INDOLE DERIVATIVES.

119.* C-ACYLATION OF METHYL 3-INDOLYLACETATE. SYNTHESIS OF 5-(3-INDOLYL)PYRIMIDINES

V. S. Rozhkov, Yu. I. Smushkevich, and N. N. Suvorov

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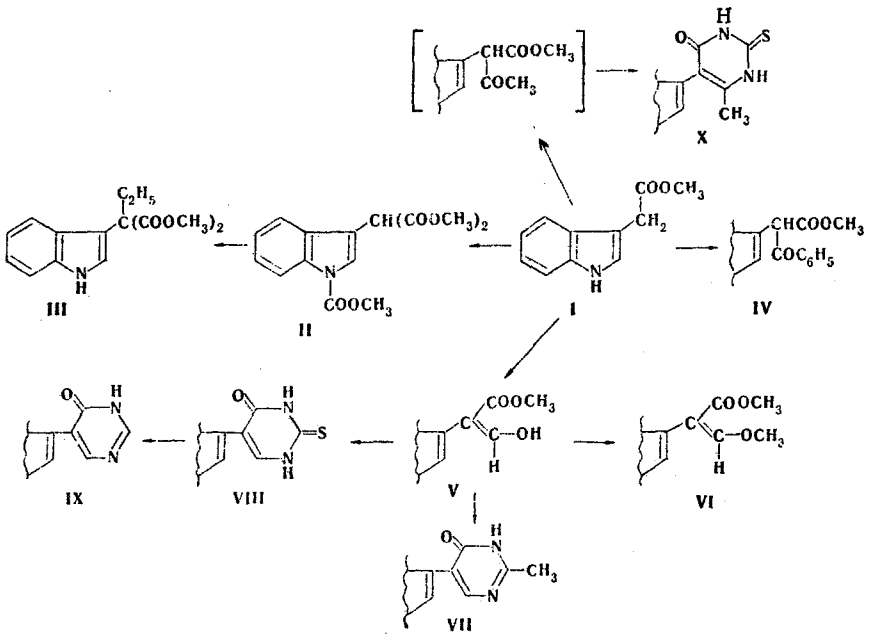
The Claisen condensation of methyl 3-indolylacetate with dimethyl carbonate, methyl benzoate, methyl formate, and methyl acetate proceeds with acylation of the CH_2 group. Only the carbomethoxy group attached to the nitrogen atom of the indole ring is retained. The corresponding 5-(3-indolyl)pyrimidines were obtained by condensation of thiourea and acetamidine with the products of acylation of methyl 3-indolylacetate with methyl formate and methyl acetate.

We have previously accomplished the C-acylation of 3-indolylacetonitrile with esters [2]. In the present research it is shown that methyl 3-indolylacetate in the presence of sodium hydride can also undergo Claisen condensation with various esters besides diethyl oxalate, the products of condensation of which with methyl and ethyl 3-indolylacetates have been described [3, 4]. Although an attempt to carbethoxylate ethyl 3-indolylacetate was unsuccessful [5], the carbomethoxylation of methyl 3-indolylacetate (I) gives dimethyl 1-carbomethoxy-3-indolylmalonate (II). Malonic ester II is alkylated by alkyl halides under ordinary conditions to give compounds of the III type.

The reaction of ester I with methyl benzoate leads to methyl 3-indolylbenzoylacetate (IV). In contrast to 3-indolylbenzoylacetonitrile, IV is not enolized and exists completely in the ketone form. A singlet of a methylidyne proton at 5.94 ppm, with an intensity of one proton unit, is observed in its PMR spectrum. Compound IV does not react with an ether



solution of diazomethane under the conditions used for the conversion of 3-indolylbenzoylacetonitrile to the methyl ether of the enol form. The reaction of ester I with methyl for-

*See [1] for Communication 118.

D. I. Mendeleev Moscow Institute of Chemical Technology, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 55-58, January, 1980. Original article submitted April 18, 1979.

mate gives 3-indolylformylacetic ester V, which exists in chloroform in the enol form. A signal of an enol proton at 11.95 ppm, which is split into a doublet by the adjacent olefinic proton (7.16 ppm) with J = 13 Hz, is observed in the PMR spectrum of V in deuterochloroform. Methyl α-(3-indolyl)-β-methoxyacrylate (VI) is obtained by treatment of enol V with diazomethane.

The condensation of formylacetic ester V with acetamidine or thiourea leads to 2-substituted 5-(3-indolyl)-4-hydroxypyrimidines VII or VIII. Despite the fact that the product of condensation of ester I with methyl acetate is an oily substance, the isolation of which in pure form is difficult, the corresponding 5-(3-indolyl)pyrimidine (X) was also obtained by condensation of this product with thiourea.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source.

Dimethyl 1-Carbomethoxy-3-indolylmalonate (II). A solution of 2.85 g (0.015 mole) of methyl 3-indolylacetate (I) in 25 ml of dimethyl carbonate was added dropwise at 35°C to a stirred suspension of 2.4 g (0.1 mole) of sodium hydride in 20 ml of absolute ether, after which the solution was sitrred for 30 min and allowed to stand for 24 h. The excess sodium hydride was decomposed, 10 ml of methanol was added dropwise with stirring, and the reaction product was isolated from the salt by the addition of 20 ml of dilute (1:1) acetic acid at 5-10°C. The mixture was extracted with ether, and the extract was dried with anhydrous $MgSO_4$. The ether was removed by distillation, 5 ml of methanol was added, and precipitated ester II was removed by filtration to give 3.8 g (82%) of a product with mp 108-110°C (from methanol). IR spectrum: 1745 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 225 (4.33), 255 (3.96), 262 (3.96), 288 nm (3.77). PMR spectrum (in $CDCl_3$), ppm: 3.75 s [$CH(COOCH_3)_2$], 4.00 s (N—$COOCH_3$), 4.88 s (α-CH), and 7.81 s (2-CH). Found: C 59.1; H 4.8; N 4.3%; M (by mass spectrometry) 305. $C_{15}H_{15}NO_6$. Calculated: C 59.0; H 4.9; N 4.6%; M 305.

Dimethyl 3-Indolylethylmalonate (III). A 3.05-g (0.01 mole) sample of II and 2.2 g (0.02 mole) of ethyl bromide were added to a solution of sodium methoxide obtained from 0.46 g (0.02 mole) of sodium in 15 ml of methanol, and the mixture was refluxed with stirring for 3-4 h. The solvent was removed by distillation in vacuo, and 50 ml of water was added to the residue. The precipitated ester (III) was extracted with ether (three 50-ml portions), and the extract was washed with water and dried with anhydrous $MgSO_4$. The ether solution was evaporated, and the precipitate was removed by filtration to give 2.24 g (81%) of a product with mp 154-155°C. IR spectrum: 1715, 1755 (C=O); 3370 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 220 (4.53), 283 (3.82), 292 nm (3.76). PMR spectrum (in $CDCl_3$), ppm: 0.9 t (CH_2CH_3), 2.44 q (CH_2CH_3), 3.70 s ($O=COCH_3$), 7.0-7.4 m (aromatic protons), and 8.44 s (NH). Found: C 65.5; H 6.1; N 5.0%. $C_{15}H_{17}NO_4$. Calculated: C 65.6; H 6.2; N 5.1%.

Methyl 3-Indolylbenzoylacetate (IV). A solution of 2.85 g (0.015 mole) of ester I and 4.1 g (0.03 mole) of methyl benzoate in 20 ml of absolute ether was added dropwise to a stirred suspension of 2.4 g (0.1 mole) of sodium hydride in 20 ml of absolute ether. To start the reaction the ether was heated to the boiling point, after which heating was stopped. After addition of the solution was complete, the reaction mixture was allowed to stand for 24 h. Methanol (10 ml) and 20 ml of 50% acetic acid were then added successively with stirring at 5-10°C, and the mixture was extracted with ether. The extract was washed with water and $NaHCO_3$ solution and dried with anhydrous $MgSO_4$, and the ether was removed by distillation to give 1.75 g (33%) of a product with mp 150-152°C. IR spectrum: 1685, 1750 (C=O); 3380 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 210 (shoulder) (4.52), 218 (4.57), 245 (4.22), 279 (3.94), 289 nm (3.86). PMR spectrum (in $CDCl_3$), ppm: 3.78 s ($COOCH_3$), 5.94 s (CH), 7.00-7.40 m (aromatic protons), and 8.44 s (NH). Found: C 73.9; H 5.6; N 4.7%; M (by mass spectrometry) 293. $C_{18}H_{15}NO_3$. Calculated: C 73.7; H 5.1; N 4.8%; M 293.

Methyl 3-Indolylformylacetate (V). A solution of 5.7 g (0.03 mole) of ester I in 25 ml of absolute ether and 24.5 g (0.41 mole) of methyl formate were added to a stirred suspension of 4.8 g (0.2 mole) of sodium hydride in 40 ml of absolute ether, and the mixture was allowed to stand for 24 h. Methanol (5 ml) and 30 ml of 50% acetic acid were then added successively at 0-5°C with stirring, and the mixture was extracted with ether. The ether

solution was washed with water and $NaHCO_3$ solution and dried with anhydrous $MgSO_4$, and the ether was removed by distillation to give 5 g (71%) of a product with mp 120-122°C. IR spectrum: 1640, 1670 (C=C–C=O); 3200 br (OH); 3400 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 205 (shoulder) (4.29), 222 (4.55), 280 (3.93), 289 nm (3.88). PMR spectrum (in $CDCl_3$), ppm: 3.68 s ($COOCH_3$), 6.8-7.5 m (aromatic protons), 8.0 s (NH), and 11.95 d (=CH–OH) with J = 13 Hz. The position of the =CH–OH olefinic proton at 7.16 ppm was determined by double resonance. Found: C 66.9; H 5.4; N 6.7%; M (by mass spectrometry) 217. $C_{12}H_{11}NO_3$. Calculated: C 66.5; H 5.1; N 6.5%; M 217.

Methyl α-(3-Indolyl)-β-methoxyacrylate (VI). A suspension of 1 g (0.0046 mole) of V in 20 ml of ether was treated with a solution of diazomethane in 50 ml of ether obtained from 2 g of nitrosomethylurea. After 3 h, the ether and excess diazomethane were removed by distillation in vacuo, 6 ml of chloroform was added to the residue, and the mixture was filtered. Petroleum ether was added to the heated filtrate, and, when crystallization was complete, the reaction product was removed by filtration to give 0.8 g (75%) with mp 103-104°C. IR spectrum: 1640, 1690 (C=C–C=O); 3365 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 205 (shoulder) (4.28), 223 (4.56), 281 (3.92), 290 nm (3.92). Found: C 67.6; H 5.9; N 6.3%; m (by mass spectrometry) 231. $C_{13}H_{13}NO_3$. Calculated: C 67.5; H 5.6; N 6.1%; M 231.

2-Methyl-4-hydroxy-5-(3-indolyl)pyrimidine (VII). A 1.45-g (0.015 mole) sample of acetamidine hydrochloride was added to a solution of sodium methoxide [from 1.05 g (0.045 g-atom) of sodium in 50 ml of methanol], and the mixture was stirred at 50°C for 15 min. A 2.2-g (0.01 mole) sample of V was added, and the mixture was refluxed with stirring for 6 h. Two-thirds of the methanol was removed by distillation, and the concentrate was heated at 85-90°C for 2 h. It was then cooled, treated successively with 15 ml of methanol and 15 ml of water, and acidified with 15 ml of acetic acid. The mixture was cooled with stirring, and the precipitate was removed by filtration, washed with a small amount of water, and recrystallized from ethanol (with clarification with charcoal) to give 0.9 g (40%) of a product with mp 270-272°C. IR spectrum: 1610, 1665 (NH, C=O); 3060, 3150, and 3350 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 207 (shoulder) (4.27), 223 (4.37), 278 (3.98), 337 nm (4.11). Found: C 69.0; H 5.0; N 18.6%; M (by mass spectrometry) 225. $C_{13}H_{11}N_3O$. Calculated: C 69.3; H 4.9; N 18.6%; M 225.

2-Thioxo-4-hydroxy-5-(3-indolyl)pyrimidine (VIII). A 2.2-g (0.01 mole) sample of V and 1 g (0.013 mole) of thiourea were added to a solution of sodium methoxide [from 0.46 g (0.02 g-atom) of sodium in 20 ml of methanol], and the mixture was heated at a bath temperature of 100°C for 4 h, after which two-thirds of the methanol was removed by distillation, and the mixture was heated with stirring for another 2 h. Methanol (15 ml) and 15 ml of water were added, and 15 ml of acetic acid was then added dropwise. The mixture was then allowed to cool slowly to precipitate crystals of VIII. After cooling to 25-30°C, they were removed by filtration and washed with small amounts of water, methanol, and ether to give 0.66 g (27%) of product. The product was dissolved in sodium methoxide solution (from 0.5 g of sodium in 10 ml of methanol), 20 ml of water was added, and the mixture was refluxed with charcoal for 5 min. It was then filtered, and the hot solution was acidified with acetic acid. The product melted above 350°C. IR spectrum: 1635, 1665 (NH, C=O); 3090, 3160, and 3420 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 208 (shoulder) (4.38), 223 (4.41), 293 (4.12), 350 nm (4.22). Found: C 59.0; H 4.0; N 16.9%; M (by mass spectrometry) 243. $C_{13}H_9N_3OS$. Calculated: C 59.3; H 3.7; N 17.3%; M 243.

4-Hydroxy-5-(3-indolyl)pyrimidine (IX). A 1-g (4.1 mmole) sample of VIII was dissolved in a mixture of 20 ml of ethanol and 10 ml of concentrated ammonium hydroxide, after which 3 g of Raney nickel in the form of a paste with ethanol was washed into the flask with 10 ml of ethanol, and the mixture was refluxed with stirring for 2 h. The still warm solution was decanted and filtered through an ordinary filter, and the filtrate was concentrated to half its original volume and allowed to stand for crystallization. Workup gave 0.52 g (60%) of a product with mp 285-287°C. IR spectrum: 1610, 1660 (NH, C=O); 3080, 3120, and 3170 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 207 (shoulder) (4.25), 222 (4.35), 278 (3.92), 340 nm (4.06); Found: C 68.7; H 4.7; N 20.3%; M (by mass spectrometry) 211. $C_{12}H_9N_3O$. Calculated: C 68.2; H 4.3; N 19.9%; M 211.

2-Thioxo-4-methyl-5-(3-indolyl)-6-hydroxypyrimidine (X). A solution of 2.85 g (0.015 mole) of ester I in 10 ml of absolute ether and 9.3 g (0.126 mole) of methyl acetate were added at 35°C to a stirred suspension of 2.4 g (0.1 mole) of sodium hydride in 20 ml of absolute ether, after which the mixture was stirred for 15 min and allowed to stand for 24 h.

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

N. A. Kogan

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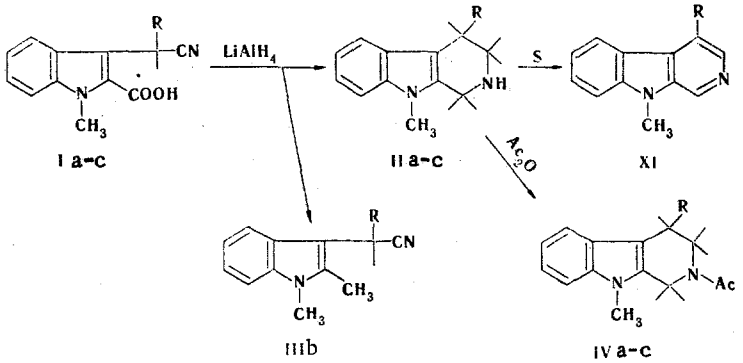
4-Aryltetrahydro-β-carbolines were synthesized from 3-substituted indole-2-carboxylic acids. The structures of the compounds obtained were proved by means of the UV, IR, and PMR spectra.

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

Leningrad Institute of Pharmaceutical Chemistry, Leningrad 197022.

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