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CYCLIZATION OF N-(2,4,6-TRIMETHYL-PHENYL)-β-ALANINES

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Reaction of 2,4,6-trimethylaniline with acrylic and itaconic acids gives the corresponding N-substituted β-alanines which can be converted to derivatives of tetrahydropyridone, dihydropyrimidinedione, and 4-carboxy-2-pyrrolidinone. Bromination of the aromatic substituent in the synthesized heterocycles has been carried out.

Keywords: dihydropyrimidinediones, N-substituted β-alanines, 4-carboxy-2-pyrrolidinones, 4(1H)-tetrahydropyridones, condensation.

One of the methods for preparing N-substituted β-amino acids, undoubtedly of interest for the synthesis of heterocyclic compounds, is the direct addition of primary amines to α,β-unsaturated acids or their derivatives [1-3]. In this work, N-(2,4,6-trimethylphenyl)-β-alanine (**2**) separated from the reaction mixture as hydrochloride was synthesized by the reaction of 2,4,6-trimethylaniline (**1**) with acrylic acid. The reaction of amine **1** with itaconic acid occurs with subsequent cyclization of the adduct 4-(2,4,6-trimethylphenylamino)-3-carboxybutanoic acid (**3**). Only 1-(2,4,6-trimethylphenyl)-4-carboxy-2-pyrrolidinone (**4**) was separated from the reaction mixture.

Condensation of β-alanine **2** with urea and potassium thiocyanate was carried out in refluxing acetic acid. The N-aryl-N-carbamoyl(thiocarbamoyl)-β-alanines **5, 6** formed in the course of the reaction were cyclized without separation to the corresponding dihydropyrimidinedione derivatives **7, 8** using concentrated hydrochloric acid. Use of a mixture of amine **1** and acrylic acid was more effective in the synthesis of 1-(2,4,6-trimethylphenyl)dihydro-2,4(1H,3H)-pyrimidinedione (**7**) or its 2-thio analog **8** without separation of the β-alanine **2** in the pure state. Compounds **7, 8** were purified by decyclization with a 5% solution of sodium hydroxide, separation of the insoluble N-substituted urea, filtration, and cyclization of the ureido acids **5, 6** using hydrochloric acid.

The N-aryl-N-carbamoyl(thiocarbamoyl)-β-alanines can be prepared in the pure state by acidification of basic solutions using acetic acid. Thus dihydropyrimidinedione **7** gave the N-carbamoyl-β-alanine **5**.

We have previously shown [4] that condensation of N-aryl-β-alanines with acetoacetic ester gives 1-aryl-3-carbethoxy-2-methyl-1,4,5,6-tetrahydro-4-pyridones, although in low yields. In this work, refluxing alanine **2** with acetoacetic ester in the presence of a catalytic amount of concentrated HCl gave the 3-carbethoxy-2-methyl-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydro-4-pyridone (**9**) and this was separated in 4.5% yield by a chromatographic method. The structure of tetrahydropyridone **9** was confirmed by ^{1}H and ^{13}C NMR spectroscopic data. Bromination of compounds **4, 7** with bromine in acetic acid at 20°C occurred in the aromatic ring to give the 1-(3-bromo-2,4,6-trimethylphenyl) derivatives **10, 11**.

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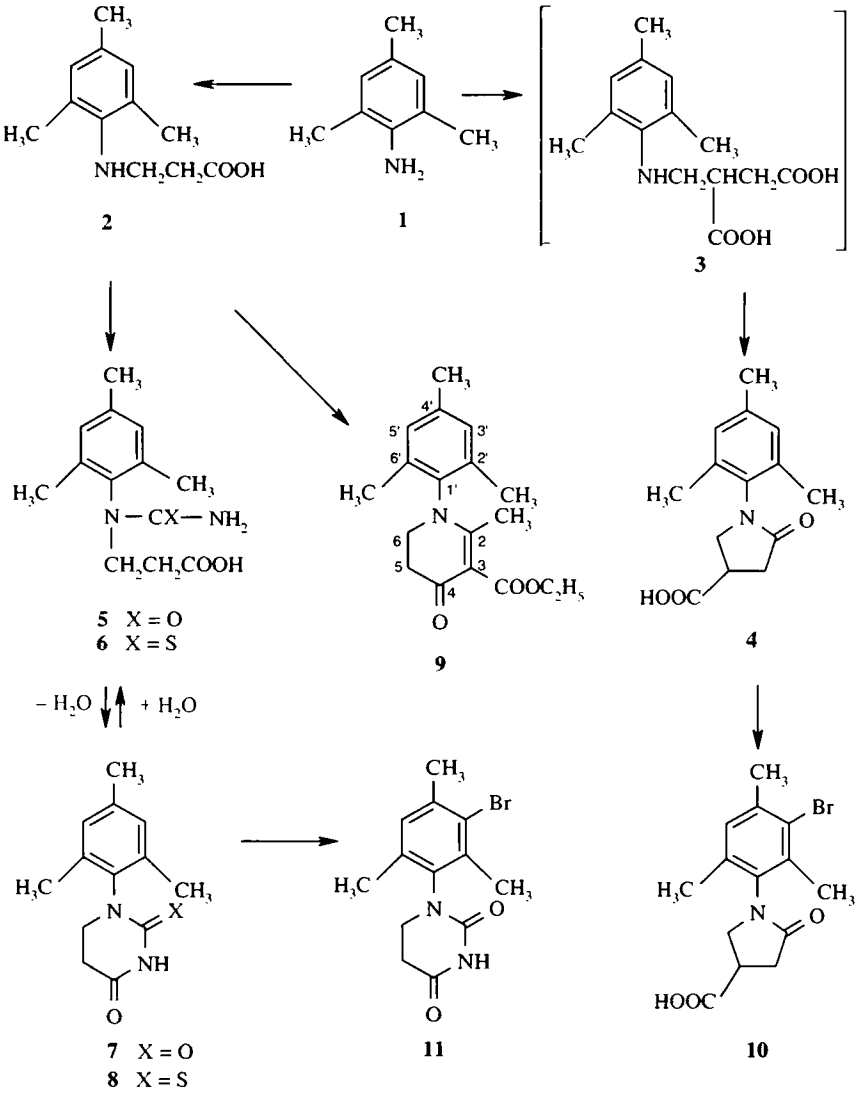

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker AC 250-P spectrometer. Chemical shifts were measured relative to an internal TMS standard. Column chromatography was performed on L 40/100 silica gel and TLC on Silufol UV-254 plates with UV light or iodine vapor visualization.

N-(2,4,6-Trimethylphenyl)-β-alanine Hydrochloride (2). 2,4,6-Trimethylaniline (**1**) (13.52 g, 0.1 mol), acrylic acid (7.2 g, 0.1 mol), hydroquinone (0.1 g), acetic acid (10 ml), and water (15 ml) were heated for 8 h at 100°C. Sodium hydroxide solution (10%, 150 ml) was added to the cooled mixture and the residue of amine **1** was extracted with diethyl ether (3 × 50 ml). The basic solution was acidified with acetic acid to pH 6 and alanine **2** was extracted with diethyl ether (3 × 70 ml). The ether extract was freeze dried (3 h at -20°C), rapidly filtered, a dry stream of HCl was passed through the filtrate to saturation, and the solution was left for 2 h at 20°C. Solvent was then decanted from the precipitate of the hydrochloride of β-alanine **2**, and the residue was thoroughly stirred with acetone (50 ml), filtered, and washed with acetone and diethyl ether. Yield 11.87 g (48.7%); mp 189-191°C

(acetic acid). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.24 (3H, s, 4-CH_3); 2.47 (6H, s, 2,6-$(CH_3)_2$); 2.95 (2H, t, α-CH_2); 3.40 (2H, t, β-CH_2); 6.98 (2H, s, ArH); 10.94 (1H, br. s, OH). Found, %: N 5.61; Cl 14.68. $C_{12}H_{17}NO_2$·HCl. Calculated, %: N 5.75; Cl 14.55.

1-(2,4,6-Trimethylphenyl)-4-carboxy-2-pyrrolidinone (4). Compound **1** (13.52 g, 0.1 mol), itaconic acid (16.25 g, 0.125 mol), and water (30 ml) were refluxed for 16 h, conc. HCl (10 ml) and water (150 ml) were added to the mixture, and the product was left for 2 h at 20°C. The separated pyrrolidinone **4** precipitate was filtered, washed with water, and recrystallized from ethanol. Yield 18.29 g (74%); mp 120-121°C. ^{1}H NMR spectrum (CF_3COOH), δ, ppm, *J* (Hz): 1.58 (6H, s, 2,6-$(CH_3)_2$); 1.67 (3H, s, 4-CH_3); 2.80 (2H, d, *J* = 7.2, CH_2CO); 3.0-3.4 (2H, m, CH); 3.61 (2H, d, *J* = 7.0, NCH_2); 6.5 (1H, s, ArH). Found, %: C 68.31; H 6.68; N 5.43 . $C_{14}H_{17}NO_3$. Calculated, %: C 68.0; H 6.93; N 5.67.

N-Carbamoyl-N-(2,4,6-trimethylphenyl)-β-alanine (5). A mixture of the pyrimidinedione **7** (2.32 g, 0.01 mol) in sodium hydroxide (5%, 10 ml) was heated to reflux and left for 2 h at 20°C. The solution was filtered, the filtrate acidified with acetic acid to pH 6, and the separated crystals of compound **5** were filtered and washed with water. Yield 1.76 g (70.3%); mp 146-148°C. Found, %: C 62.53; H 7.46; N 11.06. $C_{13}H_{18}N_2O_3$. Calculated, %: C 62.39; H 7.29; N 11.19.

1-(2,4,6-Trimethylphenyl)-5,6-dihydro-2,4(1H,3H)-pyrimidinedione (7). A. β-Alanine hydrochloride **2** (4.87 g, 0.02 mol) and urea (3 g, 0.05 mol) were refluxed in glacial acetic acid (15 ml) for 10 h, conc. HCl (10 ml) was added, and the reflux was continued for a further 30 min. The mixture was diluted with water (100 ml) and the separated crystals were filtered off and washed with water. The dry product was dissolved with warming in sodium hydroxide solution (5%, 20 ml), cooled, the insoluble admixture filtered off, the filtrate was heated to reflux, and then acidified dropwise with conc. HCl to pH 1. Reflux was continued for a further 20 min and the product was cooled, the separated crystals of **7** filtered off, and then washed with water and recrystallized from ethanol. Yield 1.09 g (23.5%); mp 219-221°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.11 (6H, s, 2,6-$(CH_3)_2$); 2.22 (3H, s, 4-CH_3); 2.70 (2H, t, 5-CH_2); 3.48 (2H, t, 6-CH_2); 6.79 (2H, s, ArH); 10.25 (1H, s, NH). Found, %: C 67.54; H 6.58; N 11.94. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.22; H 6.95; N 12.06.

B. Compound **1** (13.52 g, 0.1 mol), acrylic acid (7.2 g, 0.1 mol), hydroquinone (0.1 g), acetic acid (25 ml), and water (10 ml) were refluxed for 8 h and urea (9 g, 0.15 mol) was added. Reflux was continued for a further 12 h and the reaction mixture was acidified with conc. HCl to pH 1 and then refluxed for 20 min. The mixture was diluted with water (150 ml) and the separated precipitate was filtered off, washed with water, and dissolved in sodium hydroxide solution (5%, 150 ml). The insoluble material was separated by filtration and the filtrate was heated to reflux, cautiously acidified with concentrated HCl to pH 1, and refluxed for 15-20 min. Upon cooling, the precipitated dihydropyrimidinedione **7** was filtered and washed with water. Yield 6.44 g (27.7%).

1-(2,4,6-Trimethylphenyl)dihydro-4(1H,3H)-pyrimidinone-2-thione (8) was prepared similarly to the synthesis of the dihydropyrimidinedione **7** from β-alanine hydrochloride **2** (4.87 g, 0.02 mol) and potassium thiocyanate (3.88 g, 0.04 mol). Yield 0.96 g (19.4%); mp 225-227°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.12 (6H, s, 2,6-$(CH_3)_2$); 2.24 (3H, s, 4-CH_3); 2.78 (2H, t, 5-CH_2); 3.72 (2H, t, 6-CH_2); 6.92 (2H, s, ArH); 11.19 (1H, s, NH). Found, %: C 62.56; H 6.35; N 11.30. $C_{13}H_{16}N_2OS$. Calculated, %: C 62.87; H 6.50; N 11.28.

3-Carbethoxy-2-methyl-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydro-4(1H)-pyridone (9). β-Alanine hydrochloride **2** (12.2 g, 0.05 mol) and sodium acetate (15 g) were dissolved in water (100 ml). The solution was then extracted with diethyl ether (3 × 50 ml) and the solvent was evaporated in vacuo. The obtained N-(2,4,6-trimethylphenyl)-β-alanine was dissolved in toluene (50 ml) and there were added acetoacetic ester (13 g, 0.1 mol) and conc. HCl (4 drops). The product was refluxed for 8 h and the water evolved was removed using a Dean and Stark apparatus. Small fractions were distilled of in vacuo and the residue was treated with Na_2CO_3 solution (5%, 200 ml) and extracted with diethyl ether (3 × 70 ml). The ether extract was dried over anhydrous Na_2CO_3, the ether distilled off in vacuo, and the residue passed through an L 40/100 silica gel column collecting the fraction with R_f 0.21. The eluent was diethyl ether. Compound **9** was obtained (0.67 g, 4.5%); mp 95-97°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.20 (3H, t, $CH_2\underline{CH_3}$); 1.73 (3H, s, N–C–CH_3); 2.16 (6H, s, 2,6-$(CH_3)_2$); 2.26 (3H, s, 4-CH_3); 2.50 (2H, t, CH_2CO); 3.67 (2H, t, N–CH_2); 4.12 (2H, q, *J* = 7.2, $\underline{CH_2}CH_3$); 7.02 (2H, s, ArH). ^{13}C NMR spectrum (DMSO-d_6, 62.896 MHz): 14.12 ($\underline{CH_3}CH_2$), 17.30 (6'-CH_3), 17.30 (2'-CH_2),

17.95 (2-CH_3), 20.41 (4-CH_3), 35.34 ($C_{(5)}$), 48.48 ($C_{(6)}$), 59.40 ($\underline{CH_2}CH_3$), 105.52 ($C_{(3)}$), 129.44 ($C_{(3')}$), 129.44 ($C_{(5')}$), 134.68 ($C_{(2')}$), 134.68 $C_{(6')}$), 137.73 ($C_{(4')}$), 138.68 ($C_{(1')}$), 162.46 ($C_{(2)}$), 167.02 (COO), 186.26 ($C_{(4)}$). Found, %: C 71.93; H 7.38; N 4.55. $C_{18}H_{23}NO_3$. Calculated, %: C 71.74; H 7.69; N 4.65.

1-(3-Bromo-2,4,6-trimethylphenyl)-4-carboxy-2-pyrrolidinone (10). Pyrrolidinone **4** (2.47 g, 0.01 mol) and sodium acetate (2.52 g, 0.03 mol) were dissolved with heating in acetic acid (15 ml), cooled to 20°C, and bromine (1.1 ml, 0.02 mol) in acetic acid (5 ml) was added with stirring over 2 min. After standing for 24 h at 20°C, the mixture was diluted with water (50 ml) and the separated crystals of compound **10** were filtered and washed with water. Yield 3.10 g (95.0%); mp 133-135°C (from ethanol). ^{1}H NMR spectrum (CF_3COOH), δ, ppm, *J* (Hz): 1.50, 1.64, and 1.70 (9H, 3s, 2,4,6-(CH_3)$_3$); 2.65 (2H, d, *J* = 7.2, CH_2CO); 3.1-3.4 (1H, m, CH); 3.56 (2H, d, *J* = 7.0, NCH_2); 6.59 (1H, s, ArH). Found, %: N 4.08; Br 24.68. $C_{14}H_{15}NO_3Br$. Calculated, %: N 4.29; Br 24.50.

1-(3-Bromo-2,4,6-trimethylphenyl)dihydro-2,4-(1H,3H)-pyrimidinedione (11) was obtained similarly to the synthesis of pyrrolidinone **10** from the dihydropyrimidinedione **7** (2.32 g, 0.01 mol). Yield 1.57 g (50.5%); mp 173-175°C (ethanol). ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 1.72 and 1.85 (9H, 2s, 2,4,6-(CH_3)$_3$); 2.62 (2H, t, 5-CH_2); 3.38 (2H, t, 6-CH_2); 6.62 (2H, s, ArH); 9.05 (1H, s, NH). Found, %: N 8.95; Br 25.88. $C_{13}H_{15}BrN_2O_2$. Calculated, %: N 9.00; Br 25.68.

REFERENCES

1. J. R. Merchant and D. S. Chothia, *Indian. J. Chem.*, **12**, 351 (1974).
2. R. S. Baltrushis, V. Yu. Mitskyavichyus, I. Ch. Bilinskaite, R. M. Zolotoyabko, and E. E. Liepin'sh, *Khim. Geterotsikl. Soedin.*, No. 8, 1096 (1990).
3. V. Mitskyavichyus and B. Sapiyanskaite, *Khim. Geterotsikl. Soedin.*, No. 12, 1637 (1999).
4. V. Mickevicius and J. Bylinskaite, *Tetrahedron Lett.*, **37**, 3489 (1996).