

Rearrangement of Ethyl 2-(3-Amino-4-pyridinyl)hydrazinecarboxylate Hydrochloride to 1-Amino-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one Hydrochloride

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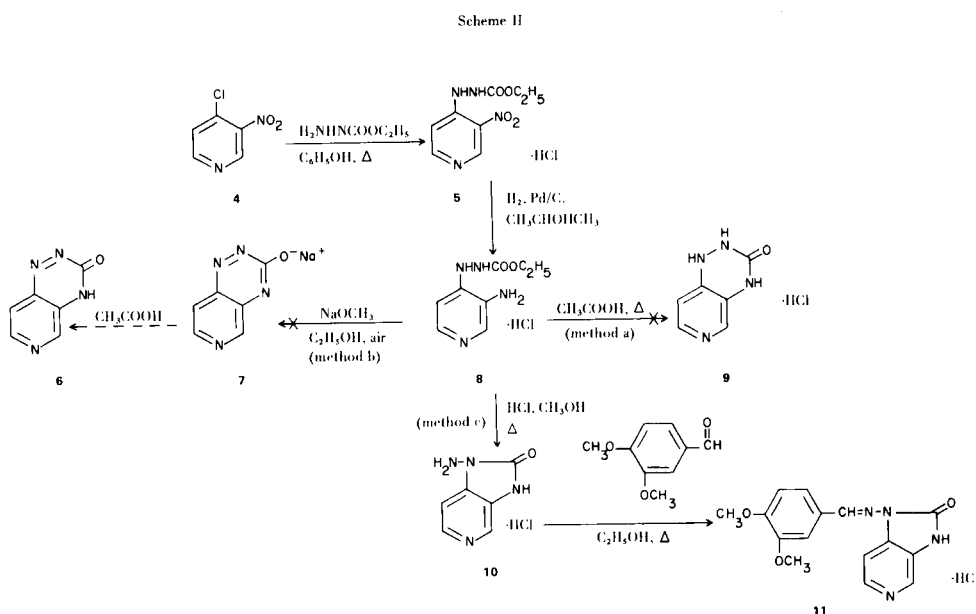
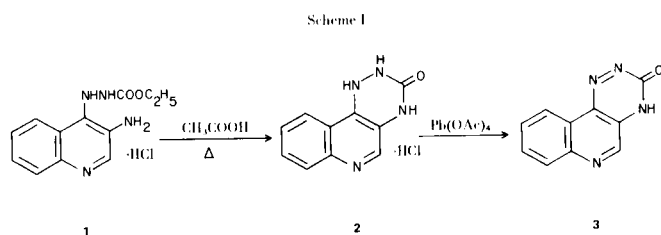
In a study of the synthesis (unsuccessful) of pyrido[3,4-*e*]-*as*-triazino-3(4*H*)one (**6**), the acidification of 2-(3-amino-4-pyridinyl)hydrazinecarboxylate hydrochloride (**8**) unexpectedly gave 1-amino-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one hydrochloride (**10**). The isolation and characterization of **10** has been described.

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It was recently reported (1) that *as*-triazino[5,6-*c*]quinolin-3(4*H*)one (**3**) was synthesized through a) the ring closure of ethyl 2-(3-amino-4-quinolinyl)hydrazinecarboxylate hydrochloride (**1**) in hot acetic acid to give 1,2-

dihydro-*as*-triazino[5,6-*c*]quinolin-3(4*H*)one hydrochloride (**2**) followed by oxidation to **3** with lead tetraacetate (Scheme I). By a second method b), **3** was obtained through oxidative-ring closure of **1** to the sodium salt of **3**, followed by acidification (1). It has more recently been shown (see Experimental) that c) the ring closure of **1** to **2** also occurs in methanolic hydrogen chloride. Subsequently the ring closure of **1** to **2** was also readily achieved through refluxing **1** in absolute ethanol.

In the present paper the results of attempted synthesis of pyrido[3,4-*e*]-*as*-triazino-3(4*H*)one (**6**), by the methods previously described (1) for **3**, are reported (Scheme II).



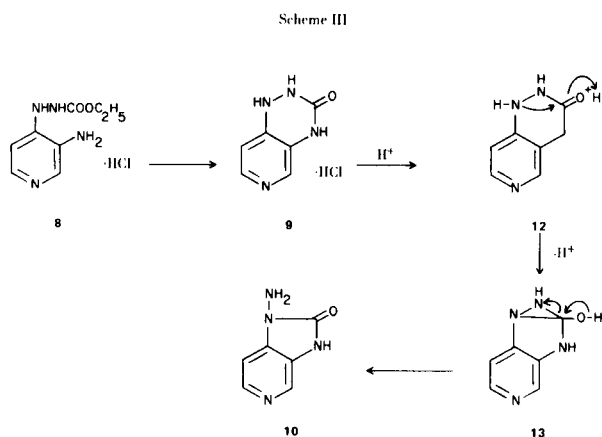
The necessary intermediate ethyl 2-(3-amino-4-pyridyl)hydrazinecarboxylate hydrochloride (**8**) was obtained by the catalytic reduction of ethyl 2-(3-nitro-4-pyridyl)hydrazinecarboxylate hydrochloride (**5**), which was prepared via the reaction of 4-chloro-3-nitropyridine (**4**) (**2**) and ethyl carbazate.

By method a) intermediate **8** was refluxed in glacial acetic acid; no identifiable product was isolated. Similarly by method b), although a semistable sodium salt was isolated from **8** upon treatment with sodium ethoxide in ethanol and air, acidification failed to provide an identifiable product.

However when **8** was heated with methanolic hydrogen chloride (method c), an unexpected product was isolated which showed infrared carbonyl absorptions at 5.67 and 5.75  $\mu$ ; the relatively higher wave length is more indicative of a 5-membered ring structure with greater ring strain than that expected for the desired *as*-triazinone (**9**).

The 1-amino-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one hydrochloride (**10**) structural assignment for the product was confirmed by reaction with veratraldehyde to give the expected 1-[(veratrylidene)amino]-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one hydrochloride (**11**).

Based on the following considerations, a mechanism (Scheme III) for the conversion of **8** to **10** has been proposed:



An unsuccessful attempt was made to isolate the postulated intermediate **9**, on the pathway from **8** to **10**, through heating **8** under mildly acidic conditions (dilution by 25 times that required for conversion of **8** to **10**); no reaction occurred. Although no direct evidence for the formation of **9** was ascertained, based on the ready conversion of **1** to **2** in the quinoline series it is assumed that **9** was an intermediate in the formation of **10**, but that **9** was unstable under the highly acidic conditions required for the reaction.

Therefore it is assumed that **8** goes directly to **9**, which

is highly protonated as depicted in **12**. The highly polarized carbonyl carbon of **12** may undergo an attack by the secondary nitrogen to give **13**, which may be expected to rearrange to **10**.

## EXPERIMENTAL

Infrared spectra were obtained with a Perkin-Elmer Infracord 137B and nmr spectra were determined in hexadeuterodimethylsulfoxide using tetramethylsilane as an internal standard on a Varian A-60A spectrometer. Melting point data were obtained on a Fisher-Johns hot stage and are uncorrected.

### 1,2-Dihydro-*as*-triazino[5,6-*c*]quinolin-3(4*H*)one Hydrochloride (**2**). Method c.

A mixture of **1** (1.0 g., 0.0035 mole) and methanolic hydrogen chloride (36%, 10 ml.) was heated on the steam bath for 5 minutes. The resultant deep yellow, crystalline solid was filtered and washed well with absolute ethanol and ether, yield, 0.8 g. (95%); the infrared absorption spectrum was identical to that of **2** previously reported (**1**).

### Ring Closure in Ethanol.

A mixture of **1** (0.30 g., 0.011 mole) and absolute ethanol was refluxed on the steam bath overnight. The resultant yellow, crystalline solid was cooled, filtered and washed with cold 2-propanol and ether, yield, 0.20 g. (77%); the infrared spectrum was nearly identical to that of **2**.

### 4-Chloro-3-nitropyridine (**4**) (**2**).

To 4-hydroxy-3-nitropyridine (**3**) (184 g., 1.31 moles) was added phosphorus oxychloride (450 ml., 4.95 moles) with mechanical stirring (**4**). Then phosphorus pentachloride (216 g., 1.04 moles) was added at 30-45° and the reaction mixture was gradually heated on a steam bath to 80° over 1.3 hours, to 108° over 1.5 hours, and refluxed for 2.5 hours until hydrogen chloride evolution ceased. The mixture was concentrated to a viscous syrup under reduced pressure on the steam bath. The residue was added to a mixture of ice (600 ml.) and chloroform (1200 ml.) and further extracted with chloroform (2 x 200 ml.).

The dried (magnesium sulfate) extract was stored in the refrigerator overnight, filtered to remove an unidentified crystalline solid, and concentrated to dryness under reduced pressure. The resultant pale yellow oil crystallized upon cooling, comparable to that previously reported (**3**), yield, 189 g. (91%).

### Ethyl 2-(3-Nitro-4-pyridinyl)hydrazinecarboxylate Hydrochloride (**5**).

To a solution of **4** (91 g., 0.57 mole) in phenol (800 ml.) was added ethyl hydrazinecarboxylate (62 g., 0.60 mole) at 40-50° with mechanical stirring. The resultant exothermic (72° over 5 minutes) reaction was further heated at 85-90° for 1.8 hours. The cooled (35-40°) reaction mixture was added to anhydrous ether (3,200 ml.) with hand stirring. The supernatant solution was decanted from the amorphous product, which was washed twice with ether, treated with 2-propanol (500 ml.), and triturated on the steam bath. After cooling in an ice bath for 10 minutes, the resultant light yellow, crystalline solid was filtered and washed well with 2-propanol and ether. Recrystallization from 95% ethanol (ether) (700 ml.) gave **5**; m.p. 203-204°, yield, 40 g. (27%). An additional 8 g. of product (m.p. 202-204°) was recovered from the ether decantate; ir (Nujol)  $\mu$ : 5.73 (C=O); 3.0, 3.2 (NH); nmr

( $\delta$ ): 1.12 and 4.25 (t and q, 5,  $\text{CH}_3\text{CH}_2$ ); 7.40 and 8.47 (2d,  $J = 7.0$  Hz, 2, heteromatic); 9.0 (broad, hydrochloric acid, exchanged with deuterium oxide); 9.32 (s, 1, heteromatic); 10.1 (broad, NHH, exchanged with deuterium oxide).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_4\text{O}_4 \cdot \text{HCl}$ : C, 36.58; H, 4.22; N, 21.33. Found: C, 36.70; H, 4.22; N, 21.65.

Ethyl 2-(3-Amino-4-pyridinyl)hydrazinecarboxylate Hydrochloride (**8**).

A mixture of **5** (59 g., 0.22 mole), 95% ethanol (methanol) (500 ml.) and 5% palladium/carbon (50% water) (7.1 g.) was hydrogenated at 50 psig. Hydrogen uptake of 100% of theory was observed. The reduction mixture was filtered to remove catalyst, and the filtrate was concentrated to a volume of 125 ml. The residue was cooled and the resultant white, crystalline product was collected and washed with 95% ethanol (methanol) (4 x 10 ml.) and ether; m.p. 222-223°, yield, 42 g. (82%). Recrystallization of 36 g. of the product from 95% ethanol (methanol) (330 ml.) gave analytically pure **8**; m.p. 223-225°, yield, 29 g.; ir (Nujol)  $\mu$ : 5.73 (C=O); 3.02, 3.1-3.2 ( $\text{NH}_2$ , NH); nmr ( $\delta$ ): 1.23 and 4.13 (t and q, 5,  $\text{CH}_2\text{CH}_3$ ); 6.03 (s,  $\text{NH}_2$ , exchanged with deuterium oxide); 6.78 and 7.90 (2d,  $J = 6.5$  Hz, 2, heteromatic C-H); 7.85 (s, 1, heteromatic C-H); 9.62 (s, NHH, exchanged with deuterium oxide); 13.8 (broad, hydrochloric acid, exchanged with deuterium oxide).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{12}\text{N}_4\text{O}_2 \cdot \text{HCl}$ : C, 41.29; H, 5.63; N, 24.08. Found: C, 41.47; H, 5.76; N, 24.14.

1-Amino-1*H*-imidazo[4,5-*c*]pyridin-2(3*H*)one Hydrochloride (**10**).

A mixture of **8** (55 g., 0.24 mole) and methanolic hydrogen chloride (36%, 245 ml.) was refluxed for 8 hours with a continuous stream of dry hydrogen chloride passed through the mixture. The stream of hydrogen chloride was discontinued and the mixture was refluxed an additional 16 hours. The mixture was cooled for 1 hour and the resultant tan solid was collected by filtration and washed with methanol (30 ml.) and ether; m.p. > 300° dec., yield, 37 g. (84%). Recrystallization twice from 67% methanol (water), using charcoal, gave **10**; m.p. 309-310° dec., yield, 20 g. (45%); ir (Nujol)  $\mu$ : 5.67, 5.75 (C=O); 3.09, 3.18 ( $\text{N}^+\text{H}_3$ ); 3.25 (NH);

nmr ( $\delta$ ): 7.55 and 8.45 (2d,  $J = 6.0$  Hz, 2, heteromatic C-H); 8.49 (s, 1, heteromatic C-H); 9.50 (broad, NH, exchanged with deuterium oxide); 12.5 (broad,  $\text{NH}_2$ , exchanged with deuterium oxide).

*Anal.* Calcd. for  $\text{C}_6\text{H}_6\text{N}_4\text{O} \cdot \text{HCl}$ : C, 38.62; H, 3.78; N, 30.03; Cl, 19.00. Found: C, 38.50; H, 3.81; N, 30.30; Cl, 18.95.

1-[(Veratrylidene)amino]-1*H*-imidazo[4,5-*c*]pyridine-2(3*H*)one Hydrochloride (**11**).

A mixture of **10** (40 g., 0.21 mole) and water (10 ml.) was treated with a solution of veratraldehyde (40 g., 0.24 mole) in 95% ethanol (methanol) (310 ml.) with mechanical stirring. The reaction mixture was refluxed for 1.8 hours, stored at room temperature for 0.5 hour, and cooled 1 hour. The resultant pale yellow solid was filtered and washed with 95% ethanol (methanol) and ether; m.p. 260-262° dec., yield, 64 g. (91%). Recrystallization from 90% methanol (water) gave analytically pure **11**, m.p. 262-265°; ir (Nujol)  $\mu$ : 5.75 (C=O); 3.25 (NH); nmr ( $\delta$ ): 3.89 (s, 6,  $\text{CH}_3\text{O}$ ); 7.0-7.7 (m, 3, aromatic C-H); 7.87 and 8.58 (2d,  $J = 6.0$  Hz, 2, heteromatic C-H); 8.61 (s, 1, methyleneamino, CH=N); 9.55 (s, 1, heteromatic).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{14}\text{N}_4\text{O}_3 \cdot \text{HCl}$ : C, 53.81; H, 4.52; N, 16.74. Found: C, 53.64; H, 4.48; N, 16.70.

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#### REFERENCES AND NOTES

- (1) G. C. Wright, J. E. Gray, and Chia-Nien Yu, *J. Med. Chem.*, 17, 244 (1974).
- (2) The compound was prepared by a modification of the procedure of Kruger and Mann (reference 3).
- (3) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 2758 (1955).
- (4) Mild cooling of the mixture is desirable to facilitate the addition of phosphorus pentachloride.