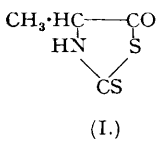
124. *Studies in the Azole Series. Part XXVI. The Action of Bases on 2-Thio-4-methyl-5-thiazolidone.*

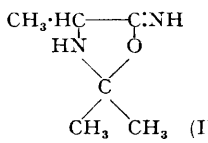
By A. H. Cook and A. L. Levy.

2-Thio-4-methyl-5-thiazolidone (I) exhibits a markedly greater stability than its analogue discussed in the preceding paper. While the ring is still readily opened by ammonia and morpholine, the products tend to revert in large part to (I) on acidification, even under anhydrous conditions. The carbon disulphide can be liberated from the ammonium dithiocarbamate, however, by very slow acidification in water under controlled conditions. (I) polymerises in boiling pyridine, but is stable to cold triethylamine.

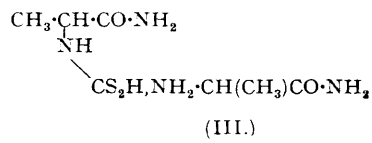
In view of the reactivity of 2-thio-5-thiazolidone and as a model for 4-substituted thiothiazolidones, (±)-2-thio-4-methyl-5-thiazolidone (I) was selected for study. The preparation of α-aminopropionitrile was improved, and the base condensed with acetone in the presence of sodium methoxide (cf. Cook, Heilbron, and Levy, Part III, *J.*, 1948, 201) to give 5-imino-2 : 2 : 4-trimethyloxazolidine (II). With carbon disulphide in wet acetone, this afforded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III), which yielded the required *thiothiazolidone* (I) in 90% yield on acidification with two equivalents of 2N-sulphuric acid. Acidification with dry hydrogen chloride in ethanol gave alanine amide hydrochloride in 60% yield, also obtained from (II) and hydrochloric acid. While α-aminopropionitrile was available, advantage was taken of the experience gained with aminoacetonitrile, to improve its condensation with carbon disulphide (Cook, Heilbron, and Levy, *J.*, 1947, 1598), and *4-amino-2-mercapto-4-methylthiazole* was obtained directly in 61% yield. It readily formed a Schiff's *base* with pyruvic acid, but could not be converted into (I) with acids.



(I.)



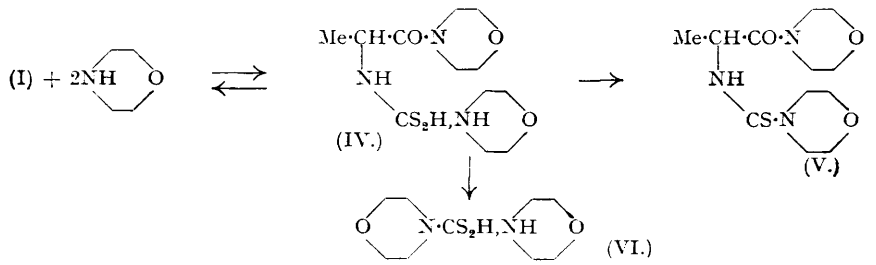
(II.)



(III.)

When (I) was treated with ammonia in ethanol, 90% of *ammonium α-carbamylethyldithiocarbamate* (cf. III) rapidly crystallised. On acidifying a solution of the ammonium salt in water, (I) was recovered in high yield, but treatment with dry hydrogen chloride in ethanol gave crude alanine amide hydrochloride in 64% yield, only 12% undergoing ring-closure to (I). Alternatively, methanolic picric acid could be used to provide crude alanine amide picrate in 70% yield, ammonium picrate being recovered quantitatively. It was of interest to see, using ammonium α-carbamylethyldithiocarbamate as a model, whether carbon disulphide could also be detached by a more controlled acidification in water. It was therefore slowly titrated against 0·05N-hydrochloric acid, the changes in pH being followed with a glass electrode. The initial pH (6·26) fell on addition of acid as the dithiocarbamic acid corresponding to (III) was liberated. Thereafter the pH began to rise, following a unimolecular curve and becoming constant after about five minutes. Clearly, this stage corresponded to loss of carbon disulphide from α-carbamylethyldithiocarbamic acid to give alanine amide, which would however be expected to neutralise at once any undecomposed acid to give (III), resulting in only half the theoretical quantity of carbon disulphide being lost for each addition of acid. This was borne out by the final titration curve which showed that two equivalents of acid were required to expel all the carbon disulphide. The course was constructed by observing the pH of the solution at an arbitrarily standardised time of three minutes after the addition of each drop of acid, *i.e.*, when about 85% of the α-carbamylethyldithiocarbamic acid had decomposed. Carbon disulphide separated from the solution during the titration, which took several hours, and no thiothiazolidone (I) was produced. For comparison, ammonium α-carbamylethyldithiocarbamate was titrated

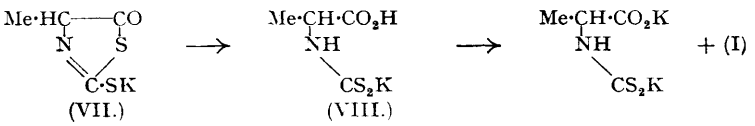
against 0·1N-hydrochloric acid during 11 minutes; in this case (I) separated from the solution, and the curve obtained was quite different from that obtained by slow titration, the first half being of the expected form for neutralisation of an ammonium salt. It appeared, therefore, that very slow acidification allowed α-carbamylethyldithiocarbamic acid to decompose before the pH became sufficiently low to cause thiothiazolidone formation. In order to gain some estimate of this pH value, the ammonium salt was acidified with a series of buffer solutions (pH 1·26—2·8). Crystallisation of (I) practically ceased at pH 2·5, though by working with a very concentrated solution a small degree of cyclisation was brought about by potassium hydrogen phthalate (pH 4). Hence, ring-closure of (III) and the corresponding ammonium salt to (I) was readily effected by such compounds as aqueous oxalic, sulphurous, and acetic acids, an 85% yield being obtained with acetic acid.



When (I) was kept with two equivalent proportions of morpholine in acetone solution, the crystalline *morpholinium* salt of *N*-dithiocarboxyalanine morpholide (IV) soon separated in a yield of 89%. Acidification of this salt regenerated (I) in a yield of 87%. The salt was remarkably labile, for when kept for a short time in solvents it was completely decomposed to a mixture of the substituted *thiourea* (V) and the morpholinium salt of 4-dithiocarboxymorpholine (VI), each of which could be isolated under appropriate conditions. When (I) was warmed with excess of morpholine, (VI) was the main product, treatment of which with aqueous acid gave the corresponding unstable free dithiocarbamic acid. Acidification of (IV) with dry hydrogen chloride in chloroform gave a poor yield of crude alanine morpholide hydrochloride, and 44% of the dithiocarbamate reverted to (I). This contrasts with the ready expulsion of carbon disulphide from the corresponding glycine derivative (preceding paper), and indicates the considerable influence of the methyl substituent in promoting ring-closure.

Again unlike 2-thio-5-thiazolidone, (I) was unaffected by triethylamine in cold acetone, and did not yield an insoluble polymer when heated under reflux with methanol However, in boiling pyridine, a high-melting, insoluble compound was produced after some time, which is probably a lower polyalanine.

The thiothiazolidone (I) dissolved in one equivalent of aqueous barium hydroxide or potassium hydroxide to give a solution of pH 8·5, which slowly became more acid on storage. When the pH had reached 7·7 (after 11 minutes) colourless needles began to separate, which increased in amount during several hours. Surprisingly, these were identified as (I), and its formation was evidently due to slow ring-opening of (VII) to give the carboxylic acid (VIII), which being a comparatively strong acid captured the limited number of potassium ions present from the weakest acid, namely (I). The salt (VII) was also decomposed by carbon dioxide to give (I).



At pH 9, approximately one-third of (I) decomposed during the first hour, and no evidence was obtained of dimerisation under the influence of alkali, as was the case with 2-thio-5-thiazolidone.

Experimental.

2-Thio-4-methyl-5-thiazolidone and Related Compounds.—In our hands, the following preparation of α-aminopropionitrile gave better results than that described in Part II (*J.*, 1947, 1598), and by Goldberg and Kelly (*J.*, 1947, 1371). Acetaldehyde (180 g.; freshly prepared from paraldehyde) and hydrogen cyanide (160 c.c.) were mixed in a large flask cooled in a freezing mixture, 50% aqueous potassium hydroxide cautiously added to initiate the vigorous autocatalytic reaction, and addition subsequently continued until no further heating effect was produced (2—3 c.c. required). After 1 hour

at room temperature, the catalyst was neutralised with concentrated sulphuric acid, and the mixture filtered and distilled at 10—12 mm. After an initial fraction, b. p. ~50° (paraldehyde), acetaldehyde cyanohydrin (105 g., 36%) distilled smoothly at 92°. Commercial acetaldehyde gave variable results by this procedure, though one batch (600 g.) gave a 60% yield of cyanohydrin. The cyanohydrin (167 g.) was added to a solution of liquid ammonia (100 g.) in methanol (500 c.c.), and the mixture kept at room temperature for 22·5 hours. Excess of methanol and ammonia was removed in a vacuum, and the residue distilled at 10—12 mm., an initial fraction (mainly water) being followed by the pure α-aminopropionitrile (78·5 g., 48%), b. p. 64°.

α-Aminopropionitrile (10 g.) in dry acetone (20 c.c.) was treated with a solution of sodium (~0·2 g.) in dry ethanol (~2 c.c.), the mixture becoming slightly warm. Next morning, the mixture was cooled in a freezing mixture and scratched, whereupon 5-imino-2 : 2 : 4-trimethyloxazolidine (9·2 g., 50%) separated, having m. p. 76°. Like the glycine analogue, it was deliquescent, but solidified again owing to carbonate or carbamate formation. With concentrated hydrochloric in ethanol, it yielded alanine amide hydrochloride, m. p. 172—173°. When the above acetone filtrate was treated with carbon disulphide, it yielded *α-carbamylethylammonium α-carbamylethyldithiocarbamate* (III) (4·0 g.), which crystallised from water on addition of a large excess of acetone, in rectangular tablets, m. p. 140° (decomp.) (varies with the rate of heating) (Found: C, 33·35; H, 6·6; N, 22·5. $C_7H_{26}O_2N_4S_2$ requires C, 33·35; H, 6·4; N, 22·2%).

When (III) was dissolved in water, and acidified, the required *2-thio-4-methyl-5-thiazolidone* rapidly separated in high yield, and recrystallised from benzene in beautiful blades, m. p. 128·5° (Found: C, 33·0; H, 3·8; N, 9·3. $C_4H_5ONS_2$ requires C, 32·65; H, 3·4; N, 9·5%). The thiothiazolidone was freely soluble in methanol, ethanol, acetone, ethyl acetate, or ether, moderately in chloroform or acetic acid, and insoluble in water or light petroleum. It dissolved readily in aqueous sodium hydroxide or carbonate, but was insoluble in sodium hydrogen carbonate. After treatment with hydroxylamine hydrochloride and sodium acetate in methanol, it afforded an intense brown colour (and a precipitate in stronger solutions) with ferric chloride. 2-Thio-5-thiazolidone gave the same colour (though the iodine–sodium acetate test is more characteristic in this case; cf. Part III, *J.*, 1948, 204), as do many other 4-substituted-5-thiazolidones and anhydrides generally (Davis and Levy, *J.*, in the press).

For the preparation of 2-thio-4-methyl-5-thiazolidone (I) in the best yield, it was not necessary to isolate α-aminopropionitrile or the above iminotrimethyloxazolidine, and a typical procedure was as follows. Acetaldehyde cyanohydrin (80 g.) was added to a mixture of liquid ammonia (40 c.c.) and methanol (40 c.c.) cooled initially in ice, and kept for 24 hours at room temperature. Excess of methanol and ammonia was then evaporated off on a water pump, until the temperature of the distilling liquid had reached 55°, and the residue was dissolved in dry acetone (150 c.c.), treated with sodium ethoxide (~0·5 g.), and kept overnight. The mixture was then diluted with acetone (250 c.c.) containing water (20 c.c.) and seeded, whereafter addition of carbon disulphide (40 c.c.) with vigorous stirring and scratching caused the dithiocarbamate (III) (47·5 g., 33% calc. on the cyanohydrin) to separate. This was dissolved in water and acidified with 2N-sulphuric acid (190 c.c.). 2-Thio-4-methyl-5-thiazolidone (25 g., 90%), m. p. 125—126°, rapidly crystallised. Recrystallisation from benzene gave 18 g., m. p. 127—128°.

The dithiocarbamate (III) (1·26 g.) was suspended in dry ethanol (10 c.c.), and a stream of dry hydrogen chloride in nitrogen (made by bubbling nitrogen through concentrated hydrochloric acid, followed by passage through anhydrous calcium chloride) passed in for 2 hours. (III) dissolved, and was replaced by crude alanine amide hydrochloride (0·74 g., 60%), m. p. 165—168°.

α-Aminopropionitrile (4·5 g.) was treated with excess of carbon disulphide in ethyl acetate, whereupon *5-amino-2-mercapto-4-methylthiazole* (5·7 g., 61%) separated on scratching, and recrystallised from ethanol in pale yellow needles which contracted and resolidified at about 150°, became dark purple at 220°, and decomposed completely at 233° (Found: C, 33·4; H, 4·0. $C_4H_6N_2S_2$ requires C, 32·9; H, 4·1%). When the reaction was carried out in ethanol, the product was incompletely soluble in hot ethanol, the residue being 2 : 4-dithio-5-methylhydantoin, m. p. 223° (decomp.) (cf. Cook, Heilbron, and Levy, *loc. cit.*). When the aminothiazole was dissolved in 2N-hydrochloric acid, it was rapidly replaced by white needles of the hydrochloride, m. p. 207° (decomp.); on the mixture being warmed to 70° for 1 minute a flocculent precipitate, m. p. 195—200° (decomp.), was deposited. The aminothiazole gave a clear solution in 2N-nitric acid, which slowly deposited the above compound, m. p. 195—200° (decomp.), in poor yield on storage for some hours; (I) was not obtained. When treated with pyruvic acid in methanol, the thiazole gave an immediate orange precipitate of *5-α-carboxyethylideneamino-2-mercapto-4-methylthiazole* which crystallised from acetic acid in clusters of needles, m. p. 199° (decomp.) (Found: C, 39·2; H, 3·8. $C_7H_8O_2N_2S_2$ requires C, 38·9; H, 3·7%).

Experiments with Ammonium α-Carbamylethyldithiocarbamate.—2-Thio-4-methyl-5-thiazolidone (2·0 g.) in ethanol (25 c.c.) was treated with liquid ammonia (3 c.c.). Ammonium α-carbamylethyldithiocarbamate (2·2 g., 90%) was collected after 45 minutes, and recrystallised from methanol–ether; it then had m. p. 143°. With aqueous silver nitrate it gave a momentary white precipitate which rapidly became yellow and then black. Lead acetate gave a yellow precipitate which began to deposit a lead sulphide " mirror " after 5 minutes, whereas mercuric chloride gave a clean, almost white derivative.

The ammonium salt (1·0 g.) was suspended in dry ethanol (10 c.c.), and dry hydrogen chloride passed in with cooling until the mixture was acid to Congo-red. Ammonium chloride (0·3 g.) was filtered off, and the filtrate evaporated to dryness in a vacuum and treated with a small volume of ethanol to give crude alanine amide hydrochloride (0·25 g.), m. p. 158° (decomp.). Re-evaporation and trituration of the residue with acetone gave a second crop (0·19 g.), m. p. 154° (decomp.). The final filtrate was evaporated, and the residue treated with water to give (I) (0·08 g., 12%), m. p. 126—128°. The combined crops of amide hydrochloride (0·44 g., 64%) were recrystallised thrice from acetic acid; the colourless needles produced had m. p. 176°, undepressed with an authentic specimen.

Picric acid (1·15 g.) was dissolved in warm methanol (10 c.c.), and a suspension of the above ammonium salt (0·45 g.) in warm methanol (7 c.c.) added. The solution became clear, whereafter cooling in a freezing mixture gave ammonium picrate (0·53 g., 87%), m. p. ~250° (decomp.). The filtrate was evaporated in a

vacuum, and four crops of crude alanine amide picrate (total : 0·58 g., 74%) were obtained by dissolution of the residue in acetone and precipitation with ether and light petroleum. The combined material was recrystallised from water; a small first crop was ammonium picrate, the remainder (0·27 g.; 36%) being alanine amide picrate, m. p. 192—200°, undepressed on admixture with an authentic sample (m. p. 197°).

The slow-titration experiment was performed at 22° on 3·997 mg. (0·0221 mg.-equivalent) of the ammonium salt in water (1·0 c.c.), in a micro-titration apparatus described by Catch, Cook, and Kitchener (*J.*, 1945, 319), using a standard Cambridge pH meter and glass electrode. Addition of 0·897 c.c. of 0·0497N-hydrochloric acid (*i.e.*, 0·0445 mg.-equivalent) was required to reach the end-point. In the rapid-titration experiment, 1·0 c.c. of 0·5N-ammonium α-carbamylethyldithiocarbamate was neutralised with 5·0 c.c. of 0·1N-hydrochloric acid in a Morton cell, stirring being effected with a fine stream of nitrogen.

Buffer solutions of pH 1·26, 1·88, 2·16, 2·5, and 2·8 were prepared by mixing 0·1N-glycine solution (0·1N. also with respect to sodium chloride) with 0·1N-hydrochloric acid in the following proportions : 2 : 8, 5 : 5, 6 : 4, 7 : 3, 8 : 2. 0·5N-Ammonium α-carbamylethyldithiocarbamate (1 c.c.) was added to each (10 c.c.); precipitation of (I) by the first two appeared to be as complete as with 0·05N-hydrochloric acid. A smaller quantity crystallised from the solution having pH 2·16, and hardly any from that having pH 2·5. α-Carbamylethylammonium α-carbamylethyldithiocarbamate (III) (5·0 g.) was dissolved in water and acidified with glacial acetic acid (*ca.* 3 c.c.), whereupon 2-thio-4-methyl-5-thiazolidone (2·45 g., 85%) separated slowly in well-formed plates. When the corresponding ammonium salt was acidified with aqueous picric acid, however, ammonium picrate was precipitated, and (I) was not produced.

Action of Morpholine on (I).—2-Thio-4-methyl-5-thiazolidone (1·5 g.) in acetone (25 c.c.) was treated with morpholine (1·8 g., 2 equivs.). Heat was evolved and the *morpholinium* salt (IV) (2·9 g., 89%) of *N*-dithiocarboxyalanine morpholide separated on scratching, and was recrystallised from chloroform by the addition of ethyl acetate containing a little ether, forming microprisms, m. p. 115° (decomp.; partly resolidifying to remelt at ~175°) (Found : C, 44·2; H, 7·3. $C_{12}H_{23}O_3N_3S_2$ requires C, 44·9; H, 7·2%). The reaction could also be carried out in methanol, the dithiocarbamate separating in well-formed rectangular prisms, m. p. 110° (decomp.), on seeding. If the solution was not seeded, however, the thiourea (V) (see below), m. p. 159°, crystallised on storage overnight, whereas, if the dithiocarbamate (IV) was dissolved in methanol, morpholinium dithiocarbamate (VI) (see below), m. p. 219° (sealed tube), separated on storage (especially if the solution had been warmed).

When the compound (IV) (2·9 g.) was dissolved in water (20 c.c.) and acidified with concentrated hydrochloric acid, 2-thio-4-methyl-5-thiazolidone (1·15 g., 87%), m. p. 123—125°, was immediately precipitated. (IV) (1·0 g.) in dry chloroform (20 c.c.) was saturated with dry hydrogen chloride, and evaporated to dryness in a vacuum. Treatment of the residue with ethanol and then acetone gave 3 crops of crystals (0·68 g., total), the final filtrate giving (I) (0·2 g., 44%), m. p. 124°, on dilution with water. Fractionation of the above crystals from ethanol cooled in a freezing mixture gave the less soluble morpholine hydrochloride, m. p. 175—176°, and crude alanine morpholide hydrochloride, m. p. 153—156°. The latter became damp on exposure to air, changing to a compound, m. p. 251° (decomp.), after crystallisation from ethanol.

In an attempted crystallisation of (IV) from methanol–ethyl acetate, very little of the required compound was obtained, and evaporation of the filtrate yielded the substituted *thiourea* (V), m. p. 159°, which recrystallised from benzene–light petroleum in clusters of rods, m. p. 161—162° (Found : C, 50·0; H, 7·7; N, 14·5. $C_{12}H_{21}O_3N_3S$ requires C, 50·2; H, 7·3; N, 14·6%). It could also be crystallised from water, or in diamond-shaped prisms from methanol or ethanol. When (I) was warmed with excess of morpholine for a few moments without a solvent, morpholinium dithiocarbamate (VI) separated; it recrystallised from water in rhombic tablets which sublimed unchanged at ~200° and melted (sealed tube) at 227° (Found : C, 43·4; H, 7·45; N, 11·1. Calc. for $C_9H_{18}O_2N_2S_2$: C, 43·2; H, 7·2; N, 11·2%). It was best prepared by the action of carbon disulphide on morpholine in acetone, in which it was highly insoluble. This, incidentally, provides a convenient method for the detection of carbon disulphide in small amounts in vapours, etc. When (VI) was dissolved in water and acidified, a white curdy precipitate was produced, which redissolved during one minute.

Action of Tertiary Amines and Aqueous Alkali on (I).—2-Thio-4-methyl-5-thiazolidone (0·73 g.) was kept with triethylamine (0·5 g., 1 equiv.) in acetone (10 c.c.) for 1 hour, and the clear yellow solution acidified with dry hydrogen chloride. Triethylamine hydrochloride was filtered off, and a further crop removed by evaporation and treatment with ether. The filtrate was evaporated, and the residue (0·45 g.), m. p. 116°, washed with water. Crystallisation from benzene gave (I), m. p. 125°, and a small insoluble residue, m. p. 210° (decomp.), soluble in aqueous sodium hydroxide and reprecipitated on acidification.

The thiazolidone (I) (1·0 g.) was heated under reflux with pyridine (10 c.c.) for 30 minutes, and the resulting gel diluted with methanol to granulate the *polymer*, which contracted considerably when dried at 100° (Found : C, 47·2; H, 7·2; N, 17·4; S, 0·38%). It was a white powder, m. p. ~290°, insoluble in common solvents. (I) (1·0 g.) was destroyed when heated under reflux with methanol (10 c.c.) for 1 hour; the product was oily and readily soluble in organic liquids.

Saturated solutions of (I) in 0·34N-barium hydroxide and 0·5N-potassium hydroxide deposited colourless needles, m. p. 126°, of (I) after a short while (see p. 643). An attempt was made to follow the decomposition of (I) with alkali, by keeping the pH constant at 9 with small progressive additions of 0·34N-barium hydroxide. The readings became variable and unreliable after about 30 minutes, but it was established that about 33% of (I) decomposed during the first hour.

We are grateful to Sir Ian Heilbron, D.S.O., F.R.S., for his interest and encouragement, and to the Department of Scientific and Industrial Research for a Senior Research Award to one of us (A. L. L.).

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7. [*Received, November 18th*, 1949.]