Studies in the Heterocyclic Series. XI. Reactions of 2-Amino-3-hydroxypyridine with 2-Chloro-3-nitropyridine (1)

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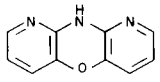
Received May 30, 1975

The reactions of 2-amino-3-hydroxypyridine and 2-chloro-3-nitropyridine in various solvents and in the presence of certain catalysts were studied. A dilute acid-catalysed procedure led to a 45% yield of 3-hydroxy-3′-nitro-2,2′-dipyridylamine which was also obtained by refluxing in alcoholic potassium hydroxide for several hours. The diarylamine was converted to 1,9-diazaphenoxazine by base-catalysed intramolecular condensation in refluxing DMSO. The same diazaphenoxazine was obtained directly by prolonged base-catalysed reaction of the starting pyridine compounds in DMSO. From a study of the infrared spectrum of the diarylamine precursor, it was found that strong NHO hydrogen bonding is responsible for the failure of the cyclization step in either aqueous or alcoholic base. This problem was overcome by the use of DMSO as the reaction solvent. Structural assignments were made by a study of their ultraviolet, infrared, nmr and mass spectra and the mechanistic pathways were also discussed.

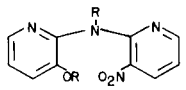
Most methods for preparing monoaza- (2-6) and diazaphenoxazines (7-8) utilize highly substituted compounds particularly halobenzenes and halopyridines bearing more than one electron-withdrawing group. The only known parent azaphenoxazine was obtained indirectly by catalytic hydrogenolysis of 10-benzyl-3-azaphenoxazine (9,10). In this article, we wish to describe some reactions of 2-amino-3-hydroxypyridine (I) and 2-chloro-3-nitropyridine (II) which culminated in a direct synthesis of the parent 1,9-diazaphenoxazine ring (III) (11).



III

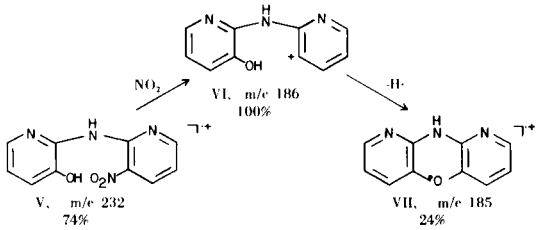
I R_1 NH_2, R_2 OH
II R_1 Cl, R_2 NO_2

2-Chloro-3-nitropyridine was mixed with 2-amino-3-hydroxypyridine and refluxed in dilute sulfuric acid medium (12) for at least 12 hours. A purple-red crystalline solid (IV) of molecular formula $C_{10}H_8N_4O_3$ melting at 169° was isolated. The field desorption mass spectrum showed the molecular ion at m/e 232 while the infrared spectrum had characteristic absorption signals at 3380s (bonded phenolic OH), 3240m (aromatic NH), 1232m (bonded phenolic C-O stretching), 1346s (aromatic NO_2), 747s and 772s (aromatic *cis*-CH) cm^{-1} (13). The product was tentatively, therefore, identified as 3-hydroxy-3′-nitro-2,2′-dipyridylamine. In a study of the mass spectrum



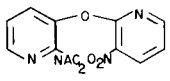
IV, R H
VIII, R Ac

of this compound, the base peak at m/e 186 was obtained by the loss of an NO_2 molecule from the molecular ion (V). Loss of a hydrogen atom from the ion (VI) led to another prominent radical (VII) at m/e 185.

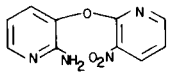


Acetylation of compound IV with acetic anhydride gave a diacetyl derivative which had two carbonyl bands at 1773 (ester) and 1695 cm^{-1} (tertiary amide) in the infrared spectrum; no OH and NH absorption bands were observed. It follows, therefore, that the amino and phenolic hydrogen atoms were replaced by acetyl groups and hence the diacetylated product is *N*-acetyl-3-acetoxy-3′-nitro-2,2′-dipyridylamine (VIII). The *N*,*N*-diacetyl derivative (IX) was rejected on the grounds that the C=O bands are too far apart for the observed signals to be due to vibrational coupling in a diacylamine. Also formation of compound III in a subsequent experiment eliminates

this possibility. The alternative oxygen-bridged structure, (2-amino-3-pyridyl)-3-nitro-2-pyridyl ether, (X), is thus ruled out as the structure of the amine (IV).



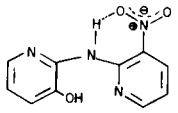
IX



X

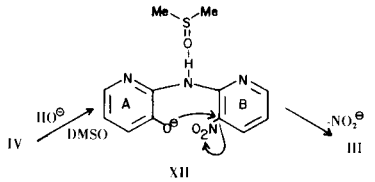
No product was obtained if the reacting compounds, I and II, were refluxed in aqueous potassium hydroxide but in alcoholic base, a small yield of compound IV was isolated. This base-catalysed reaction was, therefore, rationalized as proceeding through a diaryl ether intermediate (structure X) followed by base-catalyzed Smiles rearrangement (14,15) to give the isolated diarylamine (IV).

Cyclization of the hydroxynitrodiarylamine in aqueous or alcoholic potassium hydroxide was rather unsuccessful. The starting materials were partially recovered. The failure to cyclize was attributed to strong NHO hydrogen bonding between the amino hydrogen and the oxygen of the nitro group leading to a six-membered chelate of high stability (structure XI). Evidence for this chelation is provided by the infrared spectrum (16) in which the NH stretching frequency was shifted from 3500 to 3240 cm^{-1}. The shift in the N=O group frequency from 1370 to 1346 cm^{-1} confirms the hydrogen bonding and the chelation.



XI

As a result of the observed hydrogen bonding, the nitro group is thus not sufficiently free for interaction with the nucleophile in the cyclization step. A reagent was, therefore, sought which would compete successfully with the nitro group for the amino hydrogen and in so doing would free the nitro group. Dimethylsulfoxide (DMSO) proved to be a suitable solvent for this purpose and as a powerful ionizing aprotic solvent, it preferentially formed a hydrogen bond with the amino hydrogen thereby leaving the nitro group sufficiently free for attack by the internal nucleophile. In so doing, the nitro group was lost as a



XII

nitrite ion by an intramolecular nucleophilic attack on the positive 3-carbon centre of ring B (structure XII) leading to cyclization.

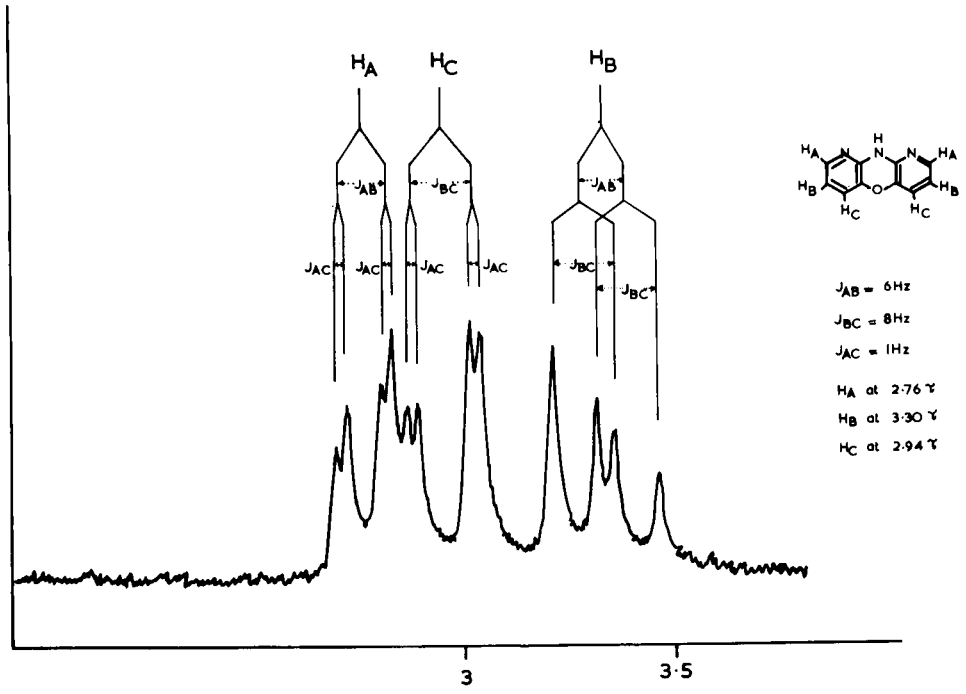
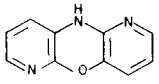


Figure 1. The nmr spectrum of the aromatic region of 1,9-diazaphenoxazine (III).

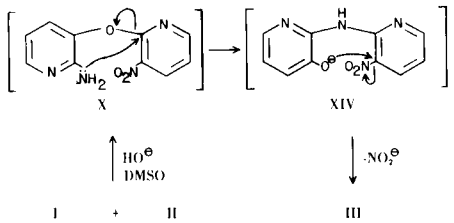
The cyclization product is a yellow crystalline solid of molecular formula $C_{10}H_7N_3O$ melting at 245°. The molecular ion appeared in the mass spectrum at m/e 185. The ultraviolet spectrum showed three intense maximum absorption bands at 338, 217 and 210 nm. The infrared spectrum had a strong absorption band at 1297 cm^{-1} (aromatic NH), another strong band at 1250 cm^{-1} (aromatic C-O-C ether linkage) and two strong signals at 741 and 772 cm^{-1} (presence of three adjacent free hydrogen atoms of pyridine). The absence of an absorption band between 1300 and 1370 cm^{-1} confirms the loss of the nitro group. The 1,9-diazaphenoxazine structure (III), was tentatively assigned to this product. The nmr spectrum provided confirmatory evidence for this structure. A singlet at τ 1.50 which disappeared with the addition of deuterium oxide was assigned to 10-NH proton. The aromatic protons appeared as a multiplet between τ 2.70 and 3.50. In Figure 1, the splitting of these aromatic protons is presented and schematically interpreted. The splitting pattern suggests that the molecule is symmetrical about the central ring nitrogen and oxygen as the symmetry axis. Thus 2H, 3H and 4H are equivalent to 8H, 7H and 6H, respectively. H_A representing the protons at C-2 and C-8 appeared as a doublet of doublets at τ 2.76, J_{AB} = 6 Hz and J_{AC} = 1 Hz. H_C (4H and 6H) appeared in the same pattern at τ 2.94, J_{AC} = 1 Hz and J_{BC} = 8 Hz. The uppermost field doublet of doublets centred at τ 3.30 is due to the absorption signals of H_B (3H and 7H), J_{AB} = 6 Hz and J_{BC} = 8 Hz. Thus the nmr spectrum is in perfect agreement with structure III which we have now assigned to the product (17). The alternative structure XIII is



XIII

expected to give a more complex spectrum due to the absence of symmetry and the non-equivalence of the six aromatic protons.

Although acid-catalysed condensation of compound I with the chloronitropyridine (II) gave the hydroxynitrodiarylamine, (IV), no crystalline product was isolated in aqueous base. In DMSO, the base-catalyzed reaction gave compound III but the overall yield is only 8%. This reaction was formulated as proceeding through a diaryl ether intermediate (X) followed by Smiles rearrangement leading to the diarylamine (XIV).



Owing to the presence of the ionizing solvent used in this base catalyzed reaction, cyclization proceeded smoothly leading to the formation of 1,9-diazaphenoxazine (III). If there were no rearrangement, direct cyclization of compound X would have led to 1,6-diazaphenoxazine, (XIII) whose nmr spectrum will be more complex than was observed.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are corrected. Uv and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells. The solvent is methanol and the absorption maxima are always given in nanometers; the figures in parenthesis are log ϵ values. Ir spectra were obtained on a Perkin Elmer Model 137 spectrophotometer using potassium bromide discs unless otherwise stated. Pmr spectra were determined on a Varian Associates A-60 instrument. Chemical shifts are reported on the τ scale relative to TMS used as an internal standard. The letters b, s, d, sh, m and dd are used to indicate broad, singlet, doublet, shoulder, multiplet and doublet of doublets, respectively. The mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer at 70 eV. Microanalyses were performed partly by the Scandinavian Microanalytical Laboratories, Herlev, Denmark and partly by the Department of Chemistry, University of Ibadan, Ibadan, Nigeria.

3-Hydroxy-3′-nitro-2,2′-dipyridylamine (IV).

Method A: Acid-Catalysed Reaction.

A mixture of 3.30 g. (30 mmoles) of 2-amino-3-hydroxypyridine (I) and 3.17 g. (20 mmoles) of 2-chloro-3-nitropyridine (II) (18) was ground in a mortar and placed in the reaction flask to which 200 ml. of water was added. About 4 ml. of concentrated sulfuric acid were added to bring down the *p*H of the solution to 1. Sodium sulfite (1.0 g.) was added and the mixture refluxed on a steam bath at 92° for 12 hours. The *p*H of the solution was checked from time to time to ensure that it remained below 2. The chloronitropyridine which sublimed and settled on the condenser was washed down to the reaction flask with a minimum amount of acidulated water. At the end of the reaction, the yellowish-red solution was cooled overnight and the unreacted 2-chloro-3-nitropyridine (200 mg.) collected by vacuum filtration. The filtrate was neutralized with concentrated ammonia solution to *p*H 8 and further cooled at 5° for 6 hours. Upon filtration and recrystallization from methanol after addition of activated charcoal (Norit A), glistening purple-red microneedles of 3-hydroxy-3′-nitro-2,2′-dipyridylamine, (IV), (2.09 g., 45%) melting at 169° were obtained; uv spectrum: λ max 400 (3.73), 355 (3.89), 312 (3.91), 240sh (4.09) and 210 (4.23); infrared spectrum: ν max 3380, 3240, 2945, 1346, 1332, 1232, 772 and 747 cm^{-1}; nmr spectrum (DMSO-d_6): τ 1.67 (m, area 3) (4H, 6H, 6′H), 2.88 (m, area 5) (4H, 5H, 5′H, OH, NH); mass spectrum m/e (relative intensity): 131 (12), 158 (25), 169 (14), 185 (24), 186 (100), 215 (10), 232 [M^+, 74] and 233 (11).

Anal. Calcd. for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.45; N, 24.14. Found: C, 51.81; H, 3.49; N, 24.13.

Method B: Alcoholic Base-catalysed Reaction.

An intimate mixture of 1.65 g. (15 mmoles) of 2-amino-3-

hydroxypyridine (I) and 1.59 g. (10 mmoles) of 2-chloro-3-nitropyridine (II) was refluxed with stirring for 10 hours in 150 ml. of ethanol to which 1.68 g. (30 mmoles) of potassium hydroxide dissolved in 20 ml. of ethanol had been added. The solution was cooled and the precipitated potassium chloride removed by filtration. The dark filtrate was concentrated to a small bulk, treated with activated charcoal, boiled and filtered. The filtrate was chilled at -10° for several days. On filtering, 200 mg. of 3-hydroxy-3'-nitro-2,2'-dipyridylamine (IV) melting at 169-170° was isolated. Mixed melting point determination with a sample obtained by acid-catalysed procedure did not show any depression; the spectra of both products were also superimposable.

N-Acetyl-3-acetoxy-3'-nitro-2,2'-dipyridylamine (VIII).

3-Hydroxy-3'-nitro-2,2'-dipyridylamine (IV) (2.32 g., 10 mmoles) was refluxed for 8 hours in 40 ml. of acetic anhydride to which 5 ml. of pyridine had been added. The resulting brown solution was cooled to room temperature and a few cubes of ice added with constant stirring and cooling. The clear solution was then neutralized with concentrated ammonia to *p*H 5 and cooled at 5° for 48 hours. Upon filtration and recrystallization of the residue from aqueous ethanol, glistening yellow plates of *N*-acetyl-3-acetoxy-3'-nitro-2,2'-dipyridylamine (VIII) (1.96 g., 62%) were obtained. The unreacted material (100 mg.) was recovered by neutralization to *p*H 8 with concentrated ammonia. The diacetyl product, (VIII), melted at 143-144°; ultraviolet spectrum: λ max 270 (3.99), 225 (4.29), 208 (4.26); infrared spectrum (Nujol): ν max 1773, 1695, 1592, 1351, 794, 769, 761 and 682 cm^{-1}; nmr (deuteriotrifluoroacetic acid): τ 2.20 (m, the 6 aromatic protons), 8.06 (m, the protons of the two methyl groups).

Anal. Calcd. for $C_{14}H_{12}N_4O_5$: C, 53.16; H, 3.80; N, 17.72. Found: C, 53.09; H, 3.76; N, 17.75.

1,9-Diazaphenoxazine (III).

Method A: Cyclization of 3-Hydroxy-3'-nitro-2,2'-dipyridylamine in DMSO.

Dried 3-hydroxy-3'-nitro-2,2'-dipyridylamine, (IV), (2.32 g., 10 mmoles) was dissolved in 20 ml. of DMSO and placed in the reaction flask equipped with a dropping funnel, a reflux condenser and a mechanical stirrer. An alcoholic solution of potassium hydroxide was made by dissolving 616 mg. (11 mmoles) of potassium hydroxide in 15 ml. of ethanol over a steam bath. The solution was transferred into the reaction flask, rinsing the beaker with 10 ml. of DMSO. The use of a near stoichiometric amount of potassium hydroxide is recommended as no product was isolated in a large excess of the base. Furthermore, a water-free condition was maintained throughout the reaction to avoid decomposition in the refluxing solvent. The reaction mixture was refluxed with constant stirring for 9 hours. The dark red solution was poured while hot into a 200 ml. beaker. Water (50 ml.) was added gradually to the hot solution and stirred. The dark residue was cooled at 5° overnight and filtered to collect the dark solid material. This residue was recrystallized from ethanol (17) after treatment with activated charcoal (Norit A). Upon cooling and filtering, glistening yellow microneedles of 1,9-diazaphenoxazine (570 mg., 31%) (19) melting at 245-246° were obtained. The analytical sample melted at 245°; λ max 338 (4.12), 217 (4.30), 210 (4.29); infrared spectrum (Nujol): ν max 1629, 1520, 1416, 1297, 1250, 772 and 741 cm^{-1}; nmr spectrum (deuteriotrifluoroacetic acid): τ 1.50 (s, 10-NH), 2.76 (dd, 2H, 8H), 2.94 (dd, 4H, 6H), 3.30 (dd, 3H, 7H).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.78; N, 22.70. Found: C, 64.91; H, 3.69; N, 22.72.

Method B: Reaction of 2-Amino-3-hydroxypyridine with 2-chloro-3-nitropyridine in DMSO.

To an intimate mixture of 2-amino-3-hydroxypyridine (I) (2.20 g., 20 mmoles) and 2-chloro-3-nitropyridine (II) (3.49 g., 22 mmoles) in 50 ml. of DMSO was added 2.46 g. (44 mmoles) of potassium hydroxide dissolved in 10 ml. of ethanol. The mixture was refluxed with constant stirring for 9 hours. Upon addition of 200 ml. of water to the hot solution, a dark precipitate was formed. The slurry was cooled overnight at 5° and filtered. The dark residue which was collected was recrystallized from ethanol after treatment with activated charcoal (Norit A) to yield 300 mg. (8%) of 1,9-diazaphenoxazine (III), m.p. 245-246°. The uv, ir, nmr and mass spectra of this compound are identical with those of the product obtained by cyclization of compound (IV) (Method A). Mixed melting point determination with these samples did not show any depression.

Acknowledgment.

We express our sincere thanks to Messrs P. I. Mowete and N. Ologun of the Department of Chemistry, University of Ibadan, Ibadan, Nigeria for the microanalyses and mass spectra, respectively. The technical assistance of Messrs. F. I. Ozoh, F. U. Ekezie and O. O. Ibe of these Laboratories is also deeply appreciated.

This project was supported by a grant from the Research Grant Committee of the University of Nigeria.

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(19) The overall yield, starting from 2-amino-3-hydroxypyridine and 2-chloro-3-nitropyridine, is 14%.