Backbone Rearrangements of Steroidal 5-Enes

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Acid-catalysed isomerisation of cholest-5-ene gives the backbone-rearranged 5,14-dimethyl-18,19-bisnor-5β,8α,9β,10α,14β-cholest-13(17)-enes with 20*R*- (1) and 20*S*- (2) configurations, respectively. Androst-5-ene and D-homoandrost-5-ene, in contrast, give products of only partial backbone rearrangement, with the olefinic bond at the 8,9-position; configurations at C-5, C-10, C-14, and in the D-homo-compound also at C-13, undergo equilibration to give mainly the more stable isomers with *cis*-fusion at the AB and CD ring junctions (Scheme 1). The symmetry characteristics of the rearranged D-homoandrost-8-enes permit racemisation, leading to total loss of optical activity after long periods of reaction. Androst-5-en-17-one rearranges in trifluoroacetic acid–dichloromethane to give 5-methyl-5β-oestr-9(11)-en-17-one (24), retaining the 14α-configuration, but methanolic sulphuric acid enforces further backbone rearrangement leading to 5-methyl-5β,14β-oestr-8-en-17-one (28) and 5-methyl-5α,10α,14β-oestr-8-en-17-one (29).

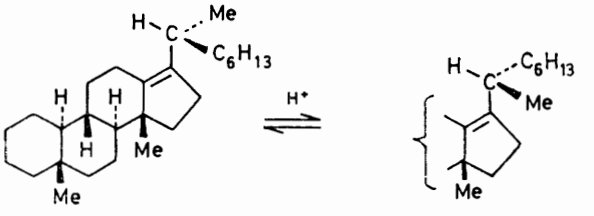
The factors influencing the stabilities of the various products are discussed, and mechanisms are proposed for the rearrangements. The ready isomerisation of D-homoandrost-5-ene shows that strain associated with the *trans*-fusion of rings C and D in ordinary steroids is *not* a requirement for backbone rearrangements to occur.

WE recently presented preliminary accounts of acid-catalysed isomerisations of cholest-5-ene,[1] androst-5-ene, and D-homoandrost-5-ene.[2] This work is now described in full, together with the results of further studies involving rearrangements of androst-5-en-17-one and androst-5-en-17β-ol.

[1] D. N. Kirk and P. M. Shaw, *Chem. Comm.*, 1970, 806.
[2] D. N. Kirk and P. M. Shaw, *Chem. Comm.*, 1971, 948.

Cholest-5-ene.—The equilibration of cholest-5-ene and cholest-4-ene in acetic acid–toluene-*p*-sulphonic acid at 80 °C was first reported by Turner and co-workers,[3] who noted that further isomerisation occurred at the b.p. of acetic acid. Blunt, Hartshorn, and Kirk [4] subsequently identified the main rearrangement product as the $\Delta^{13(17)}$ compound (1), resulting from a 'backbone' rearrangement. A further olefinic product remained unidentified at that time.

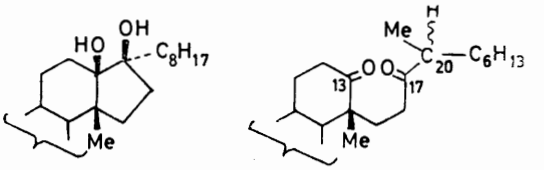
A re-examination of these reactions, by using cholesteryl *p*-phenylbenzoate as a liquid-crystalline stationary phase of high efficiency for g.l.c.,[5] gave the equilibrated ratio of cholest-5-ene and -4-ene as **39 : 61** (each ±1) in acetic acid–cyclohexane at 85 °C. (Other g.l.c. materials failed to separate these isomeric cholestenes; [5] Turner *et al.*[3] estimated a ratio of **45 : 55** by i.r. spectroscopic analysis.)



(1) (20*R*) (2) (20*S*)

Rearrangement in refluxing acetic acid (with TsOH) led first to the known $\Delta^{13(17)}$-compound (1), but the second olefinic product [4] increased in proportion until the mixture comprised essentially the two compounds in 1 : 1 ratio. N.m.r. spectra of both isomers exhibited characteristic coupling of the C-21 methyl proton signal, with the C-20 proton signal at τ *ca.* 7.58, indicating the $\Delta^{13(17)}$-structure.[4,6]

cis-Hydroxylation of each of the $\Delta^{13(17)}$-compounds with osmium tetraoxide gave crude **13,17**-diols, believed to be predominantly **13β,17β**-diols (**3**) from both olefins on the evidence of large downfield shifts [7] of the **14β**-methyl proton resonances in pyridine solution, as compared with spectra of solutions in $CDCl_3$ (see Experimental section). Cleavage of the (20*R*)- and (20*S*)-**13β,17β**-diols with lead tetra-acetate gave isomeric **13,17**-seco-diketones (**4**) and (**5**) with similar but distinguishable properties (Experimental section). Both diketones were equilibrated by acid to give a 1 : 1 mixture, consistent with their being identical except in regard to configuration at C-20. The 20*R*-configuration assigned to the first-formed $\Delta^{13(17)}$-compound corresponds to that of natural cholestanes. Equilibration of the $\Delta^{13(17)}$-compound at C-20 requires a temporary migration of unsaturation to the **17,20**-position, followed by reprotonation at C-20 from either the α- or the β-face, allowing unsaturation to return to its more stable location in the $\Delta^{13(17)}$-compounds. Attempts to enforce a similar isomerisation at C-20 in the **3β,6β**-diacetoxy-derivative [8] of the (20*R*)-$\Delta^{13(17)}$-compound led to no



(3) (4) (20*R*) (5) (20*S*)

detectable change. The polar substituents probably exert a long-range effect unfavourable to reprotonation of the $\Delta^{13(17)}$-compound, once it has been formed by a concerted backbone rearrangement.

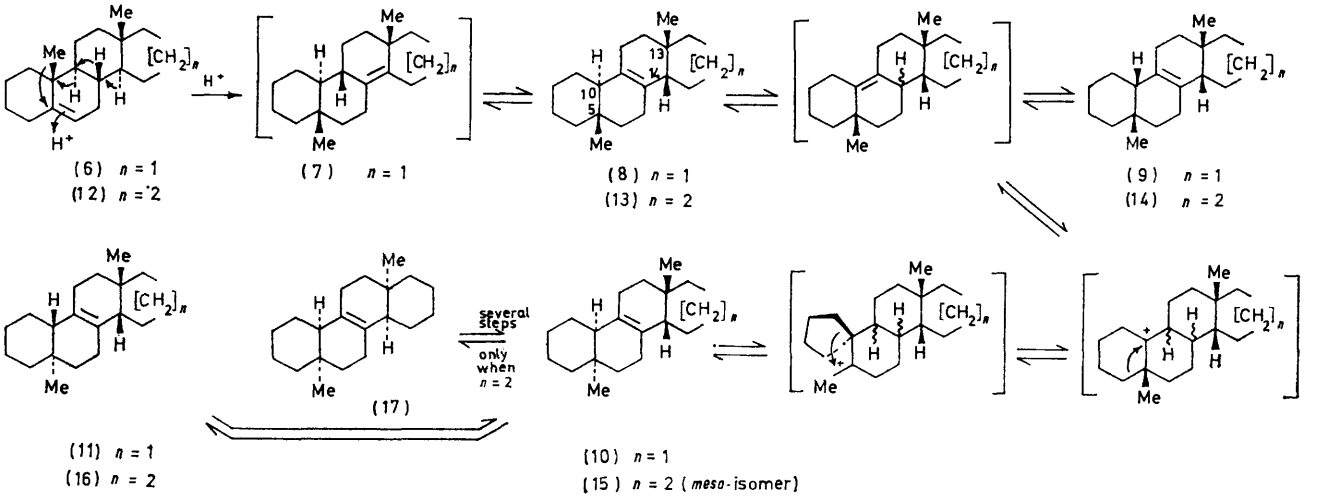
Androst-5-ene (6) *and* D-*Homoandrost-5-ene* (12).—Androst-5-ene (6) was reported [9] to rearrange with HCl in refluxing ethanol to give the 5β-methyl-19-nor-$\Delta^{8(14)}$-compound (7), although no evidence was given in support of that structure. We find that reaction of androst-5-ene in refluxing acetic acid with toluene-*p*-sulphonic acid gives a mixture containing three major olefinic products with $\Delta^{8(9)}$-structures (8)—(10). The compounds differ only in their configurations at C-5 and C-10. A $\Delta^{8(14)}$-structure was ruled out [2] on the basis of n.m.r. spectra, and for isomers (8) and (9) by the formation of 8,9-seco-8,9-diketones ($\nu_{max.}$ 1 710 cm^{-1}) by oxidative cleavage with osmium tetraoxide followed by lead tetra-acetate, or in a single step by use of ruthenium tetraoxide. Other data supporting the $\Delta^{8(9)}$-structure have already been summarized,[2] and are detailed in the Experimental section.

The order in which the three major olefinic products appeared, and their relative proportions, are consistent with the structures illustrated in Scheme 1. Product (8) appeared first, but was soon followed by isomer (9) (g.l.c.). By the time no more androst-5-ene remained (20 g) (8) and (9) were present in the ratio *ca.* **3 : 7**. With a longer reaction time, isomer (10) became detectable after 45 h. The mixture attained a constant composition between 180 and 260 h [(8), (9), and (10) in the ratio **10 : 43 : 47**]. Pure samples of olefins (8) and (9) were obtained by preparative g.l.c. Isomer (10) was not wholly separated from (9), and its properties were inferred from those of mixtures of (9) and (10). The n.m.r. characteristics were very similar to those of isomer (9), and compounds (9) and (10) were obviously of equal stability, from the composition of the equilibrated mixture. The similarity of chemical shifts of the angular methyl groups (Table 1) implied similar electronic environments, suggesting that the product (10) was a

[3] R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.
[4] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1969, **25**, 149.
[5] D. N. Kirk and P. M. Shaw, *J. Chem. Soc.* (*C*), 1971, 3979.
[6] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1966, **22**, 3195.
[7] S. Ricca, B. Rindone, and C. Scolastico, *Gazzetta*, 1969, **99**, 1284.
[8] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Letters*, 1966, 2125; J. M. Coxon, M. P. Hartshorn, G. A. Lane, K. E. Richards, and U. M. Senanayake, *Steroids*, 1969, **14**, 441.
[9] J. Bascoul, B. Cocton, and A. Crastes de Paulet, *Tetrahedron Letters*, 1969, 2401.

third Δ^8-compound. Consideration of possible mechanistic pathways for the further rearrangement of isomers (8) and (9) led to the conclusion that compound (10) must be the 5α,10α,14β-isomer, formed *via* the spiro-cation depicted in Scheme 1. Isomer (11) would also be expected as a *minor* product, but was not identified.

Each step in Scheme 1 has precedent, or is closely similar to a known reaction. The 14β-configuration of each Δ^8-product, which relieves some of the strain initially present in the CD-*trans*-ring junction,[10] received support from mass spectra (Experimental section) and n.m.r. data (Table 1). The 13β-methyl resonances, in the range τ 9.07—9.10, are close to the value observed [11] for 14β-androstanes (τ 9.01), the small upfield shift corresponding to the known effect of 8,9-unsaturation.[11] Recent work by other groups, using substituted androst-5-enes,[12] and also our own study of androst-5-en-17-one (below), have led to similar findings regarding configuration at the CD ring junction. Furthermore 14α-hydroxy-5α-androstan-3-one has been reported to give 5α,14β-androst-8-en-3-one on heating with formic acid.[13] It is now clear that the 14β-androst-8-ene system represents a particularly stable arrangement for rings C and D in the absence of a 17β-side-chain.



SCHEME 1

TABLE 1

N.m.r. data for products derived from androst-5-ene and D-homoandrost-5-ene (τ values; solvent $CDCl_3$; Me_4Si as internal standard).

	5β-Me	13β-Me	Others
Products from isomerisation of androst-5-ene			
5β,10α,14β-8-Ene (8)	9.23	9.10	
5β,10β,14β-8-Ene (9)	9.16	9.07	
5α,10α,14β-8-Ene (10)	9.14	9.07	
14-Ene (18)	9.175	9.08	4.80 (14-H)
5β,10α,14β-8α,9α-Diol from olefin (8)	9.07 (Δ_P −0.03) [a]	8.91 (Δ_P −0.03) [a]	
5β,10α,14β-8β,9β-Diol from olefin (8)	9.29 (Δ_P −0.25) [a]	8.91 (Δ_P −0.31) [a]	
5β,10β,14β-8α,9α-Diol from olefin (9)	9.07 (Δ_P −0.02) [a]	8.98 (Δ_P −0.03) [a]	
8,9-Seco-5β,10α,14β-8,9-dione from olefin (8)	9.01	8.92	
8,9-Seco-5β,10β,14β-8,9-dione from olefin (9)	9.04	8.98	
Oxidation products of olefin (9)			
5β,10β,14β-8-En-11-one [b]	9.23	8.99	
5β,10β,14β-8-En-7-one [b]	9.08	9.08	
5β,10β,14β-8-Ene-7,11-dione	9.10	8.97	7.90, 7.73, 7.58, 7.25 [c]
Products from isomerisation of D-homoandrost-5-ene			
D-Homo-5β,10α,13β,14β-8-ene (13)	9.22	9.18	
D-Homo-5β,10β,13β,14β-8-ene (14) [or racemate, (14) + (17)]	9.17	9.17	
D-Homo-5α,10α,13β,14β-8-ene (15)	9.17	9.17	

[a] Δ_P is the solvent shift in C_5D_5N [$\tau(C_5D_5N) - \tau(CDCl_3)$]. [b] Tentative assignments of position of oxo-group. [c] Unassigned signals, apparently singlets, each due to one proton deshielded by the enedione system.

The chemical shift of the 5β-methyl group (τ 9.23) corresponds almost exactly with that of the 10β-methyl group in 5α-androst-6-ene [11] (τ 9.233), supporting the assignment of an AB-*trans*-configuration. A downfield shift of the 5β-methyl resonance in changing from the *trans*-

[10] C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, 1968, **24**, 13; N. L. Allinger and M. T. Tribble, *Tetrahedron*, 1972, **28**, 1191, and references therein.

[11] N. S. Bhacca and D. H. Williams, 'Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, pp. 19 *et seq.*

[12] F. Frappier, M. Pais, and F.-X. Jarreau, *Bull. Soc. chim. France*, 1972, 610; F. Frappier, J. Boivin, and F.-X. Jarreau, *Compt. rend.*, 1972, **274C**, 2190.

[13] L. Mamlok, *Bull. Soc. chim. France*, 1967, 3827.

to the *cis*-ring junction (Table 1) is also in accord with data for normal steroids.[11] Differences in g.l.c. retention times on a cholesteryl ester column (Table 2) further

TABLE 2

G.l.c. data for androst-5-ene, D-homoandrost-5-ene, and derived compounds

Retention times relative to 5α-androstane (≡ 1.00); temperature 180 °C

	CHPB [a, b]	SE30 [b]
Androstane series		
Androst-5-ene	1.04	
Androst-4-ene	0.88	
5β,10α,14β-8-Ene (8)	0.69	0.795
5β,10β,14β-8-Ene (9)	0.47	0.61
5α,10α,14β-8-Ene (10)	0.52	0.635
14-Ene (18)	0.80	
		QF1 [b]
8-En-11-one		3.85
8-En-7-one		4.10
8-Ene-7,11-dione		6.40
D-Homoandrostane series		
D-Homoandrost-5-ene (12)	1.855	
D-Homoandrost-4-ene	1.54	
D-Homo-5β,10α,13β,14β-8-ene (13)	1.21	
D-Homo-5β,10β,13β,14β-8-ene (14)	0.745	
D-Homo-5α,10α,13β,14β-8-ene (15)	0.845	

[a] CHPB = cholesteryl *p*-phenylbenzoate. [b] Stationary phase.

support the AB-*cis*-configuration of isomers (9) and (10), their retention times being notably less than that of the AB-*trans*-isomer (8), as the consequence of a more folded molecular shape.[5]

Direct proof of structure (10) seemed difficult, but support came from a study of D-homoandrost-5-ene (12), which suffered a similar sequence of rearrangements. The symmetry characteristics of $\Delta^{8(9)}$-structures in the D-homo-series result in identical isomerisations at the AB and CD ring junctions, and afford, at equilibrium, a racemic mixture of the 5β,10β,13β,14β-isomer (14) and the 5α,10α,13α,14α-isomer (17), together with a similar mixture of AB-*trans*,CD-*cis*-products (13) and (16) in smaller quantities, and accompanied by the *meso*-(5α,10α,13β,14β-) isomer (15). As a consequence, the equilibrated mixture was devoid of both optical activity and c.d. between 700 and 185 nm, and comprised isomer (13) and its enantiomer (total *ca.* 15%), the enantiomeric pair (14) and (17) (*ca.* 40%), and the *meso*-compound (15) (30%), together with *ca.* 15% (total) of two unidentified isomers. Even more significantly, the fraction containing the 'all-*cis*-' enantiomers (14) and (17) was optically active if it was isolated from a reaction mixture which had *not* reached equilibrium, when the first-formed enantiomer (14) would be expected to predominate, but was optically inactive at equilibrium. In contrast, the *meso*-compound (15) was always optically inactive, even when isolated after only a relatively short reaction time, and while it was present in only a small proportion. The identification of the *meso*-isomer was thus unambiguous, and was helped by its ready crystallisation; all other isomers were obtained only as oils.

Further evidence for the symmetry of Δ^8-compounds of this D-homo-series came from their n.m.r. spectra (Table 1). Both the *cis,cis*-isomers (14) and (15) exhibited unusually simple spectra, the 5- and 13-methyl proton signals being coincident in each compound, and identical in chemical shift for both compounds. The non-symmetrical isomer (13), in contrast, exhibited two distinct methyl proton signals, consistent with the *trans*- and *cis*-configurations, respectively, of its two saturated ring junctions. The u.v. and n.m.r. characteristics of the various products in the androstane and D-homo-androstane series showed all the similarities required to confirm the close parallel between the two series of products, and thence the structures of the isomers of androst-5-ene.

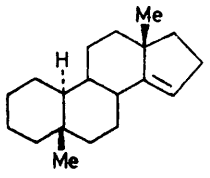
Use of other acidic catalysts. In view of the earlier report [9] that the 8(14)-ene (7) had been obtained by isomerisation of androst-5-ene with HCl–ethanol, we carried out a similar reaction and found that the product after 72 h consisted of unchanged androst-5-ene (50%) together with a mixture of the 5β,10α-$\Delta^{8(9)}$-compound (8) and the 5β,10β-isomer (9) in the ratio 1 : 9. The only obvious difference between the behaviours of toluene-*p*-sulphonic acid–acetic acid and HCl–ethanol lies in the more rapid isomerisation of (8) to (9), compared with the rate of formation of (8), when the latter reagent system was used.

Trifluoroacetic acid, with triphenylsilane in dichloromethane, has been reported to isomerise cholest-5-ene to give a mixture of the (20*R*)- and (20*S*)-$\Delta^{13(17)}$-compounds (1) and (2).[14] We found that omission of triphenylsilane did not alter the course of rearrangement, which proceeded rapidly at room temperature. Androst-5-ene in dichloromethane was also isomerised rapidly by trifluoroacetic acid to give a mixture of the same $\Delta^{8(9)}$-compounds (Scheme 1) as from the acidic reagents used previously. In both the cholest-5-ene and the androst-5-ene isomerisations, however, the i.r. spectrum of the crude product prior to chromatography revealed the presence of trifluoroacetates derived from the steroid, as well as free olefins. These trifluoroacetates decomposed to give olefins during chromatography (g.l.c., or solid–liquid).

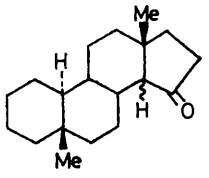
When the isomerisation of androst-5-ene with trifluoroacetic acid was followed by withdrawing samples for g.l.c. analysis, a new olefinic product could be detected as long as the isomerisation was in progress. This new compound is tentatively formulated as the Δ^{14}-substance (18), from the following evidence. One olefinic proton was evident in its n.m.r. spectrum (Table 1), which was compatible in other respects with the Δ^{14}-structure. Hydroboration, followed by oxidation with chromic acid, afforded a carbonyl compound ($\nu_{max.}$ 1 744 cm^{-1}), for which the only likely structure is that of a 15-ketone (19). In view of evidence (below) that tertiary trifluoroacetoxy-derivatives and olefins co-exist in reacting solutions containing trifluoroacetic acid, it seems probable that the Δ^{14}-substance may result from elimination of a 14-trifluoroacetoxy-group during g.l.c. separation.

[14] F. A. Carey and H. S. Tremper, *J. Org. Chem.*, 1971, **36**, 758.

Androst-5-en-17-one (20).—This compound was chosen for study in the hope of obtaining further evidence for the 14β-configuration of the isomerised androstenes



(18)

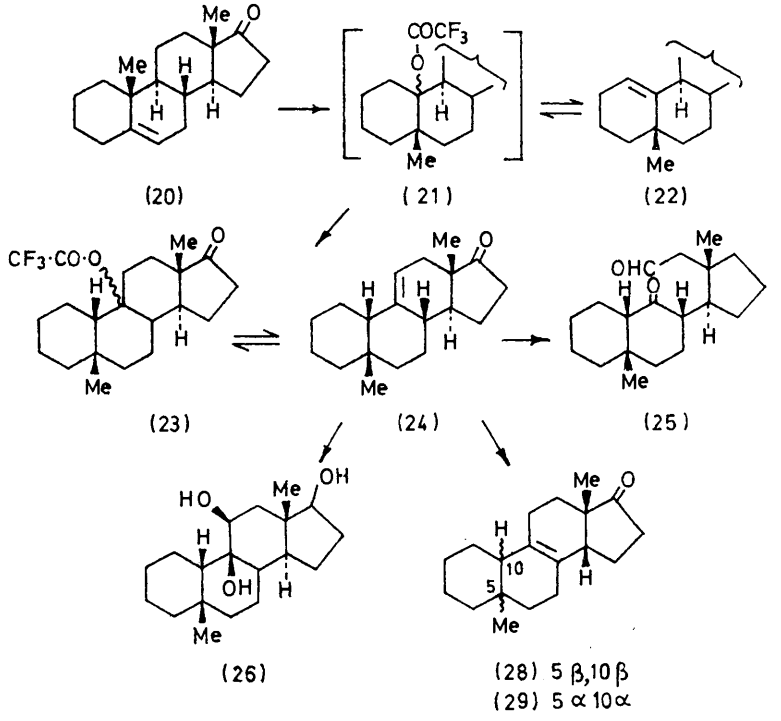


(19)

(8)—(10). The 17-oxo-group was seen as an aid to the application of c.d. and n.m.r. methods for ascertaining the configuration at the CD ring junction: deoxygenation would then allow direct correlation with the olefins.

Isomerisation of androst-5-en-17-one (20) with trifluoroacetic acid proceeded more slowly than the reactions of steroid hydrocarbons, reaching equilibrium after 4 days at room temperature. The crude product exhibited the i.r. absorption ($\nu_{max.}$ 1 780 cm^{-1}) of a trifluoroacetate, but after passage through an alumina column this i.r. band was absent. The product was then essentially one unsaturated 17-oxo-derivative ($\nu_{max.}$ 1 743 cm^{-1}), contaminated by traces of another new isomer subsequently found to be present in much larger proportion if samples were taken earlier during the reaction. The experiments described below establish the 5-methyl-5β-oestr-9(11)-en-17-one structure (24) for the final major product of isomerisation, and show that the olefin appearing at earlier stages of the reaction is probably the $\Delta^{1(10)}$-compound (22), formed wholly or in part by decomposition of an intermediate 10-trifluoroacetoxy-derivative (21) during chromatography (Scheme 2).

The $\Delta^{9(11)}$-compound (24) has one of several trisubstituted olefinic structures suggested by the i.r. spectrum [$\nu_{max.}$ 1 640 cm^{-1} (C=C str.)], and by the n.m.r. spectrum (Table 1), which revealed one olefinic proton. The chemical shifts of the 5β- and 13β-methyl protons could best be interpreted with the assumption that the olefinic bond had no significant influence, so that the $\Delta^{1(10)}$- and Δ^{14}-structures could be discounted,[11] leaving Δ^{7}- and $\Delta^{9(11)}$- as the only likely ones. The rather large carbonyl Cotton effect ($n \longrightarrow \pi^*$; $\Delta\varepsilon$ +2.5) indicated that the product still had the 14α-configuration.[15]



SCHEME 2

A decision in favour of the $\Delta^{9(11)}$- rather than the Δ^{7}-structure was reached from a study of the n.m.r. spectrum in the presence of the lanthanide shift reagent Eu(dpm)$_3$,[16] which formed a complex with the 17-oxo-group. The low-field part of the shifted spectrum contained two separate signals, each integrating for two protons. One of these signals, a triplet, was recognised from its shape [17] as being due to the C-16 protons. The other

[15] P. Crabbé, ' Applications de la Dispersion Rotatoire Optique et du Dichroisme Circulaire Optique en Chimie Organique,' Gauthier-Villars, Paris, 1968, pp. 230—237.

[16] J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, 1971, **93**, 641.

[17] J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, Sir E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1970, 250.

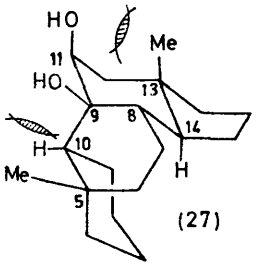
signal was a multiplet due to the C-12 protons. From a series of spectra corresponding to different proportions of $Eu(dpm)_3$, both the C-12 and the C-17 proton signals were found to lie in the low-field region of the unshifted spectrum (τ 7.9—8.2), by extrapolation to zero concentration of the reagent, implying that the protons at C-12 are allylic. Confirmation was obtained by a spin-decoupling experiment, when the C-12 proton signal in the shifted spectrum collapsed to a doublet on simultaneous irradiation at the resonance frequency of the olefinic proton at C-11. These observations are incompatible with a Δ^7-structure.

The n.m.r. spectrum did not provide convincing evidence as to the configuration of the 9(11)-en-17-one (24) at C-10, but the 10β-configuration (AB-*cis*) seemed probable from the reported 10β-configuration of a $\Delta^{9(11)}$-substance obtained by isomerisation of 'Westphalen's diacetate'.[18] Moreover, molecular models show that ring B would have to adopt a boat conformation in the 10α-configuration, whereas both rings A and B can assume chair conformations in the 10β-isomer, the molecule then having the normal conformation of a 5β-steroid. Supporting though not conclusive evidence for the 10β-configuration of compound (24) was obtained by deoxygenation at C-17 (Huang-Minlon) to give the $\Delta^{9(11)}$-compound, followed by oxidation with ruthenium tetraoxide in neutral solution. The resulting crude 9,11-seco-keto-aldehyde (25) exhibited a weakly negative Cotton effect; this could be compatible with a *cis*-1-decalone formulation for rings A and B,[19] but was contrary to expectation for the 10α-(*trans*-)configuration which would result in a strongly negative Cotton effect, particularly since the expected 8β(H)-configuration would force the ring D fragment to occupy an α-axial position in a negative octant (any contribution from the aldehyde group should be minimal, as the CH_2·CHO system would not be conformationally rigid). Acidic treatment converted the keto-aldehyde (25) into an isomer with longer retention time (g.l.c.), probably as a result of inversion of configuration at C-8 and/or C-10, but the quantity available was too small for detailed study.

Hydroxylation of the 9(11)-en-17-one with osmium tetraoxide, followed by reduction of the osmate with lithium aluminium hydride, gave a single product believed to be the 9β,11β,17β-triol (26) on the basis of large solvent shifts observed when the n.m.r. spectrum in deuteriopyridine was compared with that in deuteriochloroform. Signals due to both the 5β- and 13β-methyl groups showed large downfield shifts in deuteriopyridine, providing evidence of close proximity of hydroxy-groups [7] which are therefore assigned the β-configuration. A Dreiding model (27) showed that β-hydroxylation would be strongly preferred if the 9(11)-en-17-one has the 10β-configuration, but α-hydroxylation would be at least as favourable in the 10α-isomer.

The structure of the compound believed to be the 1(10)-en-17-one (22) is less firmly established. The n.m.r. spectrum showed the compound to possess a trisubstituted olefinic bond which was so placed as to deshield the 5β-methyl group significantly,[11] while having little if any effect on the C-18 protons. The only structure having these features and likely to appear at an intermediate stage in the isomerisation leading to the 9(11)-en-17-one (24) is the 1(10)-en-17-one (22).

To gain further information on the role of trifluoroacetic acid in the isomerisation, the reaction of androst-5-en-17-one was followed by n.m.r. study of the reacting



(27)

solution (in $CDCl_3$–CF_3·CO_2H). For comparison, the 9(11)-en-17-one (24) was subjected to the same treatment. After 8 and 5 days, respectively, the spectra were identical, and the integrated intensity of the olefinic proton signal was only about half that expected on the basis of an unsaturated ketone with a trisubstituted olefinic bond. Taken together with the i.r. evidence that trifluoroacetoxy-steroidal materials were present in crude reaction products, this result implies that the olefin (24) and its trifluoroacetic acid addition product (23) are in equilibrium (*ca.* 1 : 1) under the reaction conditions. The normal isolation and purification procedure causes elimination, to give only the olefinic product. We therefore consider the 1(10)-en-17-one (22) as likely to be in similar equilibrium with a 10(β?)-trifluoroacetate (21), and the 9(11)-en-17-one (24) with a 9-trifluoroacetate (23), of uncertain configuration at C-9.

When the isomerisation was carried out with deuteriotrifluoroacetic acid (CF_3·CO_2D) the isolated 9(11)-en-17-one (24) had incorporated up to eight atoms of deuterium, excluding any deuterium incorporated at C-16 and lost during work-up and chromatography. The n.m.r. spectrum showed no significant change in signals due to angular methyl groups but some loss in intensity of the C-11 olefinic proton signal. Deuterium atoms are probably incorporated by stepwise addition–elimination of trifluoroacetic acid as the rearrangement proceeds, *via* a series of olefinic intermediates. The nine most accessible sites for introduction of deuterium in this way are positions 1α, 1β, 4α, 4β, 6α, 6β, 8β, and 10β, and C-11, but the predominant presence of the [$^2H_5$]-species (Experimental section) showed that rearrangement occurs too rapidly to allow complete labelling at all these sites.

An attempt to isomerise androst-5-en-17-one with acetic acid–toluene-*p*-sulphonic acid led to equilibration of Δ^4- and Δ^5-isomers (*ca.* 3 : 2) at 80 °C, but at reflux temperature caused destruction of most of the steroid (g.l.c.). Methanolic sulphuric acid (1 : 1, at 40 °C), in

[18] H. Aebli, C. A. Grob, and E. Schumacher, *Helv. Chim. Acta*, 1958, **41**, 774.
[19] D. N. Kirk and W. Klyne, *J.C.S. Perkin I*, 1974, 1076.

contrast, caused rearrangement to give a mixture of two new isomers, in 1 : 1 ratio at equilibrium. The same pair of new compounds resulted when the 9(11)-en-17-one (24) was subjected to this treatment.

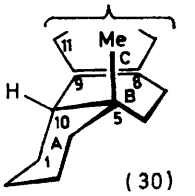
The new products were identified as the 5-methyl-14β-oestr-8-en-17-ones (28) and (29), isomeric at C-5 and C-10 (both having a *cis*-AB-ring junction). The 14β-configuration was indicated by a *small* positive Cotton effect ($n \longrightarrow \pi^*$) [15] for each compound, and by the virtual absence of a solvent shift of the C-18 proton n.m.r. signal between solutions in deuteriochloroform and deuteriobenzene. U.v., i.r., and n.m.r. spectra of the two new compounds were almost identical, and confirmed the tetrasubstituted-olefinic 17-oxo-structure. Oxidative cleavage of the olefinic bonds gave ketonic products with characteristics compatible with the 8,9-seco-8,9-diketone structure, and removal of the 17-oxo-group from the 8-en-17-ones by the Huang-Minlon procedure afforded products identical (g.l.c., n.m.r., mass spectra) with the previously prepared 8-enes (9) and (10).

Androst-5-en-17β-ol.—Treatment of androst-5-en-17β-ol with toluene-*p*-sulphonic acid–acetic acid at *ca.* 120 °C for 4 h gave two products in the ratio 5 : 1. I.r. spectra showed these to have been acetylated at C-17, and they were identified as the 17β-acetoxy-14β-androst-8(9)-ene derivatives corresponding to the 17-oxo-compounds (28) and (29), by removal of the acetate ($LiAlH_4$) and oxidation (Jones reagent), which afforded products indistinguishable from the 14β-8(9)-en-17-ones obtained from androst-5-en-17-one by the action of methanolic sulphuric acid.

DISCUSSION

From results given here, and reports elsewhere, it is clear that acid-catalysed rearrangements of suitable androstanes and D-homoandrostenes allow successive structural changes leading eventually to products rich in $\Delta^{8(9)}$-compounds, with the *cis*-configuration preferred at the AB and CD ring junctions. The products should strictly be classified as 5-methyl-14β-oestr-8-enes and 5-methyl-D-homo-oestr-8-enes, having in all cases suffered ' Westphalen-like ' migration of the 10β-methyl group to C-5. In the D-homo-series, the AB and CD parts are structurally identical, and undergo identical and almost independent equilibration of configurations at C-5, -10, -13, and -14, leading to a mixture containing all possible combinations of AB-*cis*- and CD-*cis*-configurations in the major products. The various 5-methyl-14β-oestr-8-enes with an ordinary five-membered ring D are equilibrated only at the AB ring junction, probably because the spirocation intermediate (*cf.* Scheme 1) necessary for inversion at C-5 is reasonably stable, whereas an analogous spirocation at the CD ring junction would require temporary contraction of ring D to a cyclobutane, with an unacceptable increase in strain. Evidently the *cis,cis*-Δ^8-structures are the most stable ones accessible through a multiple Wagner–Meerwein rearrangement process in which the essentially steroid-like molecular framework is retained.

The reason for the preference for *cis*-fusion of terminal rings in the Δ^8-compounds is clear from a study of Dreiding models. With ring B in the half-chair conformation required to minimise torsional (1,2) interactions, a *trans*-fusion of rings A and B forces C-1 to lie close to C-11, so that some degree of steric compression between these methylene groups is unavoidable. A *cis*-fusion of rings A and B, particularly in the ' non-steroid-



(30)

like ' conformation (30) wherein the 5β-methyl group, and the C(10)–C(1) bond are both axial to ring B, relieves the compression between C-1 and C-11. The total number of ' skew-butane ' interactions involving rings A and B and the 5β-methyl group is three for either the *cis*- or the *trans*-isomer. The experimental data suggest that the *cis*-ring junction is the more stable by *ca.* 1 kcal mol^{-1}, entirely consistent with the C-1,C-11 interaction being the decisive one.

The subtlety of the balance of steric and conformational strains which decides the relative stabilities of backbone-rearranged steroids is emphasised by the contrast between compounds of the androstene class, which favour the $\Delta^{8(9)}$-structures discussed here, and the rearranged cholestenes which prefer the $\Delta^{13(17)}$-structure, providing relief of torsional strain associated with the 17β-side chain.[9] The early impression that ring strain associated with the *trans*-fusion of rings C and D provides an essential ' driving force ' for rearrangement is no longer acceptable in view of the ready backbone isomerisation of D-homoandrost-5-ene.

Although the three acidic reagents employed in this work are all capable of equilibrating the steroidal olefins, trifluoroacetic acid is unusual in causing only incomplete isomerisation of androst-5-en-17-one. The n.m.r. demonstration that some olefinic product is always present in equilibrium with a trifluoroacetoxy-steroid precludes an explanation based upon irreversible trapping of an intermediate carbocation (at C-9) by the trifluoroacetic acid. We therefore suggest that the 17-oxo-group, by its polar effect, opposes the migration of the cationic centre towards ring D, required for generation of the 14β-isomer, although sulphuric acid is capable of achieving this key step. The $\Delta^{8(9)}$-structure seems to represent an energy minimum only for 14β-androstene derivatives, for when the material remains in the 14α-configuration the preferred location for unsaturation is the 9,11-position. This phenomenon may be analogous to the regioselectivity of unsaturation in 5α- and 5β-steroids, unsaturated about C-3.[20] The

[20] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 161—162, and references therein.

5β-(AB-*cis*-)configuration leads to a strong preference for 3,4-unsaturation, for reasons which have been discussed at length. Unsaturation in the present series of compounds has the same choice relative to the CD ring junction as unsaturation at C-3 in relation to the junction of rings A and B, so comparable control may operate in favour of the 14α-$\Delta^{9(11)}$- and the 14β-$\Delta^{8(9)}$-isomers, respectively. In no case has a $\Delta^{8(14)}$- or a Δ^{14}-isomer been found as the final stable product of backbone rearrangement. Cholest-14-ene, the product resulting from double-bond migration in the 7-ene or the 8,14-ene,[21] lies outside this generalisation because it retains the normal ' backbone ' structure and stereochemistry.

EXPERIMENTAL

G.l.c. analyses were carried out with a Hewlett–Packard 402 or Pye 104 gas-chromatograph, on columns of 1% cholesteryl *p*-phenylbenzoate (CHPB) on 80—100 mesh Chromosorb W (AW–DMCS), and with 3.8% SE30, or 3.8% QF1, each on 80—100 mesh Diatoport S. Preparative g.l.c. was performed on a Pye 105 gas chromatograph. C.d. curves (Roussel–Jouan Dichrographe II) were determined by Mrs. W. P. Mose or Mr. R. J. Mullins. T.l.c. was carried out on Merck Kieselgel G_{254}, with detection by iodine vapour. N.m.r. spectra were run at 100 MHz unless otherwise stated, in the solvent indicated: Δ_P refers to the shift in τ value on adding 10% of C_5D_5N; Δ_B is the shift on adding 10% C_6D_6.

Isomerisation of Cholest-5-ene.—(*a*) The reaction in acetic acid–toluene-*p*-sulphonic acid was carried out essentially as described in ref. 4, except that reflux temperature (*ca.* 117 °C) was maintained for 16 h; g.l.c. then showed that equilibrium had been reached. The extracted product was an oil comprising the (20*R*)- and (20*S*)-$\Delta^{13(17)}$-products (1) and (2) in 1 : 1 ratio, together with *ca.* 15% of other non-polar products (g.l.c.). Preparative g.l.c. (7 ft column; 6% SE30 on 60—70 mesh Anakrom ABS, at 210 °C) gave pure samples (*ca.* 20 mg) of olefins (1) and (2). Retention times on analytical columns at 220 °C relative to 5α-cholestane (= 1.00) were: (on SE30) (20*R*)-olefin (1), 0.56; (20*S*)-olefin (2), 0.46: (on CHPB) (1), 0.215; (2), 0.15.

(20*R*)-5,14-*Dimethyl*-18,19-*bisnor*-5β,8α,9β,10α,14β-*cholest*-13(17)-*ene* (1) was a gum, $\lambda_{max.}$ (hexane, 1 mm cell) 197 nm (ε 11 600); $\nu_{max.}$ (CS_2) 1 375, 1 362, 1 210, 1 169, 1 145, 1 125, 952, 930, and 833 cm^{-1}; Δε (hexane) −9.5 (210 nm); τ ($CDCl_3$; 60 MHz) 9.01 (d, *J* 7 Hz, 21-H_3), 9.11 (14β-Me), 9.16 (d, *J* 6 Hz, 26- and 27-H_3), and 9.17 (s, 5β-Me); *m/e* 370 (M^+, $C_{27}H_{46}$), 355 ($M^+ - CH_3$), and 257 ($M^+ - C_8H_{17}$). The (20S)-olefin (2) was a gum, $\lambda_{max.}$ (hexane, 1 mm cell) 197 nm (ε 11 900); $\nu_{max.}$ (CS_2) similar to (1), but with an extra band at 1 200 cm^{-1}, and a more intense band at 1 362 cm^{-1}; Δε (hexane) −7.1 (210 nm); τ ($CDCl_3$; 60 MHz) 9.11 (d, *J* 7 Hz, 21-H_3), otherwise identical with the spectrum of (1); mass spectrum almost indistinguishable from that of (1).

(*b*) Trifluoroacetic acid (5 ml) was added to a solution of cholest-5-ene (20 mg) in dichloromethane (2 ml). After 10 min the mixture was poured into water, and the product was isolated with ether as a gum, comprising the $\Delta^{13(17)}$-compounds (1) and (2) in the ratio *ca.* 1 : 1 (g.l.c., n.m.r., and i.r.).

Oxidation of the Olefins (1) *and* (2).—Each olefin (30 mg) in pyridine (5 ml) was treated with osmium tetraoxide (50 mg) for 7 days. The pyridine was removed under reduced pressure, and the residue was reduced with $LiAlH_4$ (20 mg) in ether under reflux for 2 h. Conventional work-up gave the two crude 13,17-diols (3), isomeric at C-20. Both products slowly solidified on standing; (20R)-5,14-*dimethyl*-18,19-*bisnor*-5β,8α,9β,10α,14β-*cholestane*-13β,17β-*diol* had m.p. 115—128°; $\nu_{max.}$ (CCl_4) 3 620, 3 560, 1 170, 1 148, 950, 940, 900, and 860 cm^{-1}; τ ($CDCl_3$; 60 MHz) 9.05, Δ_P −0.28 (s, 14β-Me), 9.12, Δ_P −0.23 (d, *J* 6 Hz, 21-H_3), 9.17, Δ_P 0.00 (d, *J* 6.5 Hz, 26- and 27-H_3), and 9.22, Δ_P 0.00 (s, 5β-Me). The (20S)-*derivative* had m.p. 85—117°, $\nu_{max.}$ (CCl_4) similar to that of the (20*R*)-isomer but lacking bands at 940 and 860 cm^{-1}; τ ($CDCl_3$; 60 MHz) 9.04, Δ_P −0.27 (s, 14β-Me), 9.07, Δ_P +0.02 (d, *J* 6 Hz, 21-H_3), 9.17, Δ_P −0.03 (d, *J* 6.5 Hz, 26- and 27-H_3), and 9.22, Δ_P 0.00 (s, 5β-Me).

Cleavage of the 13,17-*Diols with Lead Tetra-acetate.*—Each diol (20 mg) in t-butyl alcohol (2.2 ml) and acetic acid (2.2 ml) was treated with lead tetra-acetate (160 mg) for 18 h at room temperature. A few drops of ethanediol were then added to destroy the excess of reagent, and the mixture was poured into water. Extraction with ether afforded the 13,17-seco-13,17-diketones as gums, $\nu_{max.}$ 1 710 cm^{-1}. (20R)-5,14-*dimethyl*-18,19-*bisnor*-13,17-*seco*-5β,8α,9β,10α,-14β-*cholestane*-13,17-*dione* (4) showed τ ($CDCl_3$; 60 MHz) 8.93, Δ_B +0.36 (s, 14β-Me), 8.96, Δ_B 0.00 (d, *J* 7 Hz, 21-H_3), 9.15, Δ_B +0.06 (s, 5β-Me), and 9.16, Δ_B 0.00 (d, *J* 6 Hz, 26- and 27-H_3); Δε (dioxan) +0.54 (303 nm). The (20S)-*derivative* (5) showed n.m.r. data ($CDCl_3$) as the (20*R*)-isomer except τ 9.14, Δ_B +0.08 (s, 5β-Me); Δε (dioxan) +0.79 (298 nm).

The diketones were distinguishable from their g.l.c. behaviour: (20R), t_R 0.93; (20*S*), t_R 0.89 (on CHPB at 200 °C, relative to 5α-cholestane, t_R 1.00); g.l.c. on SE30 did not separate them.

Equilibration of the 13,17-seco-diketones at C-20 was achieved by heating each (20 mg) under reflux with acetic acid (3 ml), cyclohexane (1 ml), and toluene-*p*-sulphonic acid (100 mg), after allowing the cyclohexane to distil out to remove water. After 2 h each mixture had reached a 20*R* : 20*S* composition of 1 : 1 (g.l.c.).

Isomerisation of Androst-5-ene (6).—(a) *With acetic acid–toluene*-p-*sulphonic acid.* Androst-5-ene (200 mg) and toluene-*p*-sulphonic acid (500 mg) in acetic acid (32 ml) and cyclohexane (8 ml) were heated under reflux (85—88 °C) for 4 h; equilibrium had then been reached between the 5-ene and the 4-ene (ratio *ca.* 2 : 3; g.l.c.). The cyclohexane was then allowed to distil out until the temperature reached 117 °C, and refluxing was continued while samples were taken at intervals for g.l.c. analysis (see text, and Table 2). After heating for 260 h the equilibrated olefinic products [mainly (8)—(10), ratio 10 : 43 : 47], were isolated by use of ether, which afforded a gum. Passage in light petroleum through a short column of alumina removed coloured and polar by-products.

Similar experiments were carried out with interruption after shorter times, determined by g.l.c. analysis, for the convenient isolation of the intermediate olefins (8) and (9). The gums were separated into their component olefins by preparative g.l.c. (7 ft column; 6% SE30; 160 °C; with auto-injection of 3—3.5 mg samples, each in 300—350 μl of ether). A typical run using the olefin mixture from a 3 h reaction (185 mg), containing olefins (8) (35%) and (9) (44%), afforded pure (8) (53.5 mg) and pure (9) (62 mg) as gums.

[21] J. C. Eck and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 2986.

5-*Methyl*-19-*nor*-5β,10α,14β-*androst*-8-*ene* (8) showed $\nu_{max.}$ (film) 1 370, 1 346, 1 328, 1 264, 1 217, 1 185, 1 150, and 980 cm^{-1}; $\lambda_{max.}$ (hexane, 1 mm cell) 197 nm (ε 7 500); Δε (hexane) −2.74 (216 nm); for n.m.r. see Table 1; *m/e* 258 (M^+, $C_{19}H_{30}$), 243 ($M^+ - CH_3$), 175, 161, 147, 133, and 121. The 10β-*isomer* (9) showed $\nu_{max.}$ (film) 1 372, 1 355, 1 265, 1 220, 1 210, 1 160, 990, and 950 cm^{-1}; $\lambda_{max.}$ (hexane, 1 mm cell) 197 nm (ε 8 100); Δε (hexane) −2.04 (210 nm); for n.m.r. see Table 1; mass spectrum virtually indistinguishable from that of (8).

The 5α,10α-isomer (10) was not wholly separated from compound (9). The i.r. spectrum of the mixture rich in (10) was almost identical with that of (9), but contained an extra band at 1 103 cm^{-1}, attributed to (10), whereas the band at 1 160 cm^{-1} was much reduced in intensity. For g.l.c. and n.m.r. data see Tables 1 and 2.

(b) *With hydrogen chloride–ethanol.* Androst-5-ene (20 mg) in ethanol (3 ml) saturated with hydrogen chloride was heated under reflux for 72 h. After neutralisation (NaOH) the products were extracted with ether and analysed by g.l.c., which showed the presence of the olefins (8) and (9) in the ratio 1 : 9, together with androst-5-ene (50%).

(c) *With trifluoroacetic acid.* Androst-5-ene (20 mg) and trifluoroacetic acid (5 ml) in dichloromethane (2 ml) were allowed to react for 10 min, and the product was isolated by adding ether and washing with water. The crude product, in light petroleum, was passed through a short column of alumina, and afforded an oil comprising essentially the olefins (8) and (9) in the ratio 1 : 9 (g.l.c.).

A similar reaction interrupted after 1—2 min afforded a crude product showing the i.r. absorption of a trifluoroacetate ($\nu_{max.}$ *ca.* 1 775 and 1 280 cm^{-1}). Passage through alumina gave a mixture of olefins which included the Δ^{14}-isomer (18) as well as (8) and (9). Preparative g.l.c. (4% Apiezon L; 180 °C) separated the Δ^{14}-isomer (18) in *ca.* 94% purity, as a gum, $\nu_{max.}$ (CS_2) 1 645, 1 200, 1 170, 1 143, 1 120, 1 075, 1 038, 998, 980, 950, 940, 932, 920, and 795 cm^{-1}; for n.m.r. see Table 1.

This product was characterised by hydroboration of a sample (3 mg) in ether (2 ml) containing $LiBH_4$ (10 mg). The mixture was stirred at 0 °C under nitrogen while boron trifluoride–ether complex (50 μl) in ether (250 μl) was added in portions over 40 min. The mixture was stirred for 2 h, then water (100 μl) was added, followed by 8N-chromic acid (Jones' reagent; 2 drops). The mixture was heated under reflux for 2 h, then the product was extracted with ether, as an oil (1.4 mg), $\nu_{max.}$ (CCl_4) 1 744 cm^{-1}. A 15-oxo-structure (19) is assigned to this product, which was not studied further.

Oxidative Cleavage of the 8,9-*Olefins* (8) and (9).—(a) *With osmium tetraoxide followed by lead tetra-acetate.* The separated olefins were treated with OsO_4 in pyridine, followed by $LiAlH_4$, as described above for the 13,17-olefins (1) and (2), to give the corresponding crude 8,9-diols. The diol obtained from the *cis,cis*-olefin (9) was apparently a single isomer (g.l.c.), whose n.m.r. spectrum (Table 1) showed almost no shift of angular methyl signals on addition of deuteriopyridine: it is accordingly assigned the 8α,9α-diol configuration in which the hydroxy-groups are remote from the methyl groups. (Dreiding models show little strain in the 8α,9α-isomer, but excessive strain in the alternative 8β,9β-isomer, resulting from the folding of a *cis,syn,cis,-syn,cis*-conformation.)

The diol from the *trans,cis*-olefin (8) was a mixture of 8α,9α- and 8β,9β-isomers (g.l.c.; ratio *ca.* 3 : 2). The 8β,9β-isomer showed the expected large pyridine-induced shifts in the n.m.r. spectrum (Table 1), which were not observed for the 8α,9α-isomer (models show that neither isomer is unduly strained, and both sides of the 8,9-olefinic bond are reasonably accessible). Cleavage of the diols with lead tetra-acetate, as described for the cholestene derivatives (above), gave the corresponding 8,9-seco-8,9-diones. 5-*Methyl*-19-*nor*-8,9-*seco*-5β,10α,14β-*androstane*-8,9-*dione*, from the olefin (8), was an oil, $\nu_{max.}$ (CCl_4) 1 703, 1 060, and 936 cm^{-1}; *m/e* 290 (M^+, $C_{19}H_{30}O_2$), 194 ($M^+ - 96$; loss of ring A and 5β-Me), 208, 207, 179, 165, and 152; for n.m.r. see Table 1. The 8,9-*seco*-5β,10β,14β-8,9-*dione* from the olefin (9) was a solid, m.p. 40—60°, $\nu_{max.}$ 1 703, 1 100, 1 080, and 1 028 cm^{-1}, *m/e* 290 (M^+, $C_{19}H_{30}O_2$), other ions similar to those from the 10α-isomer, but with a more abundant ion at *m/e* 194; for n.m.r. see Table 1.

(b) *With ruthenium tetraoxide.* Sodium periodate (800 mg) dissolved in the minimum amount of water was added to a stirred suspension of ruthenium dioxide (200 mg) in acetone (100 ml). After 30 min a solution of the 8,9-olefins [1.7 g of a 1 : 9 mixture of (8) and (9)] in acetone (100 ml) was added during 2 h, while a solution of sodium periodate (6 g) in aqueous 50% acetone (60 ml) was added in portions to maintain the yellow colour of ruthenium tetraoxide in the solution. Finally the mixture was stirred for 17 h, then propan-2-ol (10 ml) was added to destroy the excess of reagent. The mixture was stirred for a further 2 h then filtered through Celite to collect the ruthenium dioxide, and the solvents were removed under reduced pressure. Extraction with ether gave the crude seco-diketones, $\nu_{max.}$ 1 703 cm^{-1}.

Attempts to purify the products by chromatography on silica gel led to elution of mixtures of isomers (with petroleum–benzene, 1 : 1), although early fractions were slightly enriched in the 10α-isomer.

Chromatography on deactivated alumina gave a mixture of products believed to result from internal aldol condensation of the diketone.[21] One product of uncertain structure was obtained as a solid, m.p. 50—82°, $\nu_{max.}$ (CCl_4) 3 520, 1 690, 1 140, 1 080, 1 060, and 920 cm^{-1}; τ 8.72 (s, Me) and 8.92 (s, Me). Reaction of the crude seco-diketones with KOH–MeOH at room temperature afforded a mixture of similar products, $\nu_{max.}$ 3 590 and 1 690 cm^{-1}. These compounds probably belong to the class of 'linear' steroid analogues reported recently.[21]

Allylic Oxidation of the Olefins (8) *and* (9).—(a) *With sodium dichromate–acetic acid.* In a preliminary experiment the olefins (20 mg of a 1 : 9 mixture) in benzene (1 ml) and acetic acid (2.5 ml) containing sodium dichromate dihydrate (120 mg) were heated under reflux. After 45 min, g.l.c. analysis showed the presence of the 8-en-7-one and 8-en-11-one (72% total), the 8-ene-7,11-dione (8%), and unchanged olefins (20%). Reaction for 18 h gave the mixed enones and the enedione in the ratio *ca.* 3 : 2; longer reaction caused over-oxidation with loss of recognisable products.

For preparative purposes, the pure olefin (9) (40 mg) was subjected to 16 h under reflux with reactants in the same proportions, and the ketonic products were separated by preparative g.l.c. (15% QF1 on 60—70 mesh Anakrom ABS, at 220 °C). Chromatography on alumina did not separate the products.

The monoketone fraction (5 mg) was a gum, $\nu_{max.}$ (CCl_4) 1 665 and 1 630 cm^{-1}, $\lambda_{max.}$ (EtOH) 252 nm (ε *ca.* 7 600),[22]

[22] S. Aoyama and K. Sasaki, *Chem. and Pharm. Bull. Japan*, 1970, **18**, 481, 1310.

$\Delta\varepsilon$ (EtOH) −1.54 (332 nm), +4.34 (250 nm), and −2.17 (218 nm). The n.m.r. spectrum (Table 1) showed the presence of two components in the ratio *ca.* 1 : 2, the major and minor products being tentatively assigned the 7-oxo- and 11-oxo-structures, respectively, on the basis that the 13β-methyl groups should be more deshielded by the 8-en-11-one than by the 8-en-7-one system, whereas the reverse would be expected for the 5β-methyl signal.[11] G.l.c. likewise indicated two components, in the ratio *ca.* 1 : 2, although the peaks were poorly resolved.

The 8-ene-7,11-dione (4.5 mg) solidified (yellow); m.p. 67—85°, $\nu_{max.}$ (CCl_4) 1 680 cm^{-1}, $\lambda_{max.}$ (EtOH) 270 nm (ε 5 150),[22] $\Delta\varepsilon$ −0.77 (416 nm), −0.43 (330 nm), +1.89 (264 nm), and −1.21 (212 nm), *m/e* 286 (M^+, $C_{19}H_{26}O_2$); for n.m.r. see Table 1.

A similar oxidation of the olefin (8) (40 mg) gave a complex mixture of products, most of them more polar than the enones and enedione from the olefin (9). G.l.c. analysis indicated the presence of a small amount of the monoketonic products, and preparative g.l.c. afforded two small fractions with $\lambda_{max.}$ 251 nm (ε *ca.* 4 000) and 244 nm (ε *ca.* 9 600), respectively. The products were not further characterised.

(b) *With N-bromosuccinimide–aqueous dioxan.*[23] The olefins (8) and (9) (1 : 9 mixture; 20 mg) in aqueous 5% dioxan (3 ml) were stirred with calcium carbonate (14 mg, powder) and *N*-bromosuccinimide (35 mg), during irradiation with a tungsten lamp. G.l.c. analysis of samples revealed gradual formation of the 8-ene-7,11-dione, apparently *via* intermediates which did not include the 8-en-7-one or 8-en-11-one and so seem likely to be bromination products or alcohols. After 16 h the product contained only 18% of the enedione so further *N*-bromosuccinimide (75 mg) was added, and the reaction was continued for another 16 h, giving the crude 8-en-7,11-dione (13.4 mg) as the only product isolated. Attempts to repeat the reaction on a larger scale were unsuccessful, the yield of enedione being much reduced.

D-*Homoandrost-5-ene* (12).—This olefin, m.p. 112—113° (from acetone), was prepared [24] by a conventional route (Huang-Minlon reduction, followed by reaction with thionyl chloride to give 3β-chloro-D-homoandrost-5-ene, and reduction with sodium–ethanol) from 3β-hydroxy-D-homoandrost-5-en-17a-one.[25]

Isomerisation of D-*Homoandrost-5-ene* (12).—The isomerisation in acetic acid–toluene-*p*-sulphonic acid was carried out as described for androst-5-ene. Equilibrium between structural isomers was reached after 45 h at reflux temperature (g.l.c.), but the mixed products after reaction for 45 or 70 h retained some optical activity ($[\alpha]_D$ +24° after 45 min; +10° after 70 h in $CHCl_3$). Reaction for 1 week gave a product with no measurable optical activity. The equilibrium mixture of structural isomers corresponded to *ca.* 15% of the 5β,10α,13β,14β-Δ^8-isomer (13) with its enantiomer, *ca.* 40% of the 5β,10β,13β,14β-Δ^8-isomer (14) with its enantiomer (17), and *ca.* 30% of the 5α,10α,13β,14β-Δ^8-isomer (15) (*meso*), together with two unidentified olefins in small amounts. Products, in light petroleum, were freed from polar and coloured impurities by passage through a short column of alumina.

5-*Methyl*-D-*homo*-19-*nor*-5α,10α,14β-*androst*-8-*ene* (15) was obtained from the product of a 70 h reaction by crystallisation from acetone; m.p. 130—135°; $\lambda_{max.}$ 198 nm (ε 6 700) (hexane; 1 mm cell), no c.d. from 700 to 185 nm; $\nu_{max.}$ (KBr) 1 465, 1 451, 1 432, 1 373, 1 357, 1 227, 1 207, 1 037, 1 000, 990, 970, 940, 919, 850, and 838 cm^{-1}; for n.m.r. see Table 1; *m/e* 272 (M^+, $C_{20}H_{32}$), 257, 175, 162, 147, and 121.

Other isomers were isolated from the products of 45 min or 1 week reactions by preparative g.l.c. (15% SE30 on 60—70 mesh Anakrom ABS at 200 °C). The product from a 45 min reaction gave optically active samples of the 5β,10α,13β,14β-8-ene (13) and the corresponding 10β-compound (14), each presumed to be contaminated with a little of its enantiomer. The optically inactive racemic mixture of (14) and (17) was obtained from the 1 week reaction, but was slightly contaminated with the *meso*-isomer (15) (g.l.c.). All these products were gums. The *isomer* (13) showed $\lambda_{max.}$ 200 nm (ε 6 700) (hexane, 1 mm cell); $\Delta\varepsilon$ (hexane) −1.54 (213 nm), +2.02 (191 nm); $\nu_{max.}$ (CS_2) 1 372, 1 343, 1 263, 1 214, 1 147, 980, and 940 cm^{-1}; for n.m.r. see Table 1. The *isomer* (14) and the *racemate* [(14) + (17)] showed $\lambda_{max.}$ 202 nm (ε 8 750) (hexane, 1 mm cell); optically-active sample $\Delta\varepsilon$ +0.36 (221 nm) and +7.07 (190 nm); racemate [(14) + (17)] no c.d. between 700 and 185 nm (hexane); $\nu_{max.}$ 1 373 and 940 cm^{-1}; for n.m.r. see Table 1.

Isomerisation of Androst-5-en-17-one (20).—(a) *With trifluoroacetic acid.* Trifluoroacetic acid (1 ml) was added to androst-5-en-17-one (20 mg) in dichloromethane (5 ml). The mixture became deep purple, and was left at room temperature for 4 days; the reaction was then complete (g.l.c.). The products, isolated with ether after addition of water, exhibited $\nu_{max.}$ 1 780 and 1 220 (trifluoroacetate), 1 743 [C(17)=O] and 1 640, 1 165, and 775 cm^{-1}. This material, in benzene–light petroleum (2 : 3), was passed through a short column of alumina to give the crude 9-en-17-one (24) as a gum, $\nu_{max.}$ (CS_2) 1 743 [C(17)=O], 1 640 (C=C), 1 208, 1 165, 890, 820, and 750 cm^{-1}; τ($CDCl_3$) 9.30 (s, 5β-Me), 9.18 (s, 13β-Me), 4.75 (11-H); the 13β-Me signal was shifted 0.125 p.p.m. to higher field on adding C_6D_6, but the 5β-Me signal was unaffected; $\lambda_{max.}$ *ca.* 200 nm (ε 6 200) (hexane, 1 mm cell); $\Delta\varepsilon$ +1.40sh (320 nm), +2.42 (308 nm), +2.48max (300 nm), and +2.74! (216 nm); *m/e* 272 (M^+, $C_{19}H_{28}O$), 257 ($M^+ - CH_3$), 215, 119, 109, 105, 97, and 91 (base peak); fragment ions at 105 and 91 are characteristic of $\Delta^{9(11)}$-steroids.[26]

For n.m.r. study of the isomerisation, the reaction of androst-5-en-17-one (20 mg) in $CDCl_3$ (0.1 ml) and trifluoroacetic acid (0.1 ml) was monitored at intervals for 8 days, and a similar reaction of the 9(11)-en-17-one (24) was followed for 5 days. The spectra were then identical (see text).

The intermediate product, regarded as the $\Delta^{1(10)}$-compound (22), was isolated from the product of a reaction interrupted after 19 h. The extracted product was an oil, $\nu_{max.}$ 1 780 (trifluoroacetate) and 1 743 cm^{-1}. After percolation through alumina to remove trifluoroacetate groups, the $\Delta^{1(10)}$-compound was isolated by preparative g.l.c. (15% QF1; 190 °C) as an oil (1 mg) *m/e* 272 (M^+, $C_{19}H_{28}O$), 257, 215, 147, 133, 121, 108, 95, 79, and 67. Ions characteristic of a $\Delta^{9(11)}$-compound (see above) were absent. The n.m.r. spectrum was obtained from an unseparated mixture of isomers (22) and (24), τ 8.93 (s, 5β-Me, deshielded by 1,10-double bond), 9.13 (s, 13β-Me), and 4.55 (C=C*H*).

[23] L. F. Fieser and M. Feiser, ' Steroids,' Reinhold, New York, 1959, p. 369.

[24] B. W. Finncane and J. B. Thomson, *Chem. Comm.*, 1969, 1220.

[25] D. N. Kirk, unpublished work.

[26] D. N. Kirk and M. A. Wilson, *J. Chem. Soc.* (*C*), 1971, 414.

(b) *With deuteriotrifluoroacetic acid.* The isomerisation and partial purification were carried out as in (a), but with use of $CF_3 \cdot CO_2D$. The mass spectrum of the product showed deuterium incorporation as follows: [$^2H_2$], 3.1; [$^2H_3$], 9.3; [$^2H_4$], 18.3; [$^2H_5$], 21.2; [$^2H_6$], 16.1; [$^2H_7$], 9.1; [$^2H_8$], 3.0%.

Wolff–Kishner Reduction of the 9(11)-*En*-17-*one* (24).—The ketone (24) (45 mg) was treated with hydrazine hydrate (3 ml; 100%) in diethylene glycol (3 ml) on a steam-bath for 30 min; then sodium hydroxide (0.3 g) was added and the mixture was distilled slowly under nitrogen until the liquid temperature reached 200 °C. After being heated under reflux in nitrogen for a further 1 h the cooled mixture was diluted with water, and the product was extracted with ether. The resulting crude $\Delta^{9(11)}$-compound was an oil, $\nu_{max.}$ (CS_2) 1 643, 1 375, 1 067, 990, 960, 905, 883, and 830 cm^{-1}. Oxidative cleavage of the olefin (13 mg) in CCl_4 (3 ml) was achieved by stirring with ruthenium dioxide (5 mg) and sodium periodate (20 mg) in water (3 ml), with addition in portions of more sodium periodate (50 mg) in water (1 ml), over 4.5 h. The CCl_4 layer was separated, and the aqueous layer was re-extracted with CCl_4. Propan-2-ol was added to the combined CCl_4 solutions to destroy RuO_4, and the solution was washed with sodium hydrogen carbonate solution, which coagulated colloidal RuO_2, allowing filtration. The CCl_4 layer was washed, the solvent was removed, and the residue was passed through a short column of alumina, with benzene as eluant. The crude 9,11-seco-9-keto-11-aldehyde (25) was obtained as an oil, $\nu_{max.}$ 2 700 (CHO), 1 720, and 1 714 cm^{-1}; $\Delta\varepsilon$ (MeOH) −0.26 (314 nm), *m/e* 290 (M^+, $C_{19}H_{30}O_2$).

Acidic isomerisation of the keto-aldehyde (25) (1 mg) in acetic acid (1 ml) containing toluene-*p*-sulphonic acid (20 mg) under reflux for 18 h gave a product with longer retention time (g.l.c.), which was not studied further.

Hydroxylation of the 9(11)-*En*-17-*one* (24).—Osmium tetraoxide (65 mg) and the 9(11)-en-17-one (20 mg) in pyridine (6.5 ml) were left at room temperature for 6 days; then the solvent was removed under reduced pressure and $LiAlH_4$ (100 mg) in ether (5 ml) was added to the residue. The mixture was heated under reflux for 2 h. After conventional work-up, the product was adsorbed on a short alumina column and eluted with ether–methanol (9 : 1), to give the crude 9β,11β,17β-triol (26) as a gum, $\nu_{max.}$ 3 600, 3 400, 1 070, and 1 040 cm^{-1}; τ ($CDCl_3$) 8.99 (s, 5β-Me) and 8.925 (s, 13β-Me); τ (C_5D_5N) 8.84 (s, 5β-Me) and 8.445 (s, 13β-Me).

Lead tetra-acetate (50 mg) in pyridine (1 ml) cleaved the 9β,11β,17β-triol (5 mg) at the 9,11-bond, also oxidising the 17β-hydroxy-group, on stirring in the dark for 18 h. The product had the i.r. characteristics expected of the 9,11-seco-11-aldehyde 9,17-diketone, $\nu_{max.}$ (CCl_4) 2 720 and 1 728 (CHO), 1 748 [C(17)=O] and 1 715 cm^{-1} [C(9)=O]; $\Delta\varepsilon$ (MeOH) +1.72 (293 nm).

*Isomerisation of Androst-5-en-*17-*one* (20) *with Methanolic Sulphuric Acid.*—The ketone (20 mg) in methanol (2.5 ml) and sulphuric acid (2.5 ml) was stirred at 40 °C for 30 min; g.l.c. then indicated complete reaction. The product, extracted with ether, was passed through a short column of alumina. Elution with benzene–light petroleum (2 : 3) gave a mixture comprising mainly the 5β,10β,14β-Δ^8-17-ketone (28) and the 5α,10α,14β-Δ^8-17-ketone (29), $\nu_{max.}$ (CS_2) 1 740, 1 370, 1 335, 1 282, 1 095, 1 075, 1 054, 990, 975, and 957 cm^{-1}. Preparative g.l.c. (15% QF1, 200 °C) separated small samples of these isomers, which showed almost identical i.r. spectra.

5-*Methyl*-19-*nor*-5β,14β-*androst*-8-*en*-17-*one* (28) showed τ ($CDCl_3$) 9.11 (s, 5β-Me) and 8.97 (s, 13β-Me): τ (C_6D_6) 9.10 (s, 5β-Me) and 8.975 (s, 13β-Me); $\lambda_{max.}$ (hexane, 1 mm cell) 200 nm (ε 6 700); $\Delta\varepsilon$(MeOH) +0.30 (301 and 291 nm); *m/e* 272 (M^+, $C_{19}H_{28}O$), 257, 216, 201, 176, 161, 145, 131, 119, 105, 97, 91, 83 (base peak), and 67. The 5α,10α-isomer (29) [contaminated with 25% of (28) (g.l.c.)] showed τ ($CDCl_3$) 9.10 (s, 5β-Me) and 8.95 (s, 13β-Me); τ (C_6D_6) 9.09 (s, 5β-Me) and 8.96 (s, 13β-Me); $\lambda_{max.}$ (hexane, 1 mm cell) 200 nm (ε 7 000); $\Delta\varepsilon$ (MeOH) +0.33 (292 nm); *m/e* 272 (M^+, $C_{19}H_{28}O$), 257, 216, 201, 176, 159, 145, 131, 117, 105, 97, 92, 83 (base peak), and 67.

Cleavage of the Olefinic Bonds in the 8-*En*-17-*ones* (28) *and* (29).—Each 8-en-17-one (5 and 7 mg, respectively) in pyridine (1.5 and 2 ml) was treated with osmium tetraoxide (15 and 20 mg) for 7 days, followed by $LiAlH_4$ as described above. The resulting solid 8,9,17-triols were almost insoluble in CS_2 or $CDCl_3$, so were cleaved directly with an excess of lead tetra-acetate in t-butyl alcohol–acetic acid (1 : 1) for 16 h. The extracted products were passed through short columns of silica gel, with ether–benzene (1 : 1) as eluant, to give crude 17β-hydroxy-8,9-seco-8,9-diketones, each with $\nu_{max.}$ (CCl_4) *ca.* 3 600, *ca.* 3 400, and 1 697 cm^{-1}. Oxidation of each product in acetone with Jones reagent gave the corresponding 8,9-seco-8,9,17-trione, each with $\nu_{max.}$ (CCl_4) 1 743 and 1 695 cm^{-1}. The 5β,10β,14β-8,9-seco-8,9,17-trione [from (28)] showed *m/e* 304 (M^+, $C_{19}H_{28}O_3$), 286, 223, 205, 179, 149 (base peak), 135, 124, 109, 97, 81, and 67; the 5α,10α-isomer [from (29)] showed *m/e* 304 286, 231, 208, 190, 179, 161, 149 (base peak), 135, 123, 109, 97, 81, and 67.

Wolff–Kishner Reduction of the mixed 8-*En*-17-*ones* (28) *and* (29).—The ketones (25 mg) were reduced as described for the 9(11)-en-17-one (21), and the extracted product, in light petroleum, was passed through a short column of alumina to give an olefinic mixture with all the characteristics of the mixed Δ^8-compounds (9) and (10), as well as a small proportion of the isomer (8) (g.l.c.).

*Isomerisation of Androst-5-en-*17β-*ol with Acetic Acid–Toluene-*p-*sulphonic Acid.*—The steroid (20 mg) and toluene-*p*-sulphonic acid (100 mg) in acetic acid (3 ml) and cyclohexane (1 ml) were heated with slow distillation until the temperature reached 116 °C, then under reflux for 4 h. The extracted products were passed through a short column of alumina in benzene–light petroleum (1 : 4), giving a gum with two main components in the ratio 5 : 1 (g.l.c.), $\nu_{max.}$ (CCl_4) 1 740 cm^{-1} (17-acetate).

Deacetylation (with $LiAlH_4$, in ether) followed by oxidation (Jones reagent, in acetone) gave a product with the g.l.c. characteristics expected from a 5 : 1 mixture of the 5β,10β,14β-8-en-17-one (28) and the 5α,10α,14β-8-en-17-one (29), respectively. Clearly the reaction conditions had not permitted complete equilibration of the 5β,10β- and 5α,10α-isomers, which would be expected to reach a 1 : 1 ratio by analogy with the products from rearrangement of androst-5-en-17-one with methanolic sulphuric acid.

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