Photochemical Rearrangement of α-Hydroxy-ketones to Lactones [1]

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U.v. irradiation of 3β-acetoxy-5α-hydroxycholestan-6-one (I; R = Ac) and of the 5β-epimer (VI; R = Ac) through Pyrex gives 3β-acetoxy-5α-hydroxy-5,6-secocholestan-6-oic lactone (II; R = Ac) and its 5β-epimer respectively, in almost quantitative yield. The derived 3-oxo-lactones are equilibrated heavily in favour of the *trans*-isomer (VIII). On photoisomerisation of the *O*-deuterio-compounds (I and VI; R = Ac) in *O*-deuterio-ethanol one atom of deuterium is incorporated at C-7 only in one configuration. The whole rearrangement is thus stereospecific.

Some confusion in the literature is removed by showing that in the formation of 3β,5β-dihydroxycholestan-6-one (VI; R = H) by reaction of 3β-acetoxy-5α-bromocholestan-6-one (V) with sodium hydroxide in methanol the 6,6-dimethoxy-compound (IX) is an intermediate. The product of oxidation of 3β-acetoxycholestan-6-one (XV) with perbenzoic acid, which had been described as the 5,6-lactone (VII; R = Ac), is actually a mixture containing mostly the isomeric 6,7-lactone (XVI; R = Ac).

Irradiation of *trans*-1-acetyl-4-t-butylcyclohexanol (XXII) yields almost no 4-t-butylcyclohexyl acetate, but mainly 4-t-butyl-6-methylbicyclo[3,1,1]heptane-1,6-diol (XXIII) formed through the usual six-atom transition state. 4-t-Butylcyclohexanone, which is also formed (31%), becomes the principal product (78%) from *cis*-1-acetyl-4-*t*-butylcyclohexanol (XXV).

An old photochemical reaction,[2] which has recently been revived,[3] is the photohydrolysis of cyclic ketones to seco-acids, proceeding through the corresponding ketenes. In the hope of learning something about the course of events, we have studied the photochemistry of ketones containing hydroxy-groups in various positions and configurations in the molecule, and now describe the behaviour of some α-hydroxy-ketones.

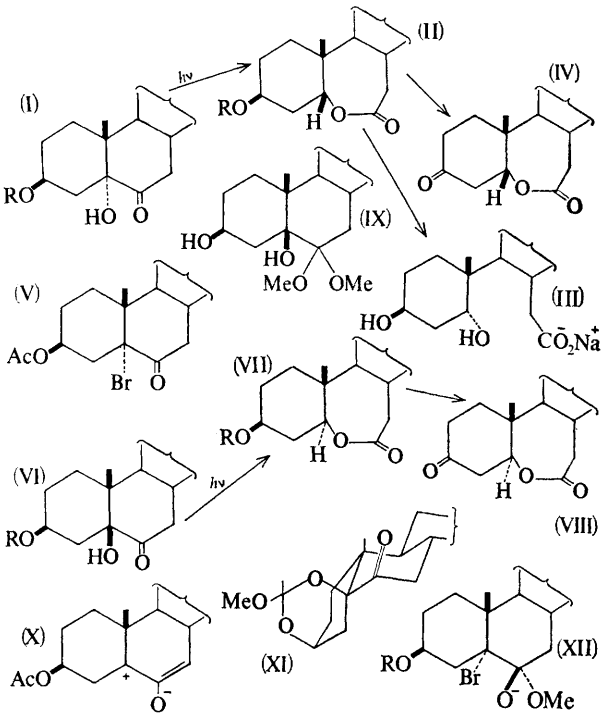
Irradiation of 3β-acetoxy-5α-hydroxycholestan-6-one [4] (I; R = Ac) through Pyrex glass in ethanol or benzene gave the isomeric lactone (II; R = Ac) in almost quantitative yield. The likely presence of the ε-lactone ring B was revealed by the band at 1708 cm.$^{-1}$ in the i.r. spectrum (in addition to the acetate absorption at 1720 cm.$^{-1}$), the circular-dichroic maximum at 224 mμ, $\Delta\varepsilon$ − 1·3 (the 3-acetate group does not absorb in that region), and the n.m.r. signals at τ 5·67 (5-H, triplet splitting 3·5 c./sec.) and 7·295 (7-methylene group, two doublets of doublets, J_{gem} 15 c./sec.). Dilute sodium hydroxide turned the lactone acetate (II; R = Ac) into the hydroxy-salt (III) (m.p. 230°) which with dilute acid gave the hydroxy-lactone (II; R = H), having the expected spectral properties. The identical compound (II; R = H) was obtained in high yield by irradiation of the dihydroxy-ketone (I; R = H) in benzene or ethanol.

To find out whether the photorearrangement was truly stereospecific the next step was obviously to examine the 5α-hydroxy-epimer (VI), but first some confusion about the compound's identity had to be cleared up. Heilbron, Jones, and Spring [5] had obtained a compound A (presumed to be 3β,5β-dihydroxycholestan-6-one), m.p. 130—140°, $[\alpha]_D$ +29°, by boiling 3β-acetoxy-5α-bromocholestan-6-one (V) in 10% methanolic potassium hydroxide. Mazur and Nussim [6] later reported that 3β,5α-dihydroxycholestan-6-one (I; R = H) gave a compound under these conditions identical with compound A (presumably identified only by the acetate, m.p. 121—122°, $[\alpha]_D$ −16°). Rowland,[7] however, could not isolate compound A under the conditions described by Heilbron *et al.*,[5] but instead obtained an oil, $[\alpha]_D$ −5° (acetate, m.p. 141°, $[\alpha]_D$ −22°), which he stated was 3β,5β-dihydroxycholestan-6-one (VI; R = H). Reaction of the bromo-ketone (V) with ethanolic potassium hydroxide at room temperature was reported [7] to yield the same oil.

We found that the bromo-ketone (V) reacted with 10%

[1] A summary of these results has been published, R. C. Cookson, *Pure Appl. Chem.*, 1964, **9**, 575.
[2] G. Ciamician and P. Silber, *Ber.*, 1903, **36**, 1582, and later papers.
[3] Reviewed by G. Quinkert, *Angew. Chem. Internat. Ed.*, 1965, **4**, 211.
[4] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[5] I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 1937, 801.
[6] Y. Mazur and M. Nussim, *Tetrahedron Letters*, 1961, 817.
[7] A. T. Rowland, *J. Org. Chem.*, 1962, **27**, 1135.

methanolic potassium hydroxide just as described by Heilbron *et al.*[5] to form compound A (55% yield) with m.p. 138°, $[\alpha]_D$ +29°. This is now considered to be the dimethyl acetal (IX) on the basis of its elemental

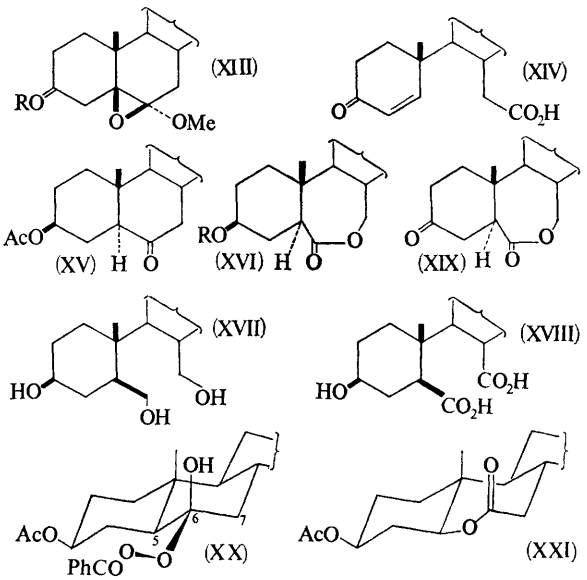


analysis, i.r. spectrum (no absorption in the carbonyl stretching region), Zeisel determination (showing two methoxy-groups), and the two singlets at τ 6·80 and 6·66 in its ^{1}H n.m.r. spectrum. Mild acid converted the acetal (IX = A) into an oil, $[\alpha]_D$ −6° (acetate, m.p. 141—142°, $[\alpha]_D$ −22°), the i.r. spectrum of which was the same as that of the compound formed under Rowland's conditions [7] (10% ethanolic potassium hydroxide at room temperature). The acetate, m.p. 141—142°, is thus authentic 3β-acetoxy-5β-hydroxy-6-one (VI; R = Ac) and the oil, which finally crystallised, m.p. 62°, $[\alpha]_D$ −6°, the true 3β,5β-dihydroxy-6-one (VI; R = H).

Treatment of the 3β,5α-dihydroxy-6-one (I; R = H) with 10% methanolic potassium hydroxide isomerised it to the *cis*-dihydroxy-ketone (VI; R = H), although the high yield reported by Mazur and Nussim [6] could not be repeated.

Identification of the intermediate in conversion of the bromo-ketone (V) into the *cis*-dihydroxy-ketone (VI; R = H) as the acetal (IX) excludes House and Thompson's [8] attractive mechanism, involving the carbonium enolate dipole (X) and ortho-ester (XI). Rather the mechanism consists in equatorial addition of methoxide (XII) and loss of bromide ion. The hypothetical intermediate methoxy-epoxide (XIII) then opens to give the acetal (IX) which is actually isolated, if acid is avoided during work-up. If the corresponding ethoxy-epoxide is formed in ethanol, it must react faster with hydroxide than ethoxide, perhaps partly for steric reasons.

Irradiation of the *cis*-acetoxy-hydroxy-ketone (VI; R = Ac) similarly produced the lactone acetate (VII; R = Ac), again in almost quantitative yield. Its spectral characteristics resembled those of its epimer: $\nu_{max.}$ 1722 (acetate) and a doublet at 1715 and 1706 cm.$^{-1}$ (ε-lactone); c.d. $\lambda_{max.}$ 223 mμ, Δε −1·3; τ 5·65 (5-H, doublet of doublets, J_{AX} 5·5, J_{BX} 11·5 c./sec.) and 7·51 (7-methylene, multiplet). Hydrolysis with dilute alkali and relactonisation with dilute acid led to the hydroxy-lactone (VII; R = H). The two epimeric lactones (II and VII; R = H) were then related to one another by oxidation of each to the corresponding oxo-lactone (IV) and (VIII). Treatment of the *cis*-lactone (IV) with dilute alkali and then cautious neutralisation afforded the crude unsaturated keto-acid (XIV), recyclisation of which in methanol containing a little acetic acid produced the *trans*-lactone (VIII) in good yield.



Although this interrelation, as well as details of the ^{1}H n.m.r. spectra, left little doubt about the structures and configurations of the lactones, a chemical proof was considered advisable at this stage. The Baeyer–Villiger oxidation of 3β-acetoxycholestan-6-one (XV) was therefore examined. While these experiments were in progress, Fonken and Miles [9] reported obtaining a compound, m.p. 162—163°, $[\alpha]_D$ +28°, in about 90% yield from oxidation of the ketone (XV) with perbenzoic acid, and gave it the structure (VII; R = Ac). We found, however, that reaction under conditions like those of Fonken and Miles [9] formed two products (separated by chromatography): B, m.p. 181°, $[\alpha]_D$ +36° (about 65% yield), and C, m.p. 176—178°, $[\alpha]_D$ +18° (about 20%). C was identical with the photochemical product (VII; R = Ac) from the *cis*-hydroxy-ketone (VI, R = Ac). The spectra of the predominant isomer B indicated that it too was an ε-lactone [$\nu_{max.}$ 1703 and 1724 cm.$^{-1}$, $\lambda_{max.}$ 225 mμ,

[8] H. O. House and H. W. Thompson, *J. Org. Chem.*, 1963, **28**, 164.

[9] G. J. Fonken and H. M. Miles, *J. Org. Chem.*, 1963, **28**, 2432.

$\Delta\varepsilon$ + 2·1 (for the derived alcohol $\nu_{max.}$ 1703 cm.$^{-1}$, $\lambda_{max.}$ 222 mμ, $\Delta\varepsilon$ + 2·1); multiplets at τ 7·08 from 5α-H and 5·98 from 7-CH_2 (at τ 7·25 and 5·95 for the alcohol)], and its structure (XVI) was proved by its reduction with lithium aluminium hydride to a triol (XVII), identical with that formed from the dimethyl ester of the 6,7-seco-diacid [10] (XVIII). Not [like (IV)] being a 3-acyloxy-cyclohexanone, the derived ketone (XIX) showed no sign of elimination with acid or base.

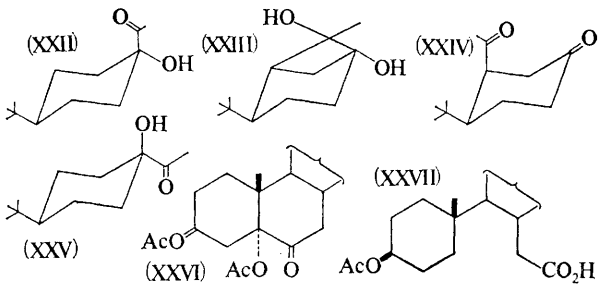
In peracid oxidation of cyclohexanones a tertiary carbon atom generally migrates in preference to a secondary one.[11] This exception must have a conformational origin. In the equatorial peracid adduct there is only slightly less repulsion in the arrangement with the O–O bond parallel to C(5)–C(6) (leading to migration of C-5) than in that with the O–O bond parallel to C(6)–C(7) (XX) (migration of C-7). However, rearrangement of the peracid adduct in the all-chair conformation (XX) will produce either lactone initially in the conformation with the carbonyl oxygen atom pointing up (β). In models shaped only by bond-angle strain, with rings A and C as chairs, because of the *trans*-ring fusions, in the conformation of ring B with the carbonyl group up the projected angle between the C(5)–O and C=O bonds in the 6,7-seco-lactone (XVI) is about 150° whereas in the 5,6-seco-lactone (VII) it is about 80° (XXI). The transition state between the peracid adduct and (XXI) therefore can derive little, if any, stabilisation from the developing ester group, whereas migration of C-7 in the intermediate (XX) can produce the isomeric lactone (XVI; R = Ac) directly in a conformation allowing full ester conjugation.

The complete stereospecificity in the photo-rearrangement of the two hydroxy-ketones (I) and (VI) raises interesting questions about its mechanism, but before they could be considered the origin of the hydrogen atom at C-5 in the lactones (II) and (VII) had to be determined. The *O*-deuterio-hydroxy-ketones were therefore irradiated in *O*-deuterioethanol to produce the two lactones as before. The presence of one atom of deuterium in each lactone acetate (II and VII; R = Ac) was shown by the mass spectra, which in each case had peaks at m/e 418 and 401 (corresponding with M — Ac and M — AcOH respectively) rather than at m/e 417 and 400 where they occurred in the isotopically normal compounds. [As in the spectra of some other acetates [12] no molecular ion could be observed for the lactone acetates (II and VII; R = Ac) or their deuteriated forms.] That the one deuterium atom incorporated was in each case linked to C-7, and only in one configuration, was shown by the ^{1}H n.m.r. spectra.

The 7-methylene protons of the *cis*-lactone (II; R = Ac) constitute the AB part of an ABM spin system, the signal from the M proton (8β-H) being obscured by other absorption at high field. The lines from both A and B appeared as well resolved doublets of doublets. First-order analysis of the 100 Mc./sec. spectrum in $CDCl_3$ gave δ_A = τ 7·07, δ_B = τ 7·56, J_{AB} (—)15, J_{AM} 9·8, J_{BM} 2 c./sec. In the deuteriated compound the signal from proton A was completely absent and that from B was a single peak of unit intensity at τ 7·59 (the coupling of 2·3 c./sec. to the deuterium and of 2 c./sec. to the vicinal proton evidently being unresolved). In the *trans*-lactone (VII; R = Ac) there was much less difference in chemical shift between the two protons in the 7-methylene group, which produced a multiplet centred at about τ 7·54. In the deuterio-derivative this was replaced by a singlet at τ 7·48, so that again the deuterium had only one configuration.

Thus in both cases the incorporation of deuterium as well as the migration of carbonyl from carbon to oxygen is completely stereospecific. Discussion of the mechanism of this remarkable reaction is deferred until more conclusive evidence is presented for the configuration of the deuterium atoms in the two lactones.

Irradiation in benzene of *trans*-1-acetyl-4-t-butylcyclohexanol (XXII), obtained by mercuric sulphate-catalysed hydration of *trans*-1-ethynyl-4-t-butylcyclohexanol, took a different course. Very little 4-t-butylcyclohexyl acetate was formed, and what there was had lost its configuration, consisting of about 0·3% of *trans*- and 1·3% of *cis*-isomer. Instead, the cyclobutanol



(XXIII) (55% yield) and 4-t-butylcyclohexanone (28%) were isolated. The structure (XXIII) of the major product is based on its molecular ion at 198 in the mass spectrum, the strong OH absorption and absence of CO absorption in the i.r. spectrum, and the ^{1}H n.m.r. spectrum. In $CDCl_3$ solution the two OH protons appeared as a singlet at τ 6·46, which moved to lower field on addition of a trace of $F_3C{\cdot}CO_2H$. The tertiary nature of the two OH groups was revealed by the spectrum in dimethyl sulphoxide, containing two unsplit singlets at τ 5·74 and 5·54. Oxidation with periodic acid confirmed the presence of the α-methyl-glycol group by forming the diketone (XXIV) which gave iodoform with hypoiodite solution and showed the methyl ketone group as a singlet in the ^{1}H n.m.r. spectrum at τ 7·73 ($CDCl_3$). The fate of the acetyl group lost in the conversion of (XXII) into 4-t-butylcyclohexanone (acetaldehyde?) was not ascertained.

Irradiation under the same conditions of *cis*-1-acetyl-4-t-butylcyclohexanol (XXV), in which the carbonyl group of the equatorial acetyl group is out of reach of a

[10] C. W. Shoppee, *J. Chem. Soc.*, 1948, 1032.
[11] C. H. Hassall, *Org. Reactions*, 1957, **9**, 73.
[12] H. Bergström, R. Ryhage, and E. Stenhagen, *Svensk. kem. Tidskr.*, 1961, **73**, 566.

γ-hydrogen atom, gave mainly 4-t-butylcyclohexanone (78% yield by extrapolation to 100% reaction, compared with 31% from the *trans*-isomer). The only other product to appear on a gas chromatogram was *cis*-4-t-butylcyclohexyl acetate (*ca.* 5%), none of the *trans*-epimer being detected in this case.

For comparison with the 5α-hydroxy-6-ketone (I; R = Ac), the parent 5α-6-ketone (XV) and the 5α-acetoxy-compound (XXVI) were also irradiated. In aqueous acetic acid the parent ketone (XV) produced the 5,6-seco-acid (XXVII; R = Ac) isolated after hydrolysis as the hydroxy-acid (XXVII; R = H), in an overall yield of 75%. The same reaction was subsequently reported by Quinkert *et al.*,[13] as part of a general survey of photo-hydrolysis of steroid ketones. Photolysis of the acetate (XXVI) in aqueous acetic acid proceeded slowly, to give the same 5,6-seco-acid (XXVII; R = Ac). On careful chromatography a small amount of 3β-acetoxy-cholestan-6-one (XV) could be isolated, which suggests its intermediacy in the formation of the seco-acid. Here too elimination of an acetoxy-radical seems to be the first step.

EXPERIMENTAL

Unless otherwise stated, i.r. spectra are of mulls in Nujol, u.v. spectra of solutions in ethanol, ^{1}H n.m.r. spectra of solutions in deuteriochloroform containing tetramethylsilane, and optical rotations of solutions in chloroform (*c* in g./l.). O.r.d. of solutions in ethanol was measured with a Bendix-Ericksson Bellingham and Stanley spectropolarimeter, and c.d. with a Roussel-Juan Dichrographe. U.v. irradiation was carried out with a 125 w medium pressure mercury arc in a Pyrex finger under nitrogen. Identity of samples was proved by mixed m.p. and i.r. spectra.

3β-*Acetoxy*-5α-*hydroxy*-5,6-*secocholestan*-6-*oic* (5 ⟶ 6)-*Lactone* (*II; R = Ac*).—3β-Acetoxy-5α-hydroxycholestan-6-one [4] (1 g.) in ethanol (200 ml.) was irradiated for 72 hr. The solvent having been removed, the residual material was crystallised from light petroleum (60—80°) or methanol to obtain the *lactone acetate* as slender needles (0·85 g., 85%), m.p. 228—229°, $[\alpha]_D$ −38° (*c*, 1·415) (Found: C, 75·1; H, 10·55. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%).

Similar irradiation of the ketone (I; R = Ac) (1 g.) in benzene (150 ml.) for 72 hr. also gave the lactone (II; R = Ac) (88—90% yield).

3β,5α-*Dihydroxy*-5,6-*secocholestan*-6-*oic* (5 ⟶ 6)-*Lactone* (*II; R = H*).—The lactone acetate (II; R = Ac) (500 mg.) was treated with 3—4% boiling methanolic NaOH (20 ml.) for about 45 min. Upon dilution with water, the sodium salt (III) separated out, m.p. 230°, $\nu_{max.}$ 3300—3400, 1565, 1036 cm.$^{-1}$. This, upon contact with dilute HCl at 80° for 15 min., gave the *lactone* (II; R = H), m.p. 164° (from methanol–water), $[\alpha]_D$ −52° (Found: C, 77·45; H, 10·85. $C_{27}H_{46}O_3$ requires C, 77·45; H, 11·1%).

5α-*Hydroxy*-3-*oxo*-5,6-*secocholestan*-6-*oic* (5 ⟶ 6)-*Lactone* (IV).—To a solution of the lactone (II; R = H) (1 g.) in acetone (150 ml.; distilled over permanganate) was introduced, rapidly and with stirring, 0·7 ml. of Jones oxidation mixture [14]—nitrogen was bubbled through the mixture during and before titration and the temperature of the contents was maintained at about 10°. The reaction mixture was diluted, at once, with cold water (1 l.) and the solid that precipitated out was filtered off, washed repeatedly with cold water, and dried (0·7 g., 70%), m.p. 124—129°. After three crystallisations from light petroleum (60—80°) the *ketone* (IV) had m.p. 138°, $[\alpha]_D$ −27° (Found: C, 78·3; H, 10·35. $C_{27}H_{44}O_3$ requires C, 77·85; H, 10·65%).

5,6-*Secocholestane*-3β,5α,6-*triol*.—A solution of the hydroxy-lactone (II; R = H) (500 mg.) in ether (50 ml.) was dropped into a stirred slurry of lithium aluminium hydride in ether (50 ml.) over about ½ hr. After 12 hr. excess of hydride was destroyed with cold water (2 ml.), and dilute H_2SO_4 (5 ml.) was then added, with stirring and external cooling. The hydrolysate was extracted with ether to give the *triol*, (315 mg., 62%), m.p. 196° (from ether) (Found: C, 76·3; H, 11·6. $C_{27}H_{50}O_3$ requires C, 76·7; H, 11·9%).

The 3,5-dinitrobenzoate was prepared from the triol (57 mg.), 3,5-dinitrobenzoyl chloride (114 mg.), and pyridine (1 ml.). This, when crystallised from ether–light petroleum (60—80°), gave a pallid material which melted at 130—140°, resolidified at 160° and remelted at 200—202°. Its i.r. spectrum showed only weak absorption in the OH stretching region (tris-3,5-dinitrobenzoate?).

Irradiation of 3β,5α-*Dihydroxycholestan*-6-*one* (*I; R = H*).—A solution of the ketone (I; R = H) (1 g.) in ethanol (200 ml.) was irradiated for 75 hr. Removal of solvent and crystallisation (from methanol–water) gave the hydroxy-lactone (II; R = H) as glistening platelets (0·87 g., 87%), m.p. 162—164°, $[\alpha]_D$ −52°, identical with the compound obtained through hydrolysis of the acetate (II; R = Ac).

Irradiation of the dihydroxy-ketone (I; R = H) (800 mg.) in anhydrous sulphur-free benzene (150 ml.) for 75 hr. gave the same hydroxy-lactone (II, R = H) (720 mg.). Acetylation with acetic anhydride in pyridine produced the lactone acetate (II; R = Ac).

6,6-*Dimethoxycholestan*-3β,5β-*diol* (*IX*).—3β-Acetoxy-5α-bromocholestan-6-one [5] (V) (2 g.) in 10% methanolic KOH (60 ml.) was boiled for 2 hr., when it developed a deep orange colour. Water was added to the cooled mixture and the organic material was taken up in ether. The solvent having been evaporated off, the residue was treated with hot methanol (75 ml.) and the mixture was filtered. To the filtrate was then added water till a turbidity appeared and the mixture was refrigerated for 24 hr. The solid (1·1 g., 55%) crystallised from methanol as colourless soft plates melting at 138° with previous softening, $[\alpha]_D$ +28° (*c*, 1·55), $\nu_{max.}$ 3450, 3400, 1145, 1053, 1000, and 945 cm.$^{-1}$ (no absorption in the C=O stretching region) (Found: C, 74·8; H, 11·3; OMe, 13·3. $C_{29}H_{52}O_4$ requires C, 74·95; H, 11·3; OMe, 13·35%).

Hydrolysis of the Acetal (IX).—The hydroxy-acetal (IX) (100 mg.) was treated with dilute HCl (5 ml.) for 20 min. at room temperature, whereafter the mixture was diluted with water and ether-extracted. The ethereal solution was washed free of acidity and dried, and the solvent was removed to leave a viscous oil, $[\alpha]_D$ −6°, $\nu_{max.}$ 3570, 3480, 1703, 1160, 1094, 1047, 996, and 924 cm.$^{-1}$.

The above oil was treated with acetic anhydride (1 ml.) and pyridine (1 ml.) at room temperature for 42 hr. The acetylation mixture, on working up in the customary manner, gave the acetate (VI; R = Ac) (75 mg.) as white

[13] G. Quinkert, B. Wegemund, F. Homburg, and G. Cimbollek, *Chem. Ber.*, 1964, **97**, 958.

[14] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39; C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

shining platelets (from methanol), m.p. 141—142°, $[\alpha]_D$ −22° (*c*, 1·635), $\nu_{max.}$ 3480, 1720, 1700, 1270, 1242, 1162, 1050, 1010, and 995 cm.$^{-1}$.

α-Hydroxy-ketone Rearrangement of 3β,5α-Dihydroxycholestan-6-one (I; R = H).—A solution of the dihydroxy-ketone (I; R = H) (2 g.) in 10% methanolic KOH (60 ml.) was refluxed for 8 hr. Most of the methanol was removed and water was added to the residual mixture. The organic material was then taken up in ether and the ethereal solution was washed free of acidity and dried. Ether having been evaporated off, the residual material was chromatographed over neutral alumina (column prepared in benzene). Elution with ethyl acetate gave 0·5—0·6 g. (25—30%) of a viscous oily material, $[\alpha]_D$ −6° (*c*, 2·05); the i.r. spectrum of the oil was identical with that of the hydrolysis product of the hydroxy-acetal (IX).

Elution with ethanol–ethyl acetate (1 : 4) gave the starting material (I; R = H). The middle fractions were mixtures. The above oil, which finally crystallised on prolonged standing in the presence of methanol, m.p. 62° with previous softening, gave the acetate (VI; R = Ac), m.p. 141—142°, $[\alpha]_D$ −22° (*c*, 1·635). The *cis*-diol acetate (VI; R = Ac) could, however, be obtained conveniently, in good yield, from 3β-acetoxy-5α-bromocholestan-6-one (V) by the procedure of Rowland,[7] involving treatment of the bromo-ketone with 5% ethanolic KOH at room temperature and subsequent acetylation of the crude material. This was identical (on the basis of mixture m.p. and i.r. spectra) with the acetoxy-ketone obtained either through the α-hydroxy-ketone rearrangement [6] or through the hydroxy-acetal (IX) as described above.

Irradiation of 3β-Acetoxy-5β-hydroxycholestan-6-one (*VI; R = Ac*).—The acetoxy-ketone (VI; R = Ac) (1 g.) in ethanol (150 ml.) was irradiated for 75 hr. Removal of the solvent and subsequent crystallisation [from light petroleum (60—80°) or cyclohexane] of the residual material yielded the *lactone acetate* (VII; R = Ac) (0·86 g., 86%) as white shining platelets, m.p. 178°, $[\alpha]_D$ +18° (*c*, 1·335) (Found: C, 75·7; H, 10·2. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%).

A solution of the acetoxy-ketone (VI; R = Ac) (1 g.) in anhydrous sulphur-free benzene (200 ml.) gave about 0·9 g. of the lactone acetate (VII, R = Ac).

Baeyer–Villiger Oxidation of 3β-Acetoxycholestan-6-one.—The acetoxy-ketone (2·7 g.) was treated with perbenzoic acid in chloroform and the mixture was left in the dark for 107 hr. Water was then added and the organic material was taken up in ether. The ethereal extract was washed successively with water, 5% $NaHCO_3$ solution, again with water, and then dried. The solvent having been removed, the residual viscous oil was dissolved in benzene (50 ml.) and chromatographed over alumina (90 g., activated Spence H). Development of the column with benzene gave *3β-acetoxy-7-hydroxy-6,7-seco-5α-cholestan-6-oic lactone* (XVI; R = Ac) (1·8 g., 65%), which crystallised from methanol in colourless woolly needles, m.p. 181°, $[\alpha]_D$ +36° (Found: C, 75·4; H, 10·55. $C_{29}H_{48}O_4$ requires C, 75·6; H, 10·5%).

After some intermediate fractions further elution of the column with benzene–ether (17 : 3) gave the isomeric lactone (VII; R = Ac) (500 mg., 20%), m.p. 176—178°, $[\alpha]_D$ +18°, identical with the photochemical product.

Hydrolysis of the lactone acetate (XVI; R = Ac) with 5% methanolic KOH followed by heating with dilute HCl at 80° formed the *hydroxy-lactone* (XVI; R = H), which separated from methanol in thin shining plates (65%), m.p. 141—142°, $[\alpha]_D$ +40° (*c*, 1·535) (Found: C, 77·0; H, 11·2. $C_{27}H_{46}O_3$ requires C, 77·45; H, 11·1%).

7-Hydroxy-3-oxo-6,7-seco-5α-cholestan-6-oic Lactone (XIX).—To a solution of the hydroxy-lactone (XVI; R = H) (600 mg.) in acetone (200 ml., distilled from permanganate) was added gradually, with cooling and stirring, Jones oxidation reagent [14] (0·6 ml.); nitrogen was bubbled through the solution before and during oxidation. On subsequent working up in the manner of (IV), the oxo-lactone (XIX) (400 mg.) was obtained, m.p. 173—175°, $[\alpha]_D$ +43°.

6,7-Seco-5α-cholestane-3β,6,7-triol (XVII).—(*a*) To lithium aluminium hydride (0·5 g.) suspended in ether (25 ml.) was introduced, with stirring, a solution of the lactone acetate (XVI; R = Ac) (200 mg.) in ether (30 ml.) at a rate to maintain gentle boiling. The mixture was then left at room temperature for 18 hr. On subsequent working up there was obtained the triol (XVII) (230 mg., 45%), m.p. 220—222° (from ether). Its i.r. spectrum showed intense absorption at 3380, 1040, 1012, and 1080 cm.$^{-1}$ (no absorption in the C=O stretching region).

(*b*) *3β-Hydroxy-6,7-seco-5α-cholestane-6,7-dioic acid* [16] (XVIII), m.p. 233°, $[\alpha]_D$ +35° (150 mg.), was dissolved in a mixture of anhydrous sulphur-free benzene (50 ml.) and absolute ethanol (10 ml.). Toluene-*p*-sulphonic acid (50 mg.) was added and the mixture refluxed (Dean–Stark) until water stopped collecting in the limb of the separator. The reaction mixture was diluted with water and ether-extracted. The organic phase was washed twice with water and dried and the solvent was removed (last traces under diminished pressure). The residual viscous oil could not be induced to crystallise.

A solution of this material in ether (100 ml.) was dropped into a stirred suspension of lithium aluminium hydride (500 mg.) in ether (20 ml.) over about ½ hr. After the addition, the mixture was refluxed and stirred for 2 hr. and was left overnight. Excess of hydride was decomposed with cold water (2 ml.), and dilute H_2SO_4 (10 ml.) was added with stirring and cooling. The organic material was then taken up in ether, which was washed free of acidity and dried, and the solvent was removed. The residual material, upon crystallisation from ether–light petroleum (60—80°), afforded white soft flakes, m.p. 220—222°, identical with the triol obtained above (method *a*).

3β,5β-Dihydroxy-5,6-seco-cholestan-6-oic (5 ⟶ 6)*-Lactone* (*VII; R = H*).—The lactone acetate (VII; R = Ac) (300 mg.) was treated on a steam bath with 2—3% aqueous KOH solution (30 ml.) for 1 hr. when the solid dissolved. To the resulting solution was added dilute HCl (10 ml.) and the mixture was kept at 80° for 15 min. The solid that precipitated was filtered off and washed free of acidity. Crystallisation from methanol–water gave the *hydroxy-lactone* (VII; R = H) (220 mg.) as white soft flakes, m.p. 215—216°, $[\alpha]_D$ +32° (Found: C, 77·45; H, 10·85. $C_{27}H_{46}O_3$ requires C, 77·45; H, 11·1%).

5β-Hydroxy-3-oxo-5,6-seco-cholestan-6-oic Lactone (VIII).—(*a*) Chromic acid solution [15] (0·8 ml.) was slowly added to a stirred solution of the hydroxy-lactone (VII; R = H) (800 mg.) in acetone (150 ml., distilled from permanganate). The mixture was diluted with water (1 l.) and the solid material that precipitated was collected and washed free of acid. Crystallisation from methanol afforded the trans-*3-oxo-lactone* (VIII) (550 mg.) as colour-

[15] R. M. Dodson and B. Riegel, *J. Org. Chem.*, 1948, **13**, 424.
[16] C. W. Shoppee, *J. Chem. Soc.*, 1948, 1032.

less needles, m.p. 202—203°, $[\alpha]_D$ +19° (Found: C, 77·2; H, 10·45. $C_{27}H_{44}O_3$ requires C, 77·85; H, 10·65%).

(*b*) The *cis*-oxo-lactone (IV) (300 mg.) was heated with 2—3% NaOH solution (20 ml.) on a water-bath for ½ hr., when it dissolved. The resulting solution was cooled and acidified with the minimum amount of dilute HCl in the cold. The semi-solid material that separated was collected and dried. It could not be obtained pure, but its i.r. spectrum exhibited bands at 1710, 1650, 1175m, and 3000—3300m cm.$^{-1}$.

To a solution of this material in methanol (50 ml.) were added a few drops of glacial acetic acid and the mixture was refluxed for 2 hr. The contents were diluted with water and the organic material was extracted with ether. The ethereal phase was washed free of acidity and then dried. The solvent having been removed, the residual pallid material was crystallised from methanol to obtain colourless needles (240 mg.), m.p. 202—203°, $[\alpha]_D$ +19°, identical with the *trans*-3-oxo-lactone obtained above (*a*). No *cis*-3-oxo-lactone (IV) was detected in the mother-liquor.

3β-*Acetoxy*-5α-[*D*]*hydroxycholestan*-6-*one*.—The ketone (I; R = Ac) (500 mg.) was dissolved, with exclusion of moisture, in a mixture of deuterioethanol [17] (4 ml.) and anhydrous ether (10 ml.) and the solution was left for a few min. The solvent mixture was then removed under reduced pressure. The residual material was treated again thrice in the same manner. The substance thus obtained showed a strong band in the i.r. spectrum at 2510 and 2530 cm.$^{-1}$ (doublet, O–D stretch).

The *O*-deuterio-compound could also be obtained by two crystallisations of the (I; R = Ac) from deuterioethanol.

3β-*Acetoxy*-7-*deuterio*-5α-*hydroxy*-5,6-*secocholestan*-6-*oic Lactone* (*II; R = Ac*, 7-*D*). A solution of the *O*-deuterio-compound (I; R = Ac) (120 mg.) in deuterioethanol (50 ml.) was irradiated as before and the product was crystallised from anhydrous light petroleum (60—80°) to obtain the 7-deuterio-lactone acetate, m.p. 228°.

The i.r. spectra of the 7-deuteriated and the unlabelled lactone acetate showed some intensity differences in the region of C–H deformation vibrations (1340—1480 cm.$^{-1}$).

3β-*Acetoxy*-5β-[*D*]*hydroxycholestan*-6-*one*.—The ketone acetate (VI; R = Ac) (400 mg.) was dissolved (moisture excluded) in deuterioethanol (2 ml.) by brief warming. After a few min. the solvent was removed under reduced pressure and the process repeated thrice to obtain the *O*-deuterio-compound. This showed strong absorption in the i.r. spectrum at 2250 cm.$^{-1}$ (O–D stretch). No co-solvent was required for effecting dissolution in this case.

3β-*Acetoxy*-7-*deuterio*-5β-*hydroxy*-5,6-*seco-cholestan*-6-*oic Lactone* (*VII; R = Ac*, 7-*D*).—The *O*-deuterio-compound (VI; R = Ac) (100 mg.) in deuterioethanol (30 ml.) was irradiated as before and the product was crystallised from anhydrous light petroleum (60—80°) or anhydrous cyclohexane to obtain the 7-labelled compound (VII; R = Ac, 7-D), m.p. 178°.

A comparison of its i.r. spectrum with that of the unlabelled lactone acetate again showed some intensity differences in the region 1340—1480 cm.$^{-1}$.

5,6-*seco-cholestane*-3β,5β,6-*triol*.—A solution of the lactone acetate (VII; R = Ac) (122 mg.) in ether (20 ml.) was added with stirring to a slurry of lithium aluminium hydride (250 mg.) in ether (25 ml.) in ½ hr. Gentle refluxing occurred during the addition. The mixture was refluxed for 1 hr. and then left overnight. Excess of hydride was decomposed with cold water (3 ml.), and dilute H_2SO_4 (3 ml.) was added. On subsequent working up in the usual way the *triol* (72 mg., 64%) was obtained as white flakes, m.p. 160—164° (from light petroleum); its i.r. spectrum exhibited bands at 3350br and 1025s cm.$^{-1}$ (Found: C, 75·35; H, 11·45. $C_{27}H_{50}O_3$ requires C, 76·7; H, 11·9%).

Irradiation of 3β-*Acetoxycholestan*-6-*one*.—A solution of ketone acetate (2 g.), m.p. 128°, $[\alpha]_D$ −17°, in a mixture of glacial acetic acid (200 ml.) and water (60 ml.) was irradiated for 90 hr. The solvent was removed under diminished pressure. The residual thick oil ($\nu_{max.}$ 3000—3400, 1728, 1707, 1230, 1040, and 1020 cm.$^{-1}$) could not be induced to crystallise. It was then hydrolysed with aqueous 4% KOH (30 ml.) on a water-bath for 2 hr. The hydrolysate was cooled and ether-extracted. The aqueous phase, upon acidification with dilute HCl, yielded 3β-hydroxy-5,6-secocholestan-6-oic acid (XXVII; R = H) (1·4 g., 75%). Crystallisation from methanol–water afforded white shining flakes, m.p. 198°, $[\alpha]_D$ +26° (*c*, 1·36) (Found: C, 77·05; H, 11·25. $C_{27}H_{48}O_3$ requires C, 77·15; H, 11·45%).

Irradiation of 3β,5α-*Diacetoxycholestan*-6-*one* (*XXVI*).—(*a*) The ketone diacetate [4] (10 g.) dissolved in a mixture of acetic acid (230 ml.) and water (30 ml.) was irradiated for 7 days. To the residual viscous material from evaporation of the solvent was added 3—4% aqueous KOH solution (80 ml.) and the mixture was refluxed for 2 hr. After cooling, the hydrolysate was extracted repeatedly with benzene. The combined benzene extract, after drying and solvent removal, gave crude 3β,5α-dihydroxycholestan-6-one (5·5 g.), m.p. 231—232° (from methanol) (i.r. spectrum identical with that of the authentic sample).

The aqueous portion of the hydrolysate, on acidification with dilute HCl, gave a brownish solid (3·2 g.) which, on 2—3 crystallisations from methanol–water, afforded colourless flakes, m.p. 195—198°, $[\alpha]_D$ +25°; its i.r. spectrum was identical with that of the 5,6-seco-acid (XXVII; R = H).

(*b*) A solution of the ketone diacetate (1·25 g.) in glacial acetic acid (200 ml.) and water (50 ml.) was irradiated for 120 hr. The solvent having been removed, the residual viscous oil was dissolved in benzene (30 ml.) and chromatographed over neutral alumina (60 g.). Development of the column with benzene gave initially 3β-acetoxycholestan-6-one (about 50 mg.), m.p. 124—126° (from methanol). Further elution of the column with benzene and benzene–ethanol (7 : 3) gave successively the starting ketone diacetate and a viscous oil, $\nu_{max.}$ 1707, 1728, and 1230 cm.$^{-1}$. The latter, on hydrolysis with 45% aqueous KOH on a water-bath for 2 hr. and subsequent acidification with dilute HCl, yielded 3β-hydroxy-5,6-secocholestan-6-oic acid (XXVII; R = H), m.p. 195—198° (white flakes from methanol–water).

Irradiation of trans-1-*Acetyl*-4-*t-butylcyclohexanol* (XXII).—The *trans*-hydroxy-ketone,[18] m.p. 101—102° (6·93 g.), was dissolved in pure benzene (300 ml.) and the solution irradiated for 86 hr. Light petroleum (40—60°) (25 ml.) was added to the viscous oil remaining from evaporation of the benzene and the mixture was refrigerated overnight. The solidified material was collected, washed with a little light petroleum (40—60°), and dried, m.p. 122° with previous softening (2·44 g.). Crystallisation from

[17] V. J. Shiner and M. L. Smith, *J. Amer. Chem. Soc.*, 1961, **83**, 593.

[18] G. F. Henion and E. J. Watson, *J. Org. Chem.*, 1958, **23**, 656.

light petroleum (60—80°) afforded the *diol* (XXIII) as colourless micro-needles, m.p. 124° (Found: C, 72·5; H, 11·05. $C_{12}H_{22}O_2$ requires C, 72·7; H, 11·2%).

The above filtrate furnished, after solvent removal and subsequent distillation in vacuum, 4-t-butylcyclohexanone (1·52 g., 28%), b.p. 80—82/4 mm. (its i.r. spectrum was identical with that of the authentic sample and a mixture m.p. of their semicarbazones was not depressed, *i.e.* 210—212°), and another 1·38 g. of the diol (XXIII), b.p. 110°/4 mm., m.p. 124°; the total yield of the diol was 55%.

Examination of gas chromatograms revealed two small peaks with the retention times of *cis*- and *trans*-4-t-butylcyclohexyl acetates. The hydroxy-ketone (XXII) (2·02 g.) in pure benzene (100 ml.) was therefore photolysed and the reaction followed by g.l.c. Comparison of the peaks from samples of the solution with those from standard solutions of the *cis*- and *trans*-acetates (5·0 μl. injections) after 24% reaction (*i.e.* reduction of the hydroxy-ketone peak to 76%) showed that the yields of acetates (extrapolated to 100% reaction) were cis $\geqslant$1·3% and trans $\geqslant$0·3%. In another experiment, the ketol (111·6 mg.) and biphenyl (104·0 mg.) as an internal standard in benzene (5·0 ml.) were irradiated with water-cooling through Pyrex. Extrapolation to 100% reaction of the early linear part (<30%) of a plot of % reaction against concentration of 4-t-butycyclohexanone formed indicated an initial yield of 31%.

Periodic Acid Oxidation of Diol (XXIII).—The diol (3 g.) was introduced to a stirred solution of $HIO_4,2H_2O$ (6·8 g.) in water (15 ml.) over 15 min. Immediately after the addition of the diol, iodine was liberated and the temperature of the mixture rose to 40—45°. The colour disappeared in a few min. and the viscous mass was then stirred for 4 hr; in the initial phase the temperature of the mixture remained slightly above room temperature. The thick oil gradually solidified and the mass was, thereafter, collected, washed repeatedly with water, superficially dried, and then crystallised from light petroleum (40—60°) to give *cis*-3-acetyl-4-t-butylcyclohexanone (XXIV) as colourless slender needles, m.p. 54°, $\nu_{max.}$ 1705, 1150, and 970 cm.$^{-1}$ (Found: C, 72·25; H, 9·7. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·25%).

Irradiation of cis-1-*Acetyl*-4-*t-butycyclohexanol* (XXV).—The *cis*-hydroxy-ketone (56·2 mg.) and biphenyl (59·5 ml.) in benzene (3 ml.) were photolysed as before. A plot of % reaction against concentration of 4-t-butylcyclohexanone, measured by g.l.c., was again linear, and extrapolation to 100% reaction indicated a yield of 78%. The only other peak on the chromatogram was from *cis*-4-t-butylcyclohexyl acetate (*ca.* 5% yield).

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