10–12 as the buffering effect of the thiol group disappears. The reactive entity undoubtedly is the thiolate ion. Rather surprisingly, salts of propiolic acid react with thiols almost as readily as do esters. The carboxylate anion would hardly be expected to activate the acetylene to nucleophilic addition as much as the ester group does, and the question is open as to whether the propiolate anion or the small amount of free propiolic acid in equilibrium with it (at pH 8–9) is the entity which actually undergoes nucleophilic addition.

The predominant initial products from reactions effected in aqueous and alcoholic solvents were the cis alkylthioacrylates. The trans isomers usually could be recovered from mother liquors, with or without deliberate or fortuitous isomerization of residual cis material. The well-known rule of trans addition[3] thus is obeyed. The generally accepted rationalization of this rule involves coordination of thiolate ion at the β carbon of the acetylene to give a resonance-stabilized anion which subsequently accepts a proton from the protic solvent (HB) on its least-hindered side.

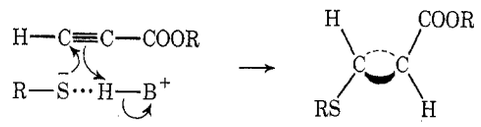


(1) A grant from Bristol Laboratories, Syracuse, N. Y. 13201, in support of this work is gratefully acknowledged.

(2) A comprehensive list of references is given in a recent paper by W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, **37**, 2391 (1972).

(3) S. Miller, *J. Chem. Chem. Soc.*, **78**, 6091 (1956); C. K. Ingold, *J. Chem. Soc.*, 2991 (1954); W. E. Truce, *J. Amer. Chem. Soc.*, **78**, 695, 2743, 2756 (1956); F. Montanari and A. Negrini, *Gazz. Chim. Ital.*, **87**, 1073 (1957).

It occurred to us that, if protonation on the less hindered side at the expense of proton donor solvent is indeed a major factor in trans addition, a change of solvent might produce a dramatic change in product stereochemistry. An aprotic solvent would be incapable of such involvement and, if, in such a solvent, the thiol and the basic catalyst were to behave as a thiolate–protobase ion pair, protonation by the protobase might, perforce, take place on the same side as thiolate coordination—a cis addition giving trans product. The lower the concentration of reactants,



moreover, the greater would be the likelihood of such quasiintramolecular reaction. This possibility promised not only a revealing test of the accepted mechanism, but also a means of tailoring the reaction, merely by change of solvent, to give a predominance of either the cis or the trans product directly, at will.

The solvent effect was explored using ethyl propiolate and methyl mercaptopropionate as reactants and a trace of triethylamine or pyridine as catalyst since these reactants, and the products, are conveniently soluble in solvents ranging from aqueous alcohol to ether and dichloromethane. Results are detailed in Table II. In dilute aqueous ethanol the

TABLE II

SOLVENT AND CONCENTRATION EFFECTS IN THE TRIETHYLAMINE-CATALYZED REACTION OF METHYL MERCAPTOPROPIONATE WITH ETHYL PROPIOLATE

Solvent	Solvent/reactant ratio (w/v)	% cis[a]	% trans[a]
None		48	52
EtOH-H_2O (1:10)	100	85	15
EtOH-H_2O (1:1)	10	85	15
EtOH	5	70	30
Et_2O	5	33	67
Et_2O	125	20	80
MeCN	5	33	67
MeCN	50	20	80
MeCN	100	20	80

[a] Determined by nmr analysis of crude mixtures after evaporation and dissolution in CCl_4.

usual product ratio (85% cis, 15% trans) was obtained. In absolute ethanol, this ratio fell to 7:3, and, in ether or acetonitrile at ordinary concentrations (20%), inverted completely to a 1:2 ratio. The extreme case, reaction in dilute (1%) solution in ether or acetonitrile gave 80% of trans and only 20% of cis product. Similar results are being obtained in other cases currently being studied, and the results obtained in a large number of thiol addition reactions which we had previously effected in aqueous, alcoholic, and aqueous–alcohol solutions, with variable isomer ratios being produced, are satisfactorily rationalized in terms of the solvent effect. We venture to predict, therefore, that base-catalyzed additions of thiols to propiolates and related activated acetylenes in dilute solution in aprotic solvents and poorly protic solvent mixtures will, in general, favor the formation of trans enesulfides.

The diacids (**3**, **4**) and their half-esters (**1**, **2**) reacted smoothly with oxalyl chloride. No indication of cis–trans isomerization was revealed by nmr spectra of the unpurified acid chlorides. The cis compounds were characterized as the anilide–ester (**14**) and the dianilide (**15**).

Experimental Section[4,5]

Structures (cis or trans) were determined by nmr,[6] vinyl proton coupling constants of 10–11 and 15–16 Hz being assigned to the cis and the trans isomers, respectively.

Ethyl 3-(2′-Carboxyethylthio)acrylate. Cis (1) and Trans (2) Isomers.—Ethyl propiolate (19.6 g, 0.2 mol) in EtOH (25 ml) was added to a solution of 3-mercaptopropionic acid (21.2 g, 0.2 mol) and KOH (11.2 g, 0.2 mol) in a water (50 ml)–EtOH (175 ml) mixture. The pH was adjusted to 8.5–9.0 and the mixture was stirred overnight, acidified with HCl (16.2 ml of 38%, 0.2 mol), and refrigerated. The white crystals (20.5 g, mp 105–106°) which were deposited were recrystallized from $CHCl_3$ (35 ml) giving *cis*-ethyl 3-(2′-carboxyethylthio)acrylate (**1**): 14.5 g (35.5%); mp 107.5–108°; ir (Nujol) 5.85, 5.95, 6.36, 14.6 μ; nmr (A-60, $CDCl_3$) δ 1.32 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.95 (m, 4 H, $-SCH_2CH_2COOH$), 4.25 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.92 (d, 1 H, J = 10.5 Hz, =CHCOOEt), 7.15 (d, 1 H, J = 10.5 Hz, –SCH=); uv $\lambda_{max}^{H_2O}$ 287 nm (ϵ 12,300). The aqueous–alcoholic mother liquor was extracted five times with $CHCl_3$; the extract was dried ($MgSO_4$), combined with the $CHCl_3$ mother liquors, and evaporated to dryness. The residue crystallized from CCl_4 (75 ml) to give additional somewhat less pure cis product (13.2 g, 33%), mp 101–106. Evaporation of the CCl_4 mother liquors gave a yellow oil (6.6 g) which was shown by nmr to be mostly the trans isomer **2**. Distillation of this was attended by considerable decomposition and afforded only 2.0 g (5%) of *trans*-ethyl 3-(2′-carboxyethylthio)acrylate (**2**): bp 152° (0.8 mm); $n^{25}D$ 1.5319; ir (liquid film) 5.87, 6.33, 7.67, 10.6 μ; nmr (A-60, $CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.94 (symmetrical multiplet, 4 H, $-SCH_2CH_2COOH$), 4.17 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.75 (d, 1 H, J = 15 Hz, =CHCOOEt), 7.67 (d, 1 H, J = 15 Hz, –SCH=); uv $\lambda_{max}^{H_2O}$ 278 nm (ϵ 18,300).

***cis*-3-(2′-Carboxyethylthio)acrylic Acid (3).**—Propiolic acid (2.0 g, 29 mmol) and 3-mercaptopropionic acid (3.03 g, 29 mmol) were dissolved in an EtOH–water (1:3) mixture (50 ml) containing KOH (3.2 g, 58 mmol). The pH was adjusted to 9 with aqueous KOH. After 4 hr the mixture was acidified with HCl (4.7 ml of 38%, 58 mmol) in water (50 ml) and chilled. The solid which separated (2.35 g, mp 182°), recrystallized from water (100 ml/g), gave *cis*-3-(2′-carboxyethylthio)acrylic acid (**3**): 2.10 g (42%); mp 187°; ir (Nujol) 5.85, 6.05, 6.38 μ; nmr (4H-100, DMSO-d_6) δ 2.60 (t, 2 H, J = 6 Hz, $-CH_2COOH$), 3.03 (t, 2 H, J = 6 Hz, $-SCH_2-$), 5.88 (d, 1 H, J = 10 Hz, =CHCOOH), 7.44 (d, 1 H, J = 10 Hz, –SCH=); uv $\lambda_{max}^{H_2O}$ 283 nm (ϵ 10,700). Partial evaporation and chilling of the combined mother liquors afforded a cis–trans mixture (2.05 g, 40%), mp 140–160°.

***trans*-3-(2′-Carboxyethylthio)acrylic Acid (4).**—A mixture similar to that used for the preparation of the cis isomer **3** was adjusted to pH 7 and kept at 25° for 30 hr prior to being acidified. Partial evaporation and chilling afforded crystals of fairly pure *trans*-3-(2′-carboxyethylthio)acrylic acid (**4**) (35%), mp 155–156°, a portion or which was recrystallized twice from water and once from C_6H_6–EtOH (10:1) mixture to give pure material: mp 158–159°; ir (KBr pellet) 5.83, 6.02, 6.33, 7.67, 10.4 μ; nmr (4H-100, DMSO-d_6) δ 2.70 (t, 2 H, J = 7 Hz, $-CH_2COOH$),

(4) See paragraph at end of paper regarding supplementary material.

(5) Spectra were determined using Varian A-60, Jeolco 4H-100, Perkin-Elmer 337, and Bausch and Lomb "Precision" instruments. Chemical shifts, δ, are ppm downfield from tetramethylsilane. Melting points are uncorrected. Solvent removal was invariably effected under reduced pressure (5–15 mm) at 30° or below.

(6) W. E. Truce and B. Groton, *J. Org. Chem.*, **27**, 128 (1962); H. Hogeveen, G. Maccagnani, and F. Taddei, *Recl. Trav. Chim. Pays-Bas*, **83**, 937 (1964).

3.14 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.83 (d, 1 H, J = 15 Hz, =CH-COOH), 7.73 (d, 1 H, J = 15 Hz, =CHS—); uv $\lambda_{max}^{H_2O}$ 275 nm (ϵ 15,800).

The cis diacid (**3**), dissolved in water containing a little H_2SO_4, was converted into the trans isomer to the extent of 95% in 2 days at 25°. Recovery of the latter acid after evaporation to dryness, washing with ice–water, and recrystallization was 65%.

cis-**Ethyl 3-(2′-Carbomethoxyethylthio)acrylate** (**5**).—Triethylamine (1 drop) was added to a solution of methyl 3-mercaptopropionate (2.4 g, 20 mmol) and ethyl propiolate (2.0 g, 20 mmol) in EtOH–water (1:1) mixture (40 ml). After 12 hr, solvent was removed by evaporation under reduced pressure to leave, in practically quantitative yield, an oil which contained (nmr) 85% of the cis and 15% of the trans product. Distillation (Nester–Faust adiabatic spinning band column, 200:1 reflux ratio) afforded *cis*-ethyl 3-(2′-carbomethoxyethylthio)-acrylate (**5**) (3.1 g, 70%, 99% pure) as a slightly yellow oil: bp 114° (0.6 mm); $n^{23}D$ 1.5141; ir (liquid film) 5.73, 5.89, 12.5, 14.1 μ; nmr (A-60, neat) δ 1.17 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.69 (slightly split triplet, 2 H, J = 5.5 Hz, $-CH_2COOMe$), 3.02 (slightly split triplet, 2 H, J = 5.5 Hz, $-SCH_2-$), 3.63 (s, 3 H, $-OCH_3$), 4.12 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.82 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.27 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 284 nm (ϵ 13,000).

trans-**Ethyl 3-(2′-Carbomethoxyethylthio)acrylate** (**6**).—Reaction effected as in the preparation of the cis isomer but in dry acetonitrile or ether (200 ml) as solvent gave an oil which contained (nmr) 80% of the trans and 20% of the cis product. Distillation gave *trans*-ethyl 3-(2′-carbomethoxyethylthio)acrylate (**6**) (2.8 g, 64%, 97% pure) as an almost colorless oil: bp 108° (0.6 mm); $n^{23}D$ 1.5107; ir (liquid film) 5.75, 5.87, 6.32, 7.67, 10.5 μ; nmr (A-60, neat) δ 1.21 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.71 (slightly split triplet, 2 H, J = 6 Hz, $-CH_2COOMe$), 3.10 (slightly split triplet, 2 H, J = 6 Hz, $-SCH_2-$), 3.61 (s, 3 H, $-OCH_3$), 4.07 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.72 (d, 1 H, J = 15 Hz, =CHCOOEt), 7.57 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 275 nm (ϵ 17,000).

Reaction effected in the absence of solvent (the mixture became quite warm) gave an equimolar mixture (nmr) of cis and trans isomers. Reactions in other solvents (Table II) gave, in all cases, weights of crude products corresponding to complete consumption of the volatile starting materials. No detectable amounts of side products were revealed by nmr.

cis-**3-(3′-Carboxypropylthio)acrylic Acid** (**7**).—γ-Thiobutyrolactone (10.2 g, 0.1 mol) was heated under reflux with NaOH (4.0 g, 0.1 mol) and phenolphthalein solution (3 drops) in water (100 ml) until a clear colorless solution was obtained (30 min). The cooled liquid was mixed with a solution of propiolic acid (7.0 g, 0.1 mol) and NaOH (4.0 g, 0.1 mol) in water (50 ml), adjusted to pH 8.5 with NaOH, kept 14 hr at 25°, acidified with HCl (16 ml of 38%, 0.2 mol), and chilled. The copious white crystalline precipitate (17.9 g, 94%) melted at 115–118° and contained (nmr) less than 5% of trans material. Pure *cis*-3-(3′-carboxypropylthio)acrylic acid (**7**), crystallized from C_6H_6 containing a little EtOH and then from water, had mp 121–122°; ir (KBr pellet) 5.92, 6.31, 6.36, 14.3 μ; nmr (4H-100, DMSO-d_6) δ 1.80 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.30 (t, 2 H, $-CH_2COOH$), 2.75 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.80 (d, 1 H, J = 10 Hz, =CHCOOH), 7.26 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 283 nm (ϵ 10,600).

trans-**3-(3′-Carboxypropylthio)acrylic Acid** (**8**).—The cis isomer (**7**) was dissolved in water (~100 ml/g) containing H_2SO_4 (~5 drops/g), and the solution was kept at 25° for 5 days and then evaporated to near-dryness. The damp solid was washed with ice–water and the crude product (mp 165–170°) was crystallized twice from CCl_4–MeOH (6:1) mixture to give pure *trans*-3-(3′-carboxypropylthio)acrylic acid (**8**) (60%), as white prisms: mp 173–174°; ir (KBr pellet) 5.87, 6.00, 6.35, 7.70, 10.4 μ; nmr (4H-100, DMSO-d_6) δ 1.80 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.32 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.85 (t, 2 H, J = 7 Hz, $-SCH_2-$), 5.68 (d, 1 H, J = 15 Hz, =CHCOOH), 7.52 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 276 nm (ϵ 14,500).

Ethyl 3-(3′-Carboxypropylthio)acrylates (**9**, **10**).—γ-Thiobutyrolactone (10.2 g, 0.1 mol) was hydrolyzed by heating (100°, 30 min) with KOH (5.6 g, 0.1 mol) in water (100 ml), and the cooled hydrolysate was mixed with a solution of ethyl propiolate (9.8 g, 0.1 mol) in EtOH (50 ml). The solution was kept 12 hr at 25° and acidified with HCl (8.1 ml of 38%, 0.1 mol), the mixture was extracted with $CHCl_3$ (4 × 50 ml), and the extracts were dried ($MgSO_4$) and evaporated to give a solid residue (19.6 g, mp 52–56°). This was crystallized from pentane (200 ml)–ether (100 ml)–$CHCl_3$ (20 ml) mixture at −20° and recrystallized by Soxhlet extraction with pentane–ether (10:1) mixture giving pure *cis*-3-(3′-carboxypropylthio)acrylic acid (**9**) (14.4 g, 66%) as fluffy white needles: mp 64–64.5°; ir (Nujol) 5.90, 6.38, 14.2 μ; nmr (4H-100, $CDCl_3$) δ 1.25 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 1.95 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.48 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.77 (t, 2 H, J = 7 Hz, $-SCH_2-$), 4.13 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.79 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.00 (d, 1 H, J = 10 Hz, —SCH=); uv $\lambda_{max}^{H_2O}$ 289 nm (ϵ 12,800). The combined mother liquors, concentrated and chilled, afforded further crystals (4.0 g, 18%, mp 25°) of largely (95%) *trans*-3-(3′-carboxypropylthio)acrylic acid (**10**). This product was not further purified and elemental analysis was not obtained: ir (liquid film) 5.85, 6.33, 7.67, 10.6 μ; nmr (4H-100, $CDCl_3$) δ 1.30 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.00 (quintet, 2 H, J = 7 Hz, $-CH_2CH_2CH_2-$), 2.52 (t, 2 H, J = 7 Hz, $-CH_2COOH$), 2.88 (t, 2 H, J = 7 Hz, $-SCH_2-$), 4.17 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.77 (d, 1 H, J = 15 Hz, =CHCOOEt), 7.63 (d, 1 H, J = 15 Hz, —SCH=); uv $\lambda_{max}^{CH_3OH}$ 278 nm (ϵ 18,000).

cis-**3-(2′-Carbomethoxyethylthio)acrylic Acid** (**11**).—Methyl 3-mercaptopropionate (2.4 g, 20 mmol) in ethanol (5 ml) was added to propiolic acid (1.4 g, 20 mmol) and KOH (1.12 g, 20 mmol) in ethanol–water (1:3) mixture (20 ml). The pH was adjusted to 8 with KOH and the solution was stirred overnight, acidified with HCl (1.6 ml of 38%, 20 mmol), and chilled, when it set to a slurry of fine white needles (2.8 g, 73%, 95% cis, mp 91.5–92°). Pure *cis*-3-(2′-carbomethoxyethylthio)acrylic acid (**11**) was crystallized from carbon tetrachloride as needles: mp 94–95°; ir (Nujol) 5.78, 5.98, 6.40 μ; nmr (A-60, $CDCl_3$) δ 2.96 (m, 4 H, $-SCH_2CH_2COOMe$), 3.75 (s, 3 H, $-OCH_3$), 5.97 (d, 1 H, J = 10.5 Hz, =CHCOOH), 7.40 (d, 1 H, J = 10.5 Hz, —SCH=), 11.18 (s, 1 H, -COOH); uv $\lambda_{max}^{H_2O}$ 275 nm (ϵ 10,000).

Dianilide (**15**) **and Diacid Chloride** (**12**) **of** *cis*-**3-(2′-Carboxyethylthio)acrylic Acid** (**3**), **and Diacid Chloride** (**13**) **of the Trans Diacid** (**4**).—The cis (**3**) and trans (**4**) diacids (0.35 g, 2 mmol) were heated under reflux 2 hr with oxalyl chloride (2 ml). Removal of excess reagent under reduced pressure gave very pale green viscous oils. The nmr spectra (A-60, $CDCl_3$, Table I, compounds **12** and **13**) of these were readily distinguishable from each other and from the starting materials, indicated the essential absence of isomerization of either to other, and were entirely consistent with smooth conversion into the desired diacid chlorides. The cis product, in ether, was treated with an ethereal solution of aniline (0.37 g, 4 mmol) and pyridine (0.32 g, 4 mmol). A gummy solid separated. After 12 hr, the supernatant ether was removed by decantation and the residue was crystallized, successively, from acetone–water (1:1) and EtOH–water (1:1) mixtures to give the cis dianilide (**15**) (0.33 g, 50%) as colorless leaflets: mp 165°; ir (Nujol) 3.03, 5.99, 6.08, 6.22, 6.27 μ.

Anilide (**14**) **of** *cis*-**Ethyl 3-(2′-carboxyethylthio)acrylate** (**1**).—The cis acid–ester (**1**) (0.36 g, 1.8 mmol) dissolved with vigorous effervescence in warm oxalyl chloride (1 ml). The solution was kept at 25° overnight and evaporated, and the residue in ether (15 ml) was treated with a solution of aniline (0.17 g, 1.9 mmol) and pyridine (0.14 g, 1.9 mmol) in ether (25 ml). Isolation with ether and recrystallization from EtOH–water (1:4) mixture gave the cis anilide–ester (**14**) (0.20 g, 38%) as white crystals with a pale-green cast: mp 125–125.5°; ir (Nujol) 3.03, 5.90, 6.00, 6.23, 6.36, 13.3, 14.4 μ; nmr (A-60, $CDCl_3$) δ 1.27 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 2.75 (t, 2 H, J = 6.5 Hz, $-CH_2CONHPh$), 3.15 (t, 2 H, J = 6.5 Hz, $-SCH_2-$), 4.21 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 5.88 (d, 1 H, J = 10 Hz, =CHCOOEt), 7.40 (m, 6 H, $-C_6H_5$ and —SCH=), 8.30 (s, 1 H, PhNH–); uv $\lambda\lambda_{max}^{CH_3OH}$ 245 nm (ϵ 16,000), 285 (15,700).

Registry No.—**1**, 41108-51-4; **2**, 41108-52-5; **3**, 41108-53-6; **4**, 41108-54-7; **5**, 41108-55-8; **6**, 41108-56-9; **7**, 41108-57-0; **8**, 41108-58-1; **9**, 41108-59-2; **10**, 41108-60-5; **11**, 41108-61-6; **12**, 41108-62-7; **13**, 41108-63-8; **14**, 41108-64-9; **15**, 41108-65-0; ethyl propiolate, 623-47-2; 3-mercaptopropionic acid, 107-96-0; methyl 3-mercaptopropionate, 2935-90-2; γ-thiobutyrolactone, 1003-10-7.

Supplementary Material Available.—Elemental analysis are given in Table III which will appear following these pages in the

microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3507.

The Stringent Requirement for Electrophiles in the Facile Solvolytic Hydrolysis of Neutral Sulfate Ester Salts[1]

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The facile desulfation of neutral sulfate ester salts in boiling moist dioxane is well known. The present studies provide evidence that the solvolysis requires initiation by traces of impurities presumably behaving as electrophiles. The surface of a glass containing vessel is adequate to initiate a reaction which is precipitously catalyzed to completion by the acidic products produced. In clean *Teflon* vessels but *not in glass*, 2-octanol (potassium sulfate) (I) and the cholestan-3β-ol analog (II) are stable for prolonged periods in hot moist dioxane, but are almost instantly solvolyzed following addition of almost any trivial potentially acidic contaminant encountered in a laboratory environment. At ambient temperature, dioxane solutions–suspensions of I and II are solvolyzed in less than 1 hr after addition of a trace of H_2SO_4 or other electrophilic reagents.

Sulfate esters of steroids,[2,3] many carbohydrates,[4,5] and simple alcohols[6,7] are notably resistant to hydrolysis in neutral or acidic aqueous systems; however, under appropriate conditions many of these are rapidly solvolyzed in relatively nonpolar, nucleophilic solvents, especially moist (<1% H_2O) ether, dioxane, and tetrahydrofuran. In these solvents, the *free acid esters* desulfate easily at *ambient temperature* while neutral alkali metal salts, with modest exceptions,[2,8] are ordinarily stable.[9]

Ammonium salts (but not sodium salts) of specific sulfatides elaborated by *Mycobacterium tuberculosis* also undergo facile solvolytic hydrolysis at ambient temperature in reagent-grade "anhydrous" ether (H_2O content ~0.005%).[10,11] The principal mycobacterial sulfatide (SL-I) is a complex tetraacyl trehalose-2-sulfate.[12] Studies with these sulfatides led us to the inference that alkali metal sulfate ester or sulfatide salts in general should ordinarily be stable in ether solvents, that a trace of mineral acid or appropriate electrophile should *initiate* solvolysis, and that the reaction would accelerate to completion, since each desulfation event generates a strongly acidic anion (HSO_4^-). For various salts of the mycobacterial SL-I, these deductions were verified.[11]

In earlier studies of steroid sulfate esters Burstein and Lieberman concluded that the species undergoing reaction is the free steroid hydrogen sulfate, and offered a probable mechanism as reproduced in Figure 1.[3] Conclusions of Batts[7] also implicate the zwitterion (of Figure 1) as the reactive species. The proposed mechanisms of our own studies and of Figure 1 have in common the requirement of an intermediate in which the sulfate ester oxygen has accepted a proton (*cf.* also Benkovic[13] and Benkovic and Dunikoski[14]).

It is well known, however, that alkali metal salts of even simple sulfate esters undergo rapid solvolysis in apparently *neutral* ether solvents at elevated temperature, as, for example, in boiling moist dioxane.[8,15,16] In the Haines' group's studies of the sulfatides of *Ochromonas danica*, the solvolysis of (+)-2-octanol (potassium sulfate) as a model compound was examined. Like many steroid sulfatides, it hydrolyzed in minutes in boiling dioxane–1% H_2O (with retention of optical configuration).[16,17] In their interpretation of the reaction, Haines, *et al.*, proposed a quite different mechanistic model in which the water participating in the reaction was assigned a prominent role in hydrating the sulfate core to generate a species proposed as reactive for the nucleophilic solvent (Figure 2). In this interpretation,[18] the intervention of electrophiles or protons is not required—a concept in contradiction with earlier conclusions. The "neutral" conditions of the solvolysis were implicitly advocated as a means of avoiding complications of acidic hydrolysis.[17]

However, reference to this high-temperature transformation as a solvolysis in *neutral* moist dioxane becomes untenable after the initial few desulfation events. The intermediate dioxane–SO_3 complex must be considered

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(18) Respecting Figure 2, Mayers, *et al.*,[17] and Haines[16] suggest that a hydrated complex in which the water molecule is bonded to two negatively charged oxygens (rather than as in the reactive complex postulated) would have greater stability. However, this would not lead to the desired products on attack by the solvent. It was suggested therefore that the "heat required for the reaction is necessary to provide the initial reacting species" as formulated in Figure 2.