Synthesis of the Insect Feeding Deterrent Peramine *via* Michael Addition of a Pyrrole Anion to a Nitroalkene[1]

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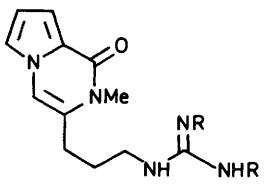
A total synthesis of peramine (**1**), the major insect feeding deterrent isolated from perennial ryegrass (*Lolium perenne L.*) infected with the endophytic fungus *Acremonium lolii* is reported. The key step involves the Michael addition of the potassium salt of methyl pyrrole-2-carboxylate (**3**) to the nitroalkene (**4**) providing access to a 3-substituted pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**10**). Displacement of the allylic bromide (**11**) by cyanomethyl cuprate provided the methodology for introducing the desired monosubstituted guanidino group *via* the nitrile (**12**).

The alkaloid peramine (**1**) has been identified[2] as the principal insect feeding deterrent isolated from perennial ryegrass (*Lolium perenne* L.) infected with the endophyte *Acremonium lolii*. Peramine (**1**) deters the feeding of adults and larvae of the Argentine stem weevil (*Listronotus bonarieusis*) at 0.1 and 10 μg/g concentrations respectively and has been implicated in the resistance of endophyte-infected ryegrass plants to this major insect pest.[3] The structure of peramine (**1**) was deduced from spectroscopic analysis of the diacetylated derivative (**2**) and



(**1**) R = H
(**2**) R = Ac

revealed the presence of the pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system together with a monosubstituted guanidino group. The presence of this interesting heterocyclic ring system, and the biological activity of peramine (**1**), prompted a synthesis. It was envisaged that a synthesis of peramine (**1**) might also lead to interesting analogues whose biological properties could be investigated.

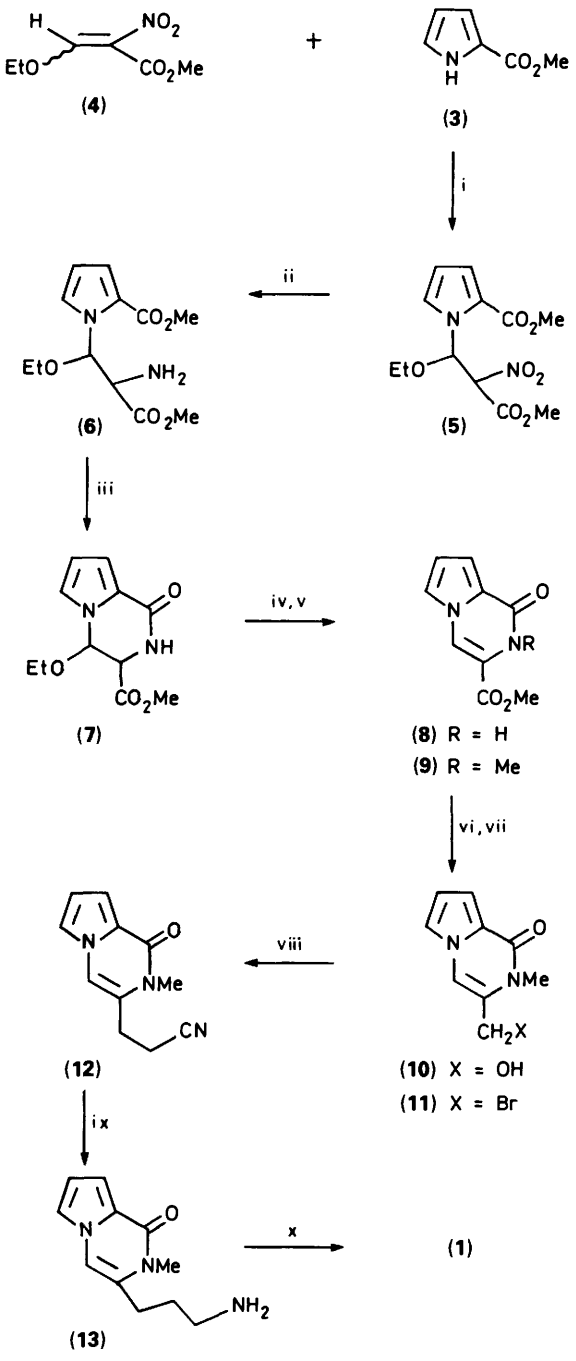
We have previously reported[4] the synthesis of the parent 2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one *via* manganese dioxide oxidation of the 2-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one. The 3,4-dihydro analogue was prepared by *N*-alkylation of methyl pyrrole-2-carboxylate with excess of 1,2-dibromoethane using potassium hydroxide in dimethyl sulphoxide followed by treatment with methylamine. Attempts to extend this model work to the synthesis of 3-substituted pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones using substituted dibromide, epoxide, or aziridine alkylating agents were unsuccessful and an alternative strategy was sought. We now report full details of our synthesis of peramine (**1**) making use of a Michael addition to a nitro-olefin to effect the key *N*-alkylation step (Scheme). Shortly after our initial communication,[1] Dumas reported[5] a second synthesis of peramine (**1**) in which the *N*-alkylation of 2-(trichloroacetyl)pyrrole with an α-halogenomethyl ketone using potassium carbonate in acetone was used.

The nitroalkene (**4**) was prepared as a mixture of stereoisomers from methyl nitroacetate using acetic anhydride and triethyl orthoformate as reported by Kamlet.[6] Nitroalkene (**4**) underwent smooth Michael addition with the potassium salt of methyl pyrrole-2-carboxylate (**3**) to provide the Michael addition product (**5**) in 82% yield. The Michael addition product (**5**), a mixture of stereoisomers that were not separated, contains all the functionality required for elaboration to peramine (**1**). This facile 1,4-addition of a pyrrole anion provided a further example of the previously reported use of nitroalkene (**4**) as a useful Michael acceptor.[7]

The nitro-group of Michael adduct (**5**) was reduced to the corresponding amine (**6**) using sodium borohydride–cobalt(II) chloride.[8] Amine (**6**) was isolated as a mixture of stereoisomers after purification by flash chromatography.[9] Difficulty was experienced when attempting to repeat this reduction on a large scale and the optimum yield (63%) was obtained using 1.2 g of the nitro-adduct (**5**). Reduction of (**5**) by catalytic hydrogenation over 5% palladium on charcoal in methanol resulted in hydrogenolysis to give methyl pyrrole-2-carboxylate (**3**) as the major product. Amine (**6**) underwent cyclization to the lactam (**7**) in 88% yield upon heating under reflux in toluene for 24 h.

Treatment of lactam (**7**) with excess of potassium hydride in tetrahydrofuran (THF) at room temperature effected elimination of the ethoxy group to give the unsaturated secondary lactam (**8**) in 80% yield. Further treatment of (**8**) with potassium hydride, using dimethylformamide (DMF) as solvent, followed by the addition of methyl iodide, afforded the tertiary lactam (**9**) in 76% yield. Attempts to effect the *N*-methylation step concurrently with the elimination step did not give as clean a reaction as was the case when each of these steps was carried out individually.

With the synthesis of the required heterocycle in place the remaining problem was the elaboration of the C-3 methoxycarbonyl group into the n-propylguanidino group. The desired oxidation level was achieved by reduction of the ester (**9**) to the alcohol (**10**) in 72% yield using sodium borohydride in methanol. The ^{1}H NMR spectrum of the alcohol (**10**) exhibited the characteristic long-range coupling between 4- and 8-H.[4] Extension of the side chain then required conversion of the alcohol (**10**) into a suitable leaving group. Conventional methods for conversion of an alcohol into a bromide such as the use of phosphorus tribromide and triphenylphosphine dibromide were unsuccessful. Finally, the bromide (**11**) was generated *in situ* from the alcohol (**10**) using methanesulphonyl



Scheme. *Reagents and conditions:* i, KH, THF, 0 °C (82%); ii, $NaBH_4$ (5.0 equiv.), $CoCl_2$ (2.0 equiv.), MeOH, room temp. (63%); iii, toluene, reflux, 24 h (88%); iv, KH, THF, room temp. (80%); v, KH, DMF, MeI (76%); vi, $NaBH_4$, MeOH, 12 h, (72%); vii, $MeSO_2Cl$ (1.1 equiv.), Et_3N, CH_2Cl_2, −60 °C, 0.25 h, then LiBr (3.0 equiv.), THF, −60 to −40 °C, 0.5 h; viii, MeCN (5.0 equiv.), Bu^nLi (5.1 equiv.), 0.5 h, −78 °C, then $CuBr{\cdot}Me_2S$ (5.2 equiv.), −78 to −40 °C, 0.5 h, then (**11**) (1.0 equiv.), −40 to −20 °C, 1 h (57% overall); ix, $NaBH_4$ (5.0 equiv.), $CoCl_2$ (2.0 equiv.), MeOH (62%); x, *S*-methylthiouronium hydrogen sulphate (5.0 equiv.), NaOH (2M), room temp., 48 h.

chloride and triethylamine at −60 °C in tetrahydrofuran followed by the addition of excess of lithium bromide at −60 to −40 °C. After an aqueous work-up to remove any salts present, the unstable bromide (**11**) was isolated, characterised by mass spectroscopy only, and quickly added to a solution of cyanomethyl cuprate at −40 to −20 °C in tetrahydrofuran. Cyanomethyl cuprate was generated by the addition of the corresponding organolithium reagent to copper(I) bromide–dimethyl sulphide complex. After purification by flash chromatography, the nitrile (**12**) was isolated in 57% yield from the alcohol (**10**).

The nitrile (**12**) was reduced using sodium borohydride–cobalt(II) chloride in methanol to give the amine (**13**) in 62% yield after purification by reverse phase chromatography as the formate salt. Amine (**13**) was converted into the guanidinylated derivative, peramine (**1**), with either excess of *S*-methylthiouronium hydrogen sulphate in sodium hydroxide (2M) at room temperature for 48 h, or 3,5-dimethyl-1-guanidinopyrazole nitrate[10] with triethylamine in dimethylformamide. This latter method proved more convenient. The synthetic material had the same chromatographic (TLC and HPLC) and spectral properties (mass, NMR) as the naturally occurring material. In summary, the synthesis of peramine (**1**) has not only confirmed the structure of the natural product but has also generated a number of analogues which are being studied for their possible feeding deterrent activity.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP3-200S spectrophotometer for Nujol mulls between sodium chloride discs. UV spectra were recorded on a Shimadzu UV 160 spectrophotometer. ^1H NMR spectra were recorded in the solvents stated using tetramethylsilane as internal standard on a Varian T-60, a Bruker WP-80SY, or a Jeol GX270 spectrometer. ^{13}C NMR spectra were recorded at 20 MHz on a Bruker WP-80SY or at 67.8 MHz on a Jeol GX270 spectrometer. Low and high resolution mass spectra were recorded on an AEI MS9 spectrometer with an ionisation potential of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago. Solvents were purified and dried according to the method of Perrin, Perrin, and Armarego.[11] Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described according to the method of Still *et al.*[9] Compounds were visualised on TLC by spraying with vanillin or Ehrlichs reagent.

Methyl 2-Nitro-3-ethoxyacrylate (**4**).—The acrylate (**4**) was prepared from methyl nitroacetate according to the method of Kamlet,[6] as a colourless liquid, b.p. 118–120 °C at 1.0 mmHg (lit.,[6] b.p. 119–121 °C at 1.0 mmHg).

Methyl 1-(1-Ethoxy-2-methoxycarbonyl-2-nitroethyl)carboxylate (**5**).—To a solution of methyl pyrrole-2-carboxylate (**3**) (1 g, 8 mmol) in dry tetrahydrofuran (100 ml) cooled to 0 °C under nitrogen was added potassium hydride (940 mg, of 35 wt % dispersion in mineral oil; 8.2 mmol). A white precipitate was formed, and the resultant mixture was stirred for 0.5 h; a solution of the acrylate (**4**) (1.4 g, 8 mmol) in dry tetrahydrofuran (30 ml) was slowly added and the white precipitate disappeared. The solution was stirred for a further 0.5 h, methanol (5 ml) was added followed by 10% sulphuric acid (10 ml), and the mixture was extracted with diethyl ether (3 × 100 ml). The ethereal extract was washed with water (25 ml) and brine (2 × 25 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluant to give the *nitroethyl compound* (**5**) (1.97 g, 82%) as a mixture of stereoisomers; compound (**5**) was a colourless oil that decomposed upon attempted distillation under reduced pressure (Found: C, 47.8; H, 5.6; N, 9.0. $C_{12}H_{16}N_2O_7$ requires C, 48.0; H, 5.4; N, 9.3%); ν_{max}(thin film) 3 120m (=CH), 1 750s, 1 700s (C=O), and 1 560s cm^{-1} (NO_2); δ_H(60 MHz; $CDCl_3$) 1.16 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.38–3.79 (8 H, m, 2 × OMe and

OCH_2), 5.42 (1 H, d, *J* 8 Hz, $CHNO_2$), 6.18–6.32 (1 H, m, 4-H), and 6.83–7.24 (3 H, m, 3-H, 5-H, and C*H*OEt); *m/z* (M^+, 27%), 269 ($M - OCH_3$, 3), 125 ($C_6H_7NO_2$, 100), and 94 (23).

Methyl 1-(2-Amino-1-ethoxy-1-methoxycarbonylethyl)-pyrrole-2-carboxylate (**6**).—To a solution of the nitroethyl derivative (**5**) (1.2 g, 4 mmol) in methanol (100 ml) was added cobalt(II) chloride (1.0 g, 8 mmol) followed by sodium borohydride (760 mg, 20 mmol) in small portions. Hydrogen gas was evolved and a black precipitate appeared. When the addition was complete stirring was continued for 1 h at room temperature. 10% Hydrochloric acid (100 ml) was added to dissolve the black precipitate and methanol removed by rotary evaporation. Concentrated ammonium hydroxide (50 ml) was added and the aqueous mixture extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed with brine (2 × 25 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded an orange oil that was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluant to give the *amino derivative* (**6**) (680 mg, 63%) as a mixture of stereoisomers, pale yellow oil (Found: M^+, 270.1227. $C_{12}H_{18}N_2O_5$ requires *M*, 270.1215); ν_{max}(thin film) 3 390m, 3 330m (NH), and 1 750s, 1 700s cm^{-1} (C=O); δ_H(60 MHz; $CDCl_3$) 1.13 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.39 br (2 H, s, NH_2), 3.43 (2 H, q, *J* 7 Hz, OCH_2), 3.56–3.68 (4 H, m, OMe and C*H*NH_2), 3.77 (3 H, s, OMe), 6.02–6.19 (1 H, m, 4-H), 6.34–6.58 (1 H, m, C*H*OEt), and 6.71–7.29 (2 H, m, 3-H and 5-H); *m/z* 270 (M^+, 1%), 182 ($C_9H_{12}NO_3$, 100), and 122 ($C_6H_4NO_2$, 70).

Ethoxy-3,4-dihydro-3-methoxycarbonylpyrrolo[1,2-a]*pyrazin-1*(2H)*-one* (**7**).—A solution of the amino derivative (**6**) (1.0 g, 3.7 mmol) in toluene (100 ml) was heated under reflux under nitrogen for 24 h. After removal of the solvent under reduced pressure the residue was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluant to give the *pyrrolopyrazine* (**7**) (775 mg, 88%) as a mixture of stereoisomers, colourless prisms, m.p. 141–146 °C (from ethyl acetate) (Found: C, 55.2; H, 6.2; N, 11.9. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%); ν_{max}(Nujol) 3 400m (NH), 1 750s (C=O ester), and 1 660s cm^{-1} (C=O lactam); δ_H(80 MHz; $CDCl_3$) 1.01, 1.09 (3 H, 2 × t, *J* 7 Hz, CH_2CH_3), 3.37, 3.45 (2 H, 2 × q, *J* 7 Hz, OCH_2), 3.62, 3.83 (3 H, 2 × s, OMe), 4.42–4.64 (1 H, m, C*H*NH), 5.48–5.58 (1 H, m, C*H*OEt), 6.13–6.24 (1 H, m, 7-H), 6.33br (1 H, s, NH), and 6.79–6.98 (2 H, m, 6-H and 8-H); *m/z* 238 (M^+, 58%), 194 ($M - C_2H_4O$, 21), 193 ($M - C_2H_5O$, 15), 182 (37), 145 (19), 122 ($C_6H_4NO_2$, 100), and 94 (64).

3-*Methoxycarbonylpyrrolo*[1,2-a]*pyrazin-1*(2H)*-one* (**8**).—To a solution of the foregoing pyrrolopyrazine (**7**) (700 mg, 2.9 mmol) in dry tetrahydrofuran (50 ml) was added potassium hydride (990 mg of 35 wt % dispersion in mineral oil, 8.7 mmol). The mixture was stirred at room temperature for 0.5 h and methanol (5 ml) was added followed by water (10 ml). The mixture was extracted with ether (3 × 50 ml) and the organic extract washed with water (10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluant to give the *title compound* (**8**) (445 mg, 80%) as colourless needles, m.p. 192–193 °C (from hexane–ethyl acetate) (Found: C, 56.0; H, 4.1; N, 14.3. $C_9H_8N_2O_3$ requires C, 56.25; H, 4.2; N, 14.6%); λ_{max}(ethanol) 314 (log ε 3.92), 280 (3.91), and 248 nm (4.50); ν_{max}(CCl_4) 3 490 (NH), 1 730s (C=O ester), and 1 680s cm^{-1} (C=O lactam); δ_H(80 MHz; $CDCl_3$) 3.93 (3 H, s, OMe), 6.66 (1 H, t, *J* 3.3 Hz, 7-H), 7.21 (2 H, d, *J* 3.3 Hz, 6-H and 8-H), 7.80 (1 H, s, 4-H), and 8.24br (1 H, s, NH); δ_C(20 MHz; $CDCl_3$) 52.8 (q, OMe), 112.6 (d, C-8), 114.0 (d, C-4), 114.7 (d, C-7), 116.7 (s, C-3), 120.6 (d, C-6), 124.5 (s, C-8a), 155.1 (s, C-1), and 161.9 (s, C=O ester); *m/z* 192 (M^+, 100%), 161 ($M - OCH_3$, 9), 134 (24), 133 ($M - C_2H_3O_2$, 17), 134 ($M - C_2H_4O_2$, 33), 104 (18), and 78 (13).

3-*Methoxycarbonyl-2-methylpyrrolo*[1,2-a]*pyrazin-1*(2H)*-one* (**9**).—To a solution of the foregoing ester (**8**) (500 mg, 2.6 mmol) in dry dimethylformamide (10 ml) was added potassium hydride (500 mg of 35 wt % dispersion in mineral oil, 4.4 mmol). The mixture was stirred at room temperature for 0.25 h, and methyl iodide (0.28 ml, 4.4 mmol) was then added followed by methanol (5 ml) after an additional 0.5 h. Water (25 ml) was added and the mixture extracted with ether (3 × 75 ml). The ethereal extract was washed with water (10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluant to give the *methyl derivative* (**9**) (407 mg, 76%) as colourless needles, m.p. 153–154 °C (from hexane–ethyl acetate) (Found: C, 58.5; H, 5.0; N, 13.4. $C_9H_{10}N_2O_3$ requires C, 58.2; H, 4.9; N, 13.6%); λ_{max}(ethanol) 312 sh (log ε 4.25), 278 (4.33), and 246 nm (4.51); ν_{max}(CCl_4) 1 730s (C=O ester) and 1 670s (C=O lactam); δ_H(270 MHz; $CDCl_3$) 3.67 (3 H, s, NMe), 3.90 (3 H, s, OMe), 6.66 (1 H, t, *J* 3.3 Hz, 7-H), 7.15 (2 H, d, *J* 3.3 Hz, 6-H and 8-H), and 7.86 (1 H, s, 4-H); δ_C(67.8 MHz; $CDCl_3$) 31.8 (q, NMe), 52.6 (q, OMe), 111.9 (d, C-8), 114.6 (d, C-7), 115.9 (d, C-4), 119.3 (d, C-6), 120.1 (s, C-3), 124.0 (s, C-8a), 156.4 (s, C-1), and 162.4 (s, C=O ester); *m/z* 206 (M^+, 100%), 191 ($M - CH_3$, 6), 147 ($M - C_2H_3O_2$, 20), 119 (11), and 78 (14).

3-*Hydroxymethyl-2-methylpyrrolo*[1,2-a]*pyrazin-1*(2H)*-one* (**10**).—To a solution of the foregoing pyrrolopyrazine (**9**) (300 mg, 1.4 mmol) in methanol (30 ml) was added sodium borohydride (160 mg, 4.2 mmol) and the reaction mixture stirred at room temperature for 12 h. 5% Hydrochloric acid (5 ml) was added and the methanol removed by rotary evaporation. After extraction of the residue with ethyl acetate (3 × 50 ml) the organic extract was washed with water (10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of solvent afforded a colourless solid that was recrystallized from ethyl acetate to give the *title alcohol* (**10**) (180 mg, 72%) as colourless needles, m.p. 157–158 °C (Found: C, 60.9; H, 5.4; N, 15.9. $C_9H_{10}N_2O_2$ requires C, 60.7; H, 5.7; N, 15.7%); λ_{max}(ethanol) 282 (log ε 3.81) and 230 nm (4.27); ν_{max}(Nujol) 3 300 (OH) and 1 630s cm^{-1} (C=O lactam); δ_H[80 MHz;$(CD_3)_2CO$] 2.19br (1 H, s, exchangeable with D_2O OH), 3.49 (3 H, s, NMe), 4.51br (2 H, s, CH_2O), 6.47 (1 H, dd, $J_{6,7}$ 2.6 and $J_{7,8}$ 3.9 Hz, 7-H), 6.89 (1 H, ddd, $J_{4,8}$ 0.7, $J_{6,8}$ 1.5, and $J_{7,8}$ 3.9 Hz, 8-H), 7.21 (1 H, dd, $J_{6,8}$ 1.5 and $J_{6,7}$ 2.6 Hz, 6-H), and 7.26br (1H, d, $J_{4,8}$ 0.7 Hz, 4-H); δ_C[20 MHz; $(CD_3)_2CO$)] 28.6 (q, NMe), 60.3 (t, CH_2OH), 108.0 (d, C-4), 109.8 (d, C-8), 112.6 (d, C-7), 118.9 (d, C-6), 124.2 (s, C-8a), 129.2 (s, C-3), and 156.7 (s, C-1); *m/z* 178 (M^+, 100%), 163 ($M - CH_3$, 28), 161 (M – OH, 11), 147 ($M - CH_2OH$, 18), 94 (19), and 78 (15).

3-(2-*Cyanoethyl*)-2-*methylpyrrolo*[1,2-a]*pyrazin-1*(2H)*-one* (**12**).—(i) *Preparation of bromide* (**11**). To a solution of the foregoing alcohol (**10**) (80 mg, 0.45 mmol) in dichloromethane (10 ml) cooled to −60 °C under nitrogen was added a solution of methanesulphonyl chloride (52 mg, 0.45 mmol) in dichloromethane (2 ml) followed by triethylamine (90 mg, 0.9 mmol). The mixture was stirred at −60 °C for 0.25 h, a solution of lithium bromide (120 mg, 1.38 mmol) in dry tetrahydrofuran (10 ml) was added, and the mixture warmed to −40 °C during 0.5 h. After dilution with ether (100 ml) the organic extract was washed with water (2 × 10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a colourless oil (82 mg) (M^+, *m/z* 240, 242) that was not purified but treated immediately with cyanomethyl cuprate.

(ii) *Preparation of nitrile* (**12**). To a solution of acetonitrile (92 mg, 2.25 mmol) in tetrahydrofuran (10 ml) cooled to −78 °C under nitrogen was added n-butyl-lithium (1.45 ml of a 1.6 mol l^{-1} solution in hexane, 2.3 mmol). The mixture was stirred at −78 °C for 0.5 h, then transferred *via* a double-ended needle to a suspension of copper(I) bromide–dimethyl sulphide complex (480 mg, 2.3 mmol) in tetrahydrofuran (5 ml) and the mixture warmed to −40 °C during 0.5 h. To the resultant yellow solution was then added a solution of the foregoing bromide (**11**) (82 mg) in tetrahydrofuran (15 ml) and the mixture warmed to −20 °C during 1 h. The reaction was quenched by the addition of 10% concentrated ammonia/saturated ammonium chloride solution (10 ml), followed by warming to room temperature and extraction with ether (3 × 30 ml). The ethereal extract was washed with water (10 ml) and brine (10 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure afforded a pale yellow oil that was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluant to give the *title nitrile* (**12**) (52 mg, 57%) as colourless needles, m.p. 170–171 °C (from hexane–ethyl acetate) (Found: C, 65.5; H, 5.4; N, 20.6. $C_{11}H_{11}N_3O$ requires C, 65.7; H, 5.5; N, 20.9%); λ_{max}(methanol) 284 (log ε 3.67) and 232 nm (4.17); $\nu_{max}(CHCl_3)$ 2 250(C≡N) and 1 630s cm^{-1} (C=O lactam); δ_H[270 MHz; $(CD_3)_2CO$] 2.83–2.88 (2 H, m, CH_2CN), 2.97–3.03 (2 H, m, allylic CH_2), 3.42 (3 H, s, NMe), 6.46 (1 H, dd, $J_{6,7}$ and $J_{7,8}$ 4.0 Hz, 7-H), 6.84 (1 H, ddd, $J_{4,8}$ 0.7, $J_{6,8}$ 1.5, and $J_{7,8}$ 4.0 Hz, 8-H, 7.24 (1 H, dd, $J_{6,8}$ 1.5 and $J_{6,7}$ 2.6 Hz, 6-H), and 7.25br (1 H, s, 4-H); δ_C(67.8 MHz; $CDCl_3$) 17.2 (t, CH_2CN), 26.9 (t, CH_2CH_2CN), 28.9 (q, NMe), 107.2 (d, C-4), 110.6 (d, C-8), 112.8 (d, C-7), 117.6 (s, C≡N), 118.1 (d, C-6), 123.0 (s, C-8a), 124.5 (s, C-3), and 156.8 (s, C-1); *m/z* 201 (M^+, 80%), 161 (M-CH_2CN, 100), 131 (14), and 104 (37).

3-(3-*Aminopropyl*)-2-*methylpyrrolo*[1,2-a]*pyrazin*-1(2H)-*one* (**13**).—Using the procedure described for the preparation of the amine (**6**) from the nitro-ester (**5**), the amine (**13**) was prepared from the nitrile (**12**) (32 mg, 0.16 mmol) using sodium borohydride (30 mg, 0.8 mmol) and cobalt(II) chloride (42 mg, 0.32 mmol). The product in 50% methanol was adsorbed onto a column of carboxymethyl silica and the column washed with 50% methanol. Elution with 80% methanol containing 5% formic acid gave the *title amine* (**13**) (20 mg, 62%) as the formate salt (Found: M^+, 205.1219. $C_{11}H_{15}N_3O$ requires M, 205.1215); λ_{max}(methanol) 298 (log ε 3.84), 226 (4.14), and 230 nm (4.49); δ_H(270 MHz; D_2O) 2.04br (2 H, quintet, $CH_2CH_2NH_2$), 2.78br (2 H, t, J 7.4 Hz, $CH_2CH_2CH_2NH_2$), 3.16br (2 H, t, J 7.7 Hz, (CH_2NH_2)), 3.50 (3 H, s, NMe), 6.72 (1 H, dd, $J_{6,7}$ 2.6 and $J_{7,8}$ 4.0 Hz, 7-H), 7.07 (1 H, m, 8-H), 7.35br (1 H, s, 4-H), and 7.38 (1 H, dd, $J_{6,7}$ 2.6 and $J_{7,8}$ 1.5 Hz, 6-H); δ_C(67.8 MHz; D_2O) 26.7 (t, $CH_2CH_2NH_2$), 27.9 (t, $CH_2CH_2CH_2NH_2$), 30.7 (q, NMe), 39.9 (t, CH_2NH_2), 109.5 (d, C-4), 110.2 (d, C-8), 114.0 (d, C-7), 120.8 (d, C-6), 122.8 (s, C-8a), 128.3 (s, C-3), and 157.3 (s, C-1); *m/z* 205 (M^+, 83%), 175 (47), 163 (100), 162 (50), 135 (27), 104 (22), and 94 (25).

3-(3-*Guanidinopropyl*)-2-*methylpyrrolo*[1,2-a]*pyrazin*-1(2H)-*one* (**1**).—To the formate salt of the foregoing amine (**13**) (20 mg, 0.08 mmol) in dimethylformamide (1.0 ml) was added 3,5-dimethyl-1-guanylpyrazole nitrate[10] (30 mg, 0.15 mmol) and triethylamine (0.2 ml). After 3.5 h at 40 °C and 2 days at room temperature, the solvent was evaporated off and the residue taken up in water (10 ml) and washed with ether (2 × 10 ml). Residual ether in the aqueous phase was removed under reduced pressure before chromatography on a column of C-18 reverse-phase silica (Sepralyte; 40 mm × 11 mm i.d.) packed in water. Elution with increasing proportions of 80% methanol containing 1% formic acid gave peramine containing fractions which were combined to yield a white solid (30 mg). Addition of potassium bromide to a concentrated aqueous solution caused crystallization of peramine hydrobromide (**1**). Recrystallization from water gave peramine hydrobromide (5.4 mg, 22%) as fine needles, m.p. 233–235 °C (lit.[12] m.p. 242–243 °C). A second crop yielded additional product (7.4 mg, 30%), m.p. 246–248 °C.

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