Chemistry Division, The Norwich Pharmacal Company

The Reaction of Imidazole and Acrylonitrile

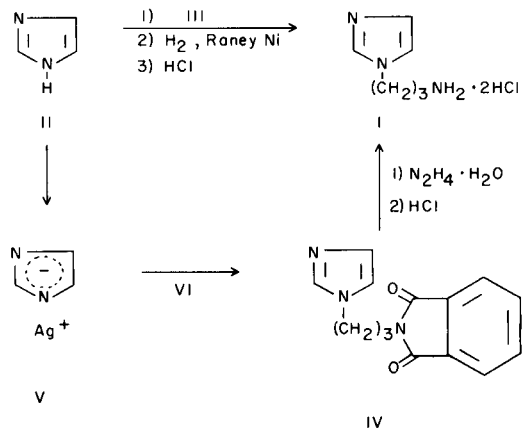
Thomas J. Schwan

As a synthetic route to 3-(1-imidazolyl)propylamine dihydrochloride (I), the previously unreported Michael reaction of imidazole (II) and acrylonitrile (III) was investigated (1).

Treatment of II with III at 90° followed by hydrogenation with Raney nickel and acidification with hydrogen chloride produced I, m.p. 149-150°. The nuclear magnetic resonance spectrum of I exhibited three aromatic protons non-exchangeable in deuterium oxide, and six aliphatic protons, indicative of *N*-alkylation.

Kochetkov *et al.* (2) previously reported the synthesis of I by a Gabriel reaction of *N*-(3-imidazolylpropyl)phthalimide (IV), prepared from the silver salt of imidazole (V) and *N*-(3-bromopropyl)phthalimide (VI). The Chemical Abstracts translation of Kochetkov's work indicates the melting point of 3-(1-imidazolyl)propylamine monohydrochloride to be 232° while the free base is described as "...base-hygroscopic crystals, m.p. 119°" (3). The original paper, on the other hand states that the phthalimido compound IV melts at 232° while a white hygroscopic crystalline compound, m.p. 117-119°, is also described. It is not specified whether this melting point refers to the free base or an amine hydrochloride. However, analytical data for the amine dihydrochloride I are included. No mention is made of a monohydrochloride (2).

Because treatment of V with VI could conceivably lead to *C*-alkyl products and thereby account for the discrepency in melting points, Kochetkov's work was repeated. It was found that the phthalimido compound IV melted at 107-109°, while the amine dihydrochloride I prepared by this method melted at 146-148°.



II I V IV

The amines prepared by the two routes exhibited identical spectral properties and were converted to the same dipicrate.

By virtue of its n.m.r. spectrum, the structure of the amine dihydrochloride I has been unequivocally established as a 1-substituted imidazole. Therefore the present investigation shows that the structural assignments of I and IV by Kochetkov *et al.* are valid and that the melting points of these compounds as described in the literature are incorrect.

EXPERIMENTAL (4)

The n.m.r. spectrum was determined on a Varian A-60A spectrometer at 60 megacycles in deuterated dimethylsulfoxide containing tetramethylsilane as an internal standard.

Infrared spectra were determined with a Perkin-Elmer 137B spectrophotometer.

Melting points were taken on a Mel-Temp block and are corrected.

3-(1-Imidazolyl)propylamine Dihydrochloride (I) (From Imidazole and Acrylonitrile).

Acrylonitrile (25 ml.) was heated to 75° and 13.6 g. (0.200 mole) of imidazole was added in small amounts. The mixture was gradually heated to 90° and stirred at 90-100° for 3 hours. The mixture was cooled, concentrated to dryness *in vacuo*, and the residue was taken up in 100 ml. of methanol. The insoluble polymeric material was removed by filtration and the methanolic solution of the product was concentrated to dryness.

The residual oil in 150 ml. of methanol and 100 ml. of concentrated aqueous ammonia was shaken with hydrogen at 3-4 atmospheres in the presence of 8 g. of Raney nickel (W. R. Grace No. 28) for 3 hours. The catalyst was filtered and washed with two 50 ml. portions of methanol. After the filtrates and combined washings were concentrated to dryness *in vacuo*, the residue was taken up in 200 ml. of methanol saturated with hydrogen chloride. After the solvent was removed, the product was crystallized from absolute ethanol to give 34.3 g. (87%) of the amine dihydrochloride, m.p. 141-145°. The analytical sample, m.p. 149-150° (lit. (3) m.p. 232°) was obtained by recrystallization from absolute ethanol; λ max (μ) (Nujol); 4.90 (NH^+), 6.20, 6.33, 6.48 (C=N and C=C); n.m.r.: singlets 9.45 δ, 7.96 δ 7.75 δ (aromatic), a triplet at 4.49 δ (methylene), multiplets at 2.25 δ and 2.80 δ (methylenes), and a broad singlet at 8.61 δ (NH_3^+) in an area ratio of 1:1:1:2:2:2:3. On admixture with deuterium oxide only the amino protons were exchanged.

Anal. Calcd. for $C_6H_{11}N_3 \cdot 2HCl$: C, 36.38; H, 6.61; Cl, 35.80; N, 21.21. Found: C, 36.45; H, 6.58; Cl, 35.77; N, 21.28.

Picrate.

To a solution of 0.40 g. (0.0020 mole) of the amine dihydrochloride (I) in 8 ml. of ethanol was added a solution of 0.92 g.

(0.0040 mole) of picric acid in 17 ml. of ethanol. The solution was heated to boiling and then cooled. The product was collected, washed with cold alcohol, and air dried to give 1.12 g. (96%) of the dipicrate, m.p. 242-243° dec.

Anal. Calcd. for $C_{18}H_{17}N_9O_{14}$: C, 37.06; H, 2.94; N, 21.61. Found: C, 37.20; H, 3.02; N, 21.40.

N-(3-Imidazolylpropyl)phthalimide (IV).

A mixture of 10.72 g. (0.040 mole) of *N*-(3-bromopropyl)-phthalimide and 8.70 g. (0.050 mole) of the silver salt of imidazole (5) in 100 ml. of xylene was stirred and refluxed for 16 hours. After the xylene was decanted the solid was extracted with three 50 ml. portions of alcohol. The combined washings were concentrated to dryness *in vacuo* and the residue was extracted with two 75 ml. portions of xylene. The combined extracts were concentrated to 50 ml. and cooled to give 4.85 g. (47%) of the crude product, m.p. 85-96°. Recrystallization from xylene gave the analytical sample, m.p. 107-109° (lit. (2) m.p. 232°); λ max (μ) (Nujol); 5.63, 5.82 (phthalimido carbonyl).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.81; H, 5.16; N, 16.36.

3-(1-Imidazolyl)propylamine Dihydrochloride (I) (from IV).

A solution of 2.55 g. (0.010 mole) of the phthalimido compound IV and 0.49 g. (0.011 mole) of 100% hydrazine hydrate in 40 ml. of ethanol was stirred and refluxed for 3 hours, cooled, and diluted with 50 ml. of 10% hydrochloric acid. The mixture was refluxed for 1 hour and then concentrated to dryness *in vacuo*. The residue was shaken with 40 ml. of 10% hydrochloric acid. The phthalhydrazide was removed by filtration and the aqueous solution was concentrated to dryness. The residue was recrystallized from absolute ethanol to afford 0.90 g. (45%) of the amine dihydrochloride, m.p. 146-148°, which exhibited infrared and n.m.r. spectra identical to that of I obtained from the Michael reaction described above. A mixture melting point of the two compounds showed no depression. The amine dihydrochloride prepared from V gave a picrate which exhibited an infrared spectrum and melting point identical to that of the picrate described above.

REFERENCES

(1) While the present investigation was in progress, the Michael reaction of several 2- substituted and 2,4-disubstituted imidazoles with acrylonitrile was reported. Japanese Patent, 8544 (1965); *Chem. Abstr.*, 63, 5657a (1965).

(2) S. I. Lure', M. G. Kuleshova, and N. K. Kochetkov, *Zh. Obshch, Khim.*, 9, 1933 (1939).

(3) *Chem. Abstr.*, 34, 4387 (1940).

(4) Elemental analyses were performed by Grant Gustin and Marvin Tefft. The n.m.r. spectrum was run by Patricia Curtis.

(5) E. Bergmann and H. Heimhold, *J. Chem. Soc.*, 505 (1936).

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