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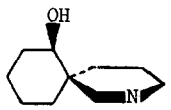
SYNTHESIS OF THE SPIROCYCLIC ALKALOID NITRAMINE

Lars H. Hellberg*, Craig Beeson
Department of Chemistry
San Diego State University
San Diego, CA 92182

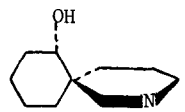
Ratnasamy Somanathan*
Centro de Graduados
Instituto Tecnologico de Tijuana
Tijuana, B.C., Mexico

Summary: The alkaloid nitramine was prepared in a four operation process using reductive cyclization of a γ-cyano ester to a spirolactam as a key step.

Recently three interesting spirocyclic alkaloids, nitramine (1), isonitramine (2) and sibirine (3), were isolated from Nitratria schoberi[1a,b] and Nitraria sibirica[1c], respectively. These Nitraria alkaloids are members of a class of alkaloids including histrionicotoxin[2] and the Erythrina alkaloids[3a], many of which exhibit marked neurophysiological activity[3b]. Also, many synthetically derived azaspiro [5.5]undecanes and [4.5]decanes exhibit various degrees of biological activities[4].



(1)



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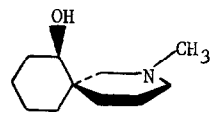
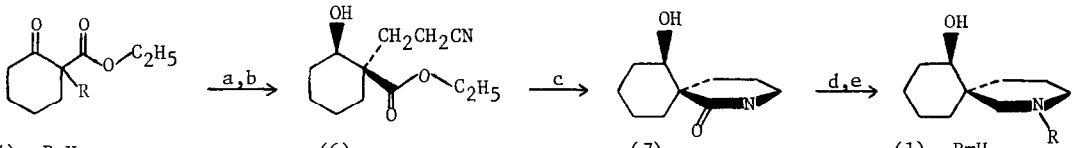


(3)

Due to their potential for biological activity, we embarked on the total synthesis of the above three Nitraria alkaloids. Two synthetic routes have appeared, one an eleven step sequence that includes a stereospecific cycloaddition of a nitrile oxide enroute to isonitramine (2)[5], the other involving a nitrone cycloaddition leading to nitramine (1) in eight steps[6].

Here we report a simple route of five steps (four operations) to nitramine (1). The readily available keto ester 4 was subjected to Michael addition with acrylonitrile[7] and subsequently reduced with $NaBH_4$[8,9] to give the alcohol 6 in a 66% yield overall. Reduction of the nitrile led to the amine, spontaneous ring closure of which gave the lactam (7)[10] in a 59% yield. The lactam was reduced with $LiAlH_4$ to give nitramine (1) in a 74% yield[11].

Methylation of 1 gave the N-methyl derivative (8)[12] whose proton NMR spectrum is consistent with the published proton NMR spectrum for N-methyl-nitramine[1b]. N-Methyl-isonitramine can be characterized by a triplet of a doublet at δ2.51 in its proton NMR spectrum due to the equatorial C-1 proton[1b]. The absence of this signal in the proton NMR spectrum of the N-methyl derivative 8 suggests that, if isonitramine (2) (ultimately arising from the epimer of 6) were present in our 1, it must represent less than 5% of the product (based on the sensitivity of the NMR spectrometer, a Magnachem A-200).



(4), R=H
(5), R=CH_2CH_2CN

(6)

(7)

(1), R=H
(8), R=CH_3

a. CH_2CHCN, KOH/CH_3CN, 11 hrs, 85%; b. $NaBH_4$, CH_3OH, 0° C/4 hrs., 78%; c. H_2/PtO_2, CH_3CH_2OH, 60° C/4 hrs., 59%; d. $LiAlH_4$, THF, 15 hrs., 74%; e. CH_3I, CH_3CN, 24 hrs., 91%.

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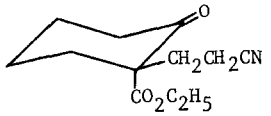
8. Reduction yields predominantly (>95%) 6, arising from the expected axial approach of the hydride to 5; its conformation is suggested by A values and minimization of dipole-dipole interactions.



9. F. Nerdel, D. Frank and G. Barth, Chem. Ber., 102, 395 (1969). We thank the referee for pointing out this reference to an earlier example of stereoselectivity with $NaBH_4$; we are trying to use $Al(O\text{-}iPr)_3$ mentioned in this paper to obtain the hydroxy epimer of 6 and thus attempt a synthesis of isonitramine.

10. The spirolactam (7) was isolated as white crystals, m.p. 118-121°C. IR (KBr)ν_{max} (cm^{-1}): 3340-3040 (-OH, -NH), 1640 (C=O). 90 MHz ^{1}H-NMR: δ6.1, (1H, br, -CONH-), 5.4 (1H, br, -OH-), 3.6 (1H, m, -CHOH-), 3.2 (2H, m, $-CONHCH_2-$), 2.1 -1.3 (10H, m, $-CH_2-$). ^{13}C-NMR ($CDCl_3$): δ179.4 (-CONH-), 71.6 (-CHOH-), 43.4, 42.1, 28.0, 27.3, 19.7, 18.9, 18.5.

11. The spectra of isolated 1 agree with published spectra[1b]. The ^{1}C and ^{13}C NMR spectra compare favorably with photocopies of the same spectra kindly supplied by Professor B. Snider[6], for which we thank him. 200 MHz 1H-NMR ($CDCl_3$): δ3.38(2H, br, -NH, -OH), 3.48 (1H, m, H-7a), 2.98 (2H, m, H-3e, H-1e), 2.62 (1H, dt, J = 11.1, 11.1, 3.3 Hz, H-3a), 2.41 (1H, d, J = 11.5 Hz, H-1a), 2.1-0.9 (12H, m, $-CH_2-$). ^{13}C-NMR ($CDCl_3$): δ78.3, 52.3, 46.9, 38.3, 36.9, 35.9, 32.4, 24.2, 23.7, 21.0.

12. The relevant 200 MHz ^{1}H NMR spectral data for 8 in $CDCl_3$ is: δ5.1 (1H, br, -OH-), 3.50 (1H, dd, J = 9.1 Hz, 4.0, H-7a), 3.15 (1H, d, J = 11.5 Hz, H-1e), 2.76 (1H, m, H-3e), 2.20.

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