Pteridine Studies. Part XLI.[1] New Routes to 4-Aminopteridines *via* 3-(Dimethylaminomethyleneamino)pyrazine-2-carbonitrile and Related Compounds

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3-Aminopyrazine-2-carboxamide was converted into 3-(dimethylaminomethyleneamino)pyrazine-2-carbonitrile (1b) with dimethylformamide and phosphoryl chloride. This amidine (1b) was produced by the same reagents also from 3-aminopyrazine-2-carbonitrile (1a), and by the action of dimethylamine on 3-ethoxymethyleneamino-pyrazine-2-carbonitrile (1c). Compound (1c) was made from 3-aminopyrazine-2-carbonitrile with triethyl orthoformate and acetic anhydride.

Compounds (1a—c) were used in several new pteridine syntheses. The amidine (1b) gave 4-amino- and 4-methylamino-pteridine (2a and b) with ammonium and methylammonium acetate, respectively. Use of the 6-chloro-derivative of amidine (1b) similarly led to 6-chloro-4-amino- and -4-methylamino-pteridine. Pteridine-4-thione was obtained from the amidine (1b) and sodium hydrosulphide. The ethoxymethylene compound (1c) gave 4-aminopteridine with ammonia but 3,4-dihydro-4-imino-3-methylpteridine (3) with cold methylamine; this imine was easily isomerized to 4-methylaminopteridine by a Dimroth reaction, but proved stable as a solid. 3-Aminopyrazine-2-carbonitrile (1a) gave 4-aminopteridine with formamidine acetate at 140°.

Some unusual pyrazine reactions were encountered. The ethoxymethylene compound (1c), after brief contact with ammonium acetate solution, gave 3-(aminomethyleneamino)pyrazine-2-carbonitrile (1e). The ethoxymethylene compound (1c) was hydrolysed by the water in cold 95% ethanol to 3-formamidopyrazine-2-carbonitrile (1d), and condensed with hydrazine hydrate to give 3-hydrazinomethyleneaminopyrazine-2-carboxamidrazone (4b). 3-Aminopyrazine-2-carbonitrile (1a) similarly gave 3-aminopyrazine-2-carboxamidrazone (4a). 3-Aminopyrazine-2-carboxamide was quantitatively brominated to give 3-amino-6-bromopyrazine-2-carboxamide.

THE amidine (1b) has now been isolated from the products of heating a mixture of 3-aminopyrazine-2-carboxamide, dimethylformamide, and phosphoryl chloride. This substance (1b) had been postulated as an intermediate in our preparation [2a] of 3-aminopyrazine-2-carbonitrile (1a) from the same starting materials. The new amidine resembles similarly substituted triazoles [4-(dimethylaminomethyleneamino)-1-(and 2-)-methyl-1,2,3-triazole-5-carbonitrile] [2b] in displaying a low basic strength and marked hypsochromy in conversion into the cation. The relation between these properties and this type of structure has been discussed in ref. 2*b*. Two alternative routes to the pyrazine amidine (1b) are given in the Experimental section, namely the reaction of 3-aminopyrazine-2-carbonitrile with dimethylformamide and phosphoryl chloride, and that of 3-ethoxymethyleneaminopyrazine-2-carbonitrile (1c) with dimethylamine. Although the yields were better in the alternative methods, the more direct original synthesis was preferred. The ethoxymethylene compound (1c) was made, in high yield, by the action of triethyl orthoformate and acetic anhydride on 3-aminopyrazine-2-carbonitrile. It was readily hydrolysed to 3-formamidopyrazine-2-carbonitrile (1d) by cold 95% ethanol, and

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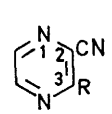
[1] Part XL, A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1971, 2357.

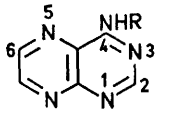
[2] (*a*) A. Albert and K. Ohta, *J. Chem. Soc.* (*C*), 1970, 1540; (*b*) A. Albert, *ibid.*, in the press.

to 3-aminopyrazine-2-carbonitrile (1a) by boiling with water.

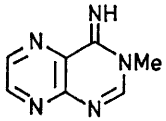
The amidine (1b) and its 6-chloro-derivative [3] proved to be excellent intermediates for a new reaction which



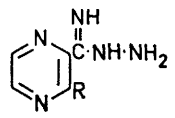
(1) a; R = NH_2
b; R = N:CH·NMe_2
c; R = N:CH·OEt
d; R = NH·CHO
e; R = N:CH·NH_2



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



(3)



(4) a; R = NH_2
b; R = N:CH·NH·NH_2

produced 4-aminopteridines in high yields. The first stage of the condensation of similarly substituted 1,2,3-triazoles with ammonia was found [2b] to be an amidine exchange, namely an electrophilic attack of the amidinium ion on the neutral species of ammonia. Because the latter was much the stronger base, far higher yields were obtained with ammonium acetate than with ammonium chloride or free ammonia (on the neutral species of the amidine in each case). Here too, highest yields were obtained with ammonium acetate, which gave 4-aminopteridine [4] (2a) with the amidine (1b) and 4-amino-6-chloropteridine with the 6-chloro-derivative of (1b). With methylamine acetate these two amidines gave 4-methylaminopteridine [5] (2b) and 6-chloro-4-methylaminopteridine, respectively. It would not have been possible to make the two chloropteridines by any known method. These applications of methylamine undoubtedly give 3,4-dihydro-4-imino-3-methylpteridines, *e.g.* (3), as first products which undergo Dimroth rearrangement [6] at the temperature required for amidine exchange. An alternative route, prior addition of methylamine across the triple bond of the cyano-group, was discounted by the failure of dimethylamine acetate to react with the amidine (1b) under the same conditions. The imine (3) was later isolated from a parallel reaction with compound (1c) (see later). The amidine (1b) and sodium hydrosulphide gave pteridine-4-thione,[7] but in only moderate yield.

Several heterocyclic *o*-ethoxymethyleneamino-carbonitriles have been condensed with ammonia in order to fuse a 4-aminopyrimidine ring on to the heterocycle.[8] Although such a reaction had not been recorded for the pyrazine series, 3-ethoxymethyleneaminopyrazine-2-carbonitrile (1c) underwent this reaction with ethanolic ammonia at room temperature, furnishing 4-aminopteridine (2a) in high yield. An intermediate in this reaction could be isolated after only 3 min. This substance, presumably 3-aminomethyleneaminopyrazine-2-carbonitrile (1e), readily cyclized to 4-aminopteridine and hence could not be purified for analysis. The ^1H n.m.r. spectrum of a solution in [$^2H_6$]dimethyl sulphoxide consisted of peaks at τ 1·18 (1H, s, methylene), 1·31 and 1·57 (total 2H, ABq, J 2·6 Hz, pyrazine ring), and 1·5br (2H, exchangeable, NH_2), and resembles that of the (stable) corresponding tertiary amidine (1b) given in the Experimental section. The i.r. spectrum (in Nujol) showed bands at 3450m, 3360w, 3250w, and 3150m (NH_2), and at 2260w cm^{-1} (CN). These spectra strongly support the suggested constitution.

With methylamine, below 10°, 3-ethoxymethyleneaminopyrazine-2-carbonitrile gave 3,4-dihydro-4-imino-3-methylpteridine (3), the hydriodide of which was identical with a specimen prepared from 5,6-diamino-1,4-dihydro-4-imino-1-methylpyrimidine and glyoxal.[9] The neutral species had not been obtained previously because when the hydriodide was warmed [9] with N-sodium hydroxide a Dimroth rearrangement [6] to 4-methylaminopteridine (2b) took place. In our work, the latter was obtained if the temperature was allowed to rise when methylamine was present in excess. However, in the solid state, the imine (3) was stable at 25° for at least 3 months.

In an attempt to prepare 4-hydrazinopteridine, 3-ethoxymethyleneaminopyrazine-2-carbonitrile (1c) was heated with hydrazine hydrate, but the sole product was 3-(hydrazinomethyleneamino)pyrazine-2-carboxamidrazone (4b). That hydrazine could react with the nitrile group under these conditions was confirmed by the formation of 3-aminopyrazine-2-carboxamidrazone (4a) from hydrazine hydrate and 3-aminopyrazine-2-carbonitrile (1a), although methylamine did not react with this nitrile under the same conditions.

3-Aminopyrazine-2-carbonitrile condensed with formamidine acetate at 140° to give 4-aminopteridine; this type of reaction is known in other heterocyclic series [8] but has not previously been used to make a pteridine.

A new and convenient preparation of 3-amino-6-bromopyrazine-2-carboxamide is reported. Usually the *C*-bromination of amides is not attempted for fear of producing *N*-bromo-derivatives. This restraint probably does not apply to π-deficient *N*-heterocycles, because 3-aminopyrazine-2-carboxamide was brominated almost quantitatively in the 6-position by bromine in acetic acid.

EXPERIMENTAL

All specimens for microanalysis were dried at 20—25° and 0·01 mmHg. I.r. spectra were taken with a Unicam SP 200

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[7] A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.
[8] E. C. Taylor and A. McKillop, 'The Chemistry of Cyclic Enamino-nitriles and *o*-Amino-nitriles,' Interscience, New York, 1970, pp. 238, 243.
[9] D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 1965, 3770.

spectrometer calibrated with polystyrene at 1603 cm^{-1} (for mulls in Nujol). U.v. and n.m.r. spectra were determined as in Part XL.[1] Yields for substances without recorded m.p. refer to material giving only one spot on paper chromatograms run in (*a*) aqueous 3% ammonium chloride and (b) butanol–5N-acetic acid. Identity of compounds prepared by different routes was established by m.p. (where applicable), i.r. spectra, and paper chromatography.

3-(*Dimethylaminomethyleneamino*)*pyrazine-2-carbonitrile* (1b).—(*a*) To a mixture of 3-aminopyrazine-2-carboxamide (Fluka; 0·28 g, 0·002 mol) and dimethylformamide (1·6 ml), cooled in ice–water, phosphoryl chloride (0·38 ml, 0·0044 mol) was added dropwise. The solution was heated at 55° (bath temp.) for 30 min, then cooled. Ice (1 g) was added and the mixture, externally cooled, was brought to pH 6 with 14N-ammonia. This mixture, on refrigeration, deposited 60% of 3-*dimethylaminomethyleneaminopyrazine-2-carbonitrile*, m.p. 86° (from ethanol–cyclohexane) (Found: C, 54·9; H, 5·3; N, 40·3. $C_8H_9N_5$ requires C, 54·8; H, 5·2; N, 40·0%), $\nu_{max.}$ 2220w (C⋮N str.), 1620s (C⋮N str.), 1555m, 1500m, 1460m, 1430m, 1380s, and 1100m cm^{-1}, τ ($CDCl_3$) 1·18 (1H, s, methylene), 1·54 and 1·70 (total 2H, ABq, J 2·6 Hz, pyrazine ring), and 6·73 (6H, s, Me_2), pK_a 2·53 ± 0·04 (10^{-4}M; 20°; analyt. wavelength 295 nm), $\lambda_{max.}$ 293 (log ε 4·41) and 352 nm (3·73) (neutral species at pH 7·0); and 254 (4·26) and 294 nm (3·75) (cation at pH 0). This ratio of dimethylformamide to amide gave the highest yield.

(*b*) A suspension of 3-aminopyrazine-2-carbonitrile [2a] (0·24 g, 0·002 mol) in dimethylformamide (0·7 ml), similarly treated with phosphoryl chloride (0·38 ml), and heated at 60° for 30 min, gave 77% of the amidine (1b), m.p. 86°. This much lower ratio of dimethylformamide to starting material gave the highest yield.

(*c*) A solution of 3-ethoxymethyleneaminopyrazine-2-carbonitrile (0·15 g; see later) in ethanolic dimethylamine (33% w/w; 2 ml), stirred at 20—25° for 15 min and evaporated to dryness, gave 67% of the amidine (1b), m.p. 86°.

3-*Ethoxymethyleneaminopyrazine-2-carbonitrile* (1c).—A suspension of 3-aminopyrazine-2-carbonitrile [2a] (1·2 g, 0·01 mol) in acetic anhydride (3 ml) and triethyl orthoformate (3 ml) was heated under reflux for 1 h. The volatile components were removed at 100° and 25 mmHg. The residue, recrystallized from benzene–cyclohexane (3 : 4; 7 ml), gave 3-*ethoxymethyleneaminopyrazine-2-carbonitrile* (82%), m.p. 105° (Found: C, 54·4; H, 4·6; N, 31·6. $C_8H_8N_4O$ requires C, 54·5; H, 4·6; N, 31·8%), $\nu_{max.}$ 2220w (C⋮N str.), 1620s (C⋮N str.), 1445m, 1425m, 1300m, 1260m, 1230m, 1110m, and 1005m cm^{-1}, τ ($CDCl_3$) 1·11 (1H, s, methylene), 1·25 (2H, s, pyrazine ring), 5·29 (2H, q, J 7·4 Hz, CH_2), and 8·49 (3H, t, J 7·4 Hz, CH_3).

3-*Formamidopyrazine-2-carbonitrile* (1d).—A suspension of the ethoxymethylene compound (1c) (0·125 g) in aqueous 95% ethanol (2 ml) was stirred at 20—25° for 3 h. Filtration gave 67% of 3-*formamidopyrazine-2-carbonitrile*, m.p. 210° (from ethanol) (Found: C, 48·35; H, 2·8; N, 37·4. $C_6H_4N_4O$ requires C, 48·65; H, 2·7; N, 37·8%), $\nu_{max.}$ 3200m, 3140m (NH str.), 2240w (C≡N str.), 1690s (C⋮O str.), 1585m, 1545m, 1490m, 1460m, 1400m, 1250m, 1230m, and 1165m cm^{-1}, τ [$(CD_3)_2SO$] −1·55 (1H, exchangeable, s, NH), 0·81 (1H, s, CHO), 1·09 and 1·23 (total 2H, ABq, J 2·6 Hz, pyrazine ring).

4-*Aminopteridine*.—A solution of 3-(dimethylaminomethyleneamino)pyrazine-2-carbonitrile (1b) (0·12 g, 0·0007 mol) and ammonium acetate (0·22 g, 4 equiv.) in water (2 ml) was heated under reflux for 30 min. The suspension, cooled and filtered, gave 96% of 4-aminopteridine, identical with material made from 4,5,6-triaminopyrimidine and glyoxal.[4]

4-*Amino*-6-*chloropteridine*.— 6-Chloro-3-(dimethylaminomethyleneamino)pyrazine-2-carbonitrile [3] (0·12 g), ammonium acetate (0·22 g), and water (2 ml), heated under reflux for 2 h, and cooled, deposited 87% of 4-*amino*-6-*chloropteridine* which, crystallized from methanol, decomposed at 186° (Found: C, 39·9; H, 2·6; Cl, 19·9; N, 38·6. $C_6H_4ClN_5$ requires C, 39·7; H, 2·2; Cl, 19·5; N, 38·6%), $\nu_{max.}$ 3430m, 3270m (NH_2), 1635s, 1545m, 1470s, 1345m, 1335m, 1120m, and 885m cm^{-1}, τ [$(CD_3)_2SO$] 0·66 (1H, s, H-7), 1·21 (1H, s, H-2), and 1·40br (2H, exchangeable, NH_2).

4-*Methylaminopteridine*.—The amidine (1b) (0·12 g, 0·0007 mol), ethanolic methylamine (23%) w/v; 0·5 ml, 0·003 mol), acetic acid (0·25 ml, 0·004 mol), and methanol (2 ml), heated under reflux for 2 h and cooled, deposited 87% of 4-methylaminopteridine, m.p. 250° (from water) (lit.,[5] 251°) (Found: C, 52·4; H, 4·5; N, 43·8. Calc. for $C_7H_7N_5$: C, 52·2; H, 4·4; N, 43·5%), $\nu_{max.}$ 3210m, 3140m (NH), 1615s, 1605s, 1570m, 1545m, 1470m, 1415m, 1365m, 1340s, 1310m, and 1265m cm^{-1}, τ [$(CD_3)_2SO$] 0·67 and 0·93 (total 2H, ABq, J 1·7 Hz, H-6 and H-7), 1·12 (1H, s, H-2), and 6·86 (3H, d, J 5·3 Hz, CH_3; signal became a singlet on deuterium exchange).

6-*Chloro*-4-*methylaminopteridine*.— 6-Chloro-3-(dimethylaminomethyleneamino)pyrazine-2-carbonitrile (0·14 g, 0·0006 mol), aqueous methylamine (40%; 0·6 ml), acetic acid (0·37 ml), and water (2 ml), heated under reflux for 1 h and cooled, deposited 65% of 6-*chloro*-4-*methylaminopteridine* (from methanol), decomp. *ca.* 221° (Found: C, 43·0; H, 3·4; N, 35·9. $C_7H_6N_5Cl$ requires C, 43·0; H, 3·1; N, 35·8%), $\nu_{max.}$ 3260m (NH), 1600s, 1425m, 1350m, 1330m, and 1120m cm^{-1}, τ [$(CD_3)_2SO$] 0·63 (1H, s, H-7), 1·11 (1H, s, H-2), and 6·87 (3H, s, CH_3).

Pteridine-4-*thione*.—A solution of the amidine (1b) (0·15 g) in freshly prepared ethanolic 1·5N-sodium hydrosulphide (5 ml) was heated under reflux for 4·5 h, then evaporated to dryness. The residue was dissolved in water (4 ml). The solution, clarified by filtration, was acidified with acetic acid (to pH 4). The resulting precipitate, recrystallized from water, gave 25% of pteridine-4-thione, identical with an authentic specimen made from 4,5-diaminopyrimidine-6-thione and glyoxal.[7]

4-*Aminopteridine from* 3-*Ethoxymethyleneaminopyrazine-2-carbonitrile* (1c).—The pyrazine (0·10 g) in 8N-ethanolic ammonia (1 ml) and chloroform (1 ml), stirred at 20—25° for 3 h, then heated under reflux for 30 min, gave 81% of 4-aminopteridine, identical with an authentic specimen.[4]

3,4-*Dihydro*-4-*imino*-3-*methylpteridine* (3).—The ethoxymethylene compound (1c) (0·18 g, 0·001 mol), suspended in ethanol (2 ml), was cooled to 1° in ice–water. Ethanolic methylamine (23% w/v; 0·19 ml, 1·5 equiv.) was added. The suspension was stirred in an ice-bath for 2 h longer and filtered, giving 65% of 3,4-*dihydro*-4-*imino*-3-*methylpteridine*, m.p. 215° (from ethanol–benzene) (Found: C, 52·3; H, 4·7; N, 43·7. $C_7H_7N_5$ requires C, 52·2; H, 4·4; N, 43·5%), $\nu_{max.}$ 3250m (NH), 1630s, 1605s, 1545m, 1440m, 1355s, 1205s, and 1140m cm^{-1}, τ [$(CD_3)_2SO$] *ca.* 0·95br (1H, exchangeable, =NH), 0·98 and 1·15 (total 2H, ABq J 2·6 Hz, H-6 and H-7), 1·48 (1H, s, H-2), and 6·48 (3H, s, CH_3).

3-*Hydrazinomethyleneaminopyrazine-2-carboxamidrazone* (4b).—To a suspension of the ethoxymethylene compound

(1c) (0·15 g) in ethanol (8 ml) was added hydrazine hydrate (1 ml) in ethanol (2 ml). The mixture, stirred for 2 h at 20—25°, deposited 82% of *3-hydrazinomethyleneamino-pyrazine-2-carboxamidrazone* (from dimethylformamide), decomp. *ca.* 240° (Found: C, 37·35; H, 5·4; N, 57·3. $C_6H_{10}N_8$ requires C, 37·1; H, 5·2; N, 57·5%), $\nu_{max.}$ 3450w, 3320m, 3200m, 1650s, 1630sh, m, 1505m, 1205m, 920m, and 855m cm^{-1}, τ [$(CD_3)_2SO$] 1·69 and 1·73 (total 2H, ABq, J 1·7 Hz, pyrazine ring), 2·10 (1H, d, J 8·6 Hz, :CH), and 3·81, 4·20, and 4·60 (total 7H, all br and exchangeable, NH).

3-Aminopyrazine-2-carboxamidrazone (4a).—A suspension of 3-aminopyrazine-2-carbonitrile (0·15 g, 0·00125 mol) in hydrazine hydrate (1 ml) and ethanol (3 ml), stirred at 20—25° for 1 h, and concentrated, deposited 84% of *3-aminopyrazine-2-carboxamidrazone*, m.p. 176° (from ethanol) (Found: C, 39·8; H, 5·4; N, 55·1. $C_5H_8N_6$ requires C, 39·5; H, 5·3; N, 55·2%), $\nu_{max.}$ 3460m, 3340m, 3280m, 3160m, 3050w, 1630s, 1605m, 1555m, 1455s, 1240m, 920m, and 895m cm^{-1}, τ [$(CD_3)_2SO$] 1·93 and 2·13 (total 2H, ABq, J 2·6 Hz, pyrazine ring), *ca.* 2·0br (2H, exchangeable, two NH), and 4·11 and 4·46 (total 4H, br and exchangeable, two NH_2).

4-Aminopteridine from 3-Aminopyrazine-2-carbonitrile (1a).—This nitrile (0·15 g) and formamidine acetate (Aldrich; 0·3 g, 2·4 equiv.) suspended in pentanol (2 ml) were heated under reflux for 1 h. On cooling, the mixture deposited 60% of 4-aminopteridine, identical with an authentic sample.[4]

3-Amino-6-bromopyrazine-2-carboxamide.—To a suspension of 3-aminopyrazine-2-carboxamide (2·8 g, 0·02 mol) in acetic acid (30 ml; anhydrous), bromine (1 ml, 0·02 mol) was added dropwise. The mixture was stirred at 25° for 15 min, then diluted with water (100 ml). Cooling produced 96% of 3-amino-6-bromopyrazine-2-carboxamide, m.p. 213° (lit.,[3] 215°) (from water), identical with an authentic sample prepared from methyl 3-amino-6-bromopyrazine-2-carboxylate.

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