The excess hydride was decomposed by the successive dropwise addition of 10 ml of methanol and 30 ml of 50% acetic acid, and the mixture was extracted with ether. The extract was washed with water and $NaHCO_3$ solution and dried with anhydrous $MgSO_4$. The ether was removed by distillation (toward the end, in vacuo at 40°C) to give 3 g (0.013 mole) of methyl 3-indolylacetate in the form of an uncrystallizable oil. The oil was dissolved in 10 ml of methanol, and sodium methoxide obtained from 0.7 g (0.03 g-atom) of sodium in 20 ml of methanol was added to the solution. A 1.15-g (0.015 mole) sample of thiourea was added, and the mixture was heated at a bath temperature of 100°C for 4 h. Two-thirds of the methanol was removed by distillation, and the concentrate was heated with stirring for another 2 h. Water (20 ml) was added, and the mixture was acidified with 20 ml of acetic acid and allowed to stand for crystallization. The precipitate was removed by filtration to give 1 g (25%) of product. Recrystallization from ethanol gave a product that decomposed at 310-312°C. IR spectrum: 1630, 1660 (NH, C=O); 3100, 3220, and 3425 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 207 (shoulder) (4.39), 219 (4.58), 285 (4.30), 315 nm (shoulder) (4.08). Found: C 60.7; H 4.8; N 16.3%; M (by mass spectrometry) 257. $C_{13}H_{11}N_3OS$. Calculated: C 60.7; H 4.3; N 16.3%; M 257.

The previously described [see Khim. Geterotsikl. Soedin., p. 942 (1975)] α-(3-indolyl)-β-phenylpropionitrile (IV) "in the form of a yellowish, uncrystallizable, very viscous mass" subsequently crystallized to give a product with mp 85-86°C.

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SYNTHESIS OF 4-ARYLTETRAHYDRO-β-CARBOLINES

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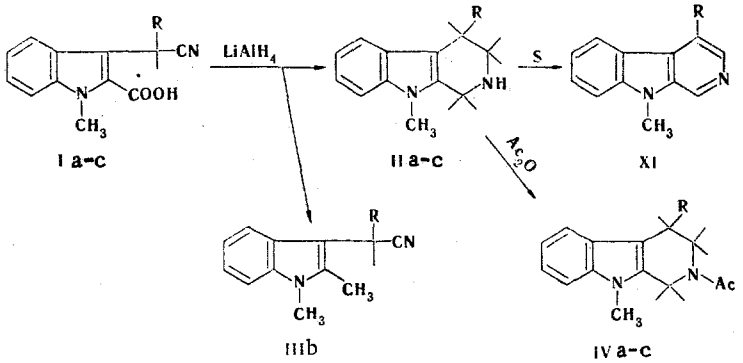
4-Aryltetrahydro-β-carbolines were synthesized from 3-substituted indole-2-carboxylic acids. The structures of the compounds obtained were proved by means of the UV, IR, and PMR spectra.

Little study has been devoted to 4-aryl- and 4-hetaryl-β-carbolines because of the difficulties involved in their preparation [1, 2]. The reduction of 1-methyl-2-carboxy-3-(α-cyanobenzyl)indoles makes it possible to obtain β-carbolines with aryl substituents in the 4 position. Treatment of acids I with lithium aluminum hydride (LAH) in ether [3] leads to the formation of a tetrahydropyridine ring without liberation of intermediates:



I–IV a R = C_6H_5; b R = *o*-C_6H_4Cl; c R = 3-pyridyl

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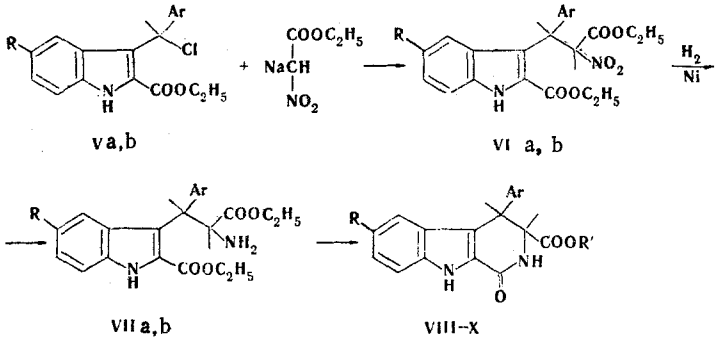
The low yields (30-32%) of tetrahydro-β-carbolines (II) are due to the multistep reduction of the cyano and carboxy groups with subsequent cyclization. 2-Carboxy-3-(α-cyanobenzyl)indoles are not capable of reducing the cyano group, evidently because of the formation of an anion due to the acidity of the NH group, although the conversion of 3-(α-cyanobenzyl)-indole to β-phenyltryptamine in high yield has been described [4]. The carboxy group of I is reduced considerably more rapidly than the cyano group. Thus, when the reaction is carried out in refluxing tetrahydrofuran (THF), 1-methyl-2-carboxy-3-(α-cyano-o-chlorobenzyl)-indole is converted to 1,2-dimethyl-3-(α-cyano-o-chlorobenzyl)indole (III), during which the cyano group is not involved. The analogous conversion of 3-formylindole to skatole has been described [5]. The PMR spectrum of tetrahydrocarboline IIb contains signals of aromatic protons at 7.6 ppm (8H) and a singlet of an N—CH_3 group (3.57 ppm, 3H). The two protons attached to C_3 and one proton attached to C_4 form an ABX system. As a consequence of merging of the inner lines, the quartet of the signals of the X proton is observed in the form of a triplet. The deshielding effect of the phenyl group shifts this signal to weak field as compared with the signals of the protons in the 1 and 3 positions [6]. The geminal AB protons give an octet of signals with $J_{AB} = J_{BA} = 15$ Hz and $J_{AX} = J_{BX} = 5$ Hz. It follows from the fact that $J_{AX} = J_{BX}$ that the geminal protons are symmetrically oriented with respect to the X proton, i.e., the X proton exists in the gauche conformation. The signals of the two geminal protons in the 1 position coincide because of the equality of the chemical shifts (s, 4.04 ppm, 2H). The signal of the proton of the NH group has the form of a broad singlet at 1.86 ppm (1H).

Heating IIb with sulfur in xylene at 130°C leads to aromatization of the tetrahydropyridine ring and the formation of carboline XI in 45% yield [7]. The UV spectrum, in which a bathochromic shift of λ_{max} from 282 nm for IIb and 289 nm (log ε 4.39) for XI was observed, underwent characteristic changes during this transformation. The spectrum of 4-(o-chlorophenyl)-9-methyl-β-carboline (XI) is similar to the spectrum of norharman [λ_{max} 289 nm (log ε 4.37)], and this indicates the similarity in their aromatic systems.

To obtain 4-aryltetrahydro-β-carbolines that do not contain a substituent in the 9 position we carried out the alkylation of the sodium salt of ethyl nitroacetate (ENA) with 3-(α-chlorobenzyl)indole derivatives V via the scheme



V-VII a R=H; b R=CH_3; VIII R=H, R'=C_2H_5; IX R=H, R'=H; X R=CH_3, R'=H; V-X Ar=o-C_6H_4Cl

The reaction was carried out in dimethyl sulfoxide (DMSO) with the reagents in an equimolar ratio at room temperature. The α-nitro-β-phenyl-β-(2-carbethoxy-3-indolyl)propionic acid esters were obtained in 78-86% yields. The formation of dialkylation products, which is characteristic in the alkylation of ENA with gramine [9], was not observed in our experiments, evidently because of the steric hindrance created by the indolylphenylmethyl substituent. The vicinal protons of the aliphatic chain have vicinal constants ($J_{\alpha\beta}$) of 13 Hz in the PMR spectrum of VIa; this indicates a trans axial orientation of the H_α and H_β protons, as in the case of the known β-(3-indolyl)-β-phenylpropionic acids [8]. According to the data from the PMR spectrum (90 MHz) and thin-layer chromatography (TLC), nitro ester VIa is one of the two possible diastereomers. It is possible that the presence of two bulky substituents (phenyl and 3-indolyl) attached to the asymmetric carbon atom of starting chloro compound V induces the preponderant formation of one of the stereomers in the reaction with the stereotopic methylene group of ENA.

The nitro group of VIa, b is reduced smoothly in alcohol on a nickel catalyst with absorption of the stoichiometric amount of hydrogen. The filtrate removed from the catalyst

TABLE 1. Properties of II-X

Compound	mp, °C	Found, %		Empirical formula	Calc., %		Yield, %
		Cl	N		Cl	N	
IIa	70—71	10,7	9,23	$C_{18}H_{16}N_2$	—	10,6	32
IIb	148—150	11,6	9,03	$C_{18}H_{17}ClN_2$	11,9	9,4	32
IIc	64—66	—	16,2	$C_{17}H_{17}N_3$	—	15,9	25
IVa	160—161	—	9,1	$C_{20}H_{20}N_2O$	—	9,2	80
IVb	176—178	10,5	8,26	$C_{20}H_{19}ClN_2O$	10,5	8,3	82
IVc	148—149	—	13,3	$C_{19}H_{19}N_3O$	—	13,7	55
VIa	152—153	7,6	6,3	$C_{22}H_{21}ClN_2O_6$	8,0	6,3	78
VIb	110—112	7,4	5,9	$C_{23}H_{23}ClN_2O_6$	7,8	6,1	86
VIIa	78—79	8,9	6,9	$C_{22}H_{23}ClN_2O_4$	8,6	6,8	56
VIIa*	160—163	15,3	6,0	$C_{22}H_{24}Cl_2N_2O_4$	15,7	6,2	88
VIIb	110—112	8,3	6,2	$C_{23}H_{25}ClN_2O_4$	8,3	6,5	52
VIIb*	153—154	14,7	5,7	$C_{23}H_{26}Cl_2N_2O_4$	15,2	6,0	80
VIII	260—263	9,5	7,4	$C_{20}H_{17}ClN_2O_3$	9,6	7,6	55
X	208—209	9,9	7,6	$C_{19}H_{15}ClN_2O_3$	10,0	7,9	52
IX	285—287	10,3	8,1	$C_{18}H_{13}ClN_2O_3$	10,4	8,2	60

*Hydrochloride.

contains ethyl β-(o-chlorophenyl)-β-(2-carbethoxy-3-indolyl)-α-aminopropionate (VIIa), which, after evaporation of the alcohol in vacuo and dissolving in ether, can be precipitated in the form of the hydrochloride and again recovered in the base from aqueous solution by precipitation with ammonia.

The data from the PMR spectrum of VIIa indicate that it is a mixture of diastereomers that have close signals of quartets at 4.4 ppm (2H, 2-carboethoxy group) and 4.13 ppm (2H, side-chain carbethoxy group). The overlapped triplets of these fragments are located at 0.88-1.55 ppm (6H, 12 lines). The signals of the protons attached to the β-carbon atoms of the side chain are doublets at 6.46 ppm (1H) and 6.77 ppm (1H) with $J_{\alpha\beta}$ = 10 Hz; the signals of H_α are found at 3.77 ppm in the form of two doublets with $J_{\alpha\beta}$ = 10 Hz.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian spectrometer (90 MHz). The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-22 spectrometer. The UV spectra of alcohol solutions of the compounds were recorded with an SF-16 spectrophotometer. The homogeneity of all of the synthesized compounds was monitored by TLC on Silufol in a hexane—ethyl acetate system (3:1).

4-Phenyl-9-methyltetrahydro-β-carboline (IIa). A 2.74-g (10 mmole) sample of 1-methyl-2-carboxy-3-(α-cyanobenzyl)indole was sprinkled into a suspension of 1.04 g (30 mmole) of $LiAlH_4$ in 200 ml of absolute ether, and the mixture was refluxed for 3 h. The excess $LiAlH_4$ was decomposed with water, and the ether layer was separated and dried with Na_2SO_4. The addition of ether saturated with HCl precipitated IIa in the form of the hydrochloride with mp 268-270°C. Found: Cl 12.4; N 9.7%. $C_{18}H_{18}N_2 \cdot HCl$. Calculated: Cl 12.7; N 10.1%. The hydrochloride of IIa was dissolved by heating in water acidified with HCl, from which IIa was isolated in the base form by the addition of ammonia to pH 9-10. Compounds IIb, c were similarly obtained. The hydrochloride of IIb had mp 258-260°C. Found: Cl 20.8; N 8.4%. $C_{18}H_{17}ClN_2 \cdot HCl$. Calculated: Cl 21.2; N 8.4%. IR spectrum: C=O absorption is absent; NH absorption at 3340 cm^{-1}. UV spectrum: λ_{max} 282 nm (log ε 3.83).

2-Acetyl-4-phenyl-9-methyltetrahydro-β-carboline (IVa). The hydrochloride of IIa [0.31 g (1 mmole)] was refluxed in 5 ml of acetic anhydride for 5 min, 3 ml of acetic acid and 10 ml of water were added, and the precipitate was removed by filtration and crystallized from alcohol. IR spectrum: C=O 1640 cm^{-1}; NH absorption is absent.

Compounds IVb, c were similarly obtained. PMR spectrum of IVb (ppm): CH_3, 3.6 s, 3H; C-CH_3, 1.4 s, 3H; CH_2, 0.5 s, 2H; signals of the $>C_{(4)}H—C_{(3)}H_2—$ ABX group [eight lines centered at 3.5 ppm (2H) and 4.5 ppm (1H)]; aromatic protons (7.6 ppm, 8H).

Ethyl α-Nitro-β-(o-chlorophenyl)-β-(2-carbethoxy-3-indolyl)propionate (VIa). A 3.48-g (10 mmole) sample of 2-carbethoxy-3-(α,o-dichlorobenzyl)indole was added to a solution of 1.7 g (11 mmole) of the sodium derivative of ethyl nitroacetate in 100 ml of dimethyl sulfoxide (DMSO), and the mixture was heated to 40-50°C and allowed to stand overnight at room

temperature. It was then diluted with water to 300 ml, and the oil that separated was washed with cold water. The oil began to crystallize when it was triturated to give 3.46 g (78%) of a solid with mp 141-143°C. Crystallization from ethanol gave a product with mp 152-153°C and R_f 0.25. PMR spectrum: 2-carbethoxy group (t, 1.45 ppm, 3H; q, 4.4 ppm, 2H), carbethoxy group of an aliphatic chain (t, 0.73 ppm, 3H; q 3.8 ppm, 2H), H_α (d, 6.75 ppm, 1H), H_β (6.40 ppm, 1H), $J_{\alpha\beta}$ = 13 Hz. IR spectrum: C=O 1750 (side chain $COOC_2H_5$) and C=O 1710 cm^{-1} (2-carbethoxy group).

Compound VIb was similarly obtained.

Ethyl α-Amino-β-(o-chlorophenyl)-β-(2-carbethoxy-3-indolyl)propionate (VIIa). The hydrogenation of 0.6 g (1.7 mmole) of VIa was carried out in 25 ml of ethanol over a Raney nickel catalyst at atmospheric pressure and room temperature. A total of 91 ml of hydrogen was consumed (the calcualted value is 92 ml). The filtrate obtained after separation of the catalyst was evaporated to dryness in vacuo, and the residue, which contained VIII, was dissolved in ether. The ether extract was treated with ether saturated with HCl, and the precipitated salt of VIIb was removed by filtration and dissolved by heating in water. The resulting solution was make alkaline to pH 9-10 with NH_4OH to precipitate 0.3 g (56%) of base VIIa with mp 78-79°C. This base was easily reconverted to the hydrochloride by the action of an ether solution of HCl.

Compounds VIIc, d were similarly obtained.

3-Carbethoxy-4-(o-chlorophenyl)tetrahydro-β-carbolinone (VIII). The alcoholic filtrate obtained after hydrogenation of VIa was refluxed for 1 h, after which the solvent was removed by distillation to give a crystalline residue that was only slightly soluble in ether and did not have basic properties. The 3-carbethoxy-4-(o-chlorophenyl)tetrahydro-β-carbolin-1-one structure was assigned to VIII. IR spectrum: 1660 (CONH) and 1750 cm^{-1} ($COOC_2H_5$). UV spectrum: λ_{max} 298 nm (log ε 4.21).

Compound VIII was refluxed in 5% alcoholic alkali for 15 min, after which the mixture was treated with water and acidified to pH 5 with CH_3COOH, and the crystals of 3-carboxy-4-(o-chlorophenyl)tetrahydro-β-carbolin-1-one (IX) were separated. IR spectrum: 1660 (CONH) and 1720 cm^{-1} (COOH). UV spectrum: λ_{max} 302 nm (log ε 4.18). Found: M_{eq} (by titration in 20% aqueous DMSO) 350. Calculated: M 341 and pK 3.75. Compound X was obtained by similar treatment of VIIb.

1,2-Dimethyl-3-(α-cyano-o-chlorobenzyl)indole (IIIb). A 0.9-g (3.3 mmole) sample of 1-methyl-2-carboxy-3-(α-cyano-o-chlorobenzyl)indole was added to a suspension of 1.04 g (30 mmole) of $LiAlH_4$ in 20 ml of tetrahydrofuran (THF), and the mixture was refluxed for 2 h. The excess $LiAlH_4$ was decomposed with water, the solid phase was removed by filtration, and the filtrate was evaporated until crystallization began. The precipitate was removed by filtration and washed with ether to give 0.56 g (60%) of a product with mp 136°C. IR spectrum: 2250 cm^{-1} (CN). UV spectrum: λ_{max} 285 nm (log ε 3.93). PMR spectrum: NCH_3 (s, 3.8 ppm, 3H), $C-CH_3$ (s, 2.2 ppm, 3H), and benzyl proton (s, 5.8 ppm, 1H). Found: C 72.9; H 5.0; N 9.3%. $C_{18}H_{15}ClN_2$. Calculated: C 73.1; H 5.1; N 9.5%.

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