Pteridine Studies. Part V. The Monosubstituted Pteridines.*

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Several new monosubstituted pteridines are described, bringing the total of such substances to 35. Previous difficulties in the replacement of hydroxyl in 7-hydroxypteridine by other groups have now been overcome.

Several methylpteridines are found, unexpectedly, to be weaker bases than the parent substance. The employment of per-acids to introduce a hydroxyl group into the 4-position of pteridine (Albert, Brown, and Cheeseman, *J.*, 1952, 4219) has been extended and used to determine the position of the methyl group in 7-methylpteridine.

Monosubstituted pteridines are of fundamental importance in any attempt to link constitution with physical and biological properties and help in understanding the properties of naturally occurring pteridines. We now report the synthesis of 13 such substances, bringing the total to 35 (cf., *e.g.*, Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 1620, 4219) : all possible mono-amino-, -dimethylamino-, -chloro-, -methoxy-, and -hydroxy-pteridines are now known, and three each of the four possible mono-acetamido-, -mercapto-, -methylthio-, and -methyl-pteridines. The new substances, and some newly determined physical properties of known pteridines (Nos. 5, 22, 23, 25), are listed in the Table.

The methylpteridines were prepared by the action of glyoxal (Nos. 6, 7), methylglyoxal (No. 8), or diacetyl (Nos. 9, 10) on 4 : 5-diaminopyrimidine or its 2- or 6-methyl derivative. That No. 8 was 7(and not 6)-methylpteridine was shown by oxidation with perphthalic acid to 4-hydroxy-7-methylpteridine followed by hydrolysis of the latter to the known 2-amino-6-methylpyrazine-3-carboxylic acid (cf. Albert *et al.*, *loc. cit.*, p. 4219). Perphthalic acid has been used to convert pteridine into 4-hydroxypteridine (*idem, ibid.*), and a third example of this reaction is now provided by the similar oxidation with perbenzoic acid of 6 : 7-dimethylpteridine (No. 9) to 4-hydroxy-6 : 7-dimethylpteridine, identical with material prepared from 5 : 6-diamino-4-hydroxypyrimidine (Albert *et al.*, *J.*, 1951, 474).

Attempts to prepare 6-methylpteridine failed. In the reaction of 4 : 5-diaminopyrimidine and methylglyoxal, 7-methylpteridine was always obtained even in the presence of sodium hydrogen sulphite which had directed the methyl group to the 6-position in the similar synthesis of 4-hydroxy-6-methylpteridine (Albert *et al.*, *J.*, 1952, 4219). Neither hydrazine nor hydroxylamine influenced the orientation favourably. 4 : 5-Diaminopyrimidine has a pK_a of 6·0, but adjustment of the pH to 4 and to 8·5 to provide different ionic species gave no 6-methylpteridine. Other unsuccessful attempts include the reaction of 4 : 5-diaminopyrimidine with hydroxyiminoacetone or dichloroacetone. It was then hoped to synthesize a 6-methylpteridine having a group which could later be removed.

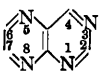
* Part IV, *J.*, 1953, 74.

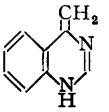
No.	Substance	Ionization [c] (H_2O; 20°) pK_a	spread ±	concn. (M)	Solubility in H_2O 20°	100°	Spectroscopy in water [f] $\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	pH
					1 in				
1	Quinazoline [a]	3·51	0·05	0·07	—	—	—	—	—
2	4-Methyl deriv.	2·52	0·02	0·07	—	—	—	—	—
3	Quinoxaline	0·72 [d]	0·10	0·1	—	—	—	—	—
4	2-Methyl deriv.	0·95 [d]	0·08	0·1	—	—	—	—	—
5	Pteridine [b]	—	—	—	7	—	230; 298 + 309 [g]	3·65; 3·87 + 3·83	6·1
	cation [b]	4·12	0·05	0·05	—	—	286 + 300	3·88 + 3·92	1·7
	Pteridines.								
6	2-Methyl	—	—	—	9	—	230 [h]; 305 + 317 [g]	3·68; 3·92 + 3·90	6·9
	cation	4·87	0·07	0·05	—	—	248; 285 + 301	3·59; 3·88 + 3·90	2·7
7	4-Methyl	—	—	—	20	—	240 [h]; 300 + 312	3·45; 3·92 + 3·86	6·1
	cation	2·94 [e]	0·13	0·05	—	—	306	3·99	1·0
8	7-Methyl	—	—	—	6	—	235 [h]; 298 + 310	3·50; 3·98 + 3·95	6·9
	cation	3·49	0·05	0·05	—	—	304	3·99	1·4
9	6 : 7-Dimethyl	—	—	—	17	—	235 [h]; 301 + 314	3·54; 4·02 + 3·98	6·0
	cation	2·93	0·04	0·05	—	—	260; 307	3·53; 4·05	1·0
10	2 : 6 : 7-Trimethyl	—	—	—	80	—	235 [h]; 307 + 320	3·74; 4·05 + 4·03	6·5
	cation	3·76	0·04	0·05	—	—	255; 307	3·65; 4·07	1·0
11	7-Chloro	[e]	—	—	45	—	220 [h]; 303 + 309 + 316	3·92; 3·97 + 3·95 + 4·01	7·0
12	7-Methoxy	—	—	—	50	4	313 + 302; 335 [h]	3·99 + 3·95; 3·32	7·0
	cation	1·64 [d]	0·05	0·02	—	—	220; 276; 299; 330 [h]	4·33; 3·80; 3·81; 3·64	−0·4
13	7-Mercapto	—	—	—	3100	900	230; 295; 386	3·83; 3·86; 4·13	3·1
	anion	5·50	0·04	0·002	—	—	259; 302; 390	3·89; 3·84; 4·10	7·9
14	2-Methylthio	—	—	—	320	40	242; 270; 360	4·18; 4·11; 3·84	5·5
	cation	2·2 [e]	—	0·01	—	—	—	—	—
15	4-Methylthio	—	—	—	1300	180	238 + 253; 283 [h]; 354	3·95 + 3·94; 3·44; 3·93	4·9
	cation	2·59	0·06	0·04	—	—	233; 335	3·97; 4·01	0·3
16	7-Methylthio	—	—	—	200	38	240; 266 [h]; 350	3·99; 3·75; 4·15	5·0
	cation	2·49	0·03	0·01	—	—	239; 278; 343	4·22; 3·65; 4·04	0·3
17	4-Methylthio-7-methyl	—	—	—	—	—	252; 289; 346	4·03; 3·56; 3·98	5·3
	cation	<2	—	0·02	—	—	—	—	—
18	4-Mercapto-7-methyl	—	—	—	—	1500	258; 384	4·11; 4·04	4·8
	anion	7·02	0·02	0·0006	—	—	—	—	—
19	7-Amino	—	—	—	1400	170	228; 262; 334	4·26; 3·80; 4·03	5·1
	cation	2·96	0·04	0·005	—	—	217; 326	4·25; 4·00	0·6
20	7-Acetamido	[e]	—	—	—	130	228; 252; 320	4·26; 3·74; 4·18	6·7
21	7-Dimethylamino	—	—	—	6	2	240; 279; 362—366	4·19; 3·98; 4·05	5·1
	cation	2·53	0·02	0·01	—	—	245; 310—314; 361	3·95; 3·96; 4·16	0·5
22	2-Acetamido	—	—	—	—	30	230; 253; 330	4·34; 4·02; 3·95	7·0
	cation	2·67 [e]	0·05	0·02	—	—	—	—	—
23	4-Acetamido	—	—	—	—	2	223; 275 [h]; 317	4·24; 3·55; 4·05	7·0
	cation	1·21 [d]	0·02	0·1	—	—	—	—	—
24	4-Hydrazino	—	—	—	450	70	230; 244; 356	3·99; 4·01; 3·77	6·5
	cation	4·00	0·05	0·005	—	—	235; 355	4·04; 3·95	1·3
25	4-Methoxy	—	—	—	—	—	—	—	—
	cation	1·04 [d]	0·04	0·033	—	—	—	—	—

[a] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [b] Albert *et al.*, *J.*, 1951, 474. [c] Determined by method of Albert *et al.*, *J.*, 1951, 474. [d] Because the pK's are low, these are reported, for greater accuracy, as thermodynamic constants (Davies's method, *J.*, 1938, 2093). [e] Sensitive to acids. [f] Determined with Hilger "Uvispek" photoelectric spectrophotometer (1-cm. cells). [g] Fine structure. [h] Shoulder.

However, 4-hydroxy-6-methylpteridine resisted chlorination with phosphorus halides, and attempts to prepare 4-mercapto-6-methylpteridine from methylglyoxal and 4 : 5-diamino-6-mercaptopyrimidine gave only the 7-methyl isomer (No. 18). In any event, 4-mercapto- and 4-methylthio-pteridine (used as models) gave no pteridine with Raney nickel. The action of methylmagnesium iodide on 6-chloropteridine, or on 6-hydroxypteridine in dibutyl ether (140°), was also unsuccessful. 4-Hydrazinopteridine (No. 24) was prepared by heating 4-methylthiopteridine (No. 15) with hydrazine. This, the first hydrazinopteridine, was used as a model for the removal of the hydrazino-group, but copper sulphate, potassium ferricyanide, and other mild oxidizing agents caused extensive decomposition.

The Table shows that the methylpteridines (except No. 6) are weaker bases than pteridine (I). The methyl group, because of its electron-releasing nature when substituted on a carbon atom, has almost invariably been found base-strengthening in heteroaromatic nuclei. For example, 2- and 4-methylpyridine are 0·8 pK unit stronger than pyridine, and 2 : 4-dimethylpyridine is stronger still (Bruehlman and Verhoek, *J. Amer. Chem. Soc.*, 1948, **70**, 1401); 4-methylpyrimidine is 0·7 unit stronger than pyrimidine (Albert, Goldacre, and Phillips, *J.*, 1948, 2240) and only strengthening effects have been found in the glyoxaline, purine, benziminazole, and pyrazole series (respectively, Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146; Albert and Brown, *J.*, 1954, 2060; Davies, Mamalis, Petrow, and Sturgeon, *J. Pharm. Pharmacol.*, 1951, **3**, 420; Dedichen, *Ber.*, 1906, **39**, 1831). The quinoline series has not been so well explored. Conductimetry has established that 2-methylquinoline is 0·7 unit stronger than quinoline (Goldschmidt and Salcher, *Z.*

(I) 

 (II)

physikal. Chem., 1899, **29**, 89). The other isomerides have not been examined by an accurate method, but 4-methylquinoline seems to show the expected base-strengthening effect (Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624; Golumbic and Orchin, *ibid.*, 1950, **72**, 4145).

Accordingly we have examined 4-methylquinazoline (No. 2), a simpler analogue of No. 7, and found a marked base-weakening effect, although 2-methylquinoxaline (No. 4), a simpler analogue of No. 8, shows base-strengthening.

*exo*Methylene tautomers, *e.g.*, (II), may be involved in these base-weakening effects. Such tautomers have been isolated in the quinoline series as intermediates in the reaction of the quaternary salts of 2- and 4-methylquinoline with aldehydes (Taylor and Baker in Sidgwick's "Organic Chemistry of Nitrogen," Oxford, 1937, pp. 557—561) and are described as highly reactive substances readily oxidized in air. The anomalously weak methylpteridines are easily oxidized by air to brown resins, whereas pteridine and 2-methylpteridine are stable if light is excluded. Attempts to condense these methylpteridines with benzaldehyde caused profound decomposition (the 4- and the 7-isomer were even resinified by 0·01 equivalent of piperidine in boiling alcohol).

Former difficulties in the preparation of 7-monosubstituted pteridines from 7-hydroxypteridine have now been overcome. Whereas 7-hydroxypteridine is rapidly converted into tar by boiling phosphorus oxychloride and the addition of phosphorus pentachloride only increases the rate of destruction, it is smoothly converted into 7-chloropteridine by long refluxing with a mixture of phosphorus penta- and tri-chloride (the latter is ineffective alone, the former gives only a poor yield when chloroform or toluene replaces the trichloride). 7-Chloropteridine rapidly polymerizes (apparently by self-quaternization) in concentrated solutions above 50°. It gave 7-methoxypteridine with sodium methoxide. A comparison of the four monochloropteridines showed that the 2-isomeride is by far the most stable to hydrolysis. 7-Methoxypteridine was quantitatively converted into the sparingly soluble sodium salt of 7-hydroxypteridine with cold N-sodium hydroxide.

Although 7-hydroxypteridine is readily destroyed by phosphorus pentasulphide (Albert *et al.*, *J.*, 1952, 1620) pyridine has been found to mitigate this effect, and an optimum temperature was found for conversion into 7-mercaptopteridine. 6-Mercaptopteridine

could not be prepared by this method, nor by the action of sodium hydrogen sulphide (or thiourea) on 6-chloropteridine, profound decomposition resulting.

7-, 4-, and 2-Methylthiopteridine and 7-methyl-4-methylthiopteridine were readily prepared by the action of methyl iodide on the corresponding mercaptopteridines in cold aqueous alkali. That the methyl group was attached to sulphur and not to nitrogen was shown by the liberation of methanethiol by boiling N-sulphuric acid. A further proof in the case of 7-methylthiopteridine is provided below. 2(and 4)-Methylthiopteridine were also prepared by the action of glyoxal on 4 : 5-diamino-2(and 6)-methylthiopyrimidine. A new synthesis of 4-mercaptopteridine (from 4 : 5-dimaino-6-mercaptopyrimidine) is reported, and is preferred to the former preparation from 2-aminopyrazine-3-carboxythioamide (Albert *et al.*, *J.*, 1951, 474). 6-Methylthiopteridine could not be prepared by the action of sodium methyl sulphide on 6-chloropteridine.

7-Methylthiopteridine was readily converted into 7-aminopteridine (with alcoholic ammonia) and into 7-dimethylaminopteridine (with methanolic dimethylamine). In the latter case it was important not to heat the mixture above 60°, to prevent alkaline destruction of the dimethylaminopteridine. 7-Acetamidopteridine was obtained by acetylation of 7-aminopteridine, and the opportunity was taken to examine the physical properties of the 2- and the 4-isomer (Albert *et al.*, *J.*, 1951, 474). The 7-isomer is by far the most sensitive of the three (Nos. 20, 22, and 23) to light and to dilute acid. 6-Aminopteridine was destroyed on attempted acetylation.

Some few general remarks about monosubstituted pteridines can now be made. It has been shown that pteridine, a highly unstable substance, is stabilized by the presence of two or more electron-releasing groups (Albert *et al.*, *J.*, 1952, 4219). The monosubstituted pteridines vary from being somewhat more stable than pteridine to somewhat less. It is to be expected that pteridines bearing substituents more electron-attracting than chlorine or methylthio will be particularly unstable, and so far we have been unable to prepare a mono-nitrile or -carboxylic acid. As regards solubility, the monosubstituted pteridines obey the general rule (*idem*, *ibid.*) that pteridines having hydrogen-bonding substituents (NH_2, OH, SH) are only sparingly soluble in water and almost insoluble in other solvents, whereas pteridines lacking such substituents are highly soluble in water and in lipophilic solvents.

The ionization constants of the amino- and methoxy-pteridines are low, like those of the methyl derivatives discussed above. The mono- and di-aza-naphthalenes undergo a considerable increase in basic strength when an amino-group is inserted in the position α or γ to a ring-nitrogen atom (Albert, Goldacre, and Phillips, *J.*, 1948, 2240). Yet, in the aminopteridines this effect is either lacking, or is actually reversed (cf. No. 5 with Nos. 19 and 21; for the remaining isomers see Albert, Brown, and Cheeseman, *locc. cit.*). Again, all four methoxypteridines are weaker bases than pteridine. Although the methoxyl group can be a little base-weakening in an aromatic ring (cf. *m*-anisidine which is 0·4 pK unit weaker than aniline), it is surprising that 4-methoxypteridine (No. 25) is no less than 3 units below pteridine. These results may imply that pteridine lacks a true aromatic structure, a hypothesis already suggested by the low chemical stability and attributed to the high ratio of doubly-bound nitrogen to carbon (Albert *et al.*, *J.*, 1952, 4219).

Experimental

The yields of substances that have no definite m. p. refer to the stage at which they became chromatographically homogeneous [ascending method on papers using (separately) aqueous ammonium chloride (3%), and butanol–5N-acetic acid (7 : 3)]. R_F values were determined by the descending method in butanol–5N-acetic acid (2 : 1), with picric acid (R_F 0·80) and 4-hydroxypteridine (R_F 0·50) as controls.

Microanalyses were by Mr. P. R. W. Baker, Beckenham.

4-Methylquinazoline was prepared by Elderfield and Serlin's method (*J. Org. Chem.*, 1951, **16**, 1669), quinoxaline by Platt's (*Nature*, 1946, **157**, 439), and 2-methylquinoxaline (b. p. 126—127°/18 mm.) by Böttcher's (*Ber.*, 1913, **46**, 3084) but with 20% methylglyoxal solution in place of hydroxyiminoacetone.

2-*Methylpteridine*.—Acetamidine hydrochloride (142 g.) and ethyl malonate (240 g.) were

refluxed with a solution of sodium (104 g.) in absolute alcohol (2 l.) for 3 hr. The precipitate was dissolved in water (850 ml.). The 4 : 6-dihydroxy-2-methylpyrimidine precipitated by 10N-hydrochloric acid (300 ml.) was washed with water, then alcohol, and dried in air. Recrystallization from water (16 l.) gave colourless needles (70%), a considerably higher yield than given by the methods of Dox and Yoder (*J. Amer. Chem. Soc.*, 1922, **44**, 361) and Ferris and Ronzio (*ibid.*, 1940, **62**, 606). This substance (99 g.) was added during 40 min. to a well stirred mixture of nitric acid (*d* 1·5; 106 ml.) and acetic acid (270 ml.) at 15—20°. After a further 30 min., the mixture was poured on ice (1 kg.). The precipitate, washed and dried as above, was recrystallized from water (2 l.), giving 85% of colourless 4 : 6-dihydroxy-2-methyl-5-nitropyrimidine. Undiluted nitric acid (as used by Hüber and Hölscher, *Ber.*, 1938, **71**, 87) gave much lower yields. This substance was converted into 4 : 6-dichloro-2-methyl-5-nitropyrimidine according to Baddiley and Topham's directions (*J.*, 1944, 678), but the use of diethylaniline in place of dimethylaniline raised their yield (38%) to 78% (m. p. 53—54°). We have consistently found diethylaniline superior in chlorinations by phosphorus oxychloride.

This pyrimidine was converted into 4-amino-6-chloro-2-methyl-5-nitropyrimidine (77%) by methanolic ammonia in ether (Boon, Jones, and Ramage, *J.*, 1951, 96). This amine (30 g.) was treated with sodium hydrogen sulphide (as for the isomer described below), giving 4 : 5-*diamino*-6-*mercapto*-2-*methylpyrimidine* as yellow needles (92%) from 450 parts of water (Found: C, 38·5; H, 4·9; N, 35·9; S, 20·6. $C_5H_8N_4S$ requires C, 38·45; H, 5·2; N, 35·9; S, 20·5%). This substance (21 g.) was treated with Raney nickel, as for the isomer (below). Recrystallization from alcohol (380 ml.) and concentration gave 4 : 5-*diamino*-2-*methylpyrimidine* (80%), yellow needles, m. p. 246—248° (Found: C, 48·8; H, 6·4; N, 45·4. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%). This diamine, treated with polyglyoxal (as below), gave 2-*methylpteridine*, sublimed at 105°/0·1 mm.), yellow leaflets, m. p. 141—142° (62%). It recrystallized from light petroleum (b. p. 60—80°; 200 parts) (Found: C, 57·4; H, 4·0; N, 38·3. $C_7H_6N_4$ requires C, 57·5; H, 4·2; N, 38·3%).

4-*Methylpteridine*.—4-Hydroxy-2-mercapto-6-methylpyrimidine (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105) was converted into 2 : 4-dihydroxy-6-methylpyrimidine (87%) by chloroacetic acid, as in the hydrolysis of thiouracil to uracil (Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353). Nitration according to Gabriel and Colman (*Ber.*, 1901, **34**, 1242) gave 88% of the 5-nitro-derivative when the temperature was kept between 5° and 10°. This product (87 g.), phosphorus oxychloride (435 ml.), and diethylaniline (105 ml.) were set aside for 20 min., then refluxed for 2 hr. (bath at 135°). The volatile compounds (300 ml.) were removed *in vacuo*, and the residue was poured slowly, with good stirring, on ice (1·5 kg.). The solution was extracted with ether (5 × 600 ml.); the extract was washed with water (200 ml.) and sodium hydrogen carbonate solution (200 ml.), dried, and freed from ether. The residual oil was distilled (125°/10 mm.), giving 2 : 4-dichloro-6-methyl-5-nitropyrimidine, m. p. 53—54° (80%). Substitution of dimethyl- for diethyl-aniline lowered the yield to 66%, and partly replaced a chlorine atom by the methylanilino-group (cf. Marshall and Walker, *J.*, 1951, 1016). Alcoholic ammonia at 0° gave 70% of 4-amino-2-chloro-6-methyl-5-nitropyrimidine, m. p. 170—171° (Gabriel and Colman, *loc. cit.*).

This amine (30 g.) was heated for 2 hr. at 95° with a saturated solution of hydrogen sulphide in 2·3N-sodium hydroxide (400 ml.). Acetic acid (about 50 ml.) was added to the hot solution, to give pH 5. After chilling overnight and filtration the precipitate was recrystallized from water (2·2 l.), giving 4 : 5-*diamino*-2-*mercapto*-6-*methylpyrimidine* (60%), as yellow needles. It recrystallized from 100 parts of water (Found: C, 38·7; H, 5·2; N, 35·7; S, 20·5%). Raney nickel catalyst (100 g., weighed wet with water) was added, in portions, to a hot mixture of the above diamine (27·5 g.), water (700 ml.), and ammonia (*d* 0·88; 28 ml.). The solution was then refluxed vigorously for 1 hr. The precipitate was extracted with boiling water (140 ml.) and the mixed filtrates were evaporated, to give 4 : 5-diamino-6-methylpyrimidine, which crystallized from *iso*butyl methyl ketone (1·2 l.) as yellow needles, m. p. 208—209° (82%). The same m. p. was obtained by Gabriel and Colman (*loc. cit.*) using a less convenient method.

4 : 5-Diamino-6-methylpyrimidine (2 g.), polyglyoxal (1·1 g.; *i.e.*, the precipitate which accumulates in bottles of syrupy glyoxal), and methanol (40 ml.) were refluxed for 20 min. The methanol was recovered at 30°, and the residue extracted with petroleum (b. p. 60—80°; 4 × 250 ml.). Evaporation of the extract, followed by sublimation at 100°/0·01 mm., gave 4-methylpteridine (60%), yellow needles, m. p. 152—153°. It recrystallized from 270 parts of light petroleum (Found: C, 57·5; H, 4·0; N, 38·3%).

7-*Methylpteridine*.—4 : 5-Diaminopyrimidine (2 g.; Brown, *J. Appl. Chem.*, 1952, **2**, 239), suspended in water (20 ml.), was added to a mixture of 20% aqueous methylglyoxal (7·4 ml.) and

sodium hydrogen sulphite solution (5 ml.; *d* 1·34). After being heated for 10 min. at 40°, the mixture was refrigerated for 2 hr. The complex was filtered off, dissolved in N-ammonia (40 ml.), and extracted with chloroform (3 × 40 ml.). The filtrate was also extracted with chloroform (3 × 40 ml.). The dried extracts were evaporated at 40°, and the product was sublimed at 95°/0·001 mm., giving 7-*methylpteridine*, m. p. 128° (60%). It recrystallized from 200 parts of light petroleum (b. p. 60—80°), giving pale yellow needles, m. p. 133—134° (Found: C, 57·9; H, 4·1; N, 38·45%). Like pteridine, all three monomethylpteridines cause sneezing.

Orientation of methyl group. 7-Methylpteridine (0·5 g.) in chloroform (2 ml.) was added to ethereal perphthalic acid (15·3 ml., 1·1 equiv.). The precipitate was recrystallized from water (14 ml.), extracted with boiling alcohol (10 ml.) to remove phthalic acid, and again recrystallized from water, giving 4-hydroxy-7-methylpteridine (70%), identical with that described by Albert *et al.* (*J.*, 1952, 4219). The identity was confirmed by degradation to 2-amino-6-methylpyrazine-3-carboxylic acid (m. p. 213°) as described there: the mixed m. p. with an authentic specimen showed no depression (2-amino-5-methylpyrazine-3-carboxylic acid, which would be given by 4-hydroxy-6-methylpteridine, has m. p. 173°).

6 : 7-*Dimethylpteridine.*—4 : 5-Diaminopyrimidine (0·5 g.) and diacetyl (0·43 g.) were refluxed in methanol (5 ml.) for 20 min. The solution was evaporated at 30°, and the residue sublimed at 100°/0·05 mm., giving 6 : 7-*dimethylpteridine*. It recrystallized from 300 parts of light petroleum (b. p. 60—80°) as pale yellow needles (90%), m. p. 148—149° (Found: C, 60·0; H, 5·1; N, 34·8. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%). Oxidation with perbenzoic acid gave 6 : 7-dimethyl-4-hydroxypteridine (75%).

4 : 5-Diamino-2-methylpyrimidine (see above) was similarly condensed with diacetyl, and purified, giving 2 : 6 : 7-*trimethylpteridine* (90%), yellow needles, m. p. 134—135° (Found: C, 62·1; H, 5·7; N, 32·4. $C_9H_{10}N_4$ requires C, 62·0; H, 5·75; N, 32·2%). It also forms a crystalline hemihydrate.

5-Amino-4 : 6-dichloro-2-methylpyrimidine was synthesized as a possible intermediate for 4 : 5-diamino-2-methylpyrimidine. 4 : 6-Dichloro-2-methyl-5-nitropyrimidine (4 g.; see above) was added to a vigorously stirred suspension of ferrous hydroxide (from 47 g. of ferrous sulphate heptahyrdate and 55 g. of barium hydroxide octahydrate in 550 ml. of water at 75°). After ½ hr. in the boiling water-bath, the mixture was filtered, and the residue extracted with boiling water. The mixed filtrates were concentrated *in vacuo* to 150 ml. The crystals were filtered off, enriched with a chloroform extract (2 × 50 ml.) of the filtrate, recrystallized from light petroleum (b. p. 60—80°, 18 ml.) and sublimed (65°/0·01 mm.), giving colourless needles of 5-*amino*-4 : 6-*dichloro*-2-*methylpyrimidine* (68%), m. p. 70—72° (Found: C, 33·8; H, 2·9; N, 23·6; Cl, 39·6. $C_5H_5N_3Cl_2$ requires C, 33·7; H, 2·8; N, 23·6; Cl, 39·85%).

7-*Chloropteridine.*—7-Hydroxypteridine (1 g.), phosphorus pentachloride (5 g.), and phosphorus trichloride (50 ml.) were refluxed for 7 hr., and the volatile compounds were removed in a vacuum. The residue was powdered in a chilled mortar, and covered with crushed ice (about 20 g.), then taken to pH 7 by the gradual addition of 5N-potassium hydroxide. The volume was measured (about 80 ml.) and the solution was shaken twice with that volume of chloroform. The extract was dried (Na_2SO_4) and evaporated below 20° to avoid polymerization, giving a pale solid. This was extracted with cold benzene (10 ml.), and the extract was at once concentrated to 0·5 ml. below 20°. Light petroleum (b. p. 80—100°; 1 ml.) was added and the mixture chilled overnight, giving a 30—50% yield of canary-yellow crystals, m. p. 95° (after contracting at 93°). Recrystallization from light petroleum (b. p. 40—60°; 500 parts) did not change the m. p. (Found: C, 43·3; H, 1·8; N, 33·6; Cl, 21·3. $C_6H_3N_4Cl$ requires C, 43·5; H, 1·6; N, 33·7; Cl, 21·2%). Treatment with ammonia in dry benzene (cf. Albert *et al.*, *J.*, 1952, 1620) gave chromatographically pure 7-aminopteridine (see below).

7-*Methoxypteridine.*—7-*Chloropteridine* (0·4 g.) in methanol (7 ml.) was added to sodium (0·06 g.) dissolved in methanol (5 ml.), refluxed for 1 hr., and evaporated under a vacuum. The residue was extracted with benzene (20 ml.), and the extract concentrated (to 1 ml.) and mixed with light petroleum (b. p. 60—80°; 2 ml.). The deposit of 7-*methoxypteridine* was recrystallized from 5 parts of methanol, giving pale yellow crystals, m. p. 130° (70% yield)(Found: C, 51·7; H, 3·7; N, 34·4. $C_7H_6ON_4$ requires C, 51·8; H, 3·7; N, 34·5%). The m. p. was profoundly depressed by the isomers 6-methoxypteridine (m. p. 124°) and 7 : 8-dihydro-8-methyl-7-oxopteridine (m. p. 125°). It is instantly converted into the insoluble sodium salt of 7-hydroxypteridine by cold N-sodium hydroxide.

7-*Mercaptopteridine.*—Phosphorus pentasulphide (3·6 g.) was added in one portion to a solution of 7-hydroxypteridine (2 g.) in dried pyridine (60 ml.) at 100° (bath). The mixture was stirred under carbon dioxide for 2 hr., and the pyridine recovered at 80°. The dark residue was

dissolved in cold N-ammonia (200 ml.). The pH was adjusted to 8 with glacial acetic acid, and the black slime discarded. The red filtrate was taken to pH 4 with 5N-sulphuric acid. The orange precipitate (1·5 g.) was recrystallized from 170 parts of 50% aqueous dimethylformamide, giving *7-mercaptopteridine* (48%) as red needles (R_F 0·90), which decomposed above 260° (Found: C, 43·9; H, 2·4; N, 34·1; S, 19·45. $C_6H_4N_4S$ requires C, 43·9; H, 2·5; N, 34·1; S, 19·5%).

7-Methylthiopteridine.—Methyl iodide (0·15 ml.; 1·25 equiv.) was shaken with 7-mercaptopteridine (0·32 g.) dissolved in 0·5N-potassium hydroxide (1·25 equiv.) for 1 hr. at 20°. The yellow crystals were filtered off and dried at 20° [when crystallization failed to occur, the solution was extracted with cold benzene (25 + 25 ml.)]. Pale yellow *7-methylthiopteridine* (80%), recrystallized from light petroleum (b. p. 60—80°; 200 parts), had m. p. 142—143° (Found: C, 47·2; H, 3·5; N, 31·4; S, 18·2. $C_7H_6N_4S$ requires C, 47·2; H, 3·4; N, 31·4; S, 18·0%).

2-Methylthiopteridine was prepared (90%) as was the 7-isomer (from 2-mercaptopteridine monohydrate; Elion and Hitchings, *J. Amer. Chem. Soc.*, 1947, **69**, 2553), giving yellow needles, m. p. 133—136° (Found: C, 47·3; H, 3·3; N, 31·4; S, 17·9%). It was also made as follows: 4 : 5-Diamino-2-methylthiopyrimidine (0·95 g.; Albert and Brown, *J.*, 1954, 2060), polyglyoxal (0·5 g.; see above), and methanol (30 ml.) were refluxed for ½ hr. The solvent was recovered *in vacuo*. The residue was extracted with boiling light petroleum (250 + 100 ml.; b. p. 60—80°), and the extract concentrated. Further recrystallization from petroleum (230 parts) gave crystals of 2-methylthiopteridine (70%), m. p. 133—136°, undepressed by material from methylation.

4-Methylthiopteridine, prepared as was the 7-isomer, but in sodium hydroxide, was dried at 110° and recrystallized from 28 parts of benzene (2 crops), giving pale yellow crystals (90%), m. p. 191° (Found: C, 47·4; H, 3·3; N, 31·5; S, 18·0%).

4-Methylthiopteridine (Direct Synthesis).—4-Amino-6-chloro-5-nitropyrimidine (10 g.; Boon, Jones, and Ramage, *J.*, 1951, 96) was refluxed for 1½ hr. with N-sodium hydroxide (330 ml.) saturated with hydrogen sulphide. The pH was then slowly adjusted to 4—5 with acetic acid (*ca.* 30 ml.). The precipitate was extracted with boiling water (400 ml.). The crystals deposited on chilling were recrystallized from water (40 parts), giving colourless 4 : 5-*diamino-6-mercaptopyrimidine* (80%), m. p. 257° (decomp.) (Found: N, 39·4; S, 22·4. $C_4H_6N_4S$ requires N, 39·4; S, 22·55%). Methyl iodide (2 ml.) was shaken vigorously for 20 min. with a solution of this pyrimidine (4 g.) in N-potassium hydroxide (32 ml.). After refrigeration, the crystals (88%) were collected and recrystallized from 12 parts of water, giving colourless needles of 4 : 5-*diamino-6-methylthiopyrimidine*, m. p. 155—157° (Found: N, 35·85; S, 20·3. $C_5H_8N_4S$ requires N, 35·9; S, 20·5%). This pyrimidine (3·9 g.), dry polyglyoxal (2·3 g., see above), and methanol (110 ml.) were refluxed for ½ hr. The solid was recrystallized from ethanol (75 parts), giving 75% of 4-methylthiopteridine, m. p. 189—191°, identical with that described above.

4-Mercaptopteridine.—4 : 5-Diamino-6-mercaptopyrimidine (1·4 g.; see above) in water (45 ml.) was heated in the boiling-water bath for 15 min. with glyoxal (50% syrup; 3 ml.). The orange solid (83%) was recrystallized from water (1·1 l.) and proved identical with that made by the former method (Albert *et al.*, *J.*, 1951, 474).

7-Methyl-4-methylthiopteridine.—Methylglyoxal (17 ml. of 30% solution) in sodium hydrogen sulphite solution (42 ml.; *d* 1·34) was added to 4 : 5-diamino-6-mercaptopyrimidine (6·3 g.) and hydrated sodium sulphite (21 g.) in water (315 ml.) at 80°. After 2 days at 30°, 10N-hydrochloric acid (105 ml.) was added (5°). After 10 min., the solid was filtered off, and recrystallized from water (1500 parts), giving *4-mercapto-7-methylpteridine* (50%) as yellow crystals (R_F 0·65), decomp. above 300°, insoluble in organic solvents (Found: N, 31·3; S, 17·9. $C_7H_6N_4S$ requires N, 31·45; S, 18·0%). The orientation of the methyl group was found by hydrolysis to 2-amino-6-methylpyrazine-3-carboxylic acid (see above) by 10N-sodium hydroxide (3 hr. at 140°). Methylation, as for 7-mercaptopteridine, and recrystallization from ethanol (30 parts) gave pale needles (80%) of *7-methyl-4-methylthiopteridine*, m. p. 187—188°, which also crystallizes from benzene (Found: N, 28·9; S, 16·4. $C_8H_8N_4S$ requires N, 29·15; S, 16·7%).

7-Aminopteridine.—7-Methylthiopteridine (0·65 g.) and saturated alcoholic ammonia (10 ml.) were heated at 125° for 6 hr. The crystals which separated on cooling were recrystallized from water (140 parts), giving *7-aminopteridine* (75%) as colourless needles (R_F 0·70) which decompose above 320° (Found: C, 48·9; H, 3·3; N, 47·2. $C_6H_5N_5$ requires C, 49·0; H, 3·4; N, 47·6%). It is much more stable to hydrolysis than the 6-isomer.

7-Dimethylaminopteridine.—Methanolic dimethylamine (8 ml.; 50% solution) was added to a solution of 7-methylthiopteridine (0·36 g.) in methanol (15 ml.). After 12 hr. at 20°, the solution was refluxed for 30 min., then evaporated. The solid, dissolved in water (25 ml.), was shaken out with benzene (5 ml., discarded). The aqueous layer was evaporated and the residue recrystallized from methanol giving *7-dimethylaminopteridine* in 85% yield as pale yellow crystals,

m. p. 204°, soluble in 12 parts of boiling methanol and 19 parts of boiling ethanol (Found: C, 55·2; H, 5·2; N, 40·0. $C_8H_9N_5$ requires C, 54·8; N, 5·2; N, 40·0%). When this preparation was carried out at 125° (4 hr.) much of the dimethylaminopteridine was destroyed.

7-*Acetamidopteridine*.—7-Aminopteridine (0·2 g.) was refluxed with acetic anhydride (12 ml.) for 30 min. The solution was chilled and filtered, and the crystals washed with a little benzene, recrystallized from 130 parts of water and dried at 110°, giving faintly yellow 7-*acetamidopteridine* (70%), R_F 0·70, decomp. above 250° (Found: C, 51·0; H, 3·9. $C_8H_7ON_5$ requires C, 50·8; H, 3·7%).

4-*Hydrazinopteridine*.—Hydrazine hydrate (90%; 2 ml.) was refluxed for 15 min. with 4-methylthiopteridine (2 g.) in methanol (110 ml.), and then chilled. The deposit, recrystallized from water, gave yellow needles of 4-*hydrazinopteridine* (90%), m. p. 215° (decomp.) (it can also be recrystallized from *iso*amyl alcohol) (Found: C, 44·8; H, 3·8; N, 51·6. $C_6H_6N_6$ requires C, 44·45; H, 3·7; N, 51·8%). The second basic pK_a is <2. An acidic ionization, indicated by increased solubility in 0·1N-sodium hydroxide, could not be measured because of rapid decomposition to a red product. 4-Mercaptopteridine did not react with hydrazine under these conditions.

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