INDOLE DERIVATIVES

CII.* C-ACYLATION OF 3-INDOLYLACETONITRILE

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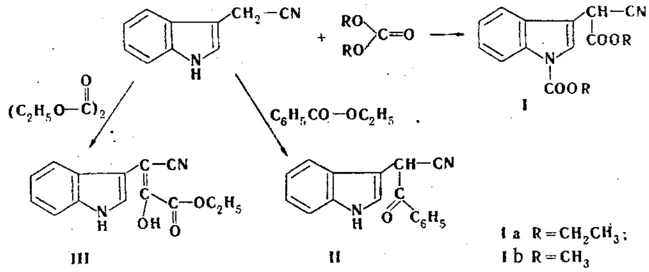
Claisen condensation of 3-indolylacetonitrile with diethyl carbonate, diethyl oxalate, and ethyl benzoate proceeds with acylation at the CH_2 group. Depending on the acylating agent, the reaction proceeds with retention or elimination of the N-acyl group.

C-Acylation of phenylacetic acid derivatives by means of the Claisen condensation is used in the preparation of important medicinal preparations [2]. The realization of this reaction in the indole series would open up a pathway to α-(3-indolyl)alkanoic acids, α-(3-indolyl) ketones, and indole analogs of known medicinal preparations.

The literature contains an indication of an unsuccessful attempt to carry out the carbethoxylation of ethyl 3-indolylacetate.

Replacement of a carbethoxy group by a stronger electron-acceptor nitrile group apparently promotes the occurrence of this sort of process. In fact, 3-indolylacetonitrile reacts with diethyl carbonate in the presence of sodium hydride to give N-carbethoxy-3-indolylcyanoacetic ester (Ia).



The UV spectrum of Ia is similar to the spectrum of 3-indolylacetonitrile. The mass spectrum of Ia contains an M^+ molecular ion peak with m/e 300 and an $(M-COOC_2H_5)^+$ fragment ion with m/e 227; this indicates the introduction of 2 carbethoxy groups into the 3-indolylacetonitrile molecule. Absorption bands of C=O and C≡N groups are observed in the IR spectrum, whereas the absorption at 3200-3400 cm^{-1} characteristic for the NH group of indole is absent; this means that one of the carbethoxy groups is attached to the nitrogen atom of indole. The PMR spectrum contains two triplets at 1.28 and 1.48 ppm and two quartets at 4.24 and 4.47 ppm, which are affiliated with the two ethoxy groups, the signal of a proton in the 2 position of the pyrrole ring at 7.82 ppm, and a signal (1H) at 4.94 ppm of a proton attached to a tertiary carbon atom. The last two signals are somewhat split (J = 1 Hz) as a result of long-range coupling.

Dimethyl carbonate reacts similarly with 3-indolylacetonitrile in the presence of sodium methoxide. The reaction also proceeds in the same way in the preparation of β-ketonitriles of the indole series with ethyl benzoate and diethyl oxalate to give 3-indolylbenzoylacetonitrile (II) and ethyl 3-indolylcyanopyruvate

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* See [1] for communication CI.

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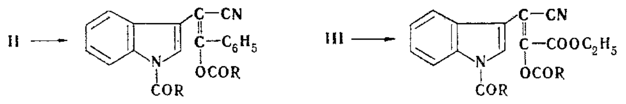
(III), respectively. According to the PMR spectral data, II is partially enolized in deuteroacetone, whereas III is completely enolized under the same conditions. The latter is also enolized in the solid state, and the absorption band of the nitrile group therefore appears at 2230 cm^{-1} in the IR spectrum as a consequence of conjugation with the double bond, whereas the maxima lie at 2260-2265 cm^{-1} in the spectra of 3-indolylacetonitrile and nonenolized Ia, Ib, and II.

Ketonitriles II and III are readily acetylated and benzoylated in pyridine to give N- and O-diacylated products IVa,b and Va,b.



IV V

IV, V a $R = CH_3$; IV, V b $R = C_6H_5$

Absorption bands at 3200-3400 cm^{-1} are absent in the IR spectra of IVa,b and Va,b: this attests to N-acylation, whereas the presence of OCOR fragments in the mass spectra and absorption bands of a nitrile group conjugated with a double bond (2225-2240 cm^{-1}) in the IR spectra indicates O-acylation of the ketonitriles.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-10 or UR-20 spectrometers. The UV spectra of ethanol solutions were recorded with a Specord spectrophotometer. The PMR spectra of the compounds were recorded with a JNM-4-100 spectrometer on the δ scale 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.

Methyl N-Carbomethoxy-3-indolylcyanoacetate (Ib). A mixture of 45 g (0.5 mole) of dimethyl carbonate, 20 ml of benzene, and 7.8 g (0.05 mole) of 3-indolyacetonitrile was added dropwise with stirring to dry sodium methoxide obtained from 3.2 g (0.14 mole) of sodium. The mixture was heated slowly with stirring while the methanol was removed by distillation and benzene (a total of 100 ml) was added simultaneously dropwise until the temperature of the vapors reached 90°. The mixture was then cooled, and 5 ml of dilute (1 : 1) acetic acid was added. The organic layer was separated, and the aqueous layer was extracted with benzene (two 50-ml portions). The combined extracts were washed successively with water, $NaHCO_3$ solution, and water, then dried with anhydrous $MgSO_4$. The benzene was removed by distillation to give 8.1 g (60%) of ester Ib with mp 140-142° (from methanol). IR spectrum; 1730 (C=O), 2265 cm^{-1} (C≡N). UV spectrum, λ_{max}, (log ε): 223 (4.42), 253 (4.21), 283 (3.82), and 293 nm (3.74). PMR spectrum (in $CDCl_3$): 3.82 (CH_3), 4.04 s* (CH_3), 4.94 s (CH-CN), 7.82 s ppm (N-CH=C). Found, %: C 6.20; H 4.4; N 10.0; M (mass spectrometrically) 272. $C_{14}H_{12}N_2O_4$. Calculated, %: C 62.0; H 4.4; N 10.3; M 272.

Ethyl N-Carbethoxy-3-indolylcyanoacetate (Ia). A solution of 7.8 g (0.05 mole) of indolylacetonitrile in 30 ml of absolute ether was added with stirring at room temperature to a suspension of 4.8 g (0.2 mole) of sodium hydride and 60 g (0.5 mole) of diethyl carbonate in 100 ml of absolute ether, and the mixture was stirred for 20-30 min, after which it was allowed to stand overnight. Ethanol (10 ml), 30 ml of water, and 30 ml of dilute 1 : 1 acetic acid were then added dropwise successively. The ether layer was separated, and the water layer was extracted with two 100-ml portions of ether. The ether extracts were washed with a saturated solution of NaCl and $NaHCO_3$ and dried with anhydrous $MgSO_4$. The ether was removed by distillation to give 7.5 g (50%) of ester Ia with mp 83-85° (from aqueous alcohol). IR spectrum: 1750 (C=O), 2265 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 223 (4.43), 255 (4.20), 283 (3.84), and 292 mm (3.63). PMR spectrum in $CDCl_3$: 1.28 t (CH_3), 148 t (CH_3), 4.24 q (CH_2), 4.48 q (CH_2), 4.94 s (CH-CN), and 7.83 s (N-CH=C). Found, %: C 64.0; H 5.0; N 9.0; M 300. $C_{16}H_{16}N_2O_4$. Calculated, %: C 64.0; H 5.3; N 9.0; M 300.

3-Indolylbenzoylacetonitrile (II). a) This compound was obtained by the method used to prepare Ia from 4.8 g (0.2 mole) of NaH, 30 g (0.2 mole) of ethyl benzoate, and 7.8 g (0.05 mole) of indolylacetonitrile. The yield of product with mp 178-180° (from chloroform) was 11 g (86%). IR spectrum: 1675 (C=O), 2260 (C≡N), and 3370 cm^{-1} (N-H). UV spectrum, λ_{max}, (log ε): 204 (4.52), 220 (4.36), 280 (3.85), and 333 nm (3.92). Found, %: C 77.8; H 4.8; N 10.6; M 260. $C_{17}H_{12}N_2O$. Calculated, %: C 78.4; H 4.6; N 10.8; M 260.

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* Here and subsequently, s is singlet, t is triplet, and q is quartet.

b) Dry sodium ethoxide obtained from 3.2 g (0.4 mole) of sodium was dissolved in 80 ml of dry diglyme at room temperature. A mixture of 60 ml (0.4 mole) of ethyl benzoate and 8 g (0.05 mole) of 3-indolylacetonitrile was then added dropwise with stirring. The mixture was then heated slowly with stirring while the alcohol was removed by distillation until the temperature of the vapors reached 110°. The mixture was poured into 150 ml of water. The organic layer was separated, and the aqueous layer was extracted with two 50-ml portions of chloroform. The combined extracts were washed successively with saturated solutions of NaCl, $NaHCO_3$, and NaCl and allowed to stand overnight. The resulting precipitate was removed by filtration and washed successively with chloroform, a small amount of alcohol, and petroleum ether to give 5 g (38.4%) of ketonitrile II with mp 178-180° (from chloroform). No melting-point depression was observed for a mixture of this product with the product obtained by method A.

Ethyl-3-Indolylcyanopyruvate (III). A solution of 7.8 g (0.05 mole) of indolylacetonitrile in 17 g (0.11 mole) of diethyl oxalate was added to a solution of sodium ethoxide obtained from 2.3 g (0.1 g-atom) of sodium and 40 ml of absolute ethanol, and the mixture was allowed to stand overnight. It was then poured into 50 ml of water, and the aqueous mixture was acidified with 10 ml of concentrated HCl. The resulting precipitate was removed by filtration and washed with a small amount of aqueous alcohol (1 : 1) and ether to give 12 g (95%) of ester III with mp 152-154° (from chloroform). IR spectrum 1610 (C=C), 1660, 1690, 1730 (C=O), 2230 (C≡N); 3250, and 3450 cm^{-1} (N–H, O–H). UV spectrum, λ_{max}, (log ε): 203 (4.36), 239 (4.29), and 280 nm (3.79). PMR spectrum [in $(CD_3)_2CO$]: 1.44 t (CH_3), 4.46 q (CH_2), and 8.06 s (NH–CH=C). Found, %: C 65.5; H 4.6; N 10.8; M 256. Calculated, %: C 65.6; H 4.7; N 10.9; M 256.

Ethyl N,O-Diacetyl-3-indolylcyanopyruvate (Va). A total of 10 ml (0.1 mole) of acetic anhydride was added to a solution of 2.6 g (0.01 mole) of ethyl ester III in 30 ml of pyridine, and the mixture was refluxed for 30 min. It was then cooled and poured into a mixture of 100 g of ice and 50 ml of concentrated HCl. The aqueous mixture was extracted with 50 ml of chloroform, and the extract was washed with 100 ml of dilute (1 : 1) hydrochloric acid and two 100-ml portions of water and dried over anhydrous $MgSO_4$. The chloroform was removed by distillation to give 1.7 g (50%) of Va with mp 135-137° (from ethanol). IR spectrum: 1540, 1610 (C=C), 1710, 1730, 1775 (C=O), and 2240 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 203 (4.39), 238 (4.51), 260 (4.18), 290 (4.04), and 300 nm (4.09). PMR spectrum (in $CDCl_3$): 7.82 s (N–CH=C). Found, %: C 63.7; H 4.9; N 8.2; M 340. $C_{18}H_{16}N_2O_5$. Calculated, %: C 63.7; H 4.7; N 8.3; M 340.

N,O-Diacetyl-3-indolylbenzoylacetonitrile (IVa). This compound was obtained by the method used to prepare Va from 2.6 g (0.01 mole) of ketonitrile II and 10 ml (0.1 mole) of acetic anhydride in 30 ml of dry pyridine. The yield of product with mp 152-154° (from ethanol) was 2.4 g (70%). IR spectrum: 1550 (C=C), 1715, 1770 (C=O), and 2230 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 204 (4.44), 220 (4.32), 268 (4.25), and 318 nm (4.16). PMR spectrum (in $CDCl_3$): 7.72 s (N–CH=C). Found, %: C 72.9; H 4.7; N 7.9; M 344. $C_{21}H_{16}N_2O_3$. Calculated, %: C 73.2; H 4.6; N 8.2; M 344.

Ethyl N,O-Dibenzoyl-3-indolylcyanopyruvate (Vb). This compound was obtained by the method used to prepare Va from 2.6 g (0.01 mole) of ethyl ester III and 12 ml (0.1 mole) of benzoyl chloride in 40 ml of dry pyridine. The yield of product with mp 147-149° (from ethanol) was 1.8 g (39%). IR spectrum: 1520 (C=C), 1695, 1725, 1750 (C=O), and 2240 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 203 (4.66), 239 (4.56), and 345 nm (4.01). Found, %: C 72.6; H 4.5; N 5.8; M 464. $C_{28}H_{20}N_2O_5$. Calculated, %: C 72.4; H 4.3; N 6.0; M 464.

N,O-Dibenzoyl-3-indolylbenzoylacetonitrile (IVb). This compound was obtained by the method used to prepare Va from 2.6 g (0.1 mole) of II and 12 ml (0.1 mole) of benzoyl chloride in 40 ml of dry pyridine. The yield of product with mp 190-192° (from ethanol) was 2.8 g (59%). IR spectrum: 1546, 1595 (C=C), 1655, 1695, 1745 (C=O), and 2225 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 203 (4.67), 225 (4.53), 267 (4.27), and 339 nm (4.08). Found, %: C 79.4; H 4.5; N 5.8; M 468. $C_{31}H_{20}N_2O_3$. Calculated, %: C 79.4; H 4.3; N 6.0; M 468.

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