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TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS PART X. AN ALTERNATIVE SYNTHESIS, AND THE NITRATION, OF 5-CARBOLINE¹

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ABSTRACT

 δ -Carboline, together with β -carboline, has been synthesized in reasonably good yield by the Fischer cyclization of cyclohexanone 3-pyridylhydrazone followed by dehydrogenation of the separated tetrahydro derivatives. The isomer ratios of products formed in this and similar reactions are discussed. Nitration of δ -carboline gives a mixture of the 6- and 8-nitro derivatives, the latter being the predominant product. The magnitude of the dipole moment of δ -carboline is appreciably higher than that predicted from molecular orbital calculations (15).

The first unambiguous synthesis of δ -carboline^{*} (I) was described in Part VIII of this series (1), in which the cyclization of 3-azido-2-phenylpyridine was reported to give variable yields of (I). In order to study the substitution reactions of this ring system a synthesis giving more reproducible yields was required. An alternative method of obtaining the δ -carboline ring system was sought and found in the Fischer cyclization of cyclohexanone 3-pyridylhydrazone (II).

The Fischer cyclization of pyridylhydrazones has been found by a number of workers to take place with greater difficulty than the cyclization of the corresponding phenylhydrazones. Perkin and Robinson were unable to effect the cyclization of acetone 2-quinolylhydrazone (2), and Fargher and Furness (3) and Okuda and Robison (4) obtained similar negative results using a number of 2-pyridylhydrazones. Clemo and Holt prepared 1-methyl-5,6,7,8-tetrahydro- β -carboline in low yield from cyclohexanone 2-methyl-3-pyridylhydrazone and zinc chloride (5). A moderate yield of 5,6,7,8-tetrahydro- α -carboline was obtained by heating cyclohexanone 2-pyridylhydrazone with polyphosphoric acid (4). Ficken and Kendall have recently examined the cyclization of the pyridylhydrazones of isopropylmethyl ketone to give the corresponding azaindole derivatives (6). They found that heating with zinc chloride to a relatively high temperature (210-250°) was necessary to effect ring closure. It is interesting to note, as well, that isopropylmethyl ketone 3-pyridylhydrazone was reported by these authors to give exclusively 2,3,3-trimethyl-3H-4-azaindole; i.e. cyclization had occurred at the α -position of the pyridine ring only. Similarly, Takahashi, Saikachi, Goto, and Shimamura (7) obtained 5-chloro-2-methyl-4-azaindole from acetone 2-chloro-5-pyridylhydrazone.

3-Hydrazinopyridine reacted with cyclohexanone to give the required cyclohexanone 3-pyridylhydrazone (II), which was somewhat unstable in air but could be kept for long periods in a closed container in the refrigerator. Cyclization was effected by fusion of (II) with zinc chloride at 250° and gave a high yield (94%) of a mixture of 6,7,8,9tetrahydro- δ -carboline (III) (63%) and 5,6,7,8-tetrahydro- β -carboline (IV) (37%). The structures of (III) and (IV) were established by dehydrogenation to the corresponding fully aromatic structures. The dehydrogenations were carried out by heating the compound with 10% palladium-charcoal in boiling mesitylene; the catalyst became poisoned

¹Part IX: R. A. Abramovitch and K. A. H. Adams. Can. J. Chem. 39, 2516 (1961).

*The trivial names α -, β -, and δ -carboline have been used throughout this paper and in previous papers in this series. They are acceptable according to the Definitive I.U.P.A.C. 1957 Rules for Nomenclature, and refer to 9H-pyrido[2,3-b]indole, 9H-pyrido[3,4-b]indole, and 5H-pyrido[3,2-b]indole (Ring Index), respectively.

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after about half the reaction had occurred and a second batch had to be added. The mixture of tetrahydro derivatives could be separated by chromatography on a column of alumina, when the δ -carboline derivative was eluted first, followed by the β -compound. The order of elution is similar to that reported by Abramovitch (8) for the separation of mixtures of *ind-N*-methyl- δ -carboline and *ind-N*-methyl- β -carboline. The cyclization of cyclohexanone 3-pyridylhydrazone was found to give very reproducible yields, thus providing a good route to the δ -carboline ring system.



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The observation that ring closure at the 2-position of the pyridine ring predominates is in agreement with the results of Ficken and Kendall (6) but differs in that these authors did not observe any cyclization to the 4-position of the pyridine nucleus. In pyridine derivatives possessing an electron-releasing group in the 3-position electrophilic attack generally leads to substitution in the 2-, rather than the 4-, position (9). This has been discussed by Schofield (10), who suggested that protonation and some form of chelation may be responsible. In the present study, attack at C2 was favored over attack at C4 to the extent of about 2:1. In contrast, the Graebe–Ullmann cyclization of $1-\beta$ -pyridylbenztriazole apparently results in exclusive substitution at C_4 of the pyridine nucleus (11). Molecular orbital calculations on the pyridine ring itself indicate that the π -electron density in the ground state is greater at the 4- than at the 2-position whereas the atom localization energies (A_e) for a Wheland-type transition state indicate (for pyridine but not pyridinium salts) that electrophilic substitution should be easier at the 2- than at the 4-position (12). A 3-amino substituent may well activate the 2- and 4-positions to different extents. Also, in the case of the Fischer cyclization, particularly that catalyzed by zinc chloride, there is no doubt that the pyridine nitrogen is coordinated with the metal atom. It would seem safe to suggest, however, that "strong" electrophilic reagents which do not make a large electron demand upon the substrate could well substitute into the pyridine ring according to the order of the ground-state π -electron densities at the nuclear carbons, whereas "weak" electrophilic reagents would probably follow the pattern suggested by the atom localization energies, with various shades possible in between, depending upon whether the transition state resembled more the starting materials or a Wheland-type intermediate structure.

The nitration of α - and β -carboline has already been studied. Thus, in the case of α -carboline it has been reported that 6-nitro- α -carboline is obtained exclusively (13), whereas mononitration of β -carboline gives mainly 6-nitro- β -carboline together with a

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lesser amount of what was suggested to be the 8-nitro derivative (14). Paoloni (15) has carried out some simple Hückel molecular orbital calculations of the ground-state π -electron densities for the four carbolines. These indicate that, in all cases, C₈ has the highest π -electron density, with C₆ the next highest.* As it is believed that in nitrations the transition state is somewhat closer in electron distribution to the unperturbed ground state than to the Wheland-type intermediate (16) it might have been expected from Paoloni's calculations that substitution at the 8-position* would have been favored (17), which is not the case. The nitration of δ -carboline with concentrated nitric acid has now been studied, and was found to lead to a mixture of two isomeric mononitro derivatives. The major product (56% after recrystallization) separated from the reaction mixture in the form of its salt. The free base did not melt below 360°. The second nitro compound (17% yield) had m.p. 232–233°.



By analogy with the nitration of carbazole (18) and of α - and β -carboline, it was initially assumed that the high-melting major product was probably 8-nitro- δ -carboline[†] (V) while the low-melting isomer was 6-nitro- δ -carboline[†] (VI). Tentative confirmation of the assignment of structure (VI) to the low-melting isomer was obtained from a study of its infrared and ultraviolet absorption spectra. It was hoped, in particular, that the infrared spectrum would show evidence of the hydrogen bonding possible between the nitro group and the indolic N-H group. The N-H group of the low-melting isomer absorbed at 3420 cm⁻¹ (dilute CHCl₃ solution), which is a lower frequency than is the N-H stretching band of δ -carboline (3450 cm⁻¹, CHCl₃ solution). The N-H group of N-methyl-o-nitroaniline absorbs at 3415 cm⁻¹. Unfortunately, the extreme insolubility in solvents suitable for infrared studies of the high-melting isomer made it impossible to determine its N-H stretching frequency under the same conditions. Spectra of the nitro compounds measured by the KBr disk technique did not give sharp N-H bands. so that the frequencies could not be accurately determined. The asymmetric and symmetric NO₂ frequencies could, however, be compared in this way. The bands for the lowmelting isomer were at 1518 and 1320 $\rm cm^{-1}$ respectively, whereas the corresponding ones for the high-melting isomer appeared at 1528 and 1328 cm⁻¹. The lower frequencies for the low-melting nitro compound could be due to hydrogen bonding, a conclusion similar to that drawn by Hathway and Flett, who studied the infrared spectra of some o-nitronaphthylamines (20). It has been reported that o-nitroaniline absorbs at longer

*Numbering here applies to the α - and β -carbolines. See also the following footnote.

†Note that the numbering in the γ - and δ -carboline ring systems is different from that in the α - and β -isomers (19).



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wavelengths in the ultraviolet than do the para and meta isomers (21). Also, 1-nitrocarbazole absorbs in the visible region at 403 m μ (22). The ultraviolet absorption spectrum of the low-melting nitro- δ -carboline has a band at 385 m μ which tails into the visible region, whereas the high-melting compound does not absorb appreciably in the visible. Finally, the hydrogen-bonded structure is supported by the *relatively* low melting point of (VI).

The structure of the high-melting nitro- δ -carboline as (V) was confirmed by reducing it to the corresponding amine, which gave a positive test for a *p*-phenylenediamine with a primary amino group (23).

An attempt was made to study the pattern of nucleophilic substitution in δ -carboline. When (I) was treated with phenyllithium an insoluble *ind-N*-lithium salt was formed and no further reaction occurred. The reaction was repeated using the very small quantity of *ind-N*-methyl- δ -carboline on hand instead of (I); a low yield of a basic product exhibiting bands at 690 and 765 cm⁻¹ (monosubstituted phenyl) was obtained, but in insufficient quantities to permit characterization. Reduction of δ -carboline with sodium and butanol proved to be difficult and in most cases starting material was recovered. Under more vigorous conditions over half of the δ -carboline was unchanged but the crude mixture (from which no other product could be isolated in a pure state) gave a positive Ehrlich test. Acetylation of the crude reaction mixture did not lead to the isolation of any pure reduction product. Catalytic reduction of δ -carboline was also attempted using 5% ruthenium on charcoal at 100° and 1350 p.s.i. of hydrogen; unchanged δ -carboline was recovered. It is not clear why δ -carboline should be more difficult to reduce than the other carbolines.

Paoloni (15) has estimated the dipole moments of the four carbolines from his molecular orbital calculations. His predicted value for δ -carboline is 3.90 D. The dipole moment of δ -carboline in benzene at 20° was kindly determined for us by Dr. G. F Wright and found to be 4.92 D, slightly more than 1 D greater than the calculated value. This result, together with the fact that there is a lack of correspondence between the calculated (15) and measured (1) ultraviolet absorption bands of δ -carboline, point to the limitations of the simple molecular orbital calculations in this case.

EXPERIMENTAL

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

Cyclohexanone 3-Pyridylhydrazone

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3-Hydrazinopyridine (3.91 g) was heated under reflux with a solution of cyclohexanone (2.8 ml) and pyridine (4 ml) in ethanol for 4 hours. The reaction mixture was poured into water and the crystalline precipitate filtered. Recrystallization of the crude product (4.82 g) from aqueous ethanol (charcoal) gave the *hydrazone* as pale yellow-brown crystals, m.p. 139–141° (decomp.). Calc. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99. Found: C, 69.73; H, 7.88.

Fischer Cyclization of Cyclohexanone 3-Pyridylhydrazone—6,7,8,9-Tetrahydro-5-carboline and 5,6,7,8-Tetrahydro-6-carboline

Cyclohexanone 3-pyridylhydrazone (2 g) was intimately mixed with zinc chloride dihydrate (7 g) and the mixture heated in a metal bath at $250-260^{\circ}$ (bath temperature) with occasional stirring. After the initial vigorous reaction was over (6 minutes) heating was continued for an additional 5 minutes. The cooled melt was dissolved in 10% hydrochloric acid, filtered to remove a small amount of brown solid, basified with 2 N sodium hydroxide, and extracted with ether. The dried (Na₂SO₄) ether solution was evaporated and left behind a brown oil which solidified (1.7 g).

The crude mixture (3.1 g) was chromatographed on a column of neutral alumina. Elution with benzene – light petroleum (b.p. $60-80^{\circ}$) (5:1) gave 6,7,8,9-tetrahydro-5-carboline (1.66 g) which, after recrystallization from benzene or from aqueous ethanol, melted at 199–200°. Calc. for C₁₁H₁₂N₂: C, 76.71; H, 7.02. Found:

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C, 76.71; H, 7.16. λ_{max} 230, 260, 290 mμ; ε×10⁻³ 28.30, 9.54, 9.32. Elution with ether-benzene (1:1) gave a brown solid (1 g) which, on recrystallization from aqueous alcohol, gave 5,6,7,8-tetrahydro- β -carboline as white leaflets, m.p. 197–198°. Found: C, 76.86; H, 7.17. λ_{max} 229, 267, 300 m μ ; $\epsilon \times 10^{-3}$ 29.00, 7.45, 5.85.

δ -Carboline

6,7,8,9-Tetrahydro-δ-carboline (1.43 g) was dissolved in hot mesitylene (15 ml), and 10% palladiumcharcoal (225 mg) added. The suspension was boiled under reflux for 8 hours, a second lot of catalyst (225 mg) was added, and heating was continued for an additional 10 hours. The reaction mixture was diluted with benzene, the catalyst filtered, and the cooled filtrate saturated with dry hydrogen chloride. The crystalline hydrochloride was filtered, washed with ether, dissolved in water, and the solution made alkaline to give δ -carboline (1.2 g), m.p. 207–208°, after recrystallization from benzene. The melting point was not depressed on admixture with an authentic sample (1) of δ -carboline. The infrared spectra of the two samples were identical. The melting point of the methiodide (249-250°) was not depressed on admixture with an authentic sample of py-N-methyl- δ -carbolinium iodide (1).

β -Carboline

Prepared similarly from 5,6,7,8-tetrahydro-\beta-carboline (300 mg), β-carboline (290 mg) was obtained as fine white needles, m.p. 197-198°. The melting point of the methiodide was not depressed on admixture with an authentic sample (1) of py-N-methyl- β -carbolinium iodide.

Nitration of δ -Carboline

 δ -Carboline (0.570 g) was stirred with concentrated nitric acid (6 ml) at room temperature for 2 hours, during which time the color of the solution changed to greenish-yellow and a precipitate separated. The precipitate was filtered, washed with water, and stirred with concentrated ammonium hydroxide. The solid was filtered, washed with water and with methanol, and recrystallized from pyridine to give 8-nitro-ôcarboline (410 mg), m.p. above 360°. An analysis sample was purified by sublimation at 250° at 0.07 mm and recrystallization from pyridine. Calc. for C11H7N3O2: C, 61.97; H, 3.31. Found: C, 61.94; H, 3.50.

The acidic filtrate from the nitration mixture was basified with ammonia and extracted with chloroform. The dried (Na_2SO_4) chloroform solution was evaporated to give a bright yellow solid (202 mg), which was purified by chromatography on a column of alumina. Elution with benzene - light petroleum (b.p. 60-80°) gave 6-nitro-ô-carboline (122 mg) which, after recrystallization from methanol, had m.p. 232-233°. Calc. for C11H7N3O2: C, 61.97; H, 3.31. Found: C, 61.66; H, 3.44. The compound was initially obtained in the form of yellow needles. On being kept under cold methanol 'these gradually changed to prisms having the same melting point.

$8-Amino-\delta$ -carboline

8-Nitro-ô-carboliue (410 mg) was suspended in concentrated hydrochloric acid (4 ml), and a solution of stannous chloride dihydrate (2.15 g) in concentrated hydrochloric acid (6 ml) was added. The mixture was heated on the steam bath with stirring for 1.5 hours, cooled, and basified. Extraction with ether gave the crude amine (347 mg), which was difficult to purify and which was discolored on standing. It gave a blue-black precipitate when oxidized with potassium persulphate in the presence of aniline, a test characteristic of a *p*-phenylenediamine derivative with a free primary amino group (23). Attempted acetylation of the amine using a procedure described in Vogel's "Practical organic chemistry" (24) led, instead, to the analytically pure amine monohydrochloride, m.p. above 300° (from methanol). Calc. for C11H9N3,HCl: C, 60.14; H, 4.56. Found: C, 60.22; H, 4.20.

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