Cubane derivatives 3.* Synthesis and molecular structure of 1,4-bis(hydroxymethyl)cubane

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An efficient procedure for the preparation of 1,4-bis(hydroxymethyl)cubane by reduction of cubane-1,4-dicarboxylic acid or its dimethyl ester with aluminum hydride was developed. The molecular structure of 1,4-bis(hydroxymethyl)cubane was established by X-ray diffraction analysis.

Key words: cubane-1,4-dicarboxylic acid and its dimethyl ester, 1,4-bis(hydroxymethyl)cubane, lithium aluminum hydride, aluminum hydride, reduction, X-ray diffraction analysis.

In view of the sharply increased interest in cubane derivatives as potential pharmaceuticals² and multistage procedures for their synthesis, the development of efficient procedures for the modification of compounds with the cubane framework is an urgent problem.

The peculiarities of structurally strained cubane derivatives often make it difficult or even impossible to use conventional methods of organic chemistry and call for the development of special procedures for performing chemical processes under rather mild conditions.

In this work, we report the results of reduction of cubane-1,4-dicarboxylic acid (1a) and its dimethyl ester (1b) with lithium aluminum hydride and aluminum hydride, which allowed the development of an efficient procedure for the synthesis of 1,4-bis(hydroxymethyl)cubane (2).

In spite of the fact that the reduction of organic compounds containing different functional groups with simple and complex metal hydrides has been studied in detail,³⁻⁶ relevant publications in the comparatively "young" chemistry of cubane derivatives are scarce, and moreover, authors usually restricted themselves to the mere preparation and identification of these derivatives.

Previously,⁷ it was found that reduction of acid 1a with LiAlH₄ under rather drastic conditions (prolonged boiling in THF) afforded diol 2 in very low yield (26%), which is associated with the fact that compound 2 readily undergoes isomerization into homocubane and bishomocubane derivatives followed by their destruction.^{7,8}

* For Part 3, see Ref. 1.

Results and Discussion

Studies of the reduction of acid 1a and its ester 1b at 16-18 °C and 65 °C (Table 1) demonstrated that temperatures of 16-18 °C are preferable to reduction of compounds 1a and 1b with LiAlH₄, while at 65 °C, diol 2 was obtained in lower yield due, apparently, to initiation of isomerization followed by destruction. The maximum yield of diol 2 obtained by reduction of acid 1a at 16-18 °C was 59%.

Reduction of compounds 1a and 1b with aluminum hydride occurred substantially faster and under milder conditions.



We carried out a series of reduction reactions of 1a and 1b (see Table 1) at different substrate to reducing agent ratios (1a : $AIH_3 = 1 : (4-6)$ and 1b : $AIH_3 = 1 :$ (2.7-4)), varying the reaction time (0.4-6.0 h), and developed an efficient procedure for the preparation of diol 2. Reduction occurred under mild conditions (16-18 °C; 1 h for 1b and 4-6 h for 1a). The subsequent

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Table 1. Dependence of the yield of diol 2 on the nature of the reducing agent and the reaction conditions

Reagents	Molar ratio of the reagents /mol	<i>T/</i> °C S	Reaction time/h	Yield of 2 (%)
LiAIH4/1a	5.0	16-18	4.0	17.2
LiAIH ₄ /1a	5.0	16-18	12.0	59.0
LiAlH ₄ /1a	5.0	65	166	26.0
LiAIH4/1b	4.5	16-18	4.0	39.6
LIAIH4/1b	4.5	65	4.0	26.2
AlH 1/1a	4.4	16-18	1.0	41.0
AlH ₁ /Ia	6.0	16-18	1.0	54.3
AlH 1/12	6.0	16-18	4.0	75.4
AlH 1/12	6.0	16-18	6.0	84.0
AlH 1/1b	2.7	16-18	0.41	46.5
AIH 1/1b	3.17	16-18	6.0	61.0
AIH ₃ /1b	4.4	16-18	1.0	94.0

workup was simple and afforded the desired product in high yield (84-95%).

We found experimentally that solutions of AlH_3 that have been prepared by different procedures could be used as a reducing agent:^{3,9,10}

3 LiAlH₄ + AlCl₃
$$\xrightarrow{El_2O}$$
 3 LiCl +
+ 4 (AlH₃ · 0.3 Et₂O) \xrightarrow{THF} AlH₃, (1)

$$2 \text{ LIAIH}_{4} + \text{H}_{2}\text{SO}_{4} \xrightarrow{\text{THF}} \text{Li}_{2}\text{SO}_{4} + + 2 \text{H}_{2} + 2 \text{ AIH}_{3}(\text{AIH}_{3})_{n}$$
(2)

$$(AIH_3)_n \xrightarrow{THF} n \cdot AIH_3$$
(3)

Table 2. Bond lengths (d) and bond angles (ω) in molecule 2



Fig. 1. Structure of molecule 2.

The essential practical advantage of methods (1) and (3) is that substantial amounts of solid aluminum hydride etherate $AIH_3 \cdot 0.3$ Et₂O or nonsolvated aluminum hydride $(AIH_3)_n$ can be prepared in advance and then used as reducing agents.

Diol 2 synthesized was identified by elemental analysis and IR and ¹H NMR spectroscopy.

The structure of 1,4-bis(hydroxymethyl)cubane 2 was established by X-ray diffraction analysis (Fig. 1, Tables 2-4). The cubane fragment of the molecule has a symmetrical structure (C-C, 1.563(3)-1.568(2) Å; the C-C-C angles in the core are $89.8(2)-90.3(2)^{\circ}$) similar to that of the initial compound 1b.¹¹ The bond

Bond	d/Å	Angle	ω/deg	Angle	ω/deg
O(1) - C(1)	1.431 (1)	C(1)-O(1)-H(10)	116.5 (7)	C(5)-C(3)-H(3)	124.1 (8)
O(1)-H(10)	0.878 (17)	O(1) - C(1) - C(2)	111.9 (2)	C(3) - C(4) - H(4)	125.3 (11)
O(1) - H(10)	1.828 (17)	O(1) - C(1) - H(1a)	[12.1 (6)	C(3) - C(4) - C(2a)	89.9 (1)
C(1) - C(2)	1.492 (3)	C(2) - C(1) - H(1a)	107.3 (12)	H(4)-C(4)-C(2a)	123.8 (16)
C(1) - H(1a)	1.034 (12)	O(1)C(1)H(1b)	110.0 (9)	C(3) - C(4) - C(5a)	90.3 (2)
C(1)-H(1b)	1.027 (17)	C(2) - C(1) - H(1b)	106.7 (13)	H(4) - C(4) - C(5a)	126.6 (8)
C(2) - C(3)	1.566 (3)	H(1a) - C(1) - H(1b)	108.6 (11)	C(2a) - C(4) - C(5a)	89.9 (1)
C(2) - C(4a)	1.568 (2)	C(1) - C(2) - C(3)	123.6 (2)	C(3)-C(5)-H(5)	123.9 (7)
C(2) - C(5a)	1.566 (3)	C(1) - C(2) - C(4a)	126.2 (2)	C(3) - C(5) - C(2a)	89.9 (1)
C(3)C(4)	1.563 (3)	C(3)-C(2)-C(4a)	90.0 (1)	H(5)-C(5)-C(2a)	125.0 (12)
C(3) - C(5)	1.566 (2)	C(1) - C(2) - C(5a)	125.8 (1)	C(3) - C(5) - C(4a)	90.1 (2)
C(3)-H(3)	0.940 (13)	C(3) - C(2) - C(5a)	90.1 (2)	H(5)-C(5)-C(4a)	127.0 (9)
C(4)-H(4)	0.928 (20)	C(4a) - C(2) - C(5a)	90.0 (2)	C(2a) - C(5) - C(4a)	89.8 (2)
C(4) - C(2a)	1.568 (2)	C(2) - C(3) - C(4)	89.8 (2)		
C(4) - C(5a)	1.565 (3)	C(2) - C(3) - C(5)	89.9 (1)		
C(5)-H(5)	1.046 (11)	C(4) - C(3) - C(5)	90.2 (2)		
C(5)-C(2a)	1.566 (3)	C(2) - C(3) - H(3)	122.4 (13)		
<u>C(5)C(4a)</u>	1.565 (3)	C(4) - C(3) - H(3)	129.2 (11)		

between the carbon atom of the cubane core and the hydroxymethyl group is rather strong (C-C, 1.492 (3) Å). The O-H bond (0.878 (17) Å) is somewhat weakened due, apparently, to the participation of the proton and the oxygen atom in intermolecular hydrogen bonding (OH...O(H), 1.828(17) Å), which leads to the formation of chains in the crystal (Fig. 2). Apparently, this fact accounts for the possibility of condensation of molecules 2 and formation of polyethers as a result of dehydration.

Experimental

Acid 1a and its ester 1b were prepared according to known procedures.^{7,12} All operations associated with the preparation of solutions of LiAlH₄ and AlH₃ and reduction of cubane derivatives with these solutions were carried out under an atmosphere of argon using procedures and techniques applied for compounds sensitive to air and atmospheric moisture.¹³

The ¹H NMR spectra were recorded on an NMR spectrometer (294 MHz) developed and built at the Institute of Chemical Physics in Chernogolovka of the Russian Academy of Sciences. The IR spectra were measured on a Specord M82 spectrometer in KBr pellets.

Reduction of dimethyl cubane-1,4-dicarboxylate (1b) with aluminum hydride. A solution of ester 1b (1.0 g, 4.54 mmol) in anhydrous THF (20 mL) was added with stirring to a solution of AlH₁ (0.6 g, 20 mmol) in anhydrous THF (55 mL), which was prepared from the etherate according to procedure (1),^{3,9} at 16-18 °C for 15 min. The reaction mixture was stirred at the same temperature for 1 h. Then a 1 : 1 THF-H₂O mixture (3.2 mL) and a saturated aqueous solution of K₂CO₃ (4 mL) were added. The transparent organic layer was separated. The aqueous solution, which contained a precipitate, was washed with ether (3×10 mL). The organic extracts were combined and dried with MgSO4. After distillation of the solvents in vacuo, compound 2 was obtained as white needle-like crystals in a yield of 0.7 g (94%), m.p. 168-170 °C (1 : 1 benzenemethanol) (cf. Ref. 6: 164-165 °C). Found (%): C, 73.97; H, 7.10. C₁₀H₁₂O₂. Calculated (%): C, 73.15; H, 7.37. ¹H NMR $(DMSO-d_6, Mc_4Si), \delta: 3.49 (t, 4 H, CH_2, {}^{3}J = 5.1 Hz); 3.60 (s, 6 H, CH); 4.42 (t, 2 H, OH, {}^{3}J = 5.1 Hz). IR, v/cm⁻¹:$ 3170 v.s (O-H); 2984 s; 2972 s; 2954 v.s (C-H); 2930 m; 2900 m; 2849 s (CH2); 1432 w (O-H); 1367 m (C-H); 1256 w; 1199 v.w; 1142 m; 1106 w; 1100 m (C-C); 1016 m; 1004 v.s (C-OH); 842 m (C-C); 830 w (O-H).

Table 3. Atomic coordinates (×10⁴) and equivalent isotropic temperature factors (×10²) for 1,4-(HOCH₂)₂C₈H₆

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Atom	x	у	ζ	Beq/Å	
O(1)	2191(1)	7007(1)	1213(3)	45(1)	
C(1)	2003(1)	7092(1)	-1142(4)	41(1)	
C(2)	1829(1)	7745(1)	-1384(3)	36(1)	
C(3)	1653(1)	8012(1)	-3774(3)	41(1)	
C(4)	945(1)	8041(1)	2636(3)	41(1)	
C(5)	2213(1)	8891(1)	-3089(3)	41(1)	
H(10)	2667(12)	7347(11)	1693(14)	70(1)	
H(1a)	1519(9)	6787(9)	-1755(13)	32(1)	
H(lb)	2472(11)	7226(11)	-2213(14)	65(1)	
H(3)	1676(9)	7790(10)	-5203(14)	47(1)	
H(4)	455(12)	7856(12)	-3319(14)	87(1)	
H(5)	2621(9)	9314(9)	~4229(13)	30(1)	



Fig. 2. Molecular packing in the crystal structure of 2.

Reduction of cubane-1,4-dicarboxylic acid with aluminum hydride. Acid 1a was reduced with AlH₃ as described above (6 h). Starting from 1a (0.1365 g, 0.71 mmol) and AlH₃ (0.128 g, 4.27 mmol), which was prepared from nonsolvated aluminum hydride by dissolving it in THF,¹⁰ compound 2 was obtained in a yield of 0.098 g (84%), m.p. 166–169 °C (1 : 1 benzene---methanol). The IR and ¹H NMR spectra of the sample obtained are identical to those of diol 2 prepared from compound 1b.

Reduction of cubane-1,4-dicarboxylic acid with lithium aluminum hydride. A solution of acid 1a (0.1 g, 0.5 mmol) in anhydrous THF (8 mL) was added dropwise with stirring and cooling with ice water to a solution of $LiAlH_4$ (0.1 g, 2.64 mmol) in anhydrous THF (4.05 mL) over several minutes. The

Table 4. Crystallographic parameters

Parameter	Value
Formula	C ₁₀ H ₁₂ O ₂
Space group	R3
a/Å	19.659(3)
c/Å	5.731(2)
V/Å ³	1918.5(8)
Ż	9
$\rho_{enic}/g \text{ cm}^{-3}$	1.279
µ/cm ⁻¹	0.88
Radiation	Mo-Ka ($\lambda = 0.71073$ Å)
0-20 scan range/deg	454
Number of measured reflections	1351
Number of reflections with $l > 4.0\sigma$	832
Weighting scheme	$w^{-1} = \sigma^2(F) + 0.0129F^2$
R	0.067
R _w	0.089

reaction mixture was stirred at 16-17 °C for 12 h. Then a 1 : 1 THF-H₂O mixture (0.6 mL) was added with stirring and cooling. When gas evolution ceased, a 15% aqueous NaOH solution (1.4 mL) was added. After the standard workup, the solvents were removed *in vacuo*, and diol 2 was obtained in a yield of 0.050 g (59%), m.p. 163-165 °C (1 : 1 benzene-methanol).

Reduction of dimethyl cubane-1,4-dicarboxylate with lithium aluminum hydride. Reduction of compound 1b in THF with lithium aluminum hydride (4 h) and subsequent workup were carried out as described above. Diol 2 was obtained from 1b (0.22 g, 1.0 mmol) and LiAlH₄ (0.17 g, 4.5 mmol) in THF (13 mL) in a yield of 0.065 g (39.6%), m.p. 164-165 °C.

X-ray diffraction analysis. Crystals suitable for X-ray structural analysis were grown by slow concentration of a solution of compound 2 in a THF--CH₂Cl₂ mixture. The X-ray intensity data were collected on an automated four-circle Siemens R3 v/m diffractometer at 22 °C (λ Mo-K α). The structure was solved by direct methods. All nonhydrogen atoms were refined anisotropically by the full-matrix least-squares method. The positions of the hydrogen atoms were located from the difference Fourier synthesis and refined isotropically. The bond lengths and bond angles are given in Table 2. The atomic coordinates are listed in Table 3. The crystallographic parameters and selected details of the refinement are given in Table 4. All calculations were carried out on a Pentium 100 computer using the SHELXTL program package.¹⁴

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