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### SYNTHESIS OF 1-(2-PYRIDINE-1-OXIDE)-2-(1-METHYL-2-PYRIDINIUM)-ETHANE CHLORIDE

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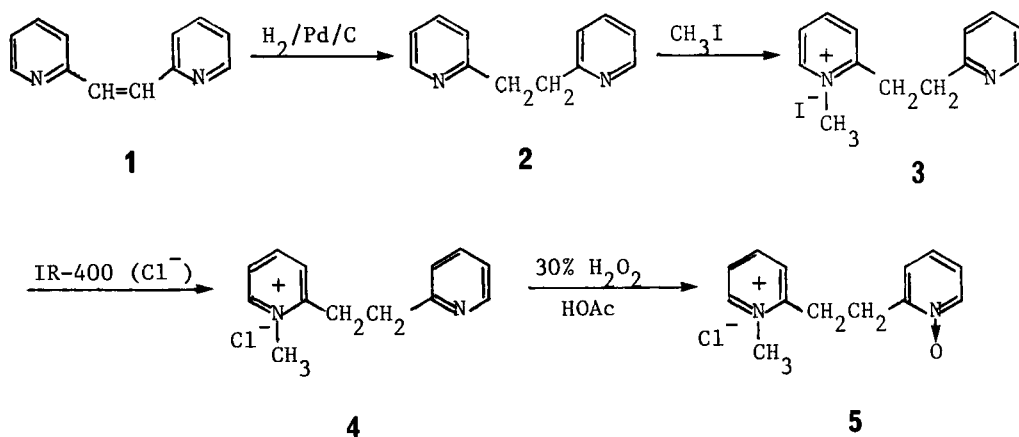
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SYNTHESIS OF 1-(2-PYRIDINE-1-OXIDE)-2-(1-METHYL-2-PYRIDINIUM)-  
ETHANE CHLORIDE

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In conjunction with the preparation of pyridine-1-oxides as potential antidotes of organophosphate intoxication, there is a need to develop a synthetic procedure to prepare compounds which contain a quaternary pyridinium and a pyridine-1-oxide function in the same molecule. The former is required for specific binding to acetylcholinesterase and the latter serves as a nucleophile to reactivate the organophosphate-inhibited enzyme.<sup>1</sup> Since both amines and amine-N-oxides are nucleophiles and both can be alkylated, selective alkylation of an amino function in the presence of an N-oxide is difficult. In this study, we have developed a facile procedure to prepare 1-(2-pyridine-1-oxide)-2-(1-methyl-2-pyridinium)ethane chloride which contains both pyridinium and pyridine-1-oxide groups.



1,2-bis-(2-Pyridyl)ethylene (**1**) was hydrogenated under the catalysis of 5% Pd/C to give 1,2-bis-(2-pyridyl)ethane (**2**) in 93% yield. Compound **2** was methylated by treatment with  $CH_3I$  in tetrahydrofuran (THF) solution at room temperature overnight to give good yield of the monomethylated quaternary pyridinium iodide salt **3** which precipitated out of the THF solution and thus was prevented from forming the bis-quaternary pyridinium salt. Since iodide ion was easily oxidizable by  $H_2O_2$  to  $I_2$ , compound **3** was converted to the corresponding chloride salt **4** by the use of an ion-exchange resin. The  $H_2O_2$  oxidation procedure of Boekelheide and Linn<sup>2</sup> was adapted to convert **4** to **5**.

## EXPERIMENTAL SECTION

1,2-bis-(2-Pyridyl)ethane (2).- To the solution of 1,2-bis-(2-pyridyl)ethylene (1, 4.5 g, 24.7 mmoles) in 100 ml of 95% EtOH was added 0.5 g of 5% Pd/C. The mixture was hydrogenated in a Parr hydrogenator at 20 psi hydrogen pressure. The catalyst was removed by filtration and the filtrate was evaporated to dryness under the reduced pressure to give an oil which crystallized from hexane to give 4.2 g (93%) of colorless prisms, mp. 50-51°, lit.<sup>3</sup> mp. 49°. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.24 (s, 4H), 7.04 (m, 4H), 7.50 (m, 2H), 8.51 (d, 2H, J = 5.4 Hz).

1-(2-Pyridyl)-2-(1-methyl-2-pyridinium)ethane Iodide (3).- To a solution of 1,2-bis-(2-pyridyl)ethane (2, 10 g, 54.4 mmoles) in 100 ml of THF was added 12 g (84.5 mmoles) of iodomethane. The mixture was stirred at room temperature overnight (17 hrs). The precipitate was collected to give 16 g (91%) of 3 which was recrystallized from CH<sub>3</sub>CN to give pale yellow crystals, mp. 173-175°. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.35-3.59 (m, 4H), 4.34 (s, 3H), 7.36 (m, 2H), 7.90 (m, 3H), 8.44 (m, 2H), 8.79 (d, 1H, J = 6.3 Hz).

Anal. Calcd. for C<sub>13</sub>H<sub>15</sub>IN<sub>2</sub>: C, 47.85; H, 4.60; N, 8.59; I, 38.96

Found: C, 47.76; H, 4.57; N, 8.56; I, 38.93

Compound 3 was converted to its chloride salt by passing its solution in a minimum of H<sub>2</sub>O through an IR-400 (Cl<sup>-</sup>) ion exchange resin. The fractions containing the product (detected by UV or iodine vapor on a silica gel plate) were pooled and lyophilized to give the corresponding chloride (4), mp. 90-93°.

Anal. Calcd. for C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>•1.4 H<sub>2</sub>O: C, 60.09; H, 6.85; N, 10.78; Cl, 13.67

Found: C, 60.32; H, 6.80; N, 10.80; Cl, 13.76

1-(2-Pyridine-1-oxide)-2-(1-methyl-2-pyridinium)ethane Chloride Hydrate (5).- To a solution of 4 (7g, 30 mmoles) in HOAc (80 ml) was added 12 ml of 30% H<sub>2</sub>O<sub>2</sub>. The solution was heated at 80° for 3 days. During the course of the reaction, two additional 5 ml portions of 30% H<sub>2</sub>O<sub>2</sub> were added at 24 hrs intervals. The solvent was removed under reduced pressure and the residual oil crystallized from CH<sub>3</sub>CN-THF. The solid mass was purified by trituration with hot CH<sub>3</sub>CN, cooled and the precipitate was collected to give 3.5 g (47%) of the desired product. Recrystallization from CH<sub>3</sub>CN-MeOH gave white crystals, mp. 222-223° (dec.). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.55 (m, 4H), 4.45 (s, 3H), 7.68 (m, 3H), 7.95 (m, 2H), 8.41 (m, 2H), 8.81 (d, 1H, J = 7.2 Hz).

Anal. Calcd. for C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>O•H<sub>2</sub>O: C, 58.10; H, 6.33; N, 10.43; Cl, 13.22

Found: C, 57.85; H, 6.69; N, 10.35; Cl, 13.10

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