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Studies on the Terpenoids and Related Alicyclic Compounds. XXXIII.[1] Acid-Catalyzed Allylic Rearrangement of 1-Hydroxy-2-en- and 3-Hydroxy-1-en-5α-cholestanes

KOJI YAMAKAWA,* KIYOSHI NISHITANI, and TOSHIHISA MASHIKO

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

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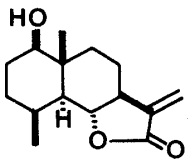
The reaction mechanism and the stereochemistry of an acid-catalyzed allylic rearrangement of four allylic alcohols of 5α-cholestane, the 3-hydroxy-1-enes (**5** and **6**) and the 1-hydroxy-2-enes (**7** and **8**), were investigated. The allylic alcohols were heated in dioxane containing a small amount of 1 N H_2SO_4. After the equilibration of the reaction, the products ratio of the four allylic alcohols, **5**:**6**:**7**:**8**, was found to be 25:20:52:3, regardless of the stereochemistry of the starting materials. The mechanism of the allylic rearrangement is of S_N1 type. The products ratio could be explained in terms of the relative stabilities of the C-1 and C-3 carbocations in the intermediates and the thermodynamic stability of each allylic alcohol.

Keywords——steroidal allylic aclohol; S_N1 mechanism; allylic rearrangement; HPLC

In the previous papers,[2a-e] chemical transformations of α-santonin to some sesquiterpene lactones have been reported. During the course of the synthesis of balchanin (**1**) from α-santonin, 1α-hydroxy-5α(*H*)-eudesm-2-en-6,13-olide (**3**) was synthesized as an intermediate by an acid-catalyzed allylic rearrangement of 3β-hydroxy-5α(*H*)-eudesm-1-en-6,13-olide (**2**).[2d,3] Compound **2** was refluxed in dioxane containing a small amount of 1 N sulfuric acid for 8 h to give the 1α-hydroxy-2-ene (**3**) in 67% yield together with the starting material (**2**) in 14% yield as reported in the previous paper.[2d]

Allylic rearrangement with retention of the stereochemistry at the γ position to the



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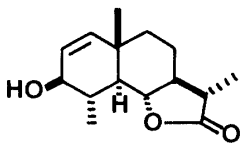

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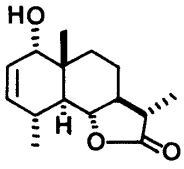

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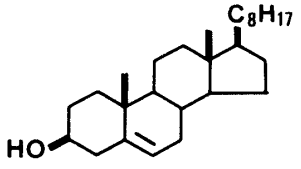

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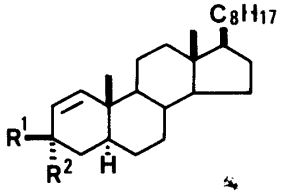
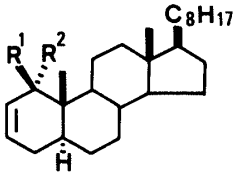


5 : R^1=OH, R^2=H
6 : R^1=H, R^2=OH



7 : R^1=H, R^2=OH
8 : R^1=OH, R^2=H

Chart 1

leaving group has been reported.[4] An example reported by Mühle *et al.*[5] is shown in Chart 2. On the other hand, few papers have appeared on the acid-catalyzed allylic rearrangement of allylic alcohols. Silversmith *et al.*[6] reported the perchloric acid-catalyzed allylic rearrangement of some cyclohexenols (Chart 3), but the stereochemistry was not determined.

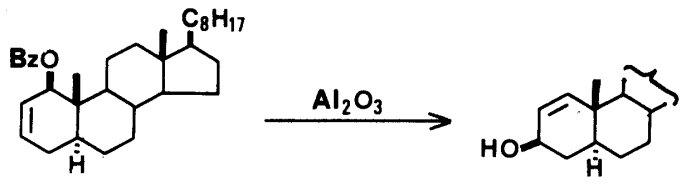


Chart 2

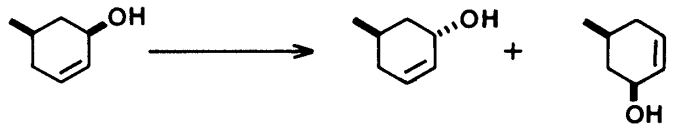


Chart 3

Now, we wish to report the stereochemistry of the acid-catalyzed rearrangement of four allylic alcohols, 3β- and 3α-hydroxy-5α-cholest-1-enes (**5** and **6**) and 1α- and 1β-hydroxy-5α-cholest-2-enes (**7** and **8**), derived from cholesterol (**4**).[7-12]

Solutions of these allylic alcohols (**5**, **6**, **7** and **8**; 130 mg) in dioxane (6 ml) containing 1 N sulfuric acid (1.3 ml) were heated at 70 °C to obtain an equilibrium mixture of the allylic alcohols, and the reaction was monitored by high performance liquid chromatography (HPLC). The results are shown in Fig. 1 and in Table I.

The ratios of the four isomers in the reaction mixture were determined from the peak heights on the HPLC chart in comparison with those of mixtures of various concentrations of the authentic allylic alcohols. The resulting reaction products were separated by preparative HPLC to give the allylic alcohols (**5**, **6**, **7** and **8**). The structures were confirmed by comparison of the spectral data with those of authentic specimens. The isolated yields of the four allylic alcohols after equilibration are shown in Table I.

The rearrangements were equilibrated within 5 h except in the case of **8**. The results can be summarized as follows. (a) The formation ratio of the allylic alcohols (**5**, **6**, **7** and **8**) was constant after equilibration regardless of the starting alcohols. This result suggests that the rearrangement proceeds through the S_N1 mechanism. (b) The formation ratio of the 1-hydroxy compounds (**7** and **8**) to the 3-hydroxy compounds (**5** and **6**) is 5:4. This result reflects the stabilities of the intermediates, carbocations A and B, as shown in Chart 4. (c) The

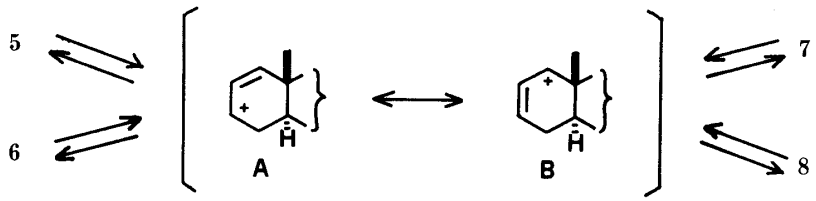


Chart 4

formation ratio of 3α- and 3β-hydroxy compounds is nearly 1 : 1, whereas that of the 1α- and 1β-hydroxy compounds is 50 : 3. These results suggest that the yields of the allylic alcohols should depend on the relative stabilities of the alcohols. Only the 1β-hydroxy compound (**8**)

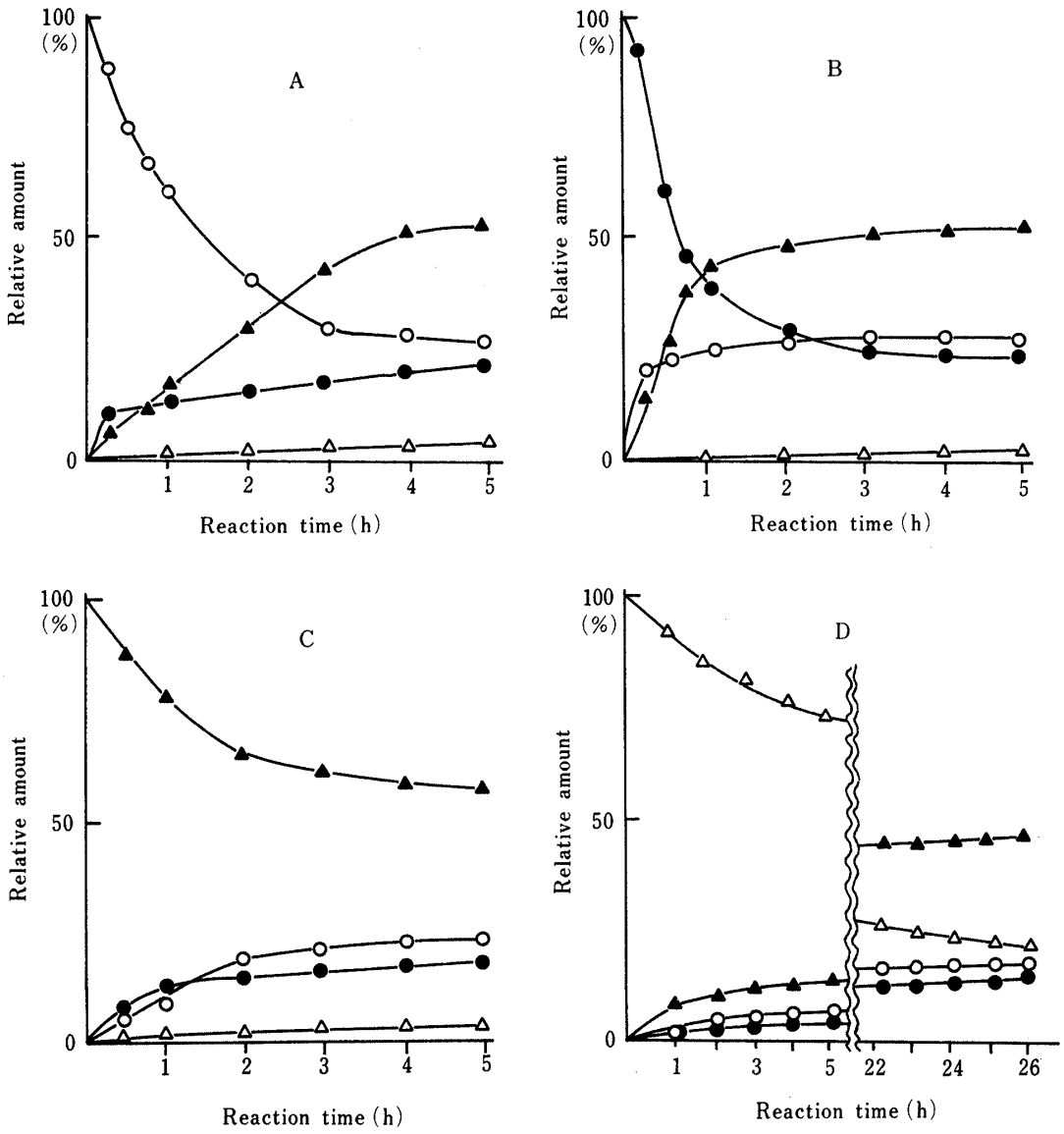


Fig. 1. The Acid Catalyzed Allylic Rearrangements of the Following Materials: A, **5** (—○—); B, **6** (—●—); C, **7** (—▲—); D, **8** (—△—)

The relative amounts in the reaction mixture were determined by HPLC.

TABLE I. Ratios of the Allylic Alcohols in the Allylic Rearrangement Equilibrium Mixtures

Starting alcohol	Reaction time (h)	Total yield of allylic alcohols (%)	Relative yields of allylic alcohol (%)			
			5	**6**	**7**	**8**
5	5	81	25	20	52	3
6	5	79	25	22	51	2
7	5	84	22	18	57	3
8[a)]	26	66	18	13	51	18

a) The reaction had not reached equilibrium after 26 h, and some elimination and/or decomposition occurred.

should be destabilized by a steric repulsion between the 11α-hydrogen and 1β-hydroxyl group.

Experimental

HPLC was done with a Hitachi 635A type instrument equipped with a 50 cm × 2.6 mm stainless-steel column packed with Merck LiChrosorb Si 60 (10 μm). Preparative-scale separation was effected by medium-pressure column chromatography with Merck Lobar prepacked silica gel columns.

Materials——The four steroidal allylic alcohols (**5**, **6**, **7** and **8**) were synthesized by the known methods[7-12] from cholesterol and purified by recrystallization or column chromatography. All the materials were identified by comparison of their spectral and physical data with those of authentic samples reported in the literature.

General Procedure for Allylic Rearrangement of the Allylic Alcohols——A solution of an allylic alcohol (130 mg) in dioxane (6 ml) containing 1 N H_2SO_4 (1.3 ml) was heated at 70 °C. The reaction was monitored by HPLC (hexane–EtOAc 10 : 1 was used as an eluant at 1.5 ml/min). The ratio of the allylic alcohols in the reaction mixture was determined by HPLC with a refractive index (RI) monitor. Retention volumes of the allylic alcohols were as follows; **8** = 2.64, **7** = 3.30, **6** = 7.55 and **5** = 9.95 ml. The ratios of the isomers were obtained from the peak heights of the isomers on the HPLC chart and were calculated on the basis of authentic mixtures of pairs of isomers (**5**/**6**, **6**/**7** and **5**/**8**) at about ten different concentrations (from 0.1 to 10 in ratio). When the reaction was complete, the dioxane was evaporated off. The residue was extracted with ether, and the extract was washed with 10% $NaHCO_3$, water and brine, then dried. Removal of the ether gave a solid, which was subjected to preparative-scale medium-pressure column chromatography with hexane–EtOAc (10 : 1), 3 ml/min, with the RI monitor. The isolated allylic alcohols were identified by spectral comparisons with authentic samples.

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