CHEMISTRY LETTERS, pp. 1159-1162, 1977. Published by the Chemical Society of Japan

PARTICIPATION OF ALLYLIC HYDROXYL GROUP IN THE BROMINE ADDITION TO CYCLOHEXENE DERIVATIVES, 1α- AND 1β-HYDROXY-2,3-DEHYDRO-5α-SANTANOLIDE[1]

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Addition of bromine to 1α-hydroxy-2,3-dehydro-5α-santanolide (6a) and its derivatives (6b and c) gave diequatorial 2α,3β-dibromides (9a, b, and c) as major products and diaxial 2β,3α-dibromides (10a, b, and c) as minor products, respectively. This bromine addition is all abnormal in the Früst-Plattner rule and its reaction mechanisms are proposed.

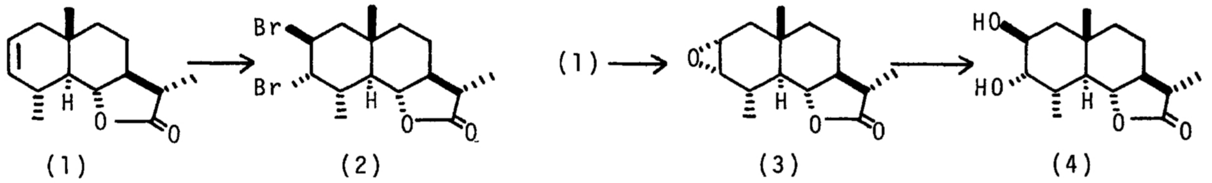
In general, bromine addition to olefins mainly gives a product of vic diaxial *trans*-dibromides.[2] In the case of steroids, the bromine addition to cholest-2-ene gave diaxial 2β,3α-dibromide as a major product (88-91% yield) together with diequatorial 2α,3β-dibromide as a minor product (12-9% yield).[3] Anti-coplaner cleavage of 2α,3α-cyclic bromonium ion from the nucleophilic attack by a bromide ion at C-2 from the β-side furnished a 2β,3α-diaxial dibromide. This result is similar to the ring-opening reaction of the epoxide ring, which can be interpreted by the Früst-Platner rule. A number of exceptions to the Früst-Plattner rule arising from the operation of inductive, conjugative, and neighboring group effects have been recorded.[4] We now report an exception to the Früst-Plattner rule in the bromine addition to cyclohexene derivatives, 1α-hydroxy-2-en-5α-santanolide and its corresponding derivatives.

The bromine addition to 2,3-dehydro-5α-santanolide[5] (1) gave predominantly 2β,-3α-dibromide (2), mp 178.5-180°C, in 80% yield. NMR spectrum of (2) showed complex signals ($W_{1/2}$=5 Hz) at δ 4.60 for 3-equatorial H, which coupled with 2α and 4β protons, and quintet signals (*J*=4, 2 Hz) at δ 4.75 for 2-equatorial H, which coupled with 1α, 1β, and 3αH's. Thus, the structure of (2) was determined as axial 2β,3α-dibromide.

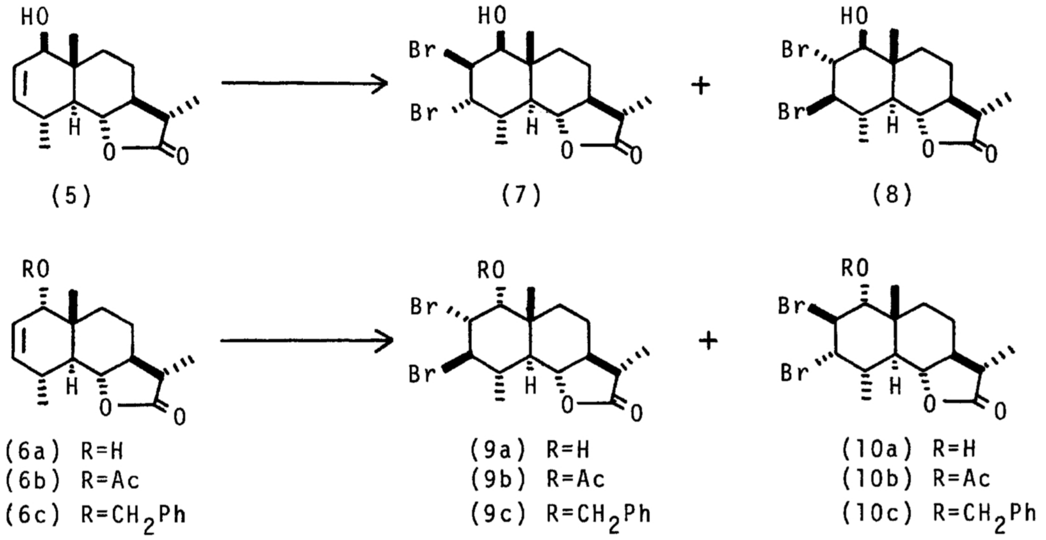
Recently, Kamat *et al.*[6] reported that the ring-opening reaction of 2α,3α-epoxy-5α-santanolide (3) gave only diaxial *trans*-2β,3α-diol (4), according to the Früst-Plattner rule. This result supported the above normal bromine addition to (1).

1α-hydroxy-5α-santan-6,12-olide (6a), mp 143-144.5°C, was previously reported as a key intermediate for the chemical transformation of α-santonin into a sesquiterpene α-methylene-γ-lactone, santamarine.[7] 1β-Hydroxy-5α-santan-6,12-olide (5), mp 128-130°C, was derived from (6a). The Jones oxidation of (6a) gave 1-oxo-2-ene, mp 113-114°C, which was reduced with $NaBH_4$ to (5). Bromine addition to 1β-hydroxy-2-ene (5) in $CHCl_3$ at 0°C furnished diaxial 2β,3α-dibromide (7), mp 172-173°C, as a major product (68% yield)[NMR δ: 4.66 (t, *J*=2.4 Hz, 3-H), 4.88 (q, *J*=2.4 Hz, 2-H)] and diequatorial 2α,3β-dibromide (8), mp 166-167.5°C, as a minor product (25% yield)[NMR δ: 3.75 (t, *J*=10 Hz, 3-H), 4.36 (t, *J*=10 Hz, 2-H)]. In this case, the diequatorial dibromide (8) was obtained but not in the case of bromine addition to (1).

Scheme 1



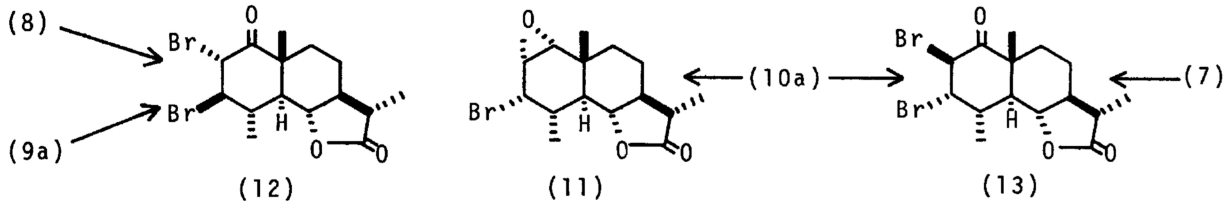
Scheme 2



Bromine addition to 1α-hydroxy-2-ene (6a) gave diequatorial 2α,3β-dibromide (9a), mp 228-230°C, as a major product (64% yield)[NMR δ: 3.98 (t, *J*=11 Hz, 3-H), 4.76 (dd, *J*=11, 2.5 Hz, 2-H)], and diaxial 2β,3α-dibromide (10a), mp 182-184°C, as a minor product (18% yield)[NMR δ: 4.60 (dd, *J*=2.5, 2 Hz, 3-H), 4.93 (t, *J*=2 Hz, 2-H)]. This result is of interest when compared with bromine addition to (5) because of the reversed ratio of major and minor products, and such a result has not been reported in the steroid chemistry. Similarly, bromine addition to 1α-acetoxy derivative (6b), mp 143-145°C, gave 2α,3β-dibromide (9b), mp 158-160°C, as a major product (44.5% yield)[NMR δ: 3.90 (t, *J*=11 Hz, 3-H), 4.65 (dd, *J*=11, 2.5 Hz, 2-H)], and 2β,3α-dibromide (10b), mp 224-226.5°C, as a minor product (17.3% yield)[NMR δ: 4.55 (bs, 3-H), 4.75 (bs, 2-H)]. Bromine addition to 1α-benzyloxy derivative (6c), an oil, with a more bulky group than hydroxyl and acetoxyl groups (6a and 6b), gave 2α,3β-dibromide (9c), an oil (51% yield)[NMR δ: 4.03 (t, *J*=10 Hz, 3-H), 4.70 (dd, *J*=10, 3 Hz, 2-H)], and 2β,3α-dibromide (10c), an oil (19.8% yield)[NMR δ: 4.57 (m, W $\frac{1}{2}$=6 Hz, 3-H), 5.00 (bt, W $\frac{1}{2}$=5 Hz, 2-H)]. The formation ratio of the major (9b and 9c) and minor bromides (10b and 10c) in the bromine addition was similar to that in 6a.

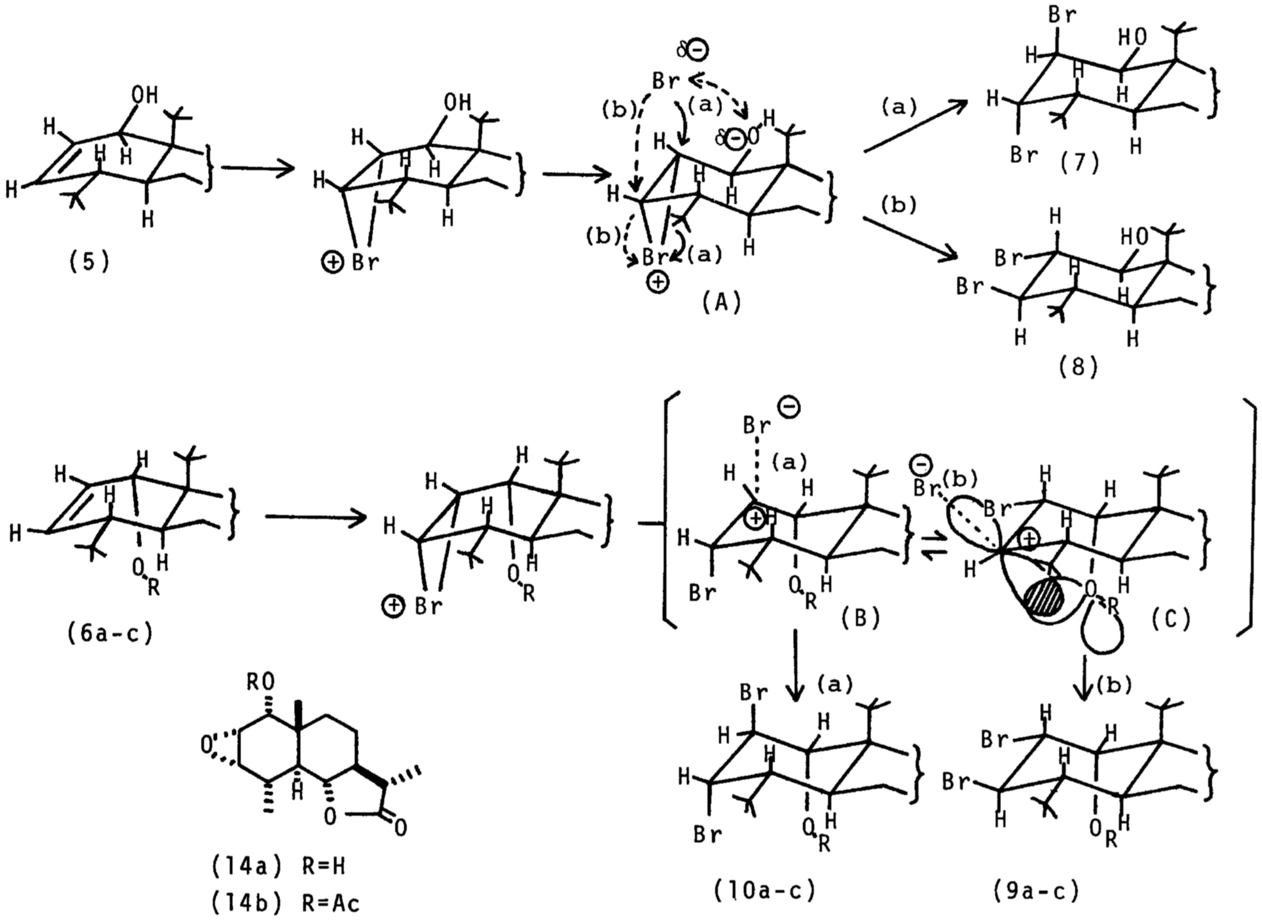
Structures of bromides (7-10) were confirmed by some transformation reactions as described below. Treatment of (10a) with KOH-MeOH gave α-epoxide (11), mp 204-205°C. This is evidence that the configuration of 1,2-bromohydrine is *trans*-diaxial 1α,2β. The Jones oxidation of the two dibromides, (8) and (9a), gave the same dibromoketone (12), mp 97°C (decomp.) [NMR δ: 3.89 (t, *J*=10 Hz, 3-H), 5.18 (d, *J*=10 Hz, 2-H)], and that of (7) and (10a) gave the same dibromoketone (13), mp 122 °C (decomp.) [NMR δ: 4.56 (t, *J*=2 Hz, 3-H), 4.64 (d, *J*=2 Hz, 2-H)]. From these results, the structureof dibromides, (8) and (9a), and (7) and (10a), was confirmed as diequatorial 2α,3β-dibromide and diaxial 2β,3α-dibromide, respectively.

Scheme 3



From the above bromination results, we propose the mechanism of bromine addition to 1β- and 1α-hydroxy-2,3-dehydro-5α-santanolide (5 and 6a) as shown in Scheme 4.

Scheme 4. Reaction Mechanism



The initial attack by "electrophilic halogen" occurs on the more exposed α-face of double bonds in (5) and (6a-c). This is supported on the basis of the epoxidation of (6a) and (6b), in which α-epoxides (14a), mp 219-222°C, and (14b), mp 185-185.5°C, were respectively obtained stereoselectively. Subsequent reaction between the halonium ion and the incoming halide ion proceeds through path (a), the energetically favored transition state (A and B) with the four atoms lying in or near the plane, and requring a *trans-anti* arrangement of the halogen atoms (7) and (10a-c). As the oxygen atom of 1β-hydroxyl group repulses the incoming halide ion in the trasition state (A), the reaction proceeds through path (b) to give the equatorial dibromide (8).

On the other hand, the initial α-halonium ion of 1α-hydroxy compound (6a) and its derivatives (6b and c) may form two cation intermediates, (B) and (C), which respectively produce diaxial 2β,3α-dibromide (10a-c) and diequatorial 2α,3β-dibromide (9a-c). It is considered that the proportion of the cation (C) produced to the normal cation (B) increases, because of the stabilization of cation (C) in terms of hybrization of C-3 cation with lone-pair orbitals oxygen atom of 1α-hydroxy and its corresponding derivatives to form the 4 membered oxonium ions. Consequently, the diequatorial 2α,3β-dibromides (9a-c) were formed as major dibromides via cation (C).

Furthermore, the bromine addition reaction to steroidal olefins are now in progress.

References and Note

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(Received July 14, 1977)