Some Reactions of 1,2-Dihydropyridines with Cyanogen Azide. Synthesis of Diazabicyclo[4.1.0]hept-4-enes.

*T. A. Ondrus and E. E. Knaus**

Faculty of Pharmacy and Pharmaceutical Sciences. University of Alberta, Edmonton, Alberta T6G 2N8

and

C. S. Giam

Department of Chemistry, Texas A&M University, College Station, Texas 77843

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The regiospecific 1,3-dipolarcycloaddition reaction of 1,2-dihydropyridines **1** with cyanogen azide **2** afford 2,7-diazabicyclo[4.1.0]hept-4-enes **3** in quantitative yield. Catalytic hydrogenation of **3** gives rise to a tautomeric mixture of piperidylidene-2-cyanamides **5** in quantitative yield. Alternatively treatment of **3** with a suspension of alumina oxide in chloroform yields 1,2,5,6-tetrahydropyridylidenes **4** which are also quantitatively reduced to **5**.

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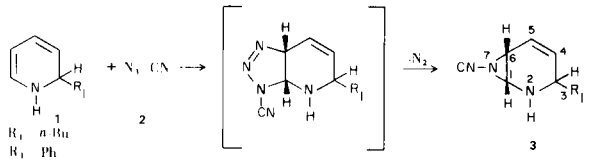
Sir:

Reaction of pyridine with organolithium reagents afford *N*-lithio-1,2-dihydropyridines (1) which on treatment with three equivalents of water (2) give 1,2-dihydropyridines **1a** and **1b**. The regiospecific 1,3-dipolar cycloaddition reaction of dienamines **1** with cyanogen azide **2** now provides a quantitative route to the pharmacologically interesting 7-cyano-2,7-diazabicyclo[4.1.0]-hept-4-enes **3**.

A typical reaction involves the dropwise addition of the dienamine **1a** (1 equivalent) in dry ether (67 ml.) to a solution of cyanogen azide **2** (1 equivalent) in dry acetonitrile (100 ml.) at 0° under an atmosphere of nitrogen. The reaction proceeds rapidly with evolution of nitrogen to yield 3-*n*-butyl-7-cyano-2,7-diazabicyclo[4.1.0]hept-4-ene **3a** (100%). Under similar conditions **1b** gave **3b** (100%). Although the cycloaddition reaction may



occur at either the C_3-C_4 and/or C_5-C_6 olefinic bonds no addition product other than **3** was detected. The mass spectrum of **3a** exhibited a molecular ion at m/e 177 (M^+ Calcd. for $C_{10}H_{15}N_3$: 177.1266: Found: 177.1265) while the ir spectrum displayed peaks at 1605 (C=C), 2180 (CN) and 3225 (NH) cm^{-1}. The pmr spectrum (δ) exhibited a broad 1H singlet at 8.63 due to NH which exchanges with deuterium, the characteristic 2H multiplet present in 1,2,3,6-tetrahydropyridines (3,4) at 5.8 due to C_4-H and C_5-H, a complex 1H multiplet at 4.17 attributed to the C_3-H (3), a complex 2H multiplet at 3.08-3.42 due to the C_1-H and C_6-H, a 6H multiplet at 1.1-1.9 attributed to $(CH_2)_3$ and a 3H distorted triplet (J = 7) due to the terminal methyl. A product resulting from addition to the C_3-C_4 olefinic bond of **1a** is not consistent with this pmr spectral data. If the intermediate triazoline formed is the product of electronic control the nitrogen atom bearing the cyano group should be directed to the carbon of the enamine double bond bearing the enamine ring nitrogen (5). The reacting species in all of these reactions is molecular cyanogen azide since loss of nitrogen to give cyanonitrene occurs above 40° (6).

In the reactions just described the presence of the isomeric alkylidene cyanamides **4** were not detected. However chromatography of **3a** on an neutral alumina (Brockman Activity 1) column gave a product which exhibited spectral data consistent with 6-*n*-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (**4a**, 79%). The mass spectrum of **4a** exhibited a molecular ion at m/e 177 (M^+ Calcd. for $C_{10}H_{15}N_3$: 177.1266; Found: 177.1265) while the ir spectrum displayed peaks at 1575 (C=C), 1645 (C=N), 2180 (CN) and 3220 (NH) cm^{-1}. The shift of the C=C absorption at 1605 cm^{-1} in **3a** to 1575 cm^{-1} in **4a** is evidence in support of the conjugated C=C-C=N system. The pmr spectrum (δ) exhibited a distorted 3H triplet (J = 7) at 0.9 due to the terminal methyl, a 6H multiplet at 1.1-2.0 due to $(CH_2)_3$, a 2H multiplet at 2.4 attributed to the C_5-H, a 1H multiplet at 3.6 due to the C_6-H, a complex 1H multiplet at 6.3 due to the C_3-H, a 1H multiplet ($J_{3,4}$ = 9, $J_{4,5}$ = 4) at 6.65 due to the C_4-H as well as a broad 1H absorption at 7.45 due to the NH which exchanges with deuterium. The isomeric structures **7** and **8** were dismissed since the C_4-H and C_5-H of **7** would be expected (3,4) to absorb in the range 5.3 to 5.9 (cf. C_4-H and C_5-H of **3a** which appear at 5.8 δ) while the C_2-H of **8** would be expected to absorb at lower field than 2.4. Stirring a suspension of neutral alumina (5 g.) (Brockman Activity 1) in 25 ml. of chloroform containing **3b** (0.216 g.) for 72 hours at 25°

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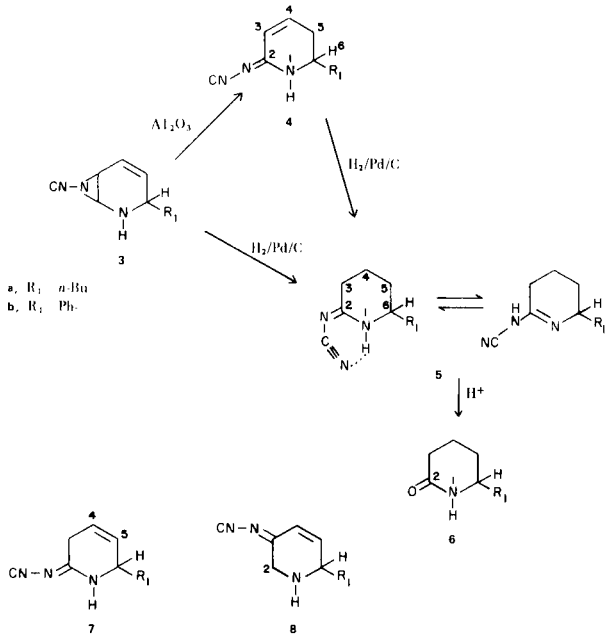

afforded **4b** in quantitative yield. Reduction of **4** with 10% palladium-charcoal and hydrogen gas at 35 psi gives a tautomeric mixture of piperidylidene cyanamides **5** in quantitative yield. The existence of a similar tautomeric equilibrium between piperidylidene-2-ethoxycarbonylamide and 3,4,5,6-tetrahydropyridyl-2-ethoxycarbonylamide has been reported (7). Reduction of **3a** and **3b** under similar conditions also afford tautomeric mixtures of **5a** and **5b** respectively in quantitative yields. Acid hydrolysis of **5b** using a 10% sulfuric acid/methanol solution (1:10 v/v) gave rise to 6-phenyl-2-piperidone (**6b**, 39%) thereby providing further evidence in support of structures **4** and **5**. The carbonyl band exhibited by **6b** at 1640 cm^{-1} is in good agreement with that of 2-piperidone which appears at 1653 cm^{-1}. The carbonyl group of *N*-ethyl-3-piperidone hydrochloride appears at 1724 cm^{-1} (8).

The reaction of other organic azides with both 1,2- and 1,4-dihydropyridines are now in progress to broaden the scope of this reaction. The broad spectrum pharmacological screening of **3a, 4a** and **5a** is currently in progress.

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REFERENCES AND NOTES

(1) C. S. Giam and J. L. Stout, *Chem. Commun.*, 142 (1969).

(2) Addition of three equivalents of water to the organolithium-pyridine adduct and drying (sodium sulfate) provides a lithium hydroxide free solution of **1**.

(3) E. E. Knaus, R. I. Marston, I. Meier and C. S. Giam, *Can. J. Pharm. Sci.*, 11, 73 (1976).

(4) K. Redda and E.E. Knaus, *J. Heterocyclic Chem.*, 13, 1237 (1976).

(5) J. F. Stephen and E. Marcus, *ibid.*, 6, 969 (1969).

(6) A. G. Anastassiou and H. E. Simmons, *J. Am. Chem. Soc.*, **89**, 3177 (1967).

(7) E. J. Moriconi and R. E. Misner, *J. Org. Chem.*, 34, 3672 (1969).

(8) Aldrich Library of IR Spectra.