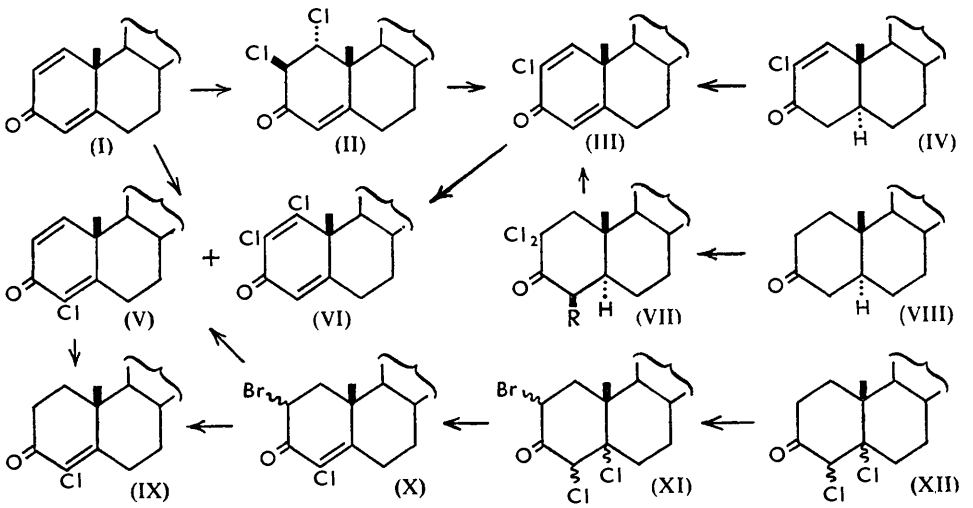
269. *Modified Steroid Hormones. Part IX.* The 2- and 4-Chloro-derivatives of 17β-Propionoxyandrosta-1 : 4-dien-3-one and -1 : 4 : 6-trien-3-one.*

By David N. Kirk and Vladimir Petrow.

Methods have been developed for the conversion of cholesta-1 : 4-dien-3-one (I) and -1 : 4 : 6-trien-3-one (XVII) into their 2- and 4-chloro-derivatives and have been applied to the preparation of the compounds named in the title, which were required for biological study.

The conversion of 3-oxo-Δ^4-steroids into 4-bromo- and 4-chloro-3-oxo-Δ^4-steroids was described in Parts I [1] and III.[2] 4-Bromo-3-oxo-Δ^4-steroids were prepared by bromination in the presence of proton-acceptors such as pyridine, ethylene oxide, or propylene oxide. The 4-chloro-derivatives were similarly obtained, by employing the same proton acceptors or dimethylformamide, and also by chlorination in ether–propionic acid to give the 4ξ : 5ξ-dichlorides, which passed readily into the 4-chloro-3-oxo-Δ^4-steroids on treatment with basic reagents such as pyridine or chromatographic alumina. An extension of these studies to the chlorination of some 1 : 4-dien-3-ones and 1 : 4 : 6-trien-3-ones is now reported.



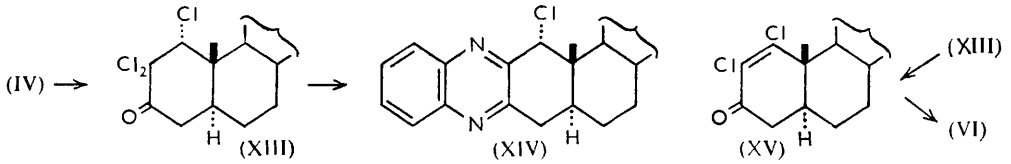
Treating the model compound cholesta-1 : 4-dien-3-one (cf. I) with 1 mol. of chlorine in ether–propionic acid caused addition of chlorine, with formation of a compound, $C_{27}H_{42}OCl_2$. That this addition involves the 1 : 2-unsaturated linkage follows from the transformations described below which lead to its formulation as 1α : 2β-dichlorocholest-4-en-3-one (II), it being assumed that this addition gives a *trans*-diaxial dichloride.[3] The axial β-orientation of the 2-chlorine atom is supported by the ultraviolet absorption maximum at 250—251 mμ, in contrast to the value of 246 mμ shown by 2α-chlorocholest-4-en-3-one:[4,5] the bathochromic shift at 4—5 mμ which occurs in passing from the equatorial α- to the axial β-configuration of the 2-halogen atom accords well with the difference of 5 mμ observed by Ellis and Petrow [5] between 2α- ($\lambda_{max.}$ 249 mμ) and 6β-bromo-2β-chlorocholest-4-en-3-one ($\lambda_{max.}$ 254 mμ).

* Part VIII, *J.*, 1958, 800.

[1] Kirk, Patel, and Petrow, *J.*, 1956, 627.
[2] *Idem*, *J.*, 1956, 1184.
[3] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, and earlier refs. therein.
[4] (*a*) Ellis and Petrow, *J.*, 1953, 3869; (*b*) Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[5] Ellis and Petrow, *J.*, 1956, 1179.

Reaction of the dichloride (II) with pyridine at room temperature led to a monochloro-derivative, $C_{27}H_{41}OCl$, considered to be 2-chlorocholesta-1 : 4-dien-3-one (III) on the basis of (i) its infrared absorption band at 6·02 μ (dienone [6]), (ii) its stability to boiling collidine and to lithium chloride in dimethylformamide, and (iii) its conversion into a 2 : 4-dinitrophenylhydrazone without loss of halogen, the last two observations being incompatible with a 6-chloro-structure.[7] This formulation (III) was finally established by comparison with authentic 2-chlorocholesta-1 : 4-dien-3-one obtained by dehydrogenation of 2-chlorocholest-1-en-3-one (IV) with selenium dioxide.[8] The same chloro-dienone (III) was also formed when either 4β-bromo-2 : 2-dichlorocholestanone (VII; R = Br), obtained by bromination of 2 : 2-dichloro- (VII; R = H) [4a] or 2 : 2 : 4β-trichloro-cholestanone (VII; R = Cl), prepared by trichlorination of cholestanone (VIII), was treated with boiling collidine. The β-configuration is assigned to the 4-halogeno-substituent in the trichloro-ketone (VII; R = Cl) by analogy with the preferred formulation of the bromo-analogue [9] (VII; R = Br).

Reaction of cholesta-1 : 4-dien-3-one (I) with 1 mol. of chlorine in dimethylformamide gave, in place of dichlorocholestenone (II), a mixture which was separated by chromatography on alumina into (i) a new monochlorocholestadienone, (ii) a dichlorocholestadienone, and (iii) unchanged material. Increasing the proportion of chlorine used led only to the disappearance of unchanged material from the product, which still consisted of the same mono- and dichloro-derivatives in approximately equal amounts: the significance of this observation is referred to below.



Formulation of the new monochloride as 4-chlorocholesta-1 : 4-dien-3-one (V) was indicated by its infrared absorption band at 6·02 μ (1 : 4-diene-3-one [6]), and its stability in boiling collidine. Evidence supporting its formulation as a 4-chloro-derivative was also obtained by its alternative preparation from 4ξ : 5ξ-dichlorocholestan-3-one [2] (XII). The last-mentioned compound in acetic acid gave 2ξ-bromo-4ξ : 5ξ-dichlorocholestan-3-one (XI), which with pyridine at room temperature afforded 2ξ-bromo-4-chlorocholest-4-en-3-one (X), readily transformed into the foregoing monochlorodienone (V) by dehydrobromination with collidine or lithium chloride–dimethylformamide. The constitution of the key intermediate (X) follows from its ultraviolet absorption spectrum ($\lambda_{max.}$ 260 mμ) and from its conversion into 4-chlorocholest-4-en-3-one (IX) by reduction with zinc dust in acetic acid. The new monochloride (V) is proved finally to be a 4-chloro-derivative by catalytic hydrogenation to 4-chlorocholest-4-en-3-one (IX). *Inter alia* we attempted to prepare the chloro-ketone (V) by dehydrogenating 4-chlorocholest-4-en-3-one with selenium dioxide, but obtained a gum.

The presence of a 1 : 4-dien-3-one system in the foregoing dichlorocholestadienone was revealed by its ultraviolet (max. at 258 mμ) and infrared (band at 6·02 μ) absorption spectra. That the chlorine atoms were situated in two of the vinylic positions 1, 2, and 4 was apparent from the stability of the compound to collidine and to lithium chloride–dimethylformamide. Recognition of a 2-chloro-ketone followed from its formation from the 2-chloro-dienone (III) by monochlorination. Its formulation as 1 : 2-dichlorocholesta-1 : 4-dien-3-one (VI) was established as follows.

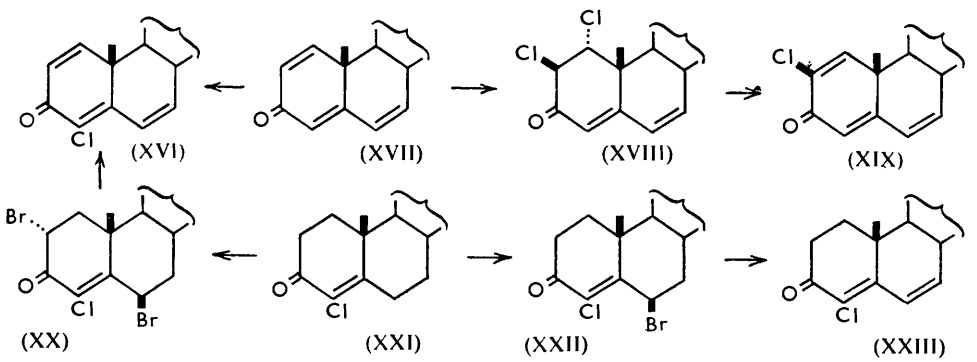
Monochlorination of cholest-1-en-3-one gave the expected 2-chlorocholest-1-en-3-one

[6] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[7] Ginsburg, *J. Amer. Chem. Soc.*, 1953, **75**, 5489.
[8] Meystre, Frey, Voser, and Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.
[9] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

(IV), there being evidence for initial formation of an unstable 1 : 2-dichloride. Further chlorination led to the stable 1α : 2 : 2-trichlorocholestan-3-one (XIII) (cf. ref. 3 for configuration at $C_{(1)}$), characterised by absorption in the *R*-band region ($\lambda_{max.}$ 296 mμ) nearly identical with that reported [10] for 2 : 2-dichlorocholestan-3-one [1] ($\lambda_{max.}$ 294 mμ) and by reaction with *o*-phenylenediamine to give the chloroquinoxaline (XIV). Dehydrochlorination of the trichloro-compound (XIII) with lithium chloride–dimethylformamide led to 1 : 2-dichlorocholest-1-en-3-one (XV), whose dinitrophenylhydrazone was formed without loss of halogen, confirming the absence of a 4-halogen atom. This ketone (XV) was smoothly dehydrogenated by selenium dioxide [8] to 1 : 2-dichlorocholesta-1 : 4-dien-3-one (VI), identical with the material obtained as above.

Substitution of chlorine at position 2 or 4 in cholestadienone (I) decreases the reactivity of the ketonic function presumably by virtue of the $-I$ effect of the halogen on the polarisation of the carbonyl group. Thus the monochloro-ketones (III) and (V) fail to react with *o*-phenylenediamine (cf. Parts I [1] and III [2]). They condense normally, though somewhat sluggishly, with 2 : 4-dinitrophenylhydrazine. The dichloro-ketone (VI), in contrast, fails to react even with the last reagent. *Inter alia*, they do not form 3 : 3-ethylenedioxy-derivatives [11] or 3-enamine derivatives.[12]

Chlorination of cholesta-1 : 4 : 6-trien-3-one (XVII) followed the pattern established for the dienone (I). In ether–propionic acid the trienone reacted additively, to give 1α : 2β-dichlorocholesta-4 : 6-dien-3-one (XVIII). The constitution assigned to this compound is supported by its ultraviolet absorption ($\lambda_{max.}$ 299 mμ) which is consistent with a cholesta-4 : 6-dien-3-one [13] ($\lambda_{max.}$ 284 mμ) substituted with an axial 2-chlorine atom but hardly consistent with an equatorial 2α-chloro-structure which would be expected from analogy with 2α-bromocholesta-4 : 6-dien-3-one [14] ($\lambda_{max.}$ 290 mμ) to absorb at a shorter



wavelength.[5] Dehydrochlorination of the dichloro-ketone (XVIII) with cold pyridine led to 2-chlorocholesta-1 : 4 : 6-trien-3-one (XIX) ($\lambda_{max.}$ 217, 268, and 307 mμ). This compound was additionally prepared by dichlorination of either 5α : 6β-dibromocholestan-3-one or 6β-bromocholest-4-en-3-one, to the corresponding 2 : 2-dichloro-derivative, and dehydrohalogenation of this with lithium chloride in dimethylformamide (cf. the similar preparation of 2-bromocholesta-1 : 4 : 6-trien-3-one [14]).

Chlorination of the trienone (XVII) in dimethylformamide gave 4-chlorocholesta-1 : 4 : 6-trien-3-one (XVI). There was no evidence for concomitant production of a dichloro-derivative under these conditions. The formulation (XVI) is supported by an alternative preparation from 4-chlorocholest-4-en-3-one (XXI). Monobromination of the last compound in acetic acid led to 6β-bromo-4-chlorocholest-4-en-3-one (XXII), converted

[10] Cookson, *J.*, 1954, 282.
[11] Fernholz and Stavely, Abs. 102nd Meeting Amer. Chem. Soc., Atlantic City, N.J., 39M (1941); Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.
[12] Johnson, Herr, Babcock, Fonken, Stafford, and Heyl, *J. Amer. Chem. Soc.*, 1956, **78**, 430.
[13] Wilds and Djerassi, *ibid.*, 1946, **68**, 1712.
[14] Fieser, Romero, and Fieser, *ibid.*, 1955, **77**, 3305.

by boiling collidine, or more efficiently by lithium chloride–dimethylformamide, into 4-chlorocholesta-4 : 6-dien-3-one (XXIII) ($\lambda_{max.}$ 298·5 mμ, revealing a bathochromic shift of 14·5 mμ due to the 4-chloro-substituent [13]). Further bromination of the 6-bromo-derivative (XXII) or dibromination of 4-chlorocholest-4-en-3-one (XXI) yielded 2α : 6β-dibromo-4-chlorocholest-4-en-3-one (XX) which passed smoothly into the foregoing 4-chlorocholesta-1 : 4 : 6-trien-3-one (XVI) on dehydrobromination with lithium chloride–dimethylformamide.

The α- and β-configurations assigned to the bromine atoms in the foregoing two compounds [(XX) and (XXII)] follow from analogy with the direct bromination of cholest-4-en-3-one,[15] which gives the 2α : 6β-dibromo-derivative.[5,14] They are supported by spectroscopic data. Thus introduction of a 4-chloro-substituent into 6β-bromocholest-4-en-3-one ($\lambda_{max.}$ 244 mμ) [15,16] leads to a bathochromic shift of 22 mμ which, though somewhat greater than that usually associated with such substitution (*ca.* 16 mμ) is nevertheless more in accord with expectation than would obtain on the basis of a 6α-bromo-formulation (cf. 6α-bromocholest-4-en-3-one,[16] $\lambda_{max.}$ 238 mμ). Absorption in the *R*-band region affords further support. The fine structure observed in the ultraviolet absorption of 4-chlorocholest-4-en-3-one (XXI) in the 300—400 mμ region is almost identical with that reported by Cookson *et al.* for cholest-4-en-3-one (cf. Table 1).

TABLE 1. $\lambda_{max.}$ (mμ) (and ε, in parentheses).

Cholest-4-en-3-one [a]	314 (45)	323·5 (49)	336 (47)	349 (34)	367 (14)
4-Chloro-4-en-3-one	313 (40)	324 (41)	337 (34)	350 [b] (19)	368 [b] (6·5)
6α-Bromo-4-en-3-one [a]	319 [b] (31)	329·5 (36)	340·5 (36)	352 [b] (28)	372 [b] (11·5)
6β-Bromo-4-en-3-one [a]	—	344 (64·5)	355 (62)	371 [b] (46·5)	391 [b] (20)
6β-Bromo-4-chlorocholest-4-en-3-one	336 (69)	345 [b] (65)	353 [b] (55)	371 [b] (31)	395 [b] (8)

[a] Values given by Bird *et al.*[17] [b] Inflexion.

Similar identity exists between the 6β-bromo-derivatives of these two ketones, which differ significantly in the *R*-band region from 6α-bromocholest-4-en-3-one.

The 2α-orientation of the bromine atom in the dibromo-ketone (XX) follows from the data in Table 2.

TABLE 2.

Compound	$\lambda_{max.}$ (mμ)	Bathochromic shift (mμ) due to 2-Br
6β-Bromocholest-4-en-3-one [15,16]	244	—
2α : 6β-Dibromocholest-4-en-3-one [14]	248	4
2β : 6β-Dibromocholest-4-en-3-one [5]	257	13
6β-Bromo-4-chlorocholest-4-en-3-one	266	—
2α : 6β-Dibromo-4-chlorocholest-4-en-3-one	270—271	4—5

Chlorination of 17β-propionoxyandrosta-1 : 4-dien-3-one (I) in ether–propionic acid furnished the 1α : 2β-dichloro-derivative (II) which was converted into 2-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one (III) by brief treatment with pyridine. By performing the chlorination in dimethylformamide, 1 : 2-dichloro- (VI) and 4-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one (V) were obtained, the last compound being also prepared from 4ξ : 5ξ-dichloro-17β-propionoxyandrostan-3-one (XII) *via* the 2ξ-bromo-derivatives (XI) and (X).

17β-Propionoxyandrosta-1 : 4 : 6-trien-3-one (XVII) in ether–propionic acid gave the 1α : 2β-dichloro-derivative (XVIII), which was converted into 2-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one (XIX). 4-Chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one (XVI) was obtained by direct chlorination of the trienone (XVII) in dimethylformamide or by dibromination of 4-chloro-17β-propionoxyandrost-4-en-3-one (XXI), followed by dehydrobromination.

[15] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.
[16] Barton and Miller, *ibid.*, p. 1066.
[17] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.

Experimental

Optical rotations refer to $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. (values in parentheses are log ε), for EtOH solutions unless otherwise stated. Infrared absorption spectra (in Nujol) were kindly determined by Mr. R. F. Branch, B.Sc., Ministry of Supply. B.D.H. alumina, chromatography grade, was employed.

1α : 2β-*Dichlorocholest*-4-*en*-3-*one* (II).—Cholesta-1 : 4-dien-3-one (2 g.) in dry ether (50 ml.) at −30° was treated with chlorine in 1·10M-propionic acid (4·8 ml.), and the mixture stored at −30° in the dark for 20 hr. The ether was washed with water, dilute sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Evaporation under reduced pressure and crystallisation of the residue from ether–methanol gave 1α : 2β-*dichlorocholest*-4-*en*-3-*one*, needles, m. p. 122—123°, $[\alpha]_D^{24}$ +25° (*c* 0·50), $\lambda_{max.}$ 250—251 mμ (4·14) (Found: C, 71·5; H, 9·3; Cl, 15·0. $C_{27}H_{42}OCl_2$ requires C, 71·5; H, 9·3; Cl, 15·6%).

2-*Chlorocholesta*-1 : 4-*dien*-3-*one* (III).—(*a*) The foregoing dichloride (400 mg.) in pyridine (2 ml.) was set aside for 4 hr., pyridine hydrochloride separating. After dilution with ether and dilute hydrochloric acid, the ether layer was washed, dried, and evaporated. The residue was purified from hexane or aqueous acetone, to give 2-*chlorocholesta*-1 : 4-*dien*-3-*one*, fibrous crystals, m. p. 128—130°, $[\alpha]_D^{23}$ +8° (*c* 0·46), $\lambda_{max.}$ 253 mμ (4·20), ν 6·02 μ (Found: C, 77·6; H, 9·8; Cl, 9·0. $C_{27}H_{41}OCl$ requires C, 77·6; H, 9·9; Cl, 9·3%).

(*b*) 2-Chlorocholest-1-en-3-one (1·72 g.) in a solution of selenium dioxide (0·6 g.) and acetic acid (0·5 ml.) in *tert.*-butyl alcohol (45 ml.) was heated under reflux under nitrogen for 12 hr., then 0·6 g. selenium dioxide was added and boiling continued for a further 20 hr. The cooled solution was diluted with ether, filtered from selenium, washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The red-brown residue in benzene–light petroleum (1 : 4) was percolated through chromatographic alumina (5 g.). Evaporation of the solvent gave 2-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 127—128° with the sample prepared above.

(*c*) 4β-Bromo-2 : 2-dichlorocholestan-3-one (VII; R = Br) (1 g.) in collidine (7 ml.) was heated under reflux under nitrogen for 30 min. The cooled mixture was poured into dilute sulphuric acid, and the product isolated with ether. The product in benzene solution was percolated through alumina (5 g.), then crystallised from hexane to give 2-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 125—128°, with samples prepared as above.

(*d*) Cholestan-3-one (2 g.) in carbon tetrachloride (20 ml.) and acetic acid (10 ml.) was treated with a 1·05M-solution of chlorine in propionic acid (15 ml.; 3 mols.) at room temperature for 72 hr. whereafter no free chlorine remained. 2 : 2 : 4β-*Trichlorocholestan*-3-*one*, isolated with ether, formed needles, m. p. 116—117° (Found: C, 66·5; H, 8·7; Cl, 19·8. $C_{27}H_{43}OCl_3$ requires C, 66·2; H, 8·8; Cl, 21·7%), after crystallisation from acetone–methanol.

The trichloro-derivative (800 mg.) in collidine (10 ml.) was heated under reflux under nitrogen for 25 min., to give the 2-chlorodienone, m. p. and mixed m. p. 126—127° on admixture with samples prepared as above.

The 2-*chlorocholesta*-1 : 4-*dien*-3-*one* 2 : 4-*dinitrophenylhydrazone* separated from chloroform–ethanol in plates, m. p. 247—250° (decomp.), $\lambda_{max.}$ 395 mμ (4·53) (Found: N, 10·2; Cl, 6·3. $C_{33}H_{45}O_4N_4Cl$ requires N, 9·4; Cl, 5·9%).

4-*Chlorocholesta*-1 : 4-*dien*-3-*one* (V) *and* 1 : 2-*Dichlorocholesta*-1 : 4-*dien*-3-*one* (VI).—Cholesta-1 : 4-dien-3-one (7 g.) in dimethylformamide (70 ml.) and dry ether (35 ml.) at −30° was treated with a 1·08M-solution of chlorine in propionic acid (17·8 ml.; 1·05 mol.). The chlorine was absorbed in 2 days at −30° in the dark. The product in light petroleum (b. p. 40—60°) was percolated through alumina (200 g.). Elution with light petroleum–benzene (7 : 3) gave 1 : 2-*dichlorocholesta*-1 : 4-*dien*-3-*one*, plates, m. p. 171—173°, $[\alpha]_D^{28}$ +23° (*c* 0·61), $\lambda_{max.}$ 258—259 mμ (4·05), ν 6·02 μ (Found: C, 71·8; H, 9·1; Cl, 15·6. $C_{27}H_{40}OCl_2$ requires C, 71·8; H, 8·9; Cl, 15·7%), after purification from methylene chloride–methanol. Further elution with light petroleum–benzene (1 : 1) gave 4-*chlorocholesta*-1 : 4-*dien*-3-*one*, needles, m. p. 129—131°, $[\alpha]_D^{24}$ +64° (*c* 0·46), $\lambda_{max.}$ 246 mμ (4·04), ν 6·02 μ (Found: C, 77·3; H, 10·0; Cl, 8·9. $C_{27}H_{41}OCl$ requires C, 77·8; H, 9·9; Cl, 8·5%), after crystallisation from methanol. Finally, elution with benzene–ether (1 : 1) gave cholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 111—113°.

4-*Chlorocholesta*-1 : 4-*dien*-3-*one* 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 254—255° (decomp.), $\lambda_{max.}$ 396 mμ (4·55) (Found: N, 9·7; Cl, 6·6%), after purification from ethyl acetate–chloroform.

2ξ-*Bromo*-4ξ : 5ξ-*dichlorocholestan*-3-*one* (XI).—4ξ : 5ξ-Dichlorocholestan-3-one (4·1 g.) in methylene chloride (50 ml.) and acetic acid (100 ml.) was treated dropwise with a 1·088M-solution of bromine in acetic acid (8·5 ml.) in 5 min. Decolorisation was complete after a further 2 min., then the mixture was diluted with water. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated. 2ξ-*Bromo*-4ξ : 5ξ-*dichlorocholestan*-3-*one* crystallised from ethanol or ether–methanol in needles, m. p. 110—111°, $[\alpha]_D^{24}$ +86° (*c* 0·76) (Found: C, 60·0; H, 8·2; Hal, 27·4. $C_{27}H_{43}OCl_2Br$ requires C, 60·7; H, 8·1; Hal, 28·2%).

2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one* (X).—A solution of the foregoing compound (1 g.) in pyridine (20 ml.) was left at room temperature for 2 hr. The solution was poured into dilute sulphuric acid, and the product extracted with ether. 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one* formed plates, m. p. 181—183°, $[\alpha]_D^{24}$ +90° (*c* 0·64), $\lambda_{max.}$ 260 mμ (4·01) (Found: C, 65·1; H, 8·7; Hal, 22·0. $C_{27}H_{42}OClBr$ requires C, 65·1; H, 8·5; Hal, 23·2%), after purification from hexane or ethanol.

Debromination of 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one*.—The foregoing compound (250 mg.) in boiling methanol (10 ml.) and acetic acid (5 ml.) was treated with zinc dust (1 g.) for ½ hr. Isolation of the product with ether, and crystallisation from ethanol, gave 4-chlorocholest-4-en-3-one, needles, m. p. and mixed m. p. 125—126°.

Dehydrobromination of 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one*.—(*a*) A solution of the 2ξ-bromo-derivative (1 g.) in collidine (10 ml.) was boiled under reflux under nitrogen for 45 min. The cooled mixture, on dilution with ether and filtration, afforded collidine hydrobromide (365 mg., 0·9 mol.). The product was decolorised by percolation in 4 : 1 light petroleum–benzene through alumina (10 g.), and crystallised from methanol to give 4-chlorocholesta-1 : 4-dien-3-one, needles, m. p. 130—131°, identical with the material prepared as above by direct chlorination of the dienone in dimethylformamide.

(*b*) The 2ξ-bromo-compound (5 g.) in dimethylformamide (50 ml.) containing lithium chloride (2 g.) was heated on the steam-bath for 4 hr., to give 4-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 129—131°.

Hydrogenation of 4-*Chlorocholesta*-1 : 4-*dien*-3-*one* (V).—The 4-chlorodienone (250 mg.) in methanol (200 ml.) was reduced in the presence of pre-reduced palladium–barium carbonate (20 mg.) until 1 mol. of hydrogen had been absorbed. The product in benzene–light petroleum (1 : 4) was chromatographed on alumina (4 g.). Elution with benzene–petroleum (1 : 1) gave 4-chlorocholest-4-en-3-one (60 mg.), m. p. 125—127°, $\lambda_{max.}$ 256 mμ (4·15), after crystallisation from ethanol.

Chlorination of 2-*Chlorocholesta*-1 : 4-*dien*-3-*one* (III).—A solution of the 2-chlorodienone (III) (1·3 g.) in ether (20 ml.) and dimethylformamide (20 ml.) at room temperature was treated with a 1·52M-solution of chlorine in propionic acid (2·25 ml.), and the mixture stored in the dark for 2 days. The product, after chromatography on alumina (40 g.), yielded 1 : 2-dichlorocholesta-1 : 4-dien-3-one, plates, m. p. and mixed m. p. 170—172°, with the sample prepared previously, $\lambda_{max.}$ 258 mμ (4·12).

The 4-chlorocholestadienone (V) resisted further chlorination.

Chlorination of Cholest-1-*en*-3-*one*.—A solution of cholest-1-en-3-one (2 g.) in ether (100 ml.) at −80° was treated with a 0·96M-solution of chlorine in propionic acid (6·5 ml., 1·03 mol.). After 6 hr. in the dark, the temperature of the mixture meanwhile rising to −30°, the chlorine-free solution was poured into ice-water. The ether was washed with ice-water and sodium hydrogen carbonate solution, dried, and evaporated at 0°. The oily residue failed to crystallise, but its solution in hexane began to evolve hydrogen chloride and subsequently afforded 2-chlorocholest-1-en-3-one, leaflets, m. p. and mixed m. p. 106—108°.

Chlorination of 2-*Chlorocholest*-1-*en*-3-*one* (IV).—The 2-chloro-compound (5 g.) in dry carbon tetrachloride (80 ml.) was treated at room temperature with a 0·935M-solution of chlorine in propionic acid (13·5 ml.). After 2 days the solution was washed with sodium hydrogen carbonate solution and water, and the solvent removed under reduced pressure. 1α : 2 : 2-*Trichlorocholestan*-3-*one* (XIII) separated from ethanol in flakes, m. p. 123—125°, $[\alpha]_D^{24}$ +78° (*c* 0·98), $\lambda_{max.}$ 296 mμ (ε 45) (in *cyclo*hexane) (Found: C, 66·0; H, 9·0; Cl, 22·4. $C_{27}H_{43}OCl_3$ requires C, 66·2; H, 8·5; Cl, 21·2%).

1 : 2-*Dichlorocholest*-1-*en*-3-*one* (XV).—A mixture of the 1α : 2 : 2-trichloride (1 g.), lithium chloride (100 mg.), and dimethylformamide (10 ml.) was heated under reflux for 30 min. The cooled solution was diluted with water and deposited 1 : 2-*dichlorocholest*-1-*en*-3-*one*, which after purification from ethanol formed blades, m. p. 153—156°, $[\alpha]_D^{25}$ +18° (*c* 0·26), $\lambda_{max.}$ 255 mμ

(4·16) (Found: C, 71·9; H, 9·4; Cl, 15·0. $C_{27}H_{42}OCl_2$ requires C, 71·5; H, 9·3; Cl, 15·6%). The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–ethanol in orange flakes, m. p. 238—240°, $\lambda_{max.}$ 394 mμ (4·47) (in $CHCl_3$) (Found: Cl, 10·3. $C_{33}H_{46}O_4N_4Cl_2$ requires Cl, 11·2%).

Reaction between 1α : 2 : 2-*Trichlorocholestan*-3-*one and* o-*Phenylenediamine.*—The trichloride (1 g.), *o*-phenylenediamine (1 g.), and acetic acid (6 ml.) were boiled under reflux in nitrogen for 30 min., then poured into water. The product, isolated with chloroform, was percolated in benzene–light petroleum (1 : 1) through alumina (20 g.). The *quinoxaline derivative* (XIV) crystallised from ethanol in light brown flakes, m. p. 174—178°, $[\alpha]_D^{28}$ +205° (*c* 0·16), $\lambda_{max.}$ 225 (4·37), 243 (4·21), 264 (4·05), 311 (3·88), 325 (3·94), 340·5 (4·01) and 357 mμ (3·94) (Found: C, 78·9; H, 8·8; N, 5·3; Cl, 7·1. $C_{33}H_{47}N_2Cl$ requires C, 78·1; H, 9·3; N, 5·5; Cl, 7·0%).

Dehydrogenation of 1 : 2-*Dichlorocholest*-1-*en*-3-*one* (XV).—The 1 : 2-dichloro-compound (1·5 g.) was heated under reflux with selenium dioxide (0·5 g.) and acetic acid (0·2 ml.) in *tert.*-butyl alcohol (20 ml.) for 9 hr., then more selenium dioxide (0·5 g.) was added. After a further 8 hours' heating, half of the solvent was removed, and the residue allowed to cool. The solids were collected, washed with methanol, and percolated in benzene through alumina (2 g.). Purification from ethanol gave 1 : 2-dichlorocholesta-1 : 4-dien-3-one, m. p. 170—171°, $[\alpha]_D^{28}$ +25° (*c* 0·24), $\lambda_{max.}$ 258—259 mμ (4·05), identified by comparison of infrared spectra with the sample obtained by direct chlorination of the dienone in dimethylformamide.

1α : 2β-*Dichlorocholesta*-4 : 6-*dien*-3-*one* (XVIII).—Cholesta-1 : 4 : 6-trien-3-one (2 g.) in dry ether (50 ml.) at −30° was treated with a 1·27M-solution of chlorine in propionic acid (4·8 ml.) and kept at −30° in the dark for 40 hr. The *product*, crystallised from ethanol, then from hexane, formed needles, m. p. 100—102°, $[\alpha]_D^{23}$ −73° (*c* 0·40), $\lambda_{max.}$ 299 mμ (4·17), ν 6·02 μ (conjugated dienone) (Found: C, 74·1; H, 8·9; Cl, 15·2. $C_{27}H_{40}OCl_2$ requires C, 73·5; H, 9·1; Cl, 16·1%).

2-*Chlorocholesta*-1 : 4 : 6-*trien*-3-*one* (XIX).—A solution of the foregoing dichloride (850 mg.) in pyridine (5 ml.) was kept at 20—25° for 4 hr., then poured into dilute hydrochloric acid. 2-*Chlorocholesta*-1 : 4 : 6-*trien*-3-*one*, isolated by means of ether, formed prisms, m. p. 153—154°, $[\alpha]_D^{23}$ −45° (*c* 0·36), $\lambda_{max.}$ 217 (4·19), 268 (4·04), and 307 mμ (4·01) (Found: C, 77·7; H, 9·2; Cl, 9·6. $C_{27}H_{39}OCl$ requires C, 78·1; H, 9·5; Cl, 8·5%), after crystallisation from ethanol.

6β-*Bromo*-2 : 2-*dichlorocholest*-4-*en*-3-*one.*—(*a*) A solution of 6β-bromocholest-4-en-3-one (10 g.) in carbon tetrachloride (50 ml.) and acetic acid (50 ml.) was treated with a 1·27M-solution of chlorine in propionic acid (35·2 ml.) in the dark overnight. The separated leaflets were washed with hexane and purified from carbon tetrachloride–hexane, to give 6β-*bromo*-2 : 2-*dichlorocholest*-4-*en*-3-*one*, leaflets, m. p. 187—188°, $[\alpha]_D^{20}$ −30° (*c* 0·20), $\lambda_{max.}$ 256 mμ (4·11) (Found: C, 60·7; H, 7·6; Hal, 30·2. $C_{27}H_{41}OCl_2Br$ requires C, 60·9; H, 7·7; Hal, 28·3%).

(*b*) 5α : 6β-Dibromocholestan-3-one (5·44 g.) in carbon tetrachloride (50 ml.) and acetic acid (100 ml.) was treated with a 1·20M-solution of chlorine in propionic acid (17·1 ml.) in the dark for 24 hr. After being washed with water the solvent was removed under reduced pressure; crystallisation of the residue from acetone gave impure 5α : 6β-dibromo-2 : 2-dichlorocholestan-3-one, needles, m. p. 130—137°, $[\alpha]_D^{24}$ −3° (*c* 0·25), not fully transparent to ultraviolet radiation at 240—260 mμ. This material was dissolved in pyridine and after 1 hr. yielded 6β-bromo-2 : 2-dichlorocholest-4-en-3-one, m. p. and mixed m. p. 184—186° with the sample prepared as in (*a*).

Dehydrohalogenation of the foregoing compound (2 g.) with lithium chloride (1 g.) in dimethylformamide (30 ml.) at 100° for 1·5 hr. yielded 2-chlorocholesta-1 : 4 : 6-trien-3-one, m. p. 150—151°, mixed m. p. 150—153° with the sample prepared previously.

4-*Chlorocholesta*-1 : 4 : 6-*trien*-3-*one* (XVI).—A solution of cholesta-1 : 4 : 6-trien-3-one (3 g.) in dimethylformamide (50 ml.) was cooled to −30°, treated with a 1·095M-solution of chlorine in propionic acid (7·6 ml.) and stored in the dark at −30° for 16 hr. The product was purified by passage in benzene–light petroleum (1 : 1) through alumina (15 g.) and crystallisation from ethanol. 4-*Chlorocholesta*-1 : 4 : 6-*trien*-3-*one* formed needles, m. p. 115—116°, $[\alpha]_D^{25}$ +40° (*c* 0·75), $\lambda_{max.}$ 229 (4·10), 311 (3·85), $\lambda_{infl.}$ 258—260 mμ (3·86) (Found: C, 78·0; H, 9·3; Cl, 8·6. $C_{27}H_{39}OCl$ requires C, 78·1; H, 9·5; Cl, 8·5%).

6β-*Bromo*-4-*chlorocholest*-4-*en*-3-*one* (XXII).—A solution of 4-chlorocholest-4-en-3-one (5 g.) in ether (100 ml.) was cooled to 5° and treated dropwise with a 1·088M-solution of bromine in acetic acid (11·5 ml.). The reaction was complete in a few minutes, then the ether was evaporated under reduced pressure and the mixture diluted with methanol. The separated solids were washed with methanol and crystallised from ethanol. 6β-*Bromo*-4-*chlorocholest*-4-*en*-3-*one*

formed needles, m. p. 170—172°, $[\alpha]_D^{24}$ −136° (*c* 0·25), $\lambda_{max.}$ 266—267 mμ (4·06) (Found: C, 63·8; H, 8·7; Hal, 26·2. $C_{27}H_{42}OClBr$ requires C, 65·1; H, 8·5; Hal, 23·2%).

4-*Chlorocholesta*-4 : 6-*dien*-3-*one* (XXIII), prepared by heating the 6β-bromo-compound (1·5 g.) with lithium chloride (250 mg.) in dimethylformamide (12 ml.) under reflux for ½ hr., crystallised from ethanol in needles, m. p. 99—100°, $[\alpha]_D^{22}$ +57° (*c* 0·19), $\lambda_{max.}$ 298·5 mμ (4·27) (Found: C, 77·2; H, 9·6; Cl, 9·1. $C_{27}H_{41}OCl$ requires C, 77·7; H, 9·9; Cl, 8·5%). Its 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 271—273°, $\lambda_{max.}$ 397 mμ (4·58) with shoulders at 406 (4·57) and 414 mμ (4·54) (in $CHCl_3$) (Found: Cl, 6·1. $C_{33}H_{45}O_4N_4Cl$ requires Cl, 5·9%).

2α : 6β-*Dibromo*-4-*chlorocholest*-4-*en*-3-*one* (XX).—4-Chlorocholest-4-en-3-one (2 g.) in dry ether (50 ml.), cooled to 0°, was stirred and treated dropwise with a 0·97M-solution of bromine in acetic acid (10·0 ml.). Decolorisation was complete after 1 hr., then the ether was removed under reduced pressure. The crystalline solids were collected and purified from methylene chloride–methanol and finally from hexane, to give 2α : 6β-*dibromo*-4-*chlorocholest*-4-*en*-3-*one*, plates, m. p. 185—187°, $[\alpha]_D^{24}$ −105° (*c* 0·92), $\lambda_{max.}$ 270—271 mμ (4·05) (Found: C, 56·1; H, 7·1; Hal, 31·4. $C_{27}H_{41}OClBr_2$ requires C, 56·2; H, 7·2; Hal, 33·9%).

Dehydrobromination of 2α : 6β-*Dibromo*-4-*chlorocholest*-4-*en*-3-*one* (XX).—A solution of the 2α : 6β-dibromide (330 mg.) and lithium chloride (200 mg.) in dimethylformamide (10 ml.) was boiled under reflux under nitrogen for 1 hr., then cooled and poured into water. 4-Chlorocholesta-1 : 4 : 6-trien-3-one was obtained, having m. p. and mixed m. p. with a previous sample 113—115°, $[\alpha]_D^{25}$ +33° (*c* 0·30), $\lambda_{max.}$ 229 (4·10), 311 (4·08), $\lambda_{infl.}$ 260 mμ (3·85).

1α : 2β-*Dichloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (II).—17β-Propionoxyandrosta-1 : 4-dien-3-one (2 g.) in dry ether (80 ml.) at −30° was treated with a 1·4M-solution of chlorine in propionic acid (4·4 ml.) and stored in the dark at −30° for 18 hr. 1α : 2β-*Dichloro*-17β-*propionoxyandrost*-4-*en*-3-*one* formed prisms, m. p. 141—144°, $[\alpha]_D^{26}$ +16° (*c* 1·23), $\lambda_{max.}$ 250 mμ (4·16) (Found: C, 63·4; H, 7·1; Cl, 16·4. $C_{22}H_{30}O_3Cl_2$ requires C, 63·9; H, 7·3; Cl, 17·1%).

2-*Chloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (III), obtained when the foregoing 1α : 2β-dichloride (600 mg.) was treated with pyridine (3 ml.) for ½ hr., separated from methylene chloride–hexane in plates, m. p. 142—144°, $[\alpha]_D^{26}$ −4° (*c* 1·52), $\lambda_{max.}$ 251 mμ (4·21) (Found: C, 69·5; H, 7·8; Cl, 9·8. $C_{22}H_{30}O_3Cl$ requires C, 70·1; H, 7·8; Cl, 9·4%).

Chlorination of 17β-*Propionoxyandrosta*-1 : 4-*dien*-3-*one in Dimethylformamide*.—A solution of the dienone (2 g.) in dimethylformamide (30 ml.) was cooled in ice and treated with a 1·11M-solution of chlorine in propionic acid (5·3 ml.) in the dark for 4 hr. The product was chromatographed in light petroleum (b. p. 40—60°) on alumina (50 g.). Elution with light petroleum–benzene (3 : 1) gave 1 : 2-*dichloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (VI), flakes, m. p. 235—237°, $[\alpha]_D^{24}$ +40° (*c* 1·19), $\lambda_{max.}$ 257·5 mμ (4·10) (Found: C, 64·1; H, 7·1; Cl, 15·3. $C_{22}H_{28}O_3Cl_2$ requires C, 64·2; H, 6·9; Cl, 17·2%), after crystallisation from methylene chloride–hexane. Elution with benzene furnished 4-*chloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (V) which separated from aqueous methanol in leaflets, m. p. 138—141°, $[\alpha]_D^{23}$ +76° (*c* 1·28), $\lambda_{max.}$ 246 mμ (4·05) (Found: C, 69·9; H, 7·5; Cl, 9·5. $C_{22}H_{29}OCl_3$ requires C, 70·1; H, 7·8; Cl, 9·4%). Continued elution with benzene and benzene–ether (4 : 1) gave some unchanged dienone, m. p. 128—130°.

2ξ-*Bromo*-4ξ : 5ξ-*dichloro*-17β-*propionoxyandrostan*-3-*one* (XI).—A 0·204M-solution of bromine in acetic acid (47·5 ml.) was added dropwise to 4ξ : 5ξ-dichloro-17β-propionoxyandrostan-3-one (4 g.) in acetic acid (60 ml.). Decolorisation was complete in 5 min., then the mixture was poured into water. 2ξ-*Bromo*-4ξ : 5ξ-*dichloro*-17β-*propionoxyandrostan*-3-*one* formed prisms, m. p. 160—163°, $[\alpha]_D^{27}$ +67° (*c* 0·86) (Found: C, 53·6; H, 6·5; Hal, 29·2. $C_{22}H_{31}O_3Cl_2Br$ requires C, 53·5; H, 6·3; Hal, 30·5%), after purification from acetone–hexane.

2ξ-*Bromo*-4-*chloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (X), prepared by treating the foregoing compound (2 g.) with pyridine (10 ml.) at room temperature for 1 hr., crystallised from methylene chloride–methanol in plates, m. p. 181—183°, $[\alpha]_D^{27}$ +61° (*c* 1·10), $\lambda_{max.}$ 260 mμ (4·08) (Found: C, 58·7; H, 6·7; Hal, 23·2. $C_{22}H_{30}O_3ClBr$ requires C, 57·7; H, 6·6; Hal, 25·2%). This compound (5 g.) with lithium chloride (2 g.) in dimethylformamide (50 ml.) on the steam-bath for 4 hr., or in collidine (6 vols.) under reflux under nitrogen gave 4-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one, m. p. and mixed m. p. 140—141°.

1α : 2β-*Dichloro*-17β-*propionoxyandrosta*-4 : 6-*dien*-3-*one* (XVIII).—17β-Propionoxyandrosta-1 : 4 : 6-trien-3-one (2 g.) in dry ether (70 ml.) at −30° was treated with a 1·16M-solution of chlorine in propionic acid (5·3 ml.) at −30° in the dark for 20 hr. The *product* separated from methylene chloride–methanol in needles, m. p. 134—135°, $[\alpha]_D^{20}$ −172° (*c* 0·43),

$\lambda_{max.}$ 296·5 mμ (4·36) (Found: C, 64·3; H, 7·0; Cl, 18·0. $C_{22}H_{28}O_3Cl_2$ requires C, 64·3; H, 6·9; Cl, 17·2%).

2-*Chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one* (XIX), prepared by keeping a solution of the preceding dichloride (1·2 g.) in pyridine (5 ml.) at 30° for 15 min., formed needles, m. p. 140—141°, $[\alpha]_D^{25}$ −7° (*c* 0·57), $\lambda_{max.}$ <220, 267·5 (4·04), and 305 mμ (4·01) (Found: C, 70·6; H, 7·5; Cl, 9·4. $C_{22}H_{27}O_3Cl$ requires C, 70·5; H, 7·3; Cl, 9·2%), after crystallisation from hexane.

4-*Chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one* (XVI).—(*a*) A solution of the trienone (XIV) (2·5 g.) in dry ether (25 ml.) and dimethylformamide (25 ml.) at −30° was treated with a 0·99M-solution of chlorine in propionic acid (7·5 ml.) for 16 hr. in the dark. The product in benzene was percolated through alumina (15 g.), to give 4-*chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one*, square plates, m. p. 97—100°, $[\alpha]_D^{24}$ +44° (*c* 0·49), $\lambda_{max.}$ 229 (4·12) and 310·5 mμ (4·11), $\lambda_{infl.}$ 255 mμ (3·85) (Found: C, 69·8; H, 7·5; Cl, 9·8. $C_{22}H_{27}O_3Cl$ requires C, 70·5; H, 7·3; Cl, 9·5%), after crystallisation from hexane.

(*b*) 4-Chloro-17β-propionoxyandrost-4-en-3-one (10 g.) in dry ether (400 ml.) was treated with a 1·04M-solution of bromine in propionic acid (52 ml.), dropwise at room temperature. A drop of 50% solution of hydrogen bromide in acetic acid was added to initiate the reaction, decolorisation being complete in 3 hr. The solution was diluted with light petroleum (b. p. 40—60°) to turbidity, and cooled in ice. The crystalline solids were collected, washed with light petroleum, and purified from methylene chloride–hexane. 2α : 6β-*Dibromo*-4-*chloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (XX) formed flakes, m. p. 197—199°, $[\alpha]_D^{24}$ −123° (*c* 1·77), $\lambda_{max.}$ 270 mμ (4·08).

The 2α : 6β-dibromide (2·5 g.) in dimethylformamide (25 ml.) containing lithium chloride (1 g.) was boiled under reflux under nitrogen for 1 hr., to give 4-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one, m. p. and mixed m. p. 98—100° with a sample prepared as in (*a*).

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