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SHORT COMMUNICATIONS

Synthesis of New Derivatives of 6-(1-Adamantylmethyl)-4(3*H*)-pyrimidinone

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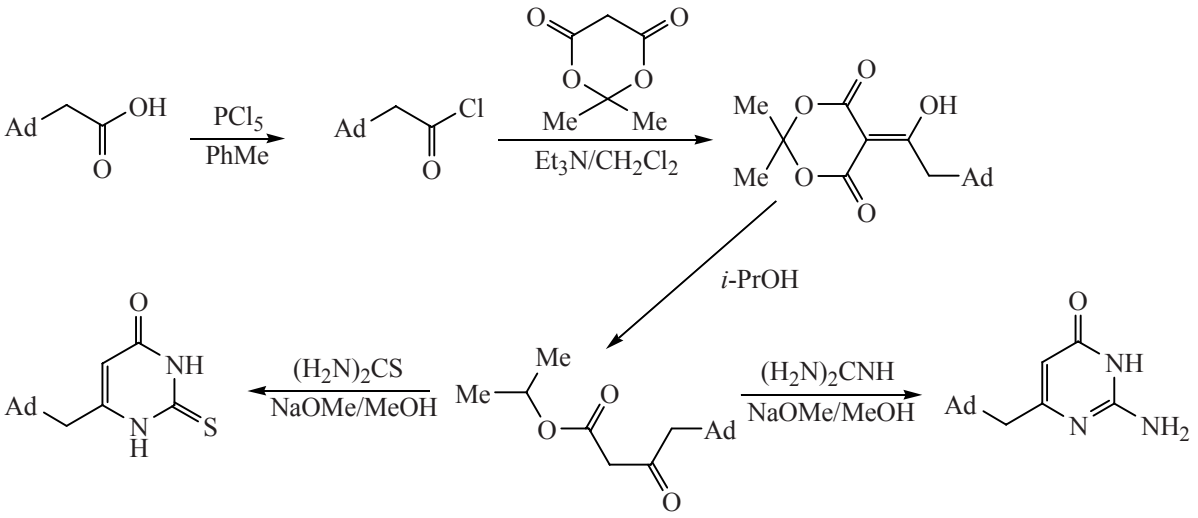
Many 6-(arylmethyl)-2-thiouracil derivatives are endowed with a pronounced anti-HIV-1 activity [1]. In this connection their analogs were synthesized, probable anti-HIV-1 agents, new derivatives of 6-(1-adamantylmethyl)-4(3*H*)-pyrimidinone: 6-(1-adamantylmethyl)isocytosine and 6-(1-adamantylmethyl)-2-thiouracil. The synthesis was performed starting with 2-(1-adamantyl)acetic acid.

Under treatment with phosphorus pentachloride the 2-(1-adamantyl)acetic acid was converted into the acid chloride that was used for acylation of 2,2-dimethyl-1,3-dioxane-4,6-dione. After the alcoholysis of the acylation product we obtained 3-oxoester that was converted into the corresponding derivatives of 4(3*H*)- pyrimidinone by the condensation with guanidine or thiourea in basic medium.



Due to the low reactivity of the 2-(1-adamantyl)acetyl chloride we failed to obtain the isopropyl 4-(1-adamantyl)-3-oxobutanoate by the previously described method [2]. using Et_3N (pK_{BH^+} 10.57, did not undergo quaternization with acyl halides) as the base instead of Py (pK_{BH^+} 5.23, underwent quaternization with acyl halides) and prolonging the reaction time made it possible to obtain the isopropyl 4-(1-adamantyl)-3-oxobutanoate in 62% yield.

Owing to strong shielding of the carbonyl group of the 3-oxoester with the adamantly fragment and to the positive inductive effect of the adamantly moiety that decreased the CH-acidity and capability to enolization of the corresponding 3-oxoester the previously described methods [3] failed to yield the desired derivatives of 2-thiouracil and isocytosine. However the application of a solvent of a higher dielectric permittivity (MeOH instead

of EtOH) and of a larger amount of base (3 equiv instead of 2 equiv) afforded the target derivatives of 4(3*H*)-pyrimidinone in high yields. This result followed from the increased reaction rate owing to the higher permittivity of the medium, and also from the higher concentration of the enolate of the initial 3-oxoester.

2-(1-Adamantyl)acetylchloride. A mixture of 10.28 g (53.0 mmol) of 2-(1-adamantyl)acetic acid, 50 ml of anhydrous PhMe, and 12.15 g (58.3 mmol) of PCl_5 was boiled for 2 h. The solvent was removed at a reduced pressure. The residue was purified by distillation in a vacuum. Yield 9.70 g (86%), bp 110–111°C (2 mm Hg).

Isopropyl 4-(1-adamantyl)-3-oxobutanoate. To a solution of 7.48 g (51.9 mmol) of 2,2-dimethyl-1,3-dioxane-4,6-dione in 20 ml of anhydrous CH_2Cl_2 at 0°C was dropwise added while stirring within 30 min 17.5 ml (12.71 g, 125.6 mmol) of anhydrous Et_3N. Then at 0°C was dropwise added while stirring within 2–2.5 h a solution of 10.70 h (50.3 mmol) of 2-(1-adamantyl)acetyl chloride in 15 ml of anhydrous CH_2Cl_2, and then the reaction mixture was left overnight. Afterwards it was diluted with 25 ml of CH_2Cl_2 and washed with 10% water solution of citric acid (200 ml). The organic layer was separated, the water layer was extracted with CH_2Cl_2 (2×25 ml). The combined organic solutions were additionally washed with 10% water solution of citric acid (100 ml) and with water, and dried with anhydrous Na_2SO_4. On removing the solvent in a vacuum the residue was mixed with anhydrous *i*-PrOH (100 ml) and boiled for 3.5 h under protection from moisture. The solvent was removed under a reduced pressure, and the residue was distilled in a vacuum. Yield 8.69 g (62%), bp 163–165°C (1.5 mm Hg). IK spectrum (thin film), cm^{-1}: 1270 [C(O)OR], 1455 (CH_2), 1710 (C=O), 2850 (CH_2), 2900 (CH_2). Mass spectrum, *m/z* (I_{rel} %): 278 (1.4) $[M]^+$, 235 (1.5), 219 (1.5), 191 (1.3), 177 (5.7), 149 (3.6), 135 (100), 107 (7.1). Found, %: C 73.29; H 9.46. M^+ 278. $C_{17}H_{26}O_3$. Calculated, %: C 73.34; H 9.41. *M* 278.39.

6-(1-Adamantylmethyl)-2-thiouracil. A solution of 16.2 g (150 mmol) of NaOMe, 7.61 g (100 mmol) of $(H_2N)_2CS$, and 13.9 g (50 mmol) of isopropyl 4-(1-adamantyl)-3-oxobutanoate in 50 ml of anhydrous MeOH was boiled at stirring for 24 h, methanol was distilled off in a vacuum on a steam bath, and the residue was dissolved in 200 ml of water, and the solution was filtered. The water filtrate was acidified to pH 3–4 with 1 N AcOH. The separated precipitate was filtered off, washed with water (100 ml), and dried in air. Yield 10.56 g (77%), mp 303–304°C (ACOH). IR spectrum (KBr), cm^{-1}: 1155 (C–O), 1195 (C=S), 1550 (NH), 1660 (C=O), 2850 (CH_2), 2900 (CH_2), 3150 (NH), 3200 (NH), 3450 (NH). ^{1}H NMR spectrum, ppm: 1.48–1.64 m (12H, 6CH_2), 1.91 s (3H, 3CH), 2.14 s (2H, CH_2), 5.52 s (1H, CH), 11.90 s (1H, NH), 12.26 s (1H, NH). Mass spectrum, *m/z* (I_{rel} %): 276 (34.6) $[M]^+$, 149 (0.77), 135 (100), 113 (5.4), 107 (9.2), 93 (20.8), 79 (27.7), 67 (12.2). Found, %: C 65.20; H 7.30; N 10.11. M^+ 276. $C_{15}H_{20}N_2OS$. Calculated, %: C 65.18; H 17.29; N 10.14. *M* 276.40.

6-(1-Adamantylmethyl)isocytosine. A mixture of a solution of 3.29 g (60.9 mmol) of NaOMe in 30 ml of anhydrous MeOH, 4.2 g (31.6 mmol) of guanidine propionate, and 5.56 g (20 mmol) of isopropyl 4-(1-adamantyl)-3-oxobutanoate was boiled for 24 h, the solvent was distilled off, and the residue was mixed with water (200 ml), acidified with 1 N AcOH to pH 6, and filtered. Yield 4.41 g (85%), mp >350°C (DMSO). IR spectrum (KBr), cm^{-1}: 1380 (CH), 1455 (CH), 1510 (NH), 1660 (C=O), 2900 (CH_2), 3080 (NH), 3350 (NH). ^{1}H NMR spectrum, ppm: 1.53–1.67 m (12H, 6CH_2), 1.92 s (3H, 3CH), 2.04 s (2H, CH_2), 5.30 s (1H, CH), 6.24 s (2H, NH_2), 10.46 br.sC (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 259 (100) $[M]^+$, 243 (2.6), 216 (4.0), 202 (8.6), 149 (3.3), 135 (60.3), 129 (28.5), 107 (7.9). Found, %: C 69.49; H 8.14; N 16.19. M^+ 259. $C_{15}H_{21}N_3O$. Calculated, %: C 69.47; H 8.16; N 16.20. *M* 259.35.

IR spectra were recorded on a spectrophotometer Perkin-Elmer 580. ^{1}H NMR spectra of compounds obtained were registered on a spectrometer Bruker DRX-500 at operating frequency 500.13 MHz in DMSO-d_6, internal reference HMDS. Mass spectra were measured on a GC-MS instrument Varian MAT-111 at direct admission of the sample into the ion source, in electron impact mode (70 eV). The melting points were measured on MelTemp 3.0 device, heating rate 10 deg/min. The homogeneity of compounds obtained was confirmed by TLC on Sorbfil plates, spots visualization under UV irradiation.

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