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TECHNICAL REPORT

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A NEW SYNTHESIS OF 2-PYRIDINE ALDOXIMES

by

Brennie E. Hackley, Jr.
Medical Research Laboratory

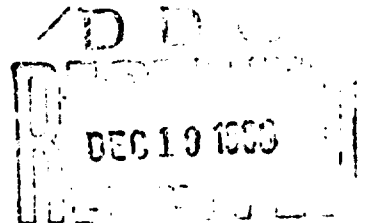
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Ash Stevens, Inc., Detroit, Michigan

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FOREWORD

The work described in this report was authorized under Task 1L013001A91A02, In-House Laboratory Independent Research, Chemical (U). This work was started in January 1965 and completed in January 1966. The experimental data are contained in notebooks MN-1826 and MN-1908 and Comprehensive Report, November 1965, Contract DA-18-035-AMC-291(A).

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DIGEST

The use of 2-pyridine aldoxime methochloride (2-PAM) in the treatment of organophosphorus poisoning has stimulated interest in finding new convenient routes for the synthesis of the precursor 2-pyridine aldoximes. We have found that the reaction of 2-chloromethyl pyridines with buffered solutions of aqueous hydroxylamine gives good yields of the corresponding 2-pyridine aldoximes.

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A NEW SYNTHESIS OF 2-PYRIDINE ALDOXIMES

I. INTRODUCTION.

The use of 2-pyridine aldoxime methochloride (2-PAM) in the treatment of organophosphorus poisoning has stimulated interest in finding new convenient routes for the synthesis of the precursor 2-pyridine aldoximes.¹

The classical method for the syntheses of these compounds involves acetic anhydride rearrangements^{2, 3} of the corresponding 2-picoline N-oxide to the acetate of 2-pyridine methanol, hydrolysis of the acetate to the alcohol, oxidation of the carbinol to the aldehyde, and then conversion of the aldehyde to the oxime. The overall yield for this multistep sequence for a series of substituted 2-picoline N-oxides is 20% to 30%.⁴ Recently Forman⁵ has reported the direct high-yield oximation of 2-picoline using sodium amide and n-butyl nitrite. The applicability of the procedure to substituted 2-picolines is not presently known.

We have found that the reaction of 2-chloromethyl pyridines with buffered solutions of aqueous hydroxylamine gives good yields of the corresponding 2-pyridine aldoximes. The procedure consists of heating the 2-chloromethyl pyridine in an aqueous ethanolic solution of hydroxylamine hydrochloride buffered to pH 7 to 8 on a steam bath for 2 to 3 hr. When the solution is cooled to room temperature, the product usually crystallizes from the solution.

II. EXPERIMENTAL.

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlabs, Inc., Indianapolis, Indiana.

The 2-chloromethyl pyridines were prepared by a modification and extension of previously reported procedures.^{6, 7} Substituted pyridine N-oxides were treated with a twofold excess of methanesulfonyl chloride or p-toluenesulfonyl chloride in refluxing dioxane for 6 to 12 hr. Best results were obtained with p-toluenesulfonyl chloride in the case of 6-methyl, 5-methyl, and 5-ethyl derivatives.

New 2-chloromethyl pyridines prepared by this procedure were as follows: 4-chloro, 51%, bp 51°C (0.9 mm Hg), n_D^{25} 1.5225, picrate, mp 123-125°C; 4-carboethoxy, 62%, bp 75°C (0.12 mm Hg), n_D^{25} 1.5208, picrate, mp 110-111°C; 5-carboethoxy, 59%, bp 64°C (0.05 mm Hg), n_D^{25} 1.5252,

picrate, mp 123-125°C; 5-chloro, 40%, bp 48°C (0.5 mm Hg), n_D^{25} 1.5293, picrate, mp 96-98°C. All compounds had acceptable elemental analyses in carbon, hydrogen, and nitrogen (chlorine).

The appropriate 2-chloromethyl pyridine (0.02 mole) was added to a solution of hydroxylamine hydrochloride (0.1 mole) in 40 ml of 50% aqueous ethanol (v/v), which had been buffered to pH 7 to 8 with 10 N sodium hydroxide solution. The solution was heated on a steam bath for 2 to 3 hr; ethanol was added from time to time to maintain a homogenous solution. When the solution was cooled, the product crystallized; it was recrystallized from either benzene or aqueous ethanol.

III. RESULTS.

The data are summarized in the following table.

Table. Conversion of Monosubstituted (R) 2-Chloromethyl Pyridines to 2-Pyridine Aldoximes

R	Yield	Melting point
	%	°C
H	50	112-114 <u>a/</u>
4-Cl	18	151-153 <u>b/</u>
5-Cl	63	194-195 <u>c/</u>
4-COOC ₂ H ₅	52	157-158 <u>d/</u>
5-COOC ₂ H ₅	72	128-129 <u>e/</u>
5-C ₂ H ₅	78	149-150 <u>f/</u>
6-CH ₃	91	170-172 <u>g/</u>

a/ Ginsberg, S., and Wilson, I. J. Am. Chem. Soc. 79, 481 (1957); report a melting point of 114°C; mixed melting point with an authentic sample was undepressed.

b/ Furukawa, S. Yakugaku Zasshi. 77, No. 1, 11 (1957); reports a melting point of 154-155°C; mixed melting point with an authentic sample was undepressed.

c/ Calcd for C₆H₅ClN₂O: C, 46.04; H, 3.22; N, 17.90.
Found: C, 45.74; H, 3.40; N, 17.63

d/ Calcd for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.42.
Found: C, 55.39; H, 5.29; N, 14.32

e/ Calcd for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.42.
Found: C, 55.86; H, 5.42; N, 14.07

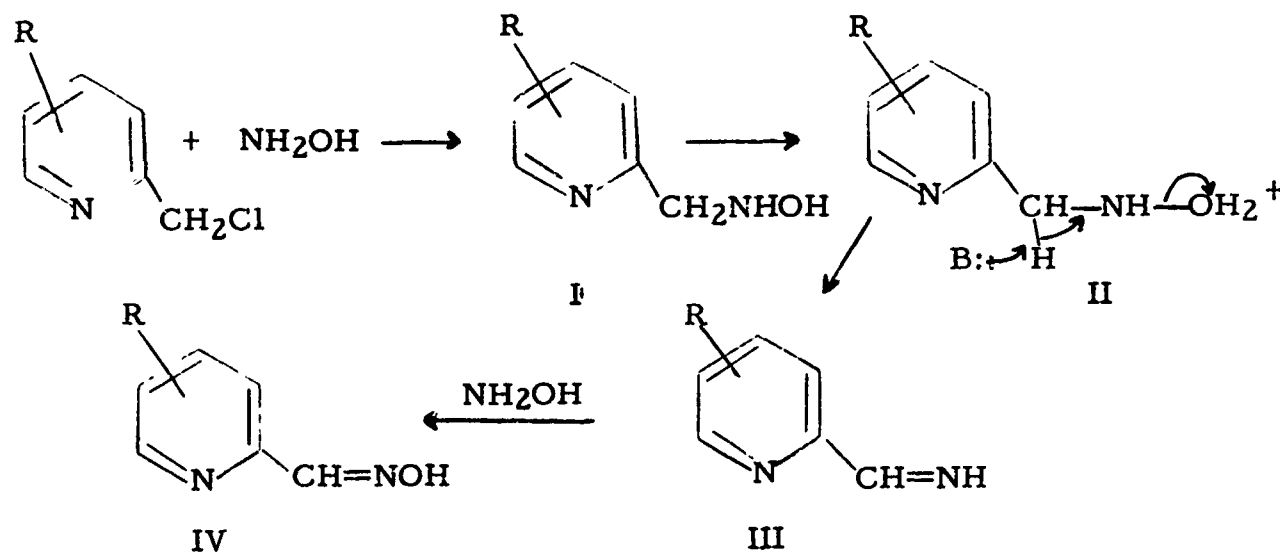
f/ Calcd for C₉H₁₀N₂O: C, 64.00; H, 6.70; N, 18.65.
Found: C, 64.17; H, 6.95; N, 18.53

g/ Ginsberg, S., and Wilson, I. J. Am. Chem. Soc. 79, 481 (1957); report a melting point of 170-171°C.

IV. DISCUSSION.

The reaction of 2-chloromethyl pyridines with buffered solutions of aqueous hydroxylamine is significant in view of the fact that treatment of *p*-chlorobenzyl chloride under identical conditions gave the dialkyl hydroxylamine as the only product. The acidity of the hydrogens alpha to the halo group seems to be important since 2-bromocyclohexanone, on treatment with buffered hydroxylamine solution, affords a 34% yield⁸ of 1,2-cyclohexane-dione dioxime.

In view of this acidity requirement, the following mechanism may be postulated: nucleophilic displacement of the chloro group yields the alkylhydroxylamine (I), subsequent protonation of the hydroxyl group of I to produce II, followed by the elimination, yields the aldimine (III),⁷ and the aldimine in the presence of excess hydroxylamine yields the product oxirne (IV).



V. CONCLUSION.

The reaction of 2-chloromethyl pyridines with buffered solutions of aqueous hydroxylamine gives good yields of the corresponding 2-pyridine aldoximes.

LITERATURE CITED

1. Heath, D. F. Organophosphorus Poisons. Pergamon Press, New York. 1961.
2. Bockleheide, V., and Linn, W. J. Am. Chem. Soc. 76, 1286 (1954).
3. Traynelis, V. J., and Pacini, P. L. J. Am. Chem. Soc. 86, 4917 (1964).
4. Furukawa, S. Yakugaku Zasshi. 77, No. 1, 11 (1957).
5. Forman, S. J. Org. Chem. 29, 3323 (1964).
6. Matsumara, E., Hirooka, T., and Imagawa, K. J. Chem. Soc. Japan, Pure Chem. Sect., 82, 616 (1961).
7. Voza, J. F. J. Org. Chem. 27, 3856 (1962).
8. Belcher, R., Hoyle, N., and West, T. S. J. Chem. Soc. 1958, 2743.

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