826. *The Synthesis of 4-Aminopteridines as Potential Anti-metabolites.*

By C. L. Leese and G. M. Timmis.

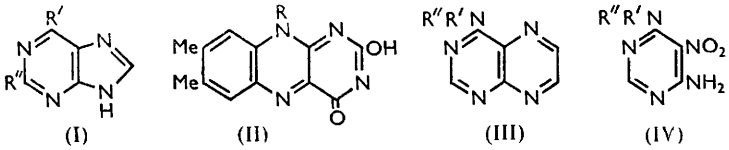
A number of pteridines which carry alkylamino- and dialkylamino-substituents in the 4-position have been synthesised.

Recently it has been shown that in the conversion of adenine [1] (I; R′ = NH_2, R″ = H) and guanine [2] (I; R′ = OH, R″ = NH_2) to riboflavine by the organism *Eremothecium ashbyii* the pyrimidine ring is transferred from the purine to riboflavine (II; R = ribityl) practically intact. This process appears to involve essentially an opening of the glyoxaline ring of the purine with loss of $C_{(8)}$ and condensation of the diaminopyrimidine so formed, perhaps after glycosidation of one amino-group, with 3 : 4-dimethyl-*o*-benzoquinone.

The ability of purines to open up to yield diaminopyrimidines was first shown *in vitro* by Albert and when this was done in the presence of suitable diketones pteridines were formed.[3] The suggestion that this sequence might occur in Nature was later confirmed [4] and this process could be a source of pteridine vitamins and co-factors. The occurrence of the 4 : 5-dimethyl-1 : 2-phenylene grouping in both riboflavine and vitamin B_{12} suggests that these two vitamins may be biosynthetically interdependent and therefore that they would depend also on purine and pteridine metabolism. Since this overall relationship would involve a balance of the four components it is likely that, for example, interference

[1] McNutt, *J. Biol. Chem.*, 1956, **219**, 365.
[2] Usama and al-Khalidi, *Fed. Proc.*, 1958, **17**, 180.
[3] Albert, *Biochem. J.*, 1954, **57**, x.
[4] Albert, *ibid.*, 1957, **65**, 124.

with the function of the normal pteridines would have interesting biological effects and we have, therefore, synthesised some simple pteridines (III) as potential antimetabolites according to the concept of structural analogy. These pteridines were selected because they are formally derivable from 6-arylalkylaminopurines [5] and from the 6-dimethylaminopurine moiety of puromycin; both these structures are associated with growth inhibition in a variety of organisms.



(I) (II) (III) (IV)

The required intermediates (IV; R′ = H, R″ = phenethyl, furfuryl, benzyl, or *cyclo*hexyl and R′ = R″ = Me) were conveniently made by condensing 4-amino-6-chloro-5-nitropyrimidine with the appropriate amine in ether, reaction being smooth at room temperature and giving excellent yields. The nitropyrimidines were reduced with hydrogen and Raney nickel, and the triamines produced then yielded the pteridines on reaction with glyoxal.

Experimental

Analyses are by Mr. P. R. W. Baker, Beckenham.

4-Amino-6-(substituted amino)-5-nitropyrimidines.—These compounds were prepared by reaction of 4-amino-6-chloro-5-nitropyrimidine with two equivalents of the appropriate primary or secondary amine in dry ether as in the following typical experiment.

4-Amino-5-nitro-6-phenethylaminopyrimidine. Phenethylamine (10 g.) in ether (50 ml.) was slowly added to 4-amino-6-chloro-5-nitropyrimidine (7 g.) in ether (200 ml.). After 12 hr. the ether was removed and the residue suspended in water (100 ml.) to remove the phenethylamine hydrochloride. Filtration afforded the essentially pure *product* (9 g., 83%), m. p. 180—181°. Recrystallisation from ethanol gave white plates, m. p. 180—181° (Found: C, 55·8; H, 4·9; N, 26·7. $C_{12}H_{13}O_2N_5$ requires C, 55·5; H, 5·0; N, 27·0%).

The following were prepared similarly: 4-Amino-6-dimethylamino-5-nitropyrimidine (7·3 g., 97%) [from 4-amino-6-chloro-5-nitropyrimidine (7 g.) and 33% w/w methanolic dimethylamine (20 ml.)], pale yellow needles (from ethanol), m. p. 162—163°. Albert *et al.*[6] give m. p. 159—161°. 4-Amino-6-benzylamino-5-nitropyrimidine (3·56 g., 96%) [from 4-amino-6-chloro-5-nitropyrimidine (2·65 g.) and benzylamine (4 g.)], needles, m. p. 202—202·5° (from dioxan) (Found: C, 54·2; H, 4·4. Calc. for $C_{11}H_{11}O_2N_5$: C, 53·8; H, 4·5%). Daly and Christensen [7] give m. p. 191—194°.

4-Amino-6-furfurylamino-5-nitropyrimidine (9·48 g., 98%) [from 4-amino-6-chloro-5-nitropyrimidine (7 g.) and furfurylamine (8 g.)], m. p. 179°, plates from ethanol (Found: C, 46·2; H, 4·2; N, 29·8. $C_9H_9O_3N_5$ requires C, 45·9; H, 3·8; N, 29·7%).

4-Amino-6-cyclohexylamino-5-nitropyrimidine (8·8 g., 96%) [from 4-amino-6-chloro-5-nitropyrimidine (7 g.) and *cyclo*hexylamine (8 g.)], needles (from ethanol), m. p. 203—204° (Found: C, 50·5; H, 6·1; N, 29·4. $C_{10}H_{15}O_2N_5$ requires C, 50·6; H, 6·3; N, 29·5%).

4 : 5-Diamino-6-(substituted amino)pyrimidines.—*4 : 5-Diamino-6-dimethylaminopyrimidine.* 4-Amino-6-dimethylamino-5-nitropyrimidine (5 g.) in ethanol (300 ml.) was shaken with hydrogen in the presence of Raney nickel. Hydrogenation was complete in 30 min. The filtered solution was evaporated *in vacuo* to yield the *product* as pale fawn crystals (3·6 g., 86%), m. p. 156—157°, obtained from benzene as white needles, m. p. 157—158° (Found: C, 47·4; H, 7·0; N, 45·7. $C_6H_{11}N_5$ requires C, 47·0; H, 7·2; N, 45·7%).

4 : 5-Diamino-6-benzylaminopyrimidine. 4-Amino-6-benzylamino-5-nitropyrimidine (1·62 g.) was suspended in boiling water (80 ml.) and treated with sodium dithionite portionwise until the nitro-compound had dissolved. The mixture was made strongly alkaline with aqueous ammonia and cooled in ice. *4 : 5-Diamino-6-benzylaminopyrimidine* (1·22 g., 86%) crystallised

[5] Ziegler-Günder, Simon, and Wacker, *Z. Naturforsch.*, 1956, **11**b, 82; Skinner and Shive, *J. Amer. Chem. Soc.*, 1955, **77**, 6692; Ham, Eakin, Skinner, and Shive, *ibid.*, 1956, **78**, 2648; Skinner, Shive, Ham, Fitzgerald, and Eakin, *ibid.*, p. 5097.

[6] Albert, Brown, and Cheesman, *J.*, 1952, 4228.

[7] Daly and Christensen, *J. Org. Chem.*, 1956, **21**, 177.

and formed needles, m. p. 153—153·5°, from benzene (Found: C, 61·5; H, 5·9; N, 32·9. $C_{11}H_{13}N_5$ requires C, 61·3; H, 6·0; N, 32·5%).

4 : 5-*Diamino*-6-*phenethylaminopyrimidine.*—4-Amino-5-nitro-6-phenethylaminopyrimidine (4 g.) suspended in ethanol (200 ml.) was catalytically reduced as above, to the *base* (3·5 g., 98%), m. p. 200°, needles from methanol (Found: C, 62·7; H, 6·2; N, 30·8. $C_{12}H_{15}N_5$ requires C, 62·8; H, 6·6; N, 30·5%). From 2N-sulphuric acid it yielded the *monosulphate* as needles, m. p. 303° (decomp.) (Found: C, 44·2; H, 5·7; N, 21·4; S, 9·6. $C_{12}H_{15}N_5,H_2SO_4$ requires C, 44·0; H, 5·2; N, 21·4; S, 9·7%).

4 : 5-*Diamino*-6-*furfurylaminopyrimidine.* 4-Amino-6-furfurylamino-5-nitropyrimidine (6 g.) in ethanol (300 ml.) was similarly reduced after which the solution was filtered and evaporated to 15 ml. *in vacuo*. Dilution with four volumes of water and ice-cooling yielded 4 : 5-*diamino*-6-*furfurylaminopyrimidine* (4·0 g., 76%), forming plates, m. p. 119—119·5°, from benzene (Found: C, 52·7; H, 5·3; N, 34·3. $C_9H_{11}ON_5$ requires C, 52·6; H, 5·4; N, 34·1%). The base (2·5 g.) in ethanol (35 ml.) with concentrated sulphuric acid (1·5 ml.) in water (5 ml.) yielded the *monosulphate* (3·1 g.), plates, m. p. 167—168° (decomp.) (from aqueous ethanol) (Found: C, 35·9; H, 4·4; N, 22·8; S, 10·3. $C_9H_{11}ON_5,H_2SO_4$ requires C, 35·6; H, 4·3; N, 23·1; S, 10·5%).

4 : 5-*Diamino*-6-cyclo*hexylaminopyrimidine.* 4-Amino-6-*cyclo*hexylamino-5-nitropyrimidine (7·5 g.), suspended in ethanol (200 ml.), was catalytically reduced and the filtrate evaporated to dryness *in vacuo* to yield 4 : 5-*diamino*-6-cyclo*hexylaminopyrimidine* (6·3 g., 98%), plates, m. p. 215° (Found: C, 57·4; H, 7·8; N, 33·9. $C_{10}H_{17}N_5$ requires C, 57·9; H, 8·3; N, 33·8%). Crystallisation of the base (4 g.) from hot 2N-sulphuric acid (150 ml.) yielded the *monosulphate* (4·6 g.), m. p. 198—202° (Found: C, 39·6; H, 6·5; N, 23·4; S, 10·5. $C_{10}H_{17}N_5,H_2SO_4$ requires C, 39·3; H, 6·2; N, 22·9; S, 10·4%).

4-(*Substituted amino*)*pteridines.*—4-*Dimethylaminopteridine.* 4 : 5-Diamino-6-dimethylaminopyrimidine (1·6 g.), glyoxal monohydrate (1·6 g.), and water (15 ml.) were heated on a steam-bath for 30 min. Ice-cooling yielded white needles of 4-dimethylaminopteridine (1·5 g., 82%), m. p. 166—167°. Recrystallisation from benzene gave pale yellow prisms, m. p. 168—169° (Found: C, 54·9; H, 4·8; N, 40·2. Calc. for $C_8H_9N_5$: C, 54·8; H, 5·2; N, 39·9%). Albert *et al.*[6] give m. p. 159—161°.

4-*Benzylaminopteridine.* 4 : 5-Diamino-6-benzylaminopyrimidine (1·25 g.), glyoxal monohydrate (2·0 g.), and water (100 ml.) were heated for 15 min. on a steam-bath. The *pteridine* (1·15 g., 72%) was rapidly precipitated and, after ice-cooling, was isolated by filtration. It was obtained from ethanol as pale yellow prisms, m. p. 160—161° (Found: C. 66·0: H 4·3: N, 29·0. $C_{13}H_{11}N_5$ requires C, 65·8; H, 4·6; N, 29·5%).

4-*Phenethylaminopteridine.* 4 : 5-Diamino-6-phenethylaminopyrimidine (2·5 g.), glyoxal monohydrate (3 g.), ethanol (30 ml.) and water (50 ml.) were heated on a steam-bath for 15 min. The mixture was cooled in ice, and the *product* (1·8 g., 65%) removed by filtration. Recrystallisation from ethanol–light petroleum (b. p. 60—80°) yielded pale yellow prisms, m. p. 159—160° (Found: C, 67·0; H, 5·2; N, 28·0. $C_{14}H_{13}N_5$ requires C, 66·9; H, 5·2; N, 27·8%).

4-*Furfurylaminopteridine.* 4 : 5-Diamino-6-furfurylaminopyrimidine (3 g.), glyoxal monohydrate (4 g.), ethanol (20 ml.) and water (40 ml.) were heated on a steam-bath for 30 min. Ice-cooling yielded the *product* (2·25 g., 68%), m. p. 141—142° (from benzene) (Found: C, 58·0; H, 3·9; N, 30·7. $C_{11}H_9ON_5$ requires C, 58·1; H, 3·9; N, 30·8%).

4-cyclo*Hexylaminopteridine.* 4 : 5-Diamino-6-*cyclo*hexylaminopyrimidine (3 g.), glyoxal monohydrate (3 g.), ethanol (30 ml.) and water (30 ml.) were heated on a steam-bath for 30 min. Evaporation of the solution *in vacuo* to half its volume followed by ice-cooling afforded 4-cyclo*hexylaminopteridine* (3·1 g., 93%), m. p. 105·5—106° (from 10% ethanol), pale yellow needles (Found: C, 62·4; H, 6·2; N, 30·8. $C_{12}H_{15}N_5$ requires C, 62·8; H, 6·6; N, 30·5%).

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Chester-Beatty Research Institute,
Institute of Cancer Research: Royal Cancer Hospital,
Fulham Road, London, S.W.3.

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