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Stereoselectivity in Hydride Reduction of [*n*.3.2]Propellanones

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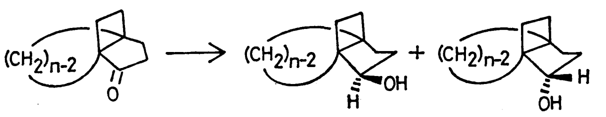
Synopsis. Stereoselectivity in hydride reduction of [*n*.3.2]propellanones is described. The observed stereoselectivity is attributed to conformational flexibility of the third ring, that is, from five- to eight-membered alicyclic rings.

Propellanes are compounds having three rings conjoined along a common σ bond and serve as good models for examination of steric and electronic effects among three dimensionally arranged rings.1) From this point of view, much works have been done on the reactivity of unsaturated propellanes such as heterocyclic2a) and [4.4.2]propellane derivatives.2b) As part of studies on relationship between structure and reactivity of propellanes,3) we wish to report here stereoselectivity in hydride reduction of [*n*.3.2]propellanones (**1**)—(**4**) involving a cyclobutane ring, a cyclopentanone moiety, and one of alicyclic rings from five to eight-membered rings as the third ring, and wish to emphasize that conformational flexibility of the third ring plays a key role in determining the stereochemistry of products.

[*n*.3.2]Propellanones **1**—**4** were prepared in good yields by photocycloaddition of the corresponding bicyclic enones to ethylene. Reduction of **1**—**4** with $LiAlH_4$ in ether or $NaBH_4$ in methanol gave two epimeric alcohols (exo; (**5X**)—(**8X**), endo; (**5N**)—(**8N**)), in quantitative yields, and the exo and endo stereochemistry of them were assigned on the basis of the α-hydroxy proton coupling constants according to the data reported for derivatives of bicyclo[3.2.0]heptan-2-ol.4) The ratios of exo and endo propellanols are summarized in Table.

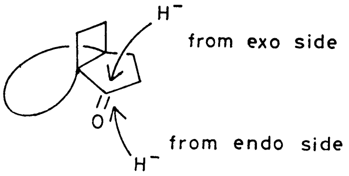


	exo	endo
1 *n*=5	**5X**	**5N**
2 *n*=6	**6X**	**6N**
3 *n*=7	**7X**	**7N**
4 *n*=8	**8X**	**8N**

Table 1. Stereoselectivity in hydride reduction of [*n*.3.2]propellanones **1**—**4**

Propellanone	Exo: endo ratio	
	$LiAlH_4$	$NaBH_4$
1	91.4:8.6	87.5:12.5
2	96.4:3.6	93.5: 6.5
3	98.6:1.4	97.2: 2.8
4	99.3:0.7	98.3: 1.7

As shown in Table 1, exo alcohols are always formed almost stereoselectively and, more interestingly, the ratio of exo alcohols increases in order as the size of the third ring increases. Taking the above facts and the mechanism for metal hydride reduction of carbonyl groups into account,6) it is reasonable to consider that endo side of propellanones **1**—**4** is sterically less hindered than exo side and the difference in the steric hindrance at exo and endo sides of each propellanones becomes greater as the third ring changes from five- to eight-membered ring. In the present system, the difference in the steric hindrance at each side of cyclopentanone moiety may be attributed to the difference in nonbonded interaction in the transition state between hydrogens of individual alicyclic ring and a hydride, which can be associated with conformational flexibility of ring systems. Namely, on account of the greater degree of conformational flexibility of the third ring in comparison with that of cyclobutane ring, such nonbonded interaction in the transition state at the endo side may be remarkably reduced compared with the exo side. In addition, the nonbonded interaction at the endo side may become smaller in order of increase in conformational flexibility of the third ring, in other words, in the increasing order in size of the third ring. Consequently, it must be concluded that conformational flexibility of the third ring plays a key role in determining the stereochemistry of the resulting alcohols in hydride reduction of [*n*.3.2]-propellanones.



Experimental

Materials. Ketones **1**,7) **2**,8) **3**, **4**, and 1,5-dimethylbicyclo[3.2.0]heptan-2-one were prepared in 51—73% yields by photocycloaddition of the corresponding bicyclic enones to ethylene in ether at −70 °C. **3**, IR 1710 cm^{-1}; NMR δ (CCl_4) 1.00—2.80 (m); MS *m/e* 178 (M^+). Semicarbazone, mp 203—204 °C; Found: C, 66.24; H, 8.87; N, 17.95%. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00; N, 17.86%. **4**, IR 1710 cm^{-1}; NMR δ (CCl_4) 1.00—2.90 (m); MS *m/e* 192 (M^+). Semicarbazone, mp 216—218 °C; Found: C, 67.31; H, 9.43; N, 16.96%. Calcd for $C_{14}H_{23}ON_3$: C, 67.43; H, 9.30; N, 16.85%. 1,5-Dimethylbicyclo[3.2.0]heptan-2-one, IR 1710 cm^{-1}; NMR δ (CCl_4) 0.95 (s, 3H), 1.15 (s, 3H), 1.40—2.80 (m, 8H); MS *m/e* 138 (M^+). Semicarbazone, mp 202—204 °C; Found: C, 61.51; H, 8.78; N, 21.52%. Calcd for $C_{10}H_{17}ON_3$: C, 61.39; H, 8.88; N, 21.33%.

$LiAlH_4$ Reduction of 1—4. A solution of a ketone in ether was added dropwise to the suspension of 5 molar excess of $LiAlH_4$ in ether and the mixture was stirred at room temperature for 12 h. Water and dilute hydrochloric acid was added carefully and the aqueous solution was extracted with

ether. The combined ethereal solution was washed with aqueous sodium hydrogencarbonate and brine, and then dried (Na_2SO_4). After evaporation of the solvent, the residue was distilled under reduced pressure to give a mixture of alcohols in 90—97% yields. Exo alcohols were separated by preparative GLC (10% FFAP or 10% DEGS) and endo ones were identified with the authentic materials prepared by Meerwein-Ponndorf reduction of ketones. The ratios of them are listed in Table.

5X, mp 95—96 °C; IR 3250, 1040 cm^{-1}; NMR δ (CCl_4) 1.00—2.40 (m, 15H), 3.72 (t, J=8.0 Hz, 1H); MS *m/e* 152 (M^+); Found: C, 77.63; H, 10.60%. Calcd for $C_{10}H_{16}O$: C, 77.89; H, 10.59%. **6X**, mp 55—57 °C; IR 3300, 1050 cm^{-1}; NMR δ (CCl_4) 1.10—2.20 (m, 16H), 3.40 (s, 1H), 3.70 (q, J=7.2 Hz, 1H); MS *m/e* 166 (M^+); Found: C, 79.15; H, 10.88. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92%. **7X**, mp 58—60 °C; IR 3350, 1165 cm^{-1}; NMR δ (CCl_4) 1.00—2.10 (m, 18H), 2.82 (s, 1H), 3.75 (q, J=7.6 Hz, 1H); MS *m/e* 180 (M^+); Found: C, 79.79; H, 11.33%. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18%. **8X**, mp 95—96 °C; IR 3300, 1040 cm^{-1}; NMR δ (CCl_4) 0.90—2.00 (m, 20H), 2.75 (s, 1H), 4.10 (q, J=7.6 Hz, 1H); MS *m/e* 194 (M^+); Found: C, 80.27; H, 11.41%. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%.

*$NaBH_4$ Reduction of **1**—**4**.* A solution of a ketone in methanol was added dropwise to a solution of 2 molar excess of $NaBH_4$ in methanol and the mixture was stirred at room temperature for 12 h. The solution was poured into dilute hydrochloric acid and extracted with ether. The organic layer was washed with aqueous sodium hydrogencarbonate and brine and then dried (Na_2SO_4). Similar work-up as above gave a mixture of alcohols in 87—90% yields. The ratios of them are listed in Table.

*Preparation of **5N**—**9N** and **9X** by Meerwein-Ponndorf Reduction.* A mixture of a ketone and 2.2 molar excess of aluminum isopropoxide in isopropyl alcohol was heated until isopropyl alcohol began to distill slowly, while more alcohol was added. Heating was continued until no ketone remained (monitored by GLC). The solution was poured into ice-cooled aqueous sodium hydroxide and extracted with ether. The ether extract was washed with water and brine, and then dried (Na_2SO_4). Evaporation of the solvent afforded a mixture of alcohol in 84—89% yields. Products were separated by column chromatography on silica gel and purified by preparative GLC. The ratios of alcohols are as follows; **5X**: **5N**=32: 68, **6X**:**6N** =32: 68, **7X**: **7N**=58: 42, **8X**: **8N**=58: 42, **9X**: **9N**=35: 65.

5N, mp 93—94 °C; IR 3250, 1040 cm^{-1}; NMR δ (CCl_4) 1.00—2.60 (m, 15 H), 3.72 (d, J=3.7 Hz, 1H); MS *m/e* 152 (M^+); Found: C, 77.63; H, 10.58%. Calcd for $C_{10}H_{16}O$: C, 77.89; H, 10.59%. **6N**, mp 53—55 °C; IR 3300, 1050 cm^{-1}; NMR δ (CCl_4) 1.10—2.40 (m, 17H), 3.75 (d, J=4.0 Hz, 1H); MS *m/e* 166 (M^+); Found: C, 79.45; H, 11.16%. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92%. **7N**, mp 55—56 °C; IR 3400, 1040 cm^{-1}; NMR δ (CCl_4) 1.00—2.60 (m, 19H), 3.55 (d, J=3.8 Hz, 1H); MS *m/e* 180 (M^+); Found: C, 80.11; H, 11.22%. Caled for $C_{12}H_{20}O$: C, 79.94; H, 11.18%. **8N**, mp 48—50 °C; IR 3300, 1050 cm^{-1}; NMR δ (CCl_4) 1.00—2.20 (m, 21H), 3.70 (d, J=3.7 Hz, 1H); MS *m/e* 194 (M^+); Found: C, 80.63; H, 11.64. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41%. **9X**, mp 77—78 °C; IR 3250, 1050 cm^{-1}; NMR δ (CCl_4) 1.05 (s, 6H), 1.30—2.20 (m, 9H), 3.62 (d, J=3.8 Hz, 1H); MS *m/e* 140 (M^+). *p*-Nitrobenzoate, mp 110—111 °C; Found: C, 66.14; H, 6.63; N, 4.83%. Calcd for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84%. **9N**, mp 78—79 °C; IR 3250, 1050 cm^{-1}; NMR δ (CCl_4) 0.96 (s, 3H), 1.02 (s, 3H), 1.10—2.10 (m, 9H), 3.53 (q, J=7.2 Hz, 1H); MS *m/e* 140 (M^+). *p*-Nitrobenzoate, mp 114—115 °C; Found: C, 66.14; H, 6.64; N, 4.89%. Calcd for $C_{16}H_{19}O_4N$: C, 66.42; H, 6.62; N, 4.84%.

References

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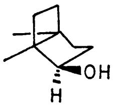
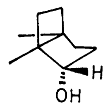
3) Previous report of this series; Y. Tobe, K. Kimura, and Y. Odaira, *J. Org. Chem.*, in press.

4) Since bicyclo[3.2.0]heptan-2-ol moiety has rigid boat conformation, endo α-hydroxy proton in exo propellanol appeared as triplet or quartet with coupling constants of 7—8 Hz and exo proton in endo propellanol appeared as doublet with coupling constants of about 4 Hz. (a) S. C. Lewis and G. H. Whitham, *J. Chem. Soc., C*, 274 (1967); (b) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **35**, 1627 (1970); (c) P. G. Gassman and J. M. Pascone, *J. Am. Chem. Soc.*, **95**, 7801 (1973); (d) E. A. Hill, R. J. Theissen, C. E. Cannon, R. Miller, R. B. Guthrie, and A. T. Chen, *J. Org. Chem.*, **41**, 1191 (1976).

Validity of this assignment is further confirmed by LIS NMR of *endo*- and *exo*-1,5-dimethylbicyclo[3.2.0]heptan-2-ol, (**9N**) and (**9X**), using Eu(dpm)$_3$. Namely, S values[5] for the methyl protons of endo isomer **9N** (exo proton, q, J=7.2 Hz) are 0.11 and 0.26 and those for exo isomer **9X** (endo proton, d, J=3.8 Hz) are 0.094 and 0.17, which are well in accord with the assigned structure.



9N



9X

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