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HETEROCYCLIZATION OF N-PROPIONYLAMINOINDOLINE

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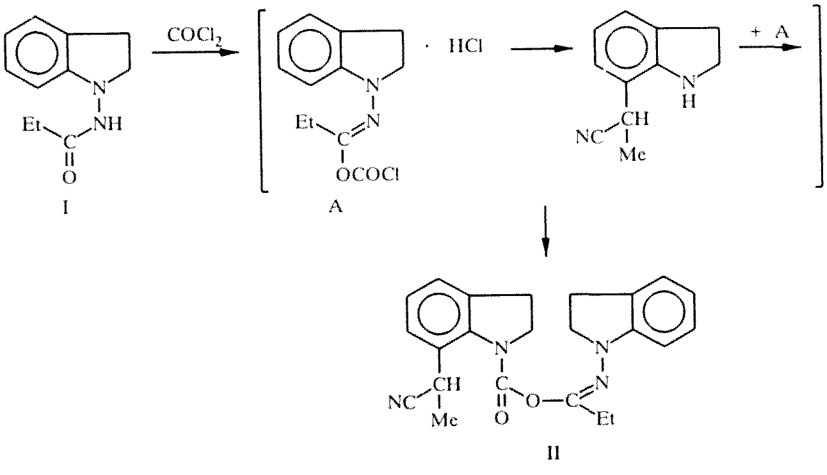
Treatment of N-propionylaminoindine with a solution of phosgene in benzene gives the 1-[(indolin-1-yl)imino]propyl ester of 7-(1-cyanoethyl)indoline-1-carboxylic acid. The structure of the compound was proved using ^1H and ^{13}C NMR spectroscopy.

The reaction of N-acylaminotetrahydroquinolines with phosphorus oxychloride under Kost conditions gives the corresponding tricyclic derivatives containing the 2-aminoindole fragment [1]. By contrast, N-acylaminoindolines form 7-cyanoindolines (analogs of ortho-aminobenzylcyanides [2]) under the same conditions. This may be due to thermodynamic instability of the corresponding tricyclic system or the rather severe reaction conditions and the phosphorus oxychloride reagent used. We have previously shown that chloroformic acid derivatives (especially phosgene) are mild and efficient reagents for the Kost rearrangement [3]. It was therefore of interest to study the reaction of N-propionylaminoindoline (I) with phosgene. The synthesis and physicochemical parameters of I have been described in [4].

The ^1H NMR spectra we obtained for I in DMSO-D_6 and $CDCl_3$ show the presence in solution of two molecular forms (the Z (anti) and E (syn) isomers) due to hindered rotation about the amide N−C bond. The ^{13}C NMR spectrum of I in $CDCl_3$ shows a series of doubled resonance signals for the carbon atoms in the molecule. Assignment of the spectral signals was made on the basis of their chemical shifts and literature data [4], the signs of the resonance signals recorded under conditions of selective irradiation of methyl, methylene, methine, and quaternary carbon atoms (using J-modulation), and pairwise comparison of the intensities of signals assigned to identical carbon atoms in the isomeric molecules. The last of these showed that the Z and E isomers exist in solution in the ratio of ≈45:55. The assignment of signals and a detailed discussion of the ^1H and ^{13}C NMR spectra of the isomers of I have been described by us earlier [5].



The reaction of I with phosgene at 45°C occurs quite rapidly and after 2-2.5 h TLC data showed the absence of starting material in the product. This product is a low polarity and TLC mobile material differing in mobility from the corresponding ortho-aminobenzylcyanide obtained by a known method [2]. After appropriate workup the product was chromatographed to

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give a yield of ca. 80%. From the physicochemical data it was assigned as the 1[(indolin-1-yl) imino]propyl ester of 7-(1-cyanoethyl)indoline-1-carboxylic acid (II).

The ^{1}H NMR spectrum of a solution of II showed signals for the protons of the ethyl group at 1.34 and 2.69 ppm, and for the methyl and methine protons in the CH_3CH fragment at 1.64 and 4.38 ppm. The presence of two indoline fragments was inferred from the presence of two signals at 4.38 and 3.74 ppm (assigned to the α-methylene protons of the dihydropyrrole rings) and of a signal at 3.11 ppm for the two β-methylene groups in the dihydropyrrole rings. The ^{13}C NMR spectrum of II showed 23 carbon signals in agreement with the proposed structure (7 quaternary carbon signals, 7 methine signals in the two aromatic rings, 1 nitrile signal, 2 signals for the α- and 2 for the β-units in the dihydropyrrole rings, 2 signals for the CH_3CH unit, and 2 signals assigned to the ethyl group). The series assignments for the ^{13}C and ^{1}H spectra are given in the experimental sections. They are based on the chemical shift values and the signs of resonance signals in the J modulated spectrum. Positive assignments of the signals for the methylenes of $CH_2N_{(2)}$, $CH_2N_{(2')}$ and the methine of $\underline{CH}CH_3$ were made by selective decoupling of the spin-spin interactions between the given carbons and the corresponding protons.

Hence reaction of aminoindoline I with phosgene does not give a tricyclic product. Evidently the intermediate A undergoes rearrangement with ring opening, converting to a benzyl cyanide which is rapidly accylated by chlorocarbonate A to give the reasonably stable product II.

EXPERIMENTAL

The IR spectrum was recorded on a Specord IR-75 instrument using a Vaseline oil suspension. ^{1}H and ^{13}NMR spectra were taken on a Bruker WH-90 instrument working at 90 MHz for protons and 22.62 MHz for carbons using 2% (proton) or 10% (carbon) solutions in $CDCl_3$ at 30°C. Chemical shifts were measured relative to TMS internal standard (0.00 ppm for ^{1}H) or $CDCl_3$ solvent (77.00 ppm for ^{13}C). J Modulated ^{13}C NMR spectra were recorded using a $90°\text{-}\tau\text{-}180°$, $\tau = 0.007$ s $\simeq 1/^1J$ pulse sequence.

Reaction monitoring and product purity were performed using TLC on Silufol UV-254 plates.

Elemental analytical data for C, H, and N agreed with that calculated.

Reaction of N-propionylamino-2,3-dihydroindole with Phosgene. A mixture of N-propionylamino-2,3-dihydroindole ([4], 0.4 g, 0.02 mole), phosgene (0.04 mole), and benzene (20 ml) was heated at 45°C for 2.5-3 h. The product was evaporated and the residue purified chromatographically on a column using L 40/100 silica gel with benzene-acetone (5:1) to give the 1-[(indolin-1-yl)imino]propyl ester of 7-(1-cyanoethyl)indoline-1-carboxylic acid (0.38 g, 85%). IR spectrum: 2240 ($C\equiv N$), 1780, 1730 ($C{=}O$), 1630, 1600 ($C{=}N$, $C{=}C$) cm^{-1}. ^{13}C NMR spectrum ($CDCl_3$): 158.58, 153.18, 147.92, 138.82, 136.56, 135.21, 134.24 ppm (s, $C{=}O$, $C{=}N$, C_9, $C_{9'}$, C_8, $C_{8'}$, C_7), 131.54, 129.81, 128.44, 128.00, 127.36, 127.21, 125.31 (d, C_4, $C_{4'}$, C_5, $C_{5'}$, C_6, $C_{6'}$, $C_{7'}$), 122.01 ppm (s, $C\equiv N$), 55.02, 44.14 ppm (t, C_2H_2, $C_{2'}H_2$), 35.21, 29.19, 20.40 ppm (t, $C_{3'}H_2$, C_3H_2, $\underline{CH_2}CH_3$), 28.44 ppm (d, $\underline{CH}CH_3$), 19.94 ppm (q, $\underline{CH_3}CH$), 9.71 ppm (q, $\underline{CH_3}CH_2$). PMR spectrum ($CDCl_3$): 1.34 (3H, t, $\underline{CH_3}CH_2$, J = 7.5 Hz), 2.69 (2H, q, $CH_3\underline{CH_2}$, J = 7.5 Hz), 1.64 (3H, d, $\underline{CH_3}CH$, J = 7.1 Hz), 4.38 (1H, q, $CH_3\underline{CH}$, J = 7.1 Hz), 4.38 (2H, t, 2-H, J = 7.5 Hz), 3.74 (2H, t, 2'-H, J = 7.5 Hz), 3.11 (4H, t, 3-H, 3'-H, J = 7.5 Hz), 7.10-7.80 ppm (7H, m, Ar).

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