Synthesis of 1-aryl(and 1-aralkyl)-β-carbolines

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Some aromatic 1-aryl(and 1-aralkyl)-β-carbolines were prepared from their tetrahydro analogues by dehydrogenation over palladium on charcoal either in a Parr bomb or in refluxing toluene. The bomb reaction appears to be a better procedure for the preparations of aromatic β-carbolines with bulky C-1 substituents such as the naphthyl group. 1-(1-Naphthyl)- and 1-(2-naphthyl)-tetrahydro-β-carbolines were obtained by the cyclization of the Schiff bases *N*-(1-naphthylmethylene)- and *N*-(2-naphthylmethylene)-tryptamines, respectively. Other tetrahydro-β-carbolines with smaller C-1 substituents were prepared by the condensation of tryptamine with the appropriate aldehydes.

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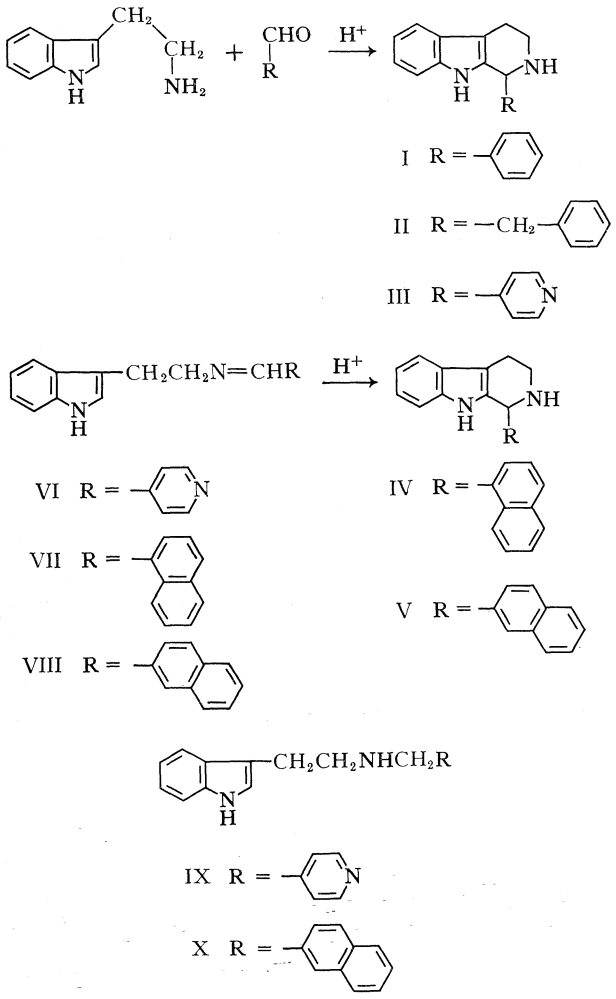
In a recent report (1) tetrahydro β-carbolines such as 1-benzyl- and 1-pyridyl-6-methoxy-1,2,3,4-tetrahydro-β-carbolines were found to possess sedative activity with little effect on blood pressure. To study the effects of C-1 aryl groups on the central nervous system activities of aromatic β-carbolines, 1-benzyl-, 1-phenyl-, 1-(4-pyridyl)-, 1-(1-naphthyl)-, and 1-(2-naphthyl)-β-carbolines as well as their tetrahydro analogues were synthesized in our laboratory.

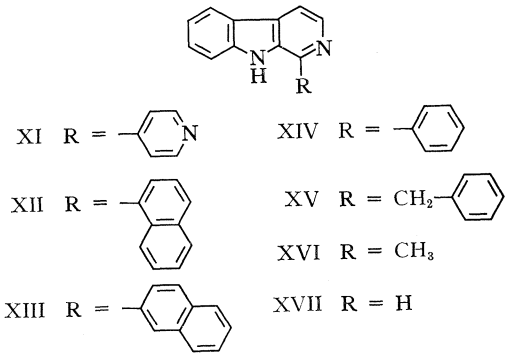
Condensation of tryptamine and the appropriate aldehydes in the presence of acid gave 1-phenyltetrahydro-β-carboline (I), 1-benzyltetrahydro-β-carboline (II), and 1-(4-pyridyl)tetrahydro-β-carboline (III), respectively. Compound III has also been prepared by the cyclization of the Schiff base *N*-(4-pyridylmethylene)tryptamine (VI) (2). Following this procedure, III was obtained in a 73% yield. This was compared with a 92% yield by the direct condensation of tryptamine and pyridine-4-aldehyde. Since the tetrahydro β-carbolines with bulky C-1 substituents such as naphthyl were obtained in very low yields from the reaction of tryptamine with aldehydes, 1-(1-naphthyl)tetrahydro-β-carboline (IV) and 1-(2-naphthyl)tetrahydro-β-carboline (V) were prepared by the cyclization of the corresponding Schiff bases *N*-(1-naphthylmethylene) tryptamine (VII) and *N*-(2-naphthylmethylene) tryptamine (VIII).

In addition to the cyclization of the Schiff bases to the tetrahydro β-carbolines, these bases were also catalytically reduced in a Parr hydrogenator. The reduction of VIII in the presence of palladium on charcoal gave a 70% yield of a solid product *N*-(2-naphthylmethyl)tryptamine (X). *N*-(4-Pyridylmethyl)tryptamine (IX) was obtained as an oil from the reduction of VI. The oil was converted to the hydrochloride salt which was too hygroscopic to be purified. The picrate derivative was then prepared for characterization. Hydrogenation of VII gave tryptamine as the only isolable product. Apparently, the C—N linkage of the reduced compound was cleaved to yield the primary amine. A reductive cleavage of the C—N bond has been reported previously in the literature (3).

The preparation of aromatic β-carbolines XI–XVII was carried out by heating a benzene solution of the corresponding tetrahydro β-carbolines in a Parr bomb at 150–160° in the presence of palladium on charcoal. The aromatization of 1-phenyltetrahydro-β-carboline (I), 1-benzyltetrahydro-β-carboline (II), 1-(4-pyridyl)tetrahydro-β-carboline (III), 1-methyltetrahydro-β-carboline, and tetrahydro-β-carboline was complete after 7 h of heating. This was indicated by the absence of the tetrahydro analogues on thin layer chromatograms. A longer heating time was required for the aromatization of IV and V. The reaction mixture still contained a small amount of unreacted starting material after



14 h of heating. The products, 1-(1-naphthyl)-β-carboline (XII) and 1-(2-naphthyl)-β-carboline (XIII), were purified by preparative thin-layer chromatography (t.l.c.). The elemental analyses of XIII checked with the calculated values whereas the percentage of hydrogen in XII was found to be too high; however, the infrared spectra of the two compounds were similar in the region between 2.9 to 7.0 μ.



Dehydrogenation of I and II was also achieved in refluxing toluene (for 4 h) with the presence of 10% palladium on charcoal; the reaction was followed by t.l.c. The aromatization of V with palladium on charcoal in refluxing toluene was investigated as well. It was found by t.l.c., however, that only a small amount of the desired product was produced. Compound II was also dehydrogenated when it was heated dry under aspirator pressure with 10% pal-

ladium on charcoal at 170–190° for 30 min. This modified procedure of Clemo and Swan (4) gave a 20% yield of XV.

In conclusion, aromatic 1-substituted β-carbolines can be prepared from the corresponding tetrahydro analogues either by heating the benzene solution in a Parr bomb in the presence of palladium on charcoal or by treating them with palladium on charcoal in refluxing toluene. The yields are generally good for the smaller substituents such as hydrogen or methyl, but considerably poorer for the larger substituents such as phenyl, pyridyl, and naphthyl. In the case of a large substituent like naphthyl, the bomb reaction seems to be the method of choice.

Studies with molecular models reveal a steric restriction in rotation of the 1-aryl group of the aromatic β-carbolines. As a result, coplanarity between the aryl group and the pyridine ring cannot be attained. When the ultraviolet spectra of these 1-aryl-β-carbolines are compared, the 1-(1-naphthyl)-β-carboline shows an absorption maximum at 354 mμ whereas a bathochromic shift by 6 mμ is observed in the 1-(2-naphthyl)-, 1-(4-pyridyl)-, and 1-phenyl-β-carbolines. This indicates a greater approach to coplanarity in the latter three compounds.

1-Substituted tetrahydro β-carbolines can be prepared either by the condensation of indolylalkylamine with the appropriate aldehydes in the presence of acid or by the cyclization of Schiff bases with mineral acid. The latter method appears to be better for compounds with large substituents, such as naphthyl, in the C-1 position.

EXPERIMENTAL

Melting points are corrected and were taken on a Fisher–Johns apparatus. Infrared spectra were obtained with a Perkin–Elmer spectrophotometer model 237 B. For qualitative ultraviolet spectra a Beckman spectrophotometer model DK 1 was used. Thin-layer chromatography was performed on silica gel GF_{254} which was purchased from the Brinkman Instruments, Inc.

Tetrahydro β-Carbolines

1-Phenyl-1,2,3,4-tetrahydro-β-carboline Hydrochloride (I)

Compound I was prepared (35% yield) according to the method of Skinner and Parkhurst (5); m.p. 270–271° (lit. m.p. 267–270°).

1-Benzyl-1,2,3,4-tetrahydro-β-carboline Hydrochloride (II)

To a hot solution of 5 g (25 mmole) of tryptamine hydrochloride in 120 ml of ethanol was added 10 ml of phenylacetaldehyde. The resulting yellow-orange solution was refluxed for 7 h. During this period a white solid separated. The product (5.7 g (90%)) was collected on a filter and washed with ethanol (4 × 10 ml) then ether (2 × 20 ml), m.p. 270–270.5°; λ_{max} (KBr) 2.95, 3.11 (NH), 3.43, 3.47, 3.63–3.66, 3.82, 3.89, 4.05, 4.10, 4.40 (CH and NH^+), 6.20, 6.25, 6.30, 6.34, 6.71 (C=C), 13.55 (indole CH), 14.35, and 15.0 μ (phenyl CH); λ_{max} (ethanol) 291, 283, 275 (shoulder), and 226 mμ. A melting point of 270° has been recorded for this compound which was prepared by the reduction of the corresponding dihydro compound (6).

1-(4-Pyridyl)-1,2,3,4-tetrahydro-β-carboline (III)

A solution of 2 g (10 mmole) of tryptamine hydrochloride and 1.2 g (11 mmole) of pyridine-4-aldehyde in 40 ml of water containing 10 ml (10 mmole) of 2 *N* sulfuric acid was refluxed for 30 min. The resulting solution was adjusted to pH 12 with 10% sodium hydroxide and the precipitate (2.3 g (92%)) was collected on a filter; m.p. 216–218°. After subsequent recrystallizations from chloroform – petroleum ether (b.p. 30–60°), benzene – petroleum ether (b.p. 30–60°), and then 95% ethanol, the product melted at 238–239°; λ_{max} (KBr) 3.22 (NH), 6.28, 6.55 (C=N and C=C), 13.5 μ (indole CH); λ_{max} (ethanol) 329, 290 (shoulder), 273 (shoulder), and 253 mμ.

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.1; H, 6.06; N, 16.9. Found for III: C, 76.9; H, 5.92; N, 16.7.

A melting point of 234–236° has been recorded for this compound which was prepared by the cyclization of Schiff base (2).

1-(2-Naphthyl)-1,2,3,4-tetrahydro-β-carboline Hydrochloride (V)

A mixture of 1.7 g (6 mmole) of *N*-(2-naphthylmethylene)tryptamine (VIII), 2 ml of concentrated hydrochloric acid, and 50 ml of absolute ethanol was heated on a steam bath for 1 h. During that period the orange color faded. The resulting mixture was allowed to stand overnight at room temperature and then it was spin-evaporated *in vacuo* to about 10 ml. The solid (1.6 g (82%)) was collected on a filter; m.p. 256–259°. One recrystallization from 95% ethanol gave an analytical sample, m.p. 261–263°; λ_{max} (KBr) 3.00, 3.12 (NH), 3.50, 3.65, 3.72, 3.84, 3.88, 3.93, 4.05, 4.08 (CH and NH^+), 6.21, 6.30, 6.40, 6.68, 6.72 (C=C), 13.59, and 13.65 μ (indole and naphthalene CH); λ_{max} (ethanol) 289 (shoulder), 274, 227, and 220 mμ.

Anal. Calcd. for $C_{21}H_{19}N_2Cl$: C, 75.3; H, 5.72; N, 8.37. Found: C, 75.2; H, 5.65; N, 8.50.

A small amount of the above hydrochloride salt was neutralized with 2 *N* sodium hydroxide and the free base, when recrystallized from aqueous ethanol, melted at 184–185°; λ_{max} (KBr) 6.21, 6.30, 6.70, 6.72

(C=C), and 13.5 μ (indole and naphthalene CH); λ_{max} (ethanol) 290 (shoulder), 274, 226, and 220 mμ.

1-(1-Naphthyl)-1,2,3,4-tetrahydro-β-carboline Hydrochloride (IV)

In a similar manner as in the preparation of V, cyclization of *N*-(1-napthylmethylene)tryptamine (VII) gave 1-(1-naphthyl)tetrahydro-β-carboline hydrochloride (79%), m.p. 240–241° (ethanol–ether); λ_{max} (ethanol) 291, 283, 275 (shoulder), and 224 mμ.

This hydrochloride salt was converted into the free base; m.p. 173–174° (aqueous ethanol).

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.5; H, 6.08; N, 9.39. Found: C, 84.4; H, 6.24; N, 9.59.

Schiff Bases

N-(2-Naphthylmethylene)tryptamine (VIII)

A solution of 1.6 g (10 mmole) of tryptamine in 25 ml of methanol was added to a solution of 1.56 g (10 mmole) of naphthalene-2-aldehyde in 25 ml of methanol. The mixture was heated on a steam bath for 10 min. The precipitate (2.8 g (94 %)) which separated was collected on a filter and washed with methanol; m.p. 166–168°. One recrystallization from 95% ethanol gave 1.9 g of needles, m.p. 167–168°; λ_{max} (KBr) 6.15 (C=N) and 13.6 μ (indole and naphthalene CH); λ_{max} (ethanol) 292, 283, 274 (shoulder), 250 (shoulder), 243, and 222 mμ.

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.5; H, 6.08; N, 9.39. Found for VIII: C, 84.5; H, 5.91; N, 9.50.

N-(1-Naphthylmethylene)tryptamine (VII)

In a similar manner as in the preparation of VIII, *N*-(1-naphthylmethylene)tryptamine, m.p. 134-135° (ethanol), was obtained (55%); λ_{max} (ethanol) 302 (shoulder), 292, 285 (shoulder), and 221 mμ.

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.5; H, 6.08; N, 9.39. Found for VII: C, 84.7; H, 6.16; N, 9.42.

N-(4-Pyridylmethylene)tryptamine (VI) was prepared (60%) according to the patent procedure (2), m.p. 180–181° (lit. m.p. 182–184°).

Aralkyltryptamines

N-(2-Naphthylmethyl)tryptamine (X)

A mixture of 500 mg of 5% palladium on charcoal and 500 mg (1.7 mmole) of *N*-(2-naphthylmethylene)-tryptamine (VIII) in 100 ml of absolute ethanol was shaken with hydrogen at the initial pressure of 3 atm until the consumption of hydrogen ceased (about 18 h). The filtered solution was spin-evaporated *in vacuo* and the oily residue crystallized overnight at 0° to give 350 mg (70%) of product; m.p. 93–94°. One recrystallization from heptane gave 175 mg, m.p. 94–95°; λ_{max} (KBr) 6.25, 6.28, 6.67 (C=C), and 13.4 μ (indole and naphthylene CH).

Anal. Calcd. for $C_{21}H_{20}N_2$: C, 84.0; H, 6.71; N, 9.33. Found for X: C, 83.7; H, 6.88, N, 9.57.

N-(4-Pyridylmethyl)tryptamine (IX)

Catalytic reduction of *N*-(4-pyridylmethylene)-tryptamine (VI), as described in the preparation of X, gave an oil. The product was characterized by its dipicrate salt, m.p. 166–167° (absolute ethanol).

Anal. Calcd. for $C_{28}H_{23}N_9O_{14}$: C, 47.4; H, 3.27; N, 17.8. Found: C, 47.3; H, 3.41; N, 17.9.

Aromatic β-Carbolines

1-(2-Naphthyl)-β-carboline (XIII)

A mixture of 1.9 g (6.4 mmole) of 1-(2-naphthyl)-1,2,3,4-tetrahydro-β-carboline (V), 500 mg of 5% palladium on charcoal, and 12 ml of benzene was heated in a Parr bomb at 150–160° for 14 h. The filtered solution was spin-evaporated *in vacuo*, and the oily residue was dissolved in hot hexane containing a small amount of benzene. After cooling, the solid (1.1 g (61%)) was collected on a filter; m.p. 61–64°. Purification of 200 mg of the product was achieved by preparative t.l.c. developed in benzene – ethyl acetate (4:1). A bright blue fluorescent band was eluted with methanol to give an oil, which was crystallized from heptane yielding 51 mg (16%); m.p. 192–194°. On a thin-layer chromatogram developed in benzene – ethyl acetate (4:1) the product travelled as a single spot with R_f = 0.48; λ_{max} (KBr) 2.93 (NH), 6.16, 6.26, 6.40, 6.70 (C=N and C=C), and 13.4 μ (indole and naphthalene CH); λ_{max} (ethanol) 360, 300 (shoulder), 292, 265, 229 (shoulder), and 221 mμ.

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.7; H, 4.79; N, 9.52. Found for XIII: C, 84.4; H, 4.93; N, 9.72.

1-(1-Naphthyl)-β-carboline (XII)

By a reaction similar to that described in the preparation of XIII, 1-(1-naphthyl)-β-carboline, m.p. 96–98° (heptane), was obtained (9%); λ_{max} (ethanol) 354, 345 (shoulder), 292, 285 (shoulder), 240 (shoulder), and 219 mμ.

Anal. Calcd. for $C_{21}H_{14}N_2$: C, 85.7; H, 4.79; N, 9.52. Found for XII: C, 85.3; H, 5.64; N, 9.48.

1-(4-Pyridyl)-β-carboline (XI)

A mixture of 1.25 g (5 mmole) of 1-(4-pyridyl)-1,2,3,4-tetrahydro-β-carboline (III) in 15 ml of benzene and 500 mg of 5% palladium on charcoal was heated in a Parr bomb at 150–160° for 7 h. After cooling yellow crystals separated. The mixture was filtered and the precipitate was washed with ethanol. The filtrate and the washings were combined and spin-evaporated *in vacuo* leaving an oil, which was dissolved in benzene and crystallized (169 mg (14%)) upon cooling; m.p. 272–273°. The white product travelled as a single spot on t.l.c. in the solvent benzene–methanol (2:1); λ_{max} (KBr) 2.95 (NH), 6.17, 6.26, 6.42, 6.48, 6.68 (C=C and C=N), and 13.35 μ (indole and naphthalene CH); λ_{max} (ethanol) 360, 290, 235 (shoulder), and 223 mμ.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.4; H, 4.52; N, 17.1. Found for XI: C, 78.6; H, 4.67; N, 16.9.

1-Methyl-β-carboline (XVI)

Dehydrogenation of 1 - methyltetrahydro - β - carboline, as in the preparation of XI, gave 1-methyl-β-carboline (36%); m.p. 233–234° (benzene), (lit. m.p. 239–241° (7). λ_{max} (ethanol) 347, 334, 287, 282 (shoulder), 255 (shoulder), 239 (shoulder), and 234 mμ.

β-Carboline (XVII)

In a similar manner as described in the preparation of XI, tetrahydro-β-carboline was dehydrogenated to give β-carboline (40%), m.p. 197–198° (benzene), (lit. m.p. 199–201° (8)); λ_{max} (ethanol) 349, 334, 289, 282, 249, and 233 mμ.

1-Phenyl-β-carboline (XIV)

Method A.—A mixture of 500 mg (2 mmole) of 1-phenyltetrahydro-β-carboline (I) in 50 ml of toluene and 250 mg of 10% palladium on charcoal catalyst was refluxed with stirring for 4 h. The filtered solution was spin-evaporated *in vacuo* leaving 350 mg of solid. One recrystallization from 95% ethanol gave 150 mg (31%) solid; m.p. 246–247°; λ_{max} (KBr) 6.19, 6.30, 6.44, 6.71 (C=N and C=C), and 13.59 μ (indole CH); λ_{max} (ethanol) 360, 347, 294, 277, and 238 mμ.

A melting point of 246° has been recorded for this compound which was prepared from the dichromate oxidative decarboxylation of 1-phenyl-1,2,3,4-tetrahydro-3-carboxylic acid (9).

Method B.—Dehydrogenation of I in a Parr bomb for 7 h, as in the preparation of XI, gave a 10% yield of 1-phenyl-β-carboline, m.p. 245–246° (benzene–heptane).

1-Benzyl-β-carboline (XV)

Method A.—From the dehydrogenation of 1-benzyltetrahydro-β-carboline (II), as described in the preparation of XIV, 1-benzyl-β-carboline, m.p. 178–179° (benzene–heptane) was obtained in a 27% yield. λ_{max} (ethanol) 350, 337, 289, 283 (shoulder), 252 (shoulder), 242 (shoulder), and 236 mμ.

A melting point of 175–176° (aqueous methanol) has been recorded for this compound which was prepared from the palladium on charcoal dehydrogenation of 1-benzyltetrahydro-β-carboline in the absence of a solvent (4).

Method B.—In a similar manner as described in the preparation of XI, 1-benzyl-β-carboline, m.p. 176–178° (benzene–heptane), was obtained in a yield of 49%.

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