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Adamantylation of 3-Nitro- and 3-Ethoxycarbonyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones*

E. N. Ulomskii[1], S. L. Deev[1], A. V. Tkachev[2], I. K. Moiseev[3], and V. L. Rusinov[2]

[1]*Ural State Technical University, Yekaterinburg, 620002 Russia*
[2]*Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, Novosibirsk, Russia*
[3]*Samara State Technical University, Samara, Russia*

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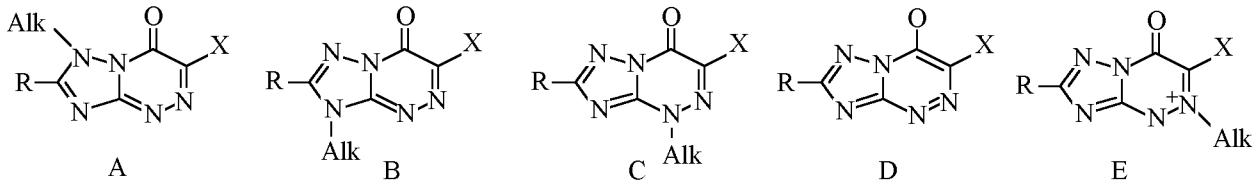
Abstract—Reaction of 3-nitro- and 3-ethoxycarbonyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones with 1-adamantanol (or 1-adamantyl nitrate) in concentrated sulfuric acid or with 1-bromoadamantane in sulfolane affords N-adamantyl derivatives. The adamantylation of 3-nitro-1,4-dihydro-7*H*-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one yields a mixture of N^8- and N^1-isomers that undergo interconversion in concentrated sulfuric acid along intermolecular mechanism.

Triazolo[5,1-*c*]-1,2,4-triazin-4-ones possess five sites sensitive to the attack of alkylating reagents that suggests a presumable formation of the following alkyl derivatives.



We established formerly that alkylation of sodium salts from 3-nitro-1,2,4-triazolo[5,1-c]-1,2,4-triazin-4-ones gave rise to a mixture of three N-alkylated products (isomers A, B, and C) [1]. We did not observe formation of O-alkylated products. With 3-ethoxycarbonyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones the reaction under the same conditions with haloalkyls afforded exclusively N^1-isomer C [2]. Besides it is known from the literature [3] that methylation of 1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (X = H) has provided O-alkylation products (isomer D) and 2-methyltriazolotriazine (isomer E).

In the present study in order to extend investigation of reactivity of 3-substituted triazolo[5,1-*c*]-1,2,4-triazin-4-ones we carried out their reactions with adamantylating reagents. Introduction of an adamantyl substituent frequently changes the biological properties of compounds, in particular, facilitates their transport through biological membranes and favors appearance of hypoglycemic, antitumor, analgetic, antipyretic, antarrhythmic, malaricidal, antibacterial activity [4].

1-adamantanol and 1-adamantyl nitrate are known to form readily in acidic media a carbocation that is an efficient alkylating agent as has been shown in experiments with 1,2,4-triazole, tetrazole, and 4-nitroimidazole [5–7].

We established that reaction of 3-substituted triazolo[5,1-*c*]-1,2,4-triazin-4-ones **Ia–f** with adamantyl cation generated from 1-adamantanol (or adamantyl nitrate) in concn. sulfuric acid gave rise predominantly to one isomer in fair yield, except reaction with compound **Ia** where formed two adamantylation products.

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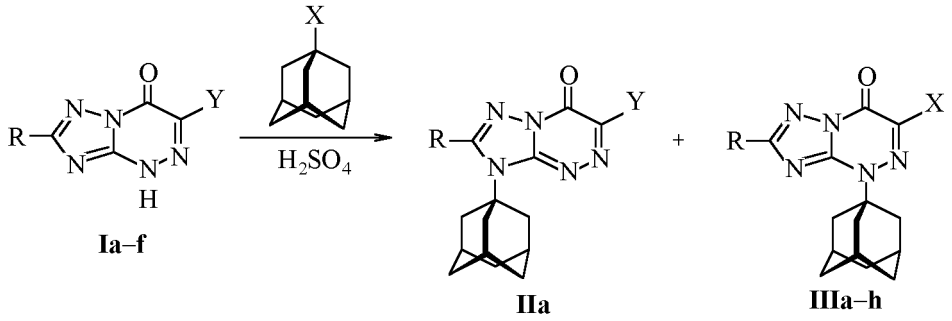
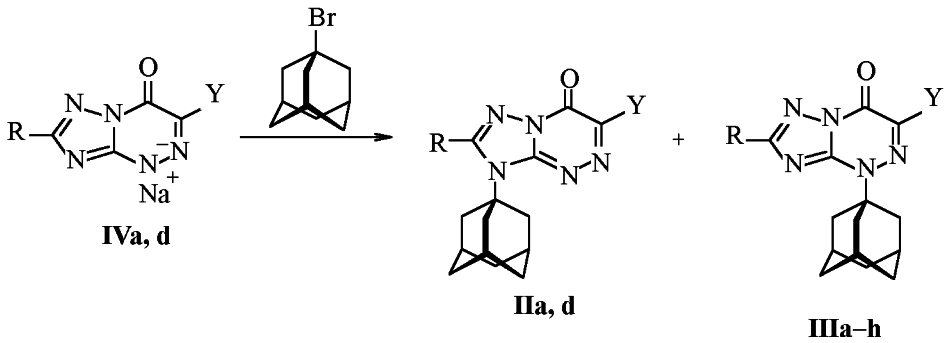


Ia–f **IIa** **IIIa–h**

I–III, R = H, Y = NO_2 (a); R = Me, Y = NO_2 (**b**); R = SMe, Y = NO_2 (**c**); R = H, Y = COOEt (**d**); R = Me, Y = COOEt (**e**); R = SMe, Y = COOEt (**f**); R = SOMe, Y = NO_2 (**g**); R = SOMe, Y = COOEt (**h**); X = OH, ONO_2.

Alkylation of 3-nitro- and 3-ethoxycarbonyl-1,4-dihydrotriazolo[5,1-*c*]-1,2,4-triazin-7-ones sodium salts (**IVa, d**) with 1-bromoadamantane proceeds in sulfolane at 180°C. This reaction yields two isomers.



IVa, d **IIa, d** **IIIa–h**

In the mass spectra of heteryladamantanes synthesized **II**, **III** is present a molecular ion peak common for the corresponding isomers (Table 1).

In the IR spectra of nitro derivatives of N-adamantyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones are observed the absorption bands from stretching vibrations of nitro group (1320–1350 and 1530–1570 cm^{-1}) and carbonyl group bands (1720–1770 cm^{-1}). In the spectra of N-adamantyl derivatives of 3-ethoxycarbonyltriazolotriazines appear both absorption bands of exocyclic and endocyclic carbonyl groups (Table 2). The presence of endocyclic carbonyl group in the IR spectra of heteryladamantanes evidences that the compounds obtained are not products of O-alkylation.

The position of N-alkyl substituent in adamantylation products of compounds **Ia–f** was derived from ^{13}C NMR spectra.

In order to be able to make correct assignment of spectral characteristics to individual isomers and to establish their structure we carried out an X-ray diffraction analysis of the sole adamantylation product of 7-methyl-3-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (**Ib**). This compound was proved to have a structure of 1-adamantyl-7-methyl-3-nitro-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (**IIIb**). The bicyclic system of compound **IIIb** is virtually planar, and only the nitro group is put out of conjugation with rotation angle around $C^{3}–N^{10}$ bond of 109.2 deg. (see figure, Table 3). The main geometrical parameters of the molecule are characteristic of the nitrogen-containing triazolo[5,1-*c*]-1,2,4-triazine heterocyclic systems [1]. The C–C bonds in the adamantyl moiety construct a tricyclic skeleton of cyclohexane rings in the *chair* conformation, and the length of the bonds vary in a relatively narrow range 1.523(2)–1.543(2) Å (Table 4).

To facilitate the assignment of spectral parameters we also synthesized adamantylation product from 6-^{15}N-3-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (**Ia***) enriched in ^{15}N to 43%. Compound **Ia*** was prepared by mixing previously described 6-^{15}N-3-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one [8] with ^{15}N content of 87% with an equivalent amount of unlabeled triazolotriazine **Ia**.

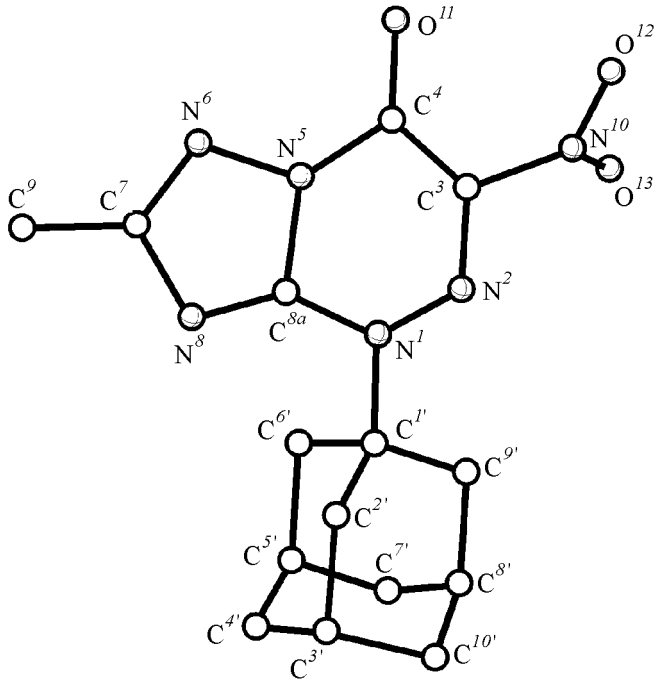
Table 1. Physicochemical characteristics of *N*-adamantyl-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones **IIa, IIa*, IId, IIIa–h, IIIa***

	Yield, % (method)	mp, °C	R_f		Found, %			Formula	Calculated, %			Found	Calcd. *M*
			[a]	[b]	C	H	N		C	H	N	M^+	
IIa (**IIa***)	45 (*a*), 29 (*b*), 3 (*c*), (20)	243–245[c]	0.02	0.53	53.16	5.04	26.50	$C_{14}H_{16}N_6O_3$ ($C_{14}H_{16}N_5{}^{15}NO_3$)	53.16	5.10	26.57	316 (317)	316.32 (317.32)
IIIa (**IIIa***)	18 (*a*), 51 (*b*), 9 (*c*), (49)	232–234[c]	0.64	0.72	53.41	5.21	26.67	$C_{14}H_{16}N_6O_3$ ($C_{14}H_{16}N_5{}^{15}NO_3$)	53.16	5.10	26.57	316 (317)	316.32 (317.32)
IIIb	18 (*a*), 52 (*b*)	270–273[d]	0.49	0.66	53.99	5.53	25.00	$C_{15}H_{18}N_6O_3$	54.54	5.49	25.44	330	330.35
IIIc	40 (*a*), 60 (*b*)	235–237[c]	0.59	0.71	49.54	4.97	23.22	$C_{15}H_{18}N_6O_3S$	49.72	4.97	23.20	362	362.41
IId	47 (*a*), 62 (*b*), 9 (*c*)	233[c]	0.05	0.54	59.42	6.10	20.42	$C_{17}H_{21}N_5O_3$	59.46	6.16	20.39	343	343.39
IIId	7 (*c*)	175–177[c]	0.58	0.79	59.40	6.16	20.51	$C_{17}H_{21}N_5O_3$	59.46	6.16	20.39	343	343.39
IIIe	22 (*a*), 40 (*b*)	209–211[d]	0.65	0.68	60.14	6.50	19.47	$C_{18}H_{23}N_5O_3$	60.49	6.49	19.59	357	357.42
IIIf	20 (*a*), 22 (*b*)	237[c]	0.56	0.72	55.74	6.04	18.00	$C_{18}H_{23}N_5O_3S$	55.53	5.91	17.99	389	389.49
IIIg	2	240–242[d]	0.55	0.64	47.44	4.75	22.11	$C_{15}H_{18}N_6O_4S$	47.62	4.75	22.22	378	378.41
IIIh	18	214[d]	0.43	0.64	53.01	5.77	17.28	$C_{18}H_{23}N_5O_4S$	53.32	5.72	17.27	405	405.48

For evaluation of R_f by TLC were used as eluents: [a] ethyl acetate, [b] ethyl ether. Solvent for crystallization: [c] ethanol, [d] 2-propanol.

Table 2. IR and ^{1}H NMR spectra of compounds synthesized

Compd. no.	IR spectrum, cm^{-1}	^{1}H NMR spectrum, δ, ppm
IIa	1720 (C=æ), 1530, 1320 (C–NO_2)	1.76 m (6H, CH_2), 2.25 m (3H, CH), 2.49 m (6H, CH_2), 9.28 s (1H, CH)
IIa*	1720 (C=æ), 1530, 1320 (C–NO_2)	1.76 m (6H, CH_2), 2.25 m (3H, CH), 2.49 m (6H, CH_2), 9.28 d [1H, ^2J(H7–^{15}N) 13.55 Hz]
IIIa	1750 (C=O), 1530, 1340 (C–NO_2)	1.74 m (6H, CH_2), 2.27 m (3H, CH), 2.49 m (6H, CH_2), 8.61 s (1H, CH)
IIIa*	1750 (C=O), 1530, 1340 (C–NO_2)	1.74 m (6H, CH_2), 2.27 m (3H, CH), 2.49 m (6H, CH_2), 8.61 d [1H, ^2J(H7–^{15}N) 15.88 Hz]
IIb	1760 (C=æ), 1530, 1350 (C–NO_2)	1.73 m (6H, CH_2), 2.26 m (3H, CH), 2.41 m (6H, CH_2), 2.51 s (3H, CH_3)
IIIc	1760 (C=æ), 1530, 1320 (C–NO_2)	1.73 m (6H, CH_2), 2.26 m (3H, CH), 2.38 m (6H, CH_2), 2.68 s (3H, SCH_3)
IId	1750, 1770 (C=O)	1.31 t (3H, CH_3), 1.75 m (6H, CH_2), 2.23 m (3H, CH), 2.42 m (6H, CH_2), 4.35 q (2H, CH_2), 9.14 c (1H, CH)
IIId	1730, 1740 (C=O)	1.31 t (3H, CH_3), 1.73 m (6H, CH_2), 2.24 m (3H, CH), 2.42 m (6H, CH_2), 4.35 q (2H, CH_2), 8.48 c (1H, CH)
IIIe	1760, 1770 (C=O)	1.31 t (3H, CH_3), 1.73 m (6H, CH_2), 2.23 m (3H, CH), 2.40 m (6H, CH_2), 2.49 s (3H, CH_3), 4.35 q (2H, CH_2)
IIIf	1730, 1760 (C=O)	1.33 t (3H, CH_3), 1.74 m (6H, CH_3), 2.25 m (3H, CH), 2.40 m (6H, CH_2), 2.53 m (3H, SCH_3), 4.40 q (2H, CH_2)
IIIg	1765 (C=O), 1530, 1350 (C–NO_2)	1.75 m (6H, CH_2), 2.28 m (3H, CH), 2.42 m (6H, CH_2), 3.13 s (3H, SæCH$_3$)
IIIh	1720, 1750 (C=O)	1.32 t (3H, CH_3), 1.74 m (6H, CH_2), 2.26 m (3H, CH), 2.49 m (6H, CH_2), 3.08 s (3H, SæCH$_3$), 4.35 q (2H, CH_2)



Molecular structure of 1-adamantyl-7-methyl-nitro-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (**IIIb**).

The similarity of ^{13}C NMR spectra of compound **IIIb** and heteryladamantanes **IIIa, c, g, IIIa*** permits the assumption that all these products are adamantylated at position *1*. The assignment of carbon signals was carried out basing on analysis of coupling constants $^{13}C–^{1}H$ that allowed unambiguous determination of atoms C^{7} and C^{8a} positions in compound **IIIa** (*d*, ^{1}J 213.6 Hz and d, ^{3}J 9.3 Hz respectively). At appearance of a substituent in the azole ring in compounds **IIIb, c, g** the C^{8a} atom signal becomes a singlet located in the same region (δ 150–152 ppm), and the signal of C^{7} is present as a quartet. The other downfield signals were assigned to C^{3} and C^{4}. The broadened singlet was attributed to C^{3} linked to the nitro group since the broadening was effected by quadrupole relaxation of ^{14}N atom in the nitro group. The validity of this assignment of the ring carbon atoms in the heterocyclic fragment of N-adamantylated triazolotriazines **IIIa, b, c, g** is confirmed by the ^{13}C NMR spectrum of compound **IIIa*** registered with C–H decoupling. Thus the signal of atom C^{7} appears as a doublet $^{1}J(C^{7}–N^{6})$ 3.71 Hz, signals of C^{4} and C^{8a} atoms also possess doublet structure $^{2}J(C^{4}–N^{6})$ 3.78 and $^{2}J(C^{8a}–N^{6})$ 1.69 Hz. The isotope shift values of the atoms C^{7} (Δδ +0.01878 ppm), C^{8a} (Δδ +0.00094 ppm), and C^{4} (Δδ +0.00015 ppm) obtained at comparison of ^{13}C NMR spectra of the labeled and unlabeled compounds **IIIa*** and **IIIa** con-

Table 3. Atomic coordinates (in fractions of unit cell axes) and thermal corrections U_{iso} and U_{eq} for 1-adamantyl-7-methyl-3-nitro-1,4-dihydro-1,2,4-triazolo-[5,1-*c*]-1,2,4-triazin-4-one (**IIIb**)

Atom	*x*	*y*	*z*	U_{iso}/U_{eq}, Å^2
O^{11}	0.5420(1)	0.8625(1)	0.0117(1)	0.0479(4)
O^{12}	0.4853(1)	0.6959(2)	–0.1158(2)	0.0837(7)
O^{13}	0.4012(1)	0.7635(2)	–0.1989(2)	0.0575(5)
N^{2}	0.3670(1)	0.8305(1)	0.0138(1)	0.0325(3)
N^{1}	0.3505(1)	0.8906(1)	0.1029(1)	0.0296(3)
N^{8}	0.3935(1)	1.0124(1)	0.2463(1)	0.0353(4)
N^{6}	0.5009(1)	0.9961(1)	0.1952(1)	0.0355(4)
N^{5}	0.4623(1)	0.9326(1)	0.1276(1)	0.0309(3)
N^{10}	0.4312(1)	0.7536(2)	–0.1165(2)	0.0426(4)
C^{4}	0.4851(1)	0.8696(1)	0.0379(2)	0.0325(4)
C^{3}	0.4278(1)	0.8206(1)	–0.0152(2)	0.0326(4)
C^{8a}	0.3983(1)	0.9453(1)	0.1609(2)	0.0301(4)
C^{7}	0.4576(1)	1.0413(2)	0.2639(2)	0.0348(4)
C^{9}	0.4773(1)	1.1173(2)	0.3537(2)	0.0485(5)
$C^{1'}$	0.2786(1)	0.8992(1)	0.1338(2)	0.0280(3)
$C^{2'}$	0.2687(1)	0.8645(2)	0.2593(2)	0.0369(4)
$C^{3'}$	0.1960(1)	0.8765(2)	0.2908(2)	0.0408(5)
$C^{4'}$	0.1753(1)	0.9912(2)	0.2752(2)	0.0434(5)
$C^{5'}$	0.1845(1)	1.0241(2)	0.1496(2)	0.0402(5)
$C^{6'}$	0.2571(1)	1.0145(1)	0.1170(2)	0.0343(4)
$C^{7'}$	0.1438(1)	0.9530(2)	0.0707(2)	0.0464(5)
$C^{8'}$	0.1657(1)	0.8381(2)	0.0871(2)	0.438(5)
$C^{9'}$	0.2385(1)	0.8276(2)	0.0544(2)	0.0390(4)
$C^{10'}$	0.1549(1)	0.8057(2)	0.2123(2)	0.0478(5)
$H_1(C^{9})$	0.523	1.126	0.351	
$H_2(C^{9})$	0.456	1.184	0.340	
$H_3(C^{9})$	0.464	1.091	0.428	
$H_1(C^{2'})$	0.294	0.907	0.309	
$H_2(C^{2'})$	0.282	0.792	0.269	
$H(C^{3'})$	0.189	0.856	0.369	
$H_1(C^{4'})$	0.201	1.035	0.324	
$H_2(C^{4'})$	0.130	0.999	0.296	
$H(C^{5'})$	0.170	1.096	0.140	
$H_1(C^{6'})$	0.263	1.034	0.037	
$H_2(C^{6'})$	0.283	1.060	0.164	
$H_1(C^{7'})$	0.150	0.973	–0.008	
$H_2(C^{7'})$	0.098	0.960	0.088	
$H(C^{8'})$	0.140	0.793	0.038	
$H_1(C^{9'})$	0.252	0.755	0.062	
$H_2(C^{9'})$	0.244	0.848	–0.024	
$H_1(C^{10'})$	0.109	0.811	0.232	
$H_2(C^{10'})$	0.167	0.733	0.222	

Table 4. Bond lengths and bond angles of 1-adamantyl-7-methyl-3-nitro-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (**IIIb**)

Bond	*d*, Å	Bond	*d*, Å
O^{11}–C^{4}	1.205(2)	C^{4}–C^{3}	1.462(3)
O^{12}–N^{10}	1.209(2)	C^{7}–C^{9}	1.473(3)
O^{13}–N^{10}	1.225(2)	$C^{1'}$–$C^{9'}$	1.530(2)
N^{2}–C^{3}	1.293(2)	$C^{1'}$–$C^{2'}$	1.533(3)
N^{2}–N^{1}	1.327(2)	$C^{1'}$–$C^{6'}$	1.537(2)
N^{2}–C^{8a}	1.374(2)	$C^{2'}$–$C^{3'}$	1.538(2)
N^{1}–$C^{1'}$	1.515(2)	$C^{3'}$–$C^{4'}$	1.523(3)
N^{8}–C^{8a}	1.309(2)	$C^{3'}$–$C^{10'}$	1.528(3)
N^{8}–C^{7}	1.377(2)	$C^{4'}$–$C^{5'}$	1.527(3)
N^{6}–C^{7}	1.321(2)	$C^{5'}$–$C^{7'}$	1.529(3)
N^{6}–N^{5}	1.371(2)	$C^{5'}$–$C^{6'}$	1.536(2)
N^{5}–C^{8a}	1.373(2)	$C^{7'}$–$C^{8'}$	1.532(3)
N^{5}–C^{4}	1.391(2)	$C^{8'}$–$C^{10'}$	1.524(3)
N^{10}–C^{3}	1.464(2)	$C^{8'}$–$C^{9'}$	1.543(3)
Angle	***w*, deg**	**Angle**	***w*, deg**
$C^{3}N^{2}N^{1}$	120.2(2)	$N^{5}C^{8a}N^{1}$	118.8(2)
$N^{2}N^{1}C^{8a}$	119.2(1)	$N^{6}C^{7}N^{8}$	115.7(2)
$N^{2}N^{1}C^{1'}$	118.2(1)	$N^{6}C^{7}C^{9}$	121.8(2)
$C^{8a}N^{1}C^{1'}$	122.6(1)	$N^{8}C^{7}C^{9}$	122.5(2)
$C^{8a}N^{8}C^{7}$	102.2(1)	$N^{1}C^{1'}C^{9'}$	109.5(1)
$C^{7}N^{6}N^{5}$	102.3(1)	$N^{1}C^{1'}C^{2'}$	109.4(1)
$N^{6}N^{5}C^{8a}$	108.6(1)	$C^{9'}C^{1'}C^{2'}$	109.4(1)
$N^{6}N^{5}C^{4}$	124.8(1)	$N^{1}C^{1'}C^{6'}$	108.4(1)
$C^{8a}N^{5}C^{4}$	126.6(2)	$C^{9'}C^{1'}C^{6'}$	109.4(2)
$O^{12}N^{10}O^{13}$	124.0(2)	$C^{2'}C^{1'}C^{6'}$	110.8(2)
$O^{12}N^{10}C^{3}$	117.3(2)	$C^{1'}C^{2'}C^{3'}$	108.9(2)
$O^{13}N^{10}C^{3}$	118.5(2)	$C^{4'}C^{3'}C^{10'}$	109.6(2)
$O^{11}C^{4}N^{5}$	123.7(2)	$C^{4'}C^{3'}C^{2'}$	109.6(2)
$O^{11}C^{4}C^{3}$	129.5(2)	$C^{10'}C^{3'}C^{2'}$	109.4(2)
$N^{5}C^{4}C^{3}$	106.8(2)	$C^{3'}C^{4'}C^{5'}$	109.8(2)
$N^{2}C^{3}C^{4}$	128.3(2)	$C^{4'}C^{5'}C^{7'}$	110.1(2)
$N^{2}C^{3}N^{10}$	113.8(2)	$C^{4'}C^{5'}C^{6'}$	109.4(2)
$C^{4}C^{3}N^{10}$	117.9(2)	$C^{7'}C^{5'}C^{6'}$	109.4(2)
$N^{8}C^{8a}N^{5}$	111.1(2)	$C^{5'}C^{6'}C^{1'}$	108.7(2)
$N^{8}C^{8a}N^{1}$	130.0(2)	$C^{5'}C^{7'}C^{8'}$	109.0(2)

firm the position of the label. According to conclusion in [9], the largest isotope shift is characteristic of the carbon atom the nearest to ^{15}N. Besides in the spectra of N-adamantylated triazolotriazines **IIIa–c, g, IIIa*** the signals of adamantyl substituent appear as four broadened singlets in the upfield region (35–70 ppm). The peak of the $C^{1'}$ is present in the region of 69–70 ppm, characteristic of all N^{1}-adamantyl derivatives obtained **IIIa–c, g, IIIa*** (Table 5).

In the 13C NMR spectrum of compound **IIa** registered without proton decoupling the peaks of atoms C^{7} and C^{8a} with the doublet structure (^{1}J 223 and ^{3}J 5.1 Hz respectively) are shifted upfield compared to the analogous signals of triazolotriazine **Ia** (Δδ 11.54 and 9.38 ppm respectively). In conformity with the concept of α-shift [10] this behavior evidences the addition of the adamantyl fragment to N^{8} atom. The spectrum of compound **IIa*** registered with decoupling from protons confirms this conclusion. Thus the peak of atom $C^{1'}$ is a doublet with a small coupling constant [$^{3}J(^{13}C–^{15}N)$ 0.5 Hz]. The value of coupling constant $^{13}C–^{15}N$ confirms the position of the adamantyl substituent at N^{8} atom since the direct coupling constant $^{1}J(^{15}N–^{13}C\text{-}sp^{3})$ has a value of 12–15 Hz [1, 11]. The chemical shifts and coupling constants $^{13}C–^{15}N$ [$^{1}J(C^{7}–N^{6})$ 3.16, $^{2}J(C^{4}–N^{6})$ 3.45, $^{2}J(C^{8a}–N^{6})$ 1.60 Hz], isotope shifts values for C^{7} (Δδ +0.02287 ppm), C^{8a} (Δδ +0.00144 ppm), C^{4} (Δδ +0.00039 ppm) and $C^{1'}$ (Δδ +0.00039 ppm) prove the conservation of the bicyclo structure in the triazolo[5,1-*c*]-1,2,4-triazine. The result obtained is well consistent with the published data [1].

The reaction of 3-substituted 1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones **Ia–f** with adamantyl cation generated from 1-adamantanol (or 1-adamantyl nitrate) in concn. H_2SO_4 occurs in the temperature range from –15 to 20°C. However the temperature affects the alkylation direction only for compound **Ia**. For instance, the adamantylation of triazolotriazine **Ia** at –15°C (procedure *a*) results in prevailing formation of alkylation product **IIa**. The ratio of compounds **IIa : IIIa** was determined from 1H NMR spectrum. The raise in temperature changes the reaction direction to formation of compound **IIIa**. For instance, at 20°C (procedure *b*) the ratio of N-adamantyl derivatives **IIa** and **IIIa** in the product is 1 : 2. For the other compounds **I** the alkylation is regioselective irrespective of the temperature. For instance, adamantylation of compound **Id** affords product **IIa** alkylated into the azole ring. The other 3-substituted triazolo[5,1-*c*]-1,2,4-triazines **Ib, c, e, f** containing a methyl or S-Me substituent at the triazole ring in reaction with adamantyl cation give rise to N^{1}-isomer. The regioselectivity is here apparently due to steric factors. Note that with compounds **Ic** and **If** the adamantylation result depends on the nature of the alkylating agent. In reaction with adamantyl nitrate in sulfuric acid alongside alkylation occurred oxidation of the S-methyl group resulting in formation of sulfoxides **IIIg, h**.

Table 5. ^{13}C NMR spectra of compounds **Ia, d, IIa, d, IIa*, IIIa–h, IIIa***

Compd.	δ, ppm (*J*, Hz)						
no.	C^{7}	R	C^{8a}	C^{3}	C^{4}	Ad	COOEt
Ia	154.60 d [^{1}J(13C–H) 213.0]		159.63 d [^{3}J(13C–H) 9.0]	144.22 br.s	143.96 s		
Id	153.33 d [^{1}J(13C–H) 211.1]		151.38 d [^{3}J(13C–H) 9.0]	147.31 s	131.55 s		160.93, 61.41, 13.96
IIa	143.04 d [^{1}J(13C–H) 223.0]		150.25 d [^{3}J(13C–H) 5.1]	148.56 br.s	141.90 s	61.24, 39.89, 28.88, 35.02	
IIa*	143.06 d [^{1}J(13C–15N) 3.16]		150.25 d [^{2}J(13C–15N) 1.60]	148.56 br.s	141.90 d [^{2}J(13C–15N) 3.45]	61.24 d [^{3}J(13C–15N) 0.5], 39.89, 28.88, 35.02	
IIIa	153.30 d [^{1}J(13C–H) 213.6]		150.45 d [^{3}J(13C–H) 9.3]	139.22 br.s	142.91 s	69.76, 39.18, 29.28, 35.23	
IIIa*	153.32 d [^{1}J(13C–15N) 3.71]		150.45 d [^{2}J(13C–15N) 1.69]	139.22 br.s	142.91 d [^{2}J(13C–15N) 3.78]	69.76, 39.18, 29.28, 35.23	
IIIb	162.82 q [^{3}J(13C–H) 7.2]	14.07 [^{1}J(13C–H) 129.3]	150.30 ©	139.01 br.s	142.01 s	69.56, 39.02, 29.16, 35.07	
IIIc	165.88 q [^{3}J(13C–H) 4.7]	13.98 q [^{1}J(13C–H) 142.60]	150.92 s	139.51 br.s	141.64 s	69.70, 39.16, 29.28, 35.36	
IId	141.83 d [^{1}J(13C–H) 221.7]		148.8 d [^{3}J(13C–H) 5.1]	145.53 s	138.39 s	60.34, 39.67, 28.80, 35.06	162.46, 60.86, 13.90
IIId	152.32 d [^{1}J(13C–H) 212.3]		149.95 d [^{3}J(13C–H) 9.3]	129.18 s	146.64 s	68.35, 39.16, 29.29, 35.36	160.65, 61.19, 13.77
IIIe	161.71 q [^{3}J(13C–H) 7.2]	14.06 [^{1}J(13C–H) 129.3]	150.00 s	129.27 s	145.89 s	68.15, 39.06, 29.15, 35.22	160.82, 61.41, 13.98
IIIf	164.51 q [^{3}J(13C–H) 5.1]	13.34 q [^{1}J(13C–H) 142.60]	150.35 s	129.81 s	145.14 s	68.25, 39.01, 29.15, 35.20	160.82, 61.41, 13.98
IIIg	168.02 q [^{3}J(13C–H) 5.1]	39.17 q [^{1}J(13C–H) 140.50]	151.20 s	139.57 br.s	142.56 s	70.35, 39.22, 29.29, 35.13	
IIIh	166.87 q [^{3}J(13C–H) 5.1]	39.10 q [^{1}J(13C–H) 140.30]	150.75 s	130.06 ©	146.16 s	68.80, 39.18, 29.22, 35.22	160.70, 61.53, 13.88

Alkylation of sodium salts **IVa, d** with 1-bromoadamantane proceeds in sulfolane at 180°C (procedure *c*) and affords N-adamantyl derivatives **IIa, d** and **IIIa, d**. However this procedure is less interesting for preparative syntheses because of low yields (Table 1).

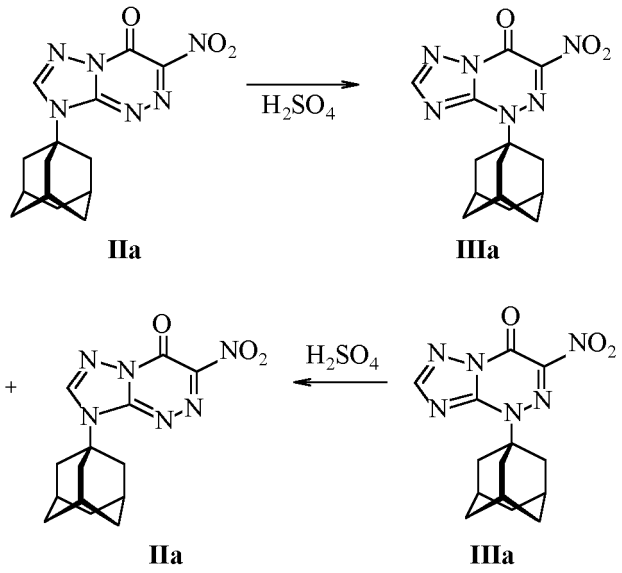
The temperature dependence of the adamantylation regioselectivity for 3-nitro-1,4-dihydro-1,2,4-triazolo-[5,1-*c*)]-1,2,4-triazin-4-one (**Ia**) was confirmed by isomerization of adamantyl derivatives **IIa** and **IIIa** in sulfuric acid. On dissolving any of the isomers in concentrated sulfuric acid at room temperature arises an equilibrium mixture of compounds **IIa** and **IIIa** in 1 : 2 ratio.

This experiment shows that adamantylation is reversible, and that it may proceed along intramolecular, intermolecular, or mixed mechanism. The intramolecular rearrangement should involve transfer of the adamantyl moiety within one molecule and may occur as [1,3]-sigmatropic shift or by formation of a tight ion pair from adamantyl cation and anion of the initial heterocycle as a result of heterolysis of the N–adamantyl bond. The intermolecular mechanism consists in transfer of the adamantyl substituent to another molecule, and it is possible only in case of formation of the initial heterocycle and adamantyl cation. Among the presumed mechanisms the sigmatropic shift of adamantyl is the least probable since [1*s*,3*s*]-sigmatropic transition is permissible in photochemical process [12] that is not the case under our rearrangement conditions. On the other hand, [1*s*,3*a*]-shift is hampered by geometrical reasons. Even less probable is a sigmatropic shift [1*a*,3*a*] [13]. A presumable under given conditions [1*a*,3*s*]-transition is hardly probable for sterical reasons due to the structure of the adamantyl substituent. Thus the rearrangement with participation of adamantyl cation seems the most probable.

Similar examples of hetaryladamantanes isomerization were found in the literature. Thus 2-(1--adamantyl)tetrazole in sulfuric acid is converted into 1-(1-adamantyl)tetrazole [14]. The mechanism assumed [14] included formation of 1,3-di(1-adamantyl)tetrazolium cation, and the mechanism was considered to be intermolecular relying on TLC data.

The details of the transadamantylation process in the derivatives of 3-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazines **IIa** and **IIIa** were elucidated by isomerization of compound **IIa** (or **IIIa**) in the presence of an equivalent amount of the labeled compound **Ia*** described before [8] (content of ^{15}N about 87%). The resulting mixture contained compounds **Ia***, **IIa***, and **IIIa*** with equal content of ^{15}N isotope (43 % according to 1H NMR data) in the ratio 3 : 1 : 2 respectively (see EXPERIMENTAL). For compounds **IIa*** and **IIIa*** the content of ^{15}N was also determined from mass spectra.

The isotope scrambling of nitrogen in compounds **Ia***, **IIa***, and **IIIa*** proves the establishing of an equilibrium and a significant contribution of the intermolecular adamantyl fragment transfer in the isomerization process. Thus the interconversion of compounds **IIa** and **IIIa** can be illustrated by the following scheme.



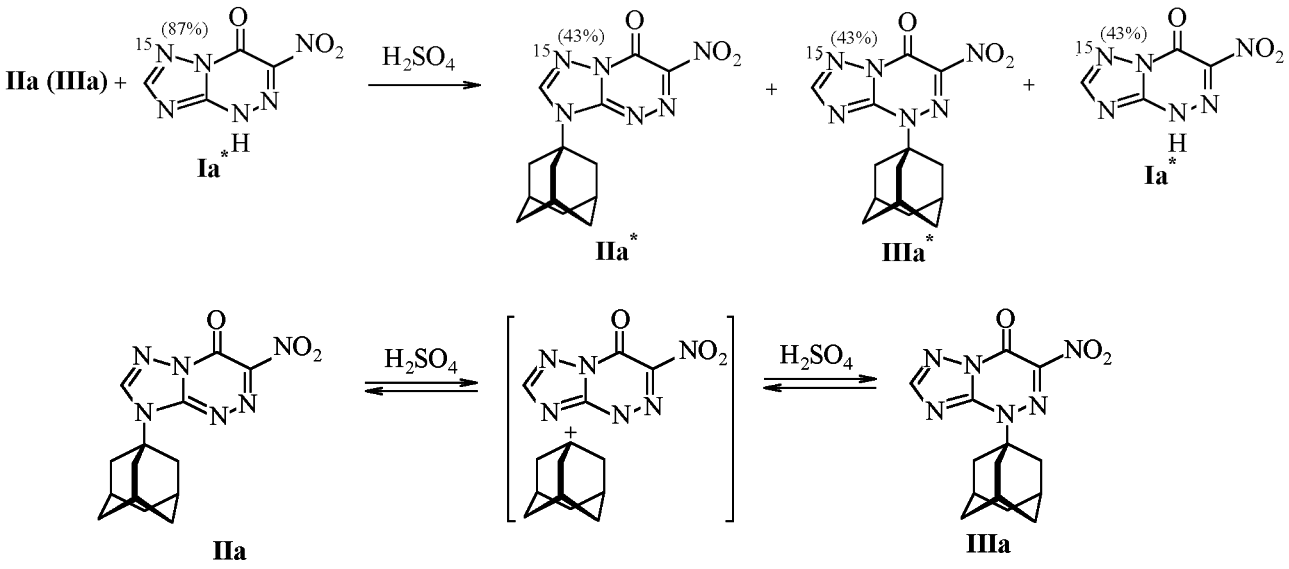
The equilibrium ratio of heteryladamantyls **IIa** and **IIIa** shows that isomer **III** is thermodymamically more favored.

EXPERIMENTAL

IR spectra of compounds obtained were recorded on spectrophotometer Specord 75IR from mulls in mineral oil. ^1H and 13C NMR spectra were registered in DMSO-d_6 on spectrometers Bruker WM-250, Bruker DRX-400, and Bruker DRX-500, internal reference TMS. Mass spectra of compounds synthesized were measured on Varian MAT-311A instrument with direct input of samples into ion source, ionizing electrons energy 70 eV, ionizing chamber temperature 100–300°C. TLC was carried out on Silufol UV-254 plate, eluent ethyl ether (100%, *c*) and ethyl acetate (100%, *d*) (Table 1), development in iodine vapor or under UV irradiation.

X-ray diffraction study. Crystals of compound **IIIb** rhombic with the following unit cell parameters:

Scheme.



a 20.437(5), *b* 12.650(3), *c* 11.594(3) Å, *Z* 8, d_{calc} 1.464 g–cm^{-3}, μ 0.106 mm^{-1}, *V* 2997(1) Å^3, space group P_{bca}. The structure was solved by the direct method and was refined by the least-squares procedure using SHELXS-86 and SHELXS-93 software in anisotropic (isotropic for H atoms) approximation to *R* 0.047 (wR_2 0.136) for 3042 reflections with $F^2 > 2\sigma$ at adjustment factor GOOF 1.071. The experiment was carried out on automatic diffractometer Inraf-Nonius, Cad-4 (λMoK_α, graphite monochromator, ω-scanning $2\theta_{max}$ 60°, 4400 reflections, among them 3042 with $F^2 > 2\sigma$).

***N*-Adamantyl-3-nitro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (IIa, IIIa).** (a). To a suspension of 0.7 g (3.7 mmol) of compound Ia in 5 ml of 96% sulfuric acid cooled to –15°C was added 4.5 mmol of 1-adamantyl nitrate (1-adamantanol), and the mixture was kept at this temperature for 3 h. The reaction mixture was then poured into water with ice and neutralized with sodium acetate solution. The separated precipitate was filtered off, washed with ethanol, and dried. Then it was extracted with hot CCl_4 (5 × 30 ml). The insoluble residue containing prevailingly compound **IIa** was filtered off and crystallized from ethanol. The extract was evaporated, and the residue was crystallized from ethanol to separate isomer **IIIa**.

(b) To a suspension of 0.7 g (3.7 mmol) of triazolotriazine **Ia** in 5 ml of 96% sulfuric acid at room temperature was added 4.5 mmol of 1-adamantyl nitrate (1-adamantanol), and the mixture was kept at this temperature for 3 h. Further workup was carried out as in procedure (a).

(c) To 0.9 g (3.7 mmol) of sodium salt **IVa** and 1.1 g (5 mmol) of 1-bromoadamantane was added 5 ml of sulfolane, the reaction mixture was heated to 150–180°C for 20–40 min. On cooling the reaction mixture was poured into water, the precipitate was filtered off, washed with ethanol, and dried. The isomers were separated as in procedure (a).

6-^{15}N-Adamantyl-3-nitro-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (IIa*, IIIa*). A mixture of 0.35 g (1.85 mmol) of compound **Ia*** enriched in ^{15}N to 87% and 0.35 g (1.85 mmol) of compound **Ia** was dispersed in 5 ml of 96% sulfuric acid, the suspension was cooled to –15°C, 4.5 mmol of 1-adamantyl nitrate (1-adamantanol) was added, and the mixture was kept at this temperature for 3 h. Further workup was carried out as in procedure (a), Compounds **IIa*** and **IIIa*** were obtained enriched in ^{15}N to 43%. 7-Methyl-*N*-adamantyl-3-substituted 1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (**IIIb, e**) were obtained along procedures *a* and *b* from 3.7 mmol of the corresponding triazolotriazine **Ib, e**. The precipitate arising of dilution the reaction mixture with ice water was filtered off and crystallized from an appropriate solvent.

7-Methylthio-*N*-adamantyl-3-substituted 1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (IIIc, f). (a) A suspension of 3.7 mmol of the corresponding triazolotriazine **Ic, f** in 5 ml of 96% sulfuric acid was cooled to −15°C, and 4.5 mmol of 1-adamantanol was added thereto. The mixture was kept at this temperature for 3 h. The reaction mixture was then poured into water with ice and neutralized with sodium acetate solution. The separated precipitate was filtered off and crystallized from an appropriate solvent.

(b) To a suspension of 3.7 mmol of the triazolotriazine **Ic, e** in 5 ml of 96% sulfuric acid was added at room temperature 4.5 mmol of 1-adamantanol. The mixture was kept at this temperature for 3 h. The reaction mixture was then poured into water with ice and neutralized with sodium acetate solution. The separated precipitate was filtered off and crystallized from an appropriate solvent.

7-Methylsulfinyl-*N*-adamantyl-3-substituted 1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (IIIg, h). A suspension of 3.7 mmol of the corresponding triazolotriazine **Ic, f** in 5 ml of 96% sulfuric acid was cooled to −15°C, and 4.5 mmol of 1-adamantyl nitrate was added thereto. The mixture was kept at this temperature for 3 h. The reaction mixture was then poured into water with ice and neutralized with sodium acetate solution. The separated precipitate was filtered off and crystallized from an appropriate solvent.

8-Adamantyl-3-ethoxycarbonyl-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-one (IId) was prepared by procedures (a) and (b) from 0.8 g (3.7 mmol) of triazolotriazine Id. The precipitate arising of dilution the reaction mixture with ice water was filtered off and crystallized from an appropriate solvent.

8-Adamantyl-3-ethoxycarbonyl-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones (IId, IIId) were prepared by procedure *c* from 0.9 g (3.7 mmol) of salt **IVd**. Isomers were separated along procedure a.

Isomerization of compounds IIa and IIIa. In concentrated sulfuric acid was dissolved 0.3 g of compound **IIa** (or **IIIa**), and the solution was left standing for 12 h at room temperature. Then the reaction mixture was poured into water with ice, the precipitate was filtered off, washed with ethanol, dried, and subjected to ^{1}H NMR measurement.

Isomerization of compounds IIa and IIIa in the presence of 6-^{15}N-adamantyl-3-nitro-1,4-dihydro-1,2,4-triazolo[5,1-*c*]-1,2,4-triazin-4-ones. In 5 ml of concentrated sulfuric acid was dissolved 0.5 g (1.6 mmol) of compound **IIa** (or **IIIa**), and 0.29 g (1.6 mmol) of compound **Ia*** was added (degree of enrichment of the latter in ^{15}N 87%). The solution was left standing for 12 h at room temperature. Then the reaction mixture was poured into water with ice, the precipitate was filtered off, washed with ethanol, dried, and subjected to ^{1}H NMR measurement. The isomers were separated as in procedure a. We obtained compounds **IIa*** and **IIIa*** enriched in 15N to 43%.

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