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QUATERNIZATION OF 1H-IMIDAZO[4,5-b]PYRIDINE AND 4-METHYL-4H-IMIDAZO[4,5-b]PYRIDINE

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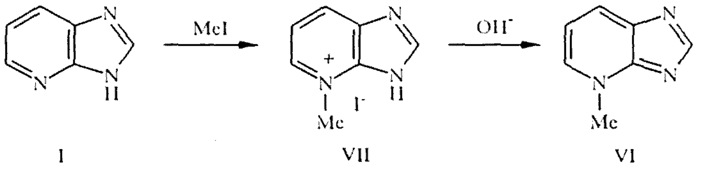
Unsubstituted imidazo[4,5-b]pyridine adds methyl iodide to the pyridine N atom. Treatment of the resulting iodide with base forms 4-methyl-4H-imidazo[4,5-b]pyridine. This nucleophile can readily add methyl iodide to form only one salt, 1,4-dimethylimidazo[4,5-b]pyridinium iodide.

Imidazo[4,5-b]pyridine (I) and its N-methylsubstituted derivatives have two nucleophilic reaction centers. It has previously been demonstrated that 1-methylimidazo[4,5-b]pyridine (II) reacts with methyl iodide to form 1,4-dimethylimidazo[4,5-b]pyridinium iodide (III) [1, 2]. However, the 3-methyl isomer (IV) is quaternized on the imidazole ring to form the iodide of 1,3-dimethylimidazolium[4,5-b]pyridine (V) [3]. The mode of quaternization of 1H-imidazo[4,5-b]pyridine (I) and 4-methyl-4H-imidazo[4,5-b]pyridine (VI) has not been reported.

A study of the prototropic tautomerism of I demonstrated that it exists in benzene solution primarily in the 3H-form [4]. Therefore, in analogy with IV, methyl iodide is expected to add to $N_{(1)}$. Moreover, I has no methyl group in the position peri to $N_{(4)}$ that can shield the nucleophilic center as in the 3-methyl derivative (IV).

Reaction of I with methyl iodide in acetone yields the monoquaternary salt. Its purity was confirmed by a constant melting point after repeated recrystallization from ethanol and also by PMR spectra.

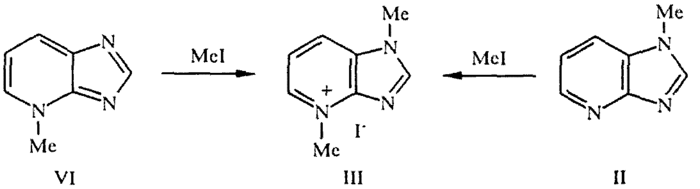
Treatment of an aqueous solution of this salt with an excess of concentrated base forms a compound with a melting point and spectral characteristics identical with 4-methyl-4H-imidazo[4,5-b]pyridine (VI). This compound was isolated earlier from a mixture of N-methylation products of 1H-imidazo[4,5-b]pyridine [5]. The evidence suggests that I reacts with methyl iodide by quaternization at $N_{(4)}$ to form 4-methylimidazo[4,5-b]pyridinium iodide (VII).



Quaternization of I at the pyridine N atom indicates that $N_{(4)}$ is the most nucleophilic center in this heteroaromatic system. The steric hindrance of the methyl group controls the direction of the quaternization of IV.

Our data on the quaternization of I at $N_{(4)}$ with subsequent conversion by base into VI makes imidazo[4,5-b]pyridines accessible for extensive study of their chemical properties. These have an azulene-like structure.

Heating VI with methyl iodide in alcohol forms exclusively 1,4-dimethylimidazo[4,5-b]pyridinium iodide (III), which has been previously produced from 1-methylimidazopyridine (II) [1].



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Since the nucleophilicity of $N_{(1)}$ and $N_{(3)}$ in VI should not differ so much that quaternization at $N_{(3)}$ is excluded, the steric effect of the methyl group can explain the selectivity of the reaction in this instance, like for the 3-methyl isomer (IV) [3].

Thus, we have demonstrated that methyl iodide quaternizes 3H-imidazo[4,5-b]pyridine at $N_{(4)}$ and 4-methyl-4H-imidazo[4,5-b]pyridine at $N_{(1)}$.

EXPERIMENTAL

A Tesla BS-467C (60 MHz) instrument was used to record PMR spectra in trifluoroacetic acid (TMS internal standard) and D_2O (internal standard tert-butanol).

Compound I was synthesized by the literature method [6].

Elemental analyses of VII and III for C, H, and N agree with the calculated values.

4-Methyl-1H-imidazo[4,5-b]pyridinium Iodide (VII). Methyl iodide (25 ml, 0.40 mole) was added to 1H-imidazo[4,5-b]pyridine (15 g, 0.13 mole) in acetone (300 ml). The mixture was stored at room temperature for 48 h. The resulting precipitate was filtered off, washed with acetone (20 ml), and dried. Melting point 216-217 °C (ethanol). PMR spectrum (D_2O): 3.27 (3H, s, N—CH_3), 6.57 (1H, q, J = 5.5, J = 8 Hz, 6-H), 7.48 (1H, d, J = 8 Hz, 7-H), 7.57 (1H, d, J = 5.5 Hz, 5-H). Yield 25.3 g (76.9%).

4-Methyl-4H-imidazo[4,5-b]pyridine (VI). Sodium hydroxide (150 ml, 40%) was added to VII (25.3 g) in H_2O. The resulting oil was extracted with $CHCl_3$ and dried over anhydrous Na_2SO_4. The solvent was distilled off. Sublimation under 2 mm Hg at 170 °C produced a white crystalline substance {7.1 g, 55.1%, mp 97-98 °C (98-100 °C [5])}.

1,4-Dimethylimidazo[4,5-b]pyridinium Iodide (III). Methyl iodide (0.14 ml, 2.2 mmole) was added to VI (0.2 g, 1.5 mmole) in ethanol (0.2 ml). The solution was boiled for 1 h. The solvent was distilled off. Diethyl ether (3 ml) was added to the salt. The precipitate was filtered off, washed with ether, and dried [mp 200-201 °C (isopropanol)]. PMR spectrum (CF_3COOH): 4.28 (3H, s, 4-N—CH_3), 4.65 (3H, s, 1-N—CH_3), 8.05 (1H, q, J = 6.5, J = 8.2 Hz, 6-H), 8.85 (1H, d, J = 6.5 Hz, 7-H), 8.89 (1H, d, J = 8.2 Hz, 5-H), 9.25 (1H, s, 2-H). Yield 0.4 g (97.6%).

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