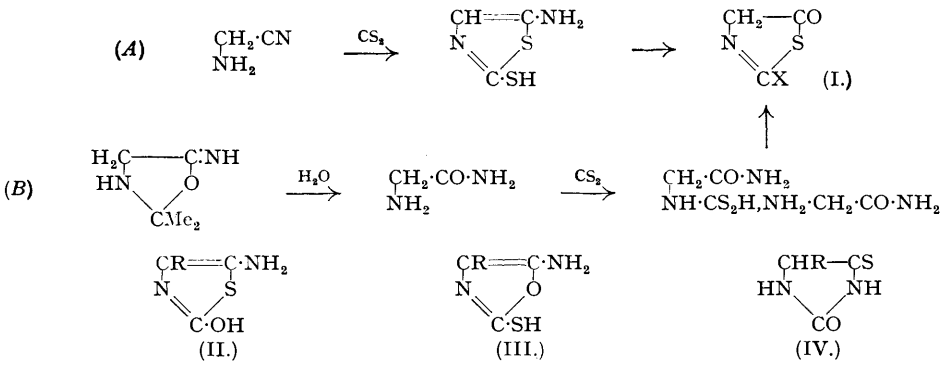
309. *Studies in the Azole Series. Part XVIII. The Interaction of α-Amino-nitriles and Carbon Oxysulphide.*

By A. H. Cook, Sir Ian Heilbron, and G. D. Hunter.

Interaction of carbon oxysulphide and α-amino-nitriles affords 5-amino-2-hydroxythiazoles (II). The latter are similar to but less stable than structurally comparable 2-mercaptothiazoles, readily undergoing cleavage or rearrangement to give 4-thiohydantoins (IV).

2-Mercapto-5-thiazolone (I; X = SH, or a tautomeride thereof) (Part III of this series, *J.*, 1948, 201) has proved useful in the synthesis of amino-acids, aminomercapto-acids, and polypeptides (Cook, Heilbron, *et al.*, *Nature*, in the press). In certain cases, however, the readiness with which the necessary ring-fissions and rearrangements take place leaves some room for improvement. It was accordingly thought that in these respects the so far unknown 2-hydroxy-5-thiazolone (2 : 5-diketothiazolidine) (I; X = OH, or its tautomeride) and its 4-substituted derivatives might exhibit the required activity, intermediate between that of *N*-carboxyglycine anhydride and of (I; X = SH). The latter compound has been prepared by two related routes (*A*) and (*B*); the present paper gives the results of experiments designed to simulate these methods with either aminoacetonitrile or other α-amino-nitriles, the carbon disulphide being replaced by carbon oxysulphide.



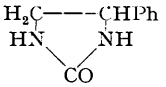
As early experiments with aminoacetonitrile and carbon oxysulphide usually led to tarry products, attention was first concentrated on the behaviour of more stable α-amino-nitriles.

Reaction between α-aminobenzyl cyanide and carbon oxysulphide in ethanolic solution led to a compound for which, on analytical evidence, structures (II and III; R = Ph) came into consideration. A more remote possibility represented by (IV; R = Ph) was eliminated by direct comparison of the new compound with 4-thio-5-phenylhydantoin (Johnson and Chernoff, *J. Amer. Chem. Soc.*, 1912, **34**, 1208). The latter substance was characterised as its *monomethyl* and its *acetyl* derivative. An attempt to desulphurise the thiohydantoin with alkaline hydrogen peroxide led to the formation of the corresponding *disulphide*. The compound (II or III; R = Ph) was indeed converted into (IV) when it was treated either with cold aqueous sodium hydroxide or with Raney nickel. Clearly, (II) is more acceptable than (III; R = Ph) as representing the immediate precursor of the 4-thio-5-phenylhydantoin, and the compound under consideration is thus regarded as 5-*amino*-2-*hydroxy*-4-*phenylthiazole* (II; R = Ph) (or a tautomeric form). A second product from the treatment of (II; R = Ph) or of (IV; R = Ph) with Raney nickel was 4-phenyl-2-iminazolidone (V); the latter had previously been obtained by a tedious method (Karewskaja, *J. pr. Chem.*, 1932, **132**, 335) but there was no doubt of the identity of the material obtained during the present work as it was hydrolysed to α-phenylethylenediamine which was characterised as its known acetyl derivative.

5-Amino-2-hydroxy-4-phenylthiazole yielded a *hydrochloride* and a *diacetyl* derivative. It condensed with benzaldehyde to give a *benzylidene* derivative, and, also like other 5-aminothiazoles (cf. Part II, *J.*, 1947, 1598), it developed a bright red colour on warming with ethanolic glyoxal.

Reaction between ethyl aminocyanoacetate and ethereal carbon oxysulphide resulted in a compound which, by analogy with one of those described above and from its behaviour, must be 5-*amino*-2-*hydroxy*-4-*carbethoxythiazole* (II; R = CO_2Et). It readily formed a *monoacetyl*

and a *benzylidene* derivative, and underwent rearrangement even more easily than the phenyl analogue above; thus in presence of either aqueous ammonia or sodium carbonate it was converted into 5-*carbethoxy*-4-*thiohydantoin* (IV; R = CO_2Et), a monohydrated *sodium* salt



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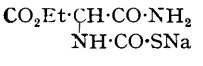

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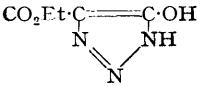
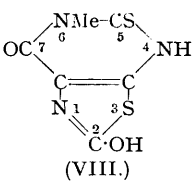


(VII.)

of the thiohydantoin being isolated as an intermediate when using sodium carbonate. Desulphurisation of either (IV; R = CO_2Et) or, with simultaneous rearrangement, of (II; R = CO_2Et) using Raney nickel afforded 2-hydroxy-4-carbethoxyglyoxaline (Hilbert, *J. Amer. Chem. Soc.*, 1932, **54**, 3413), characterised as its *acetyl* derivative. When (II; R = CO_2Et) was subjected to the action of either aqueous sodium hydroxide or hydrochloric acid the ring was cleaved with the formation, in the latter case, of *aminocarbethoxyacetamide hydrochloride*; in the former case an unstable sodium salt, probably sodium carbethoxycarbamylmethylthiolcarbamate (VI), was obtained and shown to undergo decomposition in presence of hydrochloric acid to give the hydrochloride already mentioned. Attempts to diazotise the thiazole (II; R = CO_2Et) gave rise to what is best regarded as 5-*hydroxy*-4-*carbethoxy*-1 : 2 : 3-*triazole* (VII), as it was also obtained on treating aminocarbethoxyacetamide with nitrous acid. Although 1 : 2 : 3-triazines are known to be formed on treating β-amino-amides with nitrous acid, 1 : 2 : 3-triazoles do not seem to have obtained in this way before. The method does not, however, seem to be of general utility; thus, aminoacetamide afforded glycollic acid, and α-aminophenylacetamide yielded exclusively mandelamide. The triazole (VII) is possibly identical with the compound obtained by the action of ammonia on ethyl diazomalonate (Piloty and Neresheimer, *Ber.*, 1906, **39**, 514) but not described in detail.

Attempts to prepare purine analogues *via* (II; R = CO_2Et) (cf. Parts XI—XIV, this vol., pp. 1061 *et seq.*) met with only indifferent success owing to the readiness which the thiazole underwent rearrangement. Thus on heating (II; R = CO_2Et) with methyl *iso*thiocyanate in pyridine, about 75% was converted into (IV; R = CO_2Et) and only a small yield of what is tentatively formulated as 5-*thio*-2-*hydroxy*-7-*keto*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydro*-(5 : 4-d)-*thiazolopyrimidine* (VIII) was isolated. Further, reaction of (II; R = CO_2Et) with methyl



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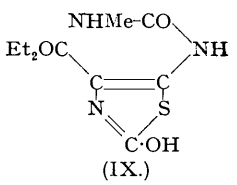


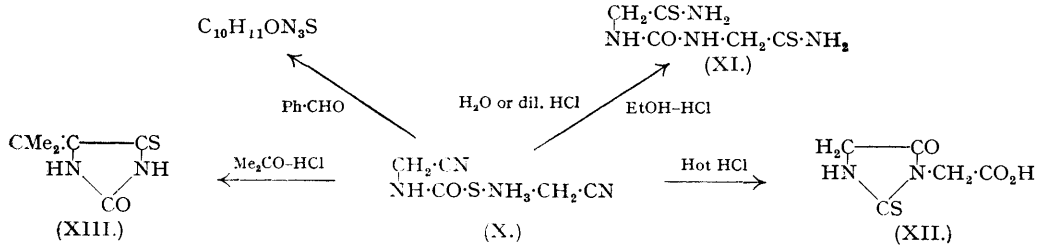
(IX.)

*iso*cyanate in pyridine afforded the expected 5-*methylureido*-2-*hydroxy*-4-*carbethoxythiazole* (IX); the latter, however, could not be cyclised to a thiazolopyrimidine in presence of alkali, undergoing instead an unelucidated change.

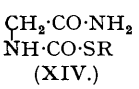
After the initial inconclusive attempts mentioned above, reaction between aminoacetonitrile and carbon oxysulphide was found to be cleanly effected in acetone solution, the immediate product being *cyanomethylammonium cyanomethylthiolcarbamate* (X), which proved to be unexpectedly reactive. For instance, on treatment with warm water, acid, or aqueous sodium carbonate, the compound liberated carbon dioxide and was converted into a new substance, $C_5H_{10}ON_4S_2$, tentatively formulated as 5-*bisthiocarbamylmethylurea* (XI). Boiling (X) or (XI) with concentrated hydrochloric acid afforded 2-thiohydantoin-1-acetic acid (XII) which was in turn converted into hydantoin-1-acetic acid (Johnson and Renfrew, *J. Amer. Chem. Soc.*, 1925, **47**, 240). Attempts to prepare 4-thiohydantoin by introduction of (X) into methanolic or ethanolic hydrogen chloride were unsuccessful, only the substance formulated as (XI) being isolated. However, when a solution of (X) in acetone was poured into aqueous mineral acid, both rearrangement and condensation occurred, 4-*thio*-5-iso*propylidenehydantoin* (XIII) being precipitated. The structure of the last compound was indicated by its oxidation by alkaline hydrogen peroxide to 4-*iso*propylidenehydantoin, identical with authentic material prepared from hydantoin. In contrast with the well-defined reaction with acetone, (X) reacted with benzaldehyde giving a crystalline *compound*, $C_{10}H_{11}ON_3S$, which was not identified.

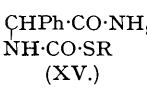
In view of these results attention was turned to the possibility of simulating the alternative

reaction (*B*, above), using carbon oxysulphide. Interaction of aminoacetamide and carbon oxysulphide in aqueous-alcoholic solution led to *carbamylmethylammonium carbamylmethylthiol-*



carbamate (XIV; R = $NH_3 \cdot CH_2 \cdot CO \cdot NH_2$). Acidification of this salt, however, in aqueous or non-aqueous media did not effect cyclisation but led only to formation of salts of aminoacetamide with loss of carbon oxysulphide. The corresponding *potassium* salt (XIV; R = K) was prepared but it also failed to undergo cyclisation as desired. It was also of interest to find that *benzyl carbamylmethylthiolcarbamate* (XIV; R = CH_2Ph) could not be dehydrated with





phosphorus tribromide or acetic anhydride, although benzyl carbamylmethyldithiocarbamate readily dehydrated under these conditions (Part III, *J.*, 1948, 201). Similarly, on treating α-aminophenylacetamide with carbon oxysulphide in the presence of potassium carbonate, a potassium salt was obtained which, on acidification, afforded only salts of α-aminophenylacetamide, potassium salts, and carbon oxysulphide. The compound is presumably potassium phenylcarbamylmethylthiocarbamate (XV; R = K); it was not analysed directly as it was very hygroscopic but, on treating it with benzyl chloride, *benzyl phenylcarbamylmethylthiolcarbamate* (XV; R = CH_2Ph) was obtained.

From these experiments it became clear that the desired compounds such as (I; X = OH) would, if accessible at all, probably have such a limited existence that they would not be useful in the manner intended, and further attempts to prepare them were therefore abandoned.

Experimental.

Reactions with α-Aminobenzyl Cyanide.—α-Aminobenzyl cyanide (21 g.) in ethanol (120 c.c.) was treated with an excess of carbon oxysulphide (30 g.), slowly bubbled through the solution during 6 hours. Bold yellow needles of *5-amino-2-hydroxy-4-phenylthiazole* (14·5 g.) were slowly formed, and a second crop (9·5 g.) was obtained from the filtrate on standing at 0° for 7 days (total yield, 24 g., 87%). The compound had m. p. 195°, immediately resolidifying and melting again at *ca.* 259° (decomp.). Although insoluble in most common organic solvents, recrystallisation was effected from pyridine–water, as pale yellow, felted needles, m. p. 255—260° (decomp.), according to the rate of heating (Found : C, 55·8; H, 4·1; S, 16·1. $C_9H_8ON_2S$ requires C, 56·2; H, 4·2; S, 16·7%). A bright red colour was obtained on warming it with ethanolic glyoxal, indicative of a 5-aminoazole structure. Acetylation by the usual procedure was very destructive, sulphur being liberated, but a 50% yield of a *diacetyl* derivative, purified by crystallisation from methanol–water, and finally aqueous acetic acid, m. p. 168—170° (decomp.), was obtained in clusters of irregular pale yellow prisms (Found : C, 56·5; H, 4·3; N, 9·8. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·3; N, 10·1%). After 5-amino-2-hydroxy-4-phenylthiazole (1·4 g.) had been shaken with saturated ethanolic hydrogen chloride (30 c.c.) for 4 hours, the almost clear yellow solution was filtered, and concentrated hydrochloric acid (60 c.c.) added. After standing at 0° for 4 days, beautiful lemon-yellow rhombohedra of the *alcoholate* of *5-amino-2-hydroxy-4-phenylthiazole hydrochloride* (1·3 g., 65%) were collected (Found : N, 10·1, 10·4. $C_9H_8ON_2S,HCl,C_2H_6O$ requires N, 10·1%). The compound rapidly lost hydrogen chloride and ethanol on standing, and in aqueous solution it immediately decomposed with deposition of starting material. On heating, it became deep orange at 120°, red-brown at 160°, dark brown at 200°, and finally melted at 260—266° (decomp.).

5-Amino-2-hydroxy-4-phenylthiazole (2·0 g.) was heated under reflux with benzaldehyde (20 c.c.) for 1 hour. The semi-solid mass was extracted with hot methanol and filtered, and the *benzylidene* derivative of 5-amino-2-hydroxy-4-phenylthiazole (0·1 g.) separated on cooling the filtrate. It recrystallised from methanol in long, yellow, hair-like needles, m. p. 271° (Found : C, 68·5; H, 4·3; N, 9·8. $C_{16}H_{12}ON_2S$ requires C, 68·6; H, 4·3; N, 10·0%).

5-Amino-2-hydroxy-4-phenylthiazole (15·0 g.) was shaken with 10% aqueous sodium hydroxide (100 c.c.) for 2 hours, a clear, pale-yellow solution being obtained. Acidification with concentrated hydrochloric acid yielded a bright yellow precipitate of 4-thio-5-phenylhydantoin (13·5 g., 90%), m. p 253—258° (decomp.), which recrystallised from 90% aqueous ethanol in small needles, m. p. 258—259° (decomp.) (Found : C, 56·6; H, 4·0. Calc. for $C_9H_8ON_2S$: C, 56·2; H, 4·2%). An alkaline solution gradually developed an orange-red colour on exposure to air. Acetylation of the thiohydantoin in the

normal way yielded a black product which on crystallisation from ethanol (charcoal) gave the *diacetyl* derivative in silvery rectangular plates, m. p. 153—154° (Found: C, 56·8; H, 4·6; N, 9·9. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·4; N, 10·1%). Methylation with diazomethane gave a yellow gum, which, after repeated crystallisations from methanol–water, formed small pale yellow prisms of the *monomethyl* derivative, m. p. 175—178° (decomp.) (Found: C, 58·1; H, 5·0; N, 13·1. $C_{10}H_{10}ON_2$ requires C, 58·2; H, 4·9; N, 13·5%). 4-Thio-5-phenylhydantoin (1·0 g.) was taken up in 10% aqueous sodium hydroxide (15 c.c.) and hydrogen peroxide solution (20-vol., 10 c.c.) added. The solution was cooled to 0° for 6 hours; it then became decolourised, and was warmed to 80°, cooled, and acidified with hydrochloric acid. A white solid precipitate of *di-5-phenylhydantoin-4 disulphide* (0·9 g., 89%) was filtered off; it recrystallised from ethanol in clusters of fine silky needles, decomposing on heating above 210° (Found: N, 14·9. $C_{18}H_{14}O_2N_4S_2$ requires N, 14·7%).

5-Amino-2-hydroxy-4-phenylthiazole (2 g.) and Raney nickel (15 g.) were heated under reflux in ethanol (30 c.c.) for 12 hours. The solution was filtered, light petroleum (30 c.c.) added, and the solution evaporated in a vacuum to small bulk, 5-phenyl-2-iminazolidone (0·6 g., 36%) being obtained. It recrystallised from water or acetone–light petroleum in colourless, glistening needles, m. p. 156—157° (Found: C, 66·6; H, 6·2; N, 17·2. Calc. for $C_9H_{10}ON_2$: C, 66·7; H, 6·2; N, 17·3%). 4-Thio-5-phenylhydantoin (1·7 g.) and Raney nickel (10 g.) in ethanol (20 c.c.) were heated under reflux for 2 hours. The solution was filtered and evaporated in a vacuum; a yellow oil was obtained, which on standing at 0° with light petroleum solidified to yield 5-phenyl-2-iminazolidone (0·3 g.). 5-Phenyl-2-iminazolidone (0·4 g.) was dissolved in concentrated hydrochloric acid (2 c.c.), the solution boiled for 5 minutes, and then evaporated to dryness. Extraction of the residue with ethanol and precipitation with ether gave α-phenylethylenediamine dihydrochloride (0·15 g., 30%), which, on recrystallisation from ethanol–ether, became yellow at 260° (cf. Karewskaja, *loc. cit.*) and finally had m. p. 313°. The hydrochloride was acylated with acetic anhydride, and the crude diacetyl derivative of α-phenylethylenediamine crystallised from benzene; m. p. 152°, in agreement with the literature value.

Reactions with Ethyl Aminocyanoacetate.—Ethyl aminocyanoacetate (27 g.) in ether (100 c.c.) was treated with an excess of carbon oxysulphide (30 g.), bubbled into the solution during 6 hours. Yellow crystals of *5-amino-2-hydroxy-4-carbethoxythiazole* (34 g., 96%) were rapidly formed, and were collected after standing at 0° for 12 hours. The compound crystallised from ethyl acetate or acetone in pale yellow tablets, m. p. 158° (Found: C, 38·6; H, 4·2; N, 14·8; S, 16·6. $C_6H_8O_3N_2S$ requires C, 38·3; H, 4·3; N, 14·9; S, 17·0%). Acetylation of the base by the usual procedure gave *5-acetamido-2-hydroxy-4-carbethoxythiazole*, which crystallised from ethanol in colourless needles, m. p. 239° (decomp.) (Found: C, 42·0; H, 4·4; N, 12·0. $C_8H_{10}O_4N_2S$ requires C, 41·7; H, 4·4; N, 12·2%).

5-Amino-2-hydroxy-4-carbethoxythiazole (2 g.) was heated for 5 minutes with benzaldehyde (20 c.c.); on cooling the solution, the *benzylidene* derivative (2·3 g., 79%) was obtained. It recrystallised from benzene in pale yellow prisms, m. p. 185° (Found: C, 57·0; H, 4·5; N, 9·8; S, 11·1. $C_{13}H_{12}O_3N_2S$ requires C, 56·5; H, 4·3; N, 10·1; S, 11·6%). A suspension of 5-amino-2-hydroxy-4-carbethoxythiazole (10 g.) in aqueous ammonia (*d* 0·880; 100 c.c.) was shaken for 12 hours, and the almost clear solution cooled to 0°. Acidification with concentrated hydrochloric acid caused precipitation of *4-thio-5-carbethoxyhydantoin* (9·9 g., 99%), which recrystallised from water, or better from ammonia–acid, in rectangular plates, m. p. 210—211° (decomp.) (Found: C, 38·4; H, 4·1; N, 14·8. $C_6H_8O_3N_2S$ requires C, 38·3; H, 4·3; N, 14·9%). An alkaline solution gave a bright cherry-red colour on exposure to air, changing overnight to a deep orange. 5-Amino-2-hydroxy-4-carbethoxythiazole (3·2 g.) was shaken with 2N-aqueous sodium carbonate (40 c.c.) for 4 hours, and the filtrate cooled to 0°; colourless massive scintillating rectangular prisms of the monohydrated *sodium* salt of 4-thio-5-carbethoxyhydantoin (1·0 g.) were filtered off and recrystallised from water–acetone, forming beautiful, long, thin, hexagonal rods which did not melt but became yellow at 170°, green at 185°, and black at 205° (Found: N, 12·2. $C_6H_9O_4N_2SNa$ requires N, 12·3%). Acidification of the salt or the filtrate gave 4-thio-5-carbethoxyhydantoin itself, identical with the product previously obtained. 4-Thio-5-carbethoxyhydantoin was characterised by acetylating it with acetic anhydride; the *diacetyl* derivative recrystallised from methanol in bundles of fine colourless needles, m. p. 160—162° (Found: C, 44·2; H, 4·4; N, 10·6. $C_{10}H_{12}O_5N_2S$ requires C, 44·1; H, 4·4; N, 10·3%). 4-Thio-5-carbethoxyhydantoin (4 g.) and Raney nickel (20 g.) in ethanol (50 c.c.) were heated under reflux for 1 hour. The hot solution was filtered, and, on cooling, colourless glistening leaflets of 2-hydroxy-4-carbethoxyiminazole (1·3 g.) appeared. A further 0·1 g. (gross yield, 59%) was obtained on adding light petroleum to the filtrate, evaporation of which gave unchanged starting material (1·1 g.). The compound crystallised from ethanol in silvery octagonal plates, m. p. 252—253° (decomp.) (Found: C, 45·9; H, 5·2; N, 17·6. Calc. for $C_6H_8O_3N_2$: C, 46·1; H, 5·1; N, 17·9%). Similar desulphurisation of 5-amino-2-hydroxy-4-carbethoxythiazole (3 g.) gave only 0·5 g. of 2-hydroxy-4-carbethoxyglyoxaline, acetylation of which with acetic anhydride gave a *monoacetyl* derivative as glistening rods, m. p. 195°, from ethanol (Found: C, 48·6; H, 5·1; N, 14·2. $C_5H_{10}O_4N_2$ requires C, 48·5; H, 5·1; N, 14·1%).

5-Amino-2-hydroxy-4-carbethoxythiazole (5 g.) was heated to 70° for 15 minutes with 4N-hydrochloric acid (40 c.c.); carbon oxysulphide was evolved, and a clear solution obtained. Evaporation to dryness in a vacuum gave an orange crystalline residue of *aminocarbethoxyacetamide hydrochloride*, which recrystallised from ethanol–ether in clusters of colourless prisms, m. p. 194—195° (decomp.) (Found: C, 32·7; H, 6·0; N, 15·1. $C_5H_{11}O_3N_2Cl$ requires C, 32·9; H, 6·0; N, 15·3%). The yield of pure hydrochloride was 3·3 g. (68%). 5-Amino-2-hydroxy-4-carbethoxythiazole (1·5 g.) dissolved readily in 10% aqueous sodium hydroxide (15 c.c.) in an atmosphere of nitrogen. Cooling to −15° for 30 minutes resulted in deposition of a colourless crystalline sodium salt (1·5 g.), m. p. 80° (decomp.), probably sodium carbethoxycarbamylmethylthiolcarbamate, which became red on exposure to air and rapidly decomposed when worked up. The experiment was repeated on the same scale, and the crystalline precipitate acidified, a clear solution being obtained. Evaporation to dryness afforded a crystalline residue from which aminocarbethoxyacetamide hydrochloride (1·0 g., 69%) was obtained by extraction with methanol and precipitation with ether.

This hydrochloride (2·0 g.) in 6N-hydrochloric acid (20 c.c.) was cooled to 0°, and a solution of sodium

nitrite (0·9 g.) in water (5 c.c.) slowly added. After cooling to 0° for 18 hours, *5-hydroxy-4-carbethoxy-1 : 2 : 3-triazole* (1·3 g., 76%) was filtered off and crystallised from benzene in colourless massive scintillating rhombohedra, m. p. 145—146° (Found : C, 38·5; H, 4·6; N, 27·6, 27·7. $C_5H_7O_3N_3$ requires C, 38·2; H, 4·5; N, 26·8%). α-Aminophenylacetamide hydrochloride (3·0 g.) in water (40 c.c.) was treated at 0° with a solution of sodium nitrite (1·3 g.) in water (6 c.c.). A vigorous effervescence occurred, and on evaporation to dryness in a vacuum, mandelamide (2·4 g.) was obtained by extraction with hot benzene. It was recrystallised from benzene–petrol, forming colourless irregular plates, m. p. 123—124° (Found : C, 63·5; H, 6·0. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0%). Aminoacetamide hydrochloride (10·0 g.) in water (20 c.c.) was treated at 0° with sodium nitrite (12 g.) in water (20 c.c.). After standing at 0° for 24 hours, the solution was evaporated to dryness, and extraction with hot ethanol then gave glycollic acid (4·3 g.), m. p. 70—75°, identical with an authentic specimen.

5-Amino-2-hydroxy-4-carbethoxythiazole (4 g.) and methyl *iso*thiocyanate (2 g.) in pyridine (30 c.c.) were heated under reflux for 1·5 hours. The solution was cooled and poured into water (100 c.c.), a black oil (1 c.c.) separating. The supernatant liquid was poured off, and after four days at 0°, 4-thio-5-carbethoxyhydantoin (3·0 g.) was collected, identical with the material described above. The black oil was dissolved in 10% aqueous sodium hydroxide (5 c.c.) and acidified with hydrochloric acid; a brown precipitate (1 g.), decomposing on heating above 300°, was obtained. Purification by trituration with methanol and crystallisation from dilute aqueous ammonia (charcoal)–dilute acid yielded *5-thio-2-hydroxy-7-keto-6-methyl-4 : 5 : 6 : 7-tetrahydro-(5 : 4-d)-thiazolopyrimidine* in masses of colourless felted needles, decomp. >310° (Found : S, 31·0. $C_6H_5O_2N_3S_2$ requires S, 31·5%), giving a positive murexide test.

5-Amino-2-hydroxy-4-carbethoxythiazole (10 g.) and methyl *iso*cyanate (8 g.) in pyridine (40 c.c.) were heated under reflux for 1·5 hours. The pyridine and excess of methyl *iso*cyanate were evaporated off in a vacuum, and a red gum was obtained. This solidified on treatment with methanol, crystallisation of the solid from methanol giving *5-methylureido-2-hydroxy-4-carbethoxythiazole* (10·1 g., 77%) as colourless needles, m. p. 185—186° (Found : C, 39·1; H, 4·8; N, 17·2. $C_8H_{11}O_4N_3S$ requires C, 39·2; H, 4·9; N, 17·1%). The latter compound (1 g.) was taken up in warm 2N-aqueous sodium hydroxide, and the solution acidified. On cooling, a crystalline *compound* (0·2 g.) deposited, crystallising from methanol in long, thin, colourless needles, m. p. 225° (decomp.) (Found : C, 38·9; H, 5·0; N, 19·6. $C_7H_{11}O_3N_3S$ requires C, 38·7; H, 5·1; N, 19·4%).

Reactions with Aminoacetonitrile.—Acetone (400 c.c.) was stirred vigorously in a 1-l. 3-necked flask in an atmosphere of nitrogen. A solution of aminoacetonitrile (20 g.) in acetone (80 c.c.) was slowly dropped into the flask during 4 hours, a strong current of carbon oxysulphide (60 g.) being simultaneously passed through the acetone. The yellow solution was stirred for a further hour, then evaporated to 80 c.c., and light petroleum (300 c.c.) added. After cooling to 0° for 2 hours, the orange precipitate of *cyanomethylammonium cyanomethylthiolcarbamate* (28 g., 91%) was filtered off, and purified by crystallisation from acetone–light petroleum; m. p. 173° (decomp.) (Found : C, 35·1; H, 5·0; N, 33·0. $C_5H_8ON_4S$ requires C, 34·9; H, 4·7; N, 32·6%). This compound (1·5 g.) was stirred with 15% hydrochloric acid; carbon dioxide was evolved, and after standing at 0° for 1·5 hours, a light brown precipitate of *5-bisthiocarbamylmethylurea* (XI) (?) (0·6 g., 66%) was filtered off; it crystallised from water in the presence of sodium hydrosulphite (dithionite) as long, thin, glistening needles, darkening rapidly when heated above 210° (Found : C, 29·2; H, 4·9; N, 27·1; S, 30·3. $C_5H_{10}ON_4S_2$ requires C, 29·1; H, 4·9; N, 27·2; S, 31·1%). Cyanomethylammonium cyanomethylthiolcarbamate (3 g.) was shaken with 2N-aqueous sodium carbonate (50 c.c.) for 2 hours in an atmosphere of nitrogen. The urea (XI) (1 g., 55%), identical with the sample previously obtained, was collected as a light-grey solid and recrystallised as above. The same compound was also obtained (yield, 42%) by boiling cyanomethylammonium cyanomethylthiocarbamate with water in the presence of sodium hydrosulphite (dithionite).

Cyanomethylammonium cyanomethylthiocarbamate (3·0 g.) was boiled for 2 minutes with concentrated hydrochloric acid (5 c.c.). The clear solution was cooled to 0°, and after 2 hours the colourless crystalline precipitate of 2-thiohydantoin-1-acetic acid and ammonium chloride (3·5 g., 87%) was collected. After purification by crystallisation from ethanol–light petroleum, 2-thiohydantoin-1-acetic acid formed beautiful spear-shaped laths with a pearly lustre, m. p. 215—216° (decomp.) (Found : C, 34·6; H, 3·6; N, 16·2. Calc. for $C_5H_6O_3N_2S$: C, 34·5; H, 3·5; N, 16·1%). The identity of the acid was further confirmed by desulphurisation with chloroacetic acid (cf. Johnson and Renfrew, *loc. cit.*) to give hydantoin-1-acetic acid, which melted in good agreement with the literature value (190—191°) after crystallisation from ethanol. Cyanomethylammonium cyanomethylthiolcarbamate (4·5 g.) in acetone (100 c.c.) was poured into 2N-hydrochloric acid (100 c.c.); after cooling to 0° for 12 hours, the bright orange precipitate of *4-thio-5-iso*propylidenehydantoin (2·0 g., 49%) was collected, and crystallised from ethanol–water in light orange, felted needles, m. p. 227—229° (decomp.) (Found : C, 46·6; H, 5·3; N, 17·7. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1; N, 17·9%). This hydantoin (0·6 g.) was dissolved in 10% aqueous sodium hydroxide, and the reddish-brown solution treated with hydrogen peroxide solution (20-vol., 10 c.c.). The solution became hot and changed to a pale yellow. After cooling to 0° for 6 hours, warming to 60°, filtering, and acidifying with hydrochloric acid, the solution was cooled to 0° for 12 hours, *5-iso*propylidenehydantoin (0·1 g., 18%) being obtained. This compound had m. p. *ca.* 245° (decomp.), on crystallisation from methanol, and was found to be identical with a specimen obtained by direct condensation of acetone with hydantoin (C.P.S., 237, 3). Cyanomethylammonium cyanomethylthiolcarbamate (5 g.) and benzaldehyde (20 c.c.) were refluxed together for 1 hour, and the deep brown solution was cooled to 0° for 16 hours. Filtering and washing with methanol afforded colourless crystals of a *compound* (4·4 g.) which recrystallised from acetic acid in colourless rectangular plates, m. p. 225—226° (decomp.) (Found : C, 54·6; H, 5·2; N, 19·5. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 5·0; N, 19·0%). The compound was easily soluble in 10% aqueous sodium hydroxide to give a light orange solution, and with hot concentrated hydrochloric acid, a small quantity of an amorphous yellow powder was obtained.

Reactions with Amino-amides.—5-Imino-2 : 2-dimethyloxazolidine (30 g.) was added to warm water (30 c.c.) to give a solution of aminoacetamide (cf. Part III, *loc. cit.*). Ethanol (70 c.c.) was added to

the solution, and an excess of carbon oxysulphide (30 g.) was passed in during 5 hours. Colourless crystals of *carbamylmethylammonium carbamylmethylthiolcarbamate* (22 g., 80%) were filtered off, and crystallised from aqueous acetone in clusters of rectangular plates, m. p. 216—218° (decomp.) (Found: C, 29·2; H, 5·9; N, 26·8. $C_5H_{12}O_3N_4S$ requires C, 28·8; H, 5·8; N, 26·9%).

5-Imino-2 : 2-dimethyloxazolidine (11·5 g.) was added to warm water (12 c.c.). Potassium carbonate (7 g.) and ethanol (40 c.c.) were added, and an excess of carbon oxysulphide passed through the solution during 4—5 hours. Unchanged potassium carbonate (0·5 g.) was filtered off, the solution evaporated to 15—20 c.c., and acetone (20 c.c.) added. Two layers formed, and the lower layer gradually crystallised on standing at 0° to give massive rhombohedra of *potassium carbamylmethylthiolcarbamate* (12·5 g., 72%), recrystallising from water–50% methanolic acetone as large, colourless, hexagonal tablets, m. p. 194—195° (decomp.) (Found: C, 21·2; H, 3·0; N, 16·2. $C_3H_5O_2N_2SK$ requires C, 20·9; H, 2·9; N, 16·3%). This compound (5 g.) in water (50 c.c.) was shaken with benzyl chloride (5 c.c.) in ether (50 c.c.) for 40 hours. Colourless needles of *benzyl carbamylmethylthiolcarbamate* (4·55 g., 71%) were collected and recrystallised from water, toluene, or ethanol in glistening plates, m. p. 170—171° (Found: C, 53·3; H, 5·3; N, 12·9. $C_{10}H_{12}O_2N_2S$ requires C, 53·6; H, 5·4; N, 12·5%).

5-Imino-4-phenyl-2 : 2-dimethyloxazolidine (14 g.) was boiled for 5 minutes with water (20 c.c.) to give a solution of α-aminophenylacetamide in water. Ethanol (80 c.c.) and potassium carbonate (7·8 g.) were added, and an excess of carbon oxysulphide (25 g.) was passed through the solution during 4 hours. Unchanged potassium carbonate was separated, the solution evaporated to 15—20 c.c., and methanol (50 c.c.) and acetone (400 c.c.) added. A potassium salt, presumably potassium phenylcarbamylmethylthiolcarbamate (12·5 g., 68%), was filtered off and recrystallised from water–90% methanolic acetone. This salt was very hygroscopic, and it was difficult even to obtain an accurate m. p. which appeared to be 110—115°. The salt (8 g.) in water (20 c.c.) was shaken with benzyl chloride (6 g.) in ether (40 c.c.); the resulting colourless crystals of *benzyl phenylcarbamylmethylthiolcarbamate* (6 g., 62%) recrystallised from toluene in colourless felted needles, m. p. 150—151° (Found: N, 9·3. $C_{16}H_{16}O_2N_2S$ requires N, 9·3%).

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