Ethyl Amidinoacetates in the Synthesis of Pyrazines

By **William F. Keir** and **Alexander H. MacLennan**, Paisley College of Technology, High Street, Paisley, Renfrewshire PA1 2BE
Hamish C. S. Wood,* Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow G1 1XL

Ethyl ethoxycarbonylacetimidate (1a) hydrochloride was converted by a one-stage process into ethyl 2-amidino-2-nitroso- (2a) or 2-amidino-2-phenylazo-acetate (2b). Reduction of these intermediates to ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride followed by cyclisation with 1,2-dicarbonyl reagents in the presence of a suitable base, yielded ethyl 3-aminopyrazine-2-carboxylates (3a—d). Phenylglyoxal afforded ethyl 3-amino-5-phenylpyrazine-2-carboxylate (3d) in contrast to 3-amino-6-phenylpyrazine-2-carboxamide (3g) which is formed with this reagent and 2-amidino-2-aminoacetamide (2h). The pyrazine-2-carboxylates were converted into a number of 3-aminopyrazine-2-(*N*-alkyl)carboxamides (3i—x).

3-Aminopyrazinecarboxylic esters are important as intermediates in the preparation of pyrazines of pharmaceutical significance, and in the synthesis of pteridines. These esters have been prepared most frequently by esterification of the acids [1,2] obtained by hydrolysis of 3-aminopyrazinecarboxamides. The carboxamides were derived either by hydrolytic degradation of a suitable lumazine [3] or by condensation of 2-amidino-2-aminoacetamide (2h) with 1,2-dicarbonyl reagents.[4] More recently, the esters have been obtained by cyclisation of a suitably substituted 2-azabuta-1,3-diene.[5] This paper describes a route to these esters similar to that of Vogl and Taylor [4] but which eliminates the hydrolysis and esterification stages.

It was noted [6,7] that 2-amidino-2-aminoacetamides, *e.g.* (2h), are useful intermediates in the synthesis of pyrazines, pteridines, and other heterocycles. The corresponding 2-amidino-2-aminoacetates, *e.g.* (2g), would be of greater synthetic value because of the more reactive ester group. Preparation of these esters required the intermediate ethyl amidinoacetate (1b) and since this highly reactive compound self-condenses at room temperature to a pyrimidine,[8] its usefulness as a synthetic intermediate seemed limited. We have found, however, that the addition of ethyl ethoxycarbonylacetimidate (1a) hydrochloride [9] to two equivalents of ethanolic ammonia followed by nitrosation or coupling with benzenediazonium chloride *in situ* precipitated ethyl 2-amidino-2-nitroso- (2a) or 2-amidino-2-phenylazo-acetate (2b) in good yield. The usefulness of the method is extended by the fact that ammonia can be replaced by amines such as benzylamine and cyclohexylamine giving rise to 2-(substituted amidino)-2-nitroso- or -2-phenylazo-acetates (2c—f). Catalytic reduction of (2a or b) in hydrochloric acid with hydrogen and palladised charcoal provided ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride. Condensation of (2g) with symmetrical 1,2-dicarbonyl reagents in aqueous sodium acetate (pH 5) yielded the corresponding ethyl 3-aminopyrazine-2-carboxylates. Glyoxal and biacetyl provided ethyl 3-aminopyrazine-2-carboxylate (3a) and ethyl 3-amino-5,6-dimethylpyrazine-2-carboxylate (3b) respectively, the structures of which were confirmed by conversion into the corresponding amide by treatment with ethanolic ammonia. The products were found to be identical in all respects with authentic samples of 3-aminopyrazine-2-carboxamide (3e) and 3-amino-5,6-dimethylpyrazine-2-carboxamide (3f) prepared by the method of Vogl and Taylor.[4] Cyclohexane-1,2-dione gave the tetrahydrobenzopyrazine (3c) which had similar spectral properties [spectral data are given in Supplementary Publication No. SUP 22284 (6 pp.) †] to the above pyrazines and was assigned a similar structure. Condensation of ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride and phenylglyoxal in aqueous sodium acetate (pH 4) below 10 °C gave a yellow solid (10%) which lacked the characteristic fluorescence in u.v. light of a pyrazine. Addition of excess of sodium acetate to the filtrate yielded another yellow solid (40%) which did fluoresce. The use of aqueous ammonia instead of sodium acetate, to give a pH of 8—9, provided the fluorescent product only (the ester group was unaffected by the ammonia under these conditions). The structure of this compound was established by hydrolysis to the corresponding acid which was not identical with 3-amino-6-phenylpyrazine-2-carboxylic acid (3z).[4] The acid did prove to be identical with a sample of 3-amino-5-phenylpyrazine-2-carboxylic acid (3y) obtained by degradative hydrolysis of 2-amino-7-phenylpteridin-4(3*H*)-one (4),[10] thus establishing the pyrazine to be ethyl 3-amino-5-phenyl-

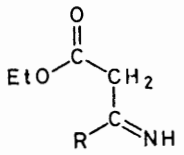
† For details of Supplementary Publication see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

[1] R. C. Ellingson, R. L. Henry, and F. G. McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711.
[2] J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, *J. Medicin. Chem.*, 1967, **10**, 598.
[3] J. Wijlard, M. Tishler, and A. E. Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.
[4] O. Vogl and E. C. Taylor, *J. Amer. Chem. Soc.*, 1959, **81**, 2472.
[5] M. Lang and J. P. Fleury, *Tetrahedron Letters*, 1974, 3967.
[6] W. F. Keir and H. C. S. Wood, *J.C.S. Perkin I*, 1976, 1847.
[7] W. F. Keir, A. H. MacLennan, and H. C. S. Wood, *J.C.S. Perkin I*, 1977, 1321.
[8] S. M. McElvain and B. E. Tate, *J. Amer. Chem. Soc.*, 1951, **73**, 2760.
[9] S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017.
[10] F. E. King and P. C. Spensley, *J. Chem. Soc.*, 1952, 2144.

pyrazine-2-carboxylate (3d). The non-fluorescing material obtained at pH 4 was rapidly converted on heating alone or in warming in ethanolic sodium ethoxide into the above pyrazine ester (3d), which suggested that it was the Schiff's base type intermediate ethyl 2-amidino-2-benzoylmethylenaminoacetate (5). This structure was supported by the n.m.r. and i.r. spectra and elemental analysis.

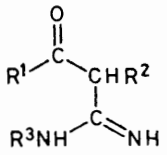
On repeating the Vogl and Taylor[4] condensation of 2-amidino-2-aminoacetamide (2h) dihydrochloride and phenylglyoxal at pH 4—5 instead of 8—9, we obtained, not an intermediate as in the case of the ester, but 3-amino-5-phenylpyrazine-2-carboxamide (3h) (54%). At the higher pH, Vogl and Taylor obtained the 6-phenyl isomer (3g). The structure of (3h) was confirmed by showing it to be identical with the carboxamide obtained by treatment of ethyl 3-amino-5-phenylpyrazine-2-carboxylate (3d) with ammonia under pressure.

It is interesting to note that at pH 8—9 the amidinoacetamide (2h) yields exclusively the 6-phenylpyrazinecarboxamide (3g), while at the same pH, the amidinoacetate (2g) yields the 5-phenylpyrazine ester (3d).



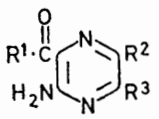
(1)

	R
a;	EtO
b;	NH_2



(2)

	R^1	R^2	R^3
a;	EtO	NO	H
b;	EtO	N_2Ph	H
c;	EtO	NO	$PhCH_2$
d;	EtO	NO	C_6H_{11}
e;	EtO	N_2Ph	$PhCH_2$
f;	EtO	N_2Ph	C_6H_{11}
g;	EtO	NH_2	H
h;	NH_2	NH_2	H



(3)

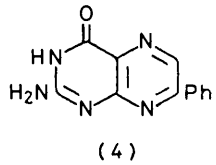
	R^1	R^2	R^3
a;	EtO	H	H
b;	EtO	CH_3	CH_3
c;	EtO	$[CH_2]_4$	
d;	EtO	H	Ph
e;	NH_2	H	H
f;	NH_2	CH_3	CH_3
g;	NH_2	Ph	H
h;	NH_2	H	Ph
i;	CH_3NH	H	H
j;	CH_3NH	CH_3	CH_3
k;	CH_3NH	$[CH_2]_4$	
l;	CH_3NH	H	Ph
m;	$PhCH_2NH$	H	H
n;	$PhCH_2NH$	CH_3	CH_3

	R^1	R^2	R^3
o;	$PhCH_2NH$	$[CH_2]_4$	
p;	$PhCH_2NH$	H	Ph
q;	$C_6H_{11}NH$	H	H
r;	$C_6H_{11}NH$	CH_3	CH_3
s;	$C_6H_{11}NH$	$[CH_2]_4$	
t;	$C_6H_{11}NH$	H	Ph
u;	$HO(CH_2)_2NH$	H	H
v;	$HO(CH_2)_2NH$	CH_3	CH_3
w;	$HO(CH_2)_2NH$	$[CH_2]_4$	
x;	$HO(CH_2)_2NH$	H	Ph
y;	HO	H	Ph
z;	HO	Ph	H

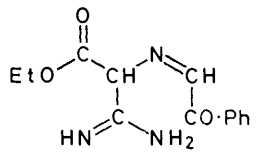
Vogl and Taylor[4] argued that the more reactive (aldehyde) carbonyl group of the dicarbonyl reagent would react selectively with the more nucleophilic amidino group of (2h). The relative nucleophilicities of the amidino and amino groups appear to be reversed in the ester. This would seem to be due to the greater electron-withdrawing property of the ester group, causing structure (6c) to be an important contributor to the ester hybrid thus weakening the nucleophilic properties of the amidino group. U.v. absorption spectra of the

amide and ester at pH 8.9 ($\lambda_{max.}$ 282 and 277 nm respectively) indicate the presence of the enamine form in both compounds, but accurate u.v. spectral analysis of these compounds is impossible due to their instability in alkaline solution.

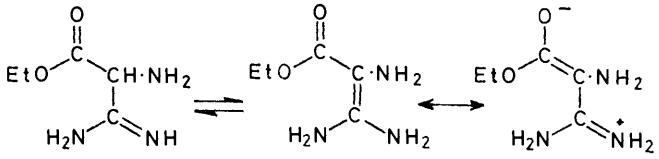
Treatment of the pyrazine esters with methylamine, benzylamine, cyclohexylamine, and ethanolamine, yielded the corresponding *N*-alkylamides (3i—x), the progress of the reaction being followed by periodic inspection of the carbonyl absorptions in the i.r. spectrum. Forcing conditions were required for the benzyl- and



(4)



(5)



(a) (b) (c)

(6)

cyclohexyl-amines, reflecting the steric influence of these groups.

The conversion of the above pyrazines into the corresponding pteridinones and the synthesis of imidazoles and hypoxanthines from the amidinoacetates, are at present being investigated.

EXPERIMENTAL

M.p.s were determined with an Electrothermal apparatus. U.v. spectra were determined with a Unicam SP 1800A spectrophotometer, i.r. spectra with a Perkin-Elmer 157G spectrophotometer (Nujol mulls unless otherwise indicated), and n.m.r. spectra with a Perkin-Elmer R12B (60 MHz) spectrometer ($CDCl_3$ as solvent unless otherwise indicated; Me_4Si as internal standard). Reaction mixtures were analysed by t.l.c. on Eastman Chromagram sheets. Spots were detected under u.v. light and the development system was chloroform–hexane (4 : 6).

Ethyl 2-Amidino-2-nitrosoacetate (2a).—Ethyl ethoxycarbonylacetimidate (1a) hydrochloride (0.25 mol) was added to vigorously stirred ethanolic ammonia (3N; 200 ml) at 0—5 °C. After stirring at this temperature for 30 min, a solution of sodium nitrite (0.275 mol) in water (50 ml) was added, and then 6N-hydrochloric acid to pH 6. A precipitate formed almost immediately and after a further 5 h at room temperature the yellow crystals were filtered off and washed with water. The *acetate* (2a) (70.0%) had m.p. >300° (from dimethylformamide) (Found: C, 38.1; H, 5.75; N, 26.4. $C_5H_9N_3O_3$ requires C, 37.75; H, 5.7; N, 26.4%).

Dissolution of the above base in excess of ethanolic hydrogen chloride, followed by evaporation to dryness *in vacuo* yielded crystals of the *hydrochloride* (2a) (100%), m.p. 224° (decomp.) (from aqueous ethanolic hydrogen chloride–ether) (Found: C, 30.75; H, 5.1; N, 21.1. $C_5H_{10}ClN_3O_3$ requires C, 30.7; H, 5.15; N, 21.5%).

Ethyl 2-Alkylamidino-2-nitrosoacetates (2c *and* d).—Ethyl ethoxycarbonylacetimidate (1a) hydrochloride (0.25 mol) was added to a vigorously stirred solution of the amine (0.5 mol) in ethanol (100 ml) at 0—5 °C. Aqueous sodium nitrite and hydrochloric acid were added as above and a similar isolation procedure gave yellow crystals. *Ethyl 2-benzylamidino-2-nitrosoacetate* (2c) (80.0%) had m.p. 175—176° (from aqueous ethanol) (Found: C, 58.25; H, 6.05; N, 16.6. $C_{12}H_{15}N_3O_3$ requires C, 57.8; H, 6.05; N, 16.85%). *Ethyl 2-cyclohexylamidino-2-nitrosoacetate* (2d) (73.0%) had m.p. 189—190° (from aqueous ethanol) (Found: C, 54.8; H, 7.9; N, 17.7. $C_{11}H_{19}N_3O_3$ requires C, 54.7; H, 7.9; N, 17.4%).

Ethyl 2-Amidino-2-phenylazoacetate (2b) *Hydrochloride*.—Ethyl ethoxycarbonylacetimidate (1a) hydrochloride (0.25 mol) was added to vigorously stirred ethanolic ammonia (3N; 200 ml) at 0 °C and the pH adjusted to 4—5 with 6N-hydrochloric acid. Benzenediazonium chloride, prepared by the addition of sodium nitrite (0.275 mol) in water (250 ml) to aniline (0.25 mol) in 6N-hydrochloric acid (125 ml) so that the temperature was maintained at 5—10 °C, was added to the stirred solution, the temperature being maintained at 5 °C during the addition. The pH was adjusted to 5, if necessary, by the addition of saturated aqueous sodium acetate. A precipitate formed almost immediately and after stirring for 5 h at room temperature, the yellow crystals were filtered off and washed with a minimum of ice-cold water. The *hydrochloride* (2b) (50.0%) had m.p. 215—217° (decomp.) (from aqueous ethanol and ether) (Found: C, 48.4; H, 5.6; N, 20.6. $C_{11}H_{15}ClN_4O_2$ requires C, 48.9; H, 5.6; N, 20.7%).

Ethyl 2-Alkylamidino-2-phenylazoacetates (2e *and* f) *Hydrochloride*.—Ethyl ethoxycarbonylacetimidate (1a) hydrochloride (0.25 mol) was added to a vigorously stirred solution of the amine (0.5 mol) at 0—5 °C. Benzenediazonium chloride was added as above and a similar isolation procedure gave yellow crystals. *Ethyl 2-benzylamidino-2-phenylazoacetate* (2e) *hydrochloride hemihydrate* (68.5%) had m.p. 167—168° (from water) (Found: C, 58.8; H, 5.75; N, 15.3. $C_{18}H_{21}ClN_4O_2,\frac{1}{2}H_2O$ requires C, 58.45; H, 6.0; N, 15.15%). *Ethyl 2-cyclohexylamidino-2-phenylazoacetate* (2f) *hydrochloride monohydrate* (70.0%) had variable m.p. *ca.* 135° (from water) (Found: C, 55.55; H, 6.85; N, 14.85. $C_{17}H_{25}ClN_4O_2,H_2O$ requires C, 55.1; H, 6.75; N, 15.15%).

Ethyl 2-Amidino-2-aminoacetate (2g) *Dihydrochloride*.—(*a*) A mixture of palladised charcoal (10%; 3.0 g) and ethyl 2-amidino-2-nitrosoacetate (2a) (0.07 mol) in ethanol (100 ml) and hydrochloric acid (4N; 100 ml) was hydrogenated at room temperature and pressure with vigorous agitation until the theoretical quantity of hydrogen had been absorbed. After removal of the catalyst, the filtrate was evaporated *in vacuo* (40 °C) to a white solid which was triturated with ethanol (100 ml) and filtered to provide white crystals. The *dihydrochloride* (2g) (87.0%) had m.p. 170—173° (decomp.) (from aqueous ethanolic hydrogen chloride) (Found: C, 27.4; H, 6.3; Cl, 32.95; N, 19.05. $C_5H_{13}Cl_2N_3O_2$ requires C, 27.55; H, 6.0; Cl, 32.5; N, 19.25%).

(*b*) Ethyl 2-amidino-2-phenylazoacetate (2b) hydrochloride was reduced as in (*a*), but the white solid was

triturated with excess ethanol (2 × 100 ml) to remove aniline hydrochloride. The product (70.0%) was identical in all respects to the material obtained in method (*a*).

Ethyl 3-Aminopyrazine-2-carboxylate (3a).—A stirred solution of ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride (0.05 mol) and glyoxal monohydrate (0.055 mol) in water (60 ml) was cooled to 10 °C and sodium acetate trihydrate was added until the pH was 5. Stirring was continued for a further 16 h at room temperature after which the red solution was evaporated to dryness *in vacuo*. The residue was extracted with chloroform (200 ml) in a Soxhlet apparatus for 48 h. After removal of the solvent, the residue was vacuum sublimed at 170 °C (12 mmHg) to provide pale yellow crystals of the *carboxylate* (3a) (22%), m.p. 99—100° [from light petroleum (b.p. 60—80°)] (Found: C, 50.15; H, 5.3; N, 24.95. $C_7H_9N_3O_2$ requires C, 50.3; H, 5.45; N, 25.15%).

Ethyl 3-Amino-5,6-dimethylpyrazine-2-carboxylate (3b).—Sodium acetate trihydrate (0.02 mol) was added to a stirred solution of ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride (0.01 mol) and biacetyl (0.011 mol) in water (35 ml) at 10 °C. A yellow solid separated almost immediately and the suspension was stirred overnight at room temperature. Filtration afforded pale yellow crystals which were washed with water. The *carboxylate* (3b) (61.3%) had m.p. 115.5—116° (from aqueous ethanol) (Found: C, 55.05; H, 6.7; N, 21.25. $C_9H_{13}N_3O_2$ requires C, 55.4; H, 6.65; N, 21.55%).

Ethyl 3-Amino-5,6,7,8-tetrahydrobenzo[b]*pyrazine-2-carboxylate* (3c).—Sodium acetate trihydrate (0.02 mol) was added to a stirred solution of ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride (0.01 mol) and cyclohexane-1,2-dione (0.011 mol) in water (15 ml) and ethanol (5 ml) at 10 °C. The mixture was stirred at this temperature for 5 h. Filtration provided orange crystals which were washed with a little ice-cold water. The *carboxylate* (3c) had m.p. 116—117.5° [from light petroleum (b.p. 80—100°)] (Found: C, 59.45; H, 6.95; N, 18.65. $C_{11}H_{15}N_3O_2$ requires C, 59.7; H, 6.85; N, 19.0%).

3-Aminopyrazine-2-carboxamides (3e *and* f).—The carboxylate (3a or b) (0.001 mol) was dissolved in saturated ethanolic ammonia (30 ml) and stirred in a sealed flask for 5 days. Evaporation *in vacuo* afforded yellow crystals. 3-Aminopyrazine-2-carboxamide (3e) (90.0%) had m.p. 239—240° (from water) and 3-amino-5,6-dimethylpyrazine-2-carboxamide (3f) (85.0%) had m.p. 255° (from ethanol). Both compounds were identical (mixed m.p., i.r., and u.v. spectra) with authentic samples.[4]

Ethyl 3-Amino-5-phenylpyrazine-2-carboxylate (3d).—A solution of phenylglyoxal monohydrate (0.011 mol) in ethanol (30 ml) was added to a solution of ethyl 2-amidino-2-aminoacetate (2g) dihydrochloride (0.01 mol) in water (10 ml).

(*a*) Sodium acetate trihydrate (0.01 mol) was added to the stirred mixture at 10 °C. After 30 min, yellow crystals of *ethyl 2-amidino-2-benzoylmethyleneaminoacetate* (5) (10.0%) were filtered off and recrystallised from chloroform (Found: C, 59.55; H, 5.8; N, 15.7. $C_{13}H_{15}N_3O_3$ requires C, 59.75; H, 5.8; N, 16.05%). The m.p. of this compound was variable due to its conversion on heating into the pyrazine (3d). Sufficient sodium acetate trihydrate was added to the filtrate of the above experiment to complete precipitation (pH 4.5) of a pale yellow solid. After stirring overnight, the crystals were filtered off and washed with water. The *carboxylate* (3d) (39.0%) had m.p. 174—175° (from ethanol) (Found: C, 63.7; H, 5.45; N, 16.85. $C_{13}H_{13}N_3O_2$ requires C, 64.2; H, 5.35; N, 17.3%).

(*b*) Concentrated ammonium hydroxide was added dropwise to the stirred mixture at 10 °C until the pH was 8—9. A yellow precipitate was formed immediately. Further small quantities of ammonium hydroxide were added frequently to maintain the pH and after stirring for 24 h at room temperature, the precipitate was filtered off and washed with water. The *carboxylate* (3d) (48.0%) had m.p. 174—175° (from ethanol) and was identical in all respects to the material obtained by method (*a*).

Conversion of Ethyl 2-Amidino-2-benzoylmethyleneaminoacetate (5) *into Ethyl 3-Amino-5-phenylpyrazine-2-carboxylate* (3d).—The acetate (5) (0.0004 mol) in boiling ethanol (6 ml) was treated dropwise with saturated ethanolic sodium ethoxide until the pH of the mixture was 10. After 2 min, the solution was refrigerated providing yellow crystals which were identical to the carboxylate (3d).

3-Amino-5-phenylpyrazine-2-carboxamide (3h).—(*a*) Ethyl 3-amino-5-phenylpyrazine-2-carboxylate (3d) (0.002 mol) was dissolved in saturated ethanolic ammonia (150 ml) and heated in an autoclave at 120 °C for 48 h. After filtering off some residual material, the solvent was removed to provide a yellow solid. The *carboxamide* (3h) (60.0%) had m.p. 178—179° (from ethanol) (Found: C, 61.9; H, 4.6; N, 26.2. $C_{11}H_{10}N_4O$ requires C, 61.65; H, 4.7; N, 26.15%).

(*b*) Sodium acetate trihydrate (0.0045 mol) was added to a stirred solution (pH 4—5) of 2-amidino-2-aminoacetamide (2h) dihydrochloride (0.003 mol) and phenylglyoxal monohydrate (0.0033 mol) in water (30 ml) at 5—10 °C. A yellow precipitate was formed almost immediately and after stirring for 3 h, the solid was filtered off and washed with water. The *carboxamide* (3h) (54.0%) had m.p. 178—179° (from ethanol) and was identical in all respects to the carboxamide obtained by method (*a*).

3-Amino-5-phenylpyrazine-2-carboxylic Acid (3y).—The carboxylate (3d) (0.001 mol) was dissolved in sodium hydroxide solution (2N; 15 ml) and heated under reflux for 6 h. On cooling bright green crystals (presumably the sodium salt) precipitated which were filtered off and dissolved in boiling water (50 ml). Acidification with 6N-hydrochloric acid gave a yellow precipitate which was filtered off and washed with water. 3-Amino-5-phenylpyrazine-2-carboxylic acid (3y) (60.0%) had m.p. 236° (from aqueous methanol), and was identical (mixed m.p., i.r., and u.v. spectra) with an authentic sample [10] (lit.,[10] 225°).

3-Aminopyrazine-2-(N-methyl)carboxamides (3i—l).—The carboxylate (3a—d) (0.003 mol) was dissolved in ethanolic methylamine (33%; 25 ml) and stirred overnight at room temperature in a sealed flask. Evaporation *in vacuo* and repeated concentration with added ethanol gave yellow crystals. *3-Aminopyrazine-2-(N-methyl)carboxamide* (3i) (90.0%) had m.p. 134—134.5° (from water) (Found: C, 47.55; H, 5.4; N, 37.05. $C_6H_8N_4O$ requires C, 47.35; H, 5.3; N, 36.8%). *3-Amino-5,6-dimethylpyrazine-2-(N-methyl)carboxamide* (3j) (92.0%) had m.p. 167—169° (from ethanol) (Found: C, 53.15; H, 6.6; N, 30.9. $C_8H_{12}N_4O$ requires C, 53.3; H, 6.7; N, 31.1%). *3-Amino-5,6,7,8-tetrahydrobenzo*[b]*pyrazine-2-(N-methyl)carboxamide* (3k) (93.0%) had m.p. 129—130° (from benzene) (Found: C, 58.15; H, 6.9; N, 26.8. $C_{10}H_{14}N_4O$ requires C, 58.25; H, 6.85; N, 27.15%). *3-Amino-5-phenylpyrazine-2-(N-methyl)carboxamide* (3l) (90.0%) had m.p. 160—161° (from ethanol) (Found: C, 63.35; H, 5.35; N, 24.15. $C_{12}H_{12}N_4O$ requires C, 63.15; H, 5.3; N, 24.55%).

3-*Aminopyrazine*-2-(N-*benzyl*)*carboxamides* (3m—p).—The carboxylate (3a—d) (0.003 mol) was dissolved in a mixture of freshly distilled benzylamine (4 ml) and ethanol (4 ml) and the solution was heated under reflux for 16 h. Evaporation *in vacuo* gave an oil to which water was added carefully until precipitation commenced. Refrigeration followed by filtration afforded yellow crystals which were washed with water. 3-Aminopyrazine-2-(*N*-benzyl)carboxamide (3m) (73.0%) had m.p. 118—119° (lit.,[11] 112°) (from aqueous ethanol) (Found: C, 63.15; H, 5.4; N, 24.75. Calc. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.3; N, 24.55%). 3-*Amino*-5,6-*dimethylpyrazine*-2-(N-*benzyl*)*carboxamide* (3n) (64.7%) had m.p. 172—174° (from ethanol) (Found: C, 65.55; H, 6.4; N, 21.75. $C_{14}H_{16}N_4O$ requires C, 65.6; H, 6.25; N, 21.85%). 3-*Amino*-5,6,7,8-*tetrahydrobenzo*[b]-*pyrazine*-2-(N-*benzyl*)*carboxamide* (3o) (78.0%) had m.p. 147—148.5° (from aqueous ethanol) (Found: C, 67.7; H, 6.4; N, 20.1. $C_{16}H_{18}N_4O$ requires C, 68.05; H, 6.45; N, 19.85%). 3-*Amino*-5-*phenylpyrazine*-2-(N-*benzyl*)*carboxamide* (3p) (70.0%) had m.p. 138—140° (from ethanol) (Found: C, 71.05; H, 5.25; N, 18.15. $C_{18}H_{16}N_4O$ requires C, 71.05; H, 5.3; N, 18.4%).

3-*Aminopyrazine*-2-(N-*cyclohexyl*)*carboxamides* (3q—t).—The carboxylate (3a—d) (0.003 mol) was dissolved in a mixture of freshly distilled cyclohexylamine (8 ml) and ethanol (8 ml) and the solution was heated under reflux for 24 h. Evaporation *in vacuo*, followed by repeated concentration with ethanol provided yellow crystals which were washed with water. 3-*Aminopyrazine*-2-(N-*cyclohexyl*)-*carboxamide* (3q) (75.0%) had m.p. 107—108° (from aqueous ethanol) (Found: C, 60.05; H, 7.55; N, 25.6. $C_{11}H_{16}N_4O$ requires C, 60.0; H, 7.30; N, 25.45%). 3-*Amino*-5,6-*dimethylpyrazine*-2-(N-*cyclohexyl*)*carboxamide* (3r) (90.0%) had m.p. 146—147° (from aqueous ethanol) (Found: C, 63.35; H, 8.05; N, 22.55. $C_{13}H_{20}N_4O$ requires C, 62.9; H, 8.1; N, 22.55%). 3-*Amino*-5,6,7,8-*tetrahydrobenzo*[b]*pyrazine*-2-(N-*cyclohexyl*)*carboxamide* (3s) (82.0%) had m.p. 160—161.5° (from aqueous ethanol) (Found: C, 65.45; H, 7.95; N, 20.2. $C_{15}H_{22}N_4O$ requires C, 65.65; H, 8.1; N, 20.4%). 3-*Amino*-5-*phenylpyrazine*-2-(N-*cyclohexyl*)*carboxamide* (3t) (87.0%) had m.p. 154—155.5° (from ethanol) (Found: C, 68.7; H, 6.85; N, 18.4. $C_{17}H_{20}N_4O$ requires C, 68.9; H, 6.8; N, 18.9%).

3-*Aminopyrazine*-2-(N-2-*hydroxyethyl*)*carboxamides* (3u—x).—The carboxylate (3a—d) (0.003 mol) was dissolved in a mixture of freshly distilled ethanolamine (0.5 ml) and ethanol (5 ml) and the solution was heated under reflux for 16 h. Evaporation *in vacuo* gave an oil which, on the careful addition of ice–water provided yellow crystals which were filtered off. 3-*Aminopyrazine*-2-N-(2-*hydroxyethyl*)*carboxamide* (3u) (91.0%) had m.p. 130—131° (from water) (Found: C, 46.45; H, 5.6; N, 31.2. $C_7H_{10}N_4O_2$ requires C, 46.15; H, 5.55; N, 30.75%). 3-*Amino*-5,6-*dimethylpyrazine*-2-N-(2-*hydroxyethyl*)*carboxamide* (3v) (86.0%) had m.p. 137—139° (from aqueous ethanol) (Found: C, 51.45; H, 6.3; N, 26.3. $C_9H_{14}N_4O_2$ requires C, 51.4; H, 6.7; N, 26.65%). 3-*Amino*-5,6,7,8-*tetrahydrobenzo*[b]*pyrazine*-2-N-(2-*hydroxyethyl*)*carboxamide* (3w) (74.0%) had m.p. 184—185° (from benzene) (Found: C, 55.8; H, 7.1; N, 23.85. $C_{11}H_{16}N_4O_2$ requires C, 55.9; H, 6.85; N, 23.7%). 3-*Amino*-5-*phenylpyrazine*-2-N-(2-*hydroxyethyl*)*carboxamide* (3x) (85.0%) had m.p. 139—140.5° [from chloroform–light petroleum (b.p. 60—80°)] (Found: C, 60.15; H, 5.5; N, 21.35. $C_{13}H_{14}N_4O_2$ requires C, 60.45; H, 5.45; N, 21.7%).

One of us (A. H. M.) thanks the S.R.C. for a research studentship. We thank Mrs. M. Muir, Paisley College of Technology, for technical assistance.

[7/1851 *Received*, 21*st October*, 1977]

[11] J. Clark, G. Neath, and C. Smith, *J. Chem. Soc.* (*C*), 1969, 1297.