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Synthesis and Cyclization of Diketones from the Adamantane Series

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Abstract—Cyclic β- and γ-diketones of the adamantane series were synthesized by reactions of chlorides of 1-adamantanecarboxylic acids and 1-adamantyl bromomethyl ketone with cyclic enamines 1-morpholino-1-cyclopentene and 1-morpholino-1-cyclohexene. Cyclization of the β-diketones obtained was performed by reaction with hydroxylamine and phenylhydrazine.

β-Diketones are well-known initial compounds in the syntheses of quite a number of heterocycles [1]. However a synthesis of β-diketones of adamantane series was considered only in a few articles. In [2, 3] was described the application of metal complexes (of copper or cobalt) from aliphatic β-diketones to the preparation of α-(1-adamantyl)-β-dicarbonyl compounds. For instance, by reaction between copper bis(3-methylpentane-2,4-dithionate) with 1-bromoadamantane at heating in chloroform or chlorobenzene for 48 h were obtained 3-(1-adamantyl)-3-methylpentane-2,4-diones [3].

Cyclic β-diketones can be prepared by Stork reaction, namely by acylation of enamines with acyl chlorides in the presence of triethylamine followed by hydrolysis [4–6]. This reaction is best studied on the cyclic enamines and acyl chlorides of aliphatic [7] and aromatic acids [8, 9]. Here in some cases were separated intermediate vinylog amides [10], the reaction course was studied with NMR spectroscopy [11], and also was elucidated the influence of various bases [12], of enamine cycle size [13], was determined the structure of β-diketones formed [14, 15], and were investigated further chemical transformations thereof [16]. The cyclic β-diketones at certain basicity of the medium can be cleaved into ketocarboxylic acids with chain elongation [17–21].

In extension of our studies [22–26] on the synthesis of carbonyl derivatives of adamantane series we carried out reactions of 1-adamantylcarbonyl chloride (**I**), 3-bromo-1-adamantylcarbonyl chloride (**II**), and 1-adamantylacetyl chloride (**III**) with cyclic enamines (1-morpholino-1-cyclopentene and 1-morpholino-1-cyclohexene) and obtained the corresponding diketones. The reactions were performed in chloroform in the presence of anhydrous triethylamine, and the subsequent hydrolyses was done with 10% hydrochloric acid. Apparently intermediately form unstable in air β-aminovinyl ketones that afford on hydrolysis 2-(1-adamantanoyl)cyclopentane-1-one (**IV**), 2-(1-adamantanoyl)cyclohexane-1-one (**Va**), 2-(3-hydroxy-1-adamantanoyl)cyclohexane-1-one (**Vb**), and 2-(1-adamantanoylmethyl)cyclohexane-1-one (**Vc**). Similar to the synthesis of 3-hydroxy-1-adamantyl methyl ketone [22] in this reaction at the hydrolysis stage the bromine is replaced by hydroxy group.

Aiming at preparation of new γ-diketones of the adamantane series we carried out a reaction of 1-adamantyl bromomethyl ketone (**VI**) with 1-morpholino-1-cyclopentene and 1-morpholino-1-cyclohexene in benzene followed by hydrolysis with 10% hydrochloric acid. As a result were isolated 2-(1-adamantanoylmethyl)cyclopentan-1-one (**VII**, $n = 0$), and 2-(1-adamantanoylmethyl)cyclohexan-1-one (**VIII**, $n = 1$).

This reaction is a continuation of the study on the chemical properties of bromoketone **VI**. Formerly was studied the behavior of ketone **VI** in N-alkylation of amines [25], C-alkylation of diethyl malonate [27], and O-alkylation with sodium or potassium methylate (ethylate, isopropylate, *tert*-butylate) [28].

In order to investigate the chemical properties of diketones from adamantane series and in extension of our studies on heterocycle synthesis we carried out reactions of β-diketone (**IV**) with hydroxylamine hydrochloride and phenylhydrazine. As a result were obtained respectively 3-(1-adamantyl)-5,6-dihydro-4*H*-cyclopenta[*c*]isoxazole (**IX**) and 3-(1-adamantyl)-2-phenyl-2,4,5,6-tetrahydro[*c*]pyrazole (**X**). Yields, properties, elemental analyses, and IR spectra of compounds synthesized are listed in Table 1, and their ^{1}H NMR spectra in Table 2.

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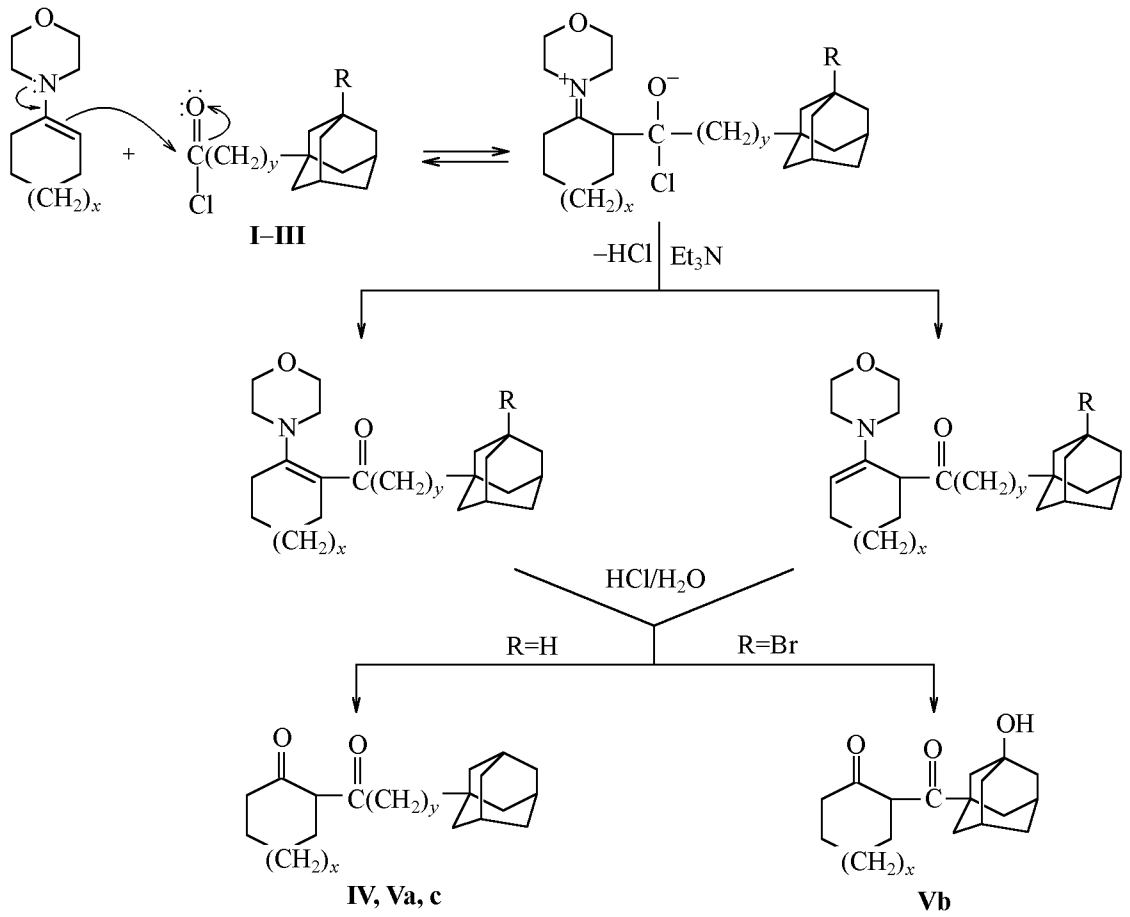
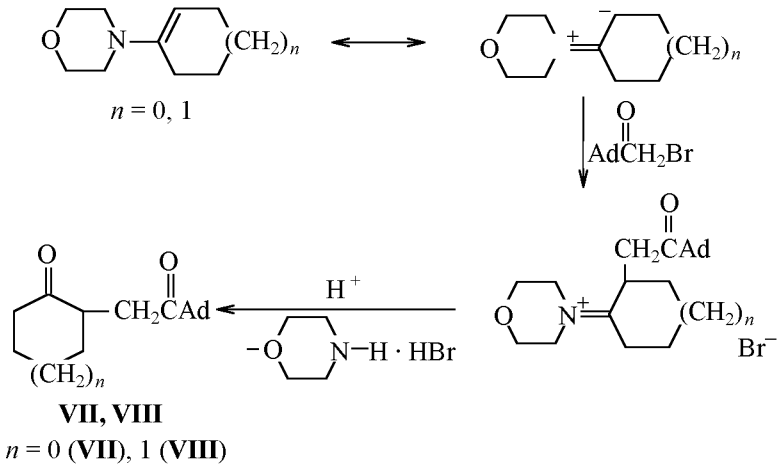


I, R = H, y = 0; **II**, R = Br, y = 0; **III**, R = H, y = 1; **IV**, x = 0, y = 0; **Va**, x = 1, y = 0; **Vb**, x = 1; **Vc**, x = 1, y = 1.



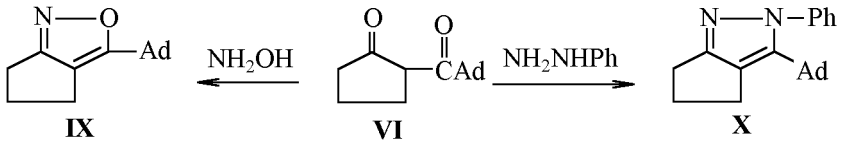


Table 1. Physico-chemical characteristics of compounds synthesized

Compd. no.	Yield, %	mp, °C	R_f (eluent)	IR spectrum, ν, cm^{-1}				Found, %			Formula	Calculated, %		
				CH_2Ad	C=O	OH	C=N	C	H	N		C	H	N
IV	51	96–98	0.37 (acetone–CCl_4, 1:4)	2900, 2850	1740	–	–	79.85	7.05	–	$C_{16}H_{17}O_2$	79.64	7.10	
Va	53	131–132	0.65 (acetone)	2920, 2870	1700	–	–	78.50	9.25	–	$C_{17}H_{24}O_2$	78.42	9.29	
Vb	50	98–100	0.54 (acetone)	2910, 2860	1690	3360	–	74.00	8.70	–	$C_{17}H_{24}O_3$	73.88	8.75	
Vc	48	115–117	0.55 (acetone–CCl_4, 1 : 4)	2890, 2840	1700	–	–	78.80	9.55	–	$C_{18}H_{26}O_2$	78.79	9.55	
VII	76	54–55	0.26 (acetone–CCl_4, 1 : 4)	2910, 2860	1730	–	–	78.00	9.15	–	$C_{17}H_{24}O_2$	78.42	9.29	
VIII	73	255–256	0.78 (acetone)	2920, 2860	1740	–	–	79.00	10.00	–	$C_{18}H_{26}O_2$	78.79	9.55	
IX	55	168–170	0.33 (acetone–CCl_4, 1 : 1)	2900, 2860	–		1650	79.00	8.95	5.50	$C_{16}H_{21}NO$	78.97	8.70	5.76
X	58	152–153	0.76 (acetone–CCl_4, 1 : 1)	2910, 2850	–	–	1610	83.10	8.50	8.90	$C_{22}H_{26}N_2$	82.97	8.23	8.80

Table 2. ^{1}H NMR spectra of compounds synthesized, δ, ppm

Compd. no.	CH_2 of adamantane	CH of adamantane	CH_2 of cycloalkane	α-CH_2 of cycloalkane	CH of cycloalkane	OH	$\underline{CH}_2$–Ad	Other signals
IV	1.65–1.75 d (12H)	2.00 s (3H)	1.40 m (4H, $2CH_2$)	2.30 q (2H)	3.85 t (1H)	–	–	–
Va	1.65–1.75 d (12H)	1.95 s (3H)	1.25 m (6H, $3CH_2$)	2.50 q (2H)	3.55 t (1H)	–	–	–
Vb	1.60–1.75 d (12H)	1.80 s (2H)	1.55 m (6H, $3CH_2$)	2.25 q (2H)	3.58 t (1H)	3.2 s (1H)	–	–
Vc	1.65–1.75 d (12H)	1.96 s (3H)	1.37 m (6H, $3CH_2$)	2.38 q (2H)	3.63 t (1H)	–	3.25 s (2H)	–
VI	1.68–1.75 d (12H)	1.80 s (3H)	1.25–1.48 m (4H, $2CH_2$)	2.38 q (2H)	3.60 m (1H)	–	–	3.25 d [2H, $C(=O)CH_2$]
VII	1.60–1.75 d (12H)	2.05 s (3H)	1.10 m (6H, $3CH_2$)	2.50 q (2H)	3.95 m (1H)	–	–	4.60 d [2H, $C(=O)CH_2$]
IX	1.75–1.80 d (12H)	1.95 s (3H)	1.05–1.2 m (4H, $2CH_2$)	2.65 t (2H)	–	–	–	–
X	1.75–1.80 d (12H)	1.90 s (3H)	1.50–1.60 m (4H, $2CH_2$)	2.48 t (2H)	–	–	–	6.60–7.05 m (5H, C_6H_5)

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Bruker AC-300 (300.13 MHz)in DMSO, internal reference HMDS. IR spectra were recorded on Specord M-80 instrument from KBr pellets. The purity of compounds was tested by TLC on Silufol UV-254 plated, development in iodine vapor.

2-(1-Adamantanoyl)cyclopentan-1-one (IV) and 2-(3-R-1-adamantanoyl)cyclohexan-1-ones (Va–c). To a solution of 4.7 mmol of enamine and 0.72 ml (5.2 mmol) of freshly distilled triethylamine in anhydrous chloroform cooled to 0°C was added dropwise a solution of 4.7 mmol of acyl chloride **I–III** in 10 ml of anhydrous chloroform. The mixture was stirred at 0°C for 6 h and left standing in refrigerator

for 24 h. Then 20 ml of 10% HCl was added, and the mixture was boiled for 6 h. The chloroform layer was separated, washed with 10% solution of Na_2CO_3, then with water, dried, the chloroform was distilled off, and the dry residue was recrystallized first from hexane and then from 50% aqueous ethanol.

2-(1-Adamantanoylmethyl)cyclopentan-1-one (VII) and 2-(1-adamantanoylmethyl)cyclohexan-1-one (VIII). A solution of 1 g (3.9 mmol) of haloketone **VI** and 4.3 mmol of enamine in 10 ml of anhydrous benzene was refluxed for 4 h. Then 10 ml of 10% HCl was added, and the mixture was refluxed for 12 h more. The benzene layer was separated, washed with water, dried on calcium chloride, the benzene was distilled off, and the residue was recrystallized from hexane.

3-(1-Adamantyl)-5,6-dihydro-4*H*-cyclopenta[*c*]-isoxazole (IX). To a solution of 1 g (4,1 mmol) of diketone **IV** in 7 ml of ethanol was added 0.35 g (5 mmol) of hydroxylamine hydrochloride in 3 ml of water. The reaction mixture was heated for 6 h, cooled, and the crystalline precipitate (fine needles) was filtered off.

3-(1-Adamantyl)-2-phenyl-2,4,5,6-tetrahydro[*c*]-pyrazole (X). A mixture of 0.5 g (2 mmol) of diketone **IV**, 0.24 ml (2.5 mmol) of phenylhydrazine, and 10 ml of ethanol was refluxed for 6 h. The precipitate separated on cooling was filtered off and washed with cold ethanol.

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