Pteridine Studies. Part XLIII.[1] Reactions of Pteridine with Some Michael Reagents

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Pteridine reacted with various Michael reagents to give three kinds of products. (i) Dimedone, barbituric acid, thiobarbituric acid, diethyl malonate, and ethyl benzoylacetate added across the 3,4-double bond to yield 4-substituted 3,4-dihydropteridines (1). (ii) Benzyl (and ethyl) acetoacetate, and acetylacetone produced 8-substituted 5,5a,8a,9-tetrahydro-7-methylfuro[2,3-*g*]pteridines (2); all were formed by simple addition of one molecule of the Michael reagent across the 5,6- and 7,8-bonds of pteridine. (iii) Malononitrile and cyanoacetamide gave pyrido[2,3-*b*]pyrazines (4) by addition across the 3,4-bond followed by scission of that bond and a nitrogen-eliminating recyclisation. Explanations of this diverse behaviour are suggested. U.v. and ^{1}H n.m.r. spectra are reported and discussed.

FOLLOWING our report [1] of the addition of alcohols to pteridine, and the earlier reported hydration of this substance,[2,3] we describe the reactions of pteridine with Michael reagents.

From solutions of pteridine, in favourable solvents (usually tetrahydrofuran or water), one (or more) equivalent(s) of dimedone, barbituric acid, and thiobarbituric acid precipitated, in good yields, the 4-substituted 3,4-dihydropteridines (1a—c). That these were 3,4-adducts of pteridine was shown by their ^{1}H n.m.r. spectra: the H-4 singlet had shifted upfield (from τ 0·2

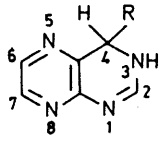
[1] Part XLII, A. Albert and H. Mizuno, *J. Chem. Soc.* (*B*), 1971, 2423.

[2] (*a*) D. D. Perrin, *J. Chem. Soc.*, 1962, 645; (*b*) Y. Inoue and D. D. Perrin, *ibid.*, 1963, 2648.

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

to 3·6—4·3) on saturation of the 3,4-double bond.[1,3] Absorption from the introduced side chains made u.v. spectra less useful for assignments than elsewhere in this work.

Under kinetic control, pteridine undergoes addition of one molecule of ethanol or water to the 3,4-bond but, under



(1)

a; R = -CH·CO·CH_2·CMe_2·CH_2·CO

b; R = -CH·CO·NH·CO·NH·CO

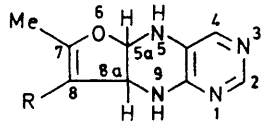
c; R = -CH·CO·NH·CS·NH·CO

d; R = -CH(CO_2Et)$_2$

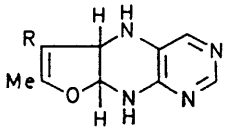
e; R = -CH(COPh)·CO_2Et

f; R = -CH(COMe)·CO_2Et

g; R = -CH(COMe)$_2$



(2)



(3)

a; R = CO_2·CH_2 Ph

b; R = CO_2Et

c; R = COMe

conditions of thermodynamic equilibrium, eventually loses it and gains two molecules of reagent across the 5,6- and 7,8-bonds.[1,3] Hence it was expected that Michael reagents might behave similarly, especially as 4-methyl-[4] and 4-hydroxy-[5] pteridine had been shown to add two molecules of Michael reagents (barbituric acid, dimedone, and acetylacetone) across the 5,6- and 7,8-bonds. Because no 2 : 1 adducts could be isolated from the reaction of pteridine with barbituric acid or dimedone, some less rigid reagents were tried. However, the only products of the reactions of pteridine with diethyl malonate and ethyl benzoylacetate were 3,4-adducts (1d and e, respectively). Their n.m.r. spectra (Table 1) and the similarity of their u.v. spectra (Table 2) to that of 3,4-dihydropteridine[6] confirmed their structure. Although compounds (1d and e) were soluble enough in the solvents used to be available for further reaction, the residues remaining after evaporation of the filtrates gave n.m.r. spectra very similar to those of compounds (1d) and (1e), respectively; no signals characteristic of 2 : 1 adducts[1] were observed. Furthermore, the n.m.r. spectrum of an equimolar mixture of diethyl malonate and compound (1d) [in $(CD_3)_2SO$] had not changed 25 days after mixing.

Hence it was surprising that some Michael reagents bearing acetyl groups [benzyl (and ethyl) acetoacetate, and acetylacetone] gave 5,6,7,8-tetrahydro-derivatives of pteridine as the first isolable products from equimolar amounts of the reagents. Elemental analysis showed that these were 1 : 1 adducts. The tetrahydrofuro[2,3-*g*]pteridine structures (2a—c), were preferred to those of the isomeric furo[3,2-*g*]pteridines (3) for the following reasons. Because the active methylene group is the stronger nucleophilic centre in these reagents, it should attack the highly electron-deficient[4] 7-position, after which the enolic hydroxy-group, a weaker nucleophile, could add across the isolated and highly polarised 5,6-double bond.[3,7] The n.m.r. spectra of these tricyclic compounds showed signals due to H-2 and H-4 at τ 1·6—1·9 and *ca.* 2·2, respectively, and those from H-5a and H-8a at τ *ca.* 4·0 and *ca.* 5·2 as a pair of doublets coupled to one another, indicating that addition involved the 6- and 7-positions of pteridine and that, in the products, the 6- and 7-carbon atoms were attached to two different substituents. This reaction recalls the formation of 1 : 1 adducts by addition of bifunctional nucleophiles (such as 1,2-diaminoethane) across the 5,6- and 7,8-bonds of ethyl pteridine-4-carboxylate.[7]

The u.v. spectral maxima of compounds (2a) and (2b) (the latter as hydrochloride) resembled those of 5,6,7,8-tetrahydropteridine[8] and its cation, respectively, above 300 nm, but the region below 300 nm was disturbed by absorption due to the Michael reagent residues. N.m.r. spectral change, with time, of a solution of pteridine and ethyl acetoacetate (or acetylacetone) in [$^2H_6$]dimethyl sulphoxide showed that the first product of the reaction was the 1 : 1 kinetically favoured 3,4-adduct (1f or g, respectively), identified by the appearance of a characteristic set of signals from H-2, H-4, H-6, and H-7; these signals gradually decreased in intensity with simultaneous increase of signals from the adduct (2b or c). The oil remaining after evaporation of the filtrate from the isolation of compound (2b) showed n.m.r. signals indicative of a mixture of compounds (2b) and (1f), but attempts to isolate the adduct (1f) were unsuccessful.

Malononitrile and pteridine gave 6-aminopyrido[2,3-*b*]-pyrazine-7-carbonitrile (4a). The presumed intermediate (5a) was not detected. Compound (4a) was synthesised independently from 3-aminopyrazine-2-carbaldehyde[9] (6) (as in the Scheme). The intermediate 3-aminopyrazin-2-ylmethylenemalononitrile (7a) was not isolated. Close similarity between the u.v. (Table 2) and

[4] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 1181.
[5] J. J. McCormack and A. Albert, Proceedings of the American Chemical Society's Spring Meeting, San Francisco, April 1968, N-65.
[6] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1970, 1540.
[7] J. Clark and F. S. Yates, *J. Chem. Soc.* (*C*), 1971, 371.
[8] P. R. Brook and G. R. Ramage, *J. Chem. Soc.*, 1957, 1.
[9] A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1971, 2357.

TABLE 1

^{1}H N.m.r. spectra at 33·3°

τ Values

Compound	Pyrazine protons	Pyrimidine protons H-2	H-4	Others	Solvent[a]
3,4-Dihydropteridine					
(1a)	1·68[b]	1·63	3·62	7·53,[c] 8·93[d]	N-DCl
(1b)	1·99, 2·08[f]	2·64	4·01		D_2O
(1c)	2·44, 2·58[g]	2·93	4·23		$(CD_3)_2SO$–8N-NaOD
(1d)	1·74[b]	2·59	4·49	5·80,[h] 5·87,[h] 8·85,[i] 8·92[i]	$(CD_3)_2SO$–D_2O
(1e)	1·95[b]	*j*	4·44	5·93,[k] 5·95,[k] 8·91,[l] 8·96[l]	$(CD_3)_2SO$–D_2O
5,5a,8a,9-Tetrahydrofuro-[2,3-*g*]pteridine					
(2a)	3·83, 5·18[m]	1·86	2·19	2·42,[n] 4·69,[o] 7·80[p]	$(CD_3)_2SO$–D_2O
(2b)[q]	3·96, 5·27[m]	1·62	2·27	5·88,[h] 7·87,[p] 8·77[i]	$(CD_3)_2SO$–D_2O
(2c)[q]	3·98, 5·13[m]	1·65	2·27	7·71,[r] 7·83[p]	$(CD_3)_2SO$–D_2O
Pyrido[2,3-*b*]pyrazine					
(4b)	0·81[b]			0·52[s]	$CF_3{\cdot}CO_2H$
(4a)	0·75[b]			0·61[s]	$CF_3{\cdot}CO_2H$

[a] For measurements in N-DCl and D_2O, sodium 3-trimethylsilylpropane-1-sulphonate was used as internal standard; tetramethylsilane was used for $(CD_3)_2SO$. [b] Two-proton singlet. [c] Singlet, two CH_2 of dimedone. [d] Singlet, two CH_3 of dimedone. [e] Sodium salt. [f] AB quartet, *J* 3·0 Hz. [g] AB quartet, *J* 2·4 Hz. [h] Quartet, *J* 7·2 Hz, $CH_2{\cdot}CH_3$. [i] Triplet, *J* 7·2 Hz, $CH_2{\cdot}CH_3$. [j] The signal due to H-2 overlapped signals from benzene ring protons (τ 2·1—2·8,m). [k] Two quartets (*J* 7·2 Hz), CH_2. [l] Two triplets (*J* 7·2 Hz), CH_3. [m] Pair of doublets (*J* 6·0 Hz) coupled to one another. [n] Singlet, benzene ring protons. [o] Centre of an AB quartet (*J* not clear). [p] Singlet, 7-CH_3. [q] Hydrochloride. [r] Singlet, CO·CH_3. [s] Singlet, H-8.

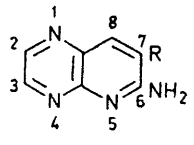
TABLE 2

Ionisation constants and u.v. spectra

Compound	Species[a]	Ionisation in water (20°) pK_a	Spread (±)	Concn. (M)	A.w.l.[b] (nm)	U.v. data[c] $\lambda_{max.}$/nm	log ε	Solvent[d]
3,4-Dihydropteridine								
(1a)	0					282, 340	4·34, 3·92	9·5
	+	7·69	0·03	$7·6 \times 10^{-5}$	345	279, 314	4·31, 4·01	5·0
(1b)	0					258, 301, 310, 337	4·25, 3·70, 3·70, 3·80	10·0
	+	7·24	0·02	$1·2 \times 10^{-4}$	258	255, 309	4·25, 3·94	5·0
(1d)	0					329	3·95	C
(1e)	0					252, 332	4·13, 3·92	C
Unsubstituted[e]	0					335	3·96	9
	+	6·36				311	3·90	4
5,6,7,8-Tetrahydropteridine[f]								
	0					268, 306	3·69, 3·81	
	+	6·63				208, 304	4·17, 3·89	
5,5a,8a,9-Tetrahydrofuro-[2,3-*g*]pteridine								
(2a)	0					245, 301	4·31, 3·93	C
(2b)	+[g]					245, 306	4·22, 3·93	E
Pyrido[2,3-*b*]pyrazine								
(4a)	0					213, 235, *258*, 383	4·43, 4·37, *3·94*, 4·01	7
	+	1·40	0·04	$1·4 \times 10^{-5}$	265	230, *266*, 361, *376*	4·35, *3·53*, 4·13, 4·05	−0·6
(4b)	0					*210*, 234, *262*, 378	*4·29*, 4·13, *3·71*, 3·87	7
	+	3·00	0·05	$1·2 \times 10^{-4}$	350	225, *260*, 356	4·21, *3·42*, 3·98	1

[a] Neutral species (0), cation (+). [b] Analytical wavelength for spectrometric determinations. [c] Inflections in italics. [d] C: Chloroform, E: ethanol, numerals refer to the pH or H_0 values of aqueous solutions. [e] All values from ref. 6. [f] All values from ref. 8. [g] Hydrochloride.

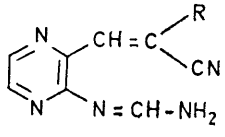
n.m.r. spectra (Table 1) of compounds (4a and b) (see later) supported the pyridopyrazine structure (4a) rather than that of the open-chain isomer (7a).



(4)

a; R = CN

b; R = CO·NH$_2$

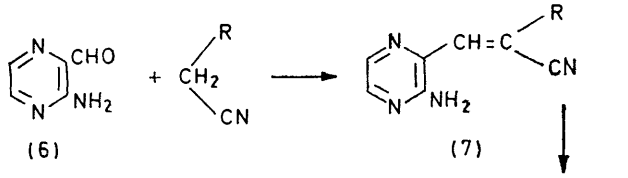


(5)

a; R = CN

b; R = CO·NH$_2$

Cyanoacetamide and pteridine gave 6-aminopyrido-[2,3-*b*]pyrazine-7-carboxamide (4b) in poorer yield (also unidentified compounds). The structure was confirmed



(6) (7) (4a and b)

a; R = CN

b; R = CO·NH$_2$

SCHEME

by synthesis as in the Scheme. The isolated intermediate (7b) (ν_{CN} 2236 cm^{-1}) was cyclised in good yield to the pyridopyrazine (4b) by N-sodium hydroxide. The absence of CN i.r. absorption distinguished compound (4b) from the open-chain isomer (7b). N.m.r. signals due to the ring protons were observed at low field (Table 1).

Because the product (4a) could be generated under anhydrous conditions, it was concluded that formation of compounds (4) from pteridine takes place by a concerted cyclisation of the amidine intermediate (5) with elimination of hydrogen cyanide, rather than through the amine (7) which could arise by hydrolysis of this amidine (*cf.* similar reactions in other fused pyrimidine series).[11]

[10] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.

[11] A. Albert and W. Pendergast, *J.C.S. Perkin I*, 1973, (*a*) following paper; (*b*) in the press.

Discussion.—In all reactions reported here, the first step was the formation of a 3,4-adduct, but in no instance did this undergo transformation to a more thermodynamically favoured 5,6,7,8-bi-adduct as did the 3,4-adducts of pteridine with alcohols[1] and water.[3] The reason seems to be that even the least nucleophilic substance (diethyl malonate) used in the present work is much more nucleophilic than are water and alcohols; hence, for Michael reagents, the 3,4-position is not only kinetically, but also thermodynamically favoured. The only exception is furnished by the *C*-acetyl compounds (acetylacetone, and benzyl and ethyl acetoacetate) which, by forming *two* links with the pyrazine ring, form a product even more firmly bound than the 3,4-adduct. Steric opposition to its approach apparently prevents ethyl benzoylacetate acting similarly.

The principal measure of nucleophilicity for Michael reagents seems to be the ease of ionisation of the active methylene group;[10] but when the tendency to ionise becomes excessive, as with reagents of p$K_a < 6$, the tendency to form a covalent bond diminishes. Hence the stability of the complexes formed by pteridine with dimedone, barbituric acid, and thiobarbituric acid (pK_a 5·3, 4·1, and 3·8, respectively) owes much to the demonstrated insolubility of the products in the reaction medium. The pK_a values of the other reagents used in this work fell between 8 and 13 and the adducts (*e.g.* that of diethyl malonate) showed no change in 25 days at 20—25° in spite of their solubility in the reaction media.

The adducts that underwent spontaneous rupture of the 3,4-bond, to give amidines of type (5), which cyclised to products of type (4), were all formed from reagents bearing strongly electron-attracting groups. Similar reactions have been reported[11] recently for the adducts of ethyl cyanoacetate, malononitrile, and cyanoacetamide with 8-azapurine (*v*-triazolo[4,5-*d*]pyrimidine), which furnish, in turn, 1,2,3-triazoles analogous to type (5), and *v*-triazolo[4,5-*b*]pyridines analogous to type (4).

EXPERIMENTAL

Pteridine was prepared as in ref. 12. Samples for microanalysis were dried at 20—25° and *ca.* 0·5 mmHg unless otherwise stated. Ionisation constants (at 20° in water) were determined spectroscopically.[13] U.v. spectra were measured on a Unicam SP 800 recording spectrophotometer; the wavelengths and intensities of maxima were confirmed with a Unicam SP 500, or an Optica CF4 manual instrument. I.r. spectra were taken (for mulls in Nujol) with a Unicam SP 200 spectrophotometer calibrated with polystyrene. N.m.r. spectra were determined with a Perkin-Elmer R10 instrument operating at 33·3° and 60 MHz.

Condensation with Dimedone.—Solutions of pteridine (0·05 g, 0·00038 mol) and dimedone (0·053 g, 0·00038 mol) in tetrahydrofuran (2 and 1 ml, respectively) were mixed and set aside at 20—25° overnight. The deposited powder, filtered off and washed with tetrahydrofuran, gave 3,4-*dihydro*-4-(4,4-*dimethyl*-2,6-*dioxocyclohexyl*)*pteridine* (1a)

[12] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 2289.

[13] A. Albert and E. P. Serjeant, 'The Determination of Ionisation Constants,' 2nd edn., Chapman and Hall, London, 1971.

(68%), m.p. 193° (decomp.) (Found: C, 62·0; H, 5·9; N, 20·4. $C_{14}H_{16}N_4O_2$ requires C, 61·75; H, 5·9; N, 20·6%).

Condensation with Barbituric Acid.—A solution of pteridine (0·05 g) in water (1 ml) was added to a hot solution of barbituric acid (0·049 g, 0·00038 mol) in water (4 ml). The mixture was set aside at 20—25° for 2 h, then crystals were collected and washed with water. To a suspension of the product in water, 4N-NaOH was added until all had dissolved. This solution was acidified to pH 5·5 with acetic acid. The deposited yellow prisms of the *trihydrate* of 3,4-*dihydro*-4-(2,4,6-*trioxohexahydropyrimidin*-5-*yl*)*pteridine* (1b) (77%) were filtered off and washed with water. The product turned grey above 220° without melting [Found: (material dried over $CaCl_2$ at 720 mmHg): C, 38·4; H, 4·3; N, 26·85. $C_{10}H_8N_6O_3,3H_2O$ requires C, 38·2; H, 4·5; N, 26·7%].

Condensation with Thiobarbituric Acid.—A solution of pteridine (0·05 g) in water (1 ml) and a hot solution of thiobarbituric acid (0·055 g, 0·00038 mol) in water (4 ml), mixed and set aside at 20—25° for 3 h, deposited yellow 3,4-*dihydro*-4-(4,6-*dioxo*-2-*thioxohexahydropyrimidin*-5-*yl*)-*pteridine* (1c) *hemihydrate* (90%), which was filtered off and washed with water. It darkened above 300° [Found (material dried at 720 mmHg): C, 42·3; H, 3·1; N, 29·3. $C_{10}H_8N_6O_2S,0{\cdot}5H_2O$ requires C, 42·1; H, 3·2; N, 29·5%].

Condensation with Diethyl Malonate.—A solution of pteridine (0·05 g) and diethyl malonate (0·061 g, 0·00038 mol) in ethanol (2 ml) was set aside at 20—25° for 4 days, and evaporated *in vacuo* to a slowly solidifying oil. Trituration with ether gave a solid, and similar trituration of the residue remaining after evaporation of the filtrate gave a second crop. Reprecipitation from ethyl acetate by ether–light petroleum (b.p. 60—80°) afforded slightly yellow prisms of 4-*bis*(*ethoxycarbonyl*)*methyl*-3,4-*dihydropteridine* (1d) (32%), m.p. 117° (Found: C, 53·7; H, 5·6; N, 19·5. $C_{13}H_{16}N_4O$ requires C, 53·4; H, 5·5; N, 19·2%).

Condensation with Ethyl Benzoylacetate.—A solution of pteridine (0·10 g) and ethyl benzoylacetate (0·146 g, 0·00076 mol) in tetrahydrofuran (2 ml) was set aside at 20—25° for 5 days. Addition of ether and light petroleum (b.p. 60—80°) followed by cooling overnight deposited a sticky solid, which was collected by decantation and triturated with ether to give a yellow solid. Three reprecipitations from ethyl acetate–ether–light petroleum (b.p. 60—80°) gave yellow crystals of 4-(1-*ethoxycarbonylphenacyl*)-3,4-*dihydropteridine* (1e) (20%), m.p. 100° (Found: C, 62·3; H, 5·3; N, 17·5. $C_{17}H_{16}N_4O_3$ requires C, 62·95; H, 5·0; N, 17·3%), $\nu_{max.}$ 1728s (CO ester) and 1691s (CO ketone) cm^{-1}.

Condensation with Benzyl Acetoacetate.—A solution of pteridine (0·20 g) and benzyl acetoacetate (0·59 g, 0·003 mol) in tetrahydrofuran (4·3 ml) was set aside at 20—25° for 7 days. The deposited crystals, filtered off and washed with benzene, gave *benzyl* 5,5a,8a,9-*tetrahydro*-7-*methylfuro*-[2,3-g]*pteridine*-8-*carboxylate* (2a) (24%), m.p. 145·5° (slight decomp.) (Found: C, 62·9; H, 5·1; N, 17·5. $C_{17}H_{16}N_4O_3$ requires C, 62·95; H, 5·0; N, 17·3%), $\nu_{max.}$ 1710s (CO) and 1641m (C=C) cm^{-1}.

Condensation with Ethyl Acetoacetate.—A solution of pteridine (0·10 g) and ethyl acetoacetate (0·099 g, 0·00076 mol) in tetrahydrofuran (2·3 ml) was set aside at 20—25° for 7 days, then chilled overnight. The deposited solid, filtered off and reprecipitated from aqueous ethanolic HCl–ether, gave the *hydrochloride* of *ethyl* 5,5a,8a,9-*tetrahydro*-7-*methylfuro*[2,3-g]*pteridine*-8-*carboxylate* (2b) (14%), m.p. 170° (decomp.) (after reprecipitation from water by ethanol–ether) (Found: C, 48·65; H, 5·3; Cl, 11·4; N, 18·6. $C_{12}H_{14}N_4O_3,HCl$ requires C, 48·2; H, 5·1; Cl, 11·9; N, 18·8%), $\nu_{max.}$ 1704s (CO), 1695m, and 1643s (C=C) cm^{-1}.

Condensation with Acetylacetone.—A solution of pteridine (0·10 g), acetylacetone (0·076 g, 0·00076 mol), and triethylamine (0·076 g, 0·00076 mol) in benzene (8 ml) was set aside at 20—25° for 15 days. The deposited prisms were filtered off and converted into the *hydrochloride* of 8-*acetyl*-5,5a,8a,9-*tetrahydro*-7-*methylfuro*[2,3-g]*pteridine* (2c) (26%), m.p. 154° (decomp.) (after reprecipitation from water–ethanol–ether) (Found: C, 48·8; H, 5·4; Cl, 12·9; N, 20·2. $C_{11}H_{12}N_4O_2,HCl,0{\cdot}25H_2O$ requires C, 48·4; H, 5·0; Cl, 13·0; N, 20·5%).

6-*Aminopyrido*[2,3-b]*pyrazine*-7-*carbonitrile* (4a).—(a) *By condensation at pteridine with malononitrile.* Pteridine (0·05 g) and malononitrile (0·05 g, 0·00076 mol) in tetrahydrofuran (1·5 ml) were set aside at 20—25° overnight. The deposit, filtered off, washed with dichloromethane, and recrystallised twice from aqueous dimethyl sulphoxide, gave the *pyridopyrazine* (48%), as fine tan needles. These darkened above 250° without melting (Found: C, 56·0; H, 3·3; N, 40·8. $C_8H_5N_5$ requires C, 56·1; H, 2·9; N, 40·9%), $\nu_{max.}$ 2230 (CN) cm^{-1}.

(b) *From* 3-*aminopyrazine*-2-*carbaldehyde* (6). This aldehyde [9] (0·06 g, 0·00049 mol) and *N*-methylpiperidine (0·05 g, 0·00050 mol) were added consecutively to a solution of malononitrile (0·04 g, 0·00061 mol) in methanol (0·5 ml). The precipitated crystals, filtered off after 1 h, washed with ethanol, and recrystallised from aqueous dimethyl sulphoxide, gave the pyridopyrazine (4a) (47%) as tan needles, m.p. >330°.

6-*Aminopyrido*[2,3-b]*pyrazine*-7-*carboxamide* (4b).—(a) *From* 3-*aminopyrazine*-2-*carbaldehyde* (6). 3-Aminopyrazine-2-carbaldehyde (0·20 g, 0·0016 mol) and *N*-methylpiperidine (0·157 g, 0·0016 mol) were added consecutively to a solution of cyanoacetamide (0·157 g, 0·0020 mol) in methanol (3 ml). Next day the suspension was filtered to give a solid which, after washing with methanol, did not melt below 350°; $\nu_{max.}$ 2236 (CN) cm^{-1}. This solid, considered to be α-(3-aminopyrazin-2-ylmethylene)-α-cyanoacetamide (7b) (99%), cyclised during recrystallisation to the pyridopyrazine (4b). Treatment of the nitrile (7b) with hot aqueous N-NaOH for 5 min gave a poorly soluble solid which, after two recrystallisations from pyridine trihydrate, furnished the *pyridopyrazine* (4b) (63%). It did not melt below 350° (Found: C, 50·7; H, 4·0; N, 37·4. $C_8H_7N_5O$ requires C, 50·8; H, 3·7; N, 37·0%).

(b) *From condensation of pteridine with cyanoacetamide.* Pteridine (0·10 g) and cyanoacetamide (0·064 g, 0·00076 mol) in water (1 ml) were set aside at 20—25° for 5 days. The precipitated solid was filtered off and washed with water. A suspension in ethanol (20 ml), stirred for 30 min, deposited the pyridopyrazine (4b) (19%).

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