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Author(s)	Kuniyoshi, Masayuki
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Study on the Reactions of Chromous Acetate with α, α'-Haloketo-steroids

Masayuki Kuniyoshi*

Synopsis

5α-cholestan-4-one and 3β-acetoxy-5α-cholestan-6-one were prepared via several synthetic pathways from cholesterol. They were further converted into dibromo-derivatives; 3α,5β-dibromo-4-oxo compound and 5α,7α-dibromo-6-oxo compound respectively, by treatment with bromine in acetic acid containing a trace of 47% boron trifluoride ethyl ether at room temparatur. While, chromous acetate was prepared from chromic chloride, zinc-amalgam and sodium acetate, and then its reactivity for the α,α'-dibrom-oketo-steroids discribed above was investigated. The reaction of chromous acetate with the dibromoketo-compounds in acetic acid-chloroform (3:1) solution gave the reductive debrominated products, i.e., monobromoketo-compounds (about 20-25%) and its parent keto-compounds (about 8-10%).

1. Introduction

Although numerous chromic salts have been utilized in organic syntheses, little has been investigated about chromous acetate[1]. We have been engaged in the study of a reductive dehalogenation of 5α- and 5β-polyhaloketo-steroids, which possess an oxo group on each position in ring A and B, by the chromous acetate. It has been reported[2] that 2α,4α-dibromo-5α-cholestan-3-one and 2β,4β-dibromo-5β-cholestan-3-one react with the chromous acetate in acetic acid to give the monobromo-keto-compounds, namely, 4α-bromo-5α-cholestan-3-one (78%) and 2β-bromo-5β-cholestan-3-one (60%), respectively. However, the reaction of other α,α'-halogenated keto-steroids with the chromous acetate has not yet been fully investigated. Therefore, we prepared the following dibromoketo-steroids; 3α,5β-dibromo-cholestan-4-one and 3β-acetoxy-5α,7α-dibromo-cholestan-6-one, and examined their reactions with the chromous acetate. The stereochemical structures of these obtained bromo derivatives were determined by the signs of the Cotton effect in optical rotatory dispersion (ORD), the shifts of C=O stretching bands in infra-red (IR) spectra, and the signal patterns of the nuclear magnetic resonance (NMR) spectra.

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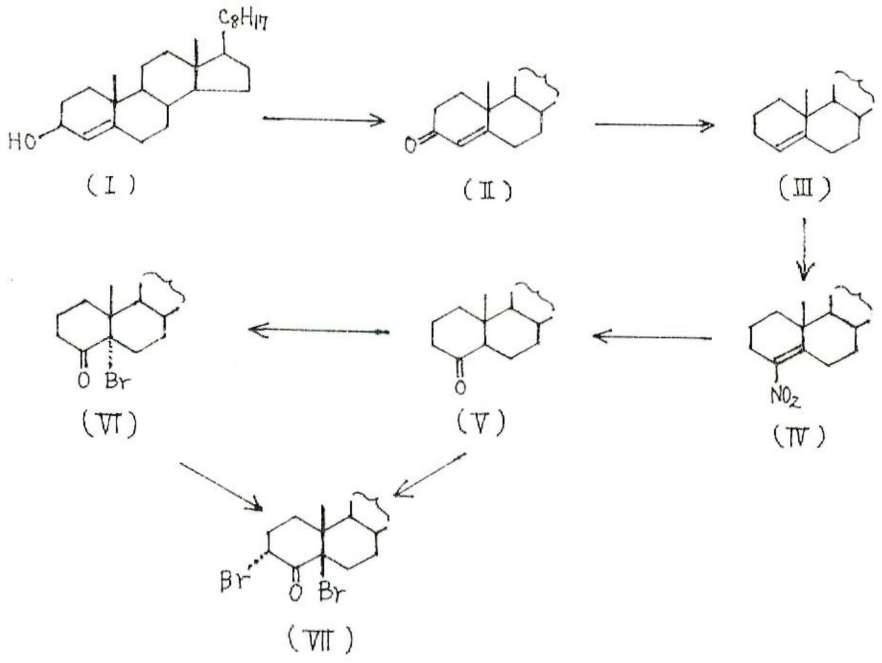
* Department of General Education, University of the Ryukyus.

2. Results and Discussion

As shown in scheme 1, 5α-cholestan-4-one (V) was prepared via several pathways from cholesterol. Moreover, the 3α,5β-dibromocholestan-4-one (VII); mp 109–110 °C, IR: 1728 cm^{-1} (νc=o), was prepared from the monobromoketo-compound (VI) by monobromination or directly from its parent keto-compound (V) by dibromination, that is, treating with two equivalent of bromine in acetic acid containing a trace of 47% boron trifluoride ethyl ether.



Scheme 1. Synthetic pathways of α,α'—Bromocholestan-4-one

The ORD spectrum (see Fig. 1) of the dibromoketone (VII) showed, in accordance with our prediction, a simple negative Cotton curve with the lst trough at (λ) 331 mμ and the NMR spectrum of this compound (VII) showed a double doublet due to the 3β-proton (1H, J=4Hz) at τ 5.82. The more detailed phisical data of VII will be presented in experimental section. Another dibromoketo-compound, i.e., 3β-acetoxy-5α,7α-dibromocholestan-6-one (IX), mp 151–152°C, IR: 1739, 1712cm^{-1} (νc=o), which was already reported in our previous paper[3], was also prepared. Chromous acetate was prepared from chromic chloride, zinc amalgam, and sodium acetate according to a modification of the procedure of Evans and his co-workers[4]. Above dibromoketo-compounds; VII and IX, reacted with chromous acetate at 10–15°C to give the corresponding dehalogenated compounds; VIII (25%), V (10%) and X (20%), XI (6%), respectively as shown in scheme 2. The ORD and the NMR spectrum of

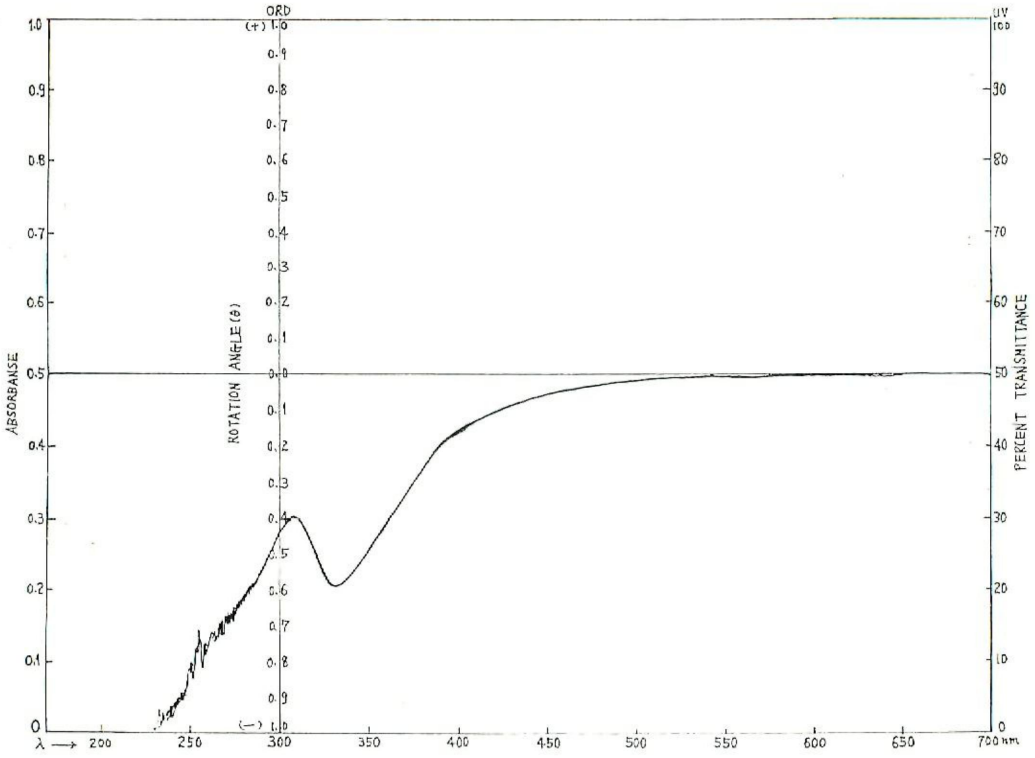
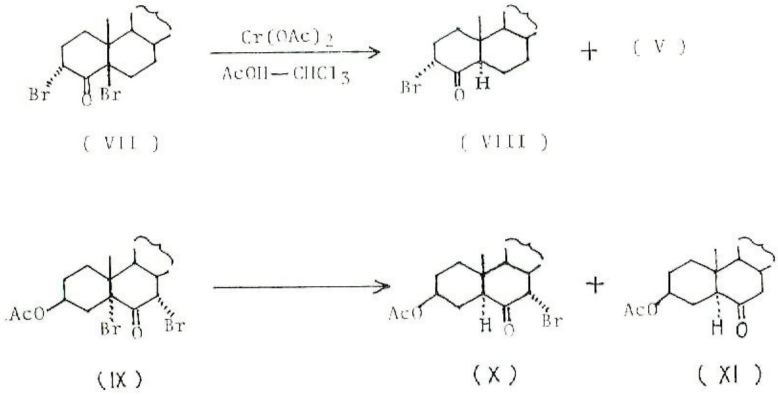


Fig. 1. ORD spectrum of 3α, 5β−Dibromocholestan-4-one
(C. 0.055 in dioxane at 22°C).



Scheme 2. Debrominations of VII and IX by Chromous Acetate

monobromoketo-compound (VIII), mp 117-118°C, are presented in the Fig. 2 and 3. The ORD spectrum of this compound (VIII) gave, in accordance with our expectation, a simple negative Cotton curve with the lst trough at (λ) 335 mμ, and the NMR spectrum showed a triplet due to the 3β-proton (1H, J=4Hz) at τ 5.71. The ORD and the NMR spectra of other compounds (X) and (VI) had been already reported in our previous paper[3].

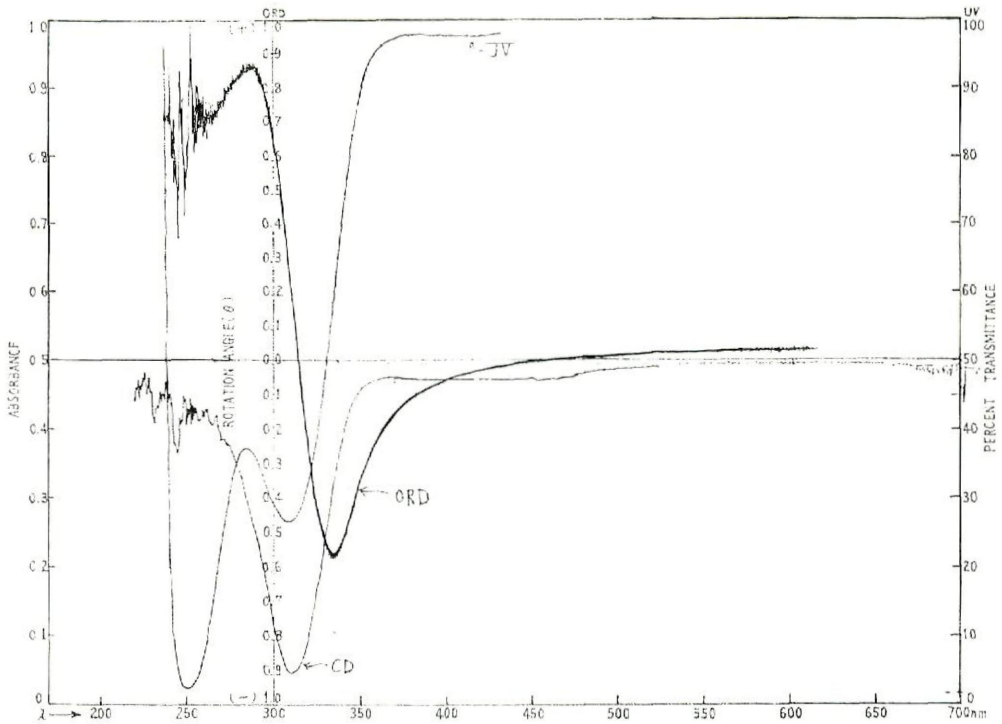


Fig. 2. ORD spectrum of 3α−Bromocholestan-4-one (C, 0.310, dioxane at 22°C)

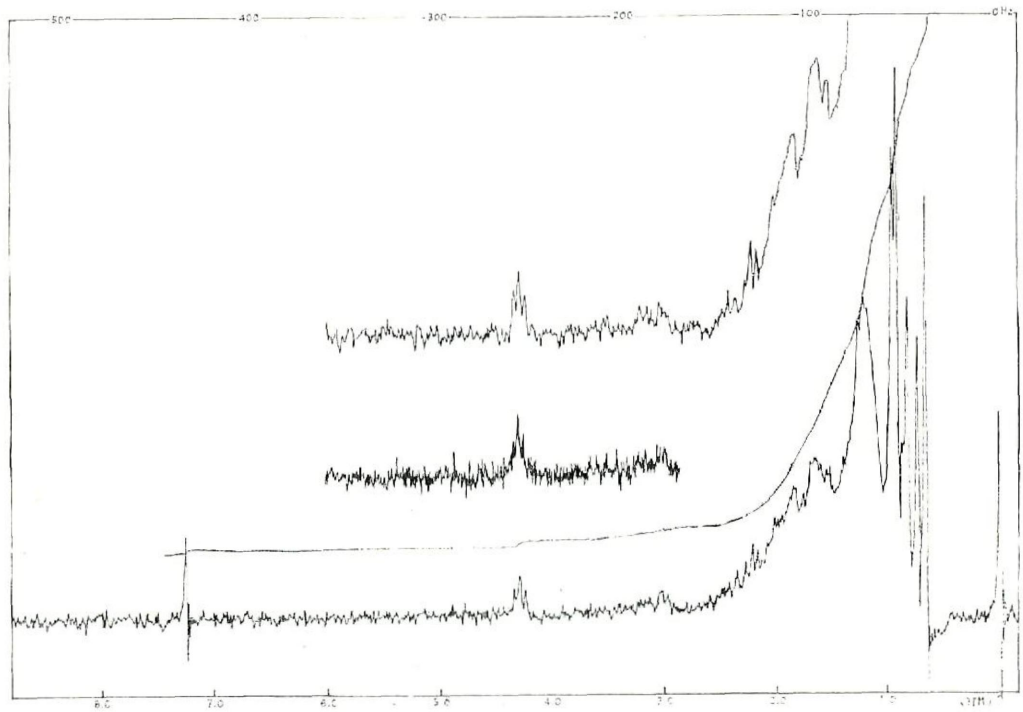


Fig. 3. NMR spectrum of 3α−Bromocholestan-4-one

When a few drops of butan thiol as hydrogen transfer agent was added to this dehalogenation reaction system, the formation of the dehalogenated monobromoketo-compound increased slightly.

From these results, it can be seen that the bromine (at C(5)-position) fixed on the tertiary-carbon is much more subject to the reductive dehalogenation reaction than the bromine (at C(3)- or C(7)-position) fixed on the secondarycarbon.

3. Experimental

Measurements. All melting points are uncorrected. The IR spectra and ORD spectra were measured with a Hitachi EPI-S-2 spectrophotometer in the region from 4000 to 650 cm^{-1} using the KBr disk and a JASCO model ORD/UV-5 spectrometer, respectively. The NMR spectra were measured in deutero-chloroform and carbon tetrachloride, with TMS as internal standard, using a Hitachi R-24 spectrometer. The mass (MS) spectra were obtained using Hitachi RMU-6L spectrometer. The each course of all reactions was monitored by thin layer chromatography (t.l.c.).

Cholest-4-en-3-one. According to the method of Eastham et al.[5], it was prepared by oxidation of cholesterol (0.26 mol.) in toluene solution (2 l.) with aluminum isopropoxide (0.14 mol.) as catalyst and cyclohexanone (500 ml.) as hydrogen acceptor. The mixture was heated with stirring, and a total of 900 ml. of toluene was distilled. Aqueous potassium-sodium tartrate was added to keep aluminum ion in solution, and the mixture was steam distilled until about 6 l. of distillate had been collected. The product was then collected by extraction with chloroform and crystallized twice to give cholest-4-en-3-one (II) (0.18 mol. 70%), mp 79–81°C, IR(KBr): 1679cm^{-1}($\nu_{C=O}$); MS: 384(M^+).

Cholest-4-ene. Lithium aluminum hydride–aluminum chloride reduction of II according to the method[6] of J.R. Bull et al., and crystallization from ethanol–hexane gave needles of cholest-4-ene (III) (about 50%), mp 83–84°C, IR(KBr): 1660 cm^{-1}($\nu_{C=O}$) and 805 cm^{-1} (δCH); NMR (CCl_4): τ 4.88(m, $W_{1/2}$=10Hz, C_4–H, 1H); MS: 370(M^+).

4-Nitro-cholest-4-ene. Following to our previous paper[3], it was prepared by adding 95% fuming nitric acid to the solution of III in absolute ether. After sterring for 2 hrs. at −7∼10°C, the reaction mixture was extracted with ether in the usual way. Washing, drying, evaporating and crystallization from ethanol gave needles of IV, mp 64–65°C, IR(KBr): 1517, 1360 cm^{-1} (ν_{NO_2}); MS: 415 (M^+). Found: C, 78.12; H, 9.98; N, 3.31%. Calcd. for $C_{27}H_{45}O_2N$: C, 78.07; H, 10.84; N, 3.37%.

5α-Cholestan-4-one and Its Bromination. The preparation and bromination of this ketone were worked up in a similar manner as discribed in our previous paper[3].

(a) Cholestan-4-one (V) crystallized from methanol, mp 97–98°C, IR(KBr): 1710 cm^{-1} ($\nu_{C=O}$); NMR (CCl_4): none signal in the vicinity of τ: 4.00 to τ: 7.00; ORD (C, 1.00, dioxane) at 22°C: $[\alpha]_{589}$+27, $[\alpha]_{307}$−560 (trough); MS: 368 (M^+).

(b) 5α-bromocholestan-4-one (VI) crystallized from methanol-acetone, mp 155–157

°C, IR(KBr): 1713 cm^{-1} ($\nu_{C=O}$); ORD (C, 0.01, di.) at 22°C: $[\alpha]_{332}$+1520 (peak), $[\alpha]_{288}$−1680 (trough).

(c) 3α,5β-dibromocholestan-4-one (VII) recrystallized twice from methanol-acetone, mp 109–110°C, IR(KBr): 1728cm^{-1}($\nu_{C=O}$), NMR ($CDCl_3$): τ5.82 (d.d., J=4Hz, C_3−H, 1F); ORD (C, 0.075, di.) at 22°C: $[\alpha]_{589}$−16, $[\alpha]_{331}$ −1730 (trough), $[\alpha]_{280}$+267 (peak), $[\alpha]_{257}$+199; MS: 544 (M^+), 546 (M+2), 548(M+4).

Found: C, 59.33; H, 8.05%. Calcd. for $C_{27}H_{44}OBr_2$: C, 59.56; H, 8.09%.

Reaction of Chromous Acetate with Dibromoketo-Compounds. On the preparation of chromous acetate, a modification[4] of the procedure of Evans and his co-workers was employed. The Jones' reductor (a 3 *cm*. diameter chromatography column filled to a height of 50 *cm*. with 20 mesh zinc which had been amalgamated with mercuric chloride) was filled with IN sulfuric acid. A solution of 3.28 g. (0.0207 mol.) of chromic chloride in 4.4 ml. of water containing 1.1 ml. of 2N sulfuric acid was run through the Jones' reductor, followed by water in such a way that the liquid level never dropped below the top surface of zinc. As soon as all the bright blue solution of chromous chloride had passed into the flask which was filled with absolute ether, the reducter was turned off and a solution of 9.2 g. (0.091 mol.) of anhydrous sodium acetate in 18 ml. of deoxygenated water was introduced into the flask from the dropping funnel without stirring, which resulted in the formation of large crystals of deep red chromous acetate. After 5 min., the solution was stirred by a magnetic stirring bar. The deep red precipitate was washed with 100 ml. portion of water; then with 50 ml. of ethanol and 50 ml. of ether. 0.01 mol. of dibromoketo-compounds, i.e., 3α, 5β-dibromo-cholest-4-one (VII) or 3β-acetoxy-5α, 7α-dibromocholest-6-one (IX), was added to this chromous acetate (0.02 mol.) dissolved in acetic acid-chloroform (3:1) solution. The reactions were carried out at 10–15°C under nitrogen, monitoring the course of the reaction by t.l.c. until the dibromoketo-compound's spot was no longer detectable on t.l.c., After stirring about 1 hr., the monobromoketo-compounds (VIII) or (X) and its parent ketone (V) or (XI) was respectively produced. The phisical properties of compound VIII was following: mp 117–118°C, IR(KBr): 1712cm^{-1}; NMR ($CDCl_3$): τ 5.71 (t., J=4Hz, C_3−H, 1H); ORD (C, 0.310, di.) at 22°C; $[\alpha]_{589}$+116, $[\alpha]_{400}$−174, $[\alpha]_{335}$−1655 (trough), $[\alpha]_{288}$ −2526 (peak); MS: 464 (M^+), 466(M+2). Found: C, 70.01; H, 9.76%. Calcd. for $C_{27}H_{45}OBr$: C, 69.83; H, 9.70%.

Addition of butan-thiol as hydrogen transfer agent to this reaction system was allowed to increase the formation of reductive dehalogenated monobromoketo-compound about a little over 10%.

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