Pteridine Studies. Part XLIV.[1] Self-condensation of Some Methylpteridines, and Reactions with Other Nucleophiles

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Treatment of 6,7-dimethylpteridine with aqueous alkali and with aliphatic amines gave 7-(3,4-dihydro-6,7-dimethylpteridin-4-ylmethyl)-3,4-dihydro-4-hydroxy-6-methyl- (1) and 7-(6,7-dimethylpteridin-4-ylmethylene)-3,7-dihydro-6-methyl-pteridine (3a), respectively. 7-Methylpteridine and an amine similarly produced 3,7-dihydro-7-(7-methylpteridin-4-ylmethylene)pteridine (3b).

6,7-Dimethylpteridine and hydroxylamine yielded 3-hydroxyiminomethylamino-5,6-dimethylpyrazine-2-carbaldehyde oxime (9a). 2,6,7-Trimethylpteridine and methoxyamine afforded 2-(1-methoxyimino)ethylamino-3-methoxyiminomethyl-5,6-dimethylpyrazine (9b). Malononitrile reacted with (*a*) 6,7-dimethyl- and 2,6,7-trimethyl-, (*b*) 4-methyl-, and (*c*) 4,6,7-trimethyl-, and 2,4,6,7-tetramethyl-pteridine to give, respectively, (*a*) the 2,3-dimethyl (13) (from the first two), (*b*) the 8-methyl (15), and (*c*) the 2,3,8-trimethyl (16) derivatives of 6-aminopyrido[2,3-*b*]pyrazine-7-carbonitrile. Cyanoacetamide and 6,7-dimethylpteridine yielded 6-amino-2,3-dimethylpyrido[2,3-*b*]pyrazine-7-carboxamide (14).

Dimedone, malonamide, and methanol (the last named only under acidic conditions) added to 6,7-dimethylpteridine across the 3,4-double bond to give 4-substituted 3,4-dihydro-6,7-dimethylpteridines [respectively (18a and b) and (17)]. 2-Methylpteridine and dimedone gave 3,4-dihydro-2-methyl-4-(4,4-dimethyl-2,6-dioxocyclohexyl)pteridine (18c). With ethyl acetoacetate, 2-methyl- and 4-methyl-pteridine yielded 2-methyl (19a) and 4-methyl derivatives of ethyl 5,5a,8a,9-tetrahydro-7-methylfuro[2,3-*g*]pteridine-8-carboxylate (19b), respectively. 4-Methylpteridine added two molecules of benzylamine across the 5,6- and 7,8-double bonds to give 6,7-bis(benzylamino)-5,6,7,8-tetrahydro-4-methylpteridine (21).

Consideration of the u.v. spectra of the dimedone adducts (18a, c, and d) revealed that the neutral species were zwitterionic.

U.v. and ^{1}H n.m.r. spectra are reported and discussed.

We have previously reported the reactions of pteridine with alcohols [2] and Michael reagents,[1] and have since examined the effects of *C*-methyl substituents on the known reactions of pteridine with nucleophiles. It soon became clear that self-condensation took place under the basic conditions favourable for the formation of nucleophilic anions.

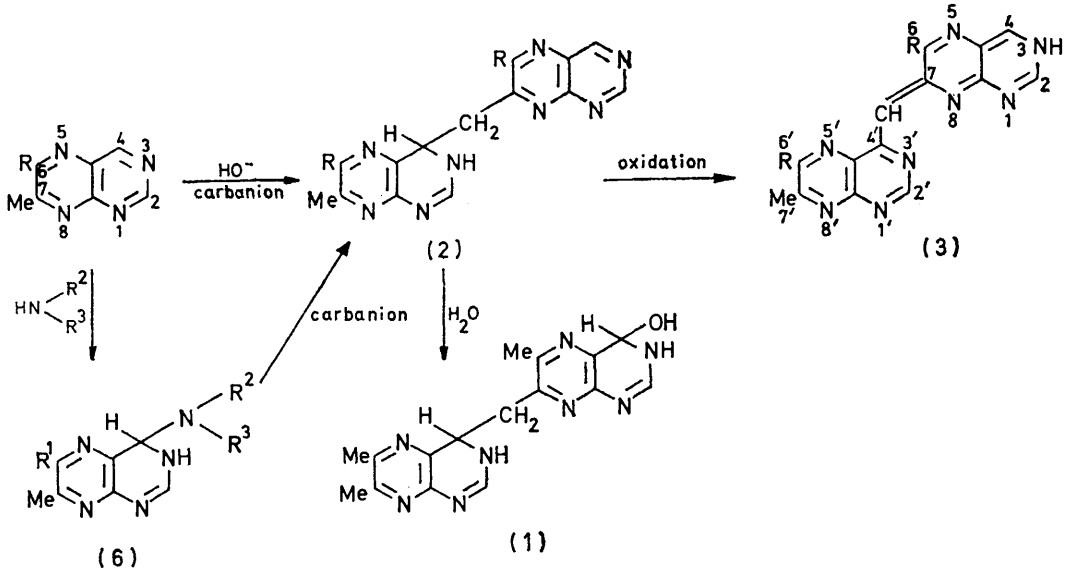
Formation of Dimers from 6,7-*Dimethyl- and* 7-*Methylpteridine.*—The hydrated dimer (1) was formed immediately when 6,7-dimethylpteridine was triturated with cold aqueous 1·5N-sodium hydroxide. Its structure was assigned on the basis of elemental analysis and u.v. spectra, and supported by the closeness of the two pK_a values (4·79 and 3·22). The u.v. spectra of the neutral species and the dication were similar to those of the

[1] Part XLIII, A. Albert and H. Mizuno, *J.C.S. Perkin I*, 1973, 1615.

[2] A. Albert and H. Mizuno, *J. Chem. Soc.* (*B*), 1971, 2423.

neutral species and the cation (respectively) of 3,4-dihydropteridine.[3] Apparently a carbanion formed from the methyl group of one molecule attacked the 4-position of another, to give the dimer (2) which was instantly hydrated to give compound (1).

An orange dehydro-derivative (3a) of the dimer (2) was slowly deposited when methylamine, dimethylamine, or triethylamine was added to 6,7-dimethylpteridine in tetrahydrofuran. The structure (3a), was indicated by

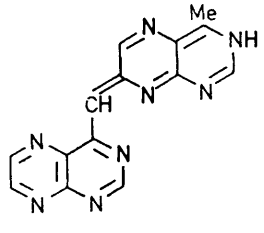


SCHEME 1
a, R (or R¹) = Me; b, R (or R¹) = H

elemental analysis and confirmed by n.m.r. and u.v. spectra. The u.v. spectrum (in 95% ethanol) was similar to that of 3,7-dihydro-4-methyl-7-(pteridin-4-ylmethylene)pteridine (4)[4] obtained by acid-catalysed self-condensation and subsequent oxidation of 4-methylpteridine. Another possible structure (5) was rejected because a conjugated dehydro-dimer (3b), with properties similar to those of compound (3a), was formed from 7-methylpteridine. The preferred structure (3a) is reasonable because the 7-methyl group is attached to a double bond that is shorter (and hence more highly polarised) than that near the 6-methyl group; hence the 7-methyl group should be the more reactive (bond lengths taken from the results of an *X*-ray crystallographic study of pteridine[5]).

Formation of the dehydro-dimers (3) is apparently helped by intervention of amine (3,4-) adducts (6) followed by displacement of the amine component by a 7-methyl carbanion to give the next intermediate (2). This hypothesis is supported by the yields obtained with various amines; thus 6,7-dimethylpteridine gave the dehydro-dimer (3a), in 65, 44, and 4% yields, in the presence of methylamine, dimethylamine, and triethylamine, respectively (these amines have similar pK_a values: 10·66, 10·73, and 10·78, respectively[6]). That triethylamine, which cannot form an intermediate of type (6), does give a small yield indicates the occurrence of a second, slower reaction, namely direct attack by the carbanion. One of the proposed amine adducts, 3,4-dihydro-7-methyl-4-methylaminopteridine (6b; R^2 = Me, R^3 = H), was deposited from a solution of 7-methylpteridine and ethanolic 33% methylamine in tetrahydrofuran immediately after mixing. The structure was assigned on the basis of elemental analysis and the i.r. spectrum ($\nu_{max.}$ 3270 and 3185 cm^{-1}). This adduct was stable only in the solid state.

Oxidation of the intermediates (2), which is necessary for the formation of the conjugated dehydro-dimers (3), was slowed but not halted when the amount of peroxide contaminating the tetrahydrofuran was decreased until the solvent did not give a blue colour with starch–iodide.[7]



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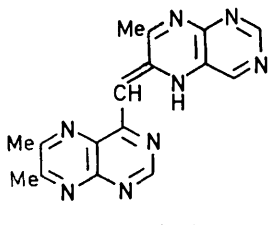


(5)

Reactions with Bifunctional Nucleophiles.—Just as in studies[8] on the reactions of bifunctional reagents such as hydroxylamine and hydrazine with other π-deficient

[3] A. Albert and K. Ohta *J. Chem. Soc.* (*C*), 1970, 1540.
[4] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 1181.
[5] T. M. Hamor and J. M. Robertson, *J. Chem. Soc.*, 1956, 3586.
[6] A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants,' 2nd edn., Chapman and Hall, London, 1971, p. 92.
[7] British Pharmacopoeia 1968, The Pharmaceutical Press, London, 1968, p. 393.
[8] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, 1625, and references therein.

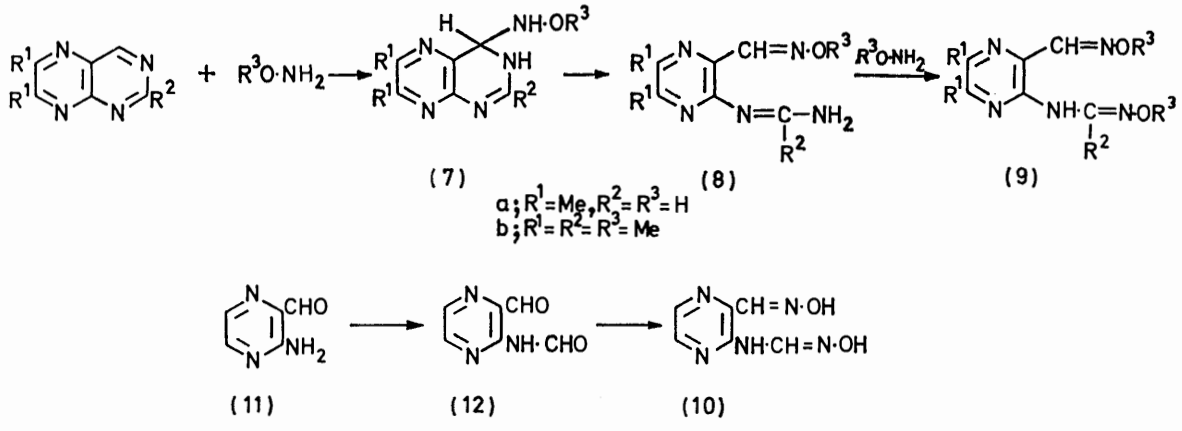
heterocycles, the present results were more complex than those encountered with ordinary nucleophiles.

Hydroxylamine and 6,7-dimethylpteridine, in cold water at pH 7, gave [apparently [9] through the intermediates (7a) and (8a)] 3-hydroxyiminomethylamino-5,6-dimethylpyrazine-2-carbaldehyde oxime (9a). This structure was confirmed by elemental analysis and the similarity of the u.v. spectrum to that of 3-hydroxyiminomethylaminopyrazine-2-carbaldehyde oxime (10) prepared [9] from 3-aminopyrazine-2-carbaldehyde (11) through 3-formamidopyrazine-2-carbaldehyde (12). An improved synthesis of the latter (12), by a Vilsmeier reaction, is described. Similarly methoxyamine, when boiled with 2,6,7-trimethylpteridine in water at pH 7, quickly deposited 2-(1-methoxyiminoethylamino)-3-methoxyiminomethyl-5,6-dimethylpyrazine (9b).

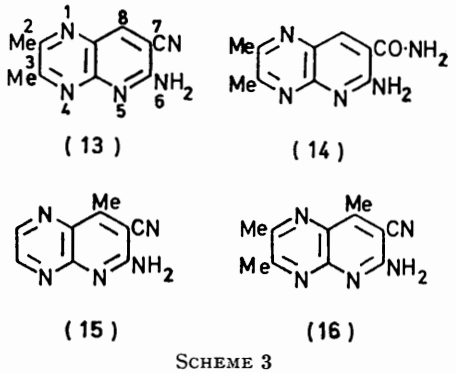
Reactions with Malononitrile.—6,7-Dimethylpteridine, with malononitrile (in tetrahydrofuran) or cyanoacetamide (in water) gave, respectively, the 7-cyano- (13) and 7-carbamoyl (14) derivatives of 6-amino-2,3-dimethylpyrido[2,3-*b*]pyrazine, by the mechanism reported [10] for similar reactions in other π-deficient series. A 4-methyl group in an annulated pyrimidine usually impedes nucleophilic addition across the 3,4-bond,[11] although some exceptions [12] have been found. With malononitrile, 4-methyl- and 4,6,7-trimethyl-pteridine gave small yields of the 8-methyl- (15) and 2,3,8-trimethyl- (16) derivatives, respectively, of 6-aminopyrido-[2,3-*b*]pyrazine-7-carbonitrile. The pyridopyrazine (13) was also obtained from 2,6,7-trimethylpteridine and malononitrile, and the pyridopyrazine (16) from 2,4,6,7-tetramethylpteridine. The presence of a 2-methyl group in these two pteridines required the expulsion of acetonitrile instead of hydrogen cyanide; [10] this proved to be a slower reaction. Moreover 2-methylpteridine did not give the expected 6-aminopyrido[2,3-*b*]pyrazine-7-carbonitrile.

Reactions with Other Nucleophiles.—6,7-Dimethylpteridine added methanol (but only under acidic conditions), dimedone, and malonamide across the 3,4-double bond to give respectively 4-methoxy- (as the hydrochloride) (17), 4-(4,4-dimethyl-2,6-dioxocyclohexyl) (18a), and 4-dicarbamoylmethyl derivatives of 3,4-dihydro-6,7-dimethylpteridine (18b). 2-Methylpteridine and dimedone yielded 3,4-dihydro-2-methyl-4-(4,4-dimethyl-2,6-dioxocyclohexyl)pteridine (18c). These structures were assigned on the basis of elemental analysis and u.v. and n.m.r. spectra; the characteristic upfield shift of the H-4 signal (τ 3·65—4·4) in the latter was conclusive.

The following consideration of the u.v. spectra of the dimedone adducts (18a and c) showed that the neutral species were zwitterionic (see also Scheme 1). Each adduct showed two pK_a values. The u.v. spectra of all three species consisted of two maxima, one at longer wavelength from the dihydropteridine residue and one at shorter wavelength typical of the dimedone residue. On change of medium from pH 11 to 6, the peak of longer wavelength showed a hypsochromic shift of 24 nm, a phenomenon also observed on protonation of 3,4-dihydropteridine; [3] however, the shorter wavelength peak did not shift significantly, but remained at the position of the anion of dimedone.[13] Hence the neutral



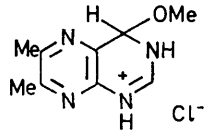
SCHEME 2



SCHEME 3

[9] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1971, 2357.
[10] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, (*a*) p. 1620; (*b*) p. 1744.
[11] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[12] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 2292.
[13] B. Eistert, E. Merkel, and W. Reiss, *Chem. Ber.*, 1954, **87**, 1513.

species is zwitterionic. Consistent with this interpretation, a change in medium from pH 6 to 1 moved



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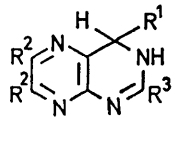


(18)

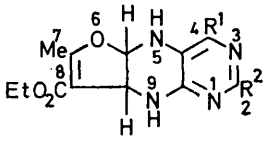
a; R^1 = –CH·CO·CH_2·CMe_2·CH_2·CO–, R^2 = Me, R^3 = H

b; R^1 = $-CH(CO{\cdot}NH_2)_2$, R^2 = Me, R^3 = H

c; R^1 = –CH·CO·CH_2·CMe_2·CH_2·CO–, R^2 = H, R^3 = Me

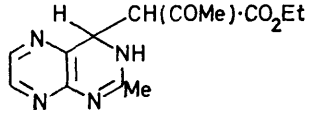
d; R^1 = –CH·CO·CH_2·CMe_2·CH_2·CO–, R^2 = R^3 = H

the shorter wavelength peak hypsochromically to the position of the neutral species of dimedone,[13] whereas the peak of the 3,4-dihydropteridine residue moved only slightly. The existence of the neutral species as a zwitterion follows from the closeness of the two constants, *cf.* the acid function of dimedone (pK_a 5·24) [14] and the

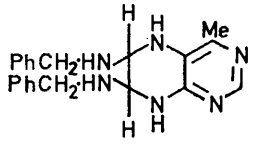


(19)

a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H



(20)

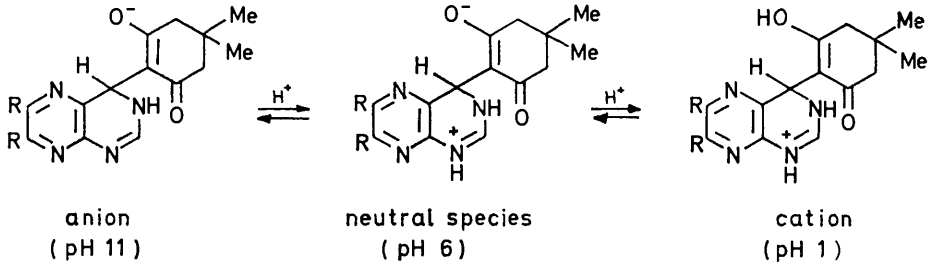


(21)

basic function of 3,4-dihydropteridine (pK_a 6·35).[3] It follows that the reported pK_a (7·69) of 4-(4,4-dimethyl-2,6-dioxocyclohexyl)-3,4-dihydropteridine [1] (18d) is actually the acidic pK_a. Similar consideration of the pK_a values (4·1 and 12·5) of barbituric acid [15,16] showed that its adduct with pteridine [1] was zwitterionic.

Similarly to the parent, 2- and 4-methylpteridine gave 1 : 1 adducts (19a and b) with ethyl acetoacetate. A series of n.m.r. spectra taken at various times showed that the first product from 2-methylpteridine was the kinetically favoured 3,4-adduct (20) and that, at equilibrium, roughly equal proportions of the two compounds (19a) and (20) were present. That these are not the isomeric furo[3,2-*g*]pteridines follows from ref. 1.

4-Methylpteridine added two molecules of benzylamine across the 5,6- and 7,8-double bonds to yield 6,7-bisbenzylamino-5,6,7,8-tetrahydro-4-methylpteridine (21); the n.m.r. spectrum supported this structure, and the u.v. spectrum (in ethanol) resembled that of 5,6,7,8-tetrahydropteridine [17] at first, but changed to that of the starting pteridine because of dissociation.



SCHEME 4

EXPERIMENTAL

2-,[18] 4-,[4], and 7-Methyl-,[18] 6,7-dimethyl-,[18] 2,6,7-[18] and 4,6,7-trimethyl-,[12] and 2,4,6,7-tetramethylpteridine [12] were prepared by the reported methods. Samples for microanalysis were dried at 65° and *ca.* 0·2 mmHg unless otherwise stated. Ionisation constants (at 20° in water) were determined spectroscopically.[6] U.v. spectra were measured on a Unicam SP 800 recording spectrophotometer; the wavelengths and intensities of maxima were confirmed with a Unicam SP 500, or an Optica CF4 manual instrument. I.r. spectra were taken (for mulls in Nujol) with a Unicam SP 200 spectrophotometer calibrated with polystyrene. N.m.r. spectra were determined with a Perkin-Elmer R10 instrument operating at 33·3° and 60 MHz.

7-(3,4-*Dihydro*-6,7-*dimethylpteridin*-4-*ylmethyl*)-3,4-*dihydro*-4-*hydroxy*-6-*methylpteridine* (1).—6,7-Dimethylpteridine (0·05 g) was triturated with aqueous 1·5N-NaOH (0·5 ml) for 5 min. The precipitate was filtered off and washed with water to give this *pteridine* (1) (95%), m.p. above 350° (Found: C, 56·7; H, 5·6; N, 33·0. $C_{16}H_{18}N_8O$ requires C, 56·8; H, 5·4; N, 33·1%).

7-(6,7-*Dimethylpteridin*-4-*ylmethylene*)-3,7-*dihydro*-6-*methylpteridine* (3a).—6,7-Dimethylpteridine (0·05 g) and ethanolic 33% methylamine (0·075 g, 2·5 equiv.) in tetrahydrofuran (2·0 ml) were set aside at 20—25° for 5 days.

[14] R. P. Bell and G. C. Davis, *J. Chem. Soc.*, 1964, 353.
[15] H. G. Mautner and E. M. Clayton, *J. Amer. Chem. Soc.*, 1959, **81**, 6270.
[16] J. J. Fox and D. Shugar, *Bull. Soc. chim. belges*, 1952, **61**, 44.
[17] P. R. Brook and G. R. Ramage, *J. Chem. Soc.*, 1957, 1.
[18] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.

TABLE 1

^{1}H N.m.r. spectra at 33·3°

τ Values

Compound	Pyrazine protons	Pyrimidine protons H-2	H-4	Ring Me	Other	Solvent [a]
(3a)		0·41,[b] −0·62 [b]	0·75 [b]	7·05 [c]	1·94 [d]	$CF_3·CO_2H$
(18a)		1·63	3·64	7·53 [e]	7·53,[e] 8·92 [f]	N-DCl
(18c)	1·70 [g]		3·65	7·51 [e]	7·51,[e] 8·92 [f]	N-DCl
(18b)		1·66	4·4	7·53 [e]	5·9 [h]	$(CD_3)_2SO$ + 10N-DCl
(17)		1·15	3·79	7·38 [e]	6·64 [i]	CD_3OD
(9b)				7·61 [j]	1·77,[k] 6·01,[l]	$(CD_3)_3SO$
				7·65 [j]	6·21 [l]	
(16)				7·09 [e]	0·55 [m]	$CF_3·CO_2H$
(13)				7·08 [e]	0·71 [m]	$CF_3·CO_2H$
(14)	0·85,[n] 1·02 [n]			6·80 [o]		$CF_3·CO_2H$
(15)				6·83,[o] 7·13 [e]		$CF_3·CO_2H$
(19a)	3·99,[p] 5·32 [p]		2·43	7·75,[q] 7·87 [r]	5·85,[s] 8·74 [t]	$(CD_3)_2SO–D_2O$
(19b)	4·00,[p] 5·31 [p]	2·11		7·84,[u] 7·88 [r]	5·80,[s] 8·74 [t]	$(CD_3)_2SO–D_2O$
(21)	5·81,[n] 5·89 [n]	2·11		7·77 [u]	2·73,[v] 6·18 [w]	$(CD_3)_2SO$

[a] For measurements in N-DCl, sodium 3-trimethylsilylpropane-1-sulphonate was used as internal standard; tetramethylsilane was used for other solvents; $(CD_3)_2SO–D_2O$ indicates that the spectrum was obtained after addition of 1 drop of D_2O. [b] Definite assignments were not made. [c] Most methyl signals appeared near this chemical shift as singlets. [d] Singlet, vinyl proton. [e] The chemical shifts of the ring methyl(s) and two CH_2 groups of the dimedone residue were coincidentally the same. [f] Singlet, two Me groups of the dimedone residue. [g] Two protons appeared as a singlet. [h] Broad singlet, CH of the malonamide residue. [i] Singlet, MeO. [j] All three methyl signals appeared as pairs of singlets. [k] Singlet, vinyl proton. [l] Pair of singlets, 2MeO. [m] Singlet, H-8. [n] AB quartet. [o] Singlet, 8-Me. [p] These two signals appeared as a pair of doublets [J 6·6 Hz for (19a) and J 6·0 Hz for (19b)] coupled to one another. [q] Singlet 2-Me. [r] Singlet, 7-Me. [s] Quartet, J 7·2 Hz, $CH_2·CH_3$. [t] Triplet, J 7·2 Hz, $CH_2·CH_3$. [u] Singlet, 4-Me. [v] Singlet, phenyl protons. [w] Benzylic protons (signal was not clear because of overlapping with the signal from water).

TABLE 2

Ionisation constants and u.v. spectra

		Ionisation in water (20°)				U.v. data [c]		
		Spread		Concn.	A.w.l.[b]			
Compound	Species [a]	pK_a	(±)	(M)	(nm)	$\lambda_{max.}$/nm	log ε	Solvent [d]
(1)	0					357	4·44	7·0
	+	4·79	0·05	$7·9 \times 10^{-5}$	350			
	++	3·22	0·04	$7·9 \times 10^{-5}$	350	324	4·63	1·0
(3a)	0					275, *293*, *315*, *454*, 483, 515	3·90, *3·82*, *3·64*, *4·24* 4·47, 4·47	AE
(3b)	0					*273*, *284*, *308*, *451*, 483, 515	*3·84*, *3·83*, *3·69*, *4·17*, 4·36, 4·39	AE
(4) [e]	0					*266*, 290, *300*, *455*, 481, 509, *550*	*3·86*, 3·94, *3·86*, *4·29*, 4·48, 4·46, *3·33*	AE
(18a)	−	8·32	0·02	$6·7 \times 10^{-5}$	350	283, 348	4·35, 4·05	10·5
	±					280, 324	4·33, 4·09	6·0
	+	3·62	0·03	$3·3 \times 10^{-5}$	280	263, 321	4·20, 4·07	1·0
(18c)	−	8·51	0·05	$5·4 \times 10^{-5}$	340	283, 342	4·34, 3·98	11·0
	±					281, 313	4·34, 4·02	6·0
	+	3·59	0·03	$5·4 \times 10^{-5}$	285	263, 312	4·19, 3·98	1·0
(18d)	−	7·69	0·03	$7·6 \times 10^{-5}$	345	282, 340	4·34, 3·92	9·5
	±					280, 315	4·31, 4·01	5·5
	+	3·55	0·05	$5·9 \times 10^{-5}$	290	262, 313	4·17, 3·96	1·0
3,4-Dihydro-pteridine [f]	0					335	3·96	9
	+	6·35				311	3·90	4
Dimedone [g]	−	5·27				282	4·38	5N-NaOH
	0					259	4·18	15% H_2SO_4
(9a)	0					222, 291, 350	4·25, 4·20, 4·02	E
(9b)	0					219, 295, 352	4·26, 4·23, 3·97	E
(10)	0					215, *221*, 287, 346	4·19, *4·18*, 4·20, 3·90	E
(14)	0					217, 236, *267*, 378	4·50, 4·25, *3·85*, 4·06	7·0
	+	3·52	0·03	$7·5 \times 10^{-5}$	355	230, *270*, 366	4·29, *3·50*, 4·22	1·0
(13)	0					217, 237, *267*, 385	4·51, 4·34, *3·95*, 4·06	7·0
	+	1·91	0·03	$1·2 \times 10^{-5}$	382	235, 269, 277, 368, 384	4·32, 3·66, 3·43, 4·18, 4·18	−0·2
(15)	0					218, 236, 257, 379	4·44, 4·28, 3·97, 3·92	7·0
	+	1·92	0·04	$1·7 \times 10^{-5}$	350	231, *343*, 356, 371	4·38, *4·07*, 4·17, 4·10	−0·2
(19a)	0					242, 304	4·16, 3·84	C
(19b)	0					243, 297	4·19, 3·87	C

[a] Neutral species (0), zwitterion (±), cation (+), dication (++), anion (−). [b] Analytical wavelength for spectrometric determinations. [c] Inflections in italics. [d] AE, 95% ethanol; E, ethanol; C, chloroform; numerals refer to the pH or H_0 values of aqueous solutions. [e] All values from ref. 4. [f] All values from ref. 3. [g] All values from ref. 13.

The deposited solid, filtered off and washed with tetrahydrofuran, gave the *dehydro-dimer* (3a) as *monohydrate* (65%), m.p. <350° (Found: C, 57·9; H, 5·1; N, 33·4. $C_{16}H_{14}N_8,H_2O$ requires C, 57·1; H, 4·8; N, 33·3%) [Found (dried at 110° and 0·02 mmHg): C, 60·5; H, 4·5; N, 35·4. $C_{16}H_{14}N_8$ requires C, 60·4; H, 4·4; N, 35·2%]. 6,7-Dimethylpteridine (0·05 g) set aside in tetrahydrofuran (3·0 ml) with ethanolic 33% dimethylamine (0·106 g, 2·5 equiv.) at 20—25° for 11 days gave the same compound (44%); also a 4% yield was obtained with triethylamine (0·063 g, 2 equiv.) 32 days after mixing.

3,7-*Dihydro*-7-(7-*methylpteridin*-4-*ylmethylene*)*pteridine* (3b).—7-Methylpteridine (0·1 g), ethylamine (0·077 g, 2·5 equiv.), and tetrahydrofuran (4 ml) were set aside at 20—25° for 3 days. The deposited solid, filtered off and washed with tetrahydrofuran then with water, gave the *dehydro-dimer* (3b) (50%), m.p. <350° [Found (material dried at 0·001 mmHg): C, 58·2; H, 4·1; N, 38·8. $C_{14}H_{10}N_8$ requires C, 57·9; H, 3·5; N, 38·6%].

3-*Hydroxyiminomethylamino*-5,6-*dimethylpyrazine*-2-*carbaldehyde Oxime* (9a).—6,7-Dimethylpteridine (0·2 g) was added to a solution of hydroxyammonium chloride (0·35 g, 4 equiv.) in 2·9% phosphate buffer (pH 7; 2·3 ml) at 20—25°, and the pH was readjusted to 7 with 20% NaOH. Next day, the deposited solid was filtered off and washed with water. It was suspended in ethanol (5 ml) overnight, filtered off, and recrystallised from ethanol to give the *oxime* (9a) (28%), m.p. 240° (decomp.) [Found (material dried at 20—25°): C, 46·25; H, 5·1; N, 33·4. $C_8H_{11}N_5O_2$ requires C, 45·9; H, 5·3; N, 33·5%].

2-(1-*Methoxyiminoethylamino*)-3-*methoxyiminomethyl*-5,6-*dimethylpyrazine* (9b).—A solution of 2,6,7-trimethylpteridine (0·05 g) and methoxyammonium chloride (0·096 g, 4 equiv.) in water (1·5 ml) was adjusted to pH 7 with 20% NaOH, then heated under reflux for 10 min and chilled for 6 h. The deposited solid, filtered off and washed with water, gave the *methoxyimino-compound* (9b) (14%), m.p. 117° [Found (material dried at 20—25°): C, 52·6; H, 6·5; N, 28·1. $C_{11}H_{17}N_5O_2$ requires C, 52·6; H, 6·8; N, 27·9%].

3-*Formamidopyrazine*-2-*carbaldehyde* (12).—Phosphoryl chloride (0·1 ml, 0·001 mol) was added to a cooled (3°), stirred suspension of 3-aminopyrazine-2-carbaldehyde [9] (0·123 g, 0·001 mol) in dimethylformamide (0·35 ml, 0·0045 mol). The mixture was stirred at 3° for 6 h, mixed with ice (0·6 g), and brought to pH 6 with aqueous 25% dimethylamine. The whole was chilled overnight, adjusted to pH 7, and extracted with chloroform (10 × 3 ml). The chloroform layer was washed with brine, dried (K_2CO_3), and evaporated to dryness. The residue was submitted to column chromatography on silica gel (eluant ethyl acetate) to give a yellow solid. Sublimation at 70—80° and 0·1 mmHg afforded 3-formamidopyrazine-2-carbaldehyde (12) (57%) as a pale yellow solid, m.p. and mixed m.p. 124° (authentic sample m.p. 126°).

3-*Hydroxyiminomethylaminopyrazine*-2-*carbaldehyde Oxime* (10).—3-Formamidopyrazine-2-carbaldehyde (12) (0·03 g), hydroxyammonium chloride (0·03 g, 2·2 equiv.), and sodium acetate trihydrate (0·060 g, 2·2 equiv.), in water (0·5 ml) were set aside at 20—25° overnight. The deposited solid, filtered off and recrystallised from aqueous ethanol, gave the *oxime* (10) (75%), m.p. 218° (decomp.) (Found: C, 39·7; H, 3·6; N, 38·5. $C_6H_7N_5O_2$ requires C, 39·8; H, 3·9; N, 38·7%).

6-*Amino*-2,3-*dimethylpyrido*[2,3-b]*pyrazine*-7-*carbonitrile* (13).—6,7-Dimethylpteridine (0·05 g) and malononitrile (0·021 g, 1 equiv.) in tetrahydrofuran (2 ml) were set aside at 20—25° for 7 days. The deposited solid, filtered off and washed with tetrahydrofuran, yielded the *pyridopyrazine* (13) (63%), m.p. 326° (decomp.) (Found: C, 60·35; H, 4·9; N, 35·3. $C_{10}H_9N_5$ requires C, 60·3; H, 4·55; N, 35·2%). This compound was independently obtained by leaving a solution of 2,6,7-trimethylpteridine (0·05 g) and malononitrile (0·019 g, 1 equiv.) in tetrahydrofuran (1 ml) at 20—25° for 14 days (7%), or under reflux for 98 h (45%).

6-*Amino*-2,3-*dimethylpyrido*[2,3-b]*pyrazine*-7-*carboxamide* (14).—6,7-Dimethylpteridine (0·05 g) and cyanoacetamide (0·027 g, 1 equiv.) in water (0·8 ml) were set aside at 4° for 7 days. The deposited solid, filtered off and washed with water, gave the *pyridopyrazine* (14) (27%), m.p. 300° (decomp.) (Found: C, 52·8; H, 5·2; N, 30·75. $C_{10}H_{11}N_5O,0·5H_2O$ requires C, 53·1; H, 5·35; N, 31·0%).

6-*Amino*-8-*methylpyrido*[2,3-b]*pyrazine*-7-*carbonitrile* (15).—4-Methylpteridine (0·05 g) and malononitrile (0·045 g, 2 equiv.) in tetrahydrofuran (2·5 ml) were set aside at 20—25° for 7 days. The deposited solid, filtered off and washed with tetrahydrofuran, gave the *pyridopyrazine* (15) (32%), m.p. 302° (decomp.) (Found: C, 58·3; H, 4·2; N, 38·0. $C_9H_7N_5$ requires C, 58·4; H, 3·8; N, 37·8%).

6-*Amino*-2,3,8-*trimethylpyrido*[2,3-b]*pyrazine*-7-*carbonitrile* (16).—A solution of 4,6,7-trimethylpteridine (0·05 g) and malononitrile (0·023 g, 1·2 equiv.) in tetrahydrofuran (1 ml) was set aside at 20—25° for 10 days. The solid deposited was filtered off and washed with tetrahydrofuran to afford the *pyridopyrazine* (16) (29%). It gradually decomposed above 330° (Found: C, 62·4; H, 5·3; N, 33·1. $C_{11}H_{11}N_5$ requires C, 61·95; H, 5·2; N, 32·85%). The yield was raised to 67% by boiling the reaction mixture for 74 h. Compound (16) (33%) was prepared independently by warming 2,4,6,7-tetramethylpteridine (0·05 g) and malononitrile (0·035 g, 2 equiv.) in dimethylformamide (1 ml) for 30 h on a steam-bath.

3,4-*Dihydro*-4-*methoxy*-6,7-*dimethylpteridine Hydrochloride* (17).—Dry hydrogen chloride was passed slowly into a cooled solution of 6,7-dimethylpteridine (0·1 g) in methanol (3 ml) until a solid began to separate. The deposit was filtered off after 2 h and washed with methanol–ether (1 : 2) to leave the *adduct* (17) (35%), m.p. <350 (Found: C, 47·1; H, 5·85; Cl, 15·5; N, 23·8. $C_9H_{12}N_4O,HCl$ requires C, 47·3; H, 5·7; Cl, 15·5; N, 24·0%).

4-(4,4-*Dimethyl*-2,6-*dioxocyclohexyl*)-3,4-*dihydro*-6,7-*dimethylpteridine* (18a).—6,7-Dimethylpteridine (0·05 g) and dimedone (0·044 g, 1 equiv.) in tetrahydrofuran (4 ml) were set aside at 20—25° overnight. The deposited solid was filtered off and washed with tetrahydrofuran to give the *cyclohexyl derivative* (18a) (69%), m.p. 195° (decomp.) (Found: C, 64·4; H, 6·7; N, 18·7. $C_{16}H_{20}N_4O_2$ requires C, 64·0; H, 6·7; N, 18·65%).

4-*Dicarbamoylmethyl*-3,4-*dihydro*-6,7-*dimethylpteridine* (18b).—6,7-Dimethylpteridine (0·1 g) and malonamide (0·064 g, 1 equiv.) in water (1 ml) were set aside at 4° for 5 days. The deposited solid, filtered off and washed with water, gave the *dicarbamoylmethylpteridine* (18b) (29%), m.p. 190° (decomp.) [Found (material dried at 20—25°): C, 50·2; H, 5·2; N, 32·1. $C_{11}H_{14}N_6O_2$ requires C, 50·4; H, 5·4; N, 32·05%].

4-(4,4-*Dimethyl*-2,6-*dioxocyclohexyl*)-3,4-*dihydro*-2-*methylpteridine* (18c).—2-Methylpteridine (0·025 g) and dimedone (0·024 g, 1 equiv.) in tetrahydrofuran (2·5 ml) were set aside at 20—25° overnight. The deposited solid, filtered off and

washed with tetrahydrofuran, gave the *cyclohexylpteridine* (18c) (69%), m.p. 205° (decomp.) (Found: C, 62·9; H, 6·3; N, 19·5. $C_{15}H_{18}N_4O_2$ requires C, 62·9; H, 6·3; N, 19·6%).

Ethyl 5,5a,8a,9-*Tetrahydro*-2,7-*dimethylfuro*[2,3-g]*pteridine*-8-*carboxylate* (19a).—2-Methylpteridine (0·5 g) and ethyl acetoacetate (0·45 g, 1 equiv.) in dimethyl sulphoxide (8 ml) were set aside at 20—25° overnight. The mixture was evaporated to an oil, from which silica gel column chromatography [eluants, in turn, ethyl acetate, ethyl acetate–acetone (1 : 1), and acetone] separated 2-methylpteridine and a brown oil. This oil, triturated with water (*ca.* 4 ml), deposited a solid which, filtered off and washed with water, gave the *furopteridine* (19a) (10%), m.p. 55° [Found (material dried at 20—25°): C, 55·7; H, 5·8; N, 19·7. $C_{13}H_{16}N_4O_3$,0·25H_2O requires C, 55·6; H, 5·9; N, 19·95%].

Ethyl 5,5a,8a,9-*Tetrahydro*-4,7-*dimethylfuro*[2,3-g]*pteridine*-8-*carboxylate* (19b).—4-Methylpteridine (0·05 g) and ethyl acetoacetate (0·045 g, 1 equiv.) in water (1 ml), shaken for 2 h, deposited a solid which, filtered off after cooling overnight and washed with water, gave the *furopteridine* (19b) (39%), m.p. 50° [Found (for material dried at 20—25°): C, 56·4; H, 6·0; N, 20·3. $C_{13}H_{16}N_4O_3$ requires C, 56·5; H, 5·8; N, 20·3%].

6,7-*Bisbenzylamino*-5,6,7,8-*tetrahydro*-4-*methylpteridine* (21).—4-Methylpteridine (0·025 g) and benzylamine (0·073 g, 4 equiv.) in tetrahydrofuran were set aside at 20—25° overnight. Addition of ether (4 ml) and light petroleum (b.p. 60—80°) (4 ml) caused slow deposition of a solid which, filtered off and washed with ether, gave the *bisbenzylaminopteridine* (21) (59%), m.p. 80° [Found (for material dried at 20—25°): C, 69·7; H, 6·5; N, 23·4. $C_{21}H_{24}N_6$ requires C, 70·0; H, 6·7; N, 23·3%].

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