Tetrahedron, 1961, Vol. 12, pp. 95 to 104. Pergamon Press Ltd. Printed in Northern Ireland

THE STEREOCHEMISTRY OF SOME HALOGENOCHOLESTAN-3-ONES

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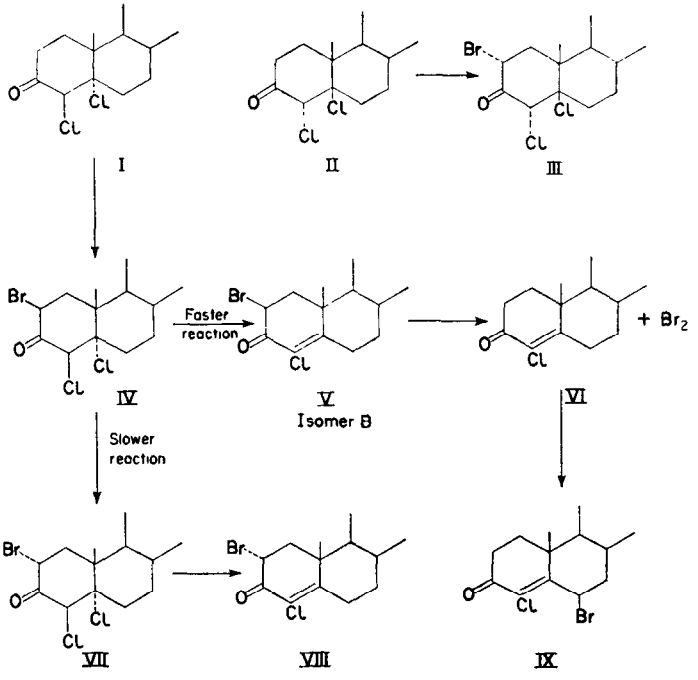
(*Received* 30 *August* 1960)

Abstract—The stereochemistry of the 4,5-dichloro- and 2-bromo-4,5-dichloro-derivatives[1] of cholestan-3-one is discussed.

THE present communication completes earlier studies[1] on 4,5-dichloro-cholestan-3-one by establishing its stereochemistry.

Information on the orientation of a halogen atom (other than fluorine) in an α-halogeno steroidal 3-ketone may generally be obtained:

(i) From the infra-red spectrum. The carbonyl stretching band found in the region 1719–1713 cm^{-1} is displaced by about +16 to +21 cm^{-1} by an equatorial halogen atom, but is hardly affected by an axial halogen atom.[2]



(ii) From the low intensity U.V. absorption band (R-band) at 280–286 mμ characteristic of an unsubstituted 3-oxo steroid. This band is displaced to a longer

[1] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1184 (1956); D. N. Kirk and V. Petrow, *Ibid.* 1334 (1958).

[2] R. N. Jones and F. Herling, *J. Org. Chem.* **19**, 1252 (1954); R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner *J. Amer. Chem. Soc.* **74**, 2828 (1952).

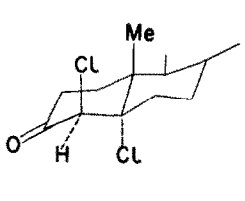
wavelength by an axial halogen atom with a concomitant marked increase in the extinction coefficient. An equatorial halogen substituent, in contrast, causes only a very small hypsochromic shift of the absorption maximum.[3]

(iii) By reduction with an alkali metal borohydride followed by treatment of the resulting halohydrin with alkali. *Trans*-halohydrins yield epoxides under these conditions, whilst *cis*-halohydrins afford ketones. Catalytic dehalogenation of the halohydrin will generally give an alcohol of known configuration, thereby permitting the stereochemistry of the halohydrin, and thence of the haloketone, to be established.[4]

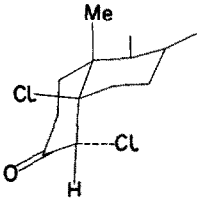
In attempting to determine the stereochemistry of 4,5-dichloro-cholestan-3-one, we turned initially to chemical procedure (iii) above. Reduction of the dihaloketone with lithium borohydride in tetrahydrofuran afforded an apparently homogeneous dichloroalcohol, which was characterized as an acetate. Reaction of the dichloroalcohol with alkali, however, failed to give indication of its structure. Thus, it was recovered unchanged after heating with 2 per cent ethanolic potassium hydroxide, whilst 20 per cent ethanolic potassium hydroxide converted it into an intractable black tar. Attention was therefore directed to physical methods.

The ultra-violet absorption of 4,5-dichlorocholestan-3-one reaches a maximum at 301 mμ, indicating an axial conformation for the 4-chloro substituent.[3] Examination of models, however, reveals the possible existence of two 4-axially substituted structures, namely 4β,4α-dichloro-cholestan-3-one (I) and 4α,5β-dichloro-5β-cholestan-3-one (II). These structures both conform to the rule of diaxial addition[5] of halogen to an ethylenic linkage. Alternative structures involving a boat-shaped Ring A may be rejected as they cannot be formed by the energetically preferred *trans*-diaxial addition of chlorine to cholest-4-en-3-one, and moreover would be destabilized by the proximity of the halogen atoms.

Bromination of 4,5-dichlorocholestan-3-one[1] (I or II) furnished a mono-substitution



I



II

product (m.p. 110–111°) formulated as a 2ξ-bromo-4,5-dichlorocholestan-3-one.[1] Its U.V. absorption spectrum showed that introduction of the bromine atom at C_2 had been accompanied by a bathochromic shift of 25 mμ in the absorption maximum, thereby indicating an axial conformation for the newly introduced halogen atom.[3] The constitution of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV), derived from structure I, was indicated for this product. At the same time the alternative 2α,4α-diaxial structure (III) could not be excluded from consideration at this stage. It is true that 3-keto-5β-steroids generally brominate at C_4. In this case, however, (i) the

[3] R. C. Cookson, *J. Chem. Soc.* 282 (1954).
[4] J. J. Beereboom and C. Djerassi, *J. Org. Chem.* **19**, 1196 (1954); L. F. Fieser and R. Ettore, *J. Amer. Chem. Soc.* **75**, 1700 (1953); L. F. Fieser and X. A. Dominguez, *Ibid* **75**, 1704 (1953); E. J. Corey, *Ibid.* **75**, 4832 (1953); L. F. Fieser and W-Y Huang, *Ibid.* **75**, 4837 (1953).
[5] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.* **72**, 370 (1950); G. H. Alt and D. H. R. Barton, *J. Chem. Soc.* 4284 (1954).

inductive effect of the 4-chloro-substituent would reduce the tendency of the 3-keto group to enolize towards C_4, and (ii) the preference for the participation of an axial hydrogen atom in the enolization of a cyclic ketone, demonstrated by Corey[6] and attributed by him to a stereoelectronic effect, would also tend to favour enolization and subsequent bromination at C_2 in the 4α-chloro ketone (II) in which the 4β-hydrogen atom has the unfavourable 4β (equatorial) conformation. A decision in favour of structure IV was ultimately reached as indicated below.

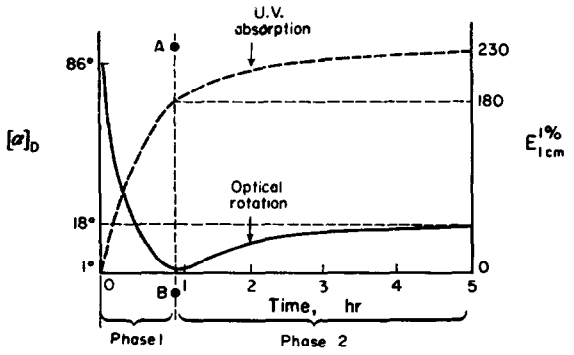


FIG. 1. Reaction between 2β-bromo-4β,5α-dichlorocholestan-3-one (of $[\alpha]_D$ + 86°) and pyridine (1% each) in chloroform (Points A and B represent the optical rotation of the pure products, isomers A and B, respectively).

TABLE 1. CHANGES OF ULTRA-VIOLET ABSORPTION IN THE DEHYDROCHLORINATION OF 2β-BROMO-4β,5α-DICHLOROCHOLESTAN-3-ONE WITH 1% PYRIDINE IN CHLOROFORM

Time (hours)	0·0	0·20	0·50	0·83	1·33	3·00	24
λ_{max} (mμ)	—	267	267	267	266	265	264·5
$E^{1\%}_{1\,cm}$ at λ_{max}	—	101	152	170	192	225	230

We had previously shown[1] that dehydrochlorination of the 2ξ-bromo-4,5-dichlorocholestan-3-one (III or IV) leads in modest yield to the formation of a 2ξ-bromo-4-chlorocholest-4-en-3-one, m.p. 183°, $[\alpha]_D$ +90° (*Isomer* A). The optical rotatory and U.V. changes occurring during its formation from the 2ξ-bromo-4,5-dichlorocholestan-3-one in a 1 per cent pyridine/chloroform solution, however, appeared to indicate the concomitant formation of a second product with a lower optical rotation and an absorption maximum at a longer wavelength (Fig. 1 and Table 1). Search for this product led to the isolation of an isomeric 2ξ-bromo-4-chlorocholest-4-en-3-one, m.p. 115°, $[\alpha]_D$ −3° (*Isomer* B). Both isomers passed into 4-chlorocholesta-1,4-dien-3-one[1] on dehydrobromination with lithium chloride/dimethyl formamide. Comparison of their ultra-violet absorption spectra (Table 2) established unequivocally the constitution of the new *Isomer* B as the 2β-(quasi axial) epimer V and that of the previously known *Isomer* A as the 2α-(quasi equatorial) epimer VIII.

The bathochromic shifts and enhancement of extinction coefficients of the peaks in the R bands of the 2β (axial) bromo-derivative are similar to those reported by

[6] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **78**, 6269 (1956).

Cookson[7] for 6β *axial*-bromo-Δ^4-3-keto steroids. Cookson's explanation of this effect in terms of overlap of the σ-bonding electron orbital, or of the p-electrons of the bromine atom, with the conjugated π-orbital system of the unsaturated ketone in the axial epimer, can be assumed to apply also to the 2-bromo-derivative. The relative positions and intensities of the K-bands support the configurations assigned to these bromo-compounds.

Following the isolation of 2β-bromo-4-chlorocholest-4-en-3-one (V) attempts

TABLE 2. PROPERTIES OF 2α- AND 2β-BROMO-4-CHLOROCHOLESTENONES

			K-band	
	M.p.	$[\alpha]_D$	λ_{max}	ε_{max}
4-Chlorocholestenone	126–7°	+106°	256 mμ	14,110
2α-Bromo-4-chlorocholestenone	181–3°	+90°	260 mμ	10,200
2β-Bromo-4-chlorocholestenone	113–5°	−3°	267 mμ	11,330

	U.V.-absorption (R-band)				
4-Chlorocholestenone	313(40[a])	324(41)	337(33)	350(19)	368(6)
2α-Bromo-4-chlorocholestenone	314(54)	326[b](45)	344[b](28)	356[b](15)	366[b](8)
2β-Bromo-4-chlorocholestenone	335(115)	346(99)	—	366(53)	374(26)

[a] Values in parentheses are extinction coefficients (ε).
[b] Inflexion.

were made to epimerize it into the 2α-*quasi-equatorial*-bromo isomer (VIII) by treatment with pyridine. Its solution in this solvent, however, failed to undergo change in optical rotation after 8 hours at room temperature. Further treatment with pyridine led to its conversion after several days into an acid-soluble product, which was probably a pyridinium compound and was not investigated further. The 2α-isomer (VIII) showed even greater stability to pyridine treatment. It was consequently mandatory to draw the unexpected conclusion that formation of *Isomer* A from 2ξ-bromo-4,5-dichlorocholestan-3-one (III or IV) does not occur through epimerization of *Isomer* B.

It was possible at this stage to interpret the reactions responsible for the optical rotatory changes given in Fig. 1. The equilibrium optical rotation of +10° recorded in Fig. 1 implies that the 2α-(*Isomer* A) and 2β-bromo (*Isomer* B)-epimers are present in the ratio 1:3 (approx). Figure 1 additionally reveals the significant fact that the first stage of the reaction (complete after ca. 1 hour) is characterized by a rapid fall in optical rotation to a value (+1°) corresponding approximately to that of *Isomer* B (−3°). At this point the ultra-violet absorption of the mixture (cf. Table 1) in the $\alpha\beta$-unsaturated ketone region also corresponds to that of *Isomer* B with only minimal quantities of *Isomer* A being present. Thereafter prolongation of the reaction leads to an increase in optical rotation and a shift in the absorption maximum to shorter wavelengths owing to the gradual appearance of *Isomer* A, which represents the minor product of the reaction and which, as shown above, is not formed from *Isomer* B by isomerization.

[7] C. W. Bird, R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.* 3675 (1956).

These changes unequivocally exclude structure III for the 2ξ-bromo-dichlorocholestan-3-one. Conversion of III into *Isomer* B would involve inversion of the bromine atom at C_2, followed by dehydrochlorination. As *Isomer* B forms the major product, these two reactions would necessarily proceed at a faster rate than the simple dehydrochlorination of the bromo-dichloro compound (III) into *Isomer* A. If this were indeed the case, then the accumulation of *Isomer* A in the solution after *Isomer* B had reached maximal concentration simply could not occur. Formula III consequently

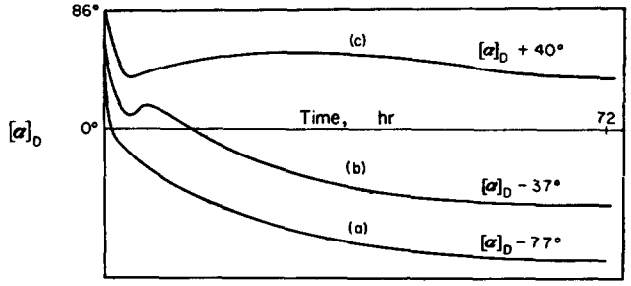


FIG. 2. Changes in optical rotation with time during reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) with HBr/acetic acid in the presence of (a) no β-naphthol, (b) 1 mole β-naphthol, (c) 5 moles β-naphthol.

fails to accommodate the observed facts. The changes revealed by Fig. 1 are, however, readily explained on the basis of structure IV for the 2ξ-bromo-4,5-dichlorocholestan-3-one. The last compound may be regarded as undergoing simultaneously two competing reactions. The faster reaction involves simple dehydrochlorination to *Isomer* B. The somewhat slower reaction involves the epimerization of the 2β-bromo-substituent to the 2α-conformation to give 2α-bromo-4β,5α-dichlorocholestan-3-one (subsequently prepared from IV by treatment with hydrochloric acid/acetic acid *vide infra*), which then undergoes dehydrochlorination. The end of the first phase of the reaction of IV with pyridine (Fig. 1) consequently represents conversion of the starting material into V and VII. Subsequently, VII undergoes dehydrochlorination into *Isomer* A which accumulates in the solution *after maximum concentration of* Isomer B *has been reached.*

After completion of this investigation towards the middle of 1957 Professor C. Djerassi kindly examined the optical rotatory dispersion of the 4,5-dichloro-ketone (I), and confirmed the 4β,5α-configuration. This conclusion depends upon the observed negative Cotton effect in the O.R.D. curve for the compound, which suggests that the axial chlorine atom at C-4 has the β-configuration.[8]

Attempts to invert the 2β-bromo substituent of the bromo-dichloro-compound (IV) with hydrobromic acid in acetic acid led to the formation of 6β-bromo-4-chlorocholest-4-en-3-one[1] (IX). The optical rotatory changes accompanying this conversion are shown in Fig. 2 (curve a). They indicate initial rapid dehydrochlorination to 2β-bromo-4-chlorocholest-4-en-3-one (V), followed by slow migration of the bromine atom to C_6. That the latter reaction involves removal of the bromine atom at C_2 with transitory formation of molecular bromine, followed by bromination at C_6, was shown by interception of the molecular bromine with β-naphthol. This procedure had been

[8] C. Djerassi and W. Klyne, *J. Amer. Chem. Soc.* **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *Ibid.* **80**, 1216 (1958).

used by Crowne *et al.*[9] to demonstrate the participation of molecular bromine in the hydrogen bromide catalysed conversion of 2,2-dibromo- into 2α,4α-dibromocholestan-3-one. In the present case the competing reaction between the steroid and the bromine could not be wholly eliminated, even in the presence of a 5-fold excess of β-naphthol, although in this instance the main steroidal product was 4-chlorocholest-4-en-3-one (VI).

The elimination of hydrogen chloride from 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) under the influence of hydrogen bromide/acetic acid to give 2β-bromo-4-chlorocholest-4-en-3-one (V, above) requires the presence of bromide ion (Br^-) and is not a general acid-catalysed process. Thus when sulphuric or toluene *p*-sulphonic acid was substituted for hydrogen bromide (all at 0·16 N), no change in optical rotation was observed after 24 hours at room temperature. When hydrogen chloride (10% w/w) or perchloric acid (2·5 N) in acetic acid were used, in contrast, the optical rotation of the solution fell from $[\alpha]_D$ +86° to $[\alpha]_D$ − 1° after 24 hours, and remained constant thereafter. The product so formed was an amorphous solid which resisted crystallization. Its spectroscopic examination revealed a 3 per cent content of αβ-unsaturated ketonic material ($\varepsilon_{261\cdot5}$ 315). Analyses showed virtually no loss of halogen. Reaction with pyridine at room temperature gave an almost quantitative yield of 2α-bromo-4-chlorocholest-4-en-3-one (VIII). The new product is accordingly formulated as 2α-bromo-4β,5α-dichlorocholestan-3-one (VII) and results from acid-catalysed inversion of the 2β-bromo substituent of IV. It represents the essential intermediate in the chain of reactions leading from IV to Isomer A (VIII) *vide supra.*

It seemed likely that the difference in behaviour of 2β-bromo-4β,5α-dichlorocholestan-3-one (IV) towards hydrobromic and hydrochloric acid/acetic acid stemmed from the greater nucleophilic reactivity of the bromide ion relative to the chloride ion. The bromide ion, acting as a base, was envisaged as abstracting a proton from the C_4 position of IV with subsequent loss of chloride ion from C_5. In order to test this hypothesis, the substitution of bromide ion by the even more nucleophilic iodide ion was examined.

Initially, a solution of hydrogen iodide in acetic acid was added to a solution of the 2β-bromo-compound (IV) dissolved in chloroform. Instantaneous reaction occurred with liberation of iodine, rendering polarimetric determinations impossible. By using the bromine-free 4β,5α-dichlorocholestan-3-one (I), however, it proved possible to examine the effect of the three halogen ions upon the analogous dehydrochlorination reaction leading to 4-chlorocholest-4-en-3-one (VI).

A one per cent solution of 4β,5α-dichlorocholestan-3-one (I) in 10 per cent of hydrogen chloride (w/w) in acetic acid/chloroform (9:1) was found to undergo change in optical rotation from $[\alpha]_D$ + 5° to $[\alpha]_D$ +96°, with a half-life period of 162 minutes to give 4-chlorocholest-4-en-3-one (VI). By using such a solution and adding to it the halide ion under examination in the form of its lithium salt, it proved possible to compare the accelerating effects of the three halide ions upon the dehydrochlorination of the dichloro-compound (I) under equivalent conditions. The results obtained (Table 3 and Fig. 3) reveal the expected order of nucleophilic reactivity for the three halide ions, with $Cl^- < Br^- < I^-$.

A somewhat different situation obtains with 2β-bromo-4β,5α-dichlorocholestan-3-one (IV). Under acidic catalysis the 3-keto group enolizes almost exclusively in the

[9] C. W. P. Crowne, R. M. Evans, G. F. H. Green and A. G. Long, *J. Chem. Soc.* 4351 (1956).

direction of C_2 *vide supra* with consequent inversion of the 2β-bromo substituent to the more stable 2α-configuration (i.e. to VII). Further reaction leading to dehydrochlorination does not occur with chloride ion, for example, which does not possess sufficient nucleophilic reactivity to enforce extrusion of a proton from C_4. In the presence of the more nucleophilic bromide ion, in contrast, the base-catalysed dehydrochlorination reaction occurs at an appreciable rate, and this reaction becomes dominant when a relatively strong base such as pyridine is employed.

TABLE 3. HALF-REACTION TIMES FOR THE DEHYDROCHLORINATION OF 4β,5α-DICHLOROCHOLESTAN-3-ONE BY HYDROGEN CHLORIDE/LITHIUM HALIDE IN ACETIC ACID/CHLOROFORM

Reagent	Concentration of lithium halide	Half-reaction time (min)
(a) 10% HCl	—	162
(b) 10% HCl + LiCl	1·0 N	84
(c) 10% HCl + LiBr	1·0 N	12
(d) 10% HCl + LiBr	0·25 N	65
(e) 10% HCl + LiI*	0·25 N	36

* LiI could not be employed at 1·0 N concentration owing to the rapid appearance in the solution of free iodine. This prevented the measurement of $[\alpha]_D$ within a few minutes.

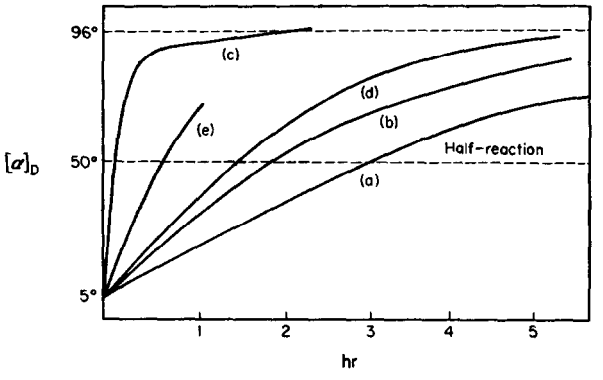


FIG. 3. Changes in optical rotation with time during dehydrochlorination of 4β,5α-dichlorocholestan-3-one by HCl in the presence of lithium halide. (a) No Li halide. (b) 1·0 N LiCl. (c) 1·0 N LiBr. (d) 0·25 N LiBr. (e) 0·25 N LiI.

The observation that 'acidic' (electrophilic) attack involves C_2, whilst 'basic' (nucleophilic) attack involves C_4 preferentially may be rationalized in terms of two distinct controlling factors. It is known that enolization of 3-oxo-5α-steroids leads to appearance of a double bond at C_2—C_3.[10] This has been attributed to hyperconjugation, the Δ^2-linkage being stabilized by one more hydrogen atom than obtains for a C_3—C_4 double bond. This essentially thermodynamic control may be expected to operate in the acid catalysed enolization of IV. Base-catalysed enolization, however,

[10] D. A. H. Taylor, *Chem. & Ind.* 250 (1954); A. S. Dreiding, *Ibid.* 1419 (1954).

is probably kinetically controlled. The C_4 hydrogen atom is more acidic in character than the one at C_2 owing to the greater polarization of the C—Cl bond compared to the C—Br bond.[11] Attack by base accordingly takes place preferentially, but not exclusively at C_4.

Yet a further effect demands recognition. Kinetic control of the rate-controlling step, viz. removal of a proton from C_4, would presumably apply in equal measure to both the 2-bromo epimers IV and VII. If this were indeed the case, then the rates of dehydrochlorination of these two isomers IV and VII would be expected to be similar.

It has been shown above that the first part of the curve in Fig. 1, representing the change in optical rotation with time in the reaction of the 2β-bromo-dichloride (IV) with pyridine corresponds approximately to the dehydrochlorination step (IV) → (V). The half-life of the 2β-bromo-dichloride (IV) estimated from this part of the curve is approximately 7 minutes. The half-life of the 2α-bromo isomer (VII) under similar conditions, however, is found to be ca. 42 minutes.

These results point to the existence of yet another rate-controlling factor which is believed to stem from stereoelectronic control associated with the centre at C_2. As already mentioned, Corey[6] has shown that enolization of cyclic ketones preferentially occurs through removal of an axial hydrogen atom. Such an axial hydrogen atom is present (at C_2) in the 2α-bromo-epimer (VII) but not in the 2β-bromo-compound (IV). Enolization towards C_4 will consequently be less marked in VII than in IV. But enolization towards C_4 is regarded as the rate-controlling step in the dehydrochlorination reaction leading to the introduction of the Δ^4-linkage. Dehydrohalogenation should consequently occur more readily in IV than in VII, which is indeed found to be the case.

The foregoing kinetic experiments were carried out under ordinary laboratory conditions, and not under strictly physico-chemical temperature control etc. The significance of the results must therefore be regarded as qualitative rather than accurately quantitative.

EXPERIMENTAL

Optical rotations were measured in $CHCl_3$ solutions in a 1 dm tube, unless otherwise stated. Ultra-violet and infra-red absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc.

Reduction of 4β,5α-dichlorocholestan-3-one with lithium borohydride

4β 5α-Dichlorocholestan-3-one (2 g) in purified tetrahydrofuran (40 ml) was added to lithium borohydride (1 g) in tetrahydrofuran (40 ml) and the mixture stirred for 4 hr at room temp, when it was poured into water. The product was isolated with ether and purified from ethanol giving 4β,5α-*dichlorocholestan-3ξ-ol* in fine needles, m.p. 163–164°, $[\alpha]_D^{24}$ +18° (*c*, 0·20). (Found: C, 71·4; H, 10·4; Cl, 15·6. $C_{27}H_{46}OCl_2$ requires: C, 70·9; H, 10·1; Cl, 15·5%).

The 3-*acetate* prepared by acetylation with acetic anhydride and pyridine on the steambath for 45 min followed by purification from ethanol formed flakes, m.p. 100–101°, $[\alpha]_D^{18}$ +1° (*c*, 0·24). (Found: C, 69·6; H, 9·7; Cl, 14·3. $C_{29}H_{48}O_2Cl_2$ requires: C, 69·7; H, 9·7; Cl, 14·2%).

Polarimetric experiments. The general procedure was as follows: The steroid was weighed into a stoppered flask, dissolved in the appropriate volume of solvent (chloroform, etc.), and treated with the required volume of reagent (hydrogen bromide solution, pyridine, etc.). After shaking, a 1 dm polarimeter tube was filled and placed in the polarimeter, and readings were taken as soon as practicable, usually within 2–5 minutes after mixing, although the first sets of readings were somewhat erratic due to striations in the solutions. The mean of 10 readings was taken as the optical rotation at the time noted after the fifth reading for each set.

[11] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 446. G. Bell and Sons, London (1953).

Reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one with pyridine

A solution of the bromodichlorocompound (1 g) in "Analar" chloroform (99 ml) was treated with pyridine (1 ml). The optical rotatory changes of a portion of the solution were observed as above. From the main bulk of the solution 5 ml portions were withdrawn at intervals, and added to an excess of dil sulphuric acid. The chloroform was washed neutral, the washings being re-extracted with chloroform. The solvent was removed *in vacuo* at 40°, and the ultra-violet absorption of the residue determined in ethanol solution. The results are recorded in Fig. 1 and Table 1.

From a similarly-composed reaction mixture the following products were isolated after 5 hr by fractional crystallization from ethanol: 2α-bromo-4-chlorocholest-4-en-3-one (195 mg), m.p. 178–180°, λ_{max} 260 mμ (ε = 10,200) in ethanol, and *2β-bromo-4-chlorocholest-4-en-3-one* (150 mg), leaflets, m.p. 113–115°, $[\alpha]_D^{25}$ −3° (*c*, 0·37), λ_{max} 267 mμ (ε = 11,330) in ethanol, R-band: see Table 2. (Found: C, 64·8; H, 8·4; Hal., 22·6. $C_{27}H_{42}OClBr$ requires: C, 65·1; H, 8·5; Hal., 23·2%).

Dehydrobromination of 2β-bromo-4-chlorocholest-4-en-3-one

The 2β-bromo compound (300 mg) and lithium chloride (30 mg) in dimethylformamide (5 ml) were heated under reflux for 30 min, then cooled and diluted with water to turbidity. The separated solids (m.p. 118–120°) were purified from aqueous methanol to give 4-chlorocholesta-1,4-dien-3-one, needles, m.p. 128–129°, identified by comparison with an authentic sample.

Reaction of 2β-bromo-4β,5α-dichlorocholestan-3-one with hydrogen bromide

A solution of the bromodichloro-compound (1 g) in methylene chloride (5 ml) was mixed with hydrogen bromide in acetic acid (45 ml of 0·18 N soln.). The optical rotation of the mixture was followed until it became constant after 72 hr (Fig. 2a). The methylene chloride was then removed under reduced pressure and the residual acetic acid solution diluted to turbidity. The solids which separated were purified from methanol to give 6β-bromo-4-chlorocholest-4-en-3-one, m.p. 168–170°, identified by comparison with an authentic sample and by its conversion into 4-chlorocholesta-4,6-dien-3-one, needles, m.p. 97–99°.

Reaction in the presence of β-naphthol. The foregoing reaction was repeated, with the preliminary addition of β-naphthol to the hydrogen bromide/acetic acid solution. Two experiments were performed employing 0·5 g of steroid, and 150 mg (1·1 moles) or 750 mg (5·5 moles) of β-naphthol, respectively, with the results recorded in Fig. 2 (b and c), and the related discussion.

Isomerization of 2β-bromo-4β,5α-dichlorocholestan-3-one with hydrogen chloride

The bromodichloro-compound (2 g) in methylene chloride (10 ml) was mixed with 11% (w/w) hydrogen chloride/acetic acid (90 ml). The optical rotation of the solution fell from $[\alpha]_D$ +86° to $[\alpha]_D$ −1° after 24 hr, when more methylene chloride was added, and the solution washed neutral. The solvent was removed under reduced press. The residual gum, which could not be crystallized, had λ_{max} 261–265 mμ (ε = 315), indicating ca. 3% of αβ-unsaturated ketonic material.

In a second experiment, omitting the methylene chloride, the acetic acid solution was poured, after 2 days at room temp, into ice-water, and the solids collected and dried. The product, consisting essentially of *2α-bromo-4β,5α-dichlorocholestan-3-one*, had m.p. 30–50°, $[\alpha]_D^{24}$ −2° (*c*. 0·26), R-band: No U.V. absorption maximum between 260 and 340 mμ in cyclohexane. (Found: C, 61·3; H, 8·1; Hal, 26·6. $C_{27}H_{43}OCl_2Br$ requires: C, 60·7; H 8·1; Hal., 28·2%).

Dehydrochlorination of 2α-Bromo-4β,5α-dichlorocholestan-3-one with pyridine

A solution of the foregoing 2α-bromo-dichloro-compound (0·5 g) in chloroform (49·5 ml) was mixed with pyridine (0·5 ml). The optical rotation of the solution changed from $[\alpha]_D$ −3° to $[\alpha]_D$ +74° after 6 hr, with a half-reaction time of 42 min. The solution was washed with dil sulphuric acid and water, dried and the solvent evaporated. Purification from ethanol gave 2α-bromo-4-chlorocholest-4-en-3-one, m.p. 178–180°, not depressed in admixture with an authentic sample.

Dehydrochlorination of 4β,5α-dichlorocholestan-3-one in the presence of hydrogen ions and halide ions

(1) *Chloride ions.* Anhydrous lithium chloride (1·06 g) in 11% (w/w) hydrogen chloride/acetic acid solution (22·5 ml) was mixed with a solution of 4β,5α-dichlorocholestan-3-one (250 mg) in

chloroform (2·5 ml), the final concentration of lithium chloride being 1·0 N. After 24 hr 4-chlorocholest-4-en-3-one was isolated.

(2) *Bromide ions.* (a) Lithium bromide (2·18 g, to give a 1·0 N soln.) was substituted for lithium chloride in (1). (b) Lithium bromide (0·55 g; 0·25 N soln.) was used as above.

(3) *Iodide ions.* Lithium iodide (0·875 g, to give a 0·25 N soln.) was substituted for lithium chloride in (1). In this case iodine was liberated slowly into the solution, but it proved possible to observe the optical rotation at intervals up to 38 min ($[\alpha]_D$ +52°). The half-reaction time was 36 min ($[\alpha]_D$ +50°).

The results are recorded in Fig. 3 and Table 3. All the above reactions gave 4-chlorocholest-4-en-3-one in high yield.