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SHORT COMMUNICATIONS

Adamantylation of Saturated Nitrogen-Containing Heterocycles

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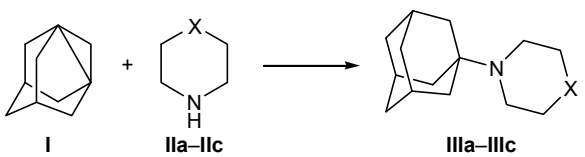
Among biologically active adamantane derivatives, a particular place is occupied by those containing nitrogen heterocycles, including saturated rings with one or two nitrogen atoms and morpholine ring, where the adamantyl radical is attached to the nitrogen atom. Derivatives of 1- and 2-aminoadamantane in which the amino nitrogen atom is a part of heterocyclic fragment attract interest as antiviral and anti-Parkinson drugs [1, 2]. The known methods of synthesis of such compounds are based on adamantylation of piperidine, piperazine, or morpholine [3] with haloadamantanes or cyclization of difunctional amines, *N*,*N*-bis(2-hydroxy- or 2-chloroethyl)adamantan-1-amines. In the first case, the reactions require high temperature, long reaction time, and the use of excess heterocyclic amine to bind liberated hydrogen halide and are accompanied by side Grob fragmentation, tarring, and other undesirable processes. The synthesis from 1-aminoadamantane [4] is multistep, and the yield of the target products is low.

With a view to develop a convenient procedure for the synthesis of saturated nitrogen heterocycles with an adamantyl group on the nitrogen atom, we tried as adamantylating agent 1,3-dehydroadamantane (**I**, tetracyclo[3.3.1.1.^{3,7}.0.^{1,3}]decane) which is classed with small-ring propellanes. We previously found that compound **I** readily reacts with various OH, SH, and CH acids [5–7], as well as with some nitrogen-containing compounds possessing NH acidity, specifically with



I **IIa–IIc** **IIIa–IIIc**

X = CH_2 (**a**), O (**b**), NH (**c**).

imidazoles, benzimidazoles [8], pyrazoles [9], and dicarboxylic acid imides [10]. These reactions involved cleavage of the propellane bond to afford a new bond between the bridgehead carbon atom of adamantane and nitrogen atom.

1,3-Dehydroadamantane (**I**) was brought into reactions with piperidine (**IIa**), morpholine (**IIb**), and piperazine (**IIc**). The reactions of **I** with saturated heterocycles **IIa**–**IIc** were expected to occur in a complicated nonselective fashion, taking into account the nature of the N–H bond in compounds **IIa**–**IIc** that are secondary amines with a higher basicity as compared to heterocycles used previously [8–10]. The NH proton in **IIa**–**IIc** is weakly acidic, and these heterocycles cannot be alkylated with unactivated alkenes or cyclopropane derivatives under mild noncatalytic conditions. There are also published data according to which some other propellanes failed to react with piperidine at the N–H bond [11, 12].

In our case, the reactions of **I** with excess heterocycles **IIa**–**IIc** were carried out at 80–100°C for 6–8 h. The products were purified by vacuum distillation. Compounds **IIIa**–**IIIc** were isolated as white crystalline substances, and their structure was confirmed by IR and ^{1}H NMR spectra and elemental analyses. The IR spectra of **IIIa** and **IIIb** lacked NH absorption at 3200–3400 cm^{-1}, typical of initial heterocycles **IIa** and **IIb**. The properties of **IIIa**–**IIIc** were consistent with the data reported in [3, 13].

The fact of alkylation of NH-heterocycles **IIa**–**IIc** with 1,3-dehydroadamantane (**I**) indicates high reactivity of the propellane bond in the latter, which makes strongly basic nitrogen heterocycles capable of reacting as proton donors.

Radical addition of some propellanes across the C–H bond of tertiary amines has been reported in [14]. In particular, [1.1.1]propellane reacted in such a way with triethylamine at the α-carbon atom. Analogous addition path was not observed in the reaction of 1,3-dehydroadamantane (**I**) with heterocycles **IIa**–**IIc**.

Thus, the results of our study allowed us to develop a convenient preparative procedure for the adamantylation of saturated nitrogen-containing heterocycles, which ensures mild one-step synthesis of heterocyclic 1-aminoadamantane derivatives with high yields and easy isolation of the products. The proposed procedure may be successfully used for the preparation of adamantyl derivatives containing other saturated rings with one or more nitrogen atoms and different numbers of carbon atoms in the ring.

1-(1-Adamantyl)piperidine (IIIa). A mixture of 10 g (0.118 mol) of piperidine (**IIa**) and 2 g (0.015 mol) of 1,3-dehydroadamantane (**I**) was heated for 6 h at 80–110°C, excess piperidine was distilled off, and the residue was distilled under reduced pressure. Yield 2.6 g (0.012 mol, 76%), bp 155°C (2 mm), mp 68°C; hydrochloride: mp 311–313°C; published data [3]: mp 312–314°C. ^{1}H NMR spectrum, δ, ppm: 1.62–1.92 m (15H, Ad), 1.32–1.40 m (6H, CH_2), 2.46–2.58 m (4H, CH_2). Found, %: C 82.19; H 11.45; N 6.36. $C_{15}H_{25}N$. Calculated, %: C 82.13; H 11.49; N 6.39.

4-(1-Adamantyl)morpholine (IIIb). From 10 g (0.104 mol) of morpholine (**IIb**) and 2 g (0.015 mol) of 1,3-dehydroadamantane (**I**) we obtained 2.48 g (0.011 mol, 75%) of compound **IIIb**, bp 145°C (1 mm); hydrochloride: mp 290–292°C; published data [3]: mp 292–294°C. ^{1}H NMR spectrum, δ, ppm: 1.61–2.05 m (15H, Ad), 2.50 t (4H, CH_2, J = 16.5 Hz), 3.52 t (4H, CH_2, J = 15.8 Hz). Found, %: C 76.02; H 10.46; N 6.29. $C_{14}H_{23}NO$. Calculated, %: C 75.97; H 10.47; N 6.33.

1-(1-Adamantyl)piperazine (IIIc). From 8.5 g (0.10 mol) of piperazine (**IIc**) and 2 g (0.015 mol) of 1,3-dehydroadamantane (**I**) we obtained 2.25 g (0.01 mol, 67%) of compound **IIIc**, bp 148–150°C (2 mm), mp 86–87°C; published data [13]: mp 86°C. ^{1}H NMR spectrum, δ, ppm: 1.68–1.95 m (15H, Ad), 2.18 s (1H, NH), 2.82–2.94 m (4H, CH_2), 3.51 t (4H, CH_2, J = 17.5 Hz). Found, %: C 76.35; H 10.92; N 12.73. $C_{14}H_{24}N_2$. Calculated, %: C 76.31; H 10.98; N 12.71.

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) from solutions in carbon tetrachloride. The chemical shifts were determined relative to hexamethyldisiloxane or tetramethylsilane.

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