[CONTRIBUTION FROM THE PROTECTIVE DEVELOPMENT DIVISION, U.S. ARMY CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Pyridine Ald-chlorimines[1]

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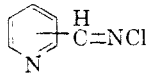
The preparation and properties of 2-(3- and 4-)pyridinalchlorimines, 4-pyridinalchlorimine hydrochloride and 4-pyridinalchlorimine dimethyl sulfate are described.

In view of the widespread interest in the general chemistry of pyridinecarboxaldehydes as exemplified in a recent review by Mathes and Sauermilch,[3] it was thought appropriate to report the synthesis and spectra of 2-(3- and 4-)pyridinalchlorimines, I(II and III).



I-III

This study was initiated primarily to obtain the above ald-chlorimines as intermediates in studies of chromogenic systems[4]; however, it is believed that this is the first report of monochloramine derivatives of pyridine carboxaldehydes and the first spectrophotometric study of any ald-chlorimine.

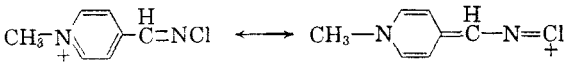
C. R. Hauser[5] with his coworkers synthesized various aromatic ald-chlorimines and studied their reaction with base. The synthesis of pyridine ald-chlorimines essentially followed the procedure outlined by Hauser, Gillaspie, and LeMaistre[5i] for aromatic ald-chlorimines in that the aldehyde was treated at 0° with a freshly prepared aqueous solution of monochloramine.

The compounds reported in this paper were quite unstable each decomposing to some extent on standing at 0° for a week. The least stable was I which turned light green on standing in the air at room temperature for an hour on a porous plate. The same compound decomposed violently with gas evolution to a brown tar on standing for less than an hour at room temperature in a loosely capped vial. Slow heating any of the heterocyclic ald-chlorimines on a spatula near an open flame resulted in decomposition with brilliant flashing.

Because of their instability characteristics, we used the compounds immediately after synthesis. If not immediately used the only recommended procedure is storage of the ald-chlorimines at 0° over potassium carbonate in a desiccator.[5i]

A study of the effect of base on III showed that with triethylamine a clean and quantitative reaction took place to yield isonicotinonitrile (IV). This represented a good synthetic route to nitriles from starting pyridine carboxaldehydes, an extension of a method by Hauser and Gillaspie[5d] for aromatic nitriles.

Passing hydrogen chloride into a dry ethereal solution of III precipitated a colorless solid whose elemental analyses corresponded to calculated values for the hydrochloride (V). Alkylation of III with dimethyl sulfate was accomplished quite readily. An excess of the alkylating agent enhanced decomposition of the ald-chlorimine function; however, an excellent yield was obtained using a slight excess of the pyridinalchlorimine. No attempts were made to quaternize the 2- or 3-derivatives. Resonance contributions of the type illustrated by structure VII are expected in the



VI VII

quaternary salts. From a stability viewpoint, however, no advantages were found in quaternizing the tertiary pyridinalchlorimine.

An excess of triethylamine with the quaternary ald-chlorimine salt (VI) caused vigorous reaction with heat generation and brilliant blue color formation. In a few minutes the blue color changed to purple and finally to red-brown. The mixture was allowed to cool to room temperature; addition of ether precipitated an uncharacterized dark red-brown gum. Titration of the quaternary ald-

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(2) (a) This paper is constructed in part from a dissertation by E. J. Poziomek submitted to the faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science, June 1960. (b) To whom inquiries should be directed at Army Chemical Center, Maryland. (c) Work done at Army Chemical Center, Maryland.

(3) W. Mathes and W. Sauermilch, *Chemiker Ztg.*, 82, 647 (1958).

(4) Details to be reported later elsewhere.

(5) (a) C. R. Hauser, *J. Am. Chem. Soc.*, 52, 1108 (1930). (b) C. R. Hauser and M. L. Hauser, *J. Am. Chem. Soc.*, 52, 2050 (1930). (c) C. R. Hauser, M. L. Hauser, and A. G. Gillaspie, *J. Am. Chem. Soc.*, 52, 4158 (1930). (d) C. R. Hauser and A. G. Gillaspie, *J. Am. Chem. Soc.*, 52, 4517 (1930). (e) C. R. Hauser, G. J. Haus, and H. A. Humble, *J. Am. Chem. Soc.*, 53, 4225 (1931). (f) C. R. Hauser, H. A. Humble, and G. J. Haus, *J. Am. Chem. Soc.*, 54, 2476 (1932). (g) C. R. Hauser, J. W. LeMaistre, and A. E. Rainsford, *J. Am. Chem. Soc.*, 57, 1056 (1935). (h) C. R. Hauser and E. Moore, *J. Am. Chem. Soc.*, 55, 4526 (1933). (i) C. R. Hauser, A. G. Gillaspie, and J. W. LeMaistre, *J. Am. Chem. Soc.*, 57, 567 (1935).

chlorimine in water with sodium hydroxide also led to a red colored solution.

The ultraviolet absorption of I–III and V (Experimental, Table I) was examined at a concentration of $1 \times 10^{-4}M$ in methanol at room temperature using a Perkin-Elmer Model 13-U spectrophotometer. The curves exhibited both highly characteristic emission and absorption peaks. The transition from absorption to emission measurements was easily effected with the Perkin-Elmer instrument (see Experimental for more details.) The position of the ald-chlorimine function in the pyridine ring did not affect the λ_{max} to any significant extent although differences in ϵ_{max} were noted; therefore, the absorption spectra do not appear to distinguish between the various isomers. The spectral determinations were repeated after allowing the sample solutions to stand overnight; it was found that wherein only emission readings were recorded after twenty-four hours the 2-isomer was the least stable. The stability of the ald-chlorimines in solution paralleled their solid state stability.

TABLE I

ULTRAVIOLET ABSORPTION OF PYRIDINALCHLORIMINES[a]

Compound	λ_{max} ($\epsilon \times 10^{-4}$)	λ_{min} ($\epsilon \times 10^{-4}$)
I[b]	227(−0.118)	233(−0.278)
	243(0.281)	263(−0.660)
	268(−0.175)	270(−0.470)
	277(0.344)	
II	243(0.646)	263(−0.316)
	267(−0.120)	270(−0.272)
	277(0.283)	
III	243(0.935)	263(−0.459)
	268(−0.247)	270(−0.540)
	282(0.157)	
V	244(0.708)	264(−0.207)
	268(0.039)	270(−0.261)
	276(0.234)	

[a] Negative values signify that measurements were made using the I_0/I scale and represent an emission of light from the irradiated sample. [b] It was evident that the 2-pyridinalchlorimine sample solution was rapidly decomposing during the absorption measurements.

Fig. 1 illustrates absorption spectra of III at $1 \times 10^{-4}M$ in methanol using the Beckman DU and the Perkin-Elmer 13-U spectrophotometers. The differences in spectra arise from incongruity of the incident light in that the sample is irradiated by monochromatic light in the Beckman instrument and polychromatic light (before collimation) in the Perkin-Elmer model. The recorded absorption with the Perkin-Elmer instrument at a particular wave length is effectively an algebraic sum of the absorption at the wave length plus the emission associated with absorption at some lower wave length. The absorption of tertiary and quaternary pyridine aldehydes and oximes[6] was measured

(6) (a) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957). (b) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

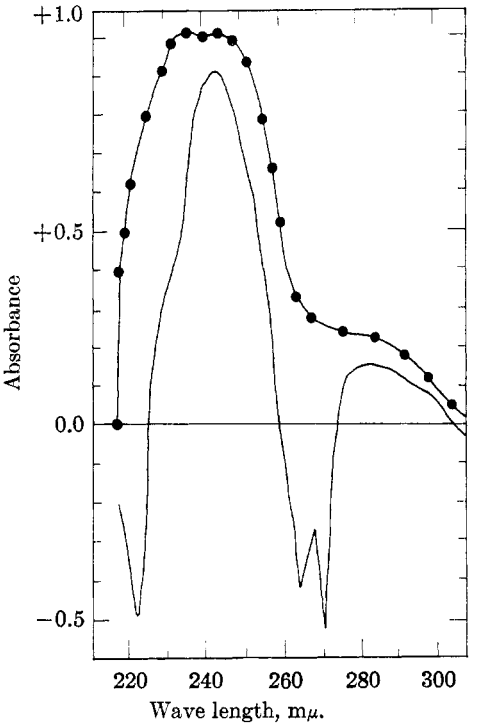

Fig. 1. Absorption spectra of 4-pyridinalchlorimine ($1 \times 10^{-4}M$ in methanol) using a Perkin-Elmer Model 13-U spectrophotometer (continuous line) and a Beckman Model DU spectrophotometer (circles)

under similar conditions; however, emission appears specific to the ald-chlorimine function or its decomposition products.

The spectrophotometric study was extended to absorption measurements of III at various concentrations. Linear plots were obtained of absorbance and emission against concentration. Fluorescence was quenched above a concentration $2.6 \times 10^{-4}M$ but predominated below $0.4 \times 10^{-4}M$. Between these concentrations both absorption and emission were measured. The observed linearity suggests that the quenching of fluorescence is a true concentration effect.

The ultraviolet data presented in this paper were not used other than in characterizing pyridinalchlorimines; however, the interesting fluorescent properties provide for an expansion of spectrophotometric studies of not only pyridine ald-chlorimines but also of the ald-chlorimine function.

EXPERIMENTAL

2-Pyridinalchlorimine (I). To a 400 ml. aqueous solution of monochloramine (0.20 mole) at 0°, freshly prepared according to the method of Hauser, Gillaspie and LeMaistre,[6i] was added 10.8 g. (0.10 mole) of pyridine-2-carboxaldehyde. The ald-chlorimine immediately precipitated and was quickly filtered. If the filtration were delayed or occurred slowly, the ald-chlorimine decomposed with solution in the slightly basic media. The precipitate was washed twice with cold distilled water and dried by pressing between porous plates. The cream-white product recrystallized from methanolic solution by cooling in the Dry Ice chest gave 5.2 g.

(yield 37%) of the ald-chlorimine as long colorless needles, m.p. 54° dec.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6. Found: C, 51.4; H, 3.8.

The following ald-chlorimines were similarly prepared:

3-Pyridinalchlorimine (II). Colorless needles (7.1 g., yield 51%) from methanol, m.p. 51–52° dec.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6; Cl, 25.2. Found: C, 51.4; H, 3.6; Cl, 25.0.

4-Pyridinalchlorimine (III). Colorless needles (10.0 g., yield 71%) from methanol. The sample melted at 104°, resolidified and finally decomposed at 175°.

Anal. Calcd. for $C_6H_5ClN_2$: C, 51.3; H, 3.6; Cl, 25.2. Found: C, 51.1; H, 3.6; Cl, 25.1.

Isonicotinonitrile (IV). To 2.8 g. (0.02 mole) of 4-pyridinalchlorimine in 20 ml. of absolute methanol was added triethylamine (5 ml.); the clear solution turned light yellow. Heat was generated and the solution was kept below reflux temperature by means of an ice bath. At the end of 1 hr. about 200 ml. of absolute ether was added. Triethylamine hydrochloride was filtered and the filtrate was evaporated to dryness in a rotating type evaporator. The residue 1.9 g. (92% yield) was recrystallized from benzene giving 1.7 g. of crystalline solid, m.p. 78–79° (m.p. reported[7] 78.5–80°).

4-Pyridinalchlorimine hydrochloride (V). A solution of 1.4 g. (0.01 mole) of freshly prepared 4-pyridinalchlorimine in 50 ml. of dry ether was maintained at room temperature while a stream of dry hydrogen chloride was added for 5 min. with stirring. The mixture was filtered and the precipitate washed twice, each time with 20 ml. of dry ether, to give the hydrochloride 1.1 g. (yield 62%) as colorless fine powder, m.p. 114° dec.

Anal. Calcd. for $C_6H_6Cl_2N_2$: Cl, 40.0; neut. equiv., 178. Found: Cl, 39.5; neut. equiv., 177.

pK_a *Value.* The pK_a value was determined to be 4.3 at room temperature (25–27°), from potentiometric data, assuming pK_a to be pH of half neutralization. Approximately 100 mg. of sample dissolved in 5 ml. of water was titrated with 0.1*N* sodium hydroxide.

4-Pyridinalchlorimine dimethyl sulfate (VI). To 5.6 g. (0.04 mole) of 4-pyridinalchlorimine in 80 ml. of acetone cooled to 0° by means of an ice-water bath was added 4.8 g. (0.038 mole) dimethyl sulfate. The clear colorless solution was allowed to warm to room temperature. At the end of 15 min. long needles were noticed growing in feather like structures at the bottom of the flask. After a total of 4 hr. standing, the mixture was filtered and gave 8.4 g. (yield 79%) of the quaternary salt as long colorless needles, m.p. 58–60° dec.

Anal. Calcd. for $C_8H_{11}Cl_1H_2O_4S$: C, 36.0; H, 4.1; Cl, 13.3. Found: C, 35.9; H, 4.7; Cl, 13.2.

Determination of ultraviolet absorption spectra. The absorption spectra were obtained using a Perkin-Elmer Model 13-U spectrophotometer unless otherwise indicated. The compounds were dissolved in anhydrous methanol and diluted to the desired concentration with additional solvent. The measurements were first performed using the I/I_0 scale, then repeated with the I_0/I scale. This gave both absorption and emission readings as a function of instrument drum readings. The readings were then converted to wave length from an available calibration curve, corrected for the air blank, and plotted to give continuous curves encompassing both absorption and emission character (see Fig. 1). To simplify assigning maxima and minima, emission readings were considered negative and the curve treated as an absorption entity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

The Synthesis of Some 2,4,5-Trisubstituted Pyrimidines[1]

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Condensation of acetamidine and *S*-alkylthioureas with diethyl ethoxymethylenemalonate and diethyl formylsuccinate by known methods gave 2-methyl- and 2-alkylthio-5-substituted 4-pyrimidones. The 4-pyrimidones were converted to the corresponding 4-alkylthio- and 4-(substituted-amino)pyrimidines, through the intermediate 4-chloropyrimidines. Several pyrimidines were converted to 2-hydrazinopyrimidines, 5-pyrimidinecarboxylic acid hydrazides, or 5-hydroxymethylpyrimidines.

The biological activity of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (methioprim),[4,5] first prepared by Ulbricht and Price[6] has prompted us to synthesize a variety of 2,4,5-trisubstituted pyrimidines.[7,8,9] Many of these compounds have been assayed for activity in experimental rodent

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