

A New Class of Heterocyclic Ring Tautomers

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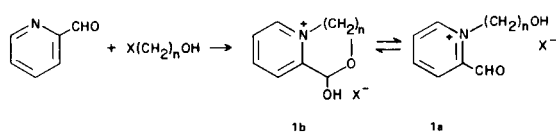
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Received July 7, 1977

Entry into the pyrido[2,1-c][1,4]oxazinium and pyrido[2,1-c][1,4]oxazepinium ring systems has been achieved by the interaction of picolinaldehyde with 2-bromoethanol and 3-bromopropanol, respectively. The products, ring-tautomeric hemiacetals, are presumably formed by rapid hemiacetalization, followed by an intramolecular Menshutkin Reaction.

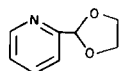
J. Heterocyclic Chem., 15, 347 (1978)

The fact that picolinaldehyde readily forms hemiacetals in alcohol solution (1,2) prompted the prediction that alkylation of picolinaldehyde with appropriately chosen halohydrins could give stable tautomers **1a** and **1b**.



This has been shown to be the case for **1b** ($n = 2,3$) where the rings are six- and seven-membered. The aldehyde and an equimolar quantity of 2-bromoethanol or 3-bromopropanol were stored under nitrogen in a desiccator at room temperature for several days. Preliminary washing of crude material was followed by recrystallization from acetonitrile to afford crystalline bromide salts. Their infrared spectra exhibited OH bands at 3100 cm^{-1} but no carbonyl absorption. The nmr spectra, measured in DMSO, were devoid of aldehyde proton but contained a characteristic methinyl proton at 6.4 or 6.5 ppm.

By comparison the methinyl proton in the (deuteriochloroform) nmr spectrum of picolinaldehyde dioxolane



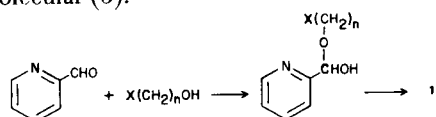
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(2) (3) appears at 5.80 ppm. One would expect a deshielding effect from the quaternary nitrogen in **1b**.

The crystalline, stable quaternary ammonium hemiacetals are designated as ring tautomers rather than polymeric structures. There is ample precedent for the formation of ring tautomers from uncharged hydroxy aldehydes (4). It is particularly noteworthy that alkylations under similar conditions with higher homologous halohydrins led to amorphous, unstable materials, very likely the products of polymerization. A case in point is the bright orange powder obtained from picolinaldehyde and 4-chlorobutanol. It could be stored under nitrogen at 0° with no apparent degradation, but exposure to the atmosphere for a few seconds caused immediate decomposition to an intractable material.

It is proposed that **1b** is formed by a sequential process of rapid hemiacetalization and alkylation, the

latter Menshutkin reaction being facilitated because it is intramolecular (5).



Support for this view comes from the observation that the aldehyde proton in the nmr spectrum diminishes rapidly upon addition of bromohydrin, with appearance of the typical methinyl peak at δ 6.1 (neat). By contrast the alkylation of pyridine with *n*-butyl bromide is sluggish, requiring pressure and heat.

The six-membered lactone corresponding to **1b** has previously been synthesized by the reaction of 2-bromoethanol with ethyl picolinate in refluxing acetonitrile (6). Although examples of five- and six-membered ring tautomeric hemiacetals, notably the sugars, are numerous, there are few cases of seven-membered ring tautomers (7-9).

To our knowledge these are the first recorded instances of ring tautomeric quaternary pyridinium hemiacetals, and the seven-membered ring compound (**1b**, $n = 3$) constitutes the first example of a pyrido[2,1-c][1,4]oxazepinium salt.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer. Nmr spectra were measured on a Jeol JMN-Mh-100 spectrometer with tetramethylsilane as an internal standard. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected.

3,4-Dihydro-1-hydroxy-1*H*-pyrido[2,1-c][1,4]oxazinium Bromide (**1b**, $n = 2$).

A mixture of 1.07 g. (0.01 mole) of picolinaldehyde and 1.25 g. (0.01 mole) of 2-bromoethanol was allowed to stand in a beaker in a desiccator flushed with nitrogen. Within four days, the solution solidified to a yellow, waxy solid. The material was pulverized under anhydrous ethyl ether to leach out unchanged starting material. Recrystallization from acetonitrile afforded 1.5 g. (65%) of nearly colorless crystals, m.p. $138-139^\circ$; ir (potassium bromide): 3100 cm^{-1} (OH); nmr (DMSO): δ 8.30-9.40 (m, 5, OH plus aromatic protons), δ 6.40 (s, 1, hemiacetal methinyl proton), δ 4.90 (m, 2, N-CH₂), δ 4.50 (m, 2, O-CH₂).

Anal. Calcd. for C₈H₁₀BrNO₂: C, 41.40; H, 4.34; Br, 34.43; N, 6.04. Found: C, 41.59; H, 4.56; Br, 34.63; N, 5.87.

1,3,4,5-Tetrahydro-1-hydroxy-pyrido[2,1-c][1,4]oxazepinium,

Bromide (**1b**, $n = 3$).

A mixture of 1.07 g. (0.01 mole) of picolinaldehyde and 1.39 g. (0.01 mole) of 3-bromopropan-1-ol was allowed to stand in a beaker in a desiccator until, after two weeks, the mixture had darkened. The addition of acetone caused the immediate precipitation of an orange solid. The acetone was decanted, and the solid was washed repeatedly with anhydrous ethyl ether until the odor of picolinaldehyde had disappeared. Recrystallization from acetonitrile was accompanied by extensive loss of material but provided 0.75 g. (30%) of product, m.p. 161-163°; ir (potassium bromide): 3100 cm^{-1} (OH); nmr (DMSO): δ 8.30-9.50 (m, 4, aromatic protons), δ 6.50 (s, 1, hemiacetal methinyl), δ 5.30 (m, 2, N-CH₂), δ 4.24 (m, 2, O-CH₂); the remaining protons were obscured by the solvent signal.

Anal. Calcd. for C₉H₁₂BrNO₂C, 43.92; H, 4.91; Br, 32.47; N, 5.69. Found: C, 43.83; H, 4.87; Br, 32.10; N, 5.89.

The Reaction of Picolinaldehyde with 4-Chlorobutan-1-ol.

A mixture of 1.07 g. (0.01 mole) of picolinaldehyde and 1.09 g. (0.01 mole) of 4-chlorobutan-1-ol was allowed to stand in a beaker in a desiccator under nitrogen. After three weeks the mixture had darkened considerably. The addition of anhydrous ethyl ether caused the formation of a flocculent, bright orange powder. This was washed repeatedly with anhydrous ether until no picolinaldehyde odor could be detected. It was necessary to centrifuge the solid between washings to avoid mechanical loss.

The solid could be stored under ether at 0° without visible decomposition, but exposure to air for a few seconds caused the solid to become a dark, brown tar.

Acknowledgment.

We are grateful to the University of New Hampshire for the awarding to J. E. D. of a Dissertation Year Fellowship.

REFERENCES AND NOTES

- (1) G. M. Steinberg, E. J. Poziomek, and B. E. Hackney, *J. Org. Chem.*, **26**, 368 (1961).
- (2) E. P. Crowell, W. A. Powell, and C. J. Varsel, *Anal. Chem.*, **35**, 184 (1963).
- (3) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).
- (4) C. D. Hurd and W. H. Saunders, *J. Am. Chem. Soc.*, **74**, 5324 (1952).
- (5) F. Bohlmann, N. Ottawa, and R. Keller, *Ann. Chem.*, **587**, 162 (1954).
- (6) F. Kröhnke, H. Schnegelberger, and W. Weis, *Chem. Ber.*, **97**, 3566 (1964).
- (7) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).
- (8) R. Escale and J. Verducci, *Bull. Soc. Chim. France*, 1203 (1974).
- (9) R. Valters, *Russ. Chem. Rev.*, **43**, 665 (1974).