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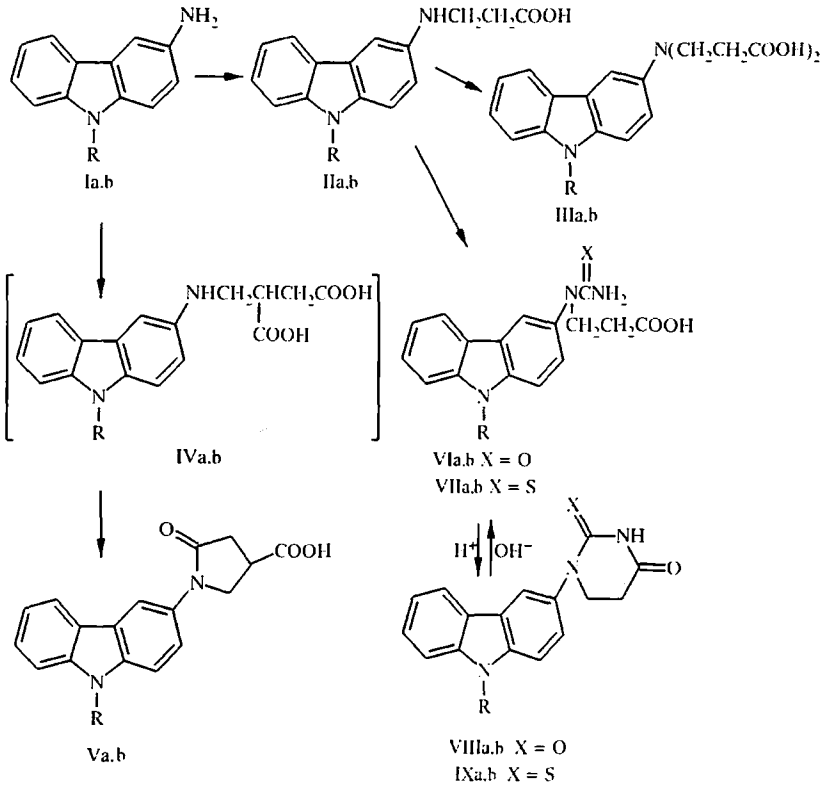
SYNTHESIS AND CYCLIZATION OF N-(9-ALKYLCARBAZOL-3-YL)-β-ALANINES

V. Mickevicius and B. Sapiyanskaite

The reaction of 3-amino-9-alkylcarbazoles with acrylic and itaconic acids yields N-substituted amino acids, which were converted into derivatives of 4-carboxy-2-pyrrolidinone and dihydropyrimidinedione.

In a continuation of a study on the synthesis and properties of N-substituted β-alanines, which are intermediates for the synthesis of heterocyclic compounds and possess biological activity [1-4], we prepared a series of compounds containing carbazole residue. N-(9-Alkylcarbazol-3-yl)-β-alanines IIa and IIb were synthesized by the nucleophilic addition of 3-amino-9-methyl- (Ia) and 3-amino-9-ethylcarbazoles (Ib) to acrylic acid. The reaction of amines Ia and Ib with acrylic acid proceeds ambigously and leads to a mixture of mono- and bisaddition products independently on the solvent and temperature. N-(9-Alkylcarbazol-3-yl)-N-carboxyethyl-β-alanines IIIa and IIIb are formed in good yield using a three-fold excess of acrylic acid relative to the amine.



Kaunas Technological University, 3028 Kaunas, Lithuania, e-mail: Vytautas.Mickevicius@ctf.ktu.lt.
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Heating 3-amino-9-alkylcarbazoles Ia,b with itaconic acid in toluene at reflux leads to 1-(9-alkylcarbazol-3-yl)-4-carboxy-2-pyrrolidinones Va,b, which are the products of cyclocondensation of intermediate 4-(9-alkylcarbazol-3-ylamino)-3-carboxybutanoic acids IVa,b, the yields being good.

Heating N-(9-alkylcarbazol-3-yl)-β-alanines IIa,b with urea in acetic acid at reflux leads to the corresponding N-carbazolyl-N-carbamoyl-β-alanines VIa,b, which are cyclized without separation under the action of hydrochloric acid to give 1-(9-alkylcarbazol-3-yl)dihydro-2,4-(1H,3H)pyrimidinediones VIIIa,b. Under analogous conditions, β-alanines IIa,b react with potassium thiocyanate to give 1-(9-alkylcarbazol-3-yl)dihydro-4-(1H,3H)pyrimidinone-2-thiones IXa,b.

Opening of the dihydrouracil ring occurs upon heating of VIIb and VIIIb in aqueous sodium hydroxide to give the corresponding sodium salts of N-carbazolyl-N-carbamoyl- and N-thiocarbamoyl-β-alanines. Free ureido acids VIb and VIIb were separated from alkaline solutions upon acidification to pH 6 by adding acetic acid. Ureido acids VI and VII are unstable in strongly acidic media and cyclize to give starting dihydropyrimidinediones VIII and IX upon heating with hydrochloric acid.

EXPERIMENTAL

The PMR spectra were taken on a Hitachi R22 spectrometer at 90 MHz with HMDS as the internal standard. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with development by UV light or iodine vapor.

N-(9-Methylcarbazol-3-yl)-β-alanine (IIa) and N-(9-Methylcarbazol-3-yl)-N-carboxyethyl-β-alanine (IIIa). Mixture of 3-amino-9-methylcarbazole (Ia) (9.8 g, 0.05 mol) and benzene (200 ml) was stirred until amine Ia was completely dissolved. Then, solution of acrylic acid (2.88 g, 0.04 mol) in benzene (30 ml) was added dropwise over 1 h and stirred for additional 8 h with formation of precipitate. The benzene layer was poured into a separatory funnel and extracted with 5% aqueous sodium hydroxide (100 ml). The alkaline solution was separated and acidified by addition of acetic acid to pH 6. The precipitate of compound IIa was filtered off and washed with water to give 5.8 g (43%) of crystalline β-alanine IIa; mp 102-103°C. PMR spectrum (CF_3CO_2H): 2.66 (2H, t, CH_2CO); 3.40 (3H, s, CH_3); 3.62 (2H, m, $NHC\underline{H}_2$); 6.6-7.9 (7H, m, H_{arom}); 8.4-8.9 ppm (2H, br. s, N^+H_2). Found, %: C 71.88; H 5.75; N 10.21. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

The pot residue was dissolved in 5% aqueous sodium hydroxide (50 ml) and filtered. The filtrate was acidified by addition of acetic acid to pH 6. The precipitate formed was filtered off and washed with water to yield 4.2 g of compound IIIa.

N-(9-Methylcarbazol-3-yl)-N-carboxyethyl-β-alanine (IIIa). Solution of amine Ia (4.9 g, 0.025 mol) and acrylic acid (5.4 g, 0.075 mol) in toluene (50 ml) was heated at reflux for 6 h and then cooled. The solvent was decanted. The residue was dissolved in 5% aqueous sodium hydroxide (50 ml) and filtered. The filtrate was brought to pH 6 by addition of acetic acid. The precipitate formed was filtered off, washed with water, and dried to give 6.1 g (72%) of compound IIIa; mp 153-154°C (dioxane). PMR spectrum (CF_3CO_2H): 2.2-2.6 (4H, m, $(CH_2CO)_2$); 3.55 (3H, s, CH_3); 3.6-4.3 (4H, m, $(NCH_2)_2$); 6.7-7.8 ppm (7H, m, H_{arom}). Found, %: C 66.84; H 5.61; N 7.99. $C_{19}H_{20}N_2O_4$. Calculated, %: C 67.04; H 5.92; N 8.23.

N-(9-Ethylcarbazol-3-yl)-β-alanine (IIb) and N-(9-Ethylcarbazol-3-yl)-N-carboxyethyl-β-alanine (IIIb) were obtained from 3-amino-9-ethylcarbazole (Ib) (10.5 g, 0.05 mol) and acrylic acid (2.88 g, 0.04 mol) by analogy to the synthesis of compound IIa. Yield of alanine IIb 9.6 g (68%); mp 136.5-137°C. PMR spectrum (CF_3CO_2H): 0.7-1.1 (3H, m, CH_3); 2.66 (2H, t, CH_2CO); 3.58 (2H, m, $NHC\underline{H}_2$); 3.94 (2H, q, J = 8 Hz, $NC\underline{H}_2CH_3$); 6.6-7.9 (7H, m, H_{arom}); 8.5-8.9 ppm (2H, br. s, N^+H_2). Found, %: C 73.45; H 6.21; N 9.15. $C_{17}H_{18}N_2O_2$. Calculated, % C 72.32; H 6.42; N 9.42. The precipitate yielded 5.6 g of compound IIIb.

N-(9-Ethylcarbazol-3-yl)-N-carboxyethyl-β-alanine (IIIb) was obtained from amine Ib (5.25 g, 0.025 mol) and acrylic acid (5.4 g, 0.075 mol) by analogy to the synthesis of compound IIIa. Yield of compound IIIb 7.7 g (87%); mp 185-187°C (dioxane). PMR spectrum (CF_3CO_2H): 0.96 (3H, t, CH_3); 2.2-2.6 (4H, m, $(CH_2CO)_2$); 3.5-4.3 (6H, m, $N(CH_2)_2$, NCH_2CH_3); 6.7-7.8 ppm (7H, m, H_{arom}). Found, %: C 67.85; H 6.54; N 7.95. $C_{20}H_{22}N_2O_4$. Calculated, %: C 67.78; H 6.26; N 7.90.

1-(9-Methylcarbazol-3-yl)-4-carboxy-2-pyrrolidinone (Va). Solution of 3-amino-9-ethylcarbazole Ia (4.9 g, 0.025 mol) and itaconic acid (6.5 g, 0.05 mol) was heated in toluene for 4 h at reflux. After cooling, the solvent was decanted and the residue was dissolved in 5% aqueous sodium hydroxide (50 ml). The alkaline solution was filtered and the filtrate was acidified to pH 1 by addition of hydrochloric acid. The precipitate formed was filtered off and washed with water to give 6.2 g (81%) of compound Va; mp 248-249.5°C (dioxane). Found, %: C 69.96; H 5.48; N 8.93. $C_{19}H_{16}N_2O_3$. Calculated, %: C 70.14; H 5.23; N 9.08.

1-(9-Ethylcarbazol-3-yl)-4-carboxy-2-pyrrolidinone (Vb) was obtained from 3-amino-9-ethylcarbazole Ib (5.25 g, 0.025 mol) and itaconic acid (6.5 g, 0.05 mol) by analogy to the synthesis of pyrrolidinone Va. Yield of compound Vb 5.8 g (72%); mp 282.5-284°C (dioxane). PMR spectrum (CF_3CO_2H): 0.98 (3H, t, CH_3); 2.95 (2H, d, J = 8 Hz, CH_2CO); 3.0-3.4 (1H, m, CH); 3.7-4.1 (4H, m, $NC\underline{H}_2CH_2$, $NC\underline{H}_2CH_3$); 6.6-7.8 ppm (7H, m, H_{arom}). Found, %: C 71.01; H 5.48; N 8.78. $C_{20}H_{18}N_2O_3$. Calculated, % C 70.79; H 5.63; N 8.69.

N-(9-Ethylcarbazol-3-yl)-N-carbamoyl-β-alanine (VIb). Mixture of dihydropyrimidinedione VIIIb (3.1 g, 0.01 mol), sodium hydroxide (2 g), and water (20 ml) was heated to reflux and left at 20°C for 20 min. The solution was filtered and acidified to pH 6. The crystalline precipitate formed was filtered off and washed with water to give 3.0 g (92%) of compound VIb; mp 285-285.5°C. PMR spectrum (DMSO-d_6): 1.17 (3H, t, CH_3); 2.42 (2H, t, CH_2CO); 3.81 (2H, t, $NC\underline{H}_2CH_2$); 4.36 (2H, q, J = 8 Hz, $NC\underline{H}_2CH_3$); 7.0-8.2 ppm (7H, m, H_{arom}). Found, %: N 12.81. $C_{18}H_{19}N_3O_3$. Calculated, %: N 12.92.

N-(9-Ethylcarbazol-3-yl)-N-thiocarbamoyl-β-alanine (VIIb) was obtained from compound IXb (3.2 g, 0.01 mol) analogously to synthesis of compound VIb. Yield of compound VIIb 3.1 g (91%); mp 273.5-274°C. PMR spectrum (DMSO-d_6): 1.29 (3H, t, CH_3); 2.3-2.85 (2H, t, CH_2CO); 3.5-4.7 (4H, m, $NC\underline{H}_2CH_2$, $NC\underline{H}_2CH_3$); 6.7-8.2 ppm (7H, m, H_{arom}). Found, %: N 12.48. $C_{18}H_{19}N_3O_2S$. Calculated, %: N 12.31.

1-(9-Methylcarbazol-3-yl)dihydro-2,4(1H,3H)-pyrimidinedione (VIIIa). Mixture of β-alanine IIa (13.4 g, 0.05 mol) and urea (6 g, 0.01 mol) in glacial acetic acid (30 ml) was heated at reflux for 12 h. Then, concentrated hydrochloric acid (15 ml) was added and the mixture was heated at reflux for additional 30 min. The mixture was diluted by adding water (120 ml). The precipitate formed was separated, washed with water, and crystallized from ethanol to give 11.2 g (76%) of compound VIIIa; mp 237.5-239°C (acetic acid). PMR spectrum (CF_3CO_2H): 2.81 (2H, t, CH_2CO); 3.41 (3H, s, CH_3); 3.92 (2H, t, NCH_2); 6.7-7.8 ppm (7H, m, H_{arom}). Found, %: C 69.98; H 5.43; N 14.15. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.61; H 5.16; N 14.33.

1-(9-Ethylcarbazol-3-yl)dihydro-2,4(1H,3H)-pyrimidinedione (VIIIb). A. Mixture of β-alanine IIb (14.1 g, 0.05 mol) and urea (6 g, 0.1 mol) in glacial acetic acid (30 ml) was heated at reflux for 12 h. Then, concentrated hydrochloric acid (15 ml) was added and the mixture was heated at reflux for additional 20 min. The product was separated out analogously to VIIIa. Yield of compound VIIIb 10.1 g (66%); mp 288-288.5°C (acetic acid). PMR spectrum (CF_3CO_2H): 1.06 (3H, t, CH_3); 2.45 (2H, t, CH_2CO); 3.7-4.2 (4H, m, $NC\underline{H}_2CH_2$, $NC\underline{H}_2CH_3$); 6.6-7.9 ppm (7H, m, H_{arom}). Found, %: C 70.25; H 5.41; N 13.48. $C_{18}H_{17}N_2O_2$. Calculated, % C 70.34; H 5.58; N 13.67.

B. Sample of N-carbamoyl-β-alanine VIb (1.6 g, 0.005 mol) was heated at reflux for 15 min in mixture of acetic acid (10 ml) and hydrochloric acid (2 ml). The mixture was diluted by addition of water (15 ml). The precipitate formed was filtered off and washed with water to give 1.3 g (85%) of compound VIIIb.

1-(9-Methylcarbazol-3-yl)dihydro-4(1H,4H)-pyrimidinone-2-thione (IXa). Mixture of β-alanine IIa (13.4 g, 0.05 mol), potassium thiocyanate (9.7 g, 0.1 mol), and acetic acid (25 ml) was heated at reflux for 12 h. Then, concentrated hydrochloric acid (15 ml) was added and the mixture was heated at reflux for additional 20 min. The mixture was diluted by addition of water (100 ml). The precipitate formed was separated, washed with water, and crystallized from ethanol to give 10.6 g (69%) of compound IXa; mp 272-273°C (acetic acid). PMR spectrum (CF_3CO_2H): 3.31 (3H, s, CH_3); 2.56 (2H, t, CH_2CO); 3.43 (2H, t, NCH_2); 6.6-8.0 (7H, m, H_{arom}); 9.13 ppm (1H, s, NH). Found, %: C 66.33; H 5.04; N 13.54. $C_{17}H_{15}N_3OS$. Calculated, %: C 66.01; H 4.89; N 13.85.

1-(9-Ethylcarbazol-3-yl)dihydro-4(1H,3H)-pyrimidinone-2-thione (IXb). A. Mixture of β-alanine IIb (14.1 g, 0.05 mol) and potassium thiocyanate (9.7 g, 0.1 mol) was heated in acetic acid (25 ml) at reflux for 12 h. Then, concentrated hydrochloric acid (15 ml) was added and the mixture was heated at reflux for additional 20 min. The product was isolated analogously to the procedure for compound IXa. Yield of compound IXb 11.5 g

(75%); mp 290-290.5°C (acetic acid). PMR spectrum (CF_3CO_2H): 1.20 (3H, t, CH_3); 2.81 (2H, t, CH_2CO); 3.7-4.2 (4H, m, $NC\underline{H}_2CH_2$, $NC\underline{H}_2CH_3$); 6.8-7.9 ppm (7H, m, H_{arom}). Found, %: C 68.54; H 5.48; N 13.11. $C_{18}H_{17}N_3OS$. Calculated, %: C 66.86; H 5.30; N 13.00.

B. Sample of N-thiocarbamoyl-β-alanine VIIb (1.7 g, 0.005 mol) in mixture of acetic acid (10 ml) and hydrochloric acid (2 ml) was heated at reflux for 15 min. After cooling, water (15 ml) was added. The precipitate formed was filtered off and washed with water to give 1.4 g (82%) of compound IXb.

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