The Bromination of Some Cholest-5-en-7-ones

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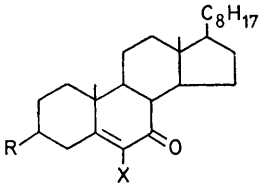
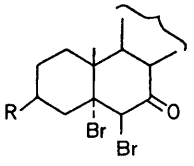
Bromination (Br_2–HBr–HOAc) of cholest-5-en-7-one (1) gives 5,6α-dibromo-5β-cholestan-7-one (4), whereas 3β-acetoxycholest-5-en-7-one (2) gives the 5α,6β-dibromo-product (5). Addition products (6) and (7) of both types are formed from the 3β-chloro-derivative (3). Products isolated from the reaction of pyridine with the 5,6-dibromides (4)—(6) and 4,5,6-tribromide (7) include a 5-en-7-one (1)—(3), a 6-bromo-5-en-7-one (8), a 6-bromo-3,5-dien-7-one (9), a 3,5-dien-7-one (10), and a 4,6-dibromo-3,5-dien-7-one (11). The structures have been established on the basis of elemental analysis and spectral properties.

HALOGENATION of ketones at the α-position and subsequent dehydrohalogenation by base is frequently employed to create unsaturated centres adjacent to ketonic functions. Such operations have been of immense utility in the field of steroids.[1] We considered it expedient to prepare some keto-steroids with bromines at both α- and β-positions and subject them to dehydrohalogenation with pyridine under reflux. The ketones chosen were cholest-5-en-7-one (1) and its 3β-acetoxy- (2) and 3β-chloro- (3) analogues.

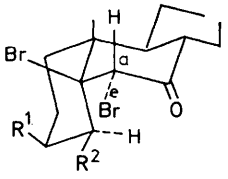


	R	X
(1)	H	H
(2)	OAc	H
(3)	Cl	H

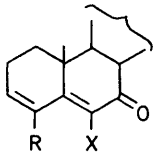


	R	X
(8)	AcO	Br

	R
(5)	OAc
(6)	Cl



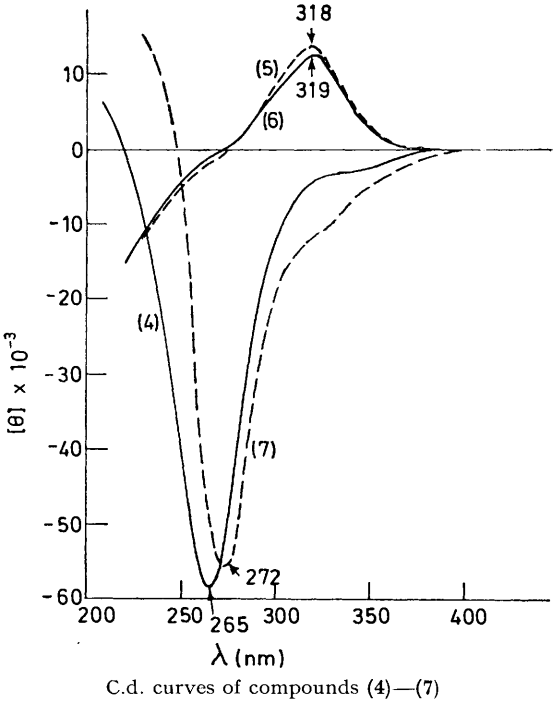
	R^1	R^2
(4)	H	H
(7)	Cl	Br



	R	X
(9)	H	Br
(10)	H	H
(11)	Br	Br

Treatment of (1) with Br_2–HBr afforded a dibromo-compound (4). The presence of bromine atoms at C-5 and -6 was proved by its debromination (Zn–AcOH) to the parent ketone (1). The location of bromine at C-6 (and not at C-8) was further supported by the ^1H n.m.r. spectrum which displayed a singlet at δ 5.39. The stereochemistry was determined by means of ^1H n.m.r., c.d., and i.r. spectral data. The bromine at C-6 has been assumed to be α-oriented in view of its c.d. curve which shows a negative Cotton effect.[2,3] In the ^1H n.m.r. spectrum the C-10 methyl signal was observed at δ 1.54. This lower field shift of the C-10 methyl signal should be explained in terms of the *cis* ring junction, since once the C-6-bromine is α-oriented (which causes a small downfield shift of the C-10 methyl signal)[4] it is the *cis* ring junction which will be responsible for the significant deshielding of C-10 methyl signals.[5] Thus, assuming the *cis* ring junction both C-5 and C-6 bromines have become equatorial. The presence of equatorial bromines was further supported by its i.r. spectrum in which the C–Br absorption frequencies occur at 720 and 710 cm^{-1}.[6]

Similar treatment of (2) gave (5). The C-6 bromine is taken to be β-oriented on the basis of the c.d. curve which shows a positive Cotton effect. The configuration (α or β) of the C-5 bromine was decided on the basis of the n.m.r. spectrum which showed a multiplet at δ 5.46 having half-height width of 18 Hz due to the proton at C-3. Evidently this proton was axial (α) and the A–B ring junction *trans*,[7] rendering the C-5 bromine an α-orientation. Zn–HOAc debromination of (5) gave back (2).



C.d. curves of compounds (4)—(7)

Reaction of (3) provided (6) and (7) in major and minor amounts respectively. In the circular dichroism (c.d.) spectrum of (6), a positive Cotton effect curve was observed. On this basis the C-6 bromine is assumed as β-oriented. The C-5 bromine is assigned α-orientation on the basis of the half-height width (20 Hz) of the C-3 proton signal, a multiplet at δ 4.60. Thus both the bromines have become diaxial. Treatment of (6) with zinc–acetic acid gave back (3).

The stereoformula of (7) is based upon elemental analysis (three bromine atoms) and spectral properties. The bromine at C-6 is α-oriented as it shows a negative Cotton effect in the c.d. spectrum. In the ^{1}H n.m.r. spectrum the C-3 proton appears as a multiplet at δ 4.93. The half-height width (6 Hz) of this signal suggests that the C-3 proton is equatorial and that the A–B ring junction is *cis*,[7] proving β-orientation of the C-5 bromine. The C-4 bromine is assigned β-orientation on the basis of a doublet-like broad signal at δ 3.17 for the proton at C-4. The half-height width (18 Hz) of this signal suggests that the C-4 proton is axial, rendering the C-4 bromine a β-orientation (equatorial).

^{1}H N.m.r. chemical shifts of the C-6 proton for compounds (4)—(7)

Compound	C-6-H configuration	Chemical shift (p.p.m.)
(4)	a	5.39
(5)	e	4.80
(6)	e	4.75
(7)	a	5.22

The chemical shifts of the hydrogen attached to C-6 of the bromo-compounds (4—7) are given in the Table. The data show that the 6-H signal for the epimer with an equatorial hydrogen appears at higher field than that for the epimer containing axial hydrogen. This is in accordance with the data given by Nickon *et al.*[8]

When refluxed with pyridine, (4) surprisingly gave back the ketone (1),[9] a result of debromination rather than dehydrobromination. A similar observation was also noticed earlier.[10,11] The role of pyridine as a debrominating agent was again in evidence as (5) in boiling pyridine provided (2)[12] along with (8), a consequence of loss of HBr from C-5–C-6, and (9) which is derived from (8) upon the removal of acetic acid. Reaction of (6) provided (3),[13] (9), and (10).[14] Loss of HCl from (3) gives (10)[14] while losses of HBr and HCl from (6) produce (9). In a similar manner (7) gives rise to (11).

EXPERIMENTAL

U.v. spectra were determined for solutions in ethanol and i.r. spectra were measured for KBr discs on a Perkin-Elmer 621 grating spectrophotometer. ^{1}H N.m.r. spectra were recorded for solutions in $CDCl_3$ on a Varian A60 instrument with Me_4Si as internal standard. C.d. curves were measured with a JASCO J-20 spectropolarimeter. T.l.c. plates were coated with silica gel and sprayed with a 20% solution of perchloric acid. Light petroleum refers to the fraction of b.p. 60—80°.

Bromination of Cholest-5-en-7-one (1).—To a solution of (1)[11] (3.0 g) in ether (35 ml) containing a few drops of HBr was added a solution of bromine (3 ml) in acetic acid (60 ml) at room temperature over a period of 30 min with shaking. The solid that separated within a few minutes after the addition of the bromine solution was filtered to give 5β,6α-*dibromocholestan-7-one* (4) (2.10 g), m.p. 142° (Found: C, 59.45; H, 7.95. $C_{27}H_{44}Br_2O$ requires C, 59.55; H, 8.0%), $\nu_{max.}$ 1 710 (C=O), 720, and 710 cm^{-1} (C–Br), δ 5.39 (s, 6-H), 1.54 (s, 10-Me), and 0.72 (s, 13-Me).

Bromination of 3β-*Acetoxycholest-5-en-7-one* (2).—Bromination of (2)[12] (5.5 g) as described above gave 3β-*acetoxy*-5α,6β-*dibromocholestan-7-one* (5) (4.2 g), m.p. 155° (Found: C, 57.85; H, 7.65. $C_{29}H_{46}Br_2O_3$ requires C, 57.80; H, 7.64%), $\nu_{max.}$ 1 730 (MeC=O), 1 712 (C=O), 1 235 (C–O), and 695 cm^{-1} (C–Br), δ 5.46 (m, 3α-H, $W_{\frac{1}{2}}$ 18 Hz), 4.8 (s, 6α-H), 2.05 (s, CH_3COO), 1.62 (s, 10-CH_3), and 0.70 (s, 13-CH_3).

Bromination of 3β-*Chlorocholest-5-en-7-one* (3).—Bromination of (3)[13] (8.0 g) under similar conditions furnished 3β-*chloro*-5α,6β-*dibromocholestan-7-one* (6) (5.2 g), m.p. 135° (Found: C, 56.0; H, 7.4. $C_{27}H_{43}Br_2ClO$ requires C, 56.05; H, 7.45%), $\nu_{max.}$ 1 725 (C=O), 760 (C–Cl), and 685, 690 cm^{-1} (C–Br), δ 4.75 (s, 6α-H), 4.60 (m, 3α-H, $W_{\frac{1}{2}}$ 20 Hz), 1.63 (s, 10-CH_3), and 0.71 (s, 13-CH_3).

The mother liquor of (6) provided 3β-*chloro*-4β,5β,6α-tribromocholestan-7-one (7) (1.2 g), m.p. 144° (homogeneous by t.l.c.) (Found: C, 49.4; H, 6.4. $C_{27}H_{42}Br_3ClO$ requires C, 49.3; H, 6.39%), $\nu_{max.}$ 1 715 (C=O), 760 (C–Cl), and 720 cm^{-1} (C–Br), δ 5.22 (s, 6β-H), 4.93 (t-like, 3α-H), 3.17 (d-like, 4α-H), 1.52 (s, 10-CH_3), and 0.72 (s, 13-CH_3).

Treatment of 5β,6α-*Dibromocholestan-7-one* (4) *with Pyridine*.—The dibromoketone (4) (1 g) in freshly distilled pyridine (10 ml) was heated under reflux for 1 h. The reaction mixture was extracted with ether and the ethereal solution washed with water, dilute sulphuric acid, water, sodium hydrogen carbonate solution (5%), and water, and dried (Na_2SO_4). Removal of the solvent gave an oil (*ca.* 1 g) which was chromatographed over silica gel (20 g). Eluates from light petroleum–ether (4 : 1) gave cholest-5-en-7-one (1) (210 mg), m.p. 128° (from methanol) (lit.,[11] 125—129°), negative Beilstein test, identical with (t.l.c.) an authentic sample.

Treatment of 3β-*Acetoxy*-5α,6β-*dibromocholestan-7-one* (5) *with Pyridine*.—The dibromoketone (5) (3.0 g) was treated with pyridine (30 ml) under reflux for 1 h. After usual work-up it gave an oil (2.8 g) which was chromatographed over silica gel (60 g). Elution with light petroleum–benzene (18 : 1) and crystallization from light petroleum gave 6-*bromocholesta*-3,5-*dien*-7-one (9) (240 mg), m.p. 148°, positive Beilstein test (Found: C, 70.1; H, 8.8. $C_{27}H_{41}BrO$ requires C, 70.3; H, 8.89%), $\lambda_{max.}$ 295 nm (ε 12 000), $\nu_{max.}$ 1 670 (C=O), 1 615 (C=C–C=C), and 700 cm^{-1} (C–Br), δ 6.48 (m, 3- and 4-H), 1.16 (s, 10-CH_3), and 0.72 (s, 13-CH_3).

Light petroleum–benzene (16 : 1) eluted 3β-*acetoxy*-6-*bromocholest-5-en-7-one* (8), which was crystallized from light petroleum, yield 160 mg, m.p. 160°, positive Beilstein test (Found: C, 66.7; H, 8.6. $C_{29}H_{45}BrO_3$ requires C, 66.8; H, 8.65%). $\lambda_{max.}$ 258 nm (ε 8 200), $\nu_{max.}$ 1 735 (MeC=O), 1 680 (C=O), 1 600 (C=C), 1 255 (C–O), and 720 cm^{-1} (C–Br), δ 4.75 (m, 3α-H), 2.02 (s, CH_3COO), 1.22 (s, 10-CH_3), and 0.68 (s, 13-CH_3).

Elution with light petroleum–benzene (12 : 1) gave 3β-acetoxycholest-5-en-7-one (2) which was crystallized from

light petroleum, yield 150 mg, m.p. and mixed m.p. 163° (lit.,[12] 164°), negative Beilstein test (Found: C, 78.7; H, 10.3. Calc. for $C_{29}H_{46}O_3$: C, 78.75; H, 10.4%), $\lambda_{max.}$ 235 nm (ε 7 000), $\nu_{max.}$ 1 730 (MeC=O), 1 675 (C=O), 1 635 (C=C), and 1 240 cm^{-1} (C–O), δ 5.71 (s, 6-H), 4.70 (m, 3α-H), 2.01 (s, CH_3COO), 1.20 (s, 10-CH_3), and 0.68 (s, 13-CH_3).

Treatment of 3β-*Chloro*-5α,6β-*dibromocholestan*-7-*one* (6) *with Pyridine*.—The dibromide (6) (4.0 g) was refluxed with pyridine (40 ml) for 1 h. After the usual work-up it was chromatographed over silica gel (80 g). Elution with light petroleum–benzene (16 : 1) furnished (9) which was crystallized from light petroleum, yield 350 mg, m.p. 148°. This compound was identical in all respects with that previously obtained from the dibromoketone (5).

Elution with light petroleum–benzene (10 : 1) gave the parent ketone (3) which was crystallized from light petroleum, yield 210 mg, m.p. and mixed m.p. 145° (lit.,[13] 145°) (Found: C, 77.3; H, 10.2. Calc. for $C_{27}H_{43}ClO$: C, 77.5; H, 10.3%), $\lambda_{max.}$ 235 nm (ε 7 200), $\nu_{max.}$ 1 675 (C=O), 1 635 (C=C), and 750 cm^{-1} (C–Cl), δ 5.55 (s, 6-*H*), 3.78 (m, 3α-*H*), 1.21 (s, 10-CH_3), and 0.70 (s, 13-CH_3).

Elution with light petroleum–benzene (5 : 1) provided cholesta-3,5-dien-7-one (10) which was crystallized from ethanol, yield 110 mg, m.p. and mixed m.p. 116° (lit.,[14] 118°), negative Beilstein test (Found: C, 84.7; H, 10.8. Calc. for $C_{27}H_{42}O$: C, 84.8; H, 11.0%), $\lambda_{max.}$ 278 nm (ε 11 000), $\nu_{max.}$ 1 660 (C=O), 1 630, and 1 600 (C=C) cm^{-1}, δ 6.1 (br s, 3- and 4-H), 5.48 (s, 6-H), 1.20 (s, 10-CH_3), and 0.70 (13-CH_3).

Dehydrohalogenation of 3β-*Chloro*-4β,5β,6α-*tribromocholestan*-7-*one* (7).—The tribromoketone (7) (1 g) was treated with pyridine (10 ml) under reflux for 2 h. After the usual work-up and chromatography, it furnished 4,6-*dibromocholesta*-3,5-*dien*-7-*one* (11) which was crystallized from petrol, yield 150 mg, m.p. 170°, positive Beilstein test (Found: C, 60.1; H, 7.4. $C_{27}H_{40}Br_2O$ requires C, 60.0; H, 7.4%), $\lambda_{max.}$ 298 nm (ε 15 000), $\nu_{max.}$ 1 690 (C=O), 1 610 (C=C–C=C), and 720 cm^{-1} (C–Br), δ 6.55 (dd, *J* 7 and 3 Hz; 3-H), 1.24 (s, 10-CH_3), and 0.70 (s, 13-CH_3).

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