5α—及び5β—コレスタン—3—オンの塩素化ならびに脱塩素化反応生成物

Chlorination and Dechlorination Products of 5α- and 5β-Cholestan-3-one

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Abstract

5α- and 5β-Cholestan-3-one derived from cholesterol were chlorinated under several reaction conditions. Depending on the reaction conditions, many kinds of chlorinated products were obtained. α, α'-Dichloroketo compounds (V, XI) could be easily prepared by dechlorination of the corresponding trichoroketones (IV, X) with chromium (II) acetate. Further dechlorination of the dichloroketones with the same reagent furnished α-monochloroketones (VI, XII) which could not be obtained by the direct monochlorination.

1. Introduction

Many groups[1-8] in the field of steroid chemistry have investigated bromination of ketosteroids as a simple and effective mothod for the functionalization of steroidal skeletones, and the stereochemistry of the brominated products has well been established. On the chlorination reaction, however, a few existing literatures[9-12] describe only mono- and dichlorination of 5α-ketosteroids. In the previous papers[13-14] we have reported the halogenation and dehalogenation reactions of various ketosteroids. In the extention of these works, we could successfully prepare 4α-chloro-5α-cholestan-3-one (VI) and 2β-chloro-5β-cholestan-3-one (XII) which are otherwise difficult to obtain by direct monochlorination of the parent ketones. In this paper, the author will describe the syntheses of these compounds together with some new polychloro derivatives which conformational assighments also discussed by means of IR, NMR, MS and ORD spectra.

Results and Discussion

Treatment of 5α-cholestan-3-one (I) with an excess of potassium chlorate in the solution of dioxane-30% aqueous sulfuric acid at 45° for 24 hr furnished 2,2,4α-trichloro-5α-cholestan-3-one (IV) in 43.1% yield. Similarly, 2β, 4, 4-trichloro-5β-cholestan-3-one (X) was obtained in 40.2% yield from 5β-cholestan-3-one (VII). Both compounds showed molecular ions at m/z 488 and characteristic istope peaks of the compounds containing three chlorine atoms. ^{1}H n. m. r. spectra of (IV) and (X) revealed signals at 4.50 (d, J 12.8 Hz, 1H, C(4)β-H) and 5.14 (dd, J 5. 2, 14.5 Hz, 1H, C(2)α-H), respectively, attributable to the protons attached to the carbons bearing chlorine atoms. These results clearly indicated the structures of (IV) and (X) as shown in Scheme 1.

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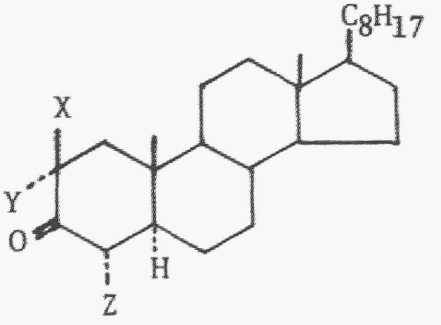
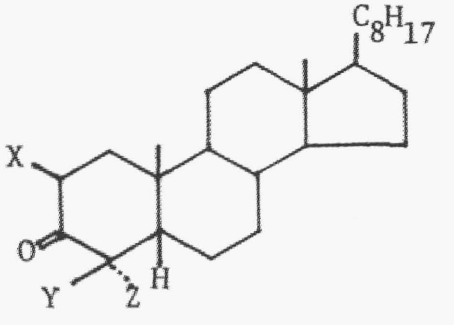


(Ⅰ) X=Y=Z=H
(Ⅱ) X=H, Y=Cl, Z=H
(Ⅲ) X=Y=Cl, Z=H
(Ⅳ) X=Y=Z=Cl
(Ⅴ) X=H, Y=Z=Cl
(Ⅵ) X=Y=H, Z=Cl



(Ⅶ) X=Y=Z=H
(Ⅷ) X=H, Y=Cl, Z=H
(Ⅸ) X=H, Y=Z=Cl
(Ⅹ) X=Y=Z=Cl
(Ⅺ) X=Y=Cl, Z=H
(Ⅻ) X=Cl, Y=Z=H

Scheme 1. Chlorination and Dechlorination of 5α- and 5β-cholestan-3-one.

Since this chlorination reaction proceeds stepwise, the intermediates, monochloro and gem-dichloro derivatives can be easily obtained by monitoring the reaction progress with t. l.c. Therefore, 2,2-dichloro-5α-cholestan-3-one(Ⅲ)[12] and 4,4-dichloro-5β-cholestan-3-one(Ⅸ) were prepared in 87.5% and 79.1% yield, respectively, by quenching the reaction in 4-5 hr. These dichloro compounds could also be prepared by reacting the parent ketones with stoichiometric amounts of chlorine. Both(Ⅲ)and(Ⅸ)showed molecular ion clusters at m/z 454 (M^+, relative-intensity 100%), 456 (M+2, 65.2), 458(M+4, 9.5), indicating the presence of two chlorine atoms. However, the absence of ^1H n.m.r. signals due to -CHCl- in both compounds demonstrated that the two chlorine atoms were geminal. It is noteworty that dichlorination always results in only gem-dichloro derivatives from both parent ketones(Ⅰ, Ⅶ), while dibromination of the katones mainly afford 2,4-dibromo compounds.[3,4] In this case it is

suggested by the authors[15] that initially formed gem-dibromo compounds, which usually isolated by kinetically controlled bromination in the presence of a large excess of potassium acetate, rearrange to 2,4-dibromo derivatives under acidic conditions. Indeed this rearrangement could be observed by acid treatment of the formers.[16,17] However, the treatment of gem-dichloro compounds (III) or (IX) under the same conditions did not undergo the expected rearrangement to furnish 2,4-dichloro derivatives. This obviously different behavior between gem-dibromo- and gem-dichloroketosteroids can probably be explained in terms of the difference of carbon-halogen bond strength and also the difference of halogen-halogen steric repulsion between gem-dibromo and gem-dichloro compound.

In this study, it was found that α, α'-dichloroketones (V, XI) can be prepared selectively from the correspondiog α,α,α'-trichloroketones (IV, X) by reductjve dehalogenation using chromium(II) acetate under nitrogen atmosphere as reported in our previous papers.[13-14] The optical rotatory dispersion of these α,α'-dichloroketones did not change the nature of Cotton effect from those of the parent ketones, but the first maximum peaks shifted toward shorter wavelength region. Considering the α-haloketone rule,[18] these results suggests that both chlorine atoms are equatorial (α-oriented in V, and β-oriented in XI). The ^{1}H n.m.r. spectrum of (V) showed peaks due to the proton attached on the carbon bearing a chlorine atom at δ 4.21 (d, J 13.6 Hz, 1H, C(4) β-H) and 4.37 (dd, J 4.8, 13.5 Hz, 1H, C(2) β-H). The ^{1}H n.m.r. spectrum of (XI) showed peaks at δ 4.67 (dd, J 6.0, 14.2 Hz, 1H, C(2)α-H) and 4.93(d, J 12.0 Hz, 1H, C(4)α-H). Accordingly, these dichloroketones were determined to be 2α-dichloro-5α-cholestan-3-one (V) and 2β, 4β-dichloro-5β-cholestan-3-one (XI), respectively. These stereochemical assignments were further supported by reasonableness of the diheadral angles calculated based on Abraham's equation[19] from the values of coupling constant(J) of -CHCl- protons in ^{1}H n.m.r. spectra, and by the observation of the carbonyl absorption bands which shifted toward higher wave number region[20] ($\triangle\nu = 35-37\,cm^{-1}$) in the IR spectra, relative to that of the parent ketones. Uulike the α,α'-dibromo analogues, these α,α'-dichloroketones could not be obtained directly from chlorination reaction of the parent ketones.[21]

Further dechlorination of (V) and (XI) furnished monochloro derivatives (VI)and (XII) which are otherwise difficult to prepare, because direct monochlorination of (I) and (XII) always occurs at the opposite position in respect to the carbonyl groups as shown in Scheme 1. Thus, - treatment of (V) with chromium(II) acetate at room temperature for about 50 min. under nitrogen atmosphere, monitoring the reaction by t.l.c., gave 4α-chloro-5α-cholestan-3-one (VI), while the same reaction of (XI) afforded 2β-chloro-5β-cholestan-3-one (XII). The optical rotatory dispersion spectrum of the monochloroketone (VI) showed a positive Cotton effect curve and a blue shift ($\triangle\lambda = 6$ nm) from that of the parent ketone. The ^{1}H n.m.r. spectrum showed a doublet at δ4.12 (J 12.5 Hz, 1H) due to -CHCl-. It's IR spectrum had a carbonyl absorption band (1735cm^{-1}) at higher wave number region relative to that (1713cm^{-1}) of the parent ketone. Moreover, its mass spectrum exhibited a molecular ion peak (M^+) at m/z 420, and a characteristic isotope ion peak at m/z 422(M+2). From these data, it was concluded that this compound (VI) was 4α-chloro-5α-cholestan-3-one. While the monochloroketone (XII) was determmined to be 2β-chloro-5β-cholestan-3-one by the sign of the negative Cotton effect in

optical rotatory dispersion spectrum, the shift of a carbonyl absorption band (1738cm^{-1}) in the IR spectrum, and the signal at δ3.34 (dd, *J* 6.0, 12.2 Hz, 1H) attributable to -CHCl- in ^{1}H n. m.r. spectrum.

Experimental

All the melting points were taken on a Yanaco model MP-J3 micro-melting points apparatus and uncorrected. Thin-layer chromatography was carried out on Wakogel B-5 (Wako Pure Chemical Industries Ltd.), and visualized with iodine or an o-phenylenediamine-ethanol solution. The IR spectra were measured as KBr disks using a Hitachi EPI-S-2 Grating Spectrophotometer. The Optical Rotatory Dispersion spectra were obtained in dioxane with a JASCO model ORD/UV-5 instrument. The ^{1}H n.m.r. spectra were recorded in carbon tetrachloride or deuterochloroform with tetramethylsilane as an internal standard, using either a JOEL model JNM-4H-100 or a Hitachi model R-24 (60 MHz) Spectrometer. The mass spectral measurement were performed by Mr. M. Higa on a Hitachi model RMU-6L Spectrometer at 70 eV.

2,2,4α-Trichloro-5α-cholestan-3-one (IV)

A mixture of 5α-cholestan-3-one (I) (2.0 g) and potassium chlorate[22] (4.50 g) in 10:1 mixture (100 ml) of dioxane and 30% surfuric acid was stirred at 45° overnight. The reaction mixture was neutralized by po pouring into ice-cold saturated sodium bicarbonate solution, and extracted with ether (3 x 200 ml). The ethereal solution was successively washed with water (3 x 100 ml) and saturated sodium chloride solution (3 x 100 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The resultant oil was purified on a silica gel (150 g) column. Elution with 10:1 pertoleum ether-benzene (3500 ml) gave a colorless oil. Three crystallizations from methanol-acetone afforded 1.09 g (43.1%) of (IV) as white needles, m.p. 115-117°. ν_{max}:1760 (C=0), 882 (C-Cl) cm^{-1}. ^{1}H n.m.r.: δ($CDCl_3$)4.50 (d, *J* 12.8 Hz, 1H, C(4) β-H). O R D.: (c 0.301) at 22°; $[\alpha]_{589}$ +125.8°, $[\alpha]_{350}$ +850.0°, $[\alpha]_{322}$ +1972° (peak), $[\alpha]_{288}$ −918.3°(trough). Mass spectrum: m/z 488 (M^+, relative intensity 100%), 490(M+2, 98.6), 492 (M+4, 30.8), 494(M+6, 3.1).(Found: C, 66.30; H, 8.56. $C_{27}H_{43}OCl_3$ requires C, 66.19; H, 8.78%). This compound was identical with a sample obtained by monochlorination of 2,2-dichloro-5α-cholestan-3-one (III).

2β,4,4-Trichloro-5 β-cholestan-3-one (X)

A mixture of 5β-cholestan-3-one (VII) (1.80 g) and potassium chlorate (4.10 g) in 10:1 dioxane-30% sulfuric acid solution (90 ml) was strirred at 45° overnight. After the usual work-up, the result oil (1.65 g) was chromatographed on silica gel. Elution with 10:1 n-hexane-benzene (2500 ml) gave 915 mg (40.2%) of colorless oil which upon recrystallization from methanol-acetona furnished white needles, m.p. 118-120°. ν_{max}:1766, 873cm^{-1}. ^{1}H n.m.r.: δ(CCl_4) 5.14 (dd, *J* 5.2, 14.5 Hz, 1H, C(2)α-H). O.R.D.: (c 0.769) at 21°; $[\alpha]_{589}$ + 31.9°, $[\alpha]_{350}$ +279.5°, $[\alpha]_{312}$ + 702.3° (peak). Mass spectrum: m/z 488 (M^+, relative intensity 100%), 490(M+2, 95.5), 492(M+4, 30.0), 494(M+6, 2.8).(Found:C, 65.98;H, 8.94. $C_{27}H_{43}OCl_3$ requires C, 66.19; H, 8.78%).

This compound was identical with a sample prepared by further monochlorination of the reaction product (9).

4β-Chloro-5β-cholestan-3-one (Ⅷ) and 4,4-Dichloro-5β-cholestan-3-one (Ⅸ)

A mixture of 1.80 g of (Ⅶ) and $KClO_3$ (1.65 g) in 10:1 dioxane-30% sulfuric acid solution (90 ml) was heated at 45° for about 50 min. and worked up in the same manner to furnish 1.77 g (90.4%) of 4β-chloro-5β-cholestan-3-one (Ⅷ).

As an alternative method, to a solution of 1.29 g (3.33 mmol) of 5β-cholestan-3-one (Ⅶ) in ml chloroform was added 0.26 g (3.67 mmol) of chlorine in 2 ml glacial acetic acid. The reaction mixture was stirrred for 30 min., poured into ice-cold water, and then extracted with ether (3 x 200 ml). The etherial solution was washed, dried, and evaporated under reduced pressure. The residue was crystallized twice from menthanol-acetone to yield 1.20 g (85.5%) of (Ⅷ) as white prisms, m.p. 123-125°. υ_{max}: 1735, 845 cm^{-1}. ^1H n.m.r.: ($CDCl_3$) 4.65 (d, J 12.0 Hz, 1H, C(4)α-H). O.R.D.: (c 0.637) at 20.5°; $[\alpha]_{589}$ +39.3°, $[\alpha]_{400}$ +41.4°, $[\alpha]_{305}$ −75.5° (trough), $[\alpha]_{294}$ +133.2° (shoulder). Mass spectrum: m/z 420(M^+, relative intensity 100%), 422 (M+2, 29.8). (Found: C, 77.21; H, 10.83. $C_{27}H_{45}OCl$ requires C, 77.05; H, 10.70%).

Further chlorination of the compound (Ⅷ) with $KClO_3$ under the same conditions (at 45° for 4-5 hr) gave 4,4-dichloro-5β-cholestan-3-one (Ⅸ) which was identical with a sample prepared by direct dichlorination of parent ketone (Ⅶ). Recrystallization from methanol-acetone gave white plates in 79.1% yield, m. p. 92-93°. υ_{max}: 1748, 850cm^{-1}. O.R.D.: (c 0.631) at 21.0; $[\alpha]_{589}$ +31.7°, $[\alpha]_{410}$ +53.9°, $[\alpha]_{315}$ +101.5° (peak), $[\alpha]_{269}$ +80.8° (trough). Mass spectrum: m/z 454 (M^+, relative intensity 100%), 456 (M+2, 65.2), 458 (M+4, 9.5). (Found: C, 71.30; H, 9.42. $C_{27}H_{44}OCl_2$ requires C, 71.21; H, 9.67%).

2α,4α-Dichloro-5α-cholestan-3-one (Ⅴ) and 4α-Chloro-5α-cholestan-3-one (Ⅵ)

To a solution of 2,2,4α-trichloro-5α-cholestan-3-one (Ⅳ) (976 mg) in 10 ml chloroform and 18 ml acetic acid, freshly prepared chromium(II) acetate (1.7 g) was quickly added under nitrogen atmosphere. The end point of the recation was cheked by t.l.c. After stirring for about 30 min., the dark slurry was taken up in ether (600 ml) and neutralized by pouring into ice-cold saturated sodium bicarbonate solution. The ether layer was successively washed with water (3 x 100 ml) and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The resultant oil was chromatographed on silica gel with a n-hexane-benzene gradient. Elution with 10:3 n-hexane-benzene afforded 230 mg (25.3%) of (Ⅴ) as white needles, m.p. 131-134°, after recrystallization from methanol-acetone. υ_{max}: 1749, 866 cm^{-1}. ^1H n.m.r.: δ($CDCl_3$) 4.21(d, J 13.6 Hz 1H, C(4)β-H), 4.37 (dd, J 4.8, 13.5 Hz, 1H, C(2)β-H). O.R.D.: (c 0.201) at 22.0°; $[\alpha]_{390}$ +71.3°, $[\alpha]_{308}$ +532.5° (peak), $[\alpha]_{270}$ −285.2° (trough). Mass spectrum : m/z 454 (M^+, relative intensity 100%), 456 (M+2, 63.5), 458 (M+4, 9.2). (Found: C, 71.02; H, 9.55. $C_{27}H_{44}OCl_2$ requires C, 71.21; H, 9.67%).

Further dechlorination of (Ⅴ) (90 mg) under the same conditions gave 38 mg (45.6%) of 4α-chloro-5α-cholestan-3-one (Ⅵ) as an amorphous solid which could not be crystallized. υ_{max}: 1735 cm^{-1}. ^1H n.m.r.: δ(CCl_4) 4.12 (d, J 12.5 Hz, 1H C(4)β-H). O.R.D.: (c 0.762) at 20.5°; $[\alpha]_{589}$ +

78.0°, $[\alpha]_{350}$ +686.6%°, $[\alpha]_{311}$ +1779° (peak), $[\alpha]_{279}$ −561.8° (trough). Mass spectrum: m/z 420 (M^+, relative intensity 100%), 422 (M+2, 30.5).

2β, 4β-Dichloro-5β-chlestan-3-one (II) and 2β-Chloro-5β-cholestan-3-one (VII)

The dichloroketone (II) was prepared from corresponding trihaloketone (X) by treatment with chromium(II) acetate as mentioned above. The reaction mixture was worked up in the usual manner. The resulting oil was prrified by eluting on silica gel column with a n-hexane-benzene gradient and crystallized from methanol-carbon tetrachloride to give (II) in 16.5% yield as white needles, m.p. 138-140°. ν_{max}: 1752, 870 cm^{-1}. ^1H n.m.r.: $\delta(CCl_4)$ 4.67 (dd, J 6.0, 14.2 Hz, 1H, C(2)α-H), 4.93 (d, J 12.0 Hz, 1H, C(4)α-H). O.R.D.: (c 0.668) at 21.0°; $[\alpha]_{400}$ + 30.1°, $[\alpha]_{350}$ +34.9°, $[\alpha]_{303}$ −83.3° (trough). Mass spectrum: m/z 454 (M^+, relative intensity 100%), 456 (M+2, 60.7), 458 (M+4, 8.7).(Found : C, 71.73; H, 9.88. $C_{27}H_{44}OCl_2$ requires C, 71.72; H, 9.67%).

Further dechlorination of (II) (303 mg) was carried out by using the technique described above. After usaual work-up, a colorless oil (XIII) was obtained. The amorphous product was purified by eluting on a silica gel column with 2:1 n-hexane-benzene. Several attempts to crystallize the product from methanol-carbon totrachloride finally gave 34 mg (12.6%) of (VII) as white needles, m.p. 112-114°. ν_{max}: 1738, 846 cm^{-1}. ^1H n.m.r.: $\delta(CDCl_3)$ 4.34 (dd, J 6.0, 12.2 Hz, 1H, C(2)α-H). O.R.D.: (c 0.622) at 21.5°; $[\alpha]_{500}$ +56.3°, $[\alpha]_{450}$ +54.4°, $[\alpha]_{305}$ −64.4° (trough). Mass spectrum : m/z 420 (M^+, relative intensity 100%), 422 (M+2, 32.7).

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