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Aromatization of Ring-A in α-Bromocholestan-6-ones

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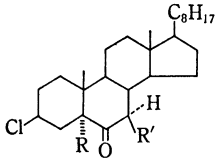
Pyridine promoted dehydrohalogenation of 3β-chloro-5-bromo-5α-cholestan-6-one resulting in ring-A aromatization with expulsion of C-10 angular methyl group to give 19-norcholesta-1,3,5(10)-trien-6-one along with 3α,5-cyclo-5α-cholest-7-en-6-one, cholesta-2,4-dien-6-one, and 5α-cholestane-3,6-dione. Similar treatment of 3β-chloro-5,7β-dibromo-5α-cholestan-6-one ends up with the aromatization of ring-A with migration of C-10 angular methyl group to give 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one.

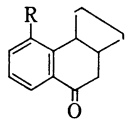
Our understanding of principles involved in selective ring-A aromatization of steroids[1] has acquired enormous attention in recent years as a result of brilliant investigations carried out by Hora,[2] Hanson,[3] and Mazur.[4] They have enlightened the mechanistic aspect of aromatization reactions. Moreover, aromatic steroids have proved their usefulness as important starting material in the synthesis of 19-norsteroids.[5] In addition to above, 10-nor-analog steroidal hormones[5] began to receive immense attention when it was realized that the presence of the angular methyl group at C-10 was not essential to biological activity and in fact, that the removal of this group, in many cases, results in great enhancement of this reactivity. This paper is the subject of outcome of the generalizations in the light of above historical background.

Results and Discussion

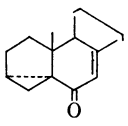
The compounds **2** ($C_{27}H_{44}OClBr$) and **7** ($C_{27}H_{43}OClBr_2$) were obtained from 3β-chloro-5α-cholestan-6-one (**1**)[6] by usual α-bromination. The identity of these products were based upon spectral and chemical evidences. In IR spectra the carbonyl frequencies at 1712 cm^{-1} was indicative for the axial (α) oriented bromine at C5 in **2** and 1725 cm^{-1} for equatorially substituted at C7 in **7**.[7,8] The NMR spectra (60 MHz, $CDCl_3$) exhibited signals at δ 4.5 ($W/2$ 21 Hz) and δ 4.39 ($W/2$ 20 Hz) for (C3-α<u>H</u>; axial) implying trans ring junction[9] in **2** and **7**. Interestingly, C3-protons of **2** and **7** display paramagnetic shifts, compared to parent ketone (**1**) where it appears at δ 3.8, ascribable to the field effect of axial bromine at C5.[10] In the spectrum of **7** a doublet at δ 5.35 (C7-α<u>H</u>) very decisively supported that the bromine at C7 is equatorially introduced and the axial hydrogen is split by C8-axial hydrogen (β) with J value of 8 Hz.[10] Singlets due to C10β-methyl and C13β-methyl appeared at δ 1.0 and 2.69 in **2** and at δ 1.1 and 0.72 in **7** respectively.



	R	R′
1	H	H
2	Br	H
7	Br	Br



	R
3	H
8	CH_3



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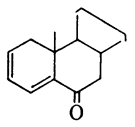

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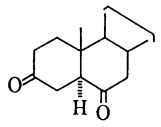

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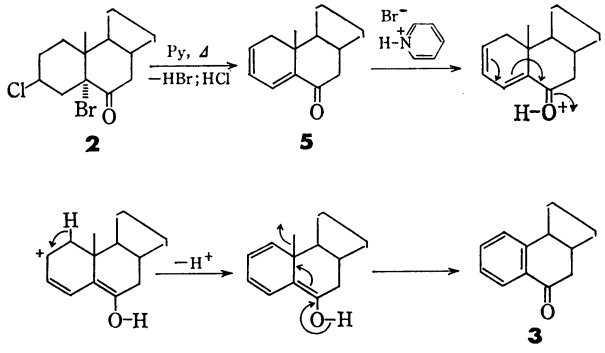
The halo ketone (**2**) on subjection to dehydrohalogenation provided **3** in about 38%, 3α,5-cyclo-5α-cholest-7-en-6-one (**4**), (9%) cholesta-2,4-dien-6-one (**5**)[11] (11%) and 5α-cholestane-3,6-dione (**6**)[12] (22%). The structures were established on spectral evidences and by comparison with authentic samples in known cases. The compound (**3**)[2] showed IR bands at 3060 (C=C–H), 1680 (C=O) and 1600 cm^{-1} (>C=C<).[10] The UV spectrum gave absorption maxima at 253 and 295 nm. Signals in the NMR spectrum were observed at δ 8.05 m (C4-<u>H</u>, J=8 Hz, o-coupled; J=2 Hz, m-coupled), 7.3m (C1-<u>H</u>, C2-<u>H</u>, C3-<u>H</u>). The multiplet at δ 8.05 strongly supported C4-<u>H</u> location β- to C6-oxo function. C13β-Methyl protons appeared as singlet at δ 0.76.

The mechanistic pathway through which **2** is converted into **3** is depicted in Scheme 1.

The product 4 in IR spectrum showed bands at 3080 (C=C–H), 1665 (C=C–C=O), 1605 cm^{-1} (>C=C<). The prominent bands at 1030 and 1010 cm^{-1} suggested the presence of cyclopropane moiety.[13] An α,β-unsaturated ketonic chromophore was also supported by absorption maximum at 253 nm (ε 8000). A signal in NMR spectrum (60 MHz) at δ 6.22s devoid of any vicinal proton, easily ascribable to a vinylic proton (C7-<u>H</u>). A multiplet at δ 2.55 was ascribable to protons at C9 and C14, allylic to C7-8 olefinic linkage. Signals due to C10β-methyl and C13β-methyl protons are at δ 1.22s and 0.76s. It is pertinent to mention that the



2 **5** **3**

Scheme 1.

nearby location of electron withdrawing C6-oxo function causes downfield shift of cyclopropane protons which merge with the methylene envelope.[14] The formation of **4** was, under the reaction conditions, rationalized on the basis of earlier report.[15]

On being refluxed with pyridine and after usual work up of the reaction mixture (**7**) provided exclusively **8** with 38% yield, a product of ring-A aromatization involving methyl migration from C10 to C1 owing to the presence of C6-oxo function.[3] The IR spectrum of **8** exhibited bands at 1685 (-C=O), 3010w (C=C-H) and 1600 cm^{-1} (>C=C<) and supported by UV absorption maxima at 255 and 300 nm. The NMR spectrum gave signals at δ 7.95d,d (C4-H; J=8 Hz; *o*-coupled, J=2 Hz; *m*-coupled; β to C6-oxo function), 7.35m (C2-H and C3-H). The C1-methyl and C13β-methyl protons appeared as singlet at δ 2.42 and 0.73 respectively.

Experimental

All melting points are uncorrected. IR spectra in Nujol were recorded with a Perkin-Elmer 237 spectrophotometer and UV spectra in 95% EtOH with a Beckmann DK2 spectrophotometer. NMR spectra were run in $CDCl_3$ with a Varian A60 instrument, chemical shifts (δ) being given in ppm relative to internal TMS and mass spectra were measured on an AEI MS-9 mass spectrometer. Light petroleum refers to fractions by 60—80 °C. TLC plates were coated with silica gel and sprayed with 20% perchloric acid solution.

3β-Chloro-5-bromo-5α-cholestan-6-one (2). The compound **1**[6] (4.0 g) in ether (50 ml) at 0 °C was treated with a solution of bromine in glacial acetic acid (40 ml, 5%); the addition of bromine solution was completed over a period of 1 h (catalysed with hydrobromic acid). Decolourization proceeded rapidly and crystalline material separated after the addition of approximately half of the bromine solution. The reaction mixture was further allowed to stand at 0 °C for 1/2 h to ensure complete crystallization. The solid was filtered under suction and recrystallized from light petroleum ether from which **2** (3.5 g) separated as white crystals, mp 124—125 °C, positive Beilstein halogen test (homogeneous by TLC, solvent petroleum ether-diethyl ether); Found: C, 65.54; H, 8.5%. Calcd for $C_{27}H_{44}OClBr$: C, 64.85; H, 8.8%; ν_{max} 765 (C-Cl), 740 cm^{-1} (C-Br).

3β-Chloro-5,7β-dibromo-5α-cholestan-6-one (7). To a solution of **1**[6] (4.0 g) in ether (20 ml) at room temperature was added bromine solution. The experimental technique was similar to that detailed under **2** except, the reaction mixture was allowed to stand at room temperature for three days. Recrystallization from petroleum ether afforded the halo ketone (**7**) (3.8 g), mp 174—175 °C, positive Beilstein halogen test (homogeneous TLC; solvent system petroleum ether-diethyl ether); Found: C, 55.85; H, 7.45%. Calcd for $C_{27}H_{43}OClBr_2$: C, 55.95; H, 7.59%; ν_{max} 768 (C-Cl), 736 and 655 cm^{-1} (C-Br).

Dehydrohalogenation of 2. The halo ketone **2** (10 g) in freshly distilled pyridine (70 ml) was heated under reflux for 10 h. Most of the solvent was removed by distillation under reduced pressure, the residue diluted with water and extracted with ether. The ethereal solution was washed successively with water, dilute hydrochloric acid, water, $NaHCO_3$ (5% aqueous solution) and water and dried over anhydrous sodium sulfate. Solid material (5.0 g) thus obtained was chromatographed over silica gel (100 g). Fractions of 10 ml were collected. Elutes from petroleum ether–benzene (20: 1) and (15: 1) gave cholesta-2,4-dien-6-one (**5**),[11] (1.1 g) mp and mixed mp 128—129 °C and 5α-cholestane-3,6-dione (**6**),[12] (2.2 g), mp and mixed mp 168 °C, respectively.

Further elution with petroleum ether–benzene (12: 1) gave 3α,5-cyclo-5α-cholest-7-en-6-one (**4**) which was crystallized from petroleum ether (0.9 g), mp 118—119 °C, negative Beilstein halogen test MS (10 eV) *m/e* 382 (80.3%) (M^+); Found: C, 84.6; H, 10.7%. Calcd for $C_{27}H_{42}O$: C, 84.8; H, 10.9%.

Elution with petroleum ether–ether (9: 1) gave 19-norcholesta-1,3,5(10)-trien-6-one (**3**) which was recrystallized from petroleum ether (3.76 g), mp 110 °C, negative Beilstein halogen test; MS (70 eV) *m/e* 366 (82.0%) (M^+); Found: C, 85.03; H, 10.5%. Calcd for $C_{27}H_{38}O$; C, 85.24; H, 10.38%.

Dehydrohalogenation of 7. The halo ketone **7** (5.0 g) in freshly distilled pyridine (35 ml) over KOH heated under reflux for 10 h. The reaction mixture worked up in the manner described under **2**. Removal of the solvent gave semi solid material (4.0 g) which was chromatographed over silica gel (80.0 g). Fractions of 10 ml were collected. Elutes from petroleum ether–benzene (6: 1) gave 1-methyl-19-norcholesta-1,3,5(10)-trien-6-one (**8**) which was recrystallized from petroleum ether (1.9 g), mp 140 °C, negative Beilstein halogen test; MS (70 eV) *m/e* 380 (100%) (M^+); Found: C, 85.06; H, 11.2%. Calcd for $C_{29}H_{40}O$: C, 85.26; H, 10.52%.

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