ALKYL N-NITRO- AND N-NITROSOPIPERIDIN-2-YLCARBAMATES

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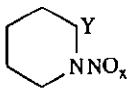
Abstract - N-Nitro- and N-nitrosopipecolic acid 1 and 6 were converted to 1-nitro- and 1-nitroso-2-aminopiperidine. The amines were isolated as methyl carbamate derivatives 4 and 11.

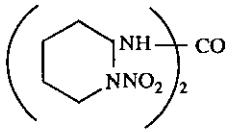
The conversions of N-nitro- 1 and N-nitrosopipecolic acid 6 gave the carbamate derivatives 4 and 11 of 1-nitro- and 1-nitroso-2-aminopiperidine. Previously two α-aminonitrosamines, isolated as ureas $R'N(NO)CH(R)NHCONH_2$, were known [1] and α-aminonitramines were unknown. The primary α-amino derivatives (masked or free) of nitramines or nitrosamines are needed for investigations on new preparations of cyclic and caged nitramines (energetic materials that are sought for explosives, propellants, and other energy storage systems).[2]

Treatment with triethyl amine and ethyl chloroformate followed by the addition of sodium azide[3] converted N-nitropipecolic acid 1 to the azide 2 that gave the isocyanate 3 quantitatively on thermolysis. The isocyanate reacted with methanol to give methyl N-(1-nitropiperidin-2-yl)carbamate 4 and with water to give N,N'-di-(1-nitropiperidin-2-yl)-urea 12. The carbamate 4 was also obtained in one operation when the acid 1 was treated with diphenyl phosphorazidate,[4] triethylamine, and methanol in benzene. A spontaneous elimination of ammonia from intermediate 1-nitro-2-aminopiperidine 5 presumably brought about the formation of 1-nitro-1,2,3,4-tetrahydropyridine 13 when the carbamate 4 was treated with trimethylsilyl iodide in methanol.[5]

The hydrazide 8 of N-nitrosopipecolic acid was readily obtained from the methyl ester 7 on treatment with hydrazine and was converted to the azide 9 in a reaction with nitrous acid. Thermolysis of the azide gave 1-nitrosopiperidin-2-yl isocyanate 10, an unstable compound that was immediately treated with methanol to give methyl N-(1-nitrosopiperidin-2-yl)carbamate 11. Attempted hydrolysis of the carbamate to 1-nitroso-2-aminopiperidine led instead to decomposition in agreement with the instability previously reported for α-aminodimethylnitrosamine and α-amino-N-nitrosopyrrolidine.[1] Treatment with triethylamine and ethyl chloroformate converted N-nitrosopipecolic acid 6 to 4,5,6,7-tetrahydro[1.2.3]oxadiazolo[3,4-*a*]pyridin-3-one 14. A similar dehydration and cyclization to the sydnone 14 occurred when the acid 6 was treated with diphenyl phosphorazidate. The expected formation of the isocyanate 10 was not detected.



(1) x = 2, Y = CO_2H
(2) x = 2, Y = CON_3
(3) x = 2, Y = NCO
(4) x = 2, Y = $NHCO_2Me$
(5) x = 2, Y = NH_2
(6) x = 1, Y = CO_2H
(7) x = 1, Y = CO_2Me
(8) x = 1, Y = CON_2H_3
(9) x = 1, Y = CON_3
(10) x = 1, Y = NCO
(11) x = 1, Y = $NHCO_2Me$



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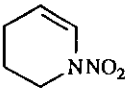

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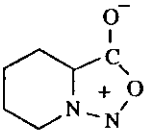

(14)

EXPERIMENTAL

Instruments included Pye-Unicam SP-200 (ir), Varian EM-360 (nmr), and Hatachi R MU-6 (ms). Elemental analyses were obtained from MicroTech Lab., Skokie, Illinois. Melting points were determined from a Thomas-Hoover mp apparatus and were uncorrected. Piperidine-2-carboxylic acid was commercially available. 1-Nitropiperidine-2-carboxylic acid 1,[6] 1-nitrosopiperidine-2-carboxylic acid 6,[7] methyl 1-nitrosopiperidine-2-carboxylate 7[8] were prepared by reported procedures.

1-Nitro-2-azidocarbonylpiperidine 2: To a solution of 1-nitropiperidine-2-carboxylic acid 1 (1.7 g, 0.01 mol) in acetone (20 ml), cooled to 0 °C, triethylamine (1.1 g, 0.011 mol) was slowly added followed by ethyl chloroformate (1.2 g, 10.0 mmol). The solution was stirred for 15 min. Sodium azide (1.3 g, 0.02 mol) in water (1.5 ml) was added and the reaction mixture was stirred at 0 °C for 30 min and poured onto crushed ice to obtain the azide 2 as a colorless solid (1.7 g, 75%), mp 62 °C (dec) after recrystallization from ether and petroleum ether; ν_{max} (KBr) 2215, 2150, 1710, 1515 and 1300 cm^{-1}; δ_H ($CDCl_3$) 5.3 (1H, m, NCH), 3.5 and 4.5 (2H, m, NCH_2), 1.2-2.2 (6H, m, CH_2). Slow decomposition at room temperature precluded elemental analysis.

1-Nitro-2-isocyanatopiperidine 3: The azide 2 (0.20 g, 1.0 mmol) was dissolved in benzene (20 ml) and heated at 80 °C for 1 h. The reaction was monitored by ir for the disappearance of azide absorption. The solvent was removed to leave the isocyanate 3 as a pale yellow liquid (0.17 g, 100%) that was extremely hygroscopic. Attempts to obtain a satisfactory elemental analysis were unsuccessful; ν_{max} (neat) 2260, 1540, 1295 cm^{-1}; δ_H ($CDC1_3$) 6.4 (1H, m, NCH), 3.3 and 4.4 (2H, m, NCH_2), 1.5-2.3 (6H, m, CH_2).

N,N′-(1-Nitropiperidin-2-yl)urea 12: The isocyanate 3 (0.17 g, 0.10 mmol) was treated with moist acetone (5 ml) and stirred at room temperature overnight. The solvents were removed and the residue was triturated with ether to give the urea 12 as a colorless solid (0.08 g, 51%), mp 198 °C (dec) (methanol); ν_{max} (KBr) 3300, 1650, 1550, 1300, 1280 cm^{-1}; δ_H (DMSO-d_6) 6.8 (2H, m, NCH), 6.3 (2H, m, NH), 4.3 and 3.3 (4H, m, NCH_2), 1.6 (12H, m, CH_2). Anal. Calcd for $C_{11}H_{20}N_6O_5$: C, 41.77; H, 6.32; N, 26.58. Found: C, 41.74; H, 6.30; N, 26.55.

Methyl N-(1-nitropiperidin-2-yl)carbamate 4: (a) The isocyanate 3 (0.17 g, 1.0 mmol) was heated at 60 °C in methanol (5 ml) for 4 h. The reaction mixture was cooled to room temperature and the carbamate 4 separated as a colorless solid (0.15 g, 65%), mp 115-116 °C (ether and petroleum ether); ν_{max} (KBr) 3300, 1725, 1690, 1540, 1300, 1280, 1255 cm^{-1}; δ_H ($CDCl_3$) 6.4 (1H, m, NCH), 5.8 (1H, m, NH), 4.4 and 3.3 (2H, m, NCH_2), 3.7 (3H, s, OCH_3), 1.8 (6H, m, CH_2). Anal. Calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.31; H, 6.39; N, 20.63. (b) A mixture of 1-nitropiperidine-2-carboxylic acid 1 (0.17 g, 1.0 mmol), diphenyl phosphorazidate (0.30 g, 1.1 mmol), triethylamine (0.102 g, 1.1 mmol) and methanol (1 ml) in benzene (10 ml) was stirred at 80 °C for 16 h. The solution was successively washed with aqueous citric acid (5%, 5 ml), water (5 ml), saturated sodium bicarbonate (5 ml) and saturated sodium chloride solution (5 ml) and dried (Na_2SO_4). Evaporation gave a colorless solid (0.11 g, 54%), mp 115-116 °C, identical in all respects with the product obtained in part (a).

Hydrolysis of the carbamate 4: To a solution of the carbamate 4 (1.0 g, 5.0 mmol) in chloroform (5 ml), trimethylsilyl iodide (1.1 g, 5.5 mmol) was added under a nitrogen atmosphere. The mixture was heated at 50-60 °C for 3 h. Methanol (0.5 ml) was added and the volatile components were removed under reduced pressure. The residue was passed through a short column of silica gel (benzene) to obtain 1-nitro-1,2,3,4-tetrahydropyridine 13 as a light brown liquid (0.13 g, 20%), that was further purified by chromatography (silica gel, benzene); ν_{max} (neat) 1645, 1515, 1325, 1305, 1295 cm^{-1}; δ_H ($CDCl_3$) 7.4 (1H, m, NCH=), 5.2 (1H, m, CH=CH), 4.1 (2H, m, NCH_2), 2.1 (4H, m, CH_2). Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86. Found: C, 47.14; H, 6.26; N, 21.18.

Hydrazide 8 of 1-nitrosopiperidine-2-carboxylic acid 6: To a solution of methyl 1-nitrosopiperidine-2-carboxylate 7 (1.72 g, 10.0 mmol) in methanol (20 ml) hydrazine hydrate (85%, 1.05 g, 20.0 mmol) was added and the mixture was heated at 65 °C for 2 h. The solvent was evaporated to give the hydrazide 8 as a viscous liquid. It was purified by chromatographic separation from a silica gel column (chloroform) (1.15 g, 60%); ν_{max} (neat) 3300, 1670, 1630, 1440 cm^{-1}; δ_H ($CDCl_3$) 7.7 (1H, br, NH), 5.6 (1H, m, NCH), 4.9 (1H, m, NCH_2), 3.9 (3H, br, NCH_2 and NH_2), 1.3-3.0 (6H, m, CH_2). Anal. Calcd for $C_6H_{12}N_4O_2$: C, 41.65; H, 6.98; N, 32.55. Found: C, 41.07; H, 7.05; N, 32.46.

1-Nitroso-2-azidocarbonylpiperidine 9: A solution of hydrazide 8 (1.72 g, 10.0 mmol) in hydrochloric acid (10%, 10 ml) was cooled at 0 °C and sodium nitrite (0.76 g, 11.0 mmol) in water (1.5 ml) was added. The reaction mixture was stirred at 0-5 °C for 1 h and poured onto crushed ice. Extraction with ether, drying (Na_2SO_4), removal of the solvent gave the azide 9 as a light yellow liquid (0.95 g, 52%). The azide slowly decomposed at room temperature and was used immediately; ν_{max} ($CHCl_3$) 2140, 1710, 1450 cm^{-1}; δ_H ($CDCl_3$) 5.6 (1H, m, NCH), 4.9 and 4.0 (2H, m, NCH_2), 1.2-3.0 (6H, m, CH_2).

1-Nitroso-2-isocyanatopiperidine 10: The azide 9 (0.18 g, 1.0 mmol) was dissolved in benzene (20 ml) and heated at 80 °C for 1 h. The reaction was monitored by ir for the disappearance of azide absorption. Solvent was removed to give the isocyanate 10 as an unstable yellow liquid (0.12 g, 70%); ν_{max} ($CHCl_3$) 2260, 1470, 1445 cm^{-1}; δ_H ($CDCl_3$) 6.4 (1H, m, NCH), 4.8 and 2.7 (2H, m, NCH_2), 1.4-2.3 (6H, m, CH_2).

Methyl N-(1-nitrosopiperidin-2-yl)carbamate 11: The azide 9 (0.18 g, 1.0 mmol) was dissolved in a mixture of benzene (5 ml) and methanol (5 ml) and heated at 80 °C for 2 h. Solvents were removed to leave the carbamate 11 as a light yellow gum (0.11 g, 50%), that decomposed upon attempted distillation at 145 °C (0.5 mm). It was purified by chromatographic separation from a silica gel column (ethyl acetate); ν_{max} (neat) 3320, 1720, 1450 cm^{-1}; δ_H (D_2O) 6.1 (1H, m, NCH), 4.4 and 3.2 (2H, m, NCH_2), 3.6 (3H, s, OCH_3), 1.6-2.2 (6H, m, CH_2). Anal. Calcd for $C_7H_{13}N_3O_3$: C, 44.91; H, 6.95; N, 22.45. Found: C, 44.78; H, 6.90; N, 22.21.

4,5,6,7-Tetrahydro-1,2,3-oxadiazolo[3,4-*a*]pyridin-3-one 14: To 1-nitrosopiperidine-2-carboxylic acid 6 (1.6 g, 10.0 mmol) in acetone (10 ml) cooled to 0 °C, triethylamine (1.1 g, 11.0 mmol) was added followed by ethyl chloroformate (1.2 g, 10.0 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and poured into ice water. The product 14 precipitated and was washed with ice water to give a colorless solid (1.4 g, 100%), mp 94-96 °C (hexane and ethyl acetate) (lit.[9] mp 104 °C); ν_{max} (KBr) 1760, 1740 cm^{-1}; δ_H ($CDCl_3$) 4.3 (2H, t, J = 6.0 Hz, CH_2), 2.6 (2H, t, J = 6.0 Hz, CH_2), 2.1 (4H, m, CH_2). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.43; H, 5.71; N, 20.00. Found: C, 51.32; H, 5.62; N, 20.63. Ei-ms (70 ev)(%): 140.2 (M^+) (28.8%), 82.0 (M^+ -CO and -NO)(100%).
Compound 14 (< 5%) was also obtained from the treatment of the acid 6 with diphenyl phosphorazidate.

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