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SYNTHESIS AND REACTIONS OF METHYL 3-(1-ADAMANTYL-CARBONYL)-4,5-DIHYDRO-1H-PYRAZOLE-5-CARBOXYLATE

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The 1,3-dipolar addition of 1-(1-adamantyl)-2-diazoethanone to methyl acrylate gave methyl 3-(1-adamantylcarbonyl)-4,5-dihydro-1H-pyrazole-5-carboxylate from which there were prepared methyl 3-(1-adamantylcarbonyl) substituted 4,5-dihydroisoxazole-5- and 1H-pyrazole-5-carboxylates as well as the products of reduction of the latter at the keto- and ester groups.

Keywords: 1-(1-adamantyl)-2-diazoethanone, methyl acrylate, methyl 3-(1-adamantylcarbonyl)-4,5-dihydroisoxazole-5-carboxylate, methyl 3-(1-adamantylcarbonyl)-4,5-dihydro-1H-pyrazole-5-carboxylate, methyl 3-(1-adamantylcarbonyl)-1H-pyrazole-5-carboxylate, 1,3-dipolar cycloaddition.

The development of methods for preparing novel adamantane derivatives is a current problem since representatives of this class of compound have a broad spectrum of physiological activity (psychostimulating, immunostimulating, anticancer, analgesic) and are used in medical practice as antiviral, anti-parkinsonian, and other preparations [1-4]. It is known that adamantyl-substituted pyrazole shows high antibacterial activity and is of interest as a chemotherapeutic agent [2].

The 1,3-dipolar cycloaddition of diazo derivatives to unsaturated compounds [5, 6] shows promise in the synthesis of five membered nitrogen heterocycles and this opens up broad possibilities for preparing novel, practically important polyfunctional materials of different structure. This methodology was used by us in the case of the synthesis of 3-aminopyrrolidin-2-ones, dihydrooxazolines, and 1,3-propylenediamines of the norbornane series [7-10].

With the aim of preparing compounds containing a nitrogen heterocycle and an adamantane fragment we have, for the first time, in this work studied the 1,3-dipolar cycloaddition of 1-(1-adamantyl)-2-diazoethanone (**1**) to methyl acrylate. On the basis of the methyl 3-(1-adamantylcarbonyl)-4,5-dihydro-1H-pyrazole-

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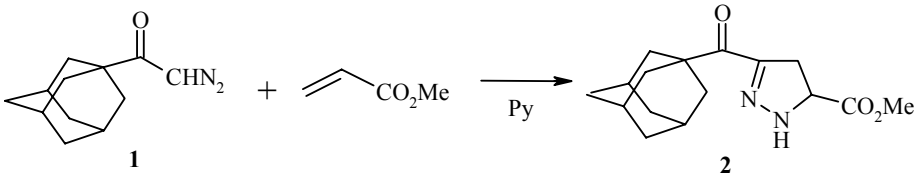
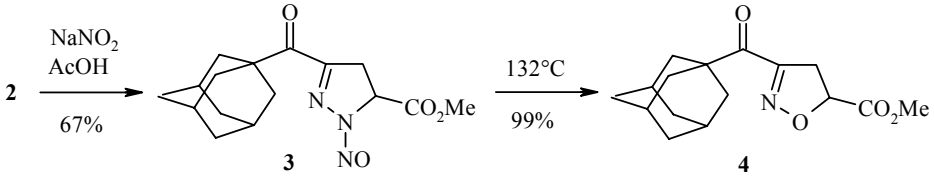
5-carboxylate obtained (**2**) we have carried out the synthesis of some other pyrazoline and pyrazole derivatives. It should be noted that this study is of interest in a scheme for developing novel routes to preparing amino acids of non natural derivation.

Based on the results of these experiments carried out under different conditions it was found that the solvent proves to have a decisive role on the nature of the reaction of diazoethanone **1** with methyl acrylate. Hence benzene as solvent gives a hard to separate mixture of products but use of pyridine solvent (successfully employed as catalyst in similar reactions [11, 12]) leads to a decrease in the reaction time and a more selective reaction process leading to the target ester **2**. The ratio of starting reagents markedly affects the yield, the highest yield (94%) being achieved with a five fold molar excess of methyl acrylate (pyridine, 60ºC, 12 h).



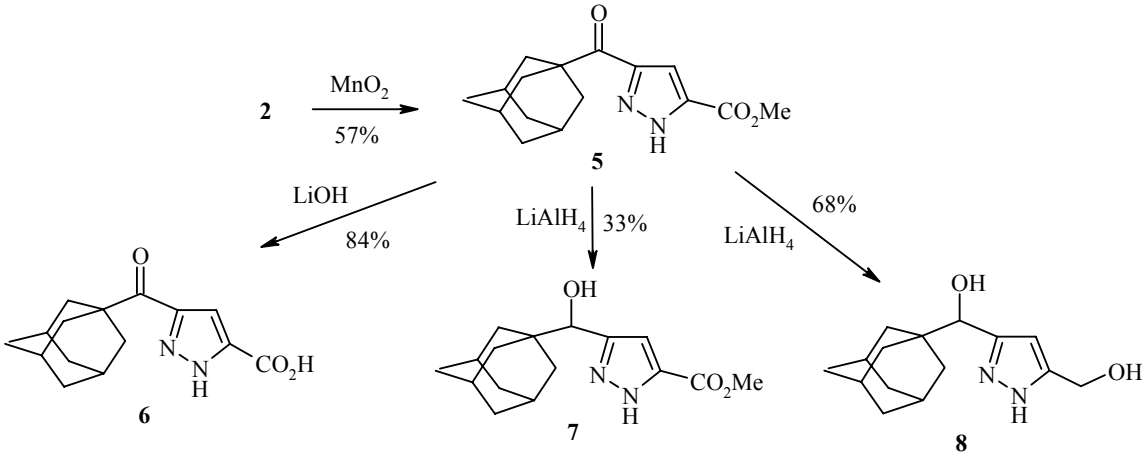
1 **2**

Treatment of the pyrazoline **2** with nitrosonium cation generated from reaction of $NaNO_2$ with AcOH at 0ºC gives the methyl 3-(1-adamantylcarbonyl)-1-nitroso-4,5-dihydro-1H-pyrazole-5-carboxylate (**3**) in 67% yield. Refluxing the ester **3** in chlorobenzene for 2 h caused the pyrazoline ring to change to a dihydroisoxazoline in 99% yield to form the methyl 3-(1-adamantylcarbonyl)-4,5-dihydroisoxazole-5-carboxylate (**4**).



3 **4**

Dehydrogenation of the pyrazoline ring of ester **2** with excess MnO_2 in benzene at room temperature gave a 57% yield of the methyl 3-(1-adamantylcarbonyl)-1H-pyrazole-5-carboxylate (**5**). Hydrolysis of ester **5** using LiOH gave an 84% yield of 3-(1-adamantylcarbonyl)-1H-pyrazole-5-carboxylate (**6**) which can be regarded as an amino acid of non natural derivation and is of great pharmacological interest.



6 **7** **8**

Treatment of pyrazole **5**, which contains keto and ester groups in the molecule, with an equimolar amount of $LiAlH_4$ in ether reduces the keto group and gives a 33% yield of methyl 3-[1-adamantyl-(hydroxy)methyl]-1H-pyrazole-5-carboxylate (**7**).

The use of a 4.6 fold molar excess of $LiAlH_4$ led to reduction of the ester function as well to give the 3-[1-adamantyl(hydroxyl)methyl]-5-hydroxymethyl-1H-pyrazole (**8**) in 68% yield. It should be noted that formation of products of hydrogenation of the pyrazole ring (pyrazolines or pyrazolidines) was not observed in any of the experiments.

The structures of the compounds **2-8** obtained were confirmed from IR and ^1H and ^{13}C NMR spectroscopic data. Hence the IR spectrum of pyrazoline **2** has absorption bands at 1560, 1640, 1740, and 3200-3450 cm^{-1} which are characteristic of the pyrazoline ring, and C=O, CO_2, and NH_2 groups [13]. The structures of pyrazoles **5-8** were proved by the presence of bands for the pyrazole fragment (1377-1610 cm^{-1} region [13]) and the NH and OH groups (3050-3450 cm^{-1} region).

The composition and structure of the novel compounds **2-8** were also confirmed by high resolution mass spectroscopic data and by IR and NMR spectroscopic data. The IR spectra contain absorption bands for the CO, CO_2, and OH substituent in these compounds and also by a set of signals characteristic of their heterocycles [13] (see Experimental section). The ^1H NMR spectra of pyrazolines **2, 3** agree with those of known 4,5-dihydro-1H-pyrazoles [14-16]. They show two signals for the H-4 ring protons each as double doublets and a similar form for the H-5 proton signal at lower field. The ^{13}C NMR spectra of compounds **2, 3** show the C-4 and C-5 atom signals at 35.3-36.8 and 57.4-59.6 ppm respectively. In the case of isoxazoline **4** the signal for the H-4 proton appears as a doublet and that of H-5 as a triplet, evidently as a result of superpositioning of the signals due to the closeness of their chemical shifts. The signals for atoms C-4 and C-5 are found at 38.69 and 77.69 ppm, i.e. shifted (particularly for the C-5 signal) to lower field relative to the analogous signals for the nitrogen analog **2**. The ^1H NMR spectra of the pyrazoles **5-8** clearly show the effect of a substituent in positions 3 and 5 on the chemical shift of the H-4 protons. Its signal in the spectra of **5-8** is shifted to high field from 7.43 to 5.97 ppm. It should also be noted that this signal is broadened with the presence in position 5 of a COOH (compound **6**) or CH_2OH substituent (compound **8**).

Hence we have developed methods for the synthesis of adamantyl substituted five membered nitrogen heterocyclic compounds as synthons for the preparation of novel, physiologically active materials.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz respectively) with TMS as internal standard. IR spectra were taken on a Specord M82-63 instrument as a thin film or in vaseline oil. Melting points were measured on a Boetius microstage. TLC analysis was preformed on Merck silica gel plates and preparative separations on a silica gel 60 column (70-230 mesh) from the Lancaster company. The solvents used in this work (Et_2O, CH_2Cl_2, benzene, hexane, pyridine, petroleum ether, THF, and AcOEt) were purified by a standard method [17]. The diazoethanone **1** used was synthesized by a known method [18].

Methyl 3-(1-Adamantylcarbonyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (2). A solution of 1-(1-adamantyl)-2-diazoethanone (**1**) (1.35 g, 6.6 mmol) and methyl acrylate (2.8 g, 33 mmol) in pyridine (4.7 ml) was held at 60ºC for 12 h. Pyridine and unreacted methyl acrylate were removed at reduced pressure to give ester **2** (1.81 g, 94%) as a light-brown oil. IR spectrum, ν, cm^{-1}: 1230, 1450, 1560 (C=N), 1640 (CO), 1740 (CO_2), 2850-3090, 3200-3450 (N–H). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.74 (6H, br. s, δ-Ad); 2.05 (9H, br. s, γ-H Ad, β-H Ad); 3.10 (1H, dd, J_{gem} = 17.5, *J* = 12.4, H-4); 3.25 (1H, dd, J_{gem} = 17.5, *J* = 5.5, H-4); 3.75 (3H, s, CH_3); 4.33 (1H, dd, *J* = 5.5, *J* = 12.4, H-5); 6.70 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.10 (γ-C Ad); 35.34 (C-4); 36.62 (δ-C Ad); 38.64 (β-C Ad); 46.56 (α-C Ad); 52.66 (CH_3O); 59.57 (C-5); 148.43 (C-3); 172.43 ($\underline{C}O_2CH_3$); 200.97 ($\underline{C}OAd$). Found, *m/z* 290.3568 $[M]^+$. $C_{16}H_{22}N_2O_3$. Calculated: M 290.3576.

Methyl 3-(1-Adamantylcarbonyl)-1-nitroso-4,5-dihydro-1H-pyrazole-5-carboxylate (3). $NaNO_2$ (0.5 g, 7.25 mmol) was added portionwise with stirring over 10 min to a cooled (0-10ºC) solution of ester **2** (0.3 g, 1.0 mmol) in AcOH (8 ml). The reaction product was stirred for 15 min at room temperature, diluted

with water, and extracted using methylene chloride. The extract was dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure. The residue was recrystallized from isopropanol to give product **3** (0.22 g, 67%) as light-brown crystals with mp 94-97ºC (isopropanol). IR spectrum, ν, cm^{-1}: 1263, 1344, 1436, 1454, 1660 (CO), 1757 (CO_2), 2850-3100. ^1H NMR spectrum (C_6D_6), δ, ppm (*J*, Hz): 1.82 (6H, br. s, δ-H Ad); 2.17 (9H, br. s, γ-H Ad, β-H Ad); 3.13 (1H, dd, J_{gem} = 19.3, *J* = 6.2, H-4); 3.41 (1H, dd, J_{gem} = 19.3, *J* = 11.9, H-4); 3.78 (3H, s, CH_3); 4.86 (1H, dd, *J* = 6.2, *J* = 11.9, H-5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.98 (γ-C Ad); 36.59 (δ-C Ad); 36.83 (C-4); 38.30 (β-C Ad); 47.26 (α-C Ad); 53.13 (OCH_3); 57.36 (C-5); 155.77 (C-3); 166.37 ($\underline{C}O_2CH_3$); 200.33 ($\underline{C}$OAd). Found *m/z* 319.3562 $[M]^+$. $C_{16}H_{21}N_3O_4$. Calculated: M 319.3558.

Methyl 3-(1-Adamantylcarbonyl)-4,5-dihydroisoxazole-5-carboxylate (4). A solution of compound **3** (0.04 g, 0.13 mmol) in chlorobenzene (2 ml) was refluxed in an argon atmosphere for 2 h. Solvent was removed at reduced pressure to give the product **4** (0.036 g, 99%) as a light-brown oil. IR spectrum, ν, cm^{-1}: 789, 1180, 1236, 1346, 1436, 1452, 1538, 1668 (CO), 1737 (CO_2), 2900-3100. ^1H NMR spectrum ($CDCl_3$+CCl_4), δ, ppm (*J*, Hz): 1.78 (6H, br. s, δ-H Ad); 2.07 (9H, br. s, γ-H and β-H Ad); 3.41 (2H, d, *J* = 9.7, two H-4); 3.83 (3H, s, CH_3); 5.00 (1H, t, *J* = 9.7, H-5). ^{13}C NMR spectrum ($CDCl_3$ + CCl_4), δ, ppm: 27.98 (γ-C Ad); 36.61 (δ-C Ad); 38.24 (β-C Ad); 38.69 (C-4); 47.24 (α-C Ad); 52.47 (OCH_3); 77.69 (C-5); 154.49 (C-3); 174.46 ($\underline{C}O_2CH_3$); 198.82 ($\underline{C}$OAd). Found: *m/z* 291.3427 $[M]^+$. $C_{16}H_{21}NO_4$. Calculated: M 291.3423.

Methyl 3-(1-Adamantylcarbonyl)-1H-pyrazole-5-carboxylate (5). MnO_2 (11.5 g, 132.25 mmol) was added to a solution of ester **2** (1.4 g, 4.82 mmol) in benzene (173 ml). The reaction product was stirred at room temperature for 5 h and filtered. The filtrate was evaporated at reduced pressure and the residue was recrystallized from toluene to give product **5** (0.8 g, 57%) as white crystals with mp 192-194ºC (toluene). IR spectrum, ν, cm^{-1}: 1197, 1240, 1442, 1454, 1558, 1658 (CO), 1739 (CO_2), 2850-3000, 3150-3400 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.80 (6H, br. s, δ-H Ad); 2.09 (9H, br. s, γ-H Ad, β-H Ad); 3.97 (3H, s, CH_3); 7.43 (1H, s, H-4); 12.30 (1H, br. s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.86 (γ-C Ad); 36.42 (δ-C Ad); 38.66 (β-C Ad); 46.28 (α-C Ad); 52.24 (OCH_3); 110.80 (C-4); 141.69 (C-5); 142.17 (C-3); 161.72 ($\underline{C}O_2CH_3$); 197.42 ($\underline{C}$OAd). Found: 288.3422 $[M]^+$. $C_{16}H_{20}N_2O_3$. Calculated: M 288.3417.

3-(1-Adamantylcarbonyl)-1H-pyrazole-5-carboxylic acid (6). An aqueous solution of LiOH (1M, 1.5 ml) was added to a solution of ester **4** (0.3 g, 1.04 mmol) in THF (1 ml) and stirred under an argon atmosphere at room temperature for 4 h. The yellow colored solution obtained was treated with a 10% aqueous $KHSO_4$ solution to neutrality and the white crystals precipitated were filtered off and dried to give the product **6** (0.24 g, 84%) as white crystals with mp 263-264ºC. IR spectrum, ν, cm^{-1}: 1211, 1257, 1271, 1456, 1593, 1666 (CO), 1737 (CO_2), 2900-3000, 3050-3250 (OH, NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.75 (6H, br. s, δ-H Ad); 2.06 (3H, br. s, γ-H Ad); 2.09 (6H, br. s, β-H Ad); 6.96 (1H, br. s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 27.66 (γ-C Ad); 36.31 (δ-C Ad); 38.25 (β-C Ad); 45.79 (α-C Ad); 109.73 (C-4); 139.42 (C-5); 148.86 (C-3); 161.43 (COOH); 199.04 ($\underline{C}$OAd). Found: *m/z* 274.3152 $[M]^+$. $C_{15}H_{18}N_2O_3$. Calculated: M 274.3151.

Methyl 3-[1-Adamantyl(hydroxy)methyl]-1H-pyrazole-5-carboxylate (7). $LiAlH_4$ (0.051 g, 1.34 mmol) was added to a solution of the pyrazole **5** (0.3 g, 1.04 mmol) in the ether (17 ml) and stirred under reflux in an argon atmosphere for 30 min. The reaction product was cooled to room temperature and 10% $NaHCO_3$ solution (1 ml) and 20% NaOH solution (2 ml) were added. The organic layer was decanted and the aqueous layer was acidified using 10% $KHSO_4$ to neutrality and then extracted with ether. The extract was combined with the organic layer and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give compound **7** (0.1 g, 33%) as white crystals. IR spectrum, ν, cm^{-1}: 1053, 1240, 1377, 1458, 1590, 1750 (CO_2), 2800-3000, 3050-3250 (OH, NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.55-1.71 (12H, m, δ-H and β-H Ad); 1.98 (3H, br. s, γ-H Ad); 3.92 (3H, s, OCH_3); 4.36 (1H, s, C$\underline{H}$OH); 6.66 (1H, s, H-4). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 27.65 (γ-C Ad); 36.43 (α-C Ad); 36.66 (δ-C Ad); 37.47 (β-C Ad); 51.22 (CH_3); 73.66 (CHOH); 105.73 (C-4); 142.13 (C-5); 145.39 (C-3); 162.73 ($\underline{C}O_2CH_3$). Found: *m/z* 290.3574 $[M]^+$. $C_{16}H_{22}N_2O_3$. Calculated: M 290.3576.

3-[1-Adamantyl(hydroxy)methyl]-5-hydroxymethyl-1H-pyrazole (8). $LiAlH_4$ (0.12 g, 3.16 mmol) was added to a solution of pyrazole **5** (0.2 g, 0.69 mmol) in diethyl ether (17 ml) and stirred under reflux in an argon atmosphere for 30 min. The reaction product was cooled to room temperature and 10% $NaHCO_3$ solution (1 ml) and 20% NaOH solution (2 ml) were added. The organic layer was decanted and the aqueous layer was extracted with ether. The extract and organic layer were combined and dried over anhydrous sodium sulfate. The aqueous layer after extraction was evaporated under reduced pressure and the solid residue was extracted in a Soxhlet apparatus using isopropanol. The alcohol extract was combined with the dried ether extract and the organic layer and evaporated under reduced pressure to give a yellowish crystalline residue (0.136 g). This was recrystallized from a mixture of ethanol and *tert*-butylmethyl ether (1: 5) to give compound **8** (0.123 g, 68%) as white crystals with mp 203-205ºC. IR spectrum, ν, cm^{-1}: 1139, 1186, 1363, 1377, 1462, 1454, 1560, 1610, 2800-3000, 3050-3450 (NH, OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38-1.65 (12H, m, δ-H and β-H Ad); 1.90 (3H, br. s, γ-H Ad); 4.05 (1H, br. s, C<u>H</u>OH); 4.40 (2H, br. s, C<u>H_2</u>OH); 4.98 (2H, br. s, OH); 5.97 (1H, br. s, H-4); 12.2 (1H, br. s, NH). ^{13}C NMR spectrum CD_3OD), δ, ppm: 29.79 (γ-C Ad); 38.14 (δ-C Ad); 39.11 (β-C Ad); 57.96 (CH_2OH); 77.21 (CHOH); 103.49 (C-4); 149.55 (C-3); 150.20 (C-5). Found: *m/z* 262.3470 $[M]^+$. $C_{15}H_{22}N_2O_2$. Calculated: M 262.3475.

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