CONDENSATION OF 2-(ACETAMIDO)CYCLOHEXANONE WITH MALONONITRILE

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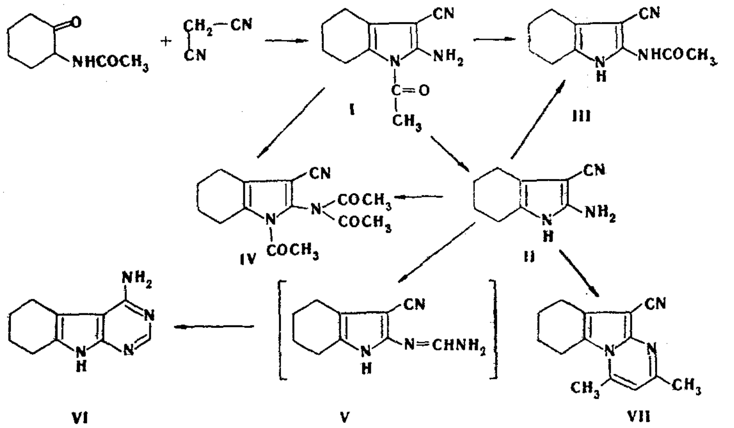
Depending on the conditions, condensation of 2-(acetamido)-cyclohexanone with malononitrile gives 1-acetyl-2-amino-3-cyano-4,5,6,7-tetrahydroindole or 2-amino-3-cyano-4,5,6,7-tetrahydroindole, from which substituted tetrahydropyrimido[1,2-*a*]indole and tetrahydropyrimido[4,5-b]indole were synthesized.

In our research (for example, see [1]) we have shown that N-acyl derivatives of α-aminothiophene behave like unsubstituted amines. In this connection, we have investigated the condensation of 2-(acetamido)cyclohexanone with malononitrile in the presence of piperidine and have found that, depending on the temperature, either 1-acetyl-2-amino-3-cyano-4,5,6,7-tetrahydroindole (I) or 2-amino-3-cyano-4,5,6,7-tetrahydroindole (II), which is probably formed by transfer of the acetyl group from I to the piperidine, is formed in high yield. When I is heated with acetic acid, 2-acetamido-3-cyano-4,5,6,7-tetrahydroindole (III) is formed; this is apparently associated with intramolecular migration of a $COCH_3$ group. A triacyl derivative (IV) is formed when I is refluxed with acetic anhydride. However, acetylation of II with acetic anhydride in benzene gives amide III, while acetylation in triethylamine gives a mixture of III and IV.



The signals of the protons of three acetyl groups of IV appear in the PMR spectrum as two singlets – 6H at 2.34 and 3H at 2.60 ppm. The spectrum of I contains a singlet signal at 2.53 ppm, which we assigned to the protons of the $COCH_3$ group attached to the ring nitrogen atom. The singlet lying at weaker field (2H, 7.10 ppm) is related to the protons of an unsubstituted amino group. The signal of the protons of the $COCH_3$ group in the spectrum of III is found at 2.10 ppm, while the signals of the protons of the NH groups appear as singlets at 10.70 and 11.16 ppm. A formamidine derivative (V) is formed when II is treated with ethyl orthoformate and then with ammonia by the method in [2]. Derivative V is cyclized to 9-amino-5,6,7,8-tetrahydropyrimido[4,5-b]indole (VI) under the influence of sodium methoxide. Condensation [3] of II with acetylacetone gives 2,4-dimethyl-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-*a*]indole (VI).

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EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer spectrometer. The UV spectra of ethanol solutions were recorded with a Hitachi EPS-3T spectrophotometer. The PMR spectra were recorded with JNM-4H-100 and JEOL C-60HL (Japan) spectrometers. The internal standards were tetramethylsilane and deuterodimethylformamide. The course of the reactions and the purities of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in acetone–heptane (1 : 1), benzene–methanol (9 : 1), and benzene–ethyl acetate (1 : 1) systems.

1-Acetyl-2-amino-3-cyano-4,5,6,7-tetrahydroindole (I). A solution of 5.3 g (0.062 mole) of malononitrile in 100 ml of absolute benzene was added to 9 g (0.062 mole) of 2-(acetamido)cyclochexanone [4] in 70 ml of absolute benzene* in such a way that the temperature of the reaction mixture did not rise above 35°. The white precipitate was removed by filtration and washed with methanol and ether to give 9.7 g (77%) of a product with mp 203-205° (from ethanol). PMR spectrum, ppm: 1.70 (5,6-H), 2.25 (4-H), 2.70 (7-H), 2.55 ($COCH_3$), 7.10 (NH_2). UV spectrum, λ_{max}, nm (log ε): 233 (4.42), 330 (3.24). IR spectrum: 3435 and 3300 (ν_{NH_2}), 2200 (ν_{CN}), 1690 ($\nu_{C=O}$) cm^{-1}. Found: C 65.1; H 6.3; N 20.4%. $C_{11}H_{13}N_3$. Calculated: C 65.0; H 6.4; N 20.7%.

2-Amino-3-cyano-4,5,6,7-tetrahydroindole (II). As above, but at 70-75°, II with mp 189-190° (from methanol) was obtained in 84% yield. PMR spectrum, ppm: 1.62 (5,6-H), 2.27 (4,7-H), 5.43 (NH_2), 9.86 (NH). UV spectrum, λ_{max}, nm (log ε): 210 (4.37), 270 (3.66). IR spectrum: 3360 (ν_{NH_2}), 3445 (ν_{NH}), 218 (ν_{CN}) cm^{-1}. Found: C 67.1; H 6.9; N 26.4%. $C_9H_{11}N_3$. Calculated: C 67.1; H 6.9; N 26.1%.

2-Acetamido-3-cyano-4,5,6,7-tetrahydroindole (III). A) A mixture of 0.8 g (5 mmole) of II, 75 ml of absolute benzene, and 0.5 ml (5 mmole) of acetic anhydride was refluxed for 1 h, after which it was cooled, and the white precipitate was removed by filtration and washed with methanol and ether to give 0.84 g (84%) of a product with mp 283-284° (dec., from methanol). PMR spectrum, ppm: 1.70 (5,6-H), 2.10 ($COCH_3$), 2.40 (4,7-H), 10.70 and 11.16 (NH). IR spectrum: 3320 (ν_{NH}), 2210 (ν_{CN}), 1640 ($\nu_{C=O}$) cm^{-1}. UV spectrum, λ_{max}, nm (log ε): 213 (4.19), 286 (3.98). Found: C 64.6; H 6.4; N 20.4%. $C_{11}H_{13}N_3O$. Calculated: C 65.0; H 6.4; N 20.7%.

B) A mixture of 0.200 g (0.9 mmole) of I and 25 ml of glacial acetic acid was refluxed for 6 h, after which it was cooled, and the precipitate was removed by filtration, washed with methanol and ether, and recrystallized from methanol to give 50% of a product with mp 283-284°.

1-Acetyl-2-diacetamido-4,5,6,7-tetrahydroindole (IV). A) A mixture of 0.5 g (0.002 mole) of I and 4 ml (0.04 mole) of acetic anhydride was refluxed for 1 h, after which the solution was cooled and poured into water. The resulting oil began to crystallize on cooling and triturating, and the solid was removed by filtration and washed with water to give 0.49 g (70%) of a product with mp 134-135° (from ethanol). PMR spectrum, ppm: 1.75 (5,6-H), 2.34 (1-$COCH_3$), 2.50 (4-H), 2.60 (2-$COCH_3$), 2.90 (7-H). UV spectrum, λ_{max}, nm (log ε): 216 (inflection) (4.17), 246 (3.91), 284 (3.44). IR spectrum: 2210 (ν_{CN}), 1760 ($\nu_{C=O}$) cm^{-1}. Found: C 62.5; H 6.0; N 15.0%. $C_{15}H_{17}N_3O_3$. Calculated: C 62.7; H 6.0; N 14.6%.

B) A mixture of 0.5 g (0.003 mole) of II, 3 ml (0.03 mole) of acetic anhydride, and 0.27 ml (0.003 mole) of triethylamine was refluxed for 2 h, cooled, and poured into water. The precipitate was removed by filtration and washed with water and a small amount of methanol to give 42.5% of III with mp 283-284° (from methanol). The methanol mother liquor yielded IV (40.2%) with mp 134-135° (from methanol).

2-Formamidino-3-cyano-4,5,6,7-tetrahydroindole (V). A suspension of 2 g (0.012 mole) of II in 25 ml of ethyl orthoformate was refluxed for 2 h, after which the mixture was evaporated to dryness in vacuo, and 25 ml of ethanol, saturated at 0° with ammonia, was added to the residue. The mixture was held at room temperature for 2 days, after which it was vacuum evaporated to dryness to give 2.34 g (100%) of a product with mp 320° (dec.). IR spectrum: 2200 cm^{-1} (ν_{CN}).

9-Amino-5,6,7,8-tetrahydropyrimido[4,5-b]indole (VI). A mixture of 2 g of V in 30 ml of methanol containing 0.7 g of sodium methoxide was refluxed for 1 h, after which it was vacuum evaporated to dryness to give 1.7 g (85%) of a product with mp > 360° (dec., from dimethylformamide). UV spectrum, λ_{max}, nm (log ε): 224 (inflection) (4.14), 285 (3.88). Found: C 63.7; H 6.4; N 29.9%. $C_{10}H_{12}N_4$. Calculated: C 63.8; H 6.4; N 29.8%.

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* The reaction can also be carried out in alcohol and in excess piperidine.

2,4-Dimethyl-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-*a*]indole (VII). A mixture of 0.4 g (2.4 mmole) of II, 2 ml of piperidine, and 0.25 ml (2.4 mmole) of acetylacetone was refluxed for 1 h, after which it was cooled, and the precipitate was removed by filtration and washed with methanol and ether to give 0.22 g (39.2%) of a product with mp 232-233° (from methanol). Found: C 75.0; H 6.9; N 18.8%. $C_{14}H_{15}N_3$. Calculated: C 75.6; H 6.7; N 18.6%.

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