207. *Pteridine Studies. Part XXIX.*[1] *The Methylation of 7-Amino- and 4,7-Diamino-pteridine.*

By D. J. Brown and N. W. Jacobsen.

Methylation of 7-aminopteridine gives a mixture of 1- and 3-methyl derivatives which are degraded for structural purposes to appropriate pyrazinealdehydes. 4,7-Diaminopteridine gives only 4(7)-amino-1,7(1,4)-dihydro-7(4)-imino-1-methylpteridine, the first iminopteridine to be isolated as a stable solid (free base). Remethylation of this (free) imine yields a 4-methylimino-derivative which is a unique example of direct extra-nuclear *N*-methylation in this series. The degradation of the imines, and the unambiguous syntheses of the products by way of 5-cyanomethylamino-pyrimidines are described. Ionization constants and ultraviolet spectra of the pteridines and other relevant compounds are recorded and discussed.

Treatment of 7-aminopteridine [2,3] (I; R = H, R′ = NH_2) with methyl iodide gave three products. Two were hydriodides of the isomers 1,7-dihydro-7-imino-1-methylpteridine (II) and 3,7-dihydro-7-imino-3-methylpteridine (III). The third was judged to be the pteridinium tri-iodide of (III) from the analytical figures, the dark red colour, and because, after treatment with silver chloride, its ultraviolet spectrum was identical with that of (III). The major products were identified as follows.

Methylation at N-5 was excluded by valency, so that there were only four possible structures for the two methylpteridines. The 8-methyl derivative (IV; R = NH) (expected by analogy [4–6]) was eliminated because acid or alkaline hydrolysis of each compound yielded neither the known 7,8-dihydro-8-methyl-7-oxopteridine [4,7] (IV: R = O) nor 5-amino-4-methylaminopyrimidine.[4,8] 7-Methylaminopteridine (I; R = H, R′ = MeNH), formed directly or by 8-methylation followed by a Dimroth rearrangement,[9] was also excluded by its unambiguous synthesis from 7-chloropteridine;[3] moreover its pK_a (2·56) differed markedly from those of the two unoriented methylpteridine hydroidides (pK_a values 8·3 and 6·8). Thus, the latter were, by elimination, the 1- and 3-methyl derivatives (II) and (III), but not necessarily respectively. They were finally orientated by their alkaline hydrolysis to hydroxypyrazine aldehydes whose constitutions were ascertained. The 1-methylpteridine (II) gave 2-formyl-5-hydroxy-3-methylaminopyrazine (V; R = Me, R′ = OH), and the isomer (III) gave 3-amino-2-formyl-5-hydroxypyrazine (V; R = H, R′ = OH). The structure of the second pyrazine was confirmed by its formation on hydrolysis of 3-amino-5-chloro-2-formylpyrazine, (V; R = H, R′ = Cl).[3] Hydrolysis of the isomer (III) at pH 4, produced 3,5-diamino-2-formylpyrazine (V; R = H, R′ = NH_2). All the aldehydes gave typical precipitates with dinitrophenylhydrazine reagent.

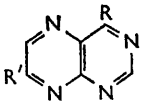
4,7-Diaminopteridine [10] (I; R = R′ = NH_2) and methyl iodide gave a single highly basic (pK_a 12·12) product, 4,(7)-Amino-1,7(1,4)-dihydro-7(4)-imino-1-methylpteridine (VI; R = H; or tautomer). In this it resembled other 4-aminopteridines.[5]

Although solutions of the imine in strong alkali were unstable ($t_{\frac{1}{2}}$ for degradation to 5-amino-2-carbamoyl-3-methylaminopyrazine was 70 sec. at pH 14·2 and 25°), it could be precipitated as a stable solid by adding cold alkali to a concentrated solution of its hydriodide. It was the first iminopteridine to be isolated as a free base. Furthermore, it could

[1] Part XXVIII, Albert and Clark, *J.*, 1965, 27.
[2] Albert, Brown, and Wood, *J.*, 1954, 3832.
[3] Albert and Clark, *J.*, 1964, 1666.
[4] Albert, Brown, and Wood, *J.*, 1956, 2066.
[5] Brown and Jacobsen, *J.*, 1960, 1978; 1961, 4413.
[6] Cheeseman, *Adv. Heterocyclic Chem.*, 1963, **2**, 222.
[7] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[8] Brown, *J. Appl. Chem.*, 1954, **4**, 72.
[9] Brown and Harper, *J.*, 1963, 1276.
[10] Osdene and Timmis, *J.*, 1955, 2036.

be methylated to give 7-amino-1,4-dihydro-1-methyl-4-methyliminopteridine (VI; R = Me; or tautomer), constituting the first example of direct extranuclear *N*-methylation in this series.

The structure of the amino-iminopteridine (VI; R = H) was proven by alkaline degradation to 5-amino-2-carbamoyl-3-methylaminopyrazine (X) which was unambiguously prepared by the following series of reactions.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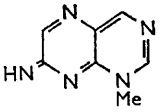
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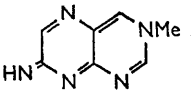
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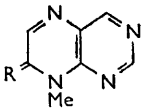
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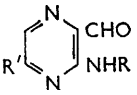
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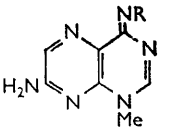
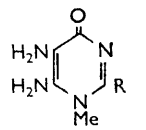

(VI)

4,5-Diamino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine [11] (VII; R = SH) was desulphurised with Raney nickel to give 4,5-diamino-3,6-dihydro-3-methyl-6-oxopyrimidine (VII; R = H). Rearrangement [12] during the treatment with nickel had not occurred because some of the diamine produced was converted with glyoxal into 1,4-dihydro-1-methyl-4-oxopteridine [4] (IX; R = H). Cyanomethylation [13] of the diamine (VII; R = H) gave 4-amino-5-cyanomethylamino-3,6-dihydro-3-methyl-6-oxopyrimidine (VIII; R = H) which, on treatment with alcoholic alkali followed by oxidation of the 7,8-dihydro-intermediate, gave 7-amino-1,4-dihydro-1-methyl-4-oxopteridine (IX; R = NH_2). On alkaline hydrolysis, this gave 5-amino-2-carbamoyl-3-methylaminopyrazine (X), identical with that from the pteridine (VI; R = H). In this reaction sequence, it was not possible to delay desulphurisation until immediately after cyanomethylation.

To confirm the structure of the pyrazine (X), it was still necessary to show that a Dimroth rearrangement [9] had not occurred during the formation or cyclisation of the cyanomethylamino-compound (VIII; R = H) to give instead the pyrimidine (XI; R = Me) or the pteridine (XII). In addition, if the latter had been formed, its subsequent rearrangement to the methylaminopteridine (I; R = OH, R′ = MeNH) had to be disproven. This was done by converting 5-amino-4-hydroxy-6-methylaminopyrimidine [14] into its cyanomethyl derivative (XI; R = Me) and cyclizing this to the 8-methylpteridine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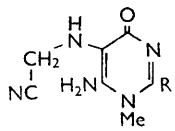
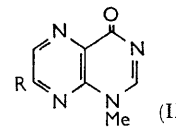

(VIII)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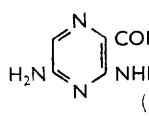
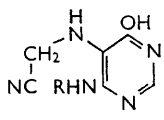

(X)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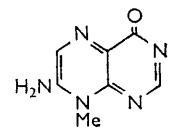

(XII)

(XII). Both compounds proved to be isomers of those postulated above as having the structures (VIII; R = H) and (IX; R = NH_2), respectively. Finally, neither of the pteridines postulated as (IX; R = NH_2) or (XII) was in fact the methylaminopteridine (I; R = OH, R′ = MeNH) because the first and second had negligible acidic properties (pK_a 14) whilst the last (yet unknown) would have an acidity approximating to the pK_a

[11] Traube and Winter, *Arch. Pharm.*, 1906, **244**, 11.
[12] Brown and Harper, *J.*, 1961, 1298.
[13] Blicke and Godt, *J. Amer. Chem. Soc.*, 1954, **76**, 2798.
[14] Brown, *J. Appl. Chem.*, 1955, **5**, 358.

8·9 of its homologue (I; R = OH, R′ = NH_2) made from 4-amino-5-cyanomethylamino-6-hydroxypyrimidine (XI; R = H).

The now proven structure of (VI; R = H) provides a basis for formulating the structure of its methylated derivative. Methylation on N-8 or quaternisation on N-5 was excluded because the dimethylpteridine was also hydrolysed by alkali to 5-amino-2-carbamoyl-3-methylaminopyrazine (X). Thus, it only remained to identify the dimethylpteridine as the methylimine (VI; R = Me) or as the quaternised N-3 pteridinium salt. The former was suggested by the similarity of its ultraviolet spectra to that of 7-amino-1,4-dihydro-4-imino-1-methylpteridine (VI: R = H; or tautomer), and this was confirmed by synthesis. 4,7-Dihydroxypteridine [15,16] (I; R = R′ = OH) was chlorinated to give 4,7-dichloropteridine (I; R = R′ = Cl). Monoamination gave a product identified as 7-amino-4-chloropteridine (I; R = Cl; R′ = NH_2) because it differed from the known 4-amino-7-chloropteridine [17] (I; R = NH_2, R′ = Cl). Methylamination then gave 7-amino-4-methylaminopteridine (I; R = MeNH, R′ = NH_2) which reacted with methyl iodide to give an hydriodide indistinguishable from that of the dimethylated product above, which must therefore be 7-amino-1,4-dihydro-1-methyl-4-methyliminopteridine hydriodide (VI; R = Me; or tautomer).

Ionization and Spectra.—The basic strength of a simple methylated iminopteridine is related both to the position of the methyl substituent and to the strength of the unmethylated base. Thus, the 1-methyl-4-iminopteridines are the strongest bases of the series, each having a pK_a value some 6 units above that of the corresponding unmethylated pteridine.[5] From the Table it can be seen that this is also true of 1,7-dihydro-7-imino-1-methylpteridine (pK_a 8·33; cf. 7-aminopteridine, pK_a 2·24) and of 7(4)-amino-1,4(1,7)-dihydro-4(7)-imino-1-methylpteridine (pK_a 12·12; cf. 4,7-diaminopteridine, pK_a 4·97). 3,7-Dihydro-7-imino-3-methylpteridine (III) is the only reported example of a 3-methylated iminopteridine. Although it is a markedly weaker base, pK_a 6·82 (cf. parent pteridine 2·24), the effect of 3-methylation (4·5 units) is between that of 1-methylation (*v.s.*) and that of 8-methylation previously reported [5,18] as 2·5—3·5 units.

The basic strength of a methylated amino-hydroxypteridine is dependent on other factors. Thus 7-amino-4,8-dihydro-8-methyl-4-oxopteridine (XII), pK_a 6·3, is a far stronger base than its 1-methyl isomer (IX; R = NH_2), pK_a 2·38, and so too is 2-amino-4,8-dihydro-8-methyl-4-oxopteridine (pK_a 5·42) in comparison with its 1-methyl- (pK_a 2·83) and 3-methyl-isomers (pK_a 2·25).[5] It seems that the 8-methylated compounds are stronger bases because, on protonation, they gain a measure of aromatic-type stability from extreme resonant forms in which the charge resides at N-8. In contrast, the 1- and 3-methyl isomers already have much of this aromatic resonance as neutral molecules and therefore gain little by protonation. In addition, or alternatively, covalent hydration in aqueous solution may be involved as a factor in these differences.

4-Amino-7-chloro- and 7-amino-4-chloro-pteridine are stable in aqueous solution over a wide range of pH. This, and their pK_a values (2·75 and 0·81, respectively) suggest that they are not covalently hydrated as are 6- and 7-chloropteridine (pK_a 4·22 and 3·79, respectively).[3] The 7-chloro-substituent lowers the basic strength of 4-aminopteridine (pK_a 3·56) by approximately 0·8 units, a change comparable with that produced when covalently hydrated pteridine (pK_a 4·79) [3] was similarly substituted in position 7. The greater change (1·4 units) observed in the pK_a value (0·81) of 7-amino-4-chloropteridine (cf. 7-aminopteridine, pK_a 2·24) suggests that the base-weakening chloro-substituent is then closer to the site of protonation (see below).

The ultraviolet spectrum of 7-methylaminopteridine (I; R = H: R′ = MeNH) differs significantly from the published spectrum of 7-aminopteridine (I; R = H; R′ =

[15] Albert and Brown, *J.*, 1953, 74.
[16] Pfleiderer, *Chem. Ber.*, 1959, **92**, 3190.
[17] Söll and Pfleiderer, *Chem. Ber.*, 1963, **96**, 2977.
[18] Brown and Jacobsen, *Tetrahedron Letters*, 1960, 17.

NH_2).[2] Repetition of the latter revealed that the spectrum of the neutral molecule was correct and the differences between it and the 7-methylamino-analogue were therefore real. However, it was soon apparent that the cation of 7-aminopteridine was far too unstable to be accurately determined by normal means. Accordingly it was redetermined at pH 0 using a rapid reaction technique,[19] and the new curve proved very similar to that of the more stable 7-methylaminopteridine. The pK_a value was also redetermined as 2·24 (cf.[2] 2·96). The time $t_{\frac{1}{2}}$, for the 7-aminopteridine to hydrolyse to 7-hydroxypteridine (I; R = H; R′ = OH) at 20° and pH 0 was 3·4 minutes; at pH 0·6 it was 9·0 minutes.

The cationic spectrum of 3,7-dihydro-7-imino-3-methylpteridine (III) is unlike that of

Ionisation constants* and spectra ($\lambda_{max.}$ in mμ)

Compound	pK_a	$\lambda_{max.}$ †	log ε †	pH
Pteridine derivatives				
7-Amino		228, 262, 334	4·26, 3·80, 4·03	5·1
cation	2·24 ± 0·02 (·01) ‡§	219, *230*, *300*, 328	4·28, *4·15*, *3·97*, *4·20*	0·0 **
7-Methylamino		223, *232*, 270, *278*, 343	4·19, *4·19*, 3·92, *3·88*, 4·05	4·8
cation	2·56 ± 0·04	215, *235*, *310*, 337	4·21, *3·91*, *4·03*, 4·14	0·2
1,7-Dihydro-7-imino-1-methyl				10·5 **
cation	8·33 ± 0·03	218, *222*, *233*, *260*, 349	4·24, *4·21*, *4·01*, *3·60*, 4·12	6·0
3,7-Dihydro-7-imino-3-methyl				9·0 **
cation	6·82 ± 0·03	215, *233*, 296, 335	4·22, *4·01*, 3·93, 4·17	4·6
4,7-Diamino		241, *254*, *263*, 339, *350*	4·38, *4·15*, *4·00*, 4·05, *3·97*	7·0
cation	4·97 ¶	233, 253, 258, 284, *335*, 342, *355*	4·12, 4·11, 4·11, 3·54, *4·00*, 4·03, *3·89*	2·0
7-Amino-4-methylamino		240, *259*, *267*, 346, *360*	4·34, *4·14*, *4·04*, 4·05, *3·94*	7·5
cation	5·11 ± 0·03 (·01) §	234, 258, *262*, 289, *296*, *340*, 351, *365*	4·17, 4·23, *4·21*, 3·78, *3·71*, *4·11*, 4·16, *4·02*	3·0
7(4)-Amino-1,4(1,7)-dihydro-4(7)-imino-1-methyl				14 **
cation	12·12 ± 0·03	237, 256, 261, 345, *360*	4·27, 4·22, 4·22, 4·15, *4·00*	9·8
7-Amino-1,4-dihydro-1-methyl-4-methylamino				14 **
cation	> 12	238, 259, 354, *368*	4·23, 4·25, 4·19, *4·08*	11·8
4-Amino-7-chloro		252, *280*, 348	4·21, *3·36*, 3·79	5·0
cation	2·75 ± 0·02	234—240, *272*, 338, *348*	4·04, *3·41*, 3·98, *3·93*	0·4
7-Amino-4-chloro		238, *262*, 339	4·27, *3·77*, 3·96	3·0
cation	0·81 ± 0·03	228, *238*, 340	4·14, *4·05*, 3·91	−1·5 **
7-Amino-1,4-dihydro-1-methyl-4-oxo		231, 248, *254*, 279, 340, *355*	4·36, 4·21, *4·18*, 3·57, 4·12, *3·95*	4·6
cation	2·38 ± 0·03	237, *243*, *288*, 293, 340	4·36, *4·33*, *3·92*, 3·92, 4·00	0·1
anion	> 14 **			
7-Amino-4,8-dihydro-8-methyl-4-oxo		220, *226*, 257, *261*, 286 296, 353	4·32, *4·22*, 3·90, *3·88*, 3·54, 3·56, 3·97	8·5
cation	6·33 ± 0·04 (·01)	219, *227*, 250, *258*, 283, 292, 340	4·33, *4·22*, 3·81, *3·73*, 3·65, 3·68, 4·00	4·0
anion	> 14 **			
7-Amino-4-hydroxy		230, *235*, 280, 288, 334	4·30, *4·30*, 3·74, 3·72, 3·95	5·0
cation	1·23 ± 0·04	*220*, 227, *239*, *283*, 290, 340	*4·23*, 4·25, *4·16*, *3·85*, 3·86, 4·00	−1·0
anion	8·87 ± 0·03	*228*, 235, *250*, 337	*4·33*, 4·35, *4·08*, 4·01	11·0

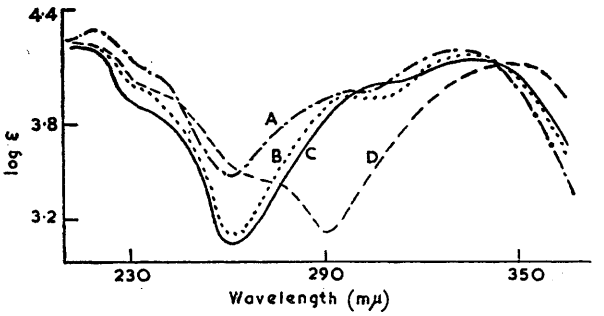
[19] Inoue and Perrin, *J. Phys. Chem.*, 1962, **66**, 1689.

TABLE (*Continued.*)

Compound	pK_a	$\lambda_{max.}$ †	log ε †	pH
Pyrazine derivatives				
5-Amino-2-carbamoyl-3-methylamino		213, 275, 363	4·26, 4·20, 4·11	4·8
cation	2·53 ± 0·05	275, 379	4·19, 4·24	0·2
3-Amino-2-formyl-5-hydroxy		*220*, 297, 341	*3·66*, 4·06, 4·24	4·2
anion	6·61 ± 0·01 (·005) §	215, 254, 289, 344	4·08, 3·87, 3·96, 4·27	8·8
2-Carbamoyl-5-hydroxy-3-methylamino		227, 277, 362	3·54, 4·21, 4·19	5·3
anion	7·48 ± 0·01 (·0025) §	211, 277, 355	4·28, 4·19, 4·12	9·7
2-Formyl-5-hydroxy-3-methylamino		232 301, 352	3·72, 4·03, 4·25	4·2
anion	6·44 ± 0·02 (·0025) §	218, 267, 289, 258	4·07, 4·03, 4·03, 4·21	8·8
3,5-Diamino-2-formyl		216, 258, 288, 353	4·14, 3·88, 4·03, 4·26	5·0
cation	1·57 ± 0·03	232, 293, 365	3·49, 3·99, 4·26	−1·0
Pyrimidine derivatives				
4-Amino-5-cyanomethylamino-3,6-dihydro-3-methyl-6-oxo		213, 268	4·39, 3·97	5·0
cation	2·83 ± 0·03 (·005) §	270	3·91	0·6
anion	>12			
4-Amino-5-cyanomethylamino-6-hydroxy		214, 267	4·36, 3·89	7·0
anion	9·79 ± 0·02 (·01) §	266	3·81	12·0
5-Cyanomethylamino-4-hydroxy-6-methylamino		221, 270, *284*	4·32, 3·96, *3·83*	5·3
cation	0·66 ± 0·03			
anion	9·90 ± 0·04 (·0025) §	219, 269	4·48, 3·88	12·1
4,5-Diamino-3,6-dihydro-3-methyl-6-oxo		212, 281	4·35, 4·04	6·4
cation	3·60 ± 0·02 (·005) §	209, 261, 285	4·33, 3·75, 3·82	1·4
anion	>14			

* Determined spectroscopically at 20° and 0·4 × 10^{-4}M except where otherwise indicated. † Inflexions in italics. ‡ This constant replaces original value given as 2·96 (ref. 2). § Determined potentiometrically at 20° (molarity given). ¶ From Albert, Lister, and Pedersen, *J.*, 1956, 4612. ** Species unstable at this pH.

its 1-methyl-isomer (II) but closely resembles those of 7-amino- and 7-methylamino-pteridine (see Fig.) indicating that each of the latter pair is probably protonated on N-3



Ultraviolet absorption spectra of cations of A, 7-aminopteridine; B, 3,7-dihydro-7-imino-3-methylpteridine; C, 7-methylaminopteridine; D, 1,7-dihydro-7-imino-1-methylpteridine.

(as has been suggested [3] for pteridine). Conversely, the cationic spectra of both 4,7-diamino- and 7-amino-4-methylamino-pteridine are very similar to those of their respective 1-methyl derivatives, from which it is concluded that they, like other pteridines [20] are protonated on N-1.

[20] Pfleiderer, Liedek, Lohrmann, and Rukwied, *Chem. Ber.*, 1960, **93**, 2015.

Experimental

Analyses were done by Dr. J. E. Fildes and her staff.

Methylation of 7-Aminopteridine.—7-Aminopteridine [2,3] (0·7 g.), methyl iodide (5 ml.), and methanol (5 ml.) were rocked at 100° for 40 min. Refrigeration gave yellow *3,7-dihydro-7-imino-3-methylpteridine hydriodide* (0·35 g.) which, recrystallized from methanol by concentration, decomposed *ca.* 250° (Found: C, 29·25; H, 2·8; N, 24·3. $C_7H_8IN_5$ requires C, 29·1; H, 2·8; N, 24·25%). The original mother-liquors were treated with charcoal and filtered. Evaporation to 3 ml. gave dark red crystals (0·1 g.) of *1,7-dihydro-7-imino-1-methylpteridinium tri-iodide*, m. p. 204° (decomp.) (from methanol with concentration) (Found: C, 15·8; H, 1·5; I, 69·5; N, 12·7. $C_7H_8I_3N_5$ requires C, 15·5; H, 1·5; I, 70·15; N, 12·9%).

Further evaporation of the original mother-liquors gave yellow-orange *1,7-dihydro-7-imino-1-methylpteridine hydriodide* (0·2 g.), m. p. *ca.* 195° (from ethanol with concentration) (Found: C, 29·05; H, 2·95; N, 24·05. $C_7H_8IN_5$ requires C, 29·1; H, 2·8; N, 24·25%).

3-Amino-2-formyl-5-hydroxypyrazine.—(*a*) 3,7-Dihydro-7-imino-3-methylpteridine hydriodide (0·25 g.) was heated in N-sodium hydroxide (10 ml.) at 100° for 1 hr. The solution, cooled and acidified to pH 2, deposited the *formylpyrazine* (0·1 g.), decomposing *ca.* 222° (from water) (Found: C, 42·9; H, 3·5; N, 29·95. $C_5H_5N_3O_2$ requires C, 43·15; H, 3·6; N, 30·2%).

(*b*) 3-Amino-5-chloro-2-formylpyrazine [3] (0·1 g.) was digested at 100° with N-sodium hydroxide (5 ml.) for 10 min. Treatment as above gave the formylpyrazine (0·06 g.), identified with that above by mixed m. p., chromatography, and infrared spectroscopy.

3,5-Diamino-2-formylpyrazine.—3,7-Dihydro-7-imino-3-methylpteridine hydriodide (0·2 g.), boiled in water (5 ml.) at pH 4 for 15 min., gave on cooling, the *diaminopyrazine* (73%), m. p. 245—247° (decomp.) (from water) (Found: C, 43·7; H, 4·5; N, 40·3. $C_5H_6N_4O$ requires C, 43·45; H, 4·4; N, 40·55%).

2-Formyl-5-hydroxy-3-methylaminopyrazine.—1,7-Dihydro-7-imino-1-methylpteridine hydriodide (0·25 g.) was degraded in alkali as above. Recrystallization from water gave the *methylaminopyrazine* (0·1 g.), m. p. 290—295° (decomp.) (Found: C, 46·8; H, 4·35; N, 27·0. $C_6H_7N_3O_2$ requires C, 47·05; H, 4·6; N, 27·4%).

7-Methylaminopteridine.—7-Chloropteridine [2,3] (1 g.) was refluxed in 10% ethanolic methylamine (18·6 ml.) for 5 min. The cooled mixture was filtered and the solid washed with 50% aqueous alcohol. The *pteridine* (82%) had m. p. 302—304° (decomp.) (from ethanol) (Found: C, 52·3; H, 4·4; N, 43·5. $C_7H_7N_5$ requires C, 52·15; H, 4·4; N, 43·45%).

Hydrolysis of 7-Aminopteridine.—The amine (0·28 g.) was shaken in N-hydrochloric acid (5 ml.) for ½ hr. The suspension was neutralised to pH 4, chilled, and the product (0·24 g.), m. p. 256° (from ethanol), collected. It was identified, (chromatography and infrared spectroscopy) as 7-hydroxypteridine [7] (Found: C, 49·1; H, 3·0; N, 37·6. Calc. for $C_6H_4N_4O$: C, 48·65; H, 2·7; N, 37·85%).

4(7)-Amino-1,7(1,4)-dihydro-7(4)-imino-1-methylpteridine.—4,7-Diaminopteridine [10] (3 g.), methanol (20 ml.), and methyl iodide (25 ml.) were rocked at 70° for 4 hr. Evaporation to a small volume and chilling afforded the *imine hydriodide* (93%). Recrystallised from water (4 parts), it had m. p. 270—272° (decomp.) (Found: C, 27·65; H, 3·1; N, 27·8. $C_7H_9IN_6$ requires C, 27·65; H, 3·0; N, 27·65%). The hydriodide (0·8 g.) in ice–water (45 ml.) was made alkaline with 10N-sodium hydroxide (5 ml.). The crystalline *imine* (80%) was washed with ice–water and ethanol (under nitrogen). It had m. p. *ca* 273° (decomp.) (Found: C, 47·6; H, 4·65; N, 47·45. $C_7H_8N_6$ requires C, 47·7; H, 4·6; N, 47·7%). The hydriodide (1·0 g.), refluxed in N-sodium hydroxide (10 ml.) for 30 min., gave 5-amino-2-carbamoyl-3-methylaminopyrazine (66%), m. p. 219°, identified with authentic material below.

4,5-Diamino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine.—4-Amino-3,6-dihydro-2-mercapto-3-methyl-5-nitroso-6-oxopyrimidine [11] (5 g.), suspended in water (30 ml.), was reduced on a steam-bath with sodium dithionite (*ca.* 8 g.). The solid (87%), recrystallised from water, had m. p. 258—259 (Traube and Winter [11] omit m. p. for material made by another method) (Found: C, 35·15; H, 4·7; N, 32·15. Calc. for $C_5H_8N_4OS$; C, 34·9; H, 4·7; N, 32·55%).

4-Amino-5-cyanomethylamino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine.—Sodium cyanide (1·25 g.) in water (5 ml.) was added to a suspension of 4,5-diamino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine hydrochloride [from the diamine (4·0 g.) and concentrated hydrochloric acid (2·3 ml.)] in methanol (10 ml.) at <30°. The suspension was adjusted to pH 5·5, warmed to 40° and treated with 37% aqueous formaldehyde (1·95 g.). After 1·5 hr., the *cyanomethylaminopyrimidine* (95%) was collected and recrystallised from water. It had

m. p. 230—232° (Found: C, 39·35; H, 4·75; N, 32·65. $C_7H_9N_5OS$ requires C, 39·8; H, 4·3; N, 33·15%).

4,5-Diamino-3,6-dihydro-3-methyl-6-oxopyrimidine.—4,5-Diamino-3,6-dihydro-2-mercapto-3-methyl-6-oxopyrimidine (6 g.), suspended in water (40 ml.), was heated at 80° for 10 min. with Raney nickel (18 g.). On concentration, the filtered solution deposited the *diamino-pyrimidine* (3·6 g.), m. p. 222—223° (from water) (Found: C, 42·85; H, 5·8; N, 39·65. $C_5H_8N_4O$ requires C, 42·85; H, 5·75; N, 39·95%).

The diamine (0·14 g.) was refluxed with glyoxal monohydrate (0·08 g.) in methanol (15 ml.) for 30 min. Evaporation gave a solid which was sublimed (180°/0·01 mm.) and recrystallised from isobutyl methyl ketone (400 parts) to give 1,4-dihydro-1-methyl-4-oxopteridine (0·09 g.), m. p. and mixed [4] m. p. 220—222°.

4-Amino-5-cyanomethylamino-3,6-dihydro-3-methyl-6-oxopyrimidine.—Cyanomethylation of 4,5-diamino-3,6-dihydro-3-methyl-6-oxopyrimidine (3 g.) as for the 2-mercapto-derivatives above, gave (after evaporation), an oil which when triturated with water (1 ml.), solidified to the *cyanomethylamino-derivative* (42%), m. p. 190—191° (from water) (Found: C, 46·9; H, 4·95; N, 38·85. $C_7H_9N_5O$ requires C, 46·9; H, 5·05; N, 39·1%).

7-Amino-1,4-dihydro-1-methyl-4-oxopteridine.—The above cyanomethylaminopyrimidine (1·3 g.) was stirred in methanol (24 ml.) containing potassium hydroxide (0·23 g.) for 18 hr. Ferrous chloride (0·02 g.) and 10% hydrogen peroxide (2·5 g.) were added. After 1 hr., the *oxopteridine* (0·9 g.), was collected, washed with water and ethanol, and recrystallised from water. It decomposed above 340° (Found: C, 47·15; H, 4·05; N, 39·3. $C_7H_7N_5O$ requires C, 47·45; H, 4·0; N, 39·55%).

5-Amino-2-carbamoyl-3-methylaminopyrazine.—The above oxopteridine (0·4 g.) was heated in N-sodium hydroxide (6 ml.) at 100° for 15 min. Chilling gave the *pyrazine* (0·25 g.), which was washed with a little water. It had m. p. 218—219° (from ethanol) (Found: C, 43·1; H, 5·4; N, 41·9. $C_6H_9N_5O$ requires C, 43·1; H, 5·45; N, 41·9%).

5-Cyanomethylamino-4-hydroxy-6-methylaminopyrimidine.—Concentrated hydrochloric acid (2·1 ml.) and a solution of sodium cyanide (1·05 g.) in water (4·9 ml.) were added separately to a suspension of 5-amino-4-hydroxy-6-methylaminopyrimidine [14] (2·9 g.) in methanol (70 ml.). After adjustment to pH 6·5. aqueous formaldehyde solution (37%; 1·75 g.) was added and the mixture was gently refluxed for 1 hr. (bath temp. 70°). The resulting *cyanomethylamino-derivative* (81%) had m. p. 211° (from water) (Found: C, 46·7; H, 5·15; N, 38·85. $C_7H_9N_5O$ requires C, 46·9; H, 5·05; N, 39·1%).

7-Amino-4,8-dihydro-8-methyl-4-oxopteridine.—The above cyanomethylaminopyrimidine (1·0 g.) was refluxed for 2·5 hr. in methanol (250 ml.) containing potassium hydroxide (0·18 g.). N-Hydrochloric acid (4 ml.) was added to the chilled solution, ferrous chloride (0·16 g.) and 10% hydrogen peroxide (2 g.) were added, and the mixture was refluxed for 30 min. The residue (0·62 g.) from evaporation was washed with water and methanol and recrystallised from water. The *oxopteridine* decomposed *ca.* 290° (Found: C, 47·5; H, 3·75; N, 39·0. $C_7H_7N_5O$ requires C, 47·45; H, 4·0; N, 39·55%).

4-Amino-5-cyanomethylamino-6-hydroxypyrimidine.—Prepared from 4,5-diamino-6-hydroxypyrimidine [21] (5·4 g.) as for the methylamino-homologue above, the *cyanomethylamino-pyrimidine* (5·2 g.) had m. p. 203—204° (from water) (Found: C, 43·55; H, 4·3; N, 42·4. $C_6H_7N_5O$ requires C, 43·65; H, 4·25; N, 42·4%).

7-Amino-4-hydroxypteridine.—The above pyrimidine (4·5 g.) and potassium hydroxide (0·83 g.) were refluxed in absolute methanol (750 ml.) for 24 hr. Ferrous chloride (0·74 g.) and 10% hydrogen peroxide (9·2 g.) were added, and the solution was again refluxed for 30 min. Evaporation gave a dark residue which was purified by dissolution in 0·5N-hydrochloric acid and reprecipitation at pH 5. The *pteridine* (0·93 g.), recrystallised from water (1000 parts), did not melt below 360° (Found: C, 44·55; H, 3·05; N, 42·75. $C_6H_5N_5O$ requires C, 44·15; H, 3·1; N, 42·95%).

7-Amino-1,4-dihydro-1-methyl-4-methyliminopteridine (*or tautomer*).—4(7)-Amino-1,7(1,4)-dihydro-7(4)-imino-1-methylpteridine (0·2 g.) was refluxed in a mixture of methanol (5 ml.) and methyl iodide (5 ml.) for 10 hr. Refrigeration gave the *methylimine hydriodide* (0·13 g.). A second crop (0·07 g.) was obtained on evaporation. Recrystallised from ethanol, it had m. p. 295—296° (decomp.) (Found: C, 30·3; H, 3·55; N, 26·15. $C_8H_{11}IN_6$ requires C, 30·2; H, 3·5; N, 26·4%). The hydriode (0·2 g.), hydrolysed in boiling N-sodium hydroxide (3 ml.)

[21] Albert, Brown, and Cheeseman, *J.*, 1951, 474.

for 15 min., gave 5-amino-2-carbamoyl-3-methylaminopyrazine (0·05 g.), identified (mixed m. p. 218—219°) with authentic material above.

4,7-*Dichloropteridine*.—4,7-Dihydroxypteridine [15,16] (1 g.) was refluxed in a solution of phosphorus pentachloride (2·6 g.) and pentachloroethane (100 ml.) for ½ hr. Evaporation *in vacuo* (0·1 mm./50°) and extraction of the residue with dry benzene (2 × 30 ml.) gave, on evaporation, a crude product (0·7 g.). Recrystallised from light petroleum (b. p. 60—80°), the *dichloropteridine* (0·23 g.) had m. p. 127—128° (Found: C, 36·7; H, 0·85; N, 27·85. $C_6H_2Cl_2N_4$ requires C, 35·85; H, 1·0; N, 27·85%).

7-*Amino*-4-*chloropteridine*.—4,7-Dichloropteridine (0·86 g.) and ammonia (0·21 g.) were stirred in ethanol (8·5 ml.) at 0—5° for 1 hr. The solid, collected, washed, and recrystallised from water, gave the *amino-chloropteridine* (0·48 g.), decomposing *ca.* 195° (Found: C, 39·6; H, 1·9; Cl, 19·55; N, 38·35. $C_6H_4ClN_5$ requires C, 39·7; H, 2·2; Cl, 19·55; N, 38·55%).

4-*Amino*-7-*chloropteridine*.—Prepared in 20% yield by the method of Soll and Pfleiderer,[17] the chloropteridine (recrystallised from benzene then water), decomposed *ca.* 204° (lit.,[17] decomp. from 60°) (Found: C, 40·0; H, 2·2; N, 38·55. Calc. for $C_6H_4ClN_5$ C, 39·7; H, 2·2; N, 38·55%).

7-*Amino*-4-*methylaminopteridine*.—7-Amino-4-chloropteridine (0·35 g.) and methylamine (0·18 g.) were refluxed in ethanol (1·1 ml.) for 15 min. The chilled product was collected, washed, and recrystallised with water (charcoal). The *methylaminopteridine* had m. p. 243—244° (Found: C, 47·6; H, 4·7; N, 47·7. $C_7H_8N_6$ requires C, 47·7; H, 4·6; N, 47·7%).

Methylation of 7-*Amino*-4-*methylaminopteridine*.—The pteridine (0·1 g.), methanol (1 ml.), and methyl iodide (1 ml.) were rocked together at 70° for 4 hr. The solution was evaporated, the residue extracted with water (5 ml.) and extract cleaned with charcoal. Evaporation gave 7-amino-1,4-dihydro-1-methyl-4-methyliminopteridine hydrioide (or tautomer) (0·08 g.), m. p. 295—296° (from ethanol with concentration) identical (mixed m. p., chromatography, and infrared and ultraviolet spectroscopy) with the hydriodide obtained above.

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