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SILVER(I) ION CATALYZED SUBSTITUTION REACTIONS: STEREOELECTRONIC CONTROL IN AN S_Ni MECHANISM

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SUMMARY: Stereochemistry of the acetolysis of 4-, 6α- and 6β-bromocholest-4-en-3-ones using silver acetate was established, and the reactions were interpreted to proceed via a stereoelectronically controlled S_Ni mechanism.

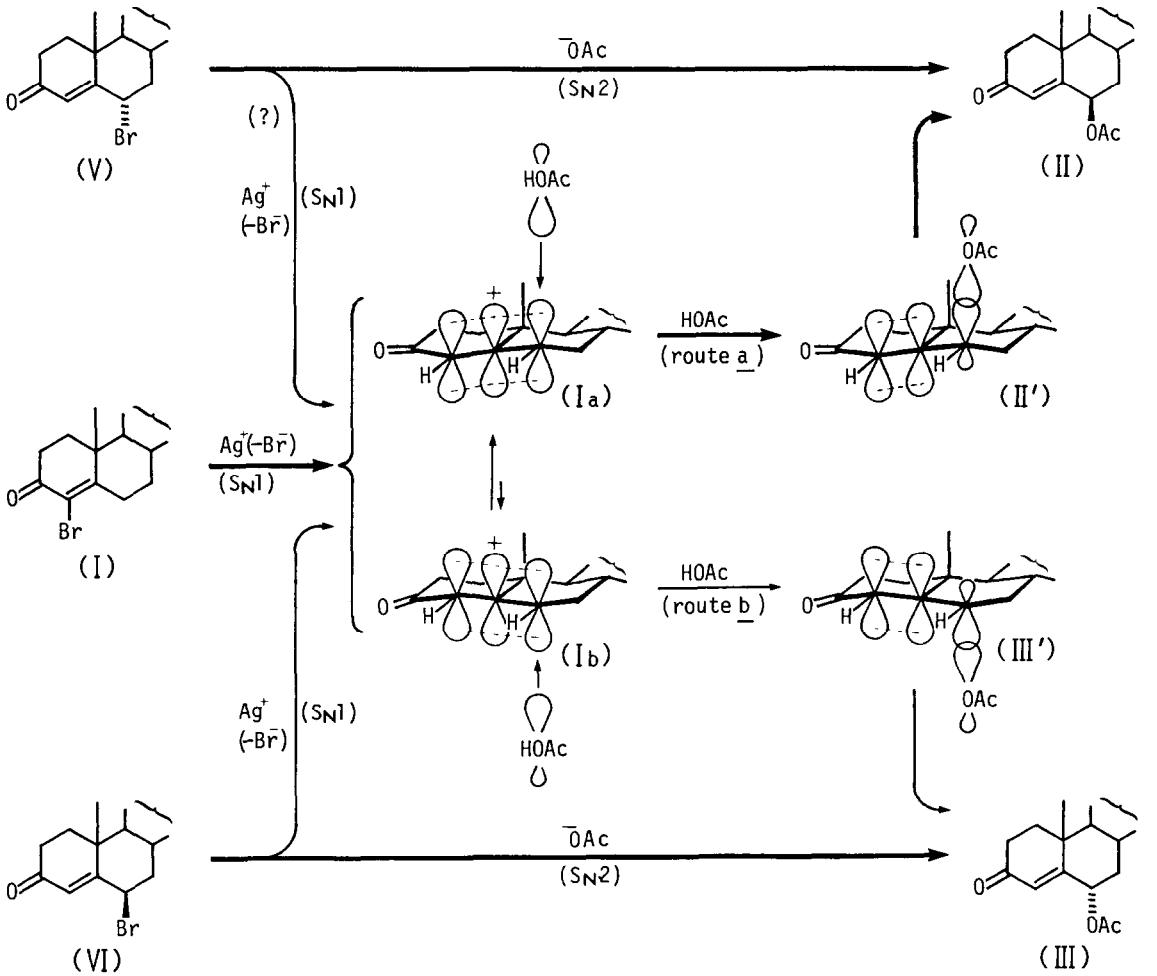
Previously we reported that the bromine atom of 4-bromocholest-4-en-3-one (I) is reactive to acetolysis in spite of its vinylic character, and the reaction resulted in a new stereospecific rearrangement of the substituent from C(4) to C(2) and C(6).[1] Namely, the reaction of I with an excess of potassium acetate in boiling acetic acid afforded 4-acetoxy (S_N2 displacement product), 2α- and 6β-acetoxy(II) compounds (S_N2' displacement products). In the S_N2' displacement, formation of the compound(II) and the intermediate product, 2β-acetate, with thermodynamically less stable axial substituent might be governed by stereoelectronic requirements around C(6) and C(2) favoring maximum overlap of the p orbital of the oxygen atom of the attacking nucleophile with the vacant p orbitals at C(6) and C(2), from the axial β-side.

We now report the new characteristic and interesting findings that silver(I) ion catalyzed acetolysis of α-bromo- and γ-bromo-4-en-3-oxo steroids affords the 6-acetoxy compounds as the displacement product, exclusively.

A solution of I[2] with a ten fold excess of silver acetate in glacial acetic acid was heated under reflux in a nitrogen atmosphere. The reaction was complete in 65 hr (t.l.c.). After usual treatment, silica gel column chromatography of the crude product gave only a mixture of 6β- (II) and

6α- (III)-acetates as the isolable displacement product in 50.0 % yield, and 4,6-dien-3-one(IV) in 26.0 % yield. The relative ratio of the isomeric products (II to III) was 13 : 1 (by g.l.c.) ; the product with thermodynamically less stable axial substituent at C(6) was extremely predominant. It was also made sure that the 6β-acetate (II) did not isomerize to its 6α-isomer (III) under such conditions, and consequently, III was formed from I directly.

The reaction can be envisaged as proceeding via mesomeric cations (Ia and Ib), which might be formed in the initial slow step including abstraction of the bromine atom at C(4) by silver(1) ion



Scheme

Nucleophilic attack of the solvent acetic acid at C(6) of the cations would occur by an S_N1 process (routes a and b in Scheme). Proceeding via a transition state with ring B in the more stable chair conformation (Ia),[3] attack of acetic acid under stereoelectronic control will, favoring axial addition, form the 6β-substituted product II. Actually, predominant formation of II clearly indicates that the route a passing through Ia is normal and favorable.

On the other hand, α bond at C(6) may become pseudoaxial in a transition state with a twist-boat conformation of ring B (Ib). In the route b, attack of the solvent under stereoelectronic control will form the 6α-substituted product III. Holland and Auret[4] suggested that for the more rigid steroid molecule, only a transition state with ring B in the chair form is feasible, but a twist-boat conformation of ring B is also considerable for 10-methyl-$\Delta^{1(9)}$-octal-2-one, which was looked on the conformationally mobile analog of the Δ^4-3-oxo steroids. Formation of the compound III in our reaction, however, clearly indicates the contribution of the twist-boat conformation (Ib) in the more rigid steroid system, and the proportion of II to III may therefore reflect the relative stability of the transition states Ia and Ib.

For further comparison of the behavior of α-bromo- and γ-bromo-enone systems under such acidic conditions, 6α-(V) and 6β-(VI)-bromocholest-4-en-3-ones were chosen and treated with silver acetate. Acetolysis of the 6-bromo-4-en-3-oxo steroids with potassium acetate is well investigated.[5] For example, Burnett and Kirk[3] obtained three acetoxy compounds, i.e. 2α-, 2β- and 6β-acetates by acetolysis of 6β-bromoandrost-4-ene-3,17-dione. A distinctive and interesting result, however, was obtained in our conditions. A solution of V with a ten fold excess of silver acetate in glacial acetic acid was kept at 70°C for 1 hr. After usual treatment, silica gel column chromatography of the crude product gave only 6β-acetate(II)(50.5 %) as the displacement product, and dienone(IV)(29.5 %) as a by-product. Under same conditions, the compound VI afforded a mixture of isomeric 6-acetates II and III (25:75) in 21.2 % yield, and also IV (48.9 %).

The acetolysis of γ-bromo-enones using silver acetate seems best explained by simultaneous operation of two reaction mechanisms (Scheme). A main route is direct substitution (S_N2) in the cases of both V and VI entailing inversion of configuration at C(6). Another is an S_N1 route with the normal stereoelectronically controlled axial attack at C(6) forming 6β-acetate (II). Formation of the compound II in the case of VI clearly indicates the contribution of the transition state (Ia) coming up to about 25 % of total displacement reactions.

Thus, in the S_N1 mechanism, the stereoelectronic effects play an important role to determine

the configuration and the relative ratio of the isomeric products at C(6).

A careful examination of the products isolated revealed that no detectable amount of the 2- and 4-substituted products was formed under the above reaction conditions; demonstrating a significant difference on the actions and the mechanisms between silver acetate and potassium acetate in acetolysis. We suspect that this is because silver acetate is slightly soluble in acetic acid and so the concentration of acetate ion in the reaction mixtures is not sufficient to cause the enolization of the keto group at C(3) toward C(2) and C(6) of the Δ^{4}-3-ketone system.

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