Thermolysis of the Reaction Products from 2-Pyridylacetohydrazide and Nitrous Acid

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2,3-Dihydroimidazo[1,5-*a*]pyridin-3-one (IV) was obtained by thermolysis of 2-pyridylacetyl azide (II) which was prepared from 2-pyridylacetohydrazide (I) on treatment with an equivalent mole of nitrous acid. Treatment of I with excess nitrous acid yielded α-oximino-α-(2-pyridyl)-acetylazide (V). Thermal decomposition of V gave 3-(2-pyridyl)-1,2,4-4*H*-oxadiazolin-5-one (VII). 2-Cyanopyridine (IX) was obtained from V by the action of alkali. 2,3-Dihydroimidazo-[1,5-*a*]pyridin-3-one (IV) was rearranged to VII upon treatment with nitrous acid.

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The imidazo[1,5-*a*]pyridine derivatives were first synthesized by Bower and Ramage in 1955 by dehydrative ring closure of the acylaminomethylpyridines in the presence of phosphoryl chloride (1). Although the related imidazo[1,5-*a*]azine system has also appeared (2,3), fewer of the derivatives of this system have been reported than those of other azaindolidines because of the poor availability of the starting aminomethyl derivatives.

In connection with our study on bridgehead nitrogen heterocyclic compounds (4), we found a novel and facile synthetic method for the preparation of the imidazo-[1,5-*a*]pyridine system starting from the readily available 2-pyridylacetohydrazide (I), where some interesting reactions have been observed.

Treatment of the hydrazide (I) with an equivamolar amount of sodium nitrite in 10% hydrochloric acid at -10~-5° and subsequent thermolysis of the resulted azide (II) in boiling chloroform solution afforded the desired bicyclic compound, 2,3-dihydroimidazo[1,5-*a*]pyridin-3-one (IV), *via* the intermediate isocyanate (III) in 40% yield.

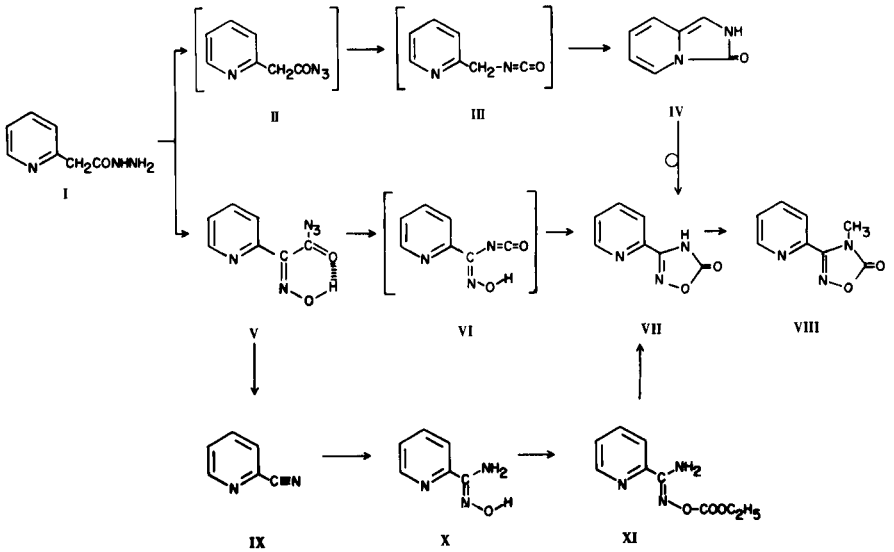
The elemental analysis and mass spectrum of IV agree with the expected molecular formula. Its ir spectrum lacked an isocyanate absorption around 2200 cm^{-1} but showed a strong carbonyl band at 1682 cm^{-1} and a NH absorption at 3100 cm^{-1}. These data indicate that the compound IV has a cyclic structure and exists predominantly in the lactam form. The nmr spectrum of IV showed the C-1 proton at 6.43 ppm as a singlet, the NH proton at 12.16 ppm as a broad singlet and others.

Attempted purification of the intermediate azide (II) failed due to its thermal instability. But the formation of II was proven by ir spectroscopy, an azide band at 2160 cm^{-1} and a carbonyl absorption at 1720 cm^{-1} (neat).

On the other hand, when I was treated with excess nitrous acid and the resulting azide allowed to decompose in boiling benzene, two products were obtained. The first compound was easily identified as 2-cyanopyridine (IX) by a comparison of its ir spectrum with that of an authentic sample. The second compound was shown to be 3-(2-pyridyl)-1,2,4-oxadiazolin-5-one (VII) by elemental analysis, spectral data and, finally, an unequivocal synthesis.

The ir spectrum of VII showed a broad hydrogen bonded NH absorption at 3150 cm^{-1} and a strong carbonyl band

Scheme I



at 1785 cm^{-1}. This characteristic band for the carbonyl group appeared in the high frequency region and was also observed in the spectrum of 3-phenyl-1,2,4-oxadiazolin-5-one (5). The unequivocal synthesis was performed as follows: 2-Pyridineamidoxime (X), prepared from 2-cyanopyridine and hydroxylamine, was treated with ethyl chloroformate in pyridine giving *O*-ethoxycarbonyl-2-pyridineamidoxime (XI). Compound XI was heated at 140-150° for 30 minutes under a nitrogen atmosphere to give 3-(2-pyridyl)-1,2,4-oxadiazolin-5-one. The ir spectrum of this compound was completely superimposable on that of compound VII. Compound VII was readily converted into its *N*-methyl derivative (VIII) by allowing it to react with methyl iodide in methanolic potassium hydroxide solution.

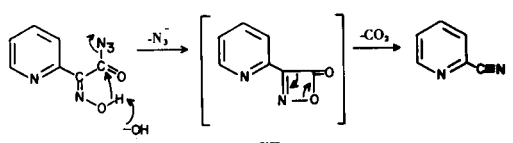
The formation of compound VII suggested α-oximino-α-(2-pyridyl)acetylazide (V) as an intermediate, which might decompose to the isocyanate (VI) and then cyclize to VII. Mechanistically, the formation of V is reasonable, because the methylene group in 2-pyridylacetylazide, which may at first be formed from I with an equivalent mole of nitrous acid, is activated to electrophilic reagents and consequently susceptible to the nitrosation reaction. In order to confirm this idea, we examined the products obtained from I with excess nitrous acid before thermolysis was carried out. As expected, the oxime (V) was obtained as a thermally unstable solid and then thermolysis of V afforded VII as the sole product. In addition, it was found that 2-cyanopyridine (IX) was already formed at this stage.

The ir spectrum of the compound V showed broad hydrogen-bonded hydroxyl bands around 2650 cm^{-1} and 1840 cm^{-1}, and azide absorption at 2160 cm^{-1} and 2140 cm^{-1} as a doublet, a carbonyl frequency at 1681 cm^{-1} and an absorption of the C=N group in the oxime at 1641 cm^{-1}. The carbonyl frequency was shifted (-39 cm^{-1}), compared with that of 2-pyridylacetylazide (II) (1720 cm^{-1}). This frequency decrease probably indicates the presence of chelation between the oxime group and the carbonyl group as shown in Scheme I. Therefore, this configuration of the oxime, *syn* to the azide-carbonyl group, is preferable for cyclization of the isocyanate (VI) to the oxadiazolinone (VII).

It is well known that certain ketoximes, for example, oximes of α-diketones and α-ketoacids, are converted to nitriles by the action of a proton or Lewis acids; *i.e.*, Beckmann fragmentation. Hence, we considered that 2-cyanopyridine (IX) was formed from the oxime (V) in acidic media for the diazotization reaction. But treatment of V with 10% hydrochloric acid did not give the nitrile (IX) but only the hydrochloride of V.

On the other hand, when V was treated with 10% aqueous sodium carbonate, it was readily converted to the nitrile (IX) with evolution of a gas. Consequently, we can now conclude that 2-cyanopyridine (IX) was formed from V by the alkali used for neutralization of the acidic media.

Scheme II

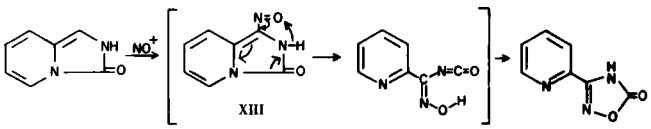


XII

This conversion can be rationalized by the intermediate formation of the oxazetinone (XII) and the subsequent elimination of carbon dioxide (Scheme II). Accordingly, the configuration of the oxime group is preferable for this reaction, too.

Finally, an interesting rearrangement of compound IV was observed. Namely, nitrosation of IV did not afford the expected nitroso derivative of IV but gave the rearranged oxadiazolinone (VII). This reaction can be envisioned to proceed by first, electrophilic attack of nitrosonium ion at the C-1 position of IV to generate XIII. Subsequent ring opening of the five membered ring and simultaneous recyclization affords VII (Scheme III).

Scheme III



XIII

Similar rearrangements for imidazo[1,5-*a*]pyridine and its 3-methyl and 3-phenyl derivatives was reported by Paudler and Kuder in 1967 (6).

The application of these reactions upon substituted pyridyl and another heteraryl acetohydrazides is under active investigation.

EXPERIMENTAL

All melting points are uncorrected. Mass spectra were recorded on a JEOL JMS-01SG spectrometer. Nmr spectra were recorded on a JEOL JNM-PS-100 spectrometer using TMS as the internal standard. Ir spectra were obtained in Nujol mulls with a Hitachi EPI-2 spectrometer. Uv spectra were determined for solutions in ethanol with a Hitachi 323 spectrometer.

2,3-Dihydroimidazo[1,5-*a*]pyridin-3-one (IV).

A solution of 4.2 g. (60 mmoles) of sodium nitrite in 20 ml. of water was added dropwise to a stirred solution of 9.1 g. (60 mmoles) of 2-pyridylacetohydrazide (I) (7) in 100 ml. of 10% hydrochloric acid, keeping the temperature between -10° and -5°. After stirring for an additional 10 minutes, the reaction mixture was made basic with sodium carbonate and extracted with chloroform. The dried chloroform extract (sodium sulfate) was refluxed for 1.5 hours and then evaporated to dryness. The residue was dissolved in 70 ml. of hot dichloromethane (charcoal) and then filtered. Ligroin was added to the filtrate and allowed to stand in a refrigerator to give 3.2 g. (40%) of brown needles of IV, m.p. 143-145°; mass spectrum: m/e 134 (M^+); nmr (deuteriochloroform): δ 6.04 (t, 1H, H_6), 6.33 (dd, 1H, H_7), 6.43 (s, 1H, H_1), 6.83 (d, 1H, H_8), 7.52 (d, 1H, H_5), 12.16 (br s, 1H, NH), $J_{5,6}$ = 7, $J_{6,7}$ = 7, $J_{7,8}$ = 10 Hz; ir: 3100 (NH) and 1682 cm^{-1} (C=O); uv λ max: 268 (ε, 6,300), 276 (ε, 6,700), 287 (ε, 4,300) and 374

nm (ε, 1,900).

Anal. Calcd. for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.45; H, 4.36; N, 20.84.

3-(2-Pyridyl)-1,2,4-oxadiazolin-5-one (VII) and 2-Cyanopyridine (IX).

A solution of 5.52 g. (80 mmoles) of sodium nitrite in 10 ml. of water was added dropwise to a stirred solution of 4.54 g. (30 mmoles) of I in 60 ml. of 10% hydrochloric acid, keeping the temperature between -10° and -5°. After stirring for an additional 10 minutes, the reaction mixture was made basic with sodium carbonate and extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated to a small volume. One hundred milliliters of benzene was added to this solution, refluxed for 2 hours and then evaporated to dryness. The residue was recrystallized from ethanol/benzene (charcoal) to give 1.60 g. of colorless needles of VII, m.p. 199-200°; mass spectrum: m/e 163 (M^+); nmr (DMSO-d_6): δ 7.61 (m, 1H, H_5'), 7.97 (m, 2H, H_3' and H_4'), 8.73 (dd, 1H, H_6'), $J_{5',6'}$ = 5, $J_{4',6'}$ = 1.5 Hz; ir: 3150 (NH, broad) and 1785 cm^{-1} (C=O); uv λ max: 222 (ε, 7,600) and 274 nm (ε, 6,400).

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.49; H, 2.92; N, 25.97.

The mother liquor of recrystallization was evaporated to dryness and the residue was washed with chloroform. The insoluble substance (0.41 g.) was found to be identical with compound VII. The chloroform solution was concentrated and passed through a column of alumina using chloroform as eluent to give 0.34 g. of colorless crystals. The ir spectrum of this compound was completely superimposable upon that of an authentic smaple of 2-cyanopyridine.

The Unequivocal Synthesis of 3-(2-Pyridyl)-1,2,4-oxadiazolin-5-one.

Ethyl chloroformate (2.39 g., 22 mmoles) was added slowly to a solution of 2.74 g. (20 mmoles) of 2-pyridineamidoxime (X) (8) under ice cooling. After stirring at room temperature for 4 hours, the reaction mixture was poured on ice water. The precipitate was collected by filtration, washed with water, dried and recrystallized from chloroform/ligroin to give 2.72 g. of XI as colorless needles, m.p. 97-98°; mass spectrum: m/e 209 (M^+); nmr (deuteriochloroform): δ 1.35 (t, 3H, CH_3), 4.32 (q, 2H, CH_2), 5.96 (br s, 2H, NH_2), 7.40 (m, 1H, H_5), 7.77 (td, 1H, H_4), 8.19 (d, 1H, H_3), 8.62 (d, 1H, H_6), J_{CH_3,CH_2} = 7, $J_{3,4}$ = 8, $J_{4,5}$ = 8, $J_{5,6}$ = 5, $J_{4,6}$ = 2 Hz; ir: 3400 (NH_2), 3290 (NH_2), 1755 (C=O), 1745 (C=O) and 1644 cm^{-1} (NH_2).

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.61; H, 5.34; N, 20.14.

Under a nitrogen atmosphere, 0.51 g. (2.4 mmoles) of compound XI was heated at 140-150° (bath temperature) for 30 minutes. The resultant solid (0.38 g.) was recrystallized from ethanol/benzene (charcoal) to give 0.18 g. of colorless needles of 3-(2-pyridyl)-1,2,4-oxadiazolin-5-one, m.p. 199-200°. A mixed melting point of this product with compound VII was not depressed. The ir spectra of these two compounds were completely superimposable.

3-(2-Pyridyl)-4-methyl-1,2,4-oxadiazolin-5-one (VIII).

A mixture of 0.50 g. (3.0 mmoles) of compound VII, 0.19 g. (3.3 mmoles) of potassium hydroxyde and 0.47 g. (3.3 mmoles) of methyl iodide in 20 ml. of methanol was stirred at room temperature for one hour and then refluxed for 3 hours. After removal of methanol by evaporation, the residue was washed with water and filtered. The filtrate was acidified with acetic acid to recover 0.19 g. of unreacted VII. The residue (0.11 g.) was recrystallized from benzene/ligroin to give colorless needles of the *N*-methyl derivative (VIII), m.p. 136.5-137.5°; mass spectrum: m/e 177 (M^+); nmr (deuteriochloroform): δ 3.64 (s, 3H, CH_3), 7.48 (m, 1H, H_5'), 7.80-8.14 (m, 2H, H_3' and H_4'), 8.78 (dd, 1H, H_6'), $J_{5',6'}$ = 5, $J_{4',6'}$ = 1.5 Hz; ir: 1785 (C=O) and 1767 cm^{-1} (C=O).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.33; H, 3.87; N, 23.95.

α-Oximino-α-(2-pyridyl)acetylazide (V).

A stirred solution of 4.54 g. (30 mmoles) of I in 60 ml. of 10% hydrochloirc acid was cooled in an ice salt bath and a solution of 5.52 g. (80 mmoles) of sodium nitrite in 10 ml. of water was added dropwise keeping the temperature between -10° and -5°. Dichloromethane (100 ml.) was added to the reaction mixture and under vigorous stirring the *p*H of the solution was adjusted to *ca.* 7 with concentrated ammonium hydroxide keeping the temperature below 0°. The organic layer was separated and the water layer was extracted with dichloromethane three times. The combined extract was washed with ice water, dried over sodium sulfate and evaporated to dryness under reduced pressure below room temperature (*ca.* 10°). The residue was washed with benzene and filtered to give 2.90 g. of crude V. From the benzene washings, 0.10 g. of 2-cyanopyridine (IX) was obtained after passing through a short column of silica gel using benzene as eluent. The crude V was dissolved in dichloromethane and filtered. The filtrate was added to *n*-hexane and allowed to stand in a refrigerator to give 1.12 g. of purified V, m.p. *ca.* 170-190° dec.; mass spectrum: m/e 163 ($M-N_2$); nmr: δ 7.50 (td, 1H, H_5), 7.98 (td, 1H, H_4), 8.26 (td, 1H, H_3), 8.54 (td, 1H, H_6), $J_{3,4}$ = 8, $J_{5,6}$ = 5, $J_{3,5}$ = 1.5 $J_{4,6}$ = 2, $J_{3,6}$ = 1 Hz; ir: 2650 (OH, broad), 1840 (OH, broad), 2160 (N_3), 2140 (N_3), 1681 (C=O) and 1641 cm^{-1} (C=N).

Anal. Calcd. for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64. Found: C, 43.61; H, 2.47; N, 35.72.

Although this product contained a slight impurity, further purification by recrystallization or chromatography failed due to its instability in solution.

Thermolysis of V.

A solution of 0.49 g. (2.5 mmoles) of V in 30 ml. of benzene was refluxed for one hour and evaporated to dryness. The residue (0.38 g.) was recrystallized from ethanol/benzene to give 0.21 g. of colorless needles, m.p. 199-200°. This compound was shown to be identical with compound VII by mixed melting point and comparison of the ir spectra.

Treatment of V with 10% Hydrochloric Acid.

A mixture of 0.50 g. (2.6 mmoles) of compound V and 12 ml. of 10% hydrochloric acid was stirred for 3 hours at room temperature. The precipitate was collected by filtration, washed with ethanol and then with ether to give 0.22 g. of the hydrochloride of compound V as a colorless powder, m.p. 200-200.5° dec.; ir: 2700 (N^+-H and OH, broad), 2150 (N_3) and 1688 cm^{-1} (C=O).

Anal. Calcd. for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.65; N, 30.76. Found: C, 36.84; H, 2.54; N, 31.10.

Treatment of V with 10% Sodium Carbonate Solution.

Compound V (0.88 g., 4.6 mmoles) was dissolved in 20 ml. of 10% sodium carbonate solution. At this time, the evolution of a gas was observed. After standing at room temperature for 3 hours, the reaction mixture was extracted with dichloromethane. The extract was washed with water, dried over sodium sulfate and evaporated to dryness leaving 0.39 g. (80%) of pale green crystals. The ir spectrum of this compound was superimposable upon that of an authentic sample of 2-cyanopyridine.

Conversion of IV to VII.

A solution of 0.34 g. (4.9 mmoles) of sodium nitrite in 2 ml. of water was added to an ice salt cooled stirred solution of 0.55 g. (4.1 mmoles) of compound IV in 10 ml. of 10% hydrochloric acid. The reaction mixture was stirred under ice salt cooling for 15 minutes and at room temperature for 2.5 hours. The precipitated substance was collected and washed with water to give 0.33 g. of colorless crystals. The filtrate and washing solution were combined and evaporated to dryness. The residue was washed with water and filtered to give 0.12 g. of same compound. Both products were combined and recrystallized from ethanol/benzene to give 0.25 g. of colorless needles, m.p. 199-200°. This compound was shown to be identical with compound VII by mixed melting point and comparison of the ir spectra.

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