Synthesis of (±)-Nitramine and (±)-Isonitramine

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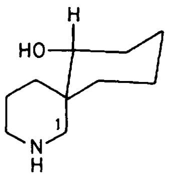
The alkaloids (±)-nitramine (**1**) and (±)-isonitramine (**2**) have been synthesised, employing an intramolecular Mannich reaction to set up the spirocyclic ring system.

Nitramine (**1**) and isonitramine (**2**), isolated recently from plants of the genus *Nitraria*,[1] are of interest because of their unusual spirocyclic structures and their structural relationship to the neurotoxic alkaloid histrionicotoxin (**3**). The structures of the new alkaloids were established by *X*-ray crystallography of crystalline salts, which showed that they are diastereoisomers;[2] in each isomer the hydroxy substituent is equatorially disposed in the cyclohexane ring. Two syntheses of (±)-nitramine[3] and one of (±)-isonitramine[4] have been recorded. We report here a direct route to both alkaloids using an intramolecular Mannich reaction to set up the spirocyclic ring system.

The readily available nitrile (**4**) was converted into the acetal (**5**) and thence into the benzylamine (**6**) by sequential $LiAlH_4$ reduction, benzoylation, and $LiAlH_4$ reduction. Cyclisation was effected by bubbling gaseous formaldehyde into a solution of amine (**6**) in methanol containing hydrochloric acid[5] and gave the spirocyclic ketone (**7**) in 60% yield. Reduction of the carbonyl group with sodium borohydride afforded a mixture of the alcohols (**8**) and (**9**) (*ca.* 1 : 1) which were separated by chromatography on silica gel. Debenzylation of (**8**) was smoothly effected with palladium–carbon in boiling methanol in the presence of ammonium formate[6] and gave (±)-nitramine (**1**) as an oil, characterised by its high



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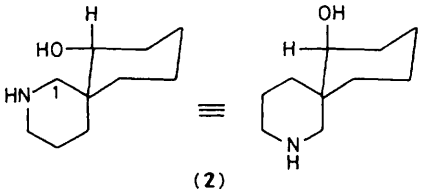

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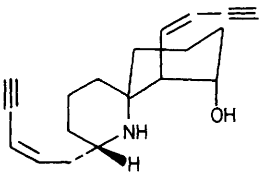

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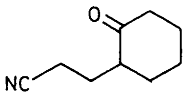

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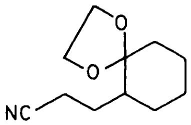

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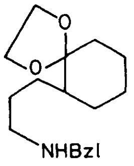

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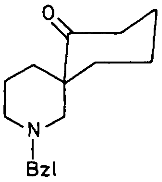

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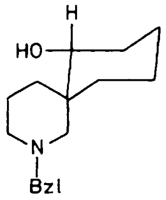

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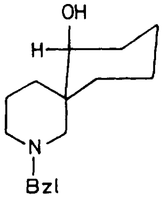

(9)

Bzl = benzyl

resolution mass spectrum and its ^{1}H and ^{13}C n.m.r. spectra, which were in close agreement with the published spectra.[2] Debenzylation of (**9**) similarly gave (±)-isonitramine (**2**) as a crystalline solid, m.p. 100.5—103 °C; its structure was fully supported by the high resolution mass spectrum and the ^{1}H and ^{13}C n.m.r. spectra. The nitramine and isonitramine were easily distinguished from each other by the C-1 ^{13}C n.m.r. signals at δ 52.32 in the former and δ 60.71 in the latter (lit.[2] δ 52.0 for nitramine and 60.3 for isonitramine).

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