

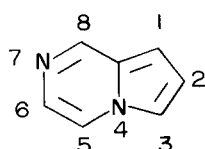
Department of Chemistry, Ohio University

Ten- π -Electron Nitrogen Heterocyclic Compounds VI: NMR Spectra, HMO Calculations and Bromination of some Diazaindenes

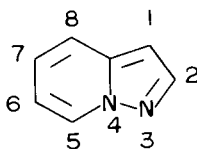
William W. Paudler and David E. Dunham

The bromination of pyrrolo[1,2-a]pyrazine and of pyrrazolo[1,2-a]pyridine yields the 1,3-dibromo and 1-bromo derivatives, respectively. These results are in agreement with the predictions based on frontier-electron density calculations. The nmr spectra of the compounds prepared in this study are analyzed in detail.

In the course of our studies on ten- π -electron nitrogen heterocyclic compounds (1-5), it became of interest to investigate pyrrolo[1,2-a]pyrazine (I) and pyrrazolo[1,2-a]pyridine (II). This paper de-



I



II

scribes the nmr analyses, HMO calculations and some substitution reactions of these compounds.

HMO Calculations.

Table I records the total π -electron densities and the frontier electron densities of pyrrolo[1,2-a]pyrazine (I) and of pyrrazolo[1,2-a]pyridine (II). The parameters employed in these calculations were those previously described (1). It is clear, that the frontier electron densities predict substitution (electrophilic) to occur at positions 1 and 3 in the pyrazine derivative (I), while position 1 is the predicted position of electrophilic substitution for the pyridine derivative (II).

Bromination of Pyrrolo[1,2-a]pyrazine.

We anticipate that bromination of pyrrolo[1,2-a]pyrazine with bromine water might yield either equal amounts of the 1- and the 3-bromo- or substantial amounts of 1,3-dibromopyrrolo[1,2-a]pyrazine.

The reaction of equal amounts of aqueous bromine and pyrrolo[1,2-a]pyrazine yields large amounts of a dibromo derivative, along with traces of two unknown materials, shown to be present by TLC (the two monobromo compounds?), and substantial amounts of starting material. The reaction of two moles of aqueous bromine with one mole of the pyrrolo-

[1,2-a]pyrazine yields larger amounts of the dibromo compound and, again, only traces of the two unknown compounds, along with small amounts of starting material.

The position of the bromine atoms in this dibromo compound can be established by an analysis of the nmr spectrum of this material and a comparison of this spectrum with that of the parent compound.

We have previously shown (2) that the replacement of H_3 by a bromine in imidazo[1,2-a]pyridines causes H_5 to become more shielded by approximately 0.1 τ units. If one of the bromine atoms in the dibromo compound is at position 3, we would anticipate that a one proton multiplet in the nmr spectrum of the parent would be shifted diamagnetically by approximately 0.1 τ . We do indeed find that a one proton multiplet at 2.11 τ of the parent compound appears at 2.19 τ in the dibromo material. Thus, one of the bromine atoms is at the predicted 3 position. A similar shielding of H_8 is expected if H_1 is replaced by a bromine. A broad singlet present in the parent at 1.09 τ is shifted to 1.29 τ in the dibromo compound. Consequently, the dibromopyrrazolo[1,2-a]pyrazine is the 1,3-dibromo compound, as predicted by the frontier electron densities. This structure assignment is further confirmed by the total analysis of the nmr spectrum of the parent compound and a comparison of this analysis (coupling constants) with that of the 1,3-dibromo compound.

Bromination of pyrrazolo[1,2-a]pyridine.

The frontier electron densities predict that electrophilic substitution in this molecule should occur at C_1 . Bromination of pyrrazolo[1,2-a]pyridine with bromine-water yields a monobromo derivative. The position of the bromine atom can readily be determined from an inspection of the nmr spectrum of this compound, and a comparison with the spectrum of the starting material (6).

The multiplet assigned to H_1 in the parent compound is no longer present in the nmr spectrum of the monobromo derivative. Consequently, the de-

rivative is the expected 1-bromopyrrazolo[1,2-a]pyridine.

NMR analysis of 1,3-dibromopyrrolo[1,2-a]pyrazine.

The most deshielded proton (1.29 τ) is coupled to another proton by 1.55 c/s. This doublet can only be due to H_8 , since *ortho* coupling requires a larger spin-spin coupling constant. The one proton singlet observed at 3.10 τ must be due to H_2 , since it is the most shielded proton in the spectrum.

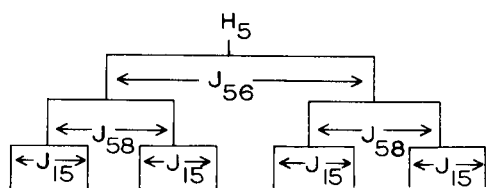
The assignment of H_5 and H_6 is based upon the observations mentioned earlier in this communication. Thus, H_5 appears at 2.19 τ and H_6 at 2.33 τ .

The H_5 and H_6 peaks are apparent as an AB system ($J_{56} = 5.0$ c/s) with the more deshielded proton (H_5) being coupled to another proton by 1.55 c/s. Since the same coupling constant is observed in H_8 , we conclude that $J_{58} = 1.55$ c/s. No other coupling is observable under the conditions of resolution available to us.

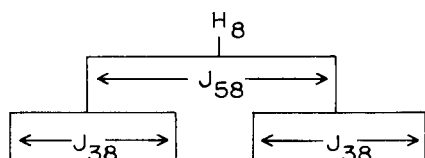
NMR analysis of pyrrolo[1,2-a]pyrazine.

The analysis of some portions of the spectrum of pyrrolo[1,2-a]pyrazine require some detailed discussion.

The proton on C_5 (2.11 τ) appears as a member of an AB system with a considerable amount of further spin-spin splitting. This pattern is diagrammed below:



The J_{56} and J_{58} coupling constants are 5.5 and 1.55 c/s, respectively. The third coupling constant (0.85 c/s) must involve either H_1 or H_3 , since this splitting is not observed in the 1,3-dibromo compound. The proton on C_8 appears (on an expanded scale spectrum) as shown:



This diagram confirms the assignment of J_{58} (1.55 c/s). That the remaining spin-spin interaction (1.0 c/s) must involve H_1 or H_3 is evident from the spectrum of the 1,3-dibromo compound, where H_8 is a simple doublet.

Analysis of the multiplet due to H_3 (2.54 τ) yields three different coupling constants. The largest of these (2.55 c/s) must be J_{23} . The 1.0 c/s coupling constant is then due to J_{38} (see above). The remaining spin-spin coupling (1.45 c/s) is as yet unassignable.

The pattern ascribed to H_1 (3.15 τ) yields three different coupling constants, 4.5, 1.45 and 0.85 c/s, respectively. The largest of these constants (4.5 c/s) is clearly J_{12} , while the 1.45 c/s constant is now ascribed to J_{13} . The remaining interaction constant (0.85 c/s) is J_{15} .

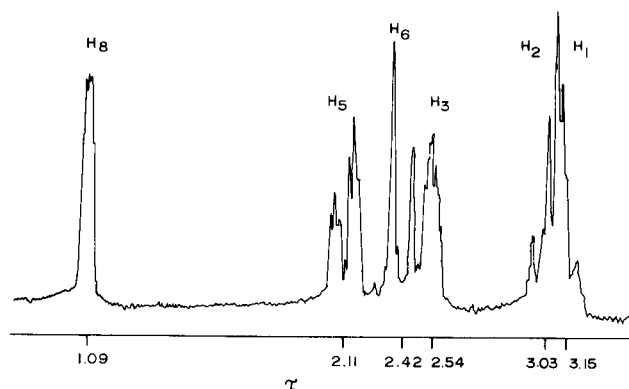
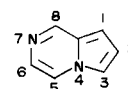
This leaves the spin-spin interactions of H_2 to be determined. The pattern centered at 3.03 τ reveals $J_{23} = 2.55$ c/s, and $J_{12} = 4.5$ c/s.

The results of this analysis are tabulated in Table II.

NMR analysis of 1-bromopyrrazolo[1,2-a]pyridine.

During the early phases of this work, a paper by Black and coworkers (7) appeared, describing the nmr spectrum of pyrrazolo[1,2-a]pyridine. Our analysis of the parent compound is in agreement with that reported by these workers. The analysis of the spectrum of the 1-bromo compound substantiates the correctness of the assignments of some of the long-range spin-spin coupling constants. These values, along with the proton chemical shifts of the various protons are reported in Table II.

It is of interest to note that H_6 and H_7 are considerably more deshielded in the 1-bromo compound than in the parent.



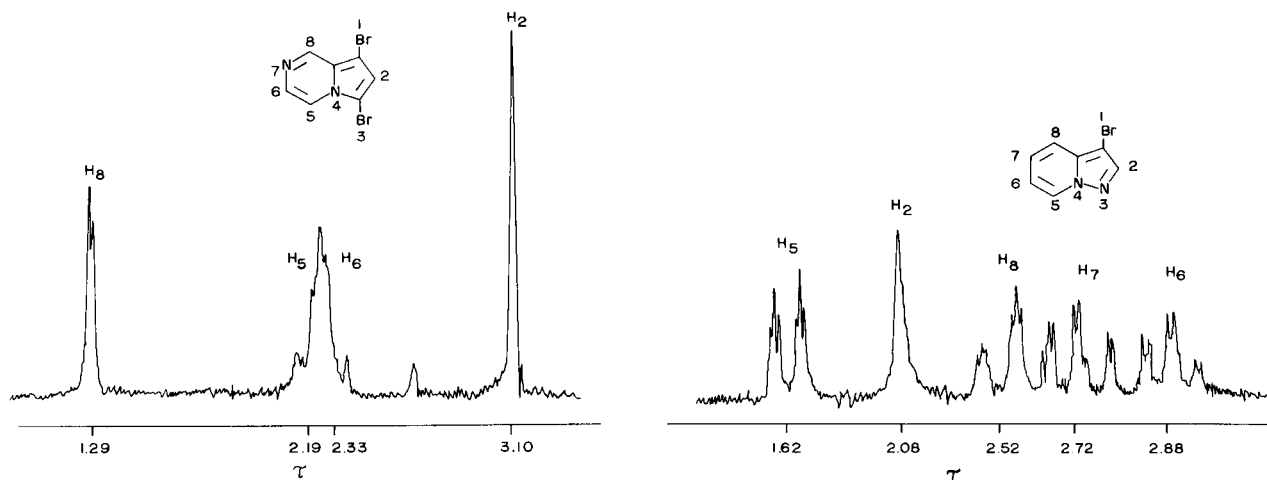


TABLE I

Total π -Electron Densities and Frontier Electron Densities of Some Diazaindenes:

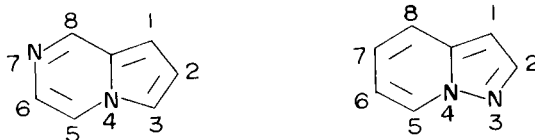


Position	Total π -Electron Densities	Frontier Electron Densities	Total (a) π -Electron Densities	Frontier (a) Electron Densities
1	1.13	0.45	1.14	0.46
2	1.07	0.00	1.01	0.02
3	1.10	0.46	1.42	0.61
4	1.50	0.04	1.49	0.01
5	0.98	0.35	0.95	0.33
6	1.02	0.17	1.02	0.10
7	1.27	0.30	0.98	0.18
8	0.88	0.13	1.01	0.26
9	1.04	0.10	0.98	0.04

(a) The N-N bond was assigned $0.85\beta^{\circ}$.

TABLE II

Chemical Shifts and Coupling Constants for Some Azaindolizines (a)



Constant	Parent	1, 3-Dibromo	Parent	1-Bromo
H ₁	3.15	----	3.62	----
H ₂	3.03	3.10	2.20	2.08
H ₃	2.54	----	----	----
H ₅	2.11	2.19	1.61	1.62
H ₆	2.42	2.33	3.38	2.88
H ₇	----	----	3.03	2.72
H ₈	1.09	1.29	2.56	2.52
J _{1,2}	4.50	----	2.18	----
J _{1,3}	1.45	----	----	----
J _{1,5}	0.85	----	0.9	----
J _{2,3}	2.55	----	----	----
J _{2,7}	----	----	0.5	0.5
J _{3,8}	1.00	----	----	----
J _{5,6}	5.5	5.0	6.93	7.0
J _{5,7}	----	----	1.00	1.2
J _{5,8}	1.55	1.55	1.02	1.2
J _{6,7}	----	----	6.79	6.8
J _{6,8}	(b)	(b)	1.17	1.6
J _{7,8}	----	----	8.94	8.3

(a) Values are for 8% solutions in deuteriochloroform, reported in τ units. (b) Probably present as indicated by the broadness of the H₆ and H₈ lines.

EXPERIMENTAL (9)

Preparation of Pyrrolo[1,2-*a*]pyrazine.

This compound was prepared by the method described by Herz and Tocker (7). The yield of pyrrolo[1,2-*a*]pyrazine was considerably improved (from 21 to 60%) by dissolving the intermediate obtained from pyrrole-2-carboxaldehyde and aminoacetaldehyde diethyl acetal in cyclohexane (50% solution), and adding this solution dropwise to the mixture of phosphorus oxychloride and polyphosphoric acid.

Bromination of Pyrrolo[1,2-*a*]pyrazine.

General Procedure.

To a stirred ethanolic solution (25 ml.) of 1.095 g. (9.28 mmole) of pyrrolo[1,2-*a*]pyrazine was added dropwise, an aqueous solution of bromine. During this addition, nitrogen gas was bubbled slowly through the solution. After addition of the bromine-water was complete (1 hour), the yellowish-brown reaction mixture was made basic (pH 11) with aqueous sodium hydroxide. The precipitated solid was then collected, and the aqueous filtrate extracted with three 100 ml. portions of chloroform. The chloroform extracts were combined and dried (anhydrous sodium carbonate). The filtered solution was evaporated and the residue combined with the precipitated solid. This solid was analyzed by TLC (silica gel G plates, 10-90 acetone-benzene). If the presence of starting material was indicated, the solid was chromatographed on neutral Grade 3 alumina. Elution with benzene yielded the pure dibromo compound, m.p. 122.0-122.4° (after vacuum sublimation at 55°/0.3 mm.). The following lists the yield of 1,3-dibromopyrrolo[1,2-*a*]pyrazine and the ratio of bromine to pyrrolo[1,2-*a*]pyrazine; 45% (1:1); 90% (2.5:1).

Anal. Calcd. for C₇H₄N₂Br₂: C, 30.47; H, 1.46; N, 10.15. Found: C, 30.60; H, 1.57; N, 10.14.

Bromination of Pyrrolo[1,2-*a*]pyridine.

The same procedure as described for the bromination of pyrrolo[1,2-*a*]pyrazine (8) was employed. The 1-bromopyrrolo[1,2-*a*]pyridine (80% of theory) obtained melted at 67.0-67.5°. The ratio of bromine to pyrrolo[1,2-*a*]pyridine employed was 2:1.

Anal. Calcd. for C₇H₅N₂Br: C, 42.67; H, 2.55; N, 14.21. Found: C, 42.54; H, 2.45; N, 13.98.

Acknowledgment.

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- (9) NMR spectra were obtained with a Varian A-60 spectrometer. The spectra are in CDCl₃ at 8% w/w. The microanalyses were performed by Mrs. C. Warner of this department. Melting points are corrected.

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Athens, Ohio 45701