Chemistry of Heterocyclic Compounds, Vol. 47, No. 8, November, 2011 (Russian Original Vol. 47, No. 8, August, 2011)

NOVEL THIAZOLONE DERIVATIVES OF *N*-ARYL-β-ALANINES

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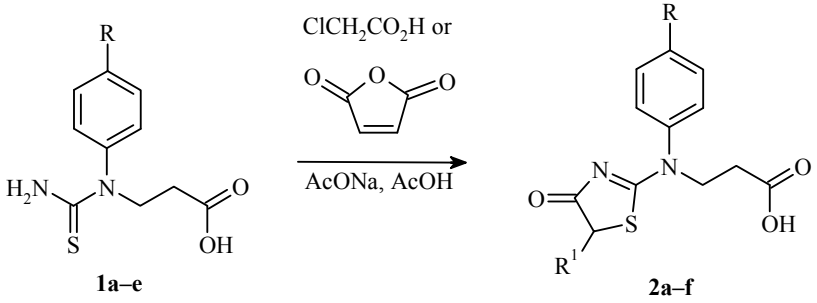
Keywords: *N*-aryl-*N*-thiocarbamoyl-β-alanines, 4-thiazolones, cyclocondensation.

Thanks to the efforts of many scientific groups in the last decade, the spectrum of pharmacological activity of 4-thiazolones has been significantly broadened. Amongst these are compounds with hypoglycemic, anticancer, anti-inflammatory, antimicrobial, antioxidant, antiviral, and antitubercular activity [1]. This has served as the basis for the synthesis and study of the named heterocycles modified by novel pharmacophoric groups with the aim of their practical use in pharmacy, medicine, agriculture, etc. One of the classical routes most often and efficiently used for the preparation of a thiazolidone ring is a [2+3] cyclocondensation reaction [2]. The reaction of the *N*-aryl-*N*-thiocarbamoyl-β-alanines **1a-e** [3] with monochloroacetic acid or maleic anhydride was carried out in acetic acid in the presence of sodium acetate to give the novel 4-thiazolone derivatives of *N*-aryl-β-alanines **2a-f**.



1a–e **2a–f**

1, 2 a, f R = H; **b** R = Me; **c** R = OMe; **d** R = NO_2; **e** R = PhNH;
2a–e R^1 = H; **f** R^1 = CH_2CO_2H

^{1}H and ^{13}C NMR spectra were recorded on a Bruker MSL-400 instrument (400 and 100 MHz respectively) at 25ºC for solutions in DMSO-d_6 and with TMS as internal standard.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1272-1274, August, 2011. Original article submitted April 21, 2011.

N-(4-Oxo-4,5-dihydro-1,3-thiazol-2-yl)-*N*-(4-R-phenyl)-β-alanines (2) (General Method). A mixture of the corresponding *N*-aryl-*N*-thiocarbamoyl-β-alanine **1** [3] (0.02 mol) and monochloroacetic acid or maleic anhydride (0.02 mol) in acetic acid (50 ml) in the presence of sodium acetate (0.02 mol) was heated at 85-90ºC for 3 h. The precipitate formed after cooling the reaction mixture was filtered off to give the novel 4-thiazolone derivatives of *N*-aryl-β-alanines **2** which were recrystallized from a 4:1 mixture of AcOH and EtOH.

***N*-(4-Oxo-4,5-dihydro-1,3-thiazol-2-yl)-*N*-phenyl-β-alanine (2a)**. Yield 68%; mp 198-199ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.72 (2H, t, *J* = 7.1, $CH_2C(O)$); 3.60 (2H, s, CH_2 thiazole); 4.03 (2H, t, *J* = 7.1, CH_2N); 7.04-7.06 (3H, m, H Ar); 7.69-7.72 (2H, m, H Ar); 10.90 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 188.2 (4-C=O); 173.9 (CO_2H); 156.5 (C-2 thiazole); 143.3 (C-1 Ar); 129.9 (C-3,5 Ar); 124.3 (C-4 Ar); 123.7 (C-2,6 Ar); 41.5 (NCH_2); 40.6 (SCH_2); 30.3 ($\underline{C}H_2CO_2H$). Found, %: C 54.61; H 4.51; N 10.71; S 12.19. $C_{12}H_{12}N_2O_3S$. Calculated, %: C 54.53; H 4.58; N 10.60; S 12.13.

***N*-(4-Methylphenyl)-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-alanine (2b)**. Yield 75%; mp 195-196ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.72 (2H, t, *J* =7.1, $CH_2C(O)$); 3.61 (2H, s, CH_2 thiazole); 4.04 (2H, t, *J* = 7.1, CH_2N); 7.20 (2H, d, *J* = 9.0, H Ar); 7.44 (2H, d, *J* = 9.0, H Ar); 10.92 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 179.7 (4-C=O); 173.7 (CO_2H); 156.1 (C-2 thiazole); 139.5 (C-1 Ar); 135.2 ($\underline{C}CH_3$); 130.6 (C-3,5 Ar); 123.1 (C-2,6 Ar); 41.8 (NCH_2); 36.1 (SCH_2); 30.2 ($\underline{C}H_2CO_2H$); 20.8 ($C\underline{C}H_3$). Found, %: C 56.15; H 5.15; N 9.99; S 11.46. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 56.10; H 5.07; N 10.06, S 11.52.

***N*-(4-Methoxyphenyl)-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-alanine (2c)**. Yield 79%; mp 189-191ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.71 (2H, t, *J* =7.1, $CH_2C(O)$); 3.62 (2H, s, CH_2 thiazole); 3.72 (3H, s, CH_3); 4.05 (2H, t, *J* = 7.1, CH_2N); 6.71 (2H, d, *J* = 9.2, H Ar); 7.02 (2H, d, *J* = 9.2, H Ar); 10.95 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 179.9 (4-C=O); 173.9 (CO_2H); 155.7 (C-2 thiazole); 155.4 (C-4 Ar); 135.6 (C-1 Ar); 126.7 (C-2,6 H Ar); 115.2 (C-3,5 Ar); 55.6 (CH_3); 41.5 (NCH_2); 36.2 (SCH_2); 30.3 ($\underline{C}H_2CO_2H$). Found, %: C 53.15; H 4.74; N 9.60; S 10.92. $C_{13}H_{14}N_2O_4S$. Calculated, %: C 53.05; H 4.79; N 9.52, S 10.89.

***N*-(4-Nitrophenyl)-*N*-(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)-β-alanine (2d)**. Yield 74%; mp 206-207ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (2H, t, *J* =7.1, $CH_2C(O)$); 3.63 (2H, s, CH_2 thiazole); 4.02 (2H, t, *J* = 7.1, CH_2N); 7.27 (2H, d, *J* = 8.9, H Ar); 8.47 (2H, d, *J* = 8.9, H Ar); 10.91 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 179.8 (4-C=O); 173.7 (CO_2H); 155.2 (C-2 thiazole); 146.7 (C-1 Ar); 142.4 (C-4 Ar); 125.1 (C-3,5 Ar); 123.8 (C-2,6 Ar); 41.2 (NCH_2); 36.0 (SCH_2); 30.1 ($\underline{C}H_2CO_2H$). Found, %: C 46.35; H 3.67; N 13.50; S 10.45. $C_{12}H_{11}N_3O_5S$. Calculated, %: C 46.60; H 3.58; N 13.59; S 10.37.

***N*-(4-Oxo-4,5-dihydro-1,3-thiazol-2-yl)-*N*-(4-(phenylamino)phenyl-β-alanine (2e)**. Yield 70%; mp 205-206ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73 (2H, t, *J* =7.1, $CH_2C(O)$); 3.61 (2H, s, CH_2 thiazole); 4.04 (2H, t, *J* = 7.1, CH_2N); 6.84-7.44 (9H, m, H Ar); 8.06 (1H, s, NH); 10.64 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 179.7 (4-C=O); 173.6 (CO_2H); 153.7 (C-2 thiazole); 146.6 (C-1' Ar); 136.8 (C-1 Ar); 136.7 (C-4 Ar); 128.8 (C-3',5' Ar); 123.4 (C-3,5 Ar); 123.3 (C-2,6 Ar); 116.9 (C-4' Ar); 113.6 (C-2',6' Ar); 41.1 (NCH_2); 36.2 (SCH_2); 30.0 ($\underline{C}H_2CO_2H$). Found, %: C 60.79; H 4.87; N 11.91; S 9.06. $C_{18}H_{17}N_3O_3S$. Calculated, %: C 60.83; H 4.82; N 11.82; S 9.02.

***N*-[5-(Carboxymethyl)-4-oxo-4,5-dihydro-1,3-thiazol-2-yl]-*N*-phenyl-β-alanine (3)**. Yield 70%; mp 223-225ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.71 (2H, t, *J* =7.1, $CH_2C(O)$); 4.02 (2H, t, *J* = 7.1, CH_2N); 3.13 (1H, dd, ^2J = 17.2, ^3J = 8.0) and 3.33 (2H, dd, ^2J = 17.2, ^3J = 6.5, CH_2); 4.53 (1H, m, CH thiazole); 7.06-7.18 (3H, m, H Ar); 7.69-7.72 (2H, m, H Ar); 10.96 (1H, s, CO_2H); 11.98 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 177.6 (4-C=O); 173.9 (CO_2H); 173.0 (CO_2H); 156.9 (C-2 thiazole); 141.5 (C-1 Ar); 131.0 (C-3,5 Ar); 126.4 (C-2,6 Ar); 125.7 (C-4 Ar); 44.3 (CHS); 42.7 ($CH\underline{C}H_2$); 41.5 (NCH_2); 30.1 ($\underline{C}H_2CO_2H$). Found, %: C 52.15; H 4.45; N 8.62; S 10.01. $C_{14}H_{14}N_2O_5S$. Calculated, %: C 52.17; H 4.38; N 8.69; S 9.95.

The work was carried out with the support of the Ministry of Education and Science of Ukraine and of Lithuania (Ukraine-Lithuania agreement M/43-2009 and Lithuania-Ukraine agreement TMP3-1/2009).

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