185. *Studies in the Steroid Series. Part LXXIII.* The Bromination of 7-Oxo-steroids.*

By E. R. H. Jones and D. J. Wluka.

Treatment of 7-oxo-5α-cholestanyl acetate (II) with acetic anhydride–toluene-*p*-sulphonic acid gives a mixture of the Δ^6- and Δ^7-eno lacetates (I and III), separable by chromatography. Bromination of these under normal conditions leads to 6-bromo-compounds (IV and V), but in the presence of bases bromination of the ketone (II) gives the hitherto unknown 8β-bromo-compound (VI).

The acid-catalysed bromination of 7-oxo-5α-cholestanyl acetate (II) yields the 6β-bromo-compound (V), transformed in the presence of hydrogen bromide into the more stable 6α(equatorial)-isomer (IV).[1,2] Further bromination of either isomer yields a 6 : 6-dibromo-compound. From these observations and other data it has been concluded [3] that enolisation of this 7-keto-steroid takes place to give the Δ^6-rather than the Δ^7-enol and suggested that the shielding of the 8β-hydrogen atom by the angular methyl groups is partly responsible. A possible explanation of the isolation of only 6-substituted bromination products is that enolisation towards the 8-position does occur, but that any 8-bromo-compound initially formed is very rapidly isomerised under the experimental conditions employed, *i.e.*, in the presence of hydrogen bromide. This view received some support from the behaviour of the 9-bromo-11-keto-compounds described in the preceding paper,[4] and some experiments with 7-keto-compounds were therefore initiated.

In this case, however, preparative indications were much less favourable and we could

* Part LXXII, preceding paper.

[1] Barr, Heilbron, Jones, and Spring, *J.*, 1938, 334.

[2] Configurations suggested by Fieser and Fieser, "Natural Products related to Phenanthrene," 1948, p. 270, and confirmed by Cookson, *J.*, 1954, 282.

[3] Corey and Sneen, *J. Amer. Chem. Soc.*, 1956, **78**, 6269.

[4] Cf. Wrigley, Ph.D. thesis, Manchester, 1956.

find no example of the production of a Δ^7-enol acetate. Hirschmann, Brown, and Wendler [5] treated methyl 3α-acetoxy-7 : 12-dioxocholanate with acetic anhydride and toluene-*p*-sulphonic acid, obtaining a 44% yield of a crystalline enol acetate, later [6] proved to be the Δ^6-isomer by oxidative degradation. There was a substantial amount of non-crystalline product from this experiment; this gave a moderate yield of the parent ketone on hydrolysis and, assuming that it was the Δ^7-isomer, we carried out similar experiments with 7-oxocholestanyl acetate.

In acetic anhydride containing toluene-*p*-sulphonic acid the ketone (II) was converted to the extent of 60% into a mixture of the Δ^6- and Δ^7-enol acetates (I and III), separated from one another and from starting material by chromatography. Although neither (I) nor (III) crystallised (not uncommon with steroid enol acetates), they were easily differentiated by their optical rotations (−55° and −10° respectively), by their behaviour on bromination (see below), and by their infrared spectra. The spectra differed most markedly in the range 1050—1180 cm.$^{-1}$ and that of the Δ^6-isomer (I) contained a pair of weak bands at 800 and 820 cm.$^{-1}$ which were assigned to the C–H of the 6 : 7-double bond. The signs of the optical rotations of (I) and (II) are in agreement with the values for Δ^6-cholestenes [7] and Δ^7-cholestenes.[8]

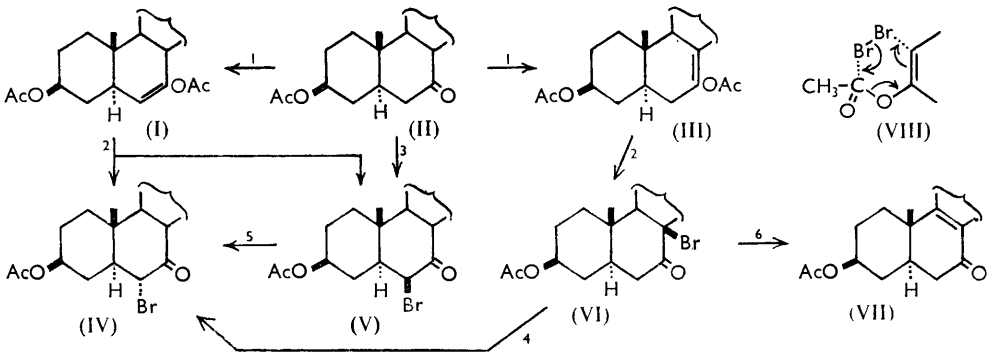
In *iso*propenyl acetate containing toluene-*p*-sulphonic acid, the Δ^6-isomer was formed in 25% yield, none of the other isomer could be detected, and most of the unconverted ketone (II) was recovered. Neither of the isomers was observed to rearrange under these conditions. A detailed study of the relative stabilities of the isomers (I) and (III) under the conditions used in their preparation was not possible because of substantial losses of material (usually *ca.* 30% of the starting material could not be eluted from deactivated alumina and this amount increased with increasing concentration of the acid catalyst). The relative yields of the two isomers (I and III) varied usually in the range 1·2—2 : 1, although in one experiment in which acetic acid was rigorously removed before addition of the ketone the ratio reached 6·5 : 1. None of the Δ^7-isomer (III) could be detected in an attempted isomerisation of (I), and only a 20% conversion (based on total recovered enol acetates) of (III) into (I) was achieved. It was concluded that both enol acetates are formed, simultaneously, in acetic anhydride and that the Δ^7-isomer is gradually converted into the more stable Δ^6-isomer.

Bromination of the Δ^6-enol acetate (I), in pyridine–acetic acid, gave a mixture (separated by chromatography) of the two monobromo-compounds (IV and V) (75% yield) together with some 7-oxocholesteryl acetate. Control experiments showed that the bromo-compounds were unaffected on alumina and, apart from partial dehydrobromination, the 6β-isomer (V) was recovered unchanged after prolonged treatment under the bromination conditions (*i.e.*, by bromine and pyridine hydrobromide in pyridine–acetic acid). Whereas direct bromination of the ketone (II) with bromine in chloroform gives *ca.* 55% of the 6β(axial)-isomer (V), a stereoelectronic factor counteracting the steric factor favouring equatorial attack of the reagent,[3] in this case the product of equatorial attack (*i.e.*, IV) predominates to the extent of 5 : 1, or 2·5 : 1 if it is assumed that the whole of the unsaturated ketone is derived from the axial isomer. It seems improbable that stereoelectronic control such as is involved in the acid-catalysed enolisation process is operative here. A cyclic transition state such as (VIII) could be operative in enol acetate brominations; this would appear to favour equatorial introduction of the 6-bromine atom.

Bromination of the Δ^7-isomer (III) in the presence of pyridine gave, in 45% yield, the new 8β-bromo-ketone (VI). Dehydrobromination with pyridine yielded 3β-acetoxy-5α-cholest-8-en-7-one (VII) with constants identical with those of Fieser [9] except in extinction

[5] Hirschmann, Brown, and Wendler, *J. Amer. Chem. Soc.*, 1951, **73**, 5373.
[6] Hirschmann and Wendler, *ibid.*, 1953, **75**, 2361.
[7] James, Rees, and Shoppee, *J.*, 1955, 1370.
[8] Barton, *J.*, 1945, 813.
[9] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4395.

coefficient (ε 10,100, compared with 15,500). The values found [10,11] for a number of compounds with the same chromophoric system in the ergosterol series do not exceed 10,000.



Reagents: 1, Ac_2O–*p*-$C_6H_4Me{\cdot}SO_3H$. 2, Br–C_5H_5N–AcOH. 3, Br–$CHCl_3$. 4, HBr–$CHCl_3$–AcOH. 5, HBr–AcOH. 6, C_5H_5N.

The effect of hydrogen bromide on the 8β-bromo-ketone (VI) was highly dependent upon the solvent. In dry chloroform this compound was recovered unchanged, in chloroform–acetic acid (1 : 1) the 6α-bromo-ketone (IV) (60%) and debrominated ketone (II) (35%) resulted, whilst in acetic acid the ratio (IV) : (II) was *ca.* 1 : 3, debromination predominating. It appears that in acetic acid alone, rebromination does not occur, in line with the original observation [1] that the ketone (II) is not brominated at an appreciable rate in acetic acid at room temperature. The absence of isomerisation in the chloroform experiment suggests that in the direct bromination experiments (although the conditions were not strictly comparable), little or no bromination occurs at position 8. It is hoped that more direct information will be forthcoming from a study of the bromination of 3β-acetoxy-8β-deuterocholestan-7-one which should now be accessible *via* (VI) by debromination with zinc and deuteroacetic acid (AcOD).

Infrared and ultraviolet absorption spectra established the axial nature of the 8-bromine atom in (VI), and complete proof of its 8β-configuration was provided by comparison of its optical rotatory dispersion curve with those of the parent ketone (II) and the isomeric 6-bromo-compounds (IV and V). As was expected the β(axial)-compounds (V and VI) showed large Cotton effects and bathochromic shifts as compared with those of the unsubstituted ketone and the 6α(equatorial)-bromo-compound (VI).[12] It was not possible to obtain chemical proof of the 8β-configuration of the bromine atom since reduction of the bromo-ketone (VI) with lithium aluminium hydride gave the parent ketone (II) together with material readily converted on treatment with base into compounds containing conjugated diene chromophores.

Experimental

General directions are given in the preceding paper.

Enol-acetylation of 7-Oxo-5α-cholestanyl Acetate (II).—(*a*) The solvent was fractionally distilled through a short column packed with glass helices from a solution of the ketone (6·6 g.) and toluene-*p*-sulphonic acid (2·85 g.) in acetic anhydride (150 c.c.), more anhydride being added periodically to keep the volume approximately constant. After 9 hr. the solvent was evaporated under reduced pressure, methanol was added to the brown gum to decompose any remaining anhydride, and the steroid was recovered in the usual manner. The product was chromatographed on alumina (600 g.); benzene–light petroleum (1 : 2; 4 × 300 c.c.) eluted 3β : 7-*diacetoxy*-5α-*cholest*-6-*ene* (I) (1·99 g.); further elution with the same solvent mixture

[10] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.
[11] Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892.
[12] Djerassi, Osiecki, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.

(7 × 300 c.c.) yielded 3β : 7-*diacetoxy*-5α-*cholest*-7-*ene* (III) (1·75 g.); finally, benzene eluted starting material (1·31 g.). Neither enol acetate crystallised. The Δ^6-enol acetate (I) had $[\alpha]_D$ −55° (*c* 0·97) (Found: C, 76·6; H, 10·4. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%), $\nu_{max.}$ 1736, 1235 (3-acetate), 1754 (sh), 1215 (7-acetate), and 1675, 800, and 820 cm.$^{-1}$ (6-ene). The Δ^7-enol acetate (III) had $[\alpha]_D$ −10° (*c* 1·13) (Found: C, 76·5; H, 10·2%), $\nu_{max.}$ 1736, 1236 (3-acetate), 1754 (sh), 1217 (7-acetate), and 1673 cm.$^{-1}$ (7-ene). The infrared spectra of the two isomers were very similar, but they could be distinguished by differences in the 1050—1180 cm.$^{-1}$ region.

(*b*) The solvent was fractionally distilled from a solution of 7-oxocholestanyl acetate (3·3 g.) and toluene-*p*-sulphonic acid (0·5 g.) in *iso*propenyl acetate (60 c.c.); the volume of the solution was maintained at *ca.* 50 c.c. by periodic addition of *iso*propenyl acetate. After 7 hr. the solvent was removed under reduced pressure and the steroid recovered in the usual manner. Starting material (1·4 g.), m. p. 151—153°, crystallised from a solution of the product in acetone–methanol, and the material (1·53 g.) from the mother-liquors was chromatographed on alumina (120 g.). Benzene–light petroleum (1 : 3) eluted 3β : 7-diacetoxycholest-6-ene (750 mg.; $[\alpha]_D$ −55°); benzene–light petroleum (1 : 1) then eluted more starting material (600 mg.), m. p. and mixed m. p. 150—152°.

Isomerisation of the Δ^7-*Enol Acetate* (III).—A solution of the Δ^7-enol acetate (910 mg.) and toluene-*p*-sulphonic acid (70 mg.; 0·2 mol.) in acetic anhydride (60 c.c.; acetic acid-free) was fractionally distilled, 20 c.c. of distillate being collected during 2 hr. After a further 1¼ hours' heating under reflux, the acetic anhydride was removed under reduced pressure and the product, recovered *via* ether, was adsorbed on alumina (90 g.). Benzene–light petroleum (1 : 3; 100 c.c.) eluted 75% pure 3β : 7-diacetoxycholest-6-ene (140 mg.; identified by its infrared absorption and $[\alpha]_D$ −42°), and further elution with the same solvent mixture (350 c.c.) afforded starting material (540 mg.; identified by its infrared absorption and $[\alpha]_D$ −10°). Finally, benzene (100 c.c.) eluted 3α-acetoxycholestan-7-one (50 mg.), plates (from acetone–methanol), m. p. and mixed m. p. 151—153°.

Attempted Isomerisation of the Δ^6-*Enol Acetate* (I).—Acetic anhydride (150 c.c.) containing toluene-*p*-sulphonic acid (180 mg.) was fractionally distilled until the still-head temperature ceased to rise. After the Δ^6-enol acetate (2·0 g.) in acetic anhydride (20 c.c.; acetic acid-free) had been added, the solution was concentrated to *ca.* 100 c.c., and then heated under reflux for 3 hr. After isolation as above, the product was adsorbed on alumina (200 g.). Benzene–light petroleum (1 : 4) eluted starting material (0·99 g.; identified by its infrared absorption), but none of the Δ^7-enol acetate could be detected. Elution with benzene–light petroleum (1 : 1) and then with benzene afforded ketonic material (300 mg.), shown by its infrared absorption to be impure 3β-acetoxycholestan-7-one.

Bromination of 3β : 7-*Diacetoxy*-5α-*cholest*-6-*ene* (I).—Bromine (220 mg., 1·5 mol.) in acetic acid (0·6 c.c.) was added to a solution of the above enol acetate (450 mg.) in 1 : 10 v/v pyridine–acetic acid (5·5 c.c.) under nitrogen. The flask was stoppered and kept in the dark at 20° for 25 hr. An aqueous solution of sodium sulphite was then added, and the product isolated *via* ether and adsorbed on alumina (50 g.). Benzene–light petroleum (1 : 2) eluted in succession 6β-bromo-7-oxocholestanyl acetate (V) (64 mg.), needles (from acetone–methanol), m. p. and mixed m. p. 172—174°, and 6α-bromo-7-oxocholestanyl acetate (IV) (310 mg.), needles (from aqueous acetic acid), m. p. and mixed m. p. 147—148°; finally, benzene eluted 7-oxocholest-5-enyl acetate (53 mg.), prisms (from acetone–methanol), m. p. and mixed m. p. 160—162°.

Bromination of 3β : 7-*Diacetoxy*-5α-*cholest*-7-*ene* (III).—Bromine (910 mg., 1·5 mol.) in acetic acid (2·5 c.c.) was added to a solution of the above enol acetate (1·85 g.) in 1 : 10 v/v pyridine–acetic acid (22 c.c.) in nitrogen. The flask was stoppered, and stored at 17° for 24 hr. in the dark. Sodium sulphite was added, and the steroid was recovered *via* ether. The product was adsorbed on a column of alumina (200 g.); benzene–light petroleum (2 : 5) eluted 8β-*bromo*-7-*oxo*-5α-*cholestanyl acetate* (VI) (900 mg.), needles (from ethyl acetate–methanol), m. p. 135—137° (decomp.; the sample being placed on the block 10° below the m. p.), $[\alpha]_D$ −113° (*c* 1·06) (Found: C, 66·7; H, 9·0; Br, 15·6. $C_{29}H_{47}O_3Br$ requires C, 66·5; H, 9·1; Br, 15·3%), $\nu_{max.}$ 1739, 1238 (acetate), and 1718 cm.$^{-1}$ (7-ketone), $\lambda_{max.}$ 3050 Å (ε 106) [ketone (II) has max. at 2830 Å (ε 40)]. Further elution with benzene yielded conjugated ketonic material, plates (from methanol), m. p. 148—154°, $\lambda_{max.}$ 2540 Å (ε 10,000) (see below).

7-*Oxocholest*-8-*enyl Acetate* (VII).—A solution of the 8β-bromo-ketone (85 mg.) in pyridine (1 c.c.) was kept overnight at 30° and then at 100° for 1 hr. After the pyridine had been

removed under reduced pressure the residue was dissolved in ether and washed several times with dilute hydrochloric acid, water, and finally aqueous sodium hydrogen carbonate. The recovered steroid (67 mg.) was adsorbed on alumina (7 g.) and eluted with benzene–light petroleum (1 : 1; 7 × 5 c.c.), and then with benzene–light petroleum (5 : 1; 10 c.c.). Each fraction showed an absorption maximum at 2525 Å, the extinction coefficient being greatest (10,000) in the last four fractions. These (35 mg.) on crystallisation from methanol gave the conjugated ketone as needles, m. p. 154—157°, $[\alpha]_D$ −34° (*c* 0·87), $\lambda_{max.}$ 2525 Å (ε 10,100). Fieser [8] gives m. p. 155—156°, $[\alpha]_D$ −32·3°, $\lambda_{max.}$ 2530 Å (ε 15,500).*

Treatment of the 8β-*Bromo-ketone* (VI) *with Hydrogen Bromide.*—(a) *In chloroform.* The rotation of a solution of the 8β-bromo-ketone (45 mg.) in dry chloroform (7 c.c.) containing hydrogen bromide (0·1 c.c.; 50% in acetic acid) did not change during 3 hr. After 7 hr., the steroid was recovered *via* ether; crystallisation from ethyl acetate–methanol gave starting material (30 mg.), m. p. and mixed m. p. 135—137° (decomp.).

(b) *In chloroform–acetic acid.* The rotation (1 dm. tube) of a solution of the 8β-bromo-ketone (140 mg.) in chloroform–acetic acid (1 : 1; 15 c.c.) containing hydrogen bromide (0·4 c.c.; 50% in acetic acid) changed from −0·80° to −0·32° in 7½ hr.; the solution had then become too dark for further observations to be made. After 10 hr., the steroid was isolated *via* ether and adsorbed on alumina (15 g.); benzene–light petroleum (1 : 2) eluted starting material (52 mg.), m. p. and mixed m. p. 134—137° (decomp.) after two recrystallisations from ethyl acetate–methanol, and 6α-bromo-7-oxo-5α-cholestanyl acetate (53 mg.), which after recrystallisation from acetone–methanol and from aqueous acetic acid had m. p. and mixed m. p. 142—146°; further elution with benzene–light petroleum (4 : 1) gave 7-oxo-5α-cholestanyl acetate (30 mg.), plates (from acetone–methanol), m. p. and mixed m. p. 151—153°.

(c) *In acetic acid.* The rotation (1 dm. tube) of a solution of the 8β-bromo-ketone (200 mg.) in acetic acid (7 c.c.) containing hydrogen bromide (0·2 c.c.; 50% in acetic acid) changed from −2·78° to −2·25° in 70 min. After 7½ hr. the product was isolated *via* ether and chromatographed on alumina (25 g.), elution being effected with benzene–light petroleum (1 : 2; 7 × 15 c.c.), and benzene–light petroleum (2 : 1; 5 × 15 c.c.). Fractions 4—12 (incl.) consisted of 7-oxo-5α-cholestanyl acetate (110 mg.), m. p. and mixed m. p. 151—153°; the first three fractions (40 mg.) contained principally 6α-bromo-7-oxo-5α-cholestanyl acetate, as shown by their infrared spectra, but a pure sample could not be obtained by crystallisation.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 23rd,* 1958.]

* Unfortunately the only sample which Professor Fieser had retained, and which he kindly sent to us, had deteriorated on storage so that further elucidation of the intensity discrepancy was not possible.