## 811. *Purines, Pyrimidines, and Glyoxalines. Part XIV.* The Preparation and Some Reactions of α-Amino-α-cyanothioacetamide, leading to 6-Mercaptopurines and Adenines.*

By G. Shaw and (in part) D. N. Butler.

α-Amino-α-cyanothioacetamide has been prepared from α-cyanothioacetamide by reaction with nitrous acid followed by sodium dithionite in aqueous solution. The aminothioamide with cyanates or isothiocyanates gave linear ureas or thioureas, but with imidic esters gives glyoxalines, thiazoles, or more complex imidates. Further reactions lead to 6-mercaptopurines, adenines, and a thiazolopyrimidine, generally simply and in good yield.

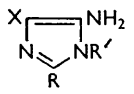
The previous paper in this series included a description of a one-step, general, unambiguous synthesis of 1-substituted 5-aminoglyoxaline-4-carboxyamides (Ia; R = H or Me) from linear imidates (II; R = H or Me) and primary amines including D-glycosylamines where the 1-substituent is derived from the amine. The ready and well-known conversion of aminoglyoxalinecarboxyamides into purines, makes the synthesis also one of 9-substituted 6-hydroxypurines of the hypoxanthine and xanthine type.

We have been interested in extending these reactions to include syntheses of similar intermediates which would lead eventually to 6-mercaptopurines and to adenines. Previous methods require relatively drastic treatment of intermediates with phosphoryl halides or phosphoric sulphide, and we sought methods which could be used under mild conditions, preferably in aqueous or alcoholic media. A much sought intermediate for the synthesis of adenines and other compounds through aminoglyoxalinenitriles has been aminomalononitrile, but many attempts to prepare this substance gave only dimeric products.[1] An alternative route would include desulphurisation of the corresponding

* Part XIII, *J.*, 1959, 1648.

[1] Cf. Cook and Smith, *J.*, 1949, 3001.

thioamide (III) which at the same time offers a route to the thiocarboxyamides (Ib). These would be expected to yield nitriles under mild conditions and to be a source of 6-mercaptopurines and adenines. We now record a convenient preparation of the thioamide (III) and some of its reactions.



(Ia) X = $CO \cdot NH_2$
(Ib) X = $CS \cdot NH_2$
(Ic) X = CN

$EtO \cdot CR{=}N \cdot CH(CN) \cdot CO \cdot NH_2$ (II)

$H_2N \cdot CH(CN) \cdot CS \cdot NH_2$ (III)

$HON{=}CH(CN) \cdot CS \cdot NH_2$ (IV)

α-Cyanothioacetamide [2] with nitrous acid gave the crystalline hydroxyimino-derivative (IV), which was reduced by sodium dithionite to the aminothioamide (III). The yield of thioamide was improved if isolation of the intermediate (IV) was omitted.

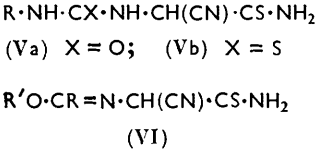
The aminothioamide (III) with cyanic acid, thiocyanic acid, and α-naphthyl isocyanate gave the ureas (Va; R = H or α-naphthyl) and the thiourea (Vb; R = H), whose behaviour with cyclising agents was complex and will not be discussed here.

The thioamide (III) with ethyl acetimidate gave the glyoxaline (Ib; R = Me, R′ = H). Initial attempts to prepare the linear imidate (VI; R = Me, R′ = Et) by reaction of the thioamide with ethyl acetimidate hydrochloride in water gave a compound which is regarded as the aminothiazole (VII; R = Me) since it could be diazotised and coupled with an alkaline solution of β-naphthol to give a red dye. However, the thioamide and benzyl acetimidate hydrochloride in water readily gave the crystalline linear imidate (VI; R = Me, R′ = $CH_2Ph$). This reacted smoothly with methylamine, ethylamine, and cyclohexylamine to give the aminoglyoxalinethiocarboxyamides (Ib; R = Me, R′ = Me, Et, and cyclohexyl respectively). These may be converted into purines by methods similar to those used for the aminocarboxyamides. Thus the glyoxaline (Ib; R = R′ = Me) with formic acid and acetic anhydride gave the 5-formamido-derivative (VIII; R = R′ = Me) which with hot dilute aqueous potassium hydrogen carbonate gave 6-mercapto-8,9-dimethylpurine (IX; R = R′ = Me). It has been recorded [3] that amidines may be prepared from thiocarboxyamides by reaction with mercuric chloride and ammonia. An attempt to apply this reaction to compound (Ib; R = R′ = Me) led to the nitrile (Ic; R = R′ = Me). The reaction was simplified and a quantitative yield of the nitrile obtained by using methylamine instead of ammonia in this reaction, the greater solubility of methylamine hydrochloride in alcohol facilitating separation of chloride from the reaction product. An attempt was also made to extend this reaction to the preparation of aminomalononitrile from the thioamide (III). Desulphurisation readily occurred and the product was a highly pungent oil which may have been the required product but its characterisation has been prevented by its instability.

It was harder to prepare aminoglyoxaline thiocarboxyamides unsubstituted at position 2 by these methods. Reaction of the hydrochlorides of ethyl, benzyl, butyl, or isobutyl formimidate and of butyl and benzyl thioformimidate with the thioamide (III) gave no useful results. However, the thioamide (III) with isopentyl formimidate hydrochloride in methyl cyanide gave the aminothiazole (VII; R = H). The required derivative (VI; R = H, R′ = isopentyl) was finally obtained in ethereal solution by ether-extraction of a mixture of the thioamide (III) and isopentyl formimidate hydrochloride in water. The ether solution with ammonia and methylamine readily gave the glyoxalines (Ib; R = H, R′ = H and Me respectively). The former compound is a probable intermediate in a synthesis of 6-mercaptopurine involving as a first step the reaction of the

[2] Howard, U.S.P. 2,733,260/1956.
[3] Bernthsen, *Annalen*, 1876, **184**, 321; 1878, **192**, 1; Skinner and Neumann, *Chem. Rev.*, 1944, **35**, 351.

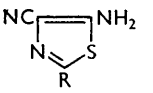
carboxyamide (Ia; R = R′ = H) with phosphoric sulphide.[4] The glyoxaline (Ib; R = H, R′ = Me) with formic acid and acetic anhydride gave a mixture of the 5-formamido-derivative (VIII; R = H, R′ = Me) and 6-mercapto-9-methylpurine (IX; R = H, R′ = Me). The mercaptopurine was also obtained by heating the formamide with aqueous



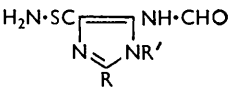
(Va) X = O; (Vb) X = S



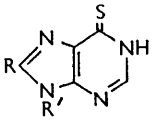
(VI)



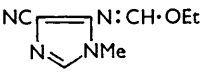
(VII)



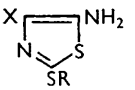
(VIII)



(IX)



(X)

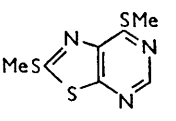


(XIa) X = $CS{\cdot}NH_2$

(XIb) X = $C(SMe){:}NH_2^+ \; MeSO_4^-$

(XIc) X = CN

(XId) X = $CO{\cdot}NH_2$



(XII)

potassium hydrogen carbonate. In addition, the corresponding amino-nitrile (Ic; R = H, R′ = Me) was readily obtained by desulphurisation of the thioamide (Ib; R = H, R′ = Me) with mercuric chloride and methylamine in ethanol. The amino-nitrile with ethyl orthoformate gave the ethoxymethylidene derivative (X) which with ammonia gave 9-methyladenine.

Purine analogues of potential value as metabolite antagonists include the thiazolo[5,4-*d*]-pyrimidines which have been prepared, *e.g.*, by completing the pyrimidine ring in an aminothiazolecarboxyamide[5] (XId; R = Me); the aminothiazole (XId; R = H) was obtained from aminocyanoacetamide and carbon disulphide.[6] In a similar manner the aminothiazole thiocarboxyamide (XIa; R = H) is formed quantitatively from the thioamide (III) and carbon disulphide. Methylation then gave a compound which from its elementary analysis and further reactions can only be the carboxythioimidate (XIb; R = Me). This salt with sodium hydroxide precipitated the amino-nitrile (XIc; R = Me) and with formic acid and acetic anhydride gave the thiazolopyrimidine (XII).

## Experimental

*α-Cyano-α-hydroxyiminothioacetamide.*—To a solution of α-cyanothioacetamide[2] (36·5 g.) and sodium nitrite (25·6 g.) in water (1 l.) at ~10° was slowly added 10N-hydrochloric acid (36·5 ml.) in water (150 ml.) with cooling. At these concentrations, more intense cooling may result in precipitation of the thioamide. An amorphous precipitate separated and was filtered off through charcoal and asbestos. The filtrate was evaporated *in vacuo* to about 400 ml., then set aside at 0° overnight. The *hydroxyimino-derivative* (17 g.) which separated recrystallised from water as dark yellow-brown needles, m. p. 156° (decomp. from 140°) (Found: C, 28·15; H, 2·45; N, 31·85. $C_3H_3ON_3S$ requires C, 27·9; H, 2·3; N, 32·55%). A further quantity (19 g.) was obtained by extraction of the aqueous solution with ether. In this preparation the evaporation may be omitted, and a similar yield of the product isolated by extraction of the initial reaction solution with ether. The compound gave an intense blue colour with sodium hydroxide solution and ferrous sulphate.

*α-Amino-α-cyanothioacetamide.*—(*a*) The hydroxyimino-compound (19 g.) in water at 50°

[4] Hitchings and Elion, U.S.P. 2,756,228/1956.

[5] Cook, Heilbron, MacDonald, and Mahadevan, *J.*, 1949, 1064; Cook, Downer, and Heilbron, *J.*, 1949, 1069; Cook, Davies, Heilbron, and Thomas, *J.*, 1949, 1071.

[6] Cook, Heilbron, and Smith, *J.*, 1949, 1440.

was treated with solid sodium dithionite (57 g.); the solution became green and its temperature rose to 73°. The solution, when cooled, gave crystals (13·05 g.), which were extracted with hot ethyl acetate, leaving a considerable residue. Addition of light petroleum (b. p. 40—60°) to the filtrate precipitated *α-amino-α-cyanothioacetamide* (6·68 g.) which recrystallised from ethyl acetate or ethyl acetate–light petroleum (b. p. 40—60°) as buff-coloured plates, m. p. 110° (decomp.) (Found: C, 31·45; H, 4·35; N, 35·8. $C_3H_5N_3S$ requires C, 31·3; H, 4·4; N, 36·5%).

(*b*) 5N-Hydrochloric acid (164 ml.) was slowly added to a solution of α-cyanothioacetamide (82 g.) and sodium nitrite (58 g.) in water (800 ml.) at 25°. Sodium dithionite (285 g.) was then added. The cooled solution gave as under (*a*) the thioamide (33 g.), m. p. and mixed m. p. 110° (decomp.).

*α-Acetamido-α-cyanothioacetamide.*—The foregoing thioamide (0·57 g.) was warmed with acetic anhydride (2 ml.) for 5 min. The solution was evaporated *in vacuo* and the residue with water gave the *acetyl derivative* (0·5 g.), needles (from ethanol), m. p. 138° (Found: C, 38·5; H, 4·3; N, 26·2. $C_5H_7ON_3S$ requires C, 38·2; H, 4·5; N, 26·7%).

*α-Cyano-α-ureidothioacetamide.*—Potassium cyanate (0·8 g.) was added to α-amino-α-cyanothioacetamide (1·1 g.) in 50% acetic acid (10 ml.) at 0°. The *product* soon crystallised and was collected after 1 hr. and washed with ice-water. It separated from ethanol as prisms (1·8 g.), m. p. 196° (decomp. from 180°) (Found: C, 30·55; H, 3·65; N, 35·4. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8; N, 35·45%).

N-α-(*Cyanothiocarbamoylmethyl*)-α-N′-α-*naphthylurea.*—α-Amino-α-cyanothioacetamide (0·57 g.) in warm ethyl acetate (15 ml.) with α-naphthyl isocyanate (0·85 g.) gave after 2 hr. a crystalline precipitate which was collected next morning. The *urea* (1·39 g.) recrystallised from aqueous methanol as needles, m. p. 203° (decomp.) (Found: C, 58·9; H, 4·2; N, 19·7. $C_{14}H_{12}ON_4S$ requires C, 59·15; H, 4·25; N, 20·3%). A solution of the urea (0·35 g.) in methanol (2·6 ml.) containing sodium (0·026 g.) was boiled under reflux for 1·5 hr., then evaporated to a gum. This largely dissolved in water (5 ml.), leaving a small amount of crystals, m. p. 80° (decomp.). The filtrate was acidified with a little dilute acetic acid to precipitate a solid which was soluble in excess of acid. This substance (0·15 g.) separated from ethanol as needles, m. p. 286° (decomp. from 230°) (Found: C, 59·25; H, 4·45; N, 16·6%). The same substance was obtained when the methanolic sodium methoxide was replaced by triethylamine in ethanol.

*α-Cyano-*N-*α-thioureidothioacetamide.*—α-Amino-α-cyanothioacetamide (2·85 g.) in water (50 ml.) with potassium thiocyanate (2·4 g.) and 10N-hydrochloric acid (2·5 ml.) gave, after 2 days, a precipitate of the *thioureide hydrate* (2·1 g.). This separated from water as pale yellow needles, m. p. >300° (with preliminary darkening) (Found: C, 25·15; H, 4·3; N, 28·9. $C_4H_6N_4S_2,H_2O$ requires C, 25·0; H, 4·2; N, 29·1%). The compound was soluble in dilute sodium hydroxide solution and recovered by acidification. It gave no colour with ferric chloride solution.

5-*Amino*-2-*methylglyoxaline*-4-*thiocarboxyamide.*—α-Amino-α-cyanothioacetamide (0·58 g.) was added to methanolic ethyl acetimidate prepared from ethyl acetimidate hydrochloride (0·62 g.) in methanol (10 ml.) and sodium (0·55 g.) in methanol (3 ml.). The solution was boiled under reflux for 10 min., cooled, and treated with methanolic picric acid. The *glyoxalinepicrate methanolate* (0·75 g.) separated from methanol as yellow needles, m. p. 206—208° (decomp.) (Found: C, 34·75; H, 3·75; N, 22·85. $C_5H_8N_4S,C_6H_3O_7N_3,CH_4O$ requires C, 34·5; H, 3·6; N, 23·5%).

5-*Amino*-4-*cyano*-2-*methylthiazole.*—α-Amino-α-cyanothioacetamide (0·5 g.), ethyl acetimidate hydrochloride (1·2 g.), and water (1 ml.) were gently warmed together for 5 min. The cooled solution precipitated a little ammonium chloride which was removed. The filtrate then quickly deposited the *thiazole.* This separated from ethanol as needles (0·2 g.), m. p. 272° (decomp.) (Found: C, 43·65; H, 3·6; N, 30·1. $C_5H_5N_3S$ requires C, 43·5; H, 3·6; N, 30·2%), and could be diazotised and then coupled with alkaline β-naphthol to give a red colour. The same compound was formed when the reaction was carried out in dry methanol.

*Benzyl* N-(*α-cyano-α-thiocarbamoylmethyl*)*acetimidate.*—α-Amino-α-cyanothioacetamide (4 g.) and benzyl acetimidate hydrochloride (9·2 g.) were shaken with water (10 ml.) for a few minutes, crystals being soon deposited. More water (10 ml.) was added and the solid collected and washed with water and a little ice-cold ethanol. The *acetimidate* (4 g.) separated from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 88° (Found: C, 58·2; H, 5·3; N, 16·75. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3; N, 17·0%).

5-*Amino*-1,2-*dimethylglyoxaline*-4-*thiocarboxyamide.*—A suspension of the foregoing imidate

(0·5 g.) in methanol (5 ml.) with 33% ethanolic methylamine (0·3 ml.) soon gave a clear solution which quickly precipitated the *glyoxaline* (0·21 g.), plates (from methanol), m. p. 244—247° (decomp.) (Found: C, 42·6; H, 5·85; N, 33·0. $C_6H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 32·95%). The compound when diazotised and coupled with an alkaline solution of β-naphthol gave a deep magneta-coloured dye. Addition of methanolic picric acid to the filtrate from the above reaction gave the *glyoxaline picrate* (0·05 g.), needles (from ethanol), m. p. 236—237° (decomp. from 210°) (Found: C, 36·15; H, 3·45; N, 24·45. $C_6H_{10}N_4S,C_6H_3O_7N_3$ requires C, 36·1; H, 3·3; N, 24·55%).

5-*Amino*-1-*ethyl*-2-*methylglyoxaline*-4-*thiocarboxyamide*.—The foregoing imidate (0·5 g.) under ethanol (5 ml.) with 20% ethanolic ethylamine precipitated the *glyoxaline* (0·23 g.) which recrystallised from ethanol as needles, m. p. 224—226° (decomp.) (Found: C, 45·85; H, 6·65; N, 30·35. $C_7H_{12}N_4S$ requires C, 45·65; H, 6·55; N, 30·45%), giving a deep red colour when diazotised and coupled with β-naphthol in alkaline solution.

5-*Amino*-1-*cyclohexyl*-2-*methylglyoxaline*-4-*thiocarboxyamide*.—The above imidate (0·25 g.) under ethanol (2 ml.) was gently warmed with cyclohexylamine (0·125 ml.) for a few minutes, to give a clear red solution whence the *glyoxaline* (0·035 g.), prisms (from ethanol), m. p. 278—280° (decomp.), soon separated (Found: C, 55·1; H, 7·55; N, 22·95. $C_{11}H_{18}N_4S$ requires C, 55·5; H, 7·6; N, 23·5%).

6-*Mercapto*-8,9-*dimethylpurine*.—5-Amino-1,2-dimethylglyoxaline-4-thiocarboxyamide (0·25 g.) was heated on a water-bath for 1 hr. with formic acid (2 ml.) and acetic anhydride (2 ml.). The solution was evaporated *in vacuo* and the residue stirred with methanol to leave a solid. 5-*Formamido*-1,2-*dimethylglyoxaline*-4-*thiocarboxyamide* (0·25 g.) separated from methanol as needles, m. p. 256—257° (decomp.) (Found: C, 42·3; H, 4·8; N, 28·5. $C_7H_{10}ON_4S$ requires C, 42·4; H, 5·1; N, 28·3%). The formamide (0·25 g.) was heated on a water-bath for 2 hr. with potassium hydrogen carbonate (0·5 g.) in water (30 ml.). The solution was then evaporated to about 5 ml. and acidified with acetic acid to precipitate 6-*mercapto*-8,9-*dimethylpurine* (0·17 g.) which separated from ethanol as hydrated rods, m. p. 250° (decomp.) (Found: C, 44·8; H, 5·2; N, 29·5. $C_7H_8N_4S,\frac{1}{2}H_2O$ requires C, 44·4; H, 4·8; N, 29·6%).

5-*Amino*-4-*cyano*-1,2-*dimethylglyoxaline*.—5-Amino-1,2-dimethylglyoxaline-4-thiocarboxyamide (1·65 g.) in methanol (200 ml.) and 33% ethanolic methylamine (5 ml.) with a solution of mercuric chloride (2·7 g.) in methanol (30 ml.) produced an immediate precipitate of mercuric sulphide. After a few minutes this was filtered off and washed with a little hot ethanol. The filtrate was evaporated to a crystalline residue which was washed with a little ethanol. The *glyoxaline* (1·3 g.) separated from ethanol as needles, m. p. 242° (Found: C, 52·95; H, 5·85; N, 41·3. $C_6H_8N_4$ requires C, 52·9; H, 5·95; N, 41·25%), giving a deep red colour when diazotised and coupled with an alkaline solution of β-naphthol. The *glyoxaline picrate* separated from ethanol as needles, m. p. 218° (decomp.) (Found: C, 39·6; H, 2·95; N, 27·2. $C_6H_8N_4,C_6H_3O_7N_3$ requires C, 39·5; H, 3·05; N, 26·8%).

5-*Amino*-4-*cyanothiazole*.—Isopentyl formimidate hydrochloride (0·85 g.) was added to a solution of α-amino-α-cyanothioacetamide (0·56 g.) in dry methyl cyanide (10 ml.). A precipitate of ammonium chloride was removed by centrifugation, and the clear solution evaporated *in vacuo* to a semi-solid residue. This partly crystallised from water to give the *thiazole* (0·1 g.) as needles, m. p. 149—150° (Found: C, 38·45; H, 2·35; N, 32·65. $C_4H_3N_3S$ requires C, 38·4; H, 2·4; N, 33·6%).

5-*Aminoglyoxaline*-4-*thiocarboxyamide*.—A mixture of α-amino-α-cyanothioacetamide (1·1 g.), isopentyl formimidate hydrochloride (3 g.), and water (5 ml.) was extracted with ether (3 × 20 ml.). The combined extracts were filtered through magnesium sulphate, then treated with excess of ethanolic ammonia to give a red solution. This was evaporated *in vacuo* to a low volume to remove ammonia, then methanolic picric acid was added to give a crystalline precipitate of the hydrated *glyoxaline picrate* (0·7 g.), rods (from methanol), m. p. 240° (after decomp.) (Found: C, 29·8; H, 3·6; N, 24·85. $C_4H_6N_4S,C_6H_3O_7N_3,2H_2O$ requires C, 29·5; H, 3·2; N, 24·1%).

5-*Amino*-1-*methylglyoxaline*-4-*thiocarboxyamide*.—Isopentyl formimidate hydrochloride (6 g.) was shaken with a suspension of α-amino-α-cyanothioacetamide (2·3 g.) in water (10 ml.) and ether (30 ml.). The ether solution was separated and the aqueous phase extracted with further ether (4 × 20 ml.). 33% Ethanolic methylamine (5 ml.) was added to the combined solutions, a vivid blue colour being produced which quickly changed to purple and then red; in this way a red oil was precipitated which soon crystallised. The solvent was decanted and the solid

washed with ethanol which removed the colour. The *glyoxaline* (1·06 g.) separated from ethanol as prisms, m. p. 252° (decomp. with shrinking from 238°) (Found: C, 38·25; H, 4·9; N, 36·0. $C_5H_8N_4S$ requires C, 38·45; H, 5·15; N, 35·85%). The compound was readily soluble in dilute hydrochloric acid, and when diazotised and coupled with an alkaline solution of β-naphthol gave a magenta-coloured dye.

*5-Amino-4-cyano-1-methylglyoxaline.*—Solutions of the foregoing glyoxaline (0·27 g.) in hot ethanol (50 ml.) and 33% ethanolic methylamine (1 ml.), and of mercuric chloride (0·47 g.) in ethanol (5 ml.), were mixed. The mercuric sulphide was filtered off, and the filtrate evaporated *in vacuo*, leaving the *glyoxaline* (0·12 g.), needles (from water), m. p. 195—196° (Found: C, 49·0; H, 4·8; N, 46·3. $C_5H_6N_4$ requires C, 49·2; H, 4·9; N, 45·9%).

*6-Mercapto-9-methylpurine.*—5-Amino-1-methylglyoxaline-4-thiocarboxyamide (0·5 g.) was dissolved in formic acid (2 ml.) and acetic anhydride (2 ml.). When the initial reaction had subsided, the solution was heated on a water-bath for 20 min. then evaporated *in vacuo* to a mixture of syrup and solid, which completely solidified when treated with water. The product was dissolved in hot ethanol, leaving an insoluble solid (0·05 g.); the cooled filtrate gave *5-formamido-1-methylglyoxaline-4-thiocarboxyamide* (0·4 g.) which separated from ethanol as pale yellow needles, which melted at 148—150° (decomp.), and resolidified, and then had m. p. >300° (Found: C, 39·6; H, 4·3; N, 30·4. $C_6H_8ON_4S$ requires C, 39·1; H, 4·4; N, 30·45%). The insoluble fraction was dissolved in dilute aqueous ammonia, the solution clarified with charcoal, and the mixture filtered. Acidification of the filtrate with dilute acetic acid gave a precipitate of *6-mercapto-9-methylpurine*, m. p. >300° (Found: C, 43·2; H, 3·7; N, 34·05. $C_6H_6N_4S$ requires C, 43·4; H, 3·65; N, 33·75%).

Also, the foregoing formamide (0·07 g.) was boiled under reflux with 0·05N-potassium hydrogen carbonate (30 ml.) for 2 hr. The cooled solution was acidified with acetic acid to precipitate the mercaptopurine (0·05 g.), m. p. >300° (Found: C, 43·1; H, 3·9; N, 34·0%).

*9-Methyladenine.*—5-Amino-4-cyano-1-methylglyoxaline (0·2 g.) in ethyl orthoformate (5 ml.) was boiled under reflux for 2 hr., then evaporated *in vacuo* to a gum which solidified when rubbed with water. *4-Cyano-5-ethoxymethylideneamino-1-methylglyoxaline* (0·15 g.) separated from water as needles, m. p. 52° (Found: C, 53·8; H, 5·5; N, 31·35. $C_8H_{10}ON_4$ requires C, 53·95; H, 5·65; N, 31·45%). The ethoxy-compound (0·1 g.) was heated in a sealed tube with saturated ethanolic ammonia (2 ml.) for 1 hr. and the solution was then evaporated. The residual 9-methyladenine (0·05 g.) separated from an excess of methanol as prisms, m. p. 298—299° (Found: C, 48·15; H, 4·9; N, 46·45. Calc. for $C_6H_7N_5$: C, 48·3; H, 4·75; N, 46·95%).

*5-Amino-2-mercaptothiazole-4-thiocarboxyamide.*—A solution of α-amino-α-cyanothioacetamide (3 g.) in methanol (30 ml.) and carbon disulphide (8 ml.) was boiled under reflux for 30 min. The *thiazole* (3·65 g.) which separated was purified by dissolution in N-sodium hydroxide and precipitation with acetic acid; it formed pale yellow prisms, m. p. 210° (decomp.) (Found: C, 25·1; H, 2·5; N, 21·9. $C_4H_5N_3S_3$ requires C, 25·15; H, 2·65; N, 22·0%).

*Methyl 5-Amino-2-methylthiothiazole-4-thiocarboxyamidate.*—A solution of the preceding thiazole (2 g.) in N-sodium hydroxide (10 ml.) was shaken with dimethyl sulphate (3 ml.) for a few minutes. The *methylthiothiazolium methyl sulphate* (2·5 g.) which separated formed pale yellow needles, m. p. 105° (decomp. and resolidified), from ethanol (Found: C, 25·25; H, 4·15; N, 12·2. $C_6H_9N_3S_3,CH_4O_4S$ requires C, 25·35; H, 3·95; N, 12·7%).

*5-Amino-4-cyano-2-methylthiothiazole.*—The foregoing sulphate (1 g.) in water (20 ml.) with 2N-sodium hydroxide (3 ml.) gave a crystalline precipitate. The *cyanothiazole* (0·4 g.) crystallised from ethanol as cream-coloured prismatic rods, m. p. 146° (Found: C, 35·2; H, 2·8; N, 24·2. $C_5H_5N_3S_2$ requires C, 35·1; H, 2·9; N, 24·5%).

*2,7-Di(methylthio)thiazolo*[5,4-d]*pyrimidine.*—The foregoing thiazole sulphate (0·4 g.) was heated on a water-bath with formic acid (2 ml.) and acetic anhydride (2 ml.) for 30 min. The solution was evaporated *in vacuo* to a syrup which crystallised when rubbed with water. The *thiazolopyrimidine* (0·2 g.) separated from ethanol as needles, m. p. 120°, which retained ethanol (Found: C, 38·6; H, 3·85; N, 16·8. $C_7H_7N_3S_3,\frac{1}{2}C_2H_6O$ requires C, 38·1; N, 4·0; N, 16·65%).

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