TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS PART VIII. δ-CARBOLINE^{1, 2}

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ABSTRACT

The first unambiguous synthesis of δ-carboline has been achieved starting with 3-amino-2phenylpyridine. This was converted to the azide which was thermally cyclized to δ -carboline. The carboline gave a py-N-methiodide which was converted to the anhydronium base. The pK_a of the anhydronium base was determined and its significance is discussed. The anhydronium base formed a methiodide which, on dry distillation, gave *ind-N*-methyl- δ -carboline. The spectral properties of the various derivatives of δ -carboline were examined and the bond structures of the anhydronium base and the methiodides are discussed.

Whereas the chemistry of α -, β -, and γ -carboline has been well studied and a number of unambiguous methods are available for the synthesis of these ring systems practically nothing is known concerning δ -carboline (I). There has appeared only one reference to the synthesis of the parent compound and that to the Graebe-Ullmann cyclization of 1- β -pyridylbenztriazole by Späth and Eiter (1), who obtained a mixture of β -carboline and what was tentatively identified as δ -carboline (since it was not identical with either α -, β -, or γ -carboline) in unspecified low yield. N-3-Pyridylaniline was also obtained in this reaction. Subsequently, Eiter (2) was unable to obtain any of the supposed δ -carboline by carrying out this reaction on a larger scale. A similar cyclication of 4-methyl-1- β pyridylbenztriazole gave 5-methyl- β -carboline as the main product together with a small amount of a compound for which the structure 5-methyl- δ -carboline was suggested (3). Gulland, Robinson, Scott, and Thornley (4) were unable to degrade 3,4-methylenedioxyquindoline to δ -carboline. However, oxidation of this compound with nitric acid gave 7-nitro-8-carboline-2-carboxylic acid in low yield.

Apart from the fact that it is the only member of the carboline family whose chemistry has not been studied to any degree δ -carboline is interesting from a number of other points of view. It is present in the ring system of the alkaloid cryptolepine (5), which is noteworthy from a biogenetic point of view (6). Also, the relative basicities of α -, β -, and γ -carboline anhydronium bases have been measured by Gray (7), who proposed an explanation for the observed order of base strengths ($\beta - \gamma - \gamma \alpha$ -) and suggested, on the basis of considerations outlined below, that the δ -carboline anhydronium base should have a dissociation constant almost as high as that of the β -isomer. It was of interest to try and test this prediction experimentally.

Smith and Bover (8) attempted to cyclize 2-o-azidophenylpyridine to δ -carboline but obtained instead 2-o-aminophenylpyridine.* When 2-o-nitrophenylpyridine was heated with ferrous oxalate, cyclization took place preferentially at the pyridine nitrogen atom to give pyrid[1,2-b] indazole (9). The Pschorr-type cyclization of 2-amino-N-methyl-N-3'-pyridylaniline gave a relatively good yield of *ind-N*-methyl- δ -carboline (II) (together with some *ind-N*-methyl- β -carboline) (10a) but attempted N-demethylation using a variety of procedures failed (10b).

 δ -Carboline has now been synthesized unambiguously from 3-amino-2-phenylpyridine

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*Our results in this reaction differ from those of Smith and Boyer and will be reported in a subsequent paper.

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(V). The amine was obtained from 2-phenyl-3-picoline (III), which was oxidized to the carboxylic acid (IV) (11); this was transformed into the amine (V) via the acid chloride and the Curtius reaction. It could also be obtained directly by the action of phenyl-lithium on 3-aminopyridine (12). It was diazotized and converted to 3-azido-2-phenyl-pyridine (VI), which on being heated in decalin, gave variable yields of δ -carboline (I).



The base formed a yellow methiodide (VII) readily but resisted all attempts at *ind-N*-methylation. Treatment of the methiodide with alkali gave the orange anhydronium base (VIII); this gave a yellow methiodide (IX) identical with that obtained from *ind-N*-methyl- δ -carboline (II), thus establishing conclusively the structure which had been assigned (10a) to (II), as well as the fact that methylation of the anhydronium base occurs at the *ind-N*-atom. Finally, dry distillation of the methiodide (IX) gave *ind-N*-methyl- δ -carboline (II) identical with the sample obtained from the Pschorr reaction (10a).



Ultraviolet Absorption Spectra and pK_a

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Gray (7) obtained the following values for the pK_a 's of the carboline anhydronium bases: α -, 7.75; β -, 11.11; and γ -, 10.54. The greater basicity of the β -derivative was ascribed to a lower stabilization energy of the β -carboline anhydronium base indicated from a consideration of the relative contributions made by quinonoid canonical forms. The low basic strength of the α - as compared with the γ -derivative was interpreted on

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the basis of two complementary factors: (a) a much increased stability of the α -anhydronium base as a result of the juxtaposition of the oppositely charged centers; 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. Support for point (a) comes from the fact that pyrid[1,2-b] indazole, in which the charged centers are even closer together, is very reluctant to form a methiodide at all (9). A consideration of the basicities of the pyridonimines led Gray to suggest that there is some slight evidence that the aromatic charge-separated forms more nearly represent the properties of all three anhydronium bases. Additional support for this suggestion comes from the high dipole moment of sempervirine (13). Paoloni and Marini-Bettòlo (14) have argued that it is unnecessary to write a formula bearing separated charges for the β -carboline anhydronium base as suggested by Schwarz (15), and have carried out calculations using the LCAO method on 1-methyl-7-azaindole and on 7-methyl-7H-pyrrolo[2,3-b]pyridine, the results of which they say support their contention. It was hoped that the determination of the pK_a and spectral properties of the δ -carboline anhydronium base would shed some light on this problem and also verify or disprove Gray's suggestion concerning its base strength.



FIG. 1. —···· δ-Carboline in 95% ethanol. – – ind-N-Methyl-δ-carboline in 95% ethanol.



The pK_a 's of the anhydronium bases prepared from the methosalts of α -, β -, and δ -carboline were determined both spectroscopically and by potentiometric titration of the methiodides in 60% ethanol with 0.1 N sodium hydroxide, the pH at half neutralization being taken as the pK_a value, no correction for the ionic strength being applied. The average values of several determinations are given in Table I.

TABLE I

Anhydronium base	py-N-Methyl-a-carboline	py-N-Methyl-β-carboline*	py-N-Methyl-δ-carboline
pK_{a}	7.55	10.88	10.77

*Methiodide kindly supplied by Dr. I. D. Spenser, McMaster University, Hamilton, Ontario.

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The values for the α - and β -bases are somewhat lower than those reported by Gray (7) but, as suggested by him, py-N-methyl- δ -carboline anhydro-base is almost as strong a base as its β -isomer. This result would seem to favor the quinonoid structure A as being an important contributor to the structure of the base, resulting in its having a lower stabilization energy as compared with its salt in which the benzenoid structure is preserved.* The infrared spectrum of p_{γ} -N-methyl- δ -carboline anhydronium base afforded some slight tentative negative evidence in support of this suggestion. In the infrared spectra of two compounds, pyrid[1,2-b] indazole (9) and anthranil (16) in which the grouping $C_6H_4N^{\ominus}$ is known to make a strong, if not predominant contribution, bands have been observed at 1650 and 1642 cm^{-1} , respectively, which have been tentatively assumed to be characteristic of such a grouping. No such band was observed for the δ -carboline anhydronium base. A medium band at 1619 cm⁻¹ might be ascribed to a highly conjugated C==N as would be present in A, or alternatively to an aromatic ring vibration as is present in A'. py-N-Methyl- α -carboline anhydronium base exhibits a band at 1630 $\rm cm^{-1}$ which is intermediate between the above values as might be expected from the suggested structure for this compound in which the benzenoid structure remains unchanged and in which the dipolar structure makes an important contribution. The evidence seems to indicate a mesomeric structure $A \leftrightarrow A'$ for the δ -anhydronium base with the quinonoid structure A making perhaps the weightier contribution to the ground state.

The analysis values of py-N-methyl- δ -carboline anhydronium base were unsatisfactory, but this seems to be characteristic of this type of compound (17). Its anhydro-base character was confirmed by its ultraviolet absorption spectrum (Fig. 2) compared with that of py-N-methyl- δ -carbolinium iodide; the bands for the anhydro-base exhibited the usual bathochromic shifts. The colors of the methiodides and anhydronium bases and of their solutions are of interest. Thus, both py-N-methyl- β - and - δ -carbolinium iodide are yellow in the solid state whereas the unmethylated bases are colorless and

*That disruption of the benzenoid structure is an important factor in the destabilization of the bases is shown by the recent work of Adler and Albert on the ionization constants of the diazaindenes (21) where this factor is not present and the order of base strengths is 1.5 > 1.6 > 1.4 > 1.7.



FIG. 2. py-N-Methyl- δ -carbolinium iodide. – – In acidified 95% ethanol. – – In alkaline 95% ethanol.

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FIG. 3. ---py-*N*-Methyl- α -carbolinium iodide (in 95% ethanol). ----py-*N*-Methyl- β -carbolinium iodide (in 95% ethanol). -----py-*N*-Methyl- δ -carbolinium iodide (in 95% ethanol).

the α -methiodide is cream-colored (see Fig. 3). The anhydronium bases are all orangecolored and give yellow solutions in hydroxylic solvents. The ultraviolet spectra of *py-N*-methyl- δ -carbolinium iodide and of its anhydronium base in 95% ethanol are identical, indicating the ease with which the anhydronium base reverts to the more stable salt structure (compare the case of the β -carboline anhydro-base (18, and references

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cited therein)). On the other hand, solutions of py-N-methyl- δ -carboline anhydronium base in non-polar solvents such as ether are darker in color than those in hydroxylic solvents and this is reflected in the ultraviolet absorption spectrum of an ethereal solution of this compound when the bands at 282, 289, 350, and 422 m μ (in alkaline 95% ethanol) are shifted to 289, doublet at 295 and 300, 362 and 464 m μ (in ether) respectively. This contrasts with the behavior of the β -carboline anaydro-base whose spectrum in alkaline ethanol is reported to be the same as that in ether solution despite the fact that the latter solution is darker than the former (18). For the δ -carboline anhydro-base the deepening of the yellow color on passing from aqueous ethanolic alkali to ether solution is undoubtedly due to the fact that the color is due to an $n \to \pi$ transition and that in aqueous ethanolic alkali the unshared electrons of the nitrogen atoms are stabilized in the ground state by hydrogen bonding. As regards the bands in the 282-350 m μ region the bathochromic shift is in the *opposite* direction to that expected for K-bands (19) which arise from $\pi \to \pi$ transitions. Such a blue shift on passing from a non-polar to a polar solvent might indicate an appreciable instantaneous change in polarity from the ground state to the excited state causing the solvating molecules of a polar solvent to be more disoriented than those of a non-polar one during such a transition. If this conclusion is valid it could be taken as providing some tenuous support for the suggestion that structure A is the more important of the two structures contributing to the resonance hybrid. Some comment may also be made concerning the vellow color of the δ -carboline methiodide as compared with the unmethylated base and the α -carboline methiodide. It seems likely that a structure such as (VII') is contributing to the structure of the ground



state of the δ -carboline methiodide, the introduction of a positive charge on the *py-N*atom producing a strong perturbation of the π -electron cloud. Similar comments will apply to the β -carboline methiodide. Due to the closeness of the two nitrogen atoms the perturbation in the α -carboline methiodide case is not as great (this is reflected in the lower p K_a of this compound).

In connection with the ultraviolet absorption spectra of the δ -carbolines it is of interest to note that Eiter and Nezval (3) claimed to have prepared 5-methyl- δ -carboline (no analysis given) and reported that this compound had two bands at 351 and 288 m μ in the ultraviolet. δ -Carboline itself has two bands at 303 and 258 m μ (Fig. 1); furthermore, the shape of the absorption curve given by Eiter and Nezval is quite different from that of δ -carboline reported here, but resembles that of 5-methyl- β -carboline (3). Horner compared the ultraviolet spectra of α - and β -carboline and found them to be similar (20). Both, however, are substantially different from the spectrum of δ -carboline. It seems unlikely therefore, that the compound isolated in very low yield by Eiter and Nezval was really 5-methyl- δ -carboline.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured with a Perkin-Elmer

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Model 21 spectrometer using sodium chloride optics. Ultraviolet absorption spectra were recorded on a Beckman DK2 spectrophotometer.

3-.4mino-2-phenylpyridine

2-Phenylpyridine-3-carboxylic acid (11) (0.5 g) was kept at room temperature with thionyl chloride (3.5 ml) for $\frac{1}{2}$ hour. The excess thionyl chloride was removed under vacuum, the residue dissolved in dry acetone, and the solvent evaporated leaving the acid chloride behind as a powder. This was dissolved in dry acetone (9 ml) and sodium azide (0.5 g) in water (1 ml) was stirred into the solution, the temperature being maintained below 20°. After 15 minutes, water (14 ml) was added and the mixture basified with 2 N sodium hydroxide. The mixture was heated on a steam bath for 3 hours, cooled, and extracted with ether. The combined extracts were dried (Na₂SO₄) and evaporated to give crude 3-amino-2-phenylpyridine (0.4 g; 92% yield) which was distilled under vacuum and had a boiling point of 119–121°/0.35 mm. The distillate solidified on cooling, and was recrystallized from benzene – light petroleum (b.p. 40–60°) to give colorless crystals, m.p. 62–64°, whose infrared spectrum was identical with that of a sample prepared from 3-aminopyridine and phenyllithium (12). The picrate, m.p. 204–206° (from ethanol), was identical (mixed melting point) with that of the specimen prepared by the 3-aminopyridine method (12).

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3-Amino-2-phenylpyridine (1.0 g) was dissolved in concentrated hydrochloric acid (2.6 ml) and water (1 ml). A solution of sodium nitrite (0.41 g) in water (1 ml) was added with stirring and cooling on ice to the above solution at such a rate that the temperature remained below 3°. The excess nitrous acid was destroyed by the addition of urea and then a solution of sodium azide (0.45 g) in water (1.5 ml) was added below 3°. At the completion of this addition the solution gave a negative alkaline β -naphthol coupling test. The reaction mixture was allowed to stand at 0° for 1 hour, the solution was then made alkaline with cold sodium hydroxide solution (temperature kept below 5° at all times) and the aqueous solution was then extracted with ether repeatedly. Acidification of the aqueous layer caused the precipitation of 3-hydroxy-2-phenyl-pyridine (0.3 g; 33% yield), m.p. 206–207°, undepressed on admixture with an authentic specimen (12). The dried (Na₂SO₄) ether extract was evaporated to give the crude azide (0.67 g) as a reddish oil which could not be purified but was used as such in the next stage. Infrared spectrum (liquid film): 2120 (s) (azide), 1580 (m), 1285 (s) (broad), 1185 (m), 802 (m), 735 (s), 695 cm⁻¹ (s).

The crude 3-azido-2-phenylpyridine (0.67 g) was dissolved in redistilled decalin (70 ml) and heated at $155-170^{\circ}$ for 3 hours. Nitrogen was evolved smoothly at this temperature. On cooling of the reaction mixture, some crystals of δ -carboline separated. The whole mixture was extracted with dilute hydrochloric acid, the acid extracts made alkaline, and the solution extracted with ether. The dried (Na₂SO₄) ether extract was evaporated to give δ -carboline (0.44 g), which was recrystallized from benzene to give colorless needles, m.p. 216°. Calc. for C₁₁H₈N₂: C, 78.55; H, 4.79. Found: C, 78.15; H, 4.72. The *monopicrate* was recrystallized from ethanol and had a melting point of 277–279°. Calc. for C₁₁H₈N₂, C₆H₃O₇N₃: C, 51.39; H, 2.79. Found: C, 51.69; H, 2.78. The yields of δ -carboline obtained in several runs varied appreciably, the one reported above being the highest obtained. In some runs, some 3-amino-2-phenylpyridine, formed undoubtedly by hydrogen abstractions from the solvent, was isolated.

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py-N-Methyl-δ-carbolinium Iodide (VII)

δ-Carboline (110 mg) in 95% ethanol (1 ml) was treated with an excess of methyl iodide (2 ml) and the solution kept overnight at room temperature. The precipitate (200 mg) was filtrated and recrystallized from methanol to give the *methiodide* as light yellow needles, m.p. 250–252°. Calc. for C₁₂H₁₁N₂I: C, 46.47; H, 3.57. Found: C, 46.27; H, 3.70. λ_{max} 262, 328 mµ; λ_{infl} 266, 348 mµ; log ϵ 4.53, 4.50, 4.35, 3.70 (in 95% ethanol).

py-N-Methyl- δ -carboline Anhydronium Base (VIII)

The above methiodide (50 mg) was dissolved in hot water (2 ml) and the solution treated with a warm 20% aqueous solution of sodium hydroxide (4 ml). The yellow precipitate (22.6 mg) which separated from the cooled suspension was filtered off and washed with a little cold water. The combined filtrates were extracted repeatedly with ether, the extracts dried (Na₂SO₄), and the ether evaporated to yield a further small quantity of base. The combined solids were recrystallized from anhydrous benzene to give the *anhydronium base* as orange-yellow plates which became almost black at ca. 200° and melted at 204–205°. The microanalytical values were unsatisfactory as is common for such substances (17). Calc. for C₁₂H₁₀N₂: C, 79.09; H, 5.53. Found (average of two determinations): C, 71.33; H, 6.00. Infrared spectrum (KBr disk) (main peaks only): 1619 (m), 1588 (m), 1335 (s), 797 (m), and 718 cm⁻¹ (ms). λ_{max} 282, 290, 350, 422 m μ ; log ϵ 4.56, 4.60, 4.38, 3.20 (in alkaline 95% ethanol).

$ind-N-Methyl-\delta$ -carboline py-N-Methiodide (IX)

A benzene solution of py-N-methyl- δ -carboline anhydronium base was treated with an excess of methyl iodide to give an immediate precipitate of the *methiodide* which was recrystallized from 95% ethanol and formed light yellow needles, m.p. 270.5–271.5°, identical with the authentic specimen obtained by treating *ind*-N-methyl- δ -carboline (10*a*) in 95% ethanol with methyl iodide and allowing the solution to stand at room temperature overnight. The melting points of the two specimens were undepressed on admixture and their infrared spectra were identical. Calc. for C₁₃H₁₃N₂I: C, 48.14; H, 4.01. Found: C, 48.08; H, 4.12.

ind-N-Methyl- δ -carboline (II)

The anhydro-base methiodide (IX) (13.7 mg) was heated at $300-310^{\circ}/0.15$ mm in a microsublimation apparatus. The methiodide decomposed smoothly and practically no residue was left. The condensate was washed off with ether and the ether evaporated to give the demethylated product (6.3 mg; 82% yield) as a colorless oil which crystallized on standing to a colorless solid, m.p. 77.5–78.5°, undepressed on admixture with an authentic specimen (10*a*). The two samples had identical infrared spectra.

$_{\rm p}K_{\rm a}$ Determinations

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The titrimetric determinations were carried out by dissolving the methiodides (ca. 26 mg) in carbon-dioxide-free 60% aqueous ethanol (6 ml) and titrating with 0.998 N sodium hydroxide. The pH measurements were carried out with a Leeds–Northrup pH meter equipped with micro pH electrodes; the solution being titrated was stirred by means of a magnetic stirrer. The *py-N*-methyl- δ -carboline anhydronium base was similarly titrated with 0.989 N sulphuric acid.

The spectrophotometric determinations were carried out by measuring the extinction coefficients of acid, alkaline, and buffered (pH 10.61) solutions of the methiodides at two or more wavelengths.

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