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Synthesis and Structural Investigation of *trans*-8-Oxabicyclo[4.3.0]nonan-3-ols

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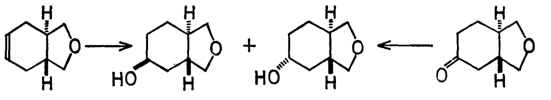
Various methods of the synthesis of *trans*-8-oxabicyclo[4.3.0]nonan-3-ols were examined; the best method for *c*-3-hydroxy-*r*-1-*trans*-8-oxabicyclo[4.3.0]nonane (**2**) was found to be the LAH reduction of the epoxide of *trans*-8-oxabicyclo[4.3.0]non-3-ene (**1**), while *t*-3-hydroxy-*r*-1-*trans*-8-oxabicyclo[4.3.0]nonane (**3**) could be obtained in a high stereoselectivity by the LAH reduction of *trans*-8-oxabicyclo[4.3.0]nonan-3-one (**4**). The structures of the two isomeric alcohols were investigated by means of nuclear magnetic resonance spectroscopy using the paramagentic shift reagent. The C-1 proton of **2** is shifted to a much greater extent than that of **3**. Much as in the case of the *cis* analogues, there is almost no difference in the coordination abilities of europium ions with the alcoholic and ethereal oxygen atoms in these compounds.

We have recently reported on the synthesis and structural investigation of *cis*-8-oxabicyclo[4.3.0]nonan-3-ols.[1] In connection with the studies of the photo-induced addition of acetic acid to *trans*-8-oxabicyclo-[4.3.0]non-3-ene (**1**),[2] the hydrolysis of the adducts has been found to afford the title compounds. As an extension of this research, and also in order to compare these results with those obtained for the *cis* compounds, the synthesis of *c*-3-hydroxy-*r*-1-*trans*-8-oxabicyclo-[4.3.0]nonane (**2**) and *t*-3-hydroxy-*r*-1-*trans*-8-oxabicyclo[4.3.0]nonane (**3**)[3] has been undertaken, and the structures of the two isomeric alcohols have been investigated by means of nuclear magnetic resonance spectroscopy using the paramagnetic shift reagent.



1 2 3 4

Scheme 1

Results and Discussion

As is shown in Table 1, the hydroboration of **1** with diborane gave almost an equal isomeric ratio of **2** and **3**, while hydroboration with diisopinocampheylborane did not improve the isomeric ratio. The lithium aluminum hydride (LAH) reduction of the epoxide of **1** obtained by the reaction of **1** with *m*-chloroperbenzoic acid gave **2** predominantly. The isomer **3** was obtained in a high isomeric ratio by the reduction of *trans*-8-oxabicyclo[4.3.0]nonan-3-one (**4**) with sodium in ethanol, lithium aluminum hydride, sodium borohydride, and catalytic hydrogenation over platinum oxide in acetic acid. To summarize these results, the LAH reduction of the epoxide of **1** seems to be the best method for the synthesis of the isomer **2**, while the LAH reduction of the ketone, **4**, provides the most convenient route to **3**.

A comparison of the above results with those for the *trans*-bicyclo[4.3.0]nonan-3-one[4] is included in Table 1; it can be deduced that, in this case, much as in

TABLE 1. REACTIONS OF **1** AND **4**

Starting materials	Methods of preparation		Alcohol ratio[a]	
			2(%)	**3**(%)
1	A	B_2H_6, H_2O_2	46	54
	B	DICB, H_2O_2[b]	43	57
	C	MCPBA, LAH[c]	93	7
4	D	LAH	6	94
	E	H_2, PtO_2/AcOH	20	80
	F	Na/EtOH	8	92
	G	$NaBH_4$	14	86
			β-ol	α-ol
	H	Na/EtOH	4	96
trans-Bicyclo[4.3.0]nonan-3-one	I	LAH	12	88
	J	H_2, PtO_2/AcOH	44	56

a) Percentage of ratio of alcohols **2** and **3** were determined by glc analysis.
b) DICB stands for diisopinocampheylborane.
c) MCPBA stands for *m*- chloroperbenzoic acid and LAH stands for lithium aluminum hydride.

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[1] K. Kimoto, T.-Y. Leong, T. Imagawa, and M. Kawanisi, *Can. J. Chem.*, **50**, 3805 (1972).

[2] T.-Y. Leong, T. Imagawa, K. Kimoto, and M. Kawanisi, This Bulletin, **46**, 596 (1973).

[3] To designate the relative configuration, the IUPAC 1968 Tentative Rules, Section E, have been adopted throughout this work. See *J. Org. Chem.*, **35**, 2849 (1970).

[4] R. Granger, J. P. Girard, J. C. Rossi, and J. Boussinesq, *Bull. Soc. Chim. Fr.*, **1967**, 4035.

that of *cis*-8-oxabicyclo[4.3.0]nonan-3-one,¹⁾ there seems to be no difference in the reactivities of the ketones in reductions even when one methylene group of the five-membered ring is replaced by an oxygen atom.

In order to determine the axial or equatorial nature of the protons adjacent to the hydroxyl or acetate moieties, it is helpful to observe the half-band widths of the proton NMR signal. The half-band widths of the carbinyl protons of **2** and **3** cannot be observed directly because of the overlapping with the signals of the protons α to the ethereal oxygen, even when the NMR shift reagent, Eu(DPM)$_3$, is added.⁵⁾ However, those of the respective acetates of **2** and **3** are observed to be 8 and 14 Hz⁶⁾ respectively, indicating the axial and equatorial arrangements for the acetoxy groups in the acetates of **2** and **3** respectively. Thus, the structures of **2** and **3** are unambiguously proved to have the structures shown in Figs. 1 and 2, since the fused systems have a *trans* configuration and since an inversion of the structure is impossible.

The above structures of **2** and **3** are further studied by the use of Eu(DPM)$_3$. The relationship between the variation in chemical shifts (δ_E) and Eu(DPM)$_3$/substrate (molar ratio) for the two isomers of **2** and **3** is shown in Figs. 1 and 2, demonstrating the linearity between δ_E and Eu(DPM)$_3$/substrate for the different protons in both isomers.

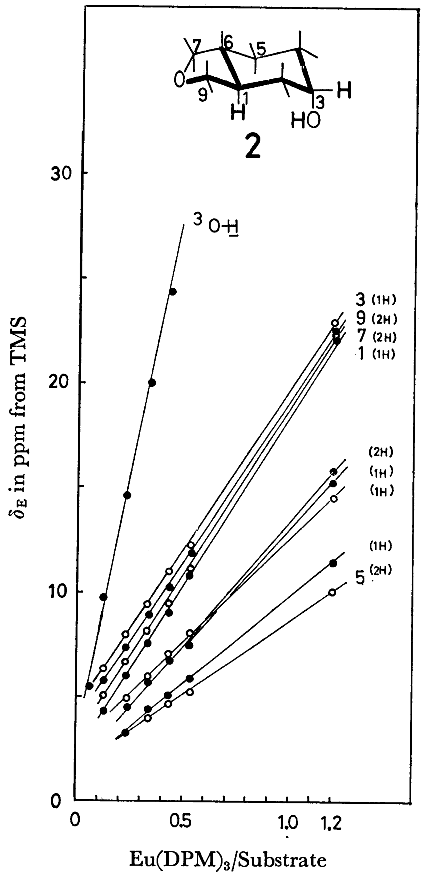

Fig. 1. Variation of chemical shift with molar ratio of Eu(DPM)$_3$/substrate for **2** in CDCl$_3$ solution.
The numerals on the lines represent protons assigned to those attached to the numbered ptorons. Numerals in parenthesis stand for the number of respective proton(s).

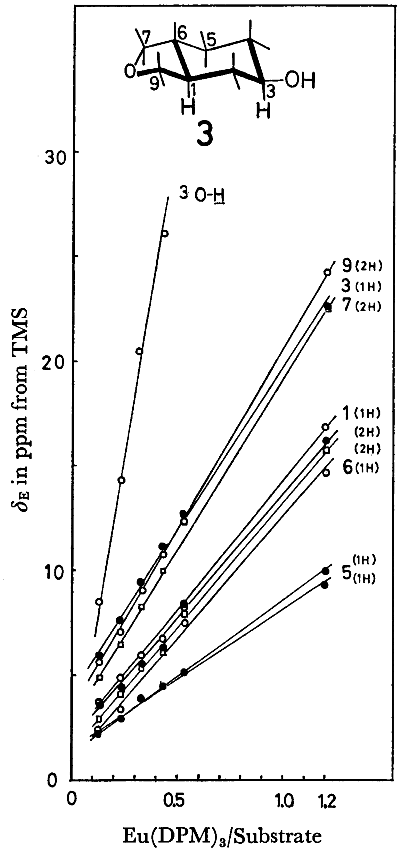

Fig. 2. Variation of chemical shift with molar ratio of Eu(DPM)$_3$/substrate for **3** in CDCl$_3$ solution.
The numerals on the lines represent protons assigned to those attached to the numbered protons. Numerals in parenthesis stand for the number of respective proton(s).

The linearities, even at the high concentration of a 1.2 molar ratio for the carbinyl protons and the four methylene protons adjacent to the oxygen atom of the five-membered rings indicate that there is no great difference in the equilibrium constants of complex formation for the alcoholic and the ethereal oxygen atoms. The same tendency has been observed in the behavior of the *cis*-8-oxabicyclo[4.3.0]nonan-3-ols toward Eu(DPM)$_3$.¹⁾

As is shown in Figs. 1 and 2, it is clear that the H_1 of **2** is shifted much more than that of **3**; this is the most distinct difference in the behavior of **2** and **3** upon the addition of Eu(DPM)$_3$. At the high concentration of a 1.2 molar ratio, the H_1 of **2** is unexpectedly shifted as much as H_3, H_7, and H_9, which are protons nearest to the two sites of coordination with the europium ions, whereas the H_1 of **3** is shifted to a much smaller degree. This observation supports the conformation of **2** and **3** as set forth in Figs. 1 and 2. It also implies that competitive coordination occurs at almost the same degree at the two sites in both **2** and **3**. This similar degree of competitive coordination for the two sites has been confirmed by an intermolecular

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5) For pertinent references, see a) J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Amer. Chem. Soc.*, **94**, 5325 (1972) and b) R. von Ammon and R. D. Fischer, *Angew. Chem.*, **84**, 737 (1972) and references cited therein.

6) See Experimental Section, lit. 2.

competitive experiment on an equal molar mixture of tetrahydrofuran and cyclohexanol, as has previously been reported.[1]

Experimental

All the temperatures are uncorrected. The microanalyses were performed by Mrs. Kiyoko Fujimoto of our laboratory. The IR spectra were obtained on a Shimadzu IR-27-C spectrophotometer. The NMR spectra were taken on a JEOL C-60H spectrometer, using tetramethylsilane as the internal standard, and $CDCl_3$ as the solvent. Tris(dipivalomethanato)europium (III), $Eu(DPM)_3$, was prepared in a manner similar to that of Eisentraut;[7] it had a mp of 189.5—190 °C (lit,[8] mp 190—191 °C). The glc analyses and separations were carried out on a Shimadzu GC-4APT apparatus using a 3 m×3 mm column of Dowfax 9N9 10% on Neopak 1A, operating at 150 °C with a He flow rate of 40 cc/min. For the preparative tlc, a 1.0 mm thickness of Merck GF-254 silica gel was employed with the solvent system of diethyl ether–benzene (50: 50). The mass spectra were recorded with a Hitachi RMS-4 mass spectrometer, with an ionizing energy of 70 eV and a source temperature of 150 °C.

Starting Material. Compound **1** was prepared from dimethyl *trans*-Δ^4-tetrahydrophthalate using the method described by Eliel;[9] it had properties identical with those reported by Christol.[10]

Reactions of trans-*8-Oxabicyclo[4.3.0]none-3-ene (1). Hydroboration with Diborane*: Dibroane generated by adding a solution of 14 g of $BF_3 \cdot Et_2O$ in 25 ml of diglyme to 1.9 g of sodium borohydride in 50 ml of diglyme was passed over a 75 min period into a stirred solution of 5.9 g of **1** in 50 ml of THF, cooled in an ice bath. The solution was then left for 75 min at room temperature, the excess diborane was decomposed with water (15 ml), 15 ml of 3M sodium hydroxide was added, and subsequently 15 ml of 30% hydrogen peroxide was added drop by drop. The reaction mixture was then stirred for an additional hour at room temperature and extracted with dichloromethane. After the evaporation of the solvent, distillation yielded 4.1 g of a mixture of **2** and **3** (bp 120 °C/10 mmHg); the isomeric ratio of **2** to **3** was shown by glc to be 46: 54.

Hydroboration with Diisopinocampheylborane: Hydroboration with diisopinocampheylborane was carried out with 680 mg of **1** according to the method of Brown;[11] a 580 mg portion of a mixture of **2** and **3** was thus obtained, its isomeric ratio being shown by glc to be 43: 57.

Reaction of 1 with m-*Chloroperbenzoic Acid Followed by Reduction with Lithium Aluminum Hydride (LAH)*: A solution of 1.8 g of 85% *m*-chloroperbenzoic acid in 40 ml of dry chloroform was added dropwise to a stirred solution of 1 g of **1** in 10 ml of dry chloroform. The reaction mixture was stirred overnight at room temperature. The solution was then washed 2 times each with 100 ml of a 10% sodium sulfite solution, 2 times each with 100 ml of a 5% sodium bicarbonate solution, and finally with a saturated sodium chloride solution, and dried (Na_2SO_4). The chloroform was driven off at reduced pressure, and a white solid was obtained on standing. Recrystallization from petroleum ether gave the epoxide of **1** in needles; mp 53.5—54 °C, IR (KBr): 2924, 2870, 1435, 1425, 1348, 1269, 1195, 1110, 1080, 990, 885, 875, 805, 780 cm^{-1}; NMR (CCl_4): δ 4.00—3.50 (m, 2H), 3.40—2.75 (m, 4H), 2.55—1.15 (m, 6H); MS: *m/e* 140 (M^+, 23%), 110 (100), 95 (69), 82 (72), 81 (70), 79 (71%). Found: C, 68.29; H, 8.59%. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

A solution of 640 mg of the above epoxide in 10 ml of ether was added dropwise to a stirred slurry of LAH in 10 ml of ether; the mixture was then stirred overnight at room temperature. Aqueous hydrochloric acid (10%) was added to destroy the excess hydride. Extraction (ether) and drying (Na_2SO_4), followed by evaporation, afforded 520 mg of a mixture of **2** and **3**, which was shown by glc to have an isomeric ratio of 93: 7.

Reduction of trans-*8-Oxabicyclo[4.3.0]nonan-3-one (4).* The ketone, **4**, was prepared by oxidizing the mixture of **2** and **3** obtained in the hydroboration (with diborane) of **1**. A solution of 2.84 g of a mixture of **2** and **3** in a small volume of dichloromethane was oxidized with the chromium trioxide-pyridine complex, as has been described by Ratcliffe,[12] to yield 2.2 g of **4**; bp 120—121 °C/18 mmHg, IR: 2955, 2900, 1720, 1420, 1322, 1201, 1072, 1020, 996 cm^{-1}; NMR (CCl_4): δ 4.06—3.70 (m, 2H), 3.55—3.07 (m, 2H), 2.70—1.15 (m, 8H); MS: *m/e* 140 (M^+, 100), 96 (22), 84 (41), 82 (70%). Found: C, 68.46; H, 8.88%. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63%.

A solution of **4** (170 mg) in 10 ml of ether was added dropwise to a stirred slurry of 60 mg of LAH in 10 ml of ether. The mixture was then stirred overnight at room temperature, dilute hydrochloric acid was added to destroy the excess hydride, and the aqueous phase was extracted with ether. After drying (Na_2SO_4), the solvent was removed; the alcohols **2** and **3** were found to have been formed in a ratio of 6: 94.

Hydrogenation of 4 over Platinum Oxide. A solution of **4** (100 mg) in 5 ml of glacial acetic acid was added to 50 mg of platinum oxide in 10 ml of glacial acetic acid, 3 drops of concentrated hydrochloric acid were added, and hydrogenation was carried out under normal atmospheric hydrogen at room temperature. A rapid uptake of hydrogen occurred, and the theoretical amount of hydrogen was absorbed in 20 min. The reaction mixture was then neutralized with aqueous sodium bicarbonate and extracted with ether. An analysis of the reaction product by glc showed that **2** and **3** were formed in a ratio of 20: 80.

Reduction of 4 with Sodium in Ethanol. A solution of 320 mg of **4** in 100 ml of absolute ethanol was placed in a flask fitted with a reflux condenser, and 1.75 g of small pieces of sodium were added to maintain reflux. After the addition of sodium had been finished, the reaction mixture was refluxed for an additional hour; it was then cooled and acidified with 10% aqueous hydrochloric acid. The ethanol was removed under diminished pressure, and the aqueous phase was extracted with ether. The ethereal solution was dried and evaporated. An analysis of the residue by glc showed that the isomers **2** and **3** were formed in a ratio of 8: 92.

Reduction of 4 with Sodium Borohydride. A solution of 170 mg of **4** in 20 ml of absolute methanol was cooled in an ice bath, and then 110 mg of sodium borohydride were slowly stirred in. After the reaction mixture had been stirred at room temperature overnight, the methanol was removed under

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[8] J. Selbin, N. Ahmad, and N. Bhacca, *Inorg. Chem.*, **10**, 1383 (1971).

[9] E. L. Eliel and C. Pillar, *J. Amer. Chem. Soc.*, **77**, 3600 (1955).

[10] H. Christol, A. Donche, and M. F. Plenar, *Bull. Soc. Chim. Fr.*, **1966**, 1315.

[11] H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964).

[12] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

diminished pressure, and ice water was added. Extraction (CH_2Cl_2) and drying (Na_2SO_4), followed by evaporation, afforded the reaction products, an analysis of which by glc showed that the isomers **2** and **3** were formed in a ratio of 14: 86.

Pure samples of **2** and **3** were secured from the reduction of epoxide of **1** and LAH reduction of **4**, respectively; by separation with preparative tlc and glc, followed by bulb-to-bulb distillation under reduced pressure, we obtained the following results, For **2**: IR (CCl_4) 3620, 3385, 2940, 2855, 1085, 1015, 995 cm^{-1}, NMR ($CDCl_3$): δ 4.40—3.80 (m, 3H), 3.60—3.18 (m, 2H), 2.40—1.30 (m, 9H), MS: *m/e* 142 (M^+, 26%), 124 (M^+-18, 30%), 69 (100%). Found: C, 67.36; H, 10.19%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93%. For **3**: IR (CCl_4) 3620, 3380, 2940, 2850, 1095, 1055, 1025, 1010 cm^{-1}, NMR ($CDCl_3$): δ 4.24—3.10 (m, 5H), 2.52—0.90 (m, 9H), MS: *m/e* 142 (M^+, 11%), 124 (M^+-18, 30%), 69 (100%). Found: C, 67.30; H, 9.92%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93%.

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