611. *The Reaction of 6-Acetoxy-3α,5-cyclo-5α-cholest-6-ene with Bromine.*

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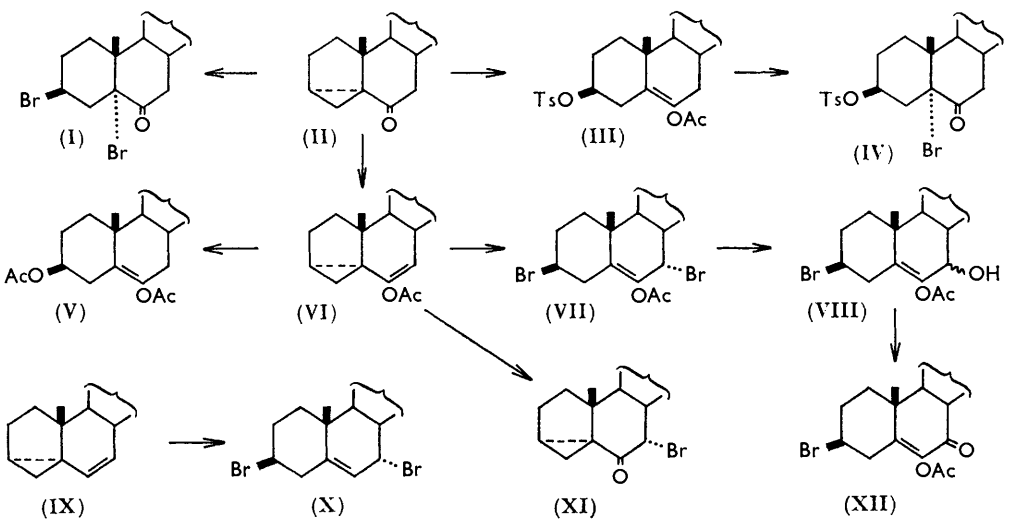
The enol acetate of 3α,5-cyclo-5α-cholestan-6-one has been prepared and has been brominated under various conditions, the products being markedly dependent on the conditions. In carbon tetrachloride the sole product is 6-acetoxy-3β,7α-dibromocholest-5-ene, but after reaction in pyridine–acetic acid considerable amounts of the 7α-bromo-ketone were also isolated.

THE reaction of 3α,5-cyclo-5α-cholestan-6-one (II) with one mol. of bromine has been shown [1] to yield 3β,5α-dibromocholestan-6-one (I). In view of the absence of 7α-bromo-3α,5-cyclo-5α-cholestan-6-one (XI) from the products, it was of interest to examine the bromination of the enol acetate (VI).

The enol acetate (VI) was prepared in good yield from the ketone (II) by using isopropenyl acetate and toluene-*p*-sulphonic acid. The structure of the enol acetate was confirmed by infrared and ultraviolet spectra. In particular, the ultraviolet spectrum ($\lambda_{max.}$ 258 mμ; ε 620) demonstrated that the cyclopropyl ring system was intact and confirmed the relative positions of this ring and the enol acetate group. A further product (III) from the reaction is discussed below.



Ts = *p*-$C_6H_4 \cdot SO_2$

Heating the enol acetate (VI) with acetic acid and a trace of sulphuric acid gave 3β,6-diacetoxycholest-5-ene (V). The β-configuration for the 3-acetoxy-group was confirmed by an independent synthesis [2] from 3β-acetoxy-5α-cholestan-6-one by treatment with boiling acetic anhydride in the presence of an acid catalyst. Since bromination of the acetate (V) has been found [2] to give only the known 3β-acetoxy-5α-bromocholestan-6-one and no 7α-bromo-ketone, the structure of the acetate (V) appears to be established.

The infrared spectrum and the analytical data of compound (III) were consistent with its being an enol-acetate toluene-*p*-sulphonate. Its bromination, to give the substance (IV)[optical rotatory dispersion, highly negative amplitude; *i.e.*, a 5α-bromo-6-ketone]

[1] Shoppee, Rees, Summers, and Phillips, *J.*, 1959, 2786.
[2] Hartshorn and Wallis, unpublished work.

proves that the ester (III) is a Δ^5- and not a Δ^6-6-acetate. It seems probable that this ester (III) was formed from the enol acetate (VI) by the addition of one mol. of toluene-*p*-sulphonic acid, a reaction analogous to the addition of acetic acid. The other mode of formation of the ester (III) would have been initial addition of toluene-*p*-sulphonic acid to the cyclo-ketone (II), to form 3β-toluene-*p*-sulphonyloxy-5α-cholestan-6-one, followed by enol acetylation of the keto-group. The latter reaction path may be excluded because enol acetylation of 6-keto-compounds by isopropenyl acetate (the reaction conditions used) has been shown [2] to yield a (*ca.* 1 : 1) mixture of Δ^5- and Δ^6-6-acetates. Thus by analogy with the addition of acetic acid to the acetate (VI), compound (III) has been formulated as 6-acetoxy-3β-toluene-*p*-sulphonyloxy-5α-cholest-5-ene.

Bromination of the enol acetate (VI) in the presence of sodium carbonate was unusual in that, although such bromination of an enol acetate is normally very fast, an enol acetate function appeared to be present (infrared spectrum) in the crude product isolated after 10 min. from the reaction mixture containing unused bromine. Chromatography on silica gel and elution with light petroleum–benzene gave a glass $C_{29}H_{46}Br_2O_2$ ($[\alpha]_D$ −128°). The infrared spectrum exhibited the characteristic enol acetate bands. By analogy with the established addition [1] of one mol. of bromine to 3α,5-cyclo-5α-cholest-6-ene (IX) to give 3β,7α-dibromocholest-5-ene (X), it is proposed that the dibromo-enol acetate obtained here by bromination of the acetate (VI) is 6-acetoxy-3β,7α-dibromocholest-5-ene (VII).

A second compound eluted from the column was a wax, $C_{29}H_{47}BrO_3$, whose infrared spectrum indicated the presence of a hydroxyl and an enol acetate group. Mild oxidation [3] of the hydroxyl group gave a compound (XII), the infrared spectrum of which was consistent with the presence of an acetylated enol form of an α-diketone. The optical rotatory dispersion of this product (XII) was similar to that for a Δ^5-7-ketone.[4] Finally, the ultraviolet spectrum was also consistent with formulation of ketone (XII) as 6-acetoxy 3β-bromocholest-5-en-7-one. Thus the alcohol would be 6-acetoxy-3β-bromocholest-5-en-7-ol. The above evidence does not allow deduction of the configuration of the 7-hydroxy-group. However, some support for the 7β-configuration may be derived from the intramolecular hydrogen bonding (3521 $cm.^{-1}$) indicated in the infrared spectrum of the alcohol (VIII); from an examination of Dreiding models, it is clear that such hydrogen bonding would occur more readily in the 7β-hydroxy-compound (*eq*-OH).

A higher yield (*ca* 95%) of pure dibromo-enol acetate (VII) ($[\alpha]_D$ −128°) was obtained after bromination of the enol acetate (VI) by rapid filtration of the crude product ($[\alpha]_D$ −120°) through a column of cellulose powder. The omission of sodium carbonate from the reactants affected neither the yield nor the quality of the product, and the difference in yields of the allylic bromide (VII) was traced to hydrolysis which occurred when the product was chromatographed on silica gel: when the pure dibromide (VII) was chromatographed on silica gel, it was hydrolysed to a variable extent, giving the alcohol (VIII).

Bromination of the enol acetate (VI) in carbon tetrachloride in the presence of epichlorohydrin [5] also gave the dibromo-enol acetate (VII) in good yield.

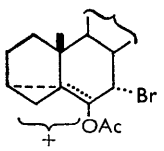
Bromination of the enol acetate (VI) in 1 : 10 pyridine–acetic acid gave an oil, the infrared spectrum of which differed markedly from the spectra of products of the previous brominations. Again there was no hydroxyl band, but, in addition to the enol acetate band, there was a strong band at 1698 $cm.^{-1}$. Adsorption of the crude material on silica gel and elution with light petroleum–benzene gave first a crystalline material whose analytical data and infrared spectrum were consistent with its being 7α-bromo-3α,5-cyclo-5α-cholestan-6-one. The change in amplitude accompanying the introduction of the bromine atom (Δa +65) is less than that normally found for (axial) bromo-ketones. This is perhaps partly due to incomplete data for the parent ketone. It is noteworthy that the 3,5-cyclo-fusion introduces a flattening of ring B. As a consequence the bromine atom is

[3] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.
[4] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6377.
[5] Hartshorn and Jones, *J.*, 1962, 1312.

splayed out from the axis of the ring and thus the p–π-orbital interaction is less intense. The data are consistent with formulation of compound (XI) as 7α-bromo-3α,5-cyclo-5α-cholestan-6-one.

In addition to the bromo-ketone (XI), further elution gave the alcohol (VIII), derived from the dibromide (VII) by hydrolysis on the column. From the rotation of the crude bromination product ($[\alpha]_D$ −45°) the ratio of the bromo-ketone (XI) to the dibromo-enol acetate (VII) formed in the reaction is *ca.* 2 : 3. Both the bromo-ketone (XI) and the dibromo-enol acetate (VII) were recovered unchanged after treatment with 1 : 10 pyridine–acetic acid.

When the solvent for the bromination was 2,6-lutidine–acetic acid (1 : 10), the infrared spectrum and rotation ($[\alpha]_D$ −21°) of the crude product showed that the ratio of bromo-ketone (XI) to the dibromo-enol acetate (VII) was *ca.* 1 : 1.



(XIII)

Thus the difference in the solvent used for bromination results in a marked difference in products. It appears likely that in each solvent the first step is α-attack of electrophilic bromine, accompanied by the incipient formation of the homoallylic cation (XIII).[6] With this particular system in carbon tetrachloride, the nucleophile, bromide ion, appears to attack the carbon-3, resulting in an overall addition, which like the addition of bromine to compound (IX) is similar to 1,4-addition across a conjugated diene system.

In 1 : 10 pyridine–acetic acid, on the other hand, a second and more usual bromination of an enol acetate becomes prominent with the formation of the bromo-ketone (XI). It appears that in pyridine–acetic acid the removal of acetyl cation from the homoallylic cation to form the bromo-ketone is assisted by the attack of a nucleophile derived from the solvent. It is unlikely that the base 2,6-lutidine or pyridine is directly concerned since in the presence of 2,6-lutidine (free from isomers) the yield of bromo-ketone was higher than that obtained when pyridine was used. However, while the attack by the stronger base 2,6-lutidine (pK_a 6·75) would be sterically more hindered than that by pyridine (pK_a 5·17), resulting in a decreased yield of bromo-ketone, there is no significant steric effect in the addition of a proton to 2,6-lutidine.[7] It seems probable that the nucleophile involved in the removal of acetyl cation is acetate ion produced in the solvent.

Experimental

M. p.s were determined on an electrothermal m. p. block and are corrected. Rotations were measured for chloroform solutions at room temperature. Infrared spectra were recorded for carbon disulphide, and ultraviolet absorption spectra for methanol solutions. The alumina used for chromatography was prepared by deactivating Peter Spence's grade " H " alumina with 5% of 10% acetic acid. The silica gel used was Hopkin and Williams's silica gel for chromatography. Light petroleum refers to the fraction with b. p. 50—70°.

3α,5-Cyclo-5α-cholestan-6-one (II).—8N-Chromic acid (7·5 c.c.; 1·1 mol.) was added dropwise to a stirred, ice-cold solution of 3α,5-cyclo-5α-cholestan-6β-ol (10 g.) in acetone (120 c.c.). The material isolated by means of ether was purified by chromatography, and crystallisation from methanol gave the ketone (8·6 g.) as needles, m. p. 96—97°, $[\alpha]_D$ +42° (*c* 0·84), $\nu_{max.}$ 1698 cm.$^{-1}$; R.D. in methanol, [*M*] (5890 Å) +50° (5000) +150°, (4000) +400° (3050) −2450° (2700) +10,300°. Heilbron, Hodges, and Spring, *J.*, 1938, 759, give m. p. 97°, $[\alpha]_D$ +40·9°.

Enol Acetylation of 3α,5-Cyclo-5α-cholestan-6-one (II).—The solvent was fractionally distilled at 96° from a solution of the ketone (2 g.) and toluene-*p*-sulphonic acid (260 mg.) in isopropenyl acetate (100 c.c.). After 6 hr. (30 c.c. of distillate) the remaining solvent was removed at 20 mm. The residue, worked up through ether, was adsorbed on alumina. Elution with light petroleum afforded *6-acetoxy-3α,5-cyclo-5α-cholest-6-ene* (VI) (1·71 g.); a sample dried at 40°/0·01 mm. was an oil, $[\alpha]_D$ −16° (*c* 0·94) (Found: C, 81·4; H, 11·0. $C_{29}H_{46}O_2$ requires

[6] Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 18.
[7] Brown, Gintis, and Podall, *J. Amer. Chem. Soc.*, 1956, **78**, 5375.

C, 81·7; H, 10·9%), $\nu_{max.}$ 1770 and 1208 (enol OAc) and 1675 cm.$^{-1}$ (C=C), $\lambda_{max.}$ 258 mμ (ε 620).

Elution with light petroleum–benzene (10 : 3) afforded starting material (169 mg.), m. p. 96—97°, $[\alpha]_D$ +42° (*c* 1·07), $\nu_{max.}$ 1698 cm.$^{-1}$.

Finally, elution with benzene gave 6-*acetoxy*-3β-*toluene*-p-*sulphonyloxy*-5α-*cholest*-5-*ene* (III) (409 mg.), which crystallised from light petroleum as needles (350 mg.), m. p. 145—146°, $[\alpha]_D$ −48° (*c* 1·00) (Found: C, 72·1; H, 9·1; S, 5·2. $C_{36}H_{54}O_5S$ requires C, 72·2; H, 9·1; S, 5·35%), $\nu_{max.}$ 1764 and 1205 (enol OAc), 1695 (C=C), 1186 and 1176 cm.$^{-1}$ (toluene-*p*-sulphonate).

Bromination of 6-*Acetoxy*-3β-*toluene*-p-*sulphonyloxycholest*-5-*ene* (III).—Bromine (57 mg., 1·1 mol.) in carbon tetrachloride (0·25 c.c.) was added to a stirred, ice-cold suspension of sodium carbonate (150 mg.) in a solution of the enol acetate (200 mg.) in carbon tetrachloride (10 c.c.). After 10 min. the excess of bromine was removed by aqueous sodium sulphite, and the product isolated by means of ether. Evaporation gave a solid (210 mg.), which crystallised from ether to give 5α-*bromo*-3β-*toluene*-p-*sulphonyloxycholestan*-6-*one* (IV) (175 mg.) as needles, m. p. 158—159° (decomp.), $[\alpha]_D$ −99° (*c* 0·41) (Found: C, 64·4; H, 8·4; Br, 12·6. $C_{34}H_{51}BrO_4S$ requires C, 64·2; H, 8·1; Br, 12·6%), $\nu_{max.}$ 1724 (*ax*-bromo-ketone), 1189 and 1179 cm.$^{-1}$ (toluene-*p*-sulphonate); R.D. in methanol, [*M*] (5890 Å) −1200°, (5000) −2200°, (4000) −4000°, (3300) −17,600°, (2850) +19,400°, (2750) +19,000°.

Addition of Acetic Acid to 6-*Acetoxy*-3α,5-*cyclo*-5α-*cholest*-6-*ene* (VI).—The enol acetate (330 mg.) was heated at 60° for 10 min. with acetic acid (15 c.c.; dry) containing 100% sulphuric acid (0·02 c.c.). The solution was cooled, and after working up by means of ether afforded an oil (301 mg.). Filtration through alumina and crystallisation from methanol gave 3β,6-*diacetoxycholest*-5-*ene* (V) (250 mg.) as needles, m. p. 91·5—92°, $[\alpha]_D$ −49° (*c* 1·08) (Found: C, 76·1; H, 10·2; O, 13·55. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·3; O, 13·2%), $\nu_{max.}$ 1761 and 1210 (enol OAc) 1742 and 1241 (3β-OAc), and 1701 cm.$^{-1}$ (C=C).

Bromination of 6-*Acetoxy*-3α,5-*cyclo*-5α-*cholest*-6-*ene* (VI).—(*a*) Bromine (104 mg., 1·1 mol.) in carbon tetrachloride (0·05 c.c.) was added to a stirred, ice-cold suspension of sodium carbonate (190 mg.) in a solution of the enol acetate (275 mg.) in carbon tetrachloride (15 c.c.). After 10 min. the excess of bromine was destroyed by aqueous sodium sulphite; the product isolated by means of ether was an oil (359 mg.), $[\alpha]_D$ −120° (*c* 0·80), $\nu_{max.}$ 1764 and 1206 (enol acetate), and 1695 cm.$^{-1}$ (C=C) (no OH band). The oil was adsorbed on silica gel (30 g.). Light petroleum–benzene (10 : 3) eluted glassy 6-*acetoxy*-3β,7α-*dibromocholest*-5-*ene* (VII) (135 mg.), $[\alpha]_D$ −129° (*c* 0·69) (Found: C, 59·4; H, 8·1; Br, 26·8. $C_{29}H_{46}Br_2O_2$ requires C, 59·4; H, 7·9; Br, 27·3%), $\nu_{max.}$ 1764 and 1206 (enol OAc) and 1695 cm.$^{-1}$ (C=C). Further elution with benzene afforded waxy 6-*acetoxy*-3β-*bromocholest*-5-*en*-7β-*ol* (VIII) (157 mg.); a sample purified by sublimation at 100°/0·01 mm. had m. p. 129—130°, $[\alpha]_D$ −32° (*c* 0·57) (Found: C, 67·0; H, 8·9; Br, 14·7; O, 9·6. $C_{29}H_{47}BrO_3$ requires C, 66·5; H, 9·0; Br, 15·3; O, 9·2%), $\nu_{max.}$ 3571 (OH), 3521 (H-bonded OH), 1751 and 1212 (enol OAc), and 1695 cm.$^{-1}$ (C=C).

(*b*) Bromine (250 mg., 1·1 mol.) in carbon tetrachloride (1·15 c.c.) was added to a stirred, ice-cold solution of the enol acetate (660 mg.) in carbon tetrachloride (30 c.c.). After 10 min. the mixture was worked up by means of ether. Evaporation gave a viscous oil (940 mg.), $[\alpha]_D$ −118° (*c* 0·99), which was dissolved in light petroleum and rapidly filtered through a column of cellulose powder (40 g.); removal of the light petroleum at 20 mm. afforded 6-acetoxy-3β,7α-dibromocholest-5-ene (VII) (830 mg.), $[\alpha]_D$ −128° (*c* 0·70), $\nu_{max.}$ 1764, 1206, and 1695 cm.$^{-1}$.

(*c*) Bromine (285 mg., 1·1 mol.) in carbon tetrachloride (1·35 c.c.) was added to a stirred, ice-cold solution of the enol acetate (750 mg.) in carbon tetrachloride (30 c.c.). After 10 min., the mixture was worked up by means of ether. Evaporation of the solvent at 20 mm. gave a viscous oil (1·135 g.), $[\alpha]_D$ −120° (*c* 1·21). Rapid filtration of a solution of the crude product in light petroleum through a column of cellulose powder and evaporation of the solvent at 20 mm. gave the above dibromo-enol acetate (VII) (950 mg.), $[\alpha]_D$ −125° (*c* 1·10), $\nu_{max.}$ 1764, 1206, and 1695 cm.$^{-1}$.

(*d*) Bromine (108 mg., 1·15 mol.) in acetic acid (0·43 c.c.) was added to a solution of the enol acetate (254 mg.) in acetic acid (3 c.c.) and pyridine (0·3 c.c.). The uptake of bromine was rapid but incomplete (10 min.); the excess of bromine was removed by aqueous sodium sulphite, and the steroidal material removed in ether. Evaporation yielded an oil (330 mg.), $[\alpha]_D$ −45° (*c* 0·95), $\nu_{max.}$ 1764 and 1211 (enol acetate), and 1698 cm.$^{-1}$ (3,5-cyclo-6-ketone superimposed on C=C) (no OH band). Adsorption of the oil on silica gel (30 g.) and elution with light petroleum–benzene (10 : 3) afforded 7α-*bromo*-3α,5-*cyclo*-5α-*cholestan*-6-*one* (XI) (124 mg.) which crystallised

from ether–methanol as needles (110 mg.), m. p. 116—117°, $[\alpha]_D$ +82° (*c* 0·62) (Found: C, 69·7; H, 9·0; Br, 17·0. $C_{27}H_{43}BrO$ requires C, 69·95; H, 9·3; Br, 17·25%), $\nu_{max.}$ 1698 cm.$^{-1}$ (C=O); R.D. in methanol, [*M*] (5890 Å) −700°, (5000) −200°, (4000) +200°, (3500) +800°, (3350) +700°, (2750) +6900°, (2700) +6700°. Further elution with benzene gave 6-acetoxy-3β-bromocholest-5-en-7β-ol (VIII) (83 mg.), identified by m. p. 128—129°, $[\alpha]_D$ −31° (*c* 0·81), $\nu_{max.}$ 3571, 3521, 1751, 1212, and 1695 cm.$^{-1}$.

(*e*) Bromine (148 mg., 1·15 mol.) in acetic acid (0·6 c.c.) was added to a solution of the enol acetate (350 mg.) in acetic acid (4 c.c.) and 2,6-lutidine (0·4 c.c.; pure, isomer-free). The product isolated by means of ether was an oil (450 mg.), $[\alpha]_D$ −21° (*c* 0·95), $\nu_{max.}$ 1764 and 1211 (enol OAc) and 1698 cm.$^{-1}$ (3,5-cyclo-6-ketone superimposed on C=C).

Oxidation of 6-Acetoxy-3β-bromocholest-5-en-7β-ol (VIII).—8N-Chromic acid (0·055 c.c., 1·1 mol.) was added dropwise to a stirred, ice-cold solution of the alcohol (103 mg.) in acetone (10 c.c.). The steroid was removed in ether. After removal of the solvent at 20 mm., crystallisation of the residue from ether–methanol gave *6-acetoxy-3β-bromocholest-5-en-7-one* (XII) as needles, m. p. 133—134°, $[\alpha]_D$ −45° (*c* 0·37) (Found: C, 66·6; H, 9·1; Br, 15·2; O, 9·6. $C_{29}H_{45}BrO_3$ requires C, 66·8; H, 8·7; Br, 15·3; O, 9·2%), $\nu_{max.}$ 1776 and 1203 (OAc), 1701 (C=C·C=O), and 1656 cm.$^{-1}$ (C=C), $\lambda_{max.}$ 243 mμ (ε 14,700); R.D. in methanol, [*M*] (5890 Å) −700°, (5000) −450°, (4000) −700°, (3925) −950°, (3500) +50°, (3000) −5000°, (2800) −7300°.

Hydrolysis of 6-Acetoxy-3β,7α-dibromocholest-5-ene (VII) *on Silica Gel.*—The dibromide (700 mg.) was adsorbed on silica gel (60 g.) in light petroleum. After 1 hr. light petroleum–benzene (10 : 3) eluted unchanged starting material (98 mg.), identified by $[\alpha]_D$ −127° (*c* 1·01), $\nu_{max.}$ 1764, 1206, and 1695 cm.$^{-1}$. Further elution with benzene afforded 6-acetoxy-3β-bromocholest-5-en-7β-ol (VIII) (414 mg.), identified by m. p. 127—129°, $[\alpha]_D$ −32° (*c* 1·05), $\nu_{max.}$ 3571, 3521, 1751, 1212, and 1695 cm.$^{-1}$.

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