View Article Online / Journal Homepage / Table of Contents for this issue

Published on 01 January 1969. Downloaded by Radboud Universiteit Nijmegen on 29/10/2014 12:26:18.

Heterocyclic Studies. Part VIII.[1] 2-Phenylpteridine and Some Related Compounds

By **Jim Clark,* P. N. T. Murdoch,** and (in part) **D. L. Roberts,** Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

Syntheses of 2-phenylpteridine and its 4- and 7-monomethyl, 4,7- and 6,7-dimethyl, and 4,6,7-trimethyl derivatives are described. Oxidation of 2-phenyl-, 7-methyl-2-phenyl-, and 6,7-dimethyl-2-phenyl-pteridine with hydrogen peroxide in glacial acetic acid gave the corresponding 4-hydroxy-derivatives. Further oxidation of 4-hydroxy-2-phenylpteridine gave 4,6,7-trihydroxy-2-phenylpteridine.

In acid solution 2-phenylpteridine gave a mixture of 3,4-monohydrated and 5,6,7,8-dihydrated cations which rapidly changed to a solution almost free of the monohydrate. 4-Methyl- and 4,7-dimethyl-2-phenylpteridine also gave essentially all 5,6,7,8-dihydrated cations but mainly 3,4-hydrated species were present in the equilibrium mixtures of cations formed from 7-methyl- and 6,7-dimethyl-2-phenylpteridine.

^{1}H N.m.r. and u.v. spectra and pK_a values are recorded.

MUCH of the early evidence for reversible covalent hydration of C=N linkages in formally heteroaromatic compounds came from the study of pteridine derivatives.[2,3] From this and closely related fields have since come examples of 'shifting hydration',[4-6] and double hydration, both in solution [5,7] and in the solid state.[5,8] Anomalous u.v. spectra and ionisation constants of complex pteridines have been rationalised on the basis of hydrate formation.[9]

The effects of substituents in pteridines and related heterocycles have provided some insight into the factors which influence hydration.[10] Although the effects of substituents on hydration equilibria are fairly well understood qualitatively and a number of kinetic studies have been made,[11] the electronic and steric effects of substituents have not always been readily separated. It is now planned to introduce a range of *meta*- or *para*-substituted phenyl groups into suitable positions in pteridine to provide, for kinetic studies, compounds with a range of substituents having varying electronic but constant steric effects.

No monosubstituted pteridine derivative with a phenyl or substituted phenyl group has been reported. This paper describes the preparation of 2-phenylpteridine and some of its methyl and hydroxy-derivatives. These syntheses should serve as models for those of analogous compounds with substituted phenyl groups which will be used in further hydration studies.

4-Amino-6-chloro-5-nitro-2-phenylpyrimidine (I; X = NH_2, Y = Cl) was prepared by passing a restricted amount of gaseous ammonia through a solution of the dichloro-compound (I; X = Y = Cl) [12] in tetrahydro-

[1] Part VII, *J. Chem. Soc.* (*C*), 1969, 1297.
[2] A. Albert, *J. Chem. Soc.*, 1955, 2690; A. Albert, D. J. Brown, and H. C. S. Wood, *ibid.*, 1956, 2066.
[3] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1956, 3443.
[4] A. Albert, Y. Inoue, and D. D. Perrin, *J. Chem. Soc.*, 1963, 5151.
[5] J. Clark, *J. Chem. Soc.* (*B*), 1968, 313.
[6] A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc.* (*B*), 1966, 1105.
[7] T. J. Batterham, *J. Chem. Soc.* (*C*), 1966, 999.
[8] J. Clark, *J. Chem. Soc.* (*C*), 1967, 1543.
[9] W. Pfleiderer, J. Bunting, D. D. Perrin, and G. Nübel, *Chem. Ber.*, 1966, **99**, 3503.
[10] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[11] D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.
[12] J. A. Hendry and R. F. Homer, *J. Chem. Soc.*, 1952, 328.

View Article Online

Published on 01 January 1969. Downloaded by Radboud Universiteit Nijmegen on 29/10/2014 12:26:18.

furan. Treatment of the amine with aqueous sodium hydrogen sulphide yielded the mercapto-diamine (II; Y = SH), which was desulphurised with Raney nickel. The product was identical with 4,5-diamino-2-phenylpyrimidine (II; Y = H), prepared previously by a different route.[13] The diamine was condensed with polyglyoxal to obtain 2-phenylpteridine (IIIa). Condensation of the same diamine with pyruvaldehyde gave 7-methyl-2-phenylpteridine (IIIb), while condensation with diacetyl gave 6,7-dimethyl-2-phenylpteridine (IIIc). 7-Methyl-2-phenylpteridine was also obtained when the diamine was treated with pyruvaldehyde in the presence of sodium hydrogen sulphite, although this reagent sometimes reverses the orientation of such condensations.[14]

It was shown, in each case, that the 7- and not the 6-methyl compound had been formed, by oxidising the pteridine to its 4-hydroxy-derivative (IIId) and cleaving this to the known 3-amino-5-methylpyrazine-2-carboxylic acid (IV).[16]

4,5-Diamino-6-methyl-2-phenylpyrimidine (II; Y = Me) was prepared by a method based on that used by Rose and others to convert chloropyrimidines into the corresponding methyl compounds.[17] 4-Amino-6-chloro-5-nitro-2-phenylpyrimidine (I; X = NH_2, Y = Cl) was condensed with diethyl malonate under alkaline conditions to give the bisethoxycarbonyl derivative [I; X = NH_2, Y = $CH(CO_2Et)_2$] which was hydrolysed, decarboxylated, and reduced. Condensation of the resulting diamine (II; Y = Me) with polyglyoxal, pyruvaldehyde, and diacetyl gave 4-monomethyl- (IIIe), 4,7-dimethyl- (IIIf), and 4,6,7-trimethyl-2-phenylpteridine (IIIg), respectively. The structures of the pteridines are confirmed by ^{1}H n.m.r. spectra (Table 1).

As already indicated, oxidation (by hydrogen peroxide) of 7-methyl-2-phenylpteridine yielded 4-hydroxy-7-methyl-2-phenylpteridine, and 6,7-dimethyl-7-phenylpteridine behaved similarly. Brief oxidation of 2-phenylpteridine gave mainly 4-hydroxy-2-phenylpteridine, but prolonged oxidation gave largely 4,6,7-trihydroxy-2-phenylpteridine (IIIh), a known compound.[15] T.l.c. indicated that a little 6,7-dihydroxy-2-phenylpteridine (IIIi) may also have been present. Similar oxidations with permanganate,[3,18] hydrogen peroxide,[19] and potassium ferricyanide [20] have been used to indicate the

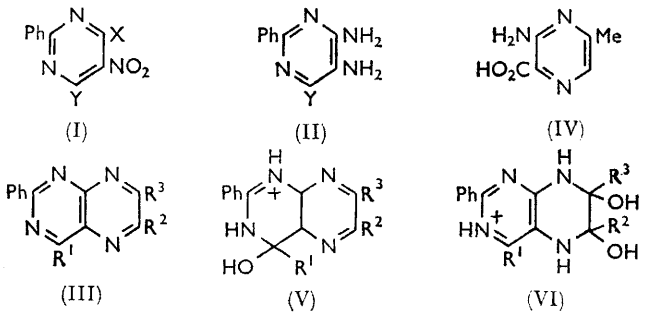
TABLE 1

^{1}H n.m.r. spectroscopy [a]

Chemical shifts (τ)

Pteridine	Solvent	7-Me	6-Me	4-Me	7-H [b]	6-H [b]	4-H	2- and 6-H of Ph [c]	3-, 4-, and 5-H of Ph [c]
(IIIa)	$CDCl_3$				0·88 [d]	1·15 [d]	0·34	1·28	2·48
	N-DCl in D_2O [e]				4·68 [f]	4·85 [f]	2·38	2·23	2·50
(IIIe)	$CDCl_3$			6·85	0·83 [d]	1·08 [d]		1·22	2·46
	N-DCl in D_2O [e]			7·60	4·70 [f]	4·85 [f]		2·23	2·50
(IIIb)	$CDCl_3$	7·14				1·19	0·32	1·27	2·48
	4N-DCl in D_2O [g,h]	7·40				1·40	3·50	2·14	2·28
(IIIc)	$CDCl_3$	7·18	7·25				0·44	1·28	2·46
	4N-DClin D_2O [g]	7·42	7·42				3·50	2·18	2·30
(IIIf)	$CDCl_3$	7·13		6·90		1·22		1·22	2·48
(IIIg)	$CDCl_3$	7·19	7·26	6·94				1·25	2·48
(IIIj)					1·10 [i]	0·90 [i]		1·75	2·37
(IIId)		7·32				1·25		1·78	2·40
(IIIk)	$[^2H_6]Me_2SO$	7·35	7·20					1·82	2·40
(IIIh)								1·95	2·45
(IIIi)							1·52	1·70	2·50

[a] Measured with a Varian A60A spectrometer. [b] Assignment of 6- and 7-protons has not been proved and may be reversed in some cases. [c] Multiplet. [d] Doublet, J 1·5 Hz. [e] 5,6,7,8-Dihydrated cation. [f] Doublet, J 2·2 Hz. [g] 3,4-Hydrated cation. [h] Also showed small peaks corresponding to about 10% of 5,6,7,8-dihydrated cations: 4-H τ 3·50, 6- and 7-H τ 1·30; signals for Ph group obscured. [i] Doublet, J 2·2 Hz.



a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = Me$
c; $R^1 = H$, $R^2 = R^3 = Me$
d; $R^1 = OH$, $R^2 = H$, $R^3 = Me$
e; $R^1 = Me$, $R^2 = R^3 = H$
f; $R^1 = Me$, $R^2 = H$, $R^3 = Me$
g; $R^1 = R^2 = R^3 = Me$
g; $R^1 = R^2 = R^3 = OH$
i; $R^1 = H$, $R^2 = R^3 = OH$
j; $R^1 = OH$, $R^2 = R^3 = H$
k; $R^1 = OH$, $R^2 = R^3 = Me$

[13] F. Bergmann, A. Kalmus, H. Ungar-Waron, and H. Kwietny-Govrin, *J. Chem. Soc.*, 1963, 3729.
[14] D. R. Seeger, D. B. Cosulich, J. M. Cosulich, J. M. Smith, jun., and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1949, **71**, 1753.
[15] F. Bergmann, M. Tamari, and H. Ungar-Waron, *J. Chem. Soc.*, 1964, 565; R. Andrisano and L. Maioli, *Gazzetta*, 1953, **83**, 264.
[16] J. Weijlard, M. Tishler, and A. E. Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 211.
[17] F. L. Rose, *J. Chem. Soc.*, 1954, 4116; R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Amer. Chem. Soc.*, 1959, **81**, 193.
[18] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1952, 1620; N. Jacobsen, *J. Chem. Soc.* (*C*), 1966, 1065.
[19] D. D. Perrin, *J. Chem. Soc.*, 1962, 645; W. L. F. Armarego, *ibid.*, 1962, 4094, 5030; A. Albert, W. L. F. Armarego, and E. Spinner, *ibid.*, 1961, 2689.
[20] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1963, 5156, 5737.

View Article Online

presence of covalent hydration. The further oxidation of 4-hydroxy-2-phenylpteridine parallels that of 4-hydroxypteridine, which was slowly oxidised to 4,6,7-trihydroxypteridine by hydrogen peroxide.[1] It is not known whether these further oxidations occur *via* covalent hydration since earlier studies had failed to reveal appreciable hydration of 4-hydroxypteridine,[3] nor pteridine and its methyl derivatives (Table 2) are too high for simple pteridines[21] so there must be some anomalous behaviour in solution. The fact that the u.v. spectra of the neutral molecules in water are closely similar, except for lack of fine structure, to their spectra in hexane suggests that the neutral molecules are normal.[10] The spectral changes on acidification are too

Published on 01 January 1969. Downloaded by Radboud Universiteit Nijmegen on 29/10/2014 12:26:18.

TABLE 2

Ionisation and u.v. spectroscopy

	Ionisation [a] (H_2O/20°)		Spectroscopy [b]			
	pK_a	Anal. λ (nm.)	Solvent	Species [c]	$\lambda_{max.}$ (nm.)	log ε
(IIIa)			Hexane	0	253 265 278 325 339 355	4·36 4·27 4·26 4·01 4·15 4·06
			H_2O, pH 6·0	0	247 *264* 335	4·31 *4·20* 4·05
	3·99 ± 0·05 [d]	305	H_2O, pH 2·0	+ [e]	253 311	4·42 4·14
(IIIb)			Hexane	0	252 273 *281* *323* 334 349	4·39 4·21 *4·16* *4·06* 4·21 4·15
			H_2O, pH 6·0	0	249 333	4·33 4·12
	2·52 ± 0·02 [d]	335	H_2O, H_0 −0·3	+ [e]	253 *290* 311	4·22 *4·04* 4·19
(IIIc)			Hexane	0	251 *257* 271 *277* *302* *322* 334 350	4·42 *4·40* 4·32 *4·30* *3·76* *4·06* 4·22 4·17
			H_2O, pH 5·0	0	248 334	4·34 4·27
	1·92 ± 0·04 [d]	340	H_2O, H_0 −0·3	+ [e]	249 *289* 313	4·11 *4·03* 4·25
(IIIe)			Hexane	0	254 *272—277* 279 323 337 352	4·43 *4·26* 4·26 4·01 4·14 4·06
			H_2O, pH 5·4	0	247 *266* 333	4·32 *4·16* 4·01
	3·30 ± 0·06 [d]	310	H_2O, pH 0·7	+ [e]	251 313	4·39 4·12
(IIIf)			Hexane	0	255 275 *321* 333 348	4·42 4·17 *4·01* 4·16 4·10
			H_2O, pH 3·9	0	248 *268* 331	4·39 *4·18* 4·15
	1·4 [d,f]	300	H_2O, H_0 −1·0	+ [e]	252 311	4·37 4·14
(IIIg)			Hexane	0	252 274 *321* 333 348	4·45 4·34 *4·02* 4·17 4·11
	Not determined [g]		H_2O, pH 2·9	0	247 *265* 332	4·38 *4·25* 4·14
(IIIj)	7·48 ± 0·05	305	H_2O, pH 5·0	0	243 285 *302*	4·14 4·15 *4·10*
			H_2O, pH 10·0	− [h]	226 268 341	4·05 4·41 3·93
(IIId)	7·72 ± 0·01	305	H_2O, pH 5·0	0	246 290 *301—305*	4·21 4·12 *4·11*
			H_2O, pH 10·0	−	227 266 341	4·00 4·41 3·99
(IIIk)	8·15 ± 0·06	305	H_2O, pH 5·0	0	244 291 *307*	4·22 4·18 *4·17*
			H_2O, pH 10·0	−	226 264 340	4·05 4·44 4·03
(II; Y = H)			H_2O, pH 7·9	0 [j]	222 296	4·14 4·07
	5·78 ± 0·02 [i]		H_2O, pH 3·8	+	248 300	4·38 4·10
(II; Y = Me)	5·84 ± 0·06	245	H_2O, pH 7·9	0	*219* 291	*4·35* 4·10
			H_2O, pH 3·5	+	245 298	4·37 4·10

[a] Determined spectrophotometrically. [b] Inflections in italics. [c] 0 Neutral molecule; + cation; − anion. [d] Equilibrium pK_a. [e] Equilibrium spectrum. [f] Approximate only, due to lack of stability of the compound under conditions of measurement. [g] Too unstable in acid. [h] Spectrum at pH 8: 226 (4·09), 266 (4·40), 338 (3·95) (ref. 15). [i] By titration of 0·002M-solution. [j] $\lambda_{max.}$ at pH 8 298 nm. (ref. 13).

TABLE 3

			Found				Required			
	M.p.	Yield (%)	C (%)	H (%)	N (%)	(M^+) *	C (%)	H (%)	N (%)	*M*
(IIIa)	132—133°	55	69·4	4·0	26·6	208	69·2	3·9	26·9	208
(IIIb)	181—182	79	70·0	4·5	25·3	222	70·2	4·5	25·2	222
(IIIc)	169—170	80	71·0	5·1	23·8	236	71·2	5·1	23·7	236
(IIIe)	150	85	69·6	4·6	25·3	222	70·2	4·5	25·2	222
(IIIf)	168—169	87	71·4	4·9	23·7	236	71·2	5·1	23·7	236
(IIIg)	192—193	82	71·5	5·8	22·6	250	72·0	5·6	22·4	250

* From mass spectrum.

was it oxidised by alkaline permanganate as are hydroxypteridines which hydrate strongly.[3,18]

Structures of the hydroxy-derivatives described were confirmed by comparison with authentic specimens when they were known compounds and, in other cases, by comparison with specimens made by unambiguous syntheses from 4,5-diamino-6-hydroxy-2-phenylpyrimidine [13] and the appropriate carbonyl compounds.

Hydration Behaviour.—The pK_a values of 2-phenylpteridine and its methyl derivatives (Table 2) are too high for simple pteridines[21] so there must be some anomalous behaviour in solution. The fact that the u.v. spectra of the neutral molecules in water are closely similar, except for lack of fine structure, to their spectra in hexane suggests that the neutral molecules are normal.[10] The spectral changes on acidification are too large to be accounted for by simple protonation of a ring nitrogen atom but are consistent with the occurrence of hydration of the cations.

The equilibrium pK_a values of 2-phenylpteridine and its 7- and 4-methyl derivatives are 3·99, 2·52, and 3·30 respectively (Table 2). The considerably larger base-weakening effect of introducing the methyl group into position 7 suggests that the most important cationic

[21] J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 319.

View Article Online

Published on 01 January 1969. Downloaded by Radboud Universiteit Nijmegen on 29/10/2014 12:26:18.

species at equilibrium is hydrated in the pyrazine ring.[10] This is confirmed by the ^{1}H n.m.r. spectrum of 2-phenylpteridine in N-deuterium chloride (Table 1), which showed only 5,6,7,8-dihydrated cations (VIa).

The cation spectrum of 2-phenylpteridine recorded in Table 2 is not observed immediately on dissolution of the pteridine in acidic solutions but is an equilibrium spectrum obtained only after a fairly rapid change ($t_{\frac{1}{2}}$ *ca.* 3 min. at pH 2·0, 20°) from that originally observed.

The initial spectrum had a peak at 289 nm. as well as one 311 nm., which suggests that a mixture of 3,4-monohydrated (Va) and 5,6,7,8-dihydrated cations (VIa) was formed at first and that a gradual change to 5,6,7,8-dihydrated cations exclusively occurred. The situation where the initial composition of a mixture of hydrated species is determined by kinetic factors and the final composition by thermodynamic stabilities has been encountered before in pteridine chemistry.[4-6]

The u.v. spectra of cations of 4-methyl- (IIIe) and 4,7-dimethyl-2-phenylpteridine (IIIf), at equilibrium, are almost identical with that of 2-phenylpteridine, suggesting that these compounds are also hydrated in the pyrazine ring [to give (VIe) and (VIf)]. However, the spectra of cations of 7-methyl- (IIIb) and 6,7-dimethyl-2-phenylpteridine (IIIc) are rather different, suggesting that in these cases hydration may occur at the 3,4-position. This view is supported by the pK_a values of 7-methyl-, 4,7-dimethyl- and 6,7-dimethyl-2-phenylpteridine (IIIb, f, and c) which are 2·52, 1·4, and 1·92 respectively (Table 2). The fact that introduction of the extra methyl group into position 4 has the larger base-weakening effect shows that 7-methyl-2-phenylpteridine is mainly hydrated at the 3,4-bond.[10] The bias towards 3,4-hydration must, of course, be even more pronounced in 6,7-dimethyl-2-phenylpteridine. The methyl-2-phenylpteridines are not very soluble in N-deuterium chloride and not very stable in stronger acid, but ^{1}H n.m.r. spectra in 4N-deuterium chloride (Table 1) indicate that 7-methyl-2-phenylpteridine is about 90% mono-hydrated as the cation (Vb) and that 6,7-dimethyl-2-phenylpteridine is exclusively monohydrated (Vc).

The fact that 2-phenylpteridine gives only 5,6,7,8-dihydrated cations (VIa) at equilibrium while pteridine gives a mixture of 3,4-mono- and 5,6,7,8-di-hydrated cations [6] suggests that a 2-phenyl group destabilises the 3,4-hydrate. This is consistent with results from the quinazoline field where electron-withdrawing 2-substituents, which reduce polarisation of the 3,4-bond, discourage 3,4-hydrate formation.[22] A recent investigation showed that 6,7-dimethyl-, 2,6,7-trimethyl- and 4,6,7-trimethylpteridine form only 3,4-hydrated cations.[23] These results reaffirm previous conclusions that 6- and 7-methyl groups strongly hinder hydration of the pyrazine ring.

EXPERIMENTAL

4-Amino-6-chloro-5-nitro-2-phenylpyrimidine.— Gaseous ammonia (2·3 equiv.) was slowly passed into a solution of 4,6-dichloro-5-nitro-2-phenylpyrimidine [12] (10 g.) in tetrahydrofuran (85 ml.). Removal of the solvent and washing of the residue with water left a crude product (8·5 g.) which contained a little 4,6-diamino-5-nitro-2-phenylpyrimidine but which was suitable for the next stage. Pure 4-Amino-6-chloro-5-nitro-2-phenylpyrimidine was obtained by chromatographing the crude material on a silica column. The material was applied in tetrahydrofuran solution and eluted with chloroform–light petroleum (b.p. 60—80°) (1 : 1). The more mobile fraction was twice crystallised from pentyl alcohol to yield the *pyrimidine* (I; X = NH_2, Y = Cl), m.p. 184° (Found: C, 48·0; H, 3·0; N, 22·5. $C_{10}H_7ClN_4O_2$ requires C, 47·9; H, 2·8; N, 22·4%).

The use of an excess of ammonia and a higher temperature in the early stages of the experiment gave *4,6-diamino-5-nitro-2-phenylpyrimidine*, m.p. 262° (from pentyl alcohol) (Found: C, 51·9; H, 3·8; N, 30·2. $C_{10}H_9N_5O_2$ requires C, 52·2; H, 3·9; N, 30·4%).

4,5-Diamino-6-mercapto-2-phenylpyrimidine.—The amine (I; X = NH_2, Y = Cl) (5 g.) was heated under reflux for 3 hr. with a saturated solution of sodium hydrogen sulphide prepared from sodium hydroxide (20 g.), water (140 ml.) and excess of hydrogen sulphide. The resulting solution was acidified with glacial acetic acid and filtered. The residue was reprecipitated from 2N-sodium hydroxide with glacial acetic acid, alkali-insoluble material being filtered off. The diamine (3·3 g.) had m.p. 238—239° (from ethanol) (lit.,[12] decomp. 270°) (Found: C, 55·1; H, 4·7; N, 25·9. Calc. for $C_{10}H_{10}N_4S$: C, 55·0; H, 4·6; N, 25·7%).

4,5-Diamino-2-phenylpyrimidine.—The mercapto-compound just described (3 g.), water (110 ml.) ammonia (5.5 ml; *d* 0·88), and Raney nickel (11 g.; settled suspension) were heated under reflux for 2 hr. The mixture was filtered hot and the spent nickel was washed with hot ethanol. Evaporation of the combined filtrates and crystallisation of the residue from benzene–light petroleum (b.p. 60—80°) yielded the diamine (1·6 g.), m.p. 144—145° (lit.,[12] 146°).

Diethyl (6-Amino-5-nitro-2-phenylpyrimidin-4-yl)malonate (I; X = NH_2, Y = $CH(CO_2Et)_2$).—A suspension of 4-amino-6-chloro-5-nitro-2-phenylpyrimidine (10 g.) in tetrahydrofuran (100 ml.) and diethyl malonate (15 ml.) was stirred and kept below 50° during the dropwise addition of 11N-sodium hydroxide (15 ml.) and for a further 0·5 hr. The solution was diluted with water (100 ml.) and acidified with glacial acetic acid, and the tetrahydrofuran was evaporated off. *The pyrimidinylmalonate* (13 g.) was filtered off; m.p. 122—124° (from pentyl alcohol) [Found: C, 54·5; H, 4·8%; *M* (mass spectrum), 374. $C_{17}H_{18}N_4O_6$ requires C, 54·5; H, 4·9%; *M*, 374].

4-Amino-6-methyl-5-nitro-2-phenylpyrimidine.—The malonate just described (7 g.) and concentrated hydrochloric acid (350 ml.) were heated under reflux for 2 hr. The solution was evaporated to dryness and the residue was sublimed and crystallised from aqueous dimethylformamide to yield the methyl compound (4·0 g.), m.p. 158—159° [Found: C, 56·9; H, 4·2%; *M* (mass spectrum), 230. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4%; *M*, 230].

4,5-Diamino-6-methyl-2-phenylpyrimidine.—A suspension of the 5-nitro-compound (4 g.) in acetone (40 ml.) was stirred vigorously with a solution of sodium hydrogen carbonate (16 g.) in water (40 ml.) during the addition over

[22] W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.* (*C*), 1966, 234.

[23] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 2292.

View Article Online

Published on 01 January 1969. Downloaded by Radboud Universiteit Nijmegen on 29/10/2014 12:26:18.

0·5 hr. of sodium dithionite (16 g.). The temperature of the mixture was allowed to reach 50° and maintained at this value for a further 0·5 hr. The acetone was evaporated off and the cooled mixture was filtered. The residue was sublimed and crystallised from benzene–light petroleum (b.p. 80—100°) to yield the *diamine* (1·6 g.), m.p. 184—185° [Found: C, 65·1; H, 5·9%; *M* (mass spectrum), 200. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0%, *M*, 200].

2-Phenylpteridine and Some Methyl Derivatives.—The relevant diamine (0·2 g.) (II; Y = H or Me) and dicarbonyl compound [polyglyoxal, diacetyl, or pyruvaldehyde (2 equiv.)] were heated, under reflux, in ethanol for 0·5 hr. Filtration and crystallisation of the residue from light petroleum (b.p. 80—100°) yielded the pteridine (Table 3).

4-Amino-6-hydroxy-5-nitro-2-phenylpyrimidine.— 4-Amino-6-chloro-5-nitro-2-phenylpyrimidine (3 g.) and concentrated hydrochloric acid (50 ml.) were heated under reflux for 1 hr. and the resulting solution was neutralised with aqueous ammonia. The solid was separated and crystallised from aqueous dimethylformamide to yield the *hydroxypyrimidine* (2·4 g.), m.p. >300° (Found: C, 52·0; H, 3·1; N, 24·0. $C_{10}H_8N_4O_3$ requires C, 51·7; H, 3·5; N, 24·1%).

4,5-Diamino-6-hydroxy-2-phenylpyrimidine.—The 5-nitro-compound (3 g.) was reduced in the same way as 4-amino-6-methyl-5-nitro-2-phenylpyrimidine to yield the diamine (II; Y = OH) (2 g.), m.p. 237—239° (from water) (lit.,[14] 228°).

4-Hydroxy-7-methyl-2-phenylpteridine.—The diamine (II; Y = OH) (0·2 g.) was dissolved in the minimum amount of boiling water and treated with pyruvaldehyde (40% aqueous solution; 0·35 ml.). The solid which gradually separated (0·3 g.) yielded *4-hydroxy-7-methyl-2-phenylpteridine*, m.p. >300° (from aqueous dimethylformamide) (Found: C, 66·0; H, 4·25; N, 24·0. $C_{13}H_{10}N_4O$ requires C, 65·5; H, 4·2; N, 23·5%).

Cleavage of 4-Hydroxy-7-methyl-2-phenylpteridine.—The hydroxypteridine just described (0·1 g.) and 2N-sodium hydroxide (5 ml.) were heated at 160° for 36 hr. The cooled mixture was filtered and the filtrate was acidified to precipitate 3-amino-5-methylpyrazine-2-carboxylic acid (0·03 g.), m.p. 206° (lit.,[16] 211—212) (from aqueous ethanol). The compound was identified by mixed m.p. and by comparison of its i.r. spectrum with that of an authentic specimen.

Oxidation of Pteridine Derivatives.—(*a*) 7-Methyl-2-phenylpteridine (0·5 g.) was suspended in glacial acetic acid (10 ml.) and hydrogen peroxide (100 vols.; 1·2 ml.) was added. After 6 hr. the pH of the mixture was adjusted to 6 by the dropwise addition of ammonia (*d* 0·88). 4-Hydroxy-7-methyl-2-phenylpteridine (0·4 g.) was filtered off and crystallised from aqueous dimethylformamide. It was shown, by comparison of u.v. and i.r. spectra and t.l.c. in two solvent systems, to be identical with that already described.

(*b*) 6,7-Dimethyl-2-phenylpteridine (0·5 g.) was similarly oxidised to 4-hydroxy-6,7-dimethyl-2-phenylpteridine (0·45 g.) identical with an authentic specimen.[14]

(*c*) Treatment of 2-phenylpteridine (0·5 g.) as in (*a*) for 3 hr. gave almost pure 4-hydroxy-2-phenylpteridine (0·4 g.), identical with an authentic specimen.[15] Extended treatment (1 week) under the same conditions gave mainly 4,6,7-trihydroxy-2-phenylpteridine, identified by comparison of its i.r. and u.v. spectra and by its t.l.c. and paper chromatographic behaviour with those of an authentic specimen.[15]

6,7-Dihydroxy-2-phenylpteridine.—4,5-Diamino-2-phenylpyrimidine (0·9 g.) and oxalic acid dihydrate (4·4 g.) were heated at *ca.* 100 mm. to 160° during 0·5 hr. and maintained at that temperature for 0·5 hr. The residue was dissolved in boiling water with the addition of sodium hydroxide to adjust the pH of the solution to 7. *6,7-Dihydroxy-2-phenylpteridine* (0·66 g.) was filtered from the cooled solution; m.p. 250° (from aqueous dimethylformamide) (Found: C 59·6; H, 3·3; N, 23·4. $C_{12}H_8N_4O_2$ requires C, 60·0; H, 3·4; N, 23·3%).

We thank Mr. A. E. Cunliffe for measuring the u.v. spectra and ionisation constants, Mr. D. Barraclough and Mr. B. Marquis for the ^1H n.m.r. spectra (Varian A60A), and Mrs. R. Maynard for the mass spectra (A. E. I. MS 12).

[9/050 *Received, January 9th,* 1969]