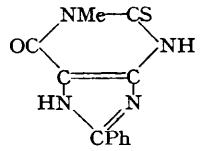
## 385. *Studies in the Azole Series. Part XXX. New Syntheses of 2- and 8-Aminopurines.*

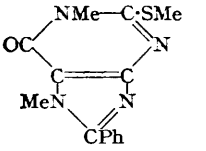
By A. H. Cook and G. H. Thomas.

Attempts to synthesise guanine derivatives from ethyl 4-aminoglyoxaline-5-carboxylates are described; more obvious routes proved unsuccessful, but a ready synthesis of dimethylguanines was developed by cyclising 4-*N'*-methylthioureidoglyoxaline-5-carboxylates with methylamine in the presence of mercuric oxide. 8-Methylaminopurines have been obtained by treatment of 5-*N'*-methylthioureido-4-aminopyrimidines with mercuric oxide.

The extension of the syntheses of purines from azoles to include adenine and some of its derivatives has been described in an earlier paper in this series (Cook and Smith, Part XXIII, *J.*, 1949, 3001). The present contribution describes some attempts to synthesise derivatives of the second important class of aminopurines, guanines, from 4-aminoglyoxaline-5-carboxylates. Such an undertaking envisaged the preliminary formation of 4-guanidinoglyoxaline-5-carboxylates, from which the guanine derivatives might be obtained by cyclisation with

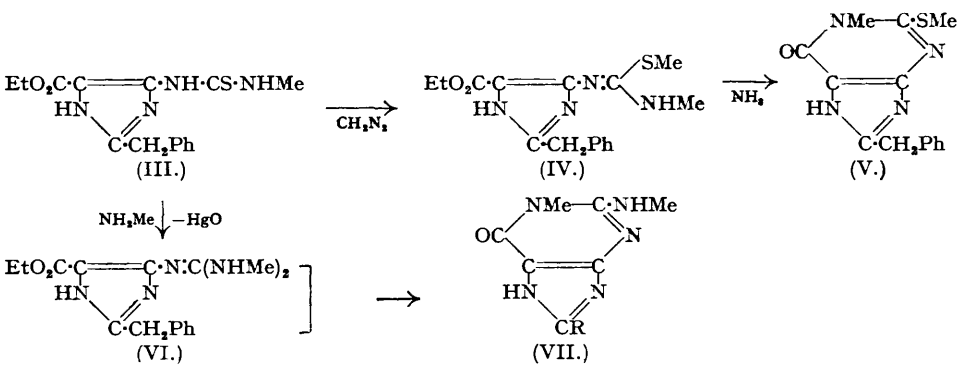
elimination of ethanol. The condensation of guanidine with the aminoglyoxalines seemed a likely route to such intermediates, but it was found that fusion of the two reactants resulted in


(I.)


(II.)

only sluggish elimination of ammonia, even at temperatures at which the glyoxaline decomposed. Similar difficulty was found with the salts of *S*-alkylthioureas. Obviously, then, a method had to be developed for synthesising the guanidinoglyoxalines under milder conditions.

Accordingly, attention was turned to the formation of the guanidino-portion of the purine by replacement of a methylthio-substituent with ammonia. 2-Thio-8-phenyl-1-methylxanthine (I) (Cook, Heilbron, Davis, and Thomas, Part XIV, *J.*, 1949, 1071) yielded 2-methylthio-8-phenyl-1 : 7-dimethylxanthine (II) on methylation with methyl sulphate in alkali, and the methylated compound was heated in ethanolic ammonia at 130° for 24 hours in an attempt to obtain 8-phenyl-1 : 7-dimethylguanine, but no methanethiol was eliminated and the purine was recovered unchanged. An obvious modification, therefore, was the use of an *S*-methyl*iso*-thioureidoglyoxaline in the place of (I), since *S*-alkyl*iso*thioureas very readily react with ammonia yielding guanidines. Ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate (III)

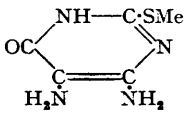

(III.) (IV.) (V.) (VI.) (VII.)

afforded ethyl 4-*N'S*-dimethyl*iso*thioureido-2-benzylglyoxaline-5-carboxylate (IV) on treatment with ethereal diazomethane. Here, again, the methylthio-group was not eliminated in ethanolic ammonia at 150° for 12 hours, 2-methylthio-8-benzyl-1-methylxanthine (V) being obtained. The stability of the methylthio-substituent may perhaps be correlated with the aromatic nature of the purine ring system, though in view of similar failures in the pyrimidine series, a complex of factors may well be responsible (see, for example, Andrews, Anand, Todd, and Topham, *J.*, 1949, 2491).

The method eventually adopted was facilitated by a recent observation that *N'*-alkyl-*N''*-*p*-chlorophenylguanidinopyrimidines could be obtained from the corresponding thioureas by treatment in ammoniacal solution with mercuric oxide, the thiol group being eliminated as the metal sulphide and replaced by an amino-group (Crowther, Curd, and Rose, *J.*, 1948, 587). It was thought that by applying the same type of reaction to the thioureido-compound (III), a guanidinoglyoxaline would result which would afford 8-benzyl-1-methylguanine on cyclisation. Unfortunately it was not possible to use ammonia in this reaction, since, like aqueous sodium hydroxide, it immediately cyclised the thioureido-compound to the ammonium salt of 2-thio-8-benzyl-1-methylxanthine (Part XIV, *loc. cit.*). Methylamine did not effect this rapid cyclisation and so, when ethyl 4-*N'*-methylthioureido-2-benzylglyoxaline-5-carboxylate and mercuric oxide were gently heated in aqueous methylamine, mercuric sulphide was precipitated and acidification of the mother-liquor yielded 8-benzyl-1 : $N^2$-dimethylguanine (VII; R = $CH_2Ph$) : cyclisation of the intermediate guanidinoglyoxaline (VI) evidently had occurred spontaneously. In a like manner, ethyl 4-*N'*-methylthioureido-glyoxaline- and -2-phenylglyoxaline-5-carboxylate afforded 1 : $N^2$-dimethyl- (VII; R = H) and 8-phenyl-1 : $N^2$-dimethyl-guanine (VII; R = Ph) respectively. These dimethylguanines gave a characteristic colour reaction under murexide conditions :

oxidation in concentrated hydrochloric acid with potassium chlorate, and evaporation to dryness left a strong mauve stain which changed to red on moistening with 10% aqueous sodium hydroxide. 1 : $N^2$-Dimethylguanine, like guanine itself (Traube, *Ber.*, 1900, **33**, 1378), left a glazed yellow residue on evaporation with nitric acid which changed to a red-violet stain when moistened with alkali.

The ability of mercuric oxide to remove hydrogen sulphide from a thioureido-compound has also provided a ready synthesis of 8-aminopurines. Johns and Baumann (*J. Biol. Chem.*, 1913, **14**, 387) found that, when 4 : 5-diamino-6-hydroxy-2-methylthiopyrimidine (VIII) was fused with thiourea, 8-amino-6-hydroxy-2-methylthiopurine (IX) was obtained instead of the expected 6-hydroxy-8-mercapto-2-methylthiopurine (X); this unique case was caused by decomposition of thiourea to guanidine *iso*thiocyanate before reaction occurred. The synthesis suggested a possible route to 8-aminopurines.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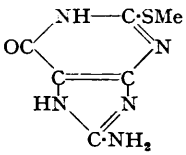
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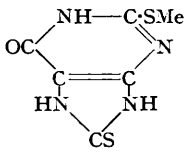
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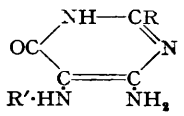
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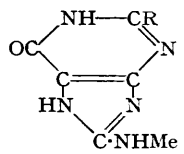
(XII.)

4 : 5-Diamino-2 : 6-dihydroxypyrimidine (XI; R = OH, R′ = H) readily reacted with methyl *iso*thiocyanate yielding the hemihydrate of 4-amino-5-*N*′-methylthioureido-2 : 6-dihydroxypyrimidine (XI; R = OH, R′ = CS·NHMe), which with mercuric oxide yielded the hemihydrate of 8-methylamino-2 : 6-dihydroxypurine (XII; R = OH). Similarly 8-methylamino-6-hydroxy-2-methylthiopurine (XII; R = SMe) was obtained from 4-amino-5-*N*′-methylthioureido-6-hydroxy-2-methylthiopyrimidine (XII; R = SMe; R′ = CS·NHMe). Both amino-purines were high-melting crystalline solids which gave a strong murexide colour on oxidation with potassium chlorate in hydrochloric acid.

## Experimental.

*2-Methylthio-8-phenyl-1 : 7-dimethylxanthine* (II).—A solution of 2-thio-8-phenyl-1 : 7-dimethylxanthine (2 g.) (Part XIV, *loc. cit.*) in 10% sodium hydroxide (10 c.c.) was shaken for 5 minutes with an excess of methyl sulphate (1 c.c.). A gummy solid separated which solidified on trituration with water at 0°; *2-methylthio-8-phenyl-1 : 7-dimethylxanthine* (1·8 g.) crystallised from ethanol as colourless threads, m. p. 235° (Found : C, 58·7; H, 5·2; N, 19·2. $C_{14}H_{14}ON_4S$ requires C, 58·7; H, 4·9; N, 19·6%). The methylated purine was heated at 130° in ethanolic ammonia for 24 hours; on acidification of the solution the starting material was isolated unchanged. The compound was also unaffected by being heated in 2N-hydrochloric acid or 20% sodium hydroxide under reflux.

*2-Methylthio-8-benzyl-1-methylxanthine* (V).—A suspension of ethyl 4-*N*′-methylthioureido-2-benzylglyoxaline-5-carboxylate (2 g.) in methanol (5 c.c.) was treated with excess of ethereal diazomethane in portions until the yellow colour persisted after stirring; all the thioureido-compound had dissolved. On evaporation to 5 c.c. and storage at 0°, a colourless solid (1·3 g.) separated which was collected and washed with light petroleum (b. p. 40—60°; 5 c.c.). The filtrate and washings left a residual gum on evaporation *in vacuo*, which was taken up in ethanol (5 c.c.). More solid (0·3 g.) was precipitated on addition of light petroleum to the ethanol solution. *Ethyl 4-N′S-dimethylisothioureido-2-benzylglyoxaline-5-carboxylate* was obtained as colourless prisms, m. p. 124—125°, on repeated crystallisation from ethanol (Found : C, 57·6; H, 5·9; N, 16·9. $C_{16}H_{20}O_2N_4S$ requires C, 57·8; H, 6·0; N, 17·2%). It (0·5 g.) was dissolved in ethanol (10 c.c.), liquid ammonia (3 c.c.) added, and the solution heated at 150° for 12 hours in a sealed tube; no methanethiol was detected and, on acidification of the alcohol solution, *2-methylthio-8-benzyl-1-methylxanthine* (0·3 g.) was precipitated. The thiopurine was dissolved in hot pyridine and the solution diluted with hot water and cooled; it separated as small laths which softened at 290° and melted at *ca.* 340° (Found : C, 58·5; H, 4·6. $C_{14}H_{14}ON_4S$ requires C, 58·7; H, 4·9%). The purine gave the murexide reaction on oxidation with potassium chlorate in hydrochloric acid.

*8-Benzyl-1 : $N^2$-dimethylguanine* (VII; R = $CH_2Ph$).—Ethyl 4-*N*′-methylthioureido-2-benzylglyoxaline-5-carboxylate (2 g.) was dissolved in cold 5% aqueous methylamine (150 c.c.). Mercuric oxide (2 g.) was then added (the suspension began to darken even in the cold) and the solution was heated over a free flame with rapid swirling until the colour had changed from red to black. Mercuric sulphide was filtered off while the solution was still hot and washed with hot water (10 c.c.). The combined filtrate and washings were acidified with excess of glacial acetic acid with stirring; a gum was precipitated which solidified in the presence of excess of acid. The solid (1·7 g.) was readily soluble in cold 2N-sodium hydroxide or concentrated hydrochloric acid, soluble in warm dilute hydrochloric acid, and moderately soluble in hot water. The crude material (1·5 g.) was heated in ethanol (150 c.c.) under reflux, the greater part dissolving to leave 2-thio-8-phenyl-1-methylxanthine (0·15 g.). The ethanol solution was concentrated (to 50 c.c.) and cooled to 0°, *8-benzyl-1 : $N^2$-dimethylguanine* (1·2 g.) separating. The guanine separated from ethanol as small crystals which darkened at 285° and had m. p. 315° (Found : C, 62·0; H, 5·7; N, 26·1. $C_{14}H_{15}ON_5$ requires C, 62·4; H, 5·6; N, 26·0%). Oxidation with potassium chlorate

in hydrochloric acid, and evaporation to dryness, left a strong mauve stain which changed to red when moistened with sodium hydroxide solution. The guanine was dissolved in a hot saturated solution of picric acid in methanol and the solution rapidly filtered; the *picrate* separated as yellow rods, m. p. 267° (decomp.) (Found: C, 48·4; H, 3·6. $C_{20}H_{18}O_8N_8$ requires C, 48·2; H, 3·6%).

8-*Phenyl*-1 : N$^2$-*dimethylguanine* (VII; R = Ph).—Ethyl 4-*N'*-methylthioureido-2-phenylglyoxaline-5-carboxylate (2 g.) and mercuric oxide (2 g.) were rapidly stirred together in 10% aqueous methylamine (150 c.c.) at 50°. After 15 minutes the colour of the suspended solid had changed from red to black; the temperature then was raised to 80° and the mercuric sulphide filtered off while the solution was still hot. When the solution was kept at 0°, long thin yellow threads of 8-*phenyl*-1 : N$^2$-*dimethylguanine* (0·8 g.) separated. Neutralisation of the mother-liquor with glacial acetic acid yielded more of the guanine (0·4 g.). The purine was purified by precipitation with acetic acid from its solution in aqueous ammonia, being obtained as colourless threads, m. p. 360° (Found: C, 61·6; H, 5·0; N, 27·5. $C_{13}H_{13}ON_5$ requires C, 61·2; H, 5·1; N, 27·5%). It was insoluble in water and readily soluble in cold alkali or warm acid. Oxidation with potassium chlorate in concentrated hydrochloric acid, and evaporation to dryness, left a strong mauve stain which changed to red when moistened with sodium hydroxide solution.

1 : N$^2$-*Dimethylguanine* (VII; R = H).—A solution of ethyl 4-*N'*-methylthioureidoglyoxaline-5-carboxylate (1 g.) in 5% aqueous methylamine (100 c.c.) was heated with mercuric oxide (1 g.) over a free flame with rapid swirling until the suspended solid became black. Mercuric sulphide was filtered off and the filtrate acidified with acetic acid; on cooling, 1 : N$^2$-*dimethylguanine* separated. It was readily soluble in aqueous sodium hydroxide and could be obtained as needles, m. p. 345—350°, on neutralisation of the alkaline solution with acetic acid and storage at 0° (Found: C, 47·2; H, 5·3; N, 38·9. $C_7H_9ON_5$ requires C, 46·9; H, 5·0; N, 39·1%); it gave the murexide reaction with potassium chlorate in hydrochloric acid. 1 : *N*$^2$-Dimethylguanine, like guanine itself (Traube, *Ber.*, 1900, **33**, 1378), left a glazed yellow residue on evaporation of a solution in nitric acid, which changed to a red-violet stain when moistened with alkali.

8-*Methylamino*-2 : 6-*dihydroxypurine* (XII; R = OH).—4 : 5-Diamino-2 : 6-dihydroxypyrimidine was prepared from 4-amino-2 : 6-dihydroxypyrimidine by nitrosation (Blitz and Schmidt, *Annalen*, 1923, **431**, 94) and reduction of the 5-nitroso-compound so formed (Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667). 4 : 5-Diamino-2 : 6-dihydroxypyrimidine sulphate (9·6 g.) was dissolved in the minimum quantity of 5% sodium hydroxide and the solution warmed with methyl *iso*thiocyanate for 30 minutes. On acidification of the hot solution with glacial acetic acid, 4-*amino*-5-*methylthioureido*-2 : 6-*dihydroxypyrimidine* (8·6 g.) separated. The pyrimidine was sparingly soluble in water and was purified by acidification of its solution in aqueous sodium hydroxide, being obtained as needles of the *hemihydrate* (Found: C, 32·0; H, 4·6; N, 31·2. $C_6H_9O_2N_5S,\frac{1}{2}H_2O$ requires C, 32·1; H, 4·5; N, 31·2%). The thioureido-compound (8 g.) was suspended in water (100 c.c.) and rapidly stirred with mercuric oxide (6 g.) at 50—60° until the colour had changed from red to black (*ca.* 30 minutes). Mercuric sulphide was filtered off while the solution was still hot, and, on cooling, the filtrate gave a lemon-yellow solid (0·5 g.). The mercuric sulphide was extracted with hot 5% sodium hydroxide; acidification of the alkaline extracts with acetic acid yielded more (4·5 g.) of the yellow precipitate. The purine was purified by acidification of its solution in aqueous ammonia, whereby it was obtained as 8-*methylamino*-2 : 6-*dihydroxypurine hemihydrate* (Found: C, 37·8; H, 4·2. $C_6H_7O_2N_5,\frac{1}{2}H_2O$ requires C, 37·9; H, 4·2%). The purine melted indefinitely above 360° and gave a strong murexide reaction on oxidation with potassium chlorate in hydrochloric acid.

8-*Methylamino*-6-*hydroxy*-2-*methylthiopurine* (XII; R = SMe).—4 : 5-Diamino-6-hydroxy-2-methylthiopyrimidine (5 g.) was suspended in pyridine (100 c.c.) at 70°, and a solution of methyl *iso*thiocyanate (2·5 g.) in pyridine was added with stirring. The reaction was exothermic and the diaminopyrimidine rapidly dissolved giving, momentarily, a clear solution from which the pyrimidine (6 g.) separated. 4-*Amino*-5-N'-*methylthioureido*-6-*hydroxy*-2-*methylthiopyrimidine hemihydrate*, crystallised from water as hexagonal plates and rods, m. p. 225—228° (Found: C, 33·0; H, 5·1; N, 27·4. $C_7H_{11}ON_5S_2,\frac{1}{2}H_2O$ requires C, 33·1; H, 4·7; N, 27·5%). The pyrimidine (4 g.) and mercuric oxide (4 g.) were rapidly stirred in water (50 c.c.) at 60° until the suspended solid was black. The hot solution was filtered, and the filtrate evaporated *in vacuo* until solid began to separate; on cooling, 8-*methylamino*-6-*hydroxy*-2-*methylthiopurine monohydrate* separated as threads. It was purified by acidification of its solution in aqueous sodium hydroxide, separating as needles, m. p. 326° (Found: C, 36·5; H, 5·2; N, 30·2. $C_7H_9ON_5S,H_2O$ requires C, 36·7; H, 4·8; N, 30·6%); *ca.* 50% of the water of crystallisation was lost on drying at 12 mm. over boiling xylene for 12 hours (Found: C, 37·5; H, 4·9; N, 32·2. $C_7H_9ON_5S,\frac{1}{2}H_2O$ requires C, 38·2; H, 4·5; H, 31·8%). The purine gave a strong murexide colour on oxidation with potassium chlorate in hydrochloric acid.

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IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY,
S. KENSINGTON, LONDON, S.W.7.

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