Imino-bridged Heterocycles. I. A Derivative of Benzo[5,6]cyclohepta[1,2-*b*]pyridin-5,11-imine

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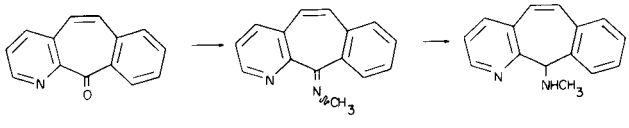
The current interest in structures that contain a tricyclic framework with a nitrogen bridged central ring has prompted us to examine the synthesis of imino-bridged benzocycloheptapyridines. Treatment of 5,6-trans-dibromobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one with anhydrous methyl amine in THF produced 6-β-bromo-5,6-dihydro-11α-hydroxy-12-methyl-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-5,11-imine, the first example of the desired bridged derivatives.

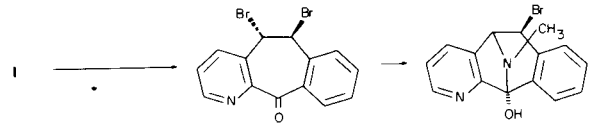
J. Heterocyclic Chem., **19**, 967 (1982).

The current interest in structures that contain a tricyclic framework with a nitrogen-bridged central ring (1) has prompted us to examine the synthesis of imino-bridged benzocycloheptapyridines. The ready availability of the tricyclic ketone (2) (**1**), from earlier work related to analogs of azatadine, (3) provided an attractive intermediate for out initial investigations.



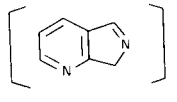
1 **2** **3**

Our original idea was to prepare the amine derivative **3** and examine possible modes of cyclization between the amino function and the ethylene bridge. Conversion of **1** to the methyl amino derivative **3** was accomplished readily using methylamine and titanium tetrachloride in toluene to generate the ketimine **2**, followed by reduction utilizing sodium borohydride in acetonitrile. Unfortunately, none of the conditions tried for inducing intramolecular ring closure between the amino function and the internal olefin was successful. However, bromination of **1** to the dibromoketone **4** could be effected with pyridine perbromide



4 **5**

in chloroform and treatment of **4** with anhydrous methylamine in THF produced a product to which we have assigned structure **5**, the first example of the desired imino-bridged derivatives. The structural assignment is based on the following arguments. Mass spectral and combustion analytical data are consistent with the formula $C_{15}H_{13}BrN_2O$. The infrared spectrum of the material diplays no carbonyl absorption and indicates loss of the ketone. The protons on the two carbon bridge display a very small coupling constant indicating the dihedral angle between them is near 0°. The proposed structure is consistent with this observation since the amine bridge and the remaining bromine should be *cis*. Consideration must be given to which bromine is displaced. The bromine adjacent to the pyridine nucleous should be the most active towards nucleophilic displacement, and we propose that the imine bridge is formed from this carbon. Mass spectral analysis suports this conclusion since fragments are formed, *i.e.*, **6**, which could arise only if the imine bridge



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is adjacent to the pyridine ring. Thus, the product may be viewed as being formed by displacement of bromine followed by intramolecular addition to the carbonyl function to provide the bridged structure (4).

Our initial attempts to generate the parent nucleus by conversion of the hydroxyl in **5** to halogen followed by reduction have been unsuccessful. We are continuing to explore this unique new class of heterocycles.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected values. ^{1}H nmr spectra were recorded on a Varian T-60 spectrometer using TMS as an internal standard. Analytical tlc was carried out on 250 μm, 2.5 cm × 10 cm, silica gel GF uniplates (Analtech, Inc.) using ultra violet light and Dragendorf spray for visualization. Mass spectra were run on an AEI MS 902 by Mr. Robert Rhodes, and microanaylses were preformed by Mr. K. B. Streeter and Mrs. Jan Stranick.

11-Methylaminobenzo[5,6]cyclohepta[1,2-*b*]pyridine (**3**).

To a stirred solution of methylamine (3.72 g, 0.12 mole) and **1** (2) (6.0 g, 0.03 mole) in toluene (150 ml) was added a solution of titanium tetrachloride (2.1 ml, 3.14 g, 0.018 mole) in toluene (50 ml) over 5 minutes. After 20 hours, anhydrous potassium carbonate was added and the reaction mixture was filtered. The residual brown oil (5.89 g), from

evaporation of the filtrate, was dissolved in acetonitrile (150 ml), treated with sodium borohydride (1.02 g, 0.0267 mole) and heated on the steam bath for 2.5 hours. After cooling to 25°, excess hydride was destroyed by the addition of 3*N* hydrochloric acid and the solvent was removed *in vacuo*. The residue was dissolved in 3*N* hydrochloroic acid (150 ml) and extracted with ether. After rendering the aqueous solution basic (*p*H > 10) by the addition of 40% sodium hydroxide solution, the organic material was extracted into ether, washed with saturated brine and dried (sodium sulfate). The residual oil (3.7 g) after removal of solvent was passed through a short pad of silica gel. After some impurities had been removed by elution with benzene-ethyl acetate (1:1), the product was eluted with chloroform-saturated with concentrated aqueous ammonia. Removal of solvent *in vacuo* left a viscous amber oil (2.2 g), homogeneous on tlc, fluorescent silica, benzene-ethyl acetate (1:1); ^{1}H nmr (deuteriochloroform) δ 2.37 (singlet, 3 H, NC*H*$_3$), 4.43 (singlet, 1 H, CH_3NH-C*H*<), 7.0-7.8 (multiplets, 9H, aromatic, pyridine 3 and 4, olefin, -NH-), 8.5 (doublet of doublets, 1 H, pyridine-2).

5,6-*trans*-Dibromobenzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**4**).

A solution of **1** (1.04 g, 5 mmoles) and pyridine perbromide (5) (2.64 g, 11 mmoles) in chloroform (25 ml) was heated on the stream bath for 24 hours. The solvent was removed *in vacuo*, the residue treated with cold aqueous sodium carbonate solution and extracted with chloroform. The combined extracts were washed with 10% sodium bisulfite solution, water, saturated sodium chloride, and dried (sodium sulfate). After removal of the dried solvent, the residue was stirred with acetone and filtered to give 0.54 g tan solid. Recrystallization from 2-propanol gave material with mp 148-158° dec; tlc, fluorescent silica, benzene silica, benzene-ethyl acetate (1:1), homogeneous; ^{1}H nmr (deuteriochloroform): δ 6.30 (doublet, 1 H, J = 7-8 Hz >C*H*Br, 6.48 (doublet, 1 H, J = 7-8 Hz, >C*H*Br), 7.20-7.73 (multiplets, 6 H, aromatic), 8.83 (doublet of doublets, 1 H, pyridine-2).

6-β-Bromo-5,6-dihydro-11α-hydroxy-12-methyl-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-5,11-imine (**5**).

A solution of methylamine (0.13 g) in THF (25 ml) was added to a stirred solution of **4** (1 g, 2.7 mmoles) in THF (100 ml). After 24 hours, the mixture was filtered and the filtrate was evaporated to dryness to give 0.75 g of tan solid. Recrystallization from benzene gave 0.50 g of white powdery solid, mp 143-145° dec; tlc fluorescent silica, benzene-ethyl acetate (1:1) homogeneous; ^{1}H nmr (deuteriochloroform): δ 2.38 (singlet, 3 H, >NC*H*$_3$) 4.65 (doublet, 1 H, J = 2 Hz >C*H*-N), 5.43 (doublet, 1 H, J = 2 Hz, >C*H*Br), 7.0-8.0 (multiplets, 6 H, aromatic), 8.27 (doublet of doublets, 1 H, pyridine-2); ms: M$^+$/e = 316.0216 ($C_{15}H_{13}N_2OBr^{79}$ = 316.02117).

Anal. Calcd. for $C_{15}H_{13}BrN_2O$: C, 56.80; H, 4.13; N, 8.83; Br, 25.20. Found: C, 56.84; H, 4.33; N, 9.17; Br, 25.49.

REFERENCES AND NOTES

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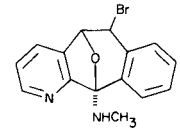
(2) F. J. Villani, P. J. L. Danielo, C. A. Ellis, T. A. Manu and K-C. Wang, *J. Heterocyclic Chem.*, **8**, 73 (1971).

(3) W. Halczenko, and K. L. Shepard, "Abstracts of Papers", 30th Southeastern Regional ACS Meeting, Savannah, Georgia, November 8-10, 1978.

(4) The alternate structure **i**, formed by addition of methyl amine to the carbonyl followed by oxygen displacement of the bromine, may be ruled out from an examination of the ^{13}C-spectrum.



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