

13. *The Abnormal Hydrolysis of Methyl β -Methylthio- and β -Ethylthio-propionate.*

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Methyl β -methylthio- and β -ethylthio-propionate, on hydrolysis with 6N-hydrochloric acid, give bis-2-carboxyethyl sulphide $S(CH_2 \cdot CH_2 \cdot CO_2H)_2$ and dimethyl and diethyl sulphide respectively. It is significant that ethyl methyl sulphide is not formed in the second reaction. Co-ordination of a proton by the sulphur atom followed by formation of dimethyl- β -propiothetin is believed to be the first stage. Two possible courses are discussed for the later stages, and the possible significance of acrylic acid. Alkaline hydrolysis yields methane- and ethane-thiol. Dimethyl sulphide is also evolved during conversion of methionine into homocystine by sulphuric acid and in the similar reaction with *S*-methylcysteine.

BARGER and COYNE¹ found that ethyl β -methylthiopropionate $Me \cdot S \cdot CH_2 \cdot CH_2 \cdot CO_2Et$ is hydrolysed by boiling N-hydrochloric acid to the expected liquid β -methylthiopropionic acid, and LIU² confirmed this result. When, however, the methyl ester³ is hydrolysed with boiling 6N-hydrochloric acid we find that the product is a white acidic solid, m. p. 129°, having the empirical formula, $C_6H_{10}O_4S$. This was identified as bis-2-carboxyethyl sulphide, $(CO_2H \cdot CH_2 \cdot CH_2)_2S$, by conversion into the sulphone. A volatile compound evolved during the hydrolysis was identified as dimethyl sulphide by conversion into the

¹ Barger and Coyne, *Biochem. J.*, 1928, **22**, 1417.

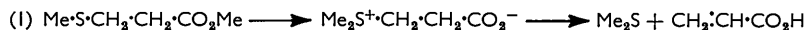
² Liu, Thesis, Leeds, 1948.

³ Hurd and Gershbein, *J. Amer. Chem. Soc.*, 1947, **69**, 2333.

mercurichloride and the sulphidimine; it was free from methanethiol, as shown by its inertness to aqueous mercuric cyanide. Traces of both products are in fact also produced from methyl β -methylthiopropionate even on use of *N*-acid. A similar experiment with 6*N*-sulphuric acid gave the same products, but also traces of methanethiol detected as its mercury derivative.

As expected, β -methylthiopropionic acid behaved in the same way with 6*N*-hydrochloric acid. β -Mercaptopropionic, methylthioacetic, and ethylthioacetic acid were stable to the hot 6*N*-acid.

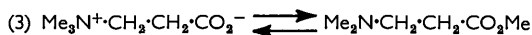
It seemed probable that the liberation of dimethyl sulphide might be due to the formation and subsequent decomposition of the chloride of the closely related compound dimethyl- β -propiothetin, $\text{Cl}^-\{\text{Me}_2\text{S}^+\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$. This might arise by isomerisation of the methyl β -methylthiopropionate, thus:



Such a mechanism recalls the interconversion of trimethylacetobetaine ("betaine") and methyl dimethylaminoacetate demonstrated by Willstätter:⁴

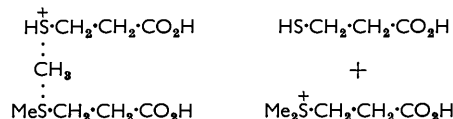


Betaine, however, is an α -derivative and although it seems possible from Willstätter's experiments that a similar relation may exist between trimethyl- β -propiobetaine and the methyl ester of β -dimethylaminopropionic acid:



the evidence for this is not so clear. Heating the β -betaine gives mainly acrylic acid and trimethylamine. We find, however, that reaction (1) of the Willstätter type is not involved in the "abnormal" hydrolysis of methyl β -methylthiopropionate with hot acid. Under similar conditions methyl β -ethylthiopropionate gives diethyl sulphide and bis-2-carboxyethyl sulphide, and not ethyl methyl sulphide which would be expected if the reaction proceeded by mechanism (1). Moreover, ethyl β -methylthiopropionate gives dimethyl sulphide, and not ethyl methyl sulphide, with hot 6*N*-hydrochloric acid.

It seems fairly certain that the "abnormal" reaction is brought about by the low pH (6*N*-acid). Presumably a proton is co-ordinated by the unshared electrons of the sulphur atom of the methylthiopropionic acid to form the complex ion $\text{MeHS}^+\cdot[\text{CH}_2]_2\cdot\text{CO}_2\text{H}$. Dr. A. T. Austin has suggested that this might then be converted into the corresponding thetin by a process in which the positive charge on the sulphur atom might attract the electrons of the methyl group so as to allow bimolecular nucleophilic attack by the sulphur atom of a second molecule of β -methylthiopropionic acid, giving a transition state leading to the formation of the thetin and β -mercaptopropionic acid:



Elimination of dimethyl sulphide from the thetin would leave the cation $^+\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ which by union with β -mercaptopropionic acid, followed by deprotonation, could give bis-2-carboxyethyl sulphide:



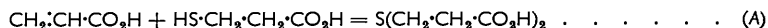
This mechanism is preferable to that according to which a positive methyl ion is detached from the positively charged complex $\text{MeHS}^+\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$ and after "independent

⁴ Willstätter, *Ber.*, 1902, **35**, 584; Willstätter and Kahn, *Ber.*, 1904, **37**, 401, 1853.

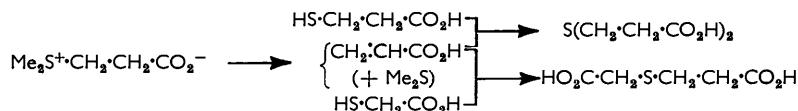
existence" is captured by a molecule of β -methylthiopropionic acid to give the thetin. Such a process, taking place in fairly strong hydrochloric acid, would be expected to give some methyl chloride. Attempts to detect this by passage of the volatile products from the abnormal hydrolysis of 10 g. of methyl β -methylthiopropionate through sulphuric acid to remove dimethyl sulphide and then through two traps at -20° and -75° , failed. Similar considerations arose in discussions of the mechanism of the mycological methylation of compounds of arsenic and selenium. If this involves a free methyl cation⁵ the formation of methanol in aqueous cultures would be expected. Attempts by Mr. F. Kieffer at Leeds in 1945 to detect this failed.⁶

An alternative, though less concise, representation of the course of the abnormal hydrolysis involves decomposition of the thetin to dimethyl sulphide and acrylic acid as shown in (1) above.

By addition of the β -mercaptopropionic acid, produced by breakdown of the transition complex, to the acrylic acid, bis-2-carboxyethyl sulphide would be formed⁷ and its production during the abnormal hydrolysis explained:



It was found⁸ that in hot 6N-hydrochloric acid β -mercaptopropionic acid reacts additively with methyl acrylate to form bis-2-carboxyethyl sulphide in good yield. A similar reaction with mercaptoacetic acid gives the unsymmetrical acid sulphide $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$. Reaction (A) is therefore possible under the conditions of the abnormal hydrolysis. Moreover, by heating dimethyl- β -propiothetin bromide and 6N-hydrochloric acid with (a) β -mercaptopropionic acid and (b) mercaptoacetic acid the two acid sulphides were readily obtained:



When β -methylthiopropionic acid, mercaptoacetic acid, and 6N-hydrochloric acid were heated as before, both the symmetrical and the unsymmetrical acid were obtained. None of these experiments, however, enables a final decision to be reached as to whether acrylic acid is an intermediate in the original abnormal hydrolysis.

Formation of acrylic acid involves elimination of hydrogen from the β -position to the methylthio-group of the propiothetin. In $\alpha\alpha$ -dimethyl- β -methylthiopropionic acid $\text{MeS}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{CO}_2\text{H}$ the β -hydrogens are replaced and this acid was recovered unchanged after long boiling with 6N-acid. Addition of thiols to unsaturated acids has usually been effected in neutral or mildly alkaline solution. Thus, Hurd and Gershbein³ found that, in presence of sodium methoxide, methyl acrylate and thiophenol give methyl β -phenylthiopropionate. Our results described above and reported in a preliminary communication⁸ show that this type of addition can occur in strongly acid solution. The same conclusion was reached almost simultaneously by Schöberl and Lange⁹ who found that in 2N-sulphuric acid containing a trace of quinol, thioacetic and acrylic acid gave high yields of 2-carboxyethyl carboxymethyl sulphide. The formation of 1–5% of the isomeric acid $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{S}\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ was also detected by Kuhn-Roth oxidation. Schöberl and Lange found that when acids of the type $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CHR}\cdot\text{S}\cdot[\text{CH}_2]_n\cdot\text{CO}_2\text{H}$ ($n = 1$ or 2) reacted with unsaturated acids, e.g., $\text{R}\cdot\text{CH}\cdot\text{CH}\cdot\text{CO}_2\text{H}$ in presence of saturated aqueous

⁵ Challenger, *Quart. Rev.*, 1955, **9**, 268.

⁶ Kieffer, unpublished observation.

⁷ Holmberg, *Arkiv Kemi, Min., Geol.*, 1946, **21**, B, No. 7, 1.

⁸ Challenger and Hollingworth, *Chem. and Ind.*, 1954, 463.

⁹ Schöberl and Lange, *Annalen*, 1956, **599**, 140.

halogen acid, sulphonium salts $\{(\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CHR})_2\cdot\text{S}^+\cdot[\text{CH}_2]_n\cdot\text{CO}_2\text{H}\}\text{X}^-$ were readily obtained. Many examples of this reaction were described. Such compounds may have been formed in our experiments with 6N-acid and have remained in the final mother-liquors. An attempt to detect β -mercaptopropionic acid when β -methylthiopropionic acid was boiled with 6N-acid and methyl α -methylacrylate failed, a viscous polymer and bis-2-carboxyethyl sulphide being obtained. The methyl derivative $\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{S}\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$ was not detected.

In hot aqueous 2N-sodium hydroxide methyl β -methylthiopropionate slowly afforded methanethiol, but not dimethyl sulphide, and after long boiling much of the acid was recovered. Acrylic acid could not be detected by addition of toluene-*p*-sulphinic acid and acidification. If formed it may have polymerised or undergone hydration to β -hydroxypropionic acid.¹⁰ Methyl β -ethylthiopropionate gave ethanethiol on alkaline hydrolysis. Much unchanged acid was recovered. Formation of alkanethiol in these two reactions may arise by β -elimination or, less probably, by hydrolysis giving as second product acrylic acid or β -hydroxypropionic acid respectively.

In bread cultures of *Scopulariopsis brevicaulis* β -methylthiopropionic acid was shown by Challenger and Liu¹¹ to give methanethiol, some of which was methylated to dimethyl sulphide. Methylthio- and ethylthio-acetic acid gave no alkanethiol in cultures of *S. brevicaulis* which suggests that a β -elimination rather than hydrolysis of the C-S bond may be concerned in the case of β -methylthiopropionic acid.

The stability of methylthio- and ethylthio-acetic acid to 6N-acid (see above) is probably due to the proximity of the electrophilic carboxyl group to the sulphur atom. The unshared electrons of the sulphur are thereby rendered unavailable and co-ordination of a proton, the first step in the abnormal hydrolysis, is hindered. In the corresponding alkylthiopropionic acids or esters this effect is damped by the second intervening $-\text{CH}_2-$ group, and protonisation of the sulphur atom can occur. It appeared, however, of interest to see whether dimethylacetothetin chloride $\text{Cl}^-\{\text{SMe}_2\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, when heated with 6N-hydrochloric acid, would (the first stage of the series of reactions being by-passed) react in accordance with the later stages postulated for the course of the "abnormal" hydrolysis. This was found to be the case, the products being dimethyl sulphide, biscarboxymethyl sulphide, methylthioacetic acid, and trimethylsulphonium chloride. The last two were characterised as the S-benzylthiuronium salt and as the mercuri-iodide, respectively. Methylthioacetic acid is also produced when the thetin chloride is boiled under reflux with water or (personal communication from Dr. D. Leaver) with aqueous sodium hydroxide (glycollic acid is also formed in the latter case).

The decomposition of the acetothetin can be explained by an adaptation of the mechanism suggested above. (1) The thetin chloride breaks down into (a) methylthioacetic acid and methyl chloride, and (b) dimethyl sulphide and the ions Cl^- and $^+\text{CH}_2\cdot\text{CO}_2\text{H}$. The cation is then co-ordinated by methylthioacetic acid, giving the complex $\text{HO}_2\text{C}\cdot\text{CH}_2\cdot^+\text{SMe}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$. By reaction with the liberated dimethyl sulphide this complex might transfer its methyl group, probably without separation as an ion, giving trimethylsulphonium chloride and biscarboxymethyl sulphide. Since acrylic acid cannot be concerned in the decomposition of dimethylacetothetin chloride, the suggestion that it is not involved in the abnormal hydrolysis gains considerably in probability.

Decomposition of Methylthio-amino-acids by Hot Mineral Acid. S-Methyl-L-cysteine.— This was unchanged after long boiling with 6N-hydrochloric acid. Only traces of methanethiol were detected and no dimethyl sulphide. In boiling 18N-sulphuric acid, however, methanethiol, dimethyl sulphide, and dimethyl disulphide were evolved. The yield of dimethyl sulphide was much greater than that from methionine under similar conditions (see below), suggesting the greater instability of the thetin from S-methylcysteine than of that from methionine. An attempt to prepare the methiodide of S-methylcysteine by the method

¹⁰ Linnemann, *Ber.*, 1875, **8**, 1095; Erlenmeyer, *Annalen*, 1878, **191**, 281.

¹¹ Challenger and Liu, *Rec. Trav. chim.*, 1950, **69**, 334.

employed for methionine methiodide,¹² reaction with methyl iodide in formic-acetic acid, yielded trimethylsulphonium iodide.

Methionine.—Butz and du Vigneaud¹³ showed that in boiling 18N-sulphuric acid methionine gave homocystine and an odour resembling that of dimethyl disulphide. Repetition of this experiment and aspiration of the volatile products through mercuric cyanide and chloride showed the presence of methanethiol, dimethyl sulphide, and dimethyl disulphide. The monosulphide very probably arose by decomposition of the thetin $\text{SO}_4^{2-}\{[{}^+\text{SMe}_2\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}(\text{NH}_2)\cdot\text{CO}_2\text{H}]_2\}$, a reaction analogous to that observed in the abnormal hydrolyses reported above. In a comprehensive investigation Lavine *et al.*¹⁴ showed that this thetin sulphate was formed during the action of sulphuric acid on methionine.

EXPERIMENTAL

Abnormal Hydrolysis of Methyl β -Methylthiopropionate.—The methyl ester³ (2 g.) was heated under reflux with 6N-hydrochloric acid (10 c.c.) until the oil disappeared. The odour of a volatile compound of sulphur was noticed. The solution on extraction with ether yielded an oil, bis-2-carboxyethyl sulphide (1 c.c., crude oil), m. p. 130° (from water) alone or mixed with material prepared by Bennett's method¹⁵ (Found: C, 40.2; H, 5.8; S, 17.7. Calc. for $\text{C}_6\text{H}_{10}\text{O}_4\text{S}$: C, 40.4; H, 5.65; S, 18.0%). It was converted by a slight excess of bromine water into bis-2-carboxyethyl sulphone, m. p. and mixed m. p. 219° (from water). Lovén¹⁶ gives m. p. 210°. The authentic sample was, therefore, analysed (Found: C, 34.4; H, 4.6; S, 15.3. Calc. for $\text{C}_6\text{H}_{10}\text{O}_6\text{S}$: C, 34.3; H, 4.8; S, 15.3%).

Hydrolysis of methyl β -methylthiopropionate (1 g.) with 6N-hydrochloric acid (6 c.c.) was repeated and volatile products aspirated in a slow stream of nitrogen through water into (a) aqueous 4% mercuric cyanide to remove thiols and (b) aqueous 3% mercuric chloride to remove sulphides. After 30 min. a white solid was formed in (b) and the odour of sulphide in the wash-water was marked. After 8 hr. formation of solid ceased; when separated it had m. p. 157° and 156—157° in admixture with authentic dimethyl sulphide¹⁷ mercurichloride of m. p. 157°. A trace of solid appeared in the mercuric cyanide which gave an odour of a thiol with hydrochloric acid, but was insufficient for determination of m. p. The dimethyl sulphide was further characterised by liberation from the mercurichloride with warm sodium hydroxide and aspiration into 10% aqueous chloramine-T. The resulting sulphidimine had m. p. 158° (from alcohol) and 157.5—158° with authentic SS-dimethyl-N-toluene-p-sulphonylsulphidimine.¹⁸ Bis-2-carboxyethyl sulphide, m. p. 130°, was again obtained.

Similar results were obtained with 6N-sulphuric acid. Dimethyl sulphide was characterised as before. The trace of precipitate, m. p. 140°, in the mercuric cyanide evolved a thiol with hydrochloric acid.

Preparation of β -Methylthiopropionic Acid and its Decomposition with Hydrochloric Acid.—Methyl β -methylthiopropionate (20 g.) was completely hydrolysed (12 hr.) under reflux with N-hydrochloric acid (40 c.c.). A slight odour of dimethyl sulphide was noticed. Extraction with ether yielded the acid, b. p. 138—140°/25 mm. Barger and Coyne¹ give b. p. 235—240°/760 mm. A small amount of non-volatile oil (0.6 g.) solidified on cooling (m. p. 129°), and was doubtless bis-2-carboxyethyl sulphide, a small amount of which is evidently produced even when N-acid is used.

β -Methylthiopropionic acid with 6N-hydrochloric acid also gave dimethyl sulphide (characterised as before) and bis-2-carboxyethyl sulphide. Traces of methanethiol were recognised. Ethyl β -methylthiopropionate¹⁹ when boiled with 6N-hydrochloric acid gave dimethyl sulphide

¹² Toennies and Kolb, *J. Amer. Chem. Soc.*, 1945, **67**, 849.

¹³ Butz and du Vigneaud, *J. Biol. Chem.*, 1932—33, **99**, 135.

¹⁴ Lavine and Floyd, *ibid.*, 1954, **207**, 97; Lavine, Floyd, and Cammaroti, *ibid.*, 1954, **207**, 107; Floyd and Lavine, *ibid.*, 1954, **207**, 119.

¹⁵ Bennett, *J.*, 1927, 196.

¹⁶ Lovén, *Ber.*, 1896, **29**, 1138.

¹⁷ Challenger and Simpson, *J.*, 1948, 1591.

¹⁸ Mann and Pope, *J.*, 1922, **121**, 1052.

¹⁹ Haagen-Smit, Kirchner, Deasy, and Prater, *J. Amer. Chem. Soc.*, 1945, **67**, 1651.

(mercurichloride, m. p. 157°) as the only volatile sulphur compound; the solid product was bis-2-carboxyethyl sulphide.

β-Mercaptopropionic Acid and Hydrochloric Acid.—The mercapto-acid,²⁰ b. p. 127°/35 mm., evolved no hydrogen sulphide or alkyl sulphur compound when boiled with the 6*N*-acid for 9 hr. and 80% of the acid was recovered. A small amount of solid, m. p. 154°, was formed, presumably bis-2-carboxyethyl disulphide (m. p. 154°) produced by oxidation.

Methyl Methylthioacetate and Hydrochloric Acid.—The ester (0.5 g.) when heated under reflux with 6*N*-hydrochloric acid (4 c.c.) gave only traces of solid in the usual absorbents and the oil recovered by ether-extraction was insufficient for further work. Methylthioacetic acid, prepared by Ramberg's method,²¹ had b. p. 111°/11.5 mm. (Holmberg²² gives b. p. 106—108°/8 mm.) (Found: C, 34.5; H, 5.6; S, 29.9. Calc. for C₃H₆O₂S: C, 34.2; H, 5.7; S, 30.2%). The acid with boiling 6*N*-hydrochloric acid yielded no precipitates in the absorbents. Ether-extraction yielded the unchanged acid, characterised as the *S*-benzylthiuronium salt, m. p. and mixed m. p. 152° (from aqueous alcohol) (Found: C, 48.7; H, 6.0; N, 10.5; S, 23.9. C₁₁H₁₆O₂N₂S₂ requires C, 48.4; H, 5.9; N, 10.4; S, 23.5%). The stability to acid of methylthioacetic acid and its ester shown by these experiments was confirmed when the acid (1.0 g.), methyl acrylate (1.0 g.), and 6*N*-hydrochloric acid (6 c.c.) were heated under reflux for 8 hr. No odour, except that of the acid, was noticed and extraction with ether yielded the unchanged acid (1 c.c.), identified as the *S*-benzylthiuronium salt, m. p. 152°. Ethylthioacetic acid (1.0 g.) was also recovered unchanged from boiling 6*N*-hydrochloric acid, and no deposit appeared in the mercuric cyanide or chloride.

Preparation and Attempted Fission of α-Dimethyl-β-methylthiopropionic Acid.—Chloropivalic acid²³ was esterified with methyl alcohol by Richard's method²⁴ for methyl pivalate. The ester had b. p. 162° (Found: C, 47.9; H, 7.4; Cl, 23.4. C₈H₁₁O₂Cl requires C, 47.8; H, 7.4; Cl, 23.6%). Sodium thiomethoxide (0.1 mol.) and sodium chloropivalate in aqueous solution were warmed at 100° for 15 min.²¹ The oil obtained on acidification was distilled at 30 mm., giving fractions, (a) b. p. 138—140° and (b) b. p. 155—160°. On redistillation, (a) boiled at 134°/12.5 mm. (Found: C, 48.8; H, 8.4; S, 21.0, 21.4. C₈H₁₃O₂S requires C, 48.6; H, 8.2; S, 21.6%). Fraction (b) partially solidified, was free from sulphur, and may have contained some hydroxypivalic acid,²⁵ m. p. 124°. Hot 6*N*-hydrochloric acid and methylthiopivalic acid (a) gave no volatile products or odour of an alkyl sulphide or thiol. Ether extracted the unchanged acid. Its *S*-benzylthiuronium salt had m. p. and mixed m. p. 134° (decomp.) (from dioxan) (Found, for the authentic sample: C, 53.2; H, 7.4; N, 9.1; S, 20.2. C₁₄H₂₂O₂N₂S₂ requires C, 53.5; H, 7.1; N, 8.9; S, 20.4%).

Dimethyl-β-propiothetin Bromide and Hydrochloric Acid.—The bromide (1.0 g.) with hot 6*N*-acid (6 c.c.) quickly gave a strong odour of sulphide. A precipitate was formed in the mercuric chloride much faster than in the case of methyl β-methylthiopropionate. This had m. p. and mixed m. p. 157—158° with dimethyl sulphide mercurichloride. Methanethiol was absent. The reaction mixture yielded an oil containing halogen which partially solidified when rubbed with either 2-chloro- or 2-bromo-propionic acid: it was probably a mixture of the two.

Interaction of Dimethyl-β-propiothetin Bromide and Hydrochloric Acid in Presence of (a) β-Mercaptopropionic Acid and (b) Mercaptoacetic Acid.—(a) The bromide (1.0 g.) was boiled under reflux with β-mercaptopropionic acid (1.1 g.) and 6*N*-hydrochloric acid (6 c.c.) for 10 hr., until dimethyl sulphide ceased to be evolved. A solid was deposited overnight which when crystallised from water had m. p. and mixed m. p. 130° with bis-2-carboxyethyl sulphide. Bromine water gave bis-2-carboxyethyl sulphone (as before), m. p. and mixed m. p. 219°. (b) When mercaptoacetic acid (0.9 g.) was used instead of β-mercaptopropionic acid, extraction with ether yielded a white solid (1.4 g.), m. p. 86°. Crystallisation from benzene gave needles, m. p. 93° not depressing the m. p. (93.5°) of 2-carboxyethyl carboxymethyl sulphide.¹⁶ This unsymmetrical acid is much more soluble than the symmetrical acid obtained as in (a) above.

Dimethylacetothetin and Hydrochloric Acid.—The thetin (1.0 g.) was boiled with 6*N*-acid (6 c.c.) for 9 hr. and volatile products were aspirated in nitrogen as before. There was no odour of methanethiol or deposit in the mercuric cyanide, but the mercurichloride of dimethyl sulphide

²⁰ Bülmann, *Annalen*, 1905, **339**, 363.

²¹ Ramberg, *Ber.*, 1907, **40**, 2588.

²² Holmberg, *Arkiv Kemi, Min., Geol.*, 1936, **12**, A, 11.

²³ Kharasch and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 925.

²⁴ Richard, *Ann. Chim. Phys.*, 1910, **21**, 335.

²⁵ Marcilly, *Bull. Soc. chim. France*, 1904, **31**, 119.

was obtained and converted into the sulphidimine, both of which were identified by m. p. and mixed m. p. The acid solution was evaporated in a vacuum to an oil which with alcohol-ether gave pale yellow needles, m. p. 140° (decomp.), presumably dimethylacetothetin chloride [m. p. 144° (decomp.)].

In a second experiment the acid solution when extracted with ether yielded a white semi-solid residue with an odour of methylthioacetic acid, which when crystallised from acetone-light petroleum formed needles, m. p. and mixed m. p. 130·5° with biscarboxymethyl sulphide (m. p. 130·5°) (Found: C, 32·0; H, 4·0; S, 21·3. Calc. for C₄H₆O₄S: C, 32·0; H, 4·2; S, 21·0%). The mother-liquor yielded methylthioacetic acid identified as the S-benzylthiuronium salt, m. p. and mixed m. p. 152°. Evaporation of the original aqueous solution gave a yellow oil which partially solidified in alcohol-ether and contained sulphur and halogen. With potassium mercuri-iodide it gave a white precipitate, m. p. 174—176°, which crystallised from acetone-ether in needles, m. p. and mixed m. p. 184° (decomp.) with authentic trimethylsulphonium mercuri-iodide (Me₃S)₂HgI₄, m. p. 184° (decomp.). The absence of an appreciable amount of biscarboxymethyl sulphide in the thetin anhydride was shown by dissolving 6 g. in dilute hydrochloric acid and extracting it six times with ether: this yielded a white solid with a sharp acidic odour in amount insufficient for a m. p. determination.

Attempts to detect Intermediate Products in the Reaction of β-Methylthiopropionic Acid and Hydrochloric Acid.—(a) *Acrylic acid.* β-Methylthiopropionic acid (5·6 g.), mercaptoacetic acid (3·0 g.), and 6N-hydrochloric acid (40 c.c.) were heated for 14 hr. (till the odour of dimethyl sulphide had disappeared). Extraction with ether yielded an oil which slowly crystallised. Since bis-2-carboxyethyl sulphide is almost insoluble in warm benzene and the unsymmetrical 2-carboxyethyl carboxymethyl sulphide is soluble, the white solid was crystallised from benzene but no homogeneous fraction could be obtained. Some fractions gave a negative test for the disulphide group with 10% aqueous sodium cyanide and sodium nitroprusside.²⁶ These were combined and crystallised from benzene-light petroleum, yielding fractions, (a) m. p. 129—130° not depressing that of authentic bis-2-carboxyethyl sulphide, and (b) m. p. and mixed m. p. 93—93·5° with 2-carboxyethyl carboxymethyl sulphide [Found for (b): C, 36·7; H, 4·4; S, 18·8. Calc. for C₅H₈O₄S: C, 36·6; H, 4·5; S, 19·8%. Calc. for C₆H₁₀O₄S: C, 40·4; H, 5·6; S, 18·0%]. Although the analysis for sulphur suggests that (b) contains 50% of bis-2-carboxyethyl sulphide the carbon and hydrogen figures do not confirm this. It is clear that the unsymmetrical acid arising from acrylic acid had been formed in large amount, a conclusion confirmed by the m. p. There was not sufficient material for a second determination of sulphur.

(b) *β-Mercaptopropionic acid.* 2-Methylthiopropionic acid (4·0 g.), methyl α-methylacrylate (1·8 g.), and 6N-hydrochloric acid (15 c.c.) were boiled in nitrogen for 14 hr. Much viscous polymer separated and the solution was extracted with ether, giving a white solid (2·0 g.) which yielded only bis-2-carboxyethyl sulphide, m. p. and mixed m. p. 130°. The unsymmetrical acid was not detected.

Methyl β-Ethylthiopropionate and Hydrochloric Acid.—The ester, prepared (yield 92%) from ethanethiol, methyl acrylate, and sodium methoxide by Hurd and Gershbein's method,³ had b. p. 103°/35 mm. (Found: C, 48·7; H, 8·0; S, 21·5. Calc. for C₈H₁₂O₂S: C, 48·6; H, 8·2; S, 21·65%). This ester (2·0 g.) was heated with 6N-hydrochloric acid (10 c.c.) in nitrogen. Only traces of solid (giving an odour of a thiol with acid but insufficient for further work) appeared in a mercuric cyanide trap. The precipitate in the mercuric chloride trap, when crystallised from benzene, did not depress the m. p. (119°) of diethyl sulphide mercurichloride. Extraction of the acid with ether yielded an oil and traces of a solid, m. p. 127—128°, presumably impure bis-2-carboxyethyl sulphide. Oxidation of the oily mixture with ferric chloride gave white needles (from water), m. p. and mixed m. p. 219° with bis-2-carboxyethyl sulphone.

Methyl β-Phenylthiopropionate and Hydrochloric Acid.—When the ester³ was boiled with hot 6N-hydrochloric acid no odour of a thiol or sulphide was noticed, no volatile products were detected, and β-phenylthiopropionic acid, m. p. 60·5°, was obtained in almost theoretical yield. Holmberg²⁷ gives m. p. 60—61°.

S-Methylcysteine and Hydrochloric Acid.—The amino-acid²⁸ had m. p. 242—244° (decomp.), [α]_D²⁵ —32·4°. du Vigneaud *et al.*²⁸ give m. p. 245° and [α]_D²⁷ —31·2°. The acid (0·5 g.) was

²⁶ Folin and Marenzi, *J. Biol. Chem.*, 1929, **83**, 103.

²⁷ Holmberg, *Arkiv Kemi, Min., Geol.*, 1942, **15**, A, 20.

²⁸ du Vigneaud, Loring, and Craft, *J. Biol. Chem.*, 1934, **105**, 481.

heated for 10 hr. under reflux with 6*N*-hydrochloric acid (5 c.c.). No volatile products were detected, the deposit in the mercuric cyanide being insufficient for a m. p. determination. The acid solution was poured into hot absolute alcohol (20 c.c.); *S*-methylcysteine, m. p. 240—242°, was precipitated with pyridine, a paper chromatogram, run in butanol-acetone and developed with ninhydrin, confirming its identity.

Attempted Preparation of S-Methylcysteine Methiodide.—Toennies and Kolb's method¹² for the corresponding methionine derivative was employed. *S*-Methylcysteine (2.7 g., 0.02 mole) in 89% formic acid (32.5 c.c.) was treated with glacial acetic acid (10 c.c.) and methyl iodide (5 c.c., 0.08 mole) and the closed flask kept at 25° in the dark for 7 days with occasional shaking, then evaporated under diminished pressure to a syrup. This when digested with methanol (20 c.c.) gave a yellow granular solid which was washed with methanol and acetone and precipitated from warm 50% ethanol with ether, forming needles, m. p. 202° (Found: I, 62.05; 61.95. Calc. for C₃H₉IS: I, 62.18%). Trimethylsulphonium iodide has m. p. 210°. The picrate, m. p. 180°, did not depress the m. p. of authentic trimethylsulphonium picrate, m. p. 180—181°.

*Decomposition of DL-Methionine with 18*N*-Sulphuric Acid.*—Methionine (5 g.) was boiled under reflux with 18*N*-sulphuric acid and the products aspirated as usual. Sulphur dioxide and dimethyl sulphide were detected by odour. Precipitates were formed in the mercuric chloride trap after 30 min. After 10 hr. sulphur dioxide was still present but the odour of dimethyl sulphide was not apparent. The precipitate in the cyanide trap had m. p. 150—155° (decomp.) and on crystallisation from ethyl acetate formed needles, m. p. and mixed m. p. 174° with mercury bithiomethoxide. The original precipitate was greenish-yellow, probably owing to traces of the compound (MeS)₂Hg.2HgS.²⁹ The mercuric chloride precipitate (0.3 g.) sintered at 145—150° but did not melt below 200°. It was treated with sodium hydroxide and the volatile products were aspirated as usual. The mercuric chloride precipitate had m. p. and mixed m. p. 157° with dimethyl sulphide mercurichloride. The alkaline residue was then acidified. Aspiration into mercuric cyanide gave mercury bithiomethoxide, m. p. and mixed m. p. 174° (from ethyl acetate). Clearly the volatile products from the reaction mixture contained dimethyl sulphide, methanethiol, and dimethyl disulphide.²⁹ Homocystine, m. p. 258—262° (decomp.), was isolated from the residual sulphuric acid according to Butz and du Vigneaud's directions.¹³

*Decomposition of S-Methylcysteine with 18*N*-Sulphuric Acid.*—*S*-Methylcysteine (1.0 g.) and 18*N*-acid (10 c.c.) were boiled under reflux and volatile products aspirated as usual. A deposit (A; 0.5 g.) was formed very quickly in the mercuric chloride and a smaller deposit (B) in the cyanide trap. (A) yielded dimethyl sulphide mercurichloride (C), m. p. and mixed m. p. 157°, on re-aspiration with sodium hydroxide into mercuric chloride. Subsequent acidification as before gave methanethiol, detected as the mercury derivative, (MeS)₂Hg, m. p. and mixed m. p. 174°. The yields of (A) and of (C) were much greater than in the corresponding experiment with methionine.

Addition of Mercapto-acids to αβ-Unsaturated Acids in Hydrochloric Acid.—(1) A mixture of β-mercaptopropionic acid (2 g., 0.02 mole) and methyl acrylate (1.6 g., 0.02 mole) was heated under reflux for 8 hr. with 6*N*-hydrochloric acid (10 c.c.). The oily layer soon disappeared. On cooling, much white solid was deposited which crystallised from water in needles (3.2 g., 91%), m. p. 130°, not depressing that of bis-2-carboxyethyl sulphide. The product was converted into the sulphone, m. p. and mixed m. p. 219°.

(2) 2-Carboxyethyl carboxymethyl sulphide was prepared by Lovén's method¹⁶ by heating β-bromopropionic acid, mercaptoacetic acid, and aqueous sodium hydroxide under reflux for 30 min. and acidifying the mixture. It crystallised from benzene as plates, m. p. 93.5° (Lovén gives m. p. 94°) (Found: C, 36.8; H, 4.5; S, 19.6. Calc. for C₅H₈O₄S: C, 36.6; H, 4.5; S, 19.8%).

The same acid was obtained when mercaptoacetic acid (2.0 g., 0.025 mole) was heated under reflux with methyl acrylate (1.7 g., 0.025 mole) and 6*N*-hydrochloric acid (10 c.c.) for 10 hr. (until oil had disappeared and the liquid gave a negative test for the thiol group with nitroprusside). Extraction with ether yielded 3.2 g. (85%) of white solid, recrystallisation from benzene giving plates, m. p. 93° alone or in admixture with 2-carboxyethyl carboxymethyl sulphide.

(3) 2-Carboxyethyl 2-carboxypropyl sulphide was obtained when β-mercaptopropionic acid

²⁹ Challenger and Rawlings, *J.*, 1937, 868.

(2.0 g., 0.02 mole) was boiled with α -methyl methacrylate (1.7 g., 0.02 mole) and 6*N*-hydrochloric acid (10 c.c.) for 8 hr. (until the clear solution gave a negative test for the thiol group). A viscous solid which appeared to be a polymer was deposited on cooling. The solution, after extraction with ether, yielded an oil, which solidified. Most solvents were unsuitable for recrystallisation, but 1:10 benzene-light petroleum yielded needles of the acid, m. p. 52.5° (Found: C, 43.5; H, 6.0; S, 16.7. $C_7H_{12}O_4S$ requires C, 43.7; H, 6.3; S, 16.7%).

Separation of $S(CH_2\cdot CH_2\cdot CO_2H)_2$ from $CO_2H\cdot CH_2\cdot CH_2\cdot S\cdot CH_2\cdot CHMe\cdot CO_2H$.—A mixture of 0.2 g. of each sulphide was prepared and fractionally crystallised from benzene. The more soluble, unsymmetrical, component was precipitated with light petroleum. Bis-2-carboxyethyl sulphide (m. p. 129—130°) and its 2-methyl derivative (m. p. 53°) were recovered.

Methyl Esters of β -Alkylthiopropionic Acids and Sodium Hydroxide.—Methyl β -methylthiopropionate (2.0 g.) was boiled with 2*N*-sodium hydroxide (10 c.c.) for 8 hr. and volatile matter was aspirated as before. Much deposit formed in the cyanide trap and crystallised from ethyl acetate, then having m. p. and mixed m. p. 175° with mercury bithiomethoxide. In the mercuric chloride trap only traces of a solid were formed: this with dilute acid evolved methanethiol and was presumably $MeS\cdot HgCl, HgCl_2$ arising from fission of dimethyl disulphide formed by oxidation of the thiol in the air-stream.

Acidification of the alkaline reaction mixture and extraction with ether yielded an oil (1.5 g.) which solidified but readily melted in air. This, on evaporation with bromine water, gave β -methylsulphonylpropionic acid as needles, m. p. 105° (Schneider³⁰ gives m. p. 105°) (Found: C, 31.8; H, 5.2; S, 21.2. Calc. for $C_4H_8O_4S$: C, 31.6; H, 5.3; S, 21.1%).

In a similar experiment (3 hr.) an attempt to detect acrylic acid by addition of toluene-*p*-sulphinic acid to the alkaline solution and acidification failed, only the sulphinic acid, m. p. 85°, being precipitated. Both methyl acrylate and methyl α -methylacrylate were appreciably polymerised in boiling alkali under comparable conditions.

In a similar experiment with methyl β -ethylthiopropionate (2 g.) and 2*N*-sodium hydroxide (10 c.c.) (8 hr.) ethanethiol was collected as the mercaptide which, after crystallisation from ethanol, had m. p. and mixed m. p. 74°. Only traces of solid were formed in the mercuric chloride trap. Acidification of the alkaline reaction mixture yielded an oil which, with bromine water, gave β -ethylsulphonylpropionic acid, needles, m. p. 118° (from hot water) (Otto and Otto³¹ give m. p. 112°) (Found: C, 36.5; H, 6.2; S, 19.6. Calc. for $C_5H_{10}O_4S$: C, 36.1; H, 6.1; S, 19.4%).

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³⁰ Schneider, *Annalen*, 1910, 375, 233.

³¹ Otto and Otto, *Ber.*, 1888, 21, 992.