SYNTHESIS OF 3-ACETAMIDOINDOLE DERIVATIVES

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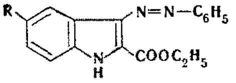
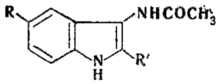
2-Carbethoxy-3-phenylazoindoles, which are reduced to 2-carbethoxy-3-acetamidoindoles, were obtained by diazo coupling of 2-carbethoxyindoles with benzene diazonium chloride. Some transformations of these compounds were studied.

Despite the definite interest in 3-aminoindole derivatives, up until now there has not been a preparative method for the synthesis of these compounds [1, 2], and 2-carbethoxy-3-acetamidoindoles have not been obtained at all. As starting compounds for the synthesis of the latter we used 2-carbethoxy-3-phenylazoindoles (I, II), which we obtained by reaction of 2-carbethoxyindoles with benzenediazonium chloride under the conditions for the diazo coupling of indole [3, 4]. The structure of I and II was confirmed by the absence of signals of the β protons of the indole ring in the PMR spectra. The reductive acetylation of I and II with zinc in acetic acid in the presence of acetic anhydride gives 2-carbethoxy-3-acetamidoindoles (III, IV).

Hydrolysis of derivatives III and IV gave 3-acetamidoindole-2-carboxylic acids (V, VI), which are converted to 3-acetamidoindoles (VII, VIII) in high yields on heating.



I–II



III–VIII

I R=H; II R=CH_3; III R=H, R′=$COOC_2H_5$; IV R=CH_3, R′=$COOC_2H_5$; V R=H, R′=COOH; VI R=CH_3, R′=COOH; VII R=H, R′=H; VIII R=CH_3, R′=H

EXPERIMENTAL METHOD

The PMR spectra of deuteroacetone solutions of the compounds were recorded with a JEOL S-60 HL spectrometer (Japan) with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The course of the reactions and the quality of the compounds obtained were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in benzene–ethyl acetate (4 : 1) and acetone–hexane (2 : 3) systems.

2-Carbethoxy-3-phenylazoindole (I). A solution of a diazonium salt obtained by the usual method [4] was added dropwise to a cooled (to −5°) solution of 36.6 g (0.194 mole) of 2-carbethoxyindole in 1 liter of dimethylformamide (DMF). During the addition of the diazonium salt solution the pH of the reaction mixture was maintained at 8.5-9.0 by the addition of a saturated aqueous sodium carbonate solution. The temperature at the instant of addition of the diazonium salt solution and for 1 h after the addition was maintained at −3 to 0°. The precipitated azo compound was removed by filtration, washed with water, dried, and recrystallized to give 36.5 g (64.5%) of I with mp 192-193° (from nitromethane). PMR spectrum, ppm: 1.4 (2-$COOCH_2\underline{CH}_3$, t*), 4.45 (2-$COO\underline{CH}_2CH_3$, q), and 11.6 (1-NH, s). Found: C 69.6; H 5.1; N 14.7%. $C_{17}H_{15}N_3O_2$. Calculated: C 69.6; H 5.1; N 14.3%.

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

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2-Carbethoxy-3-phenylazo-5-methylindole (II). This compound was similarly obtained in 58.5% yield and had mp 209-210° (from alcohol). PMR spectrum, ppm: 1.4 (2-$COOCH_2\underline{CH_3}$, t), 4.45 (2-$COO\underline{CH_2}CH_3$, q), 2.41 (5-CH_3, s), and 8.35 (1-NH, s). Found: C 70.3; H 5.6; N 13.5%. $C_{18}H_{17}N_3O_2$. Calculated: C 70.3; H 5.6; N 13.7%.

2-Carbethoxy-3-acetamidoindole (III). A total of 69 g (1.06 mole) of zinc dust was added in portions in the course of 30 min to a heated (to 90°) solution of 36.5 g (0.124 mole) of I in a mixture of 392 ml of glacial acetic acid and 29.3 g (0.29 mole) of acetic anhydride. The solution was refluxed for 1 h to complete the reaction, after which the sludge was removed by filtration and washed with hot acetic acid. The filtrate was evaporated to dryness, and the residue was washed with water, dried, and recrystallized to give 16 g (50%) of acetamidoindole III with mp 196-198° (from nitromethane). IR spectrum: 1690 (ester C=O); 1660, 1570, and 1430 (amide C=O); 750 cm^{-1}. Found: C 63.3; H 5.8; N 11.3%. $C_{13}H_{14}N_2O_3$. Calculated: C 63.4; H 5.7; N 11.4%.

2-Carbethoxy-3-acetamido-5-methylindole (IV). This compound, with mp 207.5-209° (from alcohol), was obtained in 79% yield by the method used in the preceding experiment. IR spectrum: 1690, 1660, 1340, and 800 cm^{-1}. Found: C 64.6; H 5.8; N 10.6%. $C_{14}H_{16}N_2O_3$. Calculated: C 64.6; H 6.2; N 10.8%.

3-Acetamidoindole-2-carboxylic Acid (V). A 4.44-g (0.018 mole) sample of III was refluxed with 1.15 ml (0.055 mole) of 50% potassium hydroxide and 51 ml of alcohol for 1 h, after which the solvent was removed by distillation, and the residue was diluted with 50 ml of water. The aqueous mixture was heated with activated charcoal and filtered. The filtrate was acidified with acetic acid, and the resulting precipitate was removed by filtration and washed with alcohol to give 3.33 g (82%) of acid V with mp 228-230° (dec., from acetic acid). Found: N 12.4%. $C_{11}H_{14}N_2O_3$. Calculated: N 12.8%.

3-Acetamido-5-methylindole-2-carboxylic Acid (VI). This compound was obtained under the conditions used to synthesize acid V. The yield of VI, with mp 210-211° (from 50% acetic acid), was 27%. Found: N 11.7%. $C_{12}H_{12}N_2O_3$. Calculated: N 12.0%.

3-Acetamidoindole (VII). A 3.33-g (0.015 mole) sample of acid V was heated in a flask equipped with an air condenser on a Wood's metal bath at 230-250° for 2-3 min until the evolution of gas bubbles ceased. The mixture was then cooled, and the product was recrystallized twice from water (with activated charcoal) to give 1.3 g (61%) of indole VII with mp 160-161° (from water) (mp 162-163° [1]).

3-Acetamido-5-methylindole (VIII). This compound was obtained by the method in the preceding experiment. The yield of VIII, with mp 169-170° (from 20% aqueous alcohol), was 64%. Found: C 70.2; H 6.7; N 15.0%. $C_{11}H_{12}N_2O$. Calculated: C 70.2; H 6.4; N 14.9%.

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