Pteridine Studies. Part XL.[1] The Synthesis of 4-Unsubstituted Pteridines from 3-Aminopyrazine-2-carbaldehyde

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3-Aminopyrazine-2-carbaldehyde (Ia) could be prepared by oxidizing 2-amino-3-hydroxymethylpyrazine (Ib) but not by reducing 3-aminopyrazine-2-carbonitrile (Ic), *N*-(3-aminopyrazine-2-carbonyl)piperidine (Id), or *S*-methyl 3-aminopyrazine-2-thiocarboxylate (Ie) (the latter was made by hydrolysing methyl 3-aminopyrazine-2-thiocarboximidate). The aldehyde (Ia) was converted into 2-amino-3-dimethoxymethylpyrazine (IIIa), which was acylated to give the *N*-acetyl, ethoxycarbonyl, formyl, ethoxalyl, and trifluoroacetyl derivatives. These acetals were hydrolysed to 3-acetamido-, 3-ethoxycarbonylamino-, 3-formamido-, and 3-ethoxalylamino-pyrazine-2-carbaldehyde. These aldehydes were cyclized with ammonia to 2-methylpteridine (IVc), pteridin-2-one, pteridine, and ethyl pteridine-2-carboxylate. Pteridine was shown to form a double-bond adduct with ammonia. The analogous methylamine adduct (Vb) (5,6,7,8-tetrahydro-6,7-bismethylaminopteridine) was isolated and characterized. The electronic patterns influencing these reactions are discussed.

Both mild acetylation of 2-amino-3-hydroxymethylpyrazine (Ib) and acid hydrolysis of 2-acetamido-3-acetoxymethylpyrazine gave 2-acetoxymethyl-3-aminopyrazine.

Ionization constants and u.v., i.r., and n.m.r. spectra are recorded and discussed.

THE new pteridine synthesis [1] from 2-amino-3-aminomethylpyrazine suggested a parallel synthesis from 3-aminopyrazine-2-carbaldehyde (Ia), along the lines of Bischler's quinazoline synthesis [2] (*e.g.* cyclization of 2-acetamidobenzaldehyde [3] with ammonia to give 2-methylquinazoline). The required pyrazine aldehyde

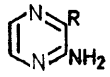
[1] Part XXXIX, A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1970, 1540.

[2] A. Bischler, *Ber.*, 1891, **24**, 506.

[3] P. Friedländer, *Ber.*, 1882, **15**, 2572.

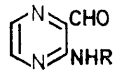
(Ia), hitherto obtained [4] only by acid hydrolysis of pteridine, was conveniently prepared by oxidizing 2-amino-3-hydroxymethylpyrazine [5] (Ib), obtained by reducing methyl 3-aminopyrazine-2-carboxylate. [An improved preparation of the alcohol (Ib) is described in the Experimental section.] Attempted preparations of the aldehyde (Ia) by appropriate reduction [6] of the following pyrazine intermediates were unsuccessful: (*a*) 3-aminopyrazine-2-carbonitrile (Ic),[1] (*b*) *N*-(3-aminopyrazine-2-carbonyl)piperidine (Id) (prepared from methyl 3-aminopyrazine-2-carboxylate), and (*c*) *S*-methyl 3-aminopyrazine-2-thiocarboxylate (Ie), prepared by first converting the nitrile (Ic) into the methyl thioimidate (If), which was then hydrolysed by acid.

It was found that this aldehyde (Ia) resisted acylation with acid chlorides and acid anhydrides other [4b] than acetic formic anhydride, which gave only a little 3-formamidopyrazine-2-carbaldehyde (IIa). This difficulty in acylating the amino-group was attributed to (*a*) the strong electron-attracting effect of the aldehyde group, and (*b*) internal hydrogen bonding of the amino-group to the carbonyl oxygen atom. To overcome these barriers to electrophilic attack, the aldehyde (Ia) was converted into the corresponding methyl acetal, 2-amino-3-dimethoxymethylpyrazine (IIIa), with boron



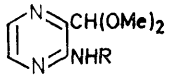
(I)

a; R = CHO
b; R = CH_2·OH
c; R = CN
d; R = CO·N·[CH_2]$_4$·CH_2
e; R = CO·SMe
f; R = C(:NH)·SMe
g; R = CH_2·OAc



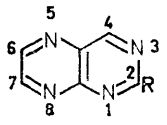
(II)

a; R = CHO
b; R = COMe
c; R = CO_2Et
d; R = CO·CO_2Et



(III)

a; R = H
b; R = Ac
c; R = CO_2Et
d; R = CHO
e; R = CO·CO_2Et
f; R = CO·CF_3



(IV)

a; R = H
b; R = CO_2Et
c; R = Me

trifluoride–methanol complex at room temperature. The ^{1}H n.m.r. spectrum of the acetal (IIIa) in deuteriochloroform consisted of peaks at τ 1·96 and 2·09 (the two pyrazine protons), a broad deuterium-exchangeable peak at τ 4·37 (NH_2), and sharp peaks at τ 4·68 (O·CH·O) and 6·52 (2 × OMe). This acetal (IIIa), being unstable, was used without purification.

Treatment with acetyl chloride at room temperature gave 2-acetamido-3-dimethoxymethylpyrazine (IIIb), which was easily hydrolysed to 3-acetamidopyrazine-2-carbaldehyde (IIb) when boiled with aqueous pyridine hydrochloride. For preparative purposes, the acetylated acetal (IIIb) was not isolated. The acetal (IIIa) was similarly acylated with ethyl chloroformate to give 2-dimethoxymethyl-3-ethoxycarbonylaminopyrazine (IIIc), which was hydrolysed to 3-ethoxycarbonylaminopyrazine-2-carbaldehyde (IIc) with aqueous pyridine hydrochloride.

Acetic formic anhydride [7] and the acetal (IIIa) gave 2-dimethoxymethyl-3-formamidopyrazine (IIId), which was hydrolysed to the known formylated aldehyde (IIa), although in only poor yield, when stirred with toluene-4-sulphonic acid in acetone. 2-Dimethoxymethyl-3-ethoxalylaminopyrazine (IIIe), similarly prepared from the acetal (IIIa) and ethoxalyl chloride, was hydrolysed (as before) to 3-ethoxalylaminopyrazine-2-carbaldehyde (IId). 2-Dimethoxymethyl-3-trifluoroacetamidopyrazine (IIIf) was similarly prepared from the acetal (IIIa) and trifluoroacetic anhydride, but all attempts at hydrolysis to 3-trifluoroacetamidopyrazine-2-carbaldehyde were unsuccessful.

An attempted synthesis of pteridine (IVa) from 3-formamidopyrazine-2-carbaldehyde (IIa) and alcoholic ammonia had caused considerable decomposition.[4b] We found that this formamido-aldehyde (IIa) gave pteridine (IVa),[8] although in only about 3% yield, when stirred in ethanolic ammonia at 0°. Similarly 3-ethoxalylaminopyrazine-2-carbaldehyde (IId) produced crude ethyl pteridine-2-carboxylate (IVb) (in about 6% yield) with ammonia in tetrahydrofuran at 0°. Better results were obtained with 3-acetamidopyrazine-2-carbaldehyde (IIb), which gave 2-methylpteridine [9] (IVc) in 34% yield in ethanolic ammonia at 0°; also 3-ethoxycarbonylaminopyrazine-2-carbaldehyde (IIc) furnished pteridin-2-one (2-hydroxypteridine),[8] in 55% yield, when stirred in ethanolic ammonia at room temperature.

It seems that, under the cyclization conditions, aminopyrazinecarbaldehydes which have a mildly electron-attracting group (acetyl or ethoxycarbonyl) are more stable to hydrolysis than those with a strongly electron-attracting group (formyl or ethoxalyl). Moreover, those resulting pteridines without an electron-releasing group were obtained in poor yields because of the greater tendency to form a covalent adduct with a nucleophilic reagent such as ammonia (see later). Also, in the preparation of the acylaminopyrazinecarbaldehydes (II), the hydrolysis of an acetal group was discouraged by a strongly electron-attracting acyl group in the 2-amino-

[4] (*a*) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1956, 2066; (*b*) A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 2289.

[5] A. Albert and S. Matsuura, *J. Chem. Soc.*, 1961, 5131.

[6] O. G. Backeberg and B. Staskun, *J. Chem. Soc.*, 1962, 3961; B. Staskun and O. G. Backeberg, *ibid.*, 1964, 5880; T. van Es and B. Staskun, *ibid.*, 1965, 5775; T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, 1951, **16**, 1121; F. Weygand, G. Eberhardt, H. Linden, F. Shäfer, and I. Eigen, *Angew. Chem.*, 1953, **65**, 525; E. Mosettig, *Org. Reactions*, 1954, **8**, 229.

[7] I. Muramatsu, M. Murakami, and T. Yoneda, *Bull. Chem. Soc. Japan*, 1965, **38**, 244.

[8] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1951, 474.

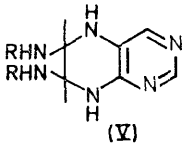
[9] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.

substituent; moreover the acylamino-group, when formed, was more easily hydrolysed.

In an attempt to prepare 2-acetamido-3-hydroxymethylpyrazine [for oxidation to 3-acetamidopyrazine-2-carbaldehyde (IIb)] by stirring 2-amino-3-hydroxymethylpyrazine (Ib) with acetic anhydride and pyridine at room temperature, only 2-acetoxymethyl-3-aminopyrazine (Ig) was formed. Also 2-acetamido-3-acetoxymethylpyrazine, obtained by refluxing 2-amino-3-hydroxymethylpyrazine (Ib) with acetic anhydride, gave mainly 2-acetoxymethyl-3-aminopyrazine (Ig) when refluxed in dilute acid solution (at pH 3).

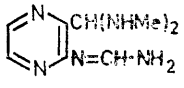
The orientation of the acetyl group in compound (Ig) was established as follows. The basic group of 2-acetoxymethyl-3-aminopyrazine (Ig) was weak (pK_a 2·42), similar to that of 2-amino-3-hydroxymethylpyrazine (pK_a 3·11) (see Table), but not weak enough to be that of the *N*-acetylated isomer. The u.v. spectrum of the neutral species of the acetoxy-derivative was almost identical with that of 2-amino-3-hydroxymethylpyrazine, but different from that of 2-acetamido-3-acetoxymethylpyrazine (see Table). The n.m.r. spectra also supported the *O*-acetyl structure.

These reactions of 3-aminopyrazine-2-carbaldehyde have opened up interesting new chemistry, but for preparing pteridines the synthesis [1] from 2-amino-3-aminomethylpyrazine is generally preferable.



(V)

a; R = H
b; R = Me



(VI)

Amine Adducts of Pteridine.—Because the reaction between 3-formamidopyrazine-2-carbaldehyde and ammonia gave a poor yield of pteridine, the behaviour of the latter towards ammonia was examined. Although the u.v. spectrum of pteridine in mildly alkaline aqueous solution (butylamine–HCl buffer; pH 11) was identical with that of a neutral solution, the spectrum of pteridine in aqueous 9N-ammonia showed a new peak (at 263 nm), similar to that of the neutral species of 5,6,7,8-tetrahydropteridine [10] (see Table). [So far, water was the only potential addend known to combine with pteridine itself [11]]. These data suggested that ammonia added across the 5,6- and 7,8-double bonds to give 6,7-diamino-5,6,7,8-tetrahydropteridine (Va).

The ammonia adduct was precipitated when pteridine was stirred in ethanolic ammonia while ammonia was slowly passed through the solution. Paper chromatography showed that small amounts of several unidentifiable compounds were also formed (they were different from 6,7-diamino-, 6-amino-7-hydroxy-, and 7-amino-6-hydroxy-pteridine, 4,5-diaminopyrimidine, and 3-aminopyrazine-2-carbaldehyde). Attempted purification of the crude ammonia adduct was unsuccessful because of a tendency to eliminate ammonia. Attempted oxidation of the ammonia adduct (Va) to the known 6,7-diaminopteridine [12] caused decomposition.

The corresponding methylamine adduct (Vb) was more easily prepared (from pteridine and ethanolic methylamine) as a pure and stable solid which gradually eliminated methylamine when dissolved in water or ethanol. Elemental analysis indicated addition of two molecules of methylamine. The u.v. spectrum of this adduct in aqueous 8N-methylamine, was almost identical with that of the ammonia adduct in aqueous 9N-ammonia (see Table). The n.m.r. spectrum of the methylamine adduct (Vb) in hexadeuteriodimethyl sulphoxide showed four sharp singlets at τ 2·02 (1H), 2·34 (1H), 7·69 (3H), and 7·74 (3H) (H-2, H-4, and *N*-methyl groups), two slightly broad singlets at τ 2·06 (1H) and 3·49 (1H) (8-H and 5-H, respectively), and three multiplets at τ 6·05 (1H), 6·17 (1H), and *ca.* 7·8br (2H) (H-6, H-7, and 2 × NH). After deuterium exchange,

Ionization constants and u.v. spectra

	Ionization in water (20°)				Spectroscopy in water [a]		
	Species [b]	pK_a	Spread (±)	Concn./M	A.w.l. [c] (λ/nm)	$\lambda_{max.}$/nm	log ε	pH
Pyrazine							
2-Amino-3-hydromethyl	0					231, 316	4·00, 3·78	6
	+	3·11	0·04	$8·0 \times 10^{-5}$	340	231, 326	4·00, 3·84	0
2-Acetamido-3-acetoxymethyl	0					274, *290*	3·81, *3·58*	6
2-Acetoxymethyl-3-amino	0	2·42	0·01	$4·5 \times 10^{-5}$	340	231, 319	4·03, 3·78	6
Pteridine								
Unsubstituted	0	4·12 [d]	0·05	0·05		*233*, 298 + 308 [e]	*3·47*, 3·875 + 3·82	7·4
Ammonia adduct (pteridine in aqueous ammonia)	0					263, 309	3·72, 3·88	A [f]
5,6,7,8-Tetrahydro [g]	0	6·63	0·02	10^{-2}		268, 306	3·69, 3·81	
5,6,7,8-Tetrahydro-6,7-bis-methylamino	0					263, 311	3·60, 3·75	B [f]

[a] Inflections in italics. [b] Neutral species (0) and cation (+). [c] Analytical wavelength for spectrometric determination (performed as in A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962). [d] Values from ref. 8. [e] Values from ref. 11. [f] A, aqueous 9N-ammonia; B, aqueous 8N-methylamine. [g] Values from ref. 10.

[10] P. R. Brook and G. R. Ramage, *J. Chem. Soc.*, 1957, 1.
[11] D. D. Perrin, *J. Chem. Soc.*, 1962, 645.
[12] A. Albert and J. Clark, *J. Chem. Soc.*, 1965, 27.

the peaks at τ 2·06, 3·49, and *ca* 7·8 had disappeared and the two multiplets at τ 6·05 and 6·17 had collapsed to a doublet (1H) (the other doublet could not be observed because of the large water peak). These data established that pteridine added two molecules of methylamine, across the 5,6- and 7,8-double bonds, to give 5,6,7,8-tetrahydro-6,7-bismethylaminopteridine (Vb). A possible ring-opened structure (VI) can be excluded because the aliphatic proton signals at τ 6·05 and 6·17, after deuterium exchange, were shown to form a doublet, and no extra vinyl proton (expected at about τ 1·2) due to an amidine group was observed.

When pteridine is dissolved in water, the neutral solution contains [11] a mixture of anhydrous pteridine and 3,4-dihydro-4-hydroxypteridine (only) in the ratio of about 3·5 : 1. However when the u.v. spectrum of pteridine was measured in various concentrations of ammonia (0—9N), the spectrum changed directly from that of pteridine to that of 6,7-diamino-5,6,7,8-tetrahydropteridine; no evidence of formation of 4-amino-3,4-dihydropteridine (expected $\lambda_{max.}$ *ca.* 320 nm) was observed. Also the n.m.r. spectrum of pteridine in aqueous ammonia, measured within 1 min after dissolution, showed the peaks characteristic of the 2 : 1 ammonia adduct almost exclusively.

EXPERIMENTAL

U.v. spectra were measured with a Unicam SP 800 spectrophotometer; the wavelength and intensity of each maximum were checked with an Optica manual instrument. I.r. spectra were taken with a Unicam SP 200 spectrophotometer calibrated with polystyrene at 1603 cm^{-1} (for mulls in Nujol) unless otherwise stated. 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.

2-*Amino*-3-*hydroxymethylpyrazine* (Ib).—The method of Albert and Matsuura [5] was modified as follows. To a suspension of methyl 3-aminopyrazine-2-carboxylate (9·0 g) in tetrahydrofuran (600 ml), lithium aluminium hydride (2·4 g) in tetrahydrofuran (70 ml) was added dropwise with stirring. The mixture was stirred at room temperature for 3 h, then heated under reflux for 20 min. Water (20 ml) was cautiously added to the cooled solution and the solid was filtered off. The filtrate was evaporated to dryness *in vacuo*, and the residue, sublimed at 110° and 0·01 mmHg, gave 2-amino-3-hydroxymethylpyrazine (61%), m.p. 110—114°, raised to 119° by crystallization from ethyl acetate (lit.,[5] 118—119·5°) (81% recovery).

3-*Aminopyrazine*-2-*carbaldehyde* (Ia).—A suspension of 2-amino-3-hydroxymethylpyrazine (4·5 g) and manganese dioxide (27 g) in chloroform (140 ml) was stirred at room temperature for 30 min. The solid was filtered off. The filtrate was evaporated to dryness, and the residue, sublimed at 100° and 0·01 mmHg, gave 3-aminopyrazine-2-carbaldehyde (84%), m.p. 117° (lit.,[4a] 119—120°), identical with an authentic sample (i.r. spectra and mixed m.p.).

N-(3-*Aminopyrazine*-2-*carbonyl*)*piperidine* (Id).—A suspension of methyl 3-aminopyrazine-2-carboxylate (1·53 g) in piperidine (18 ml) was heated under reflux for 17 h, then evaporated to dryness *in vacuo*. The residue gave *N-(3-aminopyrazine-2-carbonyl)piperidine* (45%), m.p. 153—155° (from water) [Found (material dried at 20° and 20 mmHg): C, 58·4; H, 7·1; N, 27·4. $C_{10}H_{14}N_4O$ requires C, 58·2; H, 6·8; N, 27·2%], $\nu_{max.}$ 3340m, 3150m, 1645m,sh, 1625s (C=O str.), 1575m, 1540m, 1470m, 1440m, 1165m, and 1115m cm^{-1}, τ($CDCl_3$) 1·88 and 2·04 (total 2H, ABq, *J* 2·6 Hz, pyrazine ring), *ca.* 4·3br (2H, s, NH_2), and *ca.* 6·4 and 8·32 (5H, piperidine ring).

Methyl 3-*Aminopyrazine*-2-*thiocarboximidate* (If).—To ethanol (15 ml) containing methanethiol (2·5 g) and N-sodium hydroxide (1 drop) was added 3-aminopyrazine-2-carbonitrile [1] (0·45 g). The mixture was stirred at 45° for 30 min and, on cooling, yielded *methyl* 3-*aminopyrazine*-2-*thiocarboximidate* (79%), m.p. 123° [Found (material dried at 20° and 20 mmHg): C, 43·0; H, 4·8; N, 33·9. $C_6H_8N_4S$ requires C, 42·9; H, 4·8; N, 33·9%], $\nu_{max.}$ 3280s, 3110s, 1610s, 1580m, 1560m, 1450m, 1440m, 1295m, 1160m, 920m, 860m, and 820m cm^{-1}, τ($CDCl_3$) 0·13br (1H, s, =NH), 1·86 and 2·04 (total 2H, ABq, *J* 2·6 Hz, pyrazine ring), *ca.* 2·7br (2H, s, NH_2), and 7·71 (3H, s, SMe).

S-*Methyl* 3-*Aminopyrazone*-2-*thiocarboxylate* (Ie).—A suspension of methyl 3-aminopyrazine-2-thiocarboximidate (0·45 g) in N-hydrochloric acid (10 ml) was heated under reflux for 10 min, and the pH was adjusted to 5. The cooled solution yielded the *ester* (92%), m.p. 151—153° (from ethanol) [Found (material dried at 20° and 20 mmHg): C, 42·8; H, 4·1; N, 24·9. $C_6H_7N_3OS$ requires C, 42·6; H, 4·2; N, 24·9%], $\nu_{max.}$ 3450m, 3280s, 3160s, 1655m, 1615s, 1560m, 1535m, 940s (=C–S str.), and 850s cm^{-1}, τ[$(CD_3)_2SO$] 1·58 and 2·01 (total 2H, ABq, *J* 1·7 Hz, pyrazine ring), 2·44br (2H, s, NH_2), and 7·68 (3H, s, SMe).

2-*Amino*-3-*dimethoxymethylpyrazine* (IIIa) *and* 3-*Acetamidopyrazine*-2-*carbaldehyde* (IIb).—A solution of 3-aminopyrazine-2-carbaldehyde (0·40 g) in boron trifluoride–methanol complex (3·5 ml) was stirred at room temperature for 2 h. The mixture was poured into water (3·5 ml) containing sodium carbonate (0·9 g) and extracted with chloroform (3 × 6 ml) (extract dried over Na_2SO_4). The filtered solution, evaporated to a syrup, gave crude 2-amino-3-dimethoxymethylpyrazine, which decomposed at *ca.* 100° when distilled under low vacuum. It was dissolved in chloroform (5 ml) containing pyridine (0·6 ml), then cooled in ice–water. To the mixture, acetyl chloride (0·5 ml) was added dropwise. The mixture was stirred at 0° for 30 min and evaporated to a syrup, to which was added water (3 ml). To hydrolyse the acetal group, the mixture was heated under reflux for 20 min, then cooled and extracted with chloroform (3 × 6 ml) (extract dried over Na_2SO_4). The filtered solution was evaporated and the residue, sublimed at 110° and 0·01 mmHg, gave 3-*acetamidopyrazine*-2-*carbaldehyde* (32%), m.p. 70° [benzene–light petroleum (b.p. 60—80°)] [Found (material dried at 20° and 0·01 mmHg): C, 51·0; H, 4·6; N, 25·3. $C_7H_7N_3O_2$ requires C, 50·9; H, 4·3; N, 25·5%], $\nu_{max.}$ (undiluted) 3450w, 3310m, 3060w, 3000w, 2940w, 2840w (CH str. of CHO), 1710s (NH·C=O str.), 1685s (CHO str.), 1585s, 1500m, 1380m, 1280m, 1245m, and 1225 m cm^{-1}, τ($CDCl_3$) *ca.* −0·76br (1H, s, NH, exchangeable), −0·18 (1H, s, CHO), 1·38 and 1·47 (total 2H, ABq, *J* 1·7 Hz, pyrazine ring), and 7·54 (3H, s, Ac).

In another experiment, the intermediate was isolated after stirring with acetyl chloride. The mixture was washed with water and the chloroform layer was evaporated *in vacuo* to a syrup, which was subjected to t.l.c. (silica gel; ethyl acetate). The band at R_F 0·7, which showed a dark colour under 254 nm light, was collected and extracted

with methanol. Removal of solvent *in vacuo*, followed by distillation, gave 2-*acetamido*-3-*dimethoxymethylpyrazine* (IIIb) (b.p. 132° at 0·1 mmHg) (Found: C, 50·3; H, 6·5; N, 19·6. $C_9H_{13}N_3O_3$ requires C, 50·3; H, 6·2; N, 19·9%), $\nu_{max.}$ (undiluted) 3360m, 2950m, 2840w, 1695s, 1585m, 1505s, 1470s, 1410m, 1380s, 1320s, 1300s, 1125m, 1100s, and 1065s cm^{-1}, $\tau(CDCl_3)$ 0·91br (1H, s, NH, exchangeable), 1·56 and 1·69 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·63 (1H, s, acetal), 6·47 (6H, s, 2 × OMe), and 7·58 (3H, s, Ac).

3-*Ethoxycarbonylaminopyrazine*-2-*carbaldehyde* (IIc).—Crude 2-amino-3-dimethoxymethylpyrazine [from the aldehyde (0·06 g)] was dissolved in chloroform (5 ml) containing pyridine (1 ml), then cooled in ice–water. Ethyl chloroformate (1·0 ml) was added dropwise, and the mixture was stirred at room temperature for 12 h, then ethanol was added to destroy the excess of ethyl chloroformate. The mixture was evaporated to a syrup, which was dissolved in water (5 ml) and heated under reflux for 30 min. The resulting solution was extracted with chloroform (3 × 5 ml) (extract dried over Na_2SO_4). The filtered solution was concentrated to a small volume and subjected to t.l.c. (silica gel; ethyl acetate). A band (R_F 0·8) which strongly absorbed u.v. light at 254 nm was collected and extracted with ethanol. Removal of the solvent, followed by sublimation at 110° and 0·01 mmHg, gave 3-*ethoxycarbonylaminopyrazine*-2-*carbaldehyde* (53%), m.p. 73° [from benzene–light petroleum (b.p. 60—80°)] [Found (material dried at 20° and 0·01 mmHg): C, 49·0; H, 4·4; N, 21·6. $C_8H_9N_3O_3$ requires C, 49·2; H, 4·7; N, 21·5%], $\nu_{max.}$ (undiluted) 3450w, 3300m, 2980w, 2850w (CH str. of CHO), 1750s (NH·C=O str.), 1680s (CHO str.), 1590s, 1510s, 1475m, 1210s,sh, 1195s (both C–O–C– str.), and 1065s cm^{-1}, $\tau(CDCl_3)$ −0·30br (1H, s, NH, exchangeable), −0·15 (1H, s, CHO), 1·28 and 1·47 (total 2H, ABq, J 2·6 Hz, pyrazine ring), and 5·64 (2H, q) and 8·64 (3H, t, J 7·4 Hz, Et). The intermediate 2-dimethoxymethyl-3-ethoxycarbonylaminopyrazine decomposed during attempts to separate it by t.l.c.

2-*Dimethoxymethyl*-3-*formamidopyrazine* (IIId).—Crude 2-amino-3-dimethoxymethylpyrazine [from the aldehyde (0·40 g)] and acetic formic anhydride [7] (4 ml) were stirred at 0° for 12 h, and evaporated several times with methanol. The residue, sublimed at 100° and 0·01 mmHg, gave 2-*dimethoxymethyl*-3-*formamidopyrazine* (53%), m.p. 70° [from benzene–light petroleum (b.p. 60—80°)] [Found (material dried at 20° and 0·01 mmHg): C, 48·2; H, 5·7; N, 21·3. $C_8H_{11}N_3O_3$ requires C, 48·7; H, 5·6; N, 21·3%], $\nu_{max.}$ 3290m, 1705s (C=O str.), 1585m, 1485s, 1470s, 1390m, 1370m, 1245m, 1100s, 1070s, 990m, and 975 cm^{-1}, $\tau(CDCl_3)$ 0·38* (1H, d, J 10·3 Hz, CHO), 1·65 and 1·70 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·62 (1H, s, acetal), and 6·50 (6H, s, 2 × OMe). The asterisked signal collapsed to a singlet on deuterium exchange.

3-*Formamidopyrazine*-2-*carbaldehyde* (IIa).—A suspension of 2-dimethoxymethyl-3-formamidopyrazine (0·15 g), toluene-4-sulphonic acid monohydrate (0·16 g), and sodium sulphate (0·15 g) in acetone (5 ml) was stirred at room temperature for 2 h. The solid was filtered off. The filtrate was evaporated *in vacuo* below 20°. To the residue was added M-sodium hydrogen carbonate (1 ml) and the mixture was extracted with chloroform (3 × 1 ml) (extract dried over Na_2SO_4). The filtered solution was evaporated to small volume and subjected to t.l.c. (silica gel; dichloromethane; re-run four times). The band (R_F 0·7—0·85) which showed a dark colour under 254 nm light was collected and extracted with ethanol. Removal of the solvent at 30° *in vacuo*, followed by sublimation of the residue at 100° and 0·01 mmHg, gave 3-formamidopyrazine-2-carbaldehyde (12%), m.p. 125—127° (lit.,[4b] 126—128°), identical with an authentic sample (i.r. spectra and mixed m.p.).

2-*Dimethoxymethyl*-3-*ethoxalylaminopyrazine* (IIIc).—The crude 2-amino-3-dimethoxymethylpyrazine [from the aldehyde (2·0 g)] was dissolved in chloroform (8 ml) and pyridine (6 ml), then cooled to −45°. Ethoxalyl chloride (3·2 g) was added dropwise, and the mixture was stirred at this temperature for 30 min, then washed with 4N-sodium carbonate (2 × 5 ml) and water (2 ml). The washings were extracted with chloroform (3 × 5 ml). A mixture of the original chloroform layer and the extracts (dried over Na_2SO_4) was evaporated; distillation at 148—158° and 0·01 mmHg gave 2-*dimethoxymethyl*-3-*ethoxalylaminopyrazine* (51%), m.p. 56° [from benzene–light petroleum (b.p. 60—80°)] (Found (material dried at 20° and 0·01 mmHg): C, 49·1; H, 5·9; N, 15·7. $C_{11}H_{15}N_3O_5$ requires C, 49·1; H, 5·6; N, 15·6%], $\nu_{max.}$ (undiluted) 3260m, 2990m, 2940m, 2840w, 1725s, 1590m, 1520m, 1470m, 1300m, 1185m, 1165m, 1105m, and 1055m cm^{-1}, $\tau(CDCl_3)$ 1·42 and 1·58 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·59 (1H, s, acetal), 6·47 (6H, s, 2 × OMe), and 5·56 (2H, q) and 8·61 (3H, t) (J 7·7 Hz, Et).

3-*Ethoxalylaminopyrazine*-2-*carbaldehyde* (IId).—A suspension of 2-dimethoxymethyl-3-ethoxalylaminopyrazine 0·81 g), toluene-4-sulphonic acid monohydrate (0·60 g), and sodium sulphate (1 g) in acetone (10 ml) was heated under reflux for 40 min. The solid was filtered off. The filtrate was evaporated to dryness below 30° *in vacuo*, and the residue was suspended in M-sodium hydrogen carbonate (3·5 ml) and extracted with chloroform (3 × 5 ml) (extract dried over Na_2SO_4). The filtered solution was evaporated to dryness *in vacuo*. The residue, sublimed at 120° and 0·01 mmHg, gave 3-*ethoxalylaminopyrazine*-2-*carbaldehyde* (24%), m.p. 124° (from benzene) [Found (material dried at 25° and 0·01 mmHg): C, 48·6; H, 4·3; N, 19·0. $C_9H_9N_3O_4$ requires C, 48·4; H, 4·1; N, 18·8%], $\nu_{max.}$ 3250m, 1745s, 1685s, 1590s, 1520s, 1475s, 1380m, 1320s, 1290m, 1165m, 1140m, 1065m, and 740m cm^{-1}, $\tau(CDCl_3)$ −0·42 (1H, s, CHO), 1·15 and 1·28 (total 2H, ABq, J 2·0 Hz, pyrazine ring), and 5·42 (2H, q) and 8·50 (3H, t, J 7·7 Hz, Et).

2-*Dimethoxymethyl*-3-*trifluoroacetamidopyrazine* (IIIf).—Crude 2-amino-3-dimethoxymethylpyrazine [from the aldehyde (0·60 g)] was dissolved in chloroform (5 ml) and pyridine (1 ml), then cooled to 0°. Trifluoroacetic anhydride (1·5 g) was added dropwise, and the mixture was stirred at 0° for 1 h, and washed with 4N-sodium carbonate (3 ml) then water (2 ml). The washings were extracted with chloroform (2 × 3 ml). The combined chloroform layer and extracts (dried over Na_2SO_4) were evaporated. The residue, sublimed at 140° and 0·01 mmHg, gave 2-*dimethoxymethyl*-3-*trifluoroacetamidopyrazine* (54%), m.p. 49° [from benzene–light petroleum (b.p. 60—80°)] [Found (for material dried at 20° and 0·01 mmHg): C, 40·5; H, 3·9; N, 16·0. $C_9H_{10}N_3O_3F_3$ requires C, 40·8; H, 3·8; N, 15·8%], $\nu_{max.}$ 3330s, 1745s, 1610s, 1530s, 1470s, 1370m, 1300s, 1190s, 1155s, 1105m, 1065s, 995m, 965m, and 915m cm^{-1}, $\tau(CDCl_3)$ 1·32 and 1·46 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·50 (1H, s, acetal), and 6·38 (6H, s, 2 × OMe).

2-*Methylpteridine* (IVc).—A solution of 3-acetamidopyrazine-2-carbaldehyde (0·10 g) in ethanolic ammonia

(2 ml) was stirred at 0° for 30 min and evaporated *in vacuo*. The residue, sublimed at 100° and 0·01 mmHg, gave 2-methylpteridine (34%), m.p. 137—139° (lit.,[9] 141°), identical with an authentic sample (t.l.c., i.r. spectra, and mixed m.p.).

Pteridine-2-one.—A solution of 3-ethoxycarbonylaminopyrazine-2-carbaldehyde (0·15 g) in ethanolic ammonia (2 ml) was stirred at room temperature for 45 min. The precipitate, separated by filtration, gave pteridin-2-one (55%), decomp. 241° (lit.,[8] 240°), identical with an authentic sample (paper chromatography and i.r. spectra).

2-*Acetoxymethyl-3-aminopyrazine* (Ig).—A solution of 2-amino-3-hydroxymethylpyrazine (0·125 g) in acetic anhydride (1 ml) and pyridine (1 ml) was stirred at room temperature for 18 h, then evaporated *in vacuo* to a syrup; this was dissolved in ethanol and the solution was evaporated. This operation was repeated until the smell of acetic acid had vanished. The residue, sublimed at 110° and 0·01 mmHg, gave 2-*acetoxymethyl-3-aminopyrazine* (75%), m.p. 79·5° [from benzene–light petroleum (b.p. 60—80°)] [Found (material dried at 20° and 0·01 mmHg): C, 50·8; H, 5·5; N, 25·5. $C_7H_9N_3O_2$ requires C, 50·3; H, 5·4; N, 25·1%], $\nu_{max.}$ 3420s, 3320s, 3160s, 3040s, 1715s (C=O str.), 1645s, 1585m, 1460s, 1385s, 1260s, 1235m, 1190m, 1035m, and 965m cm^{-1}, $\tau(CDCl_3)$ 1·91 and 2·02 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·76 (2H, s, CH_2), *ca.* 4·8br (2H, s, NH_2, exchangeable), and 7·89 (3H, s, Ac).

2-*Acetamido-3-acetoxymethylpyrazine*.—A solution of 2-amino-3-hydroxymethylpyrazine (0·21 g) in acetic anhydride (3 ml) was heated under reflux for 15 min, then evaporated *in vacuo* to a syrup; this was dissolved in ethanol and the solution was evaporated, as in the foregoing experiment. The residue gave 2-*acetamido-3-acetoxymethylpyrazine* (54%), m.p. 102° (from ethanol) [Found (material dried at 60° and 0·01 mmHg): C, 51·4; H, 5·5; N, 20·1. $C_9H_{11}N_3O_3$ requires C, 51·7; H, 5·3; N, 20·1%], $\nu_{max.}$ 3160m, 3100w, 1730s (C=O str. of ester), 1695s, 1530m, 1460s, 1435s, 1385s, 1290m, 1255s, 1235s (C–O–C str.), and 1030m cm^{-1}, $\tau(CDCl_3)$ *ca.* 1·2br (1H, s, NH, exchangeable), 1·51 and 1·58 (total 2H, ABq, J 2·6 Hz, pyrazine ring), 4·74 (2H, s, CH_2), 7·71 (3H, s, NAc), and 7·87 (3H, s, OAc).

Hydrolysis of 2-*Acetamido-3-acetoxymethylpyrazine*.—A solution (pH 3) of 2-acetamido-3-acetoxymethylpyrazine (0·20 g) in dilute acetic acid (2 ml) was heated under reflux for 6 h, then evaporated *in vacuo* to a syrup, which was subjected to t.l.c. (silica gel; ethyl acetate). A main band (R_F 0·5), which fluoresced blue under 254 nm light, was collected, and extracted (ethanol). Removal of the solvent gave 2-acetoxymethyl-3-aminopyrazine (22%), m.p. 79° [from benzene–light petroleum (b.p. 60—80°)], identical with the foregoing compound (i.r. spectra and mixed m.p.).

5,6,7,8-*Tetrahydro-6,7-bismethylaminopteridine* (Vb).—Pteridine (0·10 g) was stirred in ethanolic methylamine (33%; 1 ml) at room temperature for 10 min. The mixture precipitated pure 5,6,7,8-*tetrahydro-6,7-bismethylaminopteridine* (92%) [Found (material dried at 20° and 20 mmHg): C, 49·1; H, 7·1; N, 43·1. $C_8H_{14}N_6$ requires C, 49·45; H, 7·3; N, 43·3%], $\nu_{max.}$ 3240m, 3150s, 3120m,sh, 3050m, 1605s, 1550s, 1525m, 1475m, 1450m, 1415m, 1260m, 1170m, and 795m cm^{-1}.

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