253. *Steroids and the Walden Inversion. Part I. Derivatives of Androstane and Cholestane.*

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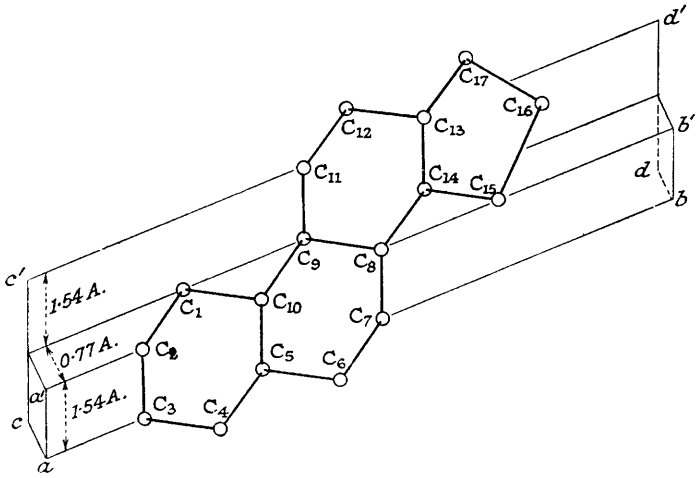
The principles enunciated by Cowdrey, Hughes, Ingold, Masterman, and Scott (*J.*, 1937, 1252) are applied to elucidate the steric orientation of replacement reactions occurring at saturated carbon atoms of the steroid nucleus.

The stereochemistry of androstane is discussed in relation to the geometry of the transition state in bimolecular steroid nuclear substitution; it is shown that the stereochemical arrangement of the steroid nucleus intrinsically favours the formation of a transition state of linear type and so reinforces the conclusion, reached on the basis of the exclusion principle, that in the replacement of ·Hal by ·OR inversion of configuration is the rule. The so-called "α"- and "β"-cholestanyl chlorides are shown to possess the constitutions 3(β)-chlorocholestane and 3(α)-chlorocholestane respectively, and the above conclusion is applied further in Section (*a*) to the extensive body of data available in respect of substitution at C_3 in saturated steroids, *e.g.*, derivatives of androstane and cholestane.

In Section (*b*), the orientation rules of Cowdrey *et al.* (*loc. cit.*) for the replacement of ·OR by ·Hal are applied to substitution at C_3 in saturated steroids, to furnish a picture which is not only self-consistent, but consistent also with the configurations assigned in Section (*a*).

During the last decade, the work of Ingold, Hughes, and their collaborators has thrown much light on the stereochemical course of substitution at a saturated carbon atom. It seems appropriate to attempt to apply the principles and diagnostic rules enunciated by these workers to some simple steroid substitution reactions with a view to assigning configurational relationships.

Fig. 1.



The androstane nucleus (omitting the angular methyl groups) seen in isometric projection at 22·5°.

As compared with simple saturated compounds of the type $CHR_1R_2R_3$, the polycyclic steroid nucleus offers both intrinsic advantages and disadvantages. Thus, whereas in molecules of the type $CHR_1R_2R_3$ sign of rotation is a direct criterion of the stereochemical arrangement, and the numerical value of the rotation an index of stereochemical purity, in steroid molecules, because of the multiplicity of asymmetric centres contributing to the observed rotation, inversion of configuration at one of these centres may cause no change in sign of rotation and may alter the numerical value by a few degrees only; the application of superposition rules to molecular rotation values, when available, may, however, afford collateral evidence of configuration. On the other hand, because of the geometrical isomerism inherent to a cyclic structure, epimerides are distinct and often well-known compounds, so that inversion must furnish one and retention of configuration must yield the other, whilst racemisation must lead to production of both epimerides, and, if extensive, should render possible their isolation.

The Geometry of the Steroid Nucleus.—Since the conclusions of Ingold, Hughes, and their co-workers as to the course of bimolecular substitution reactions at saturated carbon atoms are based partly on an examination of the geometrical form and energy of the transition state, it seems desirable to examine briefly what modifications, if any, are introduced when the substitution reaction occurs at a saturated carbon atom forming part of the steroid nucleus.

The androstane molecule is a relatively flat structure. There is much evidence available (Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **16**, 216; Ruzicka, Goldberg, Meyer, Brungger, and Eichenberger, *ibid.*, 1934, **17**, 1407; Ruzicka, Goldberg, and Wirz, *ibid.*, 1935, **18**, 61; Windaus, *Annalen*, 1926, **447**, 233; Wieland and Dane, *Z. physiol. Chem.*, 1933, **216**, 91; Dimroth and Jonsson, *Ber.*, 1941, **74**, 520; Giacomello, *Gazzetta*, 1939, **69**, 790; Bernal, Crowfoot, and Fankuchen, *Phil. Trans.*, 1940, *A*, **239**, 135; Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64) to show that the four constituent rings are linked by *trans*-unions. The essential carbon-ring structure is thus to be regarded as constructed on two parallel planes separated by a distance of about 0·77 A.

The first plane *aa'bb'* contains the carbon atoms conventionally numbered C_2, C_3, C_5, C_{10}, C_7, and C_8, and C_{15} probably lies in or very near it; the second plane *cc'dd'*, situated to the rear of the first, contains the carbon atoms C_9, C_{11}, C_{13}, and C_{14}, whilst C_{16} probably lies in or very near it. The angular methyl groups attached to C_{10} and C_{13} are omitted from Fig. 1; *trans*-fusion of rings A/B and C/D necessitates that the

angular methyl groups are similarly orientated, and they are by convention * regarded as projecting forward from the planes *aa'bb'* and *cc'dd'*. It may, however, be pointed out that the absolute configuration of no single centre of asymmetry has yet been determined despite the contrary statement of Bergmann (*J. Soc. Chem. Ind.*, 1939, **58**, 512), so that the stereochemical arrangement of the androstane molecule and of the natural steroids of the C_5-*allo*-series (rings A/B, *trans*) may actually be the mirror image of that depicted in Fig. 1. With this reservation it seems certain from the crystallographic studies summarised by Bernal, Crowfoot, and Fankuchen (*loc. cit.*) that the structure depicted in Fig. 1 represents the actual spatial arrangement of the steroid nucleus for androstane and its derivatives in the crystalline state.

Examination of a mechanical model of the androstane molecule (cf. Fig. 1), in which both ring A and ring B are chair forms, indicates that whilst rings B and C cannot undergo modification on account of double-locking by *trans*-union with rings A and C and rings B and D respectively, ring A can undergo conversion into a boat form by relative motion of carbon atoms C_2 and C_3 whereby C_3 and C_{10} become the ends of the boat without disturbance of the remainder of the tetracyclic structure. It is therefore necessary to inquire whether such a modified form of ring A can make a contribution to the stereochemistry of androstane and its derivatives in the liquid state or in solution.

There is no convincing evidence that the boat form of *cyclo*hexane itself, which is stereochemically equivalent to a plane ring, has any individuality. Thus comparison of the entropies derived from thermal data over the range 10—293° K. with those computed from molecular and spectroscopic data suggests that *cyclo*hexane, as a result of the mutual repulsions of the electrons involved in the C–H bonds, exists only as the chair form (Aston, Schumann, Fink, and Doty, *J. Amer. Chem. Soc.*, 1943, **65**, 341) (in regard to the decalins, see Bastiansen and Hassel, *Nature*, 1946, **157**, 765). From the chemical point of view, the chair form of *cyclo*hexane, being rigid, should afford two isomeric mono-substitution products; but it has been shown in an appropriate case by Wightman (*J.*, 1926, 2543) that only a single individual can be isolated, so that interconversion of the isomerides must occur in solution even if succeeded by preferential separation of one individual on packing into the crystal lattice. A very rough estimate of the height of the energy barrier opposing such interconversion (chair ⟶ boat ⟶ chair) can be made on the assumption that the principal contributions are the energies required (*a*) to overcome the mutual repulsions of the hydrogen atoms, (*b*) to deform two tetrahedral C–C–C angles to 120°, and (*c*) to accomplish the concomitant deformation of four C–C–H angles. Component (*a*) may be evaluated at 6 kg.-cals. mole^{-1} for the twelve hydrogen atoms in *cyclo*hexane, since the energy barrier, which opposes free rotation about their common axis of the methyl groups in ethane and necessitates that the structure of minimum energy is that with maximum separation of the hydrogen atoms, *i.e.*, the *trans*-configuration, has a value of 3 kg.-cals. mole^{-1} (Kemp and Pitzer, *J. Amer. Chem. Soc.*, 1937, **59**, 276; cf. Pitzer and Gwinn, *ibid.*, 1941, **63**, 33). Component (*b*) may approximately be assessed using the transformation formula $E_{(\theta - 2\alpha)} = E_\theta \cdot \cos^2\alpha$ given by Skinner (*Trans. Faraday Soc.*, 1945, **41**, 645); in each C–C bond strained through an angle $\alpha = 5°$ from the normal, we might expect the bond energy to be increased by an amount given by $\frac{L}{2}/\cos^2 5° = 1{\cdot}01\,\frac{L}{2}$ where L = the heat of sublimation of diamond, so that the energy required to effect deformation will be $1{\cdot}01\,\frac{L}{2} - \frac{L}{2}$ or about 1% of $\frac{L}{2}$. Current values of L range from 125 to 170 kg.-cals. mole^{-1}, and afford a value of 0·6 to 0·9 kg.-cals. for each C–C bond or 2·4 to 3·6 kg.-cals. for deformation of two tetrahedral angles to 120°. Component (*c*) is difficult to estimate; but if, using the geometrical expression $\cos\theta = \frac{1}{4}\{\sqrt{\cos^2\beta + 8} - \cos\beta\}$ given by Becker and Thorpe (*J.*, 1920, 1579), we assume for an endocyclic C–C–C angle $2\theta = 120°$ that the exocyclic H–C–H angle $2\beta = 107°$, so that each C–H bond is strained through an angle $\alpha = \sim 1{\cdot}5°$, and apply Skinner's transformation formula taking the C–H bond energy as $56{\cdot}5 + \frac{L}{4}$ kg.-cals. mole^{-1}, it appears that the energy needed is about 0·1 kg.-cal., or ~0·5 kg.-cal.

* The convention adopted for the representation and description of substituted steroids is that proposed by Fieser ("The Chemistry of Natural Products Related to Phenanthrene," 2nd Edition, New York, 1937, pp. 398, 399; cf. Callow, *Ann. Reports*, 1938, **35**, 281) and extended by Reichstein and Shoppee ("Vitamins and Hormones," New York, 1943, p. 349); position is specified by the number of the nuclear carbon atom bearing the substituent, configuration by the suffix (α) or (β). As emphasised by Callow (*loc. cit.*) the parentheses are important but for a different reason; they not only afford differentiation from provisional trivial indices, but also indicate a definite stereochemical orientation. Thus the position and configuration of the hydroxyl group common to cholesterol, dihydrocholesterol, and coprostanol (coprosterol) is defined by the expression 3(β); this hydroxyl group lies on the same side of the plane *aa'bb'* (Fig. 1) as does the angular methyl group attached to C_{10}, and this is conventionally represented by a full-line bond. In *epi*-cholesterol, *epi*dihydrocholesterol, and *epi*coprostanol (*epi*coprosterol) the position and configuration of the hydroxyl group is defined by the expression 3(α); the hydroxyl group and the angular methyl group attached to C_{10} lie on opposite sides of the plane *aa'bb'*, and this is conventionally expressed by use of a broken-line bond. The evidence in favour of these orientations is summarised by Ruzicka, Furter, and Goldberg (*Helv. Chim. Acta*, 1938, **21**, 498).

For substituents in steroid side chains, *e.g.*, secondary or tertiary but not primary hydroxyl groups, position is specified by the number of the carbon atom bearing the group in question, but since stereoisomerism is now no longer geometrical in character but of the classical tartaric acid type a definite spatial orientation cannot in general be assigned. The indices α and β *without* parentheses, adjacent to and following a position numeral, *e.g.*, 20α, 20β, should be employed, but *n*- and *iso*- have also been used. These suffixes without parentheses serve solely to distinguish stereoisomerides without any spatial implication; and since here suffix assignment is arbitrary, compounds labelled, *e.g.*, 20β, will not necessarily possess corresponding configuration at C_{20} (cf. Prins and Reichstein, *Helv. Chim. Acta*, 1940, **23**, 1490).

for deformation of four C–C–H angles. Summation of components (*a*), (*b*), and (*c*) gives the approximate height of the energy barrier as 9—10 kg.-cals. mole^{-1} in *cyclo*hexane.

Since the chair–boat transformation of ring A of androstane can apparently occur independently of the attached fused-ring system, the height of the energy barrier here should be of the same order of magnitude as for *cyclo*hexane; the value calculated is small compared with the activation energies of most chemical reactions, and the energy required appears to be derivable from thermal bombardment at ordinary temperatures. Stereochemistry deals with structures which retain individuality under such conditions; from the stereochemical point of view it is useless to attempt to distinguish between geometrical arrangements which are separated by energy hills so low that they will normally be traversed with great frequency in the liquid state or in solution. Very many C_3-substituted derivatives of androstane are known, but in no case have more than two individuals been reported. We conclude therefore that the possible boat form of ring A in androstane makes no contribution to the stereochemistry of this substance and its derivatives.

The nuclear carbon atoms of the androstane molecule lie in, or either side of, but never far away from, a common plane *ac'bd'* (Fig. 1) situated between the planes *aa'bb'* and *cc'dd'*. Since most of the substitution reactions to be considered later occur at C_3, we shall for the purpose of discussing the geometry of the transition state confine attention to this centre. Before the approach of a reagent Y in a bimolecular substitution of X, the situation may be approximately depicted as in Fig. 2; the bonds C_2–C_3 and C_3–C_4 will lie in, or nearly in, the common plane *ac'bd'* and are constrained by the geometry of the ring-system to remain in, or nearly in, this plane. During the attack, lateral to that plane, of the reagent Y, the bond C_3–H will suffer deformation, until, in the transition state, it too lies in or near the common plane *ac'bd'*. An idealised representation of the transition state is shown in Fig. 3; the substituting reagent Y, the saturated carbon atom C_3, at which substitution occurs, and the displaced atom X are collinearly arranged on a normal to the plane

FIG. 2.

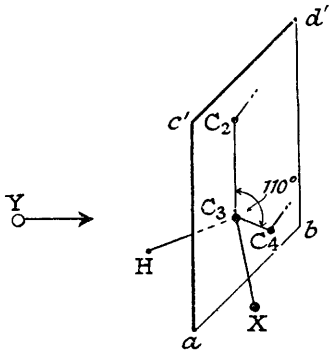


FIG. 3.

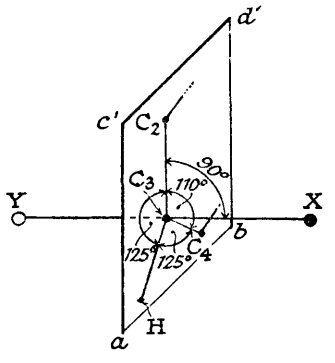
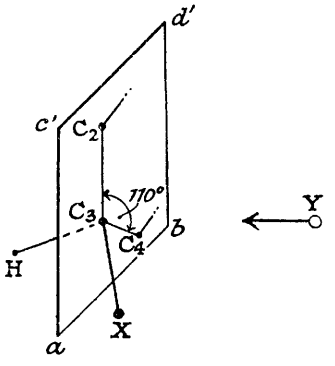


FIG. 4.



ab'cd' in which lie the other atoms C_2, C_4, and H covalently attached to C_3; the implication of C_3 in the ring-system maintains the angle $C_2C_3C_4$ at, or close to, 109·5°, wherefore the angles C_2C_3H and HC_3C_4 approximate to 125°. It follows that a transition state of the linear type $Y\cdots CR_1R_2R_3\cdots X$, which leads to inversion of configuration, will be favoured at the expense of the pyramidal type $CR_1R_2R_3{<}^{X}_{Y}$, which corresponds to retention of configuration.

The approach of the reagent may, however, be not from the far side of the plane *ac'bd'*, as depicted in Fig. 2, but from the near side of the plane *ac'bd'*, as in Fig. 4, which would lead to a transition state of pyramidal type $CR_1R_2R_2{<}^{X}_{Y}$. It has been shown (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1256) by application of the exclusion principle that the energy of activation corresponding to a linear transition state is smaller than that corresponding to the pyramidal version; therefore the number of encounters of the type illustrated in Fig. 4 (which on the basis of chance would be expected to be approximately half the total number of encounters) coming to fruition will be much smaller than those of the type illustrated in Fig. 2, and, if the energy difference is sufficiently large, may become very small. In other words, in the absence of groups or structural features which on account of either unsaturation or charge tend strongly to influence the configuration of the transition state, a large proportion of encounters leading to reaction with inversion of configuration will succeed, whilst the great majority of those encounters which would lead to reaction with retention of configuration will fail. Hence for bimolecular substitutions (S_N2, S_E2) at positions 1, 2, 3, 4, 6, 7, 11, 12, and probably at positions 15, 16, and 17, of the androstane molecule predominant inversion should be the rule.

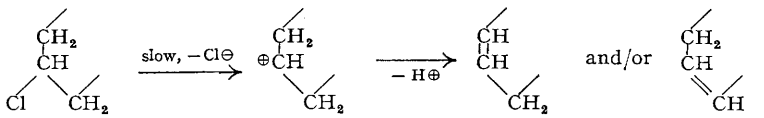
From the point of view of a reagent approaching through a surrounding medium, the most conspicuous feature differentiating the two sides of the lath-shaped androstane molecule will be the angular methyl groups at C_{10} and C_{13} projecting from the face. Except for positions 1 and 17 adjacent to the angular methyl groups and for position 11, which although not strictly adjacent to the C_{10} methyl group is known experimentally to be subject to a quite extraordinary degree of steric hindrance, there will not be a conspicuous difference

between the face and the reverse of the androstane molecule, hence the foregoing conclusion should hold for the bimolecular replacement of both (α)- and (β)-orientated groups. For one of the three cases specified in which there is a marked difference, namely position 11, there is some independent corroboratory evidence available in support of this conclusion. The 11(α)- and 11(β)-bromo-12-keto-3(α)-acetoxycholanic esters of Seebeck and Reichstein (*Helv. Chim. Acta*, 1943, **26**, 536) have both been shown (Gallagher and Long, *J. Biol. Chem.*, 1946, **162**, 521, 533) to undergo alkaline hydrolysis under the same mild conditions with inversion to afford respectively the 3(α) : 11(β)- and 3(α) : 11(α)-dihydroxy-12-ketocholanic acids; the 11(α)-configuration is subject to marked steric hindrance by the angular methyl group attached to C_{10} whilst the 11(α)-configuration is practically unhindered, and, as would be expected if replacement proceeds by the mechanism S_N2 in which steric effects operate, the reaction rates differ widely but the character of the substitution remains unaltered. There appears to be no evidence relating to positions 1 or 17; it may be pointed out that replacement reactions at C_{17} involve a system analogous to the α-methyl*neo*pentyl group, and it is hoped to deal with these in a subsequent communication.

(*a*) *Replacement of* Cl *by* OR.—On the basis of extensive kinetic studies, Cowdrey, Hughes, Ingold, Masterman, and Scott (*J.*, 1937, 1252) state that " in all homogeneous substitutions of •Hal by •OR in (saturated) alkyl halides, no matter whether the mechanism is S_N2 or S_N1, the predominating orientation will be inversion." We therefore take as our reference substances the " α "- and " β "-cholestanyl chlorides, which are typical, if complicated, alkyl halides containing besides the halogen only neutral saturated groups at the seat of substitution and formally comparable with β-*n*-octyl bromide, and consider their reactions with acetate ions in an ionising medium. The result of these reactions is described in the literature; a kinetic investigation to determine mechanism (S_N1 or S_N2) is unnecessary since it must be one or the other, and both lead to predominating inversion; further, in the present case this general conclusion is reinforced by the special conclusion reached above on grounds of steroid molecular geometry.

It has been shown by numerous methods that acid or alkaline hydrolysis of a carboxylic ester occurs by fission between the singly-bonded oxygen atom and the carbonyl group (cf. Watson, *Ann Reports*, 1940, **37**, 229 *et seq.*); unless special conditions are present, leading to suppression of acyl–oxygen fission (R–CO|O-steroid) and incursion of alkyl–oxygen fission [R–CO•O–|steroid (cf. Watson, *loc. cit.*, p. 230, footnotes 5 and *)] as in R•CO•O–C<(C)(C)(C) —a structure which never appears in steroid esters at the nuclear positions under discussion—, inversion cannot occur during hydrolysis of a steroid acetate (R = Me) to the free hydroxy-compound. A steroid alcohol and its acetate must therefore correspond in respect of the configuration of the substituent •OH and •OAc groups.

" β "-Cholestanyl chloride, m. p. 105° (Diels and Linn, *Ber.*, 1908, **41**, 260; Ruzicka, Goldberg, and Brungger, *Helv. Chim. Acta*, 1934, **17**, 1389), reacts with acetate ions in *n*-valeric acid at 185° to furnish a product yielding by alkaline hydrolysis cholestan-3(β)-ol (II) (Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358), whilst " α "-cholestanyl chloride, m. p. 115° (Mauthner, *Monatsh.*, 1896, **17**, 579; Windaus and Hossfeld, *Z. physiol. Chem.*, 1925, **145**, 177; Ruzicka, Goldberg, and Wirz, *Helv. Chim. Acta*, 1935, **18**, 998), similarly affords cholestan-3(α)-ol (Marker, Whitmore, and Kamm, *loc. cit.*); a result analogous to that last named has also been reported by Marker *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 338) for the cholestanyl bromide of m. p. 115°. These results have been confirmed and extended; treatment of " α "-cholestanyl chloride as described by Marker *et al.* leads to the isolation of 3(α)-hydroxycholestane (*epi*cholestanol), m. p. 183—185°, which was identified directly and by conversion into the acetate, m. p. 94—95°. The main product of the reaction, also isolated by direct crystallisation, is an unsaturated hydrocarbon, m. p. 70—72°, $[\alpha]_D^{20°}$ +63°±1°, which is probably identical with Δ²-cholestene, m. p. 69°, $[\alpha]_D^{20°}$ +64°, obtained by Mauthner (*Monatsh.*, 1909, **30**, 642) from the chloride by the action of hot quinoline and termed *neo*cholestene by him; [cf. also Blunschy, Hardegger, and Simon (*Helv. Chim. Acta*, 1946, **29**, 199), m. p. 73—74°, $[\alpha]_D$ +67°; Hattori and Kawasaki (*J. Pharm. Soc. Japan*, 1937, **57**, 115), m. p. 75°, $[\alpha]_D^{24°}$ +64°]; the production of Δ³-cholestene is, however, not excluded. The formation of Δ²- and/or Δ³-cholestene is not unexpected since Hughes, Ingold, and Scott (*J.*, 1937, 1271) have shown that an alkyl halide in a non-aqueous solvent and in the absence of a basic reagent can afford an olefin by a unimolecular mechanism (*E*1) :



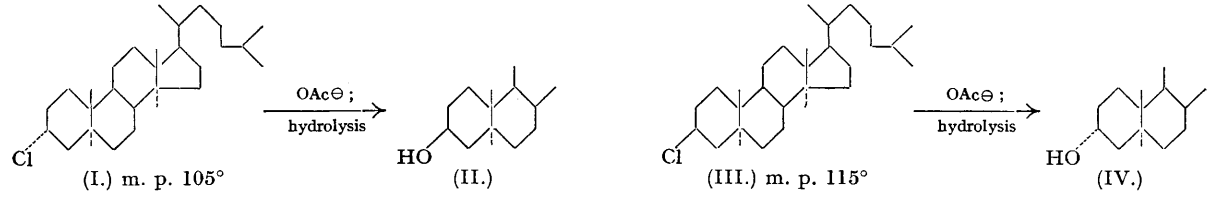
dependent on a slow halogen-ionisation, which is also the initial stage of the substitution mechanism S_N1, followed by rapid loss of a proton from the intermediate cation. From the present point of view, the process furnishing Δ²-cholestene simply puts some of the original chloride out of action; a quantitative investigation of the reaction product from " α "-cholestanyl chloride (250 mg.) was therefore undertaken. Chromatographic analysis gave Δ²-cholestene (167 mg.), 3(α)-hydroxycholestane (39 mg.), and 3(β)-hydroxycholestane (7 mg.). The elimination reaction therefore involved 73% of the original chloride, and the cholestanols isolated in pure crystalline condition represent a yield of 72% on the residual 27% of chloride. The relative proportions of the cholestanols isolated are 85% of the 3(α)- and 15% of the 3(β)-epimeride.

Similarly, a quantitative investigation of the colourless reaction product obtained by treatment of " β "-cholestanyl chloride (250 mg.) under the conditions prescribed by Marker *et al.* gave Δ^2-cholestene (176 mg.), 3(α)-hydroxycholestane (5·5 mg.), and 3(β)-hydroxycholestane (40·5 mg.); the last two were identified directly and by conversion into the acetates. The elimination reaction here involved 77% of the chloride, whilst the cholestanols isolated in pure crystalline condition correspond to a yield of 84% on the residual 23% of chloride. The relative proportions of the cholestanols isolated are 12% of the 3(α)- and 88% of the 3(β)-epimeride.

The production of *both* epimerides in both experiments, but in markedly unequal and inverse proportions, is in accord with theoretical expectation. A bimolecular acetolysis (mechanism S_N2) should proceed with inversion and practically complete absence of racemisation, whilst a unimolecular acetolysis (mechanism S_N1) should take place with predominating inversion but with some racemisation (cf. Hughes, Ingold, and Masterman, *J.*, 1937, 1196). The following table summarises the results and suggests that the substitution mechanisms S_N1 and S_N2 operate side by side, and that if racemisation is confined essentially to mechanism S_N1 then that mechanism operates to the extent of some 24—30%.

	Chloride involved in elimination reaction *E*1 (%).	Chloride involved in substitution reactions S_N1, S_N2 (%).	*epi*Cholestanol isolated (%).	Cholestanol isolated (%).
" α "-Cholestanyl chloride, m. p. 115°...	74	26	70 (S_N2) + 15 (S_N1)	15 (S_N1)
" β "-Cholestanyl chloride, m. p. 105°...	77	23	12 (S_N1)	76 (S_N2) + 12 (S_N1)

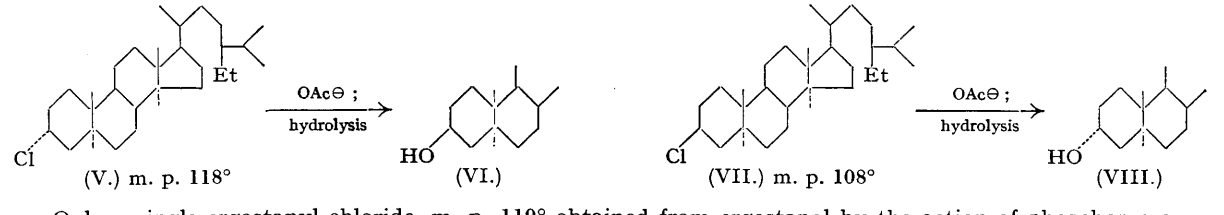
The " β "-chloride is therefore 3(α)-chlorocholestane (I), and the " α "-chloride is the epimeric 3(β)-chlorocholestane (III).



(I.) m. p. 105° (II.) (III.) m. p. 115° (IV.)

The configurations now assigned reverse the provisional trivial indices previously used for differentiation, and also reverse the stereochemical allocation suggested by Fieser (" The Chemistry of Natural Products Related to Phenanthrene," 2nd Edition, New York, 1937, pp. 392, 393) and by Barr, Heilbron, and Spring (*J.*, 1936, 737) on the basis of the rule that the m. p. of a *cis*(C_3/C_5)-compound is higher than that of its *trans*-(C_3/C_5)-isomeride, but are in harmony with the fortuitous allocation made by Sobotka (" The Chemistry of the Sterids," London, 1938, p. 61).

A similar situation exists in regard to the stigmastanyl chlorides; the so-called " β "-stigmastanyl chloride, m. p. 118°, reacts with acetate ions in *n*-valeric acid at 180° to furnish, after alkaline hydrolysis, stigmastanol (VI) (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711); this chloride is therefore 3(α)-chlorostigmastane (V). Likewise, the so-called " α "-stigmastanyl chloride, m. p. 108°, affords *epi*stigmastanol (VIII) (Marker and Lawson, *loc. cit.*) and is therefore 3(β)-chlorostigmastane (VII).



(V.) m. p. 118° (VI.) (VII.) m. p. 108° (VIII.)

Only a single ergostanyl chloride, m. p. 119° obtained from ergostanol by the action of phosphorus oxychloride, appears to be known; this [*vide infra* this Section, also Section (*b*)] is probably 3(α)-chloroergostane and should furnish ergostanol by treatment with acetate ions and subsequent alkaline hydrolysis.

For saturated compounds, in which effects arising from " vicinal action " (Barton, *J.*, 1945, 813; this vol., p. 372) are excluded, molecular rotation differences, where available, can contribute supplementary evidence of configuration, and, as will be seen from Table I, these are in agreement with the configurations now assigned.

From the configurations thus assigned to (I) and (III), it follows that the " β "-chloroandrosterone, m. p. 128°, which results from (I) by oxidation with chromium trioxide (Ruzicka, Goldberg, and Brungger, *Helv. Chim. Acta*, 1934, **17**, 1389) is 3(α)-chloroandrostan-17-one (IX). It would appear not unreasonable to consider that the polar influence of the carbonyl group at C_{17} upon the halogen at C_3 is extremely small, and to regard (IX) in respect of substitution reactions at C_3 as a secondary alkyl halide analogous to (I) and (III).

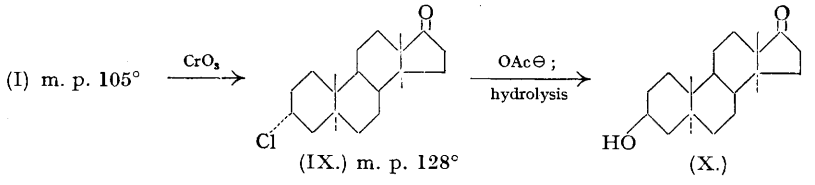
TABLE I.

(All rotations in chloroform at ~20°.)

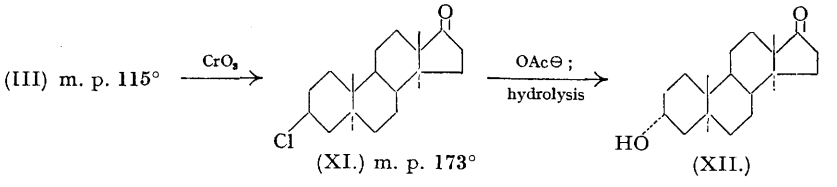
Substance.	3(α). $[\alpha]_D$.	3(α). $[M]_D$.	3(β). $[\alpha]_D$.	3(β). $[M]_D$.	$\Delta[M]_D$.
3-Chlorocholestane	+30·5° [1]	+124°	+27° [1]	+110°	+14°
3-Chlorostigmastane	—	—	—	—	—
3-Hydroxycholestane	+26 [2]	+100	+23 [3]	+ 89	+11
3-Hydroxystigmastane	+24 [4]	+108	+24 [5, 6, 7]	+100	+ 8
3-Acetoxycholestane	+30 [1]	+129	+14 [3]	+ 60	+69
3-Acetoxystigmastane	+28 [4]	+128	+15 [5, 6, 7]	+ 69	+59

[1] This paper; Mauthner (*Monatsh.*, 1909, **30**, 635) gives $[\alpha]_D^{20°}$ +29·5° (*c*, 3·138 in chloroform) for the 3(β)-chlorocholestane. [2] Linstead, *J. Amer. Chem. Soc.*, 1940, **62**, 1766. [3] Barton, private communication. [4] Barton, *J.*, 1945, 813. [5] Dalmer *et al.*, *Ber.*, 1935, **68**, 1814. [6] Discherl, *Z. physiol. Chem.*, 1935, **237**, 32. [7] Coffey, Heilbron, and Spring, *J.*, 1936, 738.

On this assumption, reaction with acetate ions should and does proceed with substantially complete inversion to give *iso*androsterone acetate and, after hydrolysis, *iso*androsterone (X); here also incursion of the elimination reaction *E*1 (cf. p. 1141) leads to the production of Δ^2- or Δ^3-androsten-17-one. Incidentally, the chloro-*allo*cholanic acid, m. p. 195°, obtained as by-product in the oxidation of (I) (compare Barr, Heilbron, and Spring, *J.*, 1936, 737) must be 3(α)-chloro*allo*cholanic acid, and the lower homologue, m. p. 213° derived from it must be 3(α)-chloronor*allo*cholanic acid. This nor*allo*-acid, characterised as the methyl ester, m. p. 158°, was also obtained by Heilbron, Samant, and Simpson (*J.*, 1933, 1410) from ergostanyl chloride, m. p. 119°, by oxidation with chromium trioxide, and the constitution now assigned to it is consistent with the formulation (*vide supra*) of the chloride, m. p. 119°, as 3(α)-chloroergostane.



Similarly, the " α "-chloroandrosterone, m. p. 173°, which is obtained from (III) by oxidation with chromium trioxide (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998; Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358) is 3(β)-chloroandrostan-17-one (XI), which by treatment with acetate ions in acetic acid undergoes inversion to afford androsterone acetate and, after hydrolysis, androsterone (XII) (Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192; Ruzicka, Wirz, and Meyer, *loc. cit.*; Marker, Whitmore, Kamm, Oakwood, and Blattermann, *J. Amer. Chem. Soc.*, 1936, **58**, 338); Butenandt and Dannenbaum record the formation of Δ^3-androsten-17-one, which again clearly arises from the inclusion of the elimin-



ation reaction *E*1. The acid, m. p. 175° (compare Windaus and Hossfeld, *Z. physiol. Chem.*, 1935, **145**, 177), accompanying (XI) must be 3(β)-chloro*allo*cholanic acid, and its lower homologues, m. p. 238° (Heilbron, Samant, and Spring, *loc. cit.*), and m. p. 231° (Marker *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 768), must be correspondingly 3(β)-chloronor- and 3(β)-chlorobisnor-*allo*cholanic acid; the latter has been degraded to a 20-ketone which must be 3(β)-chloro*allo*pregnan-20-one and which reacts with acetate ions with inversion of configuration to give 3(α)-hydroxy*allo*pregnan-20-one.

The molecular rotation differences are given in Table II, and support the configurations now assigned to the 3-chloroandrostan-17-ones.

In this case further supporting evidence can be supplied by physiological activity, which is known to be extremely susceptible to minor structural modification. *iso*Androsterone (X) is some ten times less active in the comb-growth test than androsterone (XII), *i.e.*, a 3(β)-substituent appears to depress androgenic activity as compared with the same 3(α)-substituent. On the basis of the configurations now assigned, it would therefore be expected that (IX) should exhibit greater androgenic activity than (XI). This is so; Ruzicka, Wirz, and Meyer (*Helv. Chim. Acta*, 1935, **18**, 998) have reported that (XI) is at least four times less active than (IX) in the comb-growth test.

(*b*) *Replacement of* OR *by* Cl *with* PCl_5 *and* $SOCl_2$.—The conversion of alcohols into alkyl halides was discussed by Cowdrey, Hughes, Ingold, Masterman, and Scott (*loc. cit.*) and has recently been summarised by

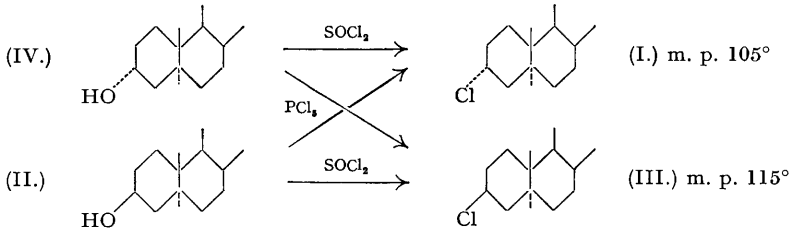
TABLE II.

(Rotations in chloroform at ~20°.)

Substance.	3(α). $[\alpha]_D$.	3(α). $[M]_D$.	3(β). $[\alpha]_D$.	3(β). $[M]_D$.	$\Delta[M]_D$.
3-Chloroandrostane-17-one	+94° [1]	+290°	+92° [1]	+284°	+ 6°
3-Hydroxyandrostane	+ 2 [2]	+ 6	+ 1 [2]	+ 3	+ 3
3-Hydroxy-Δ^{16}-androstene	+14 [2]	+ 38	+11 [2]	+ 30	+ 8
3-Hydroxyandrostan-17-one	+88 [3]	+255	+81 [3]	+235	+20
	+96 [4]	+278	+94 [5]	+273	+ 5
	—	—	+90 [6]	+261	—
3-Acetoxyandrostan-17-one	+77 [3]	+256	+65 [3]	+216	+40
	+86 [7]	+286	+76 [5]	+252	+34
	—	—	+69 [6]	+229	—

[1] This paper. [2] Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1944, **27**, 1164. [3] Reichstein and von Euw, *ibid.*, 1942, **25**, 988, determined in dioxan. [4] Butenandt and Tscherning, *Z. physiol. Chem.*, 1934, **229**, 167; David *et al.*, *ibid.*, 1935, **233**, 281; Discherl, *ibid.*, 1935, **237**, 52; Ruzicka *et al.*, *Helv. Chim. Acta*, 1934, **17**, 1389, 1395; Hirschmann, *J. Biol. Chem.*, 1940, **136**, 483, all in EtOH. [5] Barton, private communication, determined in EtOH. [6] Barton, private communication. [7] Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192, determined in EtOH.

Dostrovsky, Hughes, and Ingold (this vol., p. 188) on the supposition that the first stage is always the formation of a complex, *e.g.*, with thionyl chloride $R_1R_2R_3C{-}O{-}SOCl$, which can undergo (i) rearrangement with retention of configuration (since the transition state is of the pyramidal type) according to the capacity for electron release of R_1, R_2, R_3, to cause fission of the C–O bond (S_Ni), (ii) ionisation of the halogen atom with inversion (S_N2) or inversion accompanied by extensive racemisation (since the carbonium ion is nearly flat) (S_N1). Because thionyl halides rearrange more readily and ionise less readily than phosphorus halides, and because whenever S_Ni is possible and electronic conditions favour S_Ni in an absolute sense, S_N1 and S_N2 are superseded in a comparative sense, the cholestanols (II, IV) in both of which R_1 may be regarded as $CHMe_2$ and R_2 as $CH_2{\cdot}CH_2{\cdot}CMe_3$ (or even higher alkyl groups) might be expected to react with thionyl chloride with retention of configuration and with phosphorus pentachloride with inversion if, indeed, they afford different products with these reagents. This is in fact so; cholestan-3(α)-ol (IV) reacts with thionyl chloride (Marker, Whitmore, and Kamm, *J. Amer. Chem. Soc.*, 1935, **57**, 2358) to yield 3(α)-chlorocholestane (I) and with phosphorus pentachloride (Marker, Whitmore, and Kamm, *loc. cit.*) or phosphorus tribromide (Ruzicka, Wirz, and Meyer, *Helv. Chim. Acta*, 1935, **18**, 998; Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 340) to give 3(β)-chloro(bromo)cholestane (III); similarly, cholestan-3(β)-ol (II) reacts with thionyl chloride (Marker, Kamm, and Whitmore, *loc. cit.*) to furnish 3(β)-chlorocholestane (III), and with phosphorus pentachloride (Diels and Linn, *Ber.*, 1908, **41**, 260; Windaus, *ibid.*, 1917, **50**, 133; cf. Ruzicka, Goldberg, Brungger, *Helv. Chim. Acta*, 1934, **17**, 1392) to afford 3(α)-chlorocholestane (I).

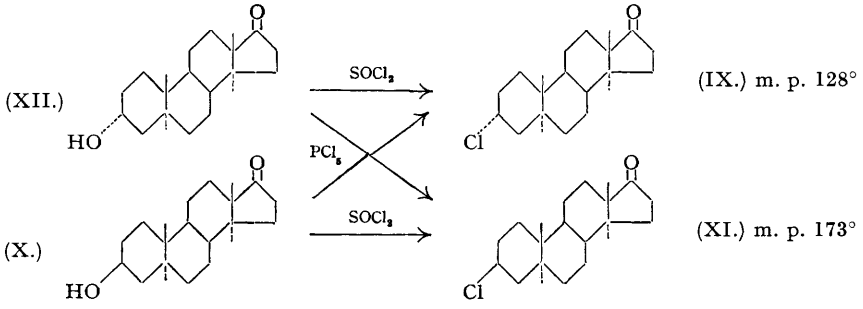


No evidence is available as to occurrence of racemisation in these reactions, but the resulting configurational relationships are in harmony with those established in section (*a*). The use of hydrochloric acid as the substituting reagent should cause inversion and furnish the same products as are obtained with phosphorus pentachloride.

A similar situation exists in respect of the stigmastanols; stigmastan-3(α)-ol (VIII) with thionyl chloride gives 3(α)-chlorostigmastane, m. p. 118° (V), and with phosphorus pentachloride yields 3(β)-chlorostigmastane, m. p. 108° (VII), whilst stigmastan-3(β)-ol (VI) furnishes 3(β)-chlorostigmastane (VII) with thionyl chloride and 3(α)-chlorostigmastane (V) with phosphorus pentachloride (Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711).

Assuming once again that the polar influence at C_3 of the carbonyl group at C_{17} is very small, similar considerations should be applicable to the reactions of androsterone (XII) and *iso*androsterone (X) with thionyl chloride and phosphorus pentachloride. *iso*Androsterone (X) reacts with thionyl chloride to give 3(β)-chloroandrostan-17-one (XI) (Marker, Whitmore, Kamm, Oakwood, and Blatterman, *J. Amer. Chem. Soc.*, 1936, **58**, 338) with retention of configuration, whilst androsterone (XII) is now found similarly to furnish 3(α)-chloroandrostan-17-one (IX) but in traces, the principal product under all conditions used being a high-melting substance, probably androsterone sulphite. Use of 1 mol. of phosphorus pentachloride is found

to convert androsterone (XII) into 3(β)-chloroandrostan-17-one (XI) * and *iso*androsterone (X) into 3(α)-chloroandrostan-17-one (IX), in accordance with the theoretical expectation of inversion of configuration,



and in good yield.† Theory suggests that use of thionyl chloride in presence of pyridine may reverse the stereochemical course of reaction and lead to inversion of configuration.

It is proposed in the near future to examine the application of the considerations developed in the foregoing to derivatives of 6-ketocholestane, ætiocholane, *allo*cholane, cholane, and coprostane.

Experimental.

(All m. ps. were thermo-electrically determined on a Kofler block and are therefore corrected; limit of error ±2°. All optical rotations were determined in chloroform.)

3(α)-Chlorocholestane (I).—3(β)-Hydroxycholestane (m. p. 139—140°, giving no colour with tetranitromethane; 165 mg.) was treated with phosphorus pentachloride (200 mg.) according to the directions of Ruzicka *et al.* (*Helv. Chim. Acta*, 1934, **17**, 1389); the product gave a faint but definite yellow colour with tetranitromethane, and was therefore dissolved in pure acetic acid (2 c.c.) and treated with a 2% solution of chromium trioxide in acetic acid (2·0 c.c. ≡1·5 atoms of oxygen) for 0·5 hour at 60°. After working up, the neutral product was dissolved in pentane and separated from neutral oxidation products by filtration through a column of aluminium oxide (Merck–Brockmann, activity III—IV; 0·5 g.) prepared in pentane. The product obtained by elution with pentane represented a yield of 90%; after recrystallisation from acetone, 3(α)-chlorocholestane was obtained as plates, m. p. 95° with partial transformation to prisms, m. p. 103—105°; $[\alpha]_D^{20°}$ +30·5°±1° (*c*, 1·377 in chloroform), giving no colour with tetranitromethane. A second preparation yielded prisms, m. p. 103—105°, the polymorphic plate-form not being observed.

Acetolysis. The chloride (I) (250 mg.), anhydrous potassium acetate (2·5 g.), and *n*-valeric acid (5 c.c.) were refluxed with exclusion of moisture for 30 hours. The product was completely colourless and was treated with 2N-sodium carbonate (25 c.c.) and extracted with ether. The extract was washed with 2N-sodium carbonate and then with water, dried (Na_2SO_4), and evaporated. The residue was hydrolysed with 4% methyl-alcoholic potassium hydroxide (2·5 c.c. ≡ *ca.* 3 mols.) for 2 hours; after addition of a few drops of water, saturation with carbon dioxide, and removal of methanol under reduced pressure, the product was extracted with ether. The ethereal extract was washed with a little water, dried (Na_2SO_4), and evaporated to give a colourless oil (231 mg.), which was dissolved in benzene (0·25 c.c.), diluted with a little pentane and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV; 7 g.) prepared in 25 c.c. of pentane. Using eluates of 25 c.c. the analysis of the product is shown in Chromatogram A. Fractions 1—3 were united and recrystallised from acetone to yield Δ²-cholestene, m. p. 69—70°, $[\alpha]_D^{20°}$ +64°±1° (*c*, 2·025 in chloroform); the upper layer remained colourless with chloroform–sulphuric acid, but developed an intense violet colour on addition of acetic anhydride. A solution of the hydrocarbon in ether–acetic acid, treated with the calculated amount of a solution of bromine in acetic acid, gave by evaporation under reduced pressure an oily dibromide, which crystallised partly when moistened with methanol and kept at 0°; the crystalline material was recrystallised from ethanol to give an impure dibromide, m. p. 100—104° (Mauthner, *loc. cit.*, gives m. p. 125°). Fractions 7 and 8 were united and recrystallised from ethanol to yield pure cholestane-3(α)-ol, m. p. 186—187°, mixed m. p. 186—187°; the crystals were boiled with acetic anhydride for 10 minutes, excess of the reagent was removed under reduced pressure, and the crystalline residue was recrystallised from methanol to yield needles of the acetate, m. p. 94—95°, mixed m. p. 94—96° with a genuine specimen. Fractions 11 and 12, consisting of pure cholestan-3(β)-ol, were identified by similar conversion into the acetate which, recrystallised from ethyl acetate–methanol, formed prisms, m. p. 109—110°, mixed m. p. 109—110°.

3(β)-Chlorocholestane (III).—Prepared by hydrogenation of cholesteryl chloride, and suitably purified (see Part II, following paper), the compound formed prisms, m. p. 114—115°, $[\alpha]_D^{20°}$ +27°±1° (*c*, 1·911 in chloroform).

Acetolysis. The chloride (III) (250 mg.), anhydrous potassium acetate (2·5 g.), and *n*-valeric acid (5 c.c.) were refluxed for 30 hours with exclusion of moisture. The product was somewhat discoloured and was isolated and hydrolysed as described above. The brown reaction product (230 mg.) was boiled with methanol in which it was not appreciably soluble and the clear colourless solution decanted from the undissolved material and allowed to crystallise. Two kinds of crystal were readily separated by hand-picking: (i) very long thin prisms, m. p. 70—72°, of Δ²-cholestene, (ii) compact prisms, m. p. 180—183°, of cholestan-3(α)-ol, mixed m. p. 181—185°, the melt recrystallising at 182° and remelting at 185°. The whole material was re-united, dissolved in benzene (0·25 c.c.), and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV, 7 gm.) prepared in pentane (25 c.c.); the details of the chromatographic analysis, using eluates of 25 c.c., are set out in chromatogram B. The Δ²-cholestene contained in fractions 1—3 was recrystallised from acetone to give prisms, m. p. 68—70°, $[\alpha]_D^{20°}$ +63°±1° (*c*, 2·015 in chloroform). Fractions 7, 8, and 9 were united and recrystallised from methanol to yield pure cholestan-3(α)-ol, m. p. 186—187°, mixed m. p. 186—187° (acetate, m. p. 94—95°, mixed m. p. 93—95°). Fractions 11 and 12 were united and recrystallised from methanol to give plates (7 mg.), m. p. *ca.* 125° with immediate recrystallisation as prisms, m. p. 141—142°; mixed m. p. determinations with pure cholestan-3(β)-ol showed a partial transition at *ca.* 125°, and melted finally at 141—142°; the material

* Since this experiment was carried out, it has been discovered that the conversion of androsterone (XII) into the chloride, m. p. 173°, now assigned the 3(β)-chloro-configuration (XI), by use of phosphorus pentachloride had already been achieved by Hirschmann (*J. Biol. Chem.*, 1940, **136**, 483).

† The apparent absence of racemisation in these reactions suggests that mechanism S_N1 is largely excluded.

gave a precipitate with digitonin in 90% methanol, and by acetylation yielded the acetate of cholestan-3(β)-ol, m. p. 109—110°, mixed m. p. 109—110°.

3(α)-*Chloroandrostan*-17-*one* (IX).—(a) *From* iso*androsterone*. *iso*Androsterone (m. p. 175—176°; 65 mg.), prepared by hydrolysis of a highly purified specimen of the acetate, double m. p. 97° and 102—104°, was dissolved in pure dry chloroform * (2·5 c.c.) at 0°, and dry precipitated calcium carbonate (65 mg.) was added, followed by phosphorus pentachloride (90 mg.) with stirring during 15 minutes. After addition of sodium bicarbonate solution (5 c.c.) and a

		Chromatogram A.		Chromatogram B.	
No.	Eluant.	Eluate.	Wt. (mg.).	Eluate.	Wt. (mg.)
1	Pentane	Cryst. spontaneously, Δ^2-cholestene, m. p. 67—69°.	135·5	Cryst. spontaneously, Δ^2-cholestene, m. p. 67—68°.	138
2	,,	Cryst. spontaneously, Δ^2-cholestene, m. p. 66—68°.	36	Cryst. spontaneously, Δ^2-cholestene, m. p. 65—68°.	25
3	,,	Cryst. by inoculation, Δ^2-cholestene, m. p. 65—66°.	3	Cryst. by inoculation, Δ^2-cholestene, m. p. 64—67°.	4
4	,,	Cryst. partially by inoculation, Δ^2-cholestene?	1·5	Trace of oil, cryst. partly by inoculation.	1
5	Benzene–pentane 1 : 4	Oil.	0·5	Oil.	1
6	,, ,, 1 : 1	Oil.	0·5	Brown gum, could not be cryst. from methanol at 0°.	5
7	,, ,, 1 : 1	Cryst. spontaneously, cholestan-3(α)-ol, m. p. 182°, the melt recryst. at 178°.	2	Cryst. spontaneously, cholestan-3(α)-ol, m. p. 185°.	27
8	,, ,, 1 : 1	Cryst. spontaneously, cholestan-3(α)-ol, m. p. 185°, the melt recryst. at 182°.	3·5	Cryst. spontaneously, cholestan-3(α)-ol, m. p. 183—185°.	5
9	,, ,, 1 : 1		—	Cryst. spontaneously, cholestan-3(α)-ol, m. p. 182—183°.	1
10	Benzene	Partly crystalline.	1	Crystalline but coloured cholestan-3(α)-ol, m. p. 178—182°.	6
11, 12	Ether.	Cryst. spontaneously, m. p. 139—141° with recryst. of the melt at 140°; cholestan-3(β)-ol.	40·5	Cryst. spontaneously, m. p. 135—140°, largely cholestan-3(β)-ol.	11·5
13	Ether	———	—	Trace of cryst. material.	0·5
		Total	224	Total	225

sufficient quantity of ether, the aqueous layer was separated, acidified with 2N-hydrochloric acid, and re-extracted with ether. The united extracts were washed with 2N-hydrochloric acid, 2N-sodium carbonate, and water, dried (Na_2SO_4), and evaporated. The product was taken up in sufficient boiling light petroleum (b. p. 80—100°), from which unchanged *iso*androsterone, m. p. 175° (38 mg.) separated on cooling. This material was retreated with phosphorus pentachloride (55 mg.), and the product was combined with the residue of reduced-pressure evaporation of the above light petroleum mother liquor and introduced on to a column of aluminium oxide (Merck–Brockmann, activity III—IV : 2 g.) prepared in pentane. Elution with benzene–pentane (1 : 4, 2 × 10 c.c. and 1 : 2, 10 c.c.) gave fractions which crystallised spontaneously after complete evaporation; further elution with benzene–pentane (1 : 2) gave only traces of material which failed to crystallise by seeding. The crystalline fractions were united and the product recrystallised from methanol to yield 3(α)-chloroandrostan-17-one (26 mg.) in characteristic stout prisms, m. p. 128°, mixed m. p. 128°. Elution of the column with dry ether (2 × 10 c.c.) yielded *iso*androsterone, m. p. 175° (28 mg.); allowance being made for this recovered material, the yield of chloride was 67%.

(b) *From androsterone*. (i) Androsterone (50 mg.) was dissolved in dry ether (2 c.c.), dry precipitated calcium carbonate (50 mg.) added, and pure redistilled thionyl chloride (1 c.c.) added dropwise with stirring at 15° during 0·5 hour. After 4 hours at room temperature, the mixture was completely evaporated under reduced pressure, and the product extracted with chloroform–ether (cf. Butenandt and Dannenbaum, *Z. physiol. Chem.*, 1934, **229**, 192). The material so obtained was chromatographed over aluminium oxide, but elution with benzene–pentane (1 : 4 and 1 : 2) gave only insignificant amounts of oil. Elution with benzene and benzene–ether mixtures yielded a substance, insoluble in methanol, which tended to separate as a jelly on concentration of the solution. The substance could not be crystallised satisfactorily, but was obtained crystalline by complete evaporation of a benzene solution and moistening of the residual oil with acetone; m. p. 200° (approx.); since hydrolysis with 4%-methyl-alcoholic potassium hydroxide in the presence of a little benzene furnished an almost quantitative yield of androsterone, the substance is regarded as androsterone sulphite.

(ii) Since under appropriate conditions cholesterol reacts with thionyl chloride to give cholesterol sulphite (Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665) and since the writer has found 3(β)-hydroxycholestane similarly to afford a quantitative yield of the *sulphite* [iridescent plates, m. p. 194°, from much hot acetone (Found: C, 79·12; H, 11·39. $C_{54}H_{94}O_3S$ requires C, 78·78; H, 11·50%)], the order of addition was reversed so that excess of thionyl chloride was always present. To a solution of thionyl chloride (2 c.c.) in dry ether (2 c.c.) containing dry calcium carbonate (100 mg.), a solution of androsterone (35 mg.) in dry ether (5 c.c.) was added dropwise at 5° during 0·25 hour. After being left for 4 hours to attain room temperature, the mixture was worked up as above, and chromatographed on aluminium oxide (Merck–Brockmann, 1 g.). Elution with benzene–pentane (1 : 4) yielded 3(α)-chloroandrostan-17-one (2 mg.), m. p. 123—125°, which did not depress the m. p. of a genuine specimen. Elution with benzene and benzene–ether mixtures yielded androsterone sulphite, which again formed the principal product of the reaction. Lack of material precluded a search for more favourable conditions.

For determination of the specific rotation, a genuine but slightly discoloured specimen, m. p. 125·5°, prepared by oxidative degradation of 3(α)-chlorocholestane and supplied by Professor Ruzicka, was purified chromatographically (*vide supra*); the product after recrystallisation from methanol formed stout colourless prisms, m. p. 128°, $[\alpha]_D^{22°}$ +94° ± 1·5° (*c*, 1·695).

* "AnalaR" chloroform was shaken for 24 hours with excess of calcium chloride, filtered, distilled, and used immediately.

3(β)-*Chloroandrostan*-17-*one* (XI).—Androsterone, m. p. 182° (54 mg.) was dissolved in chloroform at 0°, and treated with phosphorus pentachloride (80 mg.) in the presence of calcium carbonate (55 mg.) (*vide supra*). Working up yielded a product which, taken up in light petroleum (b. p. 80—100°), yielded unaltered androsterone, m. p. 180—182° (36 mg.). This material was retreated with phosphorus pentachloride (50 mg.) and the product together with the residue obtained by evaporation of the light petroleum mother-liquor submitted to chromatographic analysis on aluminium oxide; elution with benzene–pentane (1 : 4) gave fractions which crystallised spontaneously and which, united and recrystallised from ethanol, yielded 3(β)-chloroandrostan-17-one as needles, m. p. 172—173° (16 mg.), $[\alpha]_D^{20°}$ +92° ± 2° (*c*, 1·400) (Found: C, 74·0; H, 9·7. Calc. for $C_{19}H_{29}OCl$: C, 73·9; H, 9·5%). A first elution of the column with benzene–pentane (1 : 2) (10 c.c.) gave a mere trace of material and a second similar elution gave nothing; subsequent elution with dry ether (2 × 10 c.c.) afforded unchanged androsterone, m. p. 179—182° (32 mg.). Allowance being made for this recovered androsterone, the yield of chloride was 70%.

iso*Androsterone Acetate from* 3(α)-*Chloroandrostan*-17-*one* (IX).—The chloride (20 mg., m. p. 128°) was heated for 2 hours at 180° (aniline-vapour bath) with a 20% solution of fused potassium acetate in pure acetic acid in a small bomb-tube. After cooling, the contents of the tube were poured into water, and the product extracted with ether–chloroform; the extract was washed with water, sodium carbonate solution, and again with water, dried (Na_2SO_4), and evaporated. The residue (18 mg.) was partly crystalline and was introduced by a minimum of benzene on to a column of aluminium oxide (Merck–Brockmann, 0·6 g.) prepared in pentane. Elution with pentane and benzene–pentane mixtures (1 : 9, 1 : 4) gave fractions which crystallised spontaneously; these were united after appropriate examination and recrystallised from methanol to yield rectangular plates, m. p. 105°, of Δ^2 (or $\Delta^{3?}$)-androsten-17-one (Found: C, 80·0; H, 10·5. Calc. for $C_{19}H_{28}O$: C, 80·2; H, 10·3%) (cf. Marker, Kamm, Jones, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1363; Hirschmann, *J. Biol. Chem.*, 1940, **136**, 483; Venning, Hoffman, and Browne, *ibid.*, 1942, **146**, 369). Elution with benzene–pentane (1 : 1) gave a fraction which, recrystallised from dilute methanol, yielded *iso*androsterone acetate (4 mg.) as leaflets, m. p. 96—97°, with partial recrystallisation and remelting at 101—103°, which did not depress the m. p. of a genuine specimen. Subsequent elution with benzene–ether mixtures gave only traces of oil which failed to crystallise.

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