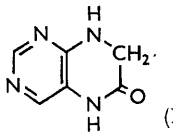
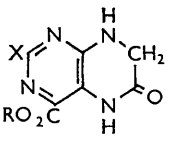
611. *Hydropteridines. Part VI.*[1] *Properties of Some 7,8-Dihydro-6-hydroxypteridine-4-carboxylic Acids and Related Compounds*

By Jim Clark, W. Kernick, and A. J. Layton.

Alkaline hydrolysis of 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids (II: R = H; X = OH, OEt, Cl, or Me_2N) gave 5-amino-4-pyrimidinylaminoacetic acid derivatives (III; R = H), which readily re-cyclised under acid conditions. Cyclisation of the diethyl esters of the latter compounds was acid-catalysed. Semi-quantitative studies of reaction rates suggest analogies with simple amide hydrolysis and formation. All the carboxylic acids were shown to exist as ions at all pH values studied. Ionisation constants and ultraviolet spectra of sixteen compounds are recorded.

Heterocyclic compounds which can adopt a tautomeric form with a hydroxy-group α or γ to a ring-nitrogen atom usually prefer the alternative amide structure.[2] The preference for the amide form is probably even more pronounced when the " hydroxy-group " is in a partly reduced ring, as in 7,8-dihydro-6-hydroxypteridine (I) which exists predominantly in the amide form in the solid state and in solution.[3] Some 2-substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids (II: R = H; X = OH, OEt, Cl, and Me_2N) were described previously [1] and these too are almost certainly cyclic amides.


(I)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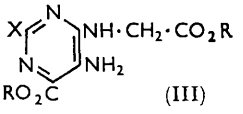

(III)

Ring-opening of Dihydropteridines.—The dihydropteridines (II; R = H) were readily hydrolysed by alkali to 5-amino-6-carboxy-4-pyrimidinylaminoacetic acid derivatives (III; R = H). The reactions were very easily reversed, *e.g.*, by acidification of the hydrolysates and crystallisation of the resulting acids from water. The ring-opened products were more stable as anions, and their nature was determined by comparison with unambiguously prepared specimens without isolating either unknown or reference compounds.

The position of ring-opening was confirmed spectroscopically in cases where the pyrimidinedicarboxylic acids could be isolated and stored as barium salts, and the necessary reference spectra determined. The spectra of solutions of 2-chloro- and 2-ethoxy-7,8-dihydro-6-hydroxypteridine-4-carboxylic acid in cold 2N-sodium hydroxide gradually changed to those of the corresponding pyrimidinecarboxylic acids (III; X = Cl or OEt, R = H) at the same pH value (Fig. 1; Table 2). The changes were quantitative but, in the case of the 2-ethoxy-compound, it was necessary to allow for the fact that the product was itself slowly attacked by alkali. This reagent rapidly decomposed the corresponding dimethylamino-derivative (III; X = Me_2N, R = H).

Unexpectedly, 7,8-dihydro-2,6-dihydroxypteridine-4-carboxylic acid (II; X = OH, R = H) (made by a simplified method) was not cleaved by cold N-sodium hydroxide. In the dark it was oxidised by air to 2,6-dihydroxypteridine-4-carboxylic acid (IV) and, in the presence of air and light, comprehensive decomposition occurred. 7,8-Dihydro-2,6-dihydroxypteridine-4-carboxylic acid was also oxidised by potassium permanganate, a reagent which is known [4] to convert 7,8-dihydro-6-hydroxypteridines into fully aromatic

[1] Part V, Clark and Layton, *J.*, 1959, 3411.
[2] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959; Katritzky and Lagowski, " Heterocyclic Chemistry," Methuen, London, 1960.
[3] Brown and Mason, *J.*, 1956, 3443.
[4] Elion, Light, and Hitchings, *J. Amer. Chem. Soc.*, 1949, **71**, 741; Albert and Brown, *J.*, 1953, 74; Albert, Lister, and Pedersen, *J.*, 1956, 4621.

TABLE 1.

Paper chromatography of alkaline hydrolysis products.

2-Substituent	Series *	R_F Values in solvent system † A	B	C	D
Me_2N	I	0·77	0·59	0·47	0·70
	II	0·77	0·59	0·47	0·70
	III	0·39	0·55	0·67	0·71
OEt	I	0·74	0·60	0·48	0·73
	II	0·74	0·60	0·48	0·73
	III	0·49	0·61	0·72	0·73
Cl	I	0·65	0·62	0·51	0·63, 0·41
	II	0·65	0·62	0·51	0·63, 0·41
	III	0·44	0·58	0·70	0·63
OH	I	0·69	0·55	0·27	" Streaked "
	II	0·69	0·55	0·27	,,
	III	0·48	0·48	0·55	,,

* " Series I " refers to solutions prepared by hydrolysis of dihydropteridines (II; R = H), " Series II " to solutions prepared by hydrolysis of pyrimidine esters (III; R = Et), and " Series III " to untreated solutions of dihydropteridines (II; R = H). † Solvent A, 0·5N-sodium carbonate solution; solvent B, diethylene glycol dimethyl ether–0·5N-sodium carbonate (1 : 2 v/v); solvent C, propan-2-ol–dimethylformamide–10% aqueous ammonia (1 : 1 : 1 v/v); solvent D, propan-2-ol–formic acid–water (3 : 2 : 1 v/v). Chromatography at 20°, by descending method, using Whatman No. 20 paper with solvent A and Whatman No. 1 paper with B, C, and D. Spots were detected by fluorescence under ultraviolet lamps giving radiation of (*a*) principally 360 mμ and (*b*) principally 256 mμ wavelength. Chromatograms run in acidic conditions were exposed to ammonia before examination.

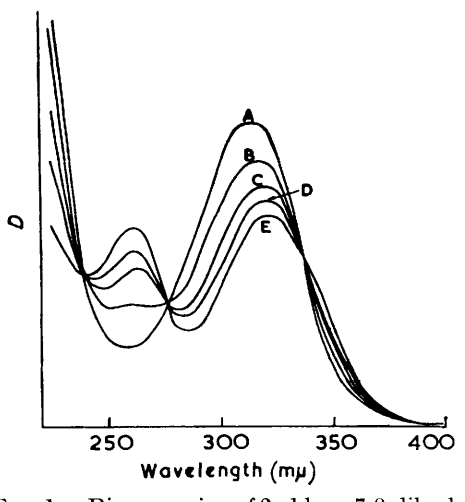


FIG. 1. Ring-opening of 2-chloro-7,8-dihydro-6-hydroxypteridine-4-carboxylic acid (II; R = H, X = Cl) in N-sodium hydroxide solution. A, after 6 min.; B, after 30 min.; C, after 60 min.; D, after 90 min.; E, after 5 hr.

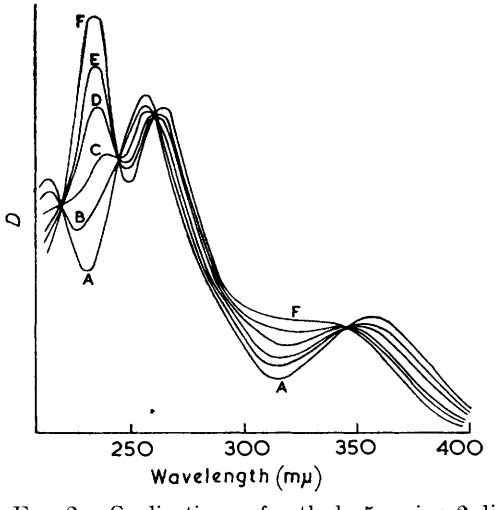
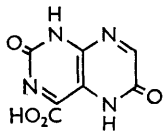


FIG. 2. Cyclisation of ethyl 5-amino-2-dimethylamino-6-ethoxycarbonyl-4-pyrimidinylaminoacetate (III; R = Et, X = Me_2N) at H_0 = 0·01. A, after 20 min.; B, after 80 min.; C, after 140 min.; D, after 260 min.; E, after 6 hr.; F, after 24 hr.

6-hydroxy-derivatives. The polyanion of 2,6-dihydroxypteridine-4-carboxylic acid absorbs at much longer wavelengths than do the species which exist at lower pH values. Similar large bathochromic shifts on anion formation have been noted with 2-, 6-, and 2,6-dihydroxypteridine, all of which are largely " covalent hydrates " as cations or neutral

molecules, but form substantially anhydrous anions.[5] By analogy, the spectrum recorded at pH 14 (Table 4) is that of the polyanion of (IV) whilst the one recorded at pH 0 is that of the cation of 7,8-dihydro-2,6,7-trihydroxypteridine-4-carboxylic acid (V).

In general the dihydropteridine-4-carboxylic acids were much more easily cleaved (Table 2) than 7,8-dihydro-6-hydroxypteridine, which was incompletely hydrolysed after treatment with boiling N-sodium hydroxide for 90 minutes.[6] The lack of stability to alkali seems to be due mainly to the (ionised) 4-carboxyl group, for it is apparent whether the 2-substituent is electron-attracting (Cl) or electron-donating (OEt and Me_2N).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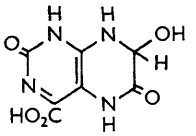
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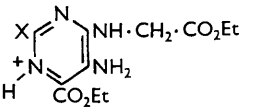
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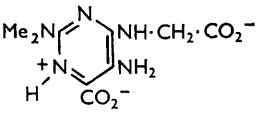
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Formation of Dihydropteridines.—The formation of dihydropteridines was also conveniently followed spectroscopically. The pyrimidine esters (III; X = Cl, OH, OEt, or Me_2N; R = Et) were stable in cold, neutral, aqueous solution, and at pH 2—4. In more acidic solution the compounds cyclised to dihydropteridines (*e.g.*, II; X = Cl, R = Et)

TABLE 2.

Alkaline degradation of 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids (II; R = H).

	Time for half-completion of ring-opening		
X	5N-NaOH	N-NaOH	0·1N-NaOH
Me_2N	45 min.*	2½ hr.*	30 hr.*
OEt	40 min.	4 hr.	36 hr.
Cl	14 min.	40 min.	6½ hr.

* Approximate because of interference from side-reactions.

TABLE 3.

Cyclisation of ethyl 5-amino-6-ethoxycarbonyl-4-pyrimidinylaminoacetates (III; R. = Et).

	Time for half-completion of cyclisation			
	H_0	H_0	pH	pH
X	−0·86	−0·01	1·05	2·11
Me_2N	80 min.	190 min.	52 hr.	slow
EtO	140 min.	13 hr.	74 hr.	slow
Cl	270 min.	205 min.	20 hr.	slow
OH	fast	12 min.	96 min.	16 hr.

Reactions followed spectroscopically at 20°.

(Fig. 2), and the rate of cyclisation increased with decreasing pH. Under most conditions the 2-chloro-compound (III; X = Cl, R = Et), which is the least basic (Table 4), cyclised least rapidly (Table 3), but the catalytic effect of acid was not closely linked with the basic strengths of the pyrimidines. For example, neither the 2-ethoxy- nor the 2-chloro-compound cyclised at any appreciable rate at pH 2·6, although the former was nearly 100% ionised and the latter almost un-ionised. Both cyclised quite rapidly at pH 0.

The results are consistent with the view that the catalytic effect of acid is concerned in making the side-chain ester group more reactive in amide formation with the 5-amino-group. The mechanism is probably analogous to that of acid-catalysed esterification of carboxylic acids or hydrolysis of esters.[7] This type of catalysis is not normally observed in amide formation because the reaction centre of the amine is also the basic centre and hence is inactivated by salt formation.[8] It is noteworthy that this restriction does not apply in the case of very weak bases.[9] In the present case the cation probably has structure (VI) by analogy with 4- and 5-aminopyrimidine [10] and the 5-amino-group is relatively unaffected by protonation. Table 3 shows that there was a progressive increase in reaction rate with increase in hydrogen ion concentration for the ethoxy- and dimethylamino-compounds, which were present as cations over the whole range examined. However the

[5] Brown and Mason, *J.*, 1956, **3443**; Albert, Inoue, and Perrin, *J.*, 1963, **5151**.
[6] Albert, *J.*, 1955, **2690**.
[7] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.
[8] Satchell, *Quart. Rev.*, 1963, **17**, 185.
[9] Snyder and Elston, *J. Amer. Chem. Soc.*, 1954, **76**, 3039.
[10] Albert, Goldacre, and Phillips, *J.*, 1948, **2240**.

chloro-compound (III; R = Et, X = Cl) cyclised faster at H_0 −0·01, where some 10% of the molecules were uncharged, than at H_0 −0·86, where nearly all the molecules were protonated. The diminution of reaction rate in spite of an increase in hydrogen-ion concentration indicates that protonation of the ring does retard cyclisation to some extent.

TABLE 4.

Spectra (in water) and ionisation constants [a] (in water at 20°).

X	pK_a	Concn. (M)	Species [b]	$\lambda_{max.}$ (mμ) [c]	log ε [c]	pH	Fluorescence [d]
Ethyl 2-substituted 5-amino-6-ethoxycarbonyl-4-pyrimidinylaminoacetates (III; R = Et)							
Cl	0·92 ± 0·05 [e]	10^{-4}	+	*215*, 242, 287, 345	*4·11*, 3·85, 3·80, 4·07	−1·38 [f]	—
			0	236, 264, 343	3·75, 3·81, 3·94	6·0	B 4+
OEt	4·58 ± 0·05	10^{-3}	+	243, 343	3·92, 4·02	2·3	P +
			0	233, 346	3·90, 3·92	6·8	B 2+
OH	3·0 [g]	—	+	Cyclises rapidly			
			0	240, 346	3·98, 3·90	6·0	BG +
Me_2N	6·51 ± 0·04 [e]	—	+	214, 257, 359	4·14, 4·25, 3·77	3·9	B 2+
			0	203, 256, 378	4·27, 4·17, 3·73	8·3	GY 3+
2-Substituted 5-amino-6-carboxy-4-pyrimidinylaminoacetic acids (III; R = H)							
Cl			+	Cyclises rapidly		−2·0 [f]	P +
	3·32 ± 0·05 [h]	5×10^{-3}	+−	*233*, 272, 338	*3·87*, 3·72, 3·99	1·3	B 2+
	4·44 ± 0·06 [h]	5×10^{-3}	+−− [i]	207, 263, 330	4·19, 3·77, 3·95	3·9	B 3+
			−−	207, 261, 323	4·27, 3·88, 3·90	7·0	B 3+
OEt	3·60 ± 0·07	2×10^{-3}	+−	Cyclises rapidly		1·6	P 2+
	7·33 ± 0·04	2×10^{-3}	+−−	238, 324	3·91, 3·99	5·4	B 4+
			−−	226, 322	3·90, 3·86	9·5	B 3+
OH [j]	—	—	−−	234, 325	4·01, 3·89	6·3	B 2+
Me_2N [j]	9·85 ± 0·08	5×10^{-3}	+−−	217, 252, 338	4·21, 4·24, 3·78	7·0	B 3+
			−−	251, 345	4·13, 3·68	11·8	G +
2-Substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylic acids (II; R = H)							
Cl	−0·19 [e]		+	221, 316, 329	4·37, 4·01, 4·02	−2·2 [f]	P +
	2·94 ± 0·04	5×10^{-3}	+−	217, *296*, 324	4·45, *3·72*, 3·88	1·5	None
	12·31 [e]		−	215, *289*, 324	4·45, *3·71*, 3·91	6·0	P 4+
			−−	314	4·02	13·3	None
OEt	0·81 [e]		+	215, 254, 328	4·41, 3·70, 4·05	−1·2	P +
	5·31 ± 0·02	4×10^{-3}	+−	288, 320	3·83, 4·03	3·1	B 4+
	12·83 [e]		−	210, 278, 327	4·43, 3·68, 3·96	7·5	P 4+
			−−	300	4·00		B +
OH			+	252, 345	3·96, 4·02	−1·0	None
	12·04 ± 0·02	9×10^{-3}	−	215, 254, 323	4·42, 4·01, 3·96	7·5	B 3+
			−−	Oxidises rapidly in air		14·0	
Me_2N	0·57 [k]		+	235, 266, 334	4·35, 4·23, 3·74		None
	7·31 ± 0·05	2×10^{-3}	+−	230, 265, 330	4·35, 4·27, 3·74	4·7	None
	>13		−	226, 285, 358	4·29, 4·03, 3·83	9·5	GB 2+
			−−	Unstable due to ring-opening			
Ethyl 2-substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylates (II; R = Et)							
Cl	−0·54 [e]	—	+	221, 318, 330	4·42, 4·06, 4·08	−2·5 [f]	P 2+
			0	215, 282, 340	4·40, 3·66, 3·97	6·0	B 4+
OEt	3·14 ± 0·08 [e]	—	+	215, 254, 331	4·42, 3·72, 4·07	0·7	P 2+
			0	211, 271, 343	4·48, 3·70, 4·07	6·0	B 3+
OH	1·75 [e]	—	+	252, 347	3·93, 4·03	−0·5 [f]	B 5+
			0	216, 256, 336	4·35, 3·91, 3·99	6·0	P 2+
Me_2N	4·71 ± 0·03 [e]	—	+	235, 266, 342	4·35, 4·22, 3·75	1·1	None
			0	231, 283, 380	4·26, 4·02, 3·78	6·8	G 2+
2,6-Dihydroxypteridine-4-carboxylic acid (IV)							
	—	—		244, 345	4·05, 3·96	0·0	
	—	—		228, *238*, 417	4·31, *4·27*, 3·84	14·0	

[a] Determined potentiometrically. [b] + = cation, 0 = neutral molecule, +− = zwitterion, +−− = triply charged species, *e.g.*, (VII), − = anion, −− = dianion. [c] Inflexions in italics. [d] Fluorescence varies from + (weak fluorescence in ultraviolet light) to 5+ (strong fluorescence in daylight); B = blue, P = purple, G = green, Y = yellow. [e] Determined spectrophotometrically. [f] H_0 in sulphuric acid. [g] Approximate because of ring-closure during determination. [h] Corrected for proximity of another pK_a by the method of Noyes (*Z. phys. Chem.*, 1893, **11**, 495). [i] Also contains 17% of zwitterion and 18% of dianion. [j] Other species cyclise rapidly. [k] Approximate because of small spectral change on ionisation.

It is probably that catalysis of the type described above is important in condensations between 4,5-diaminopyrimidines and aldehydo- or keto-acids or -esters, many of which take place in acid conditions.[11] It has been pointed out that the effect of pH on such condensations cannot be explained in terms of protonation of the pyrimidine only.[12]

Ionisation constants for the various compounds mentioned above, together with ultraviolet absorption data for those species with satisfactory stability, are given in Table 4. In the case of the dicarboxylic acids, the 2-dimethylamino-, 2-ethoxy-, and 2-chloro-derivatives (III: R = H; X = Me_2N, EtO, or Cl) resembled each other closely. Their pK_a values (9·85, 7·33, and 4·44) are associated with deprotonation of the ring and correspond to the pK_a values of the esters (III; R = Et) but with the acidity reduced in each case by the presence of an ionised carboxyl group. The change is similar to that observed in passing from ethyl picolinate (pK_a 2·21) to picolinic acid (relevant pK_a 5·32).[13] The values of 3·60 and 3·32 recorded for the 2-ethoxy- and 2-chloro-derivatives (III; R = H, X = Cl) are assigned to the side-chain carboxyl group in each case. The above assignments imply that the compounds exist as ions at all pH values. Thus, the dimethylamino-derivative (III; R = H, X = Me_2N) exists as the triply charged species (VII) in neutral solution and as a dianion at high pH values. Other species (zwitterion and cation) are unstable, and the lack of stability is associated with an un-ionised side-chain carboxyl group which readily participates in cyclisation.

Similar considerations to those applied above show that the pK_a values recorded for the dihydropteridinecarboxylic acids (II: R = H; X = Cl, OEt, or Me_2N) are associated with, in increasing order of magnitude, ionisation of the carboxyl group, deprotonation of the ring, and ionisation of the 6-hydroxy-group. This order of assignment again implies that the compounds are ionised at all pH values and this is confirmed by spectral measurements. Replacement of a non-ionised carboxyl group by an ethoxycarbonyl group causes very little change in this, as in other [13,14] series. For example, the spectra of cations of pteridinecarboxylic acids (II; R = H) are almost identical with those of cations of their esters (II; R = Et) (Table 4).

Experimental

2-Dimethylamino- and 2-Ethoxy-4-ethoxycarbonyl-7,8-dihydro-6-hydroxypteridine (II: R = Et; X = Me_2N or OEt).—The relevant pyrimidine diethyl ester (III: R = Et; X = Me_2N or OEt) (1 g.) was dissolved in the minimum volume of 2N-hydrochloric acid and the solution set aside for 5 hr., filtered (charcoal), and the filtrate adjusted to pH 7 with sodium citrate and 5N-sodium hydroxide. The product (70—80%) was filtered off and crystallised from dioxan.

Sodium Salts of 2-Substituted 7,8-Dihydro-6-hydroxypteridine-4-carboxylic Acids (II: R = H; X = Me_2N, OEt, or Cl).—Ethyl 2-chloro-7,8-dihydro-6-hydroxypteridine-4-carboxylate (1 g.) was heated under reflux with 0·5N-sodium carbonate (30 ml.) for ½ hr., cooled, and filtered. *Sodium 2-chloro-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (0·6 g.) crystallised from water as needles, m. p. >250° (Found: C, 33·7; H, 2·0; Cl, 14·1. $C_7H_4ClN_4Na$ requires C, 33·5; H, 1·6; Cl, 14·15%).

Similarly prepared were *sodium 2-dimethylamino-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (m. p. >250°) (Found: C, 39·1; H, 4·4; N, 25·2. $C_9H_{10}N_5NaO_3,H_2O$ requires C, 39·0; H, 4·4; N, 25·3%), and *sodium 2-ethoxy-7,8-dihydro-6-hydroxypteridine-4-carboxylate* (m. p. >250°) (Found: C, 39·0; H, 3·9. $C_9H_9N_4NaO_4,H_2O$ requires C, 38·9; H, 4·0%). These compounds were crystallised from water containing a little sodium carbonate.

Sodium 7,8-Dihydro-2,6-dihydroxypteridine-4-carboxylate.—Ethyl 2-chloro-6-ethoxycarbonyl-5-nitro-4-pyrimidinylaminoacetate [1] (10 g.), glacial acetic acid (25 ml.), pyridine (8 ml.), and water (75 ml.) were heated on a water-bath for ½ hr. Ethyl 6-ethoxycarbonyl-2-hydroxy-5-nitro-4-pyrimidinylaminoacetate (7 g.) was filtered off and washed with dilute hydrochloric acid, water, and ethanol.

[11] Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78; Albert, Brown, and Cheeseman, *J.*, 1952, 1620; Pfleiderer, *Chem. Ber.*, 1957, **90**, 2604.
[12] Albert, *Quart. Rev.*, 1952, **6**, 227.
[13] Green and Tong, *J. Amer. Chem. Soc.*, 1956, **78**, 4896.
[14] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127; Mason, *J.*, 1959, 1247.

The nitro-compound (3 g.) was stirred with water (50 ml.) and sodium hydrogen carbonate (6 g.) until a clear solution was obtained. Sodium dithionite (6 g.) was added during 5 min. and the mixture heated on a water-bath for 1 hr. The *sodium salt* (1·54 g.) separated from the cooled solution as pink needles, m. p. >250° (from water) (Found: C, 36·2; H, 2·6. $C_7H_5N_4NaO_4$ requires C, 36·2; H, 2·2%).

Ring-opening of 7,8-Dihydro-6-hydroxypteridine-4-carboxylic Acids.—(*a*) The sodium salt of the 2-substituted 7,8-dihydro-6-hydroxypteridine-4-carboxylic acid (0·02 g.) was heated with 2N-sodium hydroxide solution (5 ml.) on a water-bath for 1 hr. The solution was treated with sodium hydrogen carbonate (1·5 g.) and diluted to 20 ml. with water. Another series of solutions was prepared by treating the ethyl 2-substituted 5-amino-6-ethoxycarbonyl-4-pyrimidinylaminoacetate (III; R = Et) (0·02 g.) with 2N-sodium hydroxide solution (5 ml.) on a water-bath for 20 min. or at 20° for 3 hr., and adding sodium hydrogen carbonate and water as above.

Corresponding members of the two series of solutions were compared with each other and with the relevant untreated pteridine (II; R = H) by paper chromatography in three alkaline and one acidic solvent systems. R_F values are given in Table 1.

(*b*) *Spectroscopic method.* Approximately 10^{-4}M-aqueous solutions of dihydropteridines (II; R = H) containing sodium hydroxide in various concentrations were kept in the dark at 20°. The ultraviolet spectra of the solutions were measured at intervals and compared with those of the expected degradation products, namely salts of 2-substituted 5-amino-6-carboxy-4-pyrimidinylaminoacetic acids (III; R = H). The spectra of pure degradation products and starting materials are included in Table 3 and the progress of one ring-opening reaction is illustrated in Fig. 1. Times for half-completion of ring-opening are in Table 2.

Salts of 2-Substituted 5-Amino-6-carboxy-4-pyrimidinylaminoacetic Acids.—The diethyl ester (III; R = Et, X = Cl) (0·5 g.) was heated on a water-bath for 20 min. with carbonate-free 2·5N-sodium hydroxide solution (15 ml.). An excess of 2N-barium chloride solution was added and *barium 5-amino-6-carboxy-2-chloro-4-pyrimidinylaminoacetate trihydrate* (82%) was filtered off and washed with water and ethanol. Contact of the mixture with air was minimised until the product had been isolated.

Barium salts of *5-amino-6-carboxy-2-dimethylamino-*, *2-ethoxy-*, and *2-hydroxy-4-pyrimidinylaminoacetic acids* (Table 5) were similarly prepared except that only 5 ml. of 2·5N-sodium hydroxide was used.

The disodium salt of 5-amino-6-carboxy-2-chloro-4-pyrimidinylaminoacetic acid was prepared by heating the diethyl ester (III; R = Et, X = Cl) (0·5 g.) with 2·5N-sodium hydroxide (15 ml.) on a water-bath for 20 min. Ethanol was added to the hot mixture to the point of incipient precipitation. The *disodium salt* (0·6 g.) formed needles, m. p. >250° (from aqueous ethanol). Disodium salts of the other dicarboxylic acids could not be made in this way.

TABLE 5.

Analytical data for salts (III; R = Metal).

		Found (%)				Required (%)			
X	Formula	C	H	N	Ba	C	H	N	Ba
Cl	$C_7H_5BaClN_4O_4,3H_2O$	19·6	2·4	12·7	31·9	19·3	2·5	12·85	31·5
Cl	$C_7H_5ClN_4Na_2O_4,2H_2O$	26·2	2·6	17·4	—	25·7	2·8	17·2	—
OEt	$C_9H_{12}BaN_4O_5,3H_2O$	23·9	3·7	—	31·5	24·25	3·6	—	30·8
OH	$C_7H_6BaN_4O_5,7H_2O$	17·0	3·8	11·0	—	17·2	4·1	10·9	—
Me_2N	$C_9H_{11}BaN_5O_4,4H_2O$	23·3	3·9	15·1	—	23·4	4·1	15·1	—

Cyclisation of Ethyl 2-Substituted 5-Amino-6-ethoxycarbonyl-4-pyrimidinylaminoacetates (III: R = Et; X = Cl, OEt, Me_2N, or OH).—*Spectroscopic method.* Approximately 10^{-4}M-solutions of these compounds in aqueous sulphuric acid of various concentrations were kept at 20° in the dark and their ultraviolet spectra measured at intervals. The progress of one reaction is illustrated in Fig. 2 and times for half-completion of the reactions are in Table 3.

2,6-Dihydroxypteridine-4-carboxylic Acid (IV).—Sodium 7,8-dihydro-2,6-dihydroxypteridine-4-carboxylate (0·23 g.), water (10 ml.), and N-sodium hydroxide (1·2 ml.) were stirred during the addition (10 min.) of 0·1M-potassium permanganate (7 ml.), then for a further 10 min. The pH was adjusted to 2·5 with 5N-sulphuric acid and a brown solid (0·15 g.) was filtered off. The solid

was dissolved in water (10 ml.) and the minimum quantity of 0·1N-sodium hydroxide, and re-precipitated as before. The process was repeated several times, to give 2,6-*dihydroxypteridine*-4-*carboxylic acid* as a buff-coloured solid, m. p. >250° (Found: C, 36·0; H, 3·0; N, 24·0. $C_7H_4N_4O_4,1\frac{1}{2}H_2O$ requires C, 35·75; H, 3·0; N, 23·8%).

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