Some Reactions of 1-Methyl-1,2,3,4-tetrahydropyridine with Organic Azides. Synthesis of 1-Methylpiperidylidene-2-sulfon(cyan)amides

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The 1,3-dipolarcycloaddition reaction of 1-methyl-1,2,3,4-tetrahydropyridine (**1**) with organic azides **2** affords 1-methylpiperidylidene-2-sulfon(cyan)amides **4** in high yield. The reaction proceeds *via* a 2,3,4,9-tetrazabicyclo[4.3.0]non-3-ene intermediate. Acid hydrolysis of **4d** gives rise to 1-methyl-2-piperidone.

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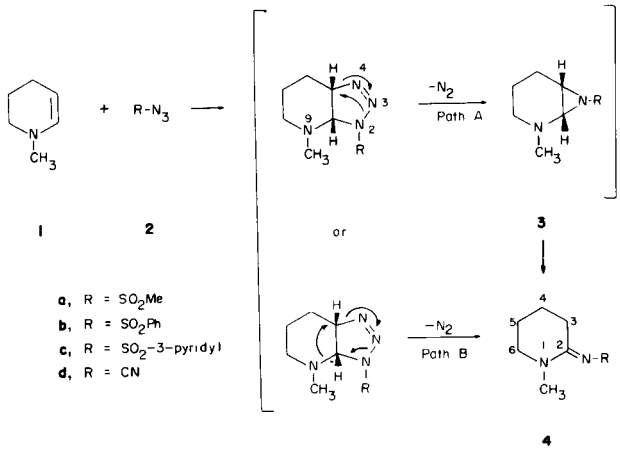
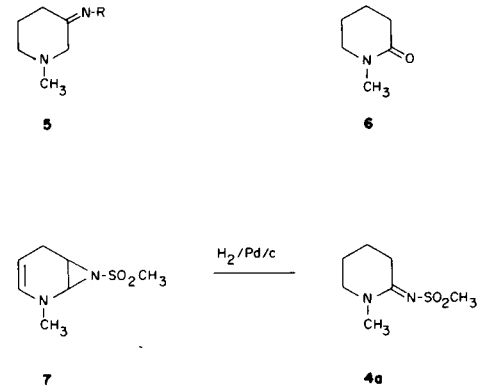
Reaction of 1-methyl-1,2,5,6-tetrahydropyridine with potassium *t*-butoxide in dimethyl sulfoxide affords 1-methyl-1,2,3,4-tetrahydropyridine (**1**) (1). The 1,3-dipolar cycloaddition reaction of the enamine **1** with organic azides **2** now provides a facile route to the pharmacologically interesting 1-methylpiperidylidene-2-sulfon(cyan)amides **4**.

A typical reaction involves the dropwise addition of a solution of methanesulfonyl azide **2a** (1 equivalent) in dry ether (10 ml) to a solution of 1-methyl-1,2,3,4-tetrahydropyridine (**1**) (1 equivalent) in dry ether (20 ml) at 25° with stirring. The reaction proceeds rapidly with evolution of nitrogen gas to yield 1-methylpiperidylidene-2-methanesulfonamide (**4a**) (82%). Under similar conditions **2b** gave



1 2 3 4

4b (71%) and **2c** gave **4c** (79%). Addition of cyanogen azide **2d** (1 equivalent) in dry acetonitrile (47 ml) to a solution of the enamine **1** (1 equivalent) in dry acetonitrile (15 ml) under an atmosphere of nitrogen affords 1-methylpiperidylidene-2-cyanamide (**4d**) (81%) (2). The mass spectrum of **4a** exhibitied a molecular ion at m/e 190 (M^+ Calcd. for $C_7H_{14}N_2O_2{}^{32}S$: 190.0776: Found: 190.0787) while the ir spectra displayed peaks at 1590 (C=N), 1270 (SO_2) and 1130 (SO_2) cm^{-1}. The pmr spectrum (δ exhibited a complex 2H multiplet at 3.39 due to the C_6-H, a complex 2H multiplet at 2.93-3.24 attributed to C_3-H, two 3H singlets at 3.02 and 3.06 due to NCH_3 and SO_2CH_3, and a complex 4H multiplet at 1.85 attributed to the C_4-H and C_5-H. No product resulting from the rearrangement of **3** to give 1-methylpiperidylidene-3-sulfon(cyan)amides **5** was observed since the C_2-H of **5** would be expected to absorb at a lower field than 3.39. Acid hydrolysis of **4d** using a 10% sulfuric acid/methanol solution (1:10) (3) gave rise to 1-methyl-2-piperidone (**6**) (55%) thus providing additional evidence in support of structures **4**. The ir and pmr spectra of **6** were identical with that of an authentic sample (4,5).



5 6 7 4a

If the intermediate triazoline adduct formed is the product of electronic control the nitrogen atom bearing the sulfono(cyano) group should be directed to the carbon of the double bond bearing the enamine ring nitrogen (6). Loss of nitrogen from the triazoline intermediate may occur by two possible mechanisms. The triazoline intermediate could eliminate nitrogen to afford the unstable 2,7-diazabicyclo[4.1.0]heptane (**3**) which then rearranges to give the stable **4** (Path A). Alternatively the triazoline adduct may fragment by a loss of nitrogen with concomitant rearrangement to yield **4** (Path B) (7). There is precedence for intermediate **3** since treatment of 1-methyl-1,4-dihydropyridine with **2a** gave 2-methyl-7-methanesulfonyl-2,7-diazabicyclo[4.1.0]hept-3-ene (**7**) in

quantitative yield (8) and subsequent reduction of **7** using 10% Palladium-on-charcoal and hydrogen gas affords **4a** (9).

The reaction of other organic azides with 1-methyl-, 1-alkyl- and 1-araalkyl-1,2,3,4-tetrahydropyridines are now in progress to broaden the scope of this reaction. The broad spectrum pharmacological screening of **4a**, **4b**, **4c** and **4d** is currently in progress. Preliminary results indicate that compounds **4** exhibit significant analgesic activity. For example, **4d** exhibits an ED_{50} of 6 mg/kg in the analgesic phenylquinone writhing assay relative to an ED_{50} of 50 for Aspirin (10).

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REFERENCES AND NOTES

(1) P. Becker and F. W. Fowler, *J. Org. Chem.*, **45**, 1336 (1980).

(2) All products gave microanalytical results within ±0.3% of theoretical values.

(3) T. A. Ondrus, E. E. Knaus and C. S. Giam, *J. Heterocyclic Chem.*, **16**, 409 (1979).

(4) Aldrich Library of IR Spectra.

(5) Aldrich Library of NMR Spectra.

(6) J. F. Stephen and E. Marcus, *J. Heterocyclic Chem.*, **6**, 969 (1969).

(7) A. C. Ritchie and M. Rosenberger, *J. Chem. Soc., C*, 277 (1968).

(8) B. K. Warren and E. E. Knaus, *J. Med. Chem.*, **24**, 462 (1981).

(9) B. K. Warren and E. E. Knaus, Unpublished results.

(10) H. O. Collier, L. C. Dineen, C. A. Johnson and C. Schneider, *Brit. J. Pharmacol. Chemotherap.*, **32**, 295 (1968).