Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1993, **3**(2), 56–57
Mendeleev Communications

Synthesis of Rimantadine from 1-Boraadamantane

Mikhail E. Gurskii, Tamara V. Potapova and Yurii N. Bubnov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation. Fax: +7 095 135 5328

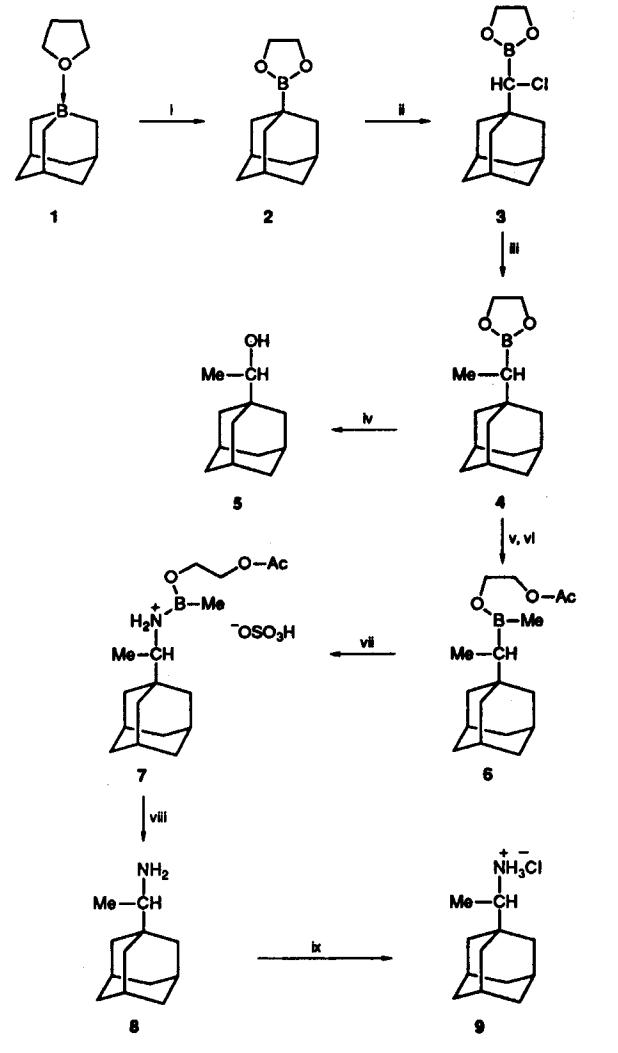
Transformations of THF–1-boraadamantane **1** into 1-(1-hydroxyethyl)adamantane **5** and the hydrochloride salt of 1-(1-aminoethyl)adamantane (rimantadine) **9**, based on a series of 1,2-anionotropic rearrangements in the corresponding 'ate'-complexes, are presented.

The elegance of the structure of the admantane molecule and the high antiviral activity of many of its derivatives, *e.g.* amantadine (1-aminoadamantane hydrochloride) and rimantadine **9** [1-(1-aminoethyl)adamantane hydrochloride)] are good reasons for furthering progress in cage compound chemistry.[1,2]

1-Boraadamantane is one of the most promising substances used in the synthesis of compounds of this type. Thus, it has been used as a starting material in convenient syntheses of 1-adamantanol[3] and 1-azaadamantane.[4a,b] In this communication we describe the preparation of 1-(1-hydroxyethyl)- **5** and 1-(1-aminoethyl)adamantane **8**, as well as rimantadine **9**, based on a series of 1,2-anionotropic rearrangements in the corresponding boron 'ate'-complexes, Scheme 1.†

Ethylene glycol 1-adamantylboronate **2** was prepared by carbonylation of THF–1-boraadamantane **1** in the presence of $(CH_2OH)_2$ according to ref. 5 (70%). Treatment of **2** with dichloromethyllithium generated *in situ*[6] led to 1-[(1-adamantyl)chloromethyl]-1,3,2-dioxaborolane **3** (δ ^{11}B 35 ppm) which was converted without isolation into 1-(1-adamantyl)ethyl-1,3,2-dioxaborolane **4** (δ ^{11}B 31 ppm) by reaction with methyllithium (yield 60% from **2**). Oxidation of **4** (H_2O_2, OH^-) gave **5** in 78% yield.

Transformation of boronic ester **4** into rimantadine **9** was performed according to a known procedure for substitution of a borylic group by an amino group[7] and involved successive treatment of **4** with methyllithium at −78°C, acetyl chloride (**4**→**6**), and hydroxylamine-*O*-sulfonic acid (**6**→**7**). Alkaline hydrolysis of the boronic salt **7** formed (cleavage of the N–B



Scheme 1 *Reagents and conditions:* i, CO, $(HOCH_2)_2$, 150°C, 1 h; ii, CH_2Cl_2, Pr^i_2NLi, 0°C, 0.5 h, 65°C, 1.5 h; iii, MeLi, −78°C, 1 h, 20°C, 2 h (70%); iv, OH^-, H_2O_2, 0°C, 1 h, 32°C, 3 h (78%); v, MeLi, −78°C, 3 h; vi, AcCl, −78°C→20°C; vii, H_2NOSO_3H, 20°C, 20 h; viii, NaOH, H_2O; ix, $HCl \cdot OEt_2$ (37%)

† Compounds **4**, **5**, **8** and **9** have satisfactory elemental analyses. NMR spectra were obtained on a 'Bruker AC-200P' spectrometer. Selected data are presented for:

4: B.p. 103–105°C (1 mm Hg); n_D^{20} 1.5080; ^{1}H NMR ($CDCl_3$) δ 0.9 (br d, CH_3), 1.5–2 (m, adamantane H), 4.2 (s, CH_2O); ^{13}C NMR ($CDCl_3$) δ 9.0 (CH_3), 28.8 (C-3), 37.2 (C-4), 40.1 (C-1), 41.5 (C-2), 65.1 (CH_2O).

5: M.p. 74–74.5°C (from hexane); ^{1}H NMR ($CDCl_3$) δ 1.1 (d, *J* 6.4 Hz, CH_3), 1.3–2 (m, adamantane H), 3.38 (q, *J* 6.4 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 16.4 (CH_3), 28.3 (C-3), 36.5 (C-1), 37.2 and 37.7 (C-2,4), 75.8 (C–O).

8: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, *J* 6.4 Hz, CH_3), 2.31 (s, NH_2), 1.4–2.0 (m, adamantane H), 2.34 (q, *J* 6.4 Hz, CH–N); ^{13}C NMR δ 16.8 (CH_3), 28.5 (C-3), 29.8 (C-1), 37.3 and 38.1 (C-2,4), 55.8 (C–N).

9: M.p. >310°C (decomp.) (*cf.* ref. 2); ^{1}H NMR (CD_3OD) δ 1.4 (d, *J* 6.7 Hz), 1.8–2.3 (m, adamantane H), 3.1 (q, 6.7 Hz, CH–N^+); ^{13}C NMR (CD_3OD) δ 13.7 (CH_3), 30.0 (C-3), 30.9 (C-1), 38.1 and 39.1 (C-2,4), 58.4 (C–N^+).

bond) resulted in 1-(1-aminoethyl)adamantane **8** (38%), which was transformed to **9** by treatment with HCl in ether.

References

1 (*a*) R. C. Fort, Jr., *Adamantane*, Marcel Dekker, Inc., New York, Basel, 1976; (*b*) E. I. Bagrii, *Adamantany* (Adamantanes), Nauka, Moscow, 1989 (in Russian).

2 P. E. Aldrich, E. C. Hermann, W. E. Meier, M. Paulschock, W. W. Prichard, J. A. Snider and J. C. Watts, *J. Med. Chem.*, 1971, **14**, 535.

3 B. M. Mikhailov and Yu. N. Bubnov, *Organoboron Compounds in Organic Synthesis*, Harwood Acad. Sci. Publ., Chur, Utrecht, London, Paris, New York, Boston, Toronto, 1984.

4 (*a*) Yu. N. Bubnov, M. E. Gurskii and D. G. Pershin, *Izv. Akad. Nauk SSSR, Ser. Khim*, 1990, 952 (*Bull Acad. Sci. USSR, Div. Chem. Sci.*, 1990, 857); (*b*) Yu. N. Bubnov, M. E. Gurskii and D. G. Pershin, *J. Organomet. Chem.*, 1991, **412**, 1.

5 T. A. Shchegoleva, E. M. Shashkova and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Ser. Khim*, 1981, 1098 (*Bull Acad. Sci. USSR, Div. Chem. Sci.*, 1981, 858).

6 H. C. Brown, S. M. Singh and M. V. Rangaishenvi, *J. Org. Chem.*, 1986, **51**, 3150.

7 H. C. Brown, T. E. Cole, K.-W. Kim and B. Singaram, *J. Am. Chem. Soc.*, 1986, **108**, 6761.

Received: Moscow, 13th November 1992
Cambridge, 24th December 1992; Com. 2/06117A