392. *Antimalarial Studies in the Pteridine Field.*

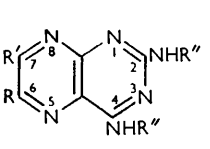
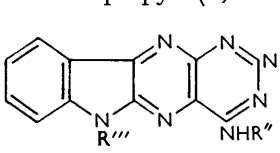
By M. D. Potter and T. Henshall.

A series of 2-, 4-, and 2 : 4-bis-(dialkylaminoalkylamino)pteridines has been prepared; preliminary pharmacological investigations indicate little or no antimalarial activity in these compounds.

New evidence is presented which contra-indicates the mechanism proposed by Taylor and Cain [1] for the reaction of an amine with 4-amino-2-mercaptopteridines.

Reports have recently appeared of activity against *Plasmodium gallinaceum* and *P. berghei* of some 6 : 7-disubstituted 2 : 4-diamino-pteridines,[2,3,4,5,6] though no extensive study of pteridine compounds as a possible source of antimalarials has so far been undertaken. Taylor [7] described the preparation of four alkylaminoalkyl derivatives of 2 : 4-diaminopteridines, but no pharmacological data were published. However, in view of the close structural similarity of 4-(dialkylaminoalkylamino)pteridines with some successful antimalarial drugs (*e.g.*, Pamaquin, Sontochin, and Chloroquine), and of the number of dialkylaminoalkyl derivatives of 2 : 4-diaminopyrimidines found to show marked antimalarial activity,[8] these compounds seemed worthy of study.

Three 2 : 4-diaminopteridines which showed antimalarial properties were chosen as the main starting materials, *viz.*, 2 : 4-diamino-6 : 7-di*iso*propyl- (I; R = R′ = Pr^{i}, R″ = H),

(I)   (II)

and 2 : 4-diamino-6 : 7-diphenyl-pteridine (I; R = R′ = Ph, R″ = H) and 2 : 4-diamino-1′-*n*-propyl(2′ : 3′-6 : 7)pteridine (II; R″ = H, R‴ = Pr^{n}). Alkylaminoalkyl groups were introduced into the 4- and the 2 : 4-positions by direct interaction in sealed tubes with four alkylaminoalkylamines in the absence or presence of small amounts of hydrochloric acid, as described by Taylor,[7] and a further three amines were used with the diphenyl compound. Attempts to prepare 2-(alkylaminoalkylamino)-4-aminopteridines by interaction of the alkylaminoalkylamine and a 4-amino-2-mercaptopteridine failed (cf. Taylor and Cain [1]). Attempts to substitute the 4-amino-group of alkyl-2 : 4-diamino-6 : 7-2′ : 3′-indolopteridines also met with little success. No reaction occurred with the *n*-propyl compound (II; R‴ = Pr^{n}), and prolonged heating (170 hours) of the corresponding methyl compound with a large excess of 3-diethylaminopropylamine gave only a very small amount of the desired product, together with a trace of the 2 : 4-dialkylated derivative. Aminoalkylation in the absence of acid also failed with 4-amino-pteridines prepared by the method described by Albert, Brown, and Cheeseman; [9] and though an apparently pure crystalline compound was isolated in good yield on reaction under acid conditions, this was not the expected 4-(dialkylaminoalkylamino)pteridine. Further, 2-(3-diethylaminopropylamino)-6 : 7-diphenyl- and -6 : 7-*cyclo*hepteno-pteridine were synthesised by the condensation of 4 : 5-diamino-2-(3-diethylaminopropylamino)pyrimidine with the appropriate α-diketone under nitrogen, but an attempt to prepare a similar derivative of 6 : 7-di*iso*propylpteridine gave only a gum.

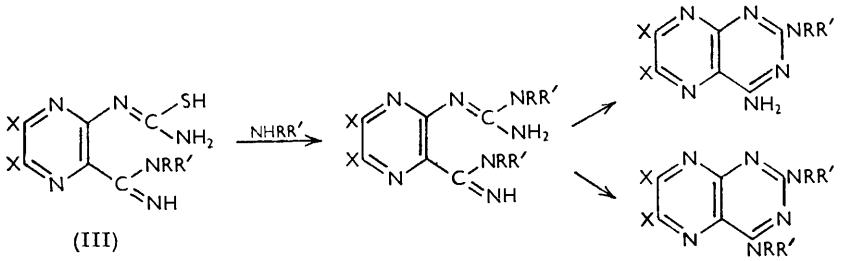
Although the corresponding unalkylated 2-aminopteridines were not required as intermediates, they were synthesised for comparison from 2 : 4 : 5-triaminopyrimidine by

[1] Taylor and Cain, *J. Amer. Chem. Soc.*, 1951, **73**, 4384.
[2] Greenberg, *J. Pharmacol.*, 1949, **97**, 484.
[3] Falco, Goodwin, Hitchings, Rollo, and Russel, *Brit. J. Pharmacol.*, 1951, **6**, 185.
[4] McConnachie, *Parasitology*, 1953, **42**, 272.
[5] H. O. J. Collier, personal communication.
[6] Thurston, *Parasitology*, 1954, **44**, 99.
[7] Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1648.
[8] Rose, *J.*, 1951, 2770.
[9] Albert, Brown, and Cheeseman, *J.*, 1952, 4219.

Albert, Brown, and Cheeseman's method,[9] but the 5-nitropyrimidine was reduced in alcohol with Raney nickel and hydrogen instead of with sodium dithionite, so that the unstable triaminopyrimidine could be used in solution without isolation.

Preliminary pharmacological tests indicated that the majority of our derivatives have much less antimalarial activity than their parent 6 : 7-disubstituted 2 : 4-diaminopteridines, except 2-amino-4-(3-diethylaminopropylamino)-6 : 7-diphenylpteridine which shows slightly increased activity. A most interesting pharmacological result, however, is the complete lack of antagonism to pteroylglutamic acid shown by 2- and 4-amino-6 : 7-di*iso*propylpteridine, with *Streptococcus faecalis* as the test organism : 2 : 4-diamino-6 : 7-di*iso*propylpteridine is one of the most powerful known pteroylglutamic acid antagonists.[10]

Attempted Preparation of 2-(Alkylaminoalkylamino)-4-aminopteridines.—Taylor and Cain [1,11] described the preparation of a number of 2-alkylamino-4-aminopteridines from 4-amino-2-mercaptopteridines and the appropriate amine. They claim that the use of a " high-boiling, strongly basic amine " leads further to alkylation of the 4-amino-group, and that in these cases attempts to limit substitution to the 2-amino-group failed. They therefore postulate the occurrence of the open-chain intermediate (III), which yields either the



(III)

2-aminoalkylated or the bis-aminoalkylated product by the reactions indicated. A similar mechanism was suggested by Taylor [7] for the reaction of an amine with a 2 : 4-diaminopteridine in the absence of acid to produce 2-amino-4-alkylaminopteridines.

However, 4-(3-diethylaminopropylamino)-2-mercapto-6 : 7-diphenylpteridine has now been isolated after reaction of 4-amino-2-mercapto-6 : 7-diphenylpteridine and 3-diethylaminopropylamine; and when further heated with the alkylaminoalkylamine, the intermediate was smoothly converted into the 2 : 4-bisaminoalkylated product. A similar intermediate was isolated from the same amine and 4-amino-2-mercapto-6 : 7-di*iso*propylpteridine. So it seems that replacement of the 2-mercapto-group occurs in the pteridine itself and that the postulated ring-opening is unnecessary; further, the fact that the substitution of the 2-mercapto-group occurs more easily after the 4-amino-group has been alkylated is almost certainly due to the increased solubility.

An attempt to prove the independence of the substitution of the 2-mercapto-group by refluxing 2-mercapto-6 : 7-diphenylpteridine with 3-diethylaminopropylamine in ethanol met with little success; for, although reaction apparently took place (evolution of hydrogen sulphide), only tars were obtained, possibly owing to the absence of the stabilising influence of the 4-amino-group.

One reason cited by Taylor and Cain [1] against the direct replacement of the 2-mercapto-group on the pteridine nucleus is based on the well-known stability of 5-amino-2-mercaptopyrimidines. This stability is not, in fact, general, since Brown [12] has shown that a 2-mercapto-5-nitropyrimidine reacts readily with methylamine under relatively mild conditions.

Finally, there appears to be little foundation for the division of amines made by Taylor and Cain into strongly basic and weakly basic amines, to account for the two possible courses of the reaction. Piperidine (pK_a 11·6) a strong base, and morpholine (pK_a 8·4) a

[10] Collier and Waterhouse, *Ann. Trop. Med. Parasitol.*, 1950, **44**, 273.
[11] Taylor and Cain, *J. Amer. Chem. Soc.*, 1952, **74**, 1644.
[12] Brown, *J. Appl. Chem.*, 1954, **4**, 72.

relatively weak base; both react with 4-amino-2-mercaptopteridines to give the 4-amino-2-alkylaminopteridine, and neither reacts with 2 : 4-diaminopteridine in the absence of acid. Ethanolamine (pK_a 9·5) and benzylamine (pK_a 9·4), on the other hand, have intermediate basicity and yet readily substitute the 4-amino-group of 4-amino-2-mercapto- and of 2 : 4-diamino-pteridines under similar conditions. Equally there appears to be little correlation between the course of the reaction and the boiling points of the amines concerned. From the evidence available it now appears that the course of these reactions is determined by the primary or secondary character of the amine. Primary alkylamines appear to react readily with the 4-amino-group of either 2 : 4-diamino- or 4-amino-2-mercapto-pteridines, while secondary amines appear to be unable to substitute this position unless " activated " by hydrochloric acid. The only exceptions so far recorded involve methyl-substituted amines.[1]

Experimental

2-*Amino*-6 : 7-*diphenylpteridine*.—A solution of benzil (1·9 g.) in ethanol (20 ml.) was added to a hot solution of 2 : 4 : 5-triaminopyrimidine sulphate [13] (2·0 g.) in acetic acid (6 ml.) and water (20 ml.), and the whole refluxed for 2 hr., then diluted with water, and basified with ammonia. The dark brown precipitate was filtered off and twice recrystallised from aqueous ethanol (charcoal), giving golden-yellow needles of 2-*amino*-6 : 7-*diphenylpteridine*, m. p. 240—241° (1·2 g., 44%) (Found: C, 72·4; H, 4·3; N, 23·2. $C_{18}H_{13}N_5$ requires C, 72·2; H, 4·4; N, 23·4%).

2-*Amino*-6 : 7-*di*iso*propylpteridine*.—A solution of 2 : 5-dimethylhexane-3 : 4-dione [14] (3·7 g.) in ethanol (50 ml.) was added to 2 : 4 : 5-triaminopyrimidine (3·2 g.) in acetic acid (12 ml.) and water (80 ml.), and the mixture refluxed for 2 hr. The alcohol was removed by distillation, and the cooled solution basified with ammonia. Crude 2-*amino*-6 : 7-*di*iso*propylpteridine* separated as green crystals. Recrystallisation from aqueous ethanol (charcoal) gave 1·9 g. (31%) of pale yellow needles, m. p. 189—190·5° (Found: C, 62·5; H, 7·6; N, 30·5. $C_{12}H_{17}N_5$ requires C, 62·4; H, 7·4; N, 30·3%).

2-*Amino*-6 : 7-cyclo*heptenopteridine*.—A suspension of 2 : 4-diamino-5-nitropyrimidine [13] (1·0 g.) in methanol (25 ml.) was shaken at room temperature in hydrogen in the presence of Raney nickel until absorption was complete (6 hr.). After removal of the catalyst under nitrogen, *cyclo*heptane-1 : 2-dione [15] (0·82 g.) was added, and the mixture refluxed for 30 min. in nitrogen. The greenish-yellow precipitate of 2-*amino*-6 : 7-cyclo*heptenopteridine* formed tan-coloured crystals m. p. 274—276° (0·5 g., 36%), from dimethylformamide (charcoal) (Found: C, 61·5; H, 6·1; N, 32·2. $C_{11}H_{13}N_5$ requires C, 61·4; H, 6·1; N, 32·6%).

4-*Amino*-6 : 7-*diphenylpteridine*.—4 : 5 : 6-Triaminopyrimidine sulphate [16] (4·0 g.) was dissolved in water (100 ml.), and sufficient sodium carbonate added to give a neutral solution. Benzil (3·8 g.) in ethanol (100 ml.) was added, and the mixture refluxed for 2 hr. and then set aside overnight. The pale yellow crystals were filtered off and dried, and unchanged benzil was removed by digestion with hot ligroin. Recrystallisation from aqueous acetone gave 3·0 g. (50%) of 4-*amino*-6 : 7-*diphenylpteridine* as yellow needles, m. p. 202—203° (Found: C, 72·4; H, 4·3; N, 23·4. $C_{18}H_{13}N_5$ requires C, 72·2; H, 4·4; N, 23·4%). M. p. of 175° is recorded [17] for this compound prepared by a different route.

4-*Amino*-6 : 7-*di*iso*propylpteridine*.—A solution of 2 : 5-dimethylhexane-3 : 4-dione (2·6 g.) in ethanol (80 ml.) was added to a hot solution of 4 : 5 : 6-triaminopyrimidine sulphate (4·0 g.) in acetic acid (10 ml.) and water (100 ml.), and the mixture refluxed for 6 hr. After removal of the alcohol, the aqueous solution was cooled and basified with ammonia. The precipitate of pale yellow needles was twice crystallised from aqueous ethanol (charcoal), affording 4-*amino*-6 : 7-*di*iso*propylpteridine* as white needles, m. p. 175—176·5° (2·0 g., 48%) (Found: C, 62·6; H, 7·4; N, 30·3. $C_{12}H_{17}N_5$ requires C, 62·4; H, 7·4; N, 30·3%).

4-*Amino*-6 : 7-cyclo*hexenopteridine*.—*cyclo*Hexane-1 : 2-dione [18] (2·1 g.) in ethanol (80 ml.) was added to a solution of 4 : 5 : 6-triaminopyrimidine sulphate (4·0 g.) in acetic acid (10 ml.) and water (80 ml.). After 6 hours' refluxing, the alcohol was removed and the aqueous solution

[13] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[14] Campbell, Dunsmuir, and Fitzgerald, *J.*, 1950, 2743.
[15] Van der Haar, Voter, and Banks, *J. Org. Chem.*, 1949, **14**, 836.
[16] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.
[17] Taylor, Carbon, and Hoff, *J. Amer. Chem. Soc.*, 1953, **75**, 1904.
[18] Rauh, Smith, Banks, and Diehl, *J. Org. Chem.*, 1945, **10**, 199.

basified with ammonia. The chocolate-brown precipitate was twice crystallised from dimethylformamide, and gave 1·1 g. (29%) of 4-*amino*-6 : 7-cyclo*hexenopteridine* as tan-coloured needles, m. p. 296—298° (decomp.) (Found : C, 60·1; H, 5·7; N, 34·1. $C_{10}H_{11}N_5$ requires C, 59·7; H, 5·5; N, 34·8%).

4-*Amino*-6 : 7-cyclo*heptenopteridine*.—This was prepared in the same way : from 2·2 g. of *cyclo*heptane-1 : 2-dione, 1·5 g. (40%) of pure 4-*amino*-6 : 7-cyclo*heptenopteridine* were obtained, forming pale yellow needles (from dimethylformamide), m. p. 304—305° (Found : C, 61·1; H, 6·1; N, 32·6. $C_{11}H_{13}N_5$ requires C, 61·4; H, 6·1; N, 32·6%).

2 : 4-*Diamino*-6 : 7-cyclo*hexenopteridine*.—Tetra-aminopyrimidine hydrogen sulphite (3·8 g.) and acetic acid (6 ml.) were heated on the steam-bath until the evolution of sulphur dioxide was complete (15 min.). Water (60 ml.) was added, followed by a solution of *cyclo*hexane-1 : 2-dione (2 g.) in ethanol (30 ml.), and the mixture refluxed for 2 hr. The pale yellow crystalline 2 : 4-*diamino*-6 : 7-cyclo*hexenopteridine* was filtered off and washed with ethanol. Owing to its sparing solubility in ordinary organic solvents, partial purification was carried out by dissolution in hot formic acid (90%) (charcoal) and reprecipitation by addition of ammonia [yield, 3·3 g., 85%; m. p. 358—360° (decomp.)] (Found : C, 54·8; H, 5·8; N, 39·6. $C_{10}H_{12}N_6$ requires C 55·5; H, 5·6; N, 38·9%).

2 : 4-*Diamino*-6 : 7-cyclo*heptenopteridine*.—Tetra-aminopyrimidine hydrogen sulphite (9·5 g.) was warmed for 15 min. with acetic acid (30 ml.), and the acetate so formed was dissolved in 150 ml. of hot water. A solution of *cyclo*heptane-1 : 2-dione (5·5 g.) in ethanol (70 ml.) was added, and the mixture refluxed for 2 hr. The cold mixture was basified with ammonia, and the pale yellow precipitate (5·7 g., 57%) filtered off. Rapid crystallisation from dimethylformamide (charcoal) gave tan crystals of 2 : 4-*diamino*-6 : 7-cyclo*heptenopteridine*, m. p. 337—339° (decomp.) (Found : C, 56·6; H, 6·2; N, 36·8. $C_{11}H_{14}N_6$ requires C, 57·4; H, 6·1; N, 36·5%).

2 : 4-*Bis*(*dialkylaminoalkylamino*)*pteridines* (Table 1).—These *compounds* were prepared by the following general method. The 2 : 4-diaminopteridine (1·0 g.), the appropriate dialkylaminoalkylamine (10 ml.) and 2 drops of concentrated hydrochloric acid were heated in a sealed tube for 24 hr. at 180°. After removal of the excess of amine under reduced pressure, the product was crystallised as indicated.

2-*Amino*-4-(*dialkylaminoalkylamino*)*pteridines* (Table 2).—A similar procedure to that for the bisaminoalkylated products was used, but no acid was added.

2-*Mercapto*-6 : 7-*diphenylpteridine*.—A solution of benzil (0·74 g.) in ethanol (25 ml.) was added to a solution of 4 : 5-diamino-2-mercaptopyrimidine [19] (0·5 g.) in water (30 ml.), whose pH was first adjusted to 9 by addition of sodium hydroxide solution. After 30 minutes' refluxing, the cooled mixture was acidified with acetic acid, and the precipitate filtered off. Two recrystallisations from aqueous dimethylformamide (charcoal) gave 1·1 g. (90%) of fawn needles of 2-*mercapto*-6 : 7-*diphenylpteridine*, m. p. 189—190° (decomp.) (Found : C, 67·0; H, 3·95; N, 18·2; S, 10·2. $C_{18}H_{12}N_4S$ requires C, 68·3; H, 3·8; N, 17·7; S, 10·1%).

4-*Amino*-2-*mercapto*-6 : 7-*di*iso*propylpteridine*.—A suspension of 4 : 5 : 6-triamino-2-mercaptopyrimidine sulphate [20] (1·0 g.) in water (25 ml.) was adjusted to pH 9 with a solution of sodium hydroxide and 2 : 5-dimethylhexane-3 : 4-dione (0·65 g.) in ethanol (10 ml.) and ethyl methyl ketone (10 ml.) was added, and the mixture refluxed for 4 hr. The cooled solution was acidified with acetic acid, and the yellow precipitate of 4-*amino*-2-*mercapto*-6 : 7-*di*iso*propylpteridine* recrystallised from aqueous dimethylformamide as yellow plates, m. p. 276—277° (0·6 g., 50%) (Found : C, 54·7; H, 6·6; N, 26·4; S, 12·0. $C_{12}H_{17}N_5S$ requires C, 54·7; H, 6·5; N, 26·6; S, 12·2%).

2-*Alkylaminoalkylaminopteridines*.—4-*Amino*-2-(3-*diethylaminopropylamino*)-5-*nitropyrimidine*. 3-Diethylaminopropylamine (11·0 g.) was shaken with 4-amino-2-chloro-5-nitropyrimidine [13] (5·0 g.) for a few minutes. The temperature rose to 90—100°. As the reaction began to slacken, the mixture was refluxed for 15 min. The cooled mixture was poured into dilute aqueous ammonia, and the tan crystals were filtered off and washed with water. Recrystallisation from aqueous ethanol (charcoal) gave 4·2 g.(55%) of 4-*amino*-2-(3-*diethylaminopropylamino*)-5-*nitropyrimidine* as pale yellow needles, m. p. 112—113° (Found : C, 49·5; H, 7·3; N, 31·4. $C_{11}H_{20}O_2N_6$ requires C, 49·3; H, 7·5; N, 31·4%).

2-(3-*Diethylaminopropylamino*)-6 : 7-*diphenylpteridine*.—A solution of 4-amino-2-(3-diethylaminopropylamino)-5-nitropyrimidine (2·0 g.) in methanol (30 ml.) was shaken in hydrogen

[19] Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553.
[20] Bendich, Tinker, and Brown, *ibid.*, 1948, **70**, 3109.

TABLE 1. 2 : 4-*Bis*(*dialkylaminoalkylamino*)*pteridines* (I) *and* (II).

Subst. R, R′	R″	Solvent *	Cryst. form †	M. p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
6 : 7-Ph_2	$[CH_2]_3{\cdot}NEt_2$	Aq. EtOH	needles	137—138° [a]	70	70·9	8·2	20·7	$C_{32}H_{44}N_8$	71·1	8·2	20·75
,,	$[CH_2]_2{\cdot}NEt_2$	Et_2O–Pet	plates	125·5—126·5	68	70·5	7·55	22·0	$C_{30}H_{40}N_8$	70·3	7·9	21·9
,,	$[CH_2]_3{\cdot}NMe_2$	Aq. $NMe_2{\cdot}CHO$	prisms	143—144 [b]	90	69·4	7·8	23·0	$C_{28}H_{36}N_8$	69·4	7·5	23·1
,,	$[CH_2]_2{\cdot}NMe_2$	Et_2O–Pet	needles	140—141	69	68·4	7·0	24·1	$C_{26}H_{32}N_8$	68·4	7·1	24·5
6 : 7-Pr^i_2	$[CH_2]_3{\cdot}NEt_2$	Aq. $NMe_2{\cdot}CHO$	plates	87—88	78	65·2	10·4	23·9	$C_{26}H_{48}N_8$	66·1	10·25	23·7
,,	$[CH_2]_2{\cdot}NEt_2$	,,	plates	95·5—97	84	64·6	10·0	25·3	$C_{24}H_{44}N_8$	64·9	10·0	25·2
,,	$[CH_2]_3{\cdot}NMe_2$	,,	needles	152—153	65	63·5	9·7	27·1	$C_{22}H_{40}N_8$	63·4	9·7	26·9
,,	$[CH_2]_2{\cdot}NMe_2$	,, [c]	needles	106—107·5	95	61·7	9·4	29·0	$C_{20}H_{36}N_8$	61·8	9·35	28·9
Indolo(2′ : 3′-6 : 7); R‴ = Me	$[CH_2]_3{\cdot}NEt_2$	EtOAc [d e f]	—	177·5—178·5	43	66·1	8·3	25·3	$C_{27}H_{41}N_9$	66·0	8·4	25·6
,, ,,	$[CH_2]_2{\cdot}NEt_2$	Aq. $NMe_2{\cdot}CHO$ [g e]	prisms	187·5—188·5	80	65·0	8·0	27·1	$C_{25}H_{37}N_9$	64·8	8·0	27·2
Indolo(2′ : 3′-6 : 7); R‴ = Pr^n	$[CH_2]_3{\cdot}NEt_2$	,,	needles	117·5—119	73	66·7	8·6	24·6	$C_{29}H_{45}N_9$	67·0	8·7	24·3
,, ,,	$[CH_2]_2{\cdot}NEt_2$	,,	needles	152·5—153·5	71	66·3	8·6	25·4	$C_{27}H_{41}N_9$	66·0	8·4	25·6
,, ,,	$[CH_2]_3{\cdot}NMe_2$	,, [e]	needles	165—166	86	65·0	8·2	27·0	$C_{25}H_{37}N_9$	64·8	8·0	27·2
,, ,,	$[CH_2]_2{\cdot}NMe_2$	,, [e]	needles	177—178	74	63·5	7·55	28·9	$C_{23}H_{33}N_9$	63·5	7·6	29·0
6 : 7-*cyclo*Hexeno-	$[CH_2]_3{\cdot}NEt_2$	Pet [h]	—	77—78	16	63·0	9·4	25·4	$C_{24}H_{42}N_8$	65·1	9·6	25·3
6 : 7-*cyclo*Hepteno-	$[CH_2]_3{\cdot}NEt_2$	Aq. $NMe_2{\cdot}CHO$ [j]	needles	71—73	27	65·8	9·5	24·6	$C_{25}H_{44}N_8$	65·8	9·72	24·6

[a] Taylor [8] records m. p. 137·3—138°. [b] Taylor [8] records m. p. 144·5—145·5°. [c] This product was more soluble in the cold solvent than in the hot, and was recrystallised by slowly warming the cold solution. [d] Reaction time was 96 hr.; scarlet product. [e] Product crystallised from the cooled reaction mixture. [f] A small quantity of 2-amino-4-(3-diethylaminopropylamino)-1′-*N*-methylindolo(2′ : 3′-6 : 7)pteridine was separated from the crude product by means of its insolubility in methylene dichloride–light petroleum (b. p. 100—120°). [g] Reaction time was 88 hr. [h] The product had an inverted temperature solubility coefficient in aqueous solvents. [j] A quantity of by-product was separated by extracting the product with light petroleum (b. p. 40°) and filtering off the undissolved impurity.

* Pet = light petroleum (b. p. 40—60°). † Yellow to orange, except as stated.[d]

TABLE 2. 2-*Amino*-4-(*dialkylaminoalkylamino*)*pteridines* (I) *and* (II). (R″ *et posn.* 2 = H.)

6 : 7-Subst. R, R′	R″ at posn. 4	Solvent [a]	M. p.	Yield (%)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
6 : 7-Ph_2	$[CH_2]_3{\cdot}NEt_2$	Aq. EtOH	195—196°	22 [b]	70·1	6·9	22·7	$C_{25}H_{29}N_7$	70·2	6·85	23·0
,,	$[CH_2]_2{\cdot}NEt_2$	Aq. ,,	194—196	59	69·6	6·8	23·6	$C_{24}H_{27}N_7$	69·7	6·6	23·7
,,	$[CH_2]_3{\cdot}NMe_2$	Aq. ,, [cd]	217—218	57	68·7	6·3	24·9	$C_{23}H_{25}N_7$	69·2	6·3	24·6
,,	$[CH_2]_2{\cdot}NMe_2$	Aq. ,, [d]	233·5—234·5	65	68·4	6·0	25·5	$C_{22}H_{23}N_7$	68·6	6·0	25·5
,,	$[CH_2]_3{\cdot}NPr_2$	Pet	139—140	34	71·2	7·2	21·4	$C_{27}H_{33}N_7$	71·2	7·3	21·5
,,	$[CH_2]_3{\cdot}NBu_2$	,, [e]	146·5—148	32 [b]	71·8	8·5	19·8	$C_{29}H_{37}N_7$	72·0	7·7	20·3
,,	$[CH_2]_4{\cdot}NEt_2$	Aq. $NMe_2{\cdot}CHO$	208—209	71	70·7	7·3	22·2	$C_{26}H_{31}N_7$	70·8	7·1	22·2
6 : 7-Pr^i_2	$[CH_2]_3{\cdot}NEt_2$	,, [g]	127·5—129	46	63·4	9·2	27·2	$C_{19}H_{33}N_7$	63·5	9·3	27·3
,,	$[CH_2]_2{\cdot}NEt_2$	,,	136·5—137·5	40	62·6	9·2	28·2	$C_{18}H_{31}N_7$	62·6	9·1	28·4
,,	$[CH_2]_3{\cdot}NMe_2$	Pet [h]	152—155 [k]	30 [b]	61·4	8·75	29·4	$C_{17}H_{29}N_7$	61·6	8·8	29·6
,,	$[CH_2]_2{\cdot}NMe_2$	,,	177—178·5	54	60·5	8·5	31·0	$C_{16}H_{27}N_7$	60·6	8·6	30·9
Indolo(2′ : 3′-6 : 7); R‴ = Me	$[CH_2]_3{\cdot}NEt_2$	Aq. EtOH [l]	211—212	7 [b]	63·2	7·0	30·4	$C_{20}H_{26}N_8$	63·5	6·9	29·6
6 : 7-*cyclo*Hepteno-	$[CH_2]_3{\cdot}NEt_2$	C_6H_6–Pet [e]	157—158	22 [b]	63·0	8·6	28·4	$C_{18}H_{29}N_7$	63·0	8·5	28·6

[a] These derivatives crystallised as needles, the colour depending on that of the parent pteridine. Pet = light petroleum (b. p. 100—120°, but in the last case 40—60°). [b] Reaction incomplete, some unchanged diaminopteridine being isolated. [c] Reaction time 48 hr. [d] The product crystallised from the cooled reaction mixture: this separation was assisted by the addition of ether. [e] Excess of amine was removed by steam-distillation of the reaction mixture, and the pteridine derivatives separated by extraction with ether. [f] With softening at 205°. [g] Reaction time 32 hr. [h] The product had an inverted temperature solubility coefficient in aqueous solvents. [k] With slow softening above 140°. [l] Reaction time 168 hr.; unchanged diaminopteridine (70%) and a little bisalkylated product were isolated.

at room temperature and pressure in the presence of Raney nickel. After 1 hr. the absorption of hydrogen had ceased and the catalyst was filtered off in nitrogen (the solution rapidly became purple in air). Benzil (1·57 g.) was added and the mixture was refluxed for 2 hr. in nitrogen. The dark brown solution was concentrated to small bulk and water was added. A brown tar was precipitated, which on scratching and cooling crystallised to a yellow solid. This was twice recrystallised from aqueous ethanol (charcoal), giving 1·2 g. (71%) of golden-yellow needles of 2-(3-*diethylaminopropylamino*)-6 : 7-*diphenylpteridine*, m. p. 136—137·5° (Found : C, 72·7; H, 6·9; N, 20·4. $C_{25}H_{28}N_6$ requires C, 72·8; H, 6·85; N, 20·4%).

2-(3-*Diethylaminopropylamino*)-6 : 7-cyclo*heptenopteridine*.—4-Amino-2-(3-diethylaminopropylamino)-5-nitropyrimidine (1·2 g.) was reduced as in the preceding experiment, and the resulting clear solution was refluxed under nitrogen with *cyclo*heptane-1 : 2-dione (0·55 g.) for 2 hr. Concentration on the steam-bath and addition of water precipitated a brown oil which slowly crystallised to a green solid and was filtered off (0·75 g.). Recrystallisation from light petroleum (b. p. 60—80°) (charcoal) gave pale yellow needles of 2-(3-*diethylaminopropylamino*)-6 : 7-cyclo*heptenopteridine*, m. p. 100—101° (Found : C, 65·7; H, 8·85; N, 25·85. $C_{18}H_{28}N_6$ requires C, 65·8; H, 8·6; N, 25·6%).

Reactions of 2-Mercaptopteridines with Alkylamines.—2 : 4-*Bis*-(3-*diethylaminopropylamino*)-6 : 7-*diphenylpteridine*. 4-Amino-2-mercapto-6 : 7-diphenylpteridine (0·5 g.) and 3-diethylaminopropylamine (5 ml.) were heated together at 120° for 10 hr. during which both hydrogen sulphide and ammonia were evolved. The excess of amine was removed under reduced pressure, and the residue recrystallised from aqueous alcohol, giving 0·5 g. (78%) of 2 : 4-bis-(3-diethylaminopropylamino)-6 : 7-diphenylpteridine, m. p. 137—138°.

4-(3-*Diethylaminopropylamino*)-2-*mercapto*-6 : 7-*diphenylpteridine*. 4-Amino-2-mercapto-6 : 7-diphenylpteridine (0·5 g.), 3-diethylaminopropylamine (2 ml.) and absolute alcohol (5 ml.) were refluxed together for 7 hr., all the solid dissolving. A little dry ether was added to the cooled solution, followed by light petroleum (b. p. 40—60°), and, after trituration and standing for a time, yellow crystals separated. These were filtered off (0·26 g.) and twice recrystallised from aqueous alcohol, to give golden-yellow needles of 4-(3-*diethylaminopropylamino*)-2-*mercapto*-6 : 7-*diphenylpteridine*, m. p. 217—218·5° (Found : C, 67·7; H, 6·3; N, 19·1; S, 7·2. $C_{25}H_{28}N_6S$ requires C, 67·5; H, 6·3; N, 18·9; S, 7·2%). 0·16 g. of 2 : 4-bis-(3-diethylaminopropylamino)-6 : 7-diphenylpteridine was isolated from the ether–light petroleum filtrate.

This compound (0·37 g.), 3-diethylaminopropylamine (3 ml.), and ethyl alcohol (4 ml.) were refluxed together for 10 hr., by which time the evolution of hydrogen sulphide appeared to be complete. The mixture was poured into water, and the yellow crystals of 2 : 4-bis-(3-diethylaminopropylamino)-6 : 7-diphenylpteridine (0·34 g.), m. p. 137—138°, were filtered off.

4-(3-*Diethylaminopropylamino*)-2-*mercapto*-6 : 7-*di*iso*propylpteridine*. 4-Amino-2-mercapto-6 : 7-di*iso*propylpteridine (0·5 g.), 3-diethylaminopropylamine (2 ml.), and absolute alcohol (5 ml.) were refluxed for 4 hr. The alcohol was then distilled off and the residue triturated with water to crystallisation. The lemon-yellow crystals (0·46 g.) were filtered off, dried, and recrystallised from chloroform–light petroleum (b. p. 40—60°). Bright yellow needles of 4-(3-*diethylaminopropylamino*)-2-*mercapto*-6 : 7-*di*iso*propylpteridine*, m. p. 162—163°, were obtained (Found : C, 60·7; H, 8·45; N, 22·4; S, 8·5. $C_{19}H_{32}N_6S$ requires C, 60·7; H, 8·6; N, 22·3; S, 8·5%).

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Research Division, Allen and Hanburys Limited, Ware, Herts.
Sir John Cass College, Aldgate, London, E.C.3.
[Present address, M. D. P. : Research Department,
Boots Pure Drug Co., Ltd., Nottingham.]

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