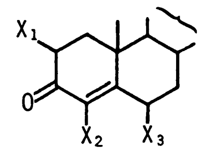
CHEMISTRY LETTERS, pp. 699-700, 1982. © The Chemical Society of Japan 1982

A NOVEL SEQUENCE OF DISPLACEMENT REACTIONS OF A DIHALOGENATED Δ^4-3-KETOSTEROID

Toshitaka KOGA,* Namiko TOH, and Yasuyoshi NOGAMI
Daiichi College of Pharmaceutical Sciences
22-1, Tamagawa-cho, Minami-ku, Fukuoka 815

Acetolysis of 2α,4-dibromocholest-4-en-3-one affords 2β,6β-disubstituted product and the reaction is explained to proceed by the successive S_N2 and S_N2' mechanisms.

As for Δ^4-3-ketosteroids having two bromine atoms around the α,β-unsaturated keto function, there are three structural isomers, α,α'-dibromo-(I), α,γ-dibromo-(II), and α',γ-dibromo-(III) enones (Fig. 1). To our knowledge, however, two cases were actually reported for their substitutions. One is a reaction of 2ξ,6β-dibromo-Δ^4-3-ketone (the system III) with potassium acetate[1] and another is an acetolysis of 4,6β-dibromo-Δ^4-3-ketone (the system II).[2] The former starts with an S_N2' displacement of 6-bromine, followed by a 1,3-elimination-rearrangement and the latter proceeds by successive S_N2' mechanisms crossed over the rings A and B. Although S_N2' reaction is a common occurrence in the displacements of the dibromo-enones, S_N2 and S_N1 reactions are not yet observed.

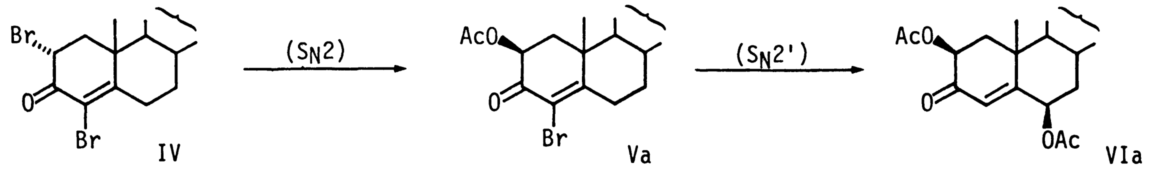


I: X_1,X_2=Br, X_3=H
II: X_2,X_3=Br, X_1=H
III: X_1,X_3=Br, X_2=H

Fig. 1

We now report the new characteristic findings that the behavior of the 2α,4-dibromo-Δ^4-3-ketone, an untried system I, is significantly different from those of the other dibromo-enones for substitution reactions. Namely, the title reaction is initiated by the facile S_N2 displacement of the 2α-bromine, followed by the S_N2' reaction of the 4-bromine: that is to say a combination of S_N2 and S_N2' reactions.

2α,4-Dibromocholest-4-en-3-one (IV)[1,3] was chosen as a substrate and was treated with a 33 fold excess of potassium acetate in acetic acid under reflux for 2 hr in a nitrogen atmosphere. By careful chromatography we obtained 2β-acetoxy-4-bromo-enone (Va:14.4%) and its α-isomer (Vb: 9.8%), 2β,6β-diacetate (VIa:11.1%) and its 2α-isomer (VIb:16.4%), and 2β-acetoxy-4,6-dienone (VIIa:trace) and its α-isomer (VIIb:14.3%).[4] Furthermore, the 4-bromo-enone (Va) afforded five products (Vb, VIa,b, and VIIa,b) under the same conditions. On the other hand, the isomeric Vb gave only two products (VIb and VIIb).



These results indicate that the 2α-bromine of IV, in marked contrast to the case of 2ξ,6β-dibromo-enone,[1] is very sensitive to substitution reactions and this reaction might start smoothly with the displacement of the bromine, proceeding by S_N2 mechanism to give the intermediate product (Va). The second step of the reaction, further acetoxylation of Va, proceeding by the stereoelectronically controlled S_N2' mechanism, can be regarded in the same way as those of 4,6β-dibromo-enone.[2]

We also inquired into the possibility that the displacement of the 2α-bromine in the first step might proceed by a stereoelectronically controlled S_N2' or S_N1 mechanism. Proceeding by these mechanisms, 6β-acetoxy-4-bromocholest-4-en-3-one (VIII) might be formed[2,5] and this species subsequently could afford observed products (VIa and VIb). To test this, VIII was prepared[6] and was subjected to the acetolysis. Thereby, the compound was found to be stable under the conditions and was surely recovered unchanged. Accordingly, the fact that no detectable amount of VIII was found in the products isolated rules out the possible involvement of the S_N2' and S_N1 mechanisms.

As well, there remains the possibility of the anchimeric assistance by participation of the C_4-C_5 π-electrons on the facile displacement of the 2α-bromine. If the participation could be effective, the reaction should be undoubtedly accelerated to give Vb as the initial product exclusively (Fig. 2).[7] It is actually indistinguishable whether Vb could be formed, at least in part, from IV directly owing to the assistance or might be only formed from Va secondarily. The following observations, however, make the possibility very improbable. In fact, Va was formed from IV predominantly and moreover, Vb could be obtained from Va secondarily under the conditions.

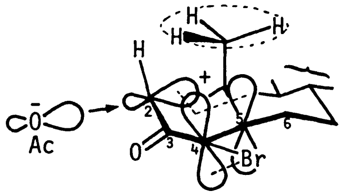


Fig. 2

It has been concluded, therefore, that the process of the S_N2 displacement is involved in the reaction sequence at the first step.

Thus, by these findings obtained, the significant difference on the behavior between the 2α,4-dibromo- and the other dibromo-enones for substitution reactions was clarified.

References

1. P.L. Julian, L. Bauer, C.L. Bell, and R.E. Hewitson, J. Am. Chem. Soc., 91, 1690 (1969), and earlier literature cited therein.
2. T. Koga, N. Toh, and Y. Nogami, Chemistry Lett. 1982, 95.
3. D.J. Collins and J.J. Hobbs, Aust. J. Chem., 18, 1049 (1965).
4. All compounds mentioned in this letter except VIII were identified by comparison (mixed m.p., i.r., u.v., and n.m.r. spectra) with authentic samples.[2]
5. a) R.D. Burnett and D.N. Kirk, J. Chem. Soc., Perkin I, 1830 (1973).
   b) T. Koga and M. Tomoeda, ibid., 1848 (1973).
   c) T. Koga and Y. Nogami, Tetrahedron Letters, 22, 3075 (1981).
6. VIII was synthesized from 4-bromocholest-4-en-3-one by the sequence (1. enol acetylation 2. epoxidation 3. cleavage of the epoxide 4. acetylation) in 60.5% over-all yield. Colorless needles, m.p. 97.5-98°; i.r. 1745, 1695, 1570 cm^{-1}; u.v. 258nm (ε :9600); n.m.r. (δ) 0.74(3H, s, 18-H), 1.33(3H, s, 19-H), 2.05(3H, s, 6β-OAc), 6.30(1H, m, W_H=6Hz, 6α-H); MS m/e 520(M^+), 478(M^+-CH_2CO), 441(M^+-Br), 399(M^+-CH_2CO-Br, base peak). Satisfactory elemental analysis has been obtained for this compound.
7. The stereochemistry of the displacement at C-2 can be controlled by the participation to give 2α-substituted product exclusively as the result of double inversion of the configuration.

(Received March 23, 1982)