SECTION C
Organic Chemistry

Pteridine Studies. Part XXXV.[1] The Structure of the Hydrated Dimer Formed by the Action of Dilute Acid on 4-Methylpteridine

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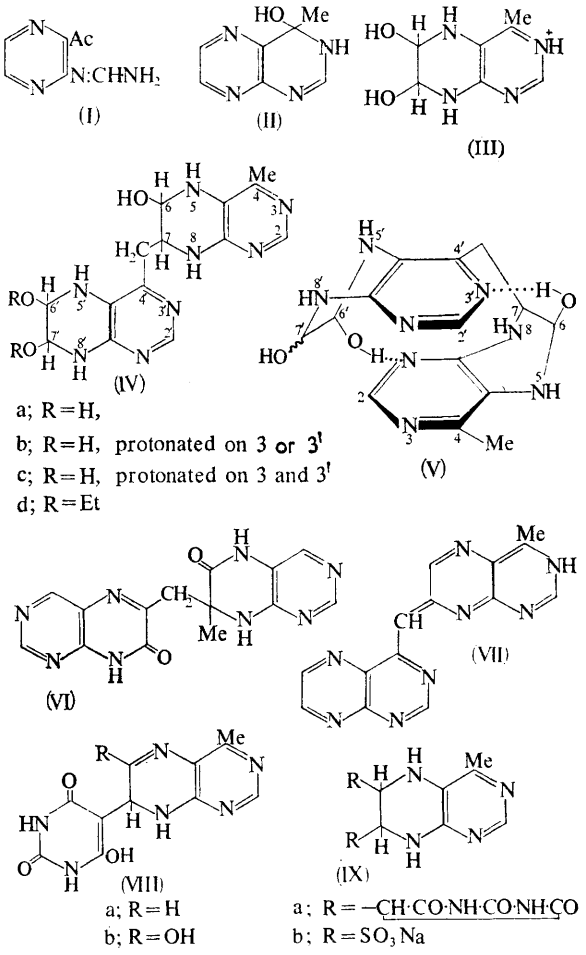
The substance formed from 4-methylpteridine by the action of hot dilute acid is assigned the structure of a hydrated dimer, namely 5,6,7,8-tetrahydro-6-hydroxy-4-methyl-7-(5,6,7,8-tetrahydro-6,7-dihydroxypteridin-4-ylmethyl)pteridine (IVa) on the basis of n.m.r., u.v., i.r., and mass spectra. 4-Methylpteridine is shown to add other nucleophiles stepwise across the 7,8- and 5,6-double bonds (in that order). An improved method for preparing 4-methylpteridine is reported.

4-METHYLPTERIDINE, treated with boiling, dilute sulphuric acid at pH 1·5, gives a stronger base for which a provisional structure *N*-(3-acetylpyrazin-2-yl)formamidine (I) has been derived [2] from elemental analysis and from analogy with the known degradation of pteridine to 2-amino-3-formylpyrazine under the same conditions. Later we found that the molecular weight in boiling water was twice that required by formula (I), and hence the structure of the degradation product was re-examined by modern physical methods.

Perrin and Inoue [3,4] found, by potentiometric and kinetic studies, that 4-methylpteridine adds water across the 3,4-double bond to give an equilibrated mixture containing a little of the hydrate, 3,4-dihydro-4-hydroxy-4-methylpteridine (II). In acid solution, as was recently shown [5] by ^{1}H n.m.r., 4-methylpteridine gives the cation (III) which is dihydrated across the pyrazine ring. The u.v. spectrum [3] of the cation, which is almost identical with that of the cation of 5,6,7,8-tetrahydro-4-methylpteridine,[6] supports structure (III) (see Table 1). Pteridine, because it lacks the sterically hindering 4-methyl group, contributes more of the 3,4-hydrate to the equilibrium states of both neutral species [3,4] and cation.[5]

It is well established that heteroaromatic rings become less sensitive to hydrolytic fission as the number of doubly bonded nitrogen atoms declines. Hence the cation of 4-methylpteridine (III) is more likely to resist acid-catalysed ring-fission than the monohydrated cation of pteridine. The reasons for our final choice of structure (IVa) for the dimer, will now be given.

The yield of this substance (previously obtained by the action of boiling 0·5N-sulphuric acid on 4-methylpteridine for 5 min.) was raised to 57% by prolonged heating at a slightly lower temperature (the reaction also took place at 25°; 12% yield after 8 days). Periodic checking by paper chromatography showed no intermediates and no other major product. The substance was isolated as the hemi-sulphate, which was basified to



give the neutral species; both species were identical (i.r. spectra) with those previously obtained.[2] Elemental

[1] Part XXXIV, A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1968, 63.
[2] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1956, 2066.
[3] D. D. Perrin, *J. Chem. Soc.*, 1962, 645.
[4] Y. Inoue and D. D. Perrin, *J. Chem. Soc.*, 1963, 2648.
[5] A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc.* (*B*), 1966, 1105.
[6] P. R. Brook and G. R. Ramage, *J. Chem. Soc.*, 1955, 896.

TABLE 1

Physical properties of some pteridines

	Ionizations (H_2O; 20°)			Spectrometry [a]		
	Species [b]	pK_a [c]	Concn. (M)	$\lambda_{max.}$ (mμ)	log ε	pH
Dimer (IVa)	++	4·19 ± 0·02	2·0 × 10^{-3}	303	4·23	2·0
	+	6·28 ± 0·02	2·9 × 10^{-3}			
	0			267, 300	4·03, 4·16	9·0
	−			*273*, 303	*4·05*, 4·16	14
4-Methyl- [d]	0 [h]	2·94 ± 0·13 [i]	5 × 10^{-2}	300, 312	3·92, 3·86	7·4
	+ *	5·51 ± 0·03		305	4·00	2·0
	0 *			258, 298	3·61, 3·86	7·4
5,6,7,8-Tetrahydro-4-methyl- [e]	+	6·74 ± 0·02	1 × 10^{-2}	213, 305	4·12, 3·93	1·0
	0			211, 300	4·18, 3·82	
6,7-Dihydroxy- [f]	0			249, 301	3·71, 4·18	4·0
	−	6·87 ± 0·03	2 × 10^{-3}	227, 268, 319	4·03, 3·71, 4·29	8·4
	−−	10·0 ± 0·08	2 × 10^{-3}	240, 324, 338	4·13, 4·30, 4·25	12
6,7-Dihydroxy-4-methyl-	0			*222*, 259, 302, *311*, *330*	*4·03*, 3·74, 4·16, *4·08*, *3·64*	4·2
	−	7·12 ± 0·06	2·5 × 10^{-3}	226, 271, *300*, 321, 337	4·09, 3·75, *4·04*, 4·28, 4·07	8·6
	−−	10·17 ± 0·08	2·5 × 10^{-3}	*220*, 240, *280*, 290, 316, 327, 341	*4·48*, 4·17, *3·66*, 3·71, 4·16, 4·32, 4·24	13
7,8-Dihydro-4,6-dimethyl- [g]	+	6·00 ± 0·03	5 × 10^{-3}	218, 293	4·13, 3·91	3
	0			218, 293	4·27, 3·73	8·3
5,6-Dihydro-4-hydroxy- [g]	+	2·94 ± 0·04		258	3·74	0
	0			286	3·78	7

[a] Inflections in italics. [b] Dication (++), cation (+), neutral species (0), anion (−), dianion (−−), the 5,6:7,8-dihydrate (*). [c] Determined potentiometrically, except for 5,6-dihydro-4-hydroxy-compound, for which spectrometric determination (ref. 7) was used (analytical wavelength 400 mμ). [d] From ref. 3. [e] From ref. 6. [f] From A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1952, 1620. [g] From A. Albert and S. Matsuura, *J. Chem. Soc.*, 1962, 2162. [h] The anhydrous cation becomes hydrated so rapidly that it has not been independently observed. [i] Equilibrium pK_a value from A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.

TABLE 2

N.m.r. spectra at 33·3° [a]

	τ Values * for protons									
	H(2′)	H(2)	H(6′)	H(7′)	H(6)	H(7)	CH_2(4′)	CH_3(4)	OEt	Solvents [b]
Dimer (IVa)	1·97s	2·09s	5·12m	5·12m	5·12m	5·97m	7·02m	7·78s		A
	1·41s	1·59s	4·66d †	4·58d †	4·54d	5·35dt	6·44dd [c]	7·47s		B
							6·20dd [c]			
			J 3	*J* 3	*J* 3	*J* 3	*J* 3·5			
						J 3·5	*J* 20			
Diethoxy-analogue (IVd)	2·09s	2·22s	5·11d †	5·29d †	5·08d	6·00m	7·0m [c]	7·81s	6·31q, 8·90t	A
									6·86q, [c] 9·20t	
			J 2·8	*J* 2·8	*J* 2				All *J* 7·0	

Pteridines	H(2)	H(4) (Me) [d]	H(6)	H(7)	
4-Methyl-	0·58s	(6·88s)	0·66d †	0·48d †	C
			J 2·8	*J* 2·8	
	1·48s	(7·45s)	4·74d †	4·59d †	D
			J 2·5	*J* 2·5	
2-Amino-4-methyl- [f,g]		(7·83s)	1·28	1·26	D
6,7-Dihydroxy-4-methyl-...	0·88s	(7·09s)			D
(VIIIa)	1·91s	(7·65s)	2·61d	4·35d	E
			J 2·5	*J* 2·5	
(VIIIb)	2·10s	(7·74s)		4·57s	E
(IXa)	1·99s	(7·73s)	5·35sbr †	4·92sbr †	E
(IXb)	1·58s	(7·53s)	4·86sbr †	4·71sbr †	F

Pyrimidine	H(2)	Me(6)	NH_2		
4,5-Diamino-6-methyl-.....	2·09s	7·79s	3·74, 5·51	—	A

* br, Broad; s, singlet; d, doublet; dd, double doublet; t, triplet; dt, double triplet; m, multiplet; *J* in c./sec. † Assignments were made according to the results of T. Goto and S. Matsuura, for monomethyl pteridines, *J. Chem. Soc.*, 1963, 1773; 1965, 623.

[a] Sodium 3-trimethylsilylpropanesulphonate as internal standard, except for solvent A, where tetramethylsilane was used. [b] A [$^2H_6$]dimethyl sulphoxide, B 3N-deuterium chloride, C deuterium oxide, D N-deuterium chloride (the solution had pH 1·0—1·5), E 10% sodium carbonate in deuterium oxide, F 5% sodium disulphite in deuterium oxide. [c] The chemical shift is approximate. [d] Values in parentheses indicate the chemical shifts of the methyl groups. [e] The material is extremely unstable in dilute alkaline solution. [f] All values from ref. 5. [g] The 3,4-hydrate.

analysis showed that both the neutral species and the hemi-sulphate contained the equivalent of two molecules of 4-methylpteridine and three molecules of tightly bound water (the hemi-sulphate had one extra molecule of water completely removable at 110° and considered to be only physically bound; see below).

The i.r. spectrum showed that the dimer (neutral species) contained hydroxy- and imino-groups ($\nu_{max.}$

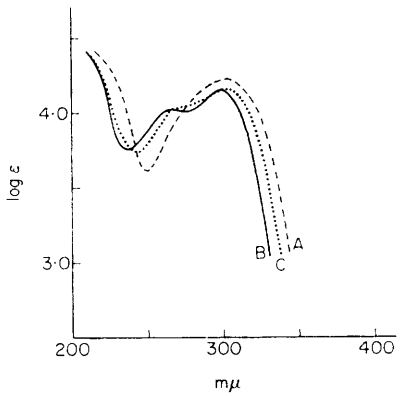


FIGURE 1 U.v. spectra of dimer at (A) pH 2·0, (B) 9·0, and (C) 14

3300sbr and 3200sbr cm.$^{-1}$). The lack of characteristic absorption for carbonyl and primary amino-groups (between 1800 and 1610 cm.$^{-1}$) completely ruled out structure (I). The characteristic absorption bands of the hemi-sulphate (monocation) were at 1100sbr (S=O) and 1640m cm.$^{-1}$ (sharp; a 4-aminopyrimidinium group involving N-3 and N-8). U.v. spectral studies in buffer solutions at various pH values (Table 1 and Figure 1), showed that the dimer existed as a neutral species between pH 8 and 11, as a dication below pH 3, and apparently as an anion above pH 13, with complete reversibility between all species. Structural similarity between the dimer and the hydrated form of the monomer is shown by the close similarity between the absorption maxima of the neutral species of the dimer and those of the (unstable) neutral species obtained by suddenly basifying the dihydrated cation (III); also between the maxima of the dication of the dimer and that of (III) (Table 1). The two overlapping pK_a values, 4·19 and 6·28 (Table 1), were obtained by potentiometric titration with acid and resolved as in ref. 7.

The ^{1}H n.m.r. spectrum (hexadeuteriodimethyl sulphoxide) consisted of peaks at τ 7·78 (3H, s), 7·02 (2H, m), 6·57 (1H, s), 5·97 (1H, m), 5·12 (3H, m), 4·68 (1H, m), 4·10 (2H, m), 2·68 (1H, m), 2·09 (1H, s), 1·97 (1H, s), and 1·96 (*ca.* 2H, m). After deuterium exchange, the singlet at τ 6·57 and the multiplets at 4·68, 4·10, 2·68, and 1·96 almost disappeared. The spectrum of 4,5-diamino-6-methylpyrimidine in the same solvent (Table 2) suggested that the dimer contained an *NN'*-disubstituted 4,5-diamino-6-methylpyrimidine ring, of which 6-Me and 2-H signals appeared at τ 7·78 and 2·09, respectively (see above). However the analyses of the multiplets at τ 7·02, 5·97, and 5·12 were difficult because of their broadness. Therefore the spectrum was examined in deuterium chloride–deuterium oxide solutions and was found to give very similar signals, thus confirming that the structure of the neutral species of the dimer persisted in the stable dication. This spectrum, obtained in 3N-deuterium chloride (cf. Figure 2), contained a singlet (3H) at τ 7·47, two double doublets (2H) around 6·32, a double triplet (1H) at 5·35, three doublets (3H) around 4·6, and singlets (1H each) at 1·59 and 1·41. When the n.m.r. spectrum of the dihydrated 4-methylpteridine cation (III) (Table 2) was taken into account, the dimer appeared to be the trihydrated molecule (IVa), namely 5,6,7,8-tetrahydro-6-hydroxy-4-methyl-7-(5,6,7,8-tetrahydro-6,7-dihydroxypteridin-4-ylmethyl)-pteridine. The possibility that the condensation occurred at the 3,4-bond was eliminated by the n.m.r. spectrum, because the signal of the 4-methyl group in a 3,4-adduct would have appeared as a singlet about 0·3 p.p.m. further up-field (cf. the chemical shift of the 3,4-hydrated 2-amino-4-methylpteridine; Table 2).

The position of substitution was assigned with reasonable certainty as C-7, rather than C-6, by analogy with the acid-catalysed Michael-type reaction product (VI) from 7-hydroxy-6-methylpteridine and 6-hydroxy-7-methylpteridine [the C(7)=N(8) bond of these hydroxypteridines was shown to be a stronger carbanion acceptor

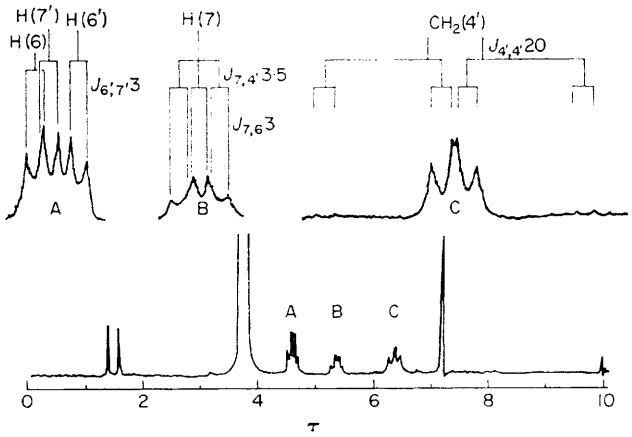


FIGURE 2 ^{1}H N.m.r. spectrum of dimer in 3N-deuterium chloride (*J* in c./sec.)

than the C(6)=N(5)].[8] Furthermore *X*-ray crystallography of pteridine has shown [9] that the 3,4-double bond is the shortest (1·28 Å), and hence it is particularly ethylenic and likely to add Michael reagents; the second shortest bond is the 7,8-bond (1·32 Å); but the 5,6-bond is much longer. Because condensation on the 3,4-double bond has been excluded by the n.m.r. spectrum (see above), the condensation is most likely to take place on the 7,8-double bond (cf. the 1 : 1 adduct of 4-methylpteridine and barbituric acid; see below). That the dication has the structure (IVc) was confirmed by the

[7] A. Albert and E. P. Serjeant, 'Ionization Constants,' Methuen, London, 1962.

[8] A. Albert and E. P. Serjeant, *J. Chem. Soc.*, 1964, 3357.

[9] T. M. Hamor and J. M. Robertson, *J. Chem. Soc.*, 1956, 3586.

complete analysis of the three expanded multiplets in the n.m.r. spectrum (Figure 2). Assignments of signals for spectra in deuterium chloride and hexadeuteriodimethyl sulphoxide are recorded in Table 2. The complexity of the signal from the 4'-methylene group can be explained in terms of non-equivalence of the geminal protons.

The intensities of the u.v. maxima of the dication and the neutral species of the dimer (Table 1) were nearly twice those of the cation (III) and its (dihydrated) neutral species, respectively, as required by the respective molecular weights; this helps to verify the structures (IVa and c). When the ionization constants of 5,6,7,8-tetrahydro-4-methylpteridine (pK_a 6·74) [6] and dihydrated 4-methylpteridine (III) (5·51) [3] were taken into account, the two overlapping pK_a values of the dimer (6·28 and 4·19) were found compatible with the proposed structure (IVa), in which the ionization of the species (IVb) exerted the usual coulombic repression on the second protonation, namely that to (IVc).

That the u.v. spectrum of the neutral species was immediately reproduced when the pH of freshly prepared acidic or alkaline solutions was rapidly adjusted to 9 indicates the presence of the same pattern and amount of covalent hydration in all species. Most of the dimer was recovered after it was heated at 70° for 17 hr. in a pH 10 buffer solution. When dissolved in 2N-sodium deuteroxide, it gradually produced a dark violet colour and decomposed (within 5 min. at 33°), but the n.m.r. spectrum measured within 3 min. showed mainly the trihydrated species (IVa). There was no signal at lower field than τ 1·8, which eliminates the possibility of dehydration to a pyrazine ring; this would be expected to give proton signals between τ 0 and 1·5 (cf. the spectrum of 4-methylpteridine in deuterium oxide in Table 2). This strong binding of water by the neutral species is in contrast to the behaviour of the neutral species of 4-methylpteridine which, when generated in the hydrated state by the action of alkali on the cation (III), gradually becomes anhydrous ($t_{\frac{1}{2}}$ *ca.* 20 min. at pH 8).[4] The unusually strong covalent binding of water by the dimer (neutral species) is best explained by strong intramolecular hydrogen bonds, as shown in the folded configuration (V) with which space models are entirely compatible. The three non-anionic species of the dimer were stable: no spectroscopic change occurred at pH 2 and 9 after storage for 1 month at 20°.

The intensity of the molecular ion region in the mass spectrum of the dimer (measured by Dr. Q. N. Porter, University of Melbourne) decreased with time, no doubt owing to dehydration. The $M - 1$ ion peak was slightly more intense than that of the molecular ion at *m/e* 346; this can probably be explained as the very ready loss of a hydrogen atom. Weak peaks were also observed in the molecular region at *m/e* 310, 292, 290, 289, 256, and 210; the first two could be the $M - 2H_2O$ and $M - 3H_2O$ ion peaks, respectively. Besides the strongest peak due to water, the spectrum below *m/e* 146 showed intense fragmentation peaks almost identical with those produced by 4-methylpteridine.[10]

Several chemical reactions were carried out to confirm the proposed structure (IVa). Although dehydration took place during the mass spectral measurement, no dehydration occurred when the specimen was dried at 150° in a high vacuum, as shown by elemental analysis and spectra (i.r. and n.m.r.). When the dimer was heated under reflux in ethanol (with a trace of toluene-*p*-sulphonic acid), a product was formed which had an elemental analysis consistent with the replacement of two hydroxy-groups by ethoxy-groups. The presence of one unreplaced hydroxy-group and of ether groups was confirmed by the i.r. spectrum [$\nu_{max.}$ 3230sbr (OH) and 1065sbr (C–O–C) cm.$^{-1}$]. The n.m.r. spectrum indicated no skeletal change and the presence of two ethoxy-groups (Table 2). Because the C(6)-hydroxy-group in (IVa) is much more sterically hindered [see (V)] than the others, this alcoholate is considered to have structure (IVd).

4-Methylpteridine, dissolved in dilute sulphuric acid, was oxidized by hydrogen peroxide to 6,7-dihydroxy-4-methylpteridine, which was unambiguously synthesized from 4,5-diamino-6-methylpyrimidine and oxalic acid. The physical properties of the product were in accord with the structure (the u.v., n.m.r., and i.r. spectra are shown in Tables 1 and 2 and in the Experimental section). The u.v. spectrum and the two anionic pK_a values were similar to those of 6,7-dihydroxypteridine [11] (Table 1). The n.m.r. spectrum indicated that 6,7-dihydroxy-4-methylpteridine formed no hydrate in acid.

However oxidation of the dimer under the same conditions gave a product the n.m.r. spectra of which in deuterium chloride–deuterium oxide and in dimethyl sulphoxide were similar to those of the starting material, and which had no carbonyl group (i.r. spectrum). Oxidation of the dimer with alkaline potassium ferricyanide or permanganate gave a mixture of several inseparable products. When manganese dioxide (or acetic anhydride) in dimethyl sulphoxide was used for the oxidation, a reddish-brown substance (m.p. >280°) was the principal product. The same substance was obtained in better yield in an attempted acylation of the dimer with acetic anhydride–pyridine (also with acetic formic anhydride–sodium formate, but in lower yield). On the evidence of the elemental analysis, and the i.r. [$\nu_{max.}$ 3400wbr (presumably an imino-group) and 1640s cm.$^{-1}$ (conjugated C=C)] and u.v. spectra (the long wavelength absorption maximum at 509 mμ denotes a long conjugated pathway), the product was assigned the structure 3,7-dihydro-4-methyl-7-(pteridin-4-ylmethylene)pteridine (VII). A compound with a similar skeletal structure has been obtained [8] by the oxidation of compound (VI) and the structure exists also in the naturally occurring pterorhodins.

[10] T. Goto, A. Tatematsu, and S. Matsuura, *J. Org. Chem.*, 1965, **30**, 1844.

[11] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1952, 1620.

Nucleophilic Addition Reactions of 4-Methylpteridine.—Much work has been done on nucleophilic addition reactions of pteridines (*e.g.* 6-hydroxy-,[12] 2-hydroxy-,[13] 7-hydroxy-,[14] and 2-amino-pteridine,[15] all of which gave 1 : 1-adducts). Because 4-methylpteridine gives a di-adduct (III) in acid solution, it was necessary to examine the behaviour of the pteridine towards bulkier nucleophiles to see whether mono-adducts were preferred, as in the suggested formation of the dimer.

We found that equivalent amounts of 4-methylpteridine and barbituric acid gave a 1 : 1 adduct quickly and almost quantitatively in dilute acid. The i.r. spectrum showed carbonyl groups ($\nu_{max.}$ 1690 and 1660 cm.$^{-1}$) and a hydroxy-group (3120). In the n.m.r. spectrum the singlet at τ 7·65, attributed to the 4-methyl group, eliminated the possibility of addition across the 3,4-bond, such as occurs with 2-hydroxy-[13] and 2-amino-pteridine.[15] The signal of such an aliphatic 4-methyl group in the adduct would be expected to appear a little up-field, by analogy with the reported chemical shift of the 4-methyl group in the 3,4-hydrate of 2-amino-4-methylpteridine (Table 2). The two coupled doublets at τ 4·35 and 2·61 proved that the addition took place on the pyrazine ring. A u.v. spectral study in solutions at various pH values showed that the 1 : 1-adduct existed as a mono-cation below pH 1, as a monoanion at pH 8—11, and mainly as a zwitterion at pH 4·5—5·5. The two approximate pK_a values were 4·0 and 6·0. The spectrum of the zwitterion of the adduct was almost identical with that of the anion (cf. Experimental section). This showed that the trihydroxy-pyrimidinyl group is in the 7- (not the 6-) position, because the cation of 7,8-dihydro-4,6-dimethylpteridine has the same long-wavelength absorption peak as the neutral species, as is usual for 7,8-dihydropteridines generally; whereas 5,6-dihydro-4-hydroxypteridine and other 5,6-dihydro-derivatives undergo a large spectral shift when converted into the cation[16] (see Table 1). This assignment of structure (VIIIa) is confirmed by analogy with substance (VI) and comparison of bond-lengths, as was done for the dimer (see above).

Use of two equivalents of barbituric acid gave a 2 : 1 adduct (IXa) after prolonged stirring, and the structure was confirmed by i.r. and n.m.r. spectra. 6-Hydroxy-4-methylpteridine and barbituric acid readily gave the 1 : 1 adduct (VIIIb), the assigned structure of which was consistent with the i.r. and the n.m.r. spectra (cf. Experimental section and Table 2). To confirm the position of the pyrimidinyl group in the adduct (VIIIa), an attempt was made to oxidise it (with hydrogen peroxide in dilute sulphuric acid at 25°) to the adduct (VIIIb) but this substance could not be detected among the many decomposition products. Treatment of 4-methylpteridine with approximately two equivalents of sodium hydrogen sulphite readily gave the 5,6:7,8-di-adduct (IXb).

To confirm that the C(7)=N(8) bond of 4-methylpteridine was involved in the formation of the dimer and in the 1 : 1-adduct with barbituric acid, a synthesis of 7- (or 6-) deuterio-4-methylpteridine was attempted by way of substitution of the hydroxy-group in 7- (or 6-) hydroxy-4-methylpteridine with a chlorine atom. However chlorination of the hydroxy-pteridine by commonly used methods (*e.g.* phosphorus pentachloride in phosphoryl chloride or in phosphorus trichloride) was unsuccessful. 7-Hydroxy-4-methylpteridine, when heated under reflux with phosphorus pentachloride in pentachloroethane, gave 7-chloro-4-dichloromethylpteridine, in poor yield (10%), and much intractable black tar. The structure of the chloropteridine was elucidated from elemental analysis, and from i.r., u.v., and n.m.r. spectra (see Experimental section).

Several attempts were made to see if the methyl-group of 4-methylpteridine reacted as a Michael-type donor with various acceptors effective at pH 2, such as 6-hydroxy-[8] or 2-amino-pteridine,[15] but no condensation took place.

EXPERIMENTAL

Microanalyses and molecular weight determination were performed by Dr. J. E. Fildes and her staff. Paper chromatography (ascending) was carried out with Whatman no. 1 paper in 3% ammonium chloride.

U.v. spectra were measured on a Shimadzu RS27 or Perkin-Elmer Spectracord 4000A recording spectrophotometer, and the maxima were checked with an Optica manual instrument. I.r. spectra (Nujol) were taken with a Unicam SP 200 spectrophotometer, and n.m.r. measurements were made with a Perkin-Elmer R10 spectrometer.

4-Methylpteridine.—Although this was previously obtained (60%) from 4,5-diamino-6-methylpyrimidine and polyglyoxal,[17] the following preparative method is more satisfactory. To the pyrimidine[17] (2·46 g.), dissolved in boiling ethanol (70 ml.) was added a boiling suspension of glyoxal monohydrate polymer[18] (B.D.H.; 1·67 g.; 1·1 equiv.) in ethanol (100 ml.), and the mixture was heated under reflux for 30 min. The solvent was evaporated at 30° under reduced pressure and the residue was covered with a layer of cotton and sublimed at 110°/0·01 mm., to give the pteridine as a yellow powder (88%), m.p. 152—153·5° (lit.,[17] 152—153°). It was necessary to interrupt the sublimation several times and grind the cake.

The Dimer (IVa).—A solution of 4-methylpteridine (1·50 g.) in 0·5N-sulphuric acid (24 ml.) was set aside for 15 min. at 30°, then heated at 95° (bath) for 40 min. (initial and final pH, 2·0). The pH of the solution was adjusted to 5·5 with sodium hydrogen carbonate and the solution was briefly warmed at 85°, then cooled. The precipitate was filtered off and washed with a little cold water, to give the *dimer hemisulphate* (57% crude). Two recrystallizations from water gave pale brown needles, decomp. *ca.* 150°

[12] A. Albert and F. Reich, *J. Chem. Soc.*, 1961, 127.
[13] A. Albert and C. F. Howell, *J. Chem. Soc.*, 1962, 1591.
[14] A. Albert and J. J. McCormack, *J. Chem. Soc.*, 1965, 6930.
[15] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117.
[16] A. Albert and S. Matsuura, *J. Chem. Soc.*, 1962, 2162.
[17] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.
[18] H. Raudnitz, *J. Chem. Soc.*, 1948, 763.

(Found, for material dried over P_2O_5 at 60°/0·01 mm.: C, 40·55; H, 5·2; N, 27·15; S, 3·8. $C_{14}H_{18}N_8O_3,\frac{1}{2}H_2SO_4,H_2O$ requires C, 40·7; H, 5·1; N, 27·1; S, 3·9%. Found for material dried over P_2O_5 at 110°/0·05 mm. for 40 min.: C, 42·45; H, 5·0; N, 28·0. $C_{14}H_{18}N_8O_3,\frac{1}{2}H_2SO_4$ requires C, 42·55; H, 4·85; N, 28·35%). Crude hemi-sulphate, twice recrystallized from very dilute 0·1N-sulphuric acid at pH 4, deposited the *sulphate* as colourless needles. It gradually became brown above 130° and decomposed above 150° (Found, for material dried over P_2O_5 at 110°/0·05 mm. for 1 hr.: C, 37·95; H, 4·6; N, 25·05. $C_{14}H_{18}N_8O_3,H_2SO_4$ requires C, 37·85; H, 4·55; N, 25·2%). Treatment of the crude hemi-sulphate with a cold 10% solution (10 ml.) of sodium carbonate–sodium hydrogen carbonate (1 : 1), followed by two recrystallizations of the precipitate from 40 parts of boiling water (carbon), gave the *base* as an ivory-white crystalline powder (47% based on 4-methylpteridine), decomp. *ca.* 190° (darkened without melting) (Found, for material dried over P_2O_5 at 110°/0·01 mm.: C, 48·25; H, 5·2; N, 31·9%; *M*, 313 (ebullioscopically in water); for material dried at 152°/0·05 mm. for 1 hr.: C, 48·95; H, 5·25; N, 32·55. $C_{14}H_{18}N_8O_3$ requires C, 48·55; H, 5·25; N, 32·35%; *M*, 346). It gives only one spot on paper chromatography (R_F 0·75) in contrast to compound (VI) which the cellulose resolved optically.[8]

Reaction of the Dimer with Ethanol.—The dimer (50 mg.), toluene-*p*-sulphonic acid monohydrate (2 mg.), and ethanol (10 ml.) were boiled for 9 hr. The solvent was evaporated and the residue was dissolved in ethanol, passed through a column of neutral alumina (5 g.), and eluted with ethanol. The elute gave 5,6,7,8-*tetrahydro*-6-*hydroxy*-4-*methyl*-7-(6,7-*diethoxy*-5,6,7,8-*tetrahydropteridin*-4-*ylmethyl*)*pteridine* (IVd) (64%) after removal of the solvent and recrystallization of the residue from ethanol–benzene; it gradually turned reddish brown above 135° without melting (Found, for material dried over P_2O_5 at 100°/0·01 mm.; C, 60·65; H, 6·25; N, 23·65. $C_{18}H_{26}N_8O_3,C_6H_6$ requires C, 60·0; H, 6·7; N, 23·35%). The presence of one molecule of benzene was confirmed by n.m.r., τ 2·64 (6H). Recrystallization of the above material from ethanol–light petroleum (b.p. 80—100°), gave the benzene-free *dimer* as an almost colourless amorphous solid, which gradually became reddish brown above 120° without melting (Found, for material dried over P_2O_5 at 80°/0·05 mm.: C, 54·8; H, 6·3; N, 27·95. $C_{18}H_{26}N_8O_3$ requires C, 53·75; H, 6·5; N, 27·85%).

6,7-*Dihydroxy*-4-*methylpteridine*.—4,5-Diamino-6-methylpyrimidine (0·25 g.) and oxalic acid dihydrate (0·65 g., 5 equiv.) were heated under a slight vacuum (40—50 cm.) to 160° during 15 min., and maintained at 160—170° for 1·5 hr. The product was extracted with boiling water (60 ml.) containing enough sodium hydroxide to maintain pH of the mixture above 10. The pH of the filtrate was brought to 4 with acetic acid; the solution was concentrated to *ca.* 10 ml. below 50° under reduced pressure and set aside at 5° overnight. The precipitate was filtered off and washed with a little cold water, to give the crude 6,7-*dihydroxy*-4-*methylpteridine* as pale brownish yellow needles (83%). Two recrystallizations from 50 parts of boiling water gave yellow prisms which turned to a colourless powder when dried at 105°; m.p. >285° (Found, for material dried at 105°/0·5 mm.: C, 47·05; H, 3·75; N, 31·2. $C_7H_6N_4O_2$ requires C, 47·2; H, 3·4; N, 31·45%). The substance, recrystallized from water, contained water of crystallization ($\nu_{max.}$ 3570 cm.$^{-1}$ etc.), lost on drying at 105°. The solubility in boiling water was about six times greater than that of 6,7-dihydroxypteridine.[11] The monosodium salt was obtained as a colourless powder by stirring the dihydroxy-methylpteridine with 10% aqueous sodium hydrogen carbonate ($\nu_{max.}$ 1690 cm.$^{-1}$).

Oxidation of 4-*Methylpteridine with Hydrogen Peroxide.*—To 4-Methylpteridine (83 mg.), dissolved in N-sulphuric acid (0·75 ml.), 30% hydrogen peroxide (0·13 ml., 2 equiv.) was added, and the mixture was set aside at 25° for 4 days (pH was 2·5 before and after). Enough solid sodium hydrogen carbonate to give a pH of 7·5 was added and the mixture was set aside overnight at 5°. The precipitate was collected and washed with a little cold water, to give the crude monosodium salt of 6,7-dihydroxy-4-methylpteridine as a light brown powder (70%). This was stirred with sodium acetate buffer solution (pH 4) and recrystallized from water to give the neutral species as a yellow powder, identical with authentic material (i.r. and chromatography).

Oxidation of the Dimer with Hydrogen Peroxide.—To the powdered dimer (0·10 g.) suspended in N-sulphuric acid (2 ml.), 30% hydrogen peroxide (0·1 ml., 3 equiv.) was added, and the mixture was shaken at 37° until the precipitate almost dissolved (*ca.* 15 min.), then filtered. The mixture was set aside for 3 days at 25°, then overnight at 5°; the sulphate was then collected and washed with a little cold water, as colourless needles (0·05 g.), which blackened without melting at *ca.* 170° (Found, for material dried over P_2O_5 at 25°/0·5 mm.: C, 37·1; H, 3·85; N, 24·55; S, 7·05%). Basification with 10% sodium hydrogen carbonate gave the neutral species which decomposed during recrystallization from water.

3,7-*Dihydro*-4-*methyl*-7-(*pteridin*-4-*ylmethylene*)*pteridine* (VII).—The finely ground dimer (80 mg.), suspended in acetic anhydride–pyridine (1 : 1) (1 ml.), was stirred at 25° for 2·5 hr. and set aside overnight at room temperature in the dark. The precipitate was filtered off and purified twice with chloroform–ethanol to give the *pteridine* as a reddish brown powder (60%). It became browner above 240° without melting (Found, for material dried over P_2O_5 at 100°/0·05 mm.: C, 58·15; H, 3·75; N, 36·9. $C_{14}H_{10}N_8$ requires C, 57·95; H, 3·5; N, 38·6%), $\lambda_{max.}$ (95% EtOH) *266*, 290, *300*, *455*, 481, 509, and *550* mμ (log ε *3·86*, 3·94, *3·86*, *4·29*, 4·48, 4·46, and *3·33*). The material is slightly soluble in chloroform–ethanol but almost insoluble in water and other common organic solvents. It gives a single yellow fluorescent spot on a paper chromatogram (R_F 0·03) under 365 mμ light, and decomposes when dissolved in N-sulphuric or trifluoroacetic acid.

4-*Methylpteridine and Barbituric Acid.*—(*a*) Solutions of the pteridine (0·17 g.) in water (5 ml.) and of barbituric acid (0·15 g., 1 equiv.) in water (25 ml.), were mixed (initial pH 2·5) and set aside at 25° for 24 hr in the dark (final pH 5·0) to give 7,8-*dihydro*-4-*methyl*-7-(2,4,6-*trihydroxypyrimidin*-5-*yl*)*pteridine* as a yellow powder (97%). This, suspended in 100 parts of water, was carefully dissolved by addition of 2N-sodium carbonate and the solution was clarified by filtration. The pH of the filtrate was adjusted to 4 by careful addition of N-sulphuric acid. The precipitate was filtered off and washed well with water to give a pale yellow powder which gradually darkened above 250° without melting (Found, for material dried over P_2O_5 at 105°/1 mm.: C, 47·4; H, 3·55; N, 30·0. $C_{11}H_{10}N_6O_3$ requires C, 48·15; H, 3·65; N, 30·65%), $\lambda_{max.}$ (pH 8·0), 218, 260, *297*, 302, and *312* mμ (log ε 4·22, 4·31, *3·86*, 3·88, and *3·82*.

(*b*) Solutions of 4-methylpteridine (0·07 g.) in water (3 ml.) and of barbituric acid (0·14 g., 2·2 equiv.) in water (25 ml.) were mixed and stirred at 25° for 24 hr. (initial and final pH 2·5 and 3·0, respectively). The pale yellow precipitate, purified as above, gave 5,6,7,8-*tetrahydro*-4-*methyl*-6,7-*di*-(2,4,6-*trihydroxypyrimidin*-5-*yl*)*pteridine* as a yellow powder (92%); above 230° it gradually became brown without melting (Found, for material dried over P_2O_5 at 110°/0·05 mm.: C, 44·6; H, 3·9; N, 27·15. $C_{15}H_{14}N_8O_6$ requires C, 44·8; H, 3·5; N, 27·85%), $\nu_{max.}$ 3300, 3200, 1740, 1710, 1690, 1660, and 1640 cm.$^{-1}$, all broad and strong.

7,8-*Dihydro*-6-*hydroxy*-4-*methyl*-7-(2,4,6-*trihydroxypyrimidin*-5-*yl*)*pteridine* was similarly obtained (70%) by the same prodedures as a yellow powder from 6-hydroxy-4-methylpteridine [12] and barbituric acid (1 equiv.). The pteridine gradually became brown above 270° without melting (Found, for material dried over P_2O_5 at 110°/0·1 mm.: C, 43·95; H, 3·75; N, 27·95. $C_{11}H_{10}N_6O_4,\frac{1}{2}H_2O$ requires C, 44·15; H, 3·7; N, 28·1%), $\nu_{max.}$ 3400mbr, 3200sbr, 1695sbr, and 1660sbr cm.$^{-1}$).

4-*Methylpteridine and Sodium Hydrogen Sulphite*.—The pteridine (0·16 g.) and sodium disulphite (0·25 g., 2·2 equiv.) were shaken in water (10 ml.) at 25° for 10 min. The solution, clarified by gravity filtration, was set aside at 25° for 30 min., then more sodium salt (0·20 g.) was added. The solution was set aside at the same temperature for 3 hr. and then at 5° for 0·5 hr. (final pH 4). Ethanol was then added to the cold solution until crystals appeared, and the mixture was chilled overnight. The colourless precipitate was filtered off and washed successively with 75% aqueous ethanol, absolute ethanol, and diethyl ether, to give the *monosodium salt of* 5,6,7,8-*tetrahydro*-4-*methylpteridine*-6,7-*disulphonate* as a colourless powder (56%). It gradually became brown above 160° without melting (Found, for material dried over P_2O_5 at 25°/20 mm.: C, 23·65; H, 3·55; N, 15·35. $C_7H_{11}N_4O_8S_2Na$ requires C, 23·0; H, 3·05; N, 15·3%).

7-*Chloro*-4-*dichloromethylpteridine*.—Finely ground 7-hydroxy-4-methylpteridine [12] (0·14 g.) was heated under reflux with pentachloroethane (20 ml.) for 15 min., phosphorus pentachloride (0·35 g.) was added, and the mixture was boiled for 30 min. The solvent was evaporated at 60° (bath)/10 mm., and the residue was extracted with cold benzene (2 × 100 ml.). After removal of the solvent at 40°/20 mm., extraction of the residue with boiling light petroleum (b.p. 40—60°; 10·0 ml.), followed by concentration of the extract to *ca.* 3 ml., deposited the *chloropteridine* (10%). One recrystallization from light petroleum gave pale yellow prisms, m.p. 84—85° (Found, for material dried over $CaCl_2$ at 25°/20 mm.: C, 33·9; H, 1·5; N, 22·25. $C_7H_3Cl_3N_4$ requires C, 33·7; H, 1·2; N, 22·45%), no i.r. absorption band at 3500—3100 or 1800—1600 cm.$^{-1}$, $\lambda_{max.}$ (cyclohexane) *222*, *297*, *302*, 307, *312*, 321, and 383 mμ (log ε *4·09*, *3·87*, *3·94*, 4·12, *4·00*, 3·95, and 2·22), τ ($CDCl_3$) 2·10 (1H, s, $CHCl_2$), 1·03 (1H, s, H-2*), and 0·34 (1H, s, H-6*) (the assignments marked * are interchangeable).

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