# An Improved Procedure for Preparing 1-Methylpyridinium-2-aldoxime Chloride

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In the therapy of poisoning by anticholinesterase chemicals, 1-methylpyridinium-2-aldoxime (2-PAM) salts are being used with increasing frequency. The iodide salt was the first one synthesized[1]; however, the limitations of this salt, because of its low water solubility and the possibility of iodism occurring in patients receiving large doses of the drug, led to the preparation of salts having more desirable properties and consequently to the selection of the chloride salt as the one of choice.[2]

The preparation of 2-PAM chloride by way of the iodide salt has been reported.[2,3] However, certain commercial samples of 2-PAM chloride that were made by treating 2-PAM iodide with silver chloride were found to contain traces of silver and iodide ions.[4] An efficient method for preparing 2-PAM chloride in good yield and in high purity is of significant importance.

## Experimental

Pyridine-2-aldoxime (2 g.) was dissolved in 20 ml. of N,N-dimethylformamide[5] contained in a pressure bottle (Fisher). Methyl chloride was added by passing the gas through a large Dewar-type condenser packed with solid carbon dioxide. After addition of 5 g. of methyl chloride[6] the bottle was closed and placed inside a steel safety jacket provided with an inlet tube and closed with a steel cap in which several small holes had been drilled. Steam was passed into the jacket for periods up to 22 hr. The temperature within the jacket reached 95–100°. Pressures up to 7 kg./cm.$^2$ developed within the bottles, as determined by a few check experi-

(1) I. B. Wilson, S. Ginsburg, and D. Nachmansohn, U. S. Patent 2,816,113 (1957).

(2) A. A. Kondritzer, R. I. Ellin, and L. J. Edberg, *J. Pharm. Sci.* **50**, 109 (1961).

(3) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

(4) R. I. Ellin and P. Zvirblis, U. S. Army Chemical R&D Laboratories Technical Memorandum 23-20 (December, 1960).

(5) Of a number of solvents tried, including ethanol, acetone, benzene, tetrahydrofuran, and a high boiling petroleum fraction consisting mainly of aromatic hydrocarbons. N,N-dimethylformamide was the only one in which a relatively pure product was obtained in good yield.

(6) Molar ratios of methyl chloride to pyridine-2-aldoxime greater than 6:1 did not increase the yield of quaternary salt.

TABLE I

PREPARATION OF 1-METHYLPYRIDINIUM-2-ALDOXIME CHLORIDE WITH N,N-DIMETHYLFORMAMIDE AS SOLVENT

| Time, hr. | 2-PAMCl, % Theory[a] | Purity, % | Color |
|---|---|---|---|
| 2 | 20 | 100 | White |
| 5 | 40 | 100 | White |
| 8 | 45 | 97 | White |
| 12 | 64 | 99 | Gray |
| 16 | 70 | 98 | Gray |
| 22 | 80 | 98 | Dark gray |

[a] Based on yield before recrystallization. When the first order rate constant of the formation of 2-PAM chloride is calculated with respect to the pyridine-2-aldoxime, using the method of least squares, a value of $6.9 \times 10^{-2}$ hr.$^{-1}$ is obtained; the half-life, $t_{1/2}$, is calculated to be 10.1 hr. The data indicate that the method could be adapted to a continuous process.

ments in which the reaction was carried out in small steel tubes with pressure gauges attached. At the end of the reaction time, the bottles were cooled to below room temperature and opened. The products were filtered off, washed, and dried.[7] The chloride salts melted within a 2° range between 235–238° dec. and had a purity of 98–100% by ultraviolet spectrophotometric analysis.[8]

For recrystallization, 1 g. of the product was dissolved in 30 ml. of 95% ethanol with heat, the solution filtered and 50 ml. of ether added to the cooled solution with stirring. Crystallization was allowed to take place in the cold; the product was collected on a filter, washed with a small volume of a cold mixture of ethanol–ether (3:5) and dried *in vacuo;* yield, 85–90%.

(7) After reaction times of 10–12 hr., the product was practically free of discoloration. From this time to 22 hr., the product had a grayish appearance.

(8) R. I. Ellin and A. A. Kondritzer, *Anal. Chem.*, **31**, 200 (1959).