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The reactions of the anions of isonicotinamide and 2-amino-5-nitropyridine with 2-chloro-5-nitropyridine and 3-nitropyridine were observed to give rise to unexpected substitution products presumably *via* a radical anion mechanism.

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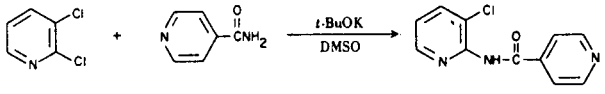
During a recent investigation into the chemistry of bipyridines, the pyrido[2,3-*h*]-2,6-naphthyridine (**2**) was obtained from the thermolysis of the bisacylazide **1** (2).

1 2

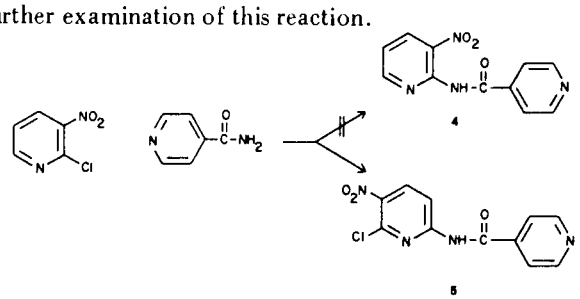
The structure of compound **2** was supported by ir, nmr, and elemental analysis; however, in order to further confirm this structure, we began to examine alternate syntheses of **2**. Two compounds, 2-(isonicotinamido)-3-chloropyridine (**3**) and 2-(isonicotinamido)-3-nitropyridine (**4**) were considered as potential precursors to **2**, and an investigation was undertaken to prepare these compounds by the reactions to isonicotinamide with 2,3-dichloropyridine and 2-chloro-3-nitropyridine, respectively.

When a solution of isonicotinamide in dimethyl sulfoxide (DMSO) was treated with potassium *t*-butoxide and then with 2,3-dichloropyridine, two compounds were isolated by means of chromatography on silicic acid; 2,3-dichloropyridine (41%) and **3** (47%).



3

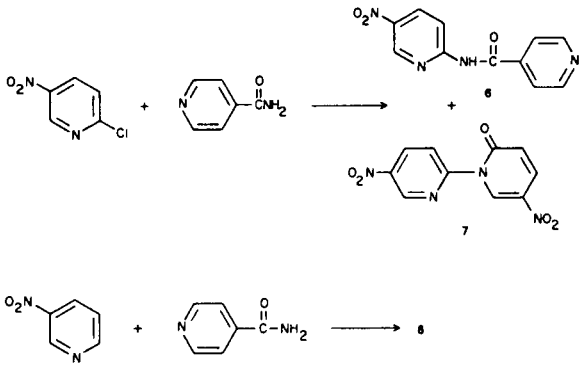
The reaction between 2-chloro-3-nitropyridine and isonicotinamide was carried out in a similar manner in an attempt to prepare the second precursor; however, we could find no evidence for the formation of **4**, but instead we isolated 7 percent of the starting 2-chloro-3-nitropyridine and the corresponding 2-chloro-3-nitro-6-(isonicotinamido)pyridine (**5**) in 6% yield. It would appear that most of the starting material had decomposed under the reaction conditions, and the isolation of **5** led us into a further examination of this reaction.



4 5

In order to avoid any steric factor, which might have contributed to the formulation of **5**, the isomeric 2-chloro-5-nitropyridine was subjected to the same reaction conditions in an effort to prepare the 2-(isonicotinamido)-5-nitropyridine (**6**). To our surprise, the expected product could only be isolated in very poor yield (0.4%). The major product (11%) of this reaction was shown to be **7**. The starting material was also present in the reaction mixture to the extent of approximately 9%.

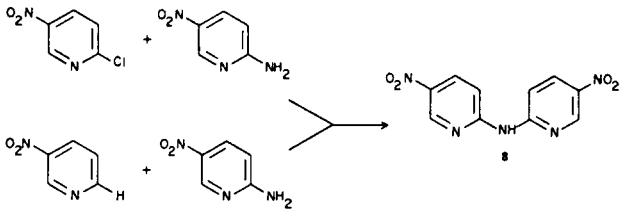
On the other hand, when 3-nitropyridine instead of 2-chloro-5-nitropyridine was used in this reaciton, **6** was obtained in 16% yield even though the substrate lacks a suitable leaving group. It was surprising to note that 3-nitropyridine gave rise to **6** in a much better yield than the 2-chloro-5-nitropyridine.



6 7

8

In order to see if this abnormal nucleophilic substitution reaction takes place with other similar anions, the anion of 2-amino-5-nitropyridine was treated with 2-chloro-5-nitropyridine and 3-nitropyridine. Interestingly enough, 3-nitropyridine afforded the higher yield (61%) of the substitution product, 5,5′-dinitro-2,2′-bipyridylamine (**8**), while the 2-chloro-5-nitropyridine gave only 38% yield of **8** (3).



In some of the reactions mentioned above, dimethylacetamide (DMAC) was also used as a reaction solvent

instead of dimethyl-sulfoxide (DMSO), and it was found that the yields in these instances were much lower than those obtained in DMSO and that the decomposition seemed to be more predominant in this solvent.

Thus, it would appear that while the chloro substituent can serve as a suitable leaving group for direct nucleophilic substitution, in many instances, a second mechanism must be operative in order to account for the abnormal substitution reactions described above. The 2-chloro-5-nitropyridine system was shown to be a good electron acceptor with the anion of 2-methyl-5-nitropyridine in a previous paper (4), and it would seem very likely that the substitution reaction involving the anion of isonicotinamide or the 2-amino-5-nitropyridine would possibly proceed *via* a similar radical anion mechanism. Presumably in this instance the mechanism may involve an electron transfer from the anion to the electron acceptor to form a radical anion in the initial step.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Mel-Temp apparatus and are uncorrected. The ir absorption spectra were recorded on either a Perkin-Elmer Model 137 or a Model 521 spectrophotometer. The nmr spectra were determined with a Varian T-60 spectrometer using tetramethylsilane as an internal reference. Analyses were performed by M-H-W Laboratories, Garden City, Michigan.

Reaction of 2,3-Dichloropyridine and Isonicotinamide.

To a solution of 2.44 g. (0.02 mole) of isonicotinamide in 20 ml. of distilled dimethyl sulfoxide was added 2.24 g. (0.02 mole) of potassium *t*-butoxide, and the mixture was stirred at room temperature. It became a clear solution after 5 minutes, and then a white precipitate began to appear. After stirring for 15 minutes, 2.96 g. (0.02 mole) of 2,3-dichloropyridine was added. The slightly yellow mixture was stirred at room temperature for 30 minutes, at 80° for 12 hours, and at 105° for 12 hours. The resulting tan solution with a small amount of insoluble material was poured into 300 ml. of water. 2,3-Dichloropyridine (1.2 g., 41%) precipitated, m.p. 65-68°, identical with an authentic sample of starting material.

The filtrate was weakly alkaline (*p*H 9-10), and the *p*H was lowered to about 8 by addition of diluted hydrochloric acid. The solution was extracted with chloroform, and the extract was washed with water. The dried extract was evaporated to give a pale tan oil, which solidified on standing at room temperature. It was recrystallized from benzene-petroleum ether to give 1.3 g. (28%; or 47% based on the consumed 2,3-dichloropyridine) of **3** as colorless needles, m.p. 125-126°; ν (potassium bromide): 3230, 1660 cm^{-1}; δ (deuteriochloroform): 7.16 [C5-H, dd (J = 8, 5 Hz)], 7.78 [C3′-H, C5′-H, dd (J = 4.7, 1.6 Hz)], 7.80 [C4-H, dd (J = 8, 1.7 Hz)], 8.38 [C6-H, dd (J = 5, 1.7 Hz)], 8.78 [C2′-H, C6′-H, dd (J = 4.7, 1.6 Hz)], 9.13 (S, amide NH) ppm.

Anal. Calcd. for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98. Found: C, 56.64; H, 3.65; N, 18.20.

Reaction of 2-Chloro-3-nitropyridine and Isonicotinamide.

Starting from 2.44 g. (0.02 mole) of isonicotinamide, 20 ml. of dimethyl sulfoxide, 2.24 g. (0.02 mole) of potassium *t*-butoxide, the anion was made in the same way. 2-Chloro-3-nitropyridine, 3.17 g. (0.02 mole), was added and the mixture was heated at 80° for 6 hours with stirring. The resulting brown mixture was washed well with water. The chloroform layer was dried and evaporated to give a light tan solid. It was chromatographed on silicic acid in chloroform solution to give 350 mg. (6%) of **5**, 210 mg. (7% recovery) of 2-chloro-3-nitropyridine, and two other fractions. After sublimation, the first fraction gave 40 mg. of a white solid that was found to be a mixture of 2-chloro-3-nitropyridine and an unidentified compound. The second fraction yielded 100 mg. of a yellow solid. On recrystallization from methanol, it gave 50 mg. of yellow needles (m.p. 164-166°) which was not able to be characterized. The unidentified compounds were, however, not compound **4**. Compound **5** was recrystallized from acetone to give very pale yellow granular crystals, m.p. 205° (decolor); ν (potassium bromide): 3200-2700 (broad), 1680 cm^{-1}; δ(DMSO-d_6): 7.90 [C3′-H, C5′-H, dd (J = 1.6 Hz)], 8.33 [C5-H, d (J = 8.7 Hz)], 8.67 [C4-H, d (J = 8.7 Hz)], 8.78 [C2′-H, C6′-H, dd (J = 4.5, 1.6 Hz)], 11.90 (S, amide NH) ppm.

Anal. Calcd. for $C_{11}H_7ClN_4O_3$: C, 47.41; H, 2.53; N, 20.11. Found: C, 47.37; H, 2.76; N, 19.96.

Reaction of 2-Chloro-5-nitropyridine and Isonicotinamide.

Starting from 2.44 g. (0.02 mole) of isonicotinamide, 20 ml. of dimethyl sulfoxide, 2.24 g. (0.02 mole) of potassium *t*-butoxide, and 3.17 g. (0.02 mole) of 2-chloro-5-nitropyridine, the reaction was carried out by the procedure described above. On chromatography, 300 mg. (9% recovery) of 2-chloro-5-nitropyridine, 70 mg. of **6**, 320 mg. of **7**, and 70 mg. of a white solid which was sublimed and then recrystallized from hexanes to give 20 mg. of unidentified colorless plates, m.p. 110-112°.

Compound **6** was purified by recrystallization from acetone to give 20 mg. (0.4%) of slightly yellow granules, m.p. 246-248°, ν (potassium bromide); 3200-3700 (broad), 1680 cm^{-1}; δ (DMSO-d_6): 7.93 [C3′-H, C5′-H, dd (J = 4.5, 1.6 Hz), 8.43 [C3-H, d (J = 9.5 Hz)], 8.73 [C4-H, dd (J = 9.5, 2.7 Hz)], 8.85 (C2′-H, C6′-H, dd (J = 4.5, 1.6 Hz)], 9.28 [C6-H, d (J = 2.7 Hz)], 11.82 (S, amide NH) ppm.

Anal. Calcd. for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94. Found: C, 54.06; H, 3.08; N, 23.09.

Compound **7** was purified by recrystallization from methanol to give 280 mg. (11%) of pure **7** as colorless needles, m.p. 168-170°; ν (potassium bromide): 1690 cm^{-1}; δ (DMSO-d_6): 6.73 (C3′-H, d (J = 10.3 Hz)], 8.23 [C3-H, d (J = 9 Hz)], 8.28 [C4′-H, dd (J = 10.3, 3 Hz)], 8.89 [C4-H, dd (J = 9, 2.7 Hz)], 9.28 [C6′-H, d (J = 3 Hz)], 9.48 [C6-H, d (J = 2.7 Hz)] ppm.

Anal. Calcd. for $C_{10}H_6N_4O_5$: C, 45.81; H, 2.31; N, 21.37. Found: C, 45.30; H, 2.21; N, 21.54.

Reaction of 3-Nitropyridine and Isonicotinamide.

The reaction was carried out by the same procedure as the above except for the use of 2.48 g. (0.02 mole) of 3-nitropyridine instead of 2-chloro-5-nitropyridine. On chromatography, 850 mg. of a light yellow solid was obtained. Recrystallization from acetone gave 780 mg. (16%) of **6**.

There were two more minor band which gave 200 mg. of a pale yellow solid. The former compound was purified by recrystallization from hexanes and sublimations to give 40 mg. of pale yellow needles, m.p. 125-127°. The latter compound was recrystallized from acetone to give 110 mg. of pale yellow needles, m.p. 270° dec. These two minor products were not characterized.

Reaction of 3-Nitropyridine and 2-Amino-5-nitropyridine.

To a solution of 1.39 g. (0.01 mole) of 2-amino-5-nitropyridine in 10 ml. of dimethyl sulfoxide was added 1.12 g. (0.01 mole) of

potassium *t*-butoxide with cooling in a water bath. The mixture was stirred at room temperature for 15 minutes to give a reddish-brown solution. 3-Nitropyridine, 1.24 g. (0.01 mole), was added to the solution with cooling in a water bath to give a deep reddish-brown mixture with a slight evolution of heat. The mixture was stirred at room temperature for 20 minutes and at 80° for 6 hours, and then 400 ml. of chloroform was added. The mixture was washed well with water, and the dried chloroform layer was evaporated to give 2.1 g. of a yellow solid. Chromatography gave 1.8 g. of a yellow solid of compound **8** and 0.16 g. (12% recovery) of 2-amino-5-nitropyridine. Compound **8** was purified by recrystallization from benzene-petroleum ether to give 1.6 g. (61%) of yellow needles, m.p. 223-226° [lit. 225-227° (2)].

Acknowledgments.

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REFERENCES AND NOTES

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