UvA-DARE (Digital Academic Repository)

Biomimetic synthesis of Nitraramine

Wanner, M.J.; Koomen, G.J.

DOI

[10.1021/jo00122a052](https://doi.org/10.1021/jo00122a052)

Publication date

1995

Published in

Journal of Organic Chemistry

[Link to publication](#)

Citation for published version (APA):

Wanner, M. J., & Koomen, G. J. (1995). Biomimetic synthesis of Nitraramine. *Journal of Organic Chemistry*, 60, 5634. <https://doi.org/10.1021/jo00122a052>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Biomimetic Synthesis of Nitraramine

Martin J. Wanner and Gerrit-Jan Koomen*

Amsterdam Institute of Molecular Studies, Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Received March 7, 1995*

The synthesis of a possible biosynthetic precursor (9) of nitraramine (1) is described, utilizing *N*-Boc-piperidone as an equivalent of didehydropiperidine 4. Heating this reactive, achiral intermediate 9 in aqueous solution results in the stereoselective formation of natural nitraramine via three successive cyclization reactions. Since nitraramine and several other *Nitraria* alkaloids are obtained from *Nitraria* species in racemic form, this synthesis provides additional support for our hypothesis of non-enzyme-catalyzed formation of these alkaloids.

Alkaloids containing a 3-spiropiperidine structural unit are exclusively obtained from plants of the *Nitraria* genus. The *Nitraria* spiroalkaloids that contain 10 carbon atoms such as nitramine (2) and isonitramine (3) are most likely biogenetically derived from two piperidine synthons.^{1,2} Nitraramine (1) was isolated in 1975 from *Nitraria schoberi*,³ and the unusual structure of this considerably more complicated alkaloid was established by X-ray analysis in 1985.⁴ Nitraramine is a 15 carbon-atom-containing spiroalkaloid and is probably derived from three piperidine equivalents. Three boat-formed rings in the center of the molecule form an oxazabicyclooctane ring system, which is surrounded by three chair-formed six-membered rings, thus creating a completely rigid structure.

Remarkable is the racemic form in which nitraramine and several other *Nitraria* alkaloids occur in nature. In a recent publication⁵ Heathcock and co-workers synthesized petrosin, a racemic bisquinolizidone sponge alkaloid containing eight stereocenters. They nicely demonstrated that postbiosynthetic equilibrations are responsible for the racemic form in which petrosin is isolated from its natural source. Nitraramine (1), however, is a

configurationally stable molecule⁶ and racemization via retroreactions is unlikely. Racemization experiments with enantiomerically pure material should give additional information in this respect; however, separation of nitraramine into enantiomers was unsuccessful until now.⁷ After some earlier synthetic approaches² we describe here a synthesis that is based on the retrobiogenetic analysis we recently proposed¹ and we will show that three successive cyclization reactions smoothly take place, once the reactive precursor anticipated is obtained. The ease with which this process occurs chemically (water, reflux) combined with the racemic form of natural nitraramine give an indication that no enzymes are involved in the stereochemically important spirocyclization reaction (Scheme 4). Another example of imine/enamine based cyclization reactions of achiral precursors in aqueous solution was recently provided by our biomimetic synthesis⁸ of the indole alkaloids nitrarine and nitramine, also obtained as racemates from *Nitraria* plants.

Biogenetic Hypothesis. Distinction should be made between the biosynthetic origin of these *Nitraria* alkaloids and for instance histrionicotoxine, which contains a 2-spiropiperidine ring system. A clear relationship exists between the Lupine alkaloids and those of the *Nitraria* family¹ (Scheme 1). Labeling studies⁹ in Lupine species have established dipiperidine 5 (tetrahydroanabasine) as the biogenetic precursor for piperidine alkaloids such as lupinine and sparteine. Although lysine, via cadaverine, is shown to be the precursor of 5, the existence of the instable didehydropiperidine 4¹⁰ as an intermediate has not been confirmed. An alternative ring opening of the saturated piperidinerings in 5 leads to 6, providing aldehyde 7 after oxidative deamination. An indication for this ring opening reaction is found in aqueous solutions of synthetic 5¹¹ (dihydrobromide), showing the presence of about 30% of the open form 6 according to ¹H-NMR spectroscopy. Condensation of 7 with the enamine form of didehydropiperidine 4 gives precursor 8, which is probably in equilibrium with the

(6) Nitraramine is for instance stable in 40% H₂SO₄ up to 80 °C during 10 h: Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1986**, 730. *Chem. Nat. Compd. (Engl. Transl.)* **1986**, 680.

(7) We attempted resolution of nitraramine by crystallization with 1 and 2 equivs of the following reagents: (S)-(+)-mandelic acid; (1R)-(-)-10-camphorsulfonic acid; (R)-(-)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.

(8) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1994**, 59, 7479.

(9) Golebiewski, W. M.; Spenser, I. D. *Can. J. Chem.* **1985**, 63, 2707.

(10) Didehydropiperidine 4 can be prepared in situ from its crystalline, symmetrical trimer α -tripiperidine: Schöpf, C.; Komzak, A.; Braun, F.; Jacobi, E.; *Chem. Ber.* **1951**, 84, 698.

(11) For an efficient synthesis of crystalline 5 see Schöpf, C.; Braun, F.; Koop, H.; Werner, G. *Liebigs Annalen* **1962**, 658, 157.

* Abstract published in *Advance ACS Abstracts*, July 15, 1995.

(1) For a review on *Nitraria* alkaloids see: Wanner, M. J.; Koomen, G. J. Stereoselectivity in Synthesis and Biosynthesis of Lupine and *Nitraria* Alkaloids. In *Studies in Natural Products Chemistry 14*; Attar-Rahman, Ed.; Elsevier: Amsterdam, 1994, p 731-768.

(2) Wanner, M. J.; Koomen, G. J. *Tetrahedron* **1992**, 48, 3935.

(3) Novgorodova, N. Yu.; Maekh, S. Kh.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1975**, 435. *Chem. Nat. Compd. (Engl. Transl.)* **1975**, 455.

(4) Tashkodzhaev, B.; Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1985**, 692; *Chem. Nat. Compd. (Engl. Transl.)* **1985**, 649.

(5) Scott, R. W.; Epperson, J. R.; Heathcock, C. H. *J. Am. Chem. Soc.* **1994**, 116, 8853.

Scheme 4

15 could not be accomplished. $NaBH_4$ in methanol, which is suitable for most *N*-Boc-piperidone reductions⁸ worked well for the saturated lactam part of **15**, but resulted in complete overreduction of the α,β -unsaturated lactam to form the corresponding ring opened allylic alcohol **17**. Among the more selective reducing agents lithium triethylborohydride is superior for reductions of *N*-acyl lactams.¹⁵ In our situation both lactam carbonyls of **15** were reduced, leading to the unstable precursor **16** in moderate yield. It should be noted that after aqueous workup the unsaturated hydroxypiperidine ring preferred the conjugated aldehyde form. 1,4-Reduction of the unsaturated lactam moiety followed by 1,2-reduction to form **18** lowered the yield. Acid-catalyzed removal of the Boc-substituents in **16** was performed with TFA in dichloromethane, leading to symmetrical dimer **9**¹⁶ probably via elimination of water from **8** as is shown in Scheme 1.

Cyclization reactions with **9** (Scheme 4) were performed at reflux temperature in buffered aqueous solutions at pH 7, leading directly to nitraramine as the only isomer. Spirocyclization of **8** completes the carbon-framework, and via cyclohexane ring-inversion of **21** the required 1,3-diaxial conformation for the two final acetal-forming steps is obtained. Although stereoisomerism is possible, especially at C1, none of these compounds was observed in ¹H NMR spectra of crude reaction mixtures. It should be noted that 1-*epi*-nitraramine was recently isolated from *Nitraria billardieri* by Quirion¹⁷ et al. The moderate yield of the last step may be caused by a cleavage reaction, which actually represents a reversion of the proposed biosynthesis. A literature example of such a hydrolytic ene-imine cleavage reaction can be found in the biomimetic deethylation of geissoschizine derivative **22** to **23** as described by Lounasmaa et al.¹⁸ (Scheme 5).

Scheme 5

Identification of nitraramine was possible by comparison of ¹H and ¹³C NMR spectra with data from the literature.^{17,19} Extensive 2D NMR-spectroscopy was performed on both nitraramine and its mono-hydrochloride, resulting in a partial revision of the literature chemical shift assignments.

In summary, it was demonstrated that water at neutral pH is an effective catalyst for biomimetic cyclization reactions with the imines and enamines that might be present in *Nitraria* species. Synthesis of the appropriate precursors, which *in vivo* would require several redox-enzymes, was accomplished with *N*-Boc-piperidone as a dihydro-piperidine equivalent.

Experimental Section

General Information. NMR spectra were obtained from a 400 MHz Bruker spectrometer. Thin layer chromatography (TLC) was performed on silica gel-coated plastic sheets. Chromatography refers to flash chromatography on silica gel (0.030–0.075 mm). When ammonia-containing eluents were used, the silica gel was pretreated with this eluent.

3-(2-Piperidinyl)-2,3-dihydropiperidine Dihydrobromide (5) and 1-Amino-5-(1,2-dihydropiperidin-3-ylidene)pentane (6). Crystalline 5·2HBr (tetrahydroanabasine, hydrate) was prepared from dihydropiperidine **4**¹⁰ as described by Schöpf et al.¹¹ ¹H NMR (DMSO-*d*₆ + 2 drops of D₂O) **5**: δ 4.8 (m), 3.46 (m, 4H), 3.1 (m, 2H), 2.15–1.4 (m, 10H). **6**: δ 8.58 (s, 1H), 7.0 (m, *J* = 7.4 Hz, 1H), 3.62 (t, *J* = 5.3 Hz, 2H), 2.49 (t, *J* = 6.2 Hz, 2H), 2.39 (dt, *J* = 7.1 Hz, 2H), 1.9–1.3 (m, 4H).

5,5-Diethoxypentanal (10a). A solution of glutaric aldehyde (25% in water, 150 mL, 0.385 mol) in EtOH (1.5 L, 99%) was stirred with Dowex 50WX8 (H⁺-form, 2.0 g) at 20 °C during 4 days. The catalyst was removed by filtration, and the resulting solution was stirred with solid NaHCO₃ during 30 min, filtered, and evaporated in vacuo. The residue was coevaporated with ethyl acetate (2 × 100 mL) and with PE 60/80 (100 mL), dissolved in PE 60/80 (200 mL), and separated by chromatography on silica (Φ 10 cm, PE 60/80/EtOAc 3/1; TLC-spots were made visible with anisaldehyde/sulfuric acid). A mixture of diacetals (open and cyclic) was eluted first, followed by monoacetal **10a**, which was obtained in pure form by distillation (8.9 g, 51.1 mmol, 13%): Bp 42–45 °C/0.6 mbar; ¹H NMR (CDCl₃)²⁰ δ 9.76 (t, *J* = 1.4 Hz, 1H), 4.48 (t, *J* = 5.2 Hz, 1H), 3.7–3.4 (m, 4H), 2.47 (dt, *J* = 1.4 Hz, *J* = 7.0 Hz, 2H), 1.74–1.61 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (CDCl₃)²⁰ δ 202.28, 102.51, 61.15, 43.52, 32.91, 17.34, 15.26; IR (CHCl₃) 1720 cm⁻¹.

1,1-Diethoxy-5-[*N*-(*tert*-butoxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (13). *N*-(*tert*-Butoxycarbonyl)-2-piperidinone (**12**)¹³ (7.96 g, 40 mmol, crystallized from hexanes at –20 °C) was added to a solution of LDA (44 mmol) in THF (120 mL) at –78 °C. The reaction mixture was allowed to warm to –20 °C, stirred at this temperature during 1 h, and cooled to –78 °C. Aldehyde **10a** (6.96 g, 40 mmol) was added dropwise, and the mixture was stirred at this temperature for

(15) (a) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447. (b) Pedregal, C.; Ezquerro, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053.

(16) Ene-imine **9** was only stable in solution and could be observed by NMR in the form of its TFA-salt; see Experimental Section.

(17) We wish to thank Dr. J.-C. Quirion for sending us spectra of nitraramine and 1-*epi*-nitraramine. Shen, M. Y.; Zuanazzi, J. A.; Kan, C.; Quirion, J.-C.; Husson, H.-P.; Bick, I. R. C. Alkaloids from *Nitraria billardieri*: *Nat. Prod. Lett.* **1995**, *6*, 119.

(18) Lounasmaa, M.; Jokela, R.; Halonen, M.; Miettinen, J. *Heterocycles* **1993**, *36*, 2523.

(19) Ibragimov, A. A.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1988**, *82*. *Chem. Nat. Compd. (Engl. Transl.)* **1988**, *71*.

(20) Traces of acid in the CDCl₃ are removed by filtration over basic Al₂O₃.

1 h and quenched with saturated NH_4Cl solution. Extractive workup (ether) yielded the crude alcohol, which was dissolved in a mixture of dry toluene (50 mL) and triethylamine (8.3 mL, 60 mmol). Methanesulfonyl chloride (3.5 mL, 45 mmol) was added dropwise at 0 °C, and the mixture was allowed to warm to room temperature. Additional triethylamine (13.8 mL, 100 mmol) was added and the mixture was refluxed during 6 h. Aqueous workup and chromatographic separation (PE 60/80/EtOAc 3/1) gave first impure **13** *Z*-isomer (0.6 g, 4%) and next **13** *E*-isomer (8.75 g, 62%) both as a syrup. *Z*-isomer: ^1H NMR (CDCl_3) δ 5.82 (t, J = 7.1 Hz); *E*-isomer: ^1H NMR (CDCl_3) δ 6.89 (m, J = 7.5 Hz), 4.41 (t, J = 5.4 Hz, 1H), 3.64–3.39 (m, 6H), 2.40 (m, 2H), 2.10 (q, J = 6.4 Hz, 2H), 1.80 (m, J = 5.4 Hz, 2H), 1.56 (m, 2H), 1.48 (s, 9H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl_3) δ 167.1, 153.2, 142.2, 130.1, 102.6, 82.65, 61.02, 45.77, 33.21, 28.06, 27.99, 24.30, 23.60, 22.22, 15.27; IR (CHCl_3) 1755, 1705, 1620 cm^{-1} ; HRMS (FAB) obs mass 378.2180 (MNa^+), calcd for $\text{C}_{19}\text{H}_{33}\text{NO}_5$ 378.2383; obs mass 356.2400 (MH^+), calcd for $\text{C}_{19}\text{H}_{34}\text{NO}_5$ 356.2503.

5-[*N*-(*tert*-Butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentanal (14). Acetal **13** (3.55 g, 10 mmol) was stirred with PPTS (0.12 g) in a mixture of water (5 mL) and acetone (150 mL) at 20 °C during 4 days. The reaction mixture was partitioned between PE 60/80 (200 mL) and dilute NaCl solution (100 mL) to remove the catalyst. Extraction and drying yielded **14** (2.8 g, 100%), which was pure enough for further transformations. ^1H NMR (CDCl_3) δ 9.72 (t, J = 1.5 Hz, 1H), 6.86 (m, J = 5.5 Hz, 1H), 3.64 (m, 2H), 2.43 (m, 4H), 2.13 (q, J = 7.5 Hz, 2H), 1.88–1.71 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (CDCl_3) δ 201.8, 165.1, 153.1, 140.8, 130.9, 82.79, 45.80, 43.07, 27.99, 27.39, 24.33, 22.17, 20.77; IR (CHCl_3) 1755, 1720, 1700, 1620 cm^{-1} ; HRMS obs mass 281.1649, calcd for $\text{C}_{15}\text{H}_{23}\text{O}_4\text{N}$ 281.1570.

1-[*N*-(*tert*-Butyloxycarbonyl)-2-oxopiperidin-3-yl]-5-hydroxy-5-[*N*-(*tert*-butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (15). A solution of the lithium enolate of *N*-(*tert*-butoxycarbonyl)-2-piperidinone (**12**) (2.2 mmol) in THF was prepared as described for **11a**. A solution of aldehyde **14** (0.56 g, 2 mmol) in THF was added at –78 °C, and the reaction mixture was stirred at this temperature during 2 h. Extractive workup (NH_4Cl , ether) and chromatography (EtOAc/PE 60/80 2/1) gave **15** (0.67 g, 70%) as a mixture of isomers: ^1H NMR (CDCl_3) δ 6.90 (m, 1H), 4.1 (b, 1H), 3.76 (m, 1H), 3.7–3.46 (m, 3H), 2.5–1.5 (m), 1.48 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (CDCl_3) δ 174.9, 173.8, 165.2, 153.2, 151.9, 142.1, 141.9, 130.2, 83.18, 82.58, 71.48, 70.22, 48.79, 45.76, 45.45, 45.08, 33.19, 32.57, 28.36, 28.10, 27.93, 25.11, 24.33, 23.94, 22.78, 22.29, 21.97, 21.69, 19.87; IR (CHCl_3) 3500 (br), 1757, 1680–1720, 1620 cm^{-1} ; HRMS (FAB) obs mass 503.2649 (MNa^+), calcd for $\text{C}_{25}\text{H}_{40}\text{N}_2\text{O}_7\text{Na}$ 503.2816; obs mass 481.2825 (MH^+), calcd for $\text{C}_{25}\text{H}_{41}\text{N}_2\text{O}_7$ 481.3010.

1,5-Bis[*N*-(*tert*-butyloxycarbonyl)-2-oxopiperidin-3-ylidene]pentane (19). Alcohol **15** (48 mg, 0.1 mmol) was eliminated with triethylamine and methanesulfonyl chloride as described for compound **13** yielding **19** *Z,E*-isomer (2 mg, 4%) and **19** *E,E*-isomer (36 mg, 78%). **19** *Z,E*-isomer: ^1H NMR (CDCl_3) δ 6.93 (m, 1H), 5.84 (m, 1H), 3.66 (m, 4H), 2.59 (m, 2H), 2.15 (m, 2H), 2.45 (m, 4H), 1.85 (m, 4H), 1.6 (m, 2H), 1.533 (s, 9H), 1.531 (s, 9H); **19** *E,E*-isomer: ^1H NMR (CDCl_3) δ 6.91 (s, 2H), 3.66 (m, 4H), 2.42 (m, 4H), 2.14 (m, 4H), 1.84 (m, 4H), 1.61 (m, 2H), 1.52 (m, 18H); ^{13}C NMR (CDCl_3) δ 165.1, 153.2, 141.3, 130.6, 82.71, 45.77, 28.04, 27.46, 27.08, 24.41, 22.28; IR (CHCl_3) 1755, 1705, 1620 cm^{-1} ; HRMS no M^+ observed.

Reduction of 15 with NaBH_4 . Excess sodium borohydride was added in portions to a solution of **15** (0.12 g, 0.25 mmol) in MeOH (5 mL) at 40–50 °C over a period of 4 h. Aqueous workup and chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOH}$ 93/7) gave **17** (0.072 g, 60%) as a mixture of isomers: ^1H NMR (CDCl_3) δ 5.42 (t, J = 7.1 Hz, 1H), 4.8 (b, 2H), 3.99 (bs, 2H), 3.9–3.4 (b, 7H), 1.41 (s, 18H); IR (CHCl_3) 3550–3200 (br), 3450, 1700, 1690 cm^{-1} ; HRMS (FAB) no M^+ observed.

Reduction of 15 to 16 with Lithium Triethylborohydride. Lithium triethylborohydride (3.8 mL of a 1 M solution in THF, 3.8 mmol) was added dropwise to a solution of **15** (0.74 g, 1.55 mmol) in THF (15 mL) at –78 °C. After a total reaction time of 2.5 h the reaction was quenched with acetic acid (0.2 mL). Aqueous NaHCO_3 workup, extraction with ethyl acetate,

and chromatography using $\text{CH}_2\text{Cl}_2/\text{EtOH}$ 93/7 as eluent yielded **16** (0.25 g, 33%) as a syrup. ^1H NMR (CDCl_3) δ 9.34 (s, 1H), 6.51 (t, J = 7.3 Hz, 1H), 5.67 (bs, 1H), 4.81 (b, 1H), 3.8–3.0 (m, 7H), 2.39 (m, 2H), 2.56 (m, 2H), 2.0–1.2 (m, 8H), 1.46–1.42 (4 x s, 18H); ^{13}C NMR (CDCl_3) δ 195.0, 155.8, 154.9, 142.8, 79.9, 73.32, 72.82; IR (CHCl_3) 3600–3200 (br) 1685, 1670 cm^{-1} ; HRMS (FAB) no M^+ observed.

Acidic Hydrolysis of 16 and Cyclization to Nitraramine. Trifluoroacetic acid (0.5 mL) was added in one portion to an ice-cold solution of **16** (0.11 g, 0.22 mmol) in CH_2Cl_2 (1 mL). After 15 min at 0 °C the mixture was stirred at room temperature for 30 min and evaporated in vacuo (bath T < 25 °C). The oily residue (**9** TFA salt) was dissolved in CDCl_3 by the addition of CD_3OD (2 drops): ^1H NMR (CDCl_3) δ 8.43 (bs, 2H), 6.87 (bt, 2H), 3.65 (m, 4H), 2.50 (m, 4H), 2.42 (m, 4H), 1.98 (m, 4H), 1.74 (m, 2H); ^{13}C NMR (CDCl_3) δ 169.2, 129.8, 43.86, 29.10, 25.53, 20.68, 18.78. This bis-iminium salt was not stable enough for further analysis and was evaporated directly after the acid-treatment and dissolved in a pH 7 phosphate buffer (20 mL). The resulting solution was refluxed under nitrogen during 20 h, made alkaline with excess solid sodium carbonate, and extracted three times with ethyl acetate. The organic layer was dried (Na_2SO_4), and removal of the solvents gave a crude alkaloid mixture, (15–30 mg) containing ca. 50% nitraramine. Chromatography ($\text{CH}_2\text{Cl}_2/\text{methanol}/\text{NH}_4\text{OH}$ 90/10/1) gave nitraramine **1** (17–22%) as a glass. An analytical pure sample was prepared from the easily crystallizing monohydrochloride. A solution of nitraramine in ethanol was treated with concd HCl. The solvents and the excess of HCl were removed by coevaporation with methanol, and the dihydrochloride was dissolved in ethanol and treated with a small excess of triethylamine. Evaporation and crystallization from $\text{CH}_2\text{Cl}_2/\text{ethyl acetate}$ produced triethylamine hydrochloride, which was removed by filtration. The filtrate was evaporated to dryness and nitraramine hydrochloride crystallized from a small amount of ethanol by precipitation with ethyl acetate. The free base was obtained in pure form by treatment of nitraramine hydrochloride with aqueous K_2CO_3 followed by ether extraction. **Nitraramine (1):** ^1H NMR (CDCl_3) δ 4.43 (m, 1H, H-7), 4.07 (d, J = 2.5 Hz, 1H, H-17), 3.34 (s, 1H, H-1), 3.11–3.07 (m, H-3eq), 3.07–3.04 (m, 1H, H-15eq), 2.79–2.71 (m, H-15ax), 2.69–2.61 (m, H-3ax), 2.19–2.14 (m, J_{gem} = 13.8 Hz, H-5eq), 2.01 (m, H-12), 1.9–1.45 (m, 7H), 1.44–1.32 (m, 3H, 2H-4, H-9ax), 1.26–1.23 (m, H-10), 1.17 (m, H-11), 1.11–1.01 (m, 2H, H-14ax, H-5ax); ^{13}C NMR (CDCl_3) δ 82.30 (C-17), 75.95 (C-1), 66.54 (C-7), 50.50 (C-15), 45.35 (C-3), 38.84 (C-11), 37.99 (C-12), 32.37 (C-6), 30.55 (C-5), 28.50 (C-8), 25.22 (C-13), 24.12 (C-10), 21.94 (C-4), 15.40 (C-9) 14.61 (C-14); MS m/z (%) 248 (100), 219 (18), 204 (30), 190 (13), 176 (15), 162 (18), 150 (35); HRMS obs mass 248.1899, calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$ 248.1857. **Nitraramine monohydrochloride:** mp: 223–225 °C; ^1H NMR (D_2O) δ 4.34 (m, 1H, H-7), 4.23 (d, 1H, J = 2.5 Hz, H-17), 4.18 (s, 1H, H-1), 3.38–3.33 (m, 1H, J_{gem} = 12.9 Hz, H-3eq), 3.12–3.07 (m, 1H, H-15eq), 3.11–3.04 (m, 1H, H-3ax), 2.83–2.77 (m, 1H, H-15ax), 2.36–2.31 (m, J_{gem} = 14.5 Hz, H-5eq), 2.19–2.16 (m, 1H, H-12), 1.85–1.6 (m, 9H), 1.51–1.48 (m, 2H, H-11), 1.44–1.36 (m, 1H, H-5ax), 1.4–1.35 (m, 1H, H-10), 1.3–1.2 (m, 1H, H-14ax); ^{13}C NMR (D_2O) δ 84.20, 77.74, 69.45, 52.90, 46.02, 39.85, 39.47, 35.22, 30.07, 29.80, 26.98, 25.63, 20.17, 16.73, 16.54; MS m/z (%) 248 (100), 231 (5), 220 (8), 204 (28), 162 (20), 150 (31); HRMS obs mass 248.1909, calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$ 248.1857. **Nitraramine dihydrochloride:** ^1H NMR (D_2O) δ 4.79 (d, J = 2.5 Hz, H-17), 4.63 (s, 1H, H-1), 4.45 (m, 1H, H-17), 3.59–3.41 (m, 2H, H-3eq, H-15eq), 3.21–3.13 (m, 2H, H-3ax, H-15ax), 2.38 (m, 1H, H-12), 2.39–2.33 (m, 1H), 1.85–1.35 (m, 14H); ^{13}C NMR (D_2O) δ 85.55, 75.05, 70.42, 54.14, 47.80, 38.39, 37.96, 35.27, 29.26, 28.28, 26.70, 25.43, 19.78, 16.39, 16.01.

Supporting Information Available: Copies of the 1D and 2D NMR spectra of nitraramine **1** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.