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A novel method of synthesis of 1-azaadamantane from 1-boraadamantane

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Abstract

A novel and convenient method for the synthesis of 1-azaadamantane (I) from the 1-boraadamantane-tetrahydrofuran complex (XIII) is described. This is based on an intramolecular reaction of organic azides with organoboron compounds. Treatment of the boron cage compound XIII with iodine and an excess of sodium azide followed by oxidation (H_2O_2, OH^-) affords 7α-hydroxymethyl-3-azabicyclo[3.3.1]nonane (VII), cyclization of which leads to I in 40% overall yield. Some new boron cage compounds were also isolated, diazidoborane (XIV) being of particular interest.

Introduction

1-Azaadamantane (I) is an attractive compound due to its unusual geometry as well as to the biological activity of its derivatives [1–4]. Progress in this field has, however, been hampered by difficulties in assembly of the 1-azaadamantane skeleton. A characteristic feature of earlier work aimed at the synthesis of I from 1,3,5-trisubstituted cyclohexanes has been discouragingly low yields [2]. A major contribution to the solution of this problem was made by Speckamp and associates [5] who developed a route to substituted 3-azabicyclo [3.3.1]nonanes from 4-piperidone enamines with cyclization of the former into derivatives of I. An original procedure for the synthesis of 4-oxo-1-azaadamantane was suggested by Black in 1982 [6]. Nevertheless, even the best of the methods described so far still require between 7 and 9 steps to prepare 1-azaadamantane, with overall yields of 4 to 6%.

A novel approach to this problem has arisen now that 1-boraadamantane (II) and its derivatives are freely available as starting materials for the synthesis of cage compounds [7]. The structural similarity of 1-boraadamantane to 1-azaadamantane suggested possible conversion of the former into the latter. This was in fact realized in 1983 by Mikhailov and Shagova [8] with a yield of 20%. Here we describe an easier and more convenient preparation of I from its boron analogue II.

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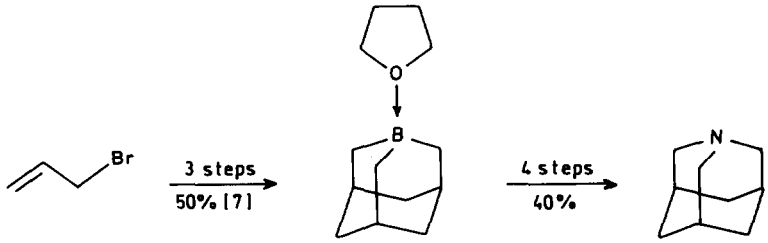
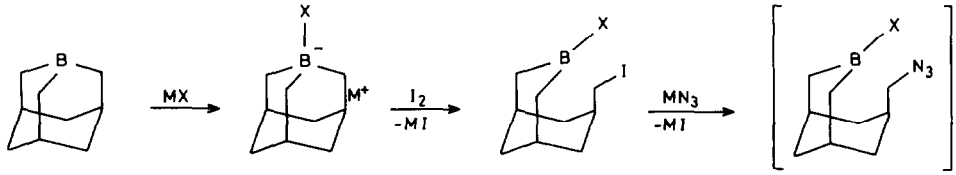


(I)

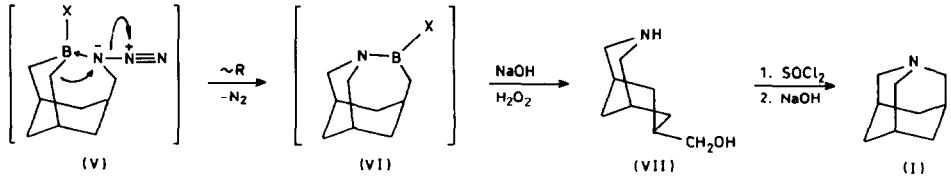
Results and discussion

The starting materials were 3-substituted 7α-iodomethyl-3-borabicyclo[3.3.1]nonanes (IV) which were prepared by iodination of the 1-boraadamantane "ate"-complexes, III [9]. The iodine atom in the bicyclic systems IV is especially prone to nucleophilic substitution [9,10] thereby facilitating its replacement by an azido-group to give unstable azides, V.



(II) (III, M = Li, Na; X = MeO (a), N_3 (b), EtO (c)) (IV) (V)

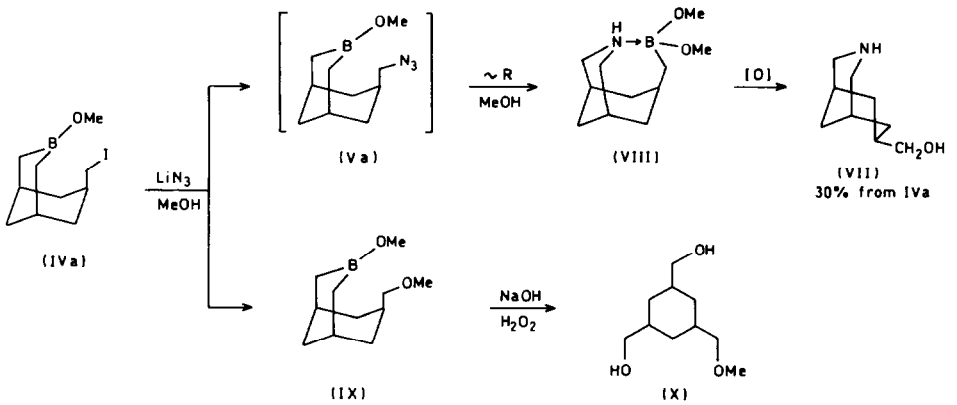
The key stage in the present scheme is an anionotropic 1,2-rearrangement of the intermediate V which proceeds with elimination of a N_2 molecule and migration of an organic moiety from boron to nitrogen [11]. This reaction in its intramolecular version has recently been employed for the preparation of pyrrolidines and piperidines [12,13]. However, this has not yet been applied to the synthesis of cage compounds. We have also demonstrated for the first time that organic azides can react with esters of dialkylborinic acids.



(V) (VI) (VII) (I)

The aminoborane rearrangement products, VI, were not isolated; oxidation with alkaline hydrogen peroxide gave bicyclic aminoalcohol VII. The latter was converted into a hydrochloride VIIa by action of HCl, and, when treated with $SOCl_2$ in benzene under reflux, afforded 1-azaadamantane (I).

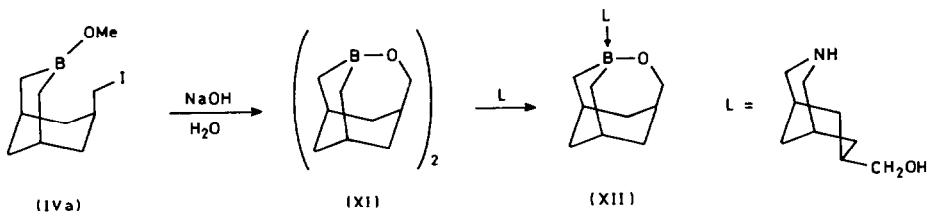
Initial experiments aimed at preparation of VII were conducted with 3-methoxy-7α-iodomethyl-3-borabicyclo[3.3.1]nonane (IVa). Its reaction with NaN_3 in DMF (130 °C, 0.5 h) resulted in a rather low yield of the target product (~ 20%) due to



concomitant side-reactions. Additional studies were undertaken to improve the synthetic procedure.

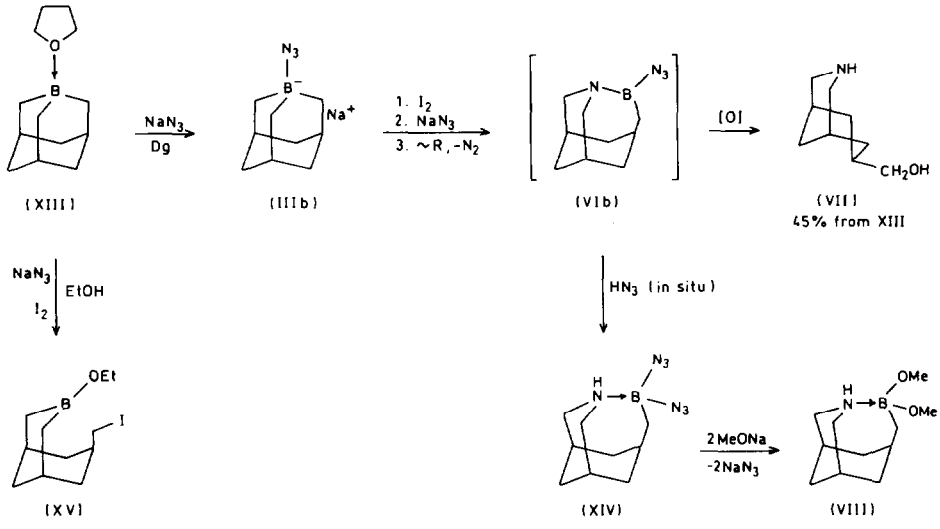
With methanol as a solvent lithium azide was used as a source of azide ions due to its greater solubility. Oxidation of the resulting internal boron–nitrogen complex VIII afforded VII in a yield of about 30% However, the proportion of one of the side products, viz. the dimethoxy derivative, IX, increased noticeably. This could result from nucleophilic substitution of the iodine atom by an methoxy group, oxidized to give the diol X.

Attempts to enhance the yield of VII by carrying out the reaction under milder conditions in the presence of Amberlite XAD-4 [14] or with a phase-transfer catalyst failed. Further, in the latter case, the drastic reaction conditions (Bu_4NI, xylene, 140 °C, 5 h) caused gradual decomposition of the catalyst. The unreacted starting material IV produced upon treatment with alkali a dimer of 4-oxa-3-bora-homoadamantane (XI) [15] which interacted with the resulting aminoalcohol VII to give a complex XII which could not be oxidized under the reaction conditions employed.



A version of the original procedure which involved iodination of the 1-boraadamantane-tetrahydrofuran complex XIII in the presence of an excess of sodium azide gave the best results. Azide ion proved to be a sufficiently strong base to form on "ate"-complex (IIIb) ($\delta^{11}B = -6.3$ ppm) which reacted readily with iodine at ambient temperature.

Diglyme was the solvent of choice and one equivalent of nitrogen evolved at 70–80 °C. The isolated reaction product was 7α-(diazidoboryl)methyl-3-aza-bicyclo[3.3.1]nonane (XIV), an interesting organoboron derivative. Unlike ordinary



azides, which decompose at 150–170 °C and are often explosive [16], the diazide XIV is thermostable up to 250 °C. Its structure was established on the basis of combustion and spectral data. Present in the ^{15}N spectrum were signals for the azido-group at −308.4, −206.2, and −138.2 ppm, as well as for the nitrogen incorporated into the bicyclic system at −335.7 ppm. This is typical for a quaternized nitrogen, $^{2}J(N-H)$ value being 73 Hz. A signal for tetracoordinated boron at +3.8 ppm was present in the ^{11}B-NMR spectrum. IR-, ^{1}H-, and ^{13}C-NMR spectral data were also in accord with this structure (cf. Experimental), a peak at m/z 191 ($M^{+} - N_3$) was present in the mass-spectrum.

Treatment of XIV with sodium methoxide (2 equiv.) gave rise to the aforementioned VIII. Oxidation of the reaction mixture without isolation of organoboron intermediates of the type XIV afforded the aminoalcohol VII in 45% yield.

As well as in diglyme, the reaction was also carried out in DMF (and was accompanied by formation of numerous by-products) and in ethanol. In the latter case the reaction was blocked at the stage of iodinolysis of the B–C bond with formation of a bicyclic derivative XV while nucleophilic substitution did not take place.

Thus we have developed a convenient and preparative-scale procedure for synthesis of 1-azaadamantane which compares favourably with existing ones: the yield of the target product is 20% from allyl bromide (7 steps) or 40% from XIII.

Experimental

All operations with organoboron compounds were performed in an atmosphere of dry argon. IR spectra were recorded on a UR-20 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker WM-250 instrument (68.69 MHz for carbon). ^{11}B and ^{15}N NMR spectra were recorded on a Bruker AM-300 spectrometer (30.42 MHz for nitrogen) relative to $BF_3 \cdot Et_2O$ and pure $CH_3{}^{15}NO_2$ (in ^{15}N NMR spectra

signals upfield to the standard are negative). Mass-spectra were measured on a Varian CH-6 instrument.

Tetrahydrofuran-1-boraadamantane (XIII) was synthesized according to a literature procedure [17].

Reaction of iodide IVa with NaN_3 in DMF

To a solution of IVa (13.3 g, 45.6 mmol) in 200 ml of DMF was added 13.0 g (200 mmol) of NaN_3 and the reaction mixture was heated at 130 °C under stirring for 0.5 h whereby 715 ml (70%) of N_2 evolved. Excess of NaN_3 was separated and DMF was distilled off *in vacuo* (30–35 °C/1mmHg). The precipitate (complex salt 6DMF · 2NaI) was washed with ether (3 × 30 ml). The combined ether filtrates were concentrated to 30 ml, stirred with NaOH (2.3 g, 57.5 mmol) in 15 ml of water and then 9.5 ml of 30% H_2O_2 were added at 0 °C. After 0.5 h at 0 °C the reaction mixture was refluxed for 0.5 h, the aqueous layer was separated, saturated with potassium carbonate, and then extracted with THF (3 × 20 ml). The combined organic extracts were concentrated *in vacuo* and the residue was chromatographed on silica gel (100/160 μm; methanol/aqueous NH_3 5/1) to give 1.4 g (20%) VII, m.p. 56–57 °C (subl.). Found: C, 69.72; H, 11.14; N, 9.15. $C_9H_{17}NO$ calc.: C, 69.63; H, 11.04; N, 9.02%. ^1H NMR (CD_3OD, δ, ppm): 1.0 (t, 2H, C(6,8) H^{β}, $J = 13.0$ Hz), 1.25 (d, 1H, C(9)H^{β}, $J = 11.9$ Hz), 1.6–1.9 (m, 3H, C(6,8,9)H^{α}), 1.9–2.05 (m, 2H, C(1,5)H), 2.50–2.70 (AB-spectrum, 4H, CH_2N, $J_{AB} = 11.9$ Hz), 3.38 (d, 2H, CH_2O, $J = 5.5$ Hz). ^{13}C NMR ($CDCl_3$, δ, ppm): 25.5 (C(1,5)), 27.6 (C9)), 29.2 (C(6,8)), 31.5 (C(7)), 52.6 (CH_2N), 67.5 (CH_2O). Mass spectrum (*m/z*): 155 [M^+].

Reaction of iodide IVa with LiN_3 in methanol

A solution of IVa (7.3 g, 25.0 mmol) and 3.8 g (77.5 mmol) of LiN_3 in 50 ml of methanol was refluxed with stirring for 15 h, 420 ml (75%) of nitrogen evolving. The mixture was concentrated *in vacuo* to 20 ml and treated with NaOH (1.1 g, 27.4 mmol) in 6 ml of water and then with 6.5 ml of 30% of H_2O_2 at 0 °C. After refluxing with stirring for 1 h the mixture was chromatographed on silica gel to give 1.3 g (34%) of VII, m.p. 55–57 °C and 1.2 g (26%) of X, m.p. 77–79 °C (subl.). Found: C, 63.61; H, 10.47. $C_{10}H_{20}O_3$ calcd.: C, 63.79; H, 10.71%. ^1H NMR ($CDCl_3$, δ, ppm): 0.55–0.70 (m, 3H, C(2,4,6)H^{ax}), 1.50–1.95 (m, 6H, C(2,4,6)H^{eq}, C(1,3,5)H), 2.12 (br.s, 2H, OH), 3.22 (d, 2H, CH_2OCH_3, $J = 6.6$ Hz), 3.33 (s, 3H, CH_3O), 3.40–3.52 (m, 4H, CH_2OH). ^{13}C NMR ($CDCl_3$, δ, ppm): 32.5 (C(4)), 32.6 (C(2,6)), 36.8 (C(1)), 39.2 (C(3,5)), 58.5(CH_3O), 67.6 (CH_2OH), 78.4 (CH_2OCH_3).

Reaction of IVa with NaN_3 in xylene in the presence of Bu_4NI

To a solution of IVa (13.1 g, 44.8 mmol) in 40 ml of xylene was added 5.9 g (91 mmol) of NaN_3 and 1.74 g (4.8 mmol) of Bu_4NI. The mixture was stirred at 140 °C for 5 h, the volume of nitrogen evolved was 540 ml (54%). Following concentration *in vacuo* (30–35 °C/1 mmHg), the residue was dissolved in 20 ml of ether. To the ether solution was added NaOH (2.4 g, 60 mmol) in 10 ml of water, then 8.5 ml of 30% H_2O_2 at 0 °C, the reaction mixture was refluxed for 0.5 h. The aqueous layer was separated, saturated with K_2CO_3, and extracted with THF (2 × 25 ml). The combined organic extracts were evaporated *in vacuo*, the brown oil obtained was dissolved in 5 ml of MeOH. After standing for a week at 0 °C a beautiful colourless

crystalline complex of 4-oxo-3-borahomoadamantane with 7α-hydroxymethyl-3-azabicyclo[3.3.1]nonane (XII) precipitated. This substance was moderately soluble in MeOH, its yield was 0.6 g (4.5%), m.p. 192–196 °C (part. decomp.). Found: C, 70.58; H, 10.48; B, 3.80; N, 4.51. $C_{18}H_{32}O_2NB$ calc.: C, 70.82; H, 10.52; B, 3.54; N, 4.59%. ^{1}H NMR (CD_3OD, δ, ppm): 0.28–0.44 (AB-spectrum, 4H, CH_2B, $J_{AB} = 13.5$ Hz), 0.95–2.12 (m, 19H, protons of cyclohexane rings), 2.58–2.82 (AB-spectrum, 4H, CH_2N, $J_{AB} = 13.8$ Hz), 3.38 (d, 2H, CH_2OH, $J = 5.0$ Hz), 3.65 (d, 2H, CH_2OB, $J = 2.8$ Hz). ^{11}B NMR (THF, δ, ppm): +6.6. Mass spectrum (m/z): 155 (VII) [M^+]; 300 (XI) [M^+]. Mother liquor was chromatographed on silica gel to give 1.4 g (21%) of VII, m.p. 55–57 °C (subl.).

Reaction of 1-boraadamantane tetrahydrofuranate (XIII) with NaN_3 and I_2 in diglyme

a. Synthesis of 7α-hydroxymethyl-3-azabicyclo[3.3.1]nonane (VII). To a stirred suspension of 5.25 g of NaN_3 (80.7 mmol) in 40 ml of diglyme at 70–80 °C solutions of 5.6 g (27.2 mmol) of XIII and 6.9 g of I_2 in 20 ml and 25 ml of diglyme, respectively, were added simultaneously from two dropping funnels over a period of 1 h. The mixture was stirred for 0.5 h at that temperature during which time 580 ml (95%) of N_2 evolved. The solvent was distilled off *in vacuo* (35–37 °C/ 1 mmHg), the solid residue was extracted with Et_2O (3 × 20 ml). The combined ether extracts were treated with 3.5 g (87 mmol) of NaOH in 10 ml of water and then with 11 ml of 30% solution of H_2O_2 under the usual conditions. By chromatography on SiO_2 (MeOH/aqueous NH_3 5/1) followed by sublimation (100 °C/1 mmHg) 1.9 g (45%) of VII was isolated, m.p. 56–57 °C.

b. 7α-(Diazidoboryl)methyl-3-azabicyclo[3.3.1]nonane (XIV). Reaction of 11.7 g (56.6 mmol) of XIII with NaN_3 and I_2 in diglyme was carried out as described above. The ether extract was not oxidized and was stored for one week. The yellow precipitate obtained was sublimated *in vacuo* (160–170 °C/0.01 mmHg) to give 0.65 g (5%) of XIV, m.p. 203–205 °C ($CHCl_3$). Found: C, 46.26; H, 6.89; B, 4.83; N 42.23. $C_9H_{17}N_7B$ calc.: C, 46,34; H, 6.92; B, 4.64; N, 42.06%. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.08 (d, 2H, CH_2B, $J = 4.8$ Hz), 1.68 (s, 3H, C(6,8,9)H$^{\beta}$), 1.95–2.08 (m, 5H, C(6,8,9)H$^{\alpha}$, C(1,5)H), 3.02 (d, 2H,C(2,4)H$^{\beta}$, $J = 12.0$ Hz), 3.53 (d, 2H, C(2,4)H$^{\alpha}$, $J = 12.0$ Hz), 4.2 (br.s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ, ppm): 25.4 (C(10)), 25.9 (C(1,5)), 28.4 (C(7)), 32.6 (C(9)), 38.5 (C(6,8)), 49.1 (C(2,4)). ^{11}B NMR (THF, δ, ppm): 3.8. ^{15}N NMR (DMSO-d_6, δ, ppm): −335.7 (NH, ^2J(N–H) = 73 Hz), −308.4 (N–B, ^4J(N–H) = 2 Hz), −206.2 (−N$^-$–$^+$N≡*N*), −138.2 (−N$^-$–$^+$*N*≡N). Mass spectrum (m/z): 191 [$M^+ - N_3$]. IR (KBr, cm^{-1}): 2100, 2125 (δ(N_3)), (comp. with $R_2Si(N_3)_2$ [14]), 3300–3500 (ν(NH)).

7α-(Dimethoxyboryl)methyl-3-azabicyclo[3.3.1]nonane (VIII)

To a solution of XIV (0.55 g, 2.3 mmol) in 6 ml of THF at 20 °C was added methanolic MeONa (3.56 ml, 4.7 mmol), and rapid precipitation of NaN_3 was observed. After stirring at 20 °C for 2 h the precipitate was filtered off, and the solvent distilled off *in vacuo*. The oil formed was dissolved in 10 ml of ether, the precipitate was filtered off; evaporation of the ether solution gave 0.39 g (80%) of white powder VIII, m.p. 84–87 °C (part. decomp.). Found:, C, 62.24; H, 10.33; B, 5.34; N 6.58. $C_{11}H_{22}O_2NB$ calc.: C, 62.58; H, 10.50; B, 5.13; N, 6.63%. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.77 (d, 2H, CH_2B, $J = 4.4$ Hz), 1.58–2.20 (m, 9H, protons of cyclohexane rings), 2.85 (d, 2H, C(2,4)H$^{\beta}$, $J = 11.4$ Hz), 3.18 (s, 3H, CH_3O), 3.44

(d, 2H, C(2,4)H$^{\alpha}$, $J = 11.4$ Hz). ^{13}C NMR ($CDCl_3$, δ, ppm): 27.1 (C(1,5)), 28.9 (C(7)), 33.7 (C(9)), 37.2 (C(6,8)), 49.0 (OCH_3), 49.2 (CH_2N). ^{11}B NMR ($CDCl_3$, δ, ppm): +7.1.

3-Ethoxy-7α-iodomethyl-3-borabicyclo[3.3.1]nonane (XV)

To a solution of 3.65 g (17.8 mmol) of XIII in 20 ml of ethanol was added first NaN_3 (5.65 g, 87.0 mmol) and then I_2 (4.45 g, 17.5 mmol) in 20 ml of ethanol at 20 °C. The reaction mixture was refluxed for 1 h, no gas evolution was observed. The excess of NaN_3 was filtered off, the solvent was evaporated *in vacuo* and the residue was extracted with hexane (3 × 30 ml). The brown hexane solution was treated with solid $Na_2S_2O_3 \cdot 5H_2O$ to decoloration. After removal of the solvent the residue was distilled to yield 3.5 g (65%) of ethoxyborane (XV), b.p. 96–98 °C/1 mmHg, n_D^{20} 1.5378. Found: C, 43.30; H, 6.54; B, 3.58; I, 41.64. $C_{11}H_{20}$OBI calc.: C, 43.17; H, 6.59; B, 3.54; I, 41.47%. ^{1}H NMR ($CDCl_3$, δ, ppm): 0.88 – 1.22 (AB-spectrum, 4H, CH_2B, $J_{AB} = 17.6$ Hz), 1.22 (t, 3H, CH_3, $J = 7.0$ Hz), 1.38–2.05 (m, 7H, C(6,7,8,9)H), 2.25 (br.s, 2H, C(1,5)H), 3.18 (d, 2H, CH_2I, $J = 7.7$ Hz), 3.92 (qr, 2H, CH_2O, $J = 7.0$ Hz). ^{13}C NMR ($CDCl_3$, δ, ppm): 17.1 (CH_2I), 17.3 (CH_3), 26.2 (CH_2B), 26.6 (C(1,5)), 34.1 (C(9)), 34.6 (C(7)), 37.0 (C(6,8)), 60.8 (CH_2O).

7α-Hydroxymethyl-3-azabicyclo[3.3.1]nonane hydrochloride (VIIa)

To a solution of 0.46 g (2.96 mmol) of VII in ether–THF (1 : 1) were added 2.2 ml of 1.4 *M* hydrogen chloride in ether. The yellow sediment obtained was reprecipitated with ether from methanol to yield 0.37 g (66%) of VIIa as a white powder, m.p. 166–168 °C. Found: C, 56.48; H, 9.60; N, 7.40; Cl, 18.55. $C_9H_{18}ONCl$ calc.: C, 56.39; H, 9.46; N, 7.31; Cl, 18.49%. ^{1}H NMR (CD_3OD, δ, ppm): 1.23 (t, 2H, C(6,8)H$^{\beta}$, $J = 11.9$ Hz), 1.42 (d, 1H, C(9)H$^{\beta}$, $J = 12.6$ Hz), 1.72–1.88 (m, 2H, C(9)H$^{\alpha}$, C(7)H), 2.10–2.24 (m, 4H, C(6,8)H$^{\alpha}$, C(1,5)H), 2.98–3.10 (m, 4H, CH_2N), 3.43 (d, 2H, CH_2O, $J = 7.0$ Hz). ^{13}C NMR (CD_3OD, δ, ppm): 25.2 (C(1,5)), 26.35 C(9)), 29.4 (C(6,8)), 32.2 (C(7)), 51.6 (CH_2N), 68.3 (CH_2OH). IR (cm^{-1}, KBr): 2300–2700 ($\nu(NH_2^+)$), 3300–3550 (ν(OH)).

1-Azaadamantane (I)

To a solution of VII (2.27 g, 14.4 mmol) in 50 ml of benzene was added with stirring for 0.5 h a solution of 3.5 ml of $SOCl_2$ in 30 ml of benzene. The reaction mixture was stirred for an additional 0.5 h at 20 °C and then it was boiled for 20 min. The precipitate of hydrochloride obtained was filtered off, washed with C_6H_6 (2 × 10 ml), dissolved in water and the solution was neutralized with 0.6 g (15 mmol) of NaOH. The aqueous layer was saturated with K_2CO_3 and extracted with ether (3 × 15 ml). The combined ether extracts were dried with Na_2SO_4, the solvent was removed and the residue sublimated *in vacuo* (80 °C/ 1 mmHg) to give 1.41 g (90%) of I, m.p. 260–262 °C (comp. with refs. 5, 8). All spectral data were identical with those described in refs. 2, 8.

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