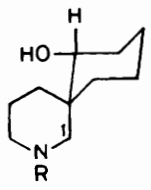
Synthesis of (±)-Nitramine and (±)-Isonitramine[1]

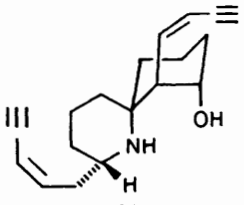
William Carruthers* and Roger C. Moses
Chemistry Department, The University, Stocker Road, Exeter, EX4 4QD

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

Nitramine (**1**; R = H) and isonitramine (**2**; R = H) were isolated recently from plants of the genus *Nitraria*[2] and 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;[3] in each isomer the hydroxy substituent is equatorially disposed in the cyclohexane ring.



(**1**)



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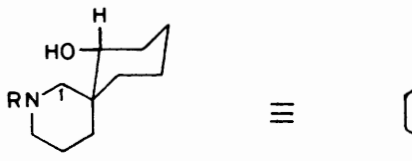
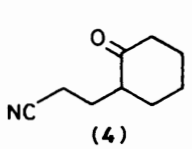


(**2**)

Two syntheses of (±)-nitramine[4] and one of (±)-isonitramine[5] have been recorded and syntheses of (+)-nitramine and of (+)- and (−)-isonitramine have been reported.[6] We describe here a direct route to (±)-nitramine and (±)-isonitramine using an intramolecular Mannich reaction to set up the spirocyclic ring system. The intramolecular Mannich reaction is widely used in biosynthesis[7] and in the laboratory[8] to make fused and bridged-bicyclic nitrogen ring compounds, but as far as we are aware it has not been much employed in the synthesis of spirocyclic compounds.

Our starting material was the readily available nitrile (**4**)[9] which was converted into the acetal (**5**) and thence into the benzylamine (**6**) by sequential reduction ($LiAlH_4$), benzoylation, and reduction ($LiAlH_4$). Attempts to isolate the free amino ketone and use it in the Mannich cyclisation were frustrated by its propensity to form the cyclic enamine (**7**). Cyclisation to the spirocycle was thus effected directly from the acetal (**6**) by reaction with gaseous formaldehyde in methanol containing hydrochloric acid,[10] affording the spirocyclic ketone (**8**) in 50—60% yield, presumably *via* a species such as compound (**9**). Reduction of the carbonyl group of the ketone (**8**) with sodium borohydride afforded a mixture of *N*-benzylnitramine (**1**; R = CH_2Ph) and *N*-benzylisonitramine (**2**; R = CH_2Ph) (7:9) which were separated by chromatography on silica. The alcohols were surprisingly resistant to debenzylation; they were unaffected on attempted hydrogenolysis with palladium–carbon in ethanol and with platinum in acetic acid, and reaction with lithium in liquid ammonia resulted in reduction of the benzene ring. Debenzylation was eventually effected with palladium–carbon and ammonium formate in boiling methanol[11] giving (±)-nitramine (**1**; R = H) and (±)-isonitramine (**2**; R = H) smoothly from the corresponding *N*-benzyl derivative. The two compounds were easily distinguished from each other by the characteristic C-1 ^{13}C n.m.r. signals at δ 52.35 in nitramine and δ 60.71 in isonitramine (lit.,[3] δ 52.0 and 60.3).



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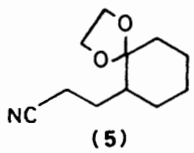
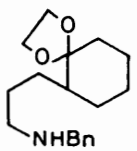
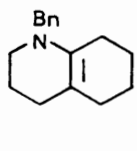


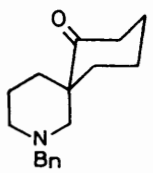
(**5**)



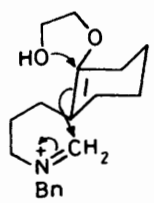
(**6**)



(**7**)



(**8**)



(**9**)

Bn = $PhCH_2$

Experimental

100 MHz ^1H N.m.r. spectra were determined using a JEOL JNM-MH 100 instrument, and 250 MHz ^1H and 62.9 MHz ^{13}C n.m.r. spectra with a Brüker AM250 instrument. Degree of substitution at carbon atoms in ^{13}C spectra was obtained by the DEPT technique. I.r. spectra were recorded on a Perkin-Elmer 398 spectrometer interfaced to a Perkin-Elmer 3600 data station. Low resolution mass spectra were obtained with a VG-Micromass MM16F mass spectrometer; high resolution mass spectra were determined at the Physico-Chemical Measurements Unit, Harwell or by the S.E.R.C. Mass Spectrometry Unit, University College, Swansea.

2-(2-*Cyanoethyl*)*cyclohexanone Ethylene Acetal* (**5**).—A solution of 2-(2-cyanoethyl)cyclohexanone (**4**)[9] (2.50 g, 16.53 mmol), ethanediol (9.7 g, 156.3 mmol), and toluene-*p*-sulphonic

acid monohydrate (0.30 g, 1.58 mmol) in benzene (80 ml) was refluxed under nitrogen for 6 h with separation of water (Dean-Stark trap). The recovered acetal was obtained as a colourless oil (3.19 g, 99%) by distillation (b.p. 98—102 °C at 0.05 mmHg); δ(100 MHz, $CDCl_3$) 1.00—2.50 (m, 13 H) and 3.91 (br s, 4 H, OCH_2CH_2O) (Found: C, 67.4; H, 9.1; N, 7.6%; M^+, 195.0. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%; *M*, 195.0).

2-(3-*Aminopropyl*)*cyclohexanone Ethylene Acetal*.—A solution of the foregoing acetal (**5**) (1.11 g, 5.67 mmol) in tetrahydrofuran (25 ml) was added to a stirred suspension of lithium aluminium hydride (0.34 g, 8.95 mmol) in tetrahydrofuran (50 ml) at room temperature under nitrogen. After 4 h the mixture was cautiously diluted with water (8 ml) and the precipitated solid was filtered off and triturated with ether (5 × 20 ml). The combined organic layers were dried and evaporated, affording the amine as a colourless oil (1.12 g, 99%), b.p. 86—88 °C at 0.19 mmHg (Found: C, 66.1; H, 10.9; N, 6.9%; M^+, 199. $C_{11}H_{21}NO_2$ requires C, 66.3; H, 10.6; N, 7.0%; *M*, 199); δ(100 MHz, $CDCl_3$) 0.80—1.95 (m, 15 H, including two exchangable by D_2O), 2.60 (t, 2 H, *J* 3.5 Hz, $CH_2CH_2NH_2$), and 3.82 (br s, 4 H, OCH_2CH_2O). Poor yields were obtained in larger scale experiments.

The corresponding benzoyl derivative was obtained by treatment of the amine (1.12 g, 5.62 mmol) with benzoyl chloride (0.87 g, 6.18 mmol) and triethylamine (0.62 g, 6.18 mmol) in benzene (20 ml) for 12 h at room temperature. It was obtained as a pale yellow glass (1.66 g, 97%) by distillation (Kugelrohr apparatus), b.p. 170—180 °C (oven temperature) at 0.25 mmHg (Found: C, 71.3; H, 8.4; N, 4.6%; M^+, 304. $C_{18}H_{25}NO_3$ requires C, 71.3; H, 8.3; N, 4.8%; *M* + 1, 304); δ(100 MHz, $CDCl_3$) 0.95—1.95 (m, 13 H), 3.40 (m, 2 H, CH_2CH_2NHCO), 3.83 (br s, 4 H, OCH_2CH_2O), 6.15 (br s, 1 H, RNHCO), and 7.24—8.10 (m, 5 H, ArH).

2-(3-*Benzylaminopropyl*)*cyclohexanone Ethylene Acetal* (**6**).—A solution of the benzoyl derivative described above (13.33 g, 43.9 mmol) in tetrahydrofuran (160 ml) was added dropwise to a suspension of lithium aluminium hydride (2.34 g, 61.5 mmol) in tetrahydrofuran (230 ml) at room temperature and the stirred mixture heated at 40 °C for 48 h under nitrogen. The cooled solution was treated successively with water (4.5 ml), aqueous sodium hydroxide (15%, 4.5 ml), and water (4.5 ml) and the solid precipitate was filtered off and triturated with ether (5 × 100 ml). The combined organic layers were dried and evaporated, affording the amine as a colourless oil (11.12 g, 88%), b.p. 152—154 °C at 0.28 mmHg (Found: C, 74.5; H, 9.6; N, 4.8%; M^+, 289. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%; *M*, 289); δ(100 MHz, $CDCl_3$) 0.85—1.85 (m, 14 H, one exchanged with D_2O), 2.56 (unresolved t, 2 H, CH_2CH_2NH), 3.70 (s, 2 H, NCH_2Ph, 3.82 (s, 4 H, OCH_2CH_2O), and 7.18 (s, 5 H, ArH).

2-*Benzyl*-2-*azaspiro*[5.5]*undecan*-7-*one* (**8**).—Gaseous formaldehyde, obtained by pyrolysis of paraformaldehyde (9.90 g) was bubbled through a solution of the above acetal (1.00 g, 3.45 mmol) in methanol (40 ml) containing concentrated hydrochloric acid (200 μl, 2.15 mmol) over 10 min. During this time the solution became cloudy and reached reflux. A further portion of concentrated hydrochloric acid (340 μl, 3.66 mmol) was added and the solution was refluxed for 24 h. Volatile material was removed under water-pump pressure, the residue was made alkaline by addition of sodium carbonate (10%; 40 ml), and the product was extracted with chloroform. The washed and dried extract was evaporated and the residue purified by dry-column flash chromatography. Elution with chloroform–methanol (49:1) gave the spiro compound as a pale yellow oil (0.42 g, 47%) (Found: M^+, 257.1777. $C_{17}H_{23}NO$ requires *M*, 257.1780); δ_H(250 MHz, $CDCl_3$) 1.23—1.83 (m, 10 H, 5 × CH_2), 2.21—2.26 (m, 3 H, CH_2CH_2CO and 1 H, of 1-CH_2), 2.39 (t, 2 H, *J* 5.4 Hz, CH_2CH_2N), 2.71 (br d, 1 H, *J* 11.5 Hz, 1 H of 1-CH_2), 3.44 (q, 2 H, *J* 13.4 Hz, NCH_2Ph), and 7.21—7.34 (m, 5 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 20.70, 21.97, 28.17, 31.49 (4 × CH_2), 36.95 (br, CH_2), 38.68 (CH_2), 49.43 (spiro qC), 55.03, 59.96, 63.29 (3 × CH_2), 127.03, 128.23, 128.89 (5 CH), 139.06 (qC of Ph), and 215.27 (CO); $\nu_{max.}$(film) 3 021, 2 930, 2 855, 2 797, 2 751, 1 703 (CO), 1 668, 1 449, 1 122, and 699 cm^{-1}.

(±)-N-*Benzylnitramine* (**1**; R = CH_2Ph). *and* (±)-N-*Benzylisonitramine* (**2**; R = CH_2Ph).—Sodium borohydride (0.68 g, 17.89 mmol) was added portionwise to a stirred solution of the amino ketone (**8**) (2.30 g, 8.94 mmol) in methanol (100 ml) at 0 °C. After 0.5 h methanol was removed under reduced pressure and the residue was dissolved in dilute hydrochloric acid (2M; 100 ml). The solution was washed with ether, basified with sodium carbonate, and the product extracted with chloroform. Evaporation of the washed and dried extract afforded a pale yellow oil (1.86 g) shown by its 250 MHz ^1H n.m.r. spectrum to contain *N*-benzyl-nitramine and -isonitramine in the ratio 7:9. (This estimation is based on the integrals of two discrete doublet signals at δ 3.24, *J* 11.5 Hz and δ 2.67, *J* 11.2 Hz, in the ^1H n.m.r. spectra of *N*-benzyl-nitramine and -isonitramine, respectively.) Short-column chromatography [12] of the mixture on 60 H silica gel and elution with chloroform eluted first *N*-benzylisonitramine (0.68 g, 29.3%). Further elution with chloroform–methanol (99:1) then gave a mixture of the two bases (0.54 g) followed by *N*-benzylnitramine (0.21 g, 9.0%).

N-Benzylnitramine was obtained as a colourless oil (Found: M^+, 259.1938. $C_{17}H_{25}NO$ requires *M*, 259.1936); δ_H(250 MHz, $CDCl_3$) 1.05—1.80 (m, 12 H, 6 × CH_2), 1.92—2.03 and 2.16—2.34 (m, 1 H, each of CH_2CH_2N), 2.88 (br d, 1 H, *J ca.* 10 Hz, 1 H of 1-CH_2), 3.26 (br d, 1 H, *J ca.* 10 Hz, 1 H of 1-CH_2, 3.36—3.52 (m, 3 H, NCH_2Ph and CHOH), and 7.31—7.43 (m, 5 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 21.11, 23.91, 24.57, 32.80 (4 × CH_2), 36.95 (spiro C), 38.20, 38.85, 54.51, 59.31, 63.67 (5 × CH_2), 79.17 (CH), 127.39, 128.32, 128.49, 129.07, 129.20 (5 × CH), and 137.89 (C, Ph).

N-Benzylisonitramine was a colourless oil (Found: M^+, 259.1923. $C_{17}H_{25}NO$ requires *M*, 259.1936); δ_H(250 MHz, $CDCl_3$) 0.87—2.28 (m, 14 H, 7 × CH_2), 2.67 (d, *J* 11.2 Hz, 1 H, of 1-CH_2), 2.90 (br d, *J* 11.2 Hz, 1 H of 1-CH_2), 3.46—3.57 (m, 3 H, NCH_2Ph) and CHOH), 5.90 (br s, 1 H, OH), and 7.23—7.36 (m, 5 H, ArH); δ_C(62.9 MHz, $CDCl_3$) 20.46, 23.25, 24.43, 28.53, 29.55, 37.30, 54.52, 63.60, 67.94 (9 × CH_2), 80.56 (CH), 127.33, 128.55, 129.07 (3 × CH), and 137.97 (C, Ph). The spiro carbon atom was not seen in this spectrum.

(±)-*Isonitramine* (**2**; R = H).—A stirred solution of *N*-benzylisonitramine (0.293 g, 1.13 mmol) and ammonium formate (0.71 g, 11.31 mmol) in methanol (9 ml) was boiled with palladium–charcoal (0.36 g) under nitrogen for 3 h. The hot solution was filtered, the residue washed with hot methanol, and the combined filtrate evaporated to dryness. The residue was purified by preparative layer chromatography on silica gel. Development with chloroform–methanol–ammonia (*d* 0.880) (40:20:1), extraction of the base from the appropriate band with hydrochloric acid, and recovery by basification and extraction with chloroform gave (±)-isonitramine (78 mg, 41%) as crystals, m.p. 100.5—103 °C (lit.,[13] m.p. 101—103 °C) (Found: M^+, 169.1469. $C_{10}H_{19}NO$ requires *M*, 169.1467); δ_H(250 MHz, $CDCl_3$) 0.88—1.76 (m, 10 H, 5 × CH_2), 1.95—2.14 (m, 1 H), 2.22 (d, 1 H, *J* 13.9 Hz), 2.52 (d, 1 H, *J* 11.3 Hz, 1-H), 2.61 (m, 1 H), 2.93 (d, 1 H, *J* 11.3 Hz, 1-H), 2.99—3.06 (m, 1 H, 3-H), 3.64 (dd, 1 H, *J* 10.8, 3.6 Hz, 7-H), and 3.72 (br s, 2 H, NH and OH); δ_C(62.9 MHz, $CDCl_3$) 20.36, 23.16, 24.33, 28.84, 29.83 (5 × CH_2), 36.31 (spiro C), 36.64 (CH_2), 47.32 (3-CH_2), 60.71 (1-CH_2), and 80.38 (1-CH).

In a larger scale experiment using 1.54 g of of *N*-benzylisonitramine, the crude product was purified by dry column flash chromatography and gave isonitramine (0.96 g, 95%), m.p. 100—102 °C.

(±)-*Nitramine* (**1**; R = H).—This was prepared from *N*-benzylnitramine (0.219 g) as described above for isonitramine. Purification of the crude product by preparative layer chromatography gave (±)-nitramine (43 mg, 31%) as a colourless oil (Found: M^+, 169.1468. $C_{10}H_{19}NO$ requires *M*, 169.1467); δ_H(250 MHz, $CDCl_3$) 0.88—2.20 (m, 12 H), 2.41 (d, 1 H, *J* 11.9 Hz, 1-H), 2.63 (m, 1 H), 2.96—3.04 (m, 1 H), 3.46 (d, 1 H, *J* 11.9 Hz, 1-H), 3.55 (dd, 1 H, *J* 10.0, 4.3 Hz, 7-H), and 3.79 (br s, 2 H, NH and OH); δ_C(62.9 MHz, $CDCl_3$) 21.12, 23.52, 24.16, 32.40 (4 × CH_2), 36.04 (spiro C), 36.86, 38.11 (2 × CH_2), 46.83 (3-CH_2), 52.32 (1-CH_2), and 78.09 (7-CH).

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