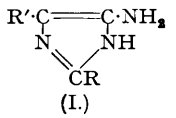
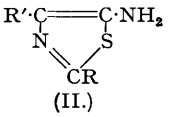
493. *Studies in the Azole Series. Part XX. Some Novel Syntheses of Purines and Thiazolopyrimidines.*

By A. H. Cook and E. Smith.

The ready cyclisation, by various procedures, of certain 5-aminoglyoxaline- and 5-aminothiazole-4-carboxyamides to the corresponding purines and thiazolopyrimidines is described.

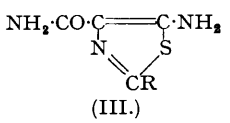
Earlier in this series (Parts XII—XIV, this vol., pp. 1064—1074) the synthesis of 5-amino-4-carbethoxy-glyoxalines (I) and -thiazoles (II; R′ = CO_2Et) and their conversion into purines and thiazolopyrimidines, respectively, was described. This approach to the purine ring system


(I.)


(II.)

appeared capable of extension to the 4-carboxyamides and 4-cyanides. Such amides have been described (Cook, Heilbron, and Smith, Part XVII, this vol., p. 1440) and thus presented a convenient alternative approach to the system under discussion.

A purine synthesis of the type here envisaged has been effected by Sarasin and Wegmann (*Helv. Chim. Acta*, 1924, **7**, 713) who obtained 7-methylxanthine by treating 5-amino-3-methylglyoxaline-4-carboxyamide with ethyl carbonate. This reaction was improved (Mann and Porter, *J.*, 1945, 752) by employing ethyl chloroformate but still required a high temperature and the presence of potassium carbonate. With the possibility in mind of using this type of approach for the synthesis of sensitive purines, a milder cyclisation procedure was accordingly sought. Modification of the alcohol residue in ethyl chloroformate by employing the thiophenyl instead of the ethoxyl group gave the desired type of reactivity, *i.e.*, ease of reaction with amines and formation of products from which subsequent smooth removal of the ester residue proved feasible. Thus, treatment of 5-amino-2-methylthiothiazole-4-carboxyamide (III; R = SMe) (cf. Part XVII, *loc. cit.*) with phenyl chlorothiolformate, Ph·S·CO·Cl (Rivière, *Bull. Soc. chim.*,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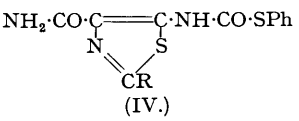
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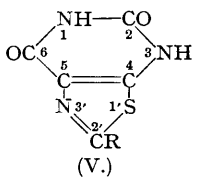
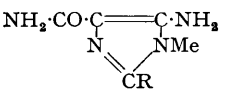

(V.)

1901, **1**, 733) at room temperature yielded 5-(*phenylthioformamido*)-2-*methylthiothiazole*-4-*carboxyamide* (IV; R = SMe). This compound on being heated above its melting point readily lost thiophenol, and the same result was obtained when it was boiled in pyridine for 10 minutes, with consequent production of 2 : 6-*diketo*-2′-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)-*pyrimidine* (V; R = SMe). This ready cyclisation was extended in a similar fashion to 5-*amino*-

2-*benzylthiothiazole*-4-*carboxyamide* and 5-amino-2-benzylthiazole-4-carboxyamide which were converted, respectively, into 5-(*phenylthioformamido*)-2-*benzylthio*- (IV; R = S·CH_2Ph) and 5-*phenylthioformamido*)-2-*benzyl*-*thiazole*-4-*carboxyamide* (IV; R = CH_2Ph), with subsequent cyclisation to 2 : 6-*diketo*-2′-*benzylthio*- (V; R = S·CH_2Ph) and to 2 : 6-*diketo*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (V; R = CH_2Ph). This route was also used for the conversion of 5-*amino*-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VI; R = SMe) through 5-(*phenylthioformamido*)-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VII) into 2 : 6-*dihydroxy*-8-*methylthio*-9-*methylpurine* (VIII). This method could doubtless be extended to the synthesis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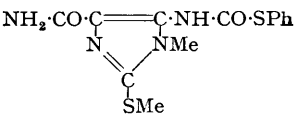
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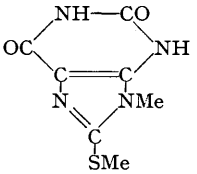
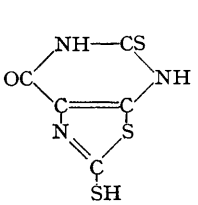

(VIII.)

of purines and thiazolopyrimidines with a mercapto-group in the 2-position by employing phenyl chlorodithioformate, but another approach to compounds of this type soon presented itself.

It has been shown that α-amino-nitriles react with carbon disulphide in non-basic solvents to give 5-amino-2-mercaptothiazoles (Cook, Heilbron, and Levy, Part II, *J.*, 1947, 1598). It was observed that on treatment of aminocyanoacetamide with carbon disulphide in pyridine a product was obtained which was not 5-amino-2-mercaptothiazole-4-carboxyamide or an isomeride thereof. Analyses of the new product showed that it was derived from aminocyanoacetamide (1 mol.) and carbon disulphide (2 mols.) with loss of hydrogen sulphide (1 mol.), and it was further shown that treatment with methyl sulphate converted it into a trimethyl derivative. It appeared likely that aminocyanoacetamide had reacted with carbon disulphide to give initially 5-amino-2-mercaptothiazole-4-carboxyamide (III; R = SH) (cf. Part XVII, *loc. cit.*) and that the latter had reacted further with carbon disulphide to give, probably through the intermediation of a dithiocarbamate, 2′-*mercapto*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (IX) which on methylation gave 6-keto-2 : 2′-dimethylthio-1-methyl-1 : 6-dihydrothiazolo(5′ : 4′-4 : 5)pyrimidine (X). Indeed, 5-amino-2-mercaptothiazole-4-carboxyamide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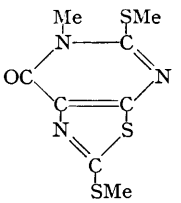
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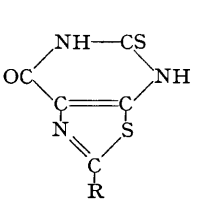
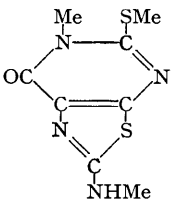

(XI.)


(XII.)

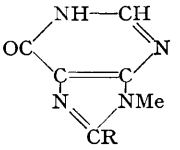
itself gave the compound (IX) when boiled under reflux with carbon disulphide in pyridine. The trimethyl derivative of this, viz. compound (X), proved in fact to be identical with the product already assigned the same structure and earlier synthesised in these laboratories by a different route (Part XII, *loc. cit.*, 1064).

This type of cyclisation was found to be applicable to other 5-aminoazole-4-carboxyamides. Treatment of 5-amino-2-methylaminothiazole-4-carboxyamide (III; R = NHMe) with carbon disulphide in pyridine gave 2′-*methylamino*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)-*pyrimidine* (XI; R = NHMe) which on methylation with methyl sulphate gave 2′-*methylamino*-6-*keto*-2-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XII). Likewise 5-amino-2-methylthio- (III; R = SMe), 5-amino-2-benzylthio- (III; R = S·CH_2Ph) and 5-amino-2-benzylthiazole-4-carboxyamide (III; R = CH_2Ph) yielded 6-*keto* 2-*thio*-2′-*methylthio*- (XI; R = SMe), 6-*keto* 2-*thio*-2′-*benzylthio*- (XI; R = S·CH_2Ph), and 6-*keto* 2-*thio*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = CH_2Ph), respectively. In a similar manner, treatment of 5-amino-2-mercapto-1-methylglyoxaline-4-carboxyamide and 5-amino-1-methylglyoxaline-4-carboxyamide with carbon disulphide yielded the corresponding purines, 6-*hydroxy*-2 : 8-*dimercapto*-9-*methyluric acid* and 6-*hydroxy*-2-*mercapto*-9-*methylpurine*, respectively.

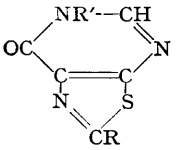
An approach to compounds of the type (XIII) containing the hypoxanthine ring system, by

treating 5-amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (VI; R = SMe) and 5-amino-1-methylglyoxaline-4-carboxyamide (VI; R = H) with formic acid led to 6-*hydroxy*-8-*methylthio*-9-*methylpurine* (XIII; R = SMe) and to 6-hydroxy-9-methylpurine (9-methylhypoxanthine) (XIII; R = H), respectively, of which products the latter had been described earlier (Fischer, *Ber.*, 1898, **31**, 114).

The attempted synthesis of compounds of the type (XIV) by interaction of 5-amino-2-methylthiothiazole-4-carboxyamide (III; R = SMe) with formic acid, however, yielded only the corresponding *N*-formyl derivative. The latter, however, was converted by acetic anhydride,



(XIII.)



(XIV.)

with elimination of water, into 6-*keto*-2'-*methylthio*-1 : 6-*dihydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (XIV; R = SMe, R' = H) which was also obtained in one stage by treating the thiazole (III; R = SMe) with ethyl orthoformate. Compound (XIV; R = SMe, R' = H) with methyl sulphate and alkali yielded a monomethyl derivative, which was formulated as 6-*kelo*-2'-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (XIV; R = SMe, R' = Me). Similar reactions were effected with 5-amino-2-benzylthiothiazole-4-carboxyamide (III; R = S·CH_2Ph) and 5-amino-2-benzylthiazole-4-carboxyamide (III; R = CH_2Ph) to give respectively, 6-*keto*-2'-*benzylthio*- (XIV; R = S·CH_2Ph) and to 6-*keto*-2'-*benzyl*-1 : 6-*dihydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (XIV) (R = CH_2Ph). It may be noted that attempted cyclisation of this type of compound carrying a reactive functional group in the 2-position (*e.g.*, R = SH, NHMe, or NHPh) led only to acetyl or ethoxymethylene derivatives and not to bicyclic products.

Experimental.

2 : 6-*Diketo*-2'-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (V; R = SMe).—5-Amino-2-methylthiothiazole-4-carboxyamide (2·5 g.) was dissolved in anhydrous dioxan (30 c.c.) and to the solution was added phenyl chlorothiolformate (1·3 g.). The solution was set aside for several hours at room temperature and then cooled to 0° for 1 hour, whereupon crystals of the hydrochloride, m. p. 195°, slowly separated. These (0·9 g.) were filtered off; the filtrate was evaporated to dryness *in vacuo*, and the residue was extracted with hot benzene (40 c.c.). This extract was evaporated to small bulk (*ca.* 5 c.c.), crystals (1·8 g.) of 5-(*phenylthioformamido*)-2-*methylthiothiazole*-4-*carboxyamide* (IV; R = SMe) separating. The product crystallised from benzene in colourless felted needles, m. p. 175° (decomp.) and 300° (Found: C, 44·6; H, 3·3; N, 13·0. $C_{12}H_{11}O_2N_3S_3$ requires C, 44·3; H, 3·4; N, 12·9%).

The above compound (2·4 g.) was dissolved in dry pyridine (5 c.c.). When this solution was boiled under reflux for 10 minutes, thiophenol was copiously evolved. The solution was cooled and acidified with 6N-hydrochloric acid (15 c.c.) and then set aside at 0°. The product, 2 : 6-*diketo*-2'-*methylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (1·5 g.), was filtered off and crystallised from glacial acetic acid in colourless small prisms, m. p. 295—300° (Found: C, 33·5; H, 2·3; N, 19·4. $C_6H_5O_2N_3S_2$ requires C, 33·5; H, 2·3; N, 19·5%).

2 : 6-*Diketo*-2'-*benzylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (V; R = S·CH_2Ph).—5-Amino-2-mercaptothiazole-4-carboxyamide (2·0 g.) was dissolved in N-sodium hydroxide (20 c.c.) and shaken for 1 hour at room temp. with excess of benzyl chloride (4 g.). The product which separated, 5-*amino*-2-*benzylthiothiazole*-4-*carboxyamide* (III; R = S·CH_2Ph) (2·4 g.), was filtered off and recrystallised from benzene, forming colourless felted needles, m. p. 143—144° (Found: N, 15·5. $C_{11}H_{11}ON_3S_2$ requires N, 15·8%).

5-Amino-2-benzylthiothiazole-4-carboxyamide (1·0 g.) was dissolved in dry acetone (40 c.c.). Phenyl chlorothiolformate (0·5 g.) was added and the solution set aside at room temperature for 6 hours and then evaporated to dryness *in vacuo*. The residue was extracted with hot benzene and filtered. Evaporation of the filtrate to a small bulk (*ca.* 5 c.c.) yielded crystals (0·6 g.) of 5-(*phenylthioformamido*)-2-*benzylthiothiazole*-4-*carboxyamide* (IV; R = S·CH_2Ph), m. p. 143°, which crystallised from benzene–light petroleum in colourless rods (Found: C, 54·0; H, 3·8; N, 10·65. $C_{18}H_{15}O_2N_3S_3$ requires C, 53·9; H, 3·8; H, 10·5%).

The above compound (0·5 g.) was dissolved in dry pyridine (2 c.c.) and the solution was boiled under reflux for 10 minutes and then evaporated to dryness *in vacuo*. The residue of 2 : 6-*diketo*-2'-*benzylthio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (0·3 g.) was collected. It crystallised from glacial acetic acid in colourless small prisms, m. p. 290—295° (Found: C, 49·4; H, 3·0; N, 14·7. $C_{12}H_9O_2N_3S_2$ requires C, 49·5; H, 3·1; N, 14·4%).

2 : 6-*Diketo*-2'-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5' : 4'-4 : 5)*pyrimidine* (V; R = CH_2Ph). 5-Amino-2-benzylthiazole-4-carboxyamide (1·0 g.) was dissolved in anhydrous dioxan (30 c.c.) and phenyl chlorothiolformate (1·0 g.) was added. After being kept at room temperature for 6 hours the solution was cooled to 0°, whereupon crystals of the hydrochloride (0·3 g.), m. p. 215°, separated The

solution was evaporated to dryness *in vacuo* and the residue extracted with hot benzene and filtered. Evaporation of this extract to small bulk yielded crystals (0·7 g.) of 5-(*phenylthioformamido*)-2-*benzylthiazole*-4-*carboxyamide* (IV; R = CH_2Ph), m. p. 148°. This crystallised from benzene–light petroleum in felted needles (Found : N, 11·2. $C_{18}H_{15}O_2N_3S_2$ requires N, 11·4%).

The above compound (0·5 g.) was dissolved in dry pyridine and the solution was boiled under reflux for 10 minutes. The solvent was then removed *in vacuo*. The residue (0·3 g.) of 2 : 6-*diketo*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* crystallised from glacial acetic acid–ether in boat-shaped small prisms, m. p. 295—300° (Found : C, 55·7; H, 3·7; N, 16·2%. $C_{12}H_9O_2N_3S$ requires C, 55·6; H, 3·5; N, 16·2%).

2 : 6-*Dihydroxy*-8-*methylthio*-9-*methylpurine* (VIII).—5-Amino-2-mercapto-1-methylglyoxaline-4-carboxyamide (1·6 g.), dissolved in N-sodium hydroxide (5 c.c.), was shaken for 30 minutes at 0° with excess of methyl sulphate. The product which separated, 5-*amino*-2-*methylthio*-1-*methylglyoxaline*-4-*carboxyamide* (VI; R = SMe) (1·1 g.) was filtered off, washed with water and then with ether. It crystallised from benzene in colourless platelets, m. p. 176° (Found : N, 29·9. $C_6H_{10}ON_4S$ requires N, 30·1%). 5-Amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (VI) (1·4 g.) was dissolved in dry acetone (100 c.c.). Phenyl chlorothiolformate (0·8 g.) was added. When the mixture was kept at room temperature for 30 minutes crystals (0·7 g.) of the *hydrochloride* separated. These were filtered off and crystallised from ethanol in colourless prisms, m. p. 217—218° (Found : C, 33·0; H, 5·3. $C_6H_{11}ON_4SCl$ requires C, 32·6; H, 5·0%). The filtrate was evaporated to dryness under diminished pressure and the residue recrystallised from *iso*butanol in colourless prisms of 5-(*phenylthioformamido*)-1-*methyl*-2-*methylthioglyoxaline*-4-*carboxyamide* (VII) which decomposed gradually up to 300° (Found : N, 17·7. $C_{13}H_{14}O_2N_4S_2$ requires N, 17·4%).

The above compound (0·3 g.) was dissolved in dry pyridine (5 c.c.), and the solution was heated under reflux for 15 minutes and then evaporated to dryness *in vacuo*. The residue of 2 : 6-*dihydroxy*-8-*methylthio*-9-*methylpurine* (0·15 g.) was collected and crystallised from pyridine–ether in colourless small prisms, m. p. 320° (decomp.) (Found : C, 41·1; H, 3·9; N, 25·9. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8; N, 26·4%).

2′-*Mercapto*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (IX).—(a) *From aminocyanoacetamide*. Aminocyanoacetamide (0·3 g.) was dissolved in pyridine (40 c.c.) and boiled under reflux for 3 hours with carbon disulphide (5 c.c.). The solution was cooled, diluted with 2N-hydrochloric acid, and after being kept at 0° was filtered. The product, 6-*hydroxy*-2′-*mercapto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (0·4 g.), crystallised from (1 : 1) quinoline–acetic acid in brownish small prisms which did not melt below 450°. The product was obtained colourless on dissolution in a large volume of N-sodium hydroxide solution, followed by precipitation with acetic acid (Found : C, 28·1; H, 1·7; N, 18·9. $C_5H_3ON_3S_3$ requires C, 27·7; H, 1·4; N, 19·3%).

(b) *From* 5-*amino*-2-*mercaptothiazole*-4-*carboxyamide*. This amide (0·5 g.) was dissolved in pyridine (40 c.c.) containing carbon disulphide (5 c.c.) and the mixture, after being heated under reflux (3 hours), was treated as in the preceding section.

The above compound (0·2 g.) was dissolved in N-sodium hydroxide solution and shaken for 1 hour with excess (1 c.c.) of methyl sulphate. The solid which separated was washed thoroughly with water and ether. This product, 6-keto-2 : 2′-dimethylthio-1-methyl-1 : 6-dihydrothiazolo(5′ : 4′-4 : 5)-pyrimidine (X), crystallised from ethanol in rosettes of needles, m. p. 222·5°, undepressed by admixture with authentic material (Cook, Heilbron, Macdonald, and Mahadevan, *loc. cit.*) (Found : C, 37·15; H, 3·55; N, 16·05. Calc. for $C_8H_9ON_3S_3$: C, 37·05; H, 3·5; N, 16·2%).

2′-*Methylamino*-6-*keto*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = NHMe).—5-Amino-2-methylaminothiazole-4-carboxyamide (0·4 g.), dissolved in pyridine (15 c.c.) was heated under reflux for 3 hours with carbon disulphide, a yellow solid being slowly deposited. The solid (0·3 g.) was filtered off and purified by dissolution in 2N-aqueous ammonia, followed by acidification with acetic acid, the *thiazolopyrimidine*, m. p. >300°, separating in small prisms (Found : C, 33·3; H, 2·9. $C_6H_6ON_4S_2$ requires C, 33·6; H, 2·8%).

The above compound (0·1 g.) was dissolved in 2N-sodium hydroxide and shaken for 30 minutes with methyl sulphate (0·5 c.c.). The yellow solid which separated, 2′-*methylamino*-6-*keto*-2-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XII) was filtered, washed thoroughly with water and ether, and crystallised from (1 : 1) glacial acetic acid–methanol in colourless prisms, m. p. 299—302° (Found : C, 39·5; H, 4·3; N, 23·5. $C_8H_{10}ON_4S_2$ requires C, 39·7; H, 4·2; N, 23·1%).

6-*Keto*-2′-*methylthio*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = SMe).—5-Amino-2-methylthiothiazole-4-carboxyamide (2·0 g.), dissolved in pyridine (5 c.c.), was heated under reflux for 8 hours with carbon disulphide (2 c.c.). The solvent was removed *in vacuo*, and the residue extracted with N-sodium hydroxide (5 c.c.) at 40°. Filtration and acidification of the extract with 2N-hydrochloric acid yielded a precipitate (0·1 g.) of the *thiazolopyrimidine*, which was purified by dissolution in N-sodium hydroxide, followed by precipitation with N-hydrochloric acid, giving small yellow prisms, m. p. 270—275° (Found : C, 31·0; H, 2·3. $C_6H_5ON_3S_3$ requires C, 31·1; H, 2·2%).

6-*Keto*-2′-*benzylthio*-2-*thio*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = S·CH_2Ph).—5-Amino-2-benzylthiothiazole-4-carboxyamide (2·0 g.), dissolved in pyridine (10 c.c.), was heated under reflux for 8 hours with carbon disulphide (2 c.c.). The solution was worked up as in the foregoing preparation to yield the thiazolopyrimidine (0·1 g.) as yellow small prisms which were purified by dissolution in alkali, followed by precipitation with acid, giving an almost white *product*, m. p. 275—280° (Found : C, 46·8; H, 3·0. $C_{12}H_9ON_3S_3$ requires C, 46·9; H, 3·0%).

6-*Keto*-2-*thio*-2′-*benzyl*-1 : 2 : 3 : 6-*tetrahydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XI; R = CH_2Ph).—5-Amino-2-benzylthiazole-4-carboxyamide (1·5 g.) in pyridine (20 c.c.) was heated under reflux for 8 hours with carbon disulphide (4 c.c.), and the solution worked up as in earlier examples, to give the *thiazolopyrimidine* (0·3 g.) which crystallised from glacial acetic acid in colourless small prisms, m. p. 280° (Found : C, 52·1; H, 3·2; N, 15·0. $C_{12}H_9ON_3S_2$ requires C, 52·35; H, 3·3; N, 15·25%).

6-*Hydroxy*-2 : 8-*dimercapto*-9-*methyluric Acid*.—5-Amino-2-mercapto-1-methylglyoxaline-4-carboxyamide (0·1 g.), dissolved in boiling pyridine (10 c.c.), was heated under reflux for 12 hours with carbon

disulphide (2 c.c.). The solution was cooled and diluted with 2N-hydrochloric acid (35 c.c.), thereby precipitating the *purine* (0·05 g.). This material had m. p. >300° and was purified by repeated dissolution in hot pyridine, followed by precipitation with 2N-hydrochloric acid (Found : C, 34·2; H, 3·1; N, 25·9. $C_6H_6ON_4S_2$ requires C, 33·6; H, 2·8; N, 26·1%).

6-*Hydroxy*-2-*mercapto*-9-*methylpurine*.—5-Amino-1-methylglyoxaline-4-carboxyamide (0·1 g.), dissolved in boiling pyridine (25 c.c.), was heated under reflux for 12 hours with carbon disulphide (2 c.c.), the purine gradually separating from the hot solution. This (0·06 g.) was filtered off, purified by dissolution in 2N-sodium hydroxide and precipitation with 2N-hydrochloric acid; it then crystallised from water in small colourless prisms of the *purine hemihydrate*, m. p. 315° (Found : C, 38·1; H, 3·8; N, 29·3. $C_6H_6ON_4S,\frac{1}{2}H_2O$ requires C, 37·7; H, 3·7; N, 29·3%). The *purine*, of unchanged m. p., was obtained from this by drying at 100° over phosphoric oxide *in vacuo* for 1 hour (Found : N, 30·7. $C_6H_6ON_4S$ requires N, 30·8%).

6-*Hydroxy*-8-*methylthio*-9-*methylpurine* (XIII; R = SMe).—5-Amino-2-methylthio-1-methylglyoxaline-4-carboxyamide (0·2 g.) was heated under reflux with formic acid (10 c.c.) and acetic anhydride (10 c.c.) for 2 hours, and the solution evaporated to dryness *in vacuo*. The residue (0·2 g.) was dissolved in boiling methanol (40 c.c.) and evaporation of this to small bulk (20 c.c.), followed by cooling, yielded the *purine* in clusters of colourless rods, m. p. 280—282°, which were recrystallised from methanol (Found : C, 42·6; H, 4·6; N, 28·1. $C_7H_8ON_4S$ requires C, 42·9; H, 4·2; N, 28·5%).

6-*Hydroxy*-9-*methylpurine* (XIII; R = H).—5-Amino-1-methylglyoxaline-4-carboxyamide (cf. Part IX, *loc. cit.*) (0·3 g.) was heated under reflux with acetic anhydride (5 c.c.) and formic acid (5 c.c.) for 2 hours and the solution evaporated to dryness *in vacuo*. The residue was dissolved in boiling glacial acetic acid (25 c.c.); evaporation of this mixture to a smaller bulk (15 c.c.), followed by dilution with ethanol (10 c.c.), gave the purine (0·2 g.) in colourless prisms which were recrystallised from glacial acetic acid and then had m. p. 375° (Found : C, 48·1; H, 4·0; N, 37·3. Calc. for $C_6H_6ON_4$: C, 48·0; H, 4·0; N, 37·3%).

6-*Keto*-2′-*methylthio*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = SMe, R′ = H).—(a) *By cyclisation of the* N-*formyl derivative*. 5-*N*-Formamido-2-methylthiothiazole-4-carboxyamide (0·5 g.) was covered with acetic anhydride (10 c.c.), and the whole heated under reflux for 1·5 hours, the solid gradually dissolving. The solvent was removed *in vacuo*, and the residue was dissolved in boiling ethanol (50 c.c.). The solution was evaporated to *ca.* 10 c.c., from which crystals (0·4 g.) appeared on cooling. The *thiazolopyrimidine* crystallised from glacial acetic acid in rosettes of colourless needles, m. p. 254—255° (Found : N, 20·7. $C_6H_5ON_3S_2$ requires N, 21·1%).

(b) *By use of ethyl orthoformate*. 5-Amino-2-methylthiothiazole-4-carboxyamide (0·5 g.) was covered with ethyl orthoformate (8 c.c.) and acetic anhydride (12 c.c.), and the whole heated under reflux for 2 hours, whereupon the solid dissolved. The solvent was removed *in vacuo*, and the residue was dissolved in boiling ethanol (50 c.c.) and treated as above. The product (0·4 g.) had m. p. 255°, undepressed when mixed with the compound prepared by route (*a*) (Found : C, 36·6; H, 2·5; N, 21·3. $C_6H_5ON_3S_2$ requires C, 36·2; H, 2·5; N, 21·1%).

The above compound (0·2 g.) was dissolved in N-sodium hydroxide (2 c.c.) at 40°. This solution was cooled to room temperature and shaken for 15 minutes with excess of methyl sulphate (1 c.c.). The solid which separated, 6-*keto*-2′-*methylthio*-1-*methyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = SMe; R′ = Me) was washed with water (5 c.c.) and ether (5 c.c.) and crystallised from ethanol in colourless scintillating needles, m. p. 228—229° (Found : N, 19·9. $C_7H_7ON_3S_2$ requires N, 19·7%).

6-*Keto*-2′-*benzylthio*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = $S{\cdot}CH_2Ph$).—5-Amino-2-benzylthiothiazole-4-carboxyamide (0·7 g.) was heated under reflux in acetic anhydride (5 c.c.) with ethyl orthoformate (5 c.c.) for 2 hours, and the solution evaporated to dryness *in vacuo*. The residue was dissolved in boiling ethanol (25 c.c.), and evaporation of this to 10 c.c., followed by cooling, yielded the *thiazolopyrimidine* in dense clusters of colourless needles (0·8 g.) which crystallised from ethanol and then had m. p. 165° (Found : C, 52·5; H, 3·7; N, 15·4. $C_{12}H_9ON_3S_2$ requires C, 52·4; H, 3·3; N, 15·3%).

6-*Keto*-2′-*benzyl*-1 : 6-*dihydrothiazolo*(5′ : 4′-4 : 5)*pyrimidine* (XIV; R = CH_2Ph).—5-Amino-2-benzylthiazole-4-carboxyamide (0·4 g.) was heated under reflux with ethyl orthoformate (4 c.c.) and acetic anhydride (4 c.c.) for 2 hours, and the excess of reactants removed *in vacuo*. The residue crystallised from methanol (*ca.* 10 c.c.), to give the *thiazolopyrimidine* (0·3 g.). This crystallised from ethanol in colourless needles, m. p. 234° (Found : C, 59·5; H, 3·9. $C_{12}H_9ON_3S$ requires C, 59·3; H, 3·7%).

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