812. *Pteridine Studies. Part III.* The Solubility and the Stability to Hydrolysis of Pteridines.*

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Two important correlations between structure and properties in the pteridine series are reported and discussed.

The introduction of OH, NH_2, and SH groups into pteridine (I) (which is highly soluble in water, hydrocarbons, and other organic solvents) greatly lowers the solubility in all solvents. Evidence is brought forward that this effect is due to unusually strong crystal-lattice forces operating through hydrogen-bonding.

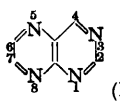
The insertion of one or (better) two electron-releasing groups into pteridine (which is readily decomposed by cold acids and alkalis) has a strong stabilizing effect. The instability of pteridine is attributed to loss of aromatic character caused by the high N : C ratio; the restoration of typical aromatic stability by OH and NH_2 groups is attributed to their ability to supply electrons to the depleted orbitals. As a practical application of this correlation, it is shown that 2-aminopyrazine-3-carboxylic acid and its derivatives can be prepared (by alkaline hydrolysis) from 4-hydroxypteridines under milder conditions than from the commonly used 2 : 4-dihydroxypteridines.

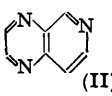
Syntheses of 2- and 4-methoxy-, 2-methylamino-, 4-dimethylamino-, 4-chloro-pteridine, 4-hydroxy-6- and -7-methylpteridine, and several 6 : 7-diethyl derivatives of hydroxy- and amino-pteridines are reported.

Ultra-violet spectra and ionization constants have been measured and correlated with structure.

Solubilities.—Insufficient attention has been paid to the decreased solubility conferred upon nitrogenous heteroaromatic substances by the insertion of amino-, hydroxy-, and thiol groups. These groups almost invariably increase the solubility in water of aliphatic and aromatic substances. For example, *m*-phenylenediamine is soluble in 1 part of water, whereas aniline and benzene (although both are liquids with no crystal-lattice forces to overcome) require 37 and 660 parts respectively. Again, 1 : 2 : 3-trihydroxybenzene requires 2 parts, 1 : 2-dihydroxybenzene 3 parts, and phenol 14 parts (all solubilities reported in this paper are for 20° unless otherwise specified).

That these groups can act in the opposite way upon heterocyclic substances was first demonstrated quantitatively in the acridine series, *e.g.*, all five monoaminoacridines are 2—5 times less soluble than acridine (Albert, "The Acridines," London, Edward Arnold and Co., 1951, pp. 152, 157). The hydroxyacridines are also less soluble than acridine. This insolubilizing effect increases as the number of amino- or hydroxy-groups is increased (4-hydroxypyridine, 1 : 1; 2 : 4-dihydroxypyridine, 1 : 160†). It also increases as the number of ring-nitrogen atoms is increased (*e.g.*, 2- and 4-hydroxy- and 2 : 4- and 4 : 6-dihydroxy-pyrimidines, 1 : 2·2,† 2·7,† 300,† and 400† respectively). This somewhat paradoxical insolubilizing effect of water-attracting groups operates even more strongly in the purine and the pteridine (I) series. The latter will now be discussed in detail.


(I)


(II)


(III)

Reference to the list of solubilities † in Table 1 shows that pteridine (No. 1) is highly soluble in water. The effect of one amino-group is to decrease the solubility 200-fold (Nos. 14—16) and of two amino-groups twice as much (No. 23). These, and the following comparisons, are made at 20° (the very high solubility of pteridine at 100° makes comparison more difficult at that temperature although the same trends are evident).

* Part II, *J.*, 1952, 1620. † New data.

The effect of one hydroxy-group is to decrease the solubility by a figure varying from 28- to 500-fold (Nos. 17—20). The effect of two hydroxy-groups is greater, varying from 100- to 700-fold (Nos. 24—27). The effect of hydroxy- is more dependent upon position than that of amino-groups, and a possible explanation will be discussed in the section on spectra, below. There appears to be a sharp rise in insolubility with three hydroxy-groups

TABLE 1. *Solubilities and melting points.*

No.	Pteridine derivative	Solubility in water 20° (±2°) 1 in	100° 1 in	M. p.	Source
1	(Unsubstituted)	7·2 †	1 ‡	140°	A
2	2-Dimethylamino	2·5 †	—	125	A
3	4-Dimethylamino	60	4	165	C
4	6-Dimethylamino *	?	—	212	B
5	2-Methoxy	80	4	150	C
6	4-Methoxy	80	9	195	C
7	6-Methoxy *	85	4	124	B
8	2-Chloro *	30	—	(dec. 106)	A
9	4-Chloro *	?	—	(dec. *ca.* 140)	C
10	6-Chloro *	80	—	(dec. 146)	B
11	3 : 4-Dihydro-4-keto-3-methyl	70	9	286	C
12	7 : 8-Dihydro-7-keto-8-methyl	50	10	125	B
13	2-Methylamino	320	35	219—220	C
14	2-Amino	1,350	100	(dec. 275)	A
15	4-Amino	1,400	80	(dec. 305)	A
16	6-Amino	1,500	110	(dec. 300)	B
17	2-Hydroxy (+1H_2O)	600	50	(dec. 240)	A
18	4-Hydroxy	200	29	>350	A
19	6-Hydroxy (+1H_2O)	3,500	230	(dec. 240)	B
20	7-Hydroxy	900	76	(dec. 230)	B
21	2-Mercapto (+1H_2O)	2,600	420	(dec. 210)	E
22	4-Mercapto	2,700	800	(dec. 290)	A
23	2 : 4-Diamino	3,000	130	(dec. 315)	C
24	2 : 4-Dihydroxy	800	120	(dec. 335)	A
25	4 : 6-Dihydroxy (+1H_2O)	5,000	300	(dec. 320)	D
26	4 : 7-Dihydroxy	4,000	600	>350	D
27	6 : 7-Dihydroxy	3,000	290	>350	B
28	4 : 6 : 7-Trihydroxy	27,000 †	7000	>350	D
29	2 : 4 : 6 : 7-Tetrahydroxy	58,000 †	—	>350	F
30	2-Amino-4-hydroxy	57,000 †	—	>350	G
31	4-Amino-2-hydroxy	14,000 †	1200	>350	C
32	2-Amino-4 : 6-dihydroxy (xanthopterin)	40,000 †	—	>350	H
33	2-Amino-4 : 6 : 7-trihydroxy (leucopterin)	750,000 †	—	>350	I
One alkyl substituent.					
34	4-Hydroxy-6-methyl	275	45	(dec. 345)	C
35	4-Hydroxy-7-methyl	225	35	(dec. >340)	C
36	4 : 7-Dihydroxy-6-methyl (+1H_2O)	800	65	>350	D
Two alkyl substituents.					
37	4-Hydroxy-6 : 7-dimethyl	1,100	100	>350	A
38	6 : 7-Diethyl	7	—	52	C
39	2-Amino-6 : 7-diethyl	5,400	—	(dec. 230)	C
40	4-Amino-6 : 7-diethyl	4,200	—	(dec. 240)	C
41	2-Hydroxy-6 : 7-diethyl (+1H_2O)	900	—	(dec. 230)	C
42	4-Hydroxy-6 : 7-diethyl	400	—	(dec. 245)	C
43	2 : 4-Diamino-6 : 7-diethyl	8,500	—	268	J
44	2 : 4-Dihydroxy-6 : 7-diethyl	1,100	—	217—219	C
45	2-Amino-4-hydroxy-6 : 7-diethyl	86,000 †	—	>350	C
46	4-Amino-2-hydroxy-6 : 7-diethyl	16,000 †	—	(dec. 290)	C
47	4-Hydroxy-6 : 7-diphenyl	5,000	—	295	C

* Substance hydrolysed by water, hence figure is only approximate. 6-Dimethylaminopteridine and 4-chloropteridine are hydrolysed too rapidly for measurement.

† Determined spectroscopically.

‡ 1 g. of pteridine is dissolved by less than 0·2 ml. of water at 100°.

Sources : A, Albert, Brown, and Cheeseman, *J.*, 1951, 474. B, *idem*, *J.*, 1952, 1620. C, Present paper. D, Forthcoming publication. E, Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553. F, Bertho and Bentler, *Annalen*, 1950, **570**, 127. G, Cain, Mallette, and Taylor, *J. Amer. Chem. Soc.*, 1946, **68**, 1996; recrystallized from water instead of formic acid. H, Elion, Light, and Hitchings, *ibid.*, 1949, **71**, 741. I, Totter, *J. Biol. Chem.*, 1944, **154**, 105. J, Kindly presented by Dr. N. R. Campbell (cf. Campbell, Dunsmuir, and Fitzgerald, *J.*, 1950, 2743).

(No. 28 is 3750-fold less soluble than pteridine). Finally, tetrahydroxypteridine (No. 29) is 8500 times less soluble than pteridine. The effect of thiol (Nos. 21—22) is even greater than that of amino- or hydroxy-groups in similar positions.

The presence of both an amino- and a hydroxy-group in the one molecule decreases solubility to a greater extent than in the corresponding homogeneously substituted molecules (compare Nos. 30 and 31 with 23 or 24; 33 with 29). Leucopterin (No. 33) is of extra interest in that the addition of four water-attracting groups to pteridine has had the effect of making it more than 100,000 times less soluble.

To explain these results the hypothesis is now advanced that crystal-lattice forces, of a strength uncommonly high for organic substances, are brought into play by hydrogen-bonding between the amino-, hydroxy-, and thiol groups on the one hand and the nitrogen atoms of the pteridine ring on the other. Thus, these very hydrophilic groups exert even more attraction for one another than they do for the molecules of water.

The weightiest evidence in support of this hypothesis comes from a study of *O*-methyl-, *N*-methyl-, and chloro-pteridines. These substituents, which are not capable of hydrogen-bonding, exert a comparatively small effect on solubility [compare the dimethylamino-pteridines (Nos. 2, 3) with the aminopteridines (14—16), or the methoxypteridines (Nos. 5—7) with the hydroxypteridines (17—20)]. Likewise, the ethylthiopteridines are much more soluble than the mercaptopteridines (Polonovski, Vieillefosse, and Pesson, *Bull. Soc. chim.*, 1945, **12**, 78). Even a water-repelling substituent like chlorine does not lower the solubility more than 10-fold (Nos. 8, 10). That the diminished solubility of hydroxypteridines does not depend greatly on their being in a special configuration (*i.e.*, keto as opposed to enol) is shown by the fact that examples of both configurations, stabilized by methylation, are highly soluble (contrast No. 11 with 18, No. 12 with 20, but note the similar solubilities of Nos. 11 and 6). Thus low solubility depends much more on the presence of a bondable hydrogen atom than on a particular tautomeric configuration.

Supporting evidence is that those pteridines which have hydrogen-bonding groups (NH_2, OH, SH) show a much reduced solubility in hydrocarbon solvents (cf. Boon, Jones, and Ramage, *J.*, 1951, 96). Pteridine and the chloro-, methoxy-, and dimethylamino-pteridines dissolve in 40 parts or less of boiling benzene and can suitably be recrystallized from light petroleum, but hydrocarbon solvents do not dissolve any demonstrable amount of the amino-, hydroxy-, or mercapto-pteridines. This lack of solubility in hydrocarbon solvents indicates that the hydrogen-bonding pteridines are very highly associated.

A tendency for pteridines with hydrogen-bonding substituents to have higher melting points can be seen in Table 1, which is what would be expected where crystal-lattice forces are abnormally strong. In this connexion, it is interesting to compare pteridine (No. 1; m. p. 140°) first with the dimethylamino- and methoxy-pteridines (Nos. 2—7), which melt between 124° and 212°, and then with those pteridines having one or more hydrogen-bonding groups (Nos. 18, 27—33) which remain unmelted at 350°. A difficulty in making these comparisons arises from the fact that the majority of pteridines with only one electron-releasing group (hydroxyl, etc.) are moderately unstable (for reasons given below) and tend to decompose before the melting point is reached.

It is noteworthy that a secondary amine, 2-methylaminopteridine (No. 13), stands intermediate in solubility and melting point between the corresponding tertiary and primary amines (Nos. 2 and 14, respectively).

Normally, alkyl groups decrease the solubility of pteridines, as can be seen by comparing No. 18 with Nos. 34, 35, 37, 42, 47; No. 17 with 41; No. 14 with 39; No. 15 with 40; No. 23 with 43; No. 24 with 44; No. 30 with 45; No. 31 with 46. A striking exception is 4 : 7-dihydroxy-6-methylpteridine (No. 36) which is more soluble than 4 : 7-dihydroxypteridine (No. 26), apparently because the 6-methyl group interferes sterically with the hydrogen-bonding by the neighbouring 7-hydroxy-group.

Alkyl groups tend to lower melting points (cf. Nos. 43 and 23; 44 and 24), an effect which increases with increasing paraffin chain length until the alkyl groups, rather than the hydrogen bonds, dictate the type of crystal lattice formed. Thus, as the series of 6 : 7-dialkyl-2 : 4-diaminopteridines is ascended, the melting point falls steadily to 132° at the di-*n*-heptyl member (Campbell, Dunsmuir, and Fitzgerald, *J.*, 1950, 2743).

Stability to Alkalis and Acids.—It is commonly believed that a high degree of chemical stability is characteristic of the pteridine series. This misconception arises from the remarkable stability of many naturally occurring pteridines. For example, xanthopterin (2-amino-4 : 6-dihydroxypteridine) is unaffected by boiling 7N-hydrochloric acid and almost unaffected by boiling 1·5N-barium hydroxide during 20 hours (Wieland and Schöpf, *Ber.*, 1925, **58**, 2178; Wieland and Purrmann, *Annalen*, 1940, **544**, 163). Leucopterin (2-amino-4 : 6 : 7-trihydroxypteridine) is practically unaffected by hot concentrated sulphuric acid during 2 hours at 150° (Wieland, Metzger, Schöpf, and Bülow, *Annalen*, 1933, **507**, 226).

However, pteridine itself is a highly unstable substance, rapidly attacked by dilute acids and alkalis, even at room temperature. The monoamino- and monohydroxy-pteridines are more stable, but only substances with two such electron-releasing groups can withstand a few minutes' boiling with N-sulphuric acid or N-sodium hydroxide. The results given in Table 2 were obtained by refluxing the pteridines with acid or alkali as described in the Experimental section. The ammonia set free was determined by titration and the percentage of material not decomposed was estimated by ultra-violet spectrophotometry, all the significant peaks of all the known ionic species of each substance being used, after adjustment to the appropriate pH values. (Tri- and tetra-hydroxypteridines, which do not lend themselves to separation into ionic species, were compared with the polyanionic spectra in 0·1N-sodium hydroxide.) Each spectroscopically determined decomposition figure recorded in Table 2 was calculated from the peak showing the greatest loss in density

TABLE 2. *The percentage decomposition of pteridines.*

(After 1 hour at 110°.) (A) From ammonia evolved; (B) from spectrophotometric estimation of unchanged material.

Pteridine derivative	N-H_2SO_4 (A)	N-H_2SO_4 (B)	N-NaOH (A)	N-NaOH (B)	10N-NaOH (A)	10N-NaOH (B)
(Unsubstituted)	*	74	57	53	‡	‡
2-Hydroxy-	5	55	7	7	5	89
4-Hydroxy-	*	60	73	57	94	80
6-Hydroxy-	<5	2	0	94	3	100
7-Hydroxy-	<9	52	15	31	50	76
2 : 4-Dihydroxy-	5	6	—	—	4	4
6 : 7-Dihydroxy-	5	7	—	—	4	12
4 : 6 : 7-Trihydroxy-	†	†	—	—	1	4
2 : 4 : 6 : 7-Tetrahydroxy-	†	†	—	—	6	6

* No figure can be quoted, because much ammonia is liberated by alkaline decomposition during steam-distillation.

† Apparently unaffected; however, the very sparing solubility of these substances in boiling N-sulphuric acid prevents a just comparison with the other substance.

‡ The formation of a large quantity of tar early in this reaction produced a non-homogeneous mass.

(compared with the corresponding peak in the corresponding species of untreated substance). Thus, 6 : 7-dihydroxypteridine, after alkaline decomposition, was examined at 249 and 301 mμ (as the neutral molecule at pH 4·00), at 268, 319, and 334 mμ (as the mono-anion at pH 8·40), and at 240, 324, and 338 mμ (as the dianion at pH 11·95). The percentage not decomposed appeared to be 89·9, 89·6, 100, 88·5, 87·7, 91·0, 89·8, and 90·4% respectively. Because the lowest of these figures is 87·7, the decomposition is given as 12% in Table 2. This examination of a number of peaks, and species, was designed to minimize error due to the possibility of the decomposition product(s) having some peaks at wave-lengths neighbouring on those of the starting material. A comparison of the results obtained by the two methods in Table 2 indicates that only in the case of 4-hydroxypteridine is more than one molecule of ammonia evolved per molecule of pteridine: on the other hand profound decomposition is seen in several cases without loss of nitrogen.

To explain the results in Table 2, the hypothesis is advanced that the instability of pteridine is due to the electron-attracting character of the four ring-nitrogen atoms. This leads to partial localization, on the nitrogens, of the ten π-electrons originating from the six carbon and four nitrogen atoms. Thus the aromatic stabilization to be expected from the presence of these π-electrons is much diminished (the possibility must even be enter-

tained that pteridine is, in consequence, non-planar). Substitution of the pteridine nucleus by electron-releasing groups apparently restores this deficit of electrons and thus permits normal aromatic stabilization. However, at least two such groups are necessary (Table 2) and their efficacy varies somewhat with the positions at which they are inserted.

In support of this hypothesis, the stability of other nuclei will be reviewed. Quinoline (with a N : C ratio of 1 : 9) is resistant to concentrated acid and alkali : it can be distilled over calcium oxide (Koenigs, *Ber.*, 1879, **12**, 97) and has been obtained (from aniline) in 90% yield in the presence of concentrated sulphuric acid at about 200° (Clarke and Davis, *Org. Synth.*, 1922, **2**, 79). *iso*Quinoline can be taken to dryness with 50% hydrobromic acid without decomposition (Bergstrom and Rodda, *J. Amer. Chem. Soc.*, 1940, **62**, 3030). Quinazoline (with a N : C ratio of 2 : 8) is more unstable, being slightly decomposed after evaporation at 100° with 10N-hydrochloric acid (Gabriel, *Ber.*, 1903, **36**, 800). No information is available for quinoxaline, but 2-methylquinoxaline behaves like quinazoline with hydrochloric acid (Böttcher, *Ber.*, 1913, **46**, 3085). Pyridino(3′ : 4′-2 : 3)pyrazine (II) (with a N : C ratio of 3 : 7) is described as rather unstable, particularly towards dilute acids (Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690). Thus the high degree of instability shown by pteridine (N : C ratio of 4 : 6) seems to be a natural extrapolation of this sequence.

If this hypothesis is correct, other 6-membered heterocyclic rings with high N : C ratios should also be unstable unless substituted with strongly electron-releasing groups. 1 : 3 : 5-Triazine (III) is such a structure, and it is noteworthy that no attempt to prepare it has yet been successful. 2 : 4 : 6-Trimethyl-1 : 3 : 5-triazine, which should be somewhat stabilized by the three methyl groups, is completely hydrolysed to ammonia by 2N-hydrochloric acid at 20° (Grundmann and Weisse, *Ber.*, 1951, **84**, 684). This behaviour stands in marked contrast to the stability of pyridine, pyrimidine, pyrazine, and their methyl derivatives. As would be expected, the corresponding trihydroxy-derivative of triazine (cyanuric acid) is extraordinarily stable : it resists N-potassium hydroxide at 100° and survives boiling with concentrated sulphuric acid (Fischer, *Ber.*, 1898, **31**, 3273; Chevallier and Lassaigne, *Ann. Chim.*, 1820, [ii], **13**, 160).

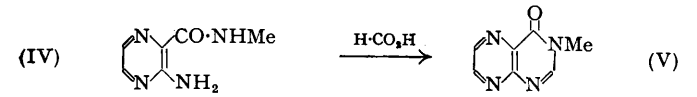
Amino-groups contribute to the stabilization of the pteridine nucleus to about the same degree as do hydroxy-groups. Furthermore the hydrolysis of amino- (and dimethylamino-) to hydroxy-compounds is itself repressed by the simultaneous presence of hydroxy-groups (see the examples of xanthopterin and leucopterin above, which stand in contrast to the easy deamination of monoaminopteridines). The stabilizing effect of amino- and hydroxy-groups is reflected in the resistance to thermal decomposition of substances containing 3 and 4 such groups (Table 1).

A small stabilizing effect from groups less powerfully electron-releasing than amino and hydroxy has been noticed. Thus 4-hydroxy-6- and -7-methylpteridine (Nos. 34, 35) require a slightly higher temperature (see below) for alkaline hydrolysis than does 4-hydroxypteridine (No. 18). 2-Amino-6 : 7-diethyl- and its 2-hydroxy-analogue (Nos. 39, 41) are not rapidly destroyed by cold 10N-hydrochloric acid or by boiling N-sodium hydroxide, but 2-amino- and 2-hydroxy-pteridine (Nos. 14, 17) are.

The outstanding stability of 6-hydroxypteridine to acid hydrolysis (Table 2) may indicate its conversion into a stable tautomer. It is noteworthy that this, alone of the monohydroxypteridines, shows hysteresis during titration (see Part II). 4-Hydroxypteridine and N-sulphuric acid gave 2-aminopyrazine-3-carboxyamide and the corresponding acid in a ratio of 1 : 2. 10N-Sodium hydroxide (at 110°) gave only 2-aminopyrazine-3-carboxylic acid. This acid is commonly prepared by heating 2 : 4-dihydroxypteridine with sodium hydroxide at 170° under pressure for 2 hours because the yield is trivial at 105° (Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802). Thus the stabilizing effect of the extra hydroxy-group is evident. 4-Hydroxy-6- and -7-methylpteridine (see below) were also readily hydrolysed by boiling 10N-sodium hydroxide (140°) to 2-amino-6- and -5-methylpyrazine-3-carboxylic acids, which, being known substances with definite melting points, enabled the positions of the methyl groups in these pteridines to be determined.

Preparation of Pteridines.—3 : 4-Dihydro-4-keto-3-methylpteridine (V) was prepared by

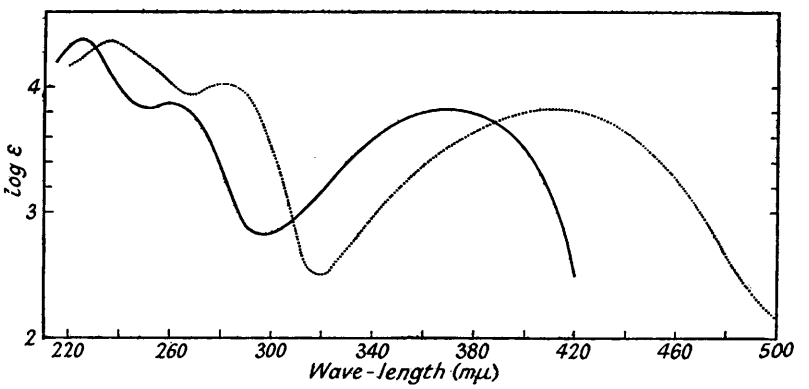
the action of formic acid on 2-aminopyrazine-3-carboxymethylamide (IV) (cf. the similar synthesis of 4-hydroxypteridine in Part I).



2- and 4-Methoxy-, 2-methylamino-, and 4-dimethylamino-pteridine were prepared by reaction of the appropriately substituted 5 : 6-diaminopyrimidines with solid polyglyoxal. Syrupy glyoxal in a neutral buffered solution was preferable for 4-chloropteridine which is more readily hydrolysed than its 2- and 6-isomers (described in Parts I and II). These conditions, applied to the synthesis of pteridine, at pH 6·5, 7·0, 7·5, and 8·0 gave a maximal yield (55%) at pH 7·0. When the synthesis of 4-chloropteridine was attempted in unbuffered methanol, a halogen-free substance was obtained, apparently glyoxylidenebis-(5-amino-4-hydroxy-6-methoxy-2-pyrimidine).

2-, 4-, and 6-Methoxypteridine were completely hydrolysed to hydroxypteridines by N-sodium hydroxide in 2 hours at 20°, or in 1 minute at the boiling point (with further

FIG. 1.



Absorption spectra in water of neutral molecules of:
———— 2-*Aminopteridine* (pH 7·1).
. . . . . 2-*Dimethylaminopteridine* (pH 7·1).

decomposition). The substance obtained in Part I by the action of perphthalic acid on pteridine in chloroform (provisionally described as pteridine *N*-oxide) has now been identified as 4-hydroxypteridine.

Methylglyoxal and 4 : 5-diamino-6-hydroxypyrimidine gave 4-hydroxy-7-methylpteridine when condensed in the presence of sodium sulphite, and 4-hydroxy-6-methylpteridine when sodium hydrogen sulphite was also present; neither product could be isolated from a reaction carried out in the absence of both these salts. The two isomers were oriented by degradation to known pyrazines.

Hexane-3 : 4-dione condensed with 4 : 5-diaminopyrimidine to give 6 : 7-diethylpteridine which has a far lower melting point (52°) than has yet been recorded for a pteridine. The dione also condensed with the appropriately substituted 4 : 5-diaminopyrimidines to give 2-(and 4-)amino-, 2-(and 4-)hydroxy-, 2 : 4-dihydroxy-, 2-amino-4-hydroxy-, and 4-amino-2-hydroxy-6 : 7-diethylpteridine. Benzil similarly gave 4-hydroxy-6 : 7-diphenylpteridine.

Spectra.—Sufficient monosubstituted pteridines are now known for preliminary investigation of tautomerism by ultra-violet spectra. The spectrum of the neutral molecule of 2-dimethylaminopteridine resembles that of 2-aminopteridine but occurs at longer wavelengths (Fig. 1). This is also true for the pair of 4- (Fig. 2) and 6-isomers (Fig. 5 of Part II), and is analogous to the shift dimethylaniline → aniline (Heertjes, Bakker, and van Kerkhof, *Rec. Trav. chim.*, 1943, **62**, 737). These results do not support an " imino "-configuration for the aminopteridines; further, recent *X*-ray crystallographic work has demonstrated the

primary character of the amino-group in 2-amino-4-methyl-6-chloropyrimidine (Clews and Cochran, *Acta Cryst.*, 1948, **1**, 4), 6-aminopurine (Broomhead, *ibid.*, p. 324), and 2 : 4 : 6-triamino-1 : 3 : 5-triazine (Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737; Knaggs and Lonsdale, *Proc. Roy. Soc.*, 1940, *A*, **177**, 140). Moreover, the primary character of 2-, 3-, and 4-aminopyridines has been demonstrated by infra-red spectroscopy (Goulden, *J.*, 1952, 2939).

It has been shown (Part II) that the spectrum of 7-hydroxypteridine resembles that of 7 : 8-dihydro-7-keto-8-methylpteridine (8-methyl-7-pteridone) (7-methoxypteridine is not

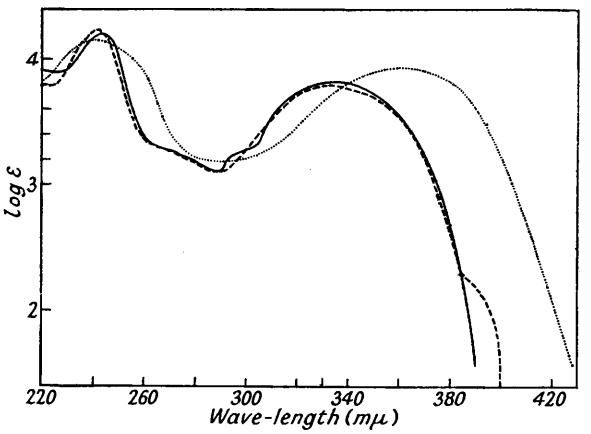


FIG. 2. *Absorption spectra in water of:*

———— 4-*Aminopteridine* (*neutral molecule*, pH 7·3).
. . . . . 4-*Dimethylaminopteridine* (*neutral molecule*, pH 7·1).
– – – – – – 4-*Hydroxypteridine* (*anion*, pH 10·0).

known). The spectrum of 4-hydroxypteridine resembles those of both 3 : 4-dihydro-4-keto-3-methylpteridine (3-methyl-4-pteridone) and 4-methoxypteridine (Fig. 4). However, Figs. 3 and 5 show that the spectra of 2- and 6-hydroxypteridines do not resemble those of their methoxy-analogues (aromatic hydroxy- and methoxy-compounds usually have almost coincident spectra; Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127). Thus 2- and 6-hydroxypteridines almost certainly have the pteridone structure; there is still insufficient evidence to indicate the

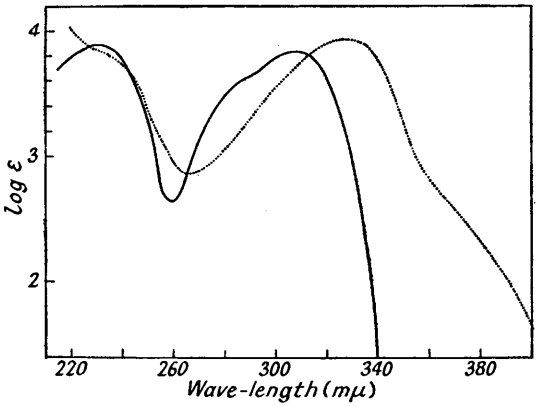


FIG. 3. *Absorption spectra in water of neutral molecules of:*

———— 2-*Hydroxypteridine* (pH 7·1).
. . . . . 2-*Methoxypteridine* (pH 6·4).

structure of the other two isomers. The unequal insolubilizing effect of hydroxy-groups (in contrast to amino-groups) in various positions in the pteridine ring (see Table 1) may be based, to some extent, on an unequal tendency to favour the " keto "-form : another factor may be hydrogen-bonding in solution between the 4-hydroxy-group and $N_{(5)}$.

The high degree of coincidence between the spectra of 4-aminopteridine (neutral molecule) and 4-hydroxypteridine (anion) is shown in Fig. 2. Similar pairs of curves were obtained for the 2-isomers (Part I) and the 6-isomers (Part II) (7-aminopteridine is unknown). Such relations are normal in aromatic compounds (Jones, *loc. cit.*) and suggest that the anions of 2-, 4-, and 6-hydroxypteridines are fairly normal too.

Other spectra, together with R_F and pH values, are given in Table 3 and should prove useful for identification. The spectra of the chloropteridines (see Part II, for 6-chloropteridine) closely resemble that of pteridine. An unexpected peak in 2-chloropteridine at 378 mμ led to a re-examination of the spectrum of pteridine (Part I) in *cyclo*hexane: an area of low intensity centred about 381 mμ (log ε = 1·93) was found.

Some anomalies in the spectra and ionization of amino-hydroxypteridines will now be discussed. The addition of a hydroxy-group to a hydroxypteridine has the expected

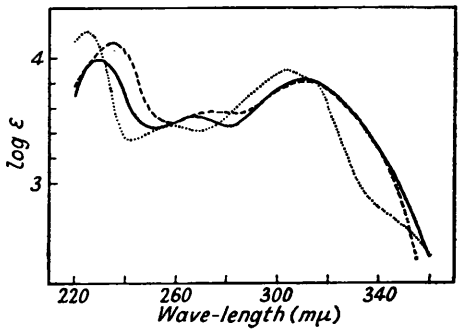


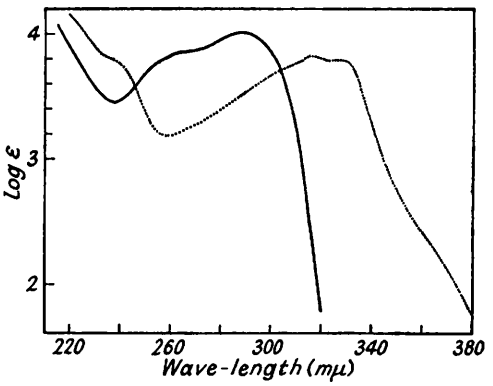
FIG. 4. *Absorption spectra in water of neutral molecules of:*

———— 4-*Hydroxypteridine* (pH 5·6).
. . . . . 4-*Methoxypteridine* (pH 5·7).
– – – – – – 3 : 4-*Dihydro-4-keto-3-methylpteridine* (3-*methyl-4-pteridone*) (pH 5·3).

bathochromic effect (see Parts I and II for spectra of 2 : 4- and 6 : 7-dihydroxypteridine; other examples will be published in Part IV). However, in 4-amino-2-hydroxypteridine, the 2-hydroxy-group exerts a large hypsochromic effect on the cation of 4-aminopteridine (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2538); moreover, Table 3 shows that, in 2-amino-4-hydroxypteridine the 4-hydroxy-group has a strong hypsochromic effect on the neutral molecule of 2-aminopteridine, although not on the cation (see Part I for spectra of monosubstituted pteridines). These two aminohydroxypteridines also have anomalous pK_a values (Table 3). In 4-amino-2-hydroxypteridine, the hydroxy-group is unexpectedly

FIG. 5. *Absorption spectra in water of neutral molecules of:*

———— 6-*Hydroxypteridine* (pH 5·2).
. . . . . 6-*Methoxypteridine* (pH 5·8).



more acidic (9·97 instead of 11·13, as in 2-hydroxypteridine, Part I) but the strength of the amino-group is little changed. On the other hand, in 2-amino-4-hydroxypteridine, the strength of the hydroxy-group is unchanged, but the amino-group has become a much weaker base (2·31 instead of 4·29). The dihydroxypteridines are acids of about the same strength as the stronger of the two monohydroxypteridines from which they are derived (Parts I and II); moreover the only known diaminopteridine (Table 3) is a stronger base than the monoaminopteridines. Hence the examples of acid-strengthening and base-weakening in the aminohydroxypteridines indicate a far-reaching electronic redistribution apparently caused by cross-conjugation. The anomalous spectra support this view, which is of special interest in the case of 2-amino-4-hydroxypteridine, because all naturally occurring pteridines are derivatives of this substance [cf., for example, the abnormally low basic pK_a of xanthopterin (Table 3)].

TABLE 3. *Other physical properties of pteridines.*

Pteridine derivative	pK_a (in water) and concn. at which determined (20°)		R_F [c]	Spectrography in water: $\lambda_{max.}$ (mμ)	Spectrography in water: log $\epsilon_{max.}$ (mol.)	Spectrography in water: pH
2-Methoxy-	—	—	0·80	<220; 325	>4·02; 3·92	6·4
cation	2·13 (±0·09)	M/100	—	—	—	—
4-Methoxy-	—	—	—	225; 258; 304	4·25; 3·45; 3·89	5·7
,,	—	—	—	(226; 262; 301 + 306 + 313 + 319 [g]) [h]	4·17; 3·46; 3·84 + 3·90 + 3·76 + 3·74	—
cation	<1·5	M/30	—	—	—	—
6-Methoxy-	—	—	—	<220; 315 + 327 [g]	>4·14; 3·82 + 3·79	5·8
cation	3·60 (±0·03)	M/100	—	—	—	—
2-Methylamino-	—	—	0·80	229; 273; 388	4·36; 3·96; 3·82	6·5
cation	3·62 (±0·03)	M/100	—	—	—	—
4-Dimethylamino-	—	—	—	241; 362	4·15; 3·93	7·1
cation	4·33 (±0·05)	M/100	—	239; 344 + 347 + 356 [g]	4·19; 4·09 + 4·10 + 4·04	2·0
2-Chloro-	—	—	—	(<220; 302 + 308 + 314 + 322; [g] 378) [h]	>4·05; 3·86 + 3·96 + 3·93 + 3·97; 2·09	—
4-Chloro-	—	—	—	(220; 296 + 303 + 315 [g]) [h]	4·24; 3·86 + 3·92 + 3·82	—
2 : 4-Diamino-	—	—	0·45	—	—	—
cation (mono)	5·32 (±0·03)	M/500	—	—	—	—
cation (di)	<0·5	M/60 [a]	—	—	—	—
2-Amino-4-hydroxy-	—	—	0·40 [f]	270; 340	4·05; 3·76	5·25
cation	2·31 (±0·05)	2×10^{-5}M [b]	—	<220; 315	>4·1; 3·88	0
anion	7·92 (±0·05)	4×10^{-5}M [b]	—	251; 358	4·31; 3·83	13
4-Amino-2-hydroxy-	—	—	0·45	—	—	—
cation	3·21 (±0·09)	M/500 [a]	—	—	—	—
anion	9·97 (±0·03)	M/500 [a]	—	—	—	—
2-Amino-4 : 6-dihydroxy- (xanthopterin)	—	—	0·40 [d]	275; 385	4·12; 3·39	4·93
cation	1·6 (±0·1)	5×10^{-5}M [b]	—	245; 355	4·07; 3·82	(70% H_2SO_4)
anion (mono)	6·3	M/1000 [a]	—	—	—	—
anion (di)	9·23 (±0·04)	M/1000 [a]	—	255; 392	4·27; 3·85	13
4-Hydroxy-6-methyl-	8·19 (±0·02)	M/100	0·55 [e]	—	—	—
4-Hydroxy-7-methyl-	8·09 (±0·02)	M/100	0·50	—	—	—
2-Amino-4 : 6 : 7-trihydroxy- (leucopterin)	—	—	0·05 [f]	(240; 285; 340) [i]	4·20; 3·84; 4·02	13
2 : 4 : 6 : 7-Tetrahydroxy-	—	—	0·05 [f]	(236; 279 + 283 + 286; [g] 347) [i]	4·27; 3·90 + 3·90 + 3·90; 4·03	13
3 : 4-Dihydro-4-keto-3-methyl	<1·3	M/20	—	233; 276; 312	4·12; 3·57; 3·81	5·3

[a] Back-titrated. [b] Determined spectrographically. [c] In butanol–5N-acetic acid (2 : 1) by descending method, 4-hydroxypteridine (R_F = 0·50) being used as a control. When samples of paper contained heavy metals (as shown by their giving more than one spot with 4-hydroxypteridine) a small crystal of sodium sulphide was added to the solvent. Papers viewed in ultra-violet light of 254 mμ. [d] As ammonium salt. [e] Not visible in Wood's light (360 mμ) unless first irradiated at 254 mμ; the 7-methyl isomer is visible directly at either wave-length. [f] As sodium salt. [g] Fine structure. [h] In *cyclo*hexane to avoid hydrolysis. [i] Poly-anion.

Experimental

M. p.s are uncorrected. The yields of substances that lack a m. p. refer to the stage at which they became chromatographically homogeneous (on paper). Microanalyses were by Mr. P. R. W. Baker, Beckenham.

Solubilities.—Those recorded in Table 1 as " determined spectroscopically " were obtained from initially supersaturated solutions centrifuged for 24 hours after crystals had formed. The maxima of the ultra-violet spectra were compared with those of solutions of known strength. The error should not exceed appreciably that of the instrument, *viz.*, $\pm 1\%$. The other solubilities in Table 1 were determined by inspection, those at 100° being the least amount of water required to dissolve the solid, those at 20° being the least amount of water preventing deposition from a seeded solution. The error here is considered not to exceed $\pm 10\%$. The expression " 1 in 2·5 " means 1 g. in 2·5 ml. of final solution.

Decomposition by Alkali.—Each pteridine (0·001 mole) was heated under reflux with N(or 10N)-sodium hydroxide (10 ml.) at 110° for 1 hour, then steam-distilled in a Kjeldahl apparatus (at constant volume) for 20 minutes. The evolved ammonia was trapped in 0·1N-hydrochloric acid (25 ml.) and back-titrated (methyl-red) with 0·1N-potassium hydroxide (carbonate-free). (In the case of pteridine, which is slightly volatile in steam, this titration was performed potentiometrically, to an end-point of pH 6·0.) The contents of the distillation-flask were then diluted (after neutralization, where necessary) with an appropriate buffer solution to 10^{-4}M. The densities at wave-lengths known to be significant for the starting material, in its various ionic species, were then compared in the " Uvispek " ultra-violet spectrophotometer, of which the solvent cell contained an aqueous solution of the same amount of the same salts brought to the same pH.

Decomposition by Acid.—The pteridines (0·001 mole) were heated as above with N-sulphuric acid (10 ml.). The resulting solution (or suspension) was diluted to 50 ml., of which 25 ml. were transferred to a Kjeldahl apparatus. 10N-Sodium hydroxide (3 ml.) was added and the contents were steam-distilled (at constant volume) for 20 minutes, the evolved ammonia being trapped and back-titrated as above. Both the acidic and the distilled halves of the acid-decomposed solution were examined spectroscopically after preparation as described above. Where a significant difference in the destruction of the two solutions was revealed spectroscopically, it was concluded that alkaline decomposition had occurred during the steam-distillation and hence the titration of ammonia was omitted.

4-*Amino*-2-*methoxy*-5-*nitropyrimidine.*—To a solution from sodium (2·5 g.) in methanol (250 ml.) was added finely ground 4-amino-2-chloro-5-nitropyrimidine (10 g., recrystallized; Part I). The suspension was refluxed with occasional shaking for 90 minutes, then refrigerated overnight. The solid was filtered off, washed by grinding in a mortar with cold water (40 ml.), and dried at 120° (yield 8 g., 82%). A sample, recrystallized from *iso*amyl alcohol (20 parts), gave colourless long needles of 4-*amino*-2-*methoxy*-5-*nitropyrimidine* with m. p. 203—204° (recovery 90%) (Found : C, 35·5; H, 3·1; N, 33·0. $C_5H_6O_3N_4$ requires C, 35·3; H, 3·5; N, 32·95%).

4-*Amino*-6-*methoxy*-5-*nitropyrimidine.*—4-Amino-6-chloro-5-nitropyrimidine (6·5 g.; Boon, Jones, and Ramage, *J.*, 1951, 96) similarly gave 4-*amino*-6-*methoxy*-5-*nitropyrimidine* (5·4 g., 85%), m. p. 238—240° (from *iso*butyl methyl ketone) (Found : N, 32·65%).

4-*Amino*-2-*methylamino*-5-*nitropyrimidine.*—4-Amino-2-chloro-5-nitropyrimidine (9·4 g.; see Part I), ethanolic methylamine (33% w/w; 26 ml.), and ethanol (50 ml.) were heated at 100° for 1 hour. After cooling, the product was filtered off, washed with cold ethanol, and dried (yield 8·9 g., 97%). After two recrystallizations of a sample from amyl alcohol (50 parts, with carbon) (80% recovery each time) pale yellow needles of 4-*amino*-2-*methylamino*-5-*nitropyrimidine*, m. p. 226—228°, were obtained (Found : C, 35·5; H, 4·2; N, 41·2. $C_5H_7O_2N_5$ requires C, 35·5; H, 4·2; N, 41·4%). It is readily soluble in dilute hydrochloric acid, hot amyl alcohol, or chlorobenzene, less soluble in ethanol or water.

4-*Amino*-6-*dimethylamino*-5-*nitropyrimidine.*—Methanolic dimethylamine (14 ml. of 50% w/w solution), methanol (40 ml.), and 4-amino-6-chloro-5-nitropyrimidine (5 g.; Boon, Jones, and Ramage, *loc. cit.*) were heated at 100° for 1 hour. After slow cooling, the long fibrous needles were filtered off (4·5 g., 86%). After three recrystallizations from ethanol (30 parts) pale yellow needles of 4-*amino*-6-*dimethylamino*-5-*nitropyrimidine* were obtained, m. p. 159—161° (Found : C, 39·2; H, 4·6; N, 38·3. $C_6H_9O_2N_5$ requires C, 39·3; H, 4·9; N, 38·2%).

4 : 5-*Diamino*-6-*chloropyrimidine.*—4-Amino-6-chloro-5-nitropyrimidine (4·87 g.) in methanol (320 ml.) was shaken with Raney nickel in hydrogen until 2100 ml. had been absorbed. The

catalyst was filtered off and extracted with boiling methanol. The combined filtrates were taken to dryness. The residue was dissolved in water (120 ml.). This solution was treated with carbon, filtered, and cooled to 0°. 4 : 5-*Diamino-6-chloropyrimidine* was deposited as needles (82%), decomp. *ca.* 248° (Found : C, 33·4; H, 3·3; N, 38·95; Cl, 25·0. $C_4H_5N_4Cl$ requires C, 33·2; H, 3·5; N, 38·8; Cl, 24·5%).

2-*Aminopyrazine-3-carboxymethylamide*.—Methyl 2-aminopyrazine-3-carboxylate (2·0 g.) was shaken with aqueous methylamine solution (25%; 20 ml.) for 10 minutes at room temperature. After a further 30 minutes with occasional shaking, it was chilled for 2 hours and the crystalline material filtered off and dried at 100° (yield 1·7 g., 92%). After two recrystallizations from alcohol (10 parts) 2-*aminopyrazine-3-carboxymethylamide* was obtained as bright yellow needles, m. p. 132—134° (Found : C, 47·4; H, 5·1; N, 37·0. $C_6H_8ON_2$ requires C, 47·35; H, 5·3; N, 36·8%). It was readily soluble in hot water and in organic solvents including boiling light petroleum.

3 : 4-*Dihydro-4-keto-3-methylpteridine*.—2-Aminopyrazine-3-carboxymethylamide (1·6 g.), acetic anhydride (20 ml.), and formic acid (20 ml.) were refluxed for 2 hours, then distilled under vacuum, and the residue was recrystallized from water (12 ml.). The crystals were finely powdered, boiled with alcohol (10 ml.) for 5 minutes, and filtered hot. The insoluble portion was taken up in 200 parts of chloroform (carbon) and filtered. The chloroform was recovered and the residue, recrystallized from 9 parts of water, gave the 4-*pteridone* as creamy-white crystals (0·8 g., 47%), m. p. 286° (Found : C, 51·85; H, 3·6; N, 34·6. $C_7H_6ON_4$ requires C, 51·8; H, 3·7; N, 34·5%). It is decomposed by cold N-hydrochloric acid.

2-*Methoxypteridine*.—Finely powdered crude 4-amino-2-methoxy-5-nitropyrimidine (7 g.), suspended in methanol (150 ml.), was hydrogenated over Raney nickel at room temperature and pressure until about 2·8 l. of hydrogen were consumed (1 hour). The nickel was filtered off and washed with methanol (40 ml.). Dry polyglyoxal (2·9 g.; Part I) was refluxed with the filtrate and washings for 30 minutes. The solution was set aside at room temperature overnight, a small precipitate was discarded, and the filtrate evaporated *in vacuo* at 40° to dryness. The residue was extracted with boiling light petroleum (b. p. 80—100°; 4 × 250 ml.). After refrigeration of the extract, the yellow solid was filtered off (4 g., 52% based on the aminomethoxynitropyrimidine) and recrystallized from light petroleum (200 parts; 90% recovery), then from benzene (6 parts; 83% recovery), giving light yellow needles of 2-*methoxypteridine*, m. p. 149—151°. It is soluble in 35 parts of benzene at 20° and very soluble in cold alcohol (Found : C, 52·15; H, 3·6; N, 34·4. $C_7H_6ON_4$ requires C, 51·85; H, 3·7; N, 34·5%). 2-Methoxypteridine instantly gives a violet colour with cold 10N-hydrochloric acid and a blue colour in boiling 6N-sodium hydroxide.

4-*Methoxypteridine*.—4-Amino-6-methoxy-5-nitropyrimidine (4·7 g.) was suspended in methanol (200 ml.) with Raney nickel and hydrogenated (about 2 l.). The filtered solution was refluxed with polyglyoxal (1·8 g.) for 40 minutes, then evaporated to dryness in a vacuum at 40°. The powdered residue was extracted by refluxing benzene (2 × 100 ml.). The slime that was deposited on standing was filtered off and the filtrate evaporated to dryness in a vacuum (yield 3·4 g., 75%). Three recrystallizations from alcohol (32 parts; charcoal) gave white needles of 4-*methoxypteridine*, m. p. 195° (recovery 80% each time) (Found : C, 51·7; H, 3·65; N, 34·9%), soluble in about 250 parts of alcohol at 0°, and in 40 parts of boiling or 100 parts of cold benzene.

Hydrolysis of Methoxypteridines.—4-Methoxypteridine (0·16 g.; 0·001 mole) was shaken with cold N-sodium hydroxide (2 ml.) for 2 hours. The solution was brought to pH 4 with acetic acid and the liberated 4-hydroxypteridine (0·13 g.; 90%) filtered off. It was identical with specimens prepared by several other methods (see Part I). 2- and 6-Methoxypteridine behaved similarly.

2-*Methylaminopteridine*.—4-Amino-2-methylamino-5-nitropyrimidine (7·7 g.) was hydrogenated in methanol (250 ml.) over Raney nickel (3300 ml.). The nickel was removed and washed with methanol (100 ml.). Polyglyoxal (2·5 g.) was dissolved in the combined filtrates and the solution refluxed for 1 hour, concentrated, and cooled, giving a total yield of 61% of solid. This was recrystallized from alcohol (190 ml.) and then from water (140 ml.; carbon), giving 3·0 g. of 2-*methylaminopteridine*, m. p. 219—220°, as very bright yellow needles, more stable to light than 2-aminopteridine (Part I) (Found : C, 52·5; H, 4·2; N, 43·6. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·45%), soluble in about 45 parts of boiling alcohol and almost insoluble in benzene. The solution in cold 10N-hydrochloric acid becomes purple in 10 minutes. Boiling 2·5N-sodium hydroxide produces a green colour in 2 minutes.

4-*Dimethylaminopteridine*.—4-Amino-6-dimethylamino-5-nitropyrimidine (3 g.) in methanol (150 ml.) was hydrogenated over Raney nickel at room temperature and pressure (1200 ml.).

The nickel was filtered off, and the filtrate was refluxed with polyglyoxal (1·2 g.) for 30 minutes. After evaporation in a vacuum at 40—45°, the residue was extracted with boiling *cyclo*hexane (3 × 200 ml.). The crystalline material was removed on cooling and the filtrate concentrated to 75 ml., to give a second crop of 4-*dimethylaminopteridine* (70% yield). Recrystallization from light petroleum gave pale yellow needles, m. p. 164—165°, soluble in 650 parts of boiling (and in approx. 4000 parts of cold) light petroleum (b. p. 60—80°), very soluble in water, alcohol, benzene, acetone, and chloroform (Found : C, 54·8; H, 4·8; N, 40·1. $C_8H_9N_5$ requires C, 54·85; H, 5·2; N, 40·0%). Boiling N-sodium hydroxide converts it into 4-hydroxypteridine.

4-*Chloropteridine*.—To 5 : 6-diamino-4-chloropyrimidine (2·15 g.), suspended in phosphate buffer (50 ml. of 1·5M; pH 7·0) at 60°, was added syrupy glyoxal neutralized with sodium hydroxide (2·0 g.; 50% w/w). The mixture was gently agitated until all the solid had gone into solution (about 7 minutes) and heated at 60° for 2 minutes longer. The solution was cooled to 20° and extracted with chloroform (7 × 25 ml.). The dried (Na_2SO_4) chloroform extracts were evaporated in a vacuum. The solid residue (0·57 g.) was extracted with light petroleum (b. p. 60—80°; 350 ml.), and the combined extracts were concentrated to 100 ml. On cooling, yellow needles of 4-*chloropteridine* (0·5 g., 20%) were deposited, decomposing about 140° when placed in a preheated bath (Found : C, 43·8; H, 1·65; Cl, 21·6. $C_6H_3N_4Cl$ requires C, 43·25; H, 1·8; Cl, 21·3%). 4-Chloropteridine darkens on exposure to light and gives a red colour on prolonged boiling in light petroleum.

Azomethine of Glyoxal and 5-*Amino*-4-*hydroxy*-6-*methoxypyrimidine*.—5 : 6-Diamino-4-chloropyrimidine (2·65 g.) and polyglyoxal (1·5 g.) were refluxed in methanol (45 ml.) for 1 hour. The solvent was evaporated in a vacuum and the residue extracted with light petroleum (b. p. 80—100°; 3 × 70 ml.). The filtrate, cooled to 0°, deposited 0·42 g. of yellow chlorine-free crystals. Crystallization from benzene (40 parts; charcoal) gave yellow plates, m. p. 168—169° (Found: C, 47·3; H, 4·0; N, 28·05. $C_{12}H_{12}O_4N_6$ requires C, 47·35; H, 4·0; N, 27·65%). This is consistent with the formulation *glyoxylidenebis*-(5-*amino*-4-*hydroxy*-6-*methoxy*-2-*pyrimidine*). The ultra-violet spectrum shows two well-separated peaks (λ_{max} 250 and 355 mμ; log ε 4·30 and 4·15 respectively). This spectrum resembles those of 1 : 4-diphenylbutadiene, cinnamaldehyde anil, and related substances described by Barany, Braude, and Pianka (*J.*, 1949, 1898). In view of the spectral interchangeability of $^-N=$ for $^-CH=$ and the bathochromic effects of OH and OMe demonstrated in the paper cited, the spectrum appears to be in good agreement with the formulation.

2 : 4-*Diaminopteridine*.—Crude 2 : 4-diaminopteridine (15 g.), prepared according to Mallette, Taylor, and Cain (*J. Amer. Chem. Soc.*, 1947, **69**, 1814), was suspended in water (200 ml.) at 40°, and 10N-sodium hydroxide (15 ml.) was added with stirring. The suspended solid, now much paler, was filtered off without cooling, washed with cold water, then with ethanol, and dried at 120° (recovery 8·6 g.). Three recrystallizations from boiling water (100 parts, with 0·5 part of carbon) gave 4·3 g. of small, bright yellow needles of chromatographically homogeneous 2 : 4-*diaminopteridine* (Found, after drying at 110° : C, 44·4; H, 3·7; N, 51·7. $C_6H_6N_6$ requires C, 44·4; H, 3·7; N, 51·8%).

4-Amino-2-hydroxypteridine was prepared according to Cain, Mallette, and Taylor (*ibid.*, 1949, **71**, 2538), but recrystallised from water.

4-*Hydroxy*-6-*methylpteridine*.—A mixture of commercial 30% methylglyoxal solution (48 ml.) and sodium hydrogen sulphite solution (*d* 1·34; 120 ml.) was added to a solution of 4-hydroxy-5 : 6-diaminopyrimidine (crude; 16 g.) and sodium sulphite (hydrated; 60 g.) in water (300 ml.) at 60°. The mixture was left at 25—30° for 12 hours. Hydrochloric acid (10N; 100 ml.) was then added and the mixture refrigerated. The resulting yellow complex was filtered off and washed with cold water and then with a little ethanol. When heated at 120° for 45 minutes, this complex lost sulphur dioxide and became grey (11·4 g., 56%). A paper chromatogram at this stage showed the presence of only a trace of the 7-methyl isomer. One recrystallization from water (45 parts; charcoal) gave 8·5 g. of faintly pink but almost pure 4-*hydroxy*-6-*methylpteridine*, free from the 7-isomer. Two further recrystallizations gave a colourless product, decomp. about 345° (Found : C, 52·25; H, 3·7; N, 34·6. $C_7H_6ON_4$ requires C, 51·8; H, 3·7; N, 34·5%).

4-*Hydroxy*-7-*methylpteridine*.—Methylglyoxal (20% solution; 48 ml.) was added to a solution of 4 : 5-diamino-6-hydroxypyrimidine (crude; 16 g.) and sodium sulphite (hydrated; 60 g.) in water (300 ml.) at 90°. The mixture was heated on a water-bath for 10 minutes, then slowly acidified to pH 2 with 10N-hydrochloric acid and cooled to 0°. The crystals were filtered off, washed, and recrystallized from water (9·6 g. of chromatographically homogeneous material). Two more recrystallizations from boiling water (35 parts, with carbon : 75% recovery) produced

long colourless needles of 4-*hydroxy*-7-*methylpteridine*, decomp. >340°, sparingly soluble in boiling amyl alcohol and almost insoluble in other common organic solvents (Found : C, 51·8; H, 3·4; N, 34·8%).

Alkaline Degradation of 4-*Hydroxypteridines*.—4-Hydroxy-7-methylpteridine (0·4 g.) was heated under reflux with 10N-sodium hydroxide (5 ml.) at 140° for 4 hours. Sulphuric acid was added to bring the pH to 2·5. The solution was evaporated and the dry residue was extracted with alcohol. The extract was taken to dryness and the residue was dissolved in one equivalent of alkali, decolorized with carbon, and adjusted to pH 2·5. The crystals which were deposited (70% yield) proved to be 2-amino-6-methylpyrazine-3-carboxylic acid [m. p. 210° (effervescence); cf. 211—212°, Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **167**, 802].

4-Hydroxy-6-methylpteridine (0·8 g.) was heated with 10N-sodium hydroxide (10 ml.) at 140° for 3 hours. The sodium salt which separated on cooling was filtered off and dissolved in hot water (3 ml.). The solution was taken to pH 2·3 with 5N-sulphuric acid and refrigerated, giving 2-amino-5-methylpyrazine-3-carboxylic acid (80%), m. p. 173° (cf. 171—172°, Mowat *et al.*, *ibid.*, 1948, **70**, 14). A mixed m. p. with the above isomeride gave 160°.

6 : 7-*Diethylpteridines*.—Except where otherwise stated the pyrimidine intermediates were prepared as in Part I (*loc. cit.*). 3-Hydroxyhexan-4-one was prepared according to Snell and McElvain (*Org. Synth.*, 1933, **13**, 26) and oxidized to hexane-3 : 4-dione with cupric acetate (Wegmann and Dahn, *Helv. Chim. Acta*, 1946, **29**, 111).

6 : 7-*Diethylpteridine*. 4 : 5-Diaminopyrimidine (0·5 g.; Brown, *J. Appl. Chem.*, 1952, **2**, 239) and hexanedione (0·6 g.) were refluxed in alcohol (10 ml.) for 30 minutes. The solvent was removed at 30—40° in a vacuum and the residue was thoroughly extracted with boiling light petroleum (b. p. 60—80°; 15 ml.). The filtered extract was concentrated to 3 ml.; on cooling, 0·45 g. (53%) of the pteridine crystallized. It was distilled (b. p. 106—108°/0·1 mm.) and gave pale yellow crystals of 6 : 7-*diethylpteridine*, m. p. 50—52° (Found : C, 63·85; H, 6·5; N, 29·8. $C_{10}H_{12}N_4$ requires C, 63·8; H, 6·4; N, 29·8%). Distillation of larger quantities gave poor recovery. It is readily soluble in water and all organic solvents. It slowly becomes pink, particularly in daylight.

2-*Amino*-6 : 7-*diethylpteridine*. Hexanedione (4·15 g.) was added to a warm solution of crude 2 : 4 : 5-triaminopyrimidine (5·5 g.) in water (90 ml.). The mixture was vigorously shaken and heated on the water-bath for 30 minutes with occasional shaking and then refrigerated. Filtration produced 6·0 g. (81%) of a yellow solid, which was recrystallized three times from alcohol (165 parts) with carbon (0·1 part), giving 2-*amino*-6 : 7-*diethylpteridine*, yellow plates, m. p. 230—234° (decomp.) (Found : C, 59·1; H, 6·6; N, 34·15. $C_{10}H_{13}N_5$ requires C, 59·1; H, 6·45; N, 34·45%). It is readily soluble in hot amyl alcohol (with steep temperature gradient), slightly soluble in cold chloroform, but almost insoluble in carbon tetrachloride. The R_F is 0·90 (see Table 3 for method).

4-*Amino*-6 : 7-*diethylpteridine*. Similarly, crude 4 : 5 : 6-triaminopyrimidine (4 g.) and hexanedione (3 g.) gave 4-*amino*-6 : 7-*diethylpteridine*, yellow prisms, decomp. *ca.* 240° (3·8 g., 71%) (from alcohol, 40 parts). It is slightly soluble in chloroform (Found : C, 59·15; H, 6·4; N, 34·0). The R_F is 0·90.

6 : 7-*Diethyl*-2-*hydroxypteridine*. Similarly, 4 : 5-diamino-2-hydroxypyrimidine (4·5 g.; Johns, *Amer. Chem. J.*, 1911, **45**, 79) and hexanedione (4 g.) gave 6 : 7-*diethyl*-2-*hydroxypteridine*, needles, m. p. 155—160° (from alcohol, 45 parts) (6·45 g.) (Found, for material dried at 120° : C, 57·8; H, 7·2; N, 22·35. $C_{10}H_{12}ON_4,C_2H_5{\cdot}OH$ requires C, 57·6; H, 7·25; N, 22·4%). It crystallized from water (100 parts) in tiny rosettes (decomp. about 230°) of the *monohydrate* (Found, for material dried at 80°/15 mm. : C, 54·2; H, 6·2; N, 25·4. $C_{10}H_{12}ON_4,H_2O$ requires C, 54·05; H, 6·35; N, 25·2%). It is slightly soluble in chloroform. The R_F is 0·95.

6 : 7-*Diethyl*-4-*hydroxypteridine*. 5 : 6-Diamino-4-hydroxypyrimidine (4·6 g.) similarly gave 6 : 7-*diethyl*-4-*hydroxypteridine*, needles, m. p. 245° (from alcohol, 30 parts) (5·4 g., 73%), soluble in 20 parts of boiling alcohol and in 350 parts at 0°, slightly soluble in cold chloroform, benzene, or acetone (Found : C, 59·0; H, 5·8; N, 27·0. $C_{10}H_{12}ON_4$ requires C, 58·8; H, 5·9; N, 27·45%). The R_F is 0·85.

2-*Amino*-6 : 7-*diethyl*-4-*hydroxypteridine*. 2 : 5 : 6-Triamino-4-hydroxypyrimidine "bisulphite" (6 g.; Cain, Mallette, and Taylor, *J. Amer. Chem. Soc.*, 1946, **68**, 1998), water (120 ml.), and hexanedione (3 g.) similarly gave 3·5 g. (64%) of cream-coloured product. This was dissolved in cold water (250 ml.) containing sodium hydroxide (2 g.), and the solution stirred with charcoal for 10 minutes, filtered, and adjusted to pH *ca.* 5. The crystals were washed with warm water, dried at 120°, and recrystallized from pure dimethylformamide (200 parts), to give almost white needles of 2-*amino*-6 : 7-*diethyl*-4-*hydroxypteridine* which did not melt below 360°. It is insoluble

in all common solvents, very slightly soluble in boiling pyridine and 2-ethoxyethanol (with steep gradient) (Found: C, 54·5; H, 6·0; N, 31·75. $C_{10}H_{13}ON_5$ requires C, 54·8; H, 6·0; N, 31·95%). The R_F is 0·85.

4-*Amino*-6 : 7-*diethyl*-2-*hydroxypteridine*. 4 : 5 : 6-Triamino-2-hydroxypyrimidine sulphate (6·5 g.; Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3112) was dissolved in hot water (350 ml.) containing 5N-sulphuric acid (7 ml.). The solution reacted with hexanedione (3 g.) to give faintly yellow needles of 4-*amino*-6 : 7-*diethyl*-2-*hydroxypteridine*, decomp. about 290° (3·65 g.) (from alcohol, 130 parts), readily soluble in boiling amyl alcohol (with steep gradient) (Found: C, 55·0; H, 5·4; N, 31·55%). The R_F is 0·85.

6 : 7-*Diethyl*-2 : 4-*dihydroxypteridine*. 5 : 6-Diamino-2 : 4-dihydroxypyrimidine sulphate (5·2 g.; Bogert and Davidson, *J. Amer. Chem. Soc.*, 1933, **55**, 1667) was dissolved in hot water (130 ml.) containing sodium hydrogen carbonate (3 g.). Hexanedione (3 g.) was added and the reaction effected as before. The pH was adjusted to 2—3 before refrigeration; 3·9 g. (67%) of crystals with m. p. *ca.* 215° were deposited. Two recrystallizations from water (45 parts) gave pale yellow 6 : 7-*diethyl*-2 : 4-*dihydroxypteridine*, m. p. 217—219°, readily soluble in warm alcohol and slightly soluble in chloroform (Found: C, 54·4; H, 6·1; N, 25·2. $C_{10}H_{12}O_2N_4$ requires C, 54·5; H, 5·5; N, 25·45%). The R_F is 0·85.

4-*Hydroxy*-6 : 7-*diphenylpteridine*. To a solution of 4 : 5-diamino-6-hydroxypyrimidine (7·0 g.) in hot aqueous alcohol (70 ml.; 50% v/v) was added a hot solution of benzil (10·5 g.) in hot alcohol (350 ml.). The mixture was refluxed on the water-bath for 20 hours (12 hours gave only a 40% yield), refrigerated, and filtered. The crystals were thoroughly stirred with cold acetone (150 ml.) to remove benzil; the yield was 9·25 g. (62%). After recrystallization from *iso*amyl alcohol (85 parts; 90% recovery) cream-coloured needles of 4-*hydroxy*-6 : 7-*diphenylpteridine* were obtained; these softened at 265° and finally melted at 295°. It is slightly soluble in hot alcohol with a steep temperature gradient (Found: C, 71·85; H, 4·0; N, 18·7. $C_{18}H_{12}ON_4$ requires C, 72·0; H, 4·0; N, 18·65%). The R_F is 0·90.

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