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SYNTHESIS AND PROPERTIES OF 3-AMINO-2-(2-BENZIMIDAZOLYL)-Δ^2-PYRROLIZIDIN-1-ONE

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2-Benzimidazolylacetonitrile is acetylated by the acid chloride derivative of N-trifluoroacetylproline to give N- and C-acyl derivatives. Removal of the trifluoroacetyl protective group in the C-acyl derivatives is accompanied by cyclization to give 3-amino-2-(2-benzimidazolyl)-Δ^2-pyrrolizidin-1-one. Exhaustive acylation of this product gives a derivative of a new heterocyclic system, namely, pyrrolizino[3',2':5,6]-pyrimido[3,4-a] benzimidazole.

Since the pyrrolizidine system is found in several alkaloids [1], synthetic derivatives of this heterocyclic system may possess biological activity. One approach to the synthesis of pyrrolizidines is acylation of 2-azahetarylacetonitriles by the acid chloride derivatives of N-protected amino acids with subsequent removal of the protective group, which is accompanied by cyclization [2]. It is interesting to study the behavior of 2-benzimidazolylacetonitrile, which has several reaction sites and is capable of acylation at both the heterocycle nitrogen atom [3] and methylene group [3-5] relative to the reaction conditions.

The reaction of 2-benzimidazolylacetonitrile with the acid chloride derivative of N-trifluoroacetylproline in dioxane in the presence of triethylamine at 80°C over 1 h gives a mixture of N-acyl (I) and C-acyl derivatives II.

N-Acyl derivative I was isolated from the mixture as a pure compound by recrystallization from nitromethane. The IR spectrum of this compound has strong bands at 1690 and 1725 cm^{-1}, corresponding to the trifluoroacetyl and carbonyl groups, while a band for the unconjugated nitrile group is not found. The methylene group protons $C\underline{H}_2CN$ are not magnetically equivalent and appear in the PMR spectrum as a two-proton doublet at 4.35 ppm. Reacylation occurs upon heating of the isomer mixture in nitromethane at reflux to give the thermodynamically more stable C-acyl derivative II. The IR spectrum of this compound has a band for the trifluoroacetyl group at 1690 cm^{-1} and a strong band is found at 2200 cm^{-1} characteristic for a conjugated cyano group.

The same transformation is observed upon heating a mixture of I and II at reflux in other solvents such as propanol, toluene, and xylene. Product III was isolated upon heating this mixture in pyridine at reflux instead of the expected α-(N-trifluoroacetylprolyl)-α-(benzimidazoliden-2-yl)acetonitrile (II). The elemental analysis data and spectral indices of III did not correspond to II. The IR spectrum of III has bands corresponding to conjugated nitrile and carbonyl groups at 2210 and 1630 cm^{-1}, respectively, but lacks a band for the trifluoroacetyl carbonyl at 1690 cm^{-1}. A strong, broad band is found at 3250-3100 cm^{-1} characteristic for chelate bonds. Removal of the trifluoroacetyl protective group clearly occurs in the presence of base (pyridine), leading to α-prolyl-α-(benzimidazoliden-2-yl)acetonitrile III.

The UV data permit facile distinction between the N-acyl (I) and C-acyl derivatives (II and III). The UV spectrum of I has low-intensity maxima at 204 (log ε = 3.2) and 243 nm (log ε = 3.1). A bathochromic shift of the long-wavelength band and increase in its intensity are found upon going to II and III (λ_{max} = 325 (log ε = 4.57) for acetonitrile II and λ_{max} = 322 nm (log ε = 4.56) for acetonitrile III) due to efficient conjugation in these molecules.

Products I (195°C), II (282°C), and III (>330°C) also differ strongly in their melting points. Carrying out the reaction at a higher temperature by heating in dioxane at reflux (101.5°C) for 1 h leads only to acetonitrile II.

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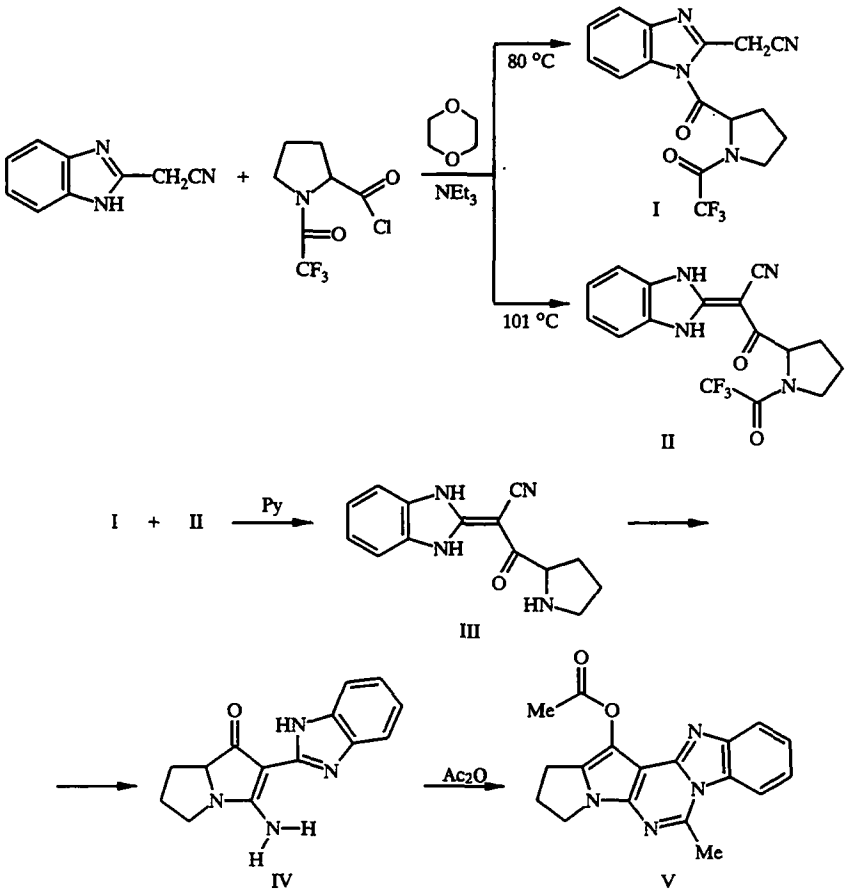

Product IV precipitates out of the reaction mixture upon heating II in n-propanol at reflux in the presence of 1,2-diaminopropane. The IR spectrum of IV lacks a nitrile group band but has strong bands for stretching vibrations of a primary amino group at 3300-3100 cm^{-1} and less intense bands for C–H stretching of the saturated molecular fragment at 2980-2870 cm^{-1} as well as band at 1610 cm^{-1}, which may be assigned to vibrations of the aminovinylketone fragment. The PMR spectrum in $CDCl_3$ has a downfield one-proton singlet for the benzimidazole N–H group at 10.56 ppm and two-proton singlet of the amino group at 7.49 ppm as well as signals for the aliphatic pyrrolizidine protons at 1.67-4.10 ppm and aromatic benzimidazole protons at 7.15-7.30 ppm.

The IR and PMR spectra indicate that, upon removal of the amino group protection, deacylated product III formed in the first step under these conditions due to addition of the N–H group at the triple bond of the nitrile group is converted to 3-amino-2-(2-benzimidazolyl)-Δ^2-pyrrolizidin-1-one (IV). Base catalysis undoubtedly facilitates cyclization.

Acylation of pyrrolizidinone IV by acetic anhydride proceeds both at the amino group and hydroxy group of the tautomeric enol form. However, this reaction does not stop at the diacetyl derivative but rather proceeds with dehydration and closure of the pyrimidine ring, leading to a new heterocyclic system, namely, pyrrolino[3′,2′:5,6]pyrimido-[3,4-*a*]benzimidazole V. The IR spectrum of V has strong bands at 1740 ($CH_3\underline{C}O$) and 1640 cm^{-1} (C=N). The stretching vibrations of the C–H bonds of the saturated fragment are seen at 2930-2840 cm^{-1}, while no absorption is found above 3050 cm^{-1}. The PMR spectrum has three-proton singlets for the acetyl group at 2.60 ppm and for the methyl group in the pyrimidine fragment at 3.51 ppm.

EXPERIMENTAL

The IR spectra were taken on a Pye Unicam SP-3-300 spectrometer for KBr pellets. The UV spectra were taken on a Specord UV-VIS spectrophotometer in methanol. The PMR spectra were taken for solutions in $CDCl_3$, DMSO-d_6, and CF_3CO_2D on a Bruker WP-100SY spectrometer.

Acylation of 2-Benzimidazolylacetonitrile by the Acid Chloride of N-Trifluoroacetylproline. A solution of 0.011 mole acid chloride of N-trifluoroacetylproline in 10 ml dioxane was added to a solution of 1.57 g (0.01 mole) 2-benzimidazolylacetonitrile and 2 ml (0.015 mole) triethylamine in 20 ml dioxane. The mixture was heated for 1 h at 80°C. The solvent was evaporated in vacuum. The dry residue was treated with water and the precipitate was filtered off to give 2.95 g (84%) mixture of isomers I and II.

1-(N-Trifluoroacetylprolyl)-2-benzimidazolylacetonitrile (I) was obtained upon recrystallization of the mixture of isomers I and II from nitromethane, mp 195°C (from nitromethane). PMR spectrum in $CDCl_3$: 1.38 (1H, m, C−H), 2.2-2.65 (3H, m, CH_2 + CH), 3.8-4.2 (2H, m, CH_2), 4.35 (2H, d, CH_2−CN), 5.51 (1H, d.d, C−H), 7.4-7.96 (2H, m, arom 5-H + 6-H), 7.65 (1H, d.d, arom 4-H), 7.90 ppm (1H, d.d, arom 7-H). Found: N, 16.2%. Calculated for $C_{16}H_{13}F_3N_4O_2$: N, 16.0%.

α-(N-Trifluoroacetylprolyl)-α-(benzimidazoliden-2-yl)acetonitrile (II) was obtained by two pathways. A. Prolonged heating of 0.35 g (1 mmole) of the mixture of isomers I and II in nitromethane at reflux gave 0.13 g (37%) II, mp 282°C (from nitromethane). Found: N, 16.2%. Calculated for $C_{16}H_{13}F_3N_4O_2$: N, 16.0%.

B. Carrying out the reaction of 2-benzimidazolylacetonitrile with N-trifluoroacetylproline in dioxane at reflux (101°C) over 1 h gave II in 81% yield. PMR spectrum (DMSO-d_6): 1.98 (2H, m, CH_2), 2.2-2.98 (m, CH_2 and DMSO), 3.75 (2H, m, CH_2), 4.96 (1H, d.d, CH), 7.2-7.7 (4H, m, arom), 12.96 (1H, br.s, NH), 13.37 ppm (1H, br.s, NH or OH).

α-Prolyl-α-(benzimidazoliden-2-yl)acetonitrile (III) was obtained by heating a mixture of I and II in pyridine at reflux for 16 h. The solvent was evaporated off. The residue was treated with water and the precipitate was filtered off, mp >330°C (from nitromethane). PMR spectrum (DMSO-d_6): 2.0-2.8 (CH_2 and DMSO), 3.73 (2H, m, CH_2), 4.76 (1H, m, CH), 7.34-7.56 (6H, m, 4 arom and 2NH), 13.33 ppm (1H, br.s, NH). Found: N, 22.2%. Calculated for $C_{14}H_{14}N_4O$: N, 22.0%.

3-Amino-2-(2-benzimidazolyl)-Δ^2-pyrrolizidin-1-one (IV). A sample of 0.7 ml (8 mmoles) 1,2-diaminopropane was added to a solution of 0.7 g (2 mmoles) nitrile II in 10 ml propanol and heated at reflux for 12 h. After cooling, the precipitate formed was filtered off. The mother liquor was evaporated and treated with water. The precipitate was filtered off to give 0.38 g (76%) IV, mp 261°C (from propanol). PMR spectrum in $CDCl_3$: 1.67 (1H, m, CH), 2.27 (3H, m, CH_2 + C−H), 3.34 (2H, m, CH_2), 4.10 (1H, m, CH), 7.15-7.30 (4H, m, arom), 7.49 (2H, br.s, NH_2), 10.56 ppm (1H, br.s, N−H). UV spectrum, λ_{max} (log ε): 206 (4.39), 304 nm (4.47). Found: C, 66.0; H, 5.6; N, 22.2%. Calculated for $C_{14}H_{14}N_4O$: C, 66.1; H, 5.5; N, 22.0%.

9H-13-Acetoxy-7-methyl-10,11-dihydro-12-pyrrolizino[3′,2′:5,6]pyrimido[[3,4-*a*]benzimidazole (V). A sample of 0.14 g (0.55 mmole) pyrrolizidinone IV in 2 ml acetic anhydride was heated at reflux for 90 min. After cooling, the precipitate was filtered off and washed with water to give 0.1 g (57%) V, mp 241°C (from acetic anhydride). PMR spectrum in CF_3CO_2D: 2.60 (3H, s, $C\underline{H}_3CO$), 2.88 (2H, m, CH_2), 3.24 (2H, m, CH_2), 3.51 (3H, s, ring CH_3), 4.51 (2H, m, CH_2−N), 7.89 (3H, m, arom), 8.43 ppm (1H, d.d, arom 5-H).

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