869. *Pteridine Studies. Part XIV.*[1] *Methylation of 2-Amino-4-hydroxypteridine and Related Compounds.*

By D. J. Brown and N. W. Jacobsen.

2-Amino-4-hydroxypteridine is shown to undergo an unprecedented transannular methylation on $N_{(8)}$, confirmed by an unambiguous synthesis of the product. 4-Amino-2-hydroxypteridine, however, forms a 1-methyl derivative, whose structure is proved by alkaline degradation to 3-methylaminopyrazine-2-carboxylic acid. 2,4-Diaminopteridine gives a mixture of 1- and 8-methyl derivatives.

pK_a values and ultraviolet spectra of the products and related compounds indicate that the predominant tautomer of " 2-amino-4-hydroxypteridine " (the fundamental unit of naturally occurring pteridines) is 2-amino-3,4-dihydro-4-oxopteridine, and that the isomeric " 4-amino-2-hydroxypteridine " is probably in the form of 4-amino-1,2-dihydro-2-oxopteridine. Application of Jones's rule suggests that the 1-methyl derivative of 2,4-diamino-6,7-dimethylpteridine exists largely as the tautomer, 4-amino-1,2-dihydro-2-imino-1,6,7-trimethylpteridine.

4-Aminopteridine is readily converted by methyl iodide into 1,4-dihydro-4-imino-1-methylpteridine [2] but attempts to isolate a product on methylation of 2-aminopteridine have so far failed. However, 4-amino-2-hydroxy-, 2-amino-4-hydroxy-, and 2,4-diaminopteridines proved more amenable to such treatment.

4-Amino-2-hydroxypteridine gave a single monomethyl derivative which was shown to be 4-amino-1,2-dihydro-1-methyl-2-oxopteridine (I; R = Me) by alkaline degradation to 1-methyl-lumazine [3] (II; R = H) and to 3-methylaminopyrazine-2-carboxylic acid (III; R = OH). The structure of the pyrazine was proved by preparation from its known [4] amide (III; $R = NH_2$). 4-Amino-2-hydroxy-6,7-dimethylpteridine (prepared from 4,5,6-triamino-2-hydroxypyrimidine and biacetyl), when methylated similarly, gave the 6,7-dimethyl derivative of (I), the structure of this being confirmed by alkaline hydrolysis to 1,6,7-trimethyl-lumazine [5] (II; R = Me) and then to the known [2] 5,6-dimethyl-3-methylaminopyrazine-2-carboxylic acid.

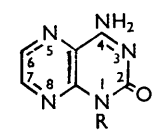
As in the above cases, other amino- and hydroxy-pteridines have always been methylated only in the ring bearing the substituents. Thus 4-methylamino-,[2] and 2- [4] and 4-hydroxypteridine give 1-methyl derivatives though the last gives also an *O*- and a 3-methyl derivative; 6- and 7-hydroxy- and 6,7-dihydroxy-pteridine [4] give, respectively, 5- and 8-methyl and 5,8-dimethyl derivatives. It was, therefore, unexpected that 2-amino-4-hydroxypteridine should undergo transannular methylation, yielding exclusively 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (IV; R = H; $R' = NH_2$). The 8-alkylated pteridines found in Nature [6] may arise in this way. The structure of the product was shown as follows.

Because methylation at position 5 is precluded by valency, there are five possible structures (V; R = H, R′ = O), (VI—VIII; R = H), and (IV; R = H, $R' = NH_2$). The first of these compounds was synthesised in another connexion (see below); 2-amino-4-methoxypteridine and 2-amino-3,4-dihydro-3-methyl-4-oxopteridine were prepared from pyrimidine precursors [7,8] by processes more simple than those recently described; [9] and

[1] Part XIII, *J.*, 1961, 127.
[2] Brown and Jacobsen, *J.*, 1960, 1978.
[3] Pfleiderer, *Chem. Ber.*, 1957, **90**, 2582.
[4] Albert, Brown, and Wood, *J.*, 1956, 2066.
[5] Sachs and Meyerheim, *Ber.*, 1908, **41**, 3957.
[6] Masuda, Kishi, Asai, and Kuwada, *Chem. and Pharm. Bull.*, 1959, **7**, 366; Taylor and Loux, *J. Amer. Chem. Soc.*, 1959, **81**, 2474.
[7] Roth, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1951, **73**, 2864, 2869.
[8] Curran and Angier, *J. Amer. Chem. Soc.*, 1958, **80**, 6095.
[9] Pfleiderer, Liedek, Lohrmann, and Rukwied, *Chem. Ber.*, 1960, **93**, 2015.

4-hydroxy-2-methylaminopteridine was made by a new route from 4-amino-6-hydroxy-2-methylaminopyrimidine by nitration, reduction to the 4,5-diamino-analogue, and condensation with glyoxal. None of these substances resembled the methylation product of 2-amino-4-hydroxypteridine, but the remaining isomer, 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (made from 2,5-diamino-4-hydroxy-6-methylaminopyrimidine [10] and glyoxal) proved identical with it (compared as hydrochlorides).

It seemed wise to confirm this with the 6,7-dimethyl homologues. 2-Amino-4-hydroxy-6,7-dimethylpteridine gave a single methyl derivative similar in spectra and pK_a values to the previous product (IV; R = H; R′ = NH_2). Identity with four of the five possible isomers, (V; R = Me, R′ = O) and (VI—VIII; R = Me), can be eliminated by their published constants.[7,8] The fifth isomer [10] (IV; R = Me, R′ = NH_2) proved, on comparison of hydrochlorides, to be identical with the methylation product, confirming that 8-alkylation had again taken place.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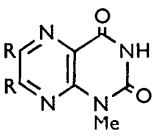
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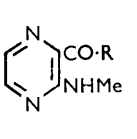
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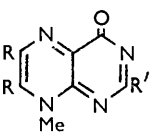
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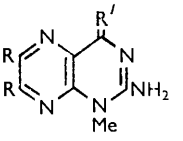
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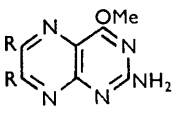
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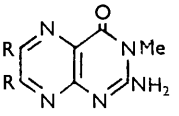
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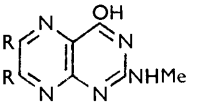
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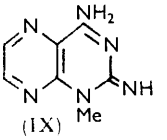

(IX)

2,4-Diaminopteridine gave two methyl derivatives. As already reported,[11] and although it has not been obtained pure, one of these has structure (IX) or (V; R = H, R′ = NH), as shown by the following degradation of impure material. With ice-cold sodium hydroxide solution it rapidly gave 2-amino-1,4-dihydro-1-methyl-4-oxopteridine (V; R = H, R′ = O) which on brief hydrolysis in warm alkali gave 1-methyl-lumazine (II; R = H). This in turn was degraded by prolonged hydrolysis to the acid (III; R = OH), which had been synthesised unambiguously as mentioned above. The possibility that the initial hydrolysis product has the 4-amino-structure (I; R = Me) rather than (V; R = H, R′ = O) is excluded by synthesis and confirmation of the structure of the former (see above), as well as by a recent unambiguous synthesis [9] of the latter. The formation of the 1-methyl derivative (IX) parallels that of its 6,7-diphenyl derivative reported by Boon and Bratt.[12]

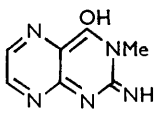
The second methylated product was obtained pure. It was not degraded by alkali and its spectrum differed from that of 4-amino-1,2-dihydro-2-imino-1,6,7-trimethylpteridine and 2,4-diaminopteridine (see Table). This precludes its being the 1-methyl derivative (IX) or 2-amino-4-methylamino- or 4-amino-2-methylamino-pteridine (the last two would resemble 2,4-diaminopteridine spectrographically). Of the remaining possibilities the 8-methylated derivative is strongly suggested by the extraordinarily long-wavelength absorption, typical of transannularly methylated imino- and oxo-pteridines shown in the Table and elsewhere.[2,10,13-15] This is confirmed by the similarity of the spectrum of its neutral molecule to that of the anion of 2-amino-4,8-dihydro-8-methyl-4-oxopteridine, as

[10] Fidler and Wood, *J.*, 1957, 4157.
[11] Brown and Jacobsen, *Tetrahedron Letters*, 1960, No. 25, p. 17.
[12] Boon and Bratt, *J.*, 1957, 2159.
[13] Brown and Mason, *J.*, 1956, 3443.
[14] Masuda, *Pharm. Bull. (Japan)*, 1957, **5**, 28.
[15] Pfleiderer and Nübel, *Chem. Ber.*, 1960, **93**, 1406.

would be expected of the 8-methyl isomer according to the R.N. Jones rule.[16] Moreover, its basic strength (pK_a 8·9) is intermediate between those of the parent pteridine (pK_a 5·3) and its 1,6,7-trimethyl derivative (pK_a 11·9), in line with analogous cases of transannularly methylated iminopteridines.[2,10] Transannular methylation was finally proved by acid hydrolysis in good yield to 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (IV; R = H, R′ = NH_2).

Like its simpler homologue, 2,4-diamino-6,7-dimethylpteridine gave two products on methylation. The major one was degraded by alkali to 1,6,7-trimethyl-lumazine[5] (II; R = Me) and is therefore the 1-methyl derivative. The minor product could not be obtained entirely free from the major one but analysis of the mixture indicated that the constituents are isomeric, and by analogy it is assumed to be the 8-methyl derivative.

The Table shows that the amino-hydroxypteridines methylated on O, $N_{(1)}$, $N_{(3)}$, or the extranuclear N-atom, are quite weak bases, of pK_a <3·5, indistinguisable in this respect from their unmethylated precursors. This indicates that the preferred tautomeric form in these cases involves an amino-form (as in VII) rather than an imino-form (as in X), which must be more strongly basic.[2,17] On the other hand, $N_{(1)}$-methylated 2,4-diamino-6,7-dimethyl-pteridine, which must involve an imine as (IX) or (V; R = Me, R′ = NH), is an exceptionally strong base of pK_a *ca.* 12.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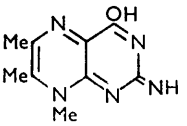
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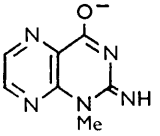
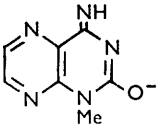

(XII)


(XIII)

The basic strengths of 8-methylated 2-amino-4-hydroxypteridines are markedly greater than those of the 1- and 3-methyl isomers. Thus the simple derivative (IV; R = H, R′ = NH_2) has pK_a 5·4, and its 6,7-dimethyl derivative has pK_a 6·1. That the basic strength of the latter approximates to that of 2,8-dihydro-2-imino-6,7,8-trimethylpteridine (5·6) led Fidler and Wood[10] to postulate the hydroxy-imino-structure (XI) for the compound, and a pK_a of 8·9 was assigned to the hydroxy-group. We have been unable to confirm the latter constant, but find an anionic pK_a 12, which is more in line with those of the 1- and 3-methyl analogues that are forced into an hydroxy-imino-form such as (XII) only at high pH values. The recorded value of 8·9 may have arisen from the formation of 6,7,8-trimethyl-lumazine (pK_a 9·8) by partial hydrolysis of the amino-group during measurement. Moreover, the enhanced basic strength of compound (IV; R = Me, R′ = NH_2) is in line with that of 4,8-dihydro-6,7,8-trimethyl-4-oxopteridine[13] (IV; R = Me, R′ = H), which can involve no imine but has a comparably enhanced basic strength (pK_a 4·7) when compared with the isomeric 1,4-dihydro-1,6,7-trimethyl-4-oxopteridine[2] (pK_a 1·7). It is, therefore unwarranted, in the face of accepted general principles,[17] to assume the hydroxy-imino-form (XI) at the expense of the usual amino-oxo-forms (IV; R = H or Me, R′ = NH_2).

It is of special interest to discover the preferred tautomeric form of 2-amino-4-hydroxypteridine in aqueous solution because this structure is common to almost all of the natural pteridines. Valency permits this substance to exist in 9 forms. The five imino-forms (three hydroxy-imino-tautomers with the mobile hydrogen atom severally at positions 1, 3, and 8, as well as two imino-oxo-tautomers each with two hydrogen atoms at positions 1,3 and 1,8) are precluded by the weakly basic nature of 2-amino-4-hydroxypteridine (pK_a 2·3) because all known pteridine and related imines are much stronger bases.[2,10]

[16] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[17] Brown, Hoerger, and Mason, *J.*, 1955, 4035; Angyal and Angyal, *J.*, 1952, 1461; Albert, "Heterocyclic Chemistry," Athlone Press, London, 1959, pp. 54 *et seq.*

This has been confirmed by the marked similarity in spectra [9] of 2-amino-4-hydroxy- and 4-hydroxy-2-dimethylamino-pteridine, the second of which cannot assume an imino-form. A similar conclusion can be drawn from a comparison of their 6,7-dimethyl derivatives.[7]

Compound	pK_a [a] and concn.	$\lambda_{max.}$ (mμ) [b]	pH	log ε
Pteridine derivatives				
4-Amino-1,2-dihydro-1-methyl-2-oxo		345; 288; 245	5·0	3·88; 3·56; 4·13
cation	2·96 ± 0·02 (M/400)	*360*; 341; 238	0·13	*3·68*; 3·87; 4·08
anion	*ca.* 12	350; 245	14·0	3·79; 4·04
4-Amino-1,2-dihydro-1,6,7-trimethyl-2-oxo		*360*; 345; 282; 248; 216	7·1	*3·93*; 4·04; 3·53; 4·24; 4·18
cation	3·66 ± 0·03 [c]	360; 343; *264*; 218	0·3	3·91; 4·02; *3·82*; 4·29
4-Amino-2-hydroxy		*350*; 337; *286*; 240	7·0	*3·87*; 3·94; *3·63*; 4·08
cation	2·99 ± 0·02 [c, d]	335; 237	0·83	3·90; 4·08
anion	9·97 [e]	375; 255	12·0	3·85; 4·31
2-Amino-1,4-dihydro-1-methyl-4-oxo		See Figure	5·0	
cation	2·83 ± 0·03 (M/200)	—[f]	—	—
anion	*ca.* 11·5	360; 258	14·0	3·90; 4·13
2-Amino-3,4-dihydro-3-methyl-4-oxo		See Figure	5·0	—
cation	2·25 ± 0·03 [c]	—[f]	—	—
2-Amino-4,8-dihydro-8-methyl-4-oxo		400; 320; 265	8·5	3·98; 3·47; 4·28
cation	5·42 ± 0·02 (M/200)	389; *283*; 261	3·0	4·01; *3·99*; 4·14
anion	*ca.* 11·5	314; 284; 239	14·0	3·91; 3·89; 4·26
2-Amino-4,8-dihydro-6,7,8-trimethyl-4-oxo		407; 315; 267	8·5	4·11; 3·43; 4·35
cation	6·10 ± 0·02 (M/200) [g]	397; 285; 254	3·0	4·12; 4·13; 4·09
anion	11·97 ± 0·02 [c]	370; 308; *301*; 228 [h]	14·0	3·88; 4·20; *4·18*; 4·33
2-Amino-4-hydroxy [i]		See Figure	5·25	
cation	2·31	315; <220		3·88; >4·1
anion	7·92	358; 251		3·83; 4·31
4-Amino-2-hydroxy-6,7-dimethyl		*350*; 340; 276; 245	6·5	*3·96*; 4·01; 3·48; 4·07
cation	3·49 ± 0·03 [c]	*350*; 338; *256*; 215	1·3	*3·97*; 4·03; *3·85*; 4·32
anion	10·69 ± 0·04	370; *274*; 254	13·8	3·88; *3·78*; 4·29
4-Amino-2,8-dihydro-2-imino-8-methyl [j]		*365*; 313; 288; 241	11·0	*3·23*; 3·92; 3·93; 4·11
cation	8·88 ± 0·04 [c]	412; 330; 270; *244*	6·0	3·98; 3·52; 4·24; *3·73*
4-Amino-1,2-dihydro-2-imino-1,6,7-trimethyl		368; 262	14·16	3·97; 4·15
cation	11·90 ± 0·05 [c]	*347*; 335; 282; *246*	7·5	*4·01*; 4·07; 3·64; *4·25*
2,4-Diamino		364; 255; 224	8·0	3·86; 4·32; 4·07
cation	5·32 [c]	*345*; 332; *318*; 284; 240	3·0	*3·90*; 3·98; *3·91*; 3·73; 4·10
1-Methyl-lumazine, anion [k]	8·57 ± 0·02 (M/200)	339; 281; 242	10·5	3·89; 3·54; 4·19
3-Methyl-lumazine, anion [k]	8·0	362; 268; 244; 215	10·0	3·81; 3·98; 4·25; 4·02
1,6,7-Trimethyl-lumazine		334; 252; *225*	7·0	3·98; 3·96; 4·07
anion	9·06 ± 0·04 (M/300)	341; *280*; 244	11·5	4·03; *3·38*; 4·25
6,7,8-Trimethyl-lumazine		404; 276; 256	7·0	4·08; 4·04; 4·16
anion	9·83 ± 0·04 (M/400)	363; 313; *304*; 243	12·0	3·78; 4·31; *4·28*; 4·19
Lumazine, dianion [m]		365; 252		3·78; 4·23

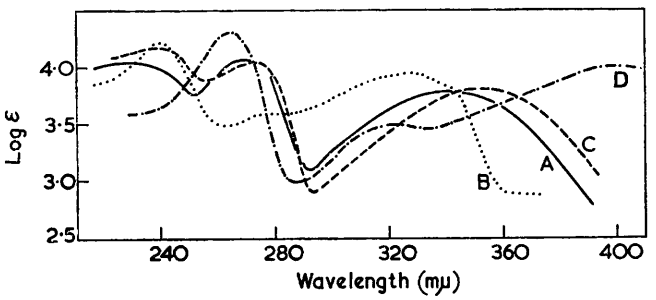
[a] By potentiometric titration in water at 20° (cf. Albert and Phillips, *J.*, 1956, 1294). For values for other compounds see Experimental section. [b] Inflexions in italics. [c] Spectrometrically determined. [d] Cf. approx. value of 3·2 by potentiometric titration, ref. 19. [e] From ref. 19. [f] For spectrum see ref. 9. [g] Cf. 5·85 given in ref. 10. [h] The peak at 268 mμ recorded by Fidler and Wood (ref. 10) at pH 13 arises from that of the neutral molecule, present to the extent of 10% in their solution. [j] Constants measured on dihydriodide with balanced I^- concentration in reference cell. [k] Spectrum from ref. 3. [l] Prep.: ref. 14 and Birch and Moye, *J.*, 1958, 2622; values determined on supplied specimens; cf. pK_a 9·86 in ref. 15. [m] Values from Albert, Brown, and Cheeseman, *J.*, 1951, 474.

The one possible amino-hydroxy-form can also be eliminated by dissimilarity in spectra [9] between 2-amino-4-hydroxy- and 2-amino-4-methoxy-pteridine. There remain the three amino-oxo-forms with hydrogen located severally at positions 1, 3, and 8. Comparison of the spectrum of 2-amino-4-hydroxypteridine as neutral molecule with those of its 1-, 3-, and 8-methyl derivatives (see Figure) leaves little doubt that the hydrogen occupies position 3 and that 2-amino-3,4-dihydro-4-oxopteridine is the predominant tautomer, at least in aqueous solution, as believed also by Pfleiderer *et al* [9] This stands in contrast to its methylation at position 8 and its reported protonation [9] at position 1, but is in line with the recorded preference [13,18] for an α-cyclic amide at the expense of a γ-vinylogous cyclic amide where the choice exists in 1,3-diazines.

Similar treatment cannot be accorded to 4-amino-2-hydroxypteridine because the range of methylated reference compounds is incomplete. However, its weak basic strength and the close similarity of its spectrum (neutral molecule) to that of 4-amino-1,2-dihydro-1-methyl-2-oxopteridine (I; R = Me) suggests that (unlike its isomer) it carries a hydrogen atom at position 1, the principal tautomer being 4-amino-1,2-dihydro-2-oxopteridine (I; R = H).

The spectrum of the neutral molecule of 4-amino-1,2-dihydro-2-imino-1,6,7-trimethylpteridine reveals the compound's tautomeric form. If allowance is made for the usual small bathochromic shift resulting from the *C*-methyl groups, the spectrum approximates more closely to that of the anion of 2-amino-1,4-dihydro-1-methyl-4-oxopteridine (XII) than to that of the anion of 4-amino-1,2-dihydro-1-methyl-2-oxopteridine (XIII). Application of Jones's rule [16] (that the spectrum of an amino-derivative is similar to that of the anion of the corresponding hydroxy-derivative) suggests that the methylated diamine

Absorption, as neutral molecules, of: A, 2-*amino*-4-*hydroxypteridine*; B, 2-*amino*-1,4-*dihydro*-1-*methyl*-4-*oxopteridine*; C, 2-*amino*-3,4-*dihydro*-3-*methyl*-4-*oxopteridine*; D, 2-*amino*-4,8-*dihydro*-8-*methyl*-4-*oxopteridine*.



is probably best represented as 4-amino-1,2-dihydro-2-imino-1,6,7-trimethylpteridine. Simple examples supporting the validity of the rule in this series are the similarity of the spectra of 2,4-diaminopteridine (neutral molecule) to those of the anions of 4-amino-2-hydroxy- and 2-amino-4-hydroxy-pteridine and the dianion of lumazine (see Table).

Experimental

Analyses were done by Dr. J. E. Fildes and staff.

3-*Methylaminopyrazine*-2-*carboxylic Acid*.—1,4-Dihydro-1-methyl-4-methyliminopteridine hydrochloride [2] (0·45 g.) was stirred in N-sodium hydroxide (10 ml.) at 100° for 2·5 hr. The solution was adjusted to pH 1 with hydrochloric acid and evaporated to dryness. The powdered residue was extracted with boiling benzene (2 × 20 ml.), and the solid obtained on evaporation was recrystallized from water (50 parts) to give the *pyrazine* (72%), m. p. 182° (decomp.) (Found: C, 47·0; H, 4·5; N, 27·4. $C_6H_7N_3O_2$ requires C, 47·05; H, 4·6; N, 27·4%). The same product

[18] Brown, Hoerger, and Mason, *J.*, 1955, 211; Brown and Mason, *J.*, 1957, 682.

was obtained similarly from 1,4-dihydro-4-imino-1-methylpteridine [3] and from 3-methylaminopyrazine-2-carboxamide.[4]

4-Amino-1,2-dihydro-1-methyl-2-oxopteridine.—4-Amino-2-hydroxypteridine [19,20] (1·35 g.), methyl iodide (5·2 ml.), and methanolic sodium methoxide (200 ml.; from sodium, 0·21 g.) were refluxed for 1 hr. Recrystallization of the solid from water (160 parts) gave the *methyl-pteridine* (75%), m. p. 324—325° (decomp.) (Found: C, 47·6; H, 4·0; N, 39·4. $C_7H_7N_5O$ requires C, 47·45; H, 4·0; N, 39·5%).

This pteridine (0·3 g.) was stirred in N-sodium hydroxide (15 ml.) for 5 hr. at 100°. The solution was adjusted to pH 1 and evaporated to dryness, and the residue continuously extracted with benzene. The extract was taken to dryness and sublimed at 120°/0·02 mm. to give 3-methylaminopyrazine-2-carboxylic acid (39%), m. p. and mixed m. p. 180°. The unsublimed part (30%), when recrystallized from ethanol and sublimed (220°/0·02 mm.), had m. p. 285°, undepressed on admixture with 1-methyl-lumazine.

4-Amino-1,2-dihydro-1,6,7-trimethyl-2-oxopteridine.—4,5,6-Triamino-2-hydroxypyrimidine sulphate [21] (4·8 g.) and sodium hydrogen carbonate (3·4 g.) in water (350 ml.) were stirred on the steam-bath with biacetyl (1·8 g.) for 15 min. The resulting solid (3·4 g.) dissolved in hot water (150 parts) on addition of hydrochloric acid to pH 2·5, and the *4-amino-2-hydroxy-6,7-dimethylpteridine*, m. p. *ca.* 340° (decomp.), crystallized on slow addition of sodium acetate to pH 5 (Found: C, 50·3; H, 4·75; N, 36·15. $C_8H_9N_5O$ requires C, 50·25; H, 4·7; N, 36·6%).

This pteridine (1 g.) and methyl iodide (2·5 ml.) were refluxed for 1 hr. in methanolic sodium methoxide (25 ml.; from sodium, 0·13 g.). After chilling, the water-washed solid (84%) recrystallized from ethanol (350 parts), to give the *trimethyloxopteridine*, m. p. 314—316° (decomp.) (Found: C, 52·65; H, 5·4; N, 33·7. $C_9H_{11}N_5O$ requires C, 52·65; H, 5·4; N, 34·1%). Hydrolysis in boiling N-sodium hydroxide (25 parts) for 15 min. gave, after adjustment to pH 5, 1,6,7-trimethyl-lumazine (83%), m. p. 328—330° (lit.,[5] 328—330°) (Found: C, 52·5; H, 4·8; N, 27·15. Calc. for $C_9H_{10}N_4O_2$: C, 52·4; H, 4·9; N, 27·15%). This substance (0·42 g.) was further heated with 2·5N-sodium hydroxide (16 ml.) at 200° for 4 hr. After treatment with charcoal and evaporation, the residue recrystallized from light petroleum (b. p. 60—80°; 165 parts) to give 5,6-dimethyl-3-methylaminopyrazine-2-carboxylic acid (35%), m. p. and mixed m. p. (ref. 2) 143—145°.

2-Amino-4,8-dihydro-8-methyl-4-oxopteridine.—2-Amino-4-hydroxypteridine (2 g.), methyl iodide (15 ml.), and methanol (60 ml.) were rocked at 110° for 12 hr. The tube was opened at −40° (dimethyl ether!), and the solution on evaporation to 15 ml. deposited red crystals (1·3 g.). Recrystallization from methanol (140 parts) with concentration gave the *oxopteridine hydriodide*, (decomp.) 265° (Found: C, 27·85; H, 2·8; I, 41·1; N, 22·55. $C_7H_8IN_5O$ requires C, 27·55; H, 2·65; I, 41·6; N, 22·95%). Treatment with silver chloride furnished the *hydrochloride* (from methanol, 330 parts, with concentration), m. p. *ca.* 285° (decomp.) (Found: C, 39·35; H, 3·9; N, 32·7. $C_7H_8ClN_5O$ requires C, 39·35; H, 3·8; N, 32·8%).

This pteridine was also made unambiguously. 2-Amino-4-hydroxy-6-methylamino-5-nitrosopyrimidine was reduced with sodium dithionite [10] or hydrogenated over Raney nickel. An equivalent amount of aqueous hydrochloric acid was added to the crude base (0·9 g.), suspended in methanol (10 ml.). Addition of ether (10 ml.) precipitated *2,5-diamino-4-hydroxy-6-methylaminopyrimidine hydrochloride* (85%), which, recrystallized from methanol, had m. p. 237—238° (decomp.) (Found: C, 31·4; H, 5·5; Cl, 18·25. $C_5H_{10}ClN_5O$ requires C, 31·35; H, 5·25; Cl, 18·5%). This hydrochloride (0·45 g.) was refluxed for 30 min. with polyglyoxal (0·14 g.) in methanol (30 ml.); evaporation to 10 ml. then gave a solid (50%) which after recrystallization was identified with the pteridine hydrochloride by mixed m. p., chromatography in six systems, and infrared spectroscopy.

2-Amino-4,8-dihydro-6,7,8-trimethyl-4-oxopteridine.—2-Amino-4-hydroxy-6,7-dimethylpteridine [22] (1·0 g.) was rocked for 5 hr. at 100° with methyl iodide (7·5 ml.) and methanol (30 ml.). Evaporation and recrystallization from methyl iodide–methanol (35 : 65) gave the *oxopteridine hydriodide* (60%), m. p. 265—270° (decomp.) (Found: C, 32·45; H, 3·5; I, 37·75; N, 20·85. $C_9H_{12}IN_5O$ requires C, 32·45; H, 3·6; I, 38·1; N, 21·0%). Silver chloride converted it into the *hydrochloride* which, recrystallized from 25% aqueous ethanol (26 parts), had m. p. 255—260° (decomp.) (Found: Cl, 14·8; N, 28·75. $C_9H_{12}ClN_5O$ requires Cl, 14·7%; N, 29·0%).

[19] Albert, Brown, and Cheeseman, *J.*, 1952, 4219.
[20] Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2538.
[21] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3109.
[22] Cain, Mallette, and Taylor, *J. Amer. Chem. Soc.*, 1946, **68**, 1996.

It was also prepared in 93% yield from 2,5-diamino-4-hydroxy-6-methylaminopyrimidine hydrochloride and biacetyl (see homologue above), and the products from both routes were identified by mixed m. p., chromatography, and spectroscopy.

2-Amino-4-methoxypteridine.—2,4,5-Triamino-6-methoxypyrimidine sulphate [7] (0·5 g.) and polyglyoxal (0·11 g.) were refluxed for 1 hr. in methanolic sodium methoxide (from sodium, 0·085 g.). The oily residue obtained on evaporation was triturated with water (5 ml.), and the resulting solid recrystallized from water (25 parts). The aminomethoxypteridine (0·14 g.) had m. p. 204—205° (lit.,[9] 207—209°) and pK_a 3·46 ± 0·02 (M/200; 20°) (Found: C, 47·4; H, 3·85; N, 39·4. Calc. for $C_7H_7N_5O$: C, 47·45; H, 4·0; N, 39·5%).

2-Amino-3,4-dihydro-3-methyl-4-oxopteridine.—2,4,5-Triamino-1,6-dihydro-1-methyl-6-oxopyrimidine hydrochloride [9] (0·5 g.), polyglyoxal (0·15 g.), and methanol (60 ml.) were refluxed for 1 hr. Evaporation to *ca.* 5 ml. gave the oxopteridine (70%) which after recrystallization from glacial acetic acid decomposed at *ca.* 320° (lit.,[9] 322°) (18%) (Found: C, 47·65; H, 4·0; N, 39·35. Calc. for $C_7H_7N_5O$: C, 47·45; H, 4·0; N, 39·5%).

4-Hydroxy-2-methylaminopteridine.—4-Amino-6-hydroxy-2-methylaminopyrimidine [7] (5 g.) was added during 30 min. to stirred nitric acid (*d* 1·5; 20 ml.) at 5—10°. After a further 30 min., the mixture was poured on ice. Washing the solid in boiling water (350 ml.) and recrystallization from water (1500 parts) gave *4-amino-6-hydroxy-2-methylamino-5-nitropyrimidine* (73%), m. p. 348—350° (decomp.) (Found: C, 32·7; H, 3·8. $C_5H_7N_5O_3$ requires C, 32·45; H, 3·8%). This nitro-compound (2·5 g.) was hydrogenated over Raney nickel in methanol (250 ml.), and the catalyst filtered off and washed with hot water (50 ml.). The filtrate and washings were added to N-hydrochloric acid (18 ml.) and evaporated to dryness. Addition of ethanol (30 ml.) to the residue (1·9 g.) in hot water (10 ml.) gave *4,5-diamino-6-hydroxy-2-methylaminopyrimidine hydrochloride*, m. p. 275—277° (decomp.) (Found: C, 31·45; H, 5·5; N, 36·3. $C_5H_{10}ClN_5O$ requires C, 31·35; H, 5·25; N, 36·55%).

The diamine hydrochloride (1 g.) and polyglyoxal (0·3 g.) were refluxed in methanol (125 ml.) for 1 hr. The solid recovered by evaporation was recrystallized by dissolution in hot water (400 parts), addition of hot alcohol (400 parts), and concentration. 4-Hydroxy-2-methylaminopteridine (0·69 g.) decomposed at *ca.* 378° (lit.,[9] >350°) and had pK_a 1·98 ± 0·03 (M/200), and 8·16 ± 0·02 (M/400) (Found: C, 47·3; H, 4·0; N, 39·3. Calc. for $C_7H_7N_5O$: C, 47·45; H, 4·0; N, 39·5%).

4-Amino-2,8-dihydro-2-imino-8-methylpteridine (or Tautomer).—2,4-Diaminopteridine [15] (4 g.), methyl iodide (40 ml.), and methanol (80 ml.) were rocked together at 110° for 1 hr. Evaporation gave a crude solid (8·4 g.) which was extracted with boiling methanol (40 ml.). The residue, twice recrystallized from methanol (160 parts) with concentration, gave the *8-methylpteridine dihydriodide* (0·5 g.) as dark red crystals, m. p. 236—237° (Found: C, 19·5; H, 2·1; I, 58·75. $C_7H_{10}I_2N_6$ requires C, 19·45; H, 2·3; I, 58·75%). The dihydriodide (0·28 g.) was heated at 100° with N-hydrochloric acid (36 ml.) for 30 min. The solution was shaken with silver chloride (*ca.* 2 g.) for 1 hr., then filtered and the filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in water (10 ml.) which was then adjusted to pH 3·5 with 5% ammonia solution and chilled. The solid precipitate (80%) recrystallised from water (80 parts), giving 2-amino-4,8-dihydro-8-methyl-4-oxopteridine hydrochloride, identified with authentic material by mixed m. p., paper chromatography in 4 solvents, and infrared and ultraviolet spectroscopy.

The initial methanol extract and the mother-liquors from the dihydriodide recrystallization gave, on evaporation, a yellow solid consisting of the 8-methylpteridine and its 1-methyl isomer. The mixture (6 g.) was dissolved in 0·5N-sodium hydroxide (125 ml.) and kept at 0° for 15 min. Recrystallization of the precipitate (1 g.) from water gave 2-amino-1,4-dihydro-1-methyl-4-oxopteridine, m. p. 336° (decomp.) (lit.,[9] 335—337°) (Found: C, 47·55; H, 4·0; N, 39·5. Calc. for $C_7H_7N_5O$: C, 47·45; H, 4·0; N, 39·5%). This pteridine (0·5 g.) was refluxed in N-sodium hydroxide (7 ml.) for 15 min. Adjustment to pH 5, followed by sublimation and recrystallization of the solid (0·44 g.) from ethanol (260 parts), gave 1-methyl-lumazine, m. p. 285° (lit.,[3] 290—291°) (Found: C, 46·95; H, 3·4; N, 31·35. Calc. for $C_7H_6N_4O_2$: C, 47·2; H, 3·4; N, 31·45%). The methyl-lumazine was refluxed in N-sodium hydroxide for 3 hr. and the solution then adjusted to pH 1—2. The residue obtained on evaporation was extracted with boiling benzene to give 3-methylaminopyrazine-2-carboxylic acid identical with authentic material.

4-Amino-1,2-dihydro-2-imino-1,6,7-trimethylpteridine (or Tautomer).—*2,4-Diamino-6,7-dimethylpteridine* was prepared according to directions by Mallette *et al.*[23] It was triturated with

[23] Mallette, Taylor, and Cain, *J. Amer. Chem. Soc.*, 1947, **69**, 1814.

dilute aqueous sodium hydroxide, washed with hot water, and recrystallised from dimethylformamide (145 parts) or glacial acetic acid (20 parts). It was then chromatographically homogeneous, and despite failure by older methods [23] it gave a satisfactory analysis for carbon and hydrogen by the " rapid combustion " method in admixture with vanadium pentoxide, and for nitrogen by the Kjeldahl method (sealed tube) (Found: C, 50·75; H, 5·35; N, 43·75. $C_8H_{10}N_6$ requires C, 50·5; H, 5·3; N, 44·2%).

This pteridine (2 g.), methyl iodide (20 ml.), and methanol (40 ml.) were rocked together at 110° for 5 hr. The tube was opened at −40° (dimethyl ether!) and the solid (27%) recrystallized from ethanol (40 parts). The *iminopteridine hydriodide* had m. p. 280—285° (decomp.) (Found: C, 32·5; H, 3·85; I, 38·15; N, 25·2. $C_9H_{13}IN_6$ requires C, 32·55; H, 3·95; I, 38·2; N, 25·3%).

The hydriodide (0·23 g.) was refluxed with N-sodium hydroxide (5 ml.) for 15 min. Adjustment to pH 5 and recrystallization from water (250 parts) then gave 1,6,7-trimethyl-lumazine (92%), m. p. and mixed m. p. 327—329°.

When the methylation mixture was heated for 1 hr. and then treated with ether (60 ml.), a solid (1·3 g.) was precipitated. Paper chromatography revealed that repeated recrystallization was ineffective in separating all the above imine from a yellow isomeric hydriodide (Found ,for the mixture: C, 32·4; H, 3·95; I, 37·65; N, 25·1%).

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