

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.

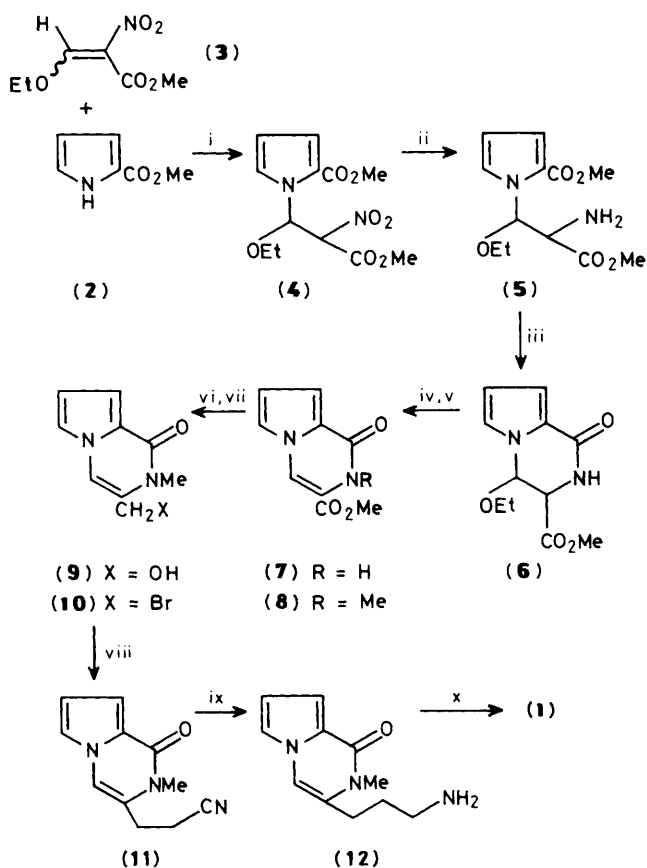
The alkaloid peramine (**1**), containing the novel 2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system together with a monosubstituted guanidino group, has recently been identified¹ as the principal insect feeding deterrent isolated from perennial ryegrass (*Lolium perenne* L.) infected with the 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) chloride³ 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) 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; ¹H n.m.r. [80 MHz; (CD₃)₂CO] δ 2.19 (1H, br. s, OH), 3.49 (3H, s, NMe), 4.51 (2H, br. s, CH₂OH), 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)}.

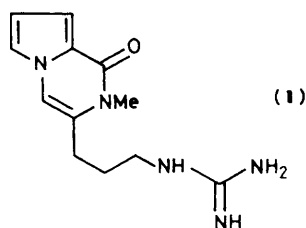
The strategy for extending the side-chain to put in place the required guanidino group focused on the displacement of the allylic bromide (**10**) by cyanomethyl cuprate [generated from the corresponding organolithium reagent with copper(I) bromide-dimethyl sulphide complex]. The bromide (**10**) (*M*⁺ 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; ¹H n.m.r. [270 MHz; (CD₃)₂CO] δ 2.83–2.88 (2H, m, CH₂CN), 2.97–3.03 (2H, m, allylic CH₂), 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); ν_{\max} . (CHCl₃) 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*-methylthiuronium hydrogen sulphate. The synthetic material had the same chromatographic properties (t.l.c. and h.p.l.c.), high resolution mass spectral fragmentations, and ¹H n.m.r. (270 MHz) spectrum as the naturally occurring material.



Scheme 1. Reagents and conditions: i, KH, THF, 0°C (82%); ii, NaBH₄ (5.0 equiv.), CoCl₂ (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, NaBH₄, MeOH, 12 h, (72%); vii, MsCl (1.1 equiv.), Et₃N, CH₂Cl₂, –60°C, 0.25 h, then LiBr (3.0 equiv.), THF, –60 to –40°C, 0.5 h; viii, MeCN (5.0 equiv.), BuⁿLi (5.1 equiv.), 0.5 h, –78°C, then CuBr·Me₂S (5.2 equiv.), –78 to –40°C, 0.5 h, then (**10**) (1.0 equiv.), –40 to –20°C, 1 h (57% overall); ix, NaBH₄ (5.0 equiv.), CoCl₂ (2.0 equiv.), MeOH (62%); x, *S*-methylthiuronium 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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