402. *Pteridine Studies. Part XII.*[1] *The Methylation of 4-Aminopteridine.*

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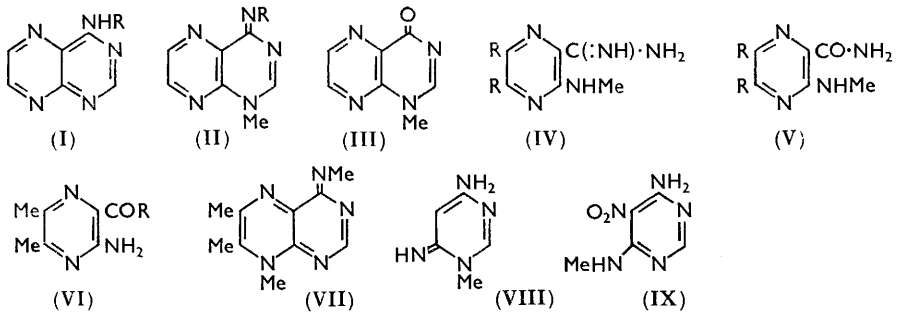
Methylation of 4-aminopteridine is found to occur on $N_{(1)}$. The resulting 1,4-dihydro-4-imino-1-methylpteridine, a strong base, is hydrolysed by acid to 1,4-dihydro-1-methyl-4-oxopteridine, and quickly degraded by hot alkali to 2-carbamoyl-3-methylaminopyrazine, whereby the structure is confirmed. However, with cold alkali, it yields 2-amidino-3-methylaminopyrazine which gives the above carbamoyl derivative only slowly in hot alkali. 4-Methylaminopteridine undergoes similar methylation and degradation. 4-Dimethylaminopteridine yields its 1-methiodide, the first quaternised pteridine to be described. The pK_a values and ultraviolet spectra of the imines and their degradation products are discussed.

An intermediate, 4-amino-1,6-dihydro-6-imino-1-methylpyrimidine, is shown to rearrange at 20° in alkali, and during nitration, to 4-amino-6-methylaminopyrimidine and its 5-nitro-derivative respectively.

With methyl iodide 4-aminopyrimidine undergoes methylation on $N_{(1)}$ only [2] to give 1,4-dihydro-4-imino-1-methylpyrimidine. Similar treatment of 4-hydroxypteridine gives a mixture of three methyl derivatives.[3] However, only a single methylation product was formed from 4-aminopteridine, namely, 1,4-dihydro-4-imino-1-methylpteridine (II; R = H), as the following evidence shows.



Methylation of the amino-group was first excluded by preparation of 4-methylaminopteridine (I; R = Me) from 4-methylthiopteridine. The pK_a (3·7) and ultraviolet spectrum of this base differed markedly from those of the methylation product (pK_a 9·5), and the hydriodides gave a depression of the melting points on admixture.

When treated at 100° for a few minutes with dilute alkali, the methylation product gave the known [3] 2-carbamoyl-3-methylaminopyrazine (V; R = H), thus indicating $N_{(1)}$ as the position of methylation in the pteridine. In an attempt to isolate the presumed intermediate pteridone (III), alkali at 0° was used. The resulting compound, which was not the expected pteridone (III), was further degraded to the pyrazine (V; R = H) only on prolonged treatment with boiling alkali. This behaviour, analysis, and a highly basic pK_a of 9 suggested that it was 2-amidino-3-methylaminopyrazine (IV; R = H) and this was confirmed by condensation with acetylacetone to give 2-(4,6-dimethylpyrimidin-2-yl)-3-methylaminopyrazine. Thus two routes of alkaline degradation operate: one, rapid at 100° but negligible at 0°, in which the amino-group is hydrolysed before ring cleavage; and another, which proceeds steadily even at 0° and involves ring cleavage to amidine and subsequent very slow hydrolysis to amide. That the presumed pteridone intermediate

[1] Part XI, *J.*, 1960, 1370.
[2] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[3] Albert, Brown, and Wood, *J.*, 1956, 2066.

(III) of the first (hot) degradation could not be isolated is not surprising as it is known [3] to be exceedingly alkali-labile. On the other hand, acid-degradation of the original methylation product readily gave this pteridone (III).

When 4-amino-6,7-dimethylpteridine was treated with methyl iodide, again a single product resulted. Brief alkaline treatment at 0° in this case gave the free unstable imine, and more prolonged treatment gave the amidine (IV; R = Me). Hot alkali gave an amide having structure (V; R = Me) or (VI; R = NHMe); the second possibility was excluded by further hydrolysis to a pyrazinecarboxylic acid which was not 3-amino-5,6-dimethylpyrazine-2-carboxylic acid (VI; R = OH) (prepared unambiguously by alkaline degradation of 4-hydroxy-6,7-dimethylpteridine). The acid, which still contained three methyl groups, was therefore 5,6-dimethyl-3-methylaminopyrazine-2-carboxylic acid, and so the original product was 1,4-dihydro-4-imino-1,6,7-trimethylpteridine. Acid-hydrolysis gave 1,4-dihydro-1,6,7-trimethyl-4-oxopteridine, degraded by alkali to the above pyrazine-amide.

4-Methylaminopteridine (I; R = Me) and its 6,7-dimethyl derivative (prepared *via* the methylthio-analogue) behaved similarly with methyl iodide, giving the 1-methyl-4-methylimino-derivative (II; R = Me) and its 1,6,7-trimethyl analogue, respectively, and these were degraded by acid and alkali to the pyrazines formed from the corresponding imines. Amidines, which would retain the extra methyl group, could not be isolated.

A representative 8-methylated imine was synthesised by reducing 4,6-bismethylamino-5-nitropyrimidine [4] to the 5-amino-derivative and condensing this with biacetyl, to give 4,8-dihydro-6,7,8-trimethyl-4-methyliminopteridine (VII). Attempts to prepare a 3-methylated imine were unsuccessful. A possible intermediate, 4,5-diamino-1,6-dihydro-6-imino-1-methylpyrimidine, was first approached by methylation of 4,6-diamino-5-nitropyrimidine, but this gave 4-amino-6-methylamino-5-nitropyrimidine (IX). Methylation of 4,6-diaminopyrimidine was more promising, giving 4-amino-1,6-dihydro-6-imino-1-methylpyrimidine (VIII) (and/or its tautomer) the structure of which was confirmed by a pK_a of 12 and by non-identity with 4-amino-6-methylaminopyrimidine prepared by successive aminations of 4,6-dichloropyrimidine.[5] Nitration of the imine under a variety of conditions, however, gave only 4-amino-6-methylamino-5-nitropyrimidine (IX), which had undergone the rearrangement familiar under alkaline conditions in the pyrimidine series [6,2] but also known under nitrating conditions in the pyridine series.[7] The imine (VIII) also rearranged rapidly in cold N-alkali to give 4-amino-6-methylaminopyrimidine in good yield.

4-Dimethylaminopteridine and its 6,7-dimethyl derivative, with methyl iodide, gave products which can be only quaternary methiodides. Methylation had taken place at $N_{(1)}$, to give the salt (X) because, when boiled at pH 10, the first product was converted through 1,4-dihydro-1-methyl-4-oxopteridine (III) into 2-carbamoyl-3-methylaminopyrazine (V; R = H), and the second methiodide gave 1,4-dihydro-1,6,7-trimethyl-4-oxopteridine.

The stability of 1,4-dihydro-4-imino-1-methylpteridine is progressively increased towards acid-hydrolysis by the introduction of methyl groups (see Table 1). In alkaline degradation, the methylimino- are not significantly different from the imino-derivatives, but the 6,7-dimethyl grouping increases stability in each case. This is understandable on the basis of electron-contribution from methyl groups to a system which is depleted of π-electrons.

Concerning the ionisation constants, Table 2 shows that 4-aminopteridine (pK_a 3·6) is made progressively more basic by *C*-methylation and by extranuclear *N*-methylation. By these means, 4-dimethylamino-6,7-dimethylpteridine reaches pK_a 4·8. Nuclear *N*-methylation, however, produces an effect of another order. The iminopteridines so

[4] Brown, *J. Appl. Chem.*, 1954, **4**, 72.
[5] Whitehead and Traverso, *J. Amer. Chem. Soc.*, 1958, **80**, 2185.
[6] Carrington, Curd, and Richardson, *J.*, 1955, 1858.
[7] Tschitschibabin and Konowalowa, *Ber.*, 1925, **58**, 1712; Tschitschibabin and Kirssanow, *Ber.*, 1928, **61**, 1223.

formed are the most strongly basic members of the series yet reported. They are some 6 pK_a units stronger than the corresponding amino-derivatives and thus resemble the analogous 1,4-dihydro-4-imino-1-methylpyrimidine and (VIII), which bear similar relations respectively to 4-aminopyrimidine [2] and to 4-amino-6-methylaminopyrimidine (Table 2). The addition of methyl groups to compound (II; R = H) increases its basic strength by the usual small increments and 1,4-dihydro-1,6,7-trimethyl-4-methyliminopteridine reaches pK_a 11·4. The basic strength of its transannular-methylated isomer (VII) is less, but still marked. That compounds (II) and (VII) are strong bases, is understandable

TABLE 1. *Optimum conditions for hydrolysis of iminopteridines.*

1,4-Dihydro-1-methyl deriv.	Reagent, time (min.), temp.	Product	Yield [a] (%)
4-Imino	2·5N-HCl; 30; 100° [b]	4-Oxo-analogue	30; 85 [c]
	2·5N-NaOH; 20; 0°	(IV; R = H)	93
	N-NaOH; 10; 100°	(V; R = H)	64
4-Imino-6,7-dimethyl	2·5N-HCl; 120; 100°	4-Oxo-analogue	79 [b]
	2·5N-NaOH; 10; 35°	(IV; R = Me)	75
	N-NaOH; 40; 100°	(V; R = Me)	70
4-Methylimino	6·3N-HCl; 240; 100° [b]	4-Oxo-analogue	55; 82 [c]
	N-NaOH; 10; 100°	(V; R = H)	60
6,7-Dimethyl-4-methylimino	6·3N-HCl; 60; 130° [d]	4-Oxo-analogue	50
	N-NaOH; 40; 100°	(V; R = Me)	70

[a] Isolated. [b] Optimum conditions determined initially by paper chromatography. [c] Yield estimated by paper chromatography, elution, and spectroscopy. [d] Sealed tube.

TABLE 2.

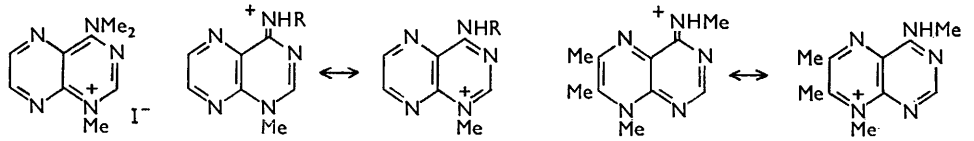
Compound	pK_a [a] and concn. (M)	$\lambda_{max.}$ (mμ) [b]	pH	log ε
Pteridine derivatives.				
4-Amino [c]		335; 244		3·82; 4·20
cation	3·56	324; 229		3·99; 4·10
4-Methylamino		352; 248; 226	5·7	3·88; 4·06; 4·05
cation	3·70 ± 0·03 (200)	*352*; 339; *251*; 232	1·7	*3·99*; 4·06; *3·68*; 4·12
4-Dimethylamino [d]		362; 241		3·93; 4·15
cation	4·33	344 + 347 + 356; 239		4·09 + 4·10 + 4·04; 4·19
4-Amino-6,7-dimethyl		330; 245	6·2	3·88; 4·25
cation	3·80 ± 0·02 (400)	337; 326; 233	1·7	3·96; 4·05; 4·18
6,7-Dimethyl-4-methylamino		346; 249	6·2	3·97; 4·15
cation	4·17 ± 0·03 (400)	*348*; 337; 234	1·7	*4·10*; 4·14; 4·19
4-Dimethylamino-6,7-dimethyl		355; 244	6·8	3·99; 4·20
cation	4·84 ± 0·03 (400)	*353*; 342; 244	2·8	*4·12*; 4·16; 4·19
1,4-Dihydro-4-imino-1-methyl [e]			12·5 [f]	
cation	9·51 ± 0·05 (200)	*350*; 333; 233	7·4	*3·87*; 4·00; 4·14
1,4-Dihydro-1-methyl-4-methylimino [e]			12·5 [f]	
cation	10·34 ± 0·04 (100)	*354*; 344; 233	8·3	*4·03*; 4·07; 4·16
1,4-Dihydro-4-imino-1,6,7-trimethyl [e]			12·5 [f]	
cation	10·47 ± 0·06 (200)	*344*; 330; 237	8·5	*3·98*; 4·06; 4·18
1,4-Dihydro-1,6,7-trimethyl-4-methylimino [e]			13·1 [f]	
cation	11·43 ± 0·05 (100)	354; 341; *255*; 237	8·5	4·06; 4·10; *3·87*; 4·15
4-Dimethylamino-1-methylpteridinium iodide [g]		352; 243		4·11; 4·17
4-Dimethylamino-1,6,7-trimethylpteridinium iodide [g]		347; 246		4·19; 4·23
4,8-Dihydro-6,7,8-trimethyl-4-methylimino		383; 284; 241; 215	8·5	3·68; 4·23; 4·06; 4·27
cation	6·64 [h] ± 0·05 (600)	410; *295*; 268; 233	4·0	4·03; *4·00*; 4·06; 4·09
1,4-Dihydro-1,6,7-trimethyl-4-oxo [i]		*340*; 325; *243*; 234	5·0	*3·92*; 4·00; *4·06*; 4·17
cation	1·73 ± 0·04 [k]	*322*; 308	−1·0	*3·87*; 4·04

TABLE 2. (*Continued.*)

Compound	pK_a [a] and concn. (M)	$\lambda_{max.}$ (mμ) [b]	pH	log ε
Pyrazine derivatives.				
2-Amidino-3-methylamino		361; 256	11·0	3·76; 4·13
cation	8·98 ± 0·06 (200)	359; 264	7·0	3·69; 3·93
2-Amidino-5,6-dimethyl-3-methylamino		370; 261	11·5	3·85; 4·11
cation	9·45 ± 0·03 (200)	370; 272	7·4	3·77; 3·92
2-(4,6-Dimethylpyrimidin-2-yl)-3-methylamino		375; 263; 223	5·7	3·85; 4·00; 4·01
cation	2·93 ± 0·03 (100)	417; 259; 223	0·9	3·85; 4·03; 4·07
2-Carbamoyl-3-methylamino		371; 256	5·0	3·74; 4·15
cation	2·11 ± 0·04 (200)	361; 247	0	3·77; 4·15
2-Carbamoyl-5,6-dimethyl-3-methylamino		377; 263	5·0	3·88; 4·17
cation	2·70 ± 0·02 (400)	380; 255	0	3·96; 4·20
2-Amino-3-carboxy-5,6-dimethyl				
proton lost	4·46 ± 0·04 (200)	343; 248	7·0	3·87; 4·00
proton gained	>1 [k]	372; 250	−1·0	4·01; 4·08
2-Carboxy-5,6-dimethyl-3-methylamino				
proton lost	4·82 ± 0·04 (200)	365; 259	7·0	3·83; 4·13
proton gained		386; 257	−1·0	3·90; 4·13
Pyrimidine derivatives.				
4-Amino-6-methylamino		260; 221	8·2	3·72; 4·58
cation	6·32 ± 0·02 (200)	268; 225	4·2	4·13; 4·38
4-Amino-6-methylamino-5-nitro		348; *227*	5·0	3·98; *4·17*
cation	2·75 ± 0·01 [k]	341; 238	−1·0	3·83; 4·36
4,5-Diamino-6-methylamino		279; 216	8·0	4·02; 4·47
cation	5·93 ± 0·01 (100)	286; 222	4·0	4·04; 4·22
4-Amino-1,6-dihydro-6-imino-1-methyl [e]			14·0 [f]	
cation	11·98 ± 0·04 (100)	265; 221	10·0	4·03; 4·52

[a] Potentiometric titration (see Albert and Phillips, *J.*, 1956, 1294) in water at 20°. [b] Inflexions in italics. [c] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [d] *Idem*, *J.*, 1952, 4219. [e] Spectra measured on buffered solutions of hydrochloride. [f] Solution too unstable for measurement of spectrum. [g] Spectrum in unbuffered water and corrected for iodide ion. [h] Cf. 5·6 for 2,8-dihydro-2-imino-6,7,8-trimethylpteridine (Fidler and Wood, *J.*, 1957, 4157). [i] Cf. 1,4-dihydro-1-methyl-4-oxopteridine (ref. 11). [k] Spectrometrically determined at 0·25 × 10^{-4}M (cf. footnote *a*).

because the cations must be resonance hybrids involving a quaternised amine of the *N*-methylpyridinium type. Resonance in the neutral molecule involves separation of charges and is therefore small enough to be neglected. Hence, to explain the high pK_a values, it will suffice to discuss factors which increase resonance in the cations. The molecule (II) gives a resonant cation having the extreme forms (XI) and (XII). Both are



(X) (XI) (XII) (XIII) (XIV)

highly stable, (XI) because it contains only Kekulé and paraquinonoid structures,[8] and (XII) because the positive charge is on the most electron-rich nitrogen atom.[9] The resonance hybrid of the cation of (VII) should be rather less stable because (XIII) has only orthoquinonoid forms (which are not as low in energy as are paraquinonoid forms),[8] and (XIV) has the positive charge on a nitrogen atom far less rich in electrons.[9] Thus although compounds (II) and (VII) are both highly basic, the former is the stronger.

[8] Gore and Phillips, *Nature*, 1949, **163**, 690.
[9] Chalvet and Sandorfy, *Compt. rend.*, 1949, **228**, 566; Pullman, *Compt. rend.*, 1958, **246**, 3290.

2-Aminopyrazine is weakly basic [10] (pK_a 3·14), and 2-methylaminopyrazine might reasonably be expected to be a little more basic. The addition of an amide grouping in 2-carbamoyl-3-methylaminopyrazine lowers the pK_a to 2·1, and the apparent figure falls to 1·5 when a carboxy-group replaces the amide. However, it is possible that the amino-acid is zwitterionic, and therefore the figure for proton gain is a measure of the enhanced acidic strength of the carboxy-group, and the figure above 4 (proton loss) is a measure of basic strength. The corresponding amidinopyrazines (IV) are quite strong bases (pK_a 9), but on cyclization to a pyrimidinylpyrazine, their pK_a falls to 2·9.

In their ultraviolet spectra, 4-aminopteridine and its closely similar 6,7-dimethyl derivative, both as neutral molecule and cation, show the usual progressive bathochromic shift of the long-wavelength band with extranuclear *N*-mono- and di-methylation. This shift is also evident in changing from the cations of 1,4-dihydro-4-imino-1-methylpteridine and its 6,7-dimethyl derivative to the methylimines. It is reasonable to expect protonation of 4-aminopteridine to occur at the same site as methylation does, provided that steric factors do not influence the latter. The implication of $N_{(1)}$ as basic centre is independently upheld by the close similarity of the cationic spectra of the amino-, methylamino-, and dimethylamino-pteridines to those of the imine cations and the two quaternary iodides in water. Exceptional is the transannular imine (VII) which, with its bathochromic shift of the long-wavelength band, bears much the same relation to the intra-annular imines as does 4,8-dihydro-6,7,8-trimethyl-4-oxopteridine [11] to 1,4-dihydro-1,6,7-trimethyl-4-oxopteridine. Unlike the other pyrazines in Table 2, the pyrimidinyl-methylamino-derivative shows a strong bathochromic shift of its long-wavelength band on forming the visibly yellow monocation.

Experimental

1,4-Dihydro-4-imino-1-methylpteridine.—4-Aminopteridine [12] (0·75 g.) and methyl iodide (7·5 ml.) were heated at 140° for 4 hr. The solid was extracted with boiling ethanol (100 ml.), and the extract treated with charcoal and evaporated to 20 ml. Addition of hot light petroleum (b. p. 60—80°; 20 ml.) and recrystallisation from a similar mixture produced the yellow *imine hydriodide* (78%), m. p. 255° (Found: C, 28·9; H, 3·0; I, 43·8. $C_7H_8IN_5$ requires C, 29·1; H, 2·8; I, 43·9%). This salt was shaken for 3 hr. with silver chloride (1 part) in water (30 parts). The filtrate was evaporated and the residue recrystallised from ethanol (80 parts) to give 79% of the *hydrochloride*, m. p. >300° (Found: C, 42·5; H, 4·1; N, 35·0. $C_7H_8ClN_5$ requires C, 42·5; H, 4·1; N, 35·4%).

1,4-Dihydro-4-imino-1,6,7-trimethylpteridine.—4,5,6-Triaminopyrimidine [13] (7·9 g.) and biacetyl (4·5 ml.) were refluxed in methanol (200 ml.) for 2 hr. The solid was recrystallised from water (160 parts), to give 90% of 4-amino-6,7-dimethylpteridine, m. p. 295° (made by another route,[14] also m. p. 295°). It was methylated as above (89%). The *imine hydriodide*, recrystallised from methanol (20 parts), had m. p. 264° (Found: C, 34·0; H, 3·9; I, 40·0; N, 21·9. $C_9H_{12}IN_5$ requires C, 34·1; H, 3·8; I, 40·0; N, 22·1%). The *hydrochloride* had m. p. 290° (decomp.) (Found: C, 48·0; H, 5·4; N, 31·1. $C_9H_{12}ClN_5$ requires C, 47·9; H, 5·4; N, 31·0%).

4-Methylaminopteridine.—4-Methylthiopteridine [15] (0·7 g.) and 3% alcoholic methylamine (35 ml.) were refluxed for 2 hr. After refrigeration, the solid (95%) was recrystallised from water (30 parts) to give *4-methylaminopteridine*, m. p. 251—252° (Found: C, 52·2; H, 4·35; N, 42·9. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·45%). Its *hydriodide* (from ethanol, 40 parts) had m. p. 234—235° (Found: C, 29·25; H, 2·8; I, 43·95; N, 24·2. $C_7H_8IN_5$ requires C, 29·1; H, 2·8; I, 43·9; N, 24·2%).

1,4-Dihydro-1-methyl-4-methyliminopteridine.—4-Methylaminopteridine was treated with methyl iodide as above, to give the orange *methyliminopteridine hydriodide* (75%), m. p. 274° (vac.) (Found: C, 31·6; H, 3·4; I, 41·75; N, 22·8. $C_8H_{10}IN_5$ requires C, 31·7; H, 3·3; I, 41·9;

[10] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[11] Brown and Mason, *J.*, 1956, 3443.
[12] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[13] Cavalieri, Tinker, and Bendich, *J. Amer. Chem. Soc.*, 1949, **71**, 533.
[14] Daly and Christensen, *J. Amer. Chem. Soc.*, 1956, **78**, 225.
[15] Albert, Brown, and Wood, *J.*, 1954, 3832.

N, 23·1%). The *hydrochloride* made from it (91%) was recrystallised from 23 parts of a mixture of ethyl acetate 70%, ethanol 20%, and water 10% (Found: C, 45·4; H, 4·9; Cl, 16·7. $C_8H_{10}ClN_5$ requires C, 45·4; H, 4·8; Cl, 16·75%).

1,4-*Dihydro*-1,6,7-*trimethyl*-4-*methyliminopteridine*.—4,5-Diamino-6-methylthiopyrimidine [15] (5 g.) and biacetyl (2·75 ml.) in methanol (38 ml.) were refluxed for 10 min. The solid (62%) was recrystallised from water (35 parts), to give 6,7-*dimethyl*-4-*methylthiopteridine*, m. p. 120—121° (Found: C, 52·2; H, 4·9; S, 15·75; N, 27·1. $C_9H_{10}SN_4$ requires C, 52·4; H, 4·9; S, 15·55; N, 27·2%). Treatment with boiling ethanolic methylamine as above, and recrystallisation from ethanol (20 parts), gave 6,7-*dimethyl*-4-*methylaminopteridine* (95%), m. p. 223° (Found: C, 57·15; H, 5·8; N, 36·6. $C_9H_{11}N_5$ requires C, 57·1; H, 5·9; N, 37·0%). Its *hydriodide* (from 1 : 1 ethyl acetate–ethanol; 15 parts) had m. p. 218—220° (Found: C, 33·8; H, 3·7; I, 40·1; N, 22·0. $C_9H_{12}IN_5$ requires C, 34·1; H, 3·8; I, 40·0; N, 22·1%). Methylation as for the analogues above, followed by recrystallisation from methanol (10 parts), gave the *methyliminopteridine hydriodide* (86%), m. p. 247° (Found: C, 36·6; H, 4·2; I, 38·4; N, 20·9. $C_{10}H_{14}IN_5$ requires C, 36·3; H, 4·3; I, 38·3; N, 21·15%). The *hydrochloride* had m. p. *ca.* 250° (decomp.) (Found: C, 50·25; H, 5·7; N, 29·1. $C_{10}H_{14}ClN_5$ requires C, 50·1; H, 5·9; N, 29·2%).

4,8-*Dihydro*-6,7,8-*trimethyl*-4-*methyliminopteridine*.—4,6-Bismethylamino-5-nitropyrimidine [4] (12 g.) was hydrogenated in methanol over Raney nickel. The filtered solution was evaporated *in vacuo* and the residue twice recrystallised by dissolution in boiled-out water (30 parts) at 25°, filtration, and cooling to 0°. When the process after hydrogenation was conducted entirely within a nitrogen box, the otherwise deep red 5-*amino*-4,6-*bismethylaminopyrimidine* was a white solid, m. p. 178—180° (Found: C, 47·0; H, 7·25; N, 45·3. $C_6H_{11}N_5$ requires C, 47·0; H, 7·25; N, 45·7%). The triamine (1 g.) was refluxed for 15 min. with biacetyl (1·1 g.) in methanol (5 ml.). The solid formed on chilling recrystallised from light petroleum (20 parts), to give the yellow *pteridine*, m. p. 113—115° (Found: C, 58·7; H, 6·5; N, 34·3. $C_{10}H_{13}N_5$ requires C, 59·1; H, 6·45; N, 34·5%).

4-*Dimethylamino*-1-*methylpteridinium Iodide*.—4-Methylthiopteridine [15] (8 g.) was refluxed for 2 hr. with 5% alcoholic dimethylamine (280 ml.). After evaporation, the residue was extracted with boiling light petroleum (b. p. 60—80°; 3 × 2 l.), and refrigeration gave 4-dimethylaminopteridine (94%), m. p. 165—166° (lit.,[16] 164—165°, by another route). The *hydriodide* [from 1 : 3 light petroleum (b. p. 60—80°)–ethanol; 85 parts] had m. p. 244—245° (Found: C, 31·8; H, 3·4; I, 41·8; N, 23·0. $C_8H_{10}IN_5$ requires C, 31·7; H, 3·3; I, 41·9; N, 23·1%). The base (0·35 g.) and methyl iodide (0·62 ml.) in methanol (6·2 ml.) were refluxed for 2 hr., the solvent was removed, and the residue recrystallised from 3 : 2 light petroleum (b. p. 80—100°)–ethanol (225 parts). The yellow quaternary *iodide* (52%) had m. p. 227—229° (Found: C, 33·7; H, 3·85; I, 40·15; N, 21·8. $C_9H_{12}IN_5$ requires C, 34·1; H, 3·8; I, 40·0; N, 22·1%).

4-*Dimethylamino*-1,6,7-*trimethylpteridinium Iodide*.—6,7-Dimethyl-4-methylthiopteridine (8·3 g.) was aminated with dimethylamine as above. The crude product was extracted with light petroleum (b. p. 60—80°; 2 × 1 l.) giving 4-*dimethylamino*-6,7-*dimethylpteridine* (90%), m. p. 138—140° (Found: C, 59·3; H, 6·4; N, 34·3. $C_{10}H_{13}N_5$ requires C, 59·1; H, 6·45; N, 34·5%). Its *hydriodide* had m. p. 206—207° (Found: C, 36·5; H, 4·4; I, 38·8; N, 20·9. $C_{10}H_{14}IN_5$ requires C, 36·3; H, 4·3; I, 38·3; N, 21·15%). After the base (0·2 g.) and methyl iodide (0·31 ml.) in ethyl acetate (20 ml.) had been kept at 20° for 12 hr., the crystals (88%) were collected, washed with ethyl acetate, and dried *in vacuo*. The quaternary *iodide* had m. p. 153—154° (Found: C, 38·3; H, 4·7; I, 37·2; N, 20·2. $C_{11}H_{16}IN_5$ requires C, 38·3; H, 4·7; I, 36·8; N, 20·3%).

1,4-*Dihydro*-1-*methyl*-4-*oxopteridine*.—Formed as indicated in Table 1, the pteridone was purified by extraction from the dry residue with isobutyl methyl ketone and sublimation at 170°/0·01 mm. It had m. p. 222°, unaltered by admixture with authentic material.[3] With alkali it gave 2-carbamoyl-3-methylaminopyrazine.

1,4-*Dihydro*-1,6,7-*trimethyl*-4-*oxopteridine*.—The acid solutions (see Table 1) were treated with charcoal, adjusted to pH 7, and evaporated to dryness, and the residues recrystallised from water (20 parts), to give the *oxopteridine*, m. p. 216—217° (Found: C, 56·5; H, 5·4; N, 29·0. $C_9H_{10}ON_4$ requires C, 56·8; H, 5·3; N, 29·45%). It was also obtained in 46% yield by boiling a solution (adjusted to pH 10) of 4-dimethylamino-1,6,7-trimethylpteridinium iodide (0·4 g.) in water (2·5 ml.) for 4 min.

[16] Albert, Brown, and Cheeseman, *J.*, 1952, 4219.

2-*Amidino*-3-*methylaminopyrazine*.—1,4-Dihydro-4-imino-1-methylpteridine hydriodide (2·54 g.) was triturated with ice-cold 2·5N-sodium hydroxide (25 ml.) for 5 min. The solid (97%) was filtered off, washed with ice-water (3 × 5 ml.), and recrystallised from light petroleum (b. p. 60—80°; 300 parts), to give the *amidine*, m. p. 108—110° (Found: C, 47·65; H, 5·9; N, 46·1. $C_6H_9N_5$ requires C, 47·7; H, 6·0; N, 46·3%). Its *hydrochloride*, from 1 : 3 ethanol–light petroleum (300 parts), had m. p. 204° (Found: C, 38·45; H, 5·4; Cl, 18·8; N, 37·0. $C_6H_{10}ClN_5$ requires C, 38·4; H, 5·4; Cl, 18·9; N, 37·3%).

2-*Amidino*-5,6-*dimethyl*-3-*methylaminopyrazine*.—1,4-Dihydro-4-imino-1,6,7-trimethylpteridine hydriodide (0·5 g.) was added to 2·5N-sodium hydroxide (5 ml.) at 0°, precipitating the free base. The temperature was raised to 35° during 5 min., the base dissolved, and an oil separated. On trituration it solidified, and recrystallised from light petroleum (b. p. 60—80°; 85 parts) to give the *amidine* (75%), m. p. 131—132° (Found: C, 53·5; H, 7·2; N, 39·1. $C_8H_{13}N_5$ requires C, 53·6; H, 7·3; N, 39·1%).

2-*Carbamoyl*-3-*methylaminopyrazine*.—This pyrazine arose from alkaline hydrolysis of 1,4-dihydro-4-imino-1-methylpteridine or its methylimino-analogue (see Table 1), or (in 30% yield) by boiling a 4% aqueous solution of 4-dimethylamino-1-methylpteridinium iodide at pH 10 for 4 min. In each case the solid had m. p. 196° undepressed on admixture with authentic material.[3]

2-*Carbamoyl*-5,6-*dimethyl*-3-*methylaminopyrazine*.—Formed as in Table 1, from an imine (1·4 g.) and sodium hydroxide solution (10 ml.), and recrystallised from water (300 parts), the *carbamoylpyrazine* had m. p. 164° (Found: C, 53·4; H, 6·75; N, 31·1. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·7; N, 31·1%). This amide (0·2 g.) was stirred at 100° for 2 hr. with N-sodium hydroxide (20 ml.). The solution was acidified to pH 1 and evaporated to dryness. The residue was extracted with, and then recrystallised from, light petroleum (b. p. 60—80°; 165 parts), giving 45% of 5,6-*dimethyl*-2-*methylaminopyrazine*-3-*carboxylic acid*, m. p. 146° (Found: C, 52·7; H, 5·9; N, 23·15. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·1; N, 23·2%).

4-Hydroxy-6,7-dimethylpteridine [12] (1·5 g.) was refluxed in 10N-sodium hydroxide (20 ml.) for 4 hr. Treatment as above and recrystallisation from water (110 parts) gave 2-amino-5,6-dimethylpyrazine-3-carboxylic acid (20%), m. p. 210—211° (cf. 209—210°, by another route [17]) (Found: C, 49·9; H, 5·3; N, 24·95. Calc. for $C_7H_9O_2N_3$: C, 50·3; H, 5·4; N, 25·1%).

2-(4,6-*Dimethylpyrimidin*-2-*yl*)-3-*methylaminopyrazine*.—2-Amidino-3-methylaminopyrazine hydrochloride (1·25 g.), acetylacetone (2·65 g.), and potassium carbonate (1·8 g.) in water (15 ml.) were shaken at 45° for 8 hr. After evaporation *in vacuo* the residue was boiled with ethanol (2 × 50 ml.), and the extract taken to dryness. Recrystallisation from light petroleum (b. p. 60—80°; 50 parts) gave the *pyrimidinylpyrazine* (40%), m. p. 89° (Found: C, 61·2; H, 6·15; N, 32·35. $C_{11}H_{13}N_5$ requires C, 61·4; H, 6·1; N, 32·5%).

4-*Amino*-1,6-*dihydro*-6-*imino*-1-*methylpyrimidine*.—4,6-Diaminopyrimidine [18] (5 g.) and methyl iodide (12 ml.) in methanol (25 ml.) were refluxed for 3 hr. The *iminopyrimidine hydriodide* (89%) crystallised from ethanol (90 parts) as needles, m. p. 284° (Found: C, 23·8; H, 3·6; I, 50·5. $C_5H_9IN_4$ requires C, 23·8; H, 3·6; I, 50·35%). It was converted with silver chloride into the *hydrochloride* which after recrystallisation from ethanol (35 parts) had m. p. 268—269° (Found: C, 37·5; H, 5·65; Cl, 22·15; N, 34·5. $C_5H_9ClN_4$ requires C, 37·4; H, 5·65; Cl, 22·1; N, 34·9%). This differed from the isomeric 4-*amino*-6-*methylaminopyrimidine hydrochloride*, m. p. 213—214°, prepared from the base [5] and recrystallised from ethanol (20 parts) (Found: C, 37·45; H, 5·6; Cl, 22·2; N, 34·7%).

The above imine hydriodide (1 g.) was dissolved in N-sodium hydroxide (12·5 ml.). After 6 hr. at 20°, the crystals (58%) were removed and the filtrate was adjusted to pH 8—9 with sulphuric acid. After vacuum-evaporation the residue was boiled with ethyl acetate (50 ml.), and the extract on evaporation gave a second crop (29%). Recrystallised from water (15 parts), the product had m. p. 209—211°, undepressed on admixture with 4-amino-6-methylaminopyrimidine [5] (Found: C, 48·3; H, 6·4; N, 45·2. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%). The hydrochloride (m. p. 213°) prepared from it was identical with the authentic salt above.

4-*Amino*-6-*methylamino*-5-*nitropyrimidine*.—(*a*) 4,6-Diamino-5-nitropyrimidine [18] (4 g.) and methyl iodide (40 ml.) were heated at 140° for 6 hr. An aqueous solution of the residue from evaporation was adjusted to pH 8—9 and after recrystallisation from water (330 parts) the

[17] Vogl and Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2472.
[18] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

nitro-compound had m. p. 248—250° undepressed by admixture with authentic material.[19] (*b*) 4-Amino-1,6-dihydro-6-imino-1-methylpyrimidine hydrochloride (2·4 g.) in concentrated sulphuric acid (11 ml.) was evacuated at 20° to remove hydrogen chloride. Nitric acid (*d* 1·5; 4·8 ml.) was added with stirring at 0°, and the mixture was heated for 30 min. at 40°, then poured on ice. Addition of ammonia gave the nitro-compound (85%). Hydrogenation in methanol over Raney nickel followed by sublimation at 120°/0·01 mm. gave pale yellow *4,5-diamino-6-methylaminopyrimidine* (60%), m. p. 187—189° (Found: C, 43·2; H, 6·65; N, 50·0. $C_5H_9N_5$ requires C, 43·15; H, 6·5; N, 50·3%).

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