Cubane derivatives

7.* Synthesis and molecular structure of 4-bromo-1-hydroxymethylcubane

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The present study concerned with reduction of methyl 4-bromocubanecarboxylate (**1**) with lithium aluminum hydride and aluminum hydride in THF. An efficient procedure was developed for the synthesis of 4-bromo-1-hydroxymethylcubane (**2**) based on reduction of compound **1** with aluminum hydride under mild conditions. The structure of **2** was established by X-ray diffraction.

Key words: methyl 4-bromocubanecarboxylate, 4-bromo-1-hydroxymethylcubane, hydroxymethylcubane, reduction, lithium aluminum hydride, aluminum hydride, X-ray diffraction study.

Cubane derivatives attract considerable interest as potential pharmaceuticals.[2—6] However, their synthesis involves many steps. Hence, the development of efficient and selective methods for modifications of compounds containing the cubane fragment and investigation of their structures are of great importance.

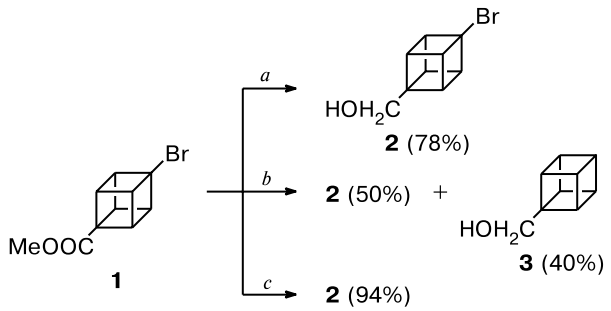
The present study continues our research on reduction of cubane derivatives containing different functional groups with light metal hydrides.[7—11]

The aim of the study was to develop a more efficient procedure (compared to a known method[12]) for the synthesis of 4-bromo-1-hydroxymethylcubane and establish its structure. This compound can be used as an intermediate for the synthesis of biologically active compounds, in particular, of nitrates of cubane-containing alcohols.

Since the synthesis of various cubane derivatives involves many steps, it is necessary to elaborate procedures for the preparation of intermediates in high yields in individual steps. Our attempts to increase the yield of carbinol **2** reported earlier (80%) in reduction of ester **1** with lithium aluminum hydride[12] by performing the reaction at higher temperature (65 °C) over a longer period of time with the use of an excess of $LiAlH_4$ failed. The yield of compound **2** was no higher than 80%. When the reaction was performed for 48—300 h, the yield decreased due to hydrodebromination (Scheme 1).

With the aim of developing a more efficient and selective procedure for the preparation of carbinol **2**, we studied reduction of ester **1** with aluminum hydride. This reaction was found to occur under mild conditions (15—25 °C) and proceed much faster (4 h at 20 °C) than the reaction with $LiAlH_4$ to give the target product in higher yield (~94%) (see Scheme 1). In addition, this process is highly selective. Thus, reduction of ester **1** with AlH_3 was not accompanied by hydrodebromination for several days.

Scheme 1



Reagents and conditions: *a*. $LiAlH_4$, THF, 65 °C, 12 h. *b*. $LiAlH_4$, THF, 65 °C, 300 h. *c*. AlH_3, THF, 20 °C, 4 h.

The structure of product **2** was established by X-ray diffraction (Fig. 1).

The 4-bromo-1-hydroxymethylcubane molecule (**2**) contains a rather symmetrical cubane core, in which the C—C bonds (1.558(4)—1.584(4) Å) are slightly longer than those (1.520—1.537 Å) observed[13] in hydrocarbons

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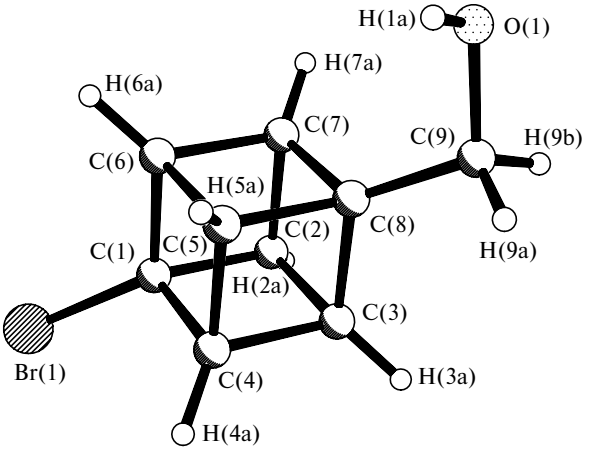

Fig. 1. Structure of 4-bromo-1-hydroxymethylcubane (**2**).

containing C atoms in a usual tetrahedral environment (Table 1). This effect is associated with the forced geometry of the cubane core, in which the angles between the C atoms are close to 90° (see Table 1). In spite of the different nature of the substituents at positions 1 and 4 (the Br atom and the CH_2OH group) in molecule **2**, the C atoms to which these fragments are bound do not differ substantially from other C atoms containing H atoms (see Table 1). Noteworthy is the crystal packing of the cubane molecules (Fig. 2). The molecules form double chains, in which the cubane molecules are linked to each other only through the hydroxy groups of the CH_2OH fragment (C(8)—C(9), 1.512(7) Å; C(9)—O(1), 1.435(6) Å). In this packing, the Br atoms (C(1)—Br(1), 1.943(5) Å) are located on the outer sides of the double chain and most likely fulfill the shielding function.

Table 1. Selected geometric characteristics (bond lengths (*d*) and bond angles (ω)) of compound **2**

Bond	*d*/Å	Bond	*d*/Å
Br(1)—C(1)	1.943(5)	C(5)—C(8)	1.575(7)
C(1)—C(6)	1.560(7)	C(7)—C(8)	1.582(7)
C(2)—C(3)	1.582(7)	C(1)—C(2)	1.558(7)
C(4)—C(5)	1.574(7)	C(2)—C(7)	1.575(7)
C(6)—C(7)	1.580(7)	C(3)—C(8)	1.584(7)
O(1)—C(9)	1.435(6)	C(5)—C(6)	1.580(7)
C(1)—C(4)	1.569(7)	C(8)—C(9)	1.512(7)
C(3)—C(4)	1.584(6)		
Angle	**ω/deg**	**Angle**	**ω/deg**
C(2)—C(1)—C(6)	91.7(4)	C(2)—C(1)—C(4)	91.5(4)
C(6)—C(1)—C(4)	91.7(4)	C(2)—C(1)—Br(1)	124.2(3)
C(6)—C(1)—Br(1)	125.4(3)	C(4)—C(1)—Br(1)	122.7(3)
C(1)—C(2)—C(7)	89.1(4)	C(1)—C(2)—C(3)	89.5(4)
C(7)—C(2)—C(3)	91.0(4)	C(2)—C(3)—C(4)	90.0(4)
C(2)—C(3)—C(8)	89.0(4)	C(4)—C(3)—C(8)	89.6(4)
C(1)—C(4)—C(5)	88.7(4)	C(1)—C(4)—C(3)	89.0(3)
C(5)—C(4)—C(3)	90.0(4)	C(4)—C(5)—C(8)	90.4(4)
C(4)—C(5)—C(6)	90.8(4)	C(8)—C(5)—C(6)	90.1(4)
C(1)—C(6)—C(7)	88.9(4)	C(1)—C(6)—C(5)	88.8(4)
C(7)—C(6)—C(5)	90.0(4)	C(2)—C(7)—C(6)	90.3(4)
C(2)—C(7)—C(8)	89.3(4)	C(6)—C(7)—C(8)	89.8(4)
C(9)—C(8)—C(5)	125.0(4)	C(9)—C(8)—C(7)	127.9(4)
C(5)—C(8)—C(7)	90.1(4)	C(9)—C(8)—C(3)	122.3(4)
C(5)—C(8)—C(3)	90.0(4)	C(7)—C(8)—C(3)	90.6(4)
O(1)—C(9)—C(8)	111.9(4)		

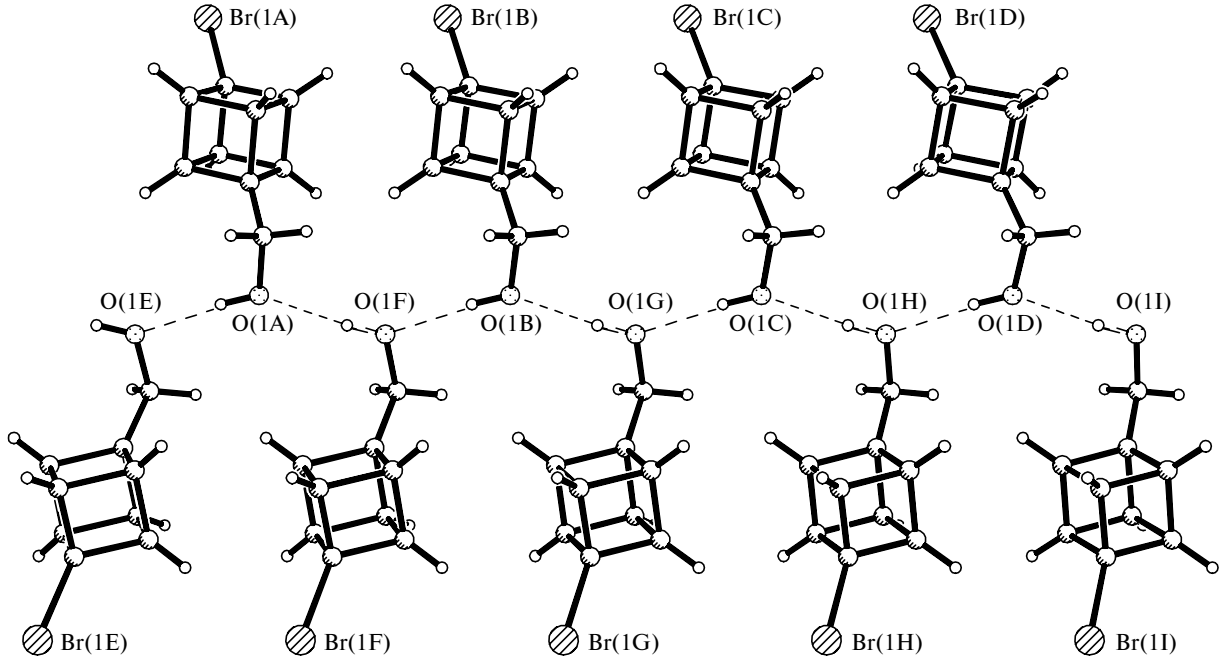

Fig. 2. Fragment of the molecular packing of **2** in the crystal along the *x* axis.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker-200 instrument in $CDCl_3$ relative to Me_4Si. The IR spectra were measured on a Specord M82 spectrophotometer (KBr pellets).

Solutions of AlH_3 in THF were prepared by dissolving etherate $AlH_3 \cdot 0.3Et_2O$, which was synthesized according to a known procedure.[14] Compound **1** was prepared according to a procedure described earlier.[15]

Reduction of ester 1 with lithium aluminum hydride. *A*. The synthesis was carried out according to a known procedure[12] with some modifications ($LiAlH_4$: **1** ≈ 3 : 1, the reaction time was 12 h, 65 °C). The yield of compound **2** was 78%, white needle-like crystals, m.p. 121—123 °C (*cf.* lit. data[12]: m.p. 124.6—126.6 °C). Found (%): C, 51.20; H, 4.52; Br, 36.48. C_9H_9BrO. Calculated (%): C, 50.73; H, 4.26; Br, 37.50. ^1H NMR, δ: 1.70 (s, 1 H, OH); 3.79 (s, 2 H, C<u>H</u>$_2$OH); 4.00 (m, 3 H, C<u>H</u>CCH$_2$, the A part of the AA′A″BB′B″ system, Δν ≈ 30 Hz); 4.18 (m, 3 H, CHCBr, the B part of the AA′A″BB′B″ system). IR, ν/cm^{-1}: 3260 v.s (OH); 2987 v.s (CH); 2922 m, 2853 m (CH_2); 1456 w (CH_2); 1432 w (OH); 1316 m (CH); 1249 w (C—C); 1203 s (C—Br); 1192 w, 1120 w, 1101 w (C—C); 1035 v.s, 1004 s (OH); 839 m (C—C); 815 m (C—Br).

***B*.** The $LiAlH_4$: **1** ratio was 10 : 1, the reaction time was 300 h, the temperature was 65 °C. Study by ^1H and ^{13}C NMR and IR spectroscopy and elemental analysis demonstrated that the reaction afforded a mixture of compounds **2** (50—55% yield) and **3** (40—45% yield). ^1H NMR of hydroxymethylcubane (**3**), δ:* 3.74 (s, 2 H, C<u>H</u>$_2$OH); 3.85—3.95 (m, 6 H, the AB part of the AA′A″BB′B″C system, δ_A 3.904, δ_B 3.925, $\Delta\nu_{AB} \approx 4$ Hz, J_o = 5.3 Hz, J_m = 2.6 Hz, J_p = 0.8 Hz); 4.04 (m, 1 H, the C part of the AA′A″BB′B″C system). The signal of the OH group is involved in a broad signal for all mobile protons averaged due to proton exchange in the sample (δ ~2.8).

Reduction of ester 1 with aluminum hydride. A solution of compound **1** (2.48 g, 10.3 mmol) in anhydrous THF (50 mL) was added with stirring to a solution of AlH_3 (0.926 g, 30.8 mmol), which was prepared by dissolution of $AlH_3 \cdot 0.3Et_2O$ [14] (1.61 g) in anhydrous THF (90 mL), at ~20 °C for 20 min. The reaction mixture was stirred for 4 h. Then a 2 : 1 THF—H_2O mixture (6.3 mL) and a saturated aqueous K_2CO_3 solution (10 mL) were successively added. The organic layer was separated, and the precipitate with the aqueous layer was extracted with diethyl ether (4×30 mL). The organic extracts were dried with $MgSO_4$, the solvents were distilled off *in vacuo*, and the residue was recrytsallized from a 1 : 1 hexane—benzene mixture. Carbinol **2** was obtained in a yield of 2.06 g (94%), m.p. 123—125 °C. Found (%): C, 50.92; H, 4.38; Br, 37.38. C_9H_9BrO. Calculated (%): C, 50.73; H, 4.26; Br, 37.50. The ^1H NMR and IR spectra are identical to those of carbinol **2**, which was prepared by reduction of ester **1** with lithium aluminum hydride according to the method *A*. ^{13}C NMR, δ: 45.18 (3 C, <u>C</u>HCCH$_2$OH); 54.19 (3 C, <u>C</u>HCBr); 59.12 (1 C, <u>C</u>CH$_2$OH); 62.99 (1 C, CH$_2$OH); 64.96 (1 C, CBr).

* The spectrum of compound **3** was extracted from the spectrum of the mixture by subtracting the signals of carbinol **2** (parameters of the protons of the cubane cage were obtained by fitting the calculated spectrum of the AA′A″BB′B″ system to the experimental spectrum until they visually coincided).

Table 2. Crystallographic parameters of compound **2**

Parameter	Characteristic
Molecular formula	C_9H_9BrO
Space group	$P2_1/c$
a/Å	12.366(5)
b/Å	5.354(2)
c/Å	12.645(5)
β/deg	109.770(7)
V/Å^3	787.8(6)
Z	4
d_{calc}/g cm^{-3}	1.796
μ/mm^{-1}	5.149
Radiation	Mo-Kα (λ = 0.71073 Å)
Number of measured reflections	4585
Number of reflections with $I > 2\sigma(I)$	2067
R_1	0.0736
wR_2	0.1900

X-ray diffraction study. The experimental X-ray diffraction data for compound **2** were collected on an automated Bruker AXS SMART diffractometer equipped with a CCD detector (graphite monochromator, 110 K, ω scanning technique with a step of 0.3°, exposure time per frame was 30 s) using a standard procedure.[16] The crystallographic parameters and details of the structure refinement are given in Table 2.

The structure of compound **2** was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters for all nonhydrogen atoms. The H atoms were revealed from a difference Fourier synthesis and refined isotropically. The calculations were carried out with the use of the SHELX97 program package.[17] Main geometric parameters are given in Table 1.

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