Steroids. I. The bromination of 1α-Methyl and 1α-Phenyl-3-keto Steroids

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1α-Phenyl-5α-cholestan-3-one was prepared from 5α-cholestan-1-en-3-one by treatment with the Grignard reagent in the presence of copper (I) chloride. In the mono- and dibromination of 1α-methyl-3-keto steroids, it was found that the position and configuration of bromine were the same as in the case of the 1-nonsubstituted 3-keto steroid. The A-ring conformations of these bromoketones were studied by means of NMR and ORD.

Synthetic and conformational studies of physiologically active 1-methyl-3-keto steroids have been made by several groups.[1] Kirk and Hartshorn[2a] stated that 3-keto-1-en-5α-steroids undergo the conjugate addition of methyl Grignard reagents to give 1β-methyl derivatives. This fact was explained by assuming that the β attack is sterically favored by the convexity of the β face of the molecule. However, other workers contend that this statement is wrong since 1α-methyl derivatives are formed. Recently, Pelc *et al.*[3] reported that the A ring of 1α-methyl-5α-androstan-3-one is in a chair conformation with the α-oriented C_1 methyl group. The α-attack of Grignard reagents is explained by the steric hindrance of the C_{10} methyl group.[4] From the fact that 1α-methyl-5β-cholestan-3-one (Va), which is derived from 1α-methyl-5α-cholestan-3-one (IIa), showed an unusual rotatory dispersion curve, Mori[5] suggested that the A ring of Va has a boat conformation. However, only very little information can be found on 1-alkyl-3-keto steroids concerning the synthesis of their derivatives and their reactivity.

In the present paper, we will describe the bromination of 1-methyl-3-keto steroids and will discuss the conformations of 1-methyl bromoketones.

Results and Discussion

The bromination of 5α- and 5β-cholestan-3-one occurred at the $C_{2\alpha}$ and $C_{4\beta}$ positions respectively.[6] The direction of bromination is dependent on that of enolization. The strong preference for a C_2-enolization in the 5α-series can be accounted for by both the 6β/19 interactions and the "hyperconjugation" of the C_1-methylene group.[2b] In the case of the 5β-series, the preference for C_4-enolization can be explained in terms of the relief of the nonbonded interactions between the 4α-hydrogen and the 7α- and 9α-hydrogens when a trigonal center is formed at C_4.[2b] Accordingly, 1-substituted 3-keto steroids are particularly interesting in the point of whether or not they show the same results as 1-unsubstituted 3-keto steroids on enolization and subsequent bromination.

Mori[5] reported that the bromination of IIa gave a C_4 brominated product, which was not purified. The bromination at the C_4-position was determined by the formation of 1α-methyl-cholest-4-en-3-one (IV) when the crude bromoketone was treated with LiCl/DMF. In our case, pure bromoketone (IIIa) was isolated; its configuration was determined by means of ORD and NMR (Tables 1 and 2).

The rotatory dispersion of this pure bromoketone

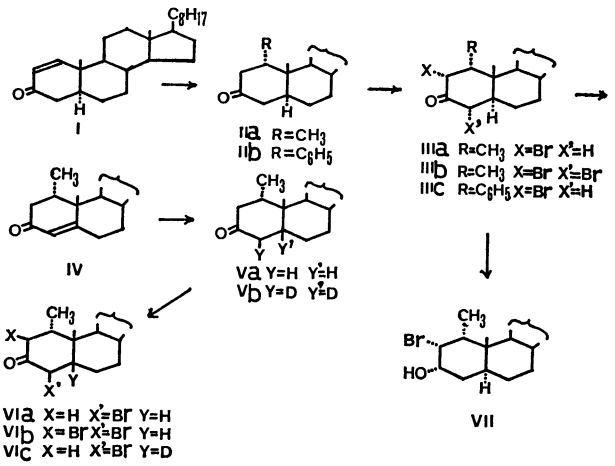

Table 1. ORD and CD data of 1-substituted 2- and 4-bromo-3-keto steroids

	$[\phi]_1$(nm)	$[\phi]_2$(nm)	a	$[\theta]$(nm)
IIa	2320(317)	−2132(273)	45	3416(296)
IIIa	1779(313)	−3319(272)	51	3531(298)
IIIb	402(310)			2112(288)
Va	848(314)	161(272)	7	848(290)
VIa	2532(313)	1204(268)	37	3029(292)
VIb	−369(367)	1285(300)	−17	−1143(337)
IIb	2897(311)	2014(285)	9	1667(297)
IIIc	3528(317)	925(277)	26	3976(294)

(IIIa) does not change the nature of the Cotton effect, and the wavelength shifts are negligible or tend toward shorter wavelength region, compared with the case of the parent ketone (IIa). The NMR spectrum showed peaks at 5.00 ppm (doublet, J=4.8 Hz) due to –CHBr–. Accordingly, the bromination product of (IIa) is concluded to be a 2α-bromo compound (IIIa) in a normal chair conformation. The dihedral angle, which was calculated using the Karplus equation from the coupling constant, also supported the results (Table 2). The dehydrobromination of IIIa with $CaCO_3$/DMF gave IV. This reaction was accompanied by a rearrangement of the bromine atom in the elimination reaction from C_2 to C_4 to give IV. If the 1,2-*trans* diaxial elimination of IIIa occurs, the A-ring requires a boat conformation in the process of elimination. In this reaction, the A-ring can not adopt a boat form by the nonbonded interaction of the 1α-methyl/11-methylene group. Therefore, the rearrangement of the substituent must have occurred.

Table 2. Chemical shifts, coupling constants, and dihedral angles of 2- and 4-bromo-3-keto steroids

Compound	CHBr (ppm)	J (Hz)	$\phi_{H_1\beta H_2}$ [c]	$\phi_{H_4H_5}$ [c]
5α-Cholestan-3-one derivative				
2α-Bromo-[a]	4.83 (dd)	6.5	44°	
2α,4α-Dibromo-[a]	4.80 (d)	12.7		161°
	4.45 (dd)	6.2	45°	
IIIa	5.00 (d)	4.8	52°	
IIIb	4.46 (d)	12.0		156°
	5.11 (d)	4.5	53°	
IIIc	5·14 (d)	6.0	46°	
5β-Cholestan-3-one derivative				
4β-Bromo-[b]	4.98 (d)	12.5		159°
2β,4β-Dibromo-[b]	4.82 (dd)	14.6	180°	
	5.08 (d)	11.4		153°
VIa	4.64 (d)	10.5		149°
VIb	4.37 (d)	13.5		166°
	4.55 (d)	8.3	35°	

a) C. W. Shoppee, T. E. Bellas, R. E. Lack, and S. Sternhell, *J. Chem. Soc.*, **1965**, 2483. b) C. W. Shoppee, A. B. Devine, and R. E. Lack, *J. Chem. Soc.*, **1965**, 6458. c) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, **1963**, 806.

The reduction of IIIa with $NaBH_4$ gave a bromohydrine as the only product. The NMR spectrum of the bromohydrine showed peaks at 4.66 ppm (d,d, J= 3.0 and 4.8 Hz) attributable to –CHBr–. Moreover, the bromohydrine was identified as 1α-methyl-2α-bromo-5α-cholestan-3α-ol (VII) on the basis of the small coupling constants (*i.e.*, not diaxial vicinal coupling constants). Because of shielding for the reducing reagent by the 1α-methyl group, the reduction of the 3-keto group occurred only on the β-side. The bromination product of IIa was also determined to be a 2α-bromo compound (IIIa) from the above fact that IIIa had no diaxial vicinal coupling constants.

The 1α-phenyl derivative, with its bulky substituent at the C_1 position, is interesting in the point of the direction of bromination. Therefore, the introduction of a phenyl group at the C_1 position was tried for the 1,4-addition with PhMgI in a manner similar to that used with CH_3MgI. The NMR spectrum of this reaction product (IIb) showed peaks at 7.10 ppm (m, 5H) and 3.25 ppm (bd, J=6.0 Hz, 1H) due to the aromatic protons and –CHPh– respectively. From the relatively small coupling constant of the C_1 proton, its configuration was equatorial. Therefore, it appears that the phenyl group was also introduced at the $C_{1\alpha}$-position, in a manner similar to that in the case of the methyl group.

The NMR spectrum of the monobromination product of IIb had peaks at 3.58 ppm (d, J=6.0 Hz, $C_{1\beta}$–H) and 5.14 ppm (d, J=6.0 Hz, C_2–H). Its ORD curve did not change the nature of the Cotton effect, and the wavelength shifts were negligible compared with those of the parent ketone (IIb) (Table 1). From this spectral evidence, the bromination product was determined to be 1α-phenyl-2α-bromo-5α-cholestan-3-one (IIIc), with an equatorial bromine atom. From the coupling constants of IIIc, the dihedral angle of C_1H_e–C_2H_a was calculated using the Karplus equation. This calculation resulted in 46°(44° in 2α-bromo-5α-cholestan-3-one[7]) (Table 2); hence, the A-ring conformation of phenyl bromoketone (IIIc) seemed to be of approximately a normal chair form.

The above results do not show any differences in the 1α-substituent with respect to the direction of bromination and A-ring conformation.

The NMR spectrum of the dibromination product of IIa revealed peaks at 4.46 ppm (d, $J_{4\beta,5\alpha}$=12.0 Hz) and 5.11 ppm (d, $J_{1\beta,2\beta}$=4.5 Hz) due to vicinal diaxial coupling and equatorial-axial coupling respectively. Accordingly, the dibromination product was determined to be 1α-methyl-2α,4α-dibromo-5α-cholestan-3-one (IIIb). The dihedral angles ($\phi_{4\beta,5\alpha}$ and $\phi_{1\beta,2\beta}$) were calculated using the Karplus equation. It was found that the A-ring conformation of IIIb is a nearly normal chair form. These values are also listed in Table 2.

1α-Methyl-5β-cholestan-3-one (Va), which has been synthesized by following the procedure of Mori,[5] was brominated. The monobrominated product (VIa) of Va showed a peak at 4.64 ppm (d, J=10.5 Hz) attributed to –CHBr– in the NMR spectrum. It can not be determined from the above NMR data whether the bromine atom is attached to the C_2 or C_4 position. In order to determine the brominated position, IV was reduced with deuterium in cyclohexane. From the fact that the mass spectrum showed a peak at *m/e* 402 [M^+], this reduced product was found to be 1α-methyl-4β,5-dideuterio-5β-cholestan-3-one (Vb). The reaction of Vb with bromine in acetic acid gave a monobromoketone, melting at 136—139 °C. This product was determined to be 1α-methyl-4-bromo-5-deuterio-5β-cholestan-3-one (VIc) from the fact that the NMR spectrum showed a singlet at 4.64 ppm due to –CHBr–. From the above facts, it was found that the bromination of Va occurs at the C_4 position. The configuration of the C_4 bromine atom was determined to be equatorial (β-linkage) in the A-ring with the boat conformation from the fact that the rotatory dispersion of 1α-methyl-4β-bromo-5β-cholestan-3-one (VIa) does not change the nature of the Cotton effect; the wavelength shifts are negligible compared with those of the parent ketone, Va. If the A-ring takes a normal chair conformation, the ORD curve can be expected to show a negative Cotton effect. The dibromination of Va produced 2,4-dibromoketone (VIb); it showed a negative Cotton curve with a small amplitude (−17) and a red shift of 53 nm from that of the parent keton (Va). From these results, we may conclude that the two bromine atoms are attached to an axial-like bond. Because of the counteraction of the opposite contribution due to 2- and 4-bromine for the Cotton effect, it seems that the amplitude is small. From the coupling constants, $J_{1,2}$=8.3 Hz and $J_{4,5}$=13.5 Hz, of the dibromoketone, the dihedral angles were calculated using the Karplus equation; we obtained 35° and 166° respectively. These values differ from those for the angles of 2β,4β-dibromo-5β-cholestan-3-one (Table 2). From these data, it was concluded that the dibromoketone was 1α-methyl-2β,4β-dibromo-5β-cholestan-3-one

(VIb), with a twist boat conformation.

All of the facts observed in these experiments with respect to the direction and orientation proved to be the same as those in the case of 1-unsubstituted 3-keto steroids; thus, these seems to be no drastic 1α-substituent effect.

Experimental

All the melting points are uncorrected. The IR spectra were measured (KBr) with a Hitachi model 215 grating infrared spectrophotometer. The ORD spectra were obtained in dioxane with a JASCO model J-20 instrument. The NMR spectra were recorded in carbon tetrachloride, with tetramethylsilane as the internal standard, using a Hitachi-Perkin Elmer R-20A apparatus. The mass spectra were obtained with a Hitachi RMU-6M spectrometer at 20 eV.

1α-Phenyl-5α-cholestan-3-one (IIb). To Mg (0.9 g) in absolute ether (24 ml), under a nitrogen atomosphere was added dropwise iodobenzene (9.6 g) with stirring. After 30 min, absolute tetrahydrofuran (40 ml) was slowly added. The solvent was distilled until the boiling point was 62 °C; the mixture was then cooled to room temperature, and CuCl (0.2 g) and 5α-cholestan-1-en-3-one (2.0 g) in tetrahydrofuran (21 ml) were added. To facilitate stirring, tetrahydrofuran (40 ml) was added. After 30 min, the mixture was cooled to 0 °C, a saturated ammonium chloride solution was added, the mixture was extracted with ether, the aqueous solution was discarded, and the organic phase was washed successively with a sodium thiosulfate solution, the saturated ammonium chloride solution, and water. After a usual work-up, the resulting oil was distilled under reduced pressure at 180 °C to remove the non-keto substance. The residue was chromatographed on silica gel. Elution with benzene afforded 1α-phenyl-5α-cholestan-3-one (IIb) (1.2 g), which crystallized from ethanol as needles; mp 140—141 °C; IR cm^{-1}: ν_{max} 1707, 1600, and 703; NMR: 3.25 ppm (bd, J=6.0 Hz, 1H) and 7.10 ppm (m, 5H); Found: C, 85.60; H, 11.00, $C_{33}H_{50}O$ requires C, 85.65; H, 10.89%.

1α-Methyl-2α-bromo-5α-cholestan-3-one (IIIa). 1α-Methyl-5α-cholestan-3-one (2 g) in acetic acid (62 ml) was treated with bromine (0.811 g) in acetic acid (19 ml) containing a few drops of 48% hydrobromic acid at room temperature for 25 min. The reaction mixture was then treated in the usual manner. The crystallization of the resulting oil from ethanol gave IIIa (1.54 g); mp 177—180 °C; IR cm^{-1}: ν_{max} 1726 and 890; NMR: 5.00 ppm (d, J= 4.8 Hz, 1H); Found: C, 70.18; H, 9.80, $C_{28}H_{47}OBr$ requires C, 70.12; H, 9.88%.

1α-Methyl-2α, 4α-dibromo-5α-cholestan-3-one (IIIb). To a solution of IIa (0.300 g) in acetic acid (18 ml) and one drop of 48% hydrobromic acid was added bromine (0.231 g) in acetic acid (15 ml) with stirring for 30 min at room temperature. The reaction mixture was then taken up in ether, and the ether extracts were washed, dried, and evaporated. On the chromatography of the residue with silica gel, elution with benzene-petroleum ether (1 : 1) gave an oily product. The crystallization of the resulting oil from ethanol afforded needles (0.125 g) of IIIb; mp 145—148 °C, IR cm^{-1}: ν_{max} 1740 and 613; NMR: 4.46 ppm (d, J=12.0 Hz, 1H) and 5.11 ppm (d, J=4.5 Hz, 1H); Found: C, 59.92; H, 8.07%, $C_{28}H_{46}OBr_2$ requires C, 60.22; H, 8.30%.

1α-Phenyl-2α-bromo-5α-cholestan-3-one (IIIc). The bromination of IIb (0.5 g) was carried out using the technique for the synthesis of IIIa. After the usual work-up, the resulting oil was chromatographed on silica gel. Elution with benzene-petroleum ether (1 : 1) afforded IIIc (0.400 g), which crystallized from ethanol-methanol as needles; mp 74—76 °C, IR cm^{-1}: ν_{max} 1723 and 789; NMR: 3.58 ppm (d, J=6.0 Hz, 1H), 5.14 ppm (d, J=6.0 Hz, 1H), and 7.20 ppm (m, 5H); Found: C, 73.35; H, 9.30%, $C_{33}H_{49}OBr$ requires C, 73.17; H, 9.12%.

1α-Methyl-4β,5-dideuterio-5β-cholestan-5-one (Vb). The synthesis was carried out following the procedure of Shapiro and Djerassi.[8] A mixture of IV (0.168 g), palladium black (0.100 g), and cyclohexane (30 ml) was shaken in a deuterium atmosphere. The deuterium uptake was completed within 7 h. The catalyst was then removed by filtration, and the filtrate was evaporated. The residue was recrystallized from methanol to give Vb (0.079 g); mp 84—85 °C, IR cm^{-1}: ν_{max} 1718 (1718, CCl_4); MS: m/e 402 (M^+).

1α-Methyl-4β-bromo-5β-cholestan-3-one (VIa). The bromination of Va (0.100 g) was carried out using the technique used for the synthesis of IIIa. The crystallization of the resulting oil from ethanol gave VIa (0.094 g); mp 136—139 °C; IR cm^{-1}: ν_{max} 1718 (1730, CCl_4) and 572; NMR: 4.64 ppm (d, J=10.5 Hz, 1H), Found: C, 70.30; H, 9.62%, $C_{28}H_{47}OBr$ requires C, 70.12; H, 9.88%.

1α-Methyl-2β, 4β-dibromo-5β-cholestan-3-one (VIb). The dibromination of Va (0.300 g) was carried out using the technique used for the synthesis of IIIb. The crystallization of the resulting oil from ethanol gave VIb (0.180 g); mp 139—144 °C; IR cm^{-1}: ν_{max} 1733 (1720, CCl_4) and 624; NMR: 4.37 ppm (d, J=13.5 Hz, 1H) and 4.55 ppm (d, J=8.3 Hz, 1H), Found: C, 60.12; H, 8.00%, $C_{28}H_{46}OBr_2$ requires C, 60.22; H, 8.30%.

1α-Methyl-4β-bromo-5-deuterio-5β-cholestan-3-one (VIc). The bromination of Vb (0.060 g) was carried out using the technique used for the synthesis of IIIa. The crystallization of the resulting oil from ethanol gave VIc (0.045 g); mp 136—139 °C, IR cm^{-1}: ν_{max} 1718 (1730, CCl_4) and 572; NMR: 4.64 ppm (s, 1H); MS: m/e 480 and 482 (M^+).

1α-Methyl-2α-bromo-3α-hydroxy-5α-cholestane (VII). The synthesis used was virtually identical with the method of Fieser.[9] A solution of IIIa (0.400 g) and sodium borohydride (0.050 g) in methanol (60 ml) was stirred at room temperature for 30 min. After the usual work-up, the crystallization of the resulting oil from ethanol gave VII (0.315 g); mp 148—152 °C; IR cm^{-1}: ν_{max} 3499 and 1030; NMR: 3.96 ppm (m, 1H) and 4.66 ppm (dd, J= 3.0 and 4.8 Hz, 1H); Found: C, 70.01; H, 10.40%, $C_{28}H_{49}OBr$ requires C, 69.83; H, 10.26%.

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