TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS

PART IX. THE CYCLIZATION OF SOME NITRO- AND AZIDO-PHENYLPYRIDINES. PYRIDO[1,2-*b*]INDAZOLE[1,2]

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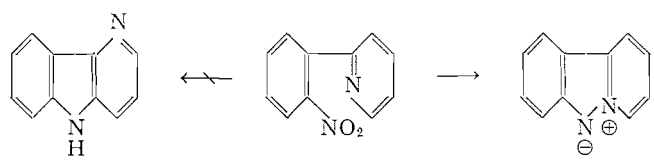
ABSTRACT

Heating 2-*o*-nitrophenylpyridine with ferrous oxalate gives rise to pyrido[1,2-*b*]indazole (III). The evidence for the structure of this compound is discussed. Similarly, heating 2-*o*-nitrophenylpyridine methiodide and *N*-oxide with ferrous oxalate gives (III), in each case, demethylation and deoxygenation preceding the cyclization. In the latter case a minute amount of δ-carboline is also formed. Heating pyridine-*N*-oxides with ferrous oxalate is a potentially general method of effecting deoxygenations of these compounds. Contrary to the results of Smith and Boyer (11), it is found that heating 2-*o*-azidophenylpyridine also gives rise to (III). On the other hand, the action of heat on 2-*o*-azidophenylpyridine-*N*-oxide gives a mixture of δ-carboline and δ-carboline-*py*-*N*-oxide in low yield. The mechanism of the cyclization of the azides and of the reaction taking place on heating nitro-compounds with ferrous oxalate is discussed briefly; the formation of a nitrene intermediate is favored.

The catalytic reduction of 2-*o*-nitrophenylpyridine-*N*-oxide giving rise to the azoxy-, azo-, and hydrazo-derivatives is described and the ultraviolet absorption spectra of these compounds are discussed. It is concluded the steric inhibition of coplanarity exists in the azoxy- and azo-compounds leading to the lack of effective conjugation across the N=N bond.

When this work was initiated no suitable method for the synthesis of the δ-carboline ring system was available. Since that time, however, δ-carboline (I) has been obtained in this laboratory by the thermal cyclization of 3-azido-2-phenylpyridine (1). The yields in this reaction are variable, however, and a better method was sought. To this end, the action of ferrous oxalate on 2-*o*-nitrophenylpyridine was investigated.

Ferrous oxalate has been used in a number of interesting cyclizations. Thus, heating it with 2-nitrodiphenyl gives rise to carbazole (2); phenazines have also been obtained from 2-nitrodiphenylamines by this method (2, 3). On the other hand, 4-nitrocarbazole was not obtained from 2,2′-dinitrodiphenyl, but instead 3,4-benzocinnoline was isolated (2). The action of ferrous oxalate on 2-*o*-nitrophenylpyridine (II) at 300° has now been examined. It was anticipated that the pyridine nuclear carbons might be relatively deactivated towards such a cyclization, but that it could conceivably occur at the 3-position of the pyridine ring to give δ-carboline. Cyclization did, in fact, occur but onto the pyridine nitrogen atom to give pyrido[1,2-*b*]indazole (III), no δ-carboline being formed.



(I) (II) (III)

The evidence for the formulation of the cyclization product as pyrido[1,2-*b*]indazole is as follows:

(i) The product is different from any of the carbolines, all of which are now known,

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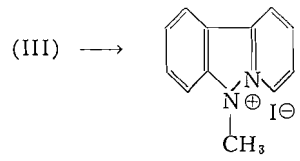
Contribution from the Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan. Part of this paper formed the subject of a lecture given at the Fifth Western Regional Conference of the Chemical Institute of Canada held in Regina in September, 1960.
[2]*Part VIII: Can. J. Chem.* **38**, *2152 (1960).*

and melts (83–84°) well below the melting point of the carbolines (~200°). It analyzed correctly for $C_{11}H_8N_2$.

(ii) The infrared spectrum of the compound did not exhibit an N—H stretching absorption and no active hydrogen could be detected. On the other hand, γ-carboline gave an atom of active hydrogen quantitatively. The compound is unaffected by boiling with mineral acids or with aqueous ethanolic alkali (no rearrangement to a more stable structure) and does not take up hydrogen in the presence of Adams' catalyst at atmospheric pressure. It does form an unstable hydrochloride and a picrate.

(iii) Unlike the carbolines, it did not form a methiodide readily, but did so to give (IV) under forcing conditions (in ethanol in a sealed tube for 18 hours at 100°). That no C-alkylation had taken place in this reaction was indicated by the absence of a C—CH_3 group (Kühn-Roth).

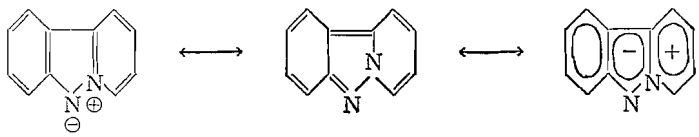
(iv) The infrared spectrum of the product showed a medium intensity band at 1650 cm^{-1}, somewhat higher than is usually found for aromatic rings. A similarly high frequency (1642 cm^{-1}) was reported (4) for anthranil in which a dipolar form $-C_6H_4-\overset{\ominus}{N}-$ contributes greatly to the structure. The ultraviolet absorption spectra of (III) and its derivatives are also interesting. The spectrum of the free base in alcohol, that of the



(IV)

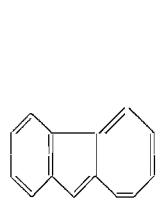
base in alcohol at pH 11, and that of the hydrochloride in alcohol are identical, pointing to the dissociation of the hydrochloride in this solvent. On the other hand, the base in aqueous hydrochloric acid at pH 1 had a spectrum very similar to that of the methiodide (IV) in alcohol, the methyl group having its usual bathochromic effect. The most striking features of the latter ultraviolet spectra are the very high extinction coefficients of the low wavelength bands ($\epsilon \times 10^{-3}$ 182.4 and 196.0 for the hydrochloride and methiodide respectively).

The heterocyclic rings in (III) are isoelectronic with azulene and one could write a number of canonical structures for this molecule:

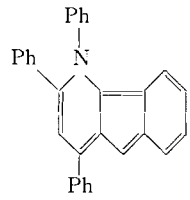


(A) (B) (C)

A number of lines of evidence point to the fact that the orthoquinonoïd anhydro-base structure (B) is probably a minor contributor to the resonance hybrid. Azulene (in which the dipolar structure plays only a small role), 1,2-benzazulene (V), and a variety to pseudo-azulenes such as 1,2,4-triphenylindeno[1,2-*b*]pyridine (VI) (5) are all highly colored; all the carboline anhydro-bases are deep yellow or orange. Paoloni and Marini-Bettòlo (6) have attributed the color of the anhydronium base of 7-azaindole to the



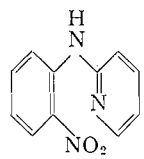
(V)



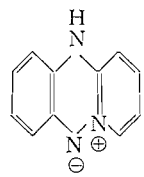
(VI)

orthoquinonoïd form and have suggested that the carboline anhydronium bases as well as sempervirine are best represented by the covalent formulae not bearing separated charges.* From a study of the spectral properties of the δ-carboline anhydronium base Abramovitch, Adams, and Notation (1) suggested that the quinonoïd structure is a more important contributor to the resonance hybrid than the dipolar one. On the other hand, pyrido[1,2-*b*]indazole is colorless, as is its methiodide. In addition, carboline anhydronium bases form *ind-N*-methiodides readily at room temperature (1, 8) whereas (III) only does so under forcing conditions. Similarly, carboline anhydronium bases can be readily hydrogenated (e.g. reduction of cryptolepine (9)) whereas pyrido[1,2-*b*]indazole is not. Gray (10) has interpreted the low base strength of the α-carboline anhydronium base (pK_a 7.75)† as compared with the γ-derivative (pK_a 10.54) on the basis of two factors: (*a*) a much increased stability of the α-anhydronium base as a result of the juxtaposition of the oppositely charged centers (presumably in the dipolar form); and (*b*) a reduced stability of the α-carboline salt owing to the inductive effect of the indole nitrogen attached to the same carbon as the positively charged pyridine nitrogen. It would be expected that in (A) ↔ (C) these effects would be greatly intensified; in fact the pK_a of pyrido[1,2-*b*]indazole has now been found to be approximately 2.48, slightly more than five p*K* units lower than the base strength of the α-carboline anhydronium base!

An attempt was made to obtain further examples of this type of cyclization onto a pyridine nitrogen atom. 2-Nitro-*N*-2′-pyridylaniline (VII) was prepared from 2-bromopyridine and *o*-nitroaniline. The action of ferrous oxalate at 300° on (VII) led to the formation of tars, no product corresponding to (VIII) being detected. This was not totally unexpected since the central ring in (VIII) would be nonaromatic (8 π electrons, compared with 6 π electrons in (III)) so that the incentive leading to its formation may have been lacking. A similar result was obtained using *N*-methyl-2-nitro-*N*-2′-pyridylaniline.



(VII)



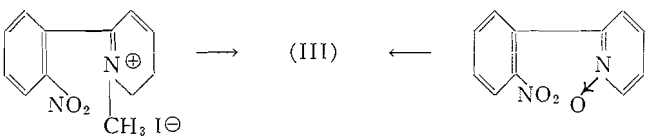
(VIII)

It was hoped to force cyclization to occur at C_3 by blocking the pyridine nitrogen atom

**Paoloni (7) has recently elaborated further on this point. Apart from the fact that his calculations do not lead to correct values for the pK_a and U.V. spectrum of δ-carboline, his conclusion that it is unnecessary to represent the carboline anhydro-bases as hybrids of dipolar and quinonoïd structures in view of the fact that his results "illustrate eloquently the compromise between the tendency to form the (aromatic) sextet and that to neutralize the charges" seems a contradiction in ideas.*

†The pK_a of this compound, as determined by us (1), was 7.55.

in (II). Thus, 2-*o*-nitrophenylpyridine methiodide (IX) and 2-*o*-nitrophenylpyridine-*N*-oxide (X) were prepared. It was realized that the *N*-oxide grouping in (X) might not survive the reducing conditions present during the cyclization reaction but it was hoped that cyclization at the 3-position would occur before reduction. In actual practice, heating either (IX) or (X) with ferrous oxalate led to the formation of pyrido[1,2-*b*]indazole. Chromatography on a column of alumina of the crude product from the cyclization of the *N*-oxide yielded, apart from (III), trace amounts of a solid which had an infrared spectrum almost identical with that of δ-carboline. Insufficient material was available to study this product further.



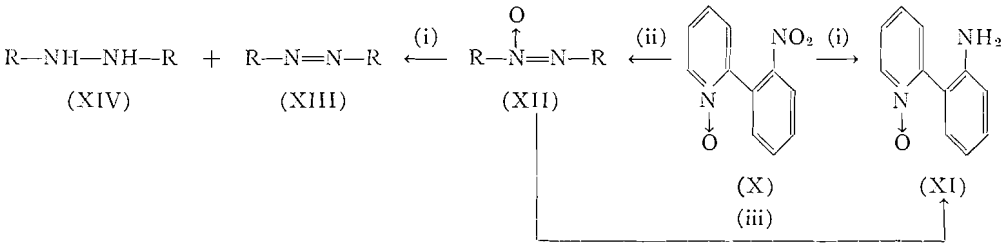
(IX) (X)

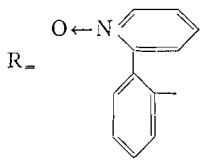
It was of interest from the point of view of the mechanism of the cyclization reaction to determine whether elimination of the protecting groups could occur prior to the cyclization, or whether some mode of concerted attack by the intermediate formed from the reduction of the nitro group and elimination of the protecting group was taking place. To this end, the action of ferrous oxalate at 300° on 2-phenylpyridine methiodide and 2-phenylpyridine-*N*-oxide was studied; in both cases 2-phenylpyridine was isolated in yields comparable to the respective reactions using (IX) and (X). In fact, 2-phenylpyridine could be obtained from the corresponding methiodide by heating it at 300° with granulated lead (used to permit the even distribution of heat in the mixture during such cyclization reactions) but without ferrous oxalate. On the other hand, 2-phenylpyridine-*N*-oxide was recovered unchanged under such conditions. It would, therefore, seem that elimination of the protecting group probably precedes cyclization onto the ring nitrogen atom, though the isolation of a trace of a second product in the *N*-oxide case suggests that conditions might be found where the reverse might be achieved. The reduction of the pyridine-*N*-oxide by ferrous oxalate may well be a general reaction of such amine oxides; this is under investigation.

Smith and Boyer (11) attempted to prepare δ-carboline by the thermal cyclization of 2-*o*-azidophenylpyridine in decalin solution but reported obtaining instead 2-*o*-aminophenylpyridine, formed presumably by hydrogen abstraction from the solvent by the intermediate involved. In the present work this reaction gave rise to a 60% yield of pyrido[1,2-*b*]indazole, only a trace of diazotizable material being detected in the crude reaction mixture. No amine could be isolated by chromatography of the crude product on alumina. Attempts at photodecomposition of the azide in solution were unsuccessful though some darkening did occur. This is similar to the experience of Smolinsky, who was working with 2,4,6-trimethyl-2′-azidodiphenyl (12).

Once again, blocking the pyridine nitrogen atom by *N*-oxide formation prior to cyclization was attempted. 2-*o*-Nitrophenylpyridine-*N*-oxide (X) could be reduced catalytically in acetic acid solution with hydrogen and palladium–charcoal to the amine (XI), the *N*-oxide grouping being unaffected. This result is in agreement with previous hydrogenations of pyridine-*N*-oxides (13, 14) which indicated that the *N*-oxide group in 2-substituted pyridine-*N*-oxides was sterically hindered and thus resisted reduction. If, on the

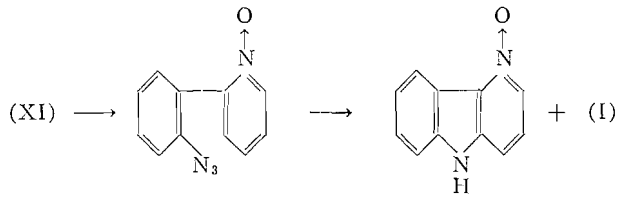
other hand, the catalytic reduction was carried out in alcohol solution the product isolated was 2,2′-di-(*N*-oxido-2-pyridyl)azoxybenzene (XII). This, on catalytic reduction in glacial acetic acid solution gave 2,2′-di-(*N*-oxido-2-pyridyl)azobenzene (λ_{max} 230, 323, 455 mμ; λ_{infl} 260 mμ; $\epsilon \times 10^{-3}$ 44.73, 19.02, 0.58, 28.70) (XIII) together with a small amount of what is probably the hydrazo-compound (XIV), though the latter proved to be very difficult to purify. Its structure was inferred from its infrared spectrum and from its ultraviolet absorption spectrum, which was similar to that of 2-*o*-aminophenylpyridine-*N*-oxide (XI). The azoxy-compound (XII) was reduced directly to the amine (XI) by stannous chloride and hydrochloric acid. These reductions are somewhat similar to those reported by Hayashi, Yamanaka, Iyima, and Matsushita (15), who studied the catalytic reduction of 4,4′-azoxypyridine 1,1′-dioxide. The amine (XI) was converted





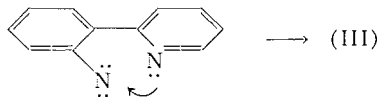
(i) 5% Pd–C in AcOH; (ii) 5% Pd–C in EtOH; (iii) $SnCl_2$–HCl.

to the azide (XV), which, on thermal decomposition in decalin solution, gave a crude mixture from which δ-carboline (I) and δ-carboline-*py*-*N*-oxide (XVI) could be isolated in low yield by chromatography on alumina. The structure of (XVI) was proved by its synthesis from authentic δ-carboline.



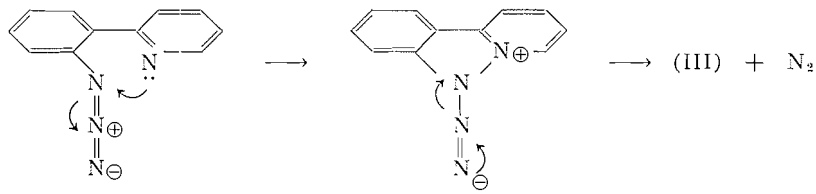
It is interesting to speculate about the mechanisms of the cyclization onto the pyridine nitrogen atom reported here. In the case of the thermal decomposition of the azides two groups of workers have very recently suggested that a nitrene, —N:, may be involved (12, 16). Such an entity, were it formed, would be isoelectronic with a carbene and could be strongly electrophilic. In support of this suggestion is the finding that thermal decomposition of 2,4,6-trimethyl-2′-azidodiphenyl gives rise to 8,10-dimethylphenanthridine (12), which can conceivably arise by attack of a benzylic C—H by a nitrene intermediate.

This may well explain the present results; such an electrophilic species would certainly tend to attack the pair of electrons on the pyridine nitrogen atom rather than the 3-position of the pyridine ring which is deactivated toward electrophilic substitution. On

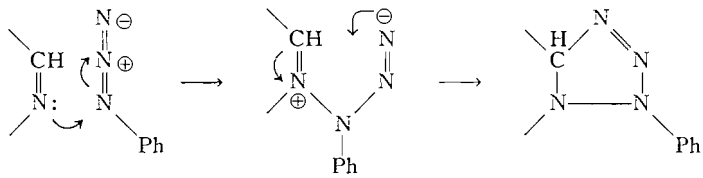


(D)

the other hand, one cannot at present eliminate a concerted or perhaps two-stage mechanism involving cyclization concurrent with, or followed by, the elimination of a nitrogen molecule:



Such a N—N bond formation has an analogy in the known reaction of aryl azides with benzaldehyde arylhydrazones which gives rise to tetrazole derivatives (17) for which one might visualize the following sequence:



We tend to prefer the "nitrene intermediate" mechanism at the present time, at least as far as the reaction leading to (XVI) and (I) goes (for arguments in favor of the formation of such an intermediate see ref. 12). A nitrene intermediate is probably formed during the ferrous oxalate cyclization of the nitro-compounds and it would be attractive to visualize a common reactive intermediate species for both of these reactions, leading as they do to the same product. The concerted mechanism for the conversion of the azide to (III) must, however, be seriously considered.

Not much is known concerning the mode of action of ferrous oxalate in these reactions. It presumably decomposes thermally to give a very reactive form of ferrous oxide (some iron may also be formed), which is the actual reducing agent (2, 3). This can either abstract both oxygen atoms from the nitro-group to give a nitrene (D), or else first give rise to a nitroso-derivative which could then add to the pyridine nitrogen atom and lose a second atom of oxygen to form the pyrido[1,2-*b*]indazole. The latter pathway seems a less likely one in view of the above azide cyclizations.

One further matter should be commented on and that is the similarity between the ultraviolet absorption spectra of the azoxybenzene (XII), the azobenzene (XIII), the hydrazo-derivative (XIV), and the amine (XI) (Fig. 1). The spectra of (XIV) and (XI) are almost superimposable (as expected), except that in the case of (XIV) the

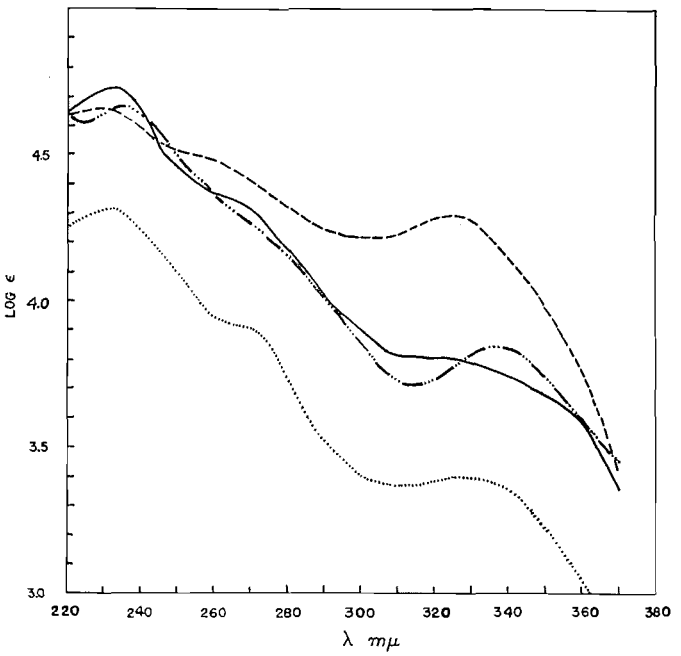


FIG. 1. Ultraviolet absorption spectra in 95% ethanol solution. —— 2,2′-Di-(*N*-oxido-2-pyridyl)azoxybenzene; – – – 2,2′-di-(*N*-oxido-2-pyridyl)azobenzene; —· · · 2,2′-di-(*N*-oxido-2-pyridyl)hydrazobenzene; · · · · 2-*o*-aminophenylpyridine-*N*-oxide.

maxima have all undergone a small bathochromic shift and the intensities are markedly greater. On the other hand, the spectra of azoxybenzene, azobenzene, and aniline are quite different from each other (18, 19), which is not the case for our compounds. One would have to attribute such a result to steric hindrance in the cases of (XII) and (XIII) preventing coplanarity of the two benzene rings and the N=N linkage and thus inhibiting effective conjugation across that linkage. This would result in each of these molecules having an absorption spectrum similar to that of the amine (XI), only more intense, which is what is actually observed.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured using a Perkin–Elmer Model 21 instrument equipped with sodium chloride optics. Ultraviolet absorption spectra were measured on a Cary Model 14 recording spectrometer.

Action of Ferrous Oxalate on 2-o-Nitrophenylpyridine–Pyrido[1,2-b]indazole

2-*o*-Nitrophenylpyridine (20) (1 g) and ferrous oxalate dihydrate (1.3 g) were mixed with granulated lead (10 g) and heated at 300° (internal temperature) (metal bath) for 45 minutes. (At the beginning of the reaction the smell of ammonia being evolved could be detected and a piece of red litmus paper held at the mouth of the flask turned blue.) The cooled mixture was extracted repeatedly with ether, and the combined extracts were dried ($MgSO_4$) and evaporated to give an oil which solidified and was recrystallized from light petroleum (b.p. 60–80°) (charcoal) giving *pyrido[1,2-b]indazole* as rods (0.5 g), m.p. 83–84°. Calc. for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.66; mol. wt. 168. Found: C,

78.47; H, 4.80; N, 16.90; mol. wt. 152. No active hydrogen was present in the product. An active hydrogen determination on γ-carboline gave 0.61% active H (calc. 0.6%). Infrared spectrum (Nujol mull) (main peaks only): 1650 (m), 1623 (m), 749 (s), 743 (s), and 719 cm^{-1} (s). Ultraviolet absorption spectrum (free base in 95% ethanol or base in alcohol at pH 11): λ_{max} 205, 229, 269, 327 mμ; $\epsilon \times 10^{-3}$ 21.0, 32.7, 23.7, 11.8.

When dry hydrogen chloride was passed through an ethereal solution of pyrido[1,2-*b*]-indazole, an impure hydrochloride, m.p. 161–164°, separated which crystallized from ethanol–ether in needles, m.p. 165–166°. Its ultraviolet absorption spectrum in 95% ethanol, however, was identical with that of the free base, indicating that in this solvent the hydrochloride dissociates to the free base. On the other hand, the base in aqueous hydrochloric acid at pH 1 had λ_{max} 208, 254, 330, 340 mμ; $\epsilon \times 10^{-3}$ 182.4, 140.7, 10.02, 11.37.

The approximate pK_a of pyrido[1,2-*b*]indazole, as determined by potentiometric titration (no solvent correction applied), was 2.48.

Pyrido[1,2-b]indazole picrate separated from alcohol and was recrystallized from acetone, giving yellow needles, m.p. 205°. Calc. for $C_{11}H_8N_2,C_6H_3O_7N_3$: C, 51.50; H, 2.77. Found: C, 51.75; H, 3.00.

The free base was recovered unchanged on:

(i) shaking with hydrogen and Adams' catalyst;
(ii) boiling with 10% hydrochloric acid for 4 hours;
(iii) boiling with 20% aqueous ethanolic potassium hydroxide for 6 hours;
(iv) treatment with an excess of methyl iodide in ethanol at room temperature.

9-Methylpyrido[1,2-b]indazolium Iodide

Pyrid[1,2-*b*]indazole (0.2 g) in ethanol (2 ml) was heated with an excess of methyl iodide (2 ml) in a sealed tube at 100° (water bath) for 18 hours. The product which crystallized out on cooling was taken up in ethanol and combined with the mother liquors and the solution was evaporated to a small volume after boiling with charcoal. Brownish plates (0.3 g) separated which were recrystallized from ethanol to give brownish shiny plates, m.p. 208–209°. These were dissolved in water and filtered from a trace of amorphous brown solid, and the filtrate evaporated to dryness to give the *methiodide*, which on recrystallization from ethanol was obtained as cream-colored prisms, m.p. 226–227°. Calc. for $C_{12}H_{11}N_2I$: C, 46.45; H, 3.55; N, 9.03; I, 40.97. Found: C, 46.88; H, 3.66; N, 8.75; I, 40.63. No C—CH_3 was found in a Kühn-Roth determination. λ_{max} 223, 256, 334, 349 mμ; $\epsilon \times 10^{-3}$ 196.0, 20.0, 9.1, 11.8 (in ethanol).

2-Nitro-N-2′-pyridylaniline

2-Bromopyridine (5 g, redistilled), *o*-nitroaniline (6 g), anhydrous potassium carbonate (4.5 g), and a trace of copper-bronze were heated at 195–210° (metal bath) for 7 hours when no more carbon dioxide was evolved. Water was added and the excess *o*-nitroaniline removed by steam distillation. The residue was extracted with chloroform, the extract dried ($MgSO_4$) and evaporated, and the residue vacuum distilled to give *2-nitro-N-2′-pyridylaniline* as a red oil (2.4 g), b.p. 140–150° at 0.05 mm, which solidified. The product could be recrystallized from light petroleum (b.p. 40–60°) and formed red rods, m.p. 68–69°. Calc. for $C_{11}H_9O_2N_3$: C, 61.39; H, 4.22. Found: C, 61.52; H, 4.00.

The *hemipicrate* separated from ethanol and was recrystallized from the same solvent to give yellow plates, m.p. 172°. Calc. for $C_{11}H_9O_2N_3,\frac{1}{2}C_6H_3O_7N_3$: C, 51.0; H, 3.2. Found: C, 51.1; H, 3.1.

2-o-Nitrophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine (0.9 g) was dissolved in glacial acetic acid (20 ml), and 35% hydrogen peroxide (0.44 g) was added. The solution was heated on a water bath at 90° for 9 hours. An additional amount of 35% hydrogen peroxide (0.44 g) was added and heating was continued at 90° for a further 9 hours. The acetic acid was removed by distillation under reduced pressure and the residue was dissolved in chloroform. Anhydrous sodium carbonate was added to neutralize the remaining acetic acid and the solution was filtered and evaporated to dryness. The residue was crystallized from benzene – light petroleum (b.p. 60–80°) and gave the *N-oxide* (0.92 g) as yellow needles, m.p. 156–157°. Calc. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73. Found: C, 61.24; H, 3.75.

1-Methyl-2-o-nitrophenylpyridinium Iodide

2-*o*-Nitrophenylpyridine (0.5 g) in 95% ethanol was treated with an excess of methyl iodide and the solution was allowed to stand at room temperature overnight. On concentration the solution yielded small orange crystals (0.55 g) which were recrystallized from methanol to give the *methiodide* as prisms, m.p. 223–224° (decomp.). Calc. for $C_{12}H_{11}O_2N_2I$: C, 42.08; H, 3.19. Found: C, 42.28; H, 3.30.

Action of Ferrous Oxalate on 2-o-Nitrophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine-*N*-oxide (1 g), ferrous oxalate dihydrate (1.2 g), and granulated lead (12 g) were intimately mixed and heated at 275–300° (internal temperature) in a metal bath. A small amount of strong-smelling gas which was basic to litmus was evolved during the heating period. The cooled mixture was extracted repeatedly with ether and then with hot benzene. The combined extracts were dried (Na_2SO_4) and evaporated to dryness to yield a brown oil (0.22 g) which was chromatographed on neutral alumina. Elution with benzene gave a light brown crystalline compound (0.19 g) which could be recrystallized from light petroleum (b.p. 60–80°) and had m.p. 84–86°. The infrared spectrum of this product was identical with that of an authentic sample of pyrido[1,2-*b*]indazole. The melting point of the base and its picrate were undepressed on admixture with authentic samples. Elution with benzene–ether yielded a tan solid (0.005 g), m.p. 202–205°, the infrared spectrum of which was almost identical with that of δ-carboline.

Action of Ferrous Oxalate on 1-Methyl-2-o-Nitrophenylpyridinium Iodide

1-Methyl-2-*o*-nitrophenylpyridinium iodide (0.6 g) was intimately mixed with ferrous oxalate dihydrate (0.7 g) and granulated lead (6 g). The mixture was heated at 275–300° (internal temperature) in a metal bath for 30 minutes. A small amount of a strong-smelling, basic (litmus) gas was evolved during the heating period. The reaction mixture was cooled and the black residue was repeatedly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give a brown oil (0.1 g) which partly solidified. This product was recrystallized from light petroleum (b.p. 60–80°) giving tan crystals (0.078 g) which proved to be identical with pyrido[1,2-*b*]indazole (mixed melting point, infrared spectrum).

Cyclization of 2-o-Azidophenylpyridine

2-*o*-Azidophenylpyridine (11) (1.2 g, not purified) was dissolved in redistilled decalin (50 ml) and the solution was heated in an oil bath at 160–170° (internal temperature). Gas bubbles began to be evolved smoothly at about 140°. After 10–15 minutes when no more gas evolution could be observed, the solution was cooled and was extracted with 10% hydrochloric acid. The acid extract was washed with ether, basified with 2 *N*

sodium hydroxide, and extracted repeatedly with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give an oil which solidified. Recrystallization from light petroleum (b.p. 60–80°) gave pyrido[1,2-*b*]indazole (0.54 g), m.p. 84.5–85.5°. The melting point was not depressed on admixture with an authentic sample. The picrate, m.p. 199–200°, did not depress the melting point of an authentic sample of pyrido[1,2-*b*]indazole picrate. The infrared spectrum of the base was identical with that of an authentic specimen.

No primary amine could be isolated when the crude reaction product was chromatographed on a column of neutral alumina.

2-o-Aminophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine-*N*-oxide (0.5 g) was dissolved in glacial acetic acid (25 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.1 g). Three molar equivalents of hydrogen were absorbed in less than 1 hour. The catalyst was removed by filtration and washed with a little acetic acid and methanol. The combined filtrates were evaporated under reduced pressure and the residue dissolved in chloroform and treated with anhydrous sodium carbonate. The filtered solution was evaporated to give an oil (0.42 g) which crystallized on trituration with methanol and was recrystallized from methanol to give the *amine* as white crystals, m.p. 181.5–182.5°. Calc. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.41. Found: C, 70.72; H, 5.38. λ_{max} 232, 325 mμ; λ_{infl} 270, 220 mμ; $\epsilon \times 10^{-3}$ 20.86, 2.54, 8.06, 17.60 (in 95% ethanol).

2-o-Azidophenylpyridine-N-oxide

2-*o*-Aminophenylpyridine-*N*-oxide (0.30 g) was dissolved in concentrated hydrochloric acid (0.6 ml) and water (1.5 ml) and the solution treated at 0° with a solution of sodium nitrite (0.12 g) in water (1 ml). An excess of a saturated aqueous solution of sodium azide was added, the temperature being maintained between 0 and 5°. The white *azide* which precipitated was filtered, washed with water, and dried. The aqueous filtrate was basified with 2 *N* sodium hydroxide, extracted with chloroform, and the extract dried (Na_2SO_4). Evaporation of the chloroform yielded an additional quantity of azide. The combined solid products (0.286 g) were recrystallized from benzene – light petroleum (b.p. 60–80°) and had m.p. 165–166°. Calc. for $C_{11}H_8ON_4$: C, 62.25; H, 3.80. Found: C, 62.60; H, 3.88.

Cyclization of 2-o-Azidophenylpyridine-N-oxide

2-*o*-Azidophenylpyridine-*N*-oxide (0.5 g) was dissolved in hot redistilled decalin (60 ml) and the solution heated in an oil bath at 175–180° (internal temperature) for 40 minutes during which time nitrogen was evolved and the solution became very dark. It was then boiled under reflux for an additional 10 minutes, cooled, and the solid which separated was filtered. The decalin solution was extracted with 10% hydrochloric acid, and the aqueous solution was basified with 2 *N* sodium hydroxide and extracted with chloroform. The dried (Na_2SO_4) chloroform extract was evaporated under reduced pressure. The residue was combined with the solid which was filtered off after the reaction (total 0.3 g), dissolved in methanol, filtered to remove some black solid (0.150 g), and the filtrate chromatographed on neutral alumina. Elution with benzene gave a solid (0.010 g) which was identified as δ-carboline by its infrared spectrum and mixed melting point with an authentic specimen. Elution with ether–methanol yielded at first a solid (0.046 g) which could be crystallized from benzene containing a small amount of methanol and had m.p. 277–278° (decomp.). Its infrared spectrum was identical

with that of an authentic sample of δ-carboline-*py*-*N*-oxide and the melting point was not depressed on admixture with a sample prepared from δ-carboline as described below. Subsequent fractions yielded only intractable dark brown residues.

δ-Carboline-py-N-oxide

δ-Carboline (0.050 g) was dissolved in glacial acetic acid (8 ml), and 35% hydrogen peroxide (0.1 g) was added. The solution was heated on a water bath at 90° for 10 hours. More 35% hydrogen peroxide (0.1 g) was added and heating was continued for an additional 9 hours. The acetic acid was evaporated under reduced pressure, and the residue was dissolved in chloroform and treated with anhydrous sodium carbonate. Evaporation of the chloroform gave the *N-oxide* (0.050 g) which was recrystallized from benzene containing some methanol (charcoal). This crude yellow product was dissolved in dilute hydrochloric acid, filtered, basified with 2 *N* sodium hydroxide, and extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform solution gave a white residue which was recrystallized from benzene containing some methanol to give white crystals which melted at 277–278° (decomp.). Calc. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38. Found: C, 71.65; H, 4.60. Infrared spectrum (KBr disk) (main peaks only): 1630 (m), 1605 (m), 1574 (m), 1215 (s), 865 (m), 782 (m), 750 (s), 705 cm^{-1} (s).

Catalytic Reduction of 2-o-Nitrophenylpyridine-N-oxide in 95% Ethanol – 2,2′-Di-(N-oxido-2-pyridyl)azoxybenzene

2-*o*-Nitrophenylpyridine-*N*-oxide (0.82 g) was dissolved in 95% ethanol (35 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.17 g). The reduction was complete in about 90 minutes. The catalyst was filtered and washed with glacial acetic acid. The combined filtrates were evaporated to a small volume under reduced pressure, the residue was dissolved in chloroform and treated with anhydrous sodium carbonate to neutralize any remaining acetic acid. The solution was filtered and evaporated to dryness and the residue recrystallized from methanol to give the *azoxy* compound (0.58 g), m.p. 236–237°. Calc. for $C_{22}H_{16}O_3N_4$: C, 68.74; H, 4.38. Found: C, 68.46; H, 4.32. Infrared spectrum (KBr disk) (main peaks only): 1600 (m), 1255 (s), 850 (s), 780 (s), 770 (s), 750 cm^{-1} (sh). λ_{max} 233, 325 mμ; λ_{infl} 220, 270 mμ; $\epsilon \times 10^{-3}$ 53.50, 6.50, 43.20, 21.00 (in 95% ethanol).

Catalytic Reduction of 2,2′-Di-(N-oxido-2-pyridyl)azoxybenzene in Glacial Acetic Acid – 2,2′-Di(N-oxido-2-pyridyl)azobenzene and 2,2′-Di-(N-oxido-2-pyridyl)hydrazobenzene

2,2′-Di-(*N*-oxido-2-pyridyl)azoxybenzene (0.050 g) was dissolved in glacial acetic acid (10 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.010 g). The reduction product was isolated as in the previous experiment. The residue was washed with methanol and crystallization took place. The crude product was separated by fractional crystallization from benzene into *2,2′-di-(N-oxido-2-pyridyl)-azobenzene* obtained as orange crystals (0.020 g), m.p. 264° (decomp.) [Calc. for $C_{22}H_{16}O_2N_4$: C, 71.72; H, 4.38. Found: C, 71.62; H, 4.71. Infrared spectrum (KBr disk) (main peaks only): 1585 (w), 1255 (s), 845 (s), 780 (s), 750 cm^{-1} (m). λ_{max} 230, 323, 455 mμ; λ_{infl} 260 mμ; $\epsilon \times 10^{-3}$ 44.73, 19.20, 0.58, 28.70 (in 95% ethanol)], and 2,2′-di-(*N*-oxido-2-pyridyl)hydrazobenzene (0.018 g), obtained as a white solid which, because of its insolubility, was very difficult to purify, m.p. 225° (decomp.). Infrared spectrum (KBr disk) (main peaks only): 3350 (m), 1595 (s), 1247 (s), 842 (s), 780 (m), 750 cm^{-1} (s). λ_{max} 236, 338 mμ; λ_{infl} 265 mμ; $\epsilon \times 10^{-3}$ 46.70, 6.88, 21.15 (in 95% ethanol).

Reduction of 2,2'-Di-(N-oxido-2-pyridyl)azoxybenzene with Stannous Chloride – 2-o-Aminophenylpyridine-N-oxide

2,2'-Di-(*N*-oxido-2-pyridyl)azoxybenzene (0.113 g) dissolved in concentrated hydrochloric acid (3 ml) was treated with a solution of stannous chloride dihydrate (0.24 g) in concentrated hydrochloric acid (1 ml). The solution was heated on the steam bath for 90 minutes. The cooled reaction mixture was basified with 2 *N* sodium hydroxide and extracted with ether. The dried (Na_2SO_4) ether solution was evaporated to give the primary amine (0.090 g) which was recrystallized from methanol–ether and had m.p. 179–181°. The melting point was not depressed on admixture with an authentic sample of 2-*o*-aminophenylpyridine-*N*-oxide and the infrared spectra of the two samples were identical.

2-Phenylpyridine Methiodide

2-Phenylpyridine and an excess of methyl iodide were kept at room temperature for 2 days in the absence of light. The *methiodide* which separated was recrystallized from ethyl acetate – methanol to give colorless needles, m.p. 143–144°. Calc. for $C_{12}H_{12}NI$: C, 48.50; H, 4.06. Found: C, 48.61; H, 4.25.

Demethylation of 2-Phenylpyridine Methiodide

(a) With Ferrous Oxalate

The methiodide (0.14 g) was mixed with ferrous oxalate dihydrate (0.16 g) and granulated lead (2 g) and the mixture heated in a metal bath at 290–300° under an air condenser for 30 minutes. The cooled reaction mixture and condensate were extracted with ether, and the ether layer was washed with sodium thiosulphate solution to remove iodine and dried (Na_2SO_4). Evaporation of the ether gave 2-phenylpyridine (0.037 g, 50%), picrate, m.p. 172–173°, undepressed on admixture with an authentic specimen.

(b) Without Ferrous Oxalate

The procedure was exactly as under (*a*) except that no ferrous oxalate was added. 2-Phenylpyridine (74% yield) was isolated.

Action of Ferrous Oxalate on 2-Phenylpyridine-N-oxide

2-Phenylpyridine-*N*-oxide (0.30 g) (21) was mixed with ferrous oxalate dihydrate (0.40 g) and granulated lead (4 g) and treated as for the methiodide reaction. 2-Phenylpyridine (0.171 g, 63%), b.p. 132–134° at 10 mm, picrate, m.p. 172–173°, undepressed on admixture with an authentic specimen, was thus obtained.

When ferrous oxalate was omitted, the starting *N*-oxide was recovered.

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REFERENCES

1. R. A. Abramovitch, K. A. H. Adams, and A. D. Notation. Can. J. Chem. **38**, 2152 (1960).
2. H. C. Waterman and D. L. Vivian. J. Org. Chem. **14**, 289 (1949).
3. D. L. Vivian, G. Y. Greenberg, and J. L. Hartwell. J. Org. Chem. **16**, 1 (1951).
4. R. A. Abramovitch. Proc. Chem. Soc. 8 (1957).
5. G. V. Boyd. J. Chem. Soc. 55 (1959).
6. L. Paoloni and G. B. Marini-Bettòlo. Nature, **179**, 41 (1957).
7. L. Paoloni. Gazzetta, **90**, 1530 (1960).

8. I. D. SPENSER. J. Chem. Soc. 3659 (1956).
9. E. GELLÉRT, RAYMOND-HAMET, and E. SCHLITTLER. Helv. Chim. Acta, **34**, 642 (1951).
10. A. P. GRAY. J. Am. Chem. Soc. **77**, 5930 (1955).
11. P. A. S. SMITH and J. H. BOYER. J. Am. Chem. Soc. **73**, 2626 (1951).
12. G. SMOLINSKY. J. Am. Chem. Soc. **82**, 4717 (1960).
13. A. R. KATRITZKY and A. M. MONRO. J. Chem. Soc. 1263 (1958).
14. A. R. KATRITZKY and P. SIMMONS. J. Chem. Soc. 1511 (1960).
15. E. HAYASHI, H. YAMANAKA, C. IYIMA, and S. MATSUSHITA. Chem. & Pharm. Bull. (Tokyo), **8**, 649 (1960).
16. E. WENKERT and B. F. BARNETT. J. Am. Chem. Soc. **82**, 4671 (1960).
17. O. DIMROTH. Ber. **35**, 4041 (1902); **40**, 2402 (1907).
18. A. E. GILLAM and E. S. STERN. An introduction to electronic absorption spectroscopy in organic chemistry. 2nd ed. E. Arnold Ltd., London. 1957. pp. 140–143.
19. G. M. BADGER and R. G. BUTTERY. J. Chem. Soc. 2156 (1953). R. J. W. LE FÈVRE and J. NORTHCOTT. J. Chem. Soc. 4082 (1952).
20. J. W. HAWORTH, I. M. HEILBRON, and D. H. HEY. J. Chem. Soc. 372 (1940).
21. A. R. HANDS and A. R. KATRITZKY. J. Chem. Soc. 1754 (1958).