Reduction of 7-Methyl- and 7-Phenyl-7-halobicyclo-[4.1.0]heptanes with Tributyltin Hydride

By

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(Received December 25, 1981)

Abstract

Each of the two geometrical isomers (**1a** and **1b**) of 7-chloro-7-methylbicyclo-[4.1.0]heptane and the *endo*-methyl isomer (**2a**) of 7-bromo-7-methylbicyclo[4.1.0]-heptane were separately reduced with tributyltin hydride in a temperature range of 0 to 140°C, to give an isomeric mixture of 7-methylbicyclo[4.1.0]heptane (**5**). The endo:exo ratio in the product was 72±2 : 28±2, irrespective of the geometry of the starting halide. The reduction of 7-chloro-7-phenylbicyclo[4.1.0]heptane (**3**) under similar conditions also proceeded nonstereospecifically to afford an isomeric mixture of 7-phenylbicyclo[4.1.0]heptane (**6**) with the endo:exo ratio of 90±2 : 10±2. The complete loss of stereospecificity in these reductions suggests that the intermediarily formed 7-methyl- and the 7-phenylbicyclo [4.1.0] hept-7-yl radicals are configurationally unstable and behave like a planar radical.

Previous work on the stereochemical behavior of α-substituted cyclopropyl radicals has revealed that the electronic nature of the substituent at the position α to the radical center has a profound effect on the configurational stability, or the energy barrier for inversion, of cyclopropyl radicals.[1-9] To our knowledge, however, there has been no systematic investigation on the effect of α-alkyl or α-aryl substituents on the configurational stability of cyclopropyl radicals. Such information would be of much importance for clarifying the substituent effect of this type.

In this paper, the stereochemical behavior of α-methyl- and α-phenyl-substituted cyclopropyl radicals is discussed, in comparison with the behavior of α-chloro-substituted radicals, on the basis of the results of the reduction of 7-chloro-7-methyl- (**1**), 7-bromo-7-methyl- (**2**), 7-chloro-7-phenyl- (**3**), and 7-bromo-7-chlorobicyclo[4.1.0]-heptane (**4**) with tributyltin hydride.

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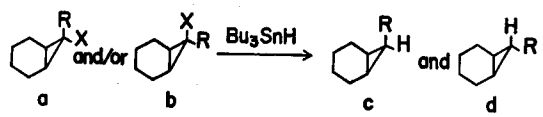
Results and Discussion

The halides employed for the present study, except **2**, were prepared as an isomeric mixture either by the addition of the corresponding carbene to cyclohexene, or by the treatment of 7, 7-dichlorobicyclo [4. 1. 0] heptane with butyllithium followed by methylation or bromination.

An isomeric mixture of **1** was separated by preparative GLC into its geometrical isomers (**1a** and **1b**), whose isomeric purities were higher than 99 %.[10] The *endo*-methyl isomer (**1a**) was obtained also by the stereoselective methylation of 7-chlorobicyclo [4. 1. 0] hept-7-yllithium with methyl iodide. A similar treatment of 7-bromobicyclo [4. 1. 0] hept-7-yllithium gave the *endo*-methyl isomer (**2a**) of 7-bromo-7-methylbicyclo [4. 1. 0] heptane. The corresponding *exo*-methyl isomer (**2b**) could not be obtained.

The treatment of an isomeric mixture of **3** with silver nitrate in methanol[11] gave pure 7-*endo*-chloro-7-*exo*-phenylbicyclo [4. 1. 0] heptane (**3b**). The treatment of an isomeric mixture of **4** with hot quinoline gave pure 7-*exo*-bromo-7-*endo*-chlorobicyclo-[4. 1. 0] heptane (**4a**). Isomerically pure 7-*endo*-bromo-7-*exo*-chlorobicyclo [4. 1. 0]-heptane (**4b**) was synthesized according to the method of Köbrich.[12]

The configurations of these compounds were determined on the basis of the stereochemical results obtained in the carbonation of 7-chlorobicyclo [4. 1. 0] hept-7-yllithium,[12] and of the difference in the rates of the ring expansion of 7, 7-dihalobicyclo-[4. 1. 0] heptanes in hot quinoline.[13] The assignments by these chemical methods are in good agreement with those based on the ^{13}C NMR analyses, which were reported previously.[14]



1: R=Me, X=Cl
2: R=Me, X=Br
3: R=Ph, X=Cl
4: R=Cl, X=Br

5: R=Me
6: R=Ph
7: R=Cl

The reduction of the halides thus obtained was conducted by treating them with 1.2 equivalents of neat tributyltin hydride under the reaction conditions shown in Tables 1 and 2. The stereochemistry of the reduction products was determined by a comparison of their spectral and other physical properties with those of authentic samples. The measurement of their ^1H and ^{13}C NMR spectra, in particular, made an unambiguous assignment possible. The yields of the reduction products were

Table 1. Reduction of Halides **1**, **2**, and **3**

Compd	Temp. (°C)	Catalyst	Time (h)	Yield (%)	Isomer ratio (c : d)
1a	80	AIBN	6	77	73 : 27
	140	DTBP	4	86	71 : 29
1b	80	AIBN	6		71 : 29
	140	DTBP	4		70 : 30
2a	0	none	12	74	74 : 26
	80	none	3	79	73 : 27
	140	none	2	86	72 : 28
3*	80	AIBN	8	64	91 : 9
	140	DTBP	4	77	89 : 11
3b	80	AIBN	8	72	90 : 10
	140	DTBP	4	73	88 : 12

* An isomeric mixture was used, **3a** : **3b**=40 : 60.

measured by the internal standard method (GLC). Where only relative yields (isomer distributions) were desired, no internal standard was added. The results of the reactions are summarized in Tables 1 and 2.

As can be seen from the data in Table 1, the isomer distributions in the products observed in the reduction of **1** and **2** (endo : exo=72±2 : 28±2) and those in the reduction of **3** (endo : exo=90±2 : 10±2) were both practically independent of the geometry of the starting halide. This implies that the 7-methyl- and the 7-phenylbicyclo [4. 1. 0] hept-7-yl radicals, which are formed intermediately in the process of the reduction, are either pyramidal but invert their configuration so rapidly that they behave as if they were planar, or are in fact planar, at temperatures used in this study (0-140°C for the methyl-substituted radical, and 80-140°C for the phenyl-substituted radical).

The predominant formation of the *endo*-substituted isomers, **5c** and **6c**, in these reductions must be due to a greater steric hindrance encountered in the hydrogen transfer from the tin hydride to the endo side of the radical than to the exo side. The slight increase in the relative amount of the *exo*-substituted isomer, **5d** or **6d**, with an increase in the reaction temperature may be explained on the same basis.

Table 1 shows that the α-methyl-substituted radical cannot retain its configuration even at 0°C. This behavior of the α-methyl radical is in sharp contrast with that of the corresponding α-chloro radical. Thus, as Table 2 shows, the reduction of the pure isomers (**4a** and **4b**) of 7-bromo-7-chlorobicyclo [4. 1. 0] heptane with tributyltin hydride at 0 or −20°C proceeded with partial retention of configuration, though the stereospecificity was lost when the reaction temperature was raised to 80°C. Evidently, the inversion of the 7-chlorobicyclo [4. 1. 0] hept-7-yl radical takes place at a rate

Table 2. Reduction of Halide **4**

Compd	Temp. (°C)	Time (h)	Yield (%)	Isomer ratio (**c** : **d**)
4a	−20	5	71	81 : 19
	0	3	75	79 : 21
	80	2	86	74 : 26
4b	−20	5	73	63 : 37
	0	3	79	69 : 31
	80	2	80	73 : 27

comparable to its hydrogen abstraction from the tin hydride at 0°C or below, and at a rate faster than the latter at 80° C or above. Analogous results have been reported by Altman and Baldwin.[5]

The difference in the behavior of the α-methyl- and the α-chloro-substituted radicals suggests that the effect of the α-chloro substituent of stabilizing the pyramidal configuration of the cyclopropyl radical is greater than that of the α-methyl substituent. Probably the difference in the electronegativity of the substituents is responsible for the difference in their configuration-stabilizing effects.[2]

The low configurational stability of the α-phenyl-substituted radical may be attributed to the p-π conjugation between the π-electrons in the phenyl substituent and the p-electron at the radical center. This should favor a planar configuration rather than a pyramidal one for the cyclopropyl radical. Other α-substituents which are capable of p-π conjugation, such as α-methoxycarbonyl or α-cyano, have been found to have no ability to stabilize the pyramidal configuration of the cyclopropyl radical even at 0° C, on the basis of the results of the reduction of 7-methoxycarbonyl- (**8**) and 7-cyano-7-halobicyclo [4. 1. 0] heptane (**9**) with tributyltin hydride.[3] To be noted is that the endo : exo ratio in the products from **3** (ca. 90 : 10) is very close to that in the products from **8** or **9**. In view of these facts, it is very probable that the configurational stability of α-phenyl-substituted cyclopropyl radicals is comparable to that of α-methoxycarbonyl- or α-cyano-substituted cyclopropyl radicals, though at present there is no direct evidence available to reveal the bahavior of the former radical at lower temperatures.

Further studies on the effect of α-substituents on the configurational stability of cyclopropyl radicals are in progress.

Experimental

General. All boiling and melting points are uncorrected. The infrared spectra were recorded on a Shimadzu IR-27 infrared spectrometer using a polystyrene film for calibration. The proton NMR (^{1}H NMR) spectra were measured with a Varian

Associates T-60 or EM-360 spectrometer (60 MHz) for solutions in carbon tetrachloride, with tetramethylsilane (Me_4Si) as an internal standard. The chemical shifts are expressed in parts per million downfield from Me_4Si. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer at an ionizing potential of 70 eV. The gas chromatographic (GLC) analyses were carried out with a Shimadzu GC-2C or GC-6A gas chromatograph by use of a glass or stainless steel column of 3 m × 3 mm. For the purpose of preparative GLC separations, a 2 m × 10 mm alumina column was used with a liquid phase of 15 % Apiezon grease L, 15 % Silicon DC 550, or 20 % tricresyl phosphate. The isomer distributions in the products were calculated from the peak areas in the gas chromatograms. The accuracy for the values of the isomer ratios listed in Tables 1 and 2 is within ±2 %.

All chemicals were of reagent grade and used without further purification. The solvents were distilled and, if necessary, were purified in the usual manner prior to use.

7-exo-Chloro-7-endo-methylbicyclo [4. 1. 0] heptane (**1a**). To a solution of 33 g (0. 2 mol) of 7, 7-dichlorobicyclo [4. 1. 0] heptane in 200 m*l* of tetrahydrofuran was added, under a nitrogen atmosphere, 250 m*l* of a 0. 8 N solution of butyllithium in hexane at −75 to −85°C. After the addition was over, the reaction mixture was stirred for 2 h at −85°C, and then an excess of methyl iodide was slowly added to it. The mixture was warmed up to room temperature, poured into ice water, and was worked up as usual. The organic fraction was distilled under reduced pressure to give 7. 6 g of 7-*exo*-chloro-7-*endo*-methylbicyclo [4. 1. 0] heptane (**1a**) as a colorless liquid : 22 % yield; bp 80-83°C (35 mmHg) ; n_D^{20} 1. 4822; IR (film) 2950 (s), 2865 (m), 1466 (m), 1169 (m), 1069 (m), 747 cm^{-1} (w) ; ^1H NMR δ 0. 7−2. 6 (complex m, 10 H) and 1. 70 (s, 3 H) ; mass spectrum *m/e* (relative intensity) 146 (M+2, 3), 144 (M, 9), 109 (72), 102 (29), 81 (63), 79 (27), 68 (66), 67 (100).

7-endo-Chloro-7-exo-methylbicyclo [4. 1. 0] heptane (**1b**). The methylation of 7-chlorobicyclo [4. 1. 0] hept-7-yllithium described above was effected at −120 to −110°C to afford a mixture of two geometrical isomers (*exo*-Me : *endo*-Me=71 : 29) in 29 % yield. The preparative GLC separation using a column with 15 % Apiezon grease L on 80-100 Celite 545 gave 7-*endo*-chloro-7-*exo*-methylbicyclo [4. 1. 0] heptane (**1b**) of more than 99 % purity: n_D^{23} 1. 4836; IR (film) 2948 (s), 2862 (m), 1445 (m), 1170 (m), 1076 (m), 796 cm^{-1} (m) ; ^1H NMR δ 0. 7-2. 6 (complex m, 10 H) and 1. 71 (s, 3 H) ; mass spectrum *m/e* (relative intensity) 146 (M+2, 3), 144 (M, 9), 109 (60), 102 (37), 81 (65), 79 (29), 68 (63), 67 (100).

7-exo-Bromo-7-endo-methylbicyclo [4. 1. 0] heptane (**2a**) was prepared by the methylation of 7-bromobicyclo [4. 1. 0] hept-7-yllithium under reaction conditions similar to those used for the preparation of **1a** : 38 % yield ; bp 95. 0-97. 0° C (28 mmHg) ;

n_D^{20} 1.5092 ; IR (film) 2935 (s), 2860 (s), 1469 (m), 1448 (m), 1440 (m), 1334 (w), 1172 (m), 1076 (m), 830 (w), 794 (m), 749 cm^{-1} (m) ; ^1H NMR δ 0.7-2.6 (complex m, 10 H) and 1.69 (s, 3 H) ; mass spectrum *m/e* (relative intensity) 190 (M+2, 6), 188 (M, 6), 148 (11), 146 (11), 135 (6), 133 (6), 109 (100), 95 (13), 81 (24), 79 (16), 68 (43), 67 (95).

7-Chloro-7-phenylbicyclo [4. 1. 0] heptane (***3a and 3b***) was prepared as an isomeric mixture by the addition of chlorophenylcarbene, generated by the reaction of benzal chloride with potassium *tert*-butoxide,[15] to cyclohexene in 58 % yield : bp 96-98° C (1.0 mmHg) (lit.[15a] 170-173° C at 33 mmHg) ; n_D^{23} 1.5559 (lit.[15a] n_D^{21} 1.5562) ; IR (film) 3020 (s), 2924 (vs), 2880 (s), 1600 (m), 1492 (s), 1444 (vs), 1175 (m), 1075 (m), 970 (m), 745 (vs), 698 cm^{-1} (vs) ; ^1H NMR δ 0.2-2.3 (complex m, 10 H) and 6.9-7.6 (m, 5 H).

A mixture of 60 g (0.3 mol) of 7-chloro-7-phenylbicyclo [4. 1. 0] heptane (mixture of isomers) and 25.5 g (0.15 mol) of silver nitrate in 200 m*l* of methanol was stirred at room temperature for 24 h. After the reaction mixture was filtered to remove the precipitates, water and ether were added to the filtrate. The organic layer was separated and the aqueous layer was extracted with ether. The ethereal extracts were combined with the organic layer and were dried over anhydrous sodium sulfate, filtered, and were concentrated *in vacuo*. Column chromatography on silica gel (Wakogel C-200) with ligroin (bp 35-70°C) gave isomerically pure **3b** as a colorless solid : mp 35.0-36.5°C (lit.[11] 36-37°C) ; IR (film) 3020 (w), 2950 (s), 2880 (m), 1603 (w), 1498 (m), 1445 (s), 1020 (m), 755 (s), 738 (s), 697 cm^{-1} (s) ; ^1H NMR δ 1.0-2.3 (complex m, 10 H) and 7.0-7.5 (m, 5 H) ; mass spectrum *m/e* (relative intensity) 208 (M+2, 10), 206 (M, 30), 171 (31), 138 (100), 129 (59), 115 (30), 103 (31), 91 (27), 77 (13).

Attempts to obtain pure 7-*exo*-chloro-7-*endo*-phenylbicyclo [4. 1. 0] heptane (**3a**) were unsuccessful.

7-exo-Bromo-7-endo-chlorobicyclo [4. 1. 0] heptane (***4a***). An isomeric mixture (*endo*-Cl : *exo*-Cl = 47 : 53) of 7-bromo-7-chlorobicyclo [4. 1. 0] heptane was prepared according to the reported method.[4] A solution of 20 g (0.1 mol) of this isomeric mixture in 100 m*l* of quinoline was stirred at 140°C for 24 h. Then, the mixture was distilled under reduced pressure to collect crude volatile products. Redistillation *in vacuo* of the products afforded pure isomer **4a** : bp 71.0-72.0°C (6 mmHg) ; n_D^{22} 1.5289 ; IR (film) 2940 (vs), 2865 (s), 1463 (m), 1445 (s), 1335 (m), 1165 (m), 1093 (m), 1081 (m), 1023 (s), 967 (m), 830 (m), 765 (s), 742 cm^{-1} (s) ; mass spectrum *m/e* (relative intensity) 212 (M+4, 1), 210 (M+2, 4), 208 (M, 3), 170 (6), 168 (24), 166 (18), 157 (1), 155 (4), 153 (3), 131 (5), 129 (15), 93 (20), 68 (100).

7-endo-Bromo-7-exo-chlorobicyclo [4. 1. 0] heptane (***4b***) was obtained by the bromi-

nation of 7-chlorobicyclo [4.1.0] hept-7-yllithium at −80° C according to the literature procedure:[12] 11 % yield ; bp 76.0-77.0°C (5 mmHg) ; n_D^{28} 1.5247 ; IR (film) 2950 (vs), 2865 (s), 1464 (m), 1448 (s), 1337 (m), 1165 (m), 1083 (m), 1023 (s), 968 (m), 838 (m), 827 (m), 782 (m), 768 cm^{-1} (s) ; mass spectrum *m/e* (relative intensity) 212 (M+4, 0.4), 210 (M+2, 2), 208 (M, 1), 170 (6), 168 (22), 166 (16), 157 (1), 155 (4), 153 (3), 131 (4), 129 (13), 93 (18), 68 (100).

*General Procedure for the Reduction of Cyclopropyl Halides (**1**, **2**, **3**, and **4**) with Tributyltin Hydride.* In a 10-m*l* flask fitted with a magnetic stirrer bar, a thermometer, an inlet tube for nitrogen, and a rubber septum for a syringe were placed 5-10 mmol of the halide and, if necessary, a catalytic amount of a radical initiator. Azobisisobutyronitrile (AIBN) and di-*tert*-butyl peroxide (DTBP) were used for reducing the chlorides (**1** or **3**) at 80 and 140° C, respectively. To this mixture was added, under a nitrogen atmosphere, 1.2 equiv of tributyltin hydride by use of a syringe at a specified temperature. After a constant time, the reaction mixture was analyzed by GLC to determine the yields and the isomer distributions, which are listed in Tables 1 and 2.

*7-Methylbicyclo [4.1.0] heptane (**5c** and **5d**)* : bp 62.0-63.0°C (55 mmHg) (lit.[16] 123-125°C at 750 mmHg) ; n_D^{20} 1.4614 (lit.[16] n_D^{26} 1.4496) ; IR (film) 3000 (m), 2930 (s), 2860 (m), 1448 (m), 1176 (m), 1015 (w), 744 cm^{-1} (m) ; ^1H NMR δ 0.4-2.4 (complex m, 11 H) and 0.94 (d, J=4.0 Hz, 3 H) for **5c**, 0.2-2.3 (complex m, 11 H) and 1.00 (d, J=5.2 Hz, 3 H) for **5d** ; mass spectrum *m/e* (relative intensity) 110 (M, 31), 95 (31), 81 (100), 79 (18), 69 (20), 67 (75) for **5c**, 110 (M, 43), 95 (31), 81 (100), 79 (23), 69 (20), 67 (82) for **5d**.

*7-Phenylbicyclo [4.1.0] heptane (**6c** and **6d**)* : bp 72.0-73.0° C (0.5 mmHg) (lit.[15a] 127-128° C at 13 mmHg) ; n_D^{25} 1.5430 (lit.[15a] n_D^{24} 1.5524) ; IR (film) 3020 (m), 2950 (s), 2880 (m), 1604 (w), 1495 (m), 1452 (m), 1070 (m), 1025 (m), 776 (s), 717 (s), 700 cm^{-1} (s) ; ^1H NMR δ 0.4-2.3 (complex m, 11 H) and 7.17 (br s, 5 H) for **6c**, 0.7-2.6 (complex m, 11 H) and 6.7-7.3 (m, 5 H) for **6d** ; mass spectrum *m/e* (relative intensity) 172 (M, 68), 130 (26), 129 (48), 128 (26), 117 (26), 115 (30), 103 (90), 91 (56), 81 (100), 80 (50), 79 (28) for **6c**, 172 (M, 76), 130 (30), 129 (50), 128 (26), 117 (30), 115 (30), 104 (100), 91 (55), 81 (87), 80 (42), 79 (24) for **6d**.

*7-Chlorobicyclo [4.1.0] heptane (**7c** and **7d**)* : bp 60.0-62.0° C (13 mmHg) (lit.[17] 56-57° C at 11 mmHg) ; n_D^{26} 1.4853 (lit.[17] n_D^{25} 1.4861) ; IR (film) 3000 (m), 2936 (s), 2860 (s), 1446 (m), 1285 (m), 1063 (w), 1010 (w), 723 (m), 685 cm^{-1} (m) ; ^1H NMR δ 0.7-2.3 (complex m, 10 H) and 3.14 (t, J=7.6 Hz, 1 H) for **7c**, 0.8-2.3 (complex m, 10 H) and 2.58 (t, J=3.4 Hz, 1 H) for **7d** ; mass spectrum *m/e* (relative intensity) 132 (M+2, 5), 130 (M, 15), 117 (0.3), 115 (0.9), 104 (2), 103 (1), 102 (5), 101 (3), 95 (53), 90 (22), 88 (66), 81 (100), 67 (53).

References and Note

1) T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.*, **89**, 5719 (1967).
2) T. Ando, H. Yamanaka, F. Namigata, and W. Funasaka, *J. Org. Chem.*, **35**, 33 (1970).
3) T. Ando, K. Wakabayashi, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, **45**, 1576 (1972).
4) T. Ishihara, K. Hayashi, T. Ando, and H. Yamanaka, *J. Org. Chem.*, **40**, 3264 (1975).
5) L. J. Altman and R. C. Baldwin, *Tetrahedron Lett.*, 2531 (1971).
6) L. J. Altman and J. C. Vederas, *J. Chem. Soc. Chem. Commun.*, 895 (1969).
7) L. A. Singer and J. Chen, *Tetrahedron Lett.*, 939 (1971).
8) J. Hatem and B. Waegell, *Tetrahedron Lett.*, 2019 (1973).
9) H. M. Walborsky, *Tetrahedron*, **37**, 1625 (1981), and references cited therein.
10) Isomers **a** and **b** of **3** and **4** were not separated by GLC in spite of a variety of liquid phases and conditions used.
11) D. B. Ledlie, R. I. Thorne, and G. Weiss, *J. Org. Chem.*, **36**, 2186 (1971).
12) G. Köbrich and W. Goyert, *Tetrahedron*, **24**, 4327 (1968).
13) T. Ando, H. Hosaka, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, **42**, 2013 (1969).
14) T. Ishihara, T. Ando, T. Muranaka, and K. Saito, *J. Org. Chem.*, **42**, 666 (1977).
15) a) J. E. Hodgkins, J. D. Woodyard, and D. L. Stephenson, *J. Am. Chem. Soc.*, **86**, 4080 (1964); b) G. L. Closs and J. J. Coyle, *J. Org. Chem.*, **31**, 2759 (1966).
16) R. T. Lalonde and M. A. Tobias, *J. Am. Chem. Soc.*, **86**, 4068 (1964).
17) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963).