Pteridine Studies. Part XXXIX.[1,2] Pteridines Unsubstituted in the 4-Position; a New Synthesis from Pyrazines, *via* 3,4-Dihydropteridines

By **Adrien Albert** and **Kyuji Ohta**, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra

3-Aminopyrazine-2-carboxamide (IIa), warmed in phosphoryl chloride and dimethylformamide, gave 3-aminopyrazine-2-carbonitrile (IV), which was hydrogenated to give 2-amino-3-aminomethylpyrazine (I). This diamine was cyclised to 3,4-dihydropteridine and its 2-methyl-, 2-hydroxy-, and 2-amino-derivatives by treatment with ethyl orthoformate, ethyl orthoacetate, ethyl chloroformate, and *S*-methylisothiouronium hydrochloride, respectively. Similarly 2-amino-3-aminomethyl-5-methylpyrazine, obtained from 3-amino-6-methylpyrazine-2-carbonitrile by hydrogenation, furnished 3,4-dihydro-6-methylpteridine. All these 3,4-dihydropteridines were selectively oxidised (*e.g.* by manganese dioxide) to the corresponding pteridines, including the long-sought 6-methylpteridine.

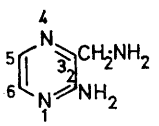
2-Amino-3-ethoxalylaminomethylpyrazine (XIII) was made from the diamine (I) and ethyl triethoxyacetate. Hydrogenation of 3-ethoxalylaminopyrazine-2-carbonitrile (XIVb), prepared from the nitrile (IV) and ethoxalyl chloride, gave ethyl 3,4-dihydropteridine-2-carboxylate (VId) and ethyl 1,2,3,4-tetrahydropteridine-2-carboxylate (XVa). The former (VId) was hydrolysed to 3,4-dihydropteridine-2-carboxylic acid (VIe) and also oxidised to ethyl pteridine-2-carboxylate. The diamine (I) and formaldehyde furnished 1,2,3,4-tetrahydropteridine (XVb).

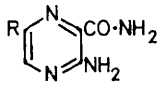
8-Aminoimidazo[1,5-*a*]pyrazine-3-thiol (XIIa), unexpectedly obtained from the diamine (I) and carbon bisulphide, was desulphurised with nickel to give 8-aminoimidazo[1,5-*a*]pyrazine.

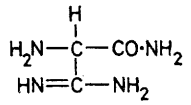
Ionisation constants and u.v. spectra are reported and discussed. The covalent hydration of 6-methylpteridine and ethylpteridine-2-carboxylate is described.

HITHERTO all reactions for converting pyrazines into pteridines have simultaneously furnished a substituent in the 4-position. This limitation is avoided in the following synthesis, based on a new class of pyrazine bases [2-amino-3-aminomethylpyrazine (I) and its derivatives], and proceeding through 3,4-dihydropteridines (for several of which this is the first practicable synthesis).

The key intermediate, 3-aminopyrazine-2-carboxamide (IIa), was conveniently prepared from 2-amidino-2-aminoacetamide (III) and glyoxal by the method of Vogl and Taylor.[3] The amidine (III) was made from ethyl cyanoacetate, first by converting[4] the cyano- and the ester group into an amidino- and an amide group respectively, then by coupling[5] the product with diazotised aniline. The resulting phenylazo-derivative has previously been converted into the compound (III) by treatment with zinc and hydrochloric acid[5] or by hydrogenation over platinium;[6] however, the yield was much improved (85%) when the azo-derivative was hydrogenated over palladium–carbon.


(I)


(II) a; R = H
b; R = Me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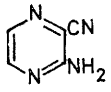
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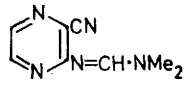

(V)

Because the amide (IIa) could not be reduced directly to the primary amine (I), *e.g.* with lithium aluminium

[1] Part XXXVIII, T. J. Batterham and J. A. Wunderlich, *J. Chem. Soc.* (*B*), 1969, 489.

[2] A preliminary account of some of this work was submitted to *Chem. Comm.*, 1969, 1168.

[3] O. Vogl and E. C. Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2472.

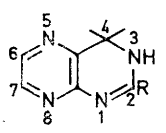
[4] E. N. Shaw and D. W. Woolley, *J. Biol. Chem.*, 1949, **181**, 89.

[5] L. H. Smith and P. Yates, *J. Amer. Chem. Soc.*, 1954, **76**, 6080.

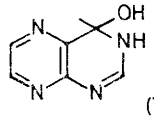
[6] J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, *J. Medicin. Chem.*, 1967, **10**, 598.

hydride, it was decided to proceed through the corresponding nitrile (IV). This dehydration has previously been accomplished [7] only with phosphorus pentoxide, but the method is troublesome and gives a poor yield. However, a 75% yield was readily obtained by heating the amide with phosphoryl chloride in dimethylformamide, followed by acidic hydrolysis of the amidine intermediate (V), a sequence which has proved useful [8] for preparing other pyrazinecarbonitriles. Hydrogenation of the nitrile (IV) over Raney nickel gave 2-amino-3-aminomethylpyrazine (I) (isolated as the phosphate). The free base (I) decomposed slowly when stored at room temperature, but remained unaltered at 5°.

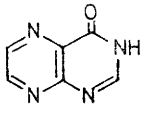
3,4-Dihydropteridine (VIa) was synthesised by heating the diamine (I) under reflux with triethyl orthoformate; triethyl orthoacetate similarly furnished the 2-methyl derivative (VIb). These pteridines had almost identical u.v. spectra (neutral species and cation respectively). The ^{1}H n.m.r. spectrum of the cation of the 2-methyl derivative (VIb) in hexadeuteriodimethyl sulphoxide and deuteriochloric acid showed an AB quartet (2H) with principal peaks at τ 1·65 and 1·71 (H-6 and H-7), a sharp peak at 5·12 (2H, CH_2), and another at 7·66 (3H, CH_3). These data confirmed that C-4 carried two hydrogen atoms, but they did not exclude a 1,4-dihydro-structure. However, it has been established [9] in the related quinazoline series that tautomerism greatly favours a 3,4- over a 1,4-dihydro-structure, most likely because an isolated double bond is thereby avoided.



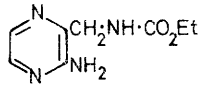
(VI) a; R = H
b; R = Me
c; R = NH_2
d; R = CO_2Et
e; R = CO_2H



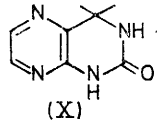
(VII)



(VIII)



(IX)



(X)

Similarly, hydrogenation of 3-amino-6-methylpyrazine-2-carbonitrile,[8] made from 3-amino-6-methylpyrazine-2-carboxamide [3] (IIb), gave 2-amino-3-aminomethyl-5-methylpyrazine, which triethyl orthoformate converted into 3,4-dihydro-6-methylpteridine. No reduction of the pyrazine ring was found in any of these hydrogenations.

All these dihydropteridines are new. It is unlikely that they could be made by the reduction of the corresponding pteridines, because pteridine itself gave only 5,6,7,8-tetrahydropteridine on reduction.[10]

Until now, attempts to oxidise 3,4-dihydropteridines to pteridines have met with little success because of the ease with which the product, if it can form a covalent hydrate [*e.g.* (VII)], is oxidised further to the pteridin-4-one [*e.g.* (VIII)]. Three reagents (see also later) have now been found that avoid such over-oxidation: the best of these for liposoluble material is activated manganese dioxide,[11] but water must be excluded.

The three dihydropteridines mentioned were accordingly oxidised by this reagent to the corresponding pteridines, of which 6-methylpteridine (m.p. 130°) was previously unknown; its preparation from 4,5-diaminopyrimidine and pyruvic aldehyde, often attempted in the presence of 'methyl-directing agents' such as sodium hydrogen sulphite or hydrazine,[12] led invariably to the isomeric 7-methylpteridine (m.p. 128°), the orientation of the methyl group of which was proved by degradation. A mixture of the two isomers melted at about 105°.

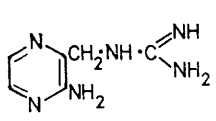
The diamine (I) and ethyl chloroformate gave a 90% yield of 2-amino-3-ethoxycarbonylaminomethylpyrazine (IX). That the *aliphatic* amino-group had been substituted was shown by the loss of basic strength (see Table 1). The original amine (I) had a highly basic group (pK_a 8·40 in water at 20°) as well as a less basic one (pK_a 2·05; *cf.* 3·14 for 2-aminopyrazine [13]). The urethane (IX) had a pK_a at value 2·8, but none of higher value. When refluxed with ethanolic sodium ethoxide, this urethane was cyclised to the known 3,4-dihydropteridin-2-one (X). This substance, previously made [14] only by reducing pteridin-2-one,[15] was oxidised to the latter by alkaline potassium ferricyanide.

The diamine (I) gave 2-amino-3-guanidinomethylpyrazine (XI) as the hydrochloride, when heated under reflux with *S*-methylisothiouronium hydrochloride in ethanol. The free base was cyclised to 2-amino-3,4-dihydropteridine (VIc) by heating at 100°. The dihydropteridine (VIc), previously obtained [16] only by reduction of 2-aminopteridine,[15] was oxidised to the latter by potassium permanganate in aqueous pyridine.

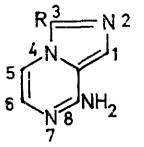
The diamine (I), when heated with carbon disulphide in pyridine, did not give the expected 3,4-dihydropteridine-2-thione,[17] but a more acidic (pK_a 8·74) compound (XIIa) (89% yield) to which we assigned the structure 8-aminoimidazo[1,5-*a*]pyrazine-3-thiol. Elemental analysis of compound (XIIa) indicated the molecular formula $C_6H_6N_4S$, and the i.r. spectrum (Nujol) showed a characteristic N–H bending primary

[7] R. C. Ellingson, R. L. Henry, and F. G. McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711.
[8] J. H. Jones and E. J. Cragoe, *J. Medicin. Chem.*, 1968, **11**, 322.
[9] W. L. F. Armarego, *J. Chem. Soc.*, 1961, 2697.
[10] E. C. Taylor and W. R. Sherman, *J. Amer. Chem. Soc.*, 1959, **81**, 2464.
[11] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and J. Walker, *J. Chem. Soc.*, 1952, 1094.
[12] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.
[13] A. Albert, R. J. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 1948, 2240.
[14] A. Albert and S. Matsuura, *J. Chem. Soc.*, 1961, 5131.
[15] A. Albert, D. J. Brown, and G. W. H. Cheeseman, *J. Chem. Soc.*, 1951, 474.
[16] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1966, 1117.
[17] A. Albert and J. J. McCormack, *J. Chem. Soc.* (*C*), 1968, 63.

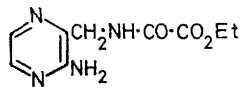
amine absorption at 1630 cm.$^{-1}$. Desulphurisation of the compound (XIIa) gave 8-aminoimidazo[1,5-*a*]-pyrazine (XIIb), the n.m.r. spectrum of which in hexadeuteriodimethyl sulphoxide showed an AB quartet (2H) with principal peaks at τ 2·37 and 3·05 (J_{AB} 5·1 Hz, H-5



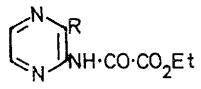
(XI)



(XII) a; R = SH
b; R = H



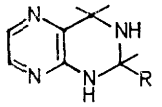
(XIII)



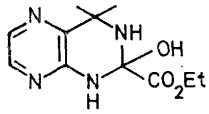
(XIV) a; R = $CH_2{\cdot}NH_2$
b; R = CN

and H-6) and three singlets at 1·67 (1H, H-3), 2·23 (1H, H-1), and 2·98 (2H, NH_2, exchangeable). The moderately strong basic property (pK_a 6·55; see Table 1) was attributed to protonation of the imidazole ring. Hence in the thiol (XIIa), the mobile proton (shown on sulphur) may be mainly on N-2. Only a few imidazopyrazines have been reported,[18] and none so simply substituted as these two derivatives.

2-Amino-3-ethoxalylaminomethylpyrazine (XIII) was prepared from the diamine (I) and ethyl triethoxyacetate.[19] The orientation of the ethoxalyl group was confirmed by the low basic strength (pK_a 2·66) and the n.m.r. assignments: τ [$(CD_3)_2SO$] 0·87br (1H, d, J 5·5 Hz, CO·NH), 2·13 and 2·29 (total 2H, ABq, J_{AB} 3·1 Hz, H-5 and H-6), 3·70br (2H, s, NH_2 on ring), 5·69 (2H, d, J 5·5 Hz, CH_2 of side chain), and 5·76 (2H, q) and 8·74 (3H, t) (both J 7·3 Hz, Et). This pyrazine (XIII) showed little tendency to cyclise into ethyl 3,4-dihydropteridine-2-carboxylate (VId) [*e.g.* when treated with phosphoryl chloride in pyridine, thionyl chloride (25°), or ethanolic sodium ethoxide]. It was thought that the isomeric 3-aminomethyl-2-ethoxalylaminopyrazine (XIVa) would cyclise more easily, because of the greater electron availability from an *aliphatic* amino-group. Accordingly 3-ethoxalylaminopyrazine-2-carbonitrile (XIVb), prepared from the nitrile (IV) and ethoxalyl chloride, was gently hydrogenated over Raney nickel, and gave ethyl 3,4-dihydropteridine-2-carboxylate (VId) directly, although in only moderate yield. Attempts to isolate the intermediate (XIVa) were unsuccessful. When hydrogenated under more vigorous conditions, the ethoxalyl derivative (XIVb) also gave some ethyl 1,2,3,4-tetrahydropteridine-2-carboxylate (XVa). Ethyl 3,4-dihydropteridine-2-carboxylate (VId) was hydrolysed to the corresponding acid (VIe) when stirred with dilute acid at room temperature. Dehydrogenation of the dihydropteridine (VId) with manganese dioxide gave ethyl pteridine-2-carboxylate (68%). These three esters are the first pteridines reported with a strongly electron-attracting group in the 2-position.



(XV) a; R = CO_2Et
b; R = H



(XVI)

Although attempts to prepare 1,2,3,4-tetrahydropteridine (XVb) from 3,4-dihydropteridine (VIa) by hydrogenation were unsuccessful, it was readily obtained by reaction of the diamine (I) with formaldehyde in alkaline solution. The tetrahydropteridine (XVb) remained unaltered at 25° for a month. These compounds (XVa and b) are the first recorded 1,2,3,4-tetrahydropteridines.

Covalent Hydration.—In dilute acid, pteridine, as shown [20] by ^{1}H n.m.r. spectroscopy, undergoes rapid covalent hydration across the 3,4-double bond to give the cation of compound (VII), and this slowly equilibrates further with water to give a mixture of the 3,4-mono- and 5,6:7,8-di-hydrates (as cations). The pK_a value and the u.v. spectra of 6-methylpteridine (both neutral species and cation at equilibrium) closely resembled those of pteridine [15] and 2- and 7-methylpteridines.[12] These data suggested that 6-methylpteridine similarly underwent covalent hydration. The ^{1}H n.m.r. spectrum showed that the neutral species of 6-methylpteridine existed mainly in the anhydrous form in water at 33·3° (assignments of peaks are shown in Table 2). On acidification (pH *ca.* 1), the cation of the 3,4-hydrate was rapidly formed, then it slowly came to equilibrium with the 5,6:7,8-dihydrate; chemical shift values agreed with those reported [20] for the cations of pteridine and 7-methylpteridine (*cf.* Table 2). The ratio of the 3,4-mono- to the 5,6:7,8-di-hydrate at equilibrium was found to be *ca.* 4 (*cf.* 0·25 for pteridine [20]).

By a rapid reaction technique,[21] the short-lived equilibrium between the (stable) hydrated cation and the (unstable) hydrated neutral species, was found to be 4·98 [expressed as pK_a (hyd)]. The loss of basic strength, shown by the fall to 3·89 [pK_a (equil)] when time-independent equilibrium was achieved, provided further evidence of hydration and permitted calculation of K_2, the ratio of hydrated to anhydrous neutral species at equilibrium (20°), from the approximation: [21]

$$-\log K_2 = \text{p}K_a\text{ (hyd)} - \text{p}K_a\text{ (equil)}.$$

K_2 was found to be 0·081 and hence 6-methylpteridine is much less hydrated than pteridine,[21] for which the corresponding ratio is 0·29. This difference might be

[18] G. B. Crippa and A. Crippa, *Il Farmaco* (*sci. Edn.*), 1955, **10**, 616; A. M. Bellini, *Ann. Chim.* (*Italy*), 1961, **51**, 1409; E. Jucker and E. Rissi, *Helv. Chim. Acta*, 1962, **45**, 2383; M. P. Merles and N. R. Patel, *J. Medicin. Chem.*, 1966, **9**, 868.

[19] R. G. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 5168.

[20] A. Albert, T. J. Batterham, and J. J. McCormack, *J. Chem. Soc.* (*B*), 1966, 1105.

[21] D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.

expected from the $+I$ character of the methyl group, because hydration is a nucleophilic reaction.

The u.v. spectrum of a fresh solution of ethyl pteridine-2-carboxylate in buffer at pH 5 closely resembled that of the anhydrous neutral species of 6-methylpteridine, were confirmed by the n.m.r. spectra. A fresh solution of ethyl pteridine-2-carboxylate in deuterium oxide showed peaks characteristic of an anhydrous species (see Table 2), but peaks at higher field and characteristic of a 5,6:7,8-dihydrate soon began to appear.

TABLE 1

Ionisation constants and u.v. spectra

		Ionisation in water (20°)				U.v. data (in water) [c]		
	Species [a]	pK_a	Spread ±	Concn. (M)	A.w.l.[b] mμ	$\lambda_{max.}$ (mμ)	log ε	pH
Pyrazine								
3-Amino-2-carbonitrile	0					245, 350	4·13, 3·82	2
	+	−0·43	0·04	$1·5 \times 10^{-4}$	376	240, 356	4·18, 3·96	−3
2-Amino-3-aminomethyl-	0					230, 313	3·96, 3·73	11
	+	8·40 [d]	0·03	1×10^{-3}	P	229, 313	4·07, 3·78	4
	2+	2·05 [e]	0·05	$7·7 \times 10^{-5}$	335	227, 321	4·07, 3·85	0
2-Amino-3-ethoxycarbonylamino-methyl-	0					230, 314	3·97, 3·78	5
	+	2·80	0·05	$5·2 \times 10^{-4}$	340	228, 322	4·01, 3·85	0
2-Amino-3-ethoxalylaminomethyl-	0					227, 316	4·10, 3·79	5
	+	2·61	0·04	$7·1 \times 10^{-5}$	340	227, 322	4·11, 3·85	0
Pteridine								
6-Methyl	0					303, 315	3·94, 3·90	6
	+[f]	3·89	0·04	1×10^{-3}	P	306	3·96	2
Ethyl 2-carboxylate	0					300, 311 [g]	3·97, 3·90	5
	0					318 [h]	4·06	5
	+	2·73 [i]	0·04	$3·0 \times 10^{-5}$	240	314	4·01	0
3,4-Dihydro	0					335	3·96	9
	+	6·36	0·04	$4·7 \times 10^{-5}$	343	311	3·90	4
3,4-Dihydro-2-methyl	0					*301*, 335	*3·66*, 3·96	10
	+	7·26	0·01	$4·6 \times 10^{-5}$	343	311	3·95	5
3,4-Dihydro-6-methyl	0					*301*, 341	*3·63*, 3·96	9
	+	6·66	0·03	$4·7 \times 10^{-5}$	343	316	4·01	4
Ethyl 3,4-dihydro-2-carboxylate	0	3·74 [j]	0·06	1×10^{-3}	P	345 [g]	3·92	7
	0					*218*, 319 [k]	*3·87*, 3·84	7
	+?					226, 319 [l]	3·86, 3·91	0
3,4-Dihydro-2-carboxylic acid	−					342 [m]	3·93	13
1,2,3,4-Tetrahydro	0					244, 287, 334	3·90, 3·20, 3·78	8
	+	5·62	0·04	1×10^{-3}	P	237, *289*, 325	3·91, *3·29*, 3·79	3
	2+	0·10	0·02	$4·7 \times 10^{-5}$	345	234, 339	3·95, 3·86	−2
Ethyl 1,2,3,4-tetrahydro-2-carboxylate	0					241, *288*, 328	3·85, *3·26*, 3·80	6
	+	3·31	0·07	1×10^{-3}	P	228, 322	3·93, 3·81	1
Imidazo[1,5-*a*]pyrazine								
8-Amino-3-thiol	−	8·74	0·05	$3·4 \times 10^{-5}$	260	259, 289, 300, 340	4·39, 4·11, 3·91, 3·40	13
	+	5·66	0·04	$1·1 \times 10^{-4}$	273	235, 273, *285*, *299*, 346	4·03, 4·27, *4·19*, *4·09*, 3·43	2
8-Amino	0					274, 283, 299	3·70, 3·73 3·68	10
	+	6·55	0·06	$7·6 \times 10^{-5}$	285	267, 278, 299	3·73, 3·70, 3·61	4

[a] Neutral species (0), cation (+), dication (2+), anion (−). [b] Analytical wavelength for spectrometric determinations (P potentiometric) as in A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962. [c] Inflections in italics. [d] Ionisation of the side-chain NH_2 group. [e] Ionisation of the ring NH_2 group. [f] The pK_a represents an equilibrium of hydrated and anhydrous species (see text). [g] This spectrum was measured immediately after dissolution. [h] This spectrum was measured after equilibration with pH 5 buffer (4 days). [i] The pK_a represents an equilibrium of hydrated neutral species and hydrated cation (see text). [j] The pK_a represents an equilibrium of anhydrous neutral species and anhydrous cation (see text). [k] This spectrum was measured after equilibration with pH 7 buffer (2 days). [l] The spectrum (cation, or cation plus neutral species) was measured after equilibration with water followed by adjustment of the pH to 0. [m] There is also a peak at 318 mμ (log ε 3·94) (pH 0). The spectrum at pH 7 was a hybrid of both species.

but gradually changed during 4 days until equilibrium with a new species was established. In acid solution (pH 0), ethyl pteridine-2-carboxylate immediately showed the spectrum of the cation of this new species, the pK_a value of which was found to be 2·73 at 20° (Table 1). These indications of covalent hydration After 48 hr. at 25° only the peaks due to the latter species remained. These n.m.r. spectra also showed that there is little tendency to form a 3,4-hydrate. This result is consistent with data [22] from the quinazoline

[22] W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.* (*C*), 1966, 234.

TABLE 2

^{1}H N.m.r. spectra at 33·3°

Pteridine	τ Values H(2)	H(4)	H(6) [a]	H(7) [a]	CH_3	Solvent [b]
Unsubstituted	0·33	0·20	0·85	0·67 [c]		A
	1·23	3·40	1·26	1·33 [d]		B *
	1·53	2·12	4·65	4·80 [d]		B †
7-Methyl	0·43	0·32	1·02		7·04 [c]	A
	1·25	3·43	1·32		7·32 [d]	B *
	1·55	2·16	5·00		8·26 [d]	B †
6-Methyl	0·46	0·31		0·56	7·04	C
	1·23	3·42		1·37	7·31	B *
	1·46	2·10		4·74	8·22	B †
Ethyl 2-carboxylate		−0·05	0·39 [e]	0·54 [e,f]		C
		2·13	4·62 [e]	4·83 [e,g]		C †

[a] Assignments for H(6) and H(7) may be interchanged. [b] A, deuteriochloroform; B, deuteriochloric acid; C, deuterium oxide. [c] Values from S. Matsuura and T. Goto, *J. Chem. Soc.*, 1963, 1773. [d] Values from ref. 20. [e] Doublet (*J* 1·7 Hz). [f] Peaks for Et at τ 5·30 (q) and 8·44 (t) (*J* 7·7 Hz). [g] Peaks for Et at τ 5·56 (q) and 8·52 (t) (*J* 7·7 Hz).

* 3,4-Hydrate. † 5,6:7,8-Dihydrate.

series in which any group that reduces polarisation of the 3,4-bond discourages hydration in the pyrimidine ring.

The covalent hydration of dihydropteridines has been little explored. Of the dihydro-compounds reported in this paper, only ethyl 3,4-dihydropteridine-2-carboxylate (VId) showed any evidence of hydration according to the criteria in ref. 23. In water at 20°, the u.v. spectrum of the compound (VId) gradually changed during 2 days, and the substance came to equilibrium with a species, the u.v. spectrum of which resembled that of ethyl 1,2,3,4-tetrahydropteridine-2-carboxylate (see Table 1). This reaction, faster in acid solution, was followed by n.m.r. spectroscopy. The freshly dissolved compound (VId) in deuteriochloric acid (pH *ca.* 1) gave a spectrum due to the cation of anhydrous ethyl 3,4-dihydropteridine-2-carboxylate cation [τ 1·47 and 1·55 (total 2H, two d, *J* 2·6 Hz, H-6 and H-7), 4·80 (2H, s, 4-CH_2), and 5·40 and 8·59 (2H, q and 3H, t, respectively, *J* 7·7 Hz, Et)]. After 1·5 hr., the spectrum showed new peaks (due to new species) as well as the former ones (integration ratio 1 : 1). The new peaks were a typical AB quartet with principal peaks at τ 1·15 and 1·29 (J_{AB} 2·6 Hz, H-6 and H-7) and a singlet at τ 5·54 (4-CH_2). Although these data suggested at first that the compound (VId) underwent covalent hydration across the 1,2-double bond to give the cation of the hydrate (XVI), it was unexpected that aromatisation of the pyrimidine ring would cause the pyrazine ring proton signals to move downfield. After 3 days at pH 1, the contents of the sample tube gave only weak signals (apart from peaks due to ethanol) because of the precipitation of 3,4-dihydropteridine-7-carboxylic acid (VIe) (see before).

The pK_a for the equilibrium of compound (VId) between the anhydrous cation and the anhydrous neutral species, obtained potentiometrically within 15 min. of dissolving the specimen, was found to be 3·74 at 20°. However no time-independent equilibrium pK_a could be obtained either potentiometrically (because of the poor solubility of the hydrate) or spectrophotometrically (there was too little u.v. spectral change between pH 0 and 7).

A comparison of the u.v. spectra (long-wavelength) of the neutral species of ethyl 3,4-dihydropteridine-2-carboxylate hydrate (XVI) with that of ethyl 1,2,3,4-tetrahydropteridine-2-carboxylate (XVa) showed a hypsochromic shift of 9 mμ. A similar shift was found between the spectrum of the neutral species of pteridine 3,4-hydrate (VII) [24] and that of 3,4-dihydropteridine (VIa) (17 mμ), also a shift of 26 mμ [25] in the case of the corresponding quinazolines. This phenomenon has been attributed to a hydrogen-bonded interaction between the hydroxy-group and the π-orbital of the aromatic ring.[23]

Ionisation Constants and U.v. Spectra.—These are presented in Table 1; some values have already been discussed. Attention is drawn to the basic strength of the 3,4-dihydropteridines, greater than that of the corresponding pteridines because of the base-strengthening amidinium-type resonance in the cation made possible by protonation on N-1. The hypsochromic shift (*ca.* 25 mμ) seen upon protonation of these 3,4-dihydropteridines, is reminiscent of that shown by 2-amino-3,4-dihydropteridine.[16]

EXPERIMENTAL

Yields refer to material sufficiently pure to give only one spot in chromatography on Whatman no. 1 paper developed with solvent A (3% aqueous ammonium chloride) or B (butanol–5N-acetic acid, 7 : 3) and viewed under 254 mμ light.

U.v. spectra were measured with a Shimadzu model RS 27 recording spectrophotometer or a Unicam SP 800 spectrophotometer; the wavelength and intensity of each maximum was then checked with an Optica manual instrument. I.r. spectra were taken (for mulls in Nujol) with a Unicam SP 200 spectrophotometer. N.m.r. spectra were determined with a Perkin-Elmer model R10 instrument operating at 33·3° and 60 MHz; tetramethylsilane was the internal standard, except for solutions in deuterium oxide, for which sodium trimethylsilylpropanesulphonate was used.

2-*Amidino*-2-*aminoacetamide* (III) *Dihydrochloride*.—To a suspension of palladium–carbon (10%; 4 g.) in 50% aqueous ethanol (400 ml.), previously saturated with hydrogen, was added 2-amidino-2-phenylazoacetamide hydrochloride (89 g.). The suspension was shaken with hydrogen at 20° and atmospheric pressure until 2 mol. of hydrogen had been absorbed. The catalyst was filtered off. The filtrate, evaporated at 40° *in vacuo* until it formed two layers, was extracted with ether (3 × 50 ml.; rejected). 10N-Hydrochloric acid was added to the aqueous layer, which was then concentrated to *ca.* 100 ml. and mixed with ethanol (200 ml.) and ether (300 ml.). Refrigeration yielded the amidinoamino-amide dihydrochloride, decomp. *ca.* 195°

[23] A. Albert, *Angew. Chem.*, 1967, **79**, 913; A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.

[24] D. D. Perrin, *J. Chem. Soc.*, 1962, 645.

[25] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 5267.

(lit.,[5] 209—210°), identical with an authentic sample (i.r. spectra) [Found (material dried at 20°): C, 19·3; H, 5·3; N, 29·5. Calc. for $C_3H_{10}Cl_2N_4O$ C: 19·1; H, 5·3; N, 29·6%].

3-*Aminopyrazine*-2-*carbonitrile* (IV).—To a mixture of 3-aminopyrazine-2-carboxamide (9·7 g., 0·08 mole) and dimethylformamide, cooled in ice–water, was added phosphonyl chloride (15 ml., 0·16 mole) dropwise. The solution was heated at 50° for 30 min. and concentrated at 20°/0·1 mm. To the residue was added water (40 ml.). The solution was boiled for 1 min., then cooled, and deposited 3-aminopyrazine-2-carbonitrile, m.p. 185—188° (189° from water) (lit.,[7] 191·9°, corr.), identical with an authentic sample (paper chromatography, mixed m.p., and i.r. spectra), $\nu_{max.}$ 3420s, 3350s, 3170s, 2230m (C≡N str.), and 1665s cm.$^{-1}$.

2-*Amino*-3-*aminomethylpyrazine* (I).—A mixture of 2-aminopyrazine-3-carbonitrile (1·0 g.) and Raney nickel (*ca.* 1 g., wet wt.) in ethanolic ammonia (100 ml.) was shaken with hydrogen at 70° and 4 atmos. After 5 hr., the catalyst was filtered off. The filtrate was evaporated to dryness at 40° *in vacuo*. The residue was rubbed with chloroform (2 × 25 ml.) and filtered, and the filtrate was evaporated to dryness at 40° *in vacuo*. To the residue in ethanol (60 ml.) was added ethanolic 1M-phosphoric acid (9 ml.). The precipitated 2-*amino*-3-*aminomethylpyrazine phosphate* (83%), after recrystallisation from 75% aqueous ethanol, decomposed at *ca.* 169° without melting [Found (material dried at 110°/0·01 mm.): C, 25·4; H, 4·9; N, 23·1. $C_5H_8N_4,H_3PO_4,0{\cdot}75H_2O$ requires C, 25·5; H, 5·4; N, 23·8%]. The pH of a solution of this phosphate (1 g.) in water (10 ml.) was adjusted to 10·5 with 0·2N-sodium hydroxide (5 ml.), and the resulting solution was evaporated to dryness at 45° *in vacuo*. The residue, further dried in a vacuum desiccator, was extracted with hot ethanol (3 × 20 ml.). The extracts were evaporated to dryness at 40° *in vacuo* and the residue, sublimed at 80°/0·003 mm., gave 2-*amino*-3-*aminomethylpyrazine* (81% based on phosphate), m.p. 84° (Found: C, 48·7; H, 6·5; N, 44·9. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%), $\nu_{max.}$ 3320s, 3150s, and 1655s cm.$^{-1}$, τ [$(CD_3)_2SO$] 2·04 and 2·20 (total 2H, q, *J* 2·6 Hz, H-5 and H-6), 3·49br (2H, s, NH_2 on ring), 6·13 (2H, s, CH_2), and 7·64 (2H, s, NH_2 on side chain).

3,4-*Dihydropteridine* (VIa).—A suspension of 2-amino-3-aminomethylpyrazine (0·18 g.) in triethyl orthoformate (2·5 ml.) was heated under reflux (at 145°) for 1 hr. The cooled mixture deposited 3,4-*dihydropteridine* (74%), decomp. *ca.* 181° (from ethanol) [Found (material dried at 20°/0·01 mm.): C, 54·2; H, 4·6; N, 41·4. $C_6H_6N_4$ requires C, 53·7; H, 4·5; N, 41·8%]. It remained unaltered when stored at 5°; τ [$(CD_3)_2SO$] 1·95 (2H, s, H-6 and H-7), 2·77 (1H, s, H-2), and 5·30 (2H, s, CH_2 at C-4).

3,4-*Dihydro*-2-*methylpteridine* (VIb).—A suspension of 2-amino-3-aminomethylpyrazine (0·15 g.) in triethyl orthoacetate (2 ml.) was heated under reflux (at 145°) for 30 min. The cooled mixture deposited 3,4-*dihydro*-2-*methylpteridine* (70%), decomp. *ca.* 177° (from ethanol) [Found (material dried at 80°/0·01 mm.): C, 56·2; H, 5·3; N, 38·0. $C_7H_8N_4$ requires C, 56·7; H, 5·4; N, 37·8%].

2-*Amino*-3-*aminomethyl*-5-*methylpyrazine*.—A suspension of 3-amino-6-methylpyrazine-2-carbonitrile (0·1 g.) in ethanol (20 ml.) was shaken with hydrogen over Raney nickel (*ca.* 0·2 g., wet wt.) at room temperature and 4 atmos. for 12 hr. The catalyst was filtered off. Ethanolic M-phosphoric acid (1·5 ml.), added to the filtrate, precipitated 2-*amino*-3-*aminomethyl*-5-*methylpyrazine phosphate* (73%), decomp. *ca.* 188° (from aqueous ethanol) [Found (material dried at 110°/0·01 mm.): C, 30·4; H, 5·8; N, 23·8. $C_6H_{13}N_4O_4P$ requires C, 30·5; H, 5·5; N, 23·7%]. The free base was prepared like 2-amino-3-aminomethylpyrazine. Sublimation of the residue gave 2-*amino*-3-*aminomethyl*-5-*methylpyrazine* (84%), m.p. 81·5° (Found: C, 52·0; H, 7·2; N, 40·7. $C_6H_{10}N_4$ requires C, 52·2; H, 7·3; N, 40·6%), τ [$(CD_3)_2SO$] 2·25 (1H, s, H-6), 3·86br (2H, s, NH_2 on ring), 6·23 (2H, s, CH_2), 6·90 (2H, s, NH_2 on side chain), and 7·75 (3H, s, Me).

3,4-*Dihydro*-6-*methylpteridine*.—A suspension of 2-amino-3-aminomethyl-5-methylpyrazine (0·09 g.) in triethyl orthoformate (1·2 ml.) was heated under reflux (at 145°) for 2 hr., then cooled. Filtration yielded 3,4-*dihydro*-6-*methylpteridine* (69%), decomp. *ca.* 181° (from ethanol) [Found (material dried at 80°/0·01 mm.): C, 56·8; H, 5·7; N, 37·7. $C_7H_8N_4$ requires C, 56·7; H, 5·4; N, 37·8%], τ [$(CD_3)_2SO$] 2·01 (1H, s, H-7), 2·77 (1H, s, H-2), 5·34 (2H, s, 4-CH_2), and 7·67 (3H, s, Me).

Pteridine.—A suspension of 3,4-dihydropteridine (0·03 g.), manganese dioxide (0·3 g., large excess), and barium oxide (0·25 g.) in tetrahydrofuran (5 ml.) was stirred at room temperature for 2 days. The residue was filtered off. The filtrate was evaporated at 30° *in vacuo*, and the residue, sublimed at 80°/0·1 mm., gave pteridine (52%), m.p. 136° [lit.,[15] 138 and 140° (two forms)], identical with an authentic sample (paper chromatography, mixed m.p., and i.r. spectra).

2-*Methylpteridine*.—3,4-Dihydro-2-methylpteridine similarly gave 2-methylpteridine (80%, after sublimation at 105°/0·1 mm.), m.p. 140° (lit.,[12] 141°), identical with an authentic sample.

6-*Methylpteridine*.—A suspension of 3,4-dihydro-6-methylpteridine (0·03 g.), manganese dioxide (0·3 g.), and anhydrous magnesium sulphate (0·2 g.) in tetrahydrofuran (3 ml.) was stirred at 5° for 2 days. The residue was filtered off. The filtrate was evaporated at 25° *in vacuo*, and the residue, sublimed at 70°/0·05 mm., gave 6-*methylpteridine* (74%), m.p. 130° (Found: C, 57·8; H, 4·4; N, 38·7. $C_7H_6N_4$ requires C, 57·5; H, 4·1; N, 38·35%).

2-*Amino*-3-*ethoxycarbonylaminomethylpyrazine* (IX).—To 2-amino-3-aminomethylpyrazine (0·25 g.), dissolved in triethylamine (0·3 ml.) and chloroform (8 ml.), was added ethyl chloroformate (0·2 ml.). The solution was stirred at 25° for 2 hr., and evaporated to dryness at 40° *in vacuo*. The residue, dissolved in hot water (3 ml.), gave on cooling 2-*amino*-3-*ethoxycarbonylaminomethylpyrazine*, m.p. 131·5° (from water) [Found (material dried at 20°): C, 49·1; H, 6·3; N, 28·7. $C_8H_{12}N_4O_2$ requires C, 49·0; H, 6·3; N, 28·6%], $\nu_{max.}$ 3420m,sh, 3360s, 3250m, 1705s (C=O str.), and 1655m cm.$^{-1}$.

3,4-*Dihydropteridin*-2-*one* (X).—To ethanolic sodium ethoxide [from sodium (21 mg.) and ethanol (2 ml.)] was added 2-amino-3-ethoxycarbonylaminomethylpyrazine (79 mg.). The mixture was heated under reflux for 1 hr., and evaporated to dryness at 40° *in vacuo*. The residue was dissolved in N-sodium hydroxide (1 ml.) and the solution was filtered (charcoal). The filtrate, acidified to pH 6 with 2N-hydrochloric acid, deposited 3,4-dihydropteridin-2-one (68%), which darkened at *ca.* 251° (from water) (lit.,[14] 250°). It was identical with an authentic sample (paper chromatography and i.r. spectra).

Pteridin-2-*one*.—To a well stirred solution of 3,4-dihydropteridin-2-one (0·03 g.) in 2N-potassium hydroxide (1 ml.) was added, dropwise, 0·4M-potassium ferricyanide (1·1

equiv.) during 40 min. The solution was then stirred for 5 hr., and neutralised with 5N-hydrochloric acid. The precipitate deposited on cooling gave pteridin-2-one (78%), decomp. *ca.* 238° (lit.,[15] 240°), identical with an authentic sample (paper chromatography and i.r. spectra).

2-*Amino*-3-*guanidinomethylpyrazine* (XI) *Hydrochloride*.—A mixture of 2-amino-3-aminomethylpyrazine (0·13 g.) and *S*-methylisothiouronium hydrochloride (0·15 g.) in ethanol (2 ml.) was heated under reflux for 1·5 hr. On cooling, 2-*amino*-3-*guanidinomethylpyrazine hydrochloride* separated (69%), decomp. *ca.* 219° [Found (material dried at 25°/0·01 mm.): C, 32·5; H, 6·2; N, 37·9. $C_6H_{11}ClN_6,H_2O$ requires C, 32·7; H, 5·9; N, 38·1%]. The less useful (because insoluble) *sulphate*, decomp. *ca.* 232°, was obtained (81% yield) when the diamine was heated under reflux with *S*-methylisothiouronium sulphate in water for 1·5 hr., τ [$(CD_3)_2SO$] 2·15 (2H, d, H-5 and H-6), 2·18br [5H, s, guanidino-group], 3·46br (2H, s, NH_2 on ring), and 5·57 (2H, s, CH_2).

2-*Amino*-3,4-*dihydropteridine* (VIc) *Toluene*-p-*sulphonate*.—To ethanolic sodium ethoxide [from ethanol (1·5 ml.) and sodium (11·4 mg.)] was added 2-amino-3-guanidinomethylpyrazine hydrochloride (0·10 g.). Sodium chloride was filtered off. The filtrate was evaporated to a syrup, which was heated at 100° for 4 hr. To the resulting solid, suspended in ethanol (10 ml.), was added toluene-*p*-sulphonic acid monohydrate (0·1 g.). The mixture was filtered hot (charcoal), and the filtrate, concentrated to 1 ml., gave 2-amino-3,4-dihydropteridine toluene-*p*-sulphonate (61%), which darkened at *ca.* 190° and melted at 210° (from ethanol) (lit.,[16] darkened at 175° and melted at *ca.* 215°). It was identical with an authentic sample (paper chromatography and i.r. spectra). The free base, liberated when the salt (0·07 g.) was dissolved in N-sodium hydroxide (2 ml.), was used for the preparation of 2-aminopteridine without purification.

2-*Aminopteridine*.—To a well stirred solution of 2-amino-3,4-dihydropteridine (15 mg.) in aqueous pyridine (trihydrate; 1 ml.) was added (dropwise) aqueous 0·2M-potassium permanganate (1·1 equiv.) during 20 min. Manganese dioxide was filtered off. The filtrate, adjusted to pH 7 and N-hydrochloric acid, was evaporated *in vacuo*. The residue was suspended in water (0·5 ml.) and the precipitate, separated by filtration, gave 2-aminopteridine (74%), decomp. >273° (lit.,[15] >275°), identical with an authentic sample (i.r. spectra and paper chromatography).

8-*Aminoimidazo*[1,5-a]*pyrazine*-3-*thiol* (XIIa).—To a suspension of 2-amino-3-aminomethylpyrazine (0·16 g.) in pyridine (2·5 ml.) was added carbon disulphide (0·25 ml.), and the mixture was heated under reflux for 30 min. A solution of the 8-*aminoimidazo*[1,5-a]*pyrazine*-3-*thiol* (deposited on cooling) in N-sodium hydroxide (1 ml.) was clarified by filtration. Adjustment of the pH to 7 with N-hydrochloric acid precipitated the pure compound, decomp. >220° [Found (material dried at 110°/0·01 mm.): C, 43·5; H, 3·8; N, 33·6; S, 19·0. $C_6H_6N_4S$ requires C, 43·4; H, 3·6; N, 33·7; S, 19·3%], $\nu_{max.}$ 3420m, 3300s, 3200s, *ca.* 2500m,br, *ca.* 1900w,br, 1630s, 1575s, and 1525s cm.$^{-1}$, τ (2N-NaOD) 2·42 (1H, d, *J* 0·9 Hz, H-1), 2·52 (1H, q, $J_{1,5}$ 0·9, $J_{5,6}$ 6·0 Hz, H-5*), and 3·15 (1H, d, *J* 6·0 Hz, H-6*) (the assignments marked * may be reversed).

8-*Aminoimidazo*[1,5-a]*pyrazine* (XIIb).—To a suspension of 8-aminoimidazo[1,5-*a*]pyrazine-3-thiol (0·12 g.) in aqueous 5N-ammonia (1·5 ml.) was added Raney nickel (*ca.* 0·1 g., wet wt.); the whole was heated under reflux for 2 hr. and filtered. The filtrate was evaporated to dryness at 40° *in vacuo*. The residue gave 8-*aminoimidazo*[1,5-a]*pyrazine* (53%), m.p. 159° [from water (1 ml.)] [Found (material dried at 80°/0·01 mm.): C, 53·15; H, 4·7; N, 42·0. $C_6H_6N_4$ requires C, 53·7; H, 4·5; N, 41·8%], $\nu_{max.}$ 3550m, 3330s, 3120s, 1655s, 1625s, and 1535s cm.$^{-1}$.

2-*Amino*-3-*ethoxyalylaminomethylpyrazine* (XIII).—A suspension of 2-amino-3-aminomethylpyrazine (0·066 g.) in ethyl triethoxyacetate (2 ml.) was stirred at 110° for 1 hr., then cooled. Filtration yielded 2-*amino*-3-*ethoxalylaminomethylpyrazine* (66%), m.p. 161° (from ethanol) [Found (material dried at 20°/20 mm.): C, 48·3; H, 5·4; N, 25·3. $C_9H_{12}N_4O_3$ requires C, 48·2; H, 5·4; N, 25·0%], $\nu_{max.}$ 3420m, 3360s, 3250m, 1730m, 1695s, 1650s, 1550m, and 1525m cm.$^{-1}$.

3-*Ethoxalylaminopyrazine*-2-*carbonitrile* (XIVb).—To a solution of 3-aminopyrazine-2-carbonitrile (1·5 g.) in pyridine (15 ml.), cooled at 1°, was added ethoxalyl chloride (2·5 ml.), dropwise. The mixture was stirred at 1° for 2 hr., then ethanol (2·5 ml.) was added. The mixture was stirred for 5 min., then evaporated to dryness at 40° *in vacuo*. The residue gave 3-*ethoxalylamidopyrazine*-2-*carbonitrile* (84%), m.p. 160° (from ethanol) [Found (material dried at 60°/0·01 mm.): C, 48·8; H, 3·6; N, 25·3. $C_9H_8N_4O_3$ requires C, 49·1; H, 3·7; N, 25·5%], $\nu_{max.}$ 3320s, 1715s, 1545m, and 1525m cm.$^{-1}$ (no peak between 2000 and 2500 cm.$^{-1}$).

Ethyl 3,4-*Dihydropteridine*-2-*carboxylate* (VId).—A suspension of 3-ethoxalylaminopyrazine-2-carbonitrile (0·22 g.) in ethanol (20 ml.) was hydrogenated over Raney nickel (*ca.* 0·6 g., wet wt.) at 20° and 1 atmos. until 2 mol. of hydrogen had been absorbed. The catalyst was filtered off. The filtrate, concentrated to a small volume at 40° *in vacuo*, was put on a thin-layer plate (silica gel; 20 × 20 cm., thickness 2 mm.) and developed with ethyl acetate. A fraction (R_F 0·18), which strongly absorbed u.v. light (254 mμ), was removed from the plate, and extracted with hot ethanol (3 × 20 ml.). The extract was evaporated to dryness at 40° *in vacuo*. The residue gave *ethyl* 3,4-*dihydropteridine*-2-*carboxylate* (17%), decomp. *ca.* 161° (from ethanol) [Found (material dried at 20°/0·01 mm.): C, 52·5; H, 4·9; N, 27·0. $C_9H_{10}N_4O_2$ requires C, 52·4; H, 4·9; N, 27·2%], $\nu_{max.}$ 3180m, 3020m, 1725s (C=O str.), and 1615s cm.$^{-1}$, τ [$(CD_3)_2SO$] 1·81 (2H, s, H-6 and H-7), 5·16 (2H, s, 4-CH_2), and 5·70 (2H, q) and 8·70 (3H, t) (Et).

Ethyl 1,2,3,4-*Tetrahydropteridine*-2-*carboxylate* (XVa).—A suspension of 3-ethoxalylamidopyrazine-2-carbonitrile (0·22 g.) in ethanol (20 ml.) was hydrogenated over Raney nickel (*ca.* 0·6 g., wet wt.) at 70° and 4 atmos. for 5 hr. The pteridine was purified by the same procedure as compound (VId) [R_F 0·20 (silica gel; ethyl acetate)]. Crystallisation from benzene–light petroleum gave *ethyl* 1,2,3,4-*tetrahydropteridine*-2-*carboxylate* (11%), m.p. 102° [Found (material dried at 20°/0·01 mm.): C, 52·4; H, 5·7; N, 27·35. $C_9H_{12}N_4O_2$ requires C, 51·9; H, 5·8; N, 26·9%], $\nu_{max.}$ 3300m, 3210s, 1735s (C=O str.), 1585m, and 1570m cm.$^{-1}$, τ ($CDCl_3$) 2·09 (2H, s, H-6 and H-7), 4·18br (1H, s, H-1), 5·01 (1H, s, H-2), 5·81 (2H, s, H-4), 7·60 br (1H, s, H-3), and 5·66 (2H, q) and 8·69 (3H, t) (Et).

Ethyl Pteridine-2-*carboxylate*.—A suspension of ethyl 3,4-dihydropteridine-2-carboxylate (0·025 g.), manganese dioxide (0·25 g.), and anhydrous magnesium sulphate (0·21 g.) in tetrahydrofuran (2 ml.) was stirred at 5° for 2 days. The residue was filtered off. The filtrate was evaporated to dryness at 25° *in vacuo*, and the residue, sublimed at 110°/0·05 mm., gave *ethyl pteridine*-2-*carboxyl*-

ate, m.p. 128·5° (Found: C, 53·0; H, 3·9; N, 27·4. $C_9H_8N_4O_2$ requires C, 52·9; H, 4·0; N, 27·4%), $\nu_{max.}$ 1735s (C=O str.), 1570m, and 1555m cm.$^{-1}$.

3,4-*Dihydropteridine*-2-*carboxylic Acid* (VIe).—A solution of ethyl 3,4-dihydropteridine-2-carboxylate (0·066 g.) in 0·1N-hydrochloric acid (2 ml.) was stirred for 2 days. The precipitate, 3,4-*dihydropteridine*-2-*carboxylic acid* (45%), crystallised from water, darkened at *ca.* 153° [Found (material dried at 20°/0·01 mm.): C, 45·9; H, 3·8; N, 30·8. $C_7H_6N_4O_2$,0·25H_2O requires C, 46·0; H, 3·6; N, 30·7%], $\nu_{max.}$ 3450s, 3120s, 1690m,sh, 1670s, 1645s, 1605m, 1575m, and 1560m cm.$^{-1}$.

1,2,3,4-*Tetrahydropteridine* (XVb).—2-Amino-3-aminomethylpyrazine (0·09 g.) dissolved in 5N-sodium hydroxide (1 ml.) and aqueous formaldehyde (37%; 1 ml.), was heated under reflux for 15 min. and extracted with chloroform (5 × 2 ml.) (extract dried over Na_2SO_4). The filtered solution was evaporated to dryness at 25° *in vacuo*, and the residue, sublimed at 110°/0·01 mm., gave 1,2,3,4-*tetrahydropteridine* (43%), decomp. 146° (Found: C, 53·4; H, 5·9; N, 41·55. $C_6H_8N_4$ requires C, 52·9; H, 5·9; N, 41·15%), $\nu_{max.}$ 3290m, 3200s, 3110m, and 1575s cm.$^{-1}$, τ($CDCl_3$) 2·09 (2H, s, H-6 and H-7), 4·27br (1H, s, H-1), 5·49 (2H, d, *J* 0·9 Hz, 2-CH_2), 5·80 (2H, s, 4-CH_2), and 7·78br (1H, s, H-3).

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