308. *Pteridine Studies. Part XVII.*[1] *Addition to 2-Hydroxypteridines.*

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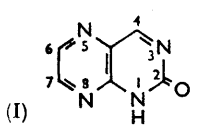
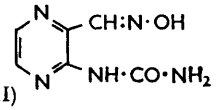
The strong tendency of 2-hydroxypteridine (I) to form the covalent hydrate (II) is greatly decreased by a methyl group in the 4-position but not elsewhere. This phenomenon is discussed with reference to other examples of covalent hydration in the pteridine and quinazoline series. Apart from water, 2-hydroxypteridine adds aliphatic alcohols across the 3,4-double bond, and also Michael reagents such as diethyl malonate.

2-Hydroxypteridine [2] (I) is a monohydrate which loses water rapidly only above 180°. The ultraviolet long-wave band is displaced 68 mμ below that of the anion (about 20 mμ would be normal), which indicates that a double bond is lost in passing from the anion to the neutral species. This unusual spectral shift, the ease of oxidation by potassium permanganate to 2,4-dihydroxypteridine, and the acidic nature of the 1- and the 3-methyl derivative, led Brown and Mason [3] to formulate the neutral species as an equilibrium mixture of which the main component is the covalent hydrate (II). This parallels the behaviour of 6-hydroxypteridine, the neutral molecule of which is, at equilibrium, largely 7,8-dihydro-6,7-dihydroxypteridine.[3]


(I)


(II)


(III)

The only difficulty in accepting formula (II) was the observed lack of hysteresis during potentiometric titration, under conditions where 6-hydroxypteridine gives a large hysteresis loop.[4] However, a more rapid titration technique recently revealed the expected hysteresis loop,[5] and gave pK_a 7·7 for the equilibrium between anhydrous anion and anhydrous neutral species, and 11·05 for that between the hydrated forms. Below pH 10 the stable species is the hydrated neutral molecule, and above pH 10 it is the anhydrous anion derived from (I). No cation has been detected. In the present work further parallels between 2- and 6-hydroxypteridine are revealed in the hindering effect of a methyl group upon hydration, and in the ease of addition of anions other than that of water, especially Michael reagents and aliphatic alcohols.

2-Hydroxy-4-methylpteridine was prepared from 4,5-diamino-2-hydroxy-6-methylpyrimidine and glyoxal. In the ultraviolet spectrum of the neutral molecule, the band at 307 mμ (long-wave), typical of 2-hydroxypteridine hydrate, had a surprisingly low extinction. A new band, at 350 mμ, denoted the presence of a significant proportion of the anhydrous substance, because anhydrous 2-hydroxypteridine (which differs in having only a transient existence) absorbs at 353 mμ. By the same criterion, 2-hydroxy-4,6,7-trimethylpteridine has an even higher proportion of the anhydrous form, in stable

[1] Part XVI, Perrin, *J.*, 1962, 645.
[2] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[3] Brown and Mason, *J.*, 1956, 3443.
[4] Albert, Brown, and Cheeseman, *J.*, 1952, 1620.
[5] Perrin and Inoue, *Proc. Chem. Soc.*, 1960, 342.

equilibrium. The ultraviolet spectra of 2-hydroxy-6- and -7-methylpteridine, by contrast, do not differ significantly from that of 2-hydroxypteridine (see Table 1). These results resemble those obtained with 6-hydroxypteridine,[6] namely, that a methyl group most effectively lowers the proportion of neutral molecules hydrated at equilibrium if it is situated on the carbon atom undergoing hydration. This effect of the 4-methyl group recalls similar behaviour in the quinazoline series.[7]

Whereas no covalent hydration can be detected for 4- and 7-hydroxypteridine,[4] even by the rapid-reaction technique, 2- and 6-hydroxypteridine become hydrated quickly. All known examples of covalent hydration of a C=N bond in a hetero-aromatic substance [1-3,5-7] occur in ring systems which have a high proportion of doubly bound nitrogen atoms which, by depleting the π-electron density primarily at one atom in the conjugated system, allows one double bond to acquire the properties of an isolated, highly

Physical properties of pteridines.

	Ionization (H_2O; 20°) [p]			Spectrometry in water [r]		
Pteridine	pK_a	Spread (±)	Concn. (M)	$\lambda_{max.}$ (mμ)	log ε	pH
2-Hydroxy (hydrate) [ab]	—	—	—	230, 307	3·88, 3·83	7·1
anion [c]	11·05 [k]	—	0·001	266, 311 [s]	3·68, 3·65	12·0
2-Hydroxy (anhyd.) [c]	—	—	—	*260*, 353 [s]	3·17, 3·68	5·6
anion [b]	7·7 [k]	—	0·001	260, 375	3·85, 3·78	13·0
2-Hydroxy-4-methyl [d] (equil., partly anhyd.)	—	—	—	231, 309, 350	3·53, 3·50, 2·96	4·5
anion (hydrated) [c]	10·85 [l]	0·02	0·001	—	—	—
anion (anhydr.) [b]	8·2 [l]	—	0·001	259, 373	3·84, 3·86	13·0
2-Hydroxy-6-methyl (hydrate) [be]	—	—	—	235, 315	4·05, 3·93	6·0
anion (hydrated) [c]	11·0 [m]	0·02	0·02	—	—	—
anion (anhyd.) [b]	—	—	—	261, 377	3·87, 3·77	13·0
2-Hydroxy-7-methyl (hydrate) [bd]	—	—	—	234, 311	3·93, 3·97	6·0
anion (hydrated) [c]	10·85 [m]	0·05	0·005	—	—	—
anion (anhyd.) [b]	—	—	—	259, 370	3·84, 3·95	13·0
2-Hydroxy-6,7-dimethyl (hydrate) [bf]	—	—	—	238, 314	3·93, 3·97	7·0
anion (hydrated) [c]	11·15 [k]	—	0·001	—	—	—
anion (anhyd.) [b]	7·95 [k]	—	0·001	*263*, 373	*3·74*, 3·85	13·0
2-Hydroxy-4,6,7-trimethyl [d] (equil., largely anhyd.)	—	—	—	215, 319, 351	4·16, 3·80, 3·73	7·0
anion (anhyd.) [b]	8·5 [k]	—	0·001	*255*, 380	*3·76*, 3·61	11·0
3,4-Dihydro-2-hydroxy [e]	—	—	—	248, 317 [e]	3·72, 3·89	7·0
anion	12·6 [e]	—	—	281, 343 [e]	3·98, 3·84	14·0
4-Acetonyl-3,4-dihydro-2-hydroxy [d]	—	—	—	246, 314	3·73, 3·90	7·0
anion	12·38	0·03	0·0002 [q]	277, 344	3·96, 3·83	14·0
4-Diacetylmethyl-3,4-dihydro-2-hydroxy [d]	—	—	—	245, 313	3·67, 3·85	6·0
anion	8·02	0·04	0·0002 [q]	—	—	—
4-(1-Ethoxycarbonyl-2-oxopropyl)-3,4-dihydro-2-hydroxy [d]	—	—	—	245, 314	3·76, 3·88	7·0
4-Di(ethoxycarbonyl)methyl-3,4-dihydro-2-hydroxy [d]	—	—	—	244, 313	3·75, 3·88	7·0
anion	11·43 [n]	0·06	0·0001 [q]	261, 320 [n]	4·16, 3·74	13·0
4-Dicarboxymethyl-3,4-dihydro-2-hydroxy (anion) [d]	—	—	—	245, 314	3·68, 3·90	9·0
4-Carboxymethyl-3,4-dihydro-2-hydroxy [d]	—	—	—	244, 313	3·69, 3·84	2·0
anion	4·14	0·02	0·005	245, 313	3·68, 3·88	7·0
4-α-Cyano-α-ethoxycarbonylmethyl-3,4-dihydro-2-hydroxy [d]	—	—	—	243, 312	3·83, 3·88	7·0
3,4-Dihydro-2-hydroxy-4-methoxy [d]	— [o]	—	—	233, 308	4·03, 3·86	— [t]
7,8-Dihydro-6-hydroxy-7-methoxy [d]	— [o]	—	—	*265*, 289	*3·85*, 3·99	— [t]
6-Hydroxy (hydrate) [bg]	—	—	—	*266*, 289 [f]	*3·85*, 4·00	5·2
4-Hydroxy [a]	—	—	—	230, 265, 310 [a]	3·98, 3·54, 3·82	5·6
nion	7·89 [a]	—	—	242, 333 [a]	4·23, 3·79	10·0

[6] Albert and Reich, *J.*, 1961, 127.

[7] Albert, Armarego, and Spinner, *J.*, 1961, 2689; Albert, Armarego, and Spinner, *J.*, 1961, 5267; Armarego, *J.*, 1962, 561.

TABLE. (*Continued*).

Pteridine	Ionization (H_2O; 20°) [p] pK_a	Spread (±)	Concn. (M)	Spectrometry in water [r] $\lambda_{max.}$ (mμ)	log ε	pH
4-Hydroxy-2-methyl [d]	—	—	—	229, 266, 315	4·07, 3·71, 3·85	6·0
anion	8·54	0·02	0·005	243, 335	4·31, 3·80	12·0
4-Hydroxy-6-methyl [h]	—	—	—	230, 266, 316	4·03, 3·73, 3·86	6·0
anion	8·19 [h]	—	—	243, 336	4·28, 3·82	10·5
4-Hydroxy-7-methyl [h]	—	—	—	232, 310	4·02, 3·92	6·0
anion	8·09 [h]	—	—	243, 330	4·24, 3·85	10·5
(2-Ureidopyrazine-3-aldoxime) [d]	—	—	—	264, 325	4·04, 3·99	7·0
anion	9·34	0·03	0·001	223, 285, 338	4·25, 4·06, 4·13	11·5
(2-Hydroxy-1,3,8-triazanaphthalene, hydrate) [bi]	—	—	—	233, 283	3·98, 3·75	7·0
anion (hydrate) [c]	11·25 [k]	—	0·001	—	—	—
anion (anhyd.) [b]	9·1 [k]	—	0·001	255, 353	3·84, 3·79	13·0
cation (hydrate)	1·81 [m]	0·03	0·05	230, 299	4·27, 4·45	−0·3
(2-Hydroxyquinazoline, equil., largely anhyd.) [j]	—	—	—	226, 275, 345	4·32, 3·65, 3·31	7·0
anion (anhyd.) [b]	10·69 [mu]	—	—	232, 355	4·63, 3·59	13·0
cation	1·30 [m]	—	—	221, 295, 384	4·49, 4·00, 3·44	−0·7

[a] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [b] Stable form. [c] Unstable form. [d] Prep. given in this paper. [e] Albert and Matsuura, *J.*, 1961, 5131. [f] Brown and Mason, *J.*, 1956, 3443. Albert, Brown, and Cheeseman, *J.*, 1952, 1620. [h] *Idem, ibid.*, p. 4219. [i] Albert and Reich, *J.*, 1960, 1370. [j] Albert and Phillips, *J.*, 1956, 1294. [k] Titration (or back-titration for anhydrous forms) completed in 3 min. (self-recording apparatus), quoted from Perrin and Inoue, *Proc. Chem. Soc.*, 1960, 342). [l] Titrations completed in 3 min. (new results). [m] Titrated at normal rate (20 min.). [n] Anion hydrolysed readily, hence pK_a was determined spectrometrically by the stopped-flow technique, and the spectrum by the continuous rapid-flow technique (for method, see Perrin, *J.*, 1962, 645); the proton comes from the side-chain. [o] Too unstable to alkali for determination. [p] Determined potentiometrically, except where marked "*q*". [q] Determined spectrometrically. In 1 and 4 cm. cells; shoulders are in italics. [r] Kindly determined by Mr. Y. Inoue, by the continous rapid-flow technique. [s] In methanol. [u] Dr. D. D. Perrin has kindly told us that the results of rapid (3 min.) titration suggest that the neutral species is about 25% hydrated.

polar, double bond. This occurs to an appreciable extent when the new substances formed by addition are stabilized by resonance. Thus the 7,8-hydration product of 6-hydroxypteridine is stabilized by a 4-aminopyridine-type resonance,[6] and the 3,4-hydration product of pteridine by an amidine-type resonance.[1] The hydration of 2-hydroxypteridine is in the 3,4-position [3] and is evidently stabilized by the urea-type resonance: R·NH·C(:O)·NHR ⟷ R·NH·C(O⁻):NHR⁺, in which $N_{(1)}$ and $N_{(3)}$ can, in turn, carry the positive charge.

Analogues of 2-hydroxypteridine with fewer ring-nitrogen atoms were also investigated (see Table). 2-Hydroxy-1,3,8-triazanaphthalene, which lacks $N_{(5)}$, undergoes strong covalent hydration, as pK_a values and spectra reveal. But 2-hydroxyquinazoline, which lacks both $N_{(5)}$ and $N_{(8)}$, showed only a slight tendency to covalent hydration.

Michael-type Additions.—Unlike 6-hydroxypteridine, 2-hydroxypteridine hydrate could not be induced to add acetone, but a careful choice of conditions permitted addition of acetylacetone, ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate. That these additions occurred at the 3,4-double bond was shown by the ultraviolet spectra (see Table) which were almost identical with that of 3,4-dihydro-2-hydroxypteridine whose constitution is well established by deuteration studies.[8] These Michael-type adducts, although stable to acid, were hydrolysed readily by alkali. Thus the acetylacetone adduct (4-diacetylmethyl-3,4-dihydro-2-hydroxypteridine) gave 4-acetonyl-3,4-dihydro-2-hydroxypteridine; the diethyl malonate adduct gave, in turn, the corresponding di- and mono-carboxylic acid; and the ethyl cyanoacetate adduct gave the corresponding carboxylic acid. More prolonged treatment with alkali gave 2-hydroxypteridine and its purple dimer [9] and (if air was not excluded) 2,4-dihydroxypteridine.

[8] Albert and Matsuura, *J.*, 1961, 5131.
[9] Albert and Reich, *J.*, 1960, 1370.

On prolonged refluxing, 2-hydroxypteridine added methanol and ethanol across the 3,4-position. The conversion of 6-hydroxypteridine into 7,8-dihydro-6-hydroxy-7-methoxypteridine was carried out similarly. Each of these alkoxy-compounds has a R_F (paper chromatography) quite different from that of the hydroxypteridine hydrate from which it was made. Relative to 3,4-dihydro-2-hydroxypteridine ($\lambda_{max.}$ 317), both 3,4-dihydro-2-hydroxy-4-methoxypteridine ($\lambda_{max.}$ 308) and 3,4-dihydro-2,4-dihydroxypteridine (*i.e.*, 2-hydroxypteridine hydrate, $\lambda_{max.}$ 307) show a small hypsochromic effect (see Table). This unusual effect also accompanies hydroxylation of the 4-position in 3,4-dihydroquinazolines.[7]

The mutual addition, in alkaline solution, of two molecules of 6-hydroxypteridine across 7,8-double bonds, which gives an orange dimer,[10] is paralleled by the similar 3,4-self-addition of 2-hydroxypteridine to give the purple dimer.[9] However, 2-hydroxypteridine does not undergo reactions equivalent to the disproportionation of 6-hydroxypteridine in alkali, or react with ammonia.[10] Whereas 6-hydroxypteridine gave 7-amino-6-hydroxypteridine with hydroxylamine in dilute alkali, 2-hydroxypteridine gave a substance $C_6H_7N_5O_2$ quite unlike 4-amino-2-hydroxypteridine. The lack of basic properties, the stability in air, and the permanent red colour given with ferrous ion indicated that the constitution was 2-ureiodpyrazine-3-aldoxime (III) and not 3,4-dihydro-2-hydroxy-4-hydroxyaminopteridine.

The synthesis of all 12 monohydroxy-monomethylpteridines (6 of which were described [6] in Part XIII) was completed by preparing 4-hydroxy-2-methylpteridine. Of these, only the 7- and 2-hydroxy-4-methyl isomers discolour (orange) on warming or storage. This colour change occurs in the absence of oxygen and appears to be due to polymerization, although no definite product could be isolated. The reaction seems to involve the 4-methyl group, as 4-methylpteridine behaves similarly. The non-reactivity of " 6-hydroxy-4-methylpteridine " can be attributed to the dihydropteridine structure caused by strong 7,8-hydration.[7]

Experimental

Elementary analyses were carried out by the Analytical Section of the Department, under Dr. J. E. Fildes. Ultraviolet spectra were measured on a Hilger " Uvispek " spectrophotometer by Mr. D. T. Light, under the supervision of Dr. E. Spinner. Ionization constants were measured by the standard methods of this Department [11] by Mr. H. Satrapa under the supervision of Dr. D. D. Perrin, who kindly performed the new rapid-flow measurements in the Table. All these colleagues are thanked for their help.

Yields are based on the stage in purification where a single spot in paper chromatography was first obtained, but further purification was carried out before analysis. The most useful chromatographic solvents were (*a*) 3% aqueous ammonium chloride, especially when run at 0°, (*b*) propan-2-ol–90% formic acid–dimethylformamide–water (65 : 2·5 : 22·5 : 10 v/v), run for 48 hr. at 20°, and (*c*) butanol–5N-acetic acid (7 : 3) run for 18 hr. at 20°. All substances were dried over calcium chloride at 20°/20 mm., except where otherwise specified.

Dehydration of 2-Hydroxypteridine Monohydrate.—This substance (dried at 120° in air) lost 10·2% of its weight when dried in air at 180° for an hour (expected for loss of $1H_2O$: 10·8%). It was rapidly rehydrated in moist air, and was then found to be unchanged in R_F and ultraviolet spectrum.

2-Hydroxy-4-methylpteridine.—4,5-Diamino-2-hydroxy-6-methylpyrimidine [13] (1·4 g., 0·01 mole) was shaken with a solution of glyoxal monohydrate (British Drug Houses powder; 0·76 g., 0·01 mole) in water (150 ml.) at 20° overnight. The liquid was filtered, shaken with charcoal (0·15 g.) for an hour, filtered, and concentrated to 10 ml. in a rotating vacuum-drier (Rinco brand) at 20°. The yellow needles (60%), purified by a similar recrystallization at 20°, became brown readily (dimerization) above 100° (Found, for material dried over P_2O_5 at 20°/0·01 mm.: C, 46·8; H, 4·6; N, 31·1. $C_7H_6N_4O,H_2O$ requires C, 46·7; H, 4·5; N, 31·1%).

[10] Albert, *J.*, 1955, 2690.
[11] Albert and Serjeant, " Ionization Constants," Methuen, London, 1962.
[12] Robins, Dille, Willits, and Christensen, *J. Amer. Chem. Soc.*, 1953, **75**, 263.
[13] Cf. Dick, Wood, and Logan, *J.*, 1956, 2131.

2-Hydroxy-7-methylpteridine.—To 4,5-diamino-2-hydroxypyrimidine [2] (0·63 g., 0·005 mole) in water (10 ml.) at 100° was added 30% aqueous methylglyoxal (1·3 ml.), and the whole was set aside at 20° for 3 hr. The precipitate (87% yield) gave white crystals of *2-hydroxy-7-methylpteridine hydrate* (from 45 parts of water) which charred at 230° (Found: C, 46·7; H, 4·6; N, 31·0%). The R_F values and ultraviolet spectra were very similar to those of 2-hydroxy-6-methylpteridine, which was unambiguously made from 2-hydroxy-5-nitro-4-pyrimidinylaminoacetone. Such resemblance is known [13] in two pteridine isomers differing solely in the 6- or 7-placement of a hydrocarbon group. The infrared spectra of the two isomers were notably different in the regions 800—1000 and 1200—1500 cm.$^{-1}$; also the NH-stretching peak occurred at 320 for the 7-methyl and at 3160 cm.$^{-1}$ for the 6-methyl isomer.

2-Hydroxy-4,5,6-trimethylpteridine [9] (*Improved Preparation*).—4,5-Diamino-2-hydroxy-6-methylpyrimidine [12] (0·8 g.) in hot water (25 ml.) was heated, under reflux, for 5 min. on the steam-bath with biacetyl (0·55 ml.). The precipitate (95% yield) was dried at 20°/20 mm. (Found: C, 56·3; H, 5·4; N, 28·9. Calc. for $C_9H_{10}N_4O$: C, 56·8; H, 5·3; N, 29·5%). It polymerized on attempted recrystallization.

Condensation with Acetylacetone.—2-Hydroxypteridine monohydrate (0·34 g., 0·002 mole), acetylacetone (1 g., 5 equiv.), sodium hydrogen carbonate (1·7 g.), and water (17 ml.) were shaken at 20—25° for 5 hr. The suspension was adjusted to pH 6 and refrigerated overnight. The precipitate (75%), when refluxed with alcohol (25 ml.) for only 5 min. and filtered off, gave colourless crystals of *4-diacetylmethyl-3,4-dihydro-2-hydroxypteridine*, decomp. 185° (Found: C, 53·1; H, 5·0; N, 22·5. $C_{11}H_{12}N_4O_3$ requires C, 53·2; H, 4·9; N, 22·6%). It was slowly hydrolyzed to 4-acetonyl-3,4-dihydro-2-hydroxypteridine by 0·5N-potassium carbonate at 20°, and rapidly decomposed to 2-hydroxypteridine by boiling water.

The adduct (1·2 g.) in N-sodium hydroxide (10 ml., 2 equiv.) was set aside for 22 hr. at 20—25°, adjusted to pH 8 and refrigerated, giving *4-acetonyl-3,4-dihydro-2-hydroxypteridine* (95%), distinguishable from the starting material by the higher R_F of the latter in 3% ammonium chloride, run at 0° (Whatman's No. 1 paper, read in 254 mμ light). Recrystallized rapidly from 120 parts of alcohol, it had m. p. 218° (Found: C, 52·5; H, 5·0; N, 26·85. $C_9H_{10}N_4O_2$ requires C, 52·4; H, 4·9; N, 27·2%). Semicarbazide hydrochloride (0·13 g., 1·1 equiv.) was added to a solution of this acetonyl derivative (0·22 g.) and sodium acetate trihydrate (0·3 g.) in boiling water (25 ml.), and the mixture was cooled at once. The needles (90%) were recrystallized from 200 parts of water, giving the *semicarbazone*, decomp. >240° (Found: C, 45·7; H, 5·0. $C_{10}H_{13}N_7O_2$ requires C, 45·6; H, 5·0%).

Condensation with Ethyl Acetoacetate.—2-Hydroxypteridine hydrate (0·85 g.) was dissolved in 0·5N-potassium carbonate (60 ml.) at 50° and cooled to 25°. This solution was shaken with ethyl acetoacetate (2·6 g., 4 equiv.) for 24 hr. The solid was filtered off, suspended in water, adjusted to pH 7, re-filtered, and recrystallized from 80 parts of alcohol, giving 80% of *4-(1-ethoxycarbonyl-2-oxopropyl)-3,4-dihydro-2-hydroxypteridine*, m. p. 178—180° (Found: C, 51·9; H, 5·2; N, 19·9. $C_{12}H_{14}N_4O_4$ requires C, 51·8; H, 5·1; N, 20·1%).

Condensation with Diethyl Malonate.—2-Hydroxypteridine (0·85 g.), dissolved as above, was shaken at 20—25° with diethyl malonate (3·2 g., 4 equiv.) for 20 hr. and filtered. The crystals of *4-di(ethoxycarbonyl)methyl-3,4-dihydro-2-hydroxypteridine* (90% yield) were recrystallized from 40 parts of alcohol, then from 150 parts of water and dried at 110° [m. p. 191° (decomp.)] (Found: C, 50·6; H, 5·2; N, 18·2. $C_{13}H_{16}N_4O_5$ requires C, 50·6; H, 5·2; N, 18·2%). This ester (1·3 g.), dissolved in N-sodium hydroxide (17 ml., 4 equiv.), was set aside at 20—25° for 4 hr., then brought to pH 2 with 5N-sulphuric acid and refrigerated overnight. An 80% yield of *4-dicarboxymethyl-3,4-dihydro-2-hydroxypteridine* was obtained. Paper chromatography reveals that it is slowly decarboxylated at 110°, but not at 100°. It was purified by dissolution in aqueous sodium hydrogen carbonate and precipitation at pH 2 (Found: C, 40·2; H, 3·7; N, 20·75; loss at 98°/15 mm., 6·8. $C_9H_8N_4O_5,H_2O$ requires C, 40·0; H, 3·7; N, 20·7; H_2O, 6·7%). This acid (1 g.; dried at 110°) was refluxed for 40 min. with propionic acid (6 vol., containing 1% w/w of sulphuric acid) and then refrigerated. The precipitate was extracted with boiling water (15 ml.). The filtrate, adjusted to pH 2 and chilled, gave 0·25 g. of white crystals which were purified from aqueous sodium hydrogen carbonate as above, then recrystallized from 30 parts of water. This *4-carboxymethyl-3,4-dihydro-2-hydroxypteridine* charred at 215° without decarboxylation (Found: C, 46·3; H, 3·8; N, 26·8. $C_8H_8N_4O_3$ requires C, 46·15; H, 3·9; N, 26·9%).

Condensation with Ethyl Cyanoacetate.—2-Hydroxypteridine hydrate (0·85 g.) was dissolved in

boiling ethyl cyanoacetate (7 ml.) and at once immersed in boiling water for 4 hr. The mixture was diluted with benzene (15 ml.) and set aside at 20° overnight. The 4-(α-*cyano*-α-*ethoxycarbonylmethyl*)-3,4-*dihydro*-2-*hydroxypteridine* (90%), recrystallized from 120 parts of ethanol, had m. p. 196—198° (decomp.) (Found: C, 50·5; H, 4·25; N, 26·3. $C_{11}H_{11}N_5O_3$ requires C, 50·6; H, 4·25; N, 26·8%). This ester (0·3 g.) was set aside in N-sodium hydroxide (1·7 ml., 1·5 equiv.) for 2½ hr. at 24°. The mixture was adjusted to pH 2 with 5N-sulphuric acid and refrigerated overnight. The 4-(α-*carboxy*-α-*cyanomethyl*)-3,4-*dihydro*-2-*hydroxypteridine* was purified from aqueous sodium hydrogen carbonate as above (Found: C, 45·5; H, 3·3; N, 29·5. $C_9H_7N_5O_3,0{\cdot}25H_2O$ requires C, 45·5; H, 3·2; N, 29·5%).

Condensation with Alcohols.—2-Hydroxypteridine hydrate (0·7 g.) and methanol (50 ml.) were refluxed for 24 hr. The refrigerated solution deposited 80% of hair-like crystals of 3,4-*dihydro*-2-*hydroxy*-4-*methoxypteridine*, which became orange at 210° without melting. The compound recrystallized from 75 parts of methanol (Found: C, 46·9; H, 4·4; N, 30·5. $C_7H_8N_4O_2$ requires C, 46·7; H, 4·5; N, 31·1%). It was rapidly hydrolyzed by boiling water to 2-hydroxypteridine. 6-Hydroxypteridine (0·3 g.) and methanol (150 ml.), refluxed for 30 hr., then concentrated to 25 ml., similarly gave 80% of 7,8-*dihydro*-6-*hydroxy*-7-*methoxypteridine*, which darkens above 230° without melting (Found: C, 46·5; H, 4·6; N, 30·7%). 2-Hydroxypteridine, refluxed for 24 hr. with 150 parts of ethanol, gave 80% of 4-*ethoxy*-3,4-*dihydro*-2-*hydroxypteridine*, which became brown at 240° without melting (Found: C, 49·3; H, 5·4; N, 28·8. $C_8H_{10}N_4O_2$ requires C, 49·5; H, 5·2; N, 28·9%). The R_F values of these three alkoxy-derivatives are greater than those of their hydroxy-analogues in 3% aqueous ammonium chloride.

Reaction with Hydroxylamine.—To 2-hydroxypteridine hydrate (1 g.) in cold N-potassium hydroxide (24 ml.) was added hydroxylamine hydrochloride (0·84 g.). The suspension was set aside at 20—25° for 60 hr., adjusted to pH 7 with phosphoric acid, and refrigerated. The precipitate was dried and extracted with boiling methanol (90 ml.). The extract, concentrated to 20 ml., deposited 66% of colourless needles of 2-*ureidopyrazine*-3-*aldoxime* (III), which, when recrystallized from 100 parts of methanol, slowly charred at 200° without melting. It was insoluble in cold 0·1N-sulphuric acid, but, when the suspension was boiled for 30 min., 2-hydroxypteridine was formed. It does not reduce cold ammoniacal silver nitrate, even after 12 hr. It can also be prepared, in lower yield, in boiling 2N-sodium carbonate (Found: C, 40·1; H, 3·8; N, 38·6. $C_6H_7N_5O_2$ requires C, 39·8; H, 3·9; N, 38·7%). When it was set aside at 20° for 7 days in 0·1N-sodium hydroxide, a little 2-aminopyrazine-3-aldoxime [14] was formed.

4-*Hydroxy*-2-*methylpteridine.*—To 5,6-diamino-4-hydroxy-2-methylpyrimidine sulphate [15] (0·76 g.) in warm 0·33N-sodium hydroxide (12 ml.) was added glyoxal hydrate (see above) (0·33 g.), and the whole was set aside at 20° for an hour. The pH was adjusted to 4·5. Refrigeration and filtration, followed by concentration of the filtrate, gave 50% of 4-*hydroxy*-2-*methylpteridine*, which sublimed at 150°/0·01 mm. and decomposed above 200° (Found: C, 52·0; H, 3·8; N, 34·5. $C_7H_6N_4O$ requires C, 51·85; H, 3·7; N, 34·6%).

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[14] Albert, Brown, and Wood, *J.*, 1956, 2066.
[15] Albert, Brown, and Wood, *J.*, 1954, 3832.