The Synthesis and Some Chemical and Spectroscopic Properties of Imidazo[1,2-*a*]pyrazine

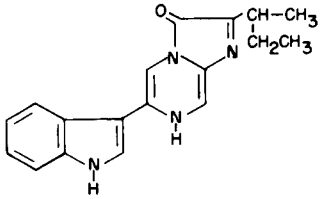
Michael F. DePompei and William W. Paudler

Department of Chemistry, The University of Alabama, University, Alabama 35486

Received May 5, 1975

The parent imidazo[1,2-*a*]pyrazine was prepared and shown to undergo electrophilic bromination at C-3, and base-catalyzed H→D exchange at C-3 and C-5. The perchloro derivative of this ring system was prepared and it was established that nucleophilic substitution by methoxide ion occurs at C-5 and C-8. Pmr spectral data for all compounds are presented.

Our interest in the chemistry of polyazaindenes has prompted us to examine the chemistry of imidazo[1,2-*a*]-pyrazine (**2**). A literature search for background information of this ring system revealed that only a few substituted imidazo[1,2-*a*]pyrazines are known. One report (1) purported to be describing the synthesis of the 5,6-diphenyl derivative, is in error since the compound prepared was actually the 2,3-dihydro derivative as shown by the structures in the publication, as well as the reported elemental analysis. A naturally occurring derivative containing this ring system is found in Cypridina Luciferin (2).

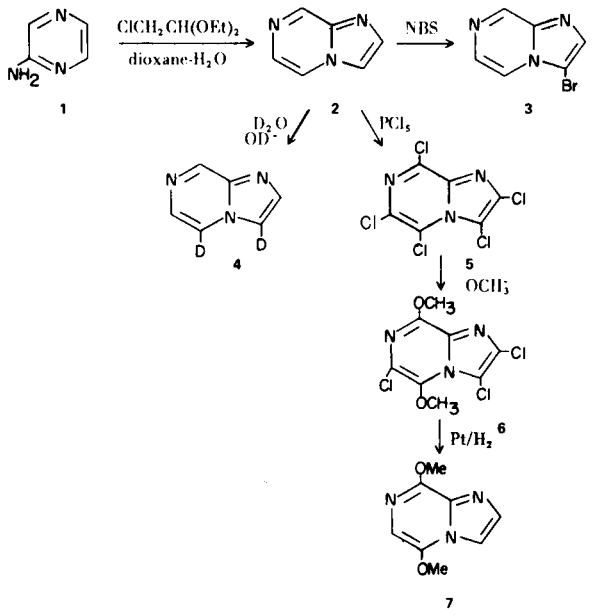


We have prepared the parent imidazo[1,2-*a*]pyrazine by the reaction delineated in Scheme I.

The structure proof of this compound rests upon its mode of synthesis, correct elemental analysis as well as mass spectrometrically determined molecular weight.

The pmr spectral analysis is relatively straight forward in that the most deshielded proton appears as a doublet (J = 1.0 Hz) this doublet finds its counterpart in the secondary splitting of one of the protons of an AB system due to H-5 and H-6. In order to decide whether this secondary splitting is caused by interaction between H-6 and H-8 or between H-5 and H-8, thus establishing which of the protons is the more deshielded one, we took recourse to an analysis of a monobromo imidazo[1,2-*a*]-pyridine prepared by electrophilic bromination of compound **2**.

Scheme I



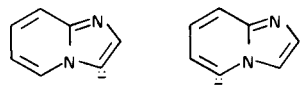
The pmr spectrum of this monobromo derivative, whose molecular formula was determined by means of an elemental analysis and mass spectrometrically determined molecular weight, still shows the ABX pattern due to H-5, H-6, and H-8. Thus, bromination has occurred at either H-2 or H-3.

Since it is well known that electrophilic bromination of imidazo[1,2-*a*]pyridine (3) occurs at C-3, we might anticipate that we are dealing with a 3-bromo-imidazo-[1,2-*a*]pyrazine. If this is indeed the case, the chemical shift of H-5 would be affected at most by a 0.15 shielding effect similar to that observed in the imidazo[1,2-*a*]-pyridine where H-5 (τ 1.95) is shifted to τ 2.10 in the 3-monobromo derivative (3). Thus, this observation not

only allows us to assign the H-5 and H-6 patterns but also proves that bromination of imidazo[1,2-*a*]pyrazine occurs at C-3. Furthermore, since the doublet of doublets at τ 1.93 is not affected, the secondary coupling is due to spin-spin interaction between H-8 and H-5 and not between H-8 and H-6.

In view of our previous work on base-catalyzed H→D exchange reactions in polyazaindenes (4), it became of interest to examine this ring system with respect to these reactions. When imidazo[1,2-*a*]pyrazine was subjected to base-catalyzed H→D exchange at 65° for a period of 12 hours, the pmr spectrum of the resulting deuterated compound had three singlets. Superposition of this spectrum upon that of the starting material showed that H-3 and H-5 were exchanged for deuterium. Thus, a 3,5-dideuteroimidazo[1,2-*a*]pyrazine (**4**) was formed.

We have, in the past, proposed that the facile H→D exchange in imidazo[1,2-*a*]pyridine and related compounds can be rationalized in terms of the potential stability of the "ylide-type" intermediates **7** and **8**.



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While the ylide-type stabilization of structure **7** is still present in imidazo[1,2-*a*]pyrazine (**4**), the presence of an sp^2 nitrogen at C-7 is expected to significantly increase the stability of the "ylide-type" intermediates **8** in the pyrazine case. Thus the facile H-5→D-5 exchange is not surprising..

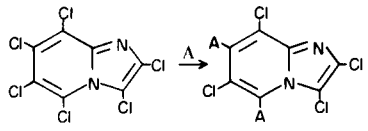
We have already described the synthesis and some chemical transformations of perchloro-imidazo[1,2-*a*]-pyridine (5). As part of a more extensive study of the chemistry of perhalogenated polyazaindenes, we treated imidazo[1,2-*a*]pyrazine (**2**) with phosphorus pentachloride to obtain perchloroimidazo[1,2-*a*]pyrazine (**5**). The structure assignment of this compound rests upon its correct elemental analysis, mass spectrometric molecular weight as well as the presence of the typical 5 chlorine peak (6) in its mass spectrum.

In order to ascertain the most reactive sites in this molecule towards nucleophilic displacement reactions, we treated it with sodium methoxide. The resulting compound gave an elemental analysis consistent with it being a dimethoxytrichloroimidazo[1,2-*a*]pyrazine. This analysis is further substantiated by the mass spectrum of the material which, in addition to giving the correct molecular weight also shows the typical 3 chlorine pattern (6).

In order to determine the sites of substitution of the two methoxy groups, the chlorine substituents were removed by catalytic reduction. The resulting compound gave a correct elemental analysis for a dimethoxyimidazo-[1,2-*a*]pyrazine. This was further confirmed by the fact that the compound had the correct molecular weight as determined by mass spectroscopy.

The pmr spectrum of this substance is extremely simple in that it shows the presence of H-2 and H-3 (see Table I), along with a sharp singlet resonating at τ 2.71. Thus, neither of the methoxy groups is substituted in the 5 membered ring.

Perchloroimidazo[1,2-*a*]pyridine (**9**) when subjected to similar transformations affords 5- and 5,7-disubstituted (**10**) derivatives (6).



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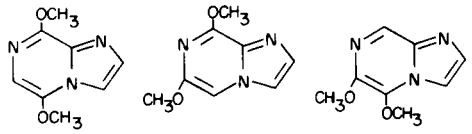
A comparison of the chemical shift of H-6 in imidazo-[1,2-*a*]pyridine (τ 3.45) with that in 5-methoxyimidazo-[1,2-*a*]pyridine (τ 4.02) shows that the introduction of a methoxy group casuses shielding of H-6 by 0.57 ppm.

In the imidazo[1,2-*a*]pyrazine instance we find that the remaining 6-membered-ring proton resonates at τ 2.71. Thus, regardless of which proton it represents, a considerable shielding effect is noted.

We are now in a position of having to decide among the following possible structures for the dimethoxy-imidazo[1,2-*a*]pyrazine. If we are dealing with structure



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12, the chemical shift of H-8 would be expected to be, at a maximum, more shielded by 1.00 ppm in comparison to H-8 (τ 0.94) in the parent compound. Yet the singlet in the dimethoxy compound resonates at τ 2.71. Thus, we can eliminate structure **12** from consideration.

In the case of imidazo[1,2-*a*]pyridine, a 5-methoxy substituent, causes shielding of H-3 by 0.40 ppm in comparison to the parent compound. A similar, but lesser effect (0.10 ppm) is observed in the imidazo[1,2-*a*]-pyrazine instance.

The shielding effect on H-6 in the imidazo[1,2-*a*]-pyridine *vs* the 5-methoxy derivative, as already noted, is 0.57 ppm. A similar effect (0.53 ppm) is observed in the

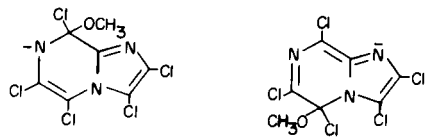

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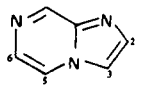
Table I
PMR Spectral Data for some Imidazo[1,2-*a*]pyrazines



		Chemical Shifts (τ)					Coupling Constants (Hz)	
		H_2	H_3	H_5	H_6	H_8	J_{56}	J_{68}
Substituent(s):	Compound							
nil	**2**	2.24	2.34	1.93	2.18	0.94	4.5	1.0
3-Br	**3**	2.24	--	1.95	1.95	0.92	4.5	0.8
3,5-di-D	**4**	2.24	--	--	2.18	0.94	--	--
5,8-diOCH_3	**7**	2.24	2.43	--	2.71	--	--	--

imidazo[1,2-*a*]pyrazine *vs* dimethoxy derivative. Thus, the latter material is the 5,8-disubstituted derivative (**7**) rather than compound **11**. This structure is also consistent with the possible intermediates (**13** and **14**) in these nucleophilic substitution reactions, which are clearly the most stable ones in comparison to nucleophilic substitution at any other position in the perchloroimidazo[1,2-*a*]-pyrazine.

EXPERIMENTAL

Imidazo[1,2-*a*]pyrazine. (**2**).

A solution of α-chlorodiethylacetal (0.1 mole) in 40 ml. of dioxane and 20 ml. of water, containing 1 ml. of concentrated hydrochloric acid, was refluxed for 1.0 hour. To the cooled solution was first added solid sodium bicarbonate (8.5 g., 0.1 mole) followed by 9.5 g. (0.1 mole) of 2-aminopyrazine. The reaction mixture was then refluxed for an additional 18 hours, and finally was cooled, made basic (*p*H = 10) with 10% sodium hydroxide and exhaustively extracted with chloroform. The combined extracts were dried (anhydrous sodium carbonate) filtered and the chloroform was removed under reduced pressure. The solid thus obtained was recrystallized from a mixture of benzene-hexane and sublimed, (100°/0.01 torr) to afford 4.65 g. (39.2%) of compound **2** (m.p. 83-85°).

Anal. Calcd. for $C_6H_5N_3$: C, 35.29; H, 4.21; N, 60.50. Found: C, 34.95; H, 4.31; N, 59.85. Mass spec. mol. wt. 119.

3-Bromoinidazo[1,2-*a*]pyrazine (**3**).

A stirred solution of 0.2 g. of **2** and 600 mg. of *N*-bromosuccinimide in 20 ml. of carbon tetrachloride was refluxed for 2 hours. The cooled solution was filtered, and the filtrate was evaporated to dryness under reduced pressure to yield 0.280 g. of crude **3**. This solid was chromatographed on grade 3 neutral alumina. Elution with chloroform yielded 0.140 g. (72%) of 3-bromoimidazo[1,2-*a*]pyrazine (m.p. 194-196°).

Anal. Calcd. for $C_6H_4N_3Br$: C, 21.20; H, 2.02; N, 37.29. Found: C, 21.23; H, 1.99; N, 37.08; Mass spec. mol. wt. 197.

Perchloroimidazo[1,2-*a*]pyrazine (**5**).

Imidazo[1,2-*a*]pyrazine (**2**) (1.0 g., 0.008 mole) and 17.5 g. (0.081 mole) of phosphorus pentachloride was placed in a sealed steel reaction bessel and heated at 265° for 4 hours. To the cooled bomb was then added 250 g. of ice and 200 ml. of chloroform. After the phosphorus pentachloride had been decomposed, the mixture was collected and boiled on a steam bath for 10 minutes. The chloroform layer was collected and boiled on a steam bath with Norite for 10 minutes and the mixture was filtered. The chloroform filtrate was concentrated to dryness *in vacuo* and the remaining solid was recrystallized from methanol to yield 1.25 g. (54.5%) of perchloroimidazo[1,2-*a*]pyrazine (**5**) (m.p. 134-136°).

Anal. Calcd. for $C_6N_3Cl_5$: C, 24.91; H, 0.00; N, 14.53. Found: C, 24.03; H, 0.02; N, 14.85. Mass spec. mol. wt. 289.

5,8-Dimethoxy-2,3,6-trichloroimidazo[1,2-*a*]pyrazine (**6**).

To 30 ml. of absolute methanol was slowly added 0.550 g. of sodium metal. When the sodium had completely reacted, the solution was cooled to 0° and 0.50 g. of perchloroimidazo[1,2-*a*]-pyrazine dissolved in 30 ml. of dry dioxane was added dropwise over a 2 hour period. After addition was completed, the solution was stirred for an additional 30 minutes. Water was then added until a material started to precipitate. This solid was collected and recrystallized from methanol to yield 0.265 g. of compound **6** (m.p. 185-187°).

Anal. Calcd. for $C_8H_6N_3O_2Cl_3$: C, 36.29; H, 2.13; N, 14.94. Found: C, 36.05; H, 2.65; N, 15.08. Mass spec. mol. wt. 281.

5,8-Dimethoxyimidazo[1,2-*a*]pyrazine (**1**).

A solution of 250 mg. of compound **6**, 100 mg. of 10% palladium on carbon and 1.0 g. of potassium hydroxide in 60 ml. of methanol was hydrogenated in a Parr apparatus at 20 psi for 18 hours. The solution was filtered, and its volume reduced to one half *in vacuo*. Upon addition of 20 ml. of water the solution was exhaustively extracted with chloroform for a period of 12 hours. The chloroform extract was dried (anhydrous sodium carbonate) and evaporated *in vacuo*. The crude product was sublimed (120°/0.01 torr) to yield 80 mg. (82%) of compound **7** (m.p. 126-128°).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.02; N, 23.46. Found: C, 53.21; H, 5.22; N, 23.68. Mass spec. mol. wt. 179.

REFERENCES

(1) R. H. Martin and Z. Tarasiejska, *Bull. Soc. Chim. Belges*, **66**, 136 (1957).

(2) Y. Kishi, S. Sugiura, S. Inoue, T. Goto, *Yakugaku Zasshi.*, **89**, 1675 (1969); *Chem. Abstr.*, 90406a (1970).

(3) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **30**, 4081 (1965).

(4) W. W. Paudler and L. Helmick, *ibid.*, **33**, 1087 (1968).

(5) W. W. Paudler, D. J. Pokorny and J. Good, *J. Heterocyclic Chem.*, **8**, 37 (1971).

(6) F. W. McLafferty, "Interpretation of Mass Spectra," W. Benjamin, N. Y., 1966.

(7) Experimental Analyses done by Analytical Services Laboratory of the Department of Chemistry, The University of Alabama.