667. *Pteridine Studies. Part IX.* The Structure of the Monohydroxypteridines and their N-Methyl Derivatives.*

By D. J. Brown and S. F. Mason.

To decide between a number of possible tautomeric structures for the four monohydroxypteridines, their infrared and ultraviolet spectra and ionisation constants have been compared with those of the *N*-methyl derivatives, including some new derivatives not obtained by direct methylation. It is concluded that all the monohydroxypteridines have the –CO·NH– structure, that is, they are cyclic amides and not vinylogous amides or hydroxy-derivatives. It is suggested that the strongly bound molecule of water in 2- and 6-hydroxypteridine and their *N*-methyl derivatives is water of constitution, and is added across the 3 : 4- and the 7 : 8-double bond respectively. The ready introduction of a hydroxyl group on gentle oxidation, but only in those cases where water of constitution has been assumed, strengthens this hypothesis.

The monohydroxypteridines may be divided into two classes. The 4- and the 7-isomers possess properties expected of tetra-azanaphthalenes with a hydroxyl group α or γ to a ring-nitrogen atom. They are acids with pK_a values of 7·89 and 6·41 respectively (Table 1), that is, they are acids some 10—1000 times stronger than the analogous hydroxytriazanaphthalenes which in turn are stronger than the corresponding diazanaphthalene derivatives.[1] The neutral molecules of 4- and 7-hydroxypteridine possess a three-banded ultraviolet absorption spectrum with the long-wavelength band just above 300 mμ, like many other bicyclic aromatic compounds. On anion formation, bathochromic shifts of 23 mμ are observed, shifts within the range of 6—34 mμ found for other (potentially tautomeric) hydroxyazanaphthalenes.[2]

The neutral molecules of 2- and 6-hydroxypteridine, on the other hand, give only a double-banded ultraviolet absorption spectrum, the long-wavelength band of the 6-isomer lying as low as 289 mμ. On anion formation, large bathochromic shifts of 68 and 67 mμ respectively are observed, suggesting that the anions are more conjugated than the neutral molecules. The spectra of the anions of all four monohydroxypteridines resemble those of the neutral molecules of the corresponding amines,[3,4] as is general for phenoxide ions and aromatic amines.[5] Thus it is likely that the anions of 2- and 6-hydroxypteridine are normal phenoxide ions, like those of the other isomers, and that the neutral molecules possess anomalous structures. 2- and 6-Hydroxypteridine differ from their isomers in that they retain a molecule of water at 110°, though their sodium salts are anhydrous. 2-Hydroxypteridine loses this water at 180°, and the 6-isomer decomposes at this temperature without prior dehydration.[6,7] Again, 2-hydroxypteridine is a much weaker acid (pK_a 11·13) than its isomers, and the 6-isomer displays hysteresis on titration, giving a pK_a value of 9·7 when titrated with alkali and the value of 6·7 when the anion is titrated with acid.

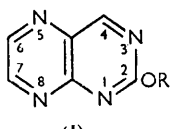
A similar contrast obtains between the *N*-methyl derivatives of the monohydroxypteridines. The known *N*-methyl derivatives of 4- and 7-hydroxypteridine are anhydrous, and when the *N*-methyl group forms a part of the ring in the pteridine nucleus to which the oxygen is attached these derivatives are not acidic. The *N*-methyl derivatives of 2- and 6-hydroxypteridine, on the other hand, all possess a strongly bound molecule of water, and they are all acidic, the *N*-methyl-2-pteridones † having pK_a values close to that of 2-hydroxypteridine itself.

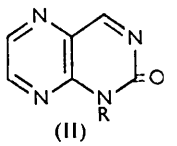
* Part VIII, *J.*, 1956, 2066.

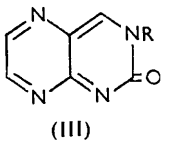
† We prefer this name to dihydro-*N*-methyl-2-oxopteridines which the Editor states is correct practice for this *Journal*; and similarly for analogous mono "amides."

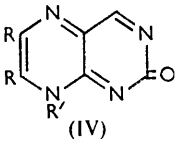
[1] Albert and Phillips, *J.*, 1956, 1294.
[2] Mason, unpublished work.
[3] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[4] *Idem*, *J.*, 1952, 1620.
[5] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[6] Albert in the Symposium report, "The Chemistry and Biology of Pteridines," Churchill, London, 1954, p. 204.
[7] Albert, *J.*, 1955, 2690.

2-Hydroxypteridine.—It has been shown [8] that the ultraviolet spectra of 2-hydroxy- and 2-methoxy-pteridine (I; R = Me) in aqueous solution are dissimilar. Hence, 2-hydroxypteridine should exist mainly as a cyclic amide in that solvent. 2-Hydroxypteridine in the solid state, and its 6 : 7-diethyl derivative in chloroform solution, show a strong band in the C:O stretching vibration region of the infrared, but its sodium salts and *O*-methyl derivative do not, and so the former compounds exist as cyclic amide under the


(I)


(II)


(III)


(IV)

conditions stated. The alternative amide structures are (II—IV; R = R′ = H), and spectroscopic comparison of 2-hydroxypteridine with the corresponding *N*-methyl derivatives (II—IV, R = R′ = Me) allows a choice to be made between them.

Of the three possible *N*-methyl-2-pteridones, the 3-isomer (III; R = Me) is known and

TABLE 1. *The ultraviolet absorption spectra of the monohydroxypteridines and their N-methyl derivatives.* (*Values in italics refer to shoulders or inflexions.*)

Compound	pK_a in H_2O at 20° and concn.	pH at which spectrum was measured	$\lambda_{max.}$ (mμ)	log ε
2-Hydroxypteridine [a] (+1H_2O)	—	7·1	230; *285*; 307	3·88; *3·59*; 3·83
anion [a]	11·13	13·0	260; 375	3·85; 3·78
cation [a]	<2	—	—	—
1-Methyl-2-pteridone (+1H_2O)	—	7·0	240; *285*; 311	3·91; *3·53*; 3·85
anion	11·43 [d]	13·0	236; 312; 375	3·89; 3·81; 2·37
cation	<1	—	—	—
3-Methyl-2-pteridone (+1H_2O)	—	7·0	230; *285*; 309	3·97; *3·59*; 3·89
anion	11·01 [d]	13·0	236; 271; 313; *350*	3·84; 3·66; 3·80; *3·53*
cation	<1	—	—	—
3 : 6 : 7-Trimethyl-2-pteridone (+1H_2O)	—	7·0	235; *290*; 317	3·95; *3·60*; 4·02
anion	11·36(±0·01), M/20	13	236; 277; 319; *355*	3·90; 3·53; 4·01; 3·23
cation	<2	—	—	—
6 : 7 : 8-Trimethyl-2-pteridone	—	7·0	239; *280*; 327	4·34; *3·70*; 4·25
anion	10·26(±0·04), M/400	12·3	240; 344	4·23; 4·19
cation	<2	—	—	—
4-Hydroxypteridine [a]	—	5·6	230; 265; 310	3·98; 3·54; 3·82
anion [a]	7·89	10·0	242; 333	4·23; 3·79
cation	−0·17(±0·07), [e] M/10	−2·5 [h]	257; 303	3·43; 3·96
1-Methyl-4-pteridone	—	7·0	232; *260*; *300*; 324	4·14; *3·34*; *3·41*; 3·96
cation	1·25(±0·05), M/20	−0·8 [i]	225; 263; 305	4·11; 3·49; 4·03
3-Methyl-4-pteridone	—	5·3	233; 276; 312	4·12; 3·57; 3·81
cation	−0·47(±0·03), [e] M/10	−2·5 [h]	221; *265*; 304	4·04; *3·46*; 4·00
6 : 7 : 8-Trimethyl-4-pteridone	—	7·0	236; 256; 301 + 311; 392	4·09; 4·14; 4·10 + 4·13; 3·55
anion	9·46(±0·05)	12·0	237; 269; 297; 334; *375*	4·24; 4·04; 3·91; 3·68; *3·45*
cation	4·70(±0·07)	2·5	246; 279; 356	3·97; 3·58; 4·02
6-Hydroxypteridine [b] (+1H_2O)	—	—	—	—
stable neutral molecule	—	5·2	*266*; 289	*3·85*; 4·00
transient neutral molecule	—	5·2	230; 305; 332	3·80; 3·65; 3·66
cation [b]	3·67	1·7	287	4·09
stable anion	6·7	13·0	224; 256; 356	4·29; 3·97; 3·84
transient anion	9·7	13·0	*265*; 289	*3·84*; 3·99
5-Methyl-6-pteridone (+1H_2O)	—	7·0	*265*; 290	*3·85*; 4·06
anion	10·6 [d]	13·0	*270*; 296	*3·78*; 3·99
cation	3·73	1·0	288	4·14

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

TABLE 1. (*Continued.*)

Compound	pK_a in H_2O at 20° and concn.	pH at which spectrum was measured	$\lambda_{max.}$ (mμ)	log ε
7 : 8-Dihydro-6-hydroxypteridine [b]	—	7·4	*275*; 293	*3·80*; 3·93
anion	10·54	13·0	*275*; 305	*3·75*; 4·07
cation [b]	4·78	2·4	292	4·01
7-Hydroxypteridine [b]	—	4·0	227; 248 + 256; 303	3·79; 3·44 + 3·45; 4·00
anion [b]	6·41	9·0	226; 260; 326	4·27; 3·76; 4·04
cation [b]	1·2	—	—	—
8-Methyl-7-pteridone [b]	—	4·0	<220; 250 + 257; 306	>4·13; 3·55 + 3·54; 3·97
cation	1·1	−2·0 [j]	295	3·97
5 : 6-Dihydro-7-hydroxypteridine [b]	—	6·0	271; 319	3·58; 3·70
anion	9·94	12·0	224; *265*; 325	4·34; *3·56*; 3·93
cation [b]	3·36	1·0	233; 284; 352	4·47; 3·74; 3·71
5 : 6-Dihydro-6 : 7-dihydroxy-5-methylpteridine	—	7·0	259; 315	3·74; 3·88
anion	9·33(±0·03), M/100	11·4	226; *268*; 322	4·26; *3·71*; 4·05
cation	2·91(±0·02), M/100	0·7	225; 275; 334	4·41; 3·78; 3·8
5 : 6-Dihydro-5 : 8-dimethyl-6-hydroxy-7-pteridone	—	7·0	219; 260; 315	4·44; 3·75; 3·93
6 : 7-Dihydroxypteridine [b]	—	4·0	249 + 255; 301	3·71 + 3·70; 4·18
anion [b]	6·87	8·4	227; 268; 319	4·03; 3·71; 4·29
dianion [b]	10·0	12·0	240; 277; *310* + 324 + 338	4·13; 3·68; *4·09* + 4·30 + 4·25
7-Hydroxy-5-methyl-6-pteridone	—	—	—	—
anion	7·02(±0·03), M/100	13·0	237; 268; 309 + 321 + 336	4·01; 3·65; 4·24 + 4·36 + 4·20
5 : 6 : 7 : 8-Tetrahydro-5 : 8-dimethyl-6 : 7-dioxopteridine	—	7·0	223; 254 + 261; 303	4·11; 3·66 + 3·68; 4·20
2-Hydroxyquinoline	—	4·7	224; 245; 270; 323	4·43; 3·93; 3·82; 3·80
anion	11·74 [f]	13·7	232; 332	4·65; 3·74
cation	−0·31 [f]	−2·5 [h]	238; 299	4·34; 3·88
2-Hydroxyquinazoline	—	5·0	220; 274; 345	4·42; 3·57; 3·25
anion	10·69 [f]	13·0	230; 322; 351	4·51; 3·35; 3·41
cation	1·30 [f]	−0·8 [i]	220; 292; 385	4·53; 3·98; 3·42
1-Methyl-5-quinolone	—	8·5	237; 273; 318 + 332; 462	4·06; 4·52; 3·09 + 3·06; 3·58
cation	6·12(±0·04), M/100	3·0	222; 254; 305 + 318; 376	3·90; 4·62; 3·20 + 3·26; 3·50
1-Methyl-7-quinolone	—	8·0	261; 311; 406	4·51; 3·19; 4·00
cation	5·56(±0·02), M/100	2·0	245; 308; 353	4·54; 3·50; 3·92
2-Methyl-6-*iso*quinolone	—	10·0	230; 267; 358	4·54; 4·36; 4·09
cation	6·10(±0·05), [e] M/10^4	2·0	227; 246; 319	4·55; 4·50; 3·96
2-Aminopyrazine	—	7·0	230; *285*; 316	4·02; *3·33*; 3·70
cation	3·14 [g]	1·0	229; 325	4·03; 3·77
2-Acetamidopyrazine	—	7·0	231; 280; 296	4·16; 3·81; 3·81
3-Aminopyrazine-2-carboxyamide	—	6·1	246; 305; 350	4·06; *3·26*; 3·80
3-Aminopyrazine-2-carboxylic acid	—	6·1	244; *295*; 340	4·01; *3·29*; 3·76
4 : 5-Diamino-2-hydroxypyrimidine [c]	—	6·98	292	3·58
anion [c]	11·45	13·0	226; 303	3·91; 3·67
cation [c]	4·37	2·3	305	3·76
4 : 5-Diamino-6-hydroxypyrimidine [c]	—	6·7	278; 372	3·95; 2·44
anion [c]	9·86	12·0	272; 370	3·87; 2·62
cation [c]	3·57; 1·34	2·45	258	3·74

[a] Albert *et al.*, *J.*, 1951, 474. [b] Albert *et al.*, *J.*, 1952, 1620. [c] Mason, *J.*, 1954, 2071. [d] Albert *et al.*, *J.*, 1956, 2066. [e] Determined spectroscopically. [f] Albert and Phillips, *J.*, 1956, 1294. [g] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [h] 10N-Sulphuric acid; these compounds slowly decompose at this pH. [i] 4N-Sulphuric acid. [j] 7·5N-Sulphuric acid.

an isomer has been obtained by the methylation of 2-hydroxypteridine.[9] Attempts to synthesise the 8-isomer (IV; R = H, R′ = Me) from 5-amino-2-hydroxy-4-methylaminopyrimidine and glyoxal did not give the required substance, but condensation of the same pyrimidine with diacetyl afforded 6 : 7 : 8-trimethyl-2-pteridone (IV; R = R′ = Me). The ultraviolet spectrum of this compound, and the infrared spectrum in the N–H and C:O stretching regions, are markedly different from those of the above two isomers (Fig. 1, Tables 1 and 2).* Thus, by elimination, the methylation product of 2-hydroxypteridine must be 1-methyl-2-pteridone.

The molecule of water held by these three *N*-methyl-2-pteridones is strongly bound; indeed, 1- and 3-methyl-2-pteridone cannot be dehydrated without fundamental change. When heated above their softening points (160—230°), the latter compounds are converted into new, water-insoluble substances, which, although very hygroscopic, do not revert to the original materials save on dissolution in alkali and reprecipitation with acid. 3 : 6 : 7-Trimethyl-2-pteridone (as hydrate or ethanolate) gives a similar compound above 190°, but the latter does not revert cleanly to the original substance when treated as above with

FIG. 1. FIG. 2.

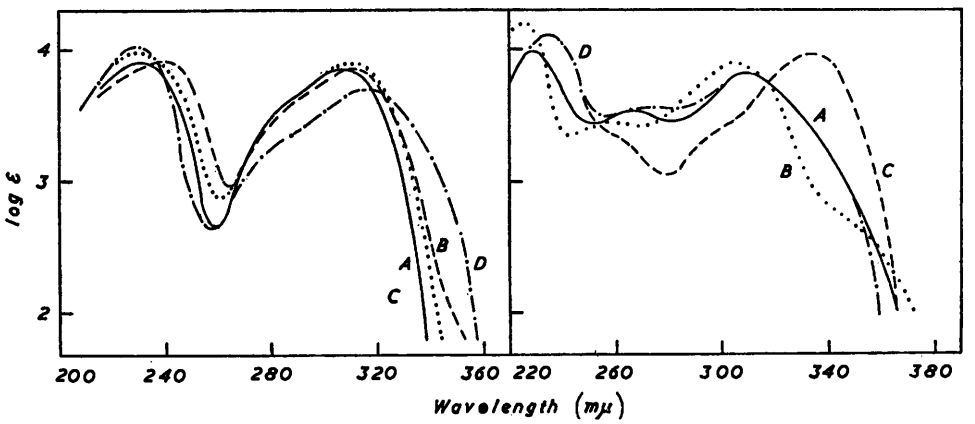


FIG. 1. *Neutral molecules of: A, 2-hydroxypteridine; B, 1-methyl-2-pteridone; C, 3-methyl-2-pteridone; and D, 2-aminopyrazine.*

FIG. 2. *Neutral molecules of: A, 4-hydroxypteridine; B, 4-methoxypteridine; C, 1-methyl-4-pteridone; and D, 3-methyl-4-pteridone.*

alkali. From their general properties, these products obtained by vigorous heating seem to be dimeric or polymeric, and they may be analogous to the dimers obtained from 6-hydroxypteridine.[7] 6 : 7 : 8-Trimethyl-2-pteridone becomes anhydrous at 120° *in vacuo*, but is readily rehydrated in air at room temperature.

The *N*-methyl-2-pteridones possess properties which suggest that the strongly bound molecule of water may be water of constitution. Their formal structures (II—IV; R = R′ = Me) show no acidic groupings or N–H linkages, yet they may be dissolved in alkali and reprecipitated unchanged with acid, and in chloroform or carbon tetrachloride solution they show a band in the infrared due to a N–H stretching vibration (Table 2). The band persists, and lies in the same position, when the molecule of water is exchanged for alcohol, an exchange effected by a few recrystallisations from ethanol in the case of the more soluble compounds, namely, 1-methyl- and 3 : 6 : 7-trimethyl-2-pteridone. The hydrates, but not the alcoholates, of these compounds also show a weak band in the O–H stretching vibration region. When 6 : 7 : 8-trimethyl-2-pteridone has been heated at 120° *in vacuo*, its infrared spectrum shows a N–H stretching vibration band much reduced in intensity, though the

* In principle, the *C*-methyl groups in positions 6 and 7 of 6 : 7 : 8-trimethyl-2-pteridone can have little effect in the spectral regions examined. In the analogous case of 3 : 6 : 7-trimethyl-2-pteridone (from diacetyl and 4 : 5-diamino-1 : 2-dihydro-1-methyl-2-oxopyrimidine) the N–H and C : O stretching frequencies, and the ultraviolet spectrum, are closely similar to those of, for example, 3-methyl-2-pteridone (Tables 1 and 2).

[9] Albert, Brown, and Wood, *J.*, 1956, 2066.

band cannot be eliminated, owing perhaps to the difficulty of maintaining the compound anhydrous. Both the "hydrate" and the "alcoholate" of 6 : 7-diethyl-2-hydroxypteridine (2-hydroxypteridine hydrate is insoluble in non-polar solvents) show two bands

TABLE 2. *The infrared spectra of the monohydroxypteridines, their sodium salts, and their N-methyl derivatives in the* O–H, N–H, *and double-bond stretching vibration regions.*

(vs = very strong, s = strong, m = moderate, w = weak.)

	O–H and N–H stretching frequencies (cm.$^{-1}$)			Double-bond stretching frequencies (cm.$^{-1}$)	
Compound	In CCl_4	In $CHCl_3$	Solid	In $CHCl_3$	Solid
2-Hydroxypteridine ($+1H_2O$)	[b]	[b]	3335 w, 3256 s	[b]	1681 vs, 1598 s
deuterated	[b]	[b]	2325 s		1672 vs, 1595 s
sodium salt	[b]	[b]	—		1614 s
2-Methoxypteridine [a]	[c]	[c]	—	[c]	1598 s
6 : 7-Diethyl-2-hydroxypteridine ($+1H_2O$ or 1EtOH)	3439 s, 3389 s	3424 s, 3382 s	—	1705 s	—
1-Methyl-2-pteridone ($+1H_2O$ or 1EtOH)	3434 s	3426 s	3350 w, 3233 s, 3124 s	1688 s	1685 s, 1555 s
3-Methyl-2-pteridone ($+1H_2O$)	[b]	3421 s	3260 s, 3180 s	1690 s	1670 s, 1600 s
3 : 6 : 7-Trimethyl-2-pteridone ($+1H_2O$ or 1EtOH)	3433 s	3423 s	3245 s, 3150 s	1690 s	1670 s, 1601 s
6 : 7 : 8-Trimethyl-2-pteridone	3422 m	3414 m	3290 w, 3183 m	1654 s	1653 s, 1595 s
4-Hydroxypteridine		[b]	3380 w, 3130 m	[b]	1710 s, 1697 s, 1586 s
deuterated	[b]	[b]	2320 m, 2205 m	[b]	1690 s, 1605 m, 1583 s
sodium salt	[b]	[b]	—	[b]	1611 w, 1584 s
4-Methoxypteridine [a]	[c]	[c]	—	[c]	1578 s
6 : 7-Diethyl-4-hydroxypteridine	3401 s	3387 s	—	1685 s	—
6 : 7-Diethyl-2 : 4-dihydroxypteridine	3421 s, 3408 s	3402 s, 3386 s	—	1703 s, 1684 s	—
1-Methyl-4-pteridone	[c]	[c]	—	1740 s, 1678	1664 s, 1607 s
3-Methyl-4-pteridone	[c]	[c]	—	1702 s	1671 s, 1595 s
6 : 7 : 8-Trimethyl-4-pteridone	[b]	3388 w	3272 w, 3140 w	1705 s, 1670 s	1681 s, 1606 s
6-Hydroxypteridine ($+1H_2O$)	[b]	[b]	3352 w, 3210 s 3172 s, 3117 s	[b]	1681 s, 1608 s
deuterated	[b]	[b]	2330 s, 2170 s	[b]	1670 s, 1594 s
sodium salt	[b]	[b]	—	[b]	1592 s
6-Methoxypteridine [a]	[c]	[c]	—	[c]	1591 s
5-Methyl-6-pteridone ($+1H_2O$)	[b]	[b]	3350 w, 3205 s 3160 s	[b]	1689 s, 1596 s
7-Hydroxypteridine	[b]	[b]	3305 w, 3242 m 3138 s	[b]	1693 s, 1580 s
deuterated	[b]	[b]	2295 m, 2270 m	[b]	1690 s, 1580 s
sodium salt	[b]	[b]	—	[b]	1605 m, 1576 s
7-Methoxypteridine [a]	[c]	[c]	—	[c]	1591 m, 1570 s
8-Methyl-7-pteridone	[c]	[c]	—	1688 s	1676 s, 1573 s
6 : 8-Dimethyl-7-pteridone			—	1685 s	1675 s, 1595 s
5 : 6-Dihydro-6-hydroxy-5-methyl-7-pteridone		[b]	3345 w, 3223 m 3165 s	[b]	1676 s, 1578 s
5 : 6-Dihydro-5 : 8-dimethyl-6-hydroxy-7-pteridone	3566 m		3275 m	1689 s	1678 s, 1582 s

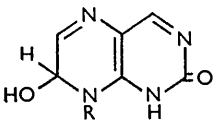
[a] Mason, *J.*, 1955, 2336. [b] Insufficiently soluble. [c] Soluble, but no band was observed in this region. [d] Region obscured by solvent absorption.

in the N–H stretching vibration region and when either form is heated at 120° *in vacuo* the band at higher frequency (3430 cm.$^{-1}$), corresponding to the band observed in the spectra of the *N*-methyl-2-pteridones, is reduced in intensity. In the solid state the *N*-methyl-2-pteridones show broad bands in the 3400—3100 cm.$^{-1}$ region due to intermolecularly hydrogen bonded O–H and N–H groups, whilst the unhydrated *N*-methyl-4- and -7-pteridones show no absorption above 3100 cm.$^{-1}$.

It is unlikely that these " hydrates " possess the open-ring structures typified by those derived by hydrolytic cleavage of the 1 : 2- or 7 : 8-double bond of (II), as they give negative tests for an aldehyde group with benzidine and are too weak both as acids (Table 1) and bases ($pK_a < 1$). More plausible are the structures (V; R or R′ = H) and (VI) in which the molecule of water has added across one of the nuclear double bonds. These structures indicate that the ultraviolet spectra of 2-hydroxypteridine and its *N*-methyl derivatives should be those of a substituted pyrimidine (VI) or a substituted pyrazine (V). 2-Hydroxypteridine hydrate and its 1- and 3-methyl derivative do indeed possess ultraviolet spectra (Fig. 1, Table 1) which are similar to those of 2-amino- and 2-acetamido-pyrazine and different from those of 2-hydroxy-quinoline and -quinazoline, the last two compounds having chromophore structures similar to that of the anhydrous 2-hydroxypteridine. 6 : 7 : 8-Trimethyl-2-pteridone, on the other hand, has an ultraviolet spectrum more akin to that of *N*-methyl-7-quinolone than to that of 4 : 5-diamino-2-hydroxypyrimidine (Table 1), though the latter compound does not provide so exact a model chromophore for (VI) as 2-acetamidopyrazine does for (V).

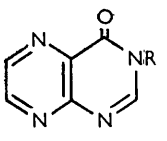
The balance of evidence accordingly suggests that 2-hydroxypteridine hydrate possesses the structure (V; R = R′ = H). The close similarity between the ultraviolet spectra of

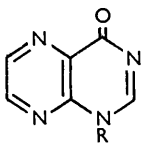

(V)

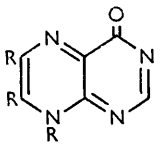

(VI)

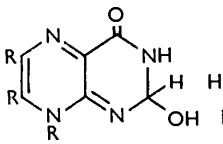
2-hydroxypteridine and those of its 1- and 3-methyl derivative indicates that they all have the same chromophoric structure (Fig. 1, Table 1). When the hydration of these compounds is taken into account, this structure is likely to be (V), for if the molecule of water had added elsewhere in the pteridine nucleus than across the 3 : 4-positions (or 1 : 4 in the case of the 3-methyl derivative) then 1- and 3-methyl-2-pteridone would form different chromophoric structures and probably would possess different ultraviolet spectra. Oxidation affords additional evidence that 2-hydroxypteridine hydrate has the structure (V; R = R′ = H), which is the dihydro-derivative of 2 : 4-dihydroxypteridine. Potassium permanganate converts it in good yield at 20° into 2 : 4-dihydroxypteridine, whilst 4-hydroxypteridine, which possesses no water of constitution, is not attacked by this reagent even at 100°.

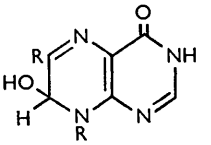
Structure (V) accounts for the weak, and nearly equal, acid strengths of 2-hydroxypteridine and its 1- and 3-methyl derivative (Table 1), for the acidity is due to the ureido-


(VII)


(VIII)


(IX)


(X)


(XI)

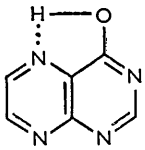
portion of (V), in which the $N_{(1)}$–H group might be expected to be nearly equivalent to the $N_{(3)}$–H group but slightly more acidic owing to the electron-withdrawing effect of the pyrazine ring. In the anions of 1- and 3-methyl-2-pteridone the 3- and the 1-nitrogen atom respectively carry a substantial negative charge, and the compounds no longer have the same chromophoric structure. Thus the ultraviolet spectra of the anions of 1- and 3-methyl-2-pteridone differ one from the other, and also from that of the anion of 2-hydroxypteridine (Table 1) which is probably a true phenoxide ion (see above), having lost the water of constitution.

4-Hydroxypteridine.—Two of the three possible *N*-methyl-4-pteridones (VII—IX; R = Me) have been prepared by the direct methylation of 4-hydroxypteridine, their

structures being confirmed by synthesis.[8,9] Attempted condensation of 5-amino-4-hydroxy-6-methylaminopyrimidine with glyoxal to provide the third isomer was not successful, but with diacetyl this pyrimidine yielded the homologue, 6 : 7 : 8-trimethyl-4-pteridone. Like the *N*-methyl-4-pteridones, this is not hydrated, though it is somewhat hygroscopic, and, unlike (VII) and (VIII), it is acidic and absorbs to a slight extent in the N–H stretching vibration region of the infrared unless it is thoroughly dried. However, the ultraviolet spectrum of 6 : 7 : 8-trimethyl-4-pteridone in neutral aqueous solution resembles that of the fully conjugated model chromophore, *N*-methyl-5-quinolone, in its qualitative features, but not those of 3-aminopyrazine-2-carboxyamide or 4 : 5-diamino-6-hydroxypyrimidine which are approximate model chromophores of the hydrated structures (X) and (XI) (Table 1).

Accordingly, 6 : 7 : 8-trimethyl-4-pteridone probably exists largely in the transannular pteridone form (IX), the acidity of the molecule arising from the union with a hydroxyl ion to give the anion of (X) or (XI). The high acid strength of the compound (pK_a 9·46), relative to that of the other *N*-methylpteridones, suggests that the resultant anion is probably that corresponding to structure (XI), for the latter is a derivative of 4 : 5-diamino-6-hydroxypyrimidine (pK_a 9·68), whilst a compound (X) is a derivative of 3-aminopyrazine-2-carboxyamide which has no acidic pK_a below 13.

4-Hydroxypteridine itself can exist to a considerable degree in the pteridone form, as it absorbs strongly in the C:O stretching vibration region of the infrared in the solid state, and so too does its 6 : 7-diethyl derivative [8] in chloroform solution. The latter compound in carbon tetrachloride solution gives rise to a single band (Table 2) in the N–H stretching vibration region, unlike the 2-hydroxy-isomer which gives two such bands, and this band lies in a range, 3370—3420 cm.$^{-1}$, which has been found to be characteristic of conjugated cyclic amides.*[2] In aqueous solution the ultraviolet spectrum of 4-hydroxypteridine resembles that of the conjugated cyclic amide (VII; R = Me), but not those of (VIII or IX; R = Me) (Fig. 2, Table 1). Some resemblances have been noted between the ultraviolet spectra of 4-hydroxypteridine and its *O*-methyl derivative,[8] and whilst these similarities are not so marked as those obtaining between the spectra of 4-hydroxypteridine and its $N_{(3)}$-methyl derivative, it is possible that an appreciable amount of the enol form (XII) exists in equilibrium with the predominant tautomer (VII; R = H). The enol form is presumably stabilised by intramolecular hydrogen bonding (XII), which is not possible with the other monohydroxypteridines. Attempts to estimate the ratio of the amounts of the isomers from the ultraviolet absorption curves of 4-hydroxypteridine and its *O*-methyl and $N_{(3)}$-methyl derivatives give results which are far from consistent at different wavelength values, and it can be concluded only that (VII; R = H) is the predominant tautomer.



(XII)

6-*Hydroxypteridine*.—The ultraviolet spectra of 6-hydroxy- and 6-methoxy-pteridine in neutral aqueous solution have been shown to be dissimilar,[4] and the former in the solid state absorbs strongly in the C:O stretching vibration region (Table 2), whilst the latter does not.[10] Thus 6-hydroxypteridine probably exists mainly in the amide form in aqueous solution and in the solid.

For valency reasons, anhydrous 6-hydroxypteridine can form only one amide structure, and thus only one *N*-methyl derivative. However, if the molecule of water bound to each molecule of 6-hydroxypteridine is constitutional, this restriction does not hold. Attempted preparation of 5-methyl-6-pteridone from 4-amino-5-methylaminopyrimidine and the hemiacetal of ethyl glyoxylate gave two products, each analysing as a hydrated "methylpteridone." One was formed by carrying out the condensation in neutral aqueous solution, the other in dilute mineral acid, and the former could be converted into

* From a study of some fifty *N*-heteroaromatic hydroxy-compounds, it has been found that those with the hydroxyl group α to a ring nitrogen atom show an N–H stretching vibration band at 3370—3420 cm.$^{-1}$, and those with a hydroxyl group γ to a ring nitrogen at 3420—3460 cm.$^{-1}$. The remainder, apart from those with an intramolecular hydrogen bond, show a band due to an O–H stretching vibration in the range 3590—3620 cm.$^{-1}$.

[10] Mason, *J.*, 1955, 2336.

the latter by treatment with dilute acid. Such behaviour is paralleled in the reaction between 4 : 5-diaminopyrimidine and ethyl glyoxylate, which gives mainly 7-hydroxypteridine under neutral conditions and the 6-isomer under acid conditions,[4] the former being converted into the latter by acid.[7]

Both of these hydrated " methylpteridones " are acids, though they are too weak (Table 1) to be carboxylic acids, and they both show negative tests for the aldehyde group with benzidine, so that they cannot possess ring-opened structures of the type derived by hydrolytic cleavage of 5-methyl-6-pteridone at the double bonds 5 : 6 or 7 : 8. The mode of formation of these " methylpteridones " suggests that they are *N*-methyl-6- and -7-hydroxypteridines. Valency considerations do not permit of a simple 5-methyl-7-pteridone, but the addition of a molecule of water of constitution to the pyrazine ring of the pteridine nucleus allows the formulation of the 7-hydroxypteridine derivative as (XIII). The hydrated " methylpteridone " formed under neutral conditions has ultraviolet spectra similar to those of 5 : 6-dihydro-7-pteridone, of which (XIII) is the

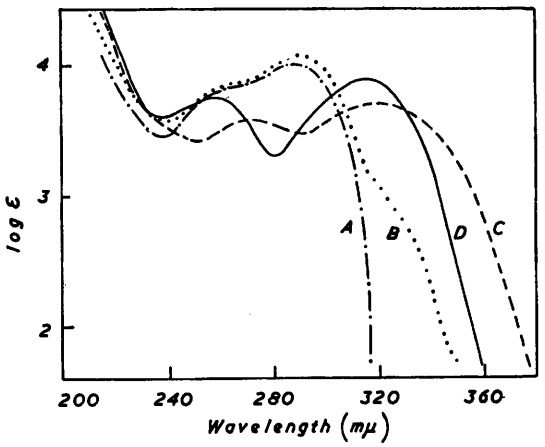
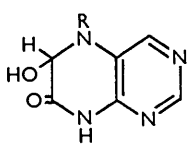
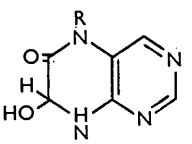


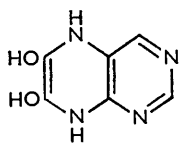
FIG. 3. *Neutral molecules of: A, 6-hydroxypteridine hydrate; B, 5-methyl-6-pteridone hydrate; C, 5 : 6-dihydro-7-hydroxypteridine; and D, 5 : 6-dihydro-6 : 7-dihydroxy-5-methylpteridine.*

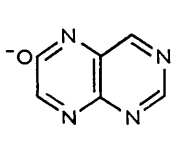
6-hydroxy-5-methyl derivative, whilst the hydrated " methylpteridone " formed under acid conditions has, in its neutral and cationic forms, ultraviolet spectra almost identical with those of the corresponding ionic species of 6-hydroxypteridine hydrate (Table 1, Fig. 3). Thus the hydrated " methylpteridone " formed under neutral conditions is taken to be 5 : 6-dihydro-6-hydroxy-5-methyl-7-pteridone (XIII; R = Me), and that formed under acid conditions to be 5-methyl-6-pteridone hydrate.

Both of these compounds were oxidised by potassium permanganate at 20° to 5 : 6 : 7 : 8-tetrahydro-5-methyl-6 : 7-dioxopteridine, which was also synthesised directly from 4-amino-5-methylaminopyrimidine and diethyl oxalate. Accordingly the water of


(XIII)


(XIV)


(XV)


(XVI)

constitution in 5-methyl-6-pteridone hydrate must be added across the 7 : 8-double bond of the pteridine nucleus, as in (XIV; R = Me). The 7 : 8-double bond in 6-hydroxypteridine is in general susceptible to additive attack. With sodium amalgam, 7 : 8-dihydro-6-hydroxypteridine is formed,[4] and hydroxylamine gives 7-amino-6-hydroxypteridine.[7] In view of the close similarity between the spectra of the cations and neutral molecules of 7 : 8-dihydro-6-hydroxypteridine, 6-hydroxypteridine hydrate, and 5-methyl-6-pteridone hydrate (Fig. 3, Table 1), it is likely that water is added across the 7 : 8-double bond in both of the latter cases, to give (XIV; R = H or Me). Structure (XIV; R = H) is the 7 : 8-dihydro-derivative of 6 : 7-dihydroxypteridine, and it is found that 6-hydroxypteridine is

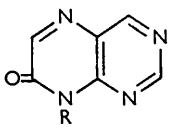
oxidised by potassium permanganate at 20° to 6 : 7-dihydroxypteridine, whilst 7-hydroxypteridine, which is not hydrated, is not attacked under these conditions.

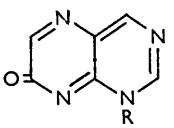
The possible ene-diol structure (XV) for 6-hydroxypteridine hydrate is in accord with many of the above observations, but it does not explain the sensitivity of the 7 : 8-bond of 6-hydroxypteridine to additive attack. Moreover, 6-hydroxypteridine does not give a blue colour with ferric chloride and ammonia and it does not reduce the E_0 indicator, alkaline dichlorophenolindophenol, tests which are specific for ene-diols.[11]

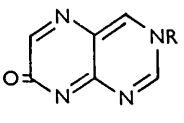
The hydrated structure (XIV; R = H) for 6-hydroxypteridine explains the hysteresis observed on the titration of the compound with alkali followed by back-titration with acid.[4] Freshly neutralised solutions of the anion of 6-hydroxypteridine give an ultraviolet spectrum (Table 1) different from that of the stable neutral molecule, though the spectrum reverts in a few minutes to that of the latter. Similarly, the spectrum of the stable anion of 6-hydroxypteridine is not observed until several minutes after a solution of the stable neutral molecule is made alkaline. The spectrum of the transient unstable anion of 6-hydroxypteridine appears to be similar to that of the stable neutral molecule, just as the spectra of the anion and neutral species of 5-methyl-6-pteridone hydrate resemble one another (Table 1), suggesting, in both cases, that the conjugated structures of the two ionic species are similar. On the other hand, the transient neutral molecule of 6-hydroxypteridine absorbs at a longer wavelength than the stable neutral molecule, indicating that the former possesses a more conjugated structure than the latter.

Evidence has been presented (see above) that the stable anion of 6-hydroxypteridine has the structure (XVI), with no water of constitution. The pK_a value (6·7) observed when this anion is titrated quickly with acid supports such a view, since the pK_a of the unhydrated 7-isomer is 6·41. The transient neutral molecule, retaining the full naphthenoid conjugation, is formed presumably by addition of a proton to the 5-nitrogen atom or the oxygen atom, but this conjugation is quickly lost upon the addition of a molecule of water, to give the stable neutral molecule (XIV; R = H). The latter is a weaker acid (pK_a 9·7) than the transient neutral molecule, as expected from the structures postulated, and under alkaline conditions the transient anion derived from (XIV; R = H) loses its water of constitution, to form the ion (XVI). Between pH 5·5 and pH 11 the molecule (XVI) and the ion (XIV; R = H) ($+H^+$) attain equilibrium, an equilibrium constant with pK 8·74 being calculated from the variation of the ultraviolet spectrum with pH.

7-Hydroxypteridine.—The ultraviolet absorption spectrum of 7-hydroxypteridine has been shown [4] to be similar to that of a *N*-methyl-7-pteridone, and the latter has been shown [9] to be 8-methyl-7-pteridone (XVII; R = Me). The spectrum of 7-methoxypteridine [12] differs from that of 7-hydroxypteridine, so the latter exists mainly in a


(XVII)


(XVIII)


(XIX)

pteridone form in aqueous solution. In the solid state 7-hydroxypteridine absorbs strongly in the C:O stretching vibration region (Table 2), whilst the sodium salt and the *O*-methyl derivative do not,[10] indicating that a pteridone form is preferred also in the solid phase.

Of the three possible pteridone forms (XVII—XIX; R = H), the first is the most likely, since the known transannular pteridones (IV and IX; R = R′ = Me) possess ultraviolet spectra which are very different from those of the simple amide pteridones (Figs. 1, 2; Table 1) and are similar in qualitative form to those of the corresponding *N*-methylquinolones (Table 1). The spectra of 1-methyl-7-quinolone and 1-methyl-6-*iso*quinolone, which have conjugated structures similar to those of (XVIII) and (XIX) respectively, show no qualitative resemblance to that of 7-hydroxypteridine, and in view

[11] Bendich and Clements, *Biochem. Biophys. Acta*, 1953, **12**, 462.
[12] Mason, ref. 6, p. 84.

of the close similarity between the spectra of 7-hydroxypteridine and 8-methyl-7-pteridone, the former may be said to exist largely in the form (XVII; R = H).

Experimental

Analyses were done by Mr. P. R. W. Baker, Wellcome Research Laboratories, Beckenham.

Ultraviolet Spectra.—These were measured with a Hilger Uvispek H700/305 Quartz Spectrophotometer. The buffer solutions were 0·01M-glycine (pH 1·5—3·5), 0·01M-acetate (pH 3·8—5·7), 0·01M-phosphate (pH 6·0—7·9 and 10·3—11·3), 0·01M-borate (pH 8·2—10·0), N- (pH 0) and 0·1N-hydrochloric acid (pH 1·0), and 0·1N- (pH 13) and 0·01N-potassium hydroxide (pH 12).

The spectra of the transient neutral molecule and anion of 6-hydroxypteridine were obtained by taking a freshly neutralised solution of the stable anion, or a solution of the stable neutral molecule made freshly alkaline, respectively, for each group of five readings at 5 mμ intervals, each group overlapping by one reading the group before and the group after. For the absorption maxima, fresh solutions were made up for each reading at 1 mμ intervals.

Infrared Spectra.—These were measured with a Perkin–Elmer model 12C spectrometer, incorporating a prism of lithium fluoride for the N–H and O–H stretching vibration region, and a prism of sodium chloride for the C:O stretching vibration region. The compounds were examined as solids included in pressed potassium bromide discs, or in chloroform or carbon tetrachloride solution, 1 cm. or 5 cm. cells respectively being used.

3 : 6 : 7-*Trimethyl-2-pteridone.**—4 : 5-Diamino-1 : 2-dihydro-1-methyl-2-oxopyrimidine[13] (0·7 g.) in boiling water (4 ml.) was mixed with diacetyl (0·5 ml.), and kept at 100° for 5 min. The solid (0·85 g.) was recrystallised from water (40 parts), giving colourless needles of 3 : 6 : 7-*trimethyl-2-pteridone hydrate* (0·65 g.). It shrinks at ~190° and melts at about 260° (decomp.) (Found, after drying at 120° : C, 51·8; H, 5·6; N, 27·1. $C_9H_{10}ON_4,H_2O$ requires C, 51·9; H, 5·8; N, 26·9%). When the hydrate was thrice recrystallised from ethanol (*ca.* 30 parts) the *ethanolate* was obtained as colourless needles (Found : C, 56·1; H, 6·85; N, 23·8. $C_9H_{10}ON_4,C_2H_5{\cdot}OH$ requires C, 55·9; H, 6·8; N, 23·7%), m. p. 163° on slow heating (lower if heated quickly). Either form, heated above 190° for 10 min., gave insoluble material resembling the product from 3-methyl-2-pteridone (see below).

6 : 7 : 8-*Trimethyl-2-pteridone.*—5-Amino-2-hydroxy-4-methylaminopyrimidine[13] (0·7 g.), water (3 ml.), and diacetyl (0·5 ml.) were kept for 5 min. at 100°. The product (0·9 g.) obtained on chilling recrystallised from water (110 parts) or ethanol (100 parts) as colourless needles of 6 : 7 : 8-*trimethyl-2-pteridone* (0·75 g.), m. p. 255—260° (decomp.) (dried at 130°) (Found : C, 56·7; H, 5·2; O, 8·6; N, 29·8. $C_9H_{10}ON_4$ requires C, 56·8; H, 5·3; O, 8·4; N, 29·45%). It dissolved in N-sodium hydroxide and at pH 7 was reprecipitated unchanged.

2-*Hydroxy*-6 : 7-*dimethylpteridine.*—Diacetyl (1 ml.) was added to 4 : 5-diamino-2-hydroxypyrimidine (1·25 g.) dissolved in boiling water (13 ml.) and kept on the water-bath for 30 min. After refrigeration, the solid (93%) was recrystallised (carbon) from water (80 parts), to give colourless needles (cf. Daly and Christensen[14]) of 2-hydroxy-6 : 7-dimethylpteridine hydrate, darkening above 200° (Found : C, 49·6; H, 4·7; O, 16·5. Calc. for $C_8H_{10}O_2N_4$: C, 49·5; H, 5·2; O, 16·5%).

Action of Heat on 3-*Methyl-2-pteridone.*—When kept at 230—240° for 30 min., 3-methyl-2-pteridone[9] gave a light brown residue almost insoluble in boiling water. Although insoluble in toluene or ethanol it was recrystallised from a mixture of these (1 : 1; 50 parts), giving a hygroscopic crystalline *product*, m. p. 285° (decomp.) [Found, for material dried at 150° : C, 51·7; H, 3·85; N, 34·2. $(C_7H_6ON_4)_x$ requires C, 51·85; H, 3·75; N, 34·55%]. Molecular-weight determination was precluded by insolubility in pure solvents, including camphor. It dissolved slowly in warm hydrochloric acid. When it was dissolved in warm 2·5N-sodium hydroxide, and the pH adjusted to *ca.* 6, 3-methyl-2-pteridone hydrate crystallised.

Action of Heat on 1-*Methyl-2-pteridone.*—When heated at 160—170°, 1-methyl-2-pteridone gave a *product* similar to the above, a white, hygroscopic amorphous powder, m. p. ~200°, from ethanol, insoluble in hot water (Found, for material dried at 110° : N, 32·85. $C_7H_6ON_4,\frac{1}{2}H_2O$ requires N, 32·7%).

6 : 7 : 8-*Trimethyl-4-pteridone.*—Diacetyl (0·25 ml.) was added to a hot solution of 5-amino-4-hydroxy-6-methylaminopyrimidine[13] (0·35 g.) in water (4 ml.). After 5 min. at 100° and chilling, the solid (0·3 g.) was filtered off and recrystallised (carbon) from ethanol (170 parts)

* See footnote on p. 3443.

[13] Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[14] Daly and Christensen, *J. Amer. Chem. Soc.*, 1956, **78**, 225.

(or from water), to give yellow needles (0·15 g.) of 6 : 7 : 8-*trimethyl*-4-*pteridone*, m. p. 235—242° (decomp.) (Found, after drying at 120° : C, 56·85; H, 5·4; N, 29·6%). It can be recovered unchanged from its solution in acid or alkali by pH adjustment.

5-*Methyl*-6-*pteridone Monohydrate* (7 : 8-*Dihydro*-7-*hydroxy*-5-*methyl*-6-*pteridone*).—Besides by the direct synthesis [9] this compound can be made by heating 5 : 6-dihydro-6 : 7-dihydroxy-5-methylpteridine (0·25 g.) with 2·5N-hydrochloric acid (5 ml.) at 100° for 1 hr. and adjusting the cooled solution to pH 6. The product (0·17 g.) was shown by its spectrum and chromatography to be identical with authentic material.

5 : 6-*Dihydro*-6 : 7-*dihydroxy*-5-*methylpteridine*.—4-Amino-5-methylaminopyrimidine [13] (1 g.) and ethyl glyoxylate ethyl hemiacetal (1·6 ml.) in water (12 ml.) were heated on the water-bath for 40 min. After chilling, the solid was recrystallised from water (80 parts), giving colourless needles (84%) of 5 : 6-*dihydro*-6 : 7-*dihydroxy*-5-*methylpteridine* (dried at 110°), m. p. 251—253° (decomp.) (Found : C, 46·9; H, 4·2; O, 17·9. $C_7H_8O_2N_4$ requires C, 46·7; H, 4·5; O, 17·8%).

7-*Hydroxy*-5-*methyl*-6-*pteridone*.—(a) *By oxidation of* 5 : 6-*dihydro*-6 : 7-*dihydroxy*-5-*methylpteridine*. This substance (0·25 g.) in water (10 ml.) at 60—70° was treated with 5% aqueous potassium permanganate (*ca.* 4·5 ml.) to a persistence of colour. This was discharged by addition of hydrogen peroxide, and the solution filtered and brought to pH ~4. The precipitate was recrystallised from water (45 parts), giving 0·16 g. of colourless 7-*hydroxy*-5-*methyl*-6-*pteridone monohydrate*, m. p. 247—249° (Found : C, 43·0; H, 4·1; N, 28·3. $C_7H_6O_2N_4,H_2O$ requires C, 42·85; H, 4·1; N, 28·55%). The anhydrous *compound* was obtained at about 180° (Found : C, 47·8; H, 3·2. $C_7H_6O_2N_4$ requires C, 47·2; H, 3·4%). Its m. p. was depressed on admixture with starting material.

(b) *By oxidation of* 5-*methyl*-6-*pteridone hydrate*. Oxidation as above gave 0·15 g. of the same product (mixed m. p.; chromatography).

(c) *By direct synthesis*. 4-Amino-5-methylaminopyrimidine [13] (0·25 g.) was heated with diethyl oxalate (2 ml.) for 6 min. at 175—180°. The cooled mixture was diluted with ethanol (0·5 ml.), and the solid filtered off, washed with ethanol (0·5 ml.), and dissolved in water (3 ml.). The solution was made just alkaline with sodium hydroxide and adjusted to pH 3—4 with acetic acid. Refrigeration and recrystallisation gave 0·05 g. of the same product (mixed m. p. and chromatography) as above. When dimethyl oxalate at 140° was used in the above synthesis, a *substance* was formed, crystallising from ethanol (20 parts) in colourless needles, m. p. 179° (decomp.) (Found, after drying at 140° *in vacuo* : C, 44·95; H, 5·4; N, 23·5. $C_9H_{14}O_4N_4$ requires C, 44·65; H, 5·8; N, 23·15%).

1 : 2 : 7 : 8-*Tetrahydro*-3 : 8-*dimethyl*-2 : 7-*dioxopteridine*.—5-Amino-1 : 2-dihydro-1-methyl-4-methylamino-2-oxopyrimidine [13] (0·8 g.) and ethyl glyoxylate ethyl hemiacetal (1·2 ml.) in water (12 ml.) were heated on the steam-bath for 1 hr. Refrigeration, followed by evaporation of mother-liquors to 3 ml., gave in all 0·7 g. of product. It was dissolved in water (110 ml.) and passed through neutral alumina (5 × 2 cm.). The solution was evaporated *in vacuo* to dryness and recrystallised from water (16 parts) (carbon), giving 0·45 g. of bright yellow needles of the *diamide*, m. p. 263° (decomp.), sparingly soluble in hot pentyl alcohol, pyridine, and *iso*butyl methyl ketone (Found : C, 49·85; H, 4·25; N, 29·15. $C_8H_8O_2N_4$ requires C, 50·0; H, 4·2; N, 29·15%).

Permanganate Oxidations.—The hydroxypteridine (0·25 g.) in 0·1N-sodium hydroxide (20 ml.) was treated with 5% potassium permanganate (*ca.* 5 ml.) at room temperature to a permanent coloration. After 20 min. excess of permanganate was destroyed with hydrogen peroxide, and the manganese dioxide filtered or centrifuged off. On adjustment of the filtrate to pH ~4—5, the product crystallised. Hot oxidations were done as for 7-hydroxy-5-methyl-6-pteridone (60—70°) :

Pteridine	Product
2-Hydroxy	2 : 4-Dihydroxypteridine [a] (cold, 72%; hot, 76%)
4-Hydroxy	Unchanged (cold and hot)
6-Hydroxy	6 : 7-Dihydroxypteridine [a] (cold, 65%)
7-Hydroxy	Unchanged (cold); 6 : 7-dihydroxypteridine [b] (hot, 15%)
Unsubst.	4-Hydroxypteridine [a] (cold, 17%)

[a] Identified by infrared spectrum, chromatography, and solubility. [b] No unchanged starting material.

We thank Professor Adrien Albert for helpful discussion and criticism and Mr. E. P. Serjeant for the pH titrations.

Department of Medical Chemistry,
The Australian National University, Canberra. [*Received, March 12th*, 1956.]