5-Aminomethyl-2,3-dimethylindole (VIII). This compound, with mp 153-154° (from heptane), was similarly obtained in 78% yield from 5-phthalimidomethyl-2,3-dimethylindole. Found: C 75.8; H 8.2%. $C_{11}H_{12}N_2$. Calculated: C 75.8; H 8.1%. UV spectrum: λ_{max} 233 and 286 nm (log ε 4.90 and 3.85).

1-Acetyl-5-acetamidomethylindoline (VI). A mixture of 2 g (6 mmole) of 1-acetyl-5-phthalimidomethylindoline and 2 ml of hydrazine hydrate in 60 ml of ethanol was refluxed for 3 h. At the end of the reaction (as monitored by TLC on aluminum oxide), the mixture was cooled and worked up as indicated above to give 0.4 g (36%) of 1-acetyl-5-aminomethylindoline. Excess (2 ml) acetic anhydride was added to the 0.4 g (2 mmole) of 5-aminomethylindoline, and the mixture was allowed to stand at room temperature for 1 h. Ether was then added to the mixture, and the resulting precipitate was removed by filtration to give 0.5 g (quantitative yield) of 1-acetyl-5-acetamidomethylindoline with mp 180° (from benzene). Found: C 67.2; H 6.9%. $C_{13}H_{16}N_2O_2$. Calculated: C 67.2; H 6.9%. UV spectrum: λ_{max} 256 and 285 nm (log ε 4.29 and 3.75). IR spectrum: 1650 (C=O) and 3300 cm^{-1} (N–H).

1-Acetyl-6-acetamidomethylindoline (III). This compound, with mp 123-124° (from benzene), was similarly obtained in 65% yield from 2 g of 6-phthalimidomethylindoline. Found: C 67.2; H 6.9%. $C_{13}H_{16}N_2O_2$. Calculated: C 67.2; H 6.9%. UV spectrum: λ_{max} 254 and 283 nm (log ε 4.17 and 3.64). IR spectrum: 1640 (C=O) and 3300 cm^{-1} (N–H).

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SYNTHESIS OF 2-INDOLYLACETIC ACID DERIVATIVES

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UDC 547.755'759.07:542.953

2-Indolylacetic acid derivatives were synthesized by condensation of diethyl acetonedicarboxylate with α-substituted arylhydrazines under the conditions of the Fischer reaction, and their transformations were studied.

Continuing our research on 2-indolylacetic acids [1], we have accomplished the Fischer synthesis of derivatives of ethyl 1-alkyl-3-carbethoxy-2-indolylacetates (I-VI, see Table 1) from diethyl acetonedicarboxylate and α-alkyl arylhydrazines. 2-(1,3-Dimethyl-2-indolyl)ethanol (VII) was obtained by reduction of ethyl-1-methyl-3-carbethoxy-2-indolylacetate with lithium aluminum hydride. Alkaline hydrolysis of esters I-IV at room temperature gives 3-carbethoxy-2-indolylacetic acids VIII-XI (see Table 1), whereas heating gives indolylcarboxylic acids XII-XIV (see Table 1).

Anhydrides XV-XVII were obtained by the usual method from acids XII-XIV, and amides (XVIII-XX) of substituted 2-indolylacetic acid were obtained from the anhydrides by the action of primary amines.

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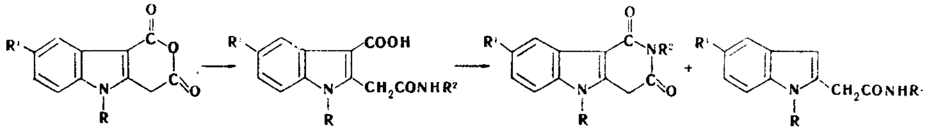


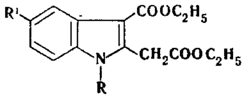
XV, XVI, XVII — XVIII, XIX, XX — XXI, XXIII + XXII, XXIV

XV R=$CH_2C_6H_5$, R^1=H; XVI R=CH_3, R^1=H; XVII R=$CH_2C_6H_5$, R^1=OCH_3; XVIII R=CH_3, R^1=H, R^2=$CH_2C_6H_5$; XIX R=$CH_2C_6H_5$, R^1=H, R^2=CH_3; XX R=$CH_2C_6H_5$, R^1=OCH_3, R^2=CH_3; XXI, XXII R=CH_3, R^1=H, R^2=$CH_2C_6H_5$; XXIII, XXIV R=$CH_2C_6H_5$, R^1=OCH_3, R^2=CH_3

Amides XVIII and XX are cyclized to γ-carboline derivatives XXI and XXIII on heating above their melting points. 2-Indolylacetamides XXII and XXIV are formed as side products in this reaction.

We also obtained 3-carbethoxy-2-indolylacetamides XXV-XXIX (see Table 2) by the action of primary amines with pK values ≥ 10 on esters I-IV. Primary amines with lower basicities and secondary amines do not undergo this reaction under the same conditions. Amides XXX-XXXIII were obtained by the action of amines on the corresponding acid chlorides (see Table 2). 2-Indolylacetyl chlorides formed by

TABLE 1. Ethyl 3-Carbethoxy-2-indolylacetates and Their Characteristics



Compound	R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
I	CH_3	H	90*	$C_{16}H_{19}NO_4$	66,5	6,8	4,9	66,4	6,6	4,8	54
II	$CH_2C_6H_5$	H	116	$C_{22}H_{23}NO_4$	72,0	6,4	4,1	72,3	6,4	3,8	40
III	$CH_2C_6H_5$	CH_3	122—123	$C_{23}H_{25}NO_4$	72,5	6,5	3,9	72,8	6,7	3,7	47
IV	$CH_2C_6H_5$	OCH_3	118—119	$C_{23}H_{25}NO_5$	70,1	5,8	3,8	69,8	6,4	3,5	42
V	4-Pyridylethyl	Cl	169—170	$C_{22}H_{24}Cl_2N_2O_4$	58,2	6,4	6,1	58,1	5,7	6,1	38
VI	4-Pyridylethyl	CH_3	172—173	$C_{23}H_{27}ClN_2O_4$	64,1	6,3	6,5	64,0	6,3	6,4	56
			3-Carbethoxy-2-indolylacetic acids								
VIII	CH_3	H	180—181	$C_{14}H_{15}NO_4$	64,9	6,1	5,3	65,1	5,9	5,4	82
IX	$CH_2C_6H_5$	H	183—184	$C_{20}H_{19}NO_4$	70,8	5,6	3,8	71,2	5,7	4,1	78
X	$CH_2C_6H_5$	CH_3	179—180	$C_{21}H_{21}NO_4$	68,9	5,9	3,4	68,6	5,8	3,8	86
XI	$CH_2C_6H_5$	OCH_3	187—188	$C_{21}H_{21}NO_4$	74,5	6,3	4,5	74,3	6,2	4,4	87
			3-Carboxy-2-indolylacetic acids								
XII	CH_3	H	262	$C_{12}H_{11}NO_4$	61,7	4,7	6,0	61,8	4,8	6,0	93
XIII	$CH_2C_6H_5$	OCH_3	230—231	$C_{19}H_{17}NO_5$	67,7	5,3	3,7	67,3	5,1	4,1	91
XIV	$CH_2C_6H_5$	H	241—243	$C_{18}H_{15}NO_4$	69,8	4,7	4,3	69,9	4,9	4,5	89

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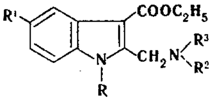
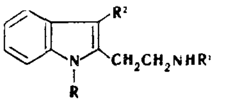
*According to the data in [5].

TABLE 2

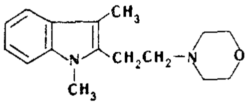


Compound	R	R^1	$N\langle^{R^3}_{R^2}$	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
XXV	CH_3	H	$NHCH_3$	185—186	$C_{15}H_{18}N_2O_3$	65,4	6,7	10,1	65,6	6,6	10,2	91
XXVI	CH_3	H	NHC_2H_5	182—183	$C_{16}H_{20}N_2O_3$	66,5	6,9	10,1	66,6	7,0	9,7	86
XXVII	$CH_2C_6H_5$	H	$NHCH_3$	167—168	$C_{21}H_{22}N_2O_3$	71,6	6,5	7,8	71,9	6,4	8,0	77
XXVIII	$CH_2C_6H_5$	OCH_3	$NHCH_3$	184—185	$C_{22}H_{24}N_2O_4$	69,8	6,5	7,3	69,5	6,4	7,4	81
XXIX	CH_3	H	$NHNH_2$	195—196	$C_{14}H_{17}N_3O_3$	61,1	6,3	15,0	61,0	6,2	15,3	69
XXX	CH_3	H	$NHCH_2C_6H_5$	153—154	$C_{21}H_{22}N_2O_3$	72,1	6,5	8,1	71,9	6,3	8,0	86
XXXI	$CH_2C_6H_5$	CH_3	$NHCH_2C_6H_5$	181—182	$C_{28}H_{28}N_2O_3$	76,4	6,6	6,3	76,3	6,4	6,4	92
XXXII	CH_3	H	NC_4H_8O	182—183	$C_{18}H_{22}N_2O_4$	65,5	6,8	8,3	65,5	6,7	8,5	89
XXXIII	$CH_2C_6H_5$	CH_3	NC_4H_8O	173—174	$C_{25}H_{28}N_2O_4$	71,4	6,7	6,3	71,4	6,7	6,7	84

the action of phosphorus pentachloride on the acids were used for the subsequent transformations without additional purification.



XXXIV, XXXV



XXXVI

XXXIV R=CH_3, R¹=R²=CH_3; XXXV R=CH_3, R¹=$CH_2C_6H_5$; R²=H

Reduction of amides XXV and XXII leads to secondary amines – 2-(2-aminoethyl)indole derivatives XXXIV-XXXV.

The tertiary amine 1,3-dimethyl-2[2-(N-morpholino)ethyl]indole (XXXVI) was obtained by alkylation of morpholine with 2-(1,3-dimethyl-2-indolyl)ethanol in the presence of Raney nickel [2].

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. Thin-layer chromatography (TLC) on a loose layer of aluminum oxide [benzene–absolute alcohol (9 : 1)] was used to evaluate the individuality of the compounds obtained.

Ethyl 1-Alkyl-3-carbethoxy-2-indolylacetates (I-VI). A mixture of 0.1 mole of α-phenylalkylhydrazine [3, 4] and 0.1 mole of diethyl acetonedicarboxylate in 100 ml of benzene was refluxed for 1 h, after which the solvent was removed by vacuum evaporation. The residue was dissolved in 50 ml of absolute alcohol, a 10% solution of hydrogen chloride in absolute alcohol was added to it, and the mixture was refluxed for 1 h. The precipitated ammonium chloride was removed by filtration, the filtrate was evaporated, and esters I-VI were recrystallized from alcohol. The physical constants and results of elementary analysis of the compounds are presented in Table 1. IR spectrum: 1700-1710 (3-$COOC_2H_5$) and 1730-1740 cm^{-1} (2-$CH_2COOC_2H_5$).

2-(1,3-Dimethyl-2-indolyl)ethanol (VII). A solution of 2.9 g (0.01 mole) of ester I in 100 ml of dry ether was added to a suspension of 1.71 g (0.04 mole) of lithium aluminum hydride in 100 ml of dry ether, and the mixture was refluxed for 8 h, after which it was decomposed with water. The ether layer was decanted, the residue was washed twice with ether, and the solvent was evaporated to give 1.2 g (63%) of VII with mp 87-88° [from hexane–ethanol (1 : 1)]. Found: C 76.5; H 7.7; N 7.0%. $C_{12}H_{15}NO$. Calculated: C 76.2; H 8.0; N 7.4%.

1-Alkyl-3-carbethoxy-2-indolylacetic Acids (VIII-XI). An aqueous alcohol solution of alkali (0.015 mole of KOH in 15 ml of 50% alcohol) was added to a solution of 0.01 mole of esters I-IV in 40 ml of dioxane, and the mixture was allowed to stand at room temperature for 24 h. The solvent was then evaporated, the residue was dissolved in water, and the aqueous solution was acidified with concentrated hydrochloric acid. The precipitated product was recrystallized from aqueous dioxane. The physical constants and results of analysis of acids VIII-XI are presented in Table 1.

1-Alkyl-3-carboxy-2-indolylacetic Acids (XII-XIV). A mixture of 0.1 mole of ethyl 1-alkyl-3-carbethoxy-2-indolylacetate (I, II, and IV) in 40 ml of dioxane and 0.3 mole of KOH in 30 ml of 50% alcohol was refluxed for 4 h, after which it was diluted with water and acidified with hydrochloric acid. The physical constants and results of analysis of acids XII-XIV are presented in Table 1.

1-Benzyl-3-carboxy-2-indolylacetic Anhydride (XV). Acetyl chloride (14 g) was added to a solution of 4.6 g (0.015 mole) of acid XIV in 50 ml of dry dioxane, and the mixture was refluxed for 1 h. The solvent was then evaporated, and the product was washed with dry acetone to give 4.1 g (95%) of anhydride XV with mp 210-211° (from dry acetone). Found: C 74.4; H 4.7; N 4.5%. $C_{18}H_{13}NO_3$. Calculated: C 74.2; H 4.5; N 4.8%.

1-Methyl-3-carboxy-2-indolylacetic Anhydride (XVI). Anhydride XVI, with mp 253-254° (from dry acetone), was similarly prepared in 91% yield. Found: C 66.8; H 4.5; N 6.2%. $C_{12}H_9NO_3$. Calculated: C 67.0; H 4.3; N 6.5%.

1-Benzyl-5-methoxy-3-carboxy-2-indolylacetic Anhydride (XVII). This compound, with mp 247° (from dry acetone), was similarly obtained in 76% yield. Found: C 71.1; H 4.9; N 4.3%. $C_{19}H_{15}NO_4$. Calculated: C 71.0; H 4.7; N 4.4%.

1-Methyl-3-carboxy-2-indolylacetic Acid N-Benzylamide (XVIII). A 2.4-g (0.022 mole) sample of benzylamine was added to a solution of 4.8 g (0.022 mole) of anhydride XVI in 300 ml of dry dioxane—acetone (1 : 1), after which the mixture was refluxed for 2 h. The solvent was then removed in vacuo, and the product was dissolved in aqueous sodium carbonate solution. The sodium carbonate solution was filtered, and the filtrate was acidified to give 6.25 g (87%) of amide XVIII with mp 219-220° (benzene). Found: C 70.7; H 5.8; N 8.7%. $C_{19}H_{18}N_2O_3$. Calculated: C 70.8; H 5.6; N 8.7%.

1-Benzyl-3-carboxy-2-indolylacetic Acid N-Methylamide (XIX). This compound, with mp 229-230° (benzene), was obtained in 92% yield by the method used to obtain XVIII. Found: C 71.1; H 5.8; N 8.8%. $C_{19}H_{18}N_2O_3$. Calculated: C 70.8; H 5.6; N 8.7%.

1-Benzyl-3-carboxy-5-methoxy-2-indolylacetic Acid N-Methylamide (XX). This compound, with mp 215-216°, was obtained in 85% yield by the method used to prepare amide XVIII. IR spectra of XVIII-XX: 1650-1655 cm^{-1} (CO—NH); the absorption band of 2-CO group was absent. Found: C 68.3; H 5.7; N 7.7%. $C_{20}H_{20}N_2O_4$. Calculated: C 68.2; H 5.7; N 8.0%.

2,4-Diketo-3-benzyl-9-methyl-1,2,3,4-tetrahydro-γ-carboline (XXI) and 1-Methyl-2-indolylacetic Acid N-Benzylamide (XXII). A 2-g sample of amide XVIII was heated on a silicone bath at 225-230° for 30 min, and the resulting mixture of XXI and XXII was dissolved in benzene and chromatographed with a column filled with Al_2O_3 by elution with benzene—absolute alcohol (9 : 1): $R_{f\,XXI}$ 0.22 and $R_{f\,XXII}$ 0.62. The yield of carboline XXI, with mp 195-196° [from alcohol—dioxane (1 : 1)], was 0.7 g (31%). Found: C 75.2; H 5.5; N 9.0%. $C_{19}H_{16}N_2O_2$. Calculated: C 74.9; H 5.3; N 9.2%. The yield of XXII with mp 129° (from benzene) was 0.9 g (43%). Found: C 77.5; H 6.6; N 9.6%. $C_{18}H_{18}N_2O$. Calculated: C 77.7; H 6.5; N 10.0%.

2,4-Diketo-3-methyl-6-methoxy-9-benzyl-1,2,3,4-tetrahydro-γ-carboline (XXIII) and 1-Benzyl-5-methoxy-2-indolylacetic Acid N-Methylamide (XXIV). Carboline XXIII, with mp 184-185°, was similarly obtained in 62% yield. Found: C 71.9; H 5.3; N 8.0%. $C_{20}H_{18}N_2O_3$. Calculated: C 71.8; H 5.4; N 8.4%. The yield of amide XXIV with mp 135-136°, was 31%. IR spectrum of XXI and XXIII: 1655 (amide CO) and 3240-3320 cm^{-1} (amide NH); XXII and XXIV: 1700 and 1650 cm^{-1} (CO). Found: C 74.4; H 6.4; N 9.3%. $C_{19}H_{20}N_2O_2$. Calculated: C 74.0; H 6.6; N 9.1%.

1-Alkyl-3-carbethoxy-2-indolylacetamides (XXV-XXXIII). A) A mixture of 0.01 mole of 1-alkyl-3-carbethoxy-2-indolylacetic acid, 20 ml of acetyl chloride, 0.011 mole of PCl_5, and 20 ml of dry ether was allowed to stand at room temperature for 1 h until the solid had dissolved completely, after which the solution was refluxed for 1 h and evaporated to dryness. The residue was dissolved in dry dioxane, 0.02 mole of amine was added to it, and the mixture was refluxed for 1 h. It was then diluted with water and filtered. The product was recrystallized from aqueous alcohol to give amides XXX-XXXIII, the characteristics of which are presented in Table 2.

B) A 0.015-mole sample of an alcohol solution of the amine was added to a solution of 0.01 mole of ethyl 1-alkyl-3-carbethoxy-2-indolylacetate in 20 ml of dioxane, and the mixture was allowed to stand at room temperature for 2 days. It was then diluted with water and filtered. The solid products were recrystallized from aqueous alcohol. Data on amides XXV-XXIX are presented in Table 2.

1,3-Dimethyl-2-(2-methylaminoethyl)indole (XXXIV). A solution of 2 g (0.0073 mole) of XXV in 50 ml of dry ether was added dropwise to a suspension of 0.84 g (0.022 mole) of lithium aluminum hydride in 50 ml of dry ether, after which the mixture was refluxed for 6 h and cooled. Water (2 ml) was gradually added, the ether layer was separated, and the solid material was washed twice with ether. The combined extracts were dried with potassium hydroxide, the solvent was evaporated, and the residue was dissolved in absolute alcohol. The alcohol solution was acidified with a solution of hydrogen chloride in absolute alcohol, and the precipitated hydrochloride was recrystallized from absolute alcohol to give 0.6 g (34%) of XXXIV with mp 254-255°. Found: C 65.1; H 7.7; N 11.4%. $C_{13}H_{19}ClN_2$. Calculated: C 65.3; H 8.0; N 11.7%.

1-Methyl-2-(2-benzylamino)indole (XXXV). This compound, with mp 246-247°, was obtained in 18% yield from XXII by the method used to prepare XXXIV. Found: C 71.7; H 7.1; N 9.0%. $C_{18}H_{21}ClN_2$. Calculated: C 71.9; H 7.0; N 9.3%.

1,3-Dimethyl-2-(2-N-morpholino)ethylindole (XXXVI). A mixture of 0.95 g of VII, 0.45 g of morpholine in 25 ml of xylene, and 10 g of an aqueous suspension of Raney nickel was refluxed for 6 h with azeotropic removal of the water by distillation. The catalyst was removed by filtration and washed with hot xylene, and the filtrate was vacuum-evaporated to give 0.72 g (49%) of XXXVI with mp 241-242° (hydrochloride). Found: C 65.6; H 8.3; N 10.0%. $C_{16}H_{23}ClN_2O$. Calculated: C 65.2; H 7.9; N 9.5%.

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BENZINDOLES

XII.* SPECTRA AND THREE-DIMENSIONAL STRUCTURES OF [6,7]- AND [4,5]BENZOSKATOLIDENEACETONES

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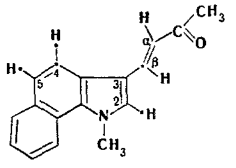
A. M. Vasil'ev, and N. N. Suvorov

UDC 547.759.3:543.422.25.4.6

It was found by means of their IR, UV, and PMR spectra that [6,7]benzoskatolideneacetones have a side chain in the trans-s-cis form, whereas the [4, 5] isomers have a side chain in the cis-s-cis form. It was concluded from the integral intensities of the bands of the vibrations of the double bond ($A_{C=C}$) and the parameters of the UV spectra that the investigated molecules have a planar structure. The $A_{C=C}$ integral intensities in the IR spectra exceed the previously observed values and, in the case of [6,7]benzoskatolideneacetones, reach ~$6 \cdot 10^4$ $\text{mole}^{-1}/\text{liter} \cdot \text{cm}^{-2}$.

In a previous paper [1] we described the synthesis of [6,7]- and [4,5]benzoskatolideneacetones, leaving open the question of their conformations.



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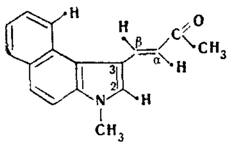

II

In the most preferable, from the point of view of electronic interactions, planar (or close-to-planar) structures I and II, first of all, transoid or cisoid orientation of the exocyclic $C_\alpha - C_\beta$ bond relative to the $C_2 - C_3$ bond and, second, an s-trans or s-cis orientation of the carbonyl group relative to the $C_\alpha - C_\beta$ bond are possible. Thus the side chains of the I and II molecules may, in principle, have four forms: trans-trans (1), trans-cis (2), cis-trans (3), and cis-cis (4). An examination of the molecular models shows that only the 3 and 4 conformations are real in the case of [4,5]benzoskatolideneacetones (II), and forms 1 and 2 are excluded because of strong nonvalence repulsions of the α-H and 8-H protons of the $C_\alpha - C_8$ bonds. The 3 and 4 forms are also sterically more favorable for [6,7]benzoskatolideneacetones, but one cannot exclude forms 1 and 2, in which there is only a relatively small nonvalence interaction of α-H and 4-H. Insofar as the mutual orientation of the exocyclic $C_\alpha - C_\beta$ bond and the carbonyl group is concerned, their orienta-

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*See [1] for communication XI.

D. I. Mendeleev Moscow Chemical and Technological Institute. Institute of Biophysics, Ministry of Public Health of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1347-1352, October, 1975. Original article submitted November 19, 1974.