459. *Hydropteridines. Part I. The Formation of 5 : 6 : 7 : 8-Tetrahydro-4 : 6-dimethylpteridines.*

By J. H. Lister and G. R. Ramage.

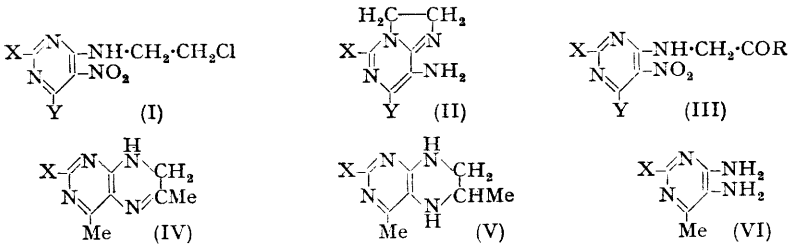
Reduction and cyclisation of 4-acetonylamino-6-methyl-5-nitropyrimidines give 7 : 8-dihydro-4 : 6-dimethylpteridines which can be further reduced to 5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridines. These have been characterised by comparing their ultra-violet spectra with those of the corresponding 4 : 5-diamino-6-methylpyrimidines.

Recent developments in the chemotherapy of anæmia have shown that the liver factor isolated by Sauberlich and Baumann (*J. Biol. Chem.*, 1948, **176**, 165), capable of supporting *Leuconostoc citrovorum* 8081, contains a reduced pteridine nucleus. This factor may undergo oxidative changes during extraction to give pteroylglutamic acid (May, Bardos, Barger, Lansford, Ravel, Sutherland, and Shive, *J. Amer. Chem. Soc.*, 1951, **73**, 3067). Simpler reduced pteridines, *e.g.* dihydro- and tetrahydro-pteridines, and the conditions necessary for their oxidation to pteridines are being investigated.

Of various possible routes to tetrahydropteridines (V) under examination one has been reported. The cyclisation of some 4-2′-chloroethylaminopyrimidines (I) gave, however, glyoxalinopyrimidines (II), and not derivatives of pteridine (Ramage and Trappe, *J.*, 1952, 4410).

Some 5-nitro-4-pyrimidylaminoacetic esters (III; R = OEt) (Boon, Jones, and Ramage, *J.*, 1951, 96) and the corresponding acetone compounds (III; R = Me) Boon and Jones,

ibid., p. 591) gave dihydropteridines on reduction. Other hydro-derivatives have been prepared from 6 : 7-dimethyl- and 6 : 7-diphenyl-pteridine by reduction (Polonovski, Pesson, and Puister, *Compt. rend.*, 1950, **230**, 2205).



The present experiments are based on the condensation of 2 : 4-dichloro-6-methyl-5-nitropyrimidine with aminoacetone, giving 4-acetonylamino-2-chloro-6-methyl-5-nitropyrimidine (III; R = Me, X = Cl, Y = Me). This was catalytically reduced in ethanol in the presence of Raney nickel, best at 55°. After removal of the catalyst from the hot solution and cooling, 2-chloro-7 : 8-dihydro-4 : 6-dimethylpteridine (IV; R = Me, X = Cl) crystallised. Boon and Jones (*loc. cit.*) reported that they were unable to isolate this product.

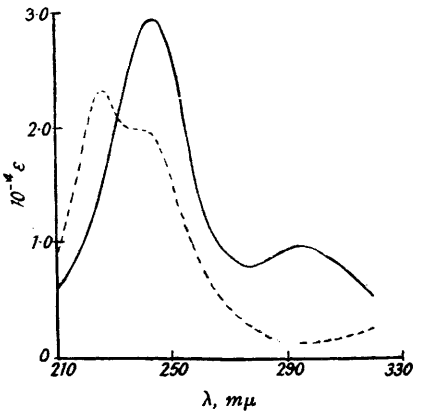


FIG. 1.

——— 2-*Diethylamino*-7 : 8-*dihydro*-4 : 6-*dimethylpteridine* (IV; X = NEt_2) *in* 0·1N-HCl.

– – – – 2-*Diethylamino*-4 : 6-*dimethylpteridine* *in* 0·1N-HCl.

Other 2-substituted 7 : 8-dihydro-4 : 6-dimethylpteridines have been prepared similarly, the required substituents being introduced before the reduction and cyclisation. Dilute acid hydrolysis of 4-acetonylamino-2-chloro-6-methyl-5-nitropyrimidine gave the 2-hydroxypyrimidine (III; R = Me, X = OH, Y = Me) whereas alcoholic ammonia, or primary or secondary amine gave (III; R = Me, X = NH_2 or substituted amino, Y = Me), and with alcoholic sodium hydrogen sulphide (III; R = Me, X = SH, Y = Me) was obtained. These were reduced in alcohol with hydrogen in the presence of Raney nickel whereupon cyclisation to the dihydropteridine occurred.

The reduction of the dihydropteridines, in glacial acetic acid, in the presence of platinum oxide has been used generally for the preparation of 2-substituted 5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridines. Even the 2-chloro-derivative (IV; X = Cl) took up one mole of hydrogen to give 2-chloro-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (V; X = Cl), and no ionic chlorine could be detected. However, further reduction in ethanol, in the presence of palladium–charcoal, gave a hydrochloride from which 5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (V; X = H) was obtained by treatment with concentrated alkali.

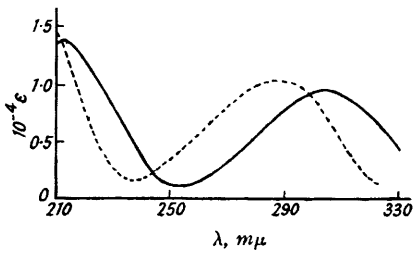
It was preferable to reduce some dihydropteridines in alcohol, under pressure, in the presence of Raney nickel, to the tetrahydropteridine, *e.g.* 2-diethylamino-7 : 8-dihydro-4 : 6-dimethylpteridine (IV; X = NEt_2) was smoothly reduced at 60 atm. to 2-diethylamino-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (V; X = NEt_2).

The 7 : 8-dihydro-4 : 6-dimethylpteridines were unstable in both 0·1N-acid and 0·05N-

alkali, oxidation back to the pteridine rapidly occurring on short exposure to the atmosphere. This conversion was followed by periodic examination of the ultra-violet spectra and comparisons of the final curves with those of the pteridines themselves (Fig. 1). In contrast no change occurred during the ageing of acid solutions of the tetrahydropteridines, and reproducible spectra were obtained after some weeks.

From the structural aspect, the tetrahydropteridines can be related to the 4 : 5-diaminopyrimidines. The two give almost identical spectra, differing only in that the bands of maximum absorption in the tetrahydropteridines are moved to longer wave-

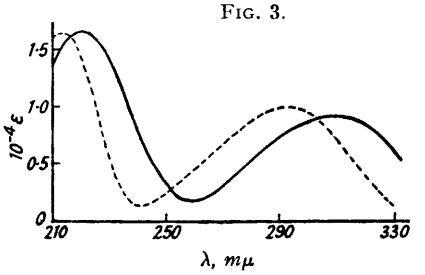
FIG. 2.



——— 5 : 6 : 7 : 8-*Tetrahydro*-4 : 6-*dimethylpteridine* (V; X = H) *in* 0·1N-HCl.

– – – – 4 : 5-*Diamino*-6-*methylpyrimidine* (VI; X = H) *in* 0·1N-HCl.

FIG. 3.



——— 2-*Chloro*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine* (V; X = Cl) *in* 0·1N-HCl.

– – – – 4 : 5-*Diamino*-2-*chloro*-6-*methylpyrimidine* (VI; X = Cl) *in* 0·1N-HCl.

lengths (Figs. 2 and 3), and such comparisons have proved to be a useful method of characterisation.

The hydropteridines described did not appear to form characteristic derivatives.

Comparative spectra of 2-*substituted* 5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridines* (V) *and related* 4 : 5-*diamino*-6-*methylpyrimidines* (VI), *in* 0·1N-*hydrochloric acid* (*wave-lengths are in* mμ; *the values in parentheses are* 10^{-4} $\varepsilon_{max.}$).

X	(V) Max.		Min.	(VI) Max.		Min.
OH	230 (0·993)	325 (0·698)	270 (0·203)	214 (1·25)	293 (0·787)	255 (0·207)
H	213 (1·36)	306 (0·936)	254 (0·112)	<210	288 (1·04)	238 (0·188)
Cl	221 (1·66)	310 (0·910)	258 (0·170)	214 (1·63)	292 (0·983)	241 (0·146)
NEt_2	235 (2·58)	—	—	233 (2·87)	290 (0·277)	274 (0·234)
NH_2	212 (2·08)	233 (1·12)	228 (1·11)	<210	277 (0·478)	261 (0·412)

7 : 8-*Dihydro*-4 : 6-*dimethylpteridines* (IV), *in* 0·1N-*hydrochloric acid.*

X	Max.		Min.
OH	<210 (—)	284 (1·24)	241 (0·278)
Cl	217 (2·48)	302 (0·7) (approx.)	256 (0·199)
NEt_2	244 (2·90)	295 (0·956)	276 (0·782)
NH_2	226 (3·17)	291 (1·02)	260 (0·444)

The determinations were made by means of a Unicam S.P. 500 quartz spectrophotometer (kindly lent by the Wool Textile Research Council).

EXPERIMENTAL

4-*Acetonylamino*-2-*amino*-6-*methyl*-5-*nitropyrimidine.*—4-Acetonylamino-2-chloro-6-methyl-5-nitropyrimidine (2 g.) (Boon and Jones, *loc. cit.*) was dissolved in warm ethanol and treated with ammonia solution (*d* 0·88; 6 c.c.). The solution was boiled under reflux for 25 min. and, on cooling in ice-water, 4-*acetonylamino*-2-*amino*-6-*methyl*-5-*nitropyrimidine* (1·1 g., 60%) separated as brown prisms, m. p. 198—200° (decomp.), from water (Found : C, 42·2; H, 5·1. $C_8H_{11}O_3N_5$ requires C, 42·7; H, 4·9%).

4-*Acetonylamino*-2-*diethylamino*-6-*methyl*-5-*nitropyrimidine.*—4-Acetonylamino-2-chloro-6-

methyl-5-nitropyrimidine (5 g.) in ethanol (80 c.c.) was treated with diethylamine (5 c.c.) dropwise, with shaking. The lemon-yellow needles (5·2 g., 90%) which quickly separated had m. p. 117—118°.

4-*Acetonylamino*-2-*hydroxy*-6-*methyl*-5-*nitropyrimidine*.—The 2-chloro-6-methyl-5-nitropyrimidine (3·0 g.) was refluxed in glacial acetic acid (20 c.c.) for 20 min. On cooling of the solution 4-*acetonylamino*-2-*hydroxy*-6-*methyl*-5-*nitropyrimidine* (2·4 g., 87%) separated and was filtered off and washed with dilute acetic acid; it formed needles (from water), m. p. 245° (decomp.) (Found: C, 42·9; H, 4·0. $C_8H_{10}O_4N_4$ requires C, 42·5; H, 4·45%).

2-*Chloro*-7 : 8-*dihydro*-4 : 6-*dimethylpteridine*.—4-Acetonylamino-2-chloro-6-methyl-5-nitropyrimidine (5 g.), in warm ethanol (100 c.c.), was hydrogenated at 45—50° and atmospheric pressure in the presence of Raney nickel catalyst (8 c.c.; settled suspension); hydrogen uptake was complete after 50 min. Cooling the concentrated filtrate gave 2-*chloro*-7 : 8-*dihydro*-4 : 6-*dimethylpteridine* (3·1 g., 77%) as plates, m. p. 215° (decomp.), from ethanol (Found: C, 48·6; H, 4·3. $C_8H_9N_4Cl$ requires C, 48·9; H, 4·6%).

2-*Amino*-7 : 8-*dihydro*-4 : 6-*dimethylpteridine*.—A suspension of 4-acetonylamino-2-amino-6-methyl-5-nitropyrimidine (2·53 g.) in ethanol (175 c.c.) was shaken with Raney nickel (10 c.c., settled suspension) in hydrogen; theoretical uptake was reached in about 90 min. The combined filtrate and washings were concentrated under reduced pressure; the resulting 2-amino-7 : 8-dihydro-4 : 6-dimethylpteridine (1·75 g.) formed brown prisms, m. p. 200° (decomp.), from water (Found: C, 49·2; H, 6·9. $C_8H_{11}N_5,H_2O$ requires C, 49·2; H, 6·7%).

2-*Diethylamino*-7 : 8-*dihydro*-4 : 6-*dimethylpteridine*.—4-Acetonylamino-2-diethylamino-6-methyl-5-nitropyrimidine (3 g.) was reduced as described for the 2-amino-compound, giving orange-yellow needles (2·0 g., 80%), m. p. 124—125°, from ligroin. Boon and Jones (*loc. cit.*) report m. p. 121°.

7 : 8-*Dihydro*-2-*hydroxy*-4 : 6-*dimethylpteridine*.—4-Acetonylamino-2-hydroxy-6-methyl-5-nitropyrimidine (1·9 g.), suspended in aqueous ethanol (75 c.c.), was hydrogenated over Raney nickel (4 c.c., settled suspension) at 50° for 30 min. The combined filtrate and aqueous washings on cooling deposited 7 : 8-*dihydro*-2-*hydroxy*-4 : 6-*dimethylpteridine* as needles (from water), which turned black but did not melt at 250° and decomposed at 294° (Found: C, 54·1; H, 5·7. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·7%).

2-*Chloro*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine*.—2-Chloro-7 : 8-dihydro-4 : 6-dimethylpteridine (2 g.), in acetic acid (50 c.c.), was hydrogenated at atmospheric temperature and pressure over Adams's catalyst (0·1 g.). Uptake ceased at 1 mol. of hydrogen after 5 hr. Evaporation of the filtered solution under reduced pressure in an atmosphere of hydrogen gave a residue which was washed with a little methanol and crystallised from amyl alcohol, giving 2-*chloro*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine* (1·55 g., 77%) as salmon-pink needles, m. p. 226—227° (Found: C, 48·6; H, 5·9; Cl, 17·9. $C_8H_{11}N_4Cl$ requires C, 48·4; H, 5·6; Cl, 17·9%). It gave no precipitate with mercuric chloride solution.

5 : 6 : 7 : 8-*Tetrahydro*-4 : 6-*dimethylpteridine*.—Hydrogenation of 2-chloro-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (1·5 g.) in ethanol (100 c.c.) in the presence of palladium–charcoal (2·0 g., 10%) proceeded smoothly with the absorption of 1 mol. of hydrogen. The combined filtrate and washings (hot ethanol) gave on evaporation a pinkish-white, crystalline hydrochloride (1·4 g.), m. p. 231° (from amyl alcohol).

The *base* (0·7 g., 56%), on crystallisation from ligroin containing a little ethyl acetate, formed pink prisms, m. p. 159° (Found: C, 58·4; H, 7·4; N, 34·2. $C_8H_{12}N_4$ requires C, 58·5; H, 7·4; N, 34·1%). It gave a product, m. p. 252—253°, with picric acid, and a white precipitate with mercuric chloride solution.

2-*Amino*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine*.—2-Amino-7 : 8-dihydro-4 : 6-dimethylpteridine (0·25 g.) was hydrogenated over Adams's catalyst (0·03 g.) in glacial acetic acid, as for the 2-chloropteridine. Removal of the solvent left a red oil which crystallised in contact with 50% potassium hydroxide solution. 2-*Amino*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine* formed brown prisms (0·15 g., 60%), m. p. 206—207°, from water (Found: C, 51·3; H, 7·5; N, 36·8. $C_8H_{13}N_5,\frac{1}{2}H_2O$ requires C, 51·1; H, 7·5; N, 37·2%). It gave a yellow precipitate with mercuric chloride solution; the picrate had m. p. 270° (decomp.).

2-*Diethylamino*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine*.—2-Diethylamino-7 : 8-dihydro-4 : 6-dimethylpteridine (2 g.) in ethanol (200 c.c.) was reduced at 45 atmospheres' pressure with hydrogen and Raney nickel (7 c.c., settled suspension) for 10 hr. Removal of the catalyst gave a straw-coloured solution with a blue fluorescence, from which the alcohol was removed under reduced pressure in an atmosphere of hydrogen, leaving a brown oil which slowly crystallised. 2-*Diethylamino*-5 : 6 : 7 : 8-*tetrahydro*-4 : 6-*dimethylpteridine* formed brown prisms,

m. p. 93° (1·7 g., 84%), from ligroin containing a little ethyl acetate, or from aqueous acetone (Found: C, 61·4; H, 8·7. $C_{12}H_{21}N_5$ requires C, 61·2; H, 9·0%).

5 : 6 : 7 : 8-*Tetrahydro-2-hydroxy-4 : 6-dimethylpteridine*.—The hydrogenation of 7 : 8-dihydro-2-hydroxy-4 : 6-dimethylpteridine (1·15 g.) in acetic acid (50 c.c.) over Adams's catalyst (0·03 g.) for 5 hr. gave 5 : 6 : 7 : 8-*tetrahydro-2-hydroxy-4 : 6-dimethylpteridine* as needles, which blackened without melting around 300° (Found: C, 53·8; H, 6·7; N, 30·2. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·7; N, 31·1%). The picrate had m. p. 235° (decomp.).

2-*Diethylamino-4 : 6-dimethylpteridine*.—(*a*) A solution of potassium permanganate (1 g.) in dry acetone (500 c.c.) was added dropwise with stirring to 2-diethylamino-7 : 8-dihydro-4 : 6-dimethylpteridine (2 g.) in dry acetone (100 c.c.). The addition was complete after 2 hr. and stirring was continued for a further 2 hr. The solvent was evaporated from the filtered solution leaving a red oil which slowly crystallised. 2-*Diethylamino-4 : 6-dimethylpteridine* (1·8 g., 91%) formed red prisms, m. p. 87—88°, from light petroleum (b. p. 40—60°) (Found: C, 62·4; H, 7·3. $C_{12}H_{17}N_5$ requires C, 62·3; H, 7·4%).

(*b*) 2-Diethylamino-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (0·5 g.) was oxidised with permanganate (0·5 g.) as above; removal of the acetone gave 2-diethylamino-4 : 6-dimethylpteridine (0·2 g.), m. p. 87—88° alone and on admixture with the sample prepared as in (*a*). The identity was confirmed by the ultra-violet spectrum.

4-*Amino-2-diethylamino-6-methyl-5-nitropyrimidine*.—4-Amino-2-chloro-6-methyl-5-nitropyrimidine (1 g.) was dissolved in ethanol (50 c.c.), and diethylamine (1·5 c.c.) added. The solution was evaporated to dryness and the yellow residue crystallised from water–ethanol (4 : 1) giving 4-*amino-2-diethylamino-6-methyl-5-nitropyrimidine* as yellow needles, m. p. 73—74° (Found: C, 48·4; H, 6·8. $C_9H_{15}O_2N_5$ requires C, 48·0; H, 6·7%).

4 : 5-*Diamino-2-diethylamino-6-methylpyrimidine*.—4-Amino-2-diethylamino-6-methyl-5-nitropyrimidine (0·2 g.) in ethanol (30 c.c.) was hydrogenated with Raney nickel (1 c.c., settled suspension), uptake being complete in 4 hr. The solution was filtered and concentrated under reduced pressure, leaving a pale brown solid. This was crystallised from ligroin giving 4 : 5-*diamino-2-diethylamino-6-methylpyrimidine* (0·1 g., 58%), m. p. 97° (Found: C, 55·3; H, 8·6. $C_9H_{17}N_5$ requires C, 55·4; H, 8·8%).

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