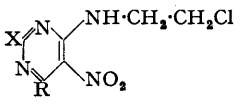
846. *Glyoxalinopyrimidines. The Cyclisation of Some 4-2′-Chloroethylaminopyrimidines.*

By G. R. Ramage and G. Trappe.

Preparations of 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine (I; R = H, X = Cl) and its 6-methyl derivative (I; R = Me, X = Cl) are described. The corresponding 5-amino-derivatives obtained on reduction have been shown to undergo cyclisation involving a pyrimidine-ring nitrogen atom in preference to the 5-amino-group. The resulting products are 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidines (VI; R = H or Me, X = Cl) and not derivatives of pteridine.

This paper describes an investigation into the reduction and cyclisation of 4-2′-chloroethylamino-5-nitropyrimidines (I), which was undertaken with a view to the synthesis of 5 : 6 : 7 : 8-tetrahydropteridines (II). Recently such a structure has been proposed for folinic acid, a factor isolated from liver, which stimulates the growth of *Leuconostoc citrovorum* and is closely related to pteroylglutamic acid (May *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 3067; Pohland *et al.*, *ibid.*, p. 3247). A similar approach to the synthesis of pteridine derivatives is the reduction and cyclisation of pyrimidine esters of type (III) (Boon, Jones, and Ramage, *J.*, 1951, 96) and related ketones (Boon and Jones, *ibid.*, p. 591), giving 7 : 8-dihydropteridines (IV).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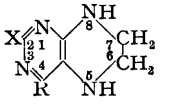
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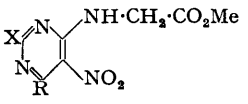
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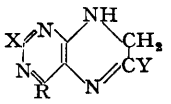
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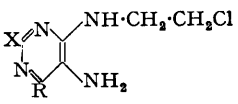
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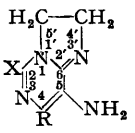

(VI)

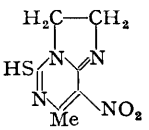
4-2′-Chloroethylamino-5-nitropyrimidines (I), however, after reduction to the corresponding 5-amino-compounds (V) could cyclise either (*a*) through the 5-amino-groups to give 5 : 6 : 7 : 8-tetrahydropteridines (II) or (*b*) by involving the pyrimidine nitrogen to give 5-amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine derivatives (VI). Cyclisations of type (*a*) have been shown to occur readily in the preparation of tetrahydroquinoxalines by a related route (see previous paper). On the other hand, cyclisations of type (*b*) occur in pyridine and quinoline derivatives possessing the 2′-chloroethylamino-group in the 2-position (Bremer, *Annalen*, 1936, **521**, 286; Osbond, *J.*, 1950, 1853). No cases appear to have been investigated in which both types of cyclisation are competing, and the present work has established that the formation of the 5-amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine occurs in preference to that of the 5 : 6 : 7 : 8-tetrahydropteridine.

Two main series of compounds were investigated, 2 : 4-dichloro-5-nitropyrimidine and its 6-methyl derivative, readily available from the corresponding 2 : 4-dihydroxypyrimidines by Baddiley and Topham's method (*J.*, 1944, 678), being used as starting materials.

By treatment of 2 : 4-dichloro-6-methyl-5-nitropyrimidine with 2-chloroethylamine hydrochloride in the presence of a suspension of sodium hydrogen carbonate, selective condensation at the 4-chloro-group gave 2-chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (I; R = Me, X = Cl) in good yield. This condensation procedure is essentially that used by Boon, Jones, and Ramage (*loc. cit.*) with glycine ester hydrochloride. 2-Chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (I; R = Me, X = Cl) was stable and showed no ready tendency to cyclisation, involving the pyrimidine nitrogen, to give a glyoxalinopyrimidine derivative.

Reduction of (I; R = Me, X = Cl) was accomplished catalytically in methanolic solution by use of Raney nickel. Without isolation of the intermediate 5-amino-2-chloro-4-2′-chloroethylamino-6-methylpyrimidine (V; R = Me, X = Cl), the methanolic solution after removal of the catalyst was refluxed and cyclisation occurred, giving the hydrochloride of 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)-pyrimidine (VI; R = Me, X = Cl). Reductive dehalogenation of this in presence of palladium on calcium carbonate gave 5-amino-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = Me, X = H). This structure was established by identity with the product obtained by the following unambiguous synthesis. Treatment of 2-chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (I; R = Me, X = Cl) with thiourea gave a thiuronium salt, which on hydrolysis to the 2-mercapto-derivative with sodium hydroxide underwent cyclisation, yielding 1 : 6 : 4′ : 5′-tetrahydro-2-mercapto-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VII). Reduction of (VII) with sodium dithionite gave the amino-compound (VIII), which was desulphurised with Raney nickel to give 5-amino-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = Me, X = H).

Similar cyclisations have occurred on attempted replacement of the 2-chloro-group in (I; R = Me, X = Cl) by other groups. On hydrolysis of the 2-chloro-group with hydrochloric acid, cyclisation occurred simultaneously to give 1 : 6 : 4′ : 5′-tetrahydro-2-hydroxy-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine (IX; X = OH). Similarly, on treatment of (I; R = Me, X = Cl) with anhydrous methanolic ammonia at low temperature, a water-insoluble product was first obtained which was apparently the desired 2-amino-compound. This product, however, cyclised with remarkable ease in the solid state when heated on the water-bath or kept in air, to give the hydrochloride of 2-amino-1 : 6 : 4′ : 5′-tetrahydro-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine (IX; X = NH_2).



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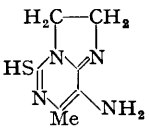

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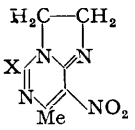


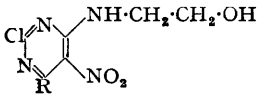
(IX)

The above cyclisations are apparently facilitated by the presence of a group, in the 2-position, capable of undergoing tautomerism, since the intermediate (I; R = Me, X = Cl) was stable, and furthermore, on treatment with piperidine, gave 4-2′-chloroethylamino-6-methyl-5-nitro-2-piperidinopyrimidine (I; R = Me, X = $C_5H_{10}N$) which was also quite stable, there being now no possibility of tautomerism at the 2-position.

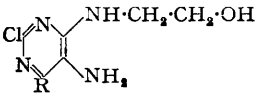
2-Chloro-4-2′-chloroethylamino-5-nitropyrimidine (I; R = H, X = Cl) was prepared from 2 : 4-dichloro-5-nitropyrimidine and 2-chloroethylamine in the same way as its 6-methyl analogue, but its reduction and cyclisation proved to be more difficult. Only about 95% of the theoretical volume of hydrogen was absorbed on catalytic reduction with Raney nickel in methanol at room temperature; the solution thus obtained was extremely sensitive to air, and, when it was refluxed in an atmosphere of carbon dioxide to effect cyclisation, considerable darkening occurred and no satisfactory product could be isolated. By raising the temperature of hydrogenation to 55° after the initial intake of hydrogen had ceased, a further quantity of hydrogen was absorbed, bringing the total intake to that required by theory. The solution thus obtained was far more stable to heat and, when it was refluxed in an atmosphere of carbon dioxide, cyclisation occurred to give the hydrochloride of 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = H, X = Cl), which by reductive dehalogenation gave 5-amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = X = H).

Some experiments have also been carried out on the cyclisation of the 4-2′-hydroxyethylamino-5-nitropyrimidines (X; R = H or Me), which were readily prepared by the action of 2-aminoethanol on 2 : 4-dichloro-5-nitropyrimidine and its 6-methyl derivative in methanolic solution at low temperature. A considerable difference in the behaviour of the two nitro-compounds was observed on reduction to the corresponding 5-amino-2-chloro-4-2′-hydroxyethylaminopyrimidines (XI; R = H or Me). 5-Amino-2-chloro-

4-2′-hydroxyethylamino-6-methylpyrimidine (XI; R = Me) was obtained from (X; R = Me) by catalytic reduction with Raney nickel in methanol, in high yield with no appreciable reduction of the 2-chloro-group. On a similar catalytic reduction of (X; R = H) the theoretical 3 mols. of hydrogen were absorbed, but the solution thus produced was extremely sensitive to air and heat. By avoidance of contact with air and removal of methanol under reduced pressure in hydrogen at room temperature, a residue was obtained which by crystallisation gave the more stable, pure 5-amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (XI; R = H). Further differences were observed between the two series in the behaviour of the 5-amino-4-2′-hydroxyethylaminopyrimidines (XI) with hydriodic acid. Treatment of 5-amino-2-chloro-4-2′-hydroxyethylamino-6-methylpyrimidine (XI; R = Me) with this acid and red phosphorus resulted in cyclisation and reduction of the 2-chloro-group to give 5-amino-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino-(1′ : 2′-1 : 6)pyrimidine (VI; R = Me, X = H), identical with that produced by cyclisation of the corresponding 4-2′-chloroethylaminopyrimidine (I; R = Me, X = Cl). Hydriodic acid and red phosphorus also directly converted the nitro-compound (X; R = Me) into (VI; R = Me, X = H), reduction of the nitro-group, cyclisation, and removal of the 2-chloro-group all occurring in the one treatment.



(X)



(XI)

Attempts to prepare 5-amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = X = H) by the hydriodic acid treatment of 5-amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (XI; R = H) or the corresponding nitro-compound (X; R = H) were unsuccessful owing to hydrolytic fission. The cleavage was evident from the isolation of ethylenediamine as its dibenzoyl derivative after hydriodic acid treatment of (XI; R = H) and the isolation of oxazolid-2-one after similar treatment of (X; R = H). Oxazolid-2-one was apparently formed from the hydrolytic fission product 2-iodoethylamine, since, in the working up, the reaction mixture was made alkaline with potassium carbonate and evaporated to dryness, and oxazolid-2-one has been prepared by the action of sodium hydrogen carbonate on 2-bromoethylamine under mild conditions (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 2494).

Substitution of hydrochloric acid (at 140—150°) for the cyclisation of 5-amino-2-chloro-4-2′-hydroxyethylamino-6-methylpyrimidine (XI; R = Me), which might be expected to give 5-amino-1 : 6 : 4′ : 5′-tetrahydro-2-hydroxy-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = Me, X = OH), caused fission with the production of 5-amino-4-methyluracil.

The 5-amino-4-2′-hydroxyethylaminopyrimidines (XI; R = H or Me) were also cyclised by conversion with thionyl chloride into the corresponding 5-amino-2-chloro-4-2′-chloroethylaminopyrimidines (V; R = H or Me, X = Cl), which were cyclised in refluxing methanol to the appropriate 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino-(1′ : 2′-1 : 6)pyrimidines (VI; R = H or Me, X = Cl). Yields were low, however, and these compounds are far better prepared by the reduction and cyclisation of the 2-chloro-4-2′-chloroethylamino-5-nitropyrimidines (I; R = H or Me, X = Cl).

Experimental

Analyses by Drs. Weiler and Strauss, Oxford.

2-Chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (I; R = Me, X = Cl).—2-Chloroethylamine hydrochloride (14 g., 0·12 mol.) was added with shaking during 20 minutes to 2 : 4-dichloro-6-methyl-5-nitropyrimidine (20·8 g., 0·1 mol.) in ether (100 c.c.) in the presence of sodium hydrogen carbonate (24 g.) in water (100 c.c.), at room temperature. After the addition, shaking was continued for a further 40 minutes before the ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed once with water and dried (Na_2SO_4). The residue, after removal of ether, was an oil which readily solidified on cooling and was crystallised from *cyclo*hexane (charcoal), to

give 2-*chloro*-4-2′-*chloroethylamino*-6-*methyl*-5-*nitropyrimidine* (18·2 g., 72%) as massive, pale yellow needles, m. p. 62—63° (Found: C, 33·7; H, 3·4; Cl, 28·2. $C_7H_8O_2N_4Cl_2$ requires C, 33·5; H, 3·2; Cl, 28·2%).

2-*Chloro*-4-2′-*hydroxyethylamino*-6-*methyl*-5-*nitropyrimidine* (X; R = Me).—A solution of 2-aminoethanol (12·2 g., 0·2 mol.) in methanol (50 c.c.) was added slowly (20 minutes) with shaking to a solution of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (20·8 g., 0·1 mol.) in methanol (60 c.c.) in a freezing mixture. During the addition the product began to separate and, after a further 2 hours in the freezing mixture, was filtered off and washed with a little methanol. Crystallisation from methanol gave 2-*chloro*-4-2′-*hydroxyethylamino*-6-*methyl*-5-*nitropyrimidine* (18·6 g., 80%), in pale yellow needles, m. p. 131° (Found: C, 36·3; H, 3·7. $C_7H_9O_3N_4Cl$ requires C, 36·1; H, 3·9%).

5-*Amino*-2-*chloro*-4-2′-*hydroxyethylamino*-6-*methylpyrimidine* (XI; R = Me).—2-Chloro-4-2′-hydroxyethylamino-6-methyl-5-nitropyrimidine (5 g.) was suspended in methanol (60 c.c.) and shaken with Raney nickel (3 c.c.; settled suspension) in hydrogen until the intake of hydrogen (theoretical amount) ceased (about 1½ hours). The catalyst was filtered off and washed with methanol, and the solvent removed from the filtrate under reduced pressure at 60°. Crystallisation of the residue from water gave 5-*amino*-2-*chloro*-4-2′-*hydroxyethylamino*-6-*methylpyrimidine* (3·77 g., 86%) as buff-coloured needles, m. p. 177—178° (Found: C, 41·2; H, 5·3; N, 28·2. $C_7H_{11}ON_4Cl$ requires C, 41·5; H, 5·5; N, 27·7%).

5-*Amino*-2-*chloro*-1 : 6 : 4′ : 5′-*tetrahydro*-4-*methylglyoxalino*(1′ : 2′-1 : 6)*pyrimidine* (VI; R = Me, X = Cl).—(*a*) 2-Chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (2 g.) in ethanol (100 c.c.) was shaken in hydrogen at room temperature and atmospheric pressure, in the presence of Raney nickel catalyst (4 c.c.; settled suspension) until the theoretical 3 mols. of hydrogen were absorbed. After filtration the filtrate was refluxed for 2½ hours, then concentrated to small bulk. The *hydrochloride* of the base (VI; R = Me, X = Cl) (1·44 g.) separated and crystallised from 90% aqueous ethanol as short needles which did not melt below 300° (Found: C, 38·5; H, 4·7; Cl, 32·0. $C_7H_9N_4Cl$,HCl requires C, 38·0; H, 4·6; Cl, 32·1%). The free *base* was precipitated from an aqueous solution of the hydrochloride with concentrated sodium hydroxide solution, and after crystallisation from water and drying in a vacuum was obtained as needles, m. p. 163° (Found: C, 45·9; H, 5·2. $C_7H_9N_4Cl$ requires C, 45·5; H, 4·9%).

(*b*) 5-Amino-2-chloro-4-2′-hydroxyethylamino-6-methylpyrimidine (4 g.) was added gradually (10 minutes) to thionyl chloride (10 c.c.) at 40°. The mixture was kept at 40° for a further 1½ hours, and the excess of thionyl chloride then removed under reduced pressure. The residue was treated with ice-water (50 c.c.), made alkaline with solid potassium carbonate, and extracted with chloroform. The extracts were dried (Na_2SO_4) and taken to dryness under reduced pressure below 40°, and the residue was dissolved in ethanol (200 c.c.) and refluxed for 2½ hours. Some hydrochloride which had separated during refluxing was taken into solution by addition of water (20 c.c.), and the hot solution treated with charcoal and filtered. Evaporation of the filtrate to dryness and crystallisation of the residue from 90% aqueous ethanol gave the hydrochloride of 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)-pyrimidine (2·41 g.), identical with that obtained above.

1 : 6 : 4′ : 5′-*Tetrahydro*-2-*mercapto*-4-*methyl*-5-*nitroglyoxalino*(1′ : 2′-1 : 6)*pyrimidine* (VII).—Thiourea (1·67 g., 0·022 mol.) in acetone (60 c.c.) was added to 2-chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (5 g., 0·02 mol.) in acetone (20 c.c.), and the mixture kept overnight and then refluxed for 2 hours. The thiuronium salt (6·05 g.) which separated was filtered off and dissolved in N-sodium hydroxide (120 c.c.) by warming on the water-bath for 2—3 minutes. The alkaline solution was cooled and acidified with glacial acetic acid, to precipitate the *compound* (VII) (3·55 g., 84%). The material was purified for analysis by twice precipitating it with acetic acid from a large volume of 0·1N-sodium hydroxide (120 c.c., to 1 g. of thio-compound) followed by crystallisation from 2-ethoxyethanol, to give orange prisms, m. p. 270° (decomp.) (Found: C, 40·1; H, 4·0. $C_7H_8O_2N_4S$ requires C, 39·6; H, 3·8%).

5-*Amino*-1 : 6 : 4′ : 5′-*tetrahydro*-2-*mercapto*-4-*methylglyoxalino*(1′ : 2′-1 : 6)*pyrimidine* (VIII).—The above nitro-compound (2 g.) was suspended in aqueous ammonia (30 c.c.; *d* 0·88), sodium dithionite (12 g.) was added during about 5 minutes, and the mixture was carefully heated to boiling. After cooling, the product was filtered off and crystallised from water containing a little sodium dithionite and ammonia, to give 5-*amino*-1 : 6 : 4′ : 5′-*tetrahydro*-2-*mercapto*-4-*methylglyoxalino*(1′ : 2′-1 : 6)*pyrimidine* (1·2 g., 71%) as colourless prisms, m. p. 300° (decomp.) (Found: C, 45·9; H, 5·7; S, 17·7. $C_7H_{10}N_4S$ requires C, 46·1; H, 5·5; S, 17·6%).

5-Amino-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = Me, X = H).—(*a*) A suspension of 5-amino-1 : 6 : 4′ : 5′-tetrahydro-2-mercapto-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (1 g.) and Raney nickel (15 c.c.; settled suspension) in ethanol (20 c.c.) was refluxed for 6 hours. The Raney nickel was removed by filtration and washed with a little ethanol, and the combined filtrates taken to dryness. The residue was crystallised from moist ethyl acetate, to give the *dihydrate* of the base (VI; R = Me, X = H) (0·25 g.) as buff-coloured needles, m. p. 108° (Found: C, 45·1; H, 7·4. $C_7H_{10}N_4,2H_2O$ requires C, 45·1; H, 7·6%). When the dihydrate was dried *in vacuo* at 65° the anhydrous base, m. p. 155°, was obtained, but its analyses were not satisfactory since it is hygroscopic and reverts to the dihydrate in air overnight. The *hydriodide* crystallised from water as prisms, m. p. 265° (decomp.) (Found: C, 30·3; H, 4·0; N, 20·4; I, 45·6. $C_7H_{10}N_4,HI$ requires C, 30·2; H, 4·0; N, 20·2; I, 45·6%). The *picrate* was sparingly soluble in ethanol and crystallised from 2-ethoxyethanol as tablets, m. p. 244° (decomp.) (Found: N, 25·6. $C_7H_{10}N_4,C_6H_3O_7N_3$ requires N, 25·9%).

(*b*) 5-Amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine (1 g.) in methanol (30 c.c.) was shaken in hydrogen in the presence of palladium on calcium carbonate (2%; 0·5 g.) at room temperature and pressure. When the intake of hydrogen ceased the catalyst was filtered off and the methanolic solution taken to dryness. The residual hydrochloride was dissolved in a little water, and 5-amino-1 : 6 : 4′ : 5′-tetrahydro-4-methylglyoxalino(1′ : 2′-1 : 6)pyrimidine precipitated with concentrated sodium hydroxide solution. Crystallisation from moist ethyl acetate gave the dihydrate (0·7 g.), m. p. 108°, identical with that obtained above.

(*c*) 5-Amino-2-chloro-4-2′-hydroxyethylamino-6-methylpyrimidine (2 g.) was added to hydriodic acid (10 c.c.; *d* 1·7) and red phosphorus (0·5 g.). After refluxing for 1½ hours the mixture was taken to dryness on the water-bath under reduced pressure, and the residue dissolved in a little hot water and filtered from excess of red phosphorus. The aqueous solution was evaporated to dryness, the residual hydriodide dissolved in hot water (4 c.c.), and the free base precipitated by making the solution alkaline with sodium hydroxide solution (30%), cooling, and then making it strongly alkaline by the further addition of sodium hydroxide. Crystallisation from moist ethyl acetate gave the above dihydrate (1·36 g.), m. p. 108°.

(*d*) 2-Chloro-4-2′-hydroxyethylamino-6-methyl-5-nitropyrimidine (4 g.), hydriodic acid (20 c.c.; *d* 1·7), and red phosphorus (2 g.) were refluxed for 1½ hours, the excess of red phosphorus filtered off, and the filtrate taken to dryness on the water-bath under reduced pressure. The residue was treated with water (10 c.c.), and the resultant suspension made strongly alkaline with sodium hydroxide solution (60%). The precipitate thus obtained was filtered off and dried in a desiccator, and contained inorganic material. The dry mixture was extracted (Soxhlet) with ethyl acetate (150 c.c.) for 6 hours, and when the extracts were cooled the dihydrate (1·26 g.), m. p. 108°, separated.

1 : 6 : 4′ : 5′-Tetrahydro-2-hydroxy-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine (IX; X = OH).—2-Chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (2 g.) was refluxed for 15 minutes with hydrochloric acid (5N; 20 c.c.). On cooling, a hydrochloride crystallised and was filtered off. This (1·4 g.) was dissolved in a little hot water, and the free base precipitated with sodium hydrogen carbonate. Crystallisation from water gave 1 : 6 : 4′ : 5′-*tetrahydro-2-hydroxy-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine* as broad needles, m. p. 286° (decomp.) (Found: C, 43·0; H, 4·1. $C_7H_8O_3N_4$ requires C, 42·9; H, 4·1%).

2-Amino-1 : 6 : 4′ : 5′-tetrahydro-4-methyl-5-nitroglyoxalino(1′ : 2′-1 : 6)pyrimidine (IX; X = NH_2).—Methanolic ammonia (2·6N; 5 c.c.) was added to a solution of 2-chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (1·25 g.) in methanol (5 c.c.). After the mixture had been kept for 1 hour at room temperature and then for 30 minutes in the refrigerator, some solid material separated and was filtered off and washed with water. The water-insoluble residue (0·3 g.) was converted into a water-soluble hydrochloride on drying either by heating it on the water-bath or keeping it in air. The free *base* (IX; X = NH_2) was precipitated from a solution of this hydrochloride with sodium hydrogen carbonate and crystallised from water in orange-coloured needles which did not melt below 300° (Found: C, 43·4; H, 4·6. $C_7H_9O_2N_5$ requires C, 43·1; H, 4·6%).

4-2′-Chloroethylamino-4-methyl-5-nitro-2-piperidinopyrimidine (I; R = Me, X = $C_5H_{10}N$).—Piperidine (0·85 g., 0·01 mol.) in methanol (4 c.c.) was added gradually with shaking to 2-chloro-4-2′-chloroethylamino-6-methyl-5-nitropyrimidine (1·25 g., 0·005 mol.) in methanol (4 c.c.) in an ice-bath. *4-2′-Chloroethylamino-4-methyl-5-nitro-2-piperidinopyrimidine* separated immediately and after 30 minutes was filtered off and washed with a little methanol (1·4 g., 93%;

m. p. 103—104°). Crystallisation from methanol gave pale yellow needles, m. p. 104—105° (Found: C, 48·5; H, 5·9. $C_{12}H_{18}O_2N_5Cl$ requires C, 48·1; H, 6·1%).

2-Chloro-4-2′-chloroethylamino-5-nitropyrimidine (I; R = H, X = Cl).—2 : 4-Dichloro-5-nitropyrimidine (19·4 g.) in ether (150 c.c.) and 2-chloroethylamine hydrochloride (14 g.) together with sodium hydrogen carbonate (24 g.) in water (100 c.c.), in a similar manner to its 6-methyl analogue above, gave *2-chloro-4-2′-chloroethylamino-5-nitropyrimidine* (17·2 g.), which crystallised from *cyclo*hexane containing a little ethyl acetate as pale yellow prisms, m. p. 75° (Found: C, 30·3; H, 2·4; Cl, 29·5. $C_6H_6O_2N_4Cl_2$ requires C, 30·4; H, 2·6; Cl, 29·9%).

2-Chloro-4-2′-hydroxyethylamino-5-nitropyrimidine (X; R = H).—2 : 4-Dichloro-5-nitropyrimidine (19·4 g.) in methanol (60 c.c.) was treated with 2-aminoethanol (12·2 g.) in methanol (50 c.c.) as described for the 6-methyl derivative. The resulting *compound* (X; R = H) (16·2 g.) crystallised from methanol in pale yellow needles, m. p. 125° (Found: C, 32·9; H, 3·3. $C_6H_7O_3N_4Cl$ requires C, 33·0; H, 3·2%).

5-Amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (XI; R = H).—The compound (X; R = H) (5 g.) was suspended in methanol (100 c.c.) and shaken with Raney nickel (3 c.c.; settled suspension) until the theoretical volume of hydrogen was absorbed. The catalyst was filtered off and washed with methanol, contact with air being reduced to a minimum. The filtrate was evaporated to dryness under reduced pressure, in an atmosphere of hydrogen, at room temperature. The residual gum slowly crystallised and was recrystallised from nitromethane (charcoal) from which the product separated as a light brown solid (3·03 g., 70%), m. p. 144—145·5°. Recrystallisation from water gave pure *5-amino-2-chloro-4-2′-hydroxyethylaminopyrimidine* as buff-coloured needles, m. p. 152—153° (Found: C, 38·3; H, 4·9; N, 29·8. $C_6H_9ON_4Cl$ requires C, 38·2; H, 4·8; N, 29·7%).

5-Amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = H, X = Cl).—(*a*) A solution of 2-chloro-4-2′-chloroethylamino-5-nitropyrimidine (4 g.) in methanol (50 c.c.) was shaken with hydrogen in the presence of Raney nickel catalyst (12 c.c.; settled suspension) at room temperature and pressure. After the initial intake of hydrogen had ceased, the temperature was raised to 55° until the intake again ceased (total, 1200 c.c. at N.T.P.; theory, 1180 c.c.). The catalyst was removed by filtration, and the filtrate diluted to 100 c.c. with methanol and refluxed for 2½ hours in an atmosphere of carbon dioxide. On concentration to about 15 c.c. the *hydrochloride* of 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino-(1′ : 2′-1 : 6)pyrimidine (2·35 g.) separated, and crystallised from aqueous ethanol in needles not melting below 300° (Found: C, 35·1; H, 3·8. $C_6H_7N_4Cl,HCl$ requires C, 34·8; H, 3·9%). The free *base* was precipitated from an aqueous solution and crystallised from ethyl acetate as needles, m. p. 157° (Found: C, 42·8; H, 3·8. $C_6H_7N_4Cl$ requires C, 42·2; H, 4·1%).

(*b*) 5-Amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (2 g.) was added during 10 minutes to thionyl chloride (12 c.c.) at room temperature, and the resulting mixture warmed on the water-bath for 15 minutes. Excess of thionyl chloride was removed under reduced pressure at 40°, and the residue dissolved in ice-water (30 c.c.). The aqueous solution was made alkaline with solid potassium carbonate and extracted with chloroform. After the extracts had been dried (Na_2SO_4), the chloroform was removed under reduced pressure, and the gummy residue dissolved in ethanol (50 c.c.) and refluxed for 2½ hours. Some hydrochloride which separated was taken into solution by addition of a little water, and the hot solution was treated with charcoal and filtered. On concentration of the filtrate to about 10 c.c., the above hydrochloride of 5-amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (0·58 g.) separated.

5-Amino-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (VI; R = X = H).—Anhydrous 5-amino-2-chloro-1 : 6 : 4′ : 5′-tetrahydroglyoxalino(1′ : 2′-1 : 6)pyrimidine (1 g.) in methanol (25 c.c.) was shaken in hydrogen with palladium on calcium carbonate (2%; 0·5 g.). When the intake of hydrogen ceased, the catalyst was filtered off and the methanolic solution taken to dryness under reduced pressure. The residual hydrochloride was treated with 1 mol. of methanolic sodium methoxide, and the sodium chloride which separated was filtered off. The filtrate was taken to dryness, and crystallisation of the residue from moist ethyl acetate gave the base (VI; R = X = H) (0·58 g.) as a hydrate, m. p. 71°. On drying in a vacuum-desiccator the anhydrous *base*, m. p. 140°, was obtained (Found: C, 53·3; H, 5·9. $C_6H_8N_4$ requires C, 52·9; H, 5·9%). The *picrate* was sparingly soluble in alcohol and crystallised from 2-ethoxyethanol; it had m. p. 240° (decomp.) (Found: C, 40·1; H, 3·1. $C_{12}H_{11}O_7N_7$ requires C, 39·5; H, 3·0%).

Hydriodic Acid Treatment of 5-Amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (XI; R = H).—5-Amino-2-chloro-4-2′-hydroxyethylaminopyrimidine (1 g.), hydriodic acid (10 c.c.; *d* 1·7), and red phosphorus (0·5 g.) were refluxed together for 1 hour. Excess of hydriodic

acid was removed on the water-bath under reduced pressure, the residue treated with water (10 c.c.), and excess of red phosphorus filtered off. After evaporation of the clarified solution to dryness, the residue was washed with hot ethanol (10 c.c.), and an ethanol-insoluble hydriodide (0·55 g.) remained. Shaking this hydriodide with benzoyl chloride (1·3 c.c.) and 5% sodium hydroxide solution (20 c.c.) for 1 hour yielded a benzoyl derivative (0·23 g.) which was filtered off. After crystallisation from ethanol it had m. p. 251° and was shown by analysis to be the dibenzoyl derivative of ethylenediamine (Found: C, 71·2; H, 6·0. Calc. for $C_{16}H_{16}O_2N_2$: C, 71·6; H, 6·0%). The m. p. was not depressed on admixture with an authentic specimen, m. p. 251°.

Hydriodic Acid Treatment of 2-Chloro-4-2′-hydroxyethylamino-5-nitropyrimidine (X; R = H).—The nitropyrimidine (2 g.) was added to a mixture of hydriodic acid (10 c.c.; *d* 1·7) and red phosphorus (1 g.). After 1 hour's refluxing, the excess of red phosphorus was removed by filtration, and the filtrate taken to dryness on the water-bath under reduced pressure and again after being made alkaline with aqueous potassium carbonate. The residual mixture was extracted with ethanol (2 × 100 c.c.) and after concentration of the extract to about 20 c.c. it was diluted with an equal volume of benzene and filtered. The filtrate was taken to dryness, and the residue sublimed at 90—120°/0·01 mm., to yield a colourless sublimate (0·28 g.), m. p. 77—84°. Crystallisation from alcohol gave colourless needles, m. p. 89—90°, of oxazolid-2-one (lit., m. p. 90—91°) (Found: C, 42·0; H, 5·6. Calc. for $C_3H_5O_2N$: C, 41·4; H, 5·8%).

Hydrochloric Acid Treatment of 5-Amino-2-chloro-4-2′-hydroxyethylamino-6-methylpyrimidine (X; R = Me).—This base (2 g.) was heated (sealed tube) with concentrated hydrochloric acid (10 c.c.) at 140° for 6 hours. On cooling, a highly crystalline hydrochloride separated (1·35 g.), which after filtration was dissolved in hot water and treated with solid sodium hydrogen carbonate to liberate the base. After crystallisation from water this had m. p. 270° (decomp.) with softening at about 250°, and was identical with 5-amino-4-methyluracil obtained by reduction of 4-methyl-5-nitrouracil with sodium dithionite (Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667). It was dried for analysis at 100° *in vacuo* (Found: C, 42·9; H, 4·7. Calc. for $C_5H_7O_2N_3$: C, 42·5; H, 5·0%).

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