Reduction of Dihaloketo-Steroids by Chromous Acetate

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Synopsis

The reaction of chromous acetate with many kinds of 5α- and 5β-dihaloketo-steroids, which possess an oxo group on each position in ring A and B, was investigated. gem-Dihaloketones were reduced rapidly with chromous acetate in acetic acid-chlorofrm solution to give corresponding monohaloketones, accompanyed further reduced products, parent ketones. α, α'-Dihaloketones were also dehalogenated reductively to monohaloketones and small amount of parent ketones. The relative yields of reduced products varyed with the structure of dihaloketones and slightly on the mode of reaction. Several new products were also obtained. The reactivity of dihaloketones toward chromous acetate decreased in the following order: gem-dihaloketones > α, α'-dihaloketones, axial-halogen > equatorial-halogen, and bromides > chlorides.

1. Introduction

Although chromous acetate have been utilized in organic syntheses as a useful reducing agent for a variety of organic compounds, only little information on application of its reagent to haloketo-compounds is found in the literature. This reagent has been received considerable attention for removing halogen from organic halides, especially for synthetic purposes in steroid and alkaloid systems[1] since the use of this reductant gives usually saturated compounds whereas other classical reducing agents,[2] such as zinc dust or ferrous, titanous, stanous, vanadous, calcium and sodium salts, sometimes gives the unsaturated compounds in relative poor yield.

A. Wilds and C. Djerassi[3] has been reported that 2α, 4α-dibromo-5α-cholestan-3-one (14) react with chromous acetate in acetic acid to give monobromoketo compound, i. e., 4α-bromo-5α-cholestan-3-one (15), in 78 % yield. On the other hand, it has been reported by J. Y. Satoh et al.[4] that 2β, 4β-dibromo-5β-cholestan-3-one (20) is reduced with chromous acetate to produce

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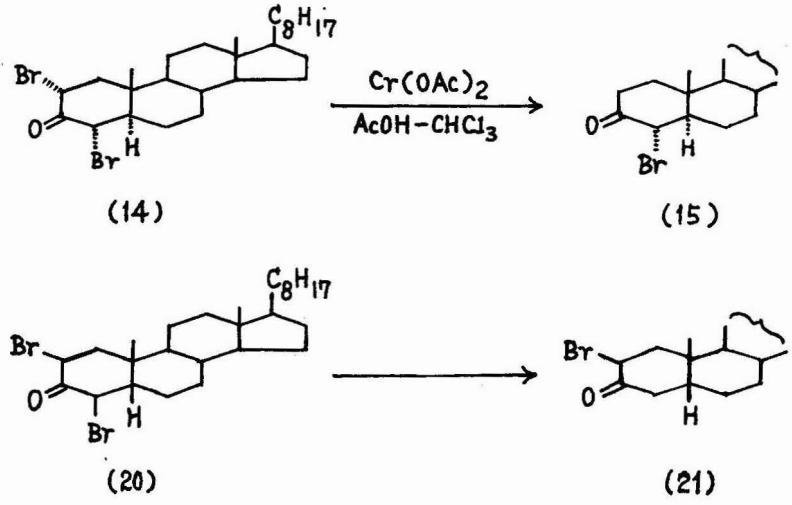
2β-bromo-5β-cholestan-3-one (21) in good yield. It is very interesting that the reductive dehalogenation of the former take place at the symmetrical C-2 position, not C-4, with respect to carbonyl group, in contrast with the latter case which occurs at the C-4 position, not C-2 (see scheme 1).



Scheme 1. $Cr(OAc)_2$ reduction of 2, 4-Dibromo-5α- and -5β-Cholestan-3-one.

However, the dehalogenation reaction of other α, α'-dihaloketosteroid compounds by means of the chromous acetate has not yet been fully investigated. Therefore, in order to study these matter, the author prepared the many kinds of 5α- and 5β-dihaloketosteroids via several synthetic pathways from cholesterol, and examined their reactions[5] with the chromous acetate.

This paper will describe the relative reducing facility among several types of 5α- and 5β-dihaloketostosteroids. Furthermore, some reaction mode for the purpose of increasing the yields of reduced products also will be reported. The mixed solvent of acetic acid and chloroform was employed throughout the present work because of the favorable solubility of the chromous acetate and haloketosteroids, and of the easy observance of a blue to green color change attendant upon the oxidation of chromous ion.

2. Results and Discussion

Reduction of gem-Dihaloketones by Chromous Acetate gem-Dihaloketones are readily reduced in acetic acid-chloroform solution for~20 minutes by freshly prepared chromous acetate to produce the corresponding

Table 1. Reaction of $Cr(OAc)_2$ with gem-Dihaloketones

Haloketone*a	Conformation of Halogen	Product*b	Conformation of Halogen	Yield
2, 2-diCl-3-one (1)	ax. eq.	2α-Cl-3-one (2)	eq.	
5α: 2α-Cl-2β-Br-3-one (3)	ax. eq.	2α-Cl-3-one (2)	eq.	~65%
2α-Br-2β-Cl-3-one (4)	ax. eq.	2α-Br-3-one (5)	eq.	
5β: 4, 4-diCl-3-one (6)	ax. eq.	4β-Cl-3-one (7)	eq.	60%

$Cr(OAc)_2$, 0.05 mol; haloketones, 0.01 mol; rection time, 10-20 min; solvent, acetic acid-chloroform (2:1) solution.

*a All haloketones are dihalogen derivatieves of 5α- and 5β-cholestan-3-one.

*b Other products were mainly parent ketone and small amount of unknown compounds.

monohaloketones in fairly good yields, as is shown in Table 1. In these reaction the chromous acetate was taken in large excess since using the theoretical amount of its reagent the yields was only 20%. It is clear from Table 1 that the conformations of halogen in the produced monohaloketones are all equatorial form, nothing about axial form. The reduction of 2α-chloro-2α-bromo-5α-cholestan-3-one (3) and 2α-bromo-2β-chloro-5α-cholestan-3-one (4)[6], which are in relation of epimer with each other, result in 2α-chloro-5α-cholestan-3-one (2) and 2α-bromo-5α-cholestan-3-one (5) respectively. These results suggest that axial halogen in the gem-haloketones is dehalogenated in preference to equatorial halogen.

The relative amounts of monohaloketone and parent ketone were somewhat dependent on the order of addition of reagents. When chromous acetate is added to a solution of 2, 2-dichloro-5α-cholestan-3-one (1), 2α-chloro-5α-cholestan-3-one (2) is formed in good yield (~65%) as shown in Table 1, accompanying small amount of 5α-cholestan-3-one(~20%). If a reverse procedure is carried out, that is, (1) is added to chromous acetate in solution, the relative yield of 5α-cholestan-3-one (~30%) is increased owing to further reduction of (2) (~55%).

The observed yields were also slightly affected by the reaction temperature. At high temperature (60℃), the amount of parent ketone was increased a little (~5%) relative to that at room temperature.

Reduction of α, α'-Dihaloketones by Chromous Acetate Although not so fast as the reduction of gem-dihaloketones in the preceding section, that of α, α'-dihaloketones proceeds easily at room temperature and affords corresponding monohaloketones, as shown in Table 2. Usually, the 5α-series haloketo compounds were reduced in good yield more than the corresponding 5β-series compounds.

The same results were also obtained substantially by other chromous salts of sulfate or chloride whereas $FeCl_2$, CuCl, and $TiCl_3$ almost in poor

Table 2. Reaction of $Cr(OAc)_2$ with α, α'-Dihaloketones

	Haloketone*a	Conformation of Halogen	Product*b	Conformation of Halogen	Yield
	$1\alpha, 3\beta$-diBr-2-one (8)	ex. eq.	3βBr-2-one (9)	eq.	
	$1\alpha, 3\alpha$-diBr-2-one (10)	ex. ax.	3αBr-2-one (11)	ex.	~70%
			1αBr-2-one (12)	ex.	
	$2\alpha, 4\alpha$-diBr-3-one (14)	eq. eq.	4αBr-3-one (15)	eq.	
5α:	2αCl-4α Br-3-one (16)	eq. eq.	2αCl-3-one (17)	eq.	~75%
	$2\alpha, 4\alpha$-diCl-3-one (18)	eq. eq.	4αCl-3-one (19)	eq.	
	3β-acetoxy-$5\alpha, 7\alpha$-diBr-6-one (28)	ax. ax.	3β-acetoxy-7αBr-6-one (29)	ax.	~45%
	$5\alpha, 7\beta$-diBr-6-one (30)	ex. eq.	7βBr-6-one (31)	eq.	
	$1\beta, 3\alpha$-diBr-2-one (13)	ax. eq.	3αBr-2-one (11)	eq.	~60%
	$2\beta, 4\beta$-diBr-3-one (20)	ep. eq.	2βBr-3-one (21)	eq.	
5β:	2β Br-4β Cl-3-one (22)	eq. eq.	4βCl-3-one (23)	eq.	~65%
	$2\beta, 4\beta$-diCl-3-one (24)	eq. eq.	2βCl-3-one (25)	eq.	
	$3\alpha, 5\beta$-diBr-4-one (26)	eq. ax.	3αBr-5α-4-one(27)	ax.	40%
	$6\alpha, 11\alpha$-diBr-7, 12-dione(32)	eq. eq.	11αBr-7, 12-dione(33)	eq.	50%

$Cr(OAc)_2$, 0.05 mol; haloketones, 0.01 mol; reaction time, 30-50 min; solvent, acetic acid-chloroform (2:1) solution.

*a All haloketones are dihalogen derivatives of 5α- and 5β-cholestanones except that the compound (32) is derived from methyl 3α-hemisuccinyloxy-7, 12-diketocholanate.

*b Other products were mainly parent ketone and small amount of unknown compounds.

yield. From the reduced products of axial-equatorial-dihalogenated compounds, i.e., 1α, 3β-dibromo-5α-cholestan-2-one (8), 5α, 7β-dibromo-5α-cholestan-6-one (30), 1β, 3α-dibromo-5β-cholestan-2-one (13) and 3α, 5β-dibromo-5β-cholestan-4-one (26), it was found that axial halogen was dehalogenated more readily than equatorial halogen as same as observed in gem-dihaloketones.

1α, 3α-dibromo-5α-cholestan-2-one (10), axial-axial-dibromoketo compound is reduced to 3α-bromo-5α-cholestan-2-one (11) and 1α-bromo-5α-cholestan-2-one (12) in about 2 : 1 ratio. In the case of 3β-acetoxy-5α, 7α-dibromo-6-one (28) the axial bromine atom (at C-5 position) fixed on the tertiary-carbon is attacked more easily than the axial bromine (at C-7 position) on the secondary-carbon. Furthermore, it can be seen from the results of Table 2 that, in the equatorial-equatorial-dihalo (Br or Cl)-5α-cholestan-3-one derivatives; (14) and (18), the halogen at C-2 position is more exclusively subject to the reductive dehalogenation reaction than the halogen at C-4 position, but in the 5β-3-one derivatives; (20) and (24), the halogen at C-4 position is preferentially reduced. However, in the bromo-chloro-3-one derivatives; (16) and (22), the bromine atom is at first reduced more easily. Commonly, it is well known[7] that in the halogenation of normal ketones enol form is intermediate and in the 5α-3-one series compounds enolization toward C-2 position is favored, while in 5β-series compounds enolization toward C-4 position predominates. Consequently, it is possible to draw the following matter; in the reduction of equatorial-equatorial-dihalo(Br or Cl) -3-ketone, the halogen (at the position of preferable direction for enolization), which is initally introduced in halogenation of the corresponding parent ketone, is attacked more easily than the halogen at another position. Moreover, this matter is also supported by the other reduced products of 2-one, 4-one, 6-one and 7, 12-dione derivatives, as shown in Table 2. The compounds obtained in the present work; (18) (19) (31) (22) (23) (24) (25) (32) and (33), are all new compounds, and the conformation and configuration of these new compound structures were determined by means of signs of the Cotton effect in optical rotatory dispersion (ORD) spectra, the shifts of C=O stretching bands in infra-red (IR) spectra, the signal patterns of nuclear magnetic resonance (NMR) spectra, and the fragmentation patterns of mass (MS) spectra. Conserning this work, however, the author would like to discuss in next paper, together with the further report regarding preparation and dehalogenation of trihaloketo compounds. Although J. K. Kochi[8] and C. E.

Castro et al.[9] have reported kinetic data demonstrating that chromium (II) dehalogenates reductively alkyl halide like allyl or benzyl chloride, we cannot, in the present situation, describe the mechanism of the reaction since our experiments are undertaken only qualitatively.

3. Experimental

Measurements. Thin-layer chromatography (t. l. c.) was carried out on Wakogel B-5, and detected by sulfuric acid. IR spectra were measured(KBr) with a Hitachi model EPI-S-2 infrared spectrophotometer. ORD spectra were obtained in dioxan with JASCO model ORD/UV-5 instrument. NMR spectra were recorded in carbon tetrachloride or deutero-chloroform with tetramethylsilane as an internal standard using a Hitachi R-24 spectrometer. The mass spectra were obtained using Hitachi RMU-6L instrument.

Reagents. On the preparation of chromous acetate, as described in our previous paper,[10] a modification of the procedure of Evans and his co-workers was employed. The chromous sulfate was prepared by reducing an aqueous solution of chromic sulfate with zinc powder.[11] The chromous chloride was prepared with chromic chloride and amalgamated zinc as described by G. Rosenkranz et al.[12] The ferrous, cuprous and titanous chloride were obtained from Wako Pure Chemical Industries Ltd.

Dihaloketones. The preparations of these haloketones were worked up by deriving from cholesterol or cholic acid in a similar manner as described in previous paper.[10]

Reduction of Dihaloketones by Chromous Acetate. To dihaloketones (0.01 mol) disssolved in acetic acid-chloroform (2:1) solution, freshly prepared chromous acetate (0.05 mol) was added. The reactions were carried out at room temperature under nitrogen atmosphere, monitoring the course of the reaction until the starting dihaloketone's spot was no longer detectable on t. l. c. The reaction mixture was then hydrolyzed with water. The products were collected by extraction with ether and isolated into each components by preparative t. l. c. (20x20cm) and/or column chromatography on silicagel.

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