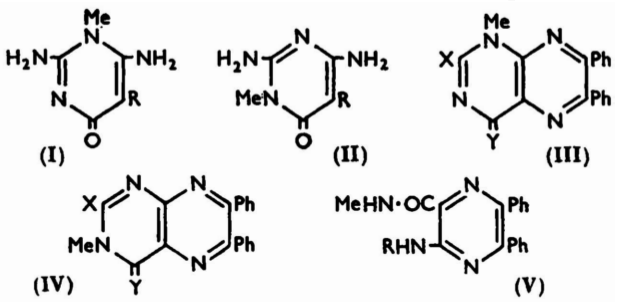
412. *Pteridines. Part V.* Derivatives of 1 : 4-Dihydro-1- and 3 : 4-Dihydro-3-methyl-6 : 7-diphenylpteridine.*

By W. R. Boon and G. Bratt.

The preparation of a number of derivatives of 1 : 4-dihydro-1- and 3 : 4-dihydro-3-methyl-6 : 7-diphenylpteridine is described. Condensation of methylguanidine with ethyl cyanoacetate gives 4-amino-6-hydroxy-2-methylaminopyrimidine and 2 : 6-diamino-1 : 4-dihydro-1-methyl-4-oxopyrimidine and not 2 : 6-diamino-3 : 4-dihydro-3-methyl-4-oxopyrimidine.

On condensation of methylguanidine with ethyl cyanoacetate, Roth, Smith, and Hultquist [1] obtained, in addition to 4-amino-6-hydroxy-2-methylaminopyrimidine, an isomeric substance to which they assigned the structure (II; R = H). This assignment was based on a comparison of the melting points of their two products with those obtained in a similar condensation of methylguanidine with ethyl acetoacetate.[2] Nitrosation of the presumed (II; R = H) followed by reduction and condensation with diacetyl gave a pteridine derivative whose infrared spectrum they considered to be in accord with the structure (IV; X = NH_2, Y = O, Me replacing Ph). We have now prepared 2-amino-1 : 4-dihydro-1-methyl-4-oxo-6 : 7-diphenylpteridine (III; X = NH_2, Y = O) and 2-amino-3 : 4-dihydro-3-methyl-4-oxo-6 : 7-diphenylpteridine (IV; X = NH_2, Y = O) by unambiguous methods for comparison with the product obtained by condensation between benzil and the triaminopyrimidine of Roth *et al.*



5 : 6-Diamino-1 : 4-dihydro-2-mercapto-1-methyl-4-oxopyrimidine [3] with benzil gave 1 : 4-dihydro-2-mercapto-1-methyl-4-oxo-6 : 7-diphenylpteridine (III; X = SH, Y = O) which on reaction with ammonia or methylamine in presence of mercuric oxide was converted into the bases (III; X = NH_2 and NHMe, Y = O). The former product was identical with that obtained by condensation of benzil with the triaminopyrimidine of Roth *et al.* which must therefore have the constitution (I; R = NH_2). Hydrolysis of the product (III; X = NH_2, Y = O) yielded 1 : 4-dihydro-2-hydroxy-1-methyl-4-oxo-6 : 7-diphenylpteridine (III; X = OH, Y = O), also obtained by oxidation of the thiol (III; X = SH, Y = O) with hydrogen peroxide and by alkaline hydrolysis of the thioamide (III; X = NH_2, Y = S).

Treatment of the amide (III; X = NH_2 or MeNH, Y = O) with phosphorus pentasulphide in pyridine gave the thioamide (III; X = NH_2 or NHMe, Y = S). This reaction product, with methylamine and ammonia, gave the imino-derivatives (III; X = NH_2, Y = MeN and NH respectively), the latter identical with the product whose hydriodide had previously been obtained in these laboratories by Richardson [4] from 2 : 4-diamino-6 : 7-diphenylpteridine and methyl iodide.

* Part IV, preceding paper.

[1] Roth, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2864.
[2] Majima, *Ber.*, 1908, **41**, 176.
[3] Traube and Winter, *Arch. Pharm.*, 1906, **244**, 16.
[4] Dora N. Richardson, personal communication.

1 : 4-Dihydro-2-mercapto-1-methyl-6 : 7-diphenyl-4-thionopteridine was readily obtained from the thiol (III; X = SH, Y = O) and phosphorus pentasulphide.

2-Amino-5 : 6-diphenylpyrazine-3-carboxylic acid [5] was converted *via* its methyl ester into the methylamide (V; R = H) which with ethyl chloroformate gave the urethane (V; R = CO_2Et). This was then cyclised to the pteridine (IV; X = OH, Y = O) with sodium ethoxide.

Experimental

1 : 4-*Dihydro*-2-*mercapto*-1-*methyl*-4-*oxo*-6 : 7-*diphenylpteridine*.—5 : 6-Diamino-1 : 4-dihydro-2-mercapto-1-methyl-4-oxopyrimidine sulphate (7 g.), benzil (6 g.), and crystalline sodium acetate (18 g.) were heated under reflux for 6 hr. in 75% aqueous ethanol. The product which separated on cooling was collected, extracted with hot light petroleum (b. p. 100—120°), and crystallised from butanol to give the *pteridine* (7·4 g.), m. p. 289° (Found: C, 66·0; H, 4·2; N, 15·6; S, 9·6. $C_{19}H_{14}ON_4S$ requires C, 65·9; H, 4·1; N, 16·2; S, 9·3%).

2-*Amino*-1 : 4-*dihydro*-1-*methyl*-4-*oxo*-6 : 7-*diphenylpteridine*.—(*a*) 2 : 5 : 6-Triamino-1 : 4-dihydro-1-methyl-4-oxopyrimidine sulphate (6·3 g.), benzil (5·8 g.), and crystalline sodium acetate (17 g.) were heated under reflux for 6 hr. in 25% v/v aqueous ethanol. The *pteridine* which separated on cooling was collected and crystallised from dimethylformamide, and had m. p. 333° (decomp.) (10 g.) (Found: C, 67·5; H, 4·8; N, 20·6. $C_{19}H_{15}ON_5,0{\cdot}5H_2O$ requires C, 67·5; H, 4·7; N, 20·7%).

(*b*) 1 : 4-Dihydro-1-methyl-2-mercapto-4-oxo-6 : 7-diphenylpteridine (0·4 g.), yellow mercuric oxide (0·5 g.), butanol (70 c.c.), and chloroform (10 c.c.) were heated under reflux for 6 hr. in a slow stream of ammonia. The mixture was then filtered hot and evaporated under reduced pressure and the residue crystallised from dimethylformamide and then from ethanol; it was identical (m. p. and mixed m. p.) with the above product.

1 : 4-*Dihydro*-1-*methyl*-2-*methylamino*-4-*oxo*-6 : 7-*diphenylpteridine*, m. p. 307° (from ethanol) (Found: C, 69·8; H, 4·9; N, 20·0. $C_{20}H_{17}ON_5$ requires C, 69·9; H, 5·0; N, 20·4%), was obtained similarly in 40% yield by using methylamine in place of ammonia.

1 : 4-*Dihydro*-2-*hydroxy*-1-*methyl*-4-*oxo*-6 : 7-*diphenylpteridine*.—(*a*) 2-Amino-1 : 4-dihydro-1-methyl-4-oxo-6 : 7-diphenylpteridine (0·5 g.) and 2N-sodium hydroxide (50 c.c.) were heated under reflux for 4 hr. After cooling and acidification with acetic acid, the *hydroxy-compound* was collected and crystallised from aqueous ethanol; it (0·16 g.) had m. p. 280° (Found: C, 68·9; H, 4·2; N, 17·1. $C_{19}H_{14}O_2N_4$ requires C, 69·1; H, 4·3; N, 17·0%).

(*b*) To 1 : 4-Dihydro-2-mercapto-1-methyl-4-oxo-6 : 7-diphenylpteridine (0·9 g.) in N-potassium hydroxide, hydrogen peroxide (10 c.c. of 100-vol.) was added dropwise with stirring at 100°. The final pale yellow solution was cooled and acidified with acetic acid, and the product (0·3 g.) collected. After crystallisation from ethanol it had the same m. p. and mixed m. p. as above.

(*c*) 2-Amino-1 : 4-dihydro-1-methyl-6 : 7-diphenyl-4-thionopteridine (3 g.) in 2N-sodium hydroxide (300 c.c.) was heated under reflux for 4 hr. The crude product obtained by acidification after cooling was fractionally crystallised from methanol, to give the 2-hydroxy-4-oxo-compound (0·5 g.). A second product, m. p. 191°, not further investigated, was obtained by chromatography on alumina of the residue obtained on evaporation of the methanol mother-liquors.

2-*Amino*-1 : 4-*dihydro*-1-*methyl*-6 : 7-*diphenyl*-4-*thionopteridine*.—2-Amino-1 : 4-dihydro-1-methyl-4-oxo-6 : 7-diphenylpteridine (15 g.), phosphorus pentasulphide (19·5 g.), and pyridine (300 c.c.) were heated under reflux for 2 hr. The dark brown solid remaining after removal of the solvent under reduced pressure was extracted with 2% aqueous sodium hydroxide and crystallised twice from dimethylformamide, to give the *thione* (7·4 g.), m. p. 295° (decomp.) (Found: C, 66·2; H, 4·4; N, 20·3; S, 9·3. $C_{19}H_{15}N_5S$ requires C, 66·2; H, 4·5; N, 20·4; S, 9·0%). 1 : 4-*Dihydro*-1-*methyl*-2-*methylamino*-6 : 7-*diphenyl*-4-*thionopteridine*, m. p. 300° (decomp.) (from dimethylformamide) (Found: C, 66·9; H, 4·6; N, 20·0; S, 9·6. $C_{20}H_{17}N_5S$ requires C, 66·8; H, 4·7; N, 19·5; S, 8·9%), was obtained similarly in 16% yield from the corresponding 2-methylamino-compound. 1 : 4-*Dihydro*-2-*mercapto*-1-*methyl*-6 : 7-*diphenyl*-4-*thionopteridine*, m. p. 375° (decomp.) (from dimethylformamide without prior extraction with sodium hydroxide) (Found: C, 63·1; H, 3·9; N, 15·3; S, 17·4. $C_{19}H_{14}N_4S_2$ requires

[5] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.

C, 63·0; H, 3·9; N, 15·5; S, 17·7%), was obtained similarly in 53% yield from 1 : 4-dihydro-2-mercapto-1-methyl-4-oxo-6 : 7-diphenylpteridine.

2-*Amino*-1 : 4-*dihydro*-4-*imino*-1-*methyl*-6 : 7-*diphenylpteridine*.—(*a*) 2 : 4-Diamino-6 : 7-diphenylpteridine (3 g.), methyl iodide (6 g.), and 2-ethoxyethanol (60 c.c.) were heated under reflux for 3 hr. The hydriodide which separated on cooling was collected [m. p. 315° (decomp.)] and boiled with 10% w/v sodium carbonate for 5 min., to give the base (1·7 g.) identical (m. p. and mixed m. p. 256°) with material prepared by method (*b*).

(*b*) 2-Amino-1 : 4-dihydro-1-methyl-6 : 7-diphenyl-4-thionopteridine (2 g.), yellow mercuric oxide (2·5 g.), ethanol (120 c.c.), and chloroform (20 c.c.) were heated under reflux in a stream of ammonia for 6 hr. After filtration of the hot mixture the *base* (0·9 g.) which separated on cooling was collected and crystallised from ethanol (m. p. 256°) (Found : C, 69·5; H, 4·7; N, 24·8. $C_{19}H_{16}N_6$ requires C, 69·5; H, 4·9; N, 25·6%).

2-*Amino*-1 : 4-*dihydro*-1-*methyl*-4-*methylimino*-6 : 7-*diphenylpteridine*, m. p. 256° (from ethanol), was obtained similarly in 21% yield (Found : C, 70·5; H, 5·8; N, 24·6. $C_{20}H_{18}N_6$ requires C, 70·2; H, 5·3; N, 24·6%).

2-*Amino*-3-(N-*methylcarbamoyl*)-5 : 6-*diphenylpyrazine*.—Methyl 3-amino-5 : 6-diphenylpyrazine-2-carboxylate (3·6 g.) and methylamine (50 g.) in ethanol (500 c.c.) were heated for 16 hr. at 160—170°. The *amide* which separated on cooling was collected and crystallised from methanol; it (2 g.) had m. p. 198° (Found : C, 71·0; H, 5·4; N, 18·5. $C_{18}H_{16}ON_4$ requires C, 71·1; H, 5·3; N, 18·4%).

2-*Ethoxycarbamoylamino*-3-(N-*methylcarbamoyl*)-5 : 6-*diphenylpyrazine*.—2-Amino-3-(*N*-methylcarbamoyl)-5 : 6-diphenylpyrazine (1·5 g.) and ethyl chloroformate (40 c.c.) were heated under reflux for 20 hr. After removal of the excess of ethyl chloroformate under reduced pressure, the *urethane* (1·7 g.), m. p. 153°, was obtained by crystallisation of the residue from chloroform–light petroleum (Found : C, 67·2; H, 5·4; N, 15·3. $C_{21}H_{20}O_3N_4$ requires C, 67·1; H, 5·3; N, 14·9%).

3 : 4-*Dihydro*-2-*hydroxy*-3-*methyl*-4-*oxo*-6 : 7-*diphenylpteridine*.—2-Ethoxycarbamoylamino-3-(*N*-methylcarbamoyl)-5 : 6-diphenylpyrazine (1·25 g.) was heated under reflux for 10 hr. with a solution of sodium ethoxide [from sodium (1·5 g.) in ethanol (200 c.c.)]. The residue obtained after removal of the solvent under reduced pressure was suspended in water and acidified with acetic acid; the *pteridine*, crystallised from ethanol, had m. p. 307° (0·7 g.) (Found : C, 69·3; H, 4·2; N, 16·5. $C_{19}H_{14}O_2N_4$ requires C, 69·1; H, 4·3; N, 16·9%).

IMPERIAL CHEMICAL (PHARMACEUTICALS) LIMITED,
HEXAGON HOUSE, BLACKLEY, MANCHESTER, 9.

[*Received, December 11th*, 1956.]