818. *The Condensation of* 4 : 5-*Diaminopyrimidines and Sugar Lactones.*

By R. HULL.

The product obtained from 4 : 5-diamino-6-diethylamino-2-methylpyrimidine and δ-D-gluconolactone is shown to be an 8-polyhydroxyalkylpurine by metaperiodate oxidation to the 8-formylpurine. The structure of this aldehyde has been confirmed by synthesis from the 8-hydroxymethylpurine. Some other pyrimidines appear to give similar products from either gluco- or ribono-lactones. Under similar conditions these lactones and 4 : 5 : 6-triamino-2-methylthiopyrimidine give the 5-acylaminopyrimidines.

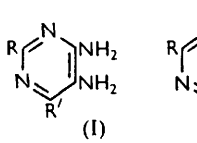
ALTHOUGH aldonic lactones have been condensed with *o*-phenylenediamines,[1] no work appears to have been described for 4 : 5-diaminopyrimidines. Ishidate and Yuki [2] reported that condensation of some 4 : 5-diamino-pyrimidines with gluconic acid yielded the 5-acylamino-derivatives but cyclisation to the purine ring was not successful. Various workers [3] have described the preparation of polyhydroxypteridines by the condensation of aldoses, ketoses, and osones with diaminopyrimidines. Reaction of δ-D-gluconolactone and some 4 : 5-diaminopyrimidines has now been shown to yield derivatives of 8-substituted purines.

[1] Richtmyer, *Adv. Carbohydrate Chem.*, 1951, **6**, 175.
[2] Ishidate and Yuki, *Pharm. Bull.* (*Japan*), 1957, **5**, 240, 244.
[3] *E.g.*, Karrer, Schwyzer, Erden, and Siegwart, *Helv. Chim. Acta*, 1947, **30**, 1031; Petering and Weisblat, *J. Amer. Chem. Soc.*, 1947, **69**, 2566; Forrest and Walker, *J.*, 1949, 79.

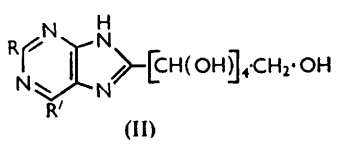
δ-D-Gluconolactone and 4 : 5-diamino-6-diethylamino-2-methylpyrimidine (I; R = Me, R′ = NEt_2) were fused together and yielded a compound $C_{15}H_{25}O_5N_5$ which on reaction with 4·4 mols. of metaperiodate, liberated 2·93 mols. of formic acid and gave an aldehyde $C_{11}H_{15}ON_5$. This result disproved formula (III; R = Me, R′ = NEt_2) which would have required 3 mols. of metaperiodate with the liberation of 2 mols. of formic acid to produce the dihydropteridine (V; R = Me, R′ = NEt_2); our result appears more consistent with formula (II; R = Me, R′ = NEt_2). The degradation product may be compared with Albert and Brown's 6-formyl-4 : 7-dihydroxypteridine [4] in that it did not reduce Fehling's solution. It resisted oxidation with alkaline peroxide, silver oxide, nitrogen peroxide, or nitric acid, and did not undergo a Cannizzaro reaction with alkali; however, treatment with 2 : 4-dinitrophenylhydrazine, (methylthio)thiocarbonylhydrazine,[5] and hydroxylamine yielded the expected condensation products. The oxime (VI) on treatment with acetic anhydride yielded the acetyl derivative (VII) which when heated above its m. p. readily evolved acetic acid and gave the nitrile (VIII).

A method similar to that used by Albert [6] for the synthesis of 8-hydroxymethylpurine, namely, interaction of 4 : 5-diaminopyrimidine with ethyl glycollate, was adapted to the synthesis of the alcohol (IX). Structure (IX) was proved to be correct since reduction with hydriodic acid in the presence of red phosphorus [7] yielded the 8-methylpurine (X), itself prepared in an unambiguous manner by fusion of the diaminopyrimidine (I; R = Me, R′ = NEt_2) with acetamidine hydrochloride. Oxidation of the hydroxymethyl group of (IX) with potassium dichromate gave a product identical with the metaperiodate fission product of (II; R = Me, R′ = NEt_2). These reactions thus established unequivocally formula (IV; R = Me, R′ = NEt_2) and therefore formula (II; R = Me, R′ = NEt_2) as the product of interaction of the diaminopyrimidine and gluconolactone.

In a similar fashion the morpholinopyrimidine (I; R = Me, R′ = morpholino) and gluconolactone yielded compound (II; R = Me, R′ = morpholino) which required 4·3 mols. of metaperiodate (theor., 4 mols.) to undergo degradation to 2·6 mols. of formic acid (theor., 3 mols.) and the 8-formylpurine (IV; R = Me, R′ = morpholino).



(I)



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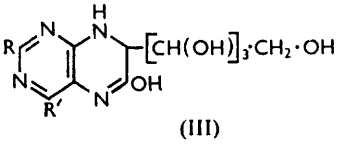

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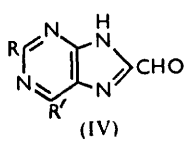
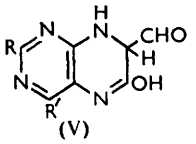
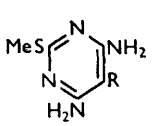
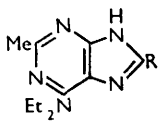


(IV)



(V)





(VI) R = CH:N·OH
(VII) R = CH:N·OAc
(VIII) R = CN
(IX) R = CH_2·OH
(X) R = Me
(XI) R = [CH(OH)]$_3$·CH_2·OH

(XII) R = NH_2
(XIII) R = NH·CO·[CH(OH)]$_n$·CH_2·OH

The same procedure applied to the pyrimidine (I; R = H, R′ = NEt_2) yielded a product in agreement with formula (II; R = H, R′ = NEt_2). Fusion of the pyrimidine (I; R = Me, R′ = NEt_2) with D-ribonolactone gave a product for which we propose formula (XI).

Finally it was found that fusion of 4 : 5 : 6-triamino-2-methylthio-pyrimidine (XII) with gluconolactone gave a product $C_{11}H_{19}O_6N_5S$ which did not appear to lose a mol.

[4] Albert and Brown, *J.*, 1953, 74.
[5] Busch, *J. prakt. Chem.*, 1916, **93**, 60.
[6] Albert, *J.*, 1955, 2690.
[7] Johnson and Chernoff, *J. Amer. Chem. Soc.*, 1914, **36**, 1742.

of water on long drying *in vacuo*. Similarly this pyrimidine (XII) with ribonolactone gave a product $C_{10}H_{17}O_5N_5S$. It was probable that in these cases only the 5-amino-group had reacted to yield the amides (XIII; $n = 4$ and 3, respectively).

The diaminopyrimidines used as starting materials were obtained by reaction of the 4-chloro-5-nitropyrimidine with the appropriate base followed by catalytic reduction of the nitro-group.

Experimental

4-Amino-6-diethylamino-2-methyl-5-nitropyrimidine.—Diethylamine (12·5 ml.) was added dropwise to a cooled stirred solution of 4-amino-6-chloro-2-methyl-5-nitropyrimidine [8] (7·56 g.) in ethyl acetate (280 ml.) and set aside for 2 days. The solvent was removed under diminished pressure and the residue (9·0 g.) was collected and washed with water. Recrystallisation from aqueous alcohol gave the *diethylaminopyrimidine* as pale yellow prismatic needles, m.p. 109·5—110·5° (Found: C, 48·15; H, 7·1; N, 30·9. $C_9H_{15}O_2N_5$ requires C, 48·0; H, 6·6; N, 31·1%).

4 : 5-Diamino-6-diethylamino-2-methylpyrimidine.—4-Amino-6-diethylamino-2-methyl-5-nitropyrimidine (8·7 g.) was reduced with hydrogen at laboratory temperature and pressure in the presence of Raney nickel. After filtration and evaporation the *diaminopyrimidine* (7·6 g.) crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 117—118° (Found: C, 55·85; H, 9·0; N, 35·5. $C_9H_{17}N_5$ requires C, 55·4; 8·7; N, 35·9%).

*6-Diethylamino-8-*D*-gluco*pentahydroxypentyl*-2-methylpurine.*—4 : 5-Diamino-6-diethylamino-2-methylpyrimidine (1·95 g.) and δ-D-gluconolactone (1·96 g.) were heated in a bath at 140—150° for 10 min. Extraction of the cooled mixture with water (charcoal) gave the *purine* (1·2 g.) which recrystallised from water in needles, m. p. 229°, $[\alpha]_D^{21} + 41°$ (*c* 3·33 in 0·1N-hydrochloric acid) (Found: C, 50·1; H, 6·4; N, 19·6. $C_{15}H_{25}O_5N_5$ requires C, 50·7; H, 7·0; N, 19·7%).

4-Amino-2-methyl-6-morpholino-5-nitropyrimidine.—Morpholine (7·6 g.) was added slowly to a stirred solution of 4-amino-6-chloro-2-methyl-5-nitropyrimidine [8] (7·6 g.) in ethyl acetate (280 ml.), then kept for 2 days. The morpholine hydrochloride was collected and washed with ethyl acetate, and the filtrates were evaporated to dryness. The *morpholinopyrimidine* (9·0 g.) recrystallised from aqueous alcohol in pale yellow prismatic needles, m. p. 193·5—195° (Found: C, 45·3; H, 5·5; N, 29·25. $C_9H_{13}O_3N_5$ requires C, 45·2; H, 5·45; N, 29·3%).

4 : 5-Diamino-2-methyl-6-morpholinopyrimidine.—4-Amino-2-methyl-6-morpholino-5-nitropyrimidine (2·25 g.), suspended in methanol (150 ml.), was reduced with hydrogen at laboratory temperature and atmospheric pressure in presence of Raney nickel. After filtration and evaporation the residue (2 g.) recrystallised from ethyl acetate to give the *diaminopyrimidine* as plates, m. p. 191° (Found: C, 52·0; H, 7·0; N, 33·95. $C_9H_{15}ON_5$ requires C, 51·7; H, 7·2; N, 33·5%).

*2-Methyl-6-morpholino-8-*D*-gluco*pentahydroxypentylpurine.*—A ground mixture of 4 : 5-diamino-2-methyl-6-morpholinopyrimidine (1·05 g.) and δ-D-gluconolactone (0·98 g.) was heated in a bath at 140° until a complete melt was obtained, then for 10 min. during which the melt began to solidify. Extraction of the mixture with boiling water (charcoal) gave the *purine* as pale yellow needles, m. p. 260°, $[\alpha]_D^{21} + 39°$ (*c* 3·093 in 0·1N-hydrochloric acid) (Found: C, 48·65; H, 6·2; N, 18·75. $C_{15}H_{23}O_6N_5$ requires C, 48·8; H, 6·25; N, 18·95%).

Fission of Hydroxyalkylpurines with Sodium Metaperiodate.—The hydroxyalkylpurine (*ca.* 0·4 millimole) was dissolved in hot water, quickly cooled, treated with 0·2039M-sodium metaperiodate (10 ml.) and set aside for 24 hr. The solution was diluted to a known volume, an aliquot part was removed, and the unchanged metaperiodate estimated iodometrically by Barneby's method [9] using 0·1N-sodium arsenite. Formic acid was estimated in an aliquot part by titration with 0·1N-sodium hydroxide (Methyl Red).

Isolation of 6-Diethylamino-8-formyl-2-methylpurine.—Neutralisation of the acid reaction mixture of 6-diethylamino-2-methyl-8-D-*gluco*pentahydroxypentylpurine and sodium metaperiodate gave a solid which was collected and washed with water. Recrystallisation from aqueous alcohol gave the *aldehyde* as colourless needles, m. p. 210·5—211° (Found: C, 56·95; H, 6·2; N, 29·9. $C_{11}H_{15}ON_5$ requires C, 56·7; H, 6·45; N, 30·0%). It does not reduce Fehling's solution, but blackens warm ammoniacal silver nitrate solution.

Isolation of 8-Formyl-2-methyl-6-morpholinopurine.—In a similar manner neutralisation of

[8] Boon, Jones, and Ramage, *J.*, 1951, 96.
[9] Barneby, *J. Amer. Chem. Soc.*, 1916, **38**, 330.

the reaction mixture from 2-methyl-6-morpholino-8-D-*gluco*pentahydroxypentylpurine and sodium metaperiodate and subsequent treatment with sodium hydrogen carbonate gave the *aldehyde* which crystallised from butanol in needles, m. p. 285° (decomp.) (Found: C, 54·15; H, 5·45; N, 27·8. $C_{11}H_{13}O_2N_5$ requires C, 53·45; H, 5·3; N, 28·3%).

Compounds from 6-*Diethylamino*-8-*formyl*-2-*methylpurine*.—The 2 : 4-*dinitrophenylhydrazone hydrochloride* crystallised from butanol as yellow needles, m. p. 294° (decomp.) (Found: C, 44·05; H, 4·85. $C_{17}H_{19}O_4N_9,HCl,H_2O$ requires C, 43·65; H, 4·7%).

The condensation *product* with (methylthio)thiocarbonylhydrazine [5] crystallised from butanol as yellow needles, m. p. 234° (decomp.) (Found: C, 46·6; H, 6·1; N, 28·7. $C_{13}H_{19}N_7S_2$ requires C, 46·3; H, 5·6; N, 29·1%).

The aldehyde (3·8 g.) in hot alcohol (120 ml.) was added to a solution of hydroxylamine [prepared by adding a solution of hydroxylamine hydrochloride (1·42 g.) in water (2 ml.) to a solution from sodium (0·47 g.) in alcohol (12 ml.) and filtering], and the whole was heated under reflux during 30 min. The *oxime* (3·8 g.) was collected from the cooled mixture. It crystallised from alcohol as needles, m. p. 238° (decomp.) (Found: C, 53·6; H, 6·8; N, 34·1. $C_{11}H_{16}ON_6$ requires C, 53·25; H, 6·45; N, 33·9%).

8-*Cyano*-6-*diethylamino*-2-*methylpurine*.—6-Diethylamino-2-methylpurine-8-aldoxime (2·75 g.) and acetic anhydride (25 ml.) were heated under reflux for 15 min. Excess of reagent was removed under diminished pressure. Recrystallisation of the residue from alcohol gave the *acetyl derivative* of the oxime (1·8 g.) as pale yellow needles, m. p. 189° (decomp.), resolidifying, and remelting at 299° (Found: C, 54·5; H, 6·1; N, 30·9. $C_{13}H_{18}O_2N_6$ requires C, 53·8; H, 6·2; N, 29·0%). The above acetyl compound (1·2 g.) was heated to 190°, acetic acid being liberated. Aqueous sodium hydrogen carbonate was added to the cooled residue and the solid (0·95 g.) was collected and washed with water. Recrystallisation from 2-ethoxyethanol gave the *cyanopurine* as needles, m. p. 302° (Found: C, 57·3; H, 6·2; N, 36·2. $C_{11}H_{14}N_6$ requires C, 57·4; H, 6·1; N, 36·5%).

6-*Diethylamino*-8-*hydroxymethyl*-2-*methylpurine*.—4 : 5-Diamino-6-diethylamino-2-methylpyrimidine (1·0 g.) and ethyl glycollate (2·15 g.) were heated together in an open flask in a bath at 140° during 2 hr. Ether was added to the cooled mixture, and the solid (0·9 g.) was collected and washed with ether. Two recrystallisations from toluene (charcoal) gave the *hydroxymethylpurine* as needles, m. p. 210° (Found: C, 55·7; H, 7·0; N, 29·2. $C_{11}H_{17}ON_5$ requires C, 56·15; H, 7·25; N, 29·8%).

6-*Diethylamino*-2 : 8-*dimethylpurine*.—A mixture of 4 : 5-diamino-6-diethylamino-2-methylpyrimidine (0·72 g.) and acetamidine hydrochloride (0·38 g.) was heated in a bath at 160° during 20 min. A slight excess of aqueous sodium hydrogen carbonate was added to the cooled melt and later the solid was collected. Recrystallisation from light petroleum (b. p. 100—120°) gave the *dimethylpurine* as needles, m. p. 166° (Found: C, 60·5; H, 7·5; N, 32·0. $C_{11}H_{17}N_5$ requires C, 60·3; H, 7·7; N, 32·0%).

Oxidation of 6-*Diethylamino*-8-*hydroxymethyl*-2-*methylpurine*.—Finely powdered potassium dichromate (0·25 g.) was added slowly to a stirred solution of 6-diethylamino-8-hydroxymethyl-2-methylpurine (0·5 g.) in acetic acid (10 ml.) in a bath at 80°. After a further 1 hr. the mixture was cooled and neutralised with sodium hydrogen carbonate, and the product (0·3 g.) was collected and washed with water. Recrystallisation from aqueous alcohol gave the 8-formyl-purine, m. p. 213°. A mixed m. p. with the periodate oxidation product (m. p. 211°) was 210°. The infrared spectrum (in Nujol) contains a band at 1700 cm.$^{-1}$ (CO); the band at 3210 cm.$^{-1}$ (OH), present in the starting material, had disappeared. The condensation product with (methylthio)-thiocarbonylhydrazine had m. p. 231° (decomp.).

Reduction of 6-*Diethylamino*-8-*hydroxymethyl*-2-*methylpurine*.—Red phosphorus (0·05 g.) was added to a solution of 8-hydroxymethyl-6-diethylamino-2-methylpurine (0·25 g.) in hydriodic acid (*d* 1·7; 4·5 ml.), and the whole was heated under reflux during 3 hr. The cooled mixture was filtered and the filtrates were neutralised with aqueous sodium hydrogen carbonate. The solid (0·14 g.; m. p. 161°) was collected and washed with water. Recrystallisation from light petroleum (b. p. 100—120°) gave 6-diethylamino-2 : 8-dimethylpurine, m. p. 165—166°. It was undepressed in admixture with and had a similar infrared absorption spectrum to an authentic sample.

6-*Diethylamino*-8-D-gluco*pentahydroxypentylpurine*.—4 : 5-Diamino-6-diethylaminopyrimidine [10] (1·0 g.) and δ-D-gluconolactone (0·99 g.) were heated in a bath at 120° during 2½ hr.

[10] Boon and Jones, *J.*, 1951, 591.

Two recrystallisations from a small quantity of water gave the *purine* as needles, m. p. 188—189·5° (Found: C, 48·7; H, 7·1; N, 20·35. $C_{14}H_{23}O_5N_5$ requires C, 49·25; H, 6·75; N, 20·5%).

6-*Diethylamino*-2-*methyl*-8-D-ribo*tetrahydroxybutylpurine*.—4 : 5-Diamino-6-diethylamino-2-methylpyrimidine (1·95 g.) and D-ribonolactone (1·62 g.) were heated in a bath at 140° ± 5° during 10 min. The cooled mixture was extracted with a small quantity of hot water. Crystallisation of the residue from butanol gave the *purine* as needles, m. p. 228—229° (sintering at 220°), $[\alpha]_D^{24}$ − 20° (*c* 3·098 in pyridine) (Found: C, 51·85; H, 7·25; N, 21·5 $C_{14}H_{23}O_4N_5$ requires C, 51·7; H, 7·1; N, 21·6%).

Reaction of δ-D-*Gluconolactone with* 4 : 5 : 6-*Triamino*-2-*methylthiopyrimidine*.—δ-D-Gluconolactone (1·04 g.) and 4 : 5 : 6-triamino-2-methylthiopyrimidine [11] (1·0 g.) were heated to fusion in a bath at 140° during 30 min. Extraction of the cooled melt with boiling water (charcoal) gave the *product* (0·97 g.) as prisms, m. p. 184—185°, $[\alpha]_D^{22}$ + 58° (*c*, 2·991 in 5% citric acid) (Found: C, 37·95; H, 5·65; N, 19·9. $C_{11}H_{19}O_6N_5S$ requires C, 37·83; H, 5·45; N, 20·0%). The compound did not appear to lose water on long drying *in vacuo*, and was probably 4 : 6-diamino-5-D-gluconamido-2-methylthiopyrimidine.

Reaction of D-*Ribonolactone with* 4 : 5 : 6-*Triamino*-2-*methylthiopyrimidine*.—A mixture of D-ribonolactone (1·56 g.) and 4 : 5 : 6-triamino-2-methylthiopyrimidine (1·71 g.) was heated to a fused mass in a bath at 140° during 15 min. Repeated crystallisation of the cooled mixture from water gave a *product* as colourless needles, m. p. 224—225°, $[\alpha]_D^{21}$ + 28° (*c* 4·029 in 5% citric acid) (Found: C, 35·05; H, 5·6; N, 21·3. $C_{10}H_{17}O_5N_5S,H_2O$ requires C, 35·6; H, 5·6; N, 20·75%). The compound was probably the monohydrate of 4 : 6-diamino-2-methylthio-5-D-ribonamidopyrimidine.

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[11] Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 385.