CARBOLINES

# VI.* INVESTIGATION OF METHODS OF SYNTHESIZING 4-HETARYL-β-CARBOLINES

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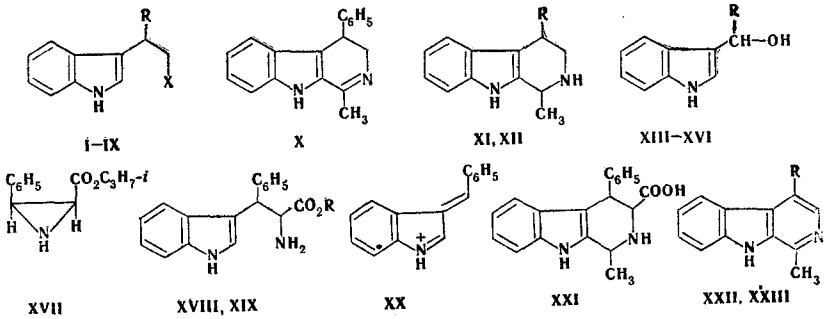
Two methods of synthesizing 4-aryl- and 4-hetaryl-β-carbolines are proposed. The reaction of indole with aryl- and hetarylnitroolefins leads to the formation of β-aryl- and β-hetaryl-nitroethylindoles, which are reduced to the corresponding tryptamines. The latter can be converted by the usual methods into 3,4-dihydro- and 1,2,3,4-tetrahydro-β-carbolines. The second route is illustrated by the reaction of indole with 3-phenylaziridine-2-carboxylic acid ester. The resulting β-phenyltryptophan, on subsequent treatment with acetaldehyde in potassium dichromate solution, is smoothly converted into 4-phenylharman.

The synthesis of 4-hetaryl-β-carbolines, analogs of the alkaloid brevicolline (XXII) [2], by the methods hitherto available presents considerable difficulties. The present paper gives the results of model experiments undertaken in order to find general methods for the synthesis of β-carbolines containing heterocyclic substituents in position 4.

It is known that indolylmagnesium halides and indole react with nitroolefins forming substituted nitroethylindoles which can be reduced to the corresponding tryptamines [3, 4]. We have established that the reaction of ω-nitrostyrene with indole can be performed conveniently under the action of formic acid. The adduct (I), after reduction, acetylation, and treatment with phosphorus pentachloride in nitrobenzene, formed 3,4-dihydro-β-carboline (X). The latter, on being heated with palladium black in glycol, was converted into the known β-carboline (XXIII) [5]. 2-Furyl- and 2-thienylnitroethylene reacted with indole similarly, giving the nitroethylindoles (IV) and (VII). The tryptamines (V) and (VIII) were obtained by their reduction, but the acetyl derivatives of these (VI and IX) could not be converted into 3,4-dihydro-β-carbolines, probably because of the instability of the heterocyclic rings under the reaction conditions. However, the tryptamines (V) and (VIII) took part smoothly in the Pictet–Spengler reaction with acetaldehyde, forming a mixture of the epimers (XI) and (XII).




R=$C_6H_5$; I X=$NO_2$; II X=$NH_2$; III X=NHCOCH$_3$
R=2-furyl; IV X=$NO_2$; V X=$NH_2$; VI X=NHCOCH$_3$
R=2-thionyl; VII X=$NO_2$; VIII X=$NH_2$; IX X=NHCOCH$_3$

XI R=2-furyl; XII R=2-thienyl XIII R=H XIV R=$C_6H_5$ XV R=pyridin-2-yl XVI R=pyridin-4-yl XVIII R=$i$-$C_3H_7$ XIX R=H XXII R=1-methylpyridin-2-yl XXIII R=$C_6H_5$

* For Communication V, see [1].

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Another possible method of solving the problem could be the replacement of the hydroxyl in carbinols of type (XIV) by a CN group, as has been described previously [6]. It is known that in an acid medium the reaction of indole with aldehydes is completed by the formation of diindolylmethane derivatives [7]. In an alkaline medium, the reaction of formaldehyde with indole gives 1- or 3-hydroxymethylindole, depending on the reaction conditions [8, 9]. We have studied the action of aldehydes on indole in the presence of benzyltriethylammonium methoxide or hydroxide. It was established by the TLC method [alumina, benzene–ether (1 : 1)] that formaldehyde reacts reversibly with the formation of 1-hydroxymethylindole. In parallel, a slower irreversible reaction takes place at position 3. When the process is continued for a long time, the equilibrium is shifted completely in the direction of the formation of (XIII). Benzaldehyde reacts directly at position 3, giving the unstable alcohol (XIV). The structure of the latter was shown spectroscopically by the presence of absorption bands of NH and OH groups in the IR spectrum, and also by independent synthesis from 3-benzoylindole. Pyridine-2-carbaldehyde and pyridine-4-carbaldehyde react similarly with the formation of the heterocyclic carbinols (XV) and XVI). Unfortunately, these alcohols could not be converted into nitriles by the action of alkali-metal cyanides, since they resinified under the reaction conditions.

Examples of the formation of tryptamine in the reaction of indole with aziridine have been described [10, 11]. However, these investigations have received no further development. We synthesized the cis-aziridinecarboxylic ester (XVII) by passing ammonia through a solution of isopropyl $\alpha,\beta$-dibromo-$\beta$-phenyl propionate in dimethyl sulfoxide. Under the action of boron trifluoride etherate, the ester (XVII) reacted with indole forming a substance containing, according to IR spectroscopy, an indole nucleus and ester and primary amino groups. The opening of the aziridine ring both at the C–N bond adjacent to the benzene ring and also at the bond adjacent to the carbonyl group might be expected. Only one product was isolated from the reaction mixture. The mass spectrum of this amino ester and of the acid corresponding to it contained the same maximum ion with m/e 206, which corresponds to structure (XX). It follows from this that the product of the reaction of indole with (XVII) is the isopropyl ester of $\beta$-phenyltryptophan (XVIII). For conversion into a $\beta$-carboline, the amino acid (XIX) was treated with acetaldehyde and converted into the tetrahydrocarbolinecarboxylic acid (XXI). When the latter was heated with potassium dichromate [12], 4-phenylharman (XXIII) was obtained in excellent yield. This latter method appears to us to be the shortest and most convenient for the synthesis of 4-aryl- and 4-hetaryl-$\beta$-carbolines. Further investigations are necessary to determine the range of its application.

## EXPERIMENTAL

All the melting points are uncorrected and were determined on a Kofler instrument. The spectroscopic information was obtained on UR-10, Specord UV VIS, and MKh-1303 instruments. The IR spectra were recorded in KBr tablets and the UV spectra in ethanolic solutions.

1-(Indol-3-yl)-2-nitro-1-phenylethane (I). To a melt of 34.4 g (0.24 mole) of nitrostyrene and 24.5 g (0.21 mole) of indole at 80-85°C, 9.8 g (0.21 mole) of 98% formic acid was added by drops. The mixture was kept at the same tempearture for 20 min and was then cooled, poured into water, and neutralized with sodium bicarbonate. After extraction with ether, elimination of the solvent, and crystallization from aqueous ethanol, 33.8 g (61%) of faintly yellowish crystals with mp 99-100°C, corresponding to literature data [4], was obtained.

1-(Indol-3-yl)-2-nitro-1-(2-thienyl)ethane (VII). This was obtained from 1-nitro-2-(2-thienyl)ethylene in a similar manner to (I). The addition of formic acid was performed at room temperature, and then the mixture was heated at 80°C for 40 min. Yield 68%, mp 92-93°C (from trichloroethane). IR spectrum, $cm^{-1}$: 3390 (NH), 1555, 1350 ($NO_2$), 755 (C–H of benzene and thiophene rings). Found: C 61.9; H 4.3; N 10.3; S 10.8%. $C_{14}H_{12}N_2O_2S$. Calculated: C 61.7; H 4.4; N 10.3; S 11.8%.

1-(2-Furyl)-1-(indol-3-yl)-2-nitroethane (IV). This was obtained from (2-furyl)nitroethylene in a similar manner to (I) in 4 h at room temperature. After purification by chromatography on alumina, the yield of unstable oil amounted to 77%. IR spectrum, $cm^{-1}$: 3410 (NH), 1540, 1380 ($NO_2$), 775 (vicinal hydrogen atoms).

2-(Indol-3-yl)-2-phenylethylamine (II). A solution of 11.3 g (0.05 mole) of (I) in 175 ml of ether was added to 8 g (0.21 mole) of lithium tetrahydroaluminate in 230 ml of anhydrous ether at such a rate that a gentle boil was maintained. Then the mixture was stirred without external heating. The ether boiled because of the heat of the reaction for about an hour. At the end of this period, sudden vigorous boiling was observed and at this moment it was desirable to cool the flask with cold water. If smaller amounts of

materials were taken, the spontaneous boiling of the ether did not take place and external heating was necessary. After the end of the reaction, the excess of reducing agent was decomposed with ethyl acetate, and the amine was isolated in the usual way. This gave 9.2 g (92%) of colorless crystals with mp 131-132°C (from ethyl acetate), which corresponds to literature data [4].

2-(Indol-3-yl)-2-(2-thienyl)ethylamine (VIII). Obtained similarly to (II) with a yield of 38%. mp 109-110°C (from benzene). IR spectrum, $cm^{-1}$: 3430 (NH), 3250, 1600 ($NH_2$), 780, 755 (vicinal hydrogen atoms). Found: C 69.3; H 5.8; N 11.4; S 13.7%. $C_{14}H_{14}N_2S$. Calculated: C 69.4; H 5.8; N 11.6; S 13.2%.

2-(2-Furyl)-2-(indol-3-yl)ethylamine (V). This was obtained from (IV) in a similar manner to (II) with a yield of 40%. mp 145-147°C (decomp., from ethyl acetate). IR spectrum, $cm^{-1}$: 3380 (NH), 3310, 1590 ($NH_2$), 775 (vicinal hydrogen atoms). Found: C 74.2; H 6.2; N 12.2%. $C_{14}H_{14}N_2O$. Calculated: C 74.3; H 6.2; N 12.4%.

2-Acetamido-1-(indol-3-yl)-1-phenylethane (III). A cooled solution of 2.0 g (85 mmoles) of (II) in 20 ml of pyridine was treated with 2.4 ml (250 mmoles) of acetic anhydride and the mixture was left overnight at room temperature. After the usual working up, 2.1 g (89%) of colorless crystals with mp 189°C (from ethyl acetate) was obtained. IR spectrum, $cm^{-1}$: 3420 (NH), 3260, 1650, 1540 (amide). Found: C 77.5; H 6.5; N 9.9%. $C_{18}H_{18}N_2O$. Calculated: C 77.4; H 6.5; N 10.1%. The acetyl derivatives of (VI) and (IX) were obtained in the form of noncrystallizing vitreous masses.

1-Methyl-4-phenyl-3,4-dihydro-$\beta$-carboline (X). In 1 min, 1.12 g (4 mmoles) of (III) was added to 2.5 g (12 mmoles) of phosphorus pentachloride in 22 ml of nitrobenzene at 70°C. After 30 sec, the reaction mixture was rapidly cooled, a few pieces of ice were added, and it was diluted with ether and extracted with dilute HCl solution. The acid extract was made alkaline and the base liberated was extracted with ether. An ethereal solution of HCl was added to the dried extract, and the crystals that deposited were separated off and crystallized from ethanol. This gave 0.66 g (56%) of the hydrochloride of (X) with mp 208°C. The picrate decomposed at 219°C without melting. Found: C 58.8; H 3.9; N 14.3%. $C_{18}H_{16}N_2 \cdot C_6H_3N_3O_7$. Calculated: C 58.9; H 3.9; N 14.3%.

1-Methyl-4-(2-thienyl)-1,2,3,4-tetrahydro-$\beta$-carboline (XII). A solution of 1 g (4.1 mmoles) of (VIII) in 50 ml of 50% formic acid was cooled with ice, and 2.2 ml (41 mmoles) of acetaldehyde was added. The reaction mixture was kept at room temperature for 2 h and was then poured into water, made alkaline with NaOH, and extracted with ether. The dried ethereal extract was evaporated in vacuum at room temperature, and the residue was crystallized from isopropanol to give 0.72 g (65%) of colorless crystals with mp 201-203°C. IR spectrum, $cm^{-1}$: 3440 (NH of an indole) and 3300 (NH). Found: C 71.7; H 6.2; N 10.7; S 12.5%. $C_{16}H_{16}N_2S$. Calculated: C 71.6; H 6.0; N 10.4; S 11.9%.

4-(2-Furyl)-1-methyl-1,2,3,4-tetrahydro-$\beta$-carboline (XI). This was obtained in a similar manner to (XII) from 1 g of (V) in 16 ml of 50% formic acid after 3 h 30 min at 10°C. Yield 63%. mp 145-147°C (from diisopropyl ether). It decomposes on storage. IR spectrum, $cm^{-1}$: 3430 (NH of an indole), 3300 (NH).

2-Acetyl-4-(2-furyl)-1-methyl-1,2,3,4-tetrahydro-$\beta$-carboline was obtained from (XI) and acetic anhydride in pyridine. mp 240-241°C (from isopropanol). Found: C 73.2; H 5.9; N 9.7%. $C_{18}H_{18}N_2O_2$. Calculated: C 73.4; H 6.2; N 9.5%.

Indol-1-ylmethyl Benzoate. To a solution of 0.73 g (6.25 mmoles) of indole in 7.5 ml of methanol were added 2.5 ml of a solution of benzyltriethylammonium hydroxide (from 2.2 mg-atoms of sodium and 2.18 mmoles of benzyltriethylammonium chloride in aqueous methanol) and 5.7 ml (68 mmoles) of formaldehyde in the form of a 32% solution. The mixture was left at 30°C for 30 min, poured into 75 ml of water, and extracted with ether. The ethereal extract was washed with water, dried with magnesium sulfate, evaporated to a volume of 5-10 ml, and stirred with 27 ml of a 2 N solution of KOH and 1.8 ml of benzoyl chloride for 5 h. Then ether was added, and the organic layer was separated off, dried, and evaporated to dryness, and crystallization of the residue from methanol gave indol-1-ylmethyl benzoate with a yield of 74%. mp 60-62°C. IR spectrum, $cm^{-1}$: 1720 (CO). Found: C 76.1; H 5.2; N 5.8%. $C_{16}H_{13}NO_2$. Calculated: C 76.5; H 5.2; N 5.6%.

Indol-3-ylmethanol (XIII). To a solution of 0.08 g (3.48 mg-atoms) of sodium in 18 ml of anhydrous methanol were added 0.79 g (3.48 mmoles) of benzyltriethylammonium chloride, 1.17 g (10 mmoles) of indole, and 0.6 g (20 mmoles) of paraformaldehyde. The resulting suspension was boiled for 5 h in a current of nitrogen, and after cooling it was poured into 180 ml of water and extracted with ether. The residue after evaporation of the dried extract was transferred to a filter and washed with benzene. This gave 1.09 g

(74%) of colorless crystals with mp 94-96°C (from benzene). They gave no depression of the melting point with a sample obtained by the method of Földeák et al. [8]. IR spectrum, $cm^{-1}$: 3200-3300 (NH, OH).

(Indol-3-yl)(phenyl)methanol (XIV). A. A mixture of 0.4 g (0.55 mmole) of 3-benzoylindole, 0.57 g (15 mmoles) of sodium tetrahydroborate, and 8 ml of 80% ethanol was stirred at room temperature for 11-12 h. Then the suspension was poured into water and extracted with ether. The dried extract was evaporated in vacuum at a temperature below 30°C. The residue was dissolved in trichloroethylene at 20-25°C, and the solution was evaporated at room temperature to small volume. The crystals that deposited were filtered off, giving 0.32 g (80%) of (XIV). The substance was stable on storage in the refrigerator. mp 101-102°C (from trichloroethylene). IR spectrum, $cm^{-1}$: 3590 (OH), 3410 (NH). Found: C 80.9; H 5.8; N 6.3%. Mol wt. 223. $C_{15}H_{13}NO$. Calculated: C 80.7; H 5.9; N 6.2%; Mol. wt. 223.

B. To a solution of benzyltriethylammonium methoxide (from 3.5 mg-atoms of sodium and 3.5 mmoles of benzyltriethylammonium chloride) in 18 ml of anhydrous methanol were added 1.17 g (10.0 mmoles) of indole and 1.58 g (14.8 mmoles) of benzaldehyde, and the mixture was left at 22°C for 24 h. The resulting solution was poured into water and extracted with ether. The extract was washed with water and, without drying, was evaporated at room temperature. The residue was treated as in method A, giving 1.05 g (47%) of (XIV).

(Indol-3-yl)(pyridin-2-yl)methanol (XV). This was obtained in a similar manner to (XIV) (method B) from indole and pyridine-2-carbaldehyde in 2 h at 22°C. After the end of the reaction, the mixture was poured into water, and the crystals that deposited were filtered off and recrystallized from ethylene chloride. Yield 67%. mp 148-150°C. An mp of 161-162°C is given in the literature [13], but on reproducing the conditions specified in this reference we obtained a compound with mp 148-150°C giving no depression of the melting point with the material obtained by our method. IR spectrum, $cm^{-1}$: 3300 (NH), 3190 (OH). Found: C 74.9; H 5.3; N 12.4%; Mol. wt. 224. $C_{14}H_{12}N_2O$. Calculated: C 75.0; H 5.4; N 12.5%; Mol. wt. 224.

(Indol-3-yl)(pyridin-4-yl)methanol (XVI). Obtained similarly to (XIV) from indole and pyridine-4-carbaldehyde. Yield 43%. mp 175-176°C (decomp.).

Isopropyl 2,3-Dibromo-3-phenylpropionate. This was obtained by the addition of bromine to isopropyl cinnamate in diethyl ether. mp 63°C (from ethanol). Found: C 41.0; H 4.0; Br 46.1%. $C_{12}H_{14}Br_2O_2$. Calculated: C 41.2; H 4.0; Br 45.7%.

Isopropyl cis-3-Phenylaziridine-2-carboxylate (XVII). A slow current of dry ammonia was passed for 60 h into a solution of 20 g of isopropyl 2,3-dibromo-3-phenylpropionate in 100 ml of unpurified dimethyl sulfoxide. At first the flask was cooled gently. The mixture was diluted with water and extracted with ether. The extract was washed with water and dried with sodium sulfate. The solid substance obtained after evaporation of the solvent was crystallized from cyclohexane with the addition of activated carbon, giving 3.15 g (27%) of colorless crystals with mp 78-79°C. IR spectrum, $cm^{-1}$: 3240 (NH), 1730, 1100 (COOR). PMR spectrum, $\delta$, ppm: 1.67 (NH, singlet), 2.93 (2-H, doublet), 3.45 (3-H, doublet), J = 6.3 Hz (cis configuration [14]). Found: C 70.4; H 7.2; N 6.7%. $C_{12}H_{15}NO_2$. Calculated: C 70.2; H 7.4; N 6.8%.

Isopropyl 2-Amino-3-(indol-3-yl)-3-phenylpropionate (XVIII). With cooling, a solution of 1.78 g of indole (0.015 mole) and 3.15 g (0.015 mole) of (XVII) in dry ether was added to 2.19 g (0.015 mole) of boron trifluoride etherate in a small amount of anhydrous ether. The solvent was rapidly eliminated in vacuum with heating to 50°C, and the residue was kept at the same temperature for 3 h 30 min. After cooling, the vitreous mass was dissolved in ether and the solution was shaken with sodium bicarbonate solution and then with 5% hydrochloric acid. Without separating the phases, the mixture was left overnight in the refrigerator, and the hydrochloride of (XVIII) that had deposited was filtered off and was crystallized from isopropanol, giving 2.75 g (51%) of colorless crystals with mp 223-225°C. IR spectrum, $cm^{-1}$: 3300 (NH of an indole), 3200 ($NH_2$), 1715 (CO). Found: C 67.4; H 6.6; N 7.7; Cl 10.2%; Mol. wt. 322. $C_{20}H_{22}N_2O_2 \cdot HCl$. Calculated: C 66.9; H 6.5; N 7.8; Cl 9.9%; Mol. wt. 322.

2-Amino-3-(indol-3-yl)-3-phenylpropionic Acid (XIX). A mixture of 1.78 g (XVIII) and 6.5 ml of a 2 N aqueous ethanolic solution of NaOH was heated in the water bath for 1 h 30 min and was then cooled, and 13 ml of 1 N $H_2SO_4$ was added. The crystals that deposited were filtered off and recrystallized from water, giving 1.34 g (87%) of (XIX) with mp 174-175°C. Found: C 73.1; H 6.0; N 10.3%. $C_{17}H_{16}N_2O_2$. Calculated: C 72.8; N 10.0%.

1-Methyl-4-phenyl-1,2,3,4-tetrahydro-$\beta$-carboline-3-carboxylic Acid (XXI). With ice cooling, 1 ml (18 mmoles) of acetaldehyde was added to a solution of 1 g (3.6 mmoles) of (XIX) in 10 ml of 50% formic

acid, and the mixture was left at room temperature for 75 min. Then the reaction mixture was diluted with an equal volume of water and was cooled in the refrigerator, and 740 mg (59%) of the formate of (XXI) was filtered off. mp 251-252°C (from isopropanol, in a sealed capillary). Found: C 68.3; H 6.7; N 8.2%. $C_{19}H_{18}N_2O_2 \cdot HCO_2H$. Calculated: C 68.2; H 5.7; N 8.0%.

1-Methyl-4-phenyl-β-carboline (XXIII). A. To a boiling suspension of 100 mg of the formate of (XXI) in 17.5 ml of water were added simultaneously 4.3 ml of a 10% aqueous solution of potassium dichromate and 0.7 ml of acetic acid. The mixture was boiled for another 20 min, after which it was cooled, treated with sodium sulfite, and neutralized with potassium carbonate. Extraction with ethyl acetate yielded 63 mg (80%) of (XXIII). Hydrochloride, mp 270-271°C.

B. The hydrochloride of (X) (1 g) was dehydrogenated over palladium black in glycol at 150°C as described by Kuchkova et al. [5], giving the hydrochloride of (XXI) with a yield of 80%. The samples obtained by methods A and B were identical in all respects with the substance synthesized previously [5].

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