Synthesis of Adamantane Derivatives. 41.[1] Synthesis of 9-Thianoradamantane by Carbon–Hydrogen Carbene Insertion Reaction and Carbon-13 Nuclear Magnetic Resonance Spectra of the Related Compounds

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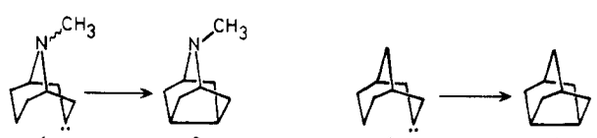
9-Thiabicyclo[3.3.1]nonan-3-one (**6**) was prepared in good yield by treatment of cycloocta-2,7-dienone (**5**) with sodium sulfide in aqueous methanol. Oxidation of **6** with *m*-chloroperbenzoic acid gave the corresponding sulfone (**7**). Reduction of **6** with $NaBH_4$ afforded *endo*-9-thiabicyclo[3.3.1]nonan-3-ol (**8a**). The predominant conformation of **8a** was shown to be chair–boat on the basis of ^{13}C NMR data. Novel skeleton 9-thianoradamantane (**11**) was obtained on pryolysis of the sodium salt of the *p*-toluenesulfonylhydrazone of **6** as the transannular C–H carbene insertion product. **11** was converted to the corresponding sulfone (**13**) and methylsulfonium iodide (**14**).

It is well known that carbene reactions are very useful for the synthesis of bridged or polycyclic compounds as well as cyclopropanes.[2] The usefulness of carbene reactions for the preparation of novel adamantane derivatives is exemplified by the reported synthesis of 2,4-dehydroadamantane,[3] 2,4,6,9-tetradehydroadamantane,[4] and 3-homoadamantene,[5] etc. Previously, we reported the facile synthesis of 9-methyl-9-azanoradamantane (**2**) by the transannular C–H insertion reaction of **1**.[6] A similar reaction of **3** is also known to afford noradamantane (**4**).[7] As an extension of our studies on the



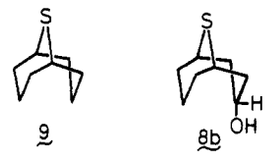
synthesis of adamantane derivatives by utilizing carbenic species, we report in this paper the synthesis of 9-thiabicyclo[3.3.1]nonan-3-one (**6**), its conversion to 9-thianoradamantane (**11**), and ^{13}C NMR spectra of the related compounds.

Results and Discussion

Synthesis, Conformations, and Carbon-13 Nuclear Magnetic Resonance Spectra of 9-Thiabicyclo[3.3.1]-nonan-3-one Derivatives. The additions of primary amines and phosphines to cycloocta-2,7-dienone (**5**)[8] are known to afford the corresponding 9-aza- and 9-phosphabicyclo[3.3.1]-nonan-3-ones, respectively.[9,10] The addition of hydrogen sulfide to **5** therefore may be one of the most promising and facile routes to 9-thiabicyclo[3.3.1]nonan-3-one (**6**).

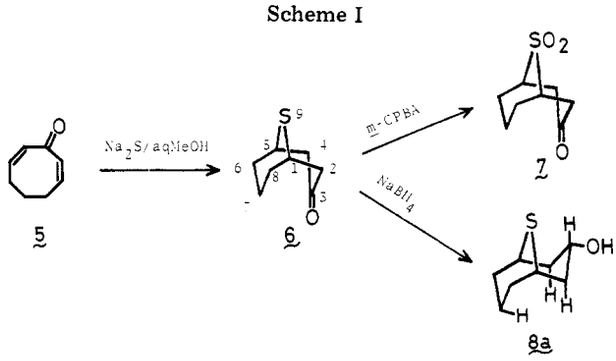
In the first attempt, **5** was treated with hydrogen sulfide in chloroform at room temperature overnight, but only **5** was recovered without change. However, treatment of **5** with a 3.3-fold excess amount of sodium sulfide in 80% aqueous methanol at room temperature afforded an adduct **6** as a sublimable solid in 75% yield which was characterized as the desired 9-thiabicyclo[3.3.1]nonan-3-one on the basis of analytical and spectral data. Compound **6** had the anticipated mass spectral molecular ion peak at *m/e* 156 and a strong IR (KBr) absorption at 1695 ($\nu_{C=O}$) cm^{-1}. In the ^1H NMR ($CDCl_3$) spectrum **6** had signals at δ 3.24 (broad s, 2 H, bridgehead protons), 2.81 (AB q, J = 16.8 Hz, $J/\Delta\delta$ = 0.774, 4 H, methylene protons at C_2 and C_4), and 2.35–1.03 (m, 6 H, other protons), and in the ^{13}C NMR spectrum **6** revealed five lines (one singlet, one doublet, and three triplets; Table I), supporting the assigned structure. Oxidation of **6** with *m*-chloroperbenzoic acid afforded the corresponding sulfone **7** in 80% yield, and reduction of **6** with sodium borohydride gave an endo alcohol **8a**, as shown in Scheme I. The assigned stereochemistry and conformation of **8a** were supported by the ^{13}C NMR data (Table I).

The ketone **6** should have a double chair conformation as supported by the appearance of C_7 at 3.8 ppm higher field than C_7 (C_3) of 9-thiabicyclo[3.3.1]nonane (**9**),[11] and hence **6**



should be attacked by borohydride on the exo face to afford the endo alcohol **8a**. The appearance of C_7 of **8a** at 6.0 ppm higher field than C_7 (C_3) of **9** and comparison of the chemical shift (15.6 ppm) with those (14.5 and 15.6 ppm, respectively) of the corresponding 9-aza and 9-phospha analogues[12,13] verified the assigned stereochemistry and chair–boat conformation of **8a**, where C_7 resonates at a high field by the gauche effect as pointed out by Wiseman and Krabbenhoft.[12,13] The double chair conformation of **8b** can not be predominant because of the presence of transannular steric repulsions.[14]

Scheme I



Synthesis of 9-Thianoradamantane (11) by Transannular C–H Carbene Insertion Reaction. The ketone **6** gave the corresponding *p*-toluenesulfonylhydrazone **10a** in 76% yield by the usual procedure. The sodium salt **10b** was obtained on treatment of **10a** with sodium methoxide in methanol, which was dried under reduced pressure and decomposed in refluxing diglyme to afford an 85:15 mixture of **11** and **12** in 67% yield after the usual workup and sublimation. Compounds **11** and **12** were isolated after chromatography on an alumina column and characterized as 9-thianoradamantane, the transannular carbene insertion product, and 9-thiabicyclo[3.3.1]non-2-ene, the hydrogen migration product,

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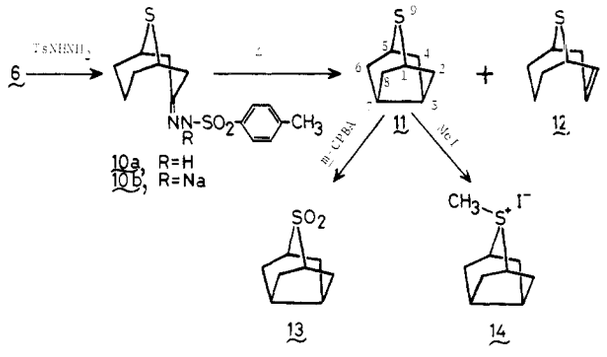
Table I. Chemical Shifts (δ) of 9-Thiabicyclo[3.3.1]nonane and Related Compounds[a]

compd	registry no.	$C_{1,5}$	$C_{2,4}$	C_3	$C_{6,8}$	C_7
6	67194-70-1	35.8 (d)	49.0 (t)	209.5 (s)	33.1 (t)	17.8 (t)
7	67194-71-2	54.3 (d)	44.2 (t)	203.4 (s)	29.8 (t)	15.3 (t)
8a	67194-72-3	32.5 (d)	34.4 (t)[b]	65.3 (d)	33.7 (t)[b]	15.6 (t)
9	281-15-2	33.2 (d)	32.1 (t)	21.6 (t)	32.1 (t)	21.6 (t)
11	67194-73-4	44.8 (d)	46.5 (t)	38.7 (d)	46.5 (t)	38.7 (d)
13	67194-74-5	65.4 (d)	39.0 (t)	35.8 (d)	39.0 (t)	35.8 (d)

[a] Downfield from internal tetramethylsilane in $CDCl_3$, and see the structural formulas for numbering of the carbon atoms. [b] These assignments may be interchangeable.

Scheme II



respectively. Compound **11** had mp 242–243 °C, mass spectral ion peaks at *m/e* 140 (M^+) and 106 ($M - H_2S$), and ^1H NMR ($CDCl_3$) signals at δ 3.08 (broad s, 2 H, C_1 H and C_5H), 2.9–2.4 (m, 2 H, C_3 H and C_7 H), and 2.4–1.55 (m, 8 H, the remaining protons). The ^{13}C NMR spectrum of **11** revealed only three lines at δ 46.5 (t, $C_{2,4,6,8}$), 44.8 (d, $C_{1,5}$), and 38.7 (d, $C_{3,7}$), which were compatible with the assigned skeleton belonging to a C_{2v} point group. The olefinic product **12** had the same IR and ^1H NMR spectra and GLC retention time as an authentic sample prepared by lithium aluminum hydride reduction of 6-chloro-9-thiabicyclo[3.3.1]non-2-ene.[11b]

The pyrolytic decomposition of **10b** without solvent did not improve the yield of **11**, affording a 74:26 mixture of **11** and **12** in 54% yield, but this procedure provides a direct isolation of the products via sublimation.

9-Thianoradamantane (**11**) afforded the corresponding sulfone **13** on oxidation with *m*-chloroperbenzoic acid in 75% yield and 9-methyl-9-thianoradamantanium iodide (**14**) on treatment with methyl iodide in 89% yield, as shown in Scheme II.

All of the above results indicate that the 9-thiabicyclo[3.3.1]nonane system is conformationally very similar to the 9-aza, 9-phospha, and carbocyclic analogues and that the 3,7 C–H carbene insertion reactions are useful also for obtaining 9-thianoradamantane (**11**) as well as previously reported 9-aza[6] and carbocyclic analogues.[7]

Experimental Section[15]

9-Thiabicyclo[3.3.1]nonan-3-one (6). A mixture of cycloocta-2,7-dienone (**5**)[8] (200 mg, 1.67 mmol) and sodium sulfide nonahydrate (1.35 g, 5.62 mmol) in 80% (v/v) aqueous methanol (25 mL) was stirred for 40 h at room temperature. After concentration to ca. 10 mL, the mixture was diluted with water (30 mL) and extracted with dichloromethane (10 mL × 4). The combined extracts were washed with water (10 mL × 2) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was purified by sublimation (150 °C, 0.2 mm) to give **6** as a colorless solid (195 mg, 74.8%): mp 194–197 °C; IR (KBr) 2940, 1695, 1440, and 1100 cm^{-1}; ^1H and ^{13}C NMR, see text; mass spectrum, *m/e* (relative intensity, %) 158 (5.0, M + 2), 157 (9.0, M + 1), 156 (100, M^+), 128 (55.5), 123 (6.5), 113 (14.4), 99 (40.0), 60 (98.5), 54 (97.5), 41 (98.0), and 39 (99.0).

Anal. Calcd for $C_8H_{12}OS$: C, 61.52; H, 7.75. Found: C, 61.27; H, 7.61.

9-Thiabicyclo[3.3.1]nonan-3-one 9,9-Dioxide (7). A mixture of **6** (78 mg, 0.50 mmol) and *m*-chloroperbenzoic acid (85% purity; 223 mg, 1.10 mmol) in dichloromethane (10 mL) was stirred at room temperature for 16 h. The mixture was washed successively with 5% aqueous sodium thiosulfate (5 mL) and 5% aqueous sodium bicarbonate (5 mL × 3) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was sublimed (150 °C, 0.2 mm) to afford **7** as a colorless solid (75 mg, 80%): mp >300 °C; IR (KBr) 1698, 1300, 1120, and 808 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (broad s, 2 H), 3.08 (AB q, J = 14.5 Hz, $J/\Delta\delta$ = 0.354, 4 H), and 2.65–1.1 (m, 6 H); ^{13}C NMR ($CDCl_3$), see Table I; mass spectrum, *m/e* (relative intensity, %) 190 (2.4, M + 2), 189 (4.4, M + 1), 188 (37.3, M^+), 124 (8.9), 122 (22.2), 97 (20.0), 96 (25.0), 82 (100), 69 (81.7), 68 (98.0), 55 (97.0), 54 (98.5), 42 (99.5), and 39 (96.0).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.04; H, 6.43. Found: C, 51.22; H, 6.24.

***endo*-9-Thiabicyclo[3.3.1]nonan-3-ol (8a).** To a stirred and ice-cooled solution of **6** (156 mg, 1.00 mmol) in methanol (5 mL) was added sodium borohydride (189 mg, 5.00 mmol), and the mixture was stirred for 40 h at room temperature and refluxed for 20 min. The cooled mixture was treated with a few drops of acetic acid. The solvent was removed to afford the crude product, which was recrystallized from chloroform–*n*-hexane and sublimed (150 °C, 0.2 mm) to give the alcohol **8a** as a colorless solid (130 mg, 82%): mp 142–145 °C; IR (KBr) 3270, 2940, 1470, 1330, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4–3.7 (m, 1 H), 3.38–2.83 (m, 3 H; 2 H in D_2O), and 2.78–1.02 (m, 10 H); ^{13}C NMR, see text and Table I; mass spectrum, *m/e* (relative intensity, %) 160 (4.0, M + 2), 159 (9.0, M + 1), 158 (100, M^+), 140 (25.0), 125 (27.0), 124 (25.0), 87 (65.0), 55 (90.0), 54 (85.0), 41 (99.5), and 39 (90.0).

Anal. Calcd for $C_8H_{14}OS$: C, 60.71; H, 8.92. Found: C, 60.85; H, 8.78.

***p*-Toluenesulfonylhydrazone (10a) of 6.** A mixture of **6** (156 mg, 1.00 mmol) and *p*-toluenesulfonyl hydrazide (400 mg, 2.15 mmol) in ethanol (5 mL) was heated under reflux for 15 h. The mixture was diluted with water to afford the crude product, which was recrystallized several times from aqueous methanol to give **10a** as colorless crystals (310 mg, 75.9%): mp 160–164 °C; IR (KBr) 3240, 1620, 1595, 1330, 1170, 735, and 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (AB q, J = 8.30 Hz, $J/\Delta\delta$ = 0.248, 4 H), 3.44–2.58 (m, 6 H), 2.87 (broad s, ca. 1 H; disappeared on shaking with D_2O), 2.43 (s, 3 H), and 2.23–1.19 (m, 6 H).

Anal. Calcd for $C_{15}H_{20}N_2O_2S_2$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.25; H, 6.17; N, 8.69.

9-Thianoradamantane (11) and 9-Thiabicyclo[3.3.1]non-2-ene (12). A. Thermal Decomposition of 10b in Diglyme. A mixture of the tosylhydrazone **10a** (310 mg, 0.956 mmmol) and freshly prepared sodium methoxide (65.9 mg, 1.22 mmol) in methanol (6 mL) was stirred for 1 h at room temperature under an argon atmosphere. After the solvent was removed under reduced pressure, the residue was dried up at 45 °C for 6 h under reduced pressure (0.2 mm) to afford the sodium salt **10b**, which was decomposed in refluxing diglyme (10 mL) for 1 h. The cooled mixture was diluted with water (50 mL) and extracted with *n*-pentane (10 mL × 5). The combined extracts were washed with water (5 mL × 5) and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was sublimed to afford an 85:15 mixture of **11** and **12** (GLC and ^1H NMR analyses) as a colorless solid (90 mg, 67%). Purification of the mixture on an alumina (Wako basic alumina, grade I) column eluting with *n*-pentane gave **11** (70 mg, 52.2%) and **12** (15 mg, 11.1%). **11** had mp 242–243 °C; IR (KBr) 2965, 2900, 2860, 1450, 1310, 1260, 1085, 955, 778, and 720 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$), see text and Table I; mass spectrum, *m/e* (relative intensity, %) 142 (5.0, M + 2), 141 (11.0, M + 1), 140 (85.0, M^+), 106 (30.0), 99 (75.0), 98 (87.5), 97 (100), 79 (70.0), 65 (50.0), 41 (90.0), and 39 (87.5).

Anal. Calcd for $C_8H_{12}S$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.54.

Compound **12** had mp 140–143 °C (lit.[11b] mp 143–143.5 °C), and its IR and ^1H NMR spectra and GLC retention time were identical with those of an authentic sample prepared by $LiAlH_4$ reduction of 6-chloro-9-thiabicyclo[3.3.1]non-2-ene.[11b]

B. Thermal Decomposition of 10b without Solvent. The sodium salt **10b**, prepared as above from **10a** (300 mg, 0.925 mmol), was well mixed with Celite 535 (0.5 g) and heated at 155–180 °C under reduced pressure (100 mm) in a sublimation flask to afford the sublimed product (90 mg, 70%), which gave a 74:26 mixture of **11** and **12** as a colorless solid (70 mg, 54%) on resublimation.

9-Thianoradamantane 9,9-Dioxide (13). A mixture of 9-thianoradamantane (**11**) (20 mg, 0.14 mmol) and *m*-chloroperbenzoic acid (85% purity; 70 mg, 0.34 mmol) in chloroform (3 mL) was stirred at room temperature for 24 h. The mixture was washed with 5% aqueous sodium thiosulfate (2 mL) and 5% aqueous sodium bicarbonate (2 mL × 3) and dried (Na_2SO_4). Removal of the solvent and sublimation (130 °C, 18 mm) afforded **13** as a colorless solid (18 mg, 75%): mp >300 °C; IR (KBr) 2960, 1450, 1285, 1110, and 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (broad s, 2 H), 2.80 (broad s, 2 H), and 2.52–1.67 (AB q type m, 8 H); ^{13}C NMR, see Table I; mass spectrum, *m/e* (relative intensity, %) 174 (1.4, M + 2), 171 (2.9, M + 1), 172 (10.5, M^+), 108 (100), 94 (30.2), 92 (68.4), 81 (99.5), 78 (67.0), 66 (63.6), 65 (46.5), 41 (93.0), and 39 (99.0).

Anal Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.00. Found: C, 56.02; H, 6.76.

9-Methyl-9-thianoradamantanium (9-Methyl-9-thiatricyclo[3.3.1.0^{3,7}]nonanium) Iodide (14). A mixture of **11** (15 mg, 0.10 mmol) and methyl iodide (340 mg, 2.4 mmol) in chloroform (3 mL) was heated under reflux for 17 h to afford a precipitate, which was filtered off and dried to give **14** as colorless crystals (25 mg, 89%): mp 242–244 °C dec; IR (KBr) 2925, 1460, 1415, 1300, 1250, 1240, 1085, 960, and 710 cm^{-1}; ^1H NMR (D_2O–$CDCl_3$) δ 3.87 (broad s, 2 H), 2.84 (s, 3 H), and 3.0–1.8 (m, 10 H).

Anal. Calcd for $C_9H_{15}SI$: C, 38.31; H, 5.36. Found: C, 38.46; H, 5.21.

Acknowledgment. We gratefully acknowledge Takeda Chemical Industries Ltd. for obtaining the mass spectral data.

Registry No.—**5**, 1073-76-3; **10a**, 67194-75-6; **10b**, 67194-76-7; **12**, 13334-79-7; **14**, 67194-77-8.

References and Notes

(1) Part 40: T. Sasaki, S. Eguchi, and F. Nakata, *Tetrahedron Lett.*, 1999 (1978).
(2) For reviews and leading references, see (a) M. Jones, Jr., and R. A. Moss, *Carbenes 1973*, **1** (1973); (b) W. Kirmse, "Carbene Chemistry", 2nd ed, Academic Press, New York, N.Y., 1971.
(3) A. C. Udding, J. Strating, H. Wynberg, and J. L. M. A. Schlatmann, *Chem. Commun.*, 657 (1966).
(4) H. W. Geluk and Th. J. DeBoer, *Tetrahedron*, **28**, 3351 (1972).
(5) M. Farcasiu, D. Farcasiu, R. T. Conlin, M. Jones, Jr., and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8207 (1973).
(6) (a) T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Am. Chem. Soc.*, **91**, 212 (1969); (b) *Tetrahedron*, **27**, 893 (1971).
(7) (a) M. R. Vegar and R. J. Wells, *Tetrahedron Lett.*, 2565 (1969); (b) M. H. Fisch and H. D. Pierce, Jr., *Appl. Spectrosc.* **23**, 637 (1969).
(8) E. W. Garbish, Jr., *J. Org. Chem.*, **30**, 2109 (1965).
(9) A. T. Bottini and J. Gal, *J. Org. Chem.*, **36**, 1718 (1971).
(10) Y. Kashman and E. Benary, *Tetrahedron*, **28**, 4091 (1972).
(11) (a) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966); (b) E. D. Weil, K. J. Smith, and R. J. Gruber, *ibid.*, **31**, 1669 (1966).
(12) J. R. Wiseman and H. O. Krabbenhoft, *J. Org. Chem.*, **40**, 322 (1975).
(13) J. R. Wiseman and H. O. Krabbenhoft, *J. Org. Chem.*, **41**, 589 (1976).
(14) For a conformational study on *endo*-bicyclo[3.3.1]nonan-3-ol, see M. Fish, S. Smallcome, J. C. Gramain, M. A. McKervey, and J. E. Anderson, *J. Org. Chem.*, **35**, 1886 (1970), and references cited therein.
(15) Microanalyses were performed with a Perkin-Elmer 240 elementanl analyzer. Melting points were determined in a sealed tube with a Yanagimoto micromelting point apparatus (hot-stage type) and are uncorrected. IR spectra were obtained with a Jasco IRA-1 spectrometer. ^1H NMR spectra were recorded on a Jeol JNM-C-60HL instrument at 60 MHz, while ^{13}C NMR spectra were recorded on a Jeol JNM-FX 60 FT NMR spectrometer at 15.04 MHz. All NMR spectral peak positions are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi RMS-4 mass spectrometer at 70 eV. GLC analyses were performed with a Jeol JGC-20K gas chromatograph on a 1 or 2 m Silicone SE-30 and/or Apiezon grease L column at 80–230 °C.

Synthesis of Adamantane Derivatives. 42.[1] Novel Synthesis of 5-Methylene-4-azahomoadamantane Derivatives from 2-Methyl-2-hydroxyadamantane and Their Carbon-13 Nuclear Magnetic Resonance Spectra

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5-Methyl-4-azahomoadamant-4-ene (**9**), readily obtainable from 2-methyl-2-hydroxyadamantane (**8**), was converted to 4-acyl-5-methylene-4-azahomoadamantanes **11a**, **11b**, and **11c** in good yields on acylation. The reaction of **9** with dichlorocarbene gave also 4-formyl-5-methylene-4-azahomoadamantane (**16**), while peracetic acid oxidation of **9** gave the corresponding oxaziridine **17**. 4,5-Dimethyl-4-azahomoadamantenium iodide (**18a**), the methiodide of **9**, gave 4-methyl-5-methylene-4-azahomoadamantane (**19**) on treatment with aqueous alkali. ^{13}C NMR data of the thus prepared 5-methylene-4-azahomoadamantane derivatives have been reported.

4-Azahomoadamantane derivatives are known as potentially biologically active compounds,[2] and several synthetic routes to this skeleton have been reported recently by many workers. The Beckmann rearrangement[3] and the Schmidt reaction[4] of the adamantanone system (**1**) are the simple routes to 4-azahomoadamantan-5-one (**2**), but these reactions are prone to suffer from side reactions such as fragmentations. The rearrangement of spirooxaziridine (**3**) is known also as a direct route to *N*-alkyl-4-azahomoadamantan-5-one (**2**).[5] On the other hand, rearrangements via 1-adamantylnitrenium ion type intermediates as in the **4** → **5**,[6] **6** → **5**,[7] and **7** → **5**[8] conversions are unique routes to 3-substituted 4-azahomoadamantanes. In this paper, we report a novel and facile synthesis of 5-methylene-4-azahomoadamantane derivatives via 5-methyl-4-azahomoadamant-4-ene (**9**) from 2-methyl-2-hydroxyadamantane (**8**).

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