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PYRROLIZIDINE SYNTHESIS BY INTRAMOLECULAR CYCLIZATION OF A SUBSTITUTED AZACYCLOOCTANE-4,5-OXIDE

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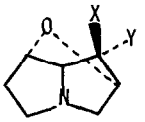
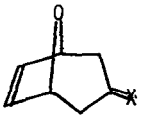
Pyrrolizidine alkaloids have been isolated from a variety of plant families.[1] In addition they have been found in several species of butterflies and moths[2] and in a millipede.[3] The pharmacology of these alkaloids has been studied extensively[1,4] and dangers to human health recognized.[4b,5] Recently, a number of synthetic results to the pyrrolizidine ring system (1-azabicyclo [3.3.0] octane) have been published.[6] A transannular route to this ring system has been communicated[7] and also used[8] in a synthesis of hemiloline 1a as described in the accompanying paper. In view of these results our related independent work is presented here.



1a, X = Y = H
b, X = H, Y = OH

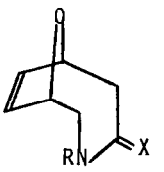
The method of Noyori et al.[9] was used to prepare 8-oxa-bicyclo [3.2.1] hept-6-en-3-one 2a. This ketone formed crystalline oxime 2b in 79% yield after purification: mp 113-114°C; IR



2a, X=O
b, X=NOH
c, X=NOTs

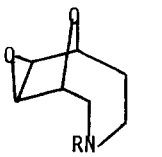
(KBr) 3306, 2951, 2901, 1540, 1406, 707 cm^{-1}; NMR ($CDCl_3$) δ 2.0-3.2 (m,4 H,CH_2), 4.87 (br d, J = 4 Hz; 2 H, OCH), 6.18 (s, 2 H, =CH), 9.17 (br, 1 H, =NOH); Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.32; H, 6.60; N, 10.18. Treatment of this oxime with p-toluenesulfonyl chloride in ether with powdered potassium hydroxide afforded crystalline

oxime tosylate 2c in 68% yield after purification: mp 104-105d°C; IR (KBr) 3068, 2962, 1596, 1351, 1183, 1170, 804 cm^{-1}; NMR ($CDCl_3$) δ 2.1-3.2 (m with s at 2.45, 7 H, CH_2, CH_3), 4.85 (br, 2 H, OCH), 6.10 (s, 2 H, =CH), 7.30 (d, J = 8 Hz, 2 H, ArH), 7.80 d, J = 8 Hz, 2 H, ArH); Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.43; H, 5.11; N, 4.74. Beckmann rearrangement of this oxime tosylate to crystalline lactam 3a in 98% yield: mp 133.5-134.5°C; IR (KBr) 3413 br, 3263, 3179, 3052, 2909, 1655, 1078, 826 cm^{-1};



3a, R=H, X=O
b, R=H, X=H_2
c, R=CF_3CO, X=H_2

NMR ($CDCl_3$) δ 2.3-2.9 (m, 4 H, CH_2), 4.83 (m, 2 H, OCH), 5.98 (d, J = 6 Hz, 1 H, =CH), 6.25 (d, J = 6 Hz, 1 H, =CH), 6.60 (br, 1 H, NH); Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.06. Found: C, 60.45; H, 6.55; N, 10.06, was conveniently carried out on a column of basic alumina.[10] The conversion of ketone 2a to lactam 3a could be accomplished most expeditiously without isolation of the intermediates in an overall yield of 73%. Reduction of lactam 3a with lithium aluminum hydride in ether gave amine 3b as an oil which was not purified but immediately treated with trifluoroacetic anhydride and anhydrous potassium carbonate to produced crystalline trifluoroacetamide 3c in 76% overall yield: mp 90-91.5°C; IR (KBr) 2932, 1666, 1140-1210 br, 1087, 1075 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (m, 2 H, CH_2), 2.9-4.7 (m, 4 H, NCH_2), 5.05 (m, 2 H, OCH), 5.87 (m, 2 H, =CH); Anal. Calcd for $C_9H_{10}NO_2F_3$: C, 48.87; H, 4.56. Found: C, 48.63; H, 4.51. Epoxidation of trifluoroacetamide 3c with m-chloroperoxybenzoic acid in methylene chloride gave crystalline epoxy amide 4a in 73% yield after purification:

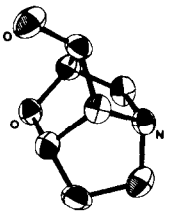


4a, R = CF_3CO
b, R = H

mp 95-97°C; IR (KBr) 2946, 1676, 1130-1200 br, 1116, 1088, 1076, 858, 844 cm^{-1}; NMR ($CDCl_3$) δ 2.0 (m, 2 H, CH_2), 2.8-4.9 (m, 8 H); Anal. Calcd for $C_9H_{10}NO_3F_3$: C, 45.58; H, 4.25. Found:

C, 45.74; H, 4.20. Epoxy amide 4a with potassium carbonate in aqueous methanol produced epoxy amine 4b as an oil. Epoxy amine 4b was not purified but transformed into crystalline hydroxy amine 1b by heating at reflux in ethanol in 60% overall yield after purification: mp 109-110°C; IR (KBr) 3300-2600 br, 2977, 2955, 2882, 1541, 1117, 1082, 1029 cm^{-1}; NMR ($CDCl_3$) δ 1.7-4.6 (m); MS m/e 141, 124, 95, 82 (base peak); Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.56; H, 7.73; N, 9.94. The cyclization of epoxy amine 4b, which is a substituted azacyclooctane-4,5-oxide, to hydroxy amine 1b is a transannular displacement on an epoxide by an amine which results in the formation of a pyrrolizidine. Interestingly, this cyclization which affords a strained oxygen-bridged pyrrolizidine occurs readily.

The structure of hydroxy amine 1b was unequivocally established by single crystal X-ray crystallographic analysis. Hydroxy amine 1b crystallizes in the orthorhombic space group $Pna2_1$ with a = 9.933(6), b = 7.305(10), c = 9.182(13) Å, Z = 4, d_{calcd} = 1.407, d_{obsd} = 1.404 g cm^{-3}. All nonhydrogen atoms were located using direct methods[11] and seven of the eleven hydrogen atoms were located by Fourier difference maps.[12] The positions of the remaining four hydrogen atoms were calculated. Full-matrix least-squares refinement[13] with the temperature factors of the nonhydrogen atoms varying anisotropically and those of the hydrogen atoms isotropic led to a conventional R factor of 0.043. A view of the molecule, without the hydrogen atoms, is shown below. This view clearly shows the distortion of the pyrrolizidine ring system.



ORTEP[14] drawing of hydroxy amine 1b. Thermal ellipsoids correspond to a 50% probability level.

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