CHEMISTRY LETTERS, pp. 995-998, 1972. Published by the Chemical Society of Japan

# THE HALOGEN REARRANGEMENT OF 1β-BROMO- AND 1β-CHLORO-5β-CHOLESTAN-2-ONE TO THE α'-POSITION

J. Yasuo SATOH, C. Akira HORIUCHI, and Akira HAGITANI
Department of Chemistry, St. Paul's (Rikkyo) University,
Nishi-Ikebukuro, Toshima-ku, Tokyo, Japan

A new phenomenon of an α-haloketone having a halogen on its secondary carbon atom in which the halogen rearranges to the α'-position occupied by a secondary carbon atom was found in the reaction of 1β-bromo- and 1β-chloro-5β-cholestan-2-one with the following reagents: i) hydrogen bromide / acetic acid, ii) hydrogen chloride / acetic acid, iii) acetic acid, iv) acetic acid / dioxane, v) boron trifluoride etherate / dioxane, vi) perchloric acid-acetic anhydride / benzene-carbon tetrachloride, vii) potassium acetate / acetic acid.

In a *gem*-dibromoketone and α-bromoketone having a bromine on its *tert*-carbon, it has been reported that, by using HBr-AcOH, the bromine rearranges to the α'-position occupied by a secondary carbon atom.$^{1)}$ Moreover, it is also known that the halogen of α-haloketone which is on a secondary carbon atom rearranges to the α'-position occupied by a tertiary carbon atom,$^{2)}$ and the one which is on a primary carbon atom likewise rearranges to the α'-position occupied by a tertiary carbon atom.$^{3)}$ However, there has been no report concerning the rearrangement to the α'-position occupied by a secondary carbon atom, of that halogen of α-bromo- and α-chloroketone which is on a secondary carbon atom. In the present paper, the authors wish to report that an α-haloketone having a special stereochemical environment is capable of undergoing such a rearrangement.

A mixture of 1β-bromo-5β-cholestan-2-one$^{4)}$ (Ia)(300 mg) and 48 % hydrogen bromide (0.2 ml) in acetic acid (30 ml) was stirred under refluxing for 1 h. After cooling, the reaction mixture was poured into water and extracted with ether.

The ethereal solution was washed with water, dried, and evaporated under reduced pressure. The resultant oil (295 mg) was chromatographed on silica gel (25 g) with petroleum ether. Elution with benzene-petroleum ether (1 : 4)(150 ml) gave plates of 3β-bromo-5β-cholestan-2-one (IIa)(100 mg), mp 139.5-142°C, IR:5) 1715 $cm^{-1}$, NMR:5) 5.66 (1H, t, J=2.9 Hz, $C_3$α-H). Found: C, 69.80; H, 9.81%. Calcd for $C_{27}H_{45}OBr$: C, 69.65; H, 9.74%.

The next fraction, eluted by benzene-petroleum ether (1 : 2)(450 ml), on crystallization from ethanol, gave plates of 3α-bromo-5β-cholestan-2-one (IIIa) (50 mg), mp 125.5-126.5°C, IR: 1723 $cm^{-1}$, NMR: 5.27 (1H, q, J=11.3 and 7.5 Hz, $C_3$β-H). Found: C, 69.93; H, 9.88%. Calcd for $C_{27}H_{45}OBr$: C, 69.65; H, 9.74%.

The rearrangement of 1β-chloro-5β-cholestan-2-one (Ib)2) (300 mg) with 35 % hydrogen chloride was carried out using the procedure described above. The reaction mixture was taken up in ether and the ether extracts were washed, dried, and evaporated. On chromatography of the residue on silica gel (25 g), elution with petroleum ether gave a yellow oil, which on crystallization from ethanol gave plates of 3β-chloro-5β-cholestan-2-one (IIb)(81 mg), mp 138.5-140°C, IR: 1715 $cm^{-1}$, NMR: 5.74 (1H, t, J=4.0 Hz, $C_3$α-H). Found: C, 76.98; H, 10.85%. Calcd for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77%.

The next fraction, eluted by benzene-petroleum ether (1 : 4)(300 ml), on crystallization from ethanol, gave plates of 3α-chloro-5β-cholestan-2-one (IIIb) (54 mg), mp 122.5-125°C, IR: 1727 $cm^{-1}$, NMR: 5.43 (1H, q, J=11.0 and 8.3 Hz, $C_3$β-H). Found: C, 76.94; H, 10.82%. Calcd for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77%.

It was also found that the reaction of both 1β-halo-5β-cholestan-2-ones with the following reagents at 90°C for 12 h formed products which exhibited the α'-position rearrangement: i) hydrogen bromide / acetic acid, ii) hydrogen chloride / acetic acid, iii) acetic acid, iv) acetic acid / dioxane, v) boron trifluoride etherate / dioxane. These results are summarized in Table.

Moreover, in the acetolysis of 1β-bromoketone (Ia) with potassium acetate in acetic acid for 4 h at 98.5°C, 3α-bromo-5β-cholestan-2-one (IIIa) was formed along with 3α-(VI)6) and 3β-acetoxy-5β-cholestan-2-one (V), mp 79.5-80°C, IR: 1748, 1719, and 1247 $cm^{-1}$, NMR: 5.13 (1H, t, J=2.4 Hz, $C_3$α-H), 7.92 (3H, s, $C_3$β-$OCOCH_3$). Found: C, 78.05; H, 10.81%. Calcd for $C_{29}H_{48}O_3$: C, 78.33; H, 10.88%.

Table

Reaction of 1β-halo-5β-cholestan-2-one ($3.21 \times 10^{-4}$ M) with some reagents ($8.59 \times 10^{-5}$ M) in acetic acid (13.5 ml) or in dioxane (13.5 ml).

| X=Br | | | | X=Cl | | | |
|---|---|---|---|---|---|---|---|
| Compositions (%) / Reagents | (Ia) | (IIa) | (IIIa) | Compositions (%) / Reagents | (Ib) | (IIb) | (IIIb) |
| HBr/AcOH[a)] | trace | 38 | 24 | HBr/AcOH[a)] | 35 | 24 | 30 |
| HCl/AcOH[a)] | 12 | 22 | 20 | HCl/AcOH[a)] | 28 | 20 | 25 |
| AcOH[a,b)] | trace | 33 | 22 | AcOH[a,b)] | 48 | 31 | 16 |
| AcOH/Di.[a)] | 28 | 30 | 20 | AcOH/Di. | 60 | 32 | 8 |
| $BF_3$/Di. | 52 | 44 | trace | $BF_3$/Di. | 55 | 30 | 8 |

a) 5β-Cholestan-2-one was contained as by-product.

b) Both 3-acetoxy-5β-cholestan-2-ones were identified from NMR spectra.

The composition of each reaction mixture was determined from the peak area due to the proton on the carbon having the halogen, using the 18-methyl group as a standard peak area.

It was found that the acetolysis of 1β-chloro-5β-cholestan-2-one yielded the rearrangement product, 3α-chloroketone, as in the case of 1β-bromoketone.

There is no report concerning the enolacetylation of an α-haloketone, except for one describing that of 4β-bromo-5β-cholestan-3-one,[7)] in which 4β-bromo-5β-cholest-2-en-3-ol acetate was obtained with acetic anhydride and perchloric acid at room temperature. However, the enolization of 1β-bromo-5β-cholestan-2-one (Ia) under the same conditions gave a rearrangement product, 3β-bromo-5β-cholest-1-en-2-ol acetate (IVa), mp 99-101°C, IR: 1774, 1659, 1291, and 710 $cm^{-1}$, NMR:[5*)] 5.14 (1H, m, W/2=7 Hz, $C_3$α-H), 4.45 (1H, s, $C_1$-H), 7.83 (3H, s, $C_2$-$OCOCH_3$). Found: C, 68.71; H, 9.23%. Calcd for $C_{29}H_{47}O_2Br$: C, 68.62; H, 9.33%.

It was also found that the enolacetylation of 1β-chloroketone (Ib) yielded the rearrangement product, 3β-chloro-5β-cholest-1-en-2-ol acetate (IVb), as in the case of 1β-bromoketone (Ia). IR (Film): 1761 and 1213 $cm^{-1}$, NMR: 5.48 (1H, m, W/2=7.5 Hz, $C_3$α-H), 4.58 (1H, s, $C_1$-H), 7.91 (3H, s, $C_2$-$OCOCH_3$).

In the reaction described above, an equilibrium was present between the 3α-(III) and 3β-haloketone (II) so that the primary product in these reactions could not be identified. From the results of the enolacetylation, however, it may be considered that the 3β-halo isomer was produced initially by cis migration.

Thus the rearrangement of the halogen of an α-haloketone in such a reaction could be demonstrated for the first time. This phenomenon is attributable to special properties of 1β-halo-5β-cholestan-2-one. An axial α-haloketone can easily epimerize to an equatorial isomer with hydrogen halide-acetic acid at room temperature, but the 1β-haloketone can not change to the 1α-isomer, probably because of the 1:3-interaction between the $C_1$-equatorial bond and the $C_9$-$C_{11}$ bond. On the other hand, the steric hindrance at the $C_3$-position is considerably less than that at $C_1$, and its position also has mobility. Consequently, the halogen in the 1β-haloketone may be forced to rearrange to the allylic position under the conditions.

On the basis of these results, it was found that the halogen in such a special stereochemical environment rearranges easily to the α'-position even in the case of an α-haloketone having a halogen on a secondary carbon atom.

We gratefully acknowledge financial support from the Ministry of Education.

## References

1) D. N. Kirk and M. P. Hartshorn, "Reaction Mechanisms in Organic Chemistry, Steroid Reaction Mechanisms", Elsevier Publ. Co., London, 1968, p. 385.
2) H. E. Zimmerman and A. Mais, J. Amer. Chem. Soc., 81, 3644 (1959).
P. Moreau, A. Casadevall, and E. Casadevall, Bull. Soc. Chim. France, 1969, 2013.
3) M. Gaudry and A. Marquet, Bull. Soc. Chim. France, 1967, 1849.
4) Y. Satoh, A. Horiuchi, and A. Hagitani, Bull. Chem. Soc. Japan, 43, 491 (1970).
5) The IR spectra were determined in KBr disk, and the NMR spectra were measured in deuteriochloroform (*: carbon tetrachloride) with tetramethylsilane as an internal standard. Their chemical shifts are presented in terms of τ values; s: singlet, t: triplet, q: quartet, m: multiplet.
6) Y. Satoh, T. Kimura, Y. Tajima, T. Takahashi, and A. Hagitani, Nippon Kagaku Zasshi, 90, 500 (1969).
7) J. Y. Satoh and T. T. Takahashi, Chem. Commun., 1970, 1714.

( Received August 19, 1972 )