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# A NOVEL REACTION OF AMMONIUM CHLORIDE AND α-AROMATIC AMINE CARBOXALDEHYDES

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A novel reaction was discovered when ammonium chloride was used to catalyze the formation of pyrazine carboxaldehye dimethyl acetal[**] from pyrazine carboxaldehye (1) and methyl orthoformate. In addition to the desired product (40%) another crystalline basic yellow compound m.p. 202-203 was formed in 10% yield. Elemental analysis supported an empirical formula of $C_{10}H_7N_5$. The infrared data indicated the lack of significant functional groups and the ultraviolet spectrum had the following maxima at 348 ($\epsilon$ =16000) and 252 ($\epsilon$ =22400).

The mass spectrum analysis exhibited abundant peaks[***] at m/e 197 ($M^+$, 100%); m/e 196 ($M^+$-1, 60%); m/e 170 ($M^+$-27, 12%); m/e 143 ($M^+$-27-27, 30%). It indicated an odd number of nitrogen atoms and a mode of fragmentation typical for unsubstituted aromatic nitrogen heterocycles (2). The n.m.r. chemical shifts in neutral and acidified ($CF_3COOH$) deuterochloroform as well as the results of proton decoupling experiments leading to their assignments are listed in Table I.

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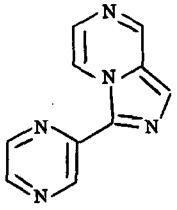
[**] The synthesis of this compound has been claimed by J. D. Behun and R. Levine, J. Org. Chem., 23, 406 (1958), by heating dichloromethyl pyrazine with sodium methoxide. Our results on the same experiment do not support the formation of the acetal but rather 2-methoxymethyl-3-methoxypyrazine or 2-methoxymethyl-5-methoxypyrazine. This finding explains the failure to hydrolyze the claimed acetal to pyrazine carboxaldehyde. Similar abnormal nucleophilic substitutions have been reported by E. J. J. Grabowski, et.al., Tetrahedron Letters, 5931 (1968).

[***] These fragmentations are supported by corresponding metastable ions.

## TABLE I

| Proton(s) | Chemical Shift, PPM |  | $\Delta\delta$ | Multiplicity | Protons decoupled |
|---|---|---|---|---|---|
|  | Neutral | Acidified |  |  |  |
| a | 7.75 | 7.78 | +0.03 | Doublet $J_{a,f} = 5$ Hz | f |
| b | 7.98 | 8.30 | +0.32 | Singlet | - |
| c & d | 8.57 | 8.67 | +0.10 | Multiplet | g |
| e | 9.10 | 9.35 | +0.25 | Doublet $J_{e,f} = 1$ Hz | f |
| f | 9.51 | 9.67 | +0.16 | Quartet $J_{a,f} = 5$ Hz; $J_{e,f} = 1$ Hz | e & a |
| g | 9.64 | 9.72 | +0.08 | Doublet $J_{g,c} = 1$ Hz | c & d |

The previous physical and chemical data strongly suggest structure (I) 3-(2-pyrazinyl)imidazo [1, 5-] pyrazine.



I

The three protons (b), (e), and (f) that are attached to the imidazo [1, 5-a] pyrazine moiety exhibited a larger downfield shift upon acidification of the solution than the remaining protons, while proton (a) was not affected and remained at a relatively high field. This is presumably due to a shielding effect exerted by the pyrazine ring, suggesting that the molecule is not completely planar (3).

Extension of the reaction to 2-pyridine carboxaldehyde, eliminating methyl orthoformate, gave a crystalline product $C_{12}H_9N_3$ m.p. 115-117 (7%). Its infrared spectrum showed lack of functionality and the ultraviolet spectrum had maxima at 344 ( $\epsilon$ = 18300) and 242 ( $\epsilon$ = 12,400).

The mass spectrum* also exhibited the loss of hydrogen cyanide as well as the pyridinium ion as follows: m/e 195 ($M^+$, 100%); m/e 194 ($M^+$-1, 79%); m/e 168 ($M^+$-27, 5.6%); m/e 141 ($M^+$-27-27, 1.68%); m/e 90 ($M^+$-27-78, 10.2%); m/e 63 ($M^+$-27-78-27, 27%).

The n.m.r. spectrum was more complicated than that of I having multiplets between 6.6-8.8 $\delta$ and a highly de-shielded one proton multiplet at 9.92 $\delta$.

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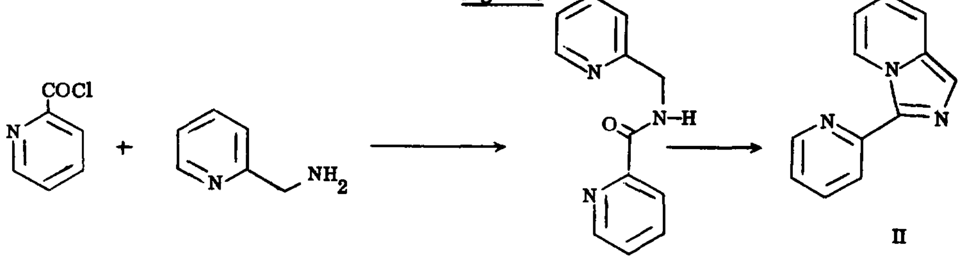
*These fragmentations are also supported by metastable ions.

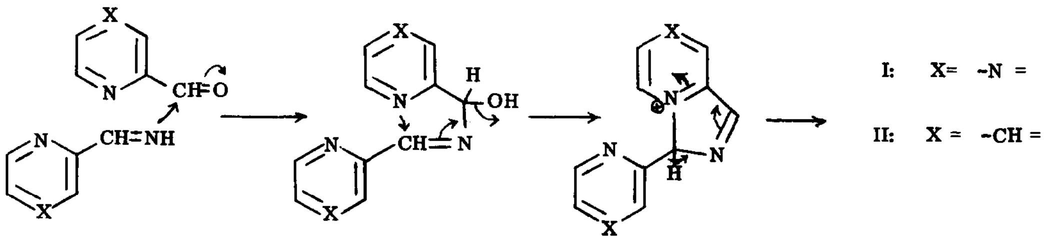
From the above data and by analogy with the pyrazine carboxaldehyde reaction, the compound was assigned the structure 3-(2-pyridinyl)imidazo [1, 5-a] pyridine (II). Full proof of the structure was provided by an unambiguous synthesis of II by the method of Bower and Ramage (4).

Figure I



Attempts to extend the reaction to aromatic carbocyclic aldehydes e.g. benzaldehyde, 3-hydroxy and 3, 5-dihydroxybenzaldehyde were not successful, the starting material was always recovered. Figure II depicts a possible mechanism for this reaction.

Figure II



References

(1) A. Hirschberg and D. P. Smith, J. Heterocyclic Chem., 3, 103 (1966).

(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, Mass Spectrometry of Organic Compounds, Holden-Day Inc., San Francisco, 1967, p. 566.

(3) In a system that is completely planar a deshielding effect would be predicted for this proton. See for example G. W. H. Cheesman and B. Tuck, Tetrahedron Letters, 4851, (1968).

(4) J. D. Bower and G. R. Ramage, J. Chem. Soc., 2834 (1955).

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