Cubane derivatives
5.* Synthesis of 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]non-4-ylcarbinol

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The reduction of 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic acid (**2**) with lithium aluminum hydride and aluminum hydride in THF was studied. A new effective method for preparing 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]-non-4-ylcarbinol (**1**) based on reduction of **2** with AlH_3 under mild conditions was developed.

Key words: 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic acid, 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]non-4-ylcarbinol, lithium aluminum hydride, aluminum hydride, reduction.

This paper continues a series of studies dealing with the reduction of cubane derivatives with various functional groups by light metal hydrides.[1] Due to the multistage character of synthesis of these compounds, the interest in cubane derivatives as potential pharmaceutic preparations, which has increased in recent years,[2,3] covers as well various homocubane derivatives serving as initial or intermediate compounds in the preparation of cubanes.

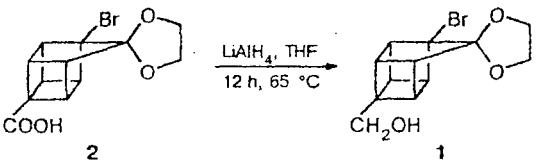
A main goal of this study was to develop an efficient method for the preparation of 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]non-4-ylcarbinol (**1**), which is used as the starting compound in the synthesis of various 1,4-substituted cubanes. Previously,[4] it has been reported that carbinol **1** was obtained by the reduction of 1-bromo-9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]-nonane-4-carboxylic acid (**2**) with $LiAlH_4$ under relatively harsh conditions (refluxing in THF for many hours). It is known[5,6] that $LiAlH_4$ is not the most selective reagent for the reduction of bromo-containing alkylcarboxylic acids, because partial hydrodebromination occurs in addition to the reduction of the carboxyl group. A much more selective reagent for the reduction of these compounds is AlH_3.[7] It is also known[4] that the reduction of cubanecarboxylic acids with $LiAlH_4$ can be accompanied by partial isomerization of the resulting carbinols to give homocubane or bishomocubane derivatives. Hence, we studied the reduction of carboxylic acid **2** with $LiAlH_4$ and AlH_3 in THF and compared the results obtained, which led us to the development of a new efficient method for the synthesis of carbinol **1**.

* For Part 4, see Ref. 1.

Results and Discussion

At the initial stage of the research, we studied the reduction of acid **2** with lithium aluminum hydride in THF (Scheme 1).

Scheme 1



2 **1**

The attempt to reproduce the synthesis of carbinol **1** by the procedure,[4] according to which the mixture obtained after the reaction was treated with AcOEt and 10% H_2SO_4 and then THF was distilled off under atmospheric pressure and the aqueous residue was extracted with chloroform, failed. The final product obtained in this way was a mixture of two compounds: carbinol **1** and, apparently, 1-bromo-9-oxopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]non-4-ylcarbinol (**3**). This is indicated by the TLC data and the IR spectrum of the final product. In addition to the absorption bands at 3415, 3250 (OH); 2985 (CH); 2925, 2855 (CH_2); 1250, 1225, 1210, 1180 (C—C); 1155, 1085, 1040 (O—C—O); 1005 (C—OH), and 845 cm^{-1} (C—Br) indicating the presence of hydroxyl and ketal groups in the homocubane derivative,[8—11] the spectrum contained an intense absorption band at 1765 cm^{-1}, corresponding to the carbonyl group of the ketone.[8—10] In our opinion, the partial deketalization of carbinol **1** occurred during the

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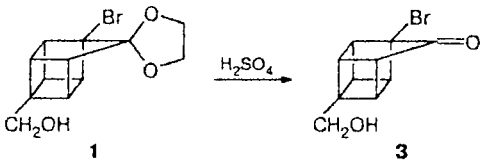
evaporation of the THF from the reaction mixture (under atmospheric pressure) in the presence of H_2SO_4 (Scheme 2).

Scheme 2



1 **3**

In order to eliminate the side processes and to simplify the procedure for the isolation of carbinol **1** from the reaction mixture, we studied several alternative variants of treatment of the reaction mixture after the reduction of acid **2** with lithium aluminum hydride (at a $LiAlH_4$: **2** molar ratio of 1 : 1):

(*A*) hydrolytic decomposition of the reaction mixture by a THF—H_2O mixture (1 : 1) followed by coagulation of the $LiAl(OH)_4$ precipitate with a saturated aqueous solution of K_2CO_3, separation of the organic and aqueous layers, and evaporation of THF from the organic layer *in vacuo*;

(*B*) a similar procedure in which coagulation is attained by adding a 15% aqueous solution of NaOH;

(*C*) treatment of the reaction mixture similar to that described previously;[4] however, evaporation of THF (after treating the residue with 10% H_2SO_4) was carried out at 15—20 °C *in vacuo* (10—15 Torr).

It was found that all the three procedures for treatment of the reaction mixture resulted in carbinol **1** being formed as the final product in 81—87% yield (no ketone **3** was obtained). However, procedure *A* (in which K_2CO_3 was used) was much simpler and required far less time.

To find out whether reduction is accompanied by competing hydrodebromination, we studied the reduction of carboxylic acid **2** with lithium aluminum hydride at the same temperature and with the same reaction times as were used in the previous study[4] (65 °C, 12 h), but the $LiAlH_4$: **2** ratio was equal to 5 : 1 (instead of 1 : 1). Analysis of the final product isolated from the reaction mixture showed that in addition to carbinol **1**, it contained about 10—15% 9,9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]non-4-ylcarbinol (**4**), *i.e.*, the reduction of the carboxyl group in compound **1** was accompanied by hydrodebromination, although the latter occurred at a much lower rate. Thus, an increase in the concentration of $LiAlH_4$ does not allow one to decrease the duration of the rather long process of reduction of **2** with lithium aluminum hydride or to use milder temperature conditions. In addition, the results obtained suggest that when compound **2** is reduced with lithium aluminum hydride (at the ratio $LiAlH_4$: **2** = 1 : 1), the final product can contain carbinol **4** as an impurity.

In order to develop a more efficient method for preparing carbinol **1**, we studied reduction of **2** with AlH_3. It was found that AlH_3 reduces carboxylic acid **2** under milder conditions (15—30 °C) and over a considerably shorter period (3—7 h) than $LiAlH_4$. For example, the reaction of **2** with AlH_3 at 30 °C in THF for 5 h affords carbinol **1** in 93% yield. Moreover, the reduction of carboxylic acid **2** with AlH_3 is highly selective (no hydrodebromination was observed during the process monitored for 24 h, though the AlH_3 : **2** ratio was greater than 5 : 1). We also showed experimentally, as in the previous study,[1] that reduction of **2** can be carried out using both solutions of AlH_3, which are prepared from $LiAlH_4$ and H_2SO_4 according to a known procedure[12] directly prior to the synthesis of carbinol **1**, and solutions of AlH_3 in THF, which are prepared from specially synthesized aluminum hydride etherate[13] or from nonsolvated aluminum hydride.[14]

Thus, the rather efficient method for the synthesis of carbinol **1** by the reduction of acid **2** with AlH_3 developed in this study makes it possible to prepare compound **1** with high selectivity, in a higher yield, over a shorter reaction time, and under milder and safer conditions than reduction with $LiAlH_4$.

Experimental

Carboxylic acid **2** was synthesized by a previously reported procedure.[11,15] Solutions of AlH_3 in THF were prepared by dissolution of the etherate $H_3Al \cdot 0.3Et_2O$ synthesized beforehand by a known procedure.[13] For some of the experiments, THF solutions of AlH_3 were prepared by a previously reported procedure[12] or from nonsolvated aluminum hydride.[14] The preparation of solutions of $LiAlH_4$ and AlH_3 and reduction of carboxylic acid **2** with these solutions were carried out under argon using techniques developed for working with substances sensitive to atmospheric oxygen and moisture.[16]

IR spectra were recorded on a Specord M82 spectrometer as pellets with KBr or $CDCl_3$ films; ^1H NMR spectra were measured on an NMR spectrometer with a superconducting magnet (294 MHz) designed and manufactured at the Institute of Chemical Physics in Chernogolovka. The composition of the products formed upon reduction of acid **2** was checked qualitatively by TLC on Silufol plates (using THF—hexane and AcOEt—$CHCl_3$ mixtures as eluents and iodine for visualization).

Reduction of 2 with lithium aluminum hydride. A solution of carboxylic acid **2** (2.1 g, 7.0 mmol) in 22 mL of anhydrous THF was added with stirring and cooling (ice water) to a solution of $LiAlH_4$ (0.27 g, 7.1 mmol) in 28 mL of anhydrous THF. The reaction mixture was refluxed for 12 h, cooled, and divided into three portions (25, 12.5, and 12.5 mL), which were treated for the isolation of the final product by different procedures.

A. The reaction mixture (12.5 mL) was quenched by 0.31 mL of a THF—H_2O (1 : 1) mixture with cooling; then 0.7 mL of a saturated aqueous solution of K_2CO_3 was added. After fast coagulation of the precipitate, the organic and aqueous layers were separated, and the aqueous layer with the precipitate was extracted with ether (3×1 mL). The organic layer was combined with the ethereal extracts and dried with $MgSO_4$. Evaporation of the solvents *in vacuo* followed by crystallization gave 0.485 g (87%) of carbinol **1**, m.p. 79—81 °C (heptane) (*cf.* Ref. 17: 80—84 °C). Found (%): C, 50.34; H, 4.50; Br, 28.01. $C_{12}H_{13}BrO_3$. Calculated (%): C, 50.54; H, 4.60; Br, 28.02. IR, KBr), ν/cm^{-1}: 3460 s, 3415 s, 3256 s, 3172 s (OH); 2990 vs, 2960 m (CH); 2907 s, 2855 m (CH_2);

1500 w, 1470 w (CH_3); 1397 w, 1360 w (OH); 1325 m, 1295 vs (CH); 1255 w, 1225 w, 1210 m, 1180 m (C—C); 1150 vs, 1130 w, 1085 s, 1005 s (C—O—C); 1040 vs (C—OH); 845 m (CBr).

B. The reaction mixture (12.5 mL) was quenched by adding 0.31 mL of a THF—H_2O (1 : 1) mixture, and 0.6 mL of 15% aqueous NaOH was added. After coagulation of the precipitate and clarification of the organic layer, the organic and aqueous layers were separated by decanting, and the aqueous layer was extracted by ether (3×1 mL). The organic solutions were combined and dried with $MgSO_4$. Evaporation of the solvents *in vacuo* followed by crystallization gave 0.405 g (81%) of carbinol **1**, m.p. 78—79 °C. The IR spectrum of this sample was identical to that of the sample prepared by procedure *A*.

C. The reaction mixture was quenched by adding AcOEt, and then 10% H_2SO_4 (28.9 mL) was added. Then the THF was evaporated under reduced pressure (10—12 Torr). The aqueous layer with the precipitate was extracted with ether (3×1 mL), the extracts were washed with a 5% aqueous solution of $NaHCO_3$ (2×10 mL) and water (3×10 mL), and dried with $MgSO_4$. Evaporation of the solvents *in vacuo* followed by crystallization gave 0.83 g (83%) of carbinol **1**, m.p. 79—80 °C. Found (%): C, 50.27; H, 4.42; Br, 27.98. The IR spectrum of this sample was identical to that given above.

Reduction of 2 with lithium aluminum hydride ($LiAlH_4$: 2 = 5 : 1). A solution of compound **2** (2.1 g, 7.0 mmol) in 15 mL of anhydrous THF was added with stirring and cooling to a solution of $LiAlH_4$ (1.36 g, 35.3 mmol) in 25 mL of anhydrous THF. Then the reaction mixture was refluxed for 12 h and quenched (with cooling with ice water) by adding 9.15 mL of a THF—H_2O (2 : 1) mixture; 7.0 mL of a saturated aqueous solution of K_2CO_3 was then added. After fast coagulation of the precipitated $LiAl(OH)_4$, the transparent organic layer was separated, and the aqueous layer was extracted with ether (3×10 mL). The organic solutions were combined and dried with $MgSO_4$. Evaporation of the solvents *in vacuo* gave 1.7 g of a solid oily substance, m.p. 65—67 °C. Found (%): C, 52.55; H, 4.92; Br, 25.06. $C_{12}H_{13}BrO_3$ (**1**). Calculated (%): C, 50.54; H, 4.60; Br, 28.02. $C_{12}H_{14}O_3$ (**4**). Calculated (%): C, 69.88; H, 6.84. The elemental analysis, the IR spectrum, and TLC behavior of the resulting sample indicated that the final product might contain hydrodebrominated carbinol **4** (~10—15%) in addition to carbinol **1**. The attempts to separate these compounds by dissolving the final product in hot hexane and filtering the solution on a hot-filtration funnel yielded 1.25 g of carbinol **1**, m.p. 78—80 °C, and 0.41 g of the oily solid residue remaining after dissolution in hexane, m.p. 49—52 °C. Analysis of the oily residue: found (%): C, 59.35; H, 5.55; Br, 14.22. $C_{12}H_{13}BrO_3$. Calculated (%): C, 50.54; H, 4.60; Br, 28.02. $C_{12}H_{14}O_3$. Calculated (%): C, 69.88; H, 6.84. The IR spectrum, TLC behavior, and elemental analysis of this sample indicated that it contained a mixture of carbinols **1** and **4**; the elemental analysis data led to the conclusion that the content of hydrodebrominated carbinol **4** was ~40—50%. Unfortunately, we did not succeed yet in separating this mixture.

Reduction of 2 with aluminum hydride. A solution of compound **2** 1.5 g (5.01 mmol) in 30 mL of anhydrous THF was added with stirring at 10—15 °C to a solution of AlH_3 (0.45 g, 1.5 mmol) prepared by dissolution of the etherate $H_3Al \cdot 0.3Et_2O$ (0.79 g), synthesized beforehand by a known procedure,[13] in 45 mL of anhydrous THF. Then the temperature was raised to 30 °C, and the reaction mixture was stirred at this temperature for 5 h and quenched by adding 19 mL of a THF—H_2O (1 : 1) mixture with cooling. When hydrolysis had been completed, 6.0 mL of a saturated aqueous solution of K_2CO_3 was added with stirring. After fast coagulation of $Al(OH)_3$, the organic layer was separated, and the aqueous layer with the precipitate was extracted with ether (3×7 mL). The organic solutions were combined and dried with $MgSO_4$. Evaporation of the solvents *in vacuo* followed by crystallization gave 1.33 g (93%) of carbinol **1**, m.p. 79—82 °C (heptane). Found (%): C, 50.41; H, 4.53; Br, 28.00. $C_{12}H_{13}BrO_3$. Calculated (%): C, 50.54; H, 4.60; Br, 28.02. ^1H NMR ($CDCl_3$), δ: 1.85 (br.s, 1 H, OH); 2.88 (m, 1 H, CH(8), $^3J_{CH-CH} \approx 5.0$ Hz); 3.40—3.60 (m, 5 H, CH(2,3,5,6,7)); 3.67 (s, 2 H, $\underline{CH_2}OH$); 4.00 (m, 2 H, OCH_2); 4.28 (m, 2 H, OCH_2). IR, KBr), ν/cm^{-1}: 3443 s, 3255 s, 3173 s (OH); 2987 vs, 2960 m (CH); 2897 s, 2856 m (CH_2); 1497 w, 1475 w (CH_2); 1398 w, 1382 w (OH); 1325 m, 1292 vs (CH); 1250 w, 1225 w, 1210 m, 1178 m (C—C); 1154 s, 1082 s, 1007 m (C—O—C); 1037 vs (C—OH); 842 m (CBr).

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