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SYNTHESIS OF NOVEL N^2-ADAMANTYL DERIVATIVES OF 2-AMINO-6-METHYL-4(3H)-PYRIMIDINONE AS POTENTIAL ACTIVATORS OF TUMOR NECROSIS FACTOR (TNF) RELEASE

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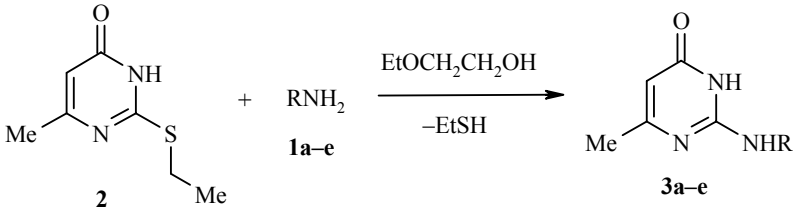
A method has been developed for the synthesis of N^2-adamantyl-2-amino-6-methyl-4(3H)-pyrimidinones based on the reaction of (adamant-1-yl)alkylamine with 2-(ethylsulfanyl)-6-methyl-4(3H)-pyrimidinone which can lead to the corresponding derivatives in which the exocyclic nitrogen atom and the adamantyl radical are separated by a hydrocarbon fragment.

Keywords: (adamant-1-yl)alkylamines, 2-(adamant-1-yl)alkylamino-6-methyl-4(3H)-pyrimidinones, 2-(ethylsulfanyl)- 6-methyl-4(3H)-pyrimidinone, aminolysis.

2-(1-Adamantylamino)-substituted hetarenes show interest as inducers of the release of tumor necrosis factor [1]. Hence they can be considered as potential agents for the immunotherapy of malignant tumors. As was shown by a group of Polish investigators the most active are the corresponding 6-methylpyrimidine [2] and 6-methylpyridine [3] derivatives, some of which have reached preclinical stage investigation. Hence the synthesis and study of novel members of this series of substances is a current goal.

The preparation of these compounds by the reaction of aminohetarenes with 1-adamantanol in the presence of trifluoroacetic acid (needed to generate the adamantyl cation *in situ*) has been reported [1, 2]. However this method does not permit the synthesis of the corresponding adamantyl derivatives in which the adamantane ring and the amino group are separated by a hydrocarbon fragment.



1, 3 a R = 1-AdCH$_2$, **b** R = 1-AdCH(Et), **c** R = 1-Ad(CH)Ph, **d** R = 1-AdCH$_2$CH$_2$, **e** R = 1-AdCH$_2$CH(Me)

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With the aim of synthesizing adamantyl-substituted aminohetarenes we have studied the reaction of a series of adamantane-containing amines **1a-e** with 2-(ethylsulfanyl)-6-methyl-4(3H)-pyrimidinone (**2**) (prepared as in [4]) and we have shown that the corresponding 2-[(1-adamantyl)alkyl]-6-methyl-4(3H)-pyrimidinones **3a-e** are formed.

The reactions were carried out by refluxing components **1** and **2** in 2-ethoxyethanol medium. The latter was used in view of its high dielectric permittivity, boiling point, and ability specifically to solvate the transition states of a series of ionic reactions.

We have shown that, while in the case of adamantylalkylamines **1a-e** the yield of the target compounds reaches 37-82%, for 4-(1-adamantyl)aniline the target compound could not be prepared, evidently connected with the markedly lower basicity and nucleophilicity of this amine when compared with the rest.

At the same time, for aliphatic amines the maximum yield is observed in cases where the amino group and the adamantane fragment were separated by a two-carbon bridge (amines **1d,e**) whereas in the 1-adamantylmethylamine derivatives **1a,b** the yield of the corresponding pyrimidinones **3a,b** was much lower. This can also be explained by the fact that the basicity of amine **1d** (pK_a of the conjugated acid 16.84 [5]) is greater than the amine **1e** (16.41). The basicities of amines **1a** and **1b** (pK_a of the conjugated acid 16.22 [5] and 16.00 respectively) are lower than amines **1d,e**. One exception is the amine **1c** in which the greater yield of the target derivative **3c** is explained by the much lower solubility and related loss upon purification.

We propose that the reaction has the character of a solvolytic fission of the starting **2**. This is indirectly confirmed by the fact that an iminothioether element is present in its chemical structure which governs its ability to undergo nucleophilic attack at the $C_{(2)}$ atom of the pyrimidine heterocycle. Such a hypothetical mechanism is indirectly confirmed by literature data for the nucleophilic substitution of the methoxy group in 2-methoxy-4(3H)-pyrimidinones in the presence of potassium alkoxide in the corresponding anhydrous alcohol medium [6-8]. The higher reactivity of thio analogs of these materials evidently determines their susceptibility to solvolytic fission by amines, having a lower basicity and nucleophilicity when compared with potassium alkoxide.

This proposal for the reaction mechanism is also confirmed by the fact that, if carried out in the absence of solvent (aiding the dissociation of the amine and pyrimidinone **2**) a sharp lowering of the yield of the target derivatives **3** is seen and a marked tarring of the reaction mixture occurs. Similarly, lowering of the yield of the target products occurs when changing 2-ethoxyethanol for 1,2-dimethoxyethane (a lower boiling solvent with a lower dielectric permittivity).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 300B (300 MHz) instrument with HMDS (δ 0.05 ppm) as internal standard. Melting points were determined on a MelTemp 3.0 instrument at a heating rate of 10°C/min. The basicities of the amines **1b,c,e** were determined by potentiometric titration using a reported method [5].

2-[1-(1-Adamantyl)propyl]amino-6-methyl-4(3H)-pyrimidinone (3b). A mixture of the pyrimidinone **2** (2 g, 11.7 mmol), amine **1b** (4.5 g, 23.6 mmol) and $EtOCH_2CH_2OH$ (10 ml) was refluxed for 6 days, solvent was distilled off under vacuum, and the residue was divided between $CHCl_3$ (120 ml) and a 10% aqueous solution of citric acid (pH 4). The organic phase was separated, washed with water (3 × 50 ml) and $NaHCO_3$ solution (50 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a Merck Kieselgel 60 silica gel (40-60 μm, 40 g) using C_6H_{14}–AcMe–EtOH (12:3:1) as eluent. The eluates containing the target material were combined and evaporated in a vacuum and the residue was crystallized twice from C_6H_{14}. Yield 1.3 g (37%); mp 217-219°C (C_6H_{14}). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 0.86 (3H, t, *J* = 7.3, CH_3); 1.13-1.24 (2H, m, CH_2); 1.56 (6H, s, CH_2 (adamantane)); 1.62 (6H, s, CH_2 (adamantane)); 1.94

(3H, s, CH (adamantane)); 2.05 (3H, s, CH_3); 3.66 (1H, t, J = 9.8, CH); 5.27 (1H, s, 5-CH); 7.02 (1H, d, J = 9.2, $N_{(2)}H$); 10.81 (1H, s, $N_{(3)}H$). Found, %: C 72.20; H 9.00; N 13.67. $C_{18}H_{27}N_3O$. Calculated, %: C 71.72; H 9.03; N 13.94.

2-(1-Adamantylmethyl)amino-6-methyl-4(3H)-pyrimidinone (3a) was prepared similarly to compound **3b** from amine **1a** and pyrimidinone **2** (duration of refluxing 3 days). Yield 46%; mp 244-246°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 1.40 (6H, d, J = 9.8, CH_2 (adamantane)); 1.65-1.49 (6H, m, CH_2 (adamantane)); 1.90-1.95 (6H, m, CH_3, CH (adamantane)); 2.94 (2H, s, CH_2); 5.32 (1H, d, J = 9.8, 5-CH); 6.27 (1H, s, $N_{(2)}H$); 10.22 (1H, d, $N_{(3)}H$). Found, %: C 70.50; H 8.47; N 15.01. $C_{16}H_{23}N_3O$. Calculated, %: C 70.30; H 8.48; N 15.37.

2-[(1-Adamantyl)(phenyl)methyl]amino-6-methyl-4(3H)-pyrimidinone (3c) was prepared from amine **1c** and pyrimidine **2** similarly to **3b**. Yield 64%; mp 297-299°C, decomp. (DMSO–water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 1.34-1.45 (6H, m, CH_2 (adamantane)); 1.50-1.57 (6H, m, CH_2 (adamantane)); 1.86 (3H, s, CH (adamantane)); 1.89 (3H, s, CH_3); 4.65 (1H, d, J = 9.4, CH); 5.34 (1H, s, 5-CH); 7.11-7.28 (6H, m, C_6H_5, $N_{(2)}H$); 10.23 (1H, br. s, $N_{(3)}H$). Found, %: C 76.00; H 7.80; N 11.84. $C_{22}H_{27}N_3O$. Calculated, %: C 75.61; H 7.79; N 12.02.

2-[2-(1-Adamantyl)ethyl]amino-6-methyl-4(3H)-pyrimidinone (3d) was prepared from amine **1d** and the pyrimidinone **2** similarly to compound **3b** (duration of refluxing 3 days). Yield 82%; mp 185-187°C, decomp. (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 1.23 (2H, t, J = 7.9, CH_2); 1.45 (6H, s, CH_2 (adamantane)); 1.60 (6H, dd, J_1 = 12.2, J_2 = 8.6, CH_2 (adamantane)); 1.88 (3H, s, CH (adamantane)); 1.97 (3H, s, CH_3); 3.19 (2H, br. s, CH_2); 5.35 (1H, s, 5-CH); 6.25 (1H, s, $N_{(2)}H$); 10.37 (1H, br. s, $N_{(3)}H$). Found, %: C 70.88; H 8.75; N 14.55. $C_{17}H_{25}N_3O$. Calculated, %: C 71.04; H 8.77; N 14.62.

2-[1-(1-Adamantyl)-2-propyl]amino-6-methyl-4(3H)-pyrimidinone (3e) was prepared from amine **1e** and pyrimidinone **2** similarly to compound **3b** (duration of refluxing 4 days). Yield 52%; mp 209-211°C (EtOH). ^{1}H NMR spectrum (CCl_4), δ, ppm (J, Hz): 1.13 (3H, d, J = 6.11, CH_3); 1.21-1.39 (2H, m, CH_2); 1.50-1.65 (12H, m, CH_2 (adamantane)); 1.90 (3H, s, CH (adamantane)); 2.12 (3H, s, CH_3); 4.13 (1H, br. s, CH); 5.39 (1H, s, 5-CH); 6.80 (1H, d, J = 6.7, $N_{(2)}H$); 10.82 (1H, br. s, $N_{(3)}H$). Found, %: C 72.00; H 9.03; N 13.89. $C_{18}H_{27}N_3O$. Calculated, %: C 71.72; H 9.03, N 13.94.

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