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INTERACTION OF 5-METHOXY-4-AZATRICYCLO[4.3.1.1^{3,8}]-UNDEC-4-ENE WITH NITROGEN-CONTAINING NUCLEOPHILES

E. A. Knyazeva[1]*, M. Yu. Skomorokhov[1], D. V. Osipov[1], and Yu. N. Klimochkin[1]

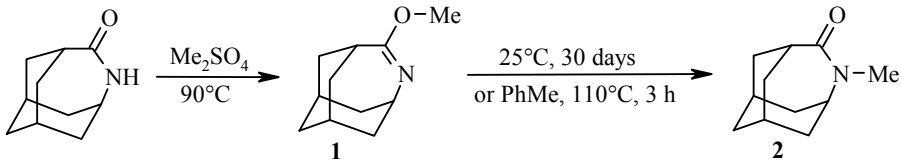
The interaction of 5-methoxy-4-azatricyclo[4.3.1.1^{3,8}]undec-4-ene with acid hydrazides has been studied. It has been established that its reaction with methoxycarbonylhydrazine leads to the formation of 6,7,8,9,10,11-hexahydro-5H-5,9:7,11-dimethano[1,2,4]triazolo[4,3-a]azocin-3-one. Special features of the alkylation of this substrate under various conditions have been studied.

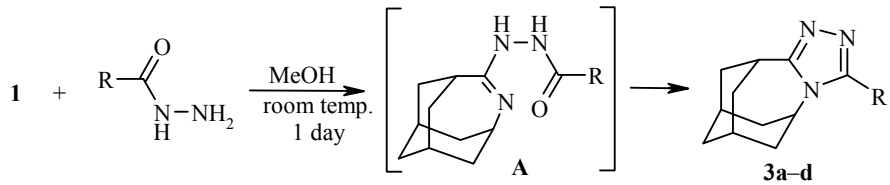
Keywords: 6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one, lactim ethers, 5-methoxy-4-azatricyclo-[4.3.1.1^{3,8}]undec-4-ene, *N*-methyl lactam, *N*- and *O*-alkylation.

The introduction of an adamantane nucleus into compounds possessing marked physiological action frequently leads to an increase in their biological activity, which is caused by the high lipophilicity of the adamantane fragment [1, 2]. In particular, certain compounds in the 4-azahomoadamantane series display antiviral, anti-inflammatory, and antihypertensive action [3-6].

We have chosen 5-methoxy-4-azatricyclo[4.3.1.1^{3,8}]undec-4-ene (**1**), obtained by a modified procedure [3] from 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one, as the starting material for obtaining heterocyclic systems based on 4-azahomoadamantane.

It is worth noting that on storage at room temperature or on heating for 3 h the lactim ether **1** undergoes rearrangement into the *N*-methyl lactam **2**.





3 a R = H, **b** R = Me, **c** R = 4-BrC_6H_4, **d** R = 4-$F_3CC_6H_4$

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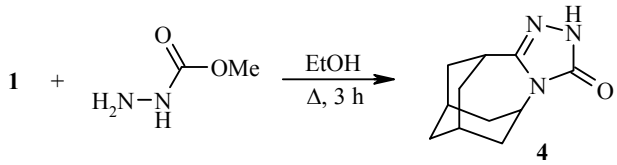
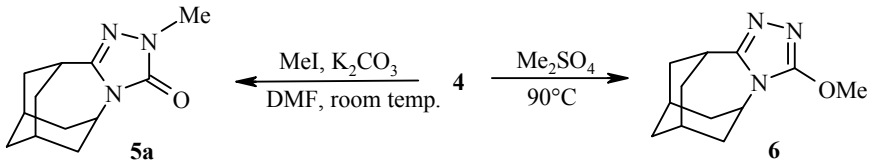
In the continuation of our investigations on lactim ether **1** interaction with acid hydrazides [7], we have extended the range of condensed triazoles **3a-d** obtained. As expected, this reaction proceeds without the possibility of isolating the amidrazone **A** formed as an intermediate and leads directly to triazoles **3a-d**.

Reaction of the lactim ether **1** with methoxycarbonylhydrazine in refluxing ethanol leads to the triazolone **4**.



Compound **4** acts as an ambiphilic agent with soft and hard nucleophilic centers. On using certain methylating agents under various conditions, we have shown the possibility of obtaining products of both *O*-and of *N*-methylation.

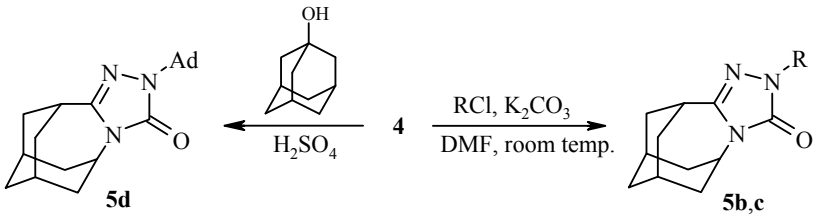
The interaction of triazolone **4** with methyl iodide proceeds at the soft nucleophilic center and leads unambiguously to the *N*-substituted compound **5a**, which is probably the product of thermodynamic control. At the same time, the reaction of triazolone **4** with dimethyl sulfate enables methoxytriazole **6** to be obtained.



In the IR spectra of both compounds intense absorption bands were observed at 2840-2930 cm^{-1}, indicating the presence of C–H bonds. Compound **5a** is characterized by stretching vibration bands of C=N and C=O bonds at 1684 and 1697 cm^{-1}, while for compound **6** only the stretching vibrations of the aromatic system at 1531 and 1666 cm^{-1} were characteristic. In the ^1H NMR spectrum of the *N*-methyl lactam **5a**, methyl group proton signals were displayed at 3.37 ppm, while in the *O*-methyl derivative **6** at 3.62 ppm. The signal of the carbonyl carbon atom in compound **5a** was observed at 152.9 ppm, while the signal of the carbon atom linked to the methoxy group in compound **6** is at 148.2 ppm.

When using other alkylating agents in the presence of calcined potassium carbonate, *N*-alkylation of triazolone **4** occurs leading to *N*-substituted triazolones **5b**,**c**.

It is necessary to mention that alkylation of triazolone **4** using 1-bromoadamantane did not permit the preparation of *N*-adamantyl-substituted triazolone **5d**. Introduction of a 1-adamantyl fragment into triazolone **4** was successfully carried out only by using 1-adamantanol in concentrated H_2SO_4.



5 b R = Bn, **c** R = 4-$F_3CC_6H_4CH_2$

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX400 spectrometer (at 400 and 100 MHz, respectively) in $CDCl_3$, internal standard was TMS. Mass spectra were obtained on a Finnigan Trace DSQ instrument, energy of ionizing electrons 70 eV. Elemental analysis was carried out on an automatic Euro Vector EA3000 CHNS analyzer. Melting points of the obtained compounds were determined by the capillary method on a PTP-M instrument.

5-Methoxy-4-azatricyclo[4.3.1.1^{3,8}]undec-4-ene (1). A mixture of 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (24.15 g, 0.146 mol) and dimethyl sulfate (18.44 g, 13.8 ml, 0.146 mol) was stirred for 6 h at 90°C. After cooling, the mixture was neutralized with a solution of Na_2CO_3 (15.50 g) in water (30 ml) until weakly alkaline, and extracted three times with $CHCl_3$. The organic layers were combined, dried over Na_2SO_4, and the solvent was distilled off in vacuum. Yield 23.00 g (89%). Pale-yellow oil, n_D^{20} 1.6383. IR spectrum, ν, cm^{-1}: 2912, 2847 (C–H$_{aliph}$), 1682 (C=N), 1439, 1362, 1234, 1180, 756. ^{1}H NMR, δ, ppm: 1.34-2.12 (12H, m, 5CH$_2$, 2CH); 2.83-2.85 (1H, m, 6-CH); 3.64-3.66 (1H, m, 3-CH); 3.83 (3H, s, OCH$_3$). Mass spectrum, *m/z* (I_{rel}, %): 179 [M]$^+$ (100), 164 [M-CH$_3$]$^+$ (53), 148 [M-OCH$_3$]$^+$ (24), 136 (25), 122 [M-NCOCH$_3$]$^+$ (23). Found, %: C 73.61; H 9.48; N 7.93. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81.

***N*-Methyl-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (2).** A solution of 5-methoxy-4-azatricyclo-[4.3.1.1^{3,8}]undec-4-ene (**1**) (12.0 g, 0.067 mol) in PhMe (40 ml) was refluxed for 3 h. After the end of the reaction, the solvent was distilled off in vacuum. Yield 11.8 g (98%). Colorless oil, n_D^{20} 1.6380. IR spectrum, ν, cm^{-1}: 2916, 2851 (C–H$_{aliph}$), 1632 (C=O), 1442, 1211, 756. ^{1}H NMR spectrum, δ, ppm: 1.55-2.18 (12H, m, 5CH$_2$, 2CH); 2.75-2.76 (1H, m, 6-CH); 2.89 (3H, s, NCH$_3$); 3.27-3.28 (1H, m, 3-CH). Mass spectrum, *m/z* (I_{rel}, %): 179 [M]$^+$ (100), 164 [M-CH$_3$]$^+$ (18), 151 [M-CO]$^+$ (17), 123 [M-CONCH$_3$]$^+$ (31). Found, %: C 73.64; H 9.51; N 7.88. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.56; N 7.81.

6,7,8,9,10,11-Hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocines 3a-d (General Method). A mixture of compound **1** (1.00 g, 5.6 mmol) and the hydrazide of the correspoding acid (5.7 mmol) in MeOH (6 ml) was maintained at room temperature for 1 day. The precipitated solid was filtered off, dried, and recrystallized.

6,7,8,9,10,11-Hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocine (3a). Yield 0.30 g (19%). Colorless crystals, mp 66-69°C (PhMe). IR spectrum, ν, cm^{-1}: 2916, 2851 (C–H$_{aliph}$), 1632, 1512, 1442, 1389, 1192. ^{1}H NMR spectrum, δ, ppm: 1.75-2.25 (12H, m, 5CH$_2$, 2CH); 3.55-3.56 (1H, m, CH–C=N); 4.36-4.37 (1H, m, N=C–N–CH); 7.95 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 26.6; 27.0; 29.6; 30.7; 32.6; 34.6; 35.2; 36.5; 50.0; 142.5; 160.5. Mass spectrum, *m/z* (I_{rel}, %): 189 [M]$^+$ (100), 161 [M-N$_2$]$^+$ (7), 148 [M-H-CN$_2$]$^+$ (10). Found, %: C 69.90; H 7.91; N 22.19. $C_{11}H_{15}N_3$. Calculated, %: C 69.81; H 7.99; N 22.20.

3-Methyl-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocine (3b). Yield 0.97 g (40%). Colorless crystals, mp 166-169°C (PhMe). IR spectrum, ν, cm^{-1}: 2928, 2854 (C–H$_{aliph}$), 1623, 1531, 1439, 1392. ^{1}H NMR spectrum, δ, ppm: 1.78-2.22 (12H, m, 5CH$_2$, 2CH); 2.39 (3H, s, CH$_3$); 3.48-3.50 (1H, m, CH–C=N); 4.23-4.25 (1H, m, N=C–N–CH). Mass spectrum, *m/z* (I_{rel}, %): 203 [M]$^+$ (100), 175 [M-N$_2$]$^+$ (7), 160 [M-N$_2$-CH$_3$]$^+$ (11). Found, %: C 70.82; H 8.49; N 20.69. $C_{12}H_{17}N_3$. Calculated, %: C 70.90; H 8.43; N 20.67.

3-(4-Bromophenyl)-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocine (3c). Yield 1.25 g (65%). White crystals, mp 254-256°C (*o*-xylene). IR spectrum, ν, cm^{-1}: 2912, 2847 (C–H$_{aliph}$), 1593, 1512, 1470, 1443, 848. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80-2.26 (12H, m, 5CH$_2$, 2CH); 3.61-3.63 (1H, m, CH–C=N); 4.41-4.42 (1H, m, N=C–N–CH); 7.39 (2H, d, *J* = 12.1, H-3',5'); 7.63 (2H, d, *J* = 12.1, H-2',6'). Mass spectrum, *m/z* (I_{rel}, %): 344 (100); 265 [M-Br]$^+$ (14), 252 (34). Found, %: C 59.43; H 5.35; N 12.28. $C_{17}H_{18}BrN_3$. Calculated, %: C 59.31; H 5.27; N 12.21.

3-(4-Trifluoromethylphenyl)-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocine (3d). Yield 0.56 g (30%). White crystals, mp 263-265°C (*o*-xylene). IR spectrum, ν, cm^{-1}: 2923, 2854

(C–H_{aliph}), 1620, 1477, 1450, 1326, 1165, 1111, 852. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80-2.30 (12H, m, 5CH_2, 2CH); 3.61-3.63 (1H, m, CH–C=N); 4.42-4.44 (1H, m, N=C–N–CH); 7.62 (2H, d, *J* = 11.8, H-3',5'); 7.65 (2H, d, *J* = 11.8, H-2',6'). Mass spectrum, *m/z* (I_{rel}, %): 333 $[M]^+$ (100), 240 (56), 252 (34). Found, %: C 64.79; H 5.53; N 12.64. $C_{18}H_{18}F_3N_3$. Calculated, %: C 64.86; H 5.44; N 12.61.

6,7,8,9,10,11-Hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one (4). A mixture of compound **1** (6.4 g, 0.036 mol) and methoxycarbonylhydrazine (3.2 g, 0.036 mol) in EtOH (20 ml) was refluxed for 3 h. The solvent was distilled off in vacuum, and the residue was crystallized from PhMe. Yield 4.1 g (56%). Colorless crystals, mp 238-240°C. IR spectrum, ν, cm^{-1}: 3167 (NH), 2928, 2851 (C–H_{aliph}), 1701 (C=O), 1674, 1585, 1381, 748. ^{1}H NMR spectrum, δ, ppm: 1.76-2.15 (12H, m, 5CH_2, 2CH); 3.01-3.03 (1H, m, CH–C=N); 4.39-4.41 (1H, m, N=C–N–CH); 10.22 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 27.1; 31.1; 33.2; 34.6; 35.1; 45.3; 154.8; 154.9. Mass spectrum, *m/z* (I_{rel}, %): 205 $[M]^+$ (100), 190 $[M\text{-}NH]^+$ (6), 177 $[M\text{-}CO]^+$ (8). Found, %: C 64.40; H 7.15; N 20.32. $C_{11}H_{15}N_3O$. Calculated, %: 64.37; H 7.37; N 20.47.

***N*-Methyl-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one (5a)**. MeI (0.15 ml, 2.4 mmol) was added to a mixture of compound **4** (0.50 g, 2.4 mmol) and calcined K_2CO_3 (0.67 g, 4.9 mmol) in DMF (5 ml) and stirred for 3 h at room temperature. The reaction mixture was poured into water, and twice extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, and the solvent distilled off in vacuum. The residue was crystallized from PhMe. Yield 0.16 g (30%). Colorless crystals, mp 92-94°C. IR spectrum, ν, cm^{-1}: 2927, 2847 (C–H_{aliph}), 1697 (C=O), 1684 (C=N), 1578, 1477, 1381. ^{1}H NMR spectrum, δ, ppm: 1.71-2.15 (12H, m, 5CH_2, 2CH); 2.94-2.97 (1H, m, CH–C=N); 3.37 (3H, s, CH_3); 4.37-4.39 (1H, m, N=C–N–CH). ^{13}C NMR spectrum, δ, ppm: 27.1; 31.2; 32.1; 33.3; 34.7; 35.1; 45.8; 152.9; 153.0. Mass spectrum, *m/z* (I_{rel}, %): 219 $[M]^+$ (100), 204 $[M\text{-}CH_3]^+$ (6), 176 $[M\text{-}CH_3\text{-}CO]^+$ (12), 140 (26), 79 (42). Found, %: C 65.90; H 7.19; N 19.12. $C_{12}H_{17}N_3O$. Calculated, %: C 65.73; H 7.81; N 19.16.

***N*-Benzyl-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one (5b)** was obtained analogously to compound **5a** using benzyl chloride as alkylating agent. Yield 0.35 g (49%). Colorless crystals, mp 84-86°C (PhMe). IR spectrum, ν, cm^{-1}: 2927, 2858 (C–H_{aliph}), 1712 (C=O), 1693, 1578, 1466, 1396, 721. ^{1}H NMR spectrum, δ, ppm: 1.75-2.16 (12H, m, 5CH_2, 2CH); 2.94-3.00 (1H, m, CH–C=N); 4.42-4.44 (1H, m, N=C–N–CH); 4.88 (2H, s, CH_2Ph); 7.25-7.33 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 27.1; 31.2; 33.3; 34.7; 35.2; 45.9; 49.0; 127.7; 128.2; 128.7; 136.8; 153.0; 153.2. Mass spectrum, *m/z* (I_{rel}, %): 295 $[M]^+$ (48), 218 $[M\text{-}C_6H_5]^+$ (36), 148 (12), 91 (100), 79 (18). Found, %: C 73.30; H 7.06; N 14.12. $C_{18}H_{21}N_3O$. Calculated, %: C 73.19; H 7.17; N 14.23.

***N*-(4-Trifluoromethylbenzyl)-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one (5c)** was obtained analogously to compound **5a**, using 4-trifluoromethylbenzyl chloride as alkylating agent. Yield 0.48 g (27%). Light-yellow crystals, mp 157-158°C (PhMe). IR spectrum, ν, cm^{-1}: 2923, 2854 (C–H_{aliph}), 1705 (C=O), 1697, 1585, 1327, 1119. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.74-2.16 (12H, m, 5CH_2, 2CH); 2.97-3.00 (1H, m, CH–C=N); 4.42-4.44 (1H, m, N=C–N-CH); 4.93 (2H, s, CH_2Ar); 7.43 (2H, d, *J* = 8.0, H-3',5'); 7.57 (2H, d, *J* = 8.0, H-2',6'). ^{13}C NMR spectrum, δ, ppm: 27.0; 31.2; 33.2; 34.6; 35.2; 46.0; 48.5; 125.7; 125.8; 128.4; 130.2; 140.7; 153.0; 153.7. Mass spectrum, *m/z* (I_{rel}, %): 363 $[M]^+$ (100), 344 $[M\text{-}F]^+$ (12), 218 $[M\text{-}C_6H_5\text{-}CF_3]^+$ (48), 159 (52). Found, %: C 62.90; H 5.39; N 11.42. $C_{19}H_{20}F_3N_3O$. Calculated, %: C 62.80; H 5.55; N 11.56.

***N*-(1-Adamantyl)-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocin-3-one (5d).** Adamantan-1-ol (0.5 g, 3.3 mmol) was dissolved with stirring in conc. H_2SO_4 (3 ml) and compound **4** (0.67 g. 3.3 mmol) was added. The mixture was heated at 60°C for 1 h. The reaction mixture was poured into water, the precipitated solid was filtered off and recrystallized from toluene. Yield 0.60 g (54%). Colorless crystals, mp > 340°C (decomp.). IR spectrum, ν, cm^{-1}: 2908, 2851 (C–H_{aliph}), 1690 (C=O), 1589, 1477, 1358. ^{1}H NMR spectrum, δ, ppm: 1.66-2.27 (27H, m, 11CH_2, 5CH); 2.98-3.02 (1H, m, CH–C=N); 4.36-4.40 (1H, m, N=C–N–CH). ^{13}C NMR spectrum, δ, ppm: 27.1; 27.5; 29.6; 31.2; 33.4; 34.8; 35.2; 36.3; 40.4; 45.0; 47.1; 151.7; 152.1. Mass spectrum, *m/z* (I_{rel}, %): 339 $[M]^+$ (66), 282 (42), 135 $[Ad]^+$ [100]. Found, %: C 74.43; H 8.39; N 12.22. $C_{21}H_{29}N_3O$. Calculated, %: C 74.30; H 8.61; N 12.38.

3-Methoxy-6,7,8,9,10,11-hexahydro-5*H*-5,9:7,11-dimethano[1,2,4]triazolo[4,3-*a*]azocine (6). A mixture of compound **4** (0.5 g, 2.4 mmol) and dimethyl sulfate (0.23 ml, 0.3 g, 2.4 mmol) was stirred at 90°C for 5 h, then cooled to room temperature and dissolved in $CHCl_3$ (5 ml). The obtained solution was added slowly to a saturated $NaHCO_3$ solution (20 ml). After the end of gas evolution, the organic layer was separated, and the aqueous layer was extracted twice with $CHCl_3$. The organic layers were combined, dried over Na_2SO_4, and the solvent distilled off in vacuum. Yield 0.19 g (36%). Colorless crystals, mp 326-328°C ($CHCl_3$). IR spectrum, ν, cm^{-1}: 2904, 2847 ($C–H_{aliph}$), 1666 (C=N), 1597, 1531, 752, 675. ^1H NMR spectrum, δ, ppm: 1.76-2.19 (12H, m, $5CH_2$, 2CH); 3.20-3.23 (1H, m, CH–C=N); 3.62 (3H, s, CH_3); 4.64-4.66 (1H, m, N–CH). ^{13}C NMR spectrum, δ, ppm: 26.8; 28.0; 32.1; 34.2; 34.3; 35.8; 45.5; 148.2; 158.9. Mass spectrum, *m/z* (I_{rel}, %): 219 $[M]^+$ (1), 205 (100). Found, %: C 65.90; H 7.49; N 19.12. $C_{12}H_{17}N_3O$. Calculated, %: C 65.73; H 7.81; N 19.16.

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