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LETTERS TO THE EDITOR

UNEXPECTED CYCLIZATION OF *N*-ARYL-*N*-CARBOXY-ETHYL-β-ALANINES TO 5,6-DIHYDROURACILS

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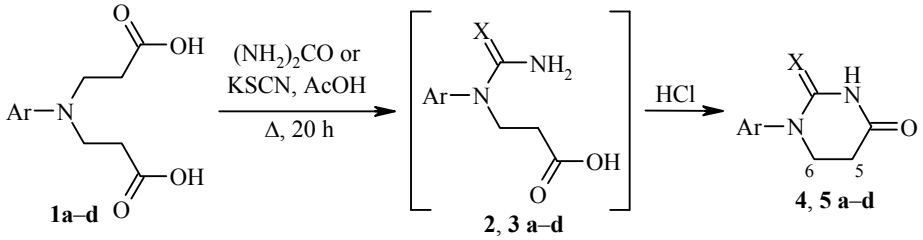
1-Substituted 5,6-dihydrouracils show certain biological activity which includes antitumor [1] and anti-retroviral [2, 3] properties. 5,6-Dihydrouracil derivatives have also been used as adrenoblocking agents [4]. It is known that 1-aryl-5,6-dihydrouracils and their 2-thio analogs are prepared by the reaction of *N*-aryl-β-alanines or their esters with urea or alkali metal thiocyanates in acidic medium [5-8]. The reactions are generally performed in refluxing acetic acid with subsequent acidification of the reaction mixture with hydrochloric acid, in order to cyclize the intermediate *N*-aryl-*N*-carbamoyl(thiocarbamoyl)-β-alanines.

We have found that *N*-aryl-*N*-carboxyethyl-β-alanines can be used in the synthesis of 1-aryl-5,6-dihydrouracils or their 2-thio analogs.



1–**5 a** Ar = 4-FC_6H_4, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-HOC_6H_4, **d** Ar = 4-$Et_2NC_6H_4$;
2, **4 a**–**d** X = O, **3**, **5 a**–**d** X = S

The reactions are carried out under the same conditions as in the synthesis of 5,6-dihydrouracils from *N*-aryl-substituted β-alanines. It is likely that initially the *N*,*N*-disubstituted amino acids **1a-d** are dealkylated to the *N*-aryl-substituted β-alanines, which are further transformed to the (thio)ureido acids **2, 3 a-d**, which readily cyclize to the derivatives **4, 5 a-d** in the presence of hydrochloric acid. The advantage of this method is the possibility of synthesizing the 1-substituted 5,6-dihydrouracils and their 2-thio analogs not only from pure *N*-aryl-substituted β-alanines, but also from their mixtures with *N*-aryl-*N*-carboxyethyl-β-alanines, which are often formed when treating aromatic amines with acrylic acid.

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^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova spectrometer (300 and 75 MHz, respectively) using DMSO-d_6 with TMS as internal standard. Elemental analysis was carried out on a CE-440 instrument (EAI Exeter Analytical, Inc.), and melting points were determined on an APA II instrument (Kleinfeld Labortechnik Gmbh).

1-Aryl-5,6-dihydrouracils 4a-d (General Method). A mixture of the corresponding *N*-aryl-*N*-carboxyethyl-β-alanine **1a-d** (10 mmol) and urea (0.90 g, 15 mmol) in glacial acetic acid (15 ml) was refluxed for 20 h, 10% HCl (40 ml) was added, and the product was refluxed for a further 30 min. The mixture was cooled, and the precipitated crystals were filtered off, washed with water, and crystallized from the corresponding solvent. In order to isolate compound **4d** from the reaction mixture, the liquid fractions were evaporated on a rotary evaporator. The residue was dissolved in water (30 ml), NaOAc (0.25 g) was added, and the mixture was stirred for 10 min. The crystals formed were filtered off, washed with water, and crystallized from MeOH.

1-(4-Fluorophenyl)-5,6-dihydrouracil (4a). Yield 0.87 g (42%). White crystals, mp 238-239ºC (EtOH) (mp 238-239ºC [6]). The ^{1}H NMR spectrum agreed with that given in the study [6].

1-(4-Bromophenyl)-5,6-dihydrouracil (4b). Yield 1.53 g (57%). Light-brown crystals, mp 228-229ºC (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.70 (2H, t, *J* = 6.6, 5-CH_2); 3.78 (2H, t, *J* = 6.6, 6-CH_2); 7.30 (2H, d, *J* = 8.7, H-2',6'); 7.57 (2H, d, *J* = 8.7, H-3',5'); 10.44 (1H, s, NH). Found, %: C 44.55; H 3.43; N 10.34. $C_{10}H_9BrN_2O_2$. Calculated, %: C 44.63; H 3.37; N 10.41.

1-(4-Hydroxyphenyl)-5,6-dihydrouracil (4c). Yield 1.18 g (57%). White crystals, mp 265-266ºC (CH_3COOH) (mp 265-266ºC [8]). The ^{1}H NMR spectrum agreed with that given in the study [8].

1-(4-Diethylaminophenyl)-5,6-dihydrouracil (4d). Yield 0.94 g (36%). Light-gray crystals, mp 183-184ºC (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (6H, t, *J* = 6.9, 2C$\underline{H}_3CH_2$); 2.67 (2H, t, *J* = 6.7, 5-CH_2); 3.32 (4H, q, *J* = 6.8, 2$CH_3C\underline{H}_2$); 3.65 (2H, t, *J* = 6.7, 6-CH_2); 6.63 (2H, d, *J* = 9.0, H-3',5'); 7.07 (2H, d, *J* = 9.0, H-2',6'); 10.22 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.3 (2$\underline{C}H_3CH_2$); 31.1 (C-5); 43.7 (C-6); 45.1 (2$CH_3\underline{C}H_2$); 111.2 (C-3',5'); 126.7 (C-2',6'); 129.9 (C-1'); 145.7 (C-4'); 152.3 (2-C=O); 170.6 (4-C=O). Found, %: C 64.42; H 7.41; N 15.95. $C_{14}H_{19}N_3O_2$. Calculated, %: C 64.35; H 7.33; N 16.08.

1-Aryl-2-thio-5,6-dihydrouracils (5a-d) (General Method). Obtained by the method for preparation of compounds **4a-d**, but using potassium thiocyanate instead of urea. Compound **5d** was isolated similarly to compound **4d**.

1-(4-Fluorophenyl)-2-thio-5,6-dihydrouracil (5a). Yield 0.94 g (42%). White crystals, mp 291-292ºC (EtOH) (mp 291-292ºC [6]). The ^{1}H NMR spectrum agreed with that given in the study [6].

1-(4-Bromophenyl)-2-thio-5,6-dihydrouracil (5b). Yield 0.88 g (31%). White crystals, mp 234-235ºC (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.81 (2H, t, *J* = 7.0, 5-CH_2); 3.90 (2H, t, *J* = 6.8, 6-CH_2); 7.34 (2H, d, *J* = 8.7, H-2',6'); 7.64 (2H, d, *J* = 8.7, H-3',5'); 11.33 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 30.3 (C-5); 48.5 (C-6); 120.2 (C-4'); 129.4 (C-2',6'); 131.9 (C-3',5'); 144.2 (C-1'); 166.9 (C=O); 179.4 (C=S). Found, %: C 42.21; H 3.09; N 9.91. $C_{10}H_9BrN_2OS$. Calculated, %: C 42.12; H 3.18; N 9.82.

1-(4-Hydroxyphenyl)-2-thio-5,6-dihydrouracil (5c). Yield 1.62 g (73%). White crystals, mp 309-311ºC (DMSO) (mp 309-311ºC [8]). The ^{1}H NMR spectrum agreed with that given in the study [8].

1-(4-Diethylaminophenyl)-2-thio-5,6-dihydrouracil (5d). Yield 0.64 g (23%). Yellow crystals, mp 206-207ºC (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (6H, t, *J* = 6.9, 2C$\underline{H}_3CH_2$); 2.76 (2H, t, *J* = 6.9, 5-CH_2); 3.34 (4H, q, *J* = 6.9, 2$CH_3C\underline{H}_2$); 3.83 (2H, t, *J* = 6.9, 6-CH_2); 6.63 (2H, d, *J* = 8.9, H-3',5'); 7.07 (2H, d, *J* = 8.9, H-2',6'); 11.10 (1H, s, NH). Found, %: C 60.72; H 6.81; N 15.07. $C_{14}H_{19}N_3OS$. Calculated, %: C 60.62; H 6.90; N 15.15.

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