

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Biosynthesis of Penicillins. VII.¹ Oxy- and Mercaptoacetic AcidsBY QUENTIN F. SOPER, CALVERT W. WHITEHEAD, OTTO K. BEHRENS, JOSEPH J. CORSE² AND REUBEN G. JONES

A continuation of the studies on the use of substituted acetic acids for the biosynthesis of penicillins has led to the preparation and testing of a large series of oxy- and mercaptoacetic acids of the types ROCH_2COOH and RSCH_2COOH and certain of their derivatives. The methods of testing^{3,4} and the isolation and characterization of some of the resulting penicillins⁵ have been covered previously.

The new compounds are listed in Tables I to VI inclusive and the stimulation tests³ using *P. notatum* NRRL 1976 and *P. chrysogenum* Q176 are reported in Tables I, III, IV, VI and VII. Certain of the aryl- and lower alkylmercaptoacetic acids and their derivatives were effectively utilized by the molds, particularly Q176. In contrast with phenylacetic acid and its derivatives, the free mercaptoacetic acids appeared to be utilized as well as and in some cases better than their valine and N-2-hydroxyethyl amides. The large number of active compounds of this series, containing both aromatic and aliphatic groupings, has made possible the preparation of an interesting variety of new penicillins. Of special interest are the penicillins derived from aliphatic mercaptoacetic acids. Aliphatic-type penicillins, with the exception of the naturally-occurring "F" and "K" types (which are very difficult to isolate in pure form), have been relatively unknown heretofore.

As a group, the oxyacetic acids and their derivatives were much less effective than the mercaptoacetic acids as penicillin precursors. Nevertheless, a number of penicillins, notably phenoxy-methyl^{5,6} and *p*-methoxyphenoxy-methylpenicillin⁵ have been obtained by the use of oxyacetic acid precursors.

In some cases in which the stimulation tests have given inconclusive results, the penicillin-containing broths have been subjected to partition analysis by the Craig technique.⁴ The cases in which such analyses have been made and the conclusions drawn therefrom as to the presence or absence of new penicillins are indicated in Tables I, III, IV, VI and VII.

Conventional methods have been employed in the preparation of the new oxyacetic acid com-

pounds of Tables I, II and III and the new mercaptoacetic acid compounds of Tables IV, V and VI.

Experimental

Oxyacetic Acids and Derivatives.—The oxyacetic acid, (Table I) were prepared by following the general procedures developed for the aryloxy^{7,8} and alkyloxy⁹ compounds.

Esterification was accomplished with alcohol using sulfuric acid as catalyst.

The 2-hydroxyethylamides and valine derivatives were synthesized as described previously.^{1,4}

Mercaptoacetic Acids and Derivatives.—In general these acids were prepared by the action of an organic halide on the sodium mercaptide. In most cases the aliphatic types were obtained by the procedure of Larsson,^{10a} from thioglycolic acid and alkyl halides, whereas the arylmercapto acids were prepared from the sodium thiophenolate and chloroacetic acid.^{10b}

The derivatives were prepared as in the case of the oxy acids.

2,3-Dibromopropylmercaptoacetic Acid.—A solution of 23.9 ml. (0.2 mole) of allylmercaptoacetic acid in 400 ml. of chloroform was cooled to 0°. To this solution was added, with stirring and cooling (< 5°), 10.3 ml. of bromine in 100 ml. of chloroform. The mixture was allowed to come to room temperature and then the solvent was removed *in vacuo*. The residual acid weighed 53.8 g.

***m*-Trifluoromethylthiophenol.**—The Grignard reagent was prepared from 140 g. (0.5 mole) of *m*-trifluoromethyliodobenzene^{10c} and 15 g. of magnesium in a total of 400 ml. of dry ether. Then 16 g. (0.5 g. atom) of powdered sulfur was added with stirring in small portions over a period of one-half hour. The mixture was stirred for an additional fifteen minutes and decomposed by the dropwise addition of 50 ml. of water followed by 125 ml. of 6 *N* hydrochloric acid. The ether layer was separated and washed with 250 ml. of 2.5 *N* sodium hydroxide solution. Acidification of this extract yielded a brown oil which was dissolved in ether and the organic solution was dried over magnesium sulfate. Distillation gave the colorless thiophenol, b. p. 84–86° (40 mm.). The yield was 57 g.

The original ether solution was evaporated to a dark, viscous oil. To this residue was added 50 ml. of glacial acetic acid and 25 g. of zinc dust. The mixture was heated on the steam-bath for one hour and then treated with 200 ml. of 6 *N* hydrochloric acid. The solution was filtered and the filtrate and precipitate extracted well with ether. This treatment yielded an additional 17 g. of *m*-trifluoromethylthiophenol bringing the total yield to 74 g. (84%).

Anal. Calcd. for $\text{C}_7\text{H}_5\text{F}_3\text{S}$: C, 47.17; H, 2.89. Found: C, 46.90; H, 2.93.

β -(2-Pyridyl)-ethylmercaptoacetic Acid, Phosphate Salt.—2-(β -Mercaptoethyl)-pyridine (50 g., 0.45 mole) was dissolved in 300 ml. of water containing 35 g. (0.88 mole) of sodium hydroxide. Chloroacetic acid (40 g., 0.43

(1) For the preceding paper of this series see Jones, Soper, Behrens and Corse, *THIS JOURNAL*, **70**, 2843 (1948).

(2) Present address: University of California at Los Angeles, Los Angeles, California.

(3) Behrens, Corse, Jones, Mann, Soper, Van Abeele and Chiang, *J. Biol. Chem.*, **175**, 751 (1948).

(4) Behrens, Corse, Huff, Jones, Soper and Whitehead, *ibid.*, **175**, 771 (1948).

(5) Behrens, Corse, Edwards, Garrison, Jones, Soper, Van Abeele and Whitehead, *ibid.*, **175**, 793 (1948).

(6) "Chemistry of Penicillin," Princeton University Press, 1948, Chapter 19.

(7) Koelsch, *THIS JOURNAL*, **53**, 304 (1931).

(8) Hayes and Branch, *ibid.*, **65**, 1555 (1943).

(9) Fuson and Wojcik, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 260.

(10) (a) Larsson, *Ber.*, **63**, 1347 (1930); (b) Behaghel, *J. prakt. Chem.*, [2] **114**, 287 (1926).

(10c) Finger and Kanowski, *Trans. Illinois State Acad. Sci.*, **37**, 66 (1944); *C. A.*, **39**, 1146 (1945).

TABLE I
OXYACETIC ACIDS, ROCH₂CO₂H

R	Yield, %	M. p., °C. ^a	Formula	Analyses, %				Stimula- tion ^b
				Calcd. C	Calcd. H	Found C	Found H	
Allyl ^{9,c}	72	B. p. 78-81 (1.2 mm.)	C ₈ H ₉ O ₃	51.72	6.94	50.37	7.11	0.6 ⁱ
<i>m</i> -Trifluoromethylphenyl ¹¹	74	92-93	C ₉ H ₇ F ₃ O ₃	49.10	3.21	49.59	3.26	
<i>m</i> -Acetylphenyl ^d	62	117	C ₁₀ H ₁₀ O ₄	61.85	5.19	61.64	4.92	
<i>p</i> - <i>s</i> -Amylphenyl ^{e,f}	71	Oil	C ₁₃ H ₁₈ O ₃	70.24	8.16	71.61	8.77	Toxic
<i>p</i> -N-Allylcarboxamidomethyl-phenyl ^g	72	137-139	C ₁₃ H ₁₅ NO ₄	(N, 5.64)		(N, 5.92)		1.0 ^j
4-Chloro-2-biphenyl ^d		118-119	C ₁₄ H ₁₁ ClO ₃	64.07	4.22	64.11	4.45	1.0
<i>p</i> -Anilinophenyl ^h	80	132.5-135	C ₁₄ H ₁₃ NO ₃	(N, 5.76)		(N, 5.97)		

^a The solid acids were recrystallized from dilute ethanol or a mixture of benzene and low-boiling petroleum ether. ^b The values represent the ratio units in experimental flask/units in control flask. ^c *n*_D²⁰ 1.4440. ^d Phenol obtained from the Dow Chemical Co. ^e Phenol supplied by Sharples Chemicals, Inc. ^f The *p*-chlorobenzylisothiuronium salt¹² crystallized from ethanol, m. p. 159-160°. *Anal.* Calcd. for C₂₁H₂₇ClN₂O₃S: N, 6.63. Found: N, 6.33. ^g Prepared in the usual manner from N-allyl-*p*-hydroxyphenylacetamide.⁴ ^h Phenol supplied by B. F. Goodrich Co. ⁱ Craig machine analysis indicated new penicillin was formed (strain Q176 and NRRL 1976). ^j Craig machine analysis did not indicate that a significant amount of new penicillin was formed (Q176).

TABLE II
OXYACETATES, ROCH₂CO₂R'

R	R'	Yield, %	M. p., °C.	Formula	Analyses, %			
					Calcd. C	Calcd. H	Found C	Found H
<i>p</i> -Bromophenyl ⁷	Methyl	90	49.5	C ₉ H ₉ BrO ₃	44.01	3.70	44.30	3.66
<i>p</i> -Arsonophenyl ¹³	Methyl		191	C ₉ H ₁₁ O ₆ As	37.23	3.82	37.63	3.93
<i>m</i> -Trifluoromethylphenyl	Methyl	89	B. p. 101 (3 mm.)	C ₁₀ H ₉ F ₃ O ₃	51.29	3.87	51.01	3.68
<i>p</i> -Carboxyphenyl ¹⁴	(di)Methyl	56	92	C ₁₁ H ₁₂ O ₅	58.92	5.40	59.42	5.45
<i>p</i> -Tolyl ⁷	Methyl	90-95	B. p. 119 (5 mm.)	C ₁₀ H ₁₂ O ₃	66.65	6.75	66.56	6.83
<i>p</i> -Methoxyphenyl ⁷	Methyl	90-95	50	C ₁₀ H ₁₂ O ₄	61.21	6.17	61.67	6.14
<i>m</i> -Acetylphenyl	Methyl	87	61-62	C ₁₁ H ₁₂ O ₄	63.45	5.81	63.51	5.61
<i>p</i> -Acetylphenyl ^c	Methyl	78	81.5	C ₁₁ H ₁₂ O ₄	63.45	5.81	63.93	5.52
<i>p</i> -Phenylene (di) ¹⁵	(di)Methyl	90-95	90-92	C ₁₂ H ₁₄ O ₅	56.68	5.56	56.57	5.62
3,4-Dimethylphenyl ¹⁶	Methyl	85	B. p. 126-128 (3 mm.)	C ₁₁ H ₁₄ O ₃	68.02	7.27	68.40	7.36
Thymyl ⁷	Methyl	87	B. p. 125-128 (3 mm.)	C ₁₃ H ₁₈ O ₃	70.24	8.16	70.61	8.63
Menthyl ¹⁷	Methyl	100	B. p. 118 (3.5 mm.)	C ₁₃ H ₂₄ O ₃	68.38	10.59	69.61	10.43
2-Biphenyl ¹⁸	Methyl	86	48	C ₁₆ H ₁₄ O ₃	74.26	5.82	74.35	5.56
<i>p</i> -Phenylazophenyl ¹⁸	Methyl	99	88-89	C ₁₆ H ₁₄ N ₂ O ₃		N, 10.37		11.05
<i>p</i> -Anilinophenyl	Ethyl	81	79-81 ^d	C ₁₆ H ₁₇ NO ₃		N, 5.16		5.33
<i>p</i> -Benzoylphenyl ¹⁹	Methyl	82	99	C ₁₆ H ₁₄ O ₄	71.10	5.22	71.00	5.24

^a References are made to the oxyacetic acids recorded in the literature. ^b The esters were crystallized from dilute ethanol, ethyl acetate or low-boiling petroleum ether. ^c Acid was not isolated. ^d Crystallized from dilute ethanol as grey needles turning to blue.

TABLE III
OXYACETIC ACID DERIVATIVES
ROCH₂CONHCH₂CH₂OH (E); ROCH₂CONHCHCH(CH₃)₂ (V)

R	Deriv.	M. p., °C.	Formula	Analyses, %				
				N, Calcd.	N, Found	C, Calcd.	C, Found	
Hydrogen	E	B. p. 195-200 (d., 1.5 mm.)	C ₄ H ₉ NO ₃	11.76	11.74	C, 40.33; H, 7.62	C, 40.38; H, 8.66	1.0
Ethyl ⁹	E	B. p. 120-126 (1.5 mm.)	C ₆ H ₁₃ NO ₃	9.08	9.43	C, 46.71; H, 9.00	C, 46.72; H, 9.35	0.8
Allyl ^a	E ^b	B. p. 149-151 (1.5 mm.)	C ₇ H ₁₃ NO ₃	8.80	8.83			0.6

(11) Swarts, *Bull. classe sci. acad. roy. Belg.*, **113**, 241 (1913); *C. A.*, **8**, 680 (1914).

(12) Dewey and Sperry, *THIS JOURNAL*, **61**, 3251 (1939).

(13) Palmer and Kester, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 75.

(14) Meyer and Duczmal, *Ber.*, **46**, 3373 (1913).

(15) Bischoff and Fröhlich, *ibid.*, **40**, 2797 (1907).

(16) Gluud and Breuer, *Chem. Centr.*, **90**, I, 626 (1919).

(17) Leffler and Calkins, "Organic Syntheses," **23**, 52 (1943).

(18) Mai and Schwabacher, *Ber.*, **34**, 3936 (1901).

(19) Torres, *Anal. soc. españ. fis. y quim.*, **24**, 82 (1926); *C. A.*, **20**, 2158 (1926).

TABLE III (Continued)

R	Deriv.	M. p., °C.	Formula	Analyses, %		Stimu- lation
				N, Calcd.	N, Found	
2,4,6-Trichlorophenyl	E ^c	128-129	C ₁₀ H ₁₀ Cl ₃ NO ₃	4.69	4.73	0.9
				C, 40.22; H, 3.88	C, 39.94; H, 3.28	
2,4,6-Trichlorophenyl	V ^c	186-187	C ₁₃ H ₁₄ Cl ₃ NO ₄	3.95	4.14	0.9
				C, 44.03; H, 3.98	C, 44.03; H, 3.93	
<i>p</i> -Bromophenyl	E	108	C ₁₀ H ₁₂ BrNO ₃	5.12	5.04	1.4
<i>p</i> -Chlorophenyl ^{7,a}	E	95-96.5	C ₁₀ H ₁₂ ClNO ₃	6.10	6.29	1.1
<i>p</i> -Chlorophenyl	V	136-138	C ₁₃ H ₁₅ ClNO ₄	4.89	4.53	1.0
<i>p</i> -Nitrophenyl ^{8,a}	E	Oil	C ₁₀ H ₁₂ N ₂ O ₅	11.66	11.79	1.15
Phenyl ^a	E	45-48	C ₁₀ H ₁₃ NO ₃	6.97	7.15	1.5
Phenyl	V ^d	109-110	C ₁₃ H ₁₇ NO ₄	5.57	5.47	1.1
<i>p</i> -Arsonophenyl	E ^{c,e}	161-164	C ₁₂ H ₂₁ N ₃ O ₇ As	7.37	7.36	1.1 ^k
<i>m</i> -Trifluoromethylphenyl	E	86	C ₁₁ H ₁₂ F ₃ NO ₃	5.32	5.44	1.0
<i>p</i> -Carboxyphenyl	E(di)	150	C ₁₃ H ₁₅ N ₂ O ₆	9.93	10.03	1.0 ^k
Benzyl ²⁰	E	Oil	C ₁₁ H ₁₅ NO ₃	6.70	6.99	1.0
<i>p</i> -Tolyl	E ^f	89-90	C ₁₁ H ₁₆ NO ₃	6.70	6.77	1.15
<i>p</i> -Methoxyphenyl	E ^g	83.5	C ₁₁ H ₁₆ NO ₄	6.22	6.30	0.7
<i>p</i> -Acetylphenyl	E ^h	138-139	C ₁₂ H ₁₆ NO ₄	6.22	6.30	0.7
<i>p</i> -Phenylene (di)	E(di) ^c	165	C ₁₄ H ₂₀ N ₂ O ₆	8.97	9.25	0.9 ^k
3,4-Dimethylphenyl	E	103	C ₁₂ H ₁₇ NO ₃	6.27	6.35	1.1
1-Naphthyl ⁷	E ⁱ	135-136	C ₁₄ H ₁₅ NO ₃	5.71	5.99	1.0
2-Naphthyl ⁷	V	145-146	C ₁₇ H ₁₉ NO ₄	4.65	4.74	1.0
Thymyl	E ^g	65	C ₁₄ H ₂₁ NO ₃	5.57	5.45	0.5
<i>l</i> -Menthyl	E	Oil	C ₁₄ H ₂₇ NO ₃	5.44	5.35	1.0
2-Biphenyl	E	82	C ₁₆ H ₁₇ NO ₃	5.16	5.21	Toxic
<i>p</i> -Phenylazophenyl	E ^f	151-152	C ₁₆ H ₁₇ N ₃ O ₃	14.04	14.32	0.8
<i>p</i> -Anilinophenyl	E ^j	81-83	C ₁₆ H ₁₈ N ₂ O ₃	9.79	9.80	0.7 ^k
<i>p</i> -Benzoylphenyl	E ^f	110.5-111	C ₁₇ H ₁₇ NO ₄	4.68	4.36	0.9

^a Intermediate(s) not isolated. ^b n_D^{22} 1.4811, the amide is soluble in water, ethanol and chloroform but is insoluble in carbon tetrachloride and ether. ^c From ethanol. ^d From ethylene chloride or ether-petroleum ether. ^e Ethanol-ammonium salt. ^f From ethyl acetate. ^g From ethyl acetate-petroleum ether. ^h From ethyl acetate-methanol. ⁱ From ether-ethanol. ^j From tetrachloroethane. ^k Craig machine analysis did not indicate that a significant quantity of new penicillin was formed.

TABLE IV

MERCAPTOACETIC ACIDS, RSCH₂CO₂H

References are to the halides from which the acetic acids were prepared. Except as noted test strain NRRL1976 was used.

R	Yield, %	B. p., °C. (mm.)	Formula	Analyses, %				Stimu- lation
				Calcd.		Found		
2-Bromoallyl ^a	76	145-148 (d.) (1.5)	C ₅ H ₇ BrO ₂ S	28.45	3.34	28.30	3.42	1.5 1.9 ^b
2-Chloroallyl ^c	83	130-131 (1)	C ₅ H ₇ ClO ₂ S	36.04	4.24	35.27	4.55	1.3 2.3 ^b
2-Cyanoethyl ^d		M. p. 73	C ₆ H ₇ NO ₂ S	N, 9.65		9.73		1.0 ^{aa}
Allyl ^e	79	103-105 (1.5)	C ₅ H ₉ O ₂ S	45.43	6.10	45.64	6.65	1.3
α -Carboxyethyl		M. p. 87-88	C ₆ H ₉ O ₄ S	36.57	4.91	36.45	4.89	1.0
2,3-Dibromopropyl ^f	92	Oil	C ₅ H ₈ Br ₂ O ₂ S	20.56	2.76	21.44	2.84	0.5 0.9 ^b
Ethylmercaptomethyl ²¹		Oil	C ₁₃ H ₂₀ N ₂ O ₂ S ₂ ^g	N, 8.43		8.23		1.6 ^b
2-Thienyl ^h	64	Oil	C ₁₄ H ₁₆ N ₂ O ₂ S ₂ ⁱ	N, 8.25		8.46		0.7 1.4 ^b
3-Thienyl ^j	90	135-140 (1)	C ₈ H ₆ O ₂ S ₂	41.36	3.47	42.33	3.50	1.2 2.1 ^b
2-Methylallyl ^k	80	114-118 (3-4)	C ₆ H ₁₀ O ₂ S	49.29	6.90	49.34	7.14	1.4
<i>s</i> -Butyl	95	118-120 (5)	C ₈ H ₁₂ O ₂ S	48.62	8.16	49.06	8.35	2.9 ^b
4,5-Dimethyl-2-thiazolyl		M. p. 127-128	C ₇ H ₉ NO ₂ S	N, 6.89		6.88		1.0
3,3-Dimethylallyl ^l	48	103-106 (0.5)	C ₇ H ₁₂ O ₂ S	52.47	7.55	50.49	8.33	1.8
Isoamyl ^m	57	102-108 (0.75)	C ₇ H ₁₄ O ₂ S	51.82	8.70	50.64	8.42	2.9 ^b
<i>n</i> -Amyl ⁿ	80	107.5-109 (0.75)	C ₈ H ₁₄ O ₂ S	51.82	8.70	51.72	8.78	1.1 ^b
<i>p</i> -Sulfamylphenyl ^f	32	M. p. 160-161	C ₈ H ₉ NO ₄ S ₂	N, 5.67		5.90		0.5 ^{bb}

(20) Rothstein, *Bull. soc. chim.*, **51**, 691 (1932).(21) Bohme, *Ber.*, **69**, 1610 (1936).

TABLE IV (Continued)

R	Yield, %	B. p., °C. (mm.)	Formula	Analyses, %				Stimu- lation
				Calcd.		Found		
Tetramethylenebis ^d		M. p. 120-121	C ₈ H ₁₄ O ₄ S ₂	40.32	5.92	40.63	6.01	0.8
				S, 26.91		27.08		0.6 ^b
<i>n</i> -Hexyl ^o	62	133-136 (2)	C ₈ H ₁₆ O ₂ S	54.51	9.15	54.51	8.98	1.0
<i>p</i> -Mercaptophenyl ^f	74	M. p. 110-111	C ₈ H ₁₆ O ₂ S ₂	47.98	4.03	48.00	4.04	0.8 ^{bb}
<i>m</i> -Trifluoromethylphenyl ^f	99	140-143 (2) (M. p. 45.5-47)	C ₉ H ₇ F ₃ O ₂ S	45.76	2.99	46.05	3.24	1.3 ^b
<i>p</i> -Chlorobenzyl ^{22,p}		M. p. 64	C ₉ H ₉ ClO ₂ S	49.89	4.15	50.47	4.35	1.7 ^b
<i>p</i> -Tolyl ^{10b,q}		M. p. 85-86	C ₉ H ₁₀ O ₂ S	59.31	5.53	59.20	5.19	1.5
β -(2-Pyridyl)-ethyl ^f	71	M. p. 117	C ₉ H ₁₁ NO ₂ S.H ₃ PO ₄	N, 4.76		4.87		0.7 ^{aa,b}
2,4-Dimethylamyl ^f	43	112-116 (1)	C ₉ H ₁₈ O ₂ S	56.80	9.53	56.13	9.28	1.0
4-Heptyl ^g	28	124-126 (1)	C ₉ H ₁₈ O ₂ S	56.80	9.53	55.57	9.10	1.4 ^b
2-Phenylethyl	75	194-195 (2) (M. p. 55-56)	C ₁₀ H ₁₂ O ₂ S	61.20	6.17	61.24	6.27	1.9 ^b
2-Phenoxyethyl	44	M. p. 47-48	C ₁₀ H ₁₂ O ₃ S	56.57	5.72	56.37	5.63	1.2
<i>n</i> -Octyl ^f	42	175-177 (5)	C ₁₀ H ₂₀ O ₂ S	58.78	9.87	59.23	9.67	Toxic
<i>s</i> -Octyl	23	130-131 (d.) (0.7)	C ₁₀ H ₂₀ O ₂ S	58.78	9.87	59.02	10.48	1.0
4-Octyl ^u	11	120-122 (0.75)	C ₁₀ H ₂₀ O ₂ S	58.78	9.87	58.09	9.93	1.0 ^b
<i>n</i> -Butoxyethoxyethyl ^v	60	160-163 (1)	C ₁₀ H ₂₀ O ₄ S	50.82	8.53	50.77	8.59	0.4 0.6 ^{b,bb}
4-Phenyl-2-thiazolyl		M. p. 95.5-96	C ₁₁ H ₉ NO ₂ S ₂	N, 5.57		5.58		0.7
Cinnamyl ^w	58	M. p. 69-72	C ₁₁ H ₁₂ O ₂ S	63.43	5.81	63.26	5.70	1.3 ^{b,aa}
<i>p</i> -(<i>N</i> -Allylsulfamyl)-phenyl ^f	66-86	M. p. 129-130	C ₁₁ H ₁₃ NO ₄ S	N, 4.87		4.88		0.8
Mesityl ^z		M. p. 95-97	C ₁₁ H ₁₄ O ₂ S	62.87	6.71	62.60	6.67	1.0
3-Phenyl- <i>n</i> -propyl	71	173-175 (1)	C ₁₁ H ₁₄ O ₂ S	62.87	6.71	62.88	6.48	1.1 ^b
3-Phenoxy- <i>n</i> -propyl	57	185 (1)	C ₁₁ H ₁₄ O ₃ S	58.36	6.24	58.09	6.25	0.75
<i>p</i> -Trimethylsilylphenyl ^f	77	M. p. 93-94	C ₁₁ H ₁₆ O ₂ SSi	54.96	6.71	54.65	6.49	0.5
2-Naphthyl ²³		M. p. 76-77	C ₁₂ H ₁₀ O ₂ S	66.03	4.61	66.23	4.67	1.6
<i>p</i> -Isopropylbenzyl ^v		160-180 (0.15)	C ₂₀ H ₂₄ N ₂ O ₂ S ₂ ^w	N, 7.36		7.02		Toxic
2,4,6-Trimethylbenzyl ^{24,q}		M. p. 95-97	C ₁₂ H ₁₆ O ₂ S	64.25	7.18	63.84	6.84	1.0 ^{b,aa}
Geranyl	55	Oil	C ₁₂ H ₂₀ O ₂ S	63.12	8.83	62.50	8.29	1.0 ^{b,aa}
<i>p</i> -[<i>N</i> -(β -Methyl- α -carboxy- <i>n</i> -propyl)-sulfamyl]-phenyl ^f		M. p. >300	C ₁₃ H ₁₇ NO ₆ S ₂	N, 4.02		3.85		1.0
<i>p</i> -Phenoxyphenyl ²⁵		M. p. 73-74	C ₁₄ H ₁₂ O ₃ S	64.58	4.58	64.26	4.49	0.7
<i>p</i> -(<i>N</i> - <i>p</i> -Arsonophenylsulfamyl)-phenyl ^f		M. p. 170 (d.)	C ₁₄ H ₁₄ NO ₇ S ₂ As	N, 3.15		3.43		1.0 ^{aa}
<i>n</i> -Tetradecyl ^z	68	M. p. 60-61	C ₁₆ H ₃₂ O ₂ S	66.61	11.18	65.90	10.60	0.7

^a n^{25D} 1.5530; m. p. 28.5-30.5. This material has a tendency to decompose after standing. ^b Strain Q176. ^c n^{24D} 1.5336. ^d From the ester by hydrolysis. ^e n^{25D} 1.5045. ^f See experimental. ^g Benzylisothiuronium salt²⁶ crystallized as white plates, m. p. 154°. ^h 2-Mercaptothiophene was prepared from 2-iodothiophene by means of the Grignard reaction in a 20% yield, b. p. 63° (1 mm.). ⁱ Benzylisothiuronium salt²⁶ white plates, m. p. 164°. ^j The sodium salt precipitated during the reaction in a 74% yield, the filtrate gave a 16% yield of acid after acidification. The *p*-chlorobenzylisothiuronium salt¹² recrystallized from dioxane melted at 148.5-149°. *Anal.* Calcd. for C₁₄H₁₆ClN₂O₂S₂: N, 7.48. Found: N, 7.21. 3-Mercaptothiophene was kindly supplied by Socony Vacuum Co. ^k n^{25D} 1.4993. ^l n^{25D} 1.5058; the benzylisothiuronium salt²⁶ crystallized from dilute ethanol in white plates, m. p. 137.5-139°. *Anal.* Calcd. for C₁₅H₂₂N₂O₂S₂: N, 8.58. Found: N, 8.67. ^m n^{25D} 1.4748; the *p*-chlorobenzylisothiuronium salt¹² melted at 155.5-157°. *Anal.* Calcd. for C₁₅H₂₀ClN₂O₂S₂: N, 7.72. Found: N, 7.71. Stimulation of mold growth of this salt was of the same order as the free acid. ⁿ n^{25D} 1.4768. ^o n^{25D} 1.4723. ^p Reported²² with no analyses except neutral equivalent. ^q From ether-petroleum ether. ^r n^{25D} 1.4734; the benzylisothiuronium salt²⁶ formed white plates from dioxane, m. p. 138.5-140°; *Anal.* Calcd. for C₁₇H₂₀N₂O₂S₂: N, 7.86. Found: N, 7.79. ^s The *p*-chlorobenzylisothiuronium salt¹² melted at 141-142° (d.). *Anal.* Calcd. for C₁₇H₂₇ClN₂O₂S₂: N, 7.17. Found: N, 7.57. ^t Rapoport, Smith and Newman, *THIS JOURNAL*, 69, 693 (1947), give no analyses but the neutral equivalent. ^u n^{25D} 1.4789; the *p*-chlorobenzylisothiuronium salt¹² white flakes, m. p. 144-145°. *Anal.* Calcd. for C₁₃H₂₃ClN₂O₂S₂: N, 6.92. Found: N, 7.02. ^v Butoxyethoxyethyl chloride was obtained from Rohm and Haas, the acid gave n^{25D} 1.4790. ^w This acid has been reported by Holmberg.²⁷ It was recrystallized from dilute ethanol. ^x An alkali-insoluble by-product from the preparation of 2,4,6-trimethylthiophenol proved to be mesityl disulfide, m. p. 116-117°, from ethanol-ether-petroleum ether. *Anal.* Calcd. for C₁₃H₂₂S₂: C, 71.46; H, 7.33. Found: C, 71.02; H, 7.44. The acid was recrystallized from ether-petroleum ether. ^y Obtained by the hydrolysis of the ester which resulted from the condensation of ethyl chloroacetate and the thiophenol. Analysis is reported for the benzylisothiuronium salt, m. p. 159°. ^z The sodium salt precipitated from the mixture and could be recrystallized from water. It melted at 184.5-185.5°. *Anal.* Calcd. for C₁₆H₂₁O₂SNa: C, 61.89; H, 10.06; Found: C, 61.73; H, 10.16. ^{aa} Craig machine analysis did not indicate that a significant quantity of new penicillin was formed. ^{bb} Craig machine analysis indicated new penicillin was formed.

(22) Newman, Fones and Renoll, *THIS JOURNAL*, 69, 718 (1947).(23) Friedlander and Woroshzow, *Ann.*, 388, 14 (1912), report a melting point of 91°.

(24) Fuson and Rabjohn, "Organic Syntheses," 25, 65 (1945).

(25) Suter, *THIS JOURNAL*, 53, 1116 (1931).(26) Donleavy, *ibid.*, 58, 1004 (1936).(27) Holmberg, *Arkiv. Kemi Mineral. Geol.*, 12A, No. 11 (1936); C. A., 31, 2170 (1937).

TABLE V
 MERCAPTOACETATES, RSCH₂CO₂R'

Yields varied from 60–90%. References are made in most cases to acids which have been reported in the literature.

R	R'	B. p., °C. (mm.)	Formula	Analyses, %				
				Calcd.		Found		
			C	H	C	H		
2-Imidazolyl ^{a,b}	Ethyl	M. p. 76	C ₇ H ₁₀ N ₂ O ₂ S	45.14	5.41	45.34	5.13	
Allyl	Ethyl	64–67 (1)	C ₇ H ₁₀ O ₂ S	^{c,d}				
<i>p</i> -Bromophenyl ^e	Methyl	175 (5)	C ₉ H ₉ BrO ₂ S	41.40	3.47	41.20	3.39	
<i>m</i> -Trifluoromethylphenyl	Methyl	100–101 (1)	C ₁₀ H ₉ F ₃ O ₂ S	48.00	3.63	48.00	3.72	
2-Benzimidazolyl ²⁸	Ethyl	Oil	C ₁₁ H ₁₂ N ₂ O ₂ S		N, 11.85		11.94	
<i>p</i> -Tolyl ^e	Ethyl	179–182 (32)	C ₁₁ H ₁₄ O ₂ S	62.82	6.71	63.00	6.53	
<i>p</i> -Methoxyphenyl ²⁹	Methyl ^e	162 (5)	C ₁₀ H ₁₂ O ₃ S	58.84	5.70	56.60	6.42	
2-Phenylethyl	Methyl	146 (4)	C ₁₁ H ₁₄ O ₂ S	62.82	6.71	62.88	6.48	
3-Phenylpropyl	Methyl	152 (3)	C ₁₂ H ₁₆ O ₂ S	64.24	7.19	63.90	7.04	
3-Phenoxypropyl	Methyl	170–178 (2–3)	C ₁₂ H ₁₆ O ₃ S	59.98	6.71	59.88	7.01	
1-Naphthyl ³⁰	Methyl	195–198 (1.6)	C ₁₃ H ₁₂ O ₂ S	^e				
2-Naphthyl ^a	Ethyl	148–150 (0.2)	C ₁₄ H ₁₄ O ₂ S	68.26	5.72	68.25	5.94	
<i>p</i> -Phenoxyphenyl	Methyl	197–200 (1.8)	C ₁₅ H ₁₄ O ₃ S	65.67	5.19	65.48	5.37	

^a Prepared directly from ethyl chloroacetate. ^b Crystallized from petroleum ether. ^c Not analyzed, used directly for preparation of the derivative. ^d *n*_D^{22.5} 1.5058. ^e Acid was not isolated.

 TABLE VI
 MERCAPTOACETIC ACID DERIVATIVES
 RSCH₂CONHCH₂CH₂OH (E), RSCH₂CONHCHCH(CH₃)₂ (V)


The ethanolamides could be recrystallized from ethyl acetate, methanol–ethyl acetate, ethylene dichloride or ethylene dichloride–petroleum ether. The valine derivatives could be recrystallized from dilute ethanol. Yields were good.

R	Deriv.	M. p., °C.	Formula	Nitrogen analyses, %		Stimulation
				Calcd.	Found	
Hydrogen	E	Oil	C ₄ H ₉ NO ₂ S	^a		
Ethyl ^b	V	85–86	C ₉ H ₁₇ NO ₃ S	6.38	6.33	1.3
2-Imidazolyl	E	125–126	C ₇ H ₁₁ N ₃ O ₂ S	20.89	20.21	1.0
Allyl	E	B. p. 172–178 1.5–2 mm., dec.	C ₇ H ₁₃ NO ₂ S	7.99	8.28	1.4
2,3-Epoxypropyl	E ^{a,c}	Orange oil	C ₇ H ₁₃ NO ₃ S	7.33	7.16	1.0
				C, 43.96; H, 6.85	C, 43.50; H, 7.53	1.3
2,3-Dihydroxypropyl	E ^{a,d}	Oil	C ₇ H ₁₅ NO ₄ S	6.69	6.92	1.0 ^d
4,5-Dimethyl-2-thiazolyl	E ^b	82.5–83	C ₉ H ₁₄ N ₂ O ₂ S ₂	11.38	11.48	
<i>p</i> -Bromophenyl	E	84–85	C ₁₀ H ₁₂ BrNO ₂ S	4.83	4.90	1.7
<i>p</i> -Nitrophenyl ^e	E ^b	89–90	C ₁₀ H ₁₂ N ₂ O ₄ S	10.93	11.19	1.2
<i>m</i> -Trifluoromethylphenyl	E	Oil	C ₁₁ H ₁₂ F ₃ NO ₂ S	5.02	5.12	1.3
2-Benzimidazolyl	E ^b	Oil	C ₁₁ H ₁₃ N ₃ O ₂ S	16.72	17.60	0.7
<i>o</i> -Carboxyphenyl	V ^{a,c}	192–193.5	C ₁₄ H ₁₇ NO ₅ S	4.50	4.79	1.1
<i>m</i> -Tolyl ^{10a}	E ^a	50	C ₁₁ H ₁₅ NO ₂ S	6.22	6.38	1.4
				C, 58.64; H, 6.71	C, 58.40; H, 7.15	
<i>p</i> -Tolyl	E	53–54	C ₁₁ H ₁₆ NO ₂ S	6.21	6.47	1.7
	V ^b	136–138	C ₁₄ H ₁₉ NO ₃ S	4.97	4.95	1.4
<i>p</i> -Methoxyphenyl	E	72–73	C ₁₁ H ₁₆ NO ₃ S	5.81	5.90	1.2
2-Phenylethyl	E	Oil	C ₁₂ H ₁₇ NO ₂ S	C, 62.81; H, 6.71	C, 62.84; H, 6.79	0.6
4-Phenyl-2-thiazolyl	E ^b	64.5–65	C ₁₃ H ₁₄ N ₂ O ₂ S ₂	9.52	9.57	
3-Phenylpropyl	E	Oil	C ₁₃ H ₁₉ NO ₂ S	5.53	5.18	1.3
3-Phenoxypropyl	E	40	C ₁₃ H ₁₉ NO ₃ S	5.20	5.33	0.75
1-Naphthyl	E	51–52	C ₁₄ H ₁₅ NO ₂ S	5.36	5.42	1.0
2-Naphthyl	E	93–95	C ₁₄ H ₁₅ NO ₂ S	5.36	5.40	1.6
2,4,6-Trimethylbenzyl	V ^b	160–161	C ₁₇ H ₂₅ NO ₃ S	4.33	4.28	1.0
<i>p</i> -Phenoxyphenyl	E	75	C ₁₆ H ₁₇ NO ₃ S	4.62	4.74	0.7

^a See experimental. ^b Intermediates were not isolated. ^c Prepared directly. ^d Craig machine analysis did not indicate that a significant quantity of new penicillin was formed (strain Q176). ^e Fromm and Wittmann, *Ber.*, 41, 2273 (1908).

(28) Everett, *J. Chem. Soc.*, 3032 (1931).

(29) Suter and Hansen, *THIS JOURNAL*, 54, 4102 (1932).

(30) German Patent 414,853, *Chem. Centr.*, 96, 11, 774 (1925).

mole) was added and the resulting solutions was heated on the steam-bath for one hour. The cooled solution was acidified with hydrochloric acid and the water evaporated

at reduced pressure. The residue was extracted with a total of 1.5 l. of 95% ethanol. Sirupy phosphoric acid was added to this solution until no more precipitate was formed. The solid was collected on a filter and recrystallized from 95% ethanol. The yield was 75 g.

***p*-Trimethylsilyloxyphenylmercaptoacetic Acid.**—The procedure used was similar to that for *m*-trifluoromethylthiophenol except for the following modifications: The Grignard solution was made from 48 g. (0.21 mole) of trimethyl-*p*-bromophenylsilicon,^{31,32} 7 g. of magnesium and 200 ml. of ether and treated with 6.7 g. of sulfur. The thiophenol was not separated from the disulfide but the mixture was treated with 50 g. of glacial acetic acid and 25 g. of zinc dust. The ether extract of the thiophenol was extracted with 200 ml. of cold 2 *N* sodium hydroxide solution. This solution was treated immediately with 18 g. (0.19 mole) of chloroacetic acid. After the exothermic reaction had subsided, the solution was acidified, the crystalline product was collected and air-dried. The yield of acid was 38.5 g.

***p*-Sulfamylphenylmercaptoacetic Acid.**—*p*-Mercapto-phenylsulfonic acid³³ (190 g., 1 mole) and 120 g. (4 moles) of sodium hydroxide were dissolved in 1 l. of water. The solution was treated with 94.5 g. of chloroacetic acid and stirred overnight. The mixture was cooled in ice, and the precipitate was collected and dried at 110°. The dry material was mixed with 450 g. of phosphorus oxychloride and allowed to stand for one week. The excess phosphorus oxychloride was removed *in vacuo* and 500 ml. of water was added to the residue. The gummy precipitate was removed and added to a cold, stirred ammonium hydroxide solution. Stirring was continued for one hour, the solution was treated with charcoal and filtered. Acidification of the filtrate yielded 78.7 g. of acid, m. p. 160–161°. The compound was recrystallized from water.

The acid was also obtained from *p*-sulfamylthiophenol³⁴ in a 6% yield based on the starting material, sulfanilamide.

***p*-[N-(β -Methyl- α -carboxy-*n*-propyl)-sulfamyl]-phenylmercaptoacetic Acid.**—A cooled solution of 5.8 g. of DL-valine and 5 g. of sodium hydroxide in 200 ml. of water was treated with 14 g. of *p*-chlorosulfonylphenylmercaptoacetic acid in portions over a period of thirty minutes. The solution was allowed to stand for one hour. Acidification with hydrochloric acid yielded 9 g. of product.

***p*-[N-(*p*-Arsonophenyl)-sulfamyl]-phenylmercaptoacetic Acid.**—This material was prepared by the above procedure from 10.7 g. of arsanic acid, 200 ml. of water, 7 g. of sodium hydroxide and 14 g. of *p*-chlorosulfonylphenylmercaptoacetic acid. The product was recrystallized from dilute ethanol, yield 14 g.

***p*-Mercaptophenylmercaptoacetic Acid.**—*p*-Chlorosulfonylphenylmercaptoacetic acid (85 g., 0.32 mole) was treated with 300 ml. of glacial acetic acid and 50 g. of zinc dust (added in portions). The mixture was heated for seven hours on the steam-bath. A small amount of *p*-mercaptophenylmercaptoacetic acid was obtained by steam distillation. The inorganic salts were removed by filtration and the filtrate was treated with hydrochloric acid. The precipitate was recrystallized from ethanol to give 94 g. of acid. The calculated molecular weight is 200.2; found, 195.3 (ebullioscopic in benzene).

***p*-(*N*-Allylsulfamyl)-phenylmercaptoacetic Acid.**—A solution of 5.7 g. (0.1 mole) of allylamine and 8 g. of sodium hydroxide in 200 ml. of water was treated with 26.6 g. (0.1 mole) of *p*-chlorosulfonylphenylmercaptoacetic acid with stirring and cooling. Addition required one hour and stirring was continued overnight. The mixture was filtered and the filtrate acidified with hydrochloric acid. The product was collected on a filter, dried and recrystallized from ethyl acetate-petroleum ether and ethyl acetate-ethylene dichloride; the yield was 16–21 g.

(31) Burkhard, *THIS JOURNAL*, **68**, 2103 (1946).

(32) The compound was prepared by the method of Grütner and Krause, *Ber.*, **50**, 1559 (1917).

(33) Waldo, *THIS JOURNAL*, **53**, 992 (1931).

(34) Northey, U. S. Patent 2,365,265; *C. A.*, **39**, 92 (1945).

N-(2'-Hydroxyethyl)-2,3-epoxypropylmercaptoacetamide.—A mixture of 50 g. of ethyl thioglycolate and 50 ml. of ethanolamine was heated on the steam-bath for two days. Excess amine was removed at 1 mm. pressure. The residue, N-2-hydroxyethylmercaptoacetamide, was added to a solution made from 11.5 g. of sodium and 500 ml. of absolute ethanol. After the solution had cooled somewhat, 40 ml. of epichlorohydrin was added with stirring (15–20°). Removal of the salt and ethanol left a thick, orange oil weighing 83.8 g. after heating at 50° and 1.5 mm. for six hours.

N-(2'-Hydroxyethyl)-2,3-dihydroxypropylmercaptoacetamide.—A solution prepared from 23 g. of sodium in 1 l. of absolute ethanol, 46 g. of thioglycolic acid and 60 g. of glycerol α -chlorohydrin was boiled under reflux for two hours. The reddish-brown, crude acid obtained by working up the mixture weighed 79.2 g. The methyl ester was obtained by esterification with 700 ml. of methanol containing 5 ml. of sulfuric acid. The brown oil weighed 68 g. and could not be distilled at 1 mm. pressure without extensive decomposition. From 60 g. of the ester and 65 ml. of ethanolamine there was obtained 58 g. of the amide.

***o*-Carboxyphenylmercaptoacetyl-DL-valine.**—Chloroacetyl-DL-valine³⁵ (8.7 g.) was added to a solution of 7.7 g. of thiosalicylic acid in 100 ml. of water containing 6 g. of sodium hydroxide. The solution was shaken well and then heated on a steam-bath for one and one-half hours. An oil separated after acidification with hydrochloric acid and solidified after cooling. The solid was collected on a filter and recrystallized from 250 ml. of 50% ethanol using charcoal. The yield of amide melting at 192.5–193.5° was 12 g.

TABLE VII

STIMULATION RESULTS ON PREVIOUSLY DESCRIBED COMPOUNDS

R (or acid)	Stimulation ^a		Differential assay ^a	
Oxyacetic Acids, ROCH ₂ COOH				
Acetone carboxymethoxime ³⁶	0.8	1.0	0.6	0.5
<i>p</i> -Arsenosophenyl ³⁷	1.0 ^b		0.8	0.6
<i>n</i> -Butyl ³⁸	0.8	1.0	0.7	0.6
2-Carboxymethyl-4-chlorophenyl ²²	1.0 ^b		0.6 ^b	
α -(<i>o</i> -Chlorophenoxy)-propionic acid ³⁹	1.0 ^b		0.8	0.5
<i>p</i> -Chlorophenyl ⁴⁰	1.0		0.6	
2-Cyanomethyl-4-chlorophenyl ²²	1.0 ^b		0.6 ^b	
3,5-Dichlorophenyl ²²	1.0 ^b		0.6 ^b	
Ethyl ⁴⁰	0.8 ^{b,c}			
Ethylenebis ⁴¹	1.0 ^b		0.7	(Q176)
Isoamyl ⁴²	1.35	(Q176)		
Methyl ⁴⁰	1.0 ^b		0.7	0.5
<i>n</i> -Propyl ³⁸	1.0 ^b		0.8	0.7
2,4,5-Trichlorophenyl ³⁹	1.0	1.4	0.8	0.6 ^d
2,4,6-Trichlorophenyl ⁴³	1.0			

(35) Abderhalden, Rindtorff and Schmitz, *Chem. Centr.*, **100**, I, 2319 (1929).

(36) Anker and Clarke, "Organic Syntheses," **27**, 15 (1947).

(37) Doak, Steinman and Eagle, *THIS JOURNAL*, **62**, 3012 (1940).

(38) Rule, Hay and Paul, *J. Chem. Soc.*, 1356 (1928).

(39) Kindly supplied by Dow Chemical Co.

(40) Eastman Kodak Co. material.

(41) Sample kindly furnished by E. I. du Pont de Nemours and Co.

(42) Purchased from Paul Kletzke, 606 N. 17, La Crosse, Wis.

(43) Bischoff, *Ber.*, **33**, 1605 (1900).

TABLE VII (Continued)

R (or acid)	Stimulation ^a	Differential assay ^a
Mercaptoacetic Acids, RSCH ₂ CO ₂ H		
<i>p</i> -Arsonophenyl ⁴⁴	1.0 ^b	0.6
2-Benzimidazolyl ²⁵	1.1 (Q176)	0.7 0.9
2,2-Bis-(carboxymethyl-mercapto)-propane ⁴⁵	1.1 ^b	0.7 ^d
<i>n</i> -Butyl ^{10a}	2.3 (Q176)	
<i>i</i> -Butyl ²⁷	1.6 (Q176)	
β -Carbomethoxyethyl ⁴⁶	1.0 ^b	0.7 0.6
β -Carboxyethyl ⁴⁷	1.0 ^b	0.6 ^b
2-Carboxymethylmercapto-4,5-dihydro-1,3,2-dithioarsenole ⁴⁸	1.0 (toxic) ^b	
<i>o</i> -Carboxyphenyl ⁴⁹	1.1 0.9	0.7 0.5 ^d
α,β' -Dicarboxydiethyl sulfide ⁴⁷	1.0 ^b	0.7 ^b
2,4-Dichlorobenzyl ²²	Toxic ^b	
Dihydro- <i>exo</i> -dicyclopentadienyl ⁵⁰	1.0 ^b	0.5 ^d
Diphenylmethyl ⁵¹	1.0 1.2	0.65 ^d (Q176)
Dithiodiglycolic acid ⁵²	1.0	0.6
Ethyl ¹⁰	1.7 (Q176)	
Ethylmercuri ⁵³	Toxic	
α -Imino- β -phenylethyl ⁵⁴	1.0	
Isopropyl ^{10a}	1.7 2.4	
Methyl ^{10a}	1.0 ^b	1.0 ^b
1-Methyl-1-cyclohexyl ⁵⁵	1.2	0.7
Methylenebis ⁵⁶	1.0 0.9	0.6 ^b

(44) German Patent 216,270; *Chem. Centr.*, **80**, II, 2105 (1909).

(45) Shriner, Cross and Dobratz, *THIS JOURNAL*, **61**, 2002 (1939).

(46) Woodward and Eastman, *ibid.*, **68**, 2232 (1946).

(47) Lovén, *Ber.*, **29**, 1136, 1140 (1896).

(48) Rueggeberg, Ginsburg and Cook, *THIS JOURNAL*, **68**, 1860 (1946).

(49) Friedländer, *Ber.*, **39**, 1062 (1906).

(50) Bruson and Reiner, U. S. Patent 2,376,340; *C. A.*, **39**, 3302 (1945).

(51) Holmberg, *J. prakt. Chem.*, **141**, 93 (1934).

(52) Billmann, *Ann.*, **339**, 351 (1905).

(53) Kharasch, U. S. Patent 1,672,615; *C. A.*, **22**, 2639 (1928).

(54) Condo, Hinkel, Fassero and Shriner, *THIS JOURNAL*, **59**, 230 (1937).

(55) Cunneen, *J. Chem. Soc.*, 36 (1947).

(56) Holmberg and Mattisson, *Ann.*, **353**, 125 (1907).

<i>p</i> -Nitrophenyl ^a	1.1 (Q176)		
Phenyl ^{10a}	2.7 (Q176)		
S-Phenylthiomalic acid ⁵⁷	1.0 ^b	0.8	0.6
<i>n</i> -Propyl ^{10a}	2.0	1.7	
Thiodiglycolic acid ⁵⁸	1.0 ^b		0.7 0.5 ^d
β -Thiodipropionic acid ⁴⁷	1.0	1.1	0.7 0.6 ^d
<i>m</i> -Tolyl ^{10b}	2.7		
Triphenylmethyl ^{10b}	1.0 ^b		0.6 (Q176)

^a Unless otherwise noted tests were performed using *P. notatum* NRRL 1976. When two values are given, the second is the result using *P. chrysogenum* Q176. ^b Both strains. ^c Craig machine analysis indicated new penicillin was formed. ^d Craig machine analysis did not indicate that a significant amount of new penicillin was formed. ^e See footnote "e" Table VI.

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Summary

A series of oxy- and mercaptoacetic acids together with many of their N-2-hydroxyethylamides or valine derivatives have been prepared and tested as penicillin precursors.

The mercaptoacetic acids have been found to be particularly well utilized by penicillin producing molds for the formation of new penicillins.

It has been shown that the aliphatic mercaptoacetic acids are valuable precursors for the preparation of aliphatic-type penicillins which are difficult to obtain otherwise.

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(57) Material obtained from National Aniline Division, Allied Chemical and Dye Corporation.

(58) Beckerts and Frericks, *J. prakt. Chem.*, **74**, 50 (1906).