A Novel Ring Closure and Amine Quaternization Under Eschweiler-Clarke Conditions

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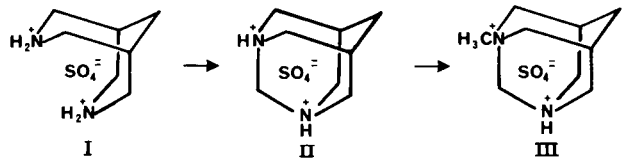
We wish to report the formation of a unique product, 1,3-diaza-adamantane methonium sulfate (III), from 3,7-diazabicyclo[3.3.1]nonane sulfate (I) under Eschweiler-Clarke reductive methylation conditions. This constitutes the first reported instance of ring closure between two secondary amino functions followed by quaternization, in formaldehyde-formic acid solution. Reports in the literature of ring formation between oxygen and nitrogen to produce oxazolidines under Eschweiler-Clarke conditions are available; however, none of these communications reported quaternized amine product (1,2).

In our case it was established by nmr that cyclization of 3,7-diazabicyclo[3.3.1]nonane (I) occurred initially to give the known 1,3-diaza-adamantane (II) which then quaternized (3).



I II III

EXPERIMENTAL (4)

1,3-Diaza-adamantane sulfate (II).

The amine was prepared according to the method of Stetter and coworkers (3) and characterized as the sulfate salt, m.p. 250-255° (gas); infrared (potassium bromide), 1100 ($SO_4^=$), and 2950 (C-H); nmr, 5.11 (singlet, N-CH_2-N), 3.91 (doublet, C-CH_2-N), 2.70 (broad singlet, -CH) 2.30 (triplet, C-CH_2-C).

Anal. Calcd. for $C_8H_{16}N_2O_4S$: C, 40.66; H, 6.82; N, 11.86. Found: C, 40.66; H, 7.07; N, 11.95.

1,3-Diaza-adamantane Methonium Sulfate (III).

To a solution containing 500 mg. (2.2 mmoles) of 3,7-diazabicyclo[3.3.1]nonane sulfate (5) dissolved in 25 ml. of 97% formic acid, was added 30 ml. of 37% formaldehyde solution. The resulting solution was refluxed for 24 hours. The reaction mixture was concentrated *in vacuo* leaving product and polymerized formaldehyde. The excess formaldehyde was removed by adding additional formic acid and again removing the volatile components *in vacuo*. The remaining white crystalline solid was recrystallized from a small amount of methanol then twice from a hot mixture of 2-propanol and methanol, 260 mg. (50% yield), m.p. 242-245° (gas); Infrared (potassium bromide), 1125 ($SO_4^=$), and 2950 (C-H); nmr, 4.80 (singlet, N-CH_2-N), 3.81 (singlet with shoulder, C-CH_2-$\overset{+}{N}$), 3.51 (singlet with shoulder, C-CH_2-N), 3.05 (singlet, N-CH_2), 2.44 (broad singlet, -CH), 2.16 (triplet, C-CH_2-C).

Anal. Calcd. for $C_9H_{18}N_2O_4S$: C, 43.18; H, 7.25; N, 11.19. Found: C, 43.63; H, 7.50; N, 11.09.

Acknowledgment

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REFERENCES

(1) M. Tomita, S. Uyeo, Jr., and T. Kikuchi, *Tetrahedron Letters*, 1053 (1964).

(2) W. L. Nelson, *J. Heterocyclic Chem.*, 5, 231 (1968).

(3) H. Stetter and H. Hennig, *Chem. Ber.*, 88, 789 (1955). H. Stetter and R. Merten, *ibid.*, 90, 868 (1957).

(4) Melting points were obtained on a Thomas Hoover Unimelt and are corrected. Infrared data were recorded on a Beckman IR 10 spectrophotometer, and values are expressed in cm^{-1}. Nmr data were recorded on a Varian Associates Model A-60 A spectrophotometer using 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard and deuterium oxide as solvent. All chemical shifts are in ppm (δ). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind.

(5) The amine was prepared according to the procedure of Stetter and coworkers (3) and characterized as the sulfate salt.

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