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Sulfur-containing Amino Acids

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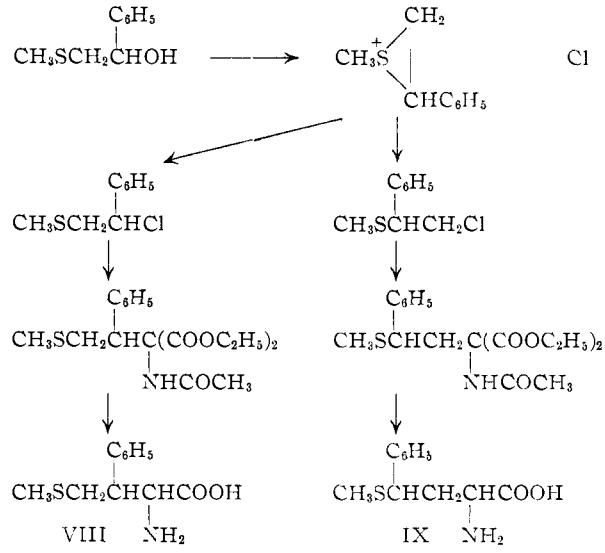
Twenty-three potential inhibitory analogs of methionine have been prepared and tested for *in vitro* inhibition of virus.

In 1949, Heathcote[1] reported that methionine sulfoximine, the toxic factor of nitrogen trichloride-treated zein, inhibits the growth of *Leuconostoc mesenteroides* P-60 by interfering[2,3] with the utilization of methionine. Later, Ackermann[4] reported that methoxinine and ethionine inhibit the growth of influenza virus in tissue culture and that their effect is countered by methionine. Thus, methionine appears to be involved in the biosynthesis of influenza virus. In view of these findings, attention has been focused on methionine sulfoximine as a possible antiviral agent.[5] Ainslie[6] investigated the effect of methionine sulfoximine on mice which had been inoculated intracerebrally with Lancing strain of poliomyelitis virus, and found that, although the methionine antagonist did not influence the morbidity or mortality rates, it did inhibit the early phase of virus growth.

We report here the synthesis of 23 potential antagonists of methionine together with the effect of these compounds on phage multiplication.

The amino acids, S-benzyl-4-methylhomocysteine[7] (V), 2-methylmethionine[8] (VI) and 4-methylmethionine (VII), were prepared by way of the hydantoins (Table I). Benzyl or methyl mercaptan was condensed with the appropriate α,β-unsaturated aldehyde or ketone by the method of Catch, *et al.*,[7] and the resulting β-mercaptocarbonyl compound was converted to the corresponding hydantoin.[9] Alkaline hydrolysis of the latter liberated the desired amino acid. 4-Methylmethionine was also prepared by debenzylation of V and methylation of the mercaptan.

For the synthesis of 3-phenylmethionine (VIII), ω-methylmercaptoacetophenone was reduced to 1-phenyl-2-methylmercaptoethanol with lithium aluminum hydride. The chloride, prepared from the alcohol and thionyl chloride, was allowed to react with ethyl sodioacetamidomalonate, and the product was hydrolyzed with dilute acid. Since reaction of 1-phenyl-2-methylmercaptoethanol and thionyl chloride can proceed in two directions *via* an intermediate sulfonium chloride, subsequent reactions can lead to the formation of either 3-phenylmethionine (VIII) or 4-phenylmethionine (IX). On the basis of earlier observations[10] on the conversion of β-hydroxysulfides to β-chlorosulfides, ring-cleavage of the sulfonium chloride was presumed to take place between the secondary carbon–sulfur bond in preference to the primary carbon–sulfur bond, suggesting that the product should have structure VIII. 4-Phenylmethionine (IX) was prepared unequivocally *via* 5-(β-methylmercapto-β-phenyl)-ethylhydantoin (IV). The decomposition points of VIII and IX were not appreciably different, and the decomposition point of a mixture of these two amino acids was not depressed. However, the R_f values for VIII and IX were different.



Further, the decomposition points and R_f values of their sulfoxides (XV and XVI) and sulfones (XXII and XXIII) were different, indicating that VIII and IX are not identical. Degradation of XXII and XXIII with N-bromosuccinimide[11] to aldehydes containing one carbon atom less and comparison of the decomposition points of their corresponding 2,4-dinitrophenylhydrazones eliminated the possibility that VIII is a second diastereoisomer of 4-phenylmethionine. Thus, VIII is 3-phenylmethionine.

Two amino acids containing sulfur in the β-position, S-methylpenicillamine (X) and S-methyl-3-phenylcysteine (XI), were prepared from their corresponding azlactones by the procedure described by Savard, *et al.*[12]

In all cases, oxidation of the sulfides to sulfoxides (Table II) was accomplished by the procedure of

(1) J. G. Heathcote, *Nature*, **164**, 439 (1949).
(2) J. G. Heathcote, *Lancet*, **257**, 1130 (1949).
(3) G. W. Newell and W. W. Carman, *Federation Proc.*, **9**, 209 (1950).
(4) W. W. Ackermann, *J. Exp. Med.*, **93**, 337 (1951).
(5) Private communications.
(6) J. D. Ainslie, *J. Exp. Med.*, **95**, 9 (1952).
(7) J. R. Catch, A. H. Cook, A. R. Graham and Sir I. Heilbron, *J. Chem. Soc.*, 1609 (1947).
(8) K. Pfister, 3rd, W. J. Leanza, J. P. Conhere, H. J. Becker, A. R. Matzuk and E. F. Rogers, THIS JOURNAL, **77**, 697 (1955), reported the synthesis of 2-methylmethionine after the present investigation was completed.
(9) E. Pierson, M. Giella and M. Tishler, *ibid.*, **70**, 1450 (1948).
(10) R. C. Fuson, C. C. Price and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946); R. C. Fuson and J. H. Koehneke, *ibid.*, **14**, 706 (1949).
(11) A. Schönherg, R. Mouhasher and M. Z. Barakat, *J. Chem. Soc.*, 2504 (1951).
(12) K. Savard, E. M. Richardson and G. A. Grant, *Can. J. Res.*, **24B**, 28 (1946).

TABLE I

HYDANTOINS $RR_1C(CONH)(HN{-}CO)$

	R	R_1	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Found
I	$C_6H_5CH_2SCH(CH_3)CH_2$	H	117–118	74.3	10.60	10.42
II	$CH_3SCH_2CH_2$	CH_3	109.5–110.5[b]	93.8	14.88	14.81
III	$CH_3SCH(CH_3)CH_2$	H	191–192	50.1	14.88	14.95
IV	$CH_3SCH(C_6H_5)CH_2$[a]	H	173–174	49.1[c]	11.20	11.09

[a] This was prepared without purification of the intermediate methylmercaptohydrocinnamaldehyde. [b] Reported[8] m.p. 109–110°. [c] Based on the amount of cinnamaldehyde used.

TABLE II

SULFUR-CONTAINING AMINO ACIDS

	Amino acids	Prepn.[b] method	Yield, %	Recrystn. solv.	M.p., °C.[d]	Nitrogen, % Calcd.	Found	R_f values[h] Butanol–acetic acid	Lutidine–collidine	Phenol–water
Sulfides										
V	S-Benzyl-4-methylhomocysteine	A	93.4	H_2O	222.5–223.5 d.[e]	5.85	5.63	0.69	0.74	0.93
VI	2-Methylmethionine	B	61	H_2O–MeOH	284–285 d.[f]	8.58	8.32	.45	.50	.77
VII	4-Methylmethionine	A	70.5	H_2O–MeOH	238–239 d.	8.58	8.46	.44	.53	.79
VIII	3-Phenylmethionine	C	61.5[c]	H_2O	203–204 d.	6.22	6.20	.61	.65	.93
IX	4-Phenylmethionine	A	49.3	H_2O	201–202 d.	6.22	6.08	.70	.66	.87
X	S-Methylpenicillamine	D	48	H_2O	282–283[g]	8.58	8.57	.38	.50	.80
XI	S-Methyl-3-phenylcysteine	D	59.3	H_2O	178–179 d.	6.63	6.62	.51	.65	.88
Sulfoxides										
XII	2-Amino-4-(henzylsulfinyl)-*n*-valeric acid	E	64.7	H_2O	214–215 d.	5.49	5.38	.45	.60	.92
XIII	2-Amino-2-methyl-4-(methylsulfinyl)-*n*-hutyric acid	E	91.8	H_2O–MeOH	239.5–240.5 d.	7.82	7.49	.14	.35	.77
XIV	2-Amino-4-(methylsulfinyl)-*n*-valeric acid	E	84.4	H_2O–MeOH	213.5–214.5 d.	7.82	7.70	.13	.40	.80
XV	2-Amino-3-phenyl-4-(methylsulfinyl)-*n*-hutyric acid	E	74.4	H_2O–MeOH	205–206 d.	5.81	5.66	.33	.59	.87
XVI	2-Amino-4-phenyl-4-(methylsulfinyl)-*n*-hutyric acid	E	87.7	H_2O–MeOH	189–190 d.	5.81	5.62	.33	.47	.85
XVII	2-Amino-3-(methylsulfinyl)-isovaleric acid	E	77.7	H_2O–MeOH	166–167	7.82	7.57	.14	.40	.76
XVIII	2-Amino-3-(methylsulfinyl)-hydrocinnamic acid	E	73.2	H_2O–MeOH	147–148 d.	6.16	6.10	.29	.54	.82
Sulfones										
XIX	2-Amino-4-(henzylsulfonyl)-*n*-valeric acid	F	70.6	H_2O	229–230 d.	5.16	5.17	.50	.65	.84
XX	2-Amino-2-methyl-4-(methylsulfonyl)-*n*-hutyric acid	G	73.6	H_2O–MeOH	288–289 d.	7.18	7.13	.16	.45	.65
XXI	2-Amino-4-(methylsulfonyl)-*n*-valeric acid	F	84.2	H_2O–MeOH	230–231 d.	7.18	7.06	.14	.50	.72
XXII	2-Amino-3-phenyl-4-(methylsulfonyl)-*n*-hutyric acid	G	50.8	H_2O	222–223 d.	5.45	5.22	.32	.61	.79
XXIII	2-Amino-4-phenyl-4-(methylsulfonyl)-*n*-hutyric acid	G	95.4	H_2O–MeOH	196.5–197.5 d.	5.45	5.39	.37	.55	.79
XXIV	2-Amino-3-(methylsulfonyl)-isovaleric acid	G	63.3	H_2O–MeOH	167–168 d.	7.18	7.07	.14	.53	.68
XXV	2-Amino-3-(methylsulfonyl)-hydrocinnamic acid	G	51.2	H_2O–MeOH	141–142 d.	5.76	5.62	.30	.52	.70
Sulfoximines										
XXVI	3-Amino-3-carhoxyhutylmethylsulfoximine	H	100	H_2O–MeOH	199–200 d.	14.45	14.15	.10	.35	.67
XXVII	1-Methyl-3-amino-3-carhoxypropyl methylsulfoximine[a]	H	98.4	H_2O–MeOH	199–200 d.	14.45	14.15	.08	.38	.71

[a] *Anal.* Calcd. for $C_6H_{14}N_2SO_3$: C, 37.10; H, 7.26. Found: C, 37.33; H, 7.28. [b] Code: A = hydrolysis of hydantoin by procedure of Pierson, *et al.*,[9] B = hydrolysis of hydantoin by procedure of J. E. Livak, E. C. Britton, J. C. Vanderweele and M. F. Murray, THIS JOURNAL, **67**, 2218 (1945), C = acid hydrolysis of substituted acetamidomalonate (see Experimental), D = see Experimental, E = oxidation with hydrogen peroxide,[13] F = oxidation of sulfoxide with hydrogen peroxide (see Experimental), G = method of Toennies and Kolb,[14] H = see Experimental. [c] 48.7% as hydrochloride and 12.8% as free amino acid. [d] Bath was preheated to 10° below m.p. [e] Reported[7] m.p. 221–222°. [f] Reported[8] m.p. 283–284° dec. [g] Reported[12] m.p. 254–256°. [h] See Experimental.

Toennies and Kolb.[13] In general, substitution of a sulfinyl group for a sulfur atom resulted in a sharp decrease in R_f values obtained with both butanol–acetic acid and lutidine–collidine systems.

Two sulfones were prepared from the sulfoxides by heating with hydrogen peroxide. All other sulfones (Table II) were prepared by treating the sulfides with hydrogen peroxide in the presence of ammonium molybdate and perchloric acid.[14] The latter method was found to proceed more readily and to be more predictable. In several trials, oxidation by the first method gave a mixture of products while the second method always yielded a chromatographically homogeneous sulfone.

(13) G. Toennies and J. J. Kolb, *J. Biol. Chem.*, **128**, 399 (1939).

(14) G. Toennies and J. J. Kolh, *ibid.*, **140**, 131 (1941).

The sulfoxides of 2- and 4-methylmethionines were converted to their corresponding sulfoximines (Table II) with hydrazoic acid in concentrated sulfuric acid as described by Misani and Reiner.[15] This procedure, when applied to sulfoxides of phenyl-substituted amino acids, gave mixtures in which the amino acids appeared to be sulfonated.

Microbiology.—The amino acids in Table II were tested, as described by Czekalowski,[16] against T_2 bacteriophage of *E. coli* strain A.T.C.C. #11303 at *p*H 7 and 37°. Of the amino acids tested, only four compounds, VI, VII, XI and XII, suppressed multiplication of phage at 100 p.p.m. or less.

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Experimental[17-20]

β-Methylmercaptobutyraldehyde.—Two drops of piperidine were added to a cooled mixture of 140 g. (2.0 moles) of crotonaldehyde and 96 g. (2.0 moles) of methyl mercaptan. The mixture was stirred at 5–10° for one-half hour and at room temperature for 3 hours. An additional 28 g. of methyl mercaptan was added, and the mixture was heated at about 90° for one hour. Ether (500 ml.) was added, and after washing with dilute hydrochloric acid and water, the solution was dried over anhydrous magnesium sulfate. The ether was removed, and the residue was distilled under reduced pressure. The product, 201 g. (85%), was collected at 80° and 23 mm.

Anal. Calcd. for $C_5H_{10}OS$: S, 27.13. Found: S, 26.85.

Methylmercaptobutane-3-one.—From 27 g. of methyl vinyl ketone and 18 g. of methyl mercaptan there was obtained 35.4 g. (80%) of product, b.p. 106° at 55 mm., $n^{25}D$ 1.4711 (reported[8] b.p. 75° at 14 mm., $n^{25}D$ 1.4772).

Anal. Calcd. for $C_5H_{10}OS$: S, 27.13. Found: S, 26.94.

5-(β-Benzylmercapto)-propylhydantoin.—This procedure represents a general method for preparing the hydantoins in Table I. A mixture of 48.5 g. (0.25 mole) of β-benzylmercaptobutyraldehyde,[7] 113 g. of ammonium carbonate, 25.5 g. of sodium cyanide, 335 ml. of ethanol, and 335 ml. of water was stirred and heated at 55° for 5 hours. The volume was reduced to about 300 ml. by distillation, and 50 ml. of concentrated hydrochloric acid was added cautiously. The mixture was heated at *ca.* 90° for 7 minutes and then chilled in the refrigerator. The solid was removed by filtration and washed with 200 ml. of water to give 49 g. of product, m.p. 117–118°. This was recrystallized from ethyl acetate without change in melting point.

4-Methylmethionine from S-Benzyl-4-methylhomocysteine.—To 7.17 g. (0.03 mole) of S-benzyl-4-methylhomocysteine in 300 ml. of liquid ammonia was added *ca.* 1.7 g. of sodium. The solution was decolorized by the addition of approximately 0.1 g. of ammonium chloride. To this solution was added 5 ml. of methyl iodide. The ammonia was then allowed to evaporate, and 125 ml. of water was added. The mixture was washed with ether, filtered and neutralized to *p*H 6 with concentrated hydrochloric acid. The volume was reduced to about 50 ml., and 50 ml. of acetone was added. After chilling in the refrigerator and recrystallizing from aqueous methanol, 4.1 g. of 4-methylmethionine, m.p. 236–237° dec., was obtained.

3-Phenylmethionine. 1-Phenyl-2-methylmercaptoethanol.—To 1.4 g. (0.037 mole) of lithium aluminum hydride in 100 ml. of dry ether a solution of 21.8 g. (0.131 mole) of ω-methylmercaptoacetophenone[21] in 50 ml. of dry ether was added with stirring. The mixture was stirred and heated under reflux for one hour and then cooled in an ice-salt-bath. About 200 ml. of ice-water and 100 ml. of 5 *N* sulfuric acid were added to the stirred mixture. The ether layer was separated, and the water layer was washed twice with 50 ml. of ether. The combined ether solutions were washed once with 75 ml. of saturated solution of sodium bicarbonate and twice with 100 ml. of water. The dried ether solution was warmed under a jet of dry air to remove the ether, and the residue (21.8 g.) was distilled at 113–114.5° and 1.8 mm. The yield was 18.4 g. (83.4%). A sample (170 mg.) was converted to the corresponding methylsulfonium iodide m.p. 134–135° dec. (reported[21] m.p. 132.5–133.5° dec.).

1-Phenyl-2-methylmercaptoethyl Chloride.—Thionyl chloride (9.2 g.) in 15 ml. of dry chloroform was added to a cooled mixture of 15.8 g. of the above alcohol and 25 ml. of dry chloroform. The mixture was cooled for an additional one-half hour and then allowed to stand overnight at room temperature. The chloroform was removed *in vacuo*, and to the residue was added 5 ml. of dry chloroform and 5 ml. of thionyl chloride. The mixture was warmed gently, and the chloroform and excess thionyl chloride were removed *in vacuo*. The residue was distilled at 105–106° and 1.8 mm. to give 14.3 g. (81.5%) of the chloride, $n^{25}D$ 1.5694. Redistillation at 106–107° and 2.8 mm. yielded 12 g. of product, $n^{25}D$ 1.5692.

Anal. Calcd. for $C_9H_{11}ClS$: Cl, 18.99; S, 17.18. Found: Cl, 18.57; S, 16.83.

Ethyl 2-Acetamido-2-carbethoxy-3-phenyl-4-methylmercaptobutyrate.—To a solution of sodium ethoxide, prepared from 1.23 g. of sodium and 100 ml. of anhydrous ethanol, were added with stirring 11.6 g. of ethyl acetamidomalonate and 200 mg. of potassium iodide. Ten grams of 1-phenyl-2-methylmercaptoethyl chloride was then added all at once to the hot solution, whereupon the solution became turbid and deposited a solid. The mixture was stirred at room temperature for 2 hours and then under reflux for 5 hours. The mixture was filtered while still hot, and the residue was washed with about 50 ml. of hot ethanol. The combined ethanol solutions were evaporated to dryness *in vacuo* to give an oil which crystallized on standing overnight at room temperature. This material was washed with dilute hydrochloric acid and with water and dried in a vacuum desiccator over potassium hydroxide pellets. The yield was 16 g., m.p. 86–92°. An analytical sample melting at 95–96° was obtained by two recrystallizations from ether–pentane (charcoal). A mixed melting point with ethyl acetamidomalonate (m.p. 94–95°) was depressed to 85–93°.

Anal. Calcd. for $C_{18}H_{25}O_5NS$: C, 58.83; H, 6.86; N, 3.81. Found: C, 58.98; H, 6.76; N, 3.79.

3-Phenylmethionine.—Following the procedure described by Goldsmith and Tishler[22] for the hydrolysis of ethyl methylmercaptoethylacetamidomalonate to methionine, a mixture of 14.4 g. of the crude ethyl 2-acetamido-2-carbethoxy-3-phenyl-4-methylmercaptobutyrate, 40 ml. of water and 10 ml. of concentrated hydrochloric acid was stirred and heated under reflux for 6 hours. An additional 40 ml. of water and 10 ml. of concentrated hydrochloric acid were added, and mixture was stirred and heated under reflux for 1.5 hours. The mixture was then allowed to cool to room temperature, and the oil that separated solidified. A sample of this material was insoluble in 10% sodium hydroxide and gave a negative test for amino acid with ninhydrin. A mixture of 80 ml. of glacial acetic acid and 10 ml. of concentrated hydrochloric acid was added, and the mixture was stirred and heated under reflux for 8 hours. The warm solution was treated with Norit and filtered. The residue was washed with water, and the combined filtrates were evaporated to dryness *in vacuo*. The residue (*ca.* 10 g.) was triturated with 50 ml. of acetone and filtered. The solid was washed with acetone and air-dried to give 5 g. (48.7%) of the amino acid hydrochloride, m.p. 208–209° dec. The acetone solutions were combined and evaporated to dryness. To the residue were added 25 ml. of water, 25 ml. of glacial acetic acid and 10 ml. of concentrated hydrochloric acid, and the mixture was heated under reflux for 6.5 hours.

(15) F. Misani and L. Reiner, *Arch. Biochem.*, **27**, 234 (1950).

(16) J. W. Czekalowski, *Brit. J. Expt. Path.*, **33**, 57 (1952).

(17) All compounds described are racemic modifications.

(18) Reactions involving amino acids were followed by means of paper chromatography, and products were isolated when the absence of unchanged starting material was indicated.

(19) The melting points of the amino acids are corrected.

(20) All analytical samples of amino acids were chromatographically homogeneous.

(21) V. Prelog, V. Hahn, H. Brauchli and H. C. Beyerman, *Helv. Chim. Acta*, **27**, 1209 (1944).

(22) D. Goldsmith and M. Tishler, THIS JOURNAL, **68**, 144 (1946).

The solution was then evaporated to dryness *in vacuo* to give 1.13 g. (12.8%) of crude amino acid after washing with acetone and neutralizing with *n*-amylamine. In order to provide an analytical sample of the amino acid, 1 g. of the first crop was dissolved in 8 ml. of water and neutralized to *p*H 6 with *n*-amylamine. Acetone (25 ml.) was added and the solid was removed by filtration and washed with 15 ml. of acetone. This material weighed 300 mg. and melted at 203–204° dec. By further addition of acetone to the filtrate a second crop weighing 350 mg. was obtained. The combined crops (650 mg.) were recrystallized from water to give an analytical sample melting at 203–204° dec.

S-Methylpenicillamine.—To a solution of 1.2 g. (0.052 gram-atom) of sodium in 150 ml. of absolute methyl alcohol was added with cooling and stirring, 14 g. (0.29 mole) of methyl mercaptan (gas). Cooling and stirring was continued and a mixture of 50 g. (0.215 mole) of methyl α-benzamidosenecioate,[12] 200 ml. of absolute methyl alcohol and 200 ml. of dry benzene was added. The mixture was stirred at room temperature for one hour and then allowed to stand overnight. Glacial acetic acid (3.12 g.) was added, and mixture was evaporated to dryness *in vacuo* and at room temperature. The residue was washed with 200-ml. and 25-ml. portions of warm, dry benzene, and the combined benzene solutions were evaporated to dryness under reduced pressure. A mixture of the residue (*ca.* 58 g.), 300 ml. of 85% formic acid, 300 ml. of concentrated hydrochloric acid and 300 ml. of water was heated under reflux for 6 hours. The solution was concentrated to about 50 ml., washed with ether and neutralized to *p*H 6.5 with *n*-amylamine. Acetone (350 ml.) was added, and mixture was refrigerated for 2 days. The white crystals were removed by filtration and washed with 300 ml. of acetone and 200 ml. of ether. The dried crystals weighed 16.8 g. (48%), m.p. 281–282°.

In another experiment, 16.5 g. (34%) of S-methylpenicillamine was obtained in the same manner as above from 60.0 g. (0.3 mole) of 2-phenyl-4-isopropylidene-5-oxazolone[23] and 30 g. of methyl mercaptan.

S-Methyl-3-phenylcysteine. Methyl 2-Benzamido-3-methylmercaptohydrocinnamate.—To 300 ml. of anhydrous methanol was added 1.2 g. of sodium, and after all of the sodium dissolved 16 g. of methyl mercaptan (gas) was added. With cooling and stirring a solution of 62.3 g. (0.25 mole) of 2-phenyl-4-benzal-5-oxazolone[24] in 500 ml. of warm, dry benzene was added. The mixture was stirred for about one hour and then allowed to stand at room temperature. Glacial acetic acid (3.12 g.) was added, and the mixture was evaporated to dryness *in vacuo*. Warm benzene (100 ml.) was added, and mixture was filtered. The filtrate was diluted with 100 ml. of warm benzene and 500 ml. of pentane. The solid was separated from the chilled mixture and washed with 150 ml. of pentane to yield 74 g. (90%) of product, m.p. 90–93°. A second crop, weighing 5.3 g. (6.4%) and melting at 90–95° was obtained by further addition of pentane to the mother liquor. Recrystallization from ethyl acetate-pentane raised the melting point to 97–98.5°.

Anal. Calcd. for $C_{18}H_{19}O_3NS$: C, 65.66; H, 5.82; N, 4.26. Found: C, 65.87; H, 5.91; N, 4.28.

S-Methyl-3-phenylcysteine.—The crude methyl 2-benzamido-3-methylmercaptohydrocinnamate (32.9 g., 0.1 mole) was hydrolyzed with a mixture of 150 ml. of water, 150 ml. of concentrated hydrochloric acid, and 150 ml. of 90% formic acid. The solution was concentrated *in vacuo* to almost dryness, and the precipitate was removed and washed three times with 100 ml. of boiling ether. The residue was dissolved in 75 ml. of water and neutralized to *p*H 6 with *n*-amylamine. The product obtained from the chilled solution was washed with acetone to give 12.5 g. (59.3%) of the amino acid, m.p. 178–179° dec. The melting point was unchanged after recrystallization from water.

Preparation of Sulfone by Oxidation of Sulfoxide.—The following procedure is typical for the preparation of two sulfones XIX and XXI. **2-Amino-4-(methylsulfonyl)-*n*-valeric Acid:** A mixture of 600 mg. of 2-amino-4-(methylsulfinyl)-*n*-valeric acid, 3 ml. of water, 2 ml. of methanol, 0.2 ml. of concentrated hydrochloric acid and 2 ml. of 30% hydrogen peroxide was heated under reflux for 2 hours. Paper chromatograms of a sample of the reaction mixture showed the presence of some unchanged sulfoxide. An additional one ml. of hydrogen peroxide was added and the mixture was heated under reflux for 2 hours; conversion to the sulfone was complete. The solution was neutralized to *p*H 6.5 with *n*-amylamine, and 100 ml. of acetone was added. The white solid was removed by filtration and was washed with 50 ml. of acetone; yield 550 mg. and m.p. 216–222° dec. Recrystallization from aqueous methanol gave 430 mg. of pure sulfone, m.p. 230–231° dec.

1-Methyl-3-amino-3-carboxypropylmethylsulfoximine.—The two sulfoximines in Table II were prepared by the following method. To 4-methylmethionine sulfoxide (6.0 g.) concentrated sulfuric acid (10.4 ml.) was added dropwise with stirring at 3°. Stirring was continued, and the mixture was heated to 45°; 54 ml. of 1.4 *N* hydrazoic acid[25] in chloroform was added over a period of 1.5 hours while the temperature was maintained at about 48°. The mixture was stirred and heated at this temperature for an additional 5 hours. Paper chromatograms of a sample of the reaction mixture indicated the presence of unchanged sulfoxide. An additional 13.5 ml. of the hydrazoic acid solution was added, and mixture was stirred and heated at 50° for 5 hours and then stirred overnight at room temperature. The mixture was poured onto 75 g. of crushed ice with stirring and neutralized to *ca. p*H 2.5 with solid barium hydroxide and then to *p*H 5 with solid barium carbonate. The mixture was centrifuged, and the liquid was decanted. The residue was mixed with water and then centrifuged and decanted. This operation was repeated until the last washings were free of amino acid (negative ninhydrin test). The combined water solutions were concentrated *in vacuo* at 50° to about 100 ml., charcoal was added, and mixture was filtered. The filtrate was concentrated to about 40 ml., filtered and evaporated to dryness. The residue weighed 6.4 g. and melted at 180–182° dec. After two recrystallizations from aqueous methanol the melting point was raised to 199–200° dec.

Degradation of XXII and XXIII.—2-Phenyl-3-(methylsulfonyl)-propionaldehyde and 3-phenyl-3-(methylsulfonyl)-propionaldehyde from XXII (100 mg.) and XXIII (80 mg.), respectively, and N-bromosuccinimide (*ca.* 60 mg.) were isolated as their corresponding 2,4-dinitrophenylhydrazones. These were triturated with hot ethanol and recrystallized from ethyl acetate to provide analytical samples.

2,4-Dinitrophenylhydrazone of 2-Phenyl-3-(methylsulfonyl)-propionaldehyde.—The purified material melted with decomposition at 188–189°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_4S$: C, 48.98; H, 4.11. Found: C, 49.27; H, 3.81.

2,4-Dinitrophenylhydrazone of 3-Phenyl-3-(methylsulfonyl)-propionaldehyde.—The purified material changed from yellow to red at 169° and decomposed at 196–198°. *Anal.* Calcd. for $C_{16}H_{16}O_6N_4S$: C, 48.98; H, 4.11. Found: C, 49.29; H, 3.90.

Paper Chromatography.—One drop of each aqueous solution of amino acid was placed on Whatman No. 1 filter paper. The paper was allowed to dry at room temperature, and ascending chromatograms were run in a solvent at 23 ± 1° for about 18 hours. The paper was removed, dried and sprayed with 0.1% ninhydrin in *i*-PrOH–H_2O (90:10).

The solvents were prepared as follows: **Butanol–Acetic Acid:** A mixture of 240 ml. of freshly distilled *n*-butyl alcohol, 60 ml. of glacial acetic acid and 300 ml. of distilled water was shaken and then allowed to stand overnight at 23 ± 1°. The upper layer was used as the solvent, and the lower layer was used to provide a water-saturated atmosphere above the solvent. **Lutidine–Collidine:** A solution of 60 ml. of freshly distilled 2,4,6-collidine, 60 ml. of 2,6-lutidine, 30 ml. of 95% alcohol and 120 ml. of distilled water was stored and used at 23 ± 1°. **Phenol–Water:** Phenol saturated with water was prepared from a mixture of equal volumes of the two solvents which had been equilibrated at 23 ± 1°.

NEWARK 1, NEW JERSEY

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