Hydropteridines. Part II. Formyl Derivatives of Some 5 : 6 : 7 : 8-Tetrahydropteridines.*

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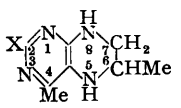
5-Formyl derivatives of 5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridines (I; X = H, Cl, OH, or NH_2) have been prepared. Their stability and some structural aspects have been studied spectroscopically. The absorption of 4-methylpteridine was found to vary with concentration in 0·1N-sodium hydroxide.

The 5 : 6 : 7 : 8-tetrahydropteridines (I) described by Lister and Ramage * have been formylated in the cold by use of anhydrous formic acid in the presence of acetic anhydride, a method used to prepare the formyl derivatives of pteroylglutamic acid and its reduced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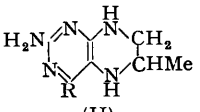
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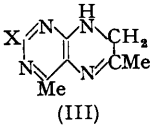
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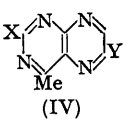

(IV)

derivatives (May *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 3067; Roth *et al.*, 1952, **74**, 3247). Reduction of 7 : 8-dihydropteridines in formic acid, followed by treatment with acetic anhydride, also gave the corresponding formylated tetrahydropteridines. By analogy

TABLE 1. *Pteridines* (IV).

This and the other Tables show the maximum and minimum wave-lengths in mμ; the values in parentheses are $10^{-4}\varepsilon_{max.}$. The determinations were made on a Unicam S.P. 500 quartz spectrophotometer (kindly lent by the Wool Textile Research Council).

		0·1N-Hydrochloric acid		0·1N-Sodium hydroxide	
X	Y	Max.	Min.	Max.	Min.
Cl	H	218 (2·20) 309 (0·981)	255 (0·261)	220 (0·744) 289 (1·67)	253 (0·317)
Cl	Me	—	—	227 (1·03) 291 (1·43)	258 (0·473)
NH_2	H	217 (1·66) 305 (0·570)	264 (0·204)	226 (2·80) 259 (0·768)	250 (0·701)
NH_2	Me	—	—	228 (2·25) 254 (0·806)	Inflection —
NEt_2	H	226 (2·20)	291 (0·115)	240 (2·41) 282 (1·23)	267 (0·952)
NEt_2	Me	226 (2·32)	298 (0·126)	240 (2·47) 281 (1·42)	267 (1·27)
OH	Me	—	—	222 (2·68) 259 (0·800)	253 (0·793)
Pteridine	—	—	—	<220 (>0·48) 266 (0·381) 312, 320 (0·668)	241 (0·292) 280 (0·368)

	Max.	Min.
Pteridine in water pH 5·9	<220 (>0·52) 230 (0·275) 298 (0·763) 309 (0·709)	248 (0·131) Inflection

In addition to the values tabulated, the substituted pteridines in alkaline solution showed a characteristic absorption band at wave-lengths greater than 350 mμ, *e.g.*, 2-diethylamino-4 : 6-dimethylpteridine 413 (0·743), 2-amino-4 : 6-dimethylpteridine 370 (0·643), and 2-chloro-4-methylpteridine 374 (0·410).

with the pteroylglutamic acid derivatives, these were 5-formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridines. Only in the case of the 2-aminotetrahydropteridines (II; R = H or Me) were diformyl derivatives obtained and these were hydrated. In general,

* Part I, *J.*, 1953, 2234.

formylation of the tetrahydropteridines caused a lowering of the melting point and where colour was shown this was less intense.

Alkaline solutions of the 7 : 8-dihydropteridines (III) gave spectra which changed on ageing, as had been observed previously with their acid solutions (Part I). In order to show that aerial oxidation to pteridines was general, 4-methylpteridines (IV; Y = H) were prepared (by condensing 4 : 5-diamino-6-methylpyrimidines with polyglyoxal), these being more accessible than the 4 : 6-dimethylpteridines (IV; Y = Me) derived by oxidation of the dihydropteridines. Comparisons were made of the spectra of these pteridines (Table 1,) in 0·1N-hydrochloric acid, and in 0·1N-sodium hydroxide, with the

TABLE 2. 7 : 8-*Dihydropteridines* (III).

	0·1N-Sodium hydroxide						
X	Max.		Min.	X	Max.		Min.
Cl [a,b]	217 (2·00)	294 (0·809)	251 (0·223)	NEt_2	240 (1·83)	320 (1·43)	274 (0·439)
NH_2	223 (2·22)	307 (1·02)	262 (0·187)	OH [c]	222 (2·29)	304 (1·17)	260 (0·301)

[a] In water, $\lambda_{max.}$ 215, 297 mμ; $\lambda_{min.}$ 247 mμ. [b] In ethanol, $\lambda_{max.}$ 217, 297 mμ; $\lambda_{min.}$ 253 mμ. [c] In water, $\lambda_{max.}$ 222, 289 mμ; $\lambda_{min.}$ 254 mμ.

TABLE 3. 5 : 6 : 7 : 8-*Tetrahydropteridines*.

Substituents in position		0·1N-Sodium hydroxide	
2	4	Max.	Min.
Me [a]	H	<215 271 (0·507), 301 (0·738)	240 (0·223), 274 (0·503)
Me [b]	Cl	<215 275 (0·602), 306 (0·760)	244 (0·254), 281 (0·586)
Me	NH_2	226 (1·22), 313 (0·850)	278 (0·352)
H	NH_2	231 (0·857), 316 (0·573)	279 (0·190)
Me	NEt_2	241 (1·32), 320 (0·732)	227 (1·12), 285 (0·416)
Me	OH	230 (0·841), 313 (0·671)	271 (0·056)

[a] In water, $\lambda_{max.}$ 210, 303 mμ; $\lambda_{min.}$ 245 mμ. [b] In water, $\lambda_{max.}$ 211, 305 mμ; $\lambda_{min.}$ 246 mμ.

TABLE 4. 5-*Formyltetrahydropteridines*.

Substituent in position		0·1N-Hydrochloric acid		0·1N-Sodium hydroxide	
2	4	Max.	Min.	Max.	Min.
Me	H	213 (1·32)	246 (0·641)	251 (1·00)	234 (0·777)
		273 (1·25)		289 (0·593)	276 (0·534)
Me	Cl	222 (1·47)	248 (0·473)	262 (0·788)	240 (0·432)
		279 (1·10)		293 (0·632)	277 (0·523)
Me	NH_2	216 (2·13)	272 (0·594)	250 (1·01)	239 (0·990)
		287 (0·735)		296 (0·885)	276 (0·578)
H	NH_2	217 (2·07)	232 (1·45)	259 (1·09)	236 (0·763)
		245 (1·71)	281 (0·430)	309 (0·800)	284 (0·374)
		297 (0·512)			
Me	OH	231 (1·40)	264 (0·252)	256 (0·816)	242 (0·711)
		301 (1·19)		296 (1·04)	274 (0·634)

corresponding spectra of aged solutions of the dihydropteridines. The similarity observed showed that 7 : 8-dihydropteridines (Table 2 and Part I) all underwent oxidation to the corresponding pteridines. These observations were in agreement with those of O'Dell and his co-workers (*ibid.*, 1947, **69**, 250) that 7 : 8-dihydroxanthopterin and 7 : 8-dihydropteroylglutamic acid, under these conditions, were similarly oxidised to pteridines.

The results observed for oxidation in alkaline solutions were more definite than those obtained for acid solutions and in every case it was possible to follow the oxidation to completion, *i.e.*, until no further change was observed in the spectrum. The rate of oxidation varied with the nature of the solvent and the groups at the 2-position; *e.g.*, 2-chloro-7 : 8-dihydro-4 : 6-dimethylpteridine (III; X = Cl) was completely oxidised in 24 hours whereas the corresponding 2-diethylamino-derivative (III; X = NEt_2) required 14 days. In certain cases the oxidation was accompanied by development of visual colour, which was often apparent shortly after preparation of the solution. This change, however, was shown not to be rapid enough to affect the spectra of the dihydropteridines whilst the

determinations were being made. The oxidation appeared to be essentially quantitative, as was indicated by the similar extinction coefficients obtained from the spectra of an aged dihydropteridine and the corresponding pteridine solutions.

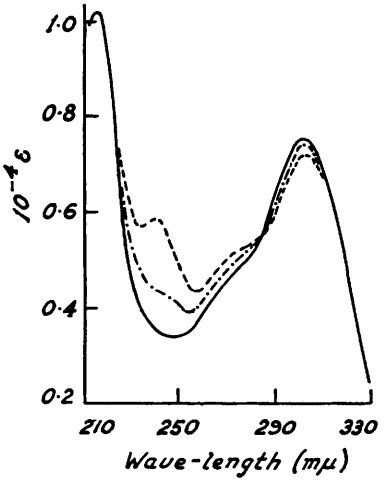
In neutral solvents there was less oxidation: the 2-chlorodihydropteridine (III; X = Cl) in alcohol gave an unchanged spectrum after six weeks, and the 2-hydroxy-derivative (III; X = OH) in water was only slightly altered after one week.

With the 5 : 6 : 7 : 8-tetrahydropteridines (Table 3) stability was confined to acid solutions (Part I). In alkaline media, the spectra for this group gradually altered, at a rate which differed according to the 2-substituent. The most rapid deterioration was noted with (I; X = OH or NH_2), the spectra being unrecognisable after 24 hours, whilst more persistent spectra were shown by (I; X = H or Cl). With (I; X = NEt_2) in alkaline solution, oxidation was complete after six days and the absorption bands corresponded with those of 2-diethylamino-4 : 6-dimethylpteridine (IV; X = NEt_2, Y = Me).

5-Formyltetrahydropteridines (Table 4) in both acid and alkaline media gradually undergo hydrolysis of the formyl group: after 24 hours the solutions give the spectra of the parent tetrahydropteridines.

Absorption of 4-methylpteridine in 0·1N-NaOH.

———— $5{\cdot}20 \times 10^{-5}$M.
—·—·— $2{\cdot}60 \times 10^{-5}$M.
— — — — $1{\cdot}30 \times 10^{-5}$M.



Comparisons of the hydropteridine spectra have also enabled some structural features to be identified. The similarity of the spectra indicated that the primary amino-group was present predominantly in the amino- rather than the imino-form (cf. Andersen and Seeger, *ibid.*, 1949, **71**, 340).

The dihydropteridine ring system exhibited no pronounced basic character; thus, the spectra of the 2-chloro-derivative (III; X = Cl) showed a maximum absorption band at a common wave-length in acid, alkali, aqueous, and ethanolic solutions. The tetrahydropteridine ring system, however, was more basic, as shown by the formation of stable hydrochlorides and by the change in spectra with acid and alkaline solutions. Whereas the 2-amino- or 2-diethylamino-dihydropteridine (III; X = NH_2 or NEt_2) showed no evidence of salt formation, similar spectra being obtained in acid and alkali, the corresponding tetrahydro-derivatives (I) gave very different spectra in the two media, indicating an appreciable degree of basic character.

For 4-methylpteridine in 0·1N-sodium hydroxide the character of the spectrum varied considerably with the concentration. It was observed (see Figure) that in dilute solution ($1{\cdot}30 \times 10^{-5}$M) the spectrum was generally similar to those of the pteridines, but in more concentrated solutions (5×10^{-5}M) resembled those of 5 : 6 : 7 : 8-tetrahydropteridines. In this connection the 4-methyl group has been reported (Albert, *Nature*, 1954, **173**, 1176) to have an anomalous base-weakening effect on pteridine.

With pteridine itself in 0·1N-sodium hydroxide, the spectrum was independent of concentration ($3-16 \times 10^{-5}$M) and in aqueous solution a spectrum in agreement with that

recorded by Albert, Brown, and Cheeseman (*J.*, 1951, 474) was obtained. The spectra in alkali and water were surprisingly different (Table 1) in view of the fact that the pK_a value for pteridine was 4·12 (*idem, loc. cit.*). It was established that the spectrum in aqueous solution was essentially reproduced from an alkaline solution by neutralisation with hydrochloric acid after 2 hours.

Experimental

Samples before analysis were dried at 100°/3 mm. for 1 hr.

2-Amino-5 : 6 : 7 : 8-tetrahydro-6-methylpteridine.—A solution of 2-amino-7 : 8-dihydro-6-methylpteridine (0·75 g.) in acetic acid (40 c.c.) was hydrogenated over Adams catalyst (0·06 g.). The straw-coloured solution, after removal of the catalyst, was evaporated in a hydrogen atmosphere under reduced pressure but darkened considerably. The dark green oil which remained solidified and after crystallisation from ethyl acetate (charcoal) gave *2-amino-5 : 6 : 7 : 8-tetrahydro-6-methylpteridine* (0·4 g., 41%) as a yellow micro-crystalline solid, m. p. 178° (Found : C, 48·8; H, 6·6. $C_7H_{11}N_5,\frac{1}{2}H_2O$ requires C, 48·3; H, 6·95%).

2-Chloro-5-formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine.—(*a*) 2-Chloro-7 : 8-dihydro-4 : 6-dimethylpteridine (0·4 g.) in formic acid (98—100%; 40 c.c.) was reduced with hydrogen over Adams catalyst (0·04 g.). After the theoretical uptake the solution was treated with acetic anhydride (3 c.c.) and left overnight under hydrogen. On evaporation, after removal of the catalyst, a red oil was obtained which solidified on cooling. Crystallisation from moist ethanol gave *2-chloro-5-formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine* (0·23 g., 50%) as an orange, micro-crystalline solid, m. p. 203—204° (Found : C, 48·1; H, 4·7; N, 24·7. $C_9H_{11}ON_4Cl$ requires C, 47·7; H, 4·9; N, 24·7%).

(*b*) 2-Chloro-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine (0·15 g.) in formic acid (98—100%; 10 c.c.) and acetic anhydride (2 c.c.) were left overnight under hydrogen. The solid obtained on evaporation, after crystallisation from ethanol, had m. p. 203—204° which was not depressed on admixture with the product above.

5-Formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine.—5 : 6 : 7 : 8-Tetrahydro-4 : 6-dimethylpteridine (0·2 g.) was treated as in method (*b*) and gave *5-formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine* (0·1 g., 43%) as colourless prisms, m. p. 201—202°, from ethyl acetate (Found : C, 56·5; H, 6·3. $C_9H_{12}ON_4$ requires C, 56·2; H, 6·3%).

2 : 5-Diformyl Derivatives of 2-Amino-5 : 6 : 7 : 8-tetrahydromethylpteridines.—2-Amino-7 : 8-dihydro-4 : 6-dimethylpteridine (0·5 g.) was hydrogenated by method (*a*), and *2-formamido-5-formyl-5 : 6 : 7 : 8-tetrahydro-4 : 6-dimethylpteridine* (0·27 g., 42%) was obtained as pale cream needles, m. p. 187°, from ethanol (Found : C, 47·7; H, 6·0; N, 28·4. $C_{10}H_{13}O_2N_5,H_2O$ requires C, 47·4; H, 6·0; N, 27·7%). In a similar manner *2-formamido-5-formyl-5 : 6 : 7 : 8-tetrahydro-6-methylpteridine* (61%) was obtained as cream crystals, m. p. 153° (Found : C, 45·4; H, 5·4; N, 29·6. $C_9H_{11}O_2N_5,H_2O$ requires C, 45·2; H, 5·5; N, 29·3%).

5-Formyl-5 : 6 : 7 : 8-tetrahydro-2-hydroxy-4 : 6-dimethylpteridine.—Reduction of 7 : 8-dihydro-2-hydroxy-4 : 6-dimethylpteridine and acetic anhydride treatment gave a brown powder. This was taken up with hot water (charcoal) and, on cooling, colourless crystals of 5-formyl-5 : 6 : 7 : 8-tetrahydro-2-hydroxy-4 : 6-dimethylpteridine (72%), m. p. 360°, were obtained (Found : C, 52·2; H, 6·0; N, 27·2. $C_9H_{12}O_2N_4$ requires C, 51·9; H, 5·8; N, 26·9%).

4-Methylpteridine.—4 : 5-Diamino-6-methylpyrimidine (0·5 g.) and polyglyoxal (0·25 g.; Albert, Brown, and Cheeseman, *loc. cit.*, p. 475) were refluxed in methanol (50 c.c.) for 1 hr. Evaporation of the solvent left an orange solid which on crystallisation from light petroleum (b. p. 100—120°) gave *4-methylpteridine* (0·25 g., 43%) as orange needles. Sublimation *in vacuo* gave yellow needles, m. p. 153° (Found : C, 57·2; H, 4·2. $C_7H_6N_4$ requires C, 57·5; H, 4·1%).

2-Chloro-4-methylpteridine.—A solution of polyglyoxal (0·15 g.) and 4 : 5-diamino-2-chloro-6-methylpyrimidine (0·45 g.) in dry ethanol (20 c.c.) was refluxed for 10 min. The yellow residue, after removal of the ethanol, was extracted with hot ligroin and the extracts concentrated. On cooling, *2-chloro-4-methylpteridine* (0·32 g., 63%) emerged as pale yellow needles, m. p. 155—156° (Found : C, 46·1; H, 2·9. $C_7H_5N_4Cl$ requires C, 46·6; H, 2·8%).

2-Amino-4-methylpteridine.—Polyglyoxal (0·14 g.) was added to a solution of 2 : 4 : 5-triamino-6-methylpyrimidine (0·28 g.) in methanol (20 c.c.) and refluxed. A precipitate formed almost immediately and after 30 min. the solution was cooled and the solid filtered off. Crystallisation from water gave *2-amino-4-methylpteridine* (0·25 g., 77%) as brown needles, m. p. 289° (Found : C, 51·8; H, 4·2; N, 43·5. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·5%).

2-*Diethylamino*-4-*methylpteridine*.—4 : 5-Diamino-2-diethylamino-6-methylpyrimidine (0·4 g.) was condensed as for the 2-chloro-compound. From light petroleum (b. p. 60—80°) 2-*diethylamino*-4-*methylpteridine* (0·23 g., 45%) was obtained as deep red prisms, m. p. 122° (Found : C, 61·1; H, 6·9. $C_{11}H_{15}N_5$ requires C, 60·8; H, 7·0%).

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