638. *Preparation of 1-Oxygenated Steroids. The Reaction of Cholest-1-en-3β-ol with Thionyl Chloride.*

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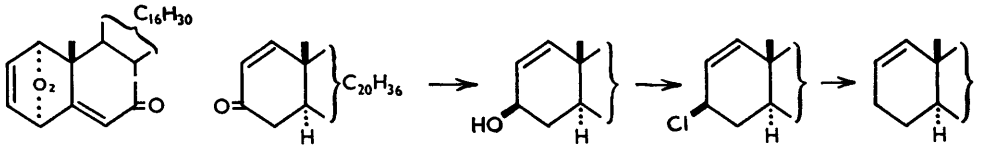
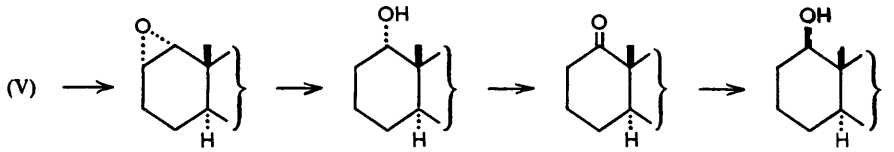
An unambiguous route to cholestan-1α-ol and related compounds is described. A key step in the synthesis involves the conversion of cholest-1-en-3β-ol into 3β-chlorocholest-1-ene by thionyl chloride. Rearrangement does not occur in this replacement, in contrast to the observations of Goering, Nevitt, and Silversmith [1] with monocyclic *cyclo*hexenols.

FOR the synthesis of 1-oxygenated steroids, unknown when this work began, two routes were considered. First, the photo-catalysed addition of oxygen to cholesta-1 : 3 : 5-trien-7-one was studied. Although the required 1 : 4-epidioxide (I) was obtained from this reaction,[2] the low yield (15%) rendered further development unattractive. The second route required a method for converting cholest-1-en-3-one (II) into cholest-1-ene (V), whereby isomerisation of the 1 : 2-double bond to the more stable 2 : 3-position could be avoided.[3,4,5] Reduction of the ketone (II) by lithium aluminium hydride gave the 3β-alcohol (III) in high yield.[5,6] In contrast to the observations of Plattner and his co-workers,[5] it was found that a crystalline chloro-compound was readily obtained from the reaction of this alcohol with thionyl chloride. Further details concerning this reaction



(I) (II) (III) (IV) (V)

and the proof of structure of the chloro-compound as (IV) are given below. For reduction of the chloro-compound without double-bond migration, lithium aluminium hydride proved to be the most effective reagent, a good yield of cholest-1-ene (V) being isolated *via* its dibromide (the infrared spectra of cholest-1-ene and related compounds have been discussed previously [3]). The ultraviolet absorption spectrum of the crude hydrocarbon from the reduction indicated that the main impurity was, not cholest-2-ene, but the as yet undescribed cholesta-1 : 3-diene, part of the hydride apparently acting as a base. Other methods of reduction tended to give more cholest-2-ene than the desired-1-ene (V); for instance, catalytic hydrogenation with palladium–strontium carbonate afforded a good yield of olefin shown by infrared analysis [3] to consist of the Δ^2-compound (75%) and the Δ^1-compound (25%).



(VI) (VII) (VIII) (IX)

Oxidation of cholest-1-ene (V) by monoperphthalic acid gave a single epoxide, assigned an α-configuration (VI) by analogy with the behaviour of cholest-2- and -3-ene which

[1] Goering, Nevitt, and Silversmith, *J. Amer. Chem. Soc.*, 1955, **77**, 4042.
[2] Henbest and Wilson, *Chem. and Ind.*, 1956, 86.
[3] Henbest, Meakins, and Wood, *J.*, 1954, 800.
[4] Turner, XIVth Internat. Congr. Pure and Appl. Chem., 1955, Abs., paper 594.
[5] Plattner, Fürst, and Els, *Helv. Chim. Acta*, 1954, **37**, 1399.
[6] Bergmann, Kita, and Giancola, *J. Amer. Chem. Soc.*, 1954, **76**, 4974.

both yield α-epoxides exclusively [7,8] and because reduction by lithium aluminium hydride gave the 1α-alcohol (VII) (the β-epoxide would have given the known 2β-alcohol), oxidised to the 1-ketone (VIII), which readily formed a 2 : 4-dinitrophenylhydrazone. Sodium–ethanol reduction of the ketone gave the equatorial 1β-alcohol (IX) in 65% yield, the remainder being the 1α-hydroxy-compound.

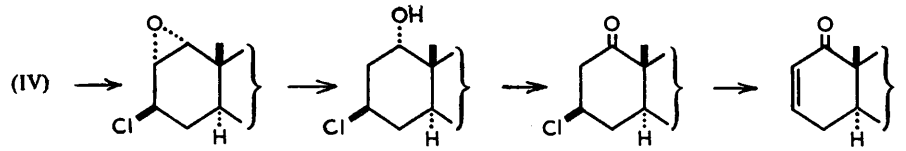
The direction of reduction of cyclic ketones by lithium aluminium hydride seems to depend on steric factors which are difficult to evaluate with precision. Previous work in the steroid series indicates that there is a general tendency for β-alcohols to be formed by reduction from the α-side (less hindered by the bulky angular methyl groups). Thus it was somewhat surprising to find that the ratio of 1α- to 1β-alcohol produced by hydride reduction of the 1-ketone was approximately 2 : 1, especially in view of the proximity of the 10β-methyl group. The present difficulty of predicting the more likely product from addition reactions of polycyclic ketones is well shown by the observations of Heusser, Wahba, and Winternitz [9] that reaction of methylmagnesium bromide with a 17*a*-oxo-homosteroid, containing a six-membered ring D, gave a 17β-methyl compound (the same direction incidentally as the major route taken by hydride reduction of the 1-ketone), whereas a similar Grignard reaction with a 17-oxosteroid containing a five-membered ring D yielded a 17α-methyl compound as the main product.

As this work was nearing completion, two publications [5,10] appeared describing syntheses of 1-oxygenated steroids. The simplicity of the present method, proceeding through four crystalline intermediates (from II), seems advantageous; the overall yields of the three routes are similar.

Molecular Rotations

Allylic chloro-compound	RCl	RH	Difference
3β-Acetoxy-7α-chlorocholest-5-ene	−762°	−166°	−596°
3β-Benzoyloxy-7α-chlorocholest-5-ene	−623	− 83	−540
3β-Benzoyloxy-7β-chlorocholest-5-ene	+319	− 83	+402
Methyl 3α-acetoxy-12α-chlorochol-9-enate	+715	+241	+464
3β-Chlorocholest-1-ene (IV)	+404	+ 48	+356

As mentioned above, reaction of cholest-1-en-3β-ol with thionyl chloride affords a crystalline chloro-compound (75% yield), reduced to cholest-1-ene by lithium aluminium hydride. However, the latter reaction does not provide unambiguous proof that chlorine is situated at $C_{(3)}$ for the Δ^1-olefin could have been formed from an isomeric 1-chloro-Δ^2-compound by a S_N2' reaction. The chloro-compound thus corresponds to one of the four possible structures depending upon whether inversion and/or rearrangement occurs during the thionyl chloride reaction. Two of the structures could be ruled out by molecular-rotation evidence. If the rotations of the steroid allylic chlorides of known structure (Table) are compared with the values given by the corresponding compounds lacking



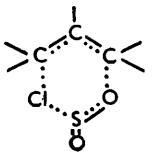
(X) (XI) (XII) (XIII)

chlorine, it is seen that the introduction of allylic chlorine produces a large rotational change in the direction predicted by Mills's rule [11] concerning cyclic allylic systems. Comparison of the rotation of the chloro-compound under discussion with those of cholest-1- and -2-ene shows (by the direction of rotational shift) that the structure is either 3β-chlorocholest-1-ene (IV) or 1α-chlorocholest-2-ene, the latter being somewhat less likely as the magnitude of the shift (+150°) would then be smaller than expected.

[7] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.
[8] Fürst and Scotoni, *ibid.*, 1953, **36**, 1332.
[9] Heusser, Wahba, and Winternitz, *ibid.*, 1954, **37**, 1052.
[10] Striebel and Tamm, *ibid.*, 1954, **37**, 1094.
[11] Mills, *J.*, 1952, 4976.

In order to distinguish between these two possibilities, the chloro-compound was converted into the epoxide (X) with perbenzoic acid, and this was transformed in turn into the axial alcohol (XI), the chloro-ketone (XII), and the known unsaturated ketone [10] (XIII). The alternative 1-chloro-Δ^2-structure would have yielded the Δ^1-3-ketone by this sequence of reactions.

Although no attempt was made to investigate further the thionyl chloride reaction leading to the formation of the chloride (IV), the observation that the hydroxyl group is largely replaced without allylic rearrangement may be contrasted with the results of Goering, Nevitt, and Silversmith [1] with a monocyclic allylic *cyclo*hexenol system. In their elegant studies with these compounds [bearing the same degree of substitution on the allylic system as (III)], they showed that thionyl chloride in ether gave rearranged chloride with a high degree of specificity, and a cyclic transition state of the type shown was suggested following the earlier proposals of Young and his co-workers.[12] However, with the steroid compounds the unrearranged chloride (IV) was the major product from the reaction in ether, dioxan, or benzene. The most probable explanation of this difference appears to be that in the monocyclic series the intermediate chlorosulphite group can assume a quasiaxial configuration from which the transition state leading to rearrangement can develop readily, whereas with the steroid compound the quasiequatorial configuration of the chlorosulphite group attached to the relatively rigid ring system causes the chlorine to be too far removed from $C_{(1)}$ for a similar transition state to be elaborated. Replacement at $C_{(3)}$ with retention of configuration (as of course with the saturated 3β-alcohol) thus becomes the predominant reaction.



Experimental

General experimental directions are as given before.[13] The infrared absorption spectra of the compounds prepared were consistent with the structures assigned.

Cholest-1-en-3β-ol (III). A solution of cholest-1-en-3-one (2·4 g.) in ether (150 c.c.) was cooled to −40° and lithium aluminium hydride (0·24 g.) in ether (30 c.c.) was added with stirring. The solution was allowed to warm to 20°, and after the addition of ethyl acetate and dilute sulphuric acid the steroid was isolated with ether. Crystallisation from methanol afforded the 3β-alcohol (1·7 g.) as needles, m. p. 130—132°, $[\alpha]_D$ +55°. The acetate had m. p. 84—86°, $[\alpha]_D$ +58°; the benzoate had m. p. 141—142°, $[\alpha]_D$ +95°.

3β-*Chlorocholest-1-ene* (IV).—Thionyl chloride (1·5 c.c.; purified by successive distillation from quinoline and linseed oil) was added to a solution of the foregoing alcohol (1·5 g.) in benzene (50 c.c.). The solution was kept at 20° for 1 hr., then the steroid was isolated in the usual way. Crystallisation from acetone afforded the *chloro-compound* (0·80 g.) as needles, m. p. 95—101°, $[\alpha]_D$ +100° (Found: C, 80·2; H, 10·9; Cl, 8·65. $C_{27}H_{45}Cl$ requires C, 80·1; H, 11·1; Cl, 8·8%). Similar results were obtained with ether or dioxan as solvent.

Treatment of the pure chloro-compound with aniline at 20° gave a quantitative yield of an anilino-steroid, m. p. 142—144°, the structure of which will be discussed in a separate communication. Similar treatment of the chloro-steroid obtained from the first mother-liquor from the crystallisation of the 3β-chloro-compound (above experiment) gave, after chromatography, the same anilino-compound (0·46 g.) together with an isomeric anilino-derivative, m. p. 163—166°, derived apparently from a second chloro-compound. Thus it is estimated that 1·2 g. (75%) of 3β-chlorocholest-1-ene was formed in the thionyl chloride reaction.

Cholest-1-ene (V).—A solution of 3β-chlorocholest-1-ene (1·4 g.) and lithium aluminium hydride (0·7 g.) in ether (120 c.c.) was heated under reflux for 16 hr. Ethyl acetate and dilute sulphuric acid were added, the steroid was isolated with light petroleum, and the solution filtered through alumina (50 g.). Crystallisation from acetone gave crude cholest-1-ene (1·0 g.) as needles, m. p. 66—69°, showing an ultraviolet absorption maximum at 2630 Å (ε 1080; the absorption being assumed due to cholesta-1 : 3-diene, the intensity value probably indicates that about 20% of the diene is present). The crude Δ^1-compound was dissolved in ether (50 c.c.) and treated with M-bromine in acetic acid (2·25 c.c.). After 10 min. the solvent was removed under reduced pressure, and the product crystallised from ethyl methyl ketone, to

[12] Young, Brandon, and Caserio, *Science*, 1953, **117**, 473.
[13] Bladon, Henbest, Jones, Wood, Eaton, and Wagland, *J.*, 1953, 2916.

give 1α : 2β-*dibromocholestane* (1·0 g.) as needles, m. p. 134—136°, $[\alpha]_D$ +32° (Found : C, 60·75; H, 8·7. $C_{27}H_{46}Br_2$ requires C, 61·1; H, 8·75%).

A solution of the dibromide (3·4 g.) in acetic acid (175 c.c.) was heated to boiling and zinc dust (16 g.) was then added in portions. The solution was heated under reflux for 1·5 hr., the solvent removed under reduced pressure, and the residue extracted with light petroleum. These extracts were filtered through alumina and evaporated, and the product was crystallised from acetone to afford *cholest-1-ene* (1·8 g.) as needles, m. p. 69—70°, $[\alpha]_D$ +13° (Found : C, 87·25; H, 12·5. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%).

1α : 2α-*Epoxycholestane* (VI).—Solutions of cholest-1-ene (0·5 g.) in ether (20 c.c.) and 2·5N-monoperphthalic acid in ether (3 c.c.) were mixed and kept at 20° for 3 days. Isolation of the product in the usual way followed by crystallisation from acetone gave the *epoxide* (0·37 g.) as prisms, m. p. 86—88°, $[\alpha]_D$ +10° (Found : C, 84·1; H, 12·2. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%).

Cholestan-1α-ol (VII).—A solution of the 1α : 2α-epoxide (1·15 g.) and lithium aluminium hydride (0·7 g.) in ether (300 c.c.) was heated under reflux for 2·5 hr. Chromatography of the product gave cholestan-1α-ol (0·85 g.), prisms (from methanol), m. p. 93—95°, remelting at 103—105°, $[\alpha]_D$ +35° (Found : C, 83·6; H, 12·6. Calc. for $C_{27}H_{48}O$: C, 83·4; H, 12·5%).

Acetylation with acetic anhydride and pyridine for 10 days at 20° yielded 1α-*acetoxycholestane*, needles (from methanol), m. p. 73—75°, $[\alpha]_D$ +43° (Found : C, 81·0; H, 11·7. $C_{29}H_{52}O_2$ requires C, 80·9; H, 11·7%). This compound was prepared but not obtained crystalline by Striebel and Tamm.[10]

Oxidation of the 1α-alcohol (0·9 g.) by the chromic acid–acetone technique,[14] followed by crystallisation of the product from methanol, afforded cholestan-1-one (0·73 g.) as prisms, m. p. 87—89°, $[\alpha]_D$ +114°. Its 2 : 4-*dinitrophenylhydrazone* crystallised from dioxan–methanol as yellow needles, m. p. 184—187° (Found : N, 9·6. $C_{33}H_{50}O_4N_4$ requires N, 9·9%).

Reduction of Cholestan-1-one.—A solution of lithium aluminium hydride (0·15 g.) and the ketone (0·25 g.) in ether (100 c.c.) was heated under reflux for 2 hr. The product was chromatographed on alumina (25 g.). Elution with light petroleum–benzene (1 : 3; 200 c.c.) gave cholestan-1α-ol (0·13 g.), m. p. and mixed m. p. 91—94°, remelting at 103—105°. Further elution with the same solvent afforded cholestan-1β-ol (70 mg.), which crystallised from methanol as needles, m. p. 82—84°, $[\alpha]_D$ +22·5°.

Sodium–ethanol reduction of the ketone (0·18 g.) followed by chromatography yielded the 1α-alcohol (60 mg.) and the 1β-alcohol (0·11 g.).

3β-*Chloro*-1α : 2α-*epoxycholestane* (X).—A 0·1M-solution of perbenzoic acid in benzene (60 c.c.) was added to a solution of 3β-chlorocholest-1-ene (0·5 g.) in benzene (30 c.c.) at 5°. The solution was kept at this temperature for 2 days, then the steroid was isolated in the usual way. Crystallisation from acetone yielded the α-*epoxide* (0·32 g.) as needles, m. p. 129—131°, $[\alpha]_D$ +27·5° (Found : C, 77·3; H, 10·9. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·8%).

3β-*Chlorocholestan-1α-ol* (XI).—A solution of the chloro-epoxide (0·2 g.) and lithium aluminium hydride (0·5 g.) in ether (50 c.c.) was heated under reflux for 3 hr. Crystallisation of the product from acetone gave the *chloro-alcohol* (0·12 g.) as needles, m. p. 119—123°, $[\alpha]_D$ +34° (Found : C, 76·4; H, 11·3. $C_{27}H_{47}OCl$ requires C, 76·7; H, 11·2%).

Cholest-2-en-1-one (XIII).—3β-Chlorocholestan-1α-ol (0·16 g.) was oxidised by the chromic acid–acetone technique.[14] The product, dissolved in benzene, was filtered through alumina (10 g.) to yield cholest-2-en-1-one (0·1 g.), which on crystallisation from methanol–acetic acid (1 : 1) had m. p. 56—57°, $[\alpha]_D$ +121°; ultraviolet absorption (in EtOH), $\lambda_{max.}$ 2240 and 3300 Å (ε 8100 and 54 respectively). Striebel and Tamm [10] record m. p. 56—57°, $[\alpha]_D$ +120°; ultraviolet absorption, $\lambda_{max.}$ 2220 and 3400 Å (ε 7940 and 52 respectively).

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[14] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.