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Synthesis of β-Aminoketones of the Adamantane Series

N. V. Makarova, I. K. Moiseev, and M. N. Zemtsova

Samara State Technical University, Samara, Russia

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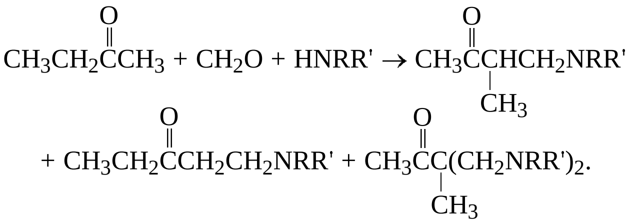
Abstract—4-(1-Adamantyl)-1-aminobutan-3-one hydrochlorides were synthesized by the Mannich reaction of (1-adamantyl)acetone with paraformaldehyde and secondary amine hydrochlorides (diethylamine, dibenzylamine, piperidine). Analogous reactions of 1-adamantyl(methyl)amine with acetone, *p*-hydroxyacetophenone, and methyl 2-thienyl ketone gave 1-[(1-adamantyl)methylamino]propan-3-one hydrochlorides.

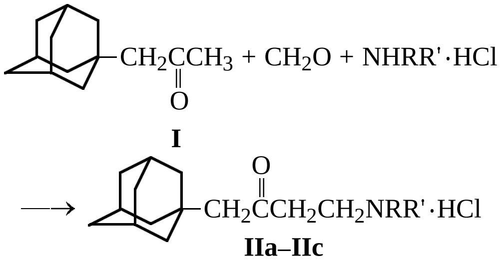
Interest in β-aminoketones (Mannich bases) is stimulated by the fact that these compounds are intermediate products in the synthesis of α,β-unsaturated ketones, β-amino alcohols, and heterocyclic compounds (dihydropyrazoles, pyridines, chroman-4-ones, isoquinolines, pyrazolo[3,4-*d*]pyridines, etc.) [1]. In addition, β-aminoketones are potential biologically active compounds with a wide spectrum of action. Some of these have found application in medical practice. For example, Phelicaine (4-propoxy-β-piperidinopropiophenone hydrochloride), Dyclonine (4-butoxy-β-piperidinopropiophenone hydrochloride), and Hexacaine (4-propoxy-β-hexamethyleneiminopropiophenone hydrochloride) are used as local anaesthetics, Mydocalm (4,α-dimethyl-β-piperidinopropiophenone) is an anticonvulsant agent, and Pyrroxan {6-[β-(3-phenyl-1-pyrrolidinyl)propionyl]-1,4-benzodioxane hydrochloride} is an α-adrenoblockator [2]. Despite increased interest (in the recent years) in the chemistry of cage-like compounds, only few data are available on the synthesis of β-aminoketones of the adamantane series. β-Aminoketones of the general formula $\mathrm{AdC(=O)CH_2CH_2NRR'\cdot HCl}$ ($R = R' = CH_3$ [3], NRR' = morpholino [4]) were obtained from 1-adamantyl methyl ketone by the Mannich reaction. Kozlov *et al.* [5] synthesized aromatic β-aminoketones of the adamantane series by reaction of 3-(1-adamantyl)-1-aryl-1-propen-3-ones with aromatic amines derived from pyridine.

β-Aminoketones can be obtained by several methods [6]: by reaction of β-haloketones with amines and by addition of amines to vinyl ketones, but the Mannich reaction is used most frequently. It involves condensation of a ketone having at least one hydrogen atom in the α position with an aldehyde (as a rule, formaldehyde) and amine. It should be noted that the Mannich reactions of unsymmetrical ketones having labile hydrogen atoms in both α and α' positions are not regioselective. For example, ethyl methyl ketone gives rise to three products [7]:



$$\mathrm{CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3 + CH_2O + HNRR' \rightarrow CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}HCH_2NRR'}$$
$$\mathrm{+\ CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_2NRR' + CH_3\overset{O}{\overset{\|}{C}}\underset{CH_3}{\underset{|}{C}}(CH_2NRR')_2.}$$

Although the Mannich reaction was the subject of extensive studies, the selectivity problem intrinsic to unsymmetrical ketones has not been solved completely. We previously [8] described the synthesis of 3-(1-adamantyl)-1-amino-1-propen-3-ones by the Mannich reaction of 1-adamantyl methyl ketone with paraformaldehyde and various secondary amine hydrochlorides [diethylamine, (1-adamantyl)ethylamine, dibenzylamine, piperidine] and their transamination with phenylhydrazine. Taking into account that (1-adamantyl)acetone (**I**) has labile hydrogen atoms in both α and α' positions, the Mannich reaction can occur at both the methyl and methylene group of ketone **I**. In the present work we examined the Mannich reaction of (1-adamantyl)acetone (**I**) with paraformaldehyde and amine hydrochlorides in isopropyl alcohol. As a result, 4-(1-adamantyl)-1-aminobutan-3-one hydrochlorides **IIa**–**IIc** were obtained.



$R = R' = C_2H_5$ (**a**), $CH_2C_6H_5$ (**b**); NRR' = piperidino (**c**).

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Table 1. Yields, melting points, IR spectra, and elemental analyses of compounds **IIa**–**IIc** and **IIIa**–**IIIc**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}		Found, %			Formula	Calculated, %		
			CH_2Ad	C=O	C	H	N		C	H	N
IIa	49	216–217	2900, 2850	1720	69.00	10.05	4.60	$C_{18}H_{32}ClNO$	68.89	10.28	4.46
IIb	70	246–248	2890, 2840	1700	76.35	8.40	3.25	$C_{28}H_{36}ClNO$	76.77	8.28	3.20
IIc	82	191–193	2900, 2850	1690	69.75	10.00	4.60	$C_{19}H_{32}ClNO$	70.02	9.90	4.30
IIIa	39	>300	2900, 2850	1710	66.50	10.00	5.50	$C_{15}H_{26}ClNO$	66.27	9.64	5.15
IIIb[a]	53	204–206	2890, 2840	1700	66.70	9.00	4.50	$C_{18}H_{28}ClNO_2$	66.33	8.66	4.30
IIIc	45	196–198	2900, 2850	1680	64.00	7.25	4.00	$C_{18}H_{26}ClNOS$	63.59	7.71	4.12

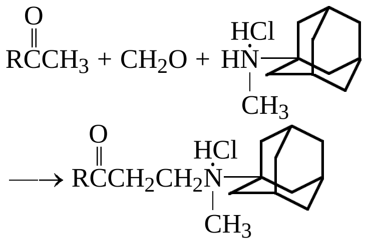
[a] ν(OH) 3100 cm^{-1}.

Table 2. ^{1}H NMR spectra of Mannich bases **IIa**–**IIc** and **IIIa**–**IIIc**, δ, ppm

Comp. no.	$CH_2(Ad)$	CH(Ad)	$CH_2C=O$	$C=OCH_2$	CH_2N	Other protons
IIa	1.55–1.65 d (12H)	1.90 s (3H)	2.50 s (2H)	2.75 t (2H)	3.20 t (2H)	1.35 m [6H, $N(CH_2\mathit{C}H_3)_2$], 2.90 m [4H, $N(\mathit{C}H_2CH_3)_2$]
IIb	1.55–1.65 d (12H)	1.90 s (3H)	2.50 s (2H)	3.00 t (2H)	3.40 t (2H)	4.05 s [4H, $N(\mathit{C}H_2C_6H_5)_2$], 7.35–7.70 m (10H, $2C_6H_5$)
IIc	1.60–1.70 d (12H)	1.95 s (3H)	2.20 s (2H)	2.80 t (2H)	3.35 t (2H)	1.12 m (2H, piperidine C^4H_2), 1.45 m (4H, piperidine $C^{3,5}H_2$), 2.50 m (4H, piperidine $C^{2,6}H_2$)
IIIa	1.65–1.70 d (12H)	1.94 s (3H)	–	3.00 t (2H)	3.35 t (2H)	2.15 s [6H, $CH_3C(=O)$, CH_3N]
IIIb	1.60–1.78 d (12H)	1.96 s (3H)	–	3.12 t (2H)	3.45 t (2H)	2.07 s (3H, CH_3H), 6.39 s (1H, OH), 6.84–7.25 m (4H, C_6H_4)
IIIc	1.65–1.75 d (12H)	2.00 s (3H)	–	2.81 t (2H)	3.20 t (2H)	2.16 s (3H, CH_3H), 6.74–7.76 m (3H, thienyl)

As follows from the product structure, only the methyl group of substrate **I** was involved. Presumably, attack on the methylene group is hindered due to the presence of bulky adamantyl group.

We also examined the possibility of involving in the Mannich reaction secondary amines of the adamantane series, using (1-adamantyl)methylamine as an example. As ketone component we used acetone, *p*-hydroxyacetophenone, and methyl 2-thienyl ketone.



IIIa–**IIIc**

R = CH_3 (**a**), 4-HOC_6H_4 (**b**), 2-thienyl (**c**).

The products were 1-[(1-adamantyl)metylamino]-propan-3-one hydrochlorides **IIIa**–**IIIc**.

Thus, our study of the Mannich reaction allowed us to synthesize new β-aminoketones having an adamantane moiety both at the ketone and at the amino group. The yields, melting points, elemental analyses, and spectral parameters of compounds **IIa**–**IIc** and **IIIa**–**IIIc** are given in Tables 1 and 2.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument in KBr. The ^{1}H NMR spectra were measured on a Bruker AC-300 spectrometer operating at 300.13 MHz; DMSO-d_6 was used as solvent, and HMDS, as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates; spots were developed with iodine vapor.

4-(1-Adamantyl)-1-aminobutan-3-one hydrochlorides IIa–**IIc** (*general procedure*)**.** A mixture of

0.5 g of ketone **I**, 0.16 g of paraformaldehyde, and 0.73 g of appropriate secondary amine hydrochloride in 10 ml of isopropyl alcohol was refluxed for 1 h. An additional 0.16 g of paraformaldehyde was added, and the mixture was refluxed for 4 h and cooled. The precipitate was filtered off and washed with ether.

1-[(1-adamantyl)methylamino]propan-3-one hydrochlorides IIIa–IIIc (*general procedure*). A mixture of 0.5 g of (1-adamantyl)methylamine, 1.3 mmol of appropriate methyl ketone, and 0.15 g of paraformaldehyde in 15 ml of isopropyl alcohol was refluxed for 18 h. The precipitate was filtered off and washed with anhydrous acetone.

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