INDOLE DERIVATIVES.

122.* NEW SYNTHESIS OF δ-CARBOLINES FROM 1-ACETYL-3-INDOLINONE

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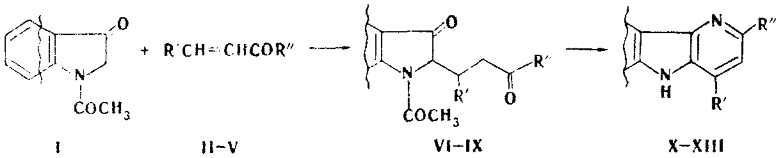
The Michael addition of 1-acetyl-3-indolinone to α,β-unsaturated aldehydes and ketones is described. The synthesis of a number of δ-carbolines that contain alkyl and aryl substituents in the 2 and 4 positions was realized on the basis of the resulting 1,5-dicarbonyl compounds.

We have previously described the synthesis of δ-carbolines from 3-aminoindole [2]. In the present paper we propose a new method for their preparation that differs favorably from the indicated method in that it makes it possible to obtain δ-carbolines that contain alkyl or aryl substituents in the 2 and 4 positions of the pyridine ring.

The synthesis takes place in two steps: 1) the synthesis of 1,5-dicarbonyl compounds by the addition of 1-acetyl-3-indolinone (I) to α,β-unsaturated carbonyl compounds; 2) cyclization of the 1,5-dicarbonyl derivatives with ammonium acetate.



II, VI, X R'=H, R''=CH$_3$; IV, VIII, XII R'=C$_6$H$_5$, R''=CH$_3$; III, VII, XI R'=CH$_3$, R''=H; V, IX, XIII R'=C$_6$H$_5$, R''=C$_6$H$_5$

Aldehydes and ketones (II-V) that differ with respect to the character of their substituents (alkyl or aryl) were used as the α,β-unsaturated compounds. The character of the substituents affects the conditions of the addition and the yields of the 1,5-dicarbonyl compounds. Thus the reaction of 1-acetyl-3-indolinone (I) with aliphatic derivatives II and III proceeds readily in alcohol in the presence of triethylamine (VI and VII were obtained in 70 and 30% yields). The reaction with ketone II proceeds at room temperature, while the reaction with aldehyde III occurs during brief heating. It is not permissible to increase the temperature in the case of ketone II, since diadduct XIV (24%) is formed in addition to monoadduct VI (57%).

The use of stronger bases (C_2H_5ONa and KOH) as the catalysts leads to products with a different structure [3]. α,β-Unsaturated ketones IV and V with aryl substituents attached to the β-carbon atom do not react with indolinone I in alcohol in the presence of triethylamine either at room temperature or upon prolonged heating. Diketones VIII and IX were obtained in 28-42% yields in the condensation of indolinone I with IV and V in acetic acid in the presence of potassium acetate.

1,5-Dicarbonyl compounds VI-IX readily undergo cyclization to δ-carbolines X-XIII when they are heated in acetic acid with excess ammonium acetate; the yields of the carbolines range from 30 to 50%.

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*See [1] for Communication 121.

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TABLE 1. 1,5-Dicarbonyl Compounds

Compound	mp, °C	Empirical formula	N, %		IR spectra, cm^{-1}	UV spectra (in alcohol)		PMR spectra, ppm			
			found	calc.	C=O	λ_{max}, nm	lg ε	$NCOCH_3$ (s)	aliphatic CH	aromatic CH	$COCH_3$ or $-CH=O$ (s)
VI	75—76*	$C_{14}H_{15}NO_3$	5,8	5,7	1680, 1715	205; 238; 259,7; 333	4,11; 4,47; 4,04; 3,47	2,41† (3H)	1,95—2,65 (4H); 4,62 (q, 1H)	7,11—7,81	1,89 (3H)
VII	94—96*	$C_{14}H_{15}NO_3$	5,6	5,7	1680; 1705; 1720 sh	204; 238; 260; 333	3,84; 4,27; 3,84; 3,26	2,44‡ (3H)	0,66 (d, 3H) 2,57—3,46 (3H); 4,49 (d, 1H)	7,08—8,39	9,78 (1H)
VIII	123—125**	$C_{20}H_{19}NO_3$	4,4	4,4	1655; 1710	210; 240; 333; 348	4,17; 4,52; 3,52; 3,50	2,75†† (3H)	3,00—4,53 (3H); 5,02 (d, 1H)	7,02—8,70	2,24 (3H)
IX	165—167**	$C_{25}H_{21}NO_3$	3,8	3,7	1670; 1685 sh 1715	207; 241 333; 348	4,44; 4,68; 3,59; 3,56	2,70†† (3H)	3,42—4,77, 4,85 (d, 1H)	6,88—8,23	—

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*From benzene-petroleum ether. †From d_5-pyridine. ‡From d_6-acetone–CCl_4. **From alcohol. ††From d_6-acetone

TABLE 2. δ-Carbolines

Compound	mp, °C*	Found, %			Empirical formula	Calc., %			IR spectra, cm^{-1} (NH)	UV spectra (in alcohol)		PMR spectra, ppm		
		C	H	N		C	H	N		λ_{max} (nm)	lg ε	CH_3 (s, 3H)	aromatic	NH (s, 1H)
X	275†	79,3	5,9	15,5	$C_{12}H_{10}N_2$	79,1	5,5	15,4	2600—3260	220; 259; 306	4,56; 4,31; 4,24	2,64‡	7,10—8,28	—
XI	264—265†	78,8	5,4	15,4	$C_{12}H_{10}N_2$	79,1	5,5	15,4	2600—3250	213; 258; 302	4,49; 4,35; 4,19	2,61‡	7,28—8,51	10,45
XII	244—246**	84,1	5,7	10,7	$C_{18}H_{14}N_2$	83,7	5,4	10,8	2600—3200	212; 228; 270; 312; 357	4,56; 4,71; 4,32; 4,17; 3,89	2,8‡	7,22—8,31	10,45
XIII	234—236††	86,7	5,2	8,6	$C_{23}H_{16}N_2$	86,2	5,0	8,7	2600—3200	207; 228; 270; 285; 362,3	4,58; 4,62; 4,55; 4,58; 3,96	—	7,12—8,31	11,41‡‡

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*In a sealed capillary. †From benzene–petroleum ether. ††From d_6-acetone. **From isopropyl alcohol. ††From ethanol. ‡‡From d_6-DMSO.

Carbolines X and XI can also be obtained by a procedure that bypasses the isolation of dicarbonyl compounds VI and VII. For this, after the first step, the alcohol is evaporated, and the second step of the reaction is carried out as described above. The yields of δ-carbolines X and XI based on indolinone I ranged from 22 to 30%.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were obtained with a CFT-20 spectrometer (80 MHz) with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing-electron energy of 50 eV in a cathode emission current of 1.25 mA.

1-Acetyl-2-(butan-3-on-1-yl)indolin-3-one (VI) and 1-Acetyl-2-bis(butan-3-on-1-yl)indolin-3-one (XIV). A) A 1-ml sample of triethylamine and 1 ml (0.01 mole) of methyl vinyl ketone II were added with stirring at 20°C to a suspension of 1.8 g (0.01 mole) of 1-acetyl-3-indolinone (I) in 50 ml of alcohol, the mixture was stirred until the solid material dissolved, and the solution was allowed to stand at room temperature for 10-12 h. The solvent was evaporated *in vacuo*, and the resulting oil crystallized after the addition of petroleum ether. The yield of diketone VI was 1.6 g (67%) (Table 1).

B) The reaction was carried out by method A with preliminary heating of the reaction mixture to 35°C. Compounds VI and XIV were isolated by chromatography on silica gel (200 g); elution with chloroform gave 1.4 g (57%) of diketone VI (Table 1) and 0.8 g (24%) of diadduct XIV with mp 91-92°C (from toluene). Found: C 68.9; H 6.9; N 4.5%; M^+ 315. $C_{18}H_{21}NO_4$. Calculated: C 68.6; H 6.7; N 4.4%; M 315.

1-Acetyl-2-(butanal-3-yl)indolin-3-one (VII). A 1-ml (0.01 mole) sample of crotonaldehyde III was added to a heated (to 35°C) solution of 1.8 g (0.01 mole) of indolinone I and 1 ml of triethylamine in 50 ml of alcohol, after which the mixture was allowed to stand at room temperature for 10-12 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (200 g); elution with chloroform gave 0.7 g (30%) of aldehyde VII (Table 1).

1-Acetyl-2-(1-phenylbutan-3-on-1-yl)indolin-3-one (VIII). A mixture of 3.5 g (0.02 mole) of indolinone I, 3.5 g (0.04 mole) of benzalacetone IV, and 2 g of CH_3CO_2K in 20 ml of CH_3CO_2H was refluxed for 24 h, after which the solvent was evaporated, 100 ml of water was added to the residue, and the precipitate was removed by filtration, washed with water, and dissolved in ethyl acetate. The solution was washed with 5% aqueous $NaHCO_3$ solution and water and dried with $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel (300 g); elution with chloroform gave 1.8 g (28%) of diketone VIII (Table 1).

1-Acetlyl-2-(3-phenylpropiophenon-3-yl)indolin-3-one (IX). A mixture of 1.8 g (0.01 mole) of indolinone I, 4.2 g (0.02 mole) of benzalacetophenone V, and 1 g of CH_3CO_2K in 10 ml of CH_3CO_2H was refluxed for 2 h, after which it was cooled, diluted with water, and extracted with ethyl acetate. The ethyl acetate layer was washed with $NaHCO_3$ solution and water, dried with $MgSO_4$, and evaporated to give 1.6 g (42%) of IX (Table 1).

δ-Carbolines (X-XIII). A 5-g sample of $(NH_4)_2CO_3$ was added to a solution of 0.01 mole of 1,5-dicarbonyl compound VI-IX in 40 ml of acetic acid, and the mixture was refluxed for 8 h. The solvent was evaporated, the reaction mass was treated with 100 ml of 10% aqeuous KOH solution, and the precipitate was removed by filtration, washed to neutrality with water, and purified by recrystallization. Carbolines X-XIII were obtained in 27, 32, 47, and 50% yields, respectively (Table 2).

δ-Carbolines X and XI were subjected to additional purification, as described below in the preparation of 2-methyl-δ-carboline (X).

2-Methyl-δ-carboline (X). A 1-ml (0.01 mole) sample of ketone II was added to 20°C to a suspension of 1.8 g (0.01 mole) of indolinone I and 1 ml of triethylamine in 50 ml of alcohol, after which the mixture was stirred until the solid material dissolved, and the solution was allowed to stand at room temperature for 10-12 h. The solvent was evaporated *in vacuo*, the residue was dissolved in 40 ml of acetic acid, 5 g of $(NH_4)_2CO_3$ was added to the solution, and the mixture was refluxed for 8 h. The solvent was evaporated, and the reaction mass was diluted with 100 ml of 10% aqueous KOH. The precipitate was removed by filtration and washed to neutrality with water. The precipitate after filtration was dissolved in isopropyl alcohol saturated with HCl, after which the solvent was evaporated. The hydrochloride of δ-carboline X was extracted from the residue by refluxing with 250 ml of water. The solution was cooled and filtered, and the filtrate was made alkaline to pH 10-11 with 10% aqueous KOH solution. The resulting precipitate was removed by filtration, washed with water, and recrystallized. The yield of carboline X was 0.5 g (30%) (Table 2).

4-Methyl-δ-carboline (XI). A 1-ml (0.01 mole) sample of aldehyde III was added to a heated (to 35°C) solution of 1.8 g (0.01 mole) of indolinone I and 1 ml of triethylamine in 50 ml of alcohol, after which the mixture was allowed to stand at room temperature for 10-12 h. The solvent was then evaporated, and the reaction mixture was worked up and δ-carboline XI was isolated as in the synthesis of X. The yield of carboline XI was 0.4 g (22%) (Table 2).

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INDOLE DERIVATIVES.

123.* EFFECT OF THE SUBSTITUENT IN THE 2 POSITION ON THE CARBOMETHOXYLATION OF 2-SUBSTITUTED 3-INDOLYLACETONITRILES

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It is shown that the size rather than the electronegativity of the substituent in the 2 position of the indole ring has an effect on the Claisen condensation of 2-substituted 3-indolylacetonitriles with dimethyl carbonate. Carbomethoxylation of the side chain is generally accompanied by methylation of the nitrogen atom of the indole ring.

It was recently established that the C-carbomethoxylation of 3-indolylacetonitrile is accompanied by N-carbomethoxylation and leads to the formation of N-carbomethoxy-3-indolylcyanoacetic ester [2]. In the present research we studied carbomethoxylation under the conditions of the Claisen condensation of 3-indolylacetonitriles that contain various substituents in the 2 position of the indole ring. It seemed of interest to ascertain the effect of both the electronic and steric properties of the substituents.

The necessary 3-indolylacetonitriles I-IV with CH_3, C_6H_5, tert-Bu, and $COOCH_3$ substituents were obtained by known methods [3-5]. 2-Cyano-3-indolylacetonitrile (V) was obtained from 2-cyano-3-methylindole [6] by the method described for 2-carbomethoxy-3-cyanomethylfuran [7].

The introduction of the substituents listed above in the 2 position of 3-indolylacetonitrole hinders carbomethyoxylation. In contrast to 3-indolylacetonitrile, its 2-substi-

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*See [1] for Communication 122.

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