Synthesis of Peramine, an Insect Feeding Deterrent Mycotoxin from *Acremonium lolii*

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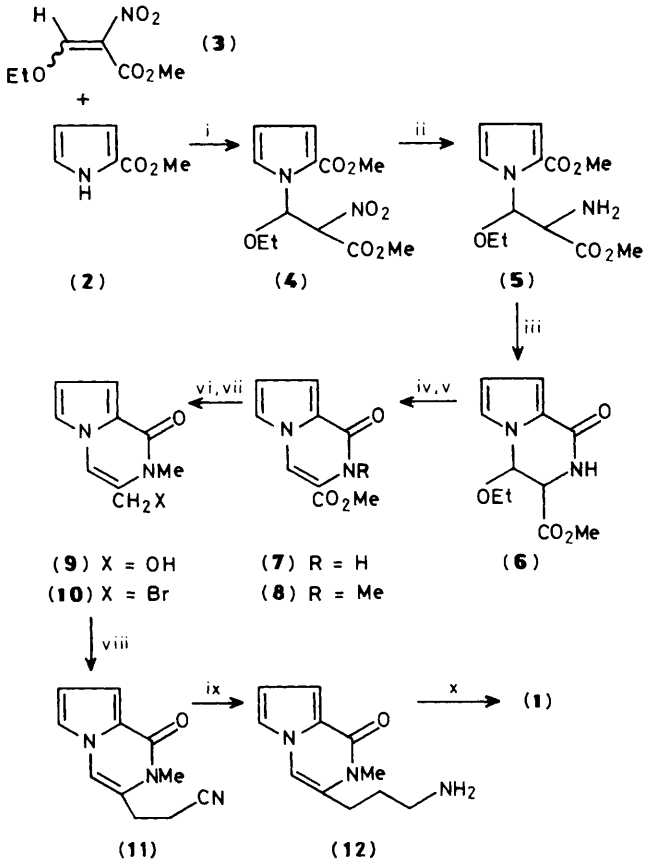
The first synthesis of peramine (**1**), the major insect feeding deterrent isolated from perennial ryegrass infected with the endophytic fungus *Acremonium lolii*, is reported.

The alkaloid peramine (**1**), containing the novel 2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system together with a monosubstituted guanidino group, has recently been identified[1] as the principal insect feeding deterrent isolated from perennial ryegrass (*Lolium perenne* L.) infected with the endophytic fungus *Acremonium lolii*. The presence of this previously unreported heterocycle together with the interesting biological activity of peramine (**1**) prompted a synthesis.

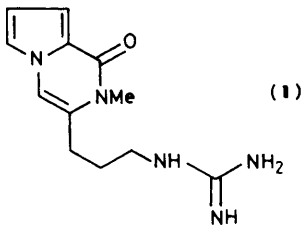
Michael addition of the potassium salt of methyl pyrrole-2-carboxylate (**2**) to the nitroalkene (**3**)[2] gave the adduct (**4**)† (82% yield) as a mixture of stereoisomers which were not separated. Reduction of the nitro group with sodium borohydride–cobalt(II) chloride[3] provided the amine (**5**) (63% yield), which cyclized to the amide (**6**) (also isolated as a mixture of stereoisomers) upon heating under reflux in toluene for 24 h. Elimination of the ethoxy group (80% yield) to give the unsaturated secondary lactam (**7**) with potassium hydride in tetrahydrofuran (THF) followed by *N*-methylation [KH, dimethylformamide (DMF), and methyl iodide (MeI)] afforded the tertiary lactam (**8**) (76%). Reduction of the α,β-unsaturated ester (**8**) was then easily effected with sodium borohydride in methanol to give the alcohol (**9**) (72%) {m.p. 157—158 °C; ^{1}H n.m.r. [80 MHz; $(CD_3)_2CO$] δ 2.19 (1H, br. s, OH), 3.49 (3H, s, NMe), 4.51 (2H, br. s, CH_2OH), 6.47 (1H, dd, $J_{6,7}$ 2.6, $J_{7,8}$ 3.9 Hz, H-7), 6.89 (1H, ddd, $J_{4,8}$ 0.7, $J_{6,8}$ 1.5, $J_{7,8}$ 3.9 Hz, H-8), 7.21 (1H, dd, $J_{6,8}$ 1.5, $J_{6,7}$ 2.6 Hz, H-6), and 7.26 (1H, br. d, $J_{4,8}$ 0.7 Hz, H-4)}.

The strategy for extending the side-chain to put in place the required guanidino group focused on the displacement of the allylic bromide (**10**) by cyanomethyl cuprate [generated from the corresponding organolithium reagent with copper(I) bromide–dimethyl sulphide complex]. The bromide (**10**) (M^+ 240/242) proved unstable and was generated *in situ* from alcohol (**9**) with methanesulphonyl chloride, triethylamine, and lithium bromide at −60 to −40 °C. The overall displacement reaction proceeded in 57% yield from the alcohol (**9**), and yielded the nitrile (**11**) which contains the necessary functionality for introduction of the guanidino group {m.p. 170—171 °C; ^{1}H n.m.r. [270 MHz; $(CD_3)_2CO$] δ 2.83—2.88 (2H, m, CH_2CN), 2.97—3.03 (2H, m, allylic CH_2), 3.42 (3H, s, NMe), 6.46 (1H, dd, $J_{6,7}$ 2.6, $J_{7,8}$ 4.0 Hz, H-7), 6.84 (1H, ddd, $J_{4,8}$ 0.7, $J_{6,8}$ 1.5, $J_{7,8}$ 4.0 Hz, H-8), 7.24 (1H, dd, $J_{6,8}$ 1.5, $J_{6,7}$ 2.6 Hz, H-6), and 7.25 (1H, br. s, H-4); $\nu_{max.}$ ($CHCl_3$) 2250 and 1620 cm^{-1}}.

The synthesis was completed by reduction of the nitrile (**11**) to the amine (**12**) with sodium borohydride–cobalt(II) chloride,[3] in 62% yield, followed by conversion into the guanidino derivative peramine (**1**) with *S*-methylthiouronium hydrogen sulphate. The synthetic material had the same chromatographic properties (t.l.c. and h.p.l.c.), high resolution mass spectral fragmentations, and ^{1}H n.m.r. (270 MHz) spectrum as the naturally occurring material.



Scheme 1. *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, MsCl (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^{n}Li (5.1 equiv.), 0.5 h, −78 °C, then CuBr.Me_2S (5.2 equiv.), −78 to −40 °C, 0.5 h, then (**10**) (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 (2 M), room temp, 48 h.



† All new compounds gave satisfactory spectral and analytical data.

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