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INTERACTION OF α,β-UNSATURATED KETONES OF THE ADAMANTANE SERIES WITH N,N'-BINUCLEOPHILES

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The influence has been established of the structure of the initial ketone, the reactants, and the reaction conditions on the direction of the interaction of α,β-unsaturated ketones of the adamantane series with hydrazine, phenylhydrazine, semicarbazide, thiosemicarbazide, urea, and thiourea. It was found that on interaction with hydrazine and phenylhydrazine both intermediate hydrazones and the final cyclization products, pyrazolines, were formed. Reaction with semicarbazide and thiosemicarbazide leads only to the synthesis of derivatives at the carbonyl group, semicarbazones and thiosemicarbazones, but with urea and thiourea leads to products of addition at the double bond.

Keywords: hydrazones, α,β-enones, ureas, α,β-unsaturated ketones, pyrazolines, semicarbazones, thioureas, thiosemicarbazones, addition.

α,β-Unsaturated ketones serve as starting materials for the synthesis of a large number of heterocyclic compounds [1,2]. In addition their use in the synthesis of heteryl-substituted adamantanes is rarely met in the literature [3-5]. The interaction of 3-(1-adamantyl)-1-aryl-1-propen-3-ones with hydroxylamine was described in [6]. The authors succeeding in isolating a substituted isoxazole only in the case of Ar = 4-$O_2NC_6H_4$.

We previously described the synthesis of 4-(1-adamantyl)-1-R-buten-3-ones from (1-adamantyl)acetone [7]. With the aim of studying the chemical properties of α,β-unsaturated ketones of the adamantane series synthesized by us we reacted 3-(1-adamantyl)-1-phenyl-1-propen-3-one (**1**) [6], 4-(1-adamantyl)-1-phenyl-1-buten-3-one (**2**) [7], and 3-(1-adamantyl)-1-(4-nitrophenyl)-1-propen-2-one **3** [6] with hydrazines. The choice of starting materials was determined by the following factors.

1) Compared with unsaturated ketones **1** and **3** ketone **2** has a methylene group between the adamantyl residue and the carbonyl which enables assessment of the degree of influence of the adamantyl residue on the cyclization process.

2) Compound **3** contains a nitro group in the phenyl residue exerting an influence on the conjugated system –C(=O)CH=CH–.

Reactions were carried out with 99% hydrazine and freshly distilled phenylhydrazine. Under acidic conditions (acetic acid, sulfuric acid) ketones **1-3** give cyclic products with 99% hydrazine, *viz*. 5-(1-adamantyl)-3-phenylpyrazoline (**4a**), 5-(1-adamantylmethyl)-3-phenylpyrazoline (**4b**), and 5-(1-adamantyl)-3-(4-nitrophenyl)pyrazoline (**4c**). Under alkaline conditions (ethyl alcohol, KOH) the reaction of ketone **3** with hydrazine leads to the synthesis of hydrazone **5**. Refluxing hydrazone **5** in acetic acid in the presence of sulfuric

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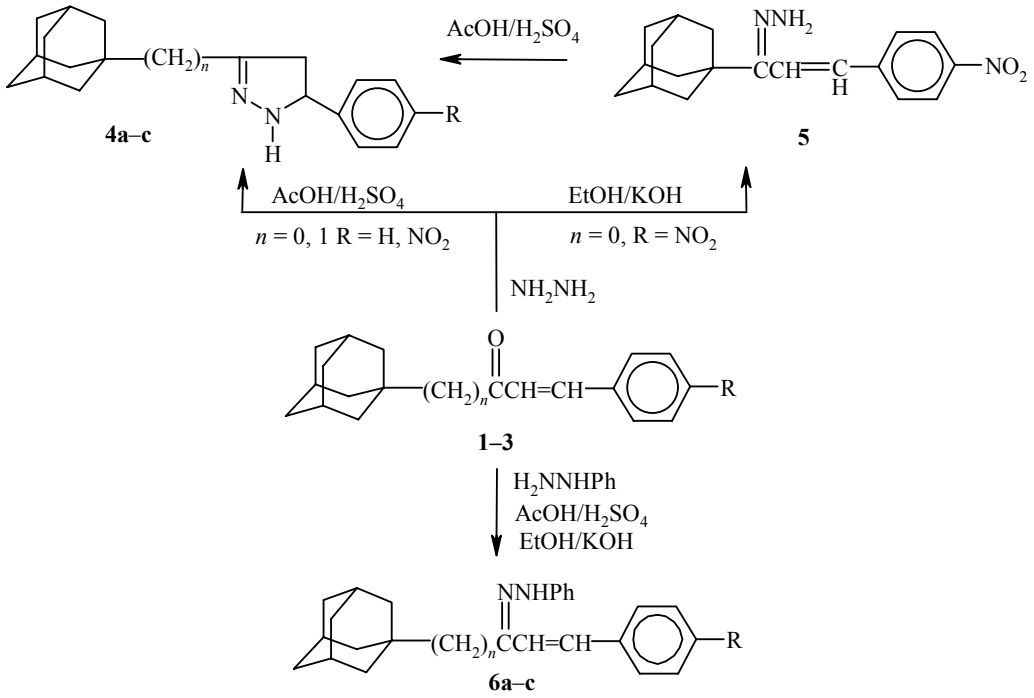
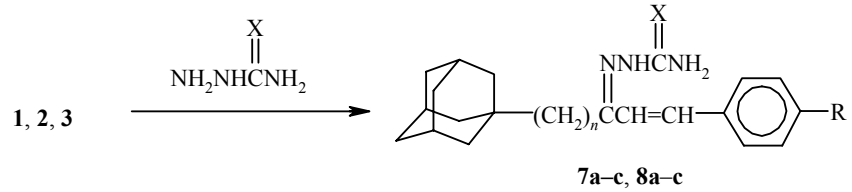
acid also leads to the synthesis of pyrazoline **4c**. On reacting the α,β-unsaturated ketones **1-3** with phenylhydrazine both under alkaline (ethyl alcohol–KOH, ethyl alcohol–EtONa, DMSO–KOH, ethyl alcohol–piperidine) and under acidic conditions (acetic acid–sulfuric acid) only hydrazones **6a-c** were obtained.



1, **4a**, **6a** n = 0, R = H; **2**, **4b**, **6b** n = 1, R = H; **3**, **4c**, **6c** n = 0, R = NO_2

The kinetics and mechanism of formation of pyrazolines from α,β-unsaturated ketones and phenylhydrazine was studied previously with the aid of polarography [8-10]. The following reaction scheme was proposed as a result, probably also valid in our case. At the first step addition of the more nucleophilic β-nitrogen atom occurs at the carbon atom of the carbonyl group of the α,β-unsaturated ketones. At the second step conversion of the addition products into hydrazones occurs. According to literature data this is the limiting stage. In the third and subsequent stages cyclization of the hydrazones into pyrazolines occurs.

In a continuation of studies on the interaction of α,β-unsaturated ketones of the adamantane series with N,N'-binucleophiles we carried out the reaction of ketones **1-3** with semicarbazide and thiosemicarbazide in alcohol in the presence of catalytic quantities of HCl. As is known, the interaction of α,β-unsaturated ketones with semicarbazide and thiosemicarbazide leads to the synthesis of pyrazolines [1,2]. However we obtained derivatives of only the carbonyl group, the new semicarbazones and thiosemicarbazones **7** and **8**, which displayed no inclination towards heterocyclization on heating either in alkaline (KOH–alcohol, piperidine–alcohol, 10% EtONa, 20% MeONa, KOH–DMSO) or acidic (AcOH–H_2SO_4, propionic acid–H_2SO_4) media.



7, 8 a n = 0, R = H, **b** n = 1, R = H, **c** n = 0, R = NO_2; **7a–c** X = O; **8a–c** X = S

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, ν, cm^{-1}		Yield, %
		C	H	N		CH_2 Ad	others	
1	2	3	4	5	6	7	8	9
4a	$C_{19}H_{24}N_2$	81.00 / 81.38	8.70 / 8.63	10.30 / 9.99	177-179	2900, 2850	1640 (C=N), 3420 (NH)	51
4b	$C_{20}H_{26}N_2$	82.00 / 81.59	9.00 / 8.90	9.00 / 9.51	96-98	2900, 2850	1670 (C=N), 3480 (NH)	42
4c	$C_{19}H_{23}N_3O_2$	70.25 / 70.13	7.15 / 7.12	12.54 / 12.91	157-158	2900, 2850	1335, 1605 (NO_2), 1665 (C=N), 3425 (NH)	63
5	$C_{19}H_{23}N_3O_2$	70.50 / 70.13	7.00 / 7.12	13.00 / 12.91	>300	2900, 2850	1610 (C=N), 3260 (NH)	89
6a	$C_{25}H_{28}N_2$	84.55 / 84.23	8.00 / 7.92	7.45 / 7.85	146-147	2900, 2850	1610 (C=N), 3150 (NH)	92
6b	$C_{26}H_{30}N_2$	84.10 / 84.28	8.60 / 8.16	7.30 / 7.56	114-116	2900, 2850	1620 (C=N), 3130 (NH)	84
6c	$C_{25}H_{27}N_3O_2$	75.10 / 74.79	6.90 / 6.78	10.55 / 10.47	278-280	2900, 2850	1305, 1600 (NO_2), 1670 (C=N), 3230 (NH)	87
7a	$C_{20}H_{25}N_3O$	74.77 / 74.27	8.00 / 7.79	12.16 / 12.99	202-204	2900, 2850	1690 (C=N), 3340, 3120 (NH, NH_2)	98

TABLE 1 (continued)

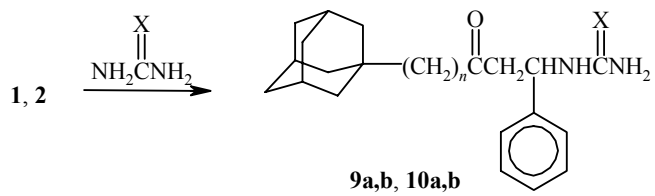
1	2	3	4	5	6	7	8	9
7b	$C_{21}H_{27}N_3O$	75.00 74.74	8.23 8.06	12.45 12.45	192-193	2900, 2850	1605 (C=N), 3480, 3170 (NH, NH_2)	96
7c	$C_{20}H_{24}N_4O_3$	65.37 65.20	6.94 6.57	15.79 15.21	284-286	2900, 2850	1325, 1615 (NO_2), 1670 (C=N), 3405, 3210 (NH, NH_2)	97
8a	$C_{20}H_{25}N_3S$	70.37 70.76	7.80 7.42	12.00 12.38	185-187	2900, 2850	1630 (C=N), 3475, 3340 (NH, NH_2)	99
8b	$C_{21}H_{27}N_3S$	71.75 71.35	8.00 7.70	12.00 11.89	184-186	2900, 2850	1610 (C=N), 3420, 3255 (NH, NH_2)	98
8c	$C_{20}H_{24}N_4O_2S$	62.84 62.48	6.00 6.29	15.12 14.57	200-201	2900, 2850	1340, 1600 (NO_2), 1610 (C=N), 3420, 3355 (NH, NH_2)	95
9a	$C_{20}H_{26}N_2O_2$	74.00 73.59	8.00 8.03	9.00 8.58	192-193	2900, 2850	1695 (C=O), 3205, 3300 (NH, NH_2)	82
9b	$C_{20}H_{26}N_2OS$	70.00 70.14	8.00 7.65	8.00 8.18	209-211	2900, 2850	1670 (C=O), 3230, 3410 (NH, NH_2)	85
10a	$C_{21}H_{28}N_2O_2$	75.00 74.08	9.00 8.28	8.00 8.23	237-239	2900, 2850	1690 (C=O), 3220, 3350 (NH, NH_2)	86
10b	$C_{21}H_{28}N_2OS$	70.55 70.75	7.90 7.92	7.75 7.86	160-161	2900, 2850	1680 (C=O), 3200, 3390 (NH, NH_2)	87

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)	
	CH_2 Ad, CH Ad, 15H, m	Other protons
4a	1.65-1.80	3.30 (1H, br. s, NH); 4.70 (2H, d, *J* = 5.6, CH_2 pyrazoline); 5.25-5.40 (1H, m, CH pyrazoline); 6.64-7.72 (5H, m, C_6H_5)
4b	1.65-1.90	2.15 (2H, s, Ad$\underline{CH_2}$); 3.50 (1H, br. s, NH); 5.20 (2H, d, *J* = 6.0, CH_2 pyrazoline); 5.45 (1H, m, CH pyrazoline); 7.00-7.42 (5H, m, C_6H_5)
4c	1.65-1.85	3.50 (1H, br. s, NH); 5.20 (2H, d, *J* = 5.8, CH_2 pyrazoline); 5.50 (1H, m, CH pyrazoline); 7.40-8.20 (4H, m, C_6H_4)
5	1.50-1.95	3.50 (2H, br. s, NH_2); 6.58 (1H, d, *J* = 15.2, CH=); 7.95 (1H, d, *J* = 15.2, =$\underline{CH}C_6H_4$); 8.00-8.30 (4H, m, C_6H_4)
6a	1.65-1.90	5.00 (1H, br. s, NH); 6.55 (1H, d, *J* = 14.4, CH=); 6.88 (1H, d, *J* = 14.4, =$\underline{CH}C_6H_5$), 7.00-7.70 (10H, m, $2C_6H_5$)
6b	1.65-1.90	2.23 (2H, s, Ad$\underline{CH_2}$); 4.60 (1H, br. s, NH); 6.98 (1H, d, *J* = 13.1, CH=); 7.18 (1H, d, *J* = 13.1, =$\underline{CH}C_6H_5$); 7.26-7.80 (10H, m, $2C_6H_5$)
6c	1.65-1.95	5.00 (1H, br. s, NH); 6.55 (1H, d, *J* = 14.4, CH=); 6.88 (1H, d, *J* = 14.4, =$\underline{CH}C_6H_5$); 7.00-7.70 (10H, m, $2C_6H_5$)
7a	1.60-1.95	3.71-3.88 (3H, br. s, NH, NH_2); 5.76 (1H, d, *J* = 13.5, CH=); 5.95 (1H, d, *J* = 13.5, =CH); 6.92-7.31 (5H, m, C_6H_5)
7b	1.55-1.80	2.10 (2H, s, Ad$\underline{CH_2}$); 3.23-3.34 (3H, br. s, NH, NH_2); 5.28 (1H, d, *J* = 12.9, CH=); 5.69 (1H, d, *J* = 12.9, =CH); 7.12-7.24 (5H, m, C_6H_5)
7c	1.52-1.83	3.95-4.09 (3H, br. s, NH, NH_2); 5.69 (1H, d, *J* = 13.5, CH=); 5.82 (1H, d, *J* = 13.5, =CH); 7.11-7.29 (4H, m, C_6H_4)
8a	1.65-1.80	3.24-3.46 (3H, br. s, NH, NH_2); 5.69 (1H, d, *J* = 13.7, CH=); 5.82 (1H, d, *J* = 13.7, =CH); 7.10-7.25 (5H, m, C_6H_5)
8b	1.54-1.85	2.10 (2H, s, Ad$\underline{CH_2}$); 3.33-3.54 (3H, br. s, NH, NH_2); 5.73 (1H, d, *J* = 12.9, CH=); 5.85 (1H, d, *J* = 12.9, =CH); 7.07-7.28 (5H, m, C_6H_5)
8c	1.65-1.80	3.57-3.69 (3H, br. s, NH, NH_2); 5.81 (1H, d, *J* = 13.7, CH=); 5.96 (1H, d, *J* = 13.7, =CH); 7.17-7.28 (4H, m, C_6H_4)
9a	1.65--.95	4.42 (2H, d, *J* = 7.3, CH_2); 4.90 (1H, m, CH); 6.95 (1H, br. s, NH); 7.20-7.50 (5H, m, C_6H_5); 7.85 (2H, br. s, NH_2)
9b	1.65-1.95	4.70 (2H, d, *J* = 7.0, CH_2); 4.95 (1H, m, CH); 7.20-7.50 (5H, m, C_6H_5); 8.80 (1H, br. s, NH); 9.05 (2H, br. s, NH_2)
10a	1.65-1.90	2.45 (2H, s, CH_2C=O); 4.35 (2H, d, *J* = 6.8, CH_2); 4.95 (1H, m, CH); 7.00 (1H, br. s, NH); 7.80 (2H, br. s, NH_2)
10b	1.65-1.90	2.50 (2H, s, CH_2C=O); 4.65 (2H, d, *J* = 7.6, CH_2); 4.95 (1H, m, CH); 7.20-7.45 (5H, m, C_6H_5); 8.75 (1H, br. s, NH); 9.15 (2H, br. s, NH_2)

The reaction of unsaturated ketones with urea and thiourea under base catalysis conditions usually leads to the preparation of hydrogenated derivatives of pyrimidine [1,2].

The interaction of compounds **1** and **2** with urea and thiourea was carried out in methanol in the presence of sodium methylate. As was shown by data of IR and ^{1}H NMR spectroscopy and elemental analysis, addition products at the double bond were obtained, *viz*. [3-(1-adamantyl)-3-oxo-1-phenylpropyl]urea (**9a**), [4-(1-adamantyl)-3-oxo-1-phenylbutyl]urea (**10a**), [3-(1-adamantyl)-3-oxo-1-phenylpropyl]thiourea (**9b**), and [4-(1-adamantyl)-3-oxo-1-phenylbutyl]thiourea (**10b**).



9a,b, **10a,b**

9 *n* = 0, **10** *n* = 1, **a** X = O, **b** X = S

The mechanism of the interaction of urea and its analogs with aromatic α,β-unsaturated ketones was considered in [11-13]. The authors assumed that the first step was always β addition to the double bond, irrespective of the type of catalyst used. The sequence of the stages of 1,2- and 1,4-addition was not proved strictly.

The conclusions were based only on the assumption that urea and its analogs have a low reactivity in relation to carbonyl compounds. The condensation of products of addition at the carbonyl group in the second stage is an intramolecular process.

The experimental data obtained by us prove that the first stage of the interaction of α,β-unsaturated ketones with urea and thiourea is addition at the double bond. Steric hindrance from the adamantyl residue makes cyclization at the carbonyl group impossible, which is the distinguishing feature of the adamantyl-containing α,β-unsaturated ketones **9** and **10** synthesized by us.

In the reaction of α,β-unsaturated ketones of the adamantane series with hydrazine and phenylhydrazine the effect has been shown of the structure of the initial ketone, of the hydrazine, and of the reaction conditions on the direction of the reaction. On interacting adamantyl-containing unsaturated ketones with semicarbazide and thiosemicarbazide the derivatives at the carbonyl group, semicarbazones and thiosemicarbazones, were obtained, and with urea and thiourea products of addition at the double bond were synthesized.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker AC 300 (300 MHz) and Bruker DS 80 (80 MHz) instruments in DMSO and $(CD_3)_2CO$, internal standard was HMDS. The IR spectra were obtained on a Specord M 80 instrument in potassium bromide. The physicochemical and spectral characteristics of compounds are given in Tables 1 and 2.

5-(1-Adamantyl)-3-phenylpyrazoline (4a), 5-(1-Adamantylmethyl)-3-phenylpyrazoline (4b), 5-(1-Adamantyl)-3-(4-nitrophenyl)pyrazoline (4c) (General Procedure). A mixture of ketone **1** [6], **2** [7], or **3** [6] (3.8 mmol), 99% hydrazine (0.12 ml, 0.12 g, 3.8 mmol), and acetic acid (10 ml) was heated to boiling, conc. H_2SO_4 (1 drop) was added, and the mixture refluxed for 8 h. The reaction mixture was then diluted with water (100 ml), the solid was filtered off, and recrystallized from ethanol.

Hydrazone of 3-(1-Adamantyl)-3-(4-nitrophenyl)-1-propen-3-one (5). A solution of ketone **3** (0.5 g, 1.6 mmol), 99% hydrazine (0.06 ml, 0.06 g, 1.6 mmol), and KOH (0.1 g, 1.8 mmol) in ethanol (10 ml) was refluxed for 1 h. The precipitated solid was filtered off, and recrystallized from DMF.

Phenylhydrazones of 3-(1-Adamantyl)-1-phenyl-1-propen-3-one (6a), 4-(1-Adamantyl-1-phenyl-1-buten-3-one (6b), and 3-(1-Adamantyl)-3-(4-nitrophenyl)-1-propen-3-one (6c) (General Procedure). Ketone **1**, **2**, or **3** (10 mmol) was dissolved with heating in ethanol (8 ml), freshly distilled phenylhydrazine (0.97 ml, 1.06 g, 10 mmol), and 20% KOH in alcohol (5 ml) were added. The mixture was refluxed for 1 h, after which the reaction mixture was cooled, the precipitated solid was filtered off, dried, and recrystallized from ethanol.

Semicarbazones (7a-c) and Thiosemicarbazones (8a-c) (General Procedure). A solution of ketone **1**, **2**, or **3** (7.5 mmol), semicarbazide (or thiosemicarbazide) (7.5 mmol), and conc. hydrochloric acid (3 ml) in alcohol (10 ml) was refluxed for 1 h, and cooled. Water (100 ml) was added, the solid was filtered off, dried, and recrystallized from ethanol.

[3(or 4)-(1-Adamantyl)-3-oxo-1-phenylpropyl(or butyl)]ureas (9a, 10a), [3(or 4)-(1-Adamantyl)-3-oxo-1-phenylpropyl(or butyl)]thioureas (9b, 10b) (General Procedure). A solution of ketone **1** or **2** (1.9 mmol) and urea (or thiourea) (1.9 mmol) in 10% sodium ethylate (15 ml) was refluxed for 5 h. The reaction mixture was cooled, the precipitated solid was filtered off, and recrystallized from ethanol.

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