574. *Glyoxalinopyrimidines. Part II.*[1]

By J. Clark and G. R. Ramage.

Methyl and ethyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate (I; X = Cl, R = Me or Et) were condensed with 2-chloroethylamine, and the products (II; X = NO_2, R = Me or Et) were reduced and cyclised. It was established by unambiguous synthesis that the cyclisations yielded tetrahydroglyoxalinopyrimidines (III; X = Cl, Y = CO_2Me or CO_2Et) and not the isomeric tetrahydropteridines (IV).

It was shown by Ramage and Trappe [1] that 4-2′-chloroethylamino-5-nitropyrimidines, *e.g.*, (V; X = H), could be readily cyclised after the introduction into the 2-position of a group capable of initiating tautomerism (*e.g.*, OH, NH_2) or after reduction of the 5-nitro-group. Some 4-2′-chloroethylamino-5-nitropyrimidines with potentially tautomeric groups in both the 2- and the 6-position were also easily cyclised.[2] However, when certain 4-(*N*-benzyl-*N*-2-chloroethylamino)-5-nitro-compounds, *e.g.*, (V; X = CH_2Ph) were reduced, the products were 8-benzyltetrahydropteridines.[3]

The cyclisation of some 5-amino-4-2′-chloroethylaminopyrimidines with electron-demanding groups in both the 2- and the 4-position has now been studied. The compounds (II; X = NH_2, R = Me or Et) had a chlorine atom in the 2-position and a methoxycarbonyl or ethoxycarbonyl group in the 6-position. Both series were prepared because the methyl esters proved to have inconveniently low solubilities and indecisive melting points at certain stages.

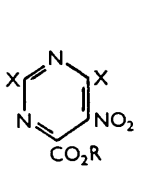
5-Nitrouracil-4-carboxylic acid (I; X = OH, R = H) has been made by a number of authors [4] who simultaneously oxidised and nitrated 4-methyluracil but the reactions were violent, even on a small scale, and gave variable yields. The same compound has also been prepared by nitration of uracil-4-carboxylic acid with fuming nitric acid.[5] When the 4-methyluracil was nitrated and the resulting 4-methyl-5-nitrouracil oxidised as a separate stage the reactions proceeded smoothly and in good yield on the largest scale attempted.

The acid was esterified and converted into the dichloro-compounds (I; X = Cl, R = Me or Et) by standard methods. Selective replacement of one of the chlorine atoms in each of these compounds by a 2-chloroethylamino-group proved to be possible and in each case an excellent yield of a compound, assumed by analogy with other 2 : 4-dichloro-5-nitropyrimidines [2,6] to be 4-substituted, was obtained. The orientation of these substances was later confirmed by demonstrating an *o*-diamine arrangement in their reduction products (II; X = NH_2, R = Me or Et) which were converted into purines

[1] Part I, Ramage and Trappe, *J.*, 1952, 4410.
[2] Martin and Mathieu, *Tetrahedron*, 1957, **1**, 75.
[3] Brook and Ramage, *J.*, 1955, 896; *J.*, 1957, 1.
[4] Behrend and Roosen, *Annalen*, 1889, **251**, 238; Behrend, *ibid.*, 1885, **229**, 32; Köhler, *ibid.*, 1886, **236**, 34.
[5] Biltz and Kramer, *ibid.*, 1924, **436**, 165.
[6] Boon, Jones, and Ramage, *J.*, 1951, 96; Bitterli and Erlenmeyer, *Helv. Chim. Acta*, 1951, **34**, 835; Polonovski and Jérome, *Compt. rend.*, 1950, **230**, 392; Rose, *J.*, 1954, 4116; Brown, *J. Appl. Chem.*, 1957, **7**, 109.

(VI; R = H, Me, or Et). The 5-amino-compounds themselves were fairly easily cyclised by heat in solution but it was possible to carry out the purine preparations using *NN*-dimethylformamide and phosphoryl chloride under very mild conditions, without interference from direct cyclisation.

Only moderate yields of amines were obtained by reducing the 5-nitro-compounds (II; X = NO_2, R = Me or Et) with Raney nickel and hydrogen. With these and certain other compounds in which an *o*-amino-ester arrangement was formed on reduction, the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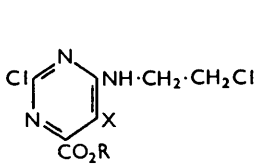
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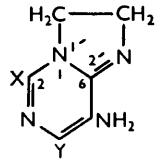
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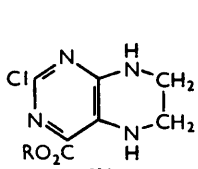
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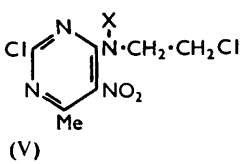
products appeared to interact with the catalyst. Better results were obtained by using powdered zinc and a little acetic or formic acid in methanol.

Methyl and ethyl 5-amino-4-2′-chloroethylaminopyrimidine-6-carboxylates (II; X = NH_2, R = Me or Et) were more stable to heat than similar compounds which did not contain two electron-demanding groups and much unchanged material was isolated from attempted cyclisations in boiling methanol as described for the preparation of a compound lacking the ester group (III; X = Cl, Y = H).[1] However, the compounds cyclised readily in boiling water and more slowly in boiling ethanol, yielding products which were shown to be tetrahydroglyoxalinopyrimidines (III; X = Cl, Y = CO_2Me or CO_2Et) and not the isomeric tetrahydropteridines.

The methyl and ethyl esters were shown to have cyclised in the same way by hydrolysing the cyclised products to the same carboxylic acid (III; X = Cl, Y = CO_2H) under conditions which did not affect the 2-chlorine atom.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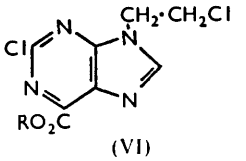
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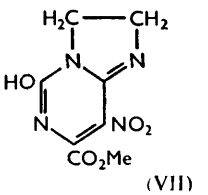
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The actual mode of cyclisation was then established by simultaneously hydrolysing the chlorine atom and the ester group of the compound (III; X = Cl, Y = CO_2Me) to obtain the hydroxy-carboxylic acid (III; X = OH, Y = CO_2H) which was then synthesised unambiguously. The alternative route involved hydrolysis and cyclisation of the pyrimidine (II; X = NO_2, R = Me). The product (VII), which could not have the pteridine ring system, was reduced by sodium dithionite to the corresponding amino-compound which yielded the required acid (III; X = OH, Y = CO_2H) on hydrolysis.

Experimental

M. p.s marked * were determined in a preheated bath, with rapid heating.

5-Nitrouracil-4-carboxylic Acid.—A mixture of 4-methyl-5-nitrouracil (40 g.) and nitric acid (100 c.c.; *d* 1·5) was heated for 4 hr. on the water-bath in a flask fitted with a short (50 cm.) air-condenser. The cooled mixture was filtered on sintered glass, and white solid which decomposed at 230° was washed successively with glacial acetic acid and ether. The yield (34—38 g.) was substantially reduced when a more efficient condenser or a less concentrated nitric acid was used.

Methyl 5-Nitrouracil-4-carboxylate.—5-Nitrouracil-4-carboxylic acid (50 g.), methanol (180 c.c.), and concentrated sulphuric acid (25 c.c.) were heated together, under reflux, for 8 hr. Next day the ester (44·5 g.) was filtered off, washed with methanol and, after drying, was suitable for use in the next stage. Crystallisation from water, followed by drying in air, gave a *monohydrate*, m. p. 199—200° (decomp.) (Found: C, 31·2; H, 3·0. $C_6H_5O_6N_3,H_2O$ requires C, 30·9; H, 3·0%). Anhydrous *methyl 5-nitrouracil-4-carboxylate* was obtained after drying at 65° *in vacuo* (Found: C, 33·7; H, 2·4; N, 19·7. $C_6H_5O_6N_3$ requires C, 33·5; H, 2·3; N, 19·5%).

Ethyl 5-nitrouracil-4-carboxylate (49 g.), m. p. 251° (decomp.), was similarly prepared from 5-nitrouracil-4-carboxylic acid (50 g.), ethanol (500 c.c.), and concentrated sulphuric acid (75 c.c.). Köhler [4] reports m. p. 250° (decomp.). The ethyl ester was much less soluble in ethanol than was the methyl ester in methanol.

Methyl 2 : 4-Dichloro-5-nitropyrimidine-6-carboxylate (I; X = Cl, R = Me).—A mixture of methyl 5-nitrouracil-4-carboxylate (15 g.), phosphoryl chloride (60 c.c.), and diethylaniline (20 c.c.) was set aside for 30 min. and then refluxed for 20 min. Excess of phosphoryl chloride was removed under reduced pressure and the cooled residue was poured on ice and extracted with ether. The ethereal solution was washed successively with N-hydrochloric acid, N-sodium hydrogen carbonate, and water, and then dried. After removal of the ether, the residue was distilled (13·8 g.; b. p. 140°/0·5 mm.); it rapidly solidified. *Methyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate* crystallised from *cyclo*hexane as prisms, m. p. 90—91° (Found: C, 29·0; H, 1·3; N, 16·5. $C_6H_3O_4N_3Cl_2$ requires C, 28·6; H, 1·2; N, 16·7%).

Ethyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate was similarly prepared from the corresponding ethyl ester but the period of reflux was advantageously extended to 1 hr. The product (15·2 g.; b. p. 128°/0·7 mm.) crystallised from *cyclo*hexane–light petroleum (b. p. 60—80°), yielding *ethyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate* as prisms, m. p. 37—38° (Found: C, 32·1; H, 1·8; Cl, 26·4. $C_7H_5O_4N_3Cl_2$ requires C, 31·6; H, 1·9; Cl, 26·7%). This compound was much more soluble in ether than was the corresponding methyl ester.

Methyl 2-Chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (II; X = NO_2, R = Me).—2-Chloroethylamine hydrochloride (6 g.) was added, with shaking, during 20 min. to a mixture of methyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate (12·6 g.) in chloroform (150 c.c.) and sodium hydrogen carbonate (12 g.) in water (40 c.c.). Shaking was continued for a further 20 min. after which the chloroform layer was separated, washed with water, and dried (Na_2SO_4). The chloroform was removed and crystallisation of the residue from methanol yielded *methyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate* (12·1 g.) as pale yellow prisms, m. p. 108° (Found: C, 32·7; H, 2·8. $C_8H_8O_4N_4Cl_2$ requires C, 32·6; H, 2·7%).

Ethyl 2 : 4-dichloro-5-nitropyrimidine-6-carboxylate (13·3 g.) was similarly condensed with 2-chloroethylamine hydrochloride (6 g.) and gave *ethyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate* (13·2 g.) which crystallised as pale yellow plates or needles, m. p. 92°, from methanol or *cyclo*hexane respectively (Found: C, 35·1; H, 3·3; N, 17·8. $C_9H_{10}O_4N_4Cl_2$ requires C, 35·0; H, 3·3; N, 18·1%).

Methyl 5-Amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate (II; X = NH_2, R = Me).—(*a*) Methyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (1 g.) in methanol (200 c.c.) was shaken with Raney nickel (3 c.c. of settled suspension) and hydrogen until the uptake reached the theoretical value for reduction of the nitro-group (3 hr.). The catalyst was removed and the solution was evaporated below 45° under reduced pressure to 10 c.c. *Methyl 5-amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate* (0·5 g., 55%) separated and crystallised from methanol as prisms which slowly decomposed above 140° (Found: C, 36·6; H, 3·9. $C_8H_{10}O_2N_4Cl_2$ requires C, 36·2; H, 3·8%).

Solutions of the amine exhibited a slight blue fluorescence in daylight and a strong blue fluorescence in ultraviolet light.

(*b*) Methyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (5 g.) in methanol (300 c.c.) was stirred vigorously and 90% formic acid (10 c.c.) was added, followed by powdered zinc (15 g.) in one addition. Stirring was continued for 5 min. and the warm mixture was then immediately filtered. The residue was washed with hot methanol (50 c.c.), and the pale yellow combined filtrates were evaporated as in (*a*) to about 15 c.c. To the partially crystallised mixture, cold water (150 c.c.) was added and the amine (3·9 g., 87%) was filtered off as well-formed white prisms identical with the product from (*a*). Further purification was unnecessary.

Methyl 5-Amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (III; X = Cl, Y = CO_2Me).—The total moist filtercake of crude material from the preceding experiment (*b*) was heated with water (60 c.c.), under reflux, for ¾ hr. The solution was cooled, made alkaline with dilute ammonia, and the *methyl 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate* (3·2 g.) which separated was filtered off. A sample crystallised from 2-ethoxyethanol as pale yellow prisms, m. p. 229° (decomp.) * (Found: C, 41·9; H, 4·0; Cl, 15·1. $C_8H_9O_2N_4Cl$ requires C, 42·0; H, 4·0; Cl, 15·5%). In solution the base exhibited a weak blue fluorescence in ultraviolet light.

The *picrate* crystallised from 2-ethoxyethanol as golden-yellow plates which slowly decomposed >230° [m. p. 246° (decomp.) *] (Found: C, 37·0; H, 2·8; Cl, 7·5. $C_8H_9O_2N_4Cl,C_6H_3O_7N_3$ requires C, 36·7; H, 2·6; Cl, 7·7%).

The stability was investigated by heating the amine (0·5 g.) in methanol (15 c.c.) under reflux for 2½ hr., the solvent being then evaporated under reduced pressure. The residue was treated with hot water (10 c.c.) to extract any cyclised hydrochloride and the water-insoluble part of the residue (0·17 g., 34%), which proved to be unchanged amine, was crystallised from methanol. The cyclised base (0·25 g., 58%), obtained by adding dilute ammonia to the solution of its hydrochloride, was identical with that prepared by cyclisation in water (above).

Ethyl 5-Amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate (II; X = NH_2, R = Et).—(*a*) Ethyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (1 g.) in ethanol (70 c.c.) was reduced with Raney nickel (1·5 c.c. of settled suspension) and hydrogen as described for the corresponding methyl ester (see above). *Ethyl 5-amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate* (0·55 g.) was obtained as prisms which partly melted, with decomposition, at 141° (Found: C, 38·9; H, 4·3; Cl, 25·5. $C_9H_{12}O_2N_4Cl_2$ requires C, 38·7; H, 4·3; Cl, 25·4%).

Solution of the substance exhibited a slight blue fluorescence in daylight and a strong blue fluorescence in ultraviolet light.

An acetyl compound was prepared by treatment with acetic anhydride at 80° for 1 hr. Excess of reagent was removed and the residue, treated with dilute ammonia, crystallised from benzene–*cyclo*hexane as needles, and dried in *vacuo* at 20°. In benzene solution, the *monoacetyl derivative*, m. p. 113—114°, exhibited an intense blue fluorescence in ultraviolet light (Found: C, 39·9, 39·7; H, 4·6, 4·6. $C_{11}H_{14}O_3N_4Cl_2,\frac{1}{2}H_2O$ requires C, 40·0; H, 4·6%).

(*b*) A solution of ethyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (2 g.) in methanol (75 c.c.) was reduced with glacial acetic acid (7·5 c.c.) and powdered zinc (5 g.) as described for the reduction, by zinc and formic acid, of the corresponding methyl ester. The amine (1·45 g., 80%) was obtained as colourless prisms, identical with those from the reduction (*a*). Pure starting material was necessary for the reduction by zinc and acetic acid and if 90% formic acid was substituted a lower yield of an impure, yellow product was obtained.

Ethyl 5-Amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (III; X = Cl, Y = CO_2Et).—(*a*) Ethyl 5-amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate (1 g.) was heated with water (10 c.c.), under reflux, for 45 min. The resulting solution was cooled, treated with excess of dilute ammonia, and kept for 3 hr., then *ethyl 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate* (0·9 g.) was filtered off. It crystallised from aqueous 2-ethoxyethanol as very pale yellow prisms which, after drying *in vacuo* for 1 hr. at 60°, were still hydrated and melted at 153—154° (Found: C, 43·2, 43·4; H, 4·8, 5·0. $C_9H_{11}O_2N_4Cl,\frac{1}{2}H_2O$ requires C, 42·9; H, 4·8%). Solutions of the base showed a weak blue fluorescence in ultraviolet light.

Other hydrates were obtained by crystallisation from water: an aqueous solution kept at 20° deposited almost colourless prismatic needles which, after air drying for 24 hr., melted when rapidly heated to 110° (Found: C, 38·9; H, 5·5. $C_9H_{11}O_2N_4Cl,2H_2O$ requires C, 38·8; H, 5·4%). A more concentrated aqueous solution, kept at 55°, deposited chunky prisms which melted when rapidly heated to 140° (Found: C, 42·2; H, 5·0. $C_9H_{11}O_2N_4Cl,H_2O$ requires C, 41·5; H, 5·0%). When slowly heated both hydrates melted at 153—154°.

The anhydrous base, m. p. 153—154°, was obtained by drying a hydrate *in vacuo* at 130° for 3 hr. (Found: C, 44·5; H, 4·3. $C_9H_{11}O_2N_4Cl$ requires C, 44·5; H, 4·6%).

The *picrate* crystallised from 2-ethoxyethanol as bright yellow needles, m. p. 242° (decomp.) (Found: C, 38·4; H, 3·1. $C_9H_{11}O_2N_4Cl,C_6H_3O_7N_3$ requires C, 38·2; H, 3·0%).

(*b*) Ethyl 5-amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate (0·25 g.) was heated, under reflux, with ethanol (10 c.c.) for 2½ hr. The hydrochloride (0·25 g.) was filtered

off from the cooled solution, dissolved in warm water, and treated with excess of dilute ammonia. A base (0·18 g.), m. p. 154°, identical with that obtained by cyclisation in water, gradually crystallised.

5-Amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylic Acid (III; X = Cl, Y = CO_2H).—Hot 2N-sodium hydroxide (15 c.c.) was well stirred during the addition of a hot solution of methyl (or ethyl) 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (1 g.) in dioxan (30 c.c.) and for a further 3 min. The mixture was cooled and the precipitated *sodium 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate* was filtered off. A sample crystallised from water as needles which gradually decomposed above 250° and was analysed after drying at 100°/0·5 mm. for 2 hr. (Found: C, 28·8; H, 4·6; N, 19·3. $C_7H_6O_2N_4ClNa,3H_2O$ requires C, 28·9; H, 4·2; N, 19·3%).

The free *acid* (0·77 g.), obtained by treating a hot aqueous solution of the sodium salt with excess of acetic acid, was very sparingly soluble in ethanol, water, 2-ethoxyethanol, dimethylformamide, or nitrobenzene. A pure sample was prepared by filtering a hot dilute solution of the pure sodium salt into hot dilute hydrochloric acid. The product slowly separated as very pale yellow plates which did not melt below 250°. The crystals were boiled with water, filtered off, washed with ethanol, and dried at 100°/0·1 mm. for 2 hr. (Found: C, 39·0; H, 3·5. $C_7H_7O_2N_4Cl$ requires C, 39·2; H, 3·3%).

The *picrate*, which was prepared by treating a warm aqueous solution of the sodium salt with an excess of picric acid in ethanol, crystallised from water as yellow needles, m. p. 244° (decomp.) * (Found: C, 36·8; H, 2·8; Cl, 10·5. $C_7H_7O_2N_4Cl,\frac{1}{2}C_6H_3O_7N_3$ requires C, 36·5; H, 2·6; Cl, 10·8%).

5-Amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxyglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylic Acid (III; X = OH, Y = CO_2H).—Methyl (or ethyl) 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (1 g.) was heated under reflux with 5N-hydrochloric acid (10 c.c.) for ½ hr. and the hydrochloride which separated on cooling was dissolved in boiling water (50 c.c.) and treated with a solution of sodium acetate trihydrate (3 g.) in water. After 24 hr., the product (0·5 g.) was filtered off and crystallised from water (charcoal). After several recrystallisations *5-amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxyglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylic acid* was obtained as yellow prisms which gradually decomposed above 240°; m. p. 268° (decomp.) * (Found: C, 43·1; H, 4·2; N, 28·8. $C_7H_8O_3N_4$ requires C, 42·9; H, 4·1; N, 28·6%).

A *picrate* was obtained as orange needles, m. p. 215° (decomp.) (Found: C, 38·9; H, 3·2; N, 24·9. $C_7H_8O_3N_4,\frac{1}{2}C_6H_3O_7N_3$ requires C, 38·7; H, 3·1; N, 24·8%). The *hydrochloride* crystallised from dilute hydrochloric acid as prismatic needles, decomp. >250° (Found: C, 34·0; H, 4·7; N, 21·9. $C_7H_8O_3N_4,HCl,H_2O$ requires C, 33·6; H, 4·4; N, 22·4%). The *mercury* salt of the *mercurichloride*, prepared by mixing hot, filtered aqueous solutions of the base and mercuric chloride, was very insoluble. It was prepared for analysis by extracting impurities with boiling *NN*-dimethylformamide and washing the residue with ethanol. The yellow needles, m. p. 236° (decomp.), were dried at 130°/1 mm. (Found: C, 19·8; H, 1·9; N, 12·6. $(C_7H_7O_3N_4)_2Hg,HgCl_2$ requires C, 19·5; H, 1·6; N, 13·0%).

(*b*) The same hydroxy-carboxylic acid (0·16 g.) was obtained when methyl 5-amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxyglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (0·2 g.) (see below) was boiled with 2N-sodium hydroxide (5 c.c.) for 2 min. and the mixture was treated with excess of acetic acid. The derivatives of this acid were identical with those previously obtained.

Methyl 1 : 6 : 4′ : 5′-Tetrahydro-2-hydroxy-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (VII).—Methyl 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine-6-carboxylate (2·5 g.) was heated, under reflux, with glacial acetic acid (7·5 c.c.), water (7·5 c.c.) and sodium acetate trihydrate (2·5 g.) for 1½ hr. *Methyl 1 : 6 : 4′ : 5′-tetrahydro-2-hydroxy-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate* (1·7 g., 84%) separated from the cooled reaction mixture and crystallised from glacial acetic acid as prisms, m. p. 215° (decomp.) (Found: C, 40·3; H, 3·5. $C_8H_8O_5N_4$ requires C, 40·0; H, 3·4%).

Methyl 5-Amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxyglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (III; X = OH, Y = CO_2Me).—Methyl 1 : 6 : 4′ : 5′-tetrahydro-2-hydroxy-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate (1 g.) was stirred with N-sodium hydrogen carbonate (20 c.c.) during addition, in 6 min., of sodium dithionite (6 g.) and then for a further

½ hr. The mixture was set aside for an hour, then filtered, and the *methyl 5-amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxyglyoxalino(1′ : 2′-1 : 6)pyrimidine-4-carboxylate* (0·55 g.) was crystallised from water. It recrystallised from 2-ethoxyethanol as very pale yellow plates, m. p. 238° (decomp.)* (Found: C, 46·1; H, 4·7. $C_8H_{10}O_3N_4$ requires C, 45·7; H, 4·8%). The *picrate* crystallised from aqueous 2-ethoxyethanol as yellow prisms, m. p. 252—253° (decomp.)* (Found: C, 38·3; H, 3·1. $C_8H_{10}O_3N_4,C_6H_3O_7N_3$ requires C, 38·3; H, 3·0%).

Methyl and Ethyl 2-Chloro-9-2′-chloroethylpurine-6-carboxylate (VI; R = Me and Et).—A solution of methyl or ethyl 5-amino-2-chloro-4-2′-chloroethylaminopyrimidine-6-carboxylate (II; X = NH_2, R = Me or Et) (0·5 g.) in *NN*-dimethylformamide (10 c.c.) and phosphoryl chloride (1 c.c.) was kept for an hour before the volatile constituents were evaporated under reduced pressure on a boiling-water bath. The residue was treated with cold water (20 c.c.), and *methyl* or *ethyl 2-chloro-9-2′-chloroethylpurine-6-carboxylate* was filtered off and crystallised from ethanol as lustrous plates. The former (0·39 g.) had m. p. 189—190° (Found: C, 39·5; H, 3·0; N, 21·0. $C_9H_8O_2N_4Cl_2$ requires C, 39·3; H, 2·9; N, 20·4%), and the latter (0·28 g.), m. p. 128—129° (Found: C, 41·6; H, 3·6; N, 19·3. $C_{10}H_{10}O_2N_4Cl_2$ requires C, 41·5; H, 3·5; N, 19·4%).

The methyl ester purine was also prepared by carrying out the treatment with phosphoryl chloride and dimethylformamide on the water-bath for an hour. When these conditions were used with the ethyl ester, the product was contaminated with an impurity which raised the m. p. After 8 hr. on the water-bath enough of the impurity was produced to enable it to be isolated by repeated crystallisation from ethanol. It crystallised as plates, m. p. 180—183°, not depressed on admixture with methyl 2-chloro-9-2′-chloroethylpurine-6-carboxylate. The methyl ester raised the melting range of a pure sample of the ethyl ester, as did the impurity which was isolated. Conversion of an ethyl into a methyl ester had occurred under the more severe conditions.

2-Chloro-9-2′-chloroethylpurine-6-carboxylic Acid.—Methyl 2-chloro-9-2′-chloroethylpurine-6-carboxylate (0·4 g.) was heated, under reflux, with 2N-hydrochloric acid (8 c.c.) during 15 min. and the cooled mixture was filtered. The residue, dissolved in 2N-sodium hydrogen carbonate, was then heated with charcoal, filtered, and treated with excess of hydrochloric acid. *2-Chloro-9-2′-chloroethylpurine-6-carboxylic acid* (0·27 g.) separated as prisms, m. p. 206° (decomp.), and for analysis was reprecipitated twice more and extracted with a little hot water and then with boiling ethanol, then dried *in vacuo* at 80° (Found: C, 37·1; H, 2·4; N, 21·6. $C_8H_6O_2N_4Cl_2$ requires C, 36·8; H, 2·3; N, 21·5%). The material crystallised slowly and with considerable loss from water or 2-ethoxyethanol and was not affected by treatment with boiling concentrated hydrochloric acid during 30 min.

Solutions of the three purines described showed a weak blue fluorescence in ultraviolet light.

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