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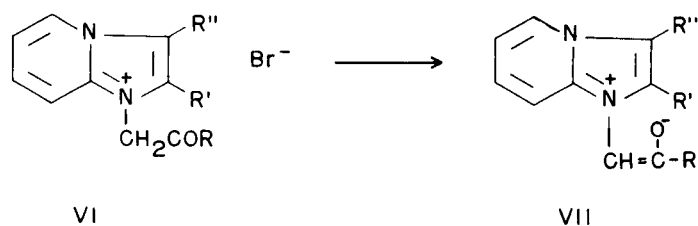
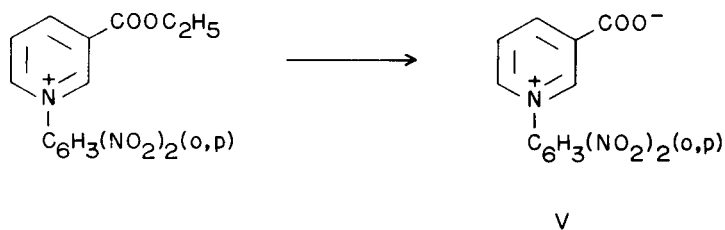
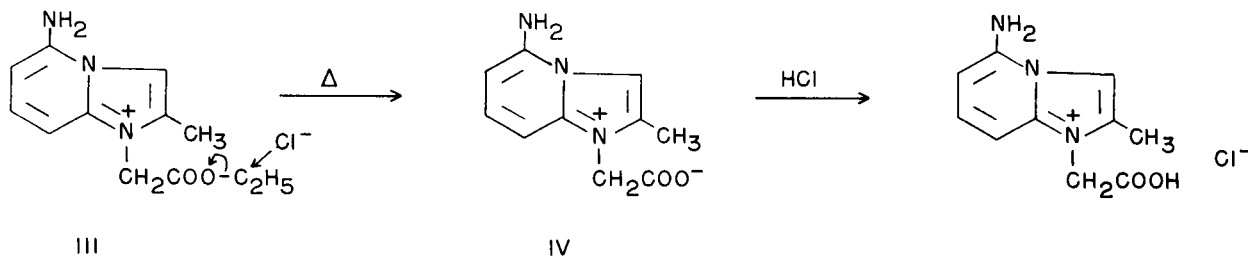
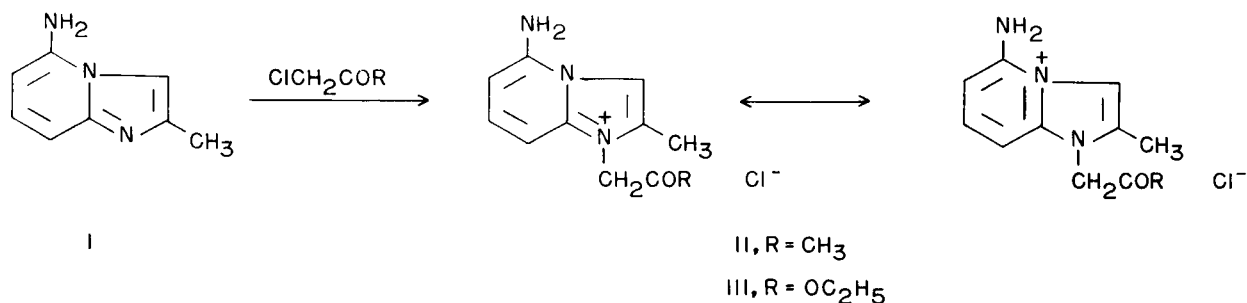
Betaine Formation in the Imidazo [1,2-a] pyridine System

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Recently the first successful synthesis of 5-aminoimidazo[1,2-a]pyridines from 2,6-diaminopyridine and α -haloketones was reported (1). One of these compounds, 5-amino-2-methylimidazo[1,2-a]pyridine (I), was prepared independently in the present work,

and was subjected to further reactions with α -halo-carbonyl compounds.

Treatment of I with chloroacetone and ethylchloroacetate gave the quaternary products II and III respectively, which exhibited carbonyl and primary



amine absorption bands in the infrared region.

Compound III subsequent to melting at 223–225° resolidifies and then does not remelt below 300°. To investigate the significance of this observation, a sample of III was heated in Dowtherm A. At 200–210° a vigorous reaction ensued with the evolution of a gas. The reaction was completed by raising the temperature to 255°. The resulting white solid was very water soluble but was insoluble in organic solvents. It was free of chloride ion, and as noted previously did not melt below 300°. Its ultraviolet absorption spectrum resembled quite closely that of III; however, the infrared spectrum lacked the ester carbonyl at 5.75 μ , and showed strong bands at 5.96 and 6.1 μ . Elemental analyses of the product and its hydrochloride salt indicated that the elements of ethyl chloride had been lost. This fact was substantiated by collecting the gas evolved in the thermal reaction, and identifying it as ethyl chloride by boiling point and gas chromatographic analysis.

The combined evidence supports the formation of the betaine IV through alkyl-oxygen bond fission of the carboxy group. The infrared band attributable to COO⁻ in the spectrum of pyridine betaine has been reported (2) to occur at 6.06 μ , which agrees well with the strong bands present in the spectrum of IV.

Vompe and Turitsyna (3) postulated the formation of the betaine V by a similar reaction; however, they did not isolate and identify the products.

The conversion of imidazo[1,2-a]pyridinium salts (VI) into "enol betaines" (VII) with strong aqueous caustic (4) represents the only other betaine synthesis in this ring system.

EXPERIMENTAL (5)

5-Amino-2-methylimidazo[1,2-a]pyridine (I).

A mixture of 109 g. (1 mole) of 2,6-diaminopyridine and 97 g. (1.05 moles) of chloroacetone in 450 ml. of absolute ethanol was heated at reflux for 8 hours. The mixture was cooled, and the solid filtered and rinsed with cold ethanol to give 44 g. (24%) of I·HCl, m.p. >300° (lit. (1) dec. above 240°). After several recrystallizations from ethanol an analytical sample was obtained; λ max (H₂O), 225 (ϵ , 30,550), 313 m μ (ϵ , 11,280); λ max (Nujol), 3.1, 3.2 and 6.02 μ .

Anal. Calcd. for C₈H₉N₃·HCl: C, 52.31; H, 5.49; Cl, 19.35. Found: C, 52.55; H, 5.28; Cl, 19.36.

The free base was prepared by dissolving the hydrochloride in water and adding ammonium hydroxide solution to give white needles, which were recrystallized from water, m.p. 156–158°; λ max (Nujol), 2.9, 2.95, 3.1 and 6.1 μ .

Anal. Calcd. for C₈H₉N₃: C, 65.28; H, 6.16. Found: C, 65.15; H, 5.96.

1-Acetyl-5-amino-2-methylimidazo[1,2-a]pyridinium Chloride (II).

A solution of 31 g. (0.21 mole) of I and 27.3 g. (0.295 mole) of

chloroacetone in 115 ml. of absolute ethanol was heated at reflux for 15 hours. The solvent was removed under reduced pressure on a steam bath, and the dark solid residue slurried with 2-propanol and then with a minimum of cold ethanol. After filtering and drying, the yield of white crystals was 45.5 g. (90%), m.p. 231–237°. Recrystallization from a 1:1 mixture of ethanol and 2-propanol raised the melting point to 239–240°; λ max (H₂O), 228 (ϵ , 28,100), 323 m μ (ϵ , 14,600); λ max (Nujol), 3.2, 3.25, 5.8 and 6.02 μ .

Anal. Calcd. for C₁₁H₁₄ClN₃O: C, 55.11; H, 5.89; Cl, 14.79; N, 17.53. Found: C, 54.70; H, 5.68; Cl, 14.46; N, 17.40.

5-Amino-1-ethoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridinium Chloride (III).

A solution of 48 g. (0.326 mole) of I and 42 g. (0.343 mole) of ethyl chloroacetate in 210 ml. of absolute ethanol was heated at reflux for 6 hours. The solution was filtered, and the filtrate was cooled to give a white solid, 54 g. (62%), m.p. 223–225°. The melting point did not change after recrystallization from a mixture of ethanol and 2-propanol; λ max (H₂O), 228 (ϵ , 28,200), 323 m μ (ϵ , 15,050); λ max (KBr), 3.15, 3.25, 5.75 and 6.02 μ .

Anal. Calcd. for C₁₂H₁₆ClN₃O₂: C, 53.42; H, 5.98; Cl, 13.15. Found: C, 53.39; H, 5.85; Cl, 13.04.

5-Amino-1-carboxymethyl-2-methylimidazo[1,2-a]pyridinium Hydroxide, Inner Salt (IV).

A suspension of 25.7 g. (0.095 mole) of III in 205 ml. of Dowtherm A was heated with stirring in a flask fitted with a reflux condenser. The top of the condenser was connected to a calcium chloride drying tube and then to a vapor trap cooled in a dry ice-acetone mixture.

At 200–210° ethyl chloride evolution began, and the internal temperature was gradually increased to 255° over a period of 45 minutes to complete the reaction. A volume of 4.5 ml. (65%) of ethyl chloride was collected, b.p. 12.5–12.8°.

The reaction mixture was cooled and the solid filtered and washed thoroughly with ethanol to give 16.9 g. (85%), m.p. >300°. Recrystallization from a mixture of ethanol and water gave white needles, m.p. >300°; λ max (H₂O), 228 (ϵ , 28,250), 320 m μ (ϵ , 14,800); λ max (KBr), 3.15, 3.25, 5.96 and 6.1 μ .

Anal. Calcd. for C₁₀H₁₁N₃O₂· $\frac{1}{2}$ H₂O: C, 56.87; H, 5.57; N, 19.89; H₂O, 2.84. Found: C, 57.15; H, 5.82; N, 19.85; H₂O, 3.00.

The hydrochloride was prepared by suspending the inner salt in boiling 2-propanol and adding concentrated hydrochloric acid until a clear solution was obtained. On cooling, the salt precipitated, and was recrystallized from a mixture of 2-propanol and water. The white solid decomposed at 270–290°; λ max (H₂O), 223 (ϵ , 28,500), 320 m μ (ϵ , 14,950); λ max (KBr), 3.05, 3.2, 5.8 and 6.02 μ .

Anal. Calcd. for C₁₀H₁₁N₃O₂·HCl·H₂O: C, 46.25; H, 5.43; Cl, 13.65. Found: C, 46.55; H, 5.49; Cl, 13.58.

Acknowledgment.

The author is indebted to Professor J. Meinwald of the Department of Chemistry, Cornell University, for his many helpful suggestions, to Mr. G. Ginther and associates for microanalyses and ultraviolet absorption spectral data, and to Mr. H. Borfitz for the gas chromatographic analysis.

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- (3) A. F. Vompe and N. F. Turitsyna, *J. Gen. Chem., USSR*, **27**, 3318 (1957).
- (4) W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 466.
- (5) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

Received December 29, 1965

Norwich, New York 13815