227. *Studies in the Azole Series. Part XIII. A Novel Synthesis of 9-Alkylpurines and Analogous Compounds.*

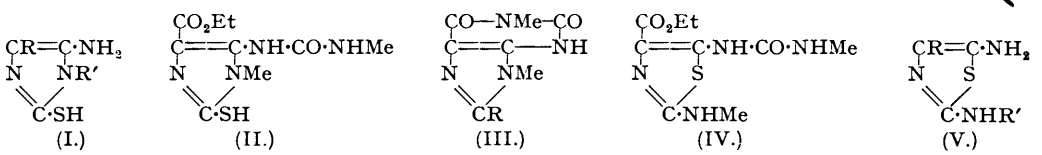
By A. H. Cook, J. D. Downer, and Sir Ian Heilbron.

A synthesis of 1 : 9-dimethyl*iso*xanthine is described starting from ethyl α-aminocyanoacetate and methyl *iso*thiocyanate. The preparation of some thiazolopyrimidines, *e.g.*, (VI) and (VIII), is also recorded.

The increasing interest shown in the polynucleosides has contributed to the evolution of several new syntheses of purines from glyoxalines (for references, see preceding paper. With the exception of that of Baxter and Spring (*J.*, 1947, 378), none of these syntheses has been employed in the building up of nucleosides owing to the fact that the appropriately orientated glyoxaline derivative is difficult of access.

Earlier work in this series (Parts VI, VIII, and IX, *J.*, 1948, 1262, 1340, 2028) described the preparation of 2 : 5-diaminothiazole derivatives (I) from α-amino-nitriles and *iso*thiocyanates and their rearrangement under the influence of mild alkalis to give 5-acylamido-2-mercaptoglyoxalines where acyl *iso*thiocyanates had been employed, and 5-amino-2-mercapto-1-alkylglyoxalines (I; R′ = alkyl) where alkyl *iso*thiocyanates had been used. In the latter case it was appreciated that the isomerisation had afforded glyoxalines suitably oriented for the synthesis of 9-alkylpurines, it being remembered that C(9) is the location of the sugar residue in nucleosides of natural origin. Pursuing this approach, the present paper describes a purine synthesis employing 5-amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (I; R = CO_2Et; R′ = Me) prepared as described in Part IX of this series.

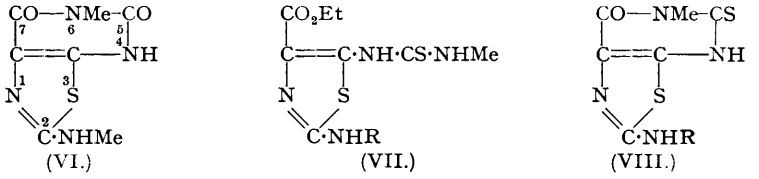
Reaction of (I; R = CO_2Et; R′ = Me) with methyl *iso*cyanate gave 5-N′-*methylureido*-2-*mercapto*-4-*carbethoxy*-1-*methylglyoxaline* (II) which readily cyclised on treatment with dilute aqueous sodium hydroxide to the known 1 : 9-dimethyl-8-thiouric acid (III; R = SH) agreeing in both physical and chemical properties with those described for this purine in the literature (Biltz and Strufe, *Annalen*, 1921, **423**, 216) : its m. p., crystalline form and solubility were in complete agreement, and furthermore, on treatment with sodium nitrite it gave 1 : 9-dimethyl-*iso*xanthine (III; R = H), also identical with that prepared by Biltz and Strufe (*loc. cit.*). Finally, analysis and m. p. of the aurichloride of the synthetic compound (III; R = H) were compatible with the structure assigned.



(I.) (II.) (III.) (IV.) (V.)

The identification of the above product with 1 : 9-dimethyl-8-thiouric acid further confirms the structure of the glyoxalines prepared by rearrangement of 5-amino-2-alkylaminothiazoles (see Part IX).

This facile formation of the pyrimidine ring with dilute aqueous alkali was first employed by Cook, Heilbron, Mahadevan, and Macdonald (preceding paper) for the formation of thiazolopyrimidines. A number of related compounds have now been made from 2 : 5-diaminothiazole



(VI.) (VII.) (VIII.)

derivatives by employing this facile cyclisation. Attempts to rearrange the thiazole ring at this stage to the respective purine proved abortive. Thus, on reaction of the thiazole (V; R = CO_2Et, R′ = Me) (see Part IX) with methyl *iso*cyanate, 2-*methylamino*-5-N′-*methylureido*-4-*carbethoxythiazole* (IV) was obtained, which readily cyclised in dilute aqueous alkali to 2-*methylamino*-5 : 7-*diketo*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI), isomeric with 1 : 9-dimethylthiouric acid. Long heating, under reflux, of (VI) with 10% aqueous sodium

hydroxide gave two products, *viz.*, a *compound*, $C_6H_9O_2N_3S$, m. p. 226°, which appeared to possess pseudo-acidic properties and gave colour reactions for a thiol group, and a *compound*, m. p. 371°, isomeric with both (III; R = SH) and (VI). The latter compound was distinguished from the isomeride (VI) in that it dissolved in dilute aqueous hydrochloric acid; as it also gave a positive murexide test it may be 1 : 7-dimethyl-8-thiouric acid.

The *thiazolopyrimidines* (VIII; R = Me and CO_2Et) were made from the thiazoles (V; R = CO_2Et; R′ = Me and CO_2Et, respectively) by formation of the *methylthioureido*-derivatives (VII; R = Me and CO_2Et respectively) using methyl *iso*thiocyanate followed by cyclisation in alkali. It is of interest that the thioureido-compounds slowly cyclised when heated under reflux in pyridine, whereas (IV) did not do so under these conditions. The ease of formation of these thiazolopyrimidines is shown by the direct preparation of (VIII; R = Me) from ethyl α-aminocyanoacetate in one operation within a few minutes.

Experimental.

1 : 9-*Dimethyl*iso*xanthine*.—5-Amino-2-mercapto-4-carbethoxy-1-methylglyoxaline (2·2 g.) (Cook, Downer, and Heilbron, *J.*, 1948, 1262), in pyridine (5 c.c.), and methyl *iso*cyanate (2 c.c.) were heated under reflux for 3 hours, methyl *iso*cyanate (1 c.c. portions) being added after the first and the second hour. The cold, clear, dark red solution was diluted with ethanol (5 c.c.) and ether (500 c.c.), and the crude precipitate purified from ethanol–ether to give light fawn needles (1·75 g.). Crystallisation from ethanol gave colourless, elongated, irregular prisms of *5-methylureido-2-mercapto-4-carbethoxy-1-methylglyoxaline* (II), m. p. 242° (decomp.) (Found: C, 42·1; H, 5·4; N, 22·0; S, 12·1. $C_9H_{14}O_3N_4S$ requires C, 41·8; H, 5·5; N, 21·7; S, 12·4%). It did not give a positive murexide test.

The preceding glyoxaline (1·4 g.), in 7·5% aqueous sodium hydroxide (15 c.c.), was boiled for 2 minutes, and the solution acidified with acetic acid. The crude product (0·7 g.), m. p. 371° (decomp.), was filtered off from the cold mixture and purified by repeated acid precipitation of its solution in dilute aqueous ammonia (100 vols.), to give almost colourless prismatic clusters of 1 : 9-dimethyl-8-thiouric acid (III; R = SH), m. p. 371° (decomp.) [Biltz and Strufe, *loc. cit.*, quote m. p. 370° (decomp.)] (Found: C, 39·3; H, 3·6; N, 26·2; S, 15·2. Calc. for $C_7H_8O_2N_4S$: C, 39·6; H, 3·8; N, 26·4; S, 15·1%). It gave a positive murexide test.

The above 1 : 9-dimethyl-8-thiouric acid (0·5 g.) was suspended in 6N-hydrochloric acid (2 c.c.), and powdered sodium nitrite (1·3 g.) added in small portions with stirring during 3 hours, according to the method described by Biltz and Strufe (*loc. cit.*). After this had stood overnight, water (5 c.c.) and concentrated hydrochloric acid (1·5 c.c.) were added, the whole warmed to effect solution, and the solution filtered. The filtrate was acidified with acetic acid, cooled, and filtered. The crude product (0·4 g.) was purified by repeated acid precipitation from its solution in dilute aqueous ammonia to give creamy needles of 1 : 9-dimethyl*iso*xanthine (0·3 g.), m. p. 350° (decomp.) [Biltz and Strufe, *loc. cit.*, quote m. p. 350° (decomp.)] (Found: N, 31·3. Calc. for $C_7H_8O_2N_4$: N, 31·1%). It gave a positive murexide test.

1 : 9-Dimethyl*iso*xanthine (0·1 g.), from the previous preparation, dissolved in concentrated hydrochloric acid (3 c.c.), was added to a solution of auric chloride (0·25 g., 0·12 mol. Au) in concentrated hydrochloric acid (10 c.c.), and the golden-yellow needles of the aurichloride of 1 : 9-dimethyl*iso*xanthine (0·2 g.), m. p. 254° (decomp.), were collected [Biltz and Strufe, *loc. cit.*, give m. p. 255° (decomp.)] (Found: Au, 37·9. Calc. for $C_7H_8O_2N_4,HAuCl_4$: Au, 37·9%).

2-*Methylamino*-5 : 7-*diketo*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VI).—5-Amino-2-methylamino-4-carbethoxythiazole (4 g.) (Cook, Downer, and Heilbron, *loc. cit.*), in a mixture of pyridine (8 c.c.) and methyl *iso*cyanate (3 c.c.), was heated under reflux for 1 hour. The cold solution was diluted with ethanol (10 c.c.) and ether (300 c.c.) to give a cream-coloured solid (4·5 g.), m. p. 209° (decomp.). Crystallisation of the crude product from ethyl acetate (100 vols.) gave almost colourless prisms of *2-methylamino-5-N′-methylureido-4-carbethoxythiazole* (IV), m. p. 214° (decomp.) (Found: N, 21·5. $C_9H_{14}O_2N_4S$ requires N, 21·7%). It did not give a positive murexide test.

The preceding methylureidothiazole (1·3 g.) was boiled for 5 minutes in 5% aqueous sodium hydroxide (20 c.c.) and acidified while hot with acetic acid, giving a colourless solid (1 g.), m. p. 368—370°, which was purified by repeated precipitation from its solution in aqueous ammonia with acid, giving colourless, fine, isolated, hairy needles of the *thiazolopyrimidine*, m. p. 370—372° (decomp.) (Found: C, 39·7; H, 4·1. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8%). This gave a positive murexide test, and was insoluble in dilute aqueous hydrochloric acid; it did not give 1 : 9-dimethyl*iso*xanthine with nitrous acid, nor did it yield 1 : 9-dimethyl-8-iodo*iso*xanthine on treatment with iodine (Biltz and Beck, *loc. cit.*).

On heating the above thiazolopyrimidine (4 g.) for 1 hour under reflux with 10% aqueous sodium hydroxide (120 c.c.), much ammonia and methylamine were evolved. The product was acidified with concentrated hydrochloric acid and cooled to give colourless needles of a *compound* (A) (2·2 g.), which became red and yellow at *ca.* 210° and melted at 226° (decomp.) (Found: C, 38·7; H, 4·9; S, 16·4. $C_6H_9O_2N_3S$ requires C, 38·5; H, 4·8; S, 17·0%). It could be crystallised from hot water and was soluble in dilute aqueous sodium hydroxide with red coloration on standing or heating. The filtrate from (*A*) was made alkaline with ammonia, filtered from impurities, acidified while hot with acetic acid, and filtered while still lukewarm to give colourless prisms (1 g.) of another *compound* (1 : 7-dimethyl-8-thiouric acid ?), m. p. 371° (decomp.) (Found: C, 39·9; H, 3·9; N, 26·2; S, 15·3. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8; N, 26·4; S, 15·1%). It gave a positive murexide test, was soluble in dilute aqueous hydrochloric acid (cf. VI), but failed to give 8-iodo-1 : 9-dimethyl*iso*xanthine on treatment with iodine.

2-*Methylamino*-7-*keto*-5-*thiono*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VIII; R = Me).—A mixture of 5-amino-2-methylamino-4-carbethoxythiazole (2 g.) and methyl *iso*thiocyanate

(0·7 c.c.), in pyridine (4 c.c.), was heated under reflux for 45 minutes, cooled, and filtered; the residual brownish solid (0·7 g.), m. p. 192° (decomp.) (a further 0·8 g. was obtained on keeping the filtrate overnight), on fractional crystallisation from pyridine (8 c.c.), gave colourless micro-needles (*B*) (0·2 g.), m. p. >360°, which were purified by extraction of the impurites with boiling alcohol (Soxhlet), and repeated acid precipitation from solution in dilute aqueous ammonia to give long, thin, hairy needles of the *thiazolopyrimidine*, decomposing above 325° but not melting below 360° (Found: C, 36·3; H, 4·0; N, 24·1; S, 28·5. $C_7H_8ON_4S_2$ requires C, 36·8; H, 3·6; N, 24·5; S, 28·1%). It gave a positive murexide test, and was insoluble in water and dilute acids, but soluble in aqueous alkalis. The pyridine filtrate from (*B*) was diluted with much water, and the resulting yellow solid (0·4 g.), m. p. 195°, crystallised from ethanol (15 c.c.) (charcoal) to give pale yellow, irregular, prismatic, silky needles of 2-*methylamino*-5-N′-*methylthioureido*-4-*carbethoxythiazole* (VII; R = Me), m. p. 199° (decomp.) (Found: N, 20·7. $C_9H_{14}O_2N_4S$ requires N, 20·4%). It did not give a positive murexide test.

The above methylthioureido-thiazole (2·6 g.), on boiling for 4 minutes with 7·5% aqueous sodium hydroxide (45 c.c.), dilution with water (300 c.c.), and acidification at the boil with acetic acid, gave colourless needles of the derived thiazolopyrimidine.

The last-named thiazolopyrimidine was also obtained directly from ethyl α-aminocyanoacetate as follows: This ester (2·5 g.), methyl *iso*thiocyanate (4 c.c.), and pyridine (5 c.c.) in ether (22 c.c.) were heated on the steam-bath for 5 minutes, most of the ether then having evaporated. 7·5% Aqueous sodium hydroxide (30 c.c.) was added, the mixture brought to the boil, acidified whilst hot with acetic acid, and the thiazolopyrimidine filtered off and washed (1 g.), m. p. >360°.

2-*Carbethoxyamino*-7-*keto*-5-*thiono*-6-*methyl*-4 : 5 : 6 : 7-*tetrahydrothiazolo*[5 : 4-d]*pyrimidine* (VIII; R = CO_2Et).—5-Amino-2-carbethoxyamino-4-carbethoxythiazole (4 g.) (Capp, Cook, Downer, and Heilbron, *J.*, 1948, 2028) and methyl *iso*thiocyanate (1·2 c.c.) in pyridine (7 c.c.) were heated under reflux for 2 hours. The yellow solid (1·9 g.), sintering at *ca.* 190°, which separated on standing, was rubbed with ethanol (10 c.c.), and collected. Boiling the crude solid with methanol (30 c.c.) and filtering left the crude thiazolopyrimidine (0·05 g.), m. p. 290—300° (see below), which gave a positive murexide test. The methanol filtrate on concentration and dilution with ether gave a crude product (1·2 g.), which crystallised from ethanol–water (1 : 1; 50 c.c.) in pale yellow micro-crystals of 5-N′-*methylthioureido*-2-*carbethoxyamino*-4-*carbethoxythiazole* (VII; R = CO_2Et), m. p. 199° (decomp.) (Found: C, 39·4; H, 4·9; N, 16·6; S, 18·8. $C_{11}H_{16}O_4N_4S$ requires C, 39·7; H, 4·9; N, 16·9; S, 19·3%). It did not give a positive murexide test.

The last-named methylthioureidothiazole (0·7 g.), when boiled for 5 minutes with 8% aqueous sodium hydroxide (30 c.c.), followed by acidification with acetic acid, cooling and filtration, gave a crude solid (0·65 g.), m. p. >360° (decomp.), which was purified by repeated acid precipitation of its solution in dilute aqueous ammonia to give pale cream micro-needles of the *thiazolopyrimidine* (Found: N, 19·4. $C_9H_{10}O_3N_4S_2$ requires N, 19·6%). It gave a positive murexide test.

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

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