D-Homo-steroids. Part IV.[1] Acetolysis of D-Homo-5α-androstan-17aβ-yl Tosylate: a Novel Rearrangement involving the Steroid Backbone

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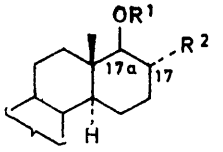
Buffered acetolysis of the title compound (5) gave the corresponding 17aβ-yl acetate (6), along with olefinic products, but unbuffered acetolysis additionally gave D-homo-5α,13α-androstan-17aα-yl acetate (10), with inversion at C-13. The inversion reaction appears to proceed through a series of carbocation and olefinic intermediates, derived from the 14(13 ⟶ 17a)*abeo* skeleton (7) by migration of unsaturation involving the steroid backbone. When the acetolysis was performed in acetic [^{2}H]acid, the 13α-product contained up to 17 deuterium atoms.

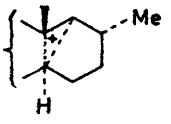
Photoisomerisation of D-homo-5α-androstan-17a-one (15) gave the 17a-ketone (12) of the 13α-series in low yield.

ACETOLYSIS or formolysis of the 17a-tosylate (1) of a 17aβ-hydroxy-17α-methyl-D-homoandrostane derivative was reported by Hirschmann and his co-workers in 1966 [2] to give the corresponding 17aβ-acyloxy-derivative [*e.g.* (2)] as the major product. To explain the retention of configuration, these authors suggested that a non-classical cation of type (3) might be formed as an intermediate in the solvolysis, through participation of the C(13)–C(14) bonding electrons, although this interpretation has since been questioned.[3]

Having a supply of the monofunctional D-homo-17aβ-alcohol (4),[1,4] without the 17α-methyl substituent, we examined the acetolysis of the 17aβ-tosylate (5), and



(1) R^1 = Ts, R^2 = Me
(2) R^1 = Ac, R^2 = Me
(4) R^1 = R^2 = H
(5) R^1 = Ts, R^2 = H
(6) R^1 = Ac, R^2 = H



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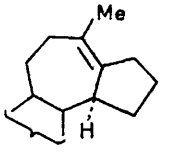


(7)

found in this case also that the 17aβ-acetate (6) was the major polar product, although a second acetate (see below), and a substantial olefinic fraction, were also formed, depending upon the conditions. Acetolysis was chosen rather than formolysis because the monofunctional tosylate was only sparingly soluble in formic acid.

An investigation of the kinetics of the acetolysis of the 17aβ-tosylate (5) showed that the rate of reaction was normal, the first-order rate constant ($3{\cdot}44 \times 10^{-4}$ s^{-1} at 100°) being similar in magnitude to those reported for *trans*-4-t-butylcyclohexyl tosylate ($6{\cdot}04 \times 10^{-4}$ s^{-1} at 99·6° [5]), *trans*-(*eq*)-1-decalyl and -2-decalyl tosylate ($2{\cdot}84 \times 10^{-4}$ s^{-1} at 103·7° and $5{\cdot}01 \times 10^{-4}$ at 103·6°, respectively [6]), and 5α-cholestan-3β-yl tosylate ($3{\cdot}98 \times 10^{-4}$ s^{-1} at 100° [7]). This finding excludes any likelihood of anchimeric assistance to the ionisation of the 17aβ-tosylate from the migration of the C(13)–C(14) bond to form a non-classical cation of type (3). Hirschmann [2] reached the same conclusion from kinetic data for formolysis. Our subsequent investigation of products has shown, however, that the migration of the 13,14-bond is an important part of the total reaction scheme. The situation appears to be similar to others in the steroid field described by Shoppee [8] and Bancroft [9] and their co-workers, and interpreted as the unassisted ionisation of a tosylate to give a classical carbocation, which may subsequently undergo bond delocalisation to form a non-classical structure, from which the final products are derived.

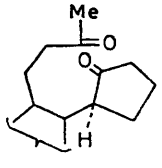
Kinetic data, being unexceptional, are not reported in detail, but we outline in the Experimental section a convenient indirect spectroscopic method which we developed for following the solvolysis of a tosylate when the small quantity available precludes use of the usual methods (titration with use of an indicator,[5,6,10] potentiometric titration,[11] or i.r.[2] or u.v. spectroscopy [12]).

Analysis of Products.—When the D-homo-17aβ-tosylate (5) was solvolysed in refluxing acetic acid

[1] Part III, D. N. Kirk and M. A. Wilson, *J. Chem. Soc.* (*C*), 1971, 414.
[2] H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, 1966, **31**, 375.
[3] M. Leboeuf, A. Cave, and R. Goutarel, *Bull. Soc. chim. France*, 1969, 2100.
[4] D. N. Kirk, W. Klyne, C. M. Peach, and M. A. Wilson, *J. Chem. Soc.* (*C*), 1970, 1454.
[5] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 1955, **77**, 5562.
[6] I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, 1959, **81**, 3420.
[7] R. Baker and J. Hudec, *Chem. Comm.*, 1967, 479; *cf.* also S. Nishida, *J. Amer. Chem. Soc.*, 1960, **82**, 4290.
[8] C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 1961, 3261.
[9] G. Bancroft, Y. M. Y. Haddad, and G. H. R. Summers, *J. Chem. Soc.*, 1961, 3295.
[10] S. Winstein, F. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 812, 821; K. Takeda, H. Tomida, and K. Horiki, *J. Org. Chem.*, 1966, **31**, 734.
[11] J. Mathieu, M. Legrand, and J. Valls, *Bull. Soc. chim. France*, 1960, 549.
[12] C. G. Swain and C. R. Mogran, *J. Org. Chem.*, 1964, **29**, 2097; D. S. Noyce and G. A. Selter, *ibid.*, 1971, **36**, 3458; *cf.* Ch. R. Engel, K. F. Jennings, and G. Just, *J. Amer. Chem. Soc.*, 1956, **78**, 6153.

buffered by potassium acetate, two major products were formed. The larger fraction (*ca.* 60%) after chromatography was essentially a single hydrocarbon, but was seen from g.l.c. analysis to be contaminated with traces of at least six other hydrocarbons, together comprising *ca.* 15% of the fraction. The other major product was the known 17aβ-acetate (6) (*ca.* 40%).

The principal hydrocarbon is believed to be the 14(13 → 17a)*abeo*-12a(13)-ene (7). The ^{1}H n.m.r. spectrum showed only one sharp singlet attributable to an angular methyl group (10β-CH_3), and a broadened three-proton singlet (τ 8·32; $W_{\frac{1}{2}}$ 4 Hz) indicating the



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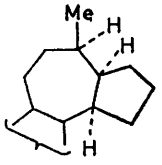

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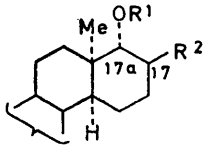
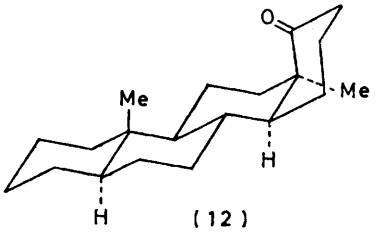


(10) R^1 = Ac, R^2 = H
(11) R^1 = R^2 = H
(13) R^1 = CHO, R^2 = Me

system CH_3·C=C. There were no olefinic protons, but unsaturation was confirmed by epoxidation (*m*-chloroperbenzoic acid), and by ozonolysis, which gave a diketone (8) containing a cyclopentanone ring ($\nu_{max.}$ 1736 cm^{-1}) and a methyl ketone function [$\nu_{max.}$ 1712 cm^{-1}; τ 7·89 (CH_3·CO)]. Hydrogenation converted the crude olefinic mixture essentially into a single saturated hydrocarbon, apparently contaminated by only a trace of an isomeric hydrocarbon (g.l.c.). The n.m.r. spectrum revealed a doublet (τ 9·25, *J* 6·5 Hz) due to the 12a-methyl group. The doublet collapsed to a singlet on simultaneous irradiation 1·07 ± 0·05 p.p.m. downfield, revealing the location of the 12a-proton signal. The hydrocarbon seems likely to have the 12aβ-methyl-13α-configuration (9), assuming attack from the less hindered α-face of the olefin (7) (Dreiding model).

Acetolysis of the 17aβ-tosylate (5) in the absence of a buffer gave significantly different results: the olefinic fraction was of more complex composition (g.l.c.), and the polar fraction was essentially a mixture of the 17aβ-acetate (6) and another acetoxy-compound. The inverted 17aα-acetoxy-derivative was present only in minute traces, from g.l.c. evidence. Acetolyses carried out at various temperatures (75, 85, and 95°, and at reflux) showed that the formation of the new acetoxy-compound is favoured by lower temperatures, but the reaction at 75° required *ca.* 200 h for its completion, so that still lower temperatures were impracticable. At 75° the new compound was formed to the extent of 20%. Higher temperatures increased the proportions of olefinic products at the expense of the acetates (see Experimental section).

The new acetoxy-compound differed from the known 17aα-, 17β-, 17α-, 16β-, and 16α-acetoxy-D-homo-5α-androstanes,[4] and was identified as 17aα-acetoxy-D-homo-5α,13α-androstane (10) * on the basis of the following observations.[13] The n.m.r. spectrum showed the 17a-proton signal as an unresolved multiplet of width 10 Hz, indicating an axial rather than an equatorial conformation, and hence an equatorial acetoxy-group. The acetoxy-group was nevertheless unusually hindered compared with other acetates in ring D,[4] for the compound exhibited lower polarity (t.l.c.) and retention time (g.l.c.) than the known isomers, and its hydrolysis (KOH–MeOH) was unusually slow. The derived 17aα-alcohol (11), which also exhibited a broad (10 Hz) signal for the axial 17aβ-proton, was oxidised to give D-homo-5α,13α-androstan-17a-one (12). The ketone was characterised by an exceptionally large downfield shift of the signal due to the 13α-methyl protons in comparison with the 17a-, 17-, and 16-ketones in the normal (13β) series, and by a small *up-field* shift of the 10β-methyl signal in comparison either with D-homo-5α-androstane, or with the 17aα-alcohol of the 13α-series. This slight shielding of the 10β-methyl group by the carbonyl group is consistent with the folded 13α-structure (12), for the 10β-methyl group lies in a direction roughly perpendicular to the internuclear axis of the C=O bond.[14]



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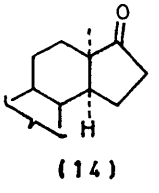

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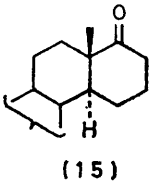

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The c.d. curve for the new ketone (Δε +2·6 in MeOH) agrees tolerably well with the value calculated (+2·1) on the basis of our recent analysis of c.d. data for extended decalones.[15] The dominant effect is that of the axial 13α-methyl group in a positive octant. Reduction of the ketone with sodium borohydride gave a mixture of

* This structure was first proposed by M. A. W. (Ph.D. Thesis, London, 1969).

[13] Preliminary communication, I. Khattak, D. N. Kirk, C. M. Peach, and M. A. Wilson, *J.C.S. Chem. Comm.*, 1973, 341.

[14] J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1970, **26**, 119.

[15] D. N. Kirk and W. Klyne, *J.C.S. Perkin I*, 1974, 1076.

the 17aα-alcohol (11) (38%) and another product assumed to be the axial 17aβ-alcohol (62%) on the evidence of its greater mobility (t.l.c. and g.l.c.). Predominant formation of the axial alcohol is consistent with the hindered nature of the 17a-ketone in the 13α-series.[16]

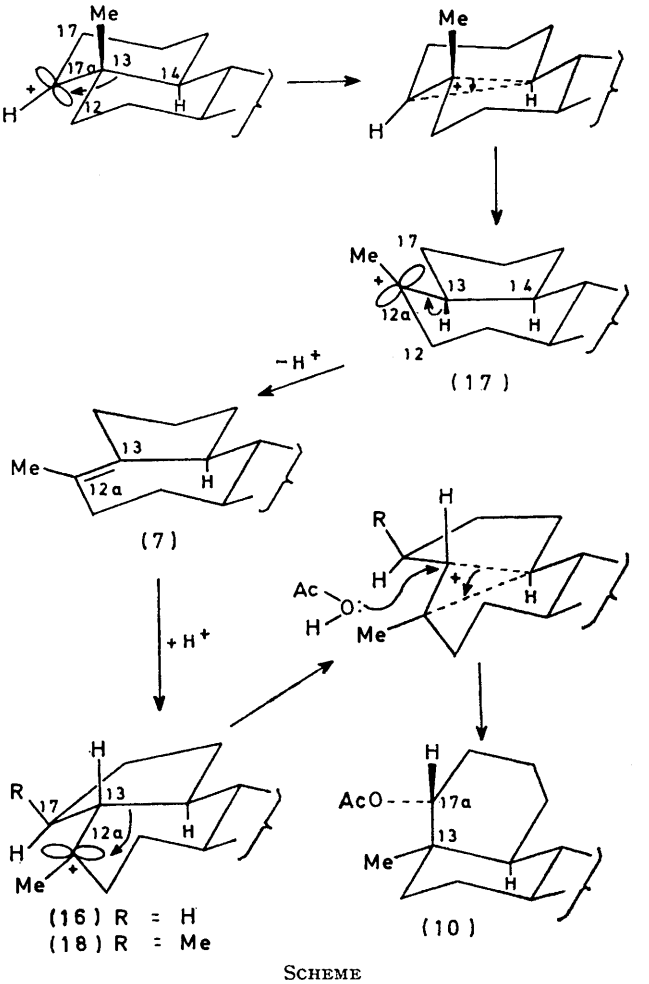
At this stage, the assignment of the 13α-configuration to our product received support from related findings of Hirschmann and Hirschmann.[17,*] These workers, extending their earlier studies on the formolysis of the 17α-methyl-D-homo-17aβ-tosylate (1), identified a by-product as the 17β-methyl-D-homo-13α-androstan-17aα-yl formate (13), their material having undergone isomerisation in part at both C-13 and C-17 during the formolysis. The structure (13) was confirmed by an independent synthesis.

In pursuance of an alternative route to our compounds of the 13α-series, we first attempted the D-homo-annulation of 5α,13α-androstan-17-one (14), which is available by photoisomerisation of 5α-androstan-17-one.[18] However, attempts to convert the ketone of the 13α-series into the required intermediate for Demjanov ring enlargement, a 17-aminomethyl-17-hydroxy-derivative, were wholly unsuccessful. The ketone failed to form a spiro-oxiran [1] either with dimethyloxosulphonium methylide or with the more reactive dimethylsulphonium methylide, and was unreactive towards the Wittig reagent methylenetriphenylphosphorane, and also towards phenylthiomethyl-lithium, a reagent recently employed [19] in an alternative synthesis of methylene compounds from ketones. Similar low reactivity of the *cis*-fused 17-ketone has been found by Hirschmann,[17] and also earlier by Nambara and his co-workers.[20]

We therefore had recourse to the photochemical isomerisation of D-homo-5α-androstan-17a-one (15). Unlike the photoisomerisation of 5α-androstan-17-one [18] the D-homo-ketone reacted with low efficiency, probably as a result of its normal thermodynamic preference for the original *trans*-fusion of rings C and D, but the required 13α-isomer (12) was obtained in 12—15% yield under optimum conditions, along with four non-ketonic by-products which were not identified. The ketone (12), isolated by preparative g.l.c., was identical with the sample derived *via* the solvolysis route.

Mechanism of Acetolysis of the Tosylate (5).—The formation of the rearranged acetate only in unbuffered acetic acid hinted at the involvement of liberated toluene-*p*-sulphonic acid in the process leading to inversion of configuration at C-13, and this impression was supported by an analysis (g.l.c.) of samples withdrawn at intervals from the reacting solution (see Experimental section). The proportion of olefinic products reached a maximum between 50 and 100 h at 75°, and declined thereafter while the proportion of the rearranged acetate continued to increase. Extra toluene-*p*-sulphonic acid added initially did not, however, cause any significant change in the rate of acetolysis or in the ultimate proportions of products.

It seems probable that the 14(13 ⟶ 17a)*abeo*-$\Delta^{12a(13)}$ olefin (7) is the precursor of the 13α-compound (10), which could be envisaged as arising by protonation of the olefinic bond at the 13β-position to give the 12a-carbocation (16). The conformational change imposed upon the seven-membered ring would then



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present the α-face of C-12a for attack by the 13,14-bonding electrons, so that a return to the original ring sizes would leave the angular methyl group in the 13α-position, and generate a *cis*-fusion of the six-membered rings C and D (Scheme).

To test the feasibility of this mechanism, the acetolysis was carried out in acetic [^{2}H]acid on the assumption

* We are grateful to Professor H. Hirschmann for sending us a copy of the manuscript some months before publication.

[16] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 135.

[17] F. B. Hirschmann and H. Hirschmann, *J. Org. Chem.*, 1973, **38**, 1270.

[18] M. Fetizon and J. C. Gramain, *Bull. Soc. chim. France*, 1967, 1003.

[19] R. L. Sowerby and R. M. Coates, *J. Amer. Chem. Soc.*, 1972, **94**, 4758.

[20] T. Nambara, H. Hosoda, and S. Goya, *Chem. and Pharm. Bull. Japan*, 1968, **16**, 1266; T. Nambara and J. Goto, *ibid.*, 1971, **19**, 1308.

that the protonation of an intermediate olefin of type (7) would lead to the incorporation of at least one atom of deuterium in the rearranged product. To our surprise, a mass spectrometric analysis of the separated D-homo-13α-androstan-17aα-yl acetate (10) revealed the incorporation of *up to seventeen* deuterium atoms, some of which could be located from study of the ^1H n.m.r. spectrum of the acetate, and of the derived alcohol and ketone. The most obvious features were the virtual absence of proton signals due to the 13α-methyl group (C-18), as well as to the 17aβ-H, although the 10β-methyl signal was unaffected. Other features of the spectrum of the labelled 17aα-acetate could not be interpreted directly, although pronounced changes in the methylene envelope were evident. Hydrolysis to the 17aα-alcohol, and careful Jones oxidation, gave a sample of the 17a-ketone (12) which also lacked proton signals for the 13α-methyl group. Moreover the spectrum of this ketone showed no significant signals in the region below τ 8·0, where the unlabelled ketone exhibited a two-proton multiplet centred at τ 7·62 due to the C-17 protons, which are deshielded by the 17a-carbonyl group. Treatment of the deuterium-labelled ketone with ethanolic hydrochloric acid gave a sample in the spectrum of which these C-17 proton signals were restored. Mass spectra confirmed that the acid treatment of the ketone had reduced the main molecular-ion peak by two mass units, by exchanging the two deuterium atoms adjacent to the carbonyl group for hydrogen.

These findings pointed to a rearrangement mechanism which was much more extensive than had originally been considered, and which seemed likely to involve a series of short-lived olefinic intermediates with temporary unsaturation covering at least C-17, C-17a, and the angular methyl group (C-18), and extending further into the ring structure to account for as many as seventeen deuterium atoms.

The other sites of deuterium labelling have not been identified unambiguously, but we offer a scheme which provides for the exchange of precisely seventeen protons, based upon the following mechanistic considerations:

(*a*) Centres of unsaturation are known [21] to move along the steroid 'backbone,' either as a result of hydride migrations or by alternating protonation and deprotonation steps, under conditions of the type used in the present acetolysis; several examples of extensive deuterium incorporation *via* backbone rearrangements have been described.[21c,d]

(*b*) Carbocations at the 'backbone' carbon atoms (*e.g.* C-8, -9, -13, and -14) may be deprotonated to give either tetrasubstituted [*e.g.* $\Delta^{8(14)}$] or trisubstituted [*e.g.* $\Delta^{9(11)}$ or Δ^{14}] olefinic bonds, but reactions of this type have not been observed to give the much less stable disubstituted olefinic bonds (*e.g.* Δ^{6} or Δ^{11}), which could arise from secondary carbocations.

[21] 'Terpenoids and Steroids,' ed. K. H. Overton, Chem Soc. Specialist Periodical Reports, (*a*) 1971, vol. 1, p. 361; (*b*) 1972, vol. 2, p. 301; (*c*) 1973, vol. 3, p. 378; (*d*) 1974, vol. 4, p. 373.

With this constraint, the process of protonation–deprotonation, starting from the 14(13 ⟶ 17a)*abeo* structure (7), could transfer unsaturation temporarily to each of the carbon atoms in rings C and D *except* C-16. The further assumption that backbone rearrangement in the present case does not extend beyond C-9 (*i.e.* does not include migration of the 10β-methyl group to C-9), leads to the possibility of deuterium exchange at exactly seventeen sites (Figure 1), including all the carbon atoms bearing hydrogen from C-7 to C-18, inclusive, with the exception of C-16. The olefinic intermediates which would account for the postulated distribution of deuterium are indicated collectively in Figure 2.

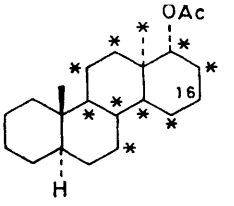

FIGURE 1 D-Homo-5α,13α-androstan-17aα-yl acetate (6), with asterisks indicating sites of deuterium labelling

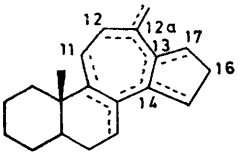

FIGURE 2 Olefins of the 14(13 ⟶ 17a)*abeo*-series; dotted lines indicate possible locations for the olefinic bond as a result of acid-catalysed rearrangements

This tentative conclusion could not be verified with certainty, for the complex mass spectra of the labelled compounds showed that all molecular species with from about ten up to seventeen deuterium atoms were present in significant proportions. However, an n.m.r. study of the labelled 17aα-alcohol (11), with added shift reagent [Eu(fod)$_3$],[22] afforded evidence consistent with the view that the C-16 protons were the only ones in the vicinity of ring D *not* substantially exchanged by deuterium. Using the unlabelled 17aα-alcohol (11) initially, sufficient shift reagent was added, stepwise, to move downfield out of the methylene envelope those signals which are due to the fourteen protons closest to the 17aα-hydroxy-group, including those at C-18. The labelled sample was then treated similarly, and as expected the low-field region of its shifted spectrum showed only very weak signals due to residual protons, including those at C-18; a single two-proton signal, however, remained at full intensity. A crude estimate of the expected induced shift for the C-16 protons agreed well with the location of this signal. The estimate was obtained by using the measured shifts of the C-18 protons, as well as those of a pair of strongly shifted signals attributed to the two C-17 protons, to obtain an approximate value for the proportionality constant k in the expression: induced

[22] R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, 1971, **93**, 1522.

shift $= k/r^3$. (The angular term in the more accurate McConnell–Robertson equation [23] was ignored in view of uncertainties regarding the position and orientation of the lanthanide complex.[24]) To obtain a reasonable fit with shifts observed for protons at C-17 and C-18, the europium atom was considered to be located *ca.* 2·5 Å from oxygen, and 1·0 Å off the C(17a)–O axis, in the direction eclipsing the C(17a)–C(17) bond. Measurements of Eu · · · H distances, including those for protons at C-16, were made with the aid of the Dreiding model. The induced shifts for the C-16, C-17, and C-18 protons, respectively, were calculated to be in the ratio 0·40 : 1·37 : 1, and found from the spectra to be in the ratio 0·37 : 1·37 : 1, a satisfactory agreement in view of the approximations involved.

The mechanism outlined above therefore seems to provide a satisfactory pathway for the inversion of configuration at C-13, and for the incorporation of up to seventeen deuterium atoms. It was surprising, however, to find that the normal (unrearranged) product, D-homo-5α-androstan-17aβ-yl acetate (6), when obtained from the reaction in acetic [^{2}H]acid, contained no detectable deuterium. Clearly the substitution of a 17aβ-acetoxy- for a 17aβ-tosyloxy-substituent occurs by a more direct mechanism, not involving skeletal rearrangements.

Inspection of Dreiding models suggested a possible reason for the non-reversion of the rearranged olefinic intermediates to the normal (13β) D-homoandrostane skeleton. The initial migration of the C(13)–C(14) bond to form the C-homo-D-nor-structure must occur in the sense which leads to a *cis*-fusion of rings C and D in the 12a-carbocation (17), and a model shows that the conformation in which this ion is initially formed involves a considerable increase in compression between the C-7 and C-15 positions (the 7,8- and 14,15-bonds become more nearly eclipsed). The driving force for the rearrangement presumably comes from the conversion of a secondary into a tertiary carbocation. Microscopic reversibility demands that a return to the original 13β-configuration should proceed through 13α-protonation of the olefin (7) to the same strained cation, as well as being contrary to the trend of cation stabilities. An alternative is available, however, if the olefin (7) is protonated at the 13β-position, giving the C/D-*trans*-fused 12a-carbocation (16). A model shows that the C/D-*trans* geometry forces the C-18 methyl group to the ' rear ' of the molecule, which is now essentially strain-free. Return to a D-homoandrostane structure from this conformation (16) results in generation of the 13α-configuration, and may be assisted by concerted nucleophilic attack of acetic acid at the 17a-position. The cation (16) possesses the correct geometry for this process, which would afford the 17aα-acetoxy-D-homo-5α,13α-androstane (10) uniquely (Scheme).

Hirschmann's observation [17] that the 17α-methyl-substituted compound (1) afforded the 17β-methyl derivative (13) in the 13α-series can be explained in similar terms. The intermediacy at one stage of a C-homo-$\Delta^{13(17)}$-olefin, implied by our deuterium-labelling results (*cf.* Figure 2), provides a mechanism for inversion at C-17 by protonation of the $\Delta^{13(17)}$-olefin at the 17α- instead of the 17β-position. Moreover the 17-methyl-substituted derivative of the C/D-*trans*-C-homo-12a-cation can only adopt the conformation required for rearrangement to the final 13a-product if the 17-methyl substituent has the β-configuration (18), for a 17α-methyl group would be close enough to ring C to impede the conformational change required to bring the 12a-methyl group towards the rear of the molecule.

EXPERIMENTAL

N.m.r. spectra were obtained for solutions in $CDCl_3$ at 100 MHz. Alumina refers to Spence, Grade H. Light petroleum refers to the fraction of b.p. 60—80°.

Buffered Acetolysis of D-*Homo-5α-androstan-17aβ-yl Tosylate* (5).—The tosylate (500 mg) was added to a refluxing solution of potassium acetate (0·7 g) in acetic acid (50 ml). After 2 h under reflux the solution was poured into water, and the products were isolated with ether–light petroleum (4 : 1) to give an oil (368 mg). This product, in light petroleum, was chromatographed on alumina (10 g) to give mixed olefins (197 mg) as an oil containing 85% (g.l.c.) of the 13(14 → 17a)*abeo*-12a(13)-ene (7), τ 9·26 (s, 10β-Me) and 8·32br (s, $W_{\frac{1}{2}}$ 4 Hz, 12a-CH_3).

Elution with light petroleum–ether (100 : 1) gave the 17aβ-acetate (6) (154 mg), m.p. 137—139°, identical with an authentic sample.[1]

Reactions of the Crude Olefin (7).—(a) *Hydrogenation.* The oily olefins (15 mg) were hydrogenated in hexane over 5% Pd–C for 5 h. The resulting oil (15 mg) gave one main peak (g.l.c. on 3·8% SE30 at 210°) with retention time 0·93 relative to the olefin (7) (= 1·00). A very minor component with slightly shorter retention time was also formed. The major component was assigned structure (9); τ 9·31 (s, 10β-Me) and 9·25 (d, *J* 6·5 Hz, 12a-Me) (the latter signal collapsed to a singlet, τ 9·25, on irradiation 1·07 ± 0·05 p.p.m. downfield); M^+ 274 ($C_{20}H_{34}$).

(b) *Epoxidation.* The olefins (40 mg) in chloroform (50 ml) were treated with *m*-chloroperbenzoic acid (100 mg) for 5 min; g.l.c. then showed that reaction was complete. The isolated crude epoxide was a gum, characterised only by its n.m.r. spectrum, τ 9·23 (10β-Me) and 8·77 (12a-Me).

(c) *Ozonolysis.* The olefins (100 mg) in chloroform (50 ml) were treated with ozonised oxygen for 30 min, then methanol (5 ml), water (1 ml), acetic acid (1 ml), and zinc dust (1 g) were added and the mixture was stirred at room temperature for 4 h. After filtration and washing, the solvents were removed under reduced pressure to leave the crude diketone (8) as an oil (72 mg), $\nu_{max.}$ (CCl_4) 1736, 1712, and 1368 cm^{-1}; τ 9·15 (10β-Me) and 7·89 (CH_3CO).

Unbuffered Acetolysis of D-*Homo-5α-androstan-17aβ-yl Tosylate* (5).—(a) *G.l.c. study.* The tosylate (5 mg) in anhydrous acetic acid (5 ml) was maintained at 75°, and samples (0·2 ml) were taken at intervals (Table) up to 216 h. The solvent was removed from each sample under reduced pressure, and the residue, in chloroform, was analysed by

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g.l.c. Similar reactions at 85 and 95° afforded products relatively richer in olefins, and containing smaller proportions of the rearranged acetate (10).

Products from unbuffered acetolysis of D-homo-5α-androstan-17aβ-yl tosylate (5) at 75°

Time (h)	D-Homo-5α-androstan-17αβ-yl acetate (6) (%)	D-Homo-5α, 13α-androstan-17aα-yl acetate (10) (%)	Olefins (%)
17	10	2·5	
33	14	3·6	
46	17	5·1	
66	20	7·7	
90	22	8	70
120	28	13	58
150	33	16	51
200	32	20	48
216	26	20	52

(b) *Preparation of* D-*homo*-5α,13α-*androstan*-17aα-*yl acetate* (10). The tosylate (200 mg) and anhydrous acetic acid (150 ml) were heated at 75° for 9 days. The products, isolated by extraction with chloroform, were dissolved in light petroleum and passed through alumina (4 g). Elution with light petroleum separated the mixture of olefins from relatively polar products. Elution with benzene then gave a mixture of D-homo-5α-androstan-17aβ-yl acetate and D-homo-5α,13α-androstan-17aα-yl acetate. The mixture was chromatographed on a second column of alumina (20 g). Light petroleum first eluted the 13α,17aα-*acetate* (18 mg), m.p. 103—105° (from methanol), $\nu_{max.}$ (Nujol) 1733 and 1245 cm^{-1}; τ 9·02 (s, 13α-Me), 9·22 (s, 10β-Me), 8·00 (s, Ac), and 5·74 (m, $W_{\frac{1}{2}}$ 10 Hz, 17a-H) (Found: M^+, 332·2727. $C_{22}H_{36}O_2$ requires M, 332·2715).

Further elution with light petroleum and benzene gave the 17aβ-acetate (6) (40 mg).

Deuteriated D-*Homo*-5α,13α-*androstan*-17aα-*yl Acetate*.—D-Homo-5α-androstan-17aβ-yl tosylate (200 mg) in acetic [^{2}H]acid (99% $MeCO_2D$) (100 ml) was heated at 75° for 9 days, and the products were isolated as in the previous experiment, to give deuteriated D-homo-5α,13α-androstan-17aα-yl acetate (20 mg), M^+ 349·3775 (main molecular ion peak; $C_{22}H_{19}D_{17}O_2$ requires 349·3782).

The 17aβ-acetate (6) (45 mg) isolated from this experiment had M^+ 332, showing that no appreciable deuterium incorporation had occurred.

Hydrolysis of D-*Homo*-5α,13α-*androstan*-17aα-*yl Acetate*.—The acetate (9 mg) in ethanolic 5% potassium hydroxide (10 ml) was heated under reflux for 4 h; reaction was then complete (t.l.c.). After work-up with ether, the product crystallised from hexane, giving D-*homo*-5α,13α-*androstan*-17aα-*ol*, m.p. 186—188°, $\nu_{max.}$ 3325 cm^{-1}. A portion (3 mg) of the alcohol sublimed at 140° under reduced pressure gave the pure product (2 mg), m.p. 187—188°; τ 9·09 (s, 13α-Me), 9·24 (s, 10β-Me), and 6·10 (m, $W_{\frac{1}{2}}$ 10 Hz, 17a-H); Δε (hexane) +0·37 (184 nm) and −0·058 (204 nm), M^+ 290 ($C_{20}H_{34}O$).

Oxidation of D-*Homo*-5α,13α-*androstan*-17aα-*ol*.—D-Homo-5α,13α-androstan-17aα-ol (4·5 mg) in acetone (2 ml) was oxidised with Jones reagent to give D-*homo*-5α,13α-*androstan*-17a-*one* (4 mg), m.p. 139°, $\nu_{max.}$ 1710 cm^{-1}; Δε (MeOH) +2·6 (297 nm); τ 8·81 (s, 13α-Me), 9·31 (s, 10β-Me), and 7·75 (m, 17-H_2); M^+ 288 ($C_{20}H_{32}O$).

Reduction of D-*Homo*-5α,13α-*androstan*-17a-*one with Sodium Borohydride*.—D-Homo-5α,13α-androstan-17a-one (2 mg) in propan-2-ol (5 ml) was treated with sodium borohydride for 2 h. Two products were indicated by t.l.c. and g.l.c. One (38%; longer retention time) was identified as D-homo-5α,13α-androstan-17aα-ol by comparison (g.l.c. and t.l.c.) with an authentic sample. The other (61%) was probably D-homo-5α,13α-androstan-17aβ-ol. It had unusually low mobility on t.l.c. for an alcohol, running parallel with D-homo-5α,13α-androstan-17a-one, but was clearly distinguished from the ketone by g.l.c.

The n.m.r. spectrum of the mixture of the two epimeric alcohols exhibited four distinct methyl signals, two corresponding to those for the 13α-17aα-alcohol. The other signals, τ 8·74 (s, 13α-Me) and 9·10 (s, 10β-Me), are assigned to the 13α-17aβ-alcohol, although this product was not isolated in pure condition.

Hydrolysis of Deuteriated D-*Homo*-5α,13α-*androstan*-17aα-*yl Acetate*.—Deuteriated D-homo-5α,13α-androstan-17aα-yl acetate (18 mg) was hydrolysed in the manner described for the unlabelled material, to give deuteriated D-homo-5α,13α-androstan-17aα-ol (14·6 mg), m.p. 186—188° (from acetone). The dominant molecular ion, at *m/e* 307, requires a formula of $C_{20}H_{17}D_{17}O$.

Oxidation of the Deuteriated D-*Homo*-5α,13α-*androstan*-17aα-*ol with Jones Reagent*.—The deuteriated D-homo-5α,13α-androstan-17aα-ol (12 mg) was oxidised as above to give deuteriated D-homo-5α,13α-androstan-17a-one (10·5 mg), $\nu_{max.}$ 1695 cm^{-1}; τ 9·31 (10β-Me). The presence of 16 deuterium atoms in the major component species was indicated by mass spectral analysis [M^+ 304 ($C_{20}H_{16}D_{16}O$)].

Reaction of Deuteriated D-*Homo*-5a,13α-*androstan*-17a-*one with Acidified Ethanol*.—The deuteriated D-homo-5α,13α-androstan-17a-one (3 mg) in ethanol (3 ml) and concentrated hydrochloric acid (1 drop), was heated on a steam-bath for 30 min and the product was worked up in the usual way to recover the 17a-one (2·5 mg), $\nu_{max.}$ 1695 cm^{-1}. The n.m.r. spectrum exhibited a two-proton multiplet centred at τ 7·75 which was absent from the spectrum of the untreated ketone and is assigned to protons at C-17; the 10β-methyl signal at τ 9·31 remained unaffected. The mass spectrum showed the principal molecular ion at *m/e* 302 ($C_{20}H_{18}D_{14}O$).

Photolysis of D-*Homo*-5α-*androstan*-17a-*one* (15).—D-Homo-5α-androstan-17a-one (40 mg) in anhydrous dioxan (10 ml) was irradiated in a Pyrex vessel with a high-pressure mercury lamp (Hanau Q81) for 2 h. The reaction was followed by g.l.c. D-Homo-5α-androstan-17a-one was the major of six products and was the most polar component of the mixture (t.l.c.). D-Homo-5α-androstan-17a-one (6 mg), D-homo-5α,13α-androstan-17a-one (3 mg), and three of the other four components (<1 mg each) were separated by preparative g.l.c. (3% QF1 column). The ketones were characterised by crystallisation and comparison with samples prepared previously. The most polar of the three minor products exhibited $\nu_{max.}$ 1745, 1725, and 1120 cm^{-1}, but was not identified.

Kinetics.—Acetolyses were performed in anhydrous acetic acid at 74, 81, 86·5, and 100° (each ±0·1°), with *ca.* 10 mg of tosylate in acetic acid (0·05%; 20 ml). Rapidly chilled samples (2 ml) of solution, taken at suitable intervals, were added to a solution (1 ml) of *p*-naphtholbenzein (8 mg) in acetic acid (50 ml). The indicator is in its basic form in pure acetic acid ($\lambda_{max.}$ 454 nm; orange-brown solution), but is partially converted by toluene-*p*-sulphonic acid into its acidic form ($\lambda_{max.}$ 464 and 625 nm; green). The optical density at 625 nm is linearly related to the concentration of

toluene-*p*-sulphonic acid over the range required for measurements. The optical density was plotted graphically against time, giving a smooth curve for the reaction at 100°. The first-order rate constant was obtained from this curve by the Swinbourne procedure,[25] which proved more satisfactory than the Guggenheim method.[26] Graphs for reactions at 86·5° and below were not smooth curves, probably because these conditions favour the reprotonation of olefinic intermediates, leading to backbone rearrangement processes, and thereby disturb the accumulation of acid in the solution. The experimental rate constant was $3{\cdot}44 \times 10^{-4}$ s^{-1} at 100° ($t_{\frac{1}{2}}$ 33·6 min). Accurate rate constants could not be evaluated for the reactions at lower temperatures: half-lives were *ca.* 140 min at 86·5°, 220 min at 81°, and 400 min at 74°.

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