D-Homosteroids. 5.[1] Formolysis of an Equatorial Tosylate with Two Vicinal Axial Methyls[2]

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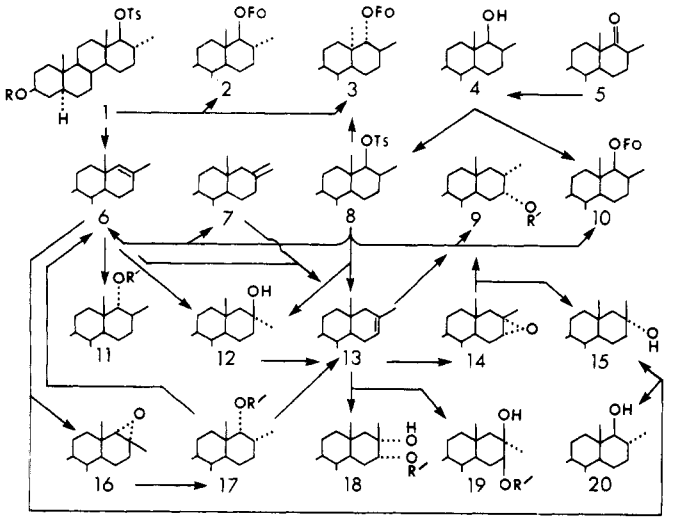
Compared to its 17-epimer, uranediol 3-acetate 17a-tosylate (**1a**), 3β-acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**8a**) formolyzed 2.2 times faster and yielded 17 times more olefins. The main products were 17-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (**13a**, 84%), the product of the addition of formic acid to this olefin [3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-16α-yl formate (**9e**), 3.3%], the substitution product with retained configuration [3β-acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl formate (**10a**), 4.6%], and a 13α-isomer, 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate (**3a**, 0.8%). Solvolysis in buffered acetic acid gave an even higher proportion of olefins and at least 82% of the reaction involved a shift of the 17α-hydrogen. When compared to the solvolyses of a related pair of equatorial cyclohexyl tosylates with an adjacent axial or equatorial methyl but lacking the vicinal quaternary carbon, the results were taken to indicate that **1a** formolyzes in the chair form, while most of the formolysis of **8a** involves a transition state with a nonchair conformation. On this basis the rate of **1a** was judged to be accelerated and to be consistent with anchimeric assistance. The products of the formolysis of **8a** were identified by relating them to known compounds. Two of these reactions gave noteworthy results. The hydroboration–oxidation of the 17(17a)-olefin (**6a**) gave more tertiary than secondary alcohols and the hydrogenolysis of the 17β-methyl-*D*-homo-16α,17α-epoxide (**14a**) with lithium aluminum hydride proceeded predominantly with an equatorial attack on C-16.

The formolysis of uranediol 3-acetate 17a-tosylate (**1a**) yielded two equatorial formates: the major one (**2a**) had the same configuration as the starting material at C-13 and C-17, the two centers adjacent to the locus of metathesis,[3] whereas the lesser product (**3a**) differed in both these configurations.[4] No isomer was detected which showed configurational changes at only one of these sites. These inversions may or may not have a prescribed order. As any information on this point might help to elucidate the mechanism of the 13α-*D*-homosteroid rearrangement, we examined the formolysis of the 17a-tosylate (**8a**) of a new isomer of uranediol 3-acetate that



a) R=Ac c) R=R'=Ac e) R=Ac; R'=Fo
b) R=H d) R=R'=H f) R=Ac; R'=H
g) R=Ac; R'=Ts

differs from it in the configuration at C-17. This change introduces a 1,3-syn interaction of the methyl groups and thus could be expected to facilitate any process which reduces this large strain in the transition state. Therefore, if mechanisms exist for inversion at either C-13 or C-17, their products (**2a**, **3a**) should be thermodynamically favored and readily observed.

Fukushima and co-workers[5] have provided access to *D*-homosteroids with the 17β-methyl group by converting 3β-acetoxy-17α-hydroxy-5α-pregnan-20-one to ketones of type **5**. They found these to be unstable[6] toward acid and alkali and to assume a nonchair conformation of the *D* ring.[5b] Reduction of **5a** with lithium tri-*tert*-butoxyaluminohydride[9] gave the 17a-carbinol **4a**. Its 17a-hydrogen had a coupling constant of 5.6 Hz, a value to be expected[10] if this hydrogen was axial and if the *D* ring was a chair. The alternative 17aα-hydroxy-17β-methyl configuration was definitely excluded when **4a** was found to differ from another new stereoisomer which must be assigned structure **11f** (see below). When compared to the 17-epimer, uranediol 3-acetate,[3] carbinol **4a** showed considerable steric hindrance in its reaction with tosyl chloride in pyridine, which gave **8a**. The hydroxyl group was esterified readily, however, in formic acid to yield **10a**.

The main product of the formolysis of **8a** was the same olefin we had obtained previously from the 17aα-tosylate **17g** with formic acid.[3] A product with the same spectrographic characteristics of the double bond and its environment but without a substituent at C-3 was obtained more recently from the corresponding olefin **6** with formic acid by Leboeuf and co-workers[11] who were able to assign structure **13** to their product.

The esters resulting from the formolysis of **8a** were difficult to separate. The main product was the formate with retained configuration (**10a**) and a faster moving component of this mixture proved to be identical with the known 13α-*D*-homosteroid, **3a**. In addition there were at least two formates present that had not been encountered before. Experiments aimed at their identification and at the preparation of other required[12] reference compounds also provided a full verification of the structures that had been deduced[11,13] for the two olefins **6** and **13**.

If the tosylate **8a** behaved like an ordinary cyclohexyl sulfonate, its formolysis should have yielded the ester with inverted configuration (**11e**). A reference sample seemed accessible through hydroboration–oxidation of the 17-olefin **6a**. We obtained this intermediate by treating tosylate **1a** with sodium iodide in hexamethylphosphotriamide. This modification of two older methods[11,13] proceeds from a readily available starting material at a temperature low enough to furnish a good product without recourse to chromatography. Its epoxidation yielded **16a** which must be the α-epoxide because hydrogenolysis with lithium aluminum hydride gave the known[3] 3β,17aα-diol (**17d**). This identity fully confirmed the structure of the olefin. Like the epoxidation, the hydroboration showed a preference for α attack[14] but displayed a most

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unusual regiospecificity.[15] The desired secondary alcohol **11f** was obtained by the usual oxidation of the boranes but only in a modest yield. There was also a trace of the secondary alcohol with the β configuration (**20a**) while the dominant reaction was toward the tertiary alcohols (**12a** and **15a**). The major one was identified as the equatorial alcohol **15a** on the following evidence. It was eluted more slowly than its epimer **12a**,[16] it showed an O—H stretching vibration at a lower frequency,[17] and it gave further evidence for the α orientation of its hydroxyl group by the near constancy of the NMR signals for the 18-hydrogens when the solvent was changed from deuteriochloroform to pyridine-d_5.[18] This alcohol provided the link to the second olefin (**13a**) and its epoxide (**14a**). When the latter was subjected to reduction with lithium aluminum hydride followed by acetylation, two products were obtained. As one was the 17α-carbinol, the other, a diacetate, must have the 16α-acetoxy structure shown in **9c.** Although the parent diol (**9d**) of this diacetate results from the normal[16] diaxial opening of an α-epoxide, it was the lesser product in a reaction that left much of the epoxide ring intact. Presumably this inhibition of the normal cleavage results from the tertiary character of C-17[19] and from the 1,3 interaction of the entering hydride reagent with the methyl at C-13. Under these conditions an equatorial attack on C-16 becomes competitive and yields the tertiary alcohol besides the normal product. Although the same considerations should apply to an axial attack on C-17 of the epoxide **16a,** no tertiary alcohol could be isolated. Evidently there is an even greater resistance to an attack on C-17a which is of the neopentyl type and therefore particularly slow to react by an S_N2 process. The formation of the diacetate **9c** from **14a** thus constitutes further evidence for the α orientation of the C—O bonds; had they been β, the appropriate tertiary alcohol should have been the sole product.[19] Accordingly we regard the α configuration of the epoxide and its products as firmly established.[20]

When one of the new formates obtained in the solvolysis of tosylate **8a** was hydrolyzed and acetylated, the product was identical with the 16α-acetoxy compound **9c.** Suspecting the 16-olefin (**13a**) to be the intermediate in the conversion of **8a** to the formate **9e** we dissolved the olefin in formic acid and observed its conversion to the formate **9e.**[22] Presumably all of this ester that was obtained from the tosylate was formed in this manner, but as we failed to observe simple kinetics for the addition reaction even in the absence of toluenesulfonic acid, this point has not been established.

As expected[10] the main secondary alcohol (**11f**) that resulted from the cis hydration of the 17–17a double bond of **6a** had a smaller coupling constant for its 17a-proton than the 17a-epimer (**4a**) in which this hydrogen is axial. Its signal was found at a higher field if the 17a-hydroxyl group is axial. While this is contrary to a frequently cited generalization or to our observations on the pair with the 17α-methyl group (**20a** and **17f**),[3] the pattern is consistent with that presented by the four

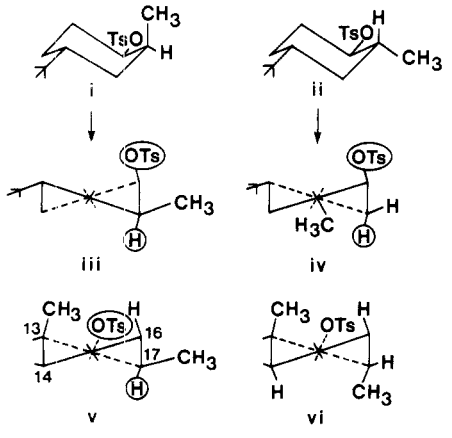

Table I. Products of Formolysis of 3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (8a)

	registry no.	structure[a]	% yield
		olefins	84.7
13a	68151-33-7	17-Me-16-ene	83.7
7a	62797-25-5	17-methylene	0.4
		unidentified	0.6
		formates	10.3
3a	38456-48-3	13α-17aα-FoO-17β-Me	0.8
		unidentified	0.4
10a	68199-18-8	17aβ-FoO-17β-Me	4.6
9e	68151-34-8	16α-FoO-17α-Me	3.3

[a] All that were identified are derivatives of 3β-acetoxy-*D*-homo-5α-androstane.

3-hydroxy-4-methyl-5α-androstan-17β-yl acetates and accounted for by a modification of the McConnell equation.[23] The 17aα-carbinol **11f** was converted to the formate **11e** which moved faster on TLC than its 17a-epimer **10a.** Although the solvolysis products of **8a** included a formate with similar chromatographic mobility, its spectrum was distinct from that of **11e,** which is readily detected by an unusually intense peak at 903 cm^{-1}.

The yields of the various formolysis products are listed in Table I. The results demonstrate a major effect of the configuration of the center that bears the secondary methyl group. If this methyl is equatorial (**1a**), only 5% of the final products are olefins,[12] whereas their yields rose to 85% in the present case, a fairly typical value for a cyclohexyl tosylate. As in the case of **1a,** the major formate was the one that retained the configuration of the starting tosylate at all its chiral centers (**10a**). Of the two processes which would relieve the strain of interaction between the two methyl groups only the inversion of C-13 was observed. It gave **3a** in higher yield relative to **10a** than the proportion of **3a** and **2a** derived from **1a**.[3] Nevertheless, it is evident that the nature and ratio of stereoisomers is controlled by kinetic and not by thermodynamic factors. The mechanism of the isomerizations will be discussed in the succeeding paper[12] which presents observations consistent with our failure to find the most stable of the formates (**2a**) among the reaction products of **8a.**

The rate of formolysis of **8a** was only 2.2 times faster than that of a tosylate of type **1**.[3] This compares with a much larger rate ratio for solvolysis (78 for acetolysis) of the two 4-*tert*-butylcyclohexyl tosylates that bear an axial (i) or equatorial (ii) methyl adjacent to an equatorial tosylate.[24] Pánková and co-workers explained this large ratio by proposing that both isomers solvolyze mainly, or exclusively, through a nonchair transition state. This state would be assumed more readily by i because the conformational change (as in iii) would relieve the strain associated with the axial orientation of the methyl and because it would result in a geometry favorable to the participation of a methine hydrogen in the ionization, whereas in the epimer only a methylene hydrogen could play such a role (e.g., iv). The only twist form available to **8a** (v) would relieve the even larger ground state energy of the interaction of two methyl groups, but this accelerating effect is opposed by at least two factors. The methyl at C-13 would shorten its distance from the 16β-hydrogen, and the dihedral angle between the carbon bonds to the tosyloxy group and to the participating hydrogen would be significantly less favorable[25,26] than in iii. The compression effect of the 13-methyl is also present in vi which has acquired an additional one from the like position of the 17-methyl. As to dihedral angles, vi has no hydrogen in an orientation that permits participation.

While these and other differences between **8** and i allow no easy answer about their relative rates, the comparison between

the two members of each pair leads us to expect that the rate ratio of 8 to 1 should be much larger than of the pair studied by Pánková, if the steroids also utilize nonchair transition states. As the reverse was observed, at least one stereoisomer should react by a different mechanism. The nature of the products strongly suggests that **8a** solvolyzes like i. Formic acid is not the best solvent for such a study because any 17-olefin (**6a**) formed initially would isomerize to the 16-isomer (**13a**).[11] This reaction does not occur in buffered acetic acid.[12] Even in this solvent **13a** was the main product and its ratio to **6a** was distinctly higher than the ratio of these compounds when formed from the tosylate **1a**.[12] In addition **8a** gave two products which had not been obtained from **1a**: a trace of an alcohol with the spectrum of **12a** and an olefin with relatively intense peaks at 3067 and 1649 and a very strong one at 887 cm^{-1}. This combination is diagnostic for a 1,1-dialkylated methylene[27] and strongly indicated the presence of the 17-methylene **7a**. This structure was confirmed by a conversion of this product to **13a** in formic acid.[28] Therefore, as in Pánková's experiments solvolysis strongly favors a shift of the methine hydrogen if it is trans to the tosyloxy group.[29] This difference between **8a** and **1a** seems explicable only if the preferred transition state of **8a** has a nonchair conformation.

After the hydride shift from C-17 to C-17a has occurred, the bonding differences that exist between **1a** and **8a** have been abolished and if no conformational differences developed during the ionization it would be difficult to explain why only the 17-cation derived form **8a** gave readily detectable amounts of the 17-methylene (**7a**).

It is evident that isomer **1a** is the one that solvolyzes differently from its analogue in Pánková's pair and that **1a**, therefore, retains its chair conformation during solvolysis. This leaves its tosyloxy group in the equatorial orientation. According to Campbell[30] the solvolysis of such a bond "is known to be slow and may possibly be very slow". As the formolysis of 1 is somewhat faster[3] than that of a reference compound (*trans*-4-*tert*-butylcyclohexyl tosylate) now widely believed to utilize a nonchair transition state extensively,[30] some other factor must compensate for the intrinsic inertness of the equatorial bond. This could be a particularly effective solvation from the rear. This possibility can be dismissed because the neighboring atoms are extensively substituted and because the reaction shows a very high preference for retention. The remaining alternative appears to be participation of a neighboring bond in the ionization process. Both the 13,14 and the 16,17 bonds have the appropriate antiparallel orientations. Their roles will be discussed in the succeeding paper.[12]

The *substitution* reaction of the tosylate **8a** at C-17a resembles that of **1a** in giving both the ester with retained configurations at all centers (**10a**) and the 13α-*D*-homosteroid **3a**. We presume, therefore, that this relatively small fraction of the formolysis of **8a** (like that of **1a**) utilizes the chair conformation. Its rate relative to that of **1a** is significantly retarded (~2.2 × 0.06 = 0.13). Evidently the proximity of the methyl groups strains this transition state even more than the ground state. In going from **1a** to **8a**, a blocking group, the 17-methyl, has been removed from the α side. Nevertheless there was no demonstrable increase in the normal substitution process by solvation from the rear. This further strengthens our earlier contention that steric hindrance does not provide an adequate explanation for the steric preferences that we have observed.[3,4]

Experimental Section

General Procedures. These were the same as were described in the accompanying paper[12] except that the adsorbent in column chromatography was a 2:1 mixture of silica gel (E. Merck, Darmstadt, finer than 200 mesh) and Celite, prewashed as described.[31]

3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17a-one (5a). Two batches of 3β-acetoxy-17α-hydroxy-5-pregnen-20-one obtained from different commercial suppliers were hydrogenated with palladium–calcium carbonate and separately converted to **5a** according to the procedures of Fukushima[5] except that the elimination of methanesulfonic acid was carried out by heating with hexamethylphosphotriamide (3 h, 100 °C) in the case of batch 2. Each elimination product had mp 206–208 °C (reported 206.5–210 °C[5b] and 204.5–206.5 °C[32]) and $[\alpha]_D$ −66° (measured for second batch only) (reported[5b] −71.2°). Hydrogenation gave **5a**: first batch, mp 143–144.5 °C, $[\alpha]_D$ +70°, acetone; second batch 142–143 °C, $[\alpha]_D$ +74°, acetone, $[\alpha]_\lambda$ (CCl_3H) +77° (589), +82° (578), +97° (546), +221° (436), and +569° (365 nm). Reported:[5b] mp 150.5–153 °C; $[\alpha]_D$ + 48.2°, acetone. A sample that was kept in boiling methanolic potassium hydroxide and reacetylated[5b] showed the IR spectrum of the 17-epimer.

3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-ol (4a). A solution of 73 mg of **5a** in 2.5 mL of tetrahydrofuran was mixed with one of 150 mg of lithium tri-*tert*-butoxyaluminohydride in 2.5 mL of the same solvent. The mixture was kept in ice for 30 min and at room temperature for 45 min. The excess hydride was decomposed with hydrochloric acid and the neutral product was isolated by ether extraction. Two recrystallizations from hexane gave 62 mg of **4a** with mp 164.5–165.5 °C (or occasionally at 133–134 °C). (The mother liquors were recrystallized and the resulting mother liquor (1.1 mg) gave an IR spectrum in good accord with that of the analytical sample.) Rotation $[\alpha]^{28}_\lambda$ +14° (589), +17° (546), +28° (436) and +42° (365 nm); IR 3621 (ν_+/ν_- 0.58),[3] 1039 (OH); 1737, 1242, 1028 cm^{-1} (OAc); NMR δ 0.80 (19-H), 0.82 (18-H), 0.98 (d, J = 7.4 Hz, 17-Me), 2.01 (Ac), 3.25 (d, J = 5.6 Hz). Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.12; H, 10.98.

3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl Formate (10a). A solution of 10 mg of carbinol **4a** in 2 mL of formic acid was kept at room temperature for 4 h. The product (**10a**) after recrystallization from acetone had double mp 165.5–166 and 169.5–170.5 °C: IR 1737, 1240, 1026 (3β-OAc) and 3096, 1723 cm^{-1} (OFo); the following served to distinguish **10a** from other formates, 1214, 1176, 1163, 1014, 956, 948, 911, 897, 886 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.87; H, 9.85.

3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (8a). A solution of 51 mg of carbinol **4a** and of 850 mg of *p*-toluenesulfonyl chloride in 1 mL of pyridine was kept at room temperature for 24 h. The excess tosyl chloride was hydrolyzed with aqueous pyridine and the product (**8a**) isolated by extraction with benzene and purified by recrystallization from 90% acetone: mp 137–138.5 °C; IR 1736, 1240, 1027 (3β-OAc) and 1305, 1187, 1176, 1099, 1020 cm^{-1} (general tosylate bands);[3] major specific tosylate bands were at 940, 918, 873, 813, 744, 667, 601, and 563 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_5S$: C, 69.73; H, 8.58. Found: C, 69.78; H, 8.49. Even at this high concentration of tosyl chloride the crude reaction product still showed some of the OH stretching band of **4a** and good yields required further tosylation of the mother liquors.

Formolysis of 3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (8a). A solution of 85.9 mg of tosylate **8a** in 0.5 mL of benzene was diluted with 170 mL of formic acid, kept at 25 °C for 18 h, and distributed between benzene and water. The neutral product was chromatographed on 4.8 g of silica gel–Celite. Elution with benzene–hexane (1:1) gave 46.6 mg of crystals with the IR spectrum of pure **13a**. These gave 41.8 mg with mp 116.5–118 °C after recrystallization from acetone. The analytical sample of **17-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (13a)** had mp 117.5–118.5 °C: $[\alpha]_\lambda$ −76° (589), −90° (546), −154° (436), and −246° (365 nm) (Calcd[7] from Leboeuf's analogue:[11] $[\alpha]_D$ −77°); IR 1735, 1733, 1241, 1026 cm^{-1} (3β-OAc), 3039 (=CH), 808, 800 cm^{-1}; the additional olefinic band at 795 cm^{-1} described by Leboeuf[11] for the compound unsubstituted at C-3 could not be seen. For NMR see ref 3 and 11. Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 79.77; H, 10.67.

Elution with benzene gave 1.8 mg of material of a mixture containing mainly **13a** and at least three other olefins, one of which had the IR peaks (3067, 1649, 887 cm^{-1}) described below for **7a**. The other two had ^1H NMR peaks characteristic of an olefinic methyl (1.56 and 1.58 ppm, respectively). (These spectrographic details were obtained from fractions prepared on a larger scale.)

Elution with benzene containing 1% ether gave 6.7 mg of formates, with benzene containing 5–10% ether 1.9 mg of products of autoxidation were obtained. The fractionation of the formates was carried out with 75.0 mg of like material derived from 959.4 mg of tosylate. Recrystallization of the largest eluate (64 mg) from methanol gave

22.3 mg of formate **10a**. Its melting point (171–172.5 °C) was not depressed by admixture of a reference sample prepared from **4a**. The IR spectra agreed.

The material in the mother liquors and the earlier and later eluates were combined and subjected to one or more chromatographic separations. As no complete separations were achieved, the yields given in Table I were determined by IR analyses. The products are listed in the order of their elution. **3β-Acetoxy-17β-methyl-5α,13α-androstan-17aα-yl formate (3a)** was recrystallized from methanol. Its mp (178–181 °C) was not depressed by admixture of an authentic sample.[3] The IR spectra agreed. The next formate was purified by TLC (20% hexane in methylene chloride, three runs). Its principal formate peaks were at 1199, 1177, and 1160 cm^{-1}. It was not identified. The next eluates contained additional amounts of **10a** and finally **3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-16α-yl formate (9e)**. Its mp (97.5–100.5 °C) was not depressed by admixture of a sample prepared from **13a**. The IR spectra agreed.

17-Methyl-*D*-homo-5α-androst-17-en-3β-yl Acetate (6a). A solution of 95.5 mg of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**1a**) and of 195 mg of sodium iodide in 3.9 mL of hexamethylphosphotriamide was heated under dry conditions in an oil bath maintained at 109 °C for 3 h. The mixture was distributed between benzene and water and the organic phase washed with water, hydrochloric acid, sodium bisulfite, sodium carbonate, and water. The product (63.8 mg) was recrystallized twice from methanol to give 49.1 mg of **6a** with mp 122.5–123.5 °C (reported[13] 119.5–120 °C) and an additional 7.5 mg from the mother liquors. Rotation $[\alpha]^{28}_{\lambda}$ +36° (589), +42° (546), +72° (436), +111° (365 nm). Reported[13] $[\alpha]^{20}_{D}$ +21.3°; calculated from rotation of **6b**[13] with standard shifts[7] + 36° and from that of **6** with C-3 = CH_2,[11] +25°. Repetition of our synthesis gave sample with $[\alpha]^{25}_{D}$ +37°. The IR band at 834 cm^{-1} serves best to estimate **6a** in mixtures with **13a**. Although the curve between 3100 and 3000 cm^{-1} is not entirely smooth, no absorption maximum could be seen (as had been reported[3] for a less pure sample obtained from **17g**).

17α,17aα-Epoxy-17-methyl-*D*-homo-5α-androstan-3β-yl Acetate (16a). 17-Methyl-*D*-homo-5α-androst-17-en-3β-yl acetate (**6a**) (30 mg) was treated with *m*-chloroperoxybenzoic acid as described below for **13a**. The product was recrystallized from methanol to yield the epoxide **16a** with mp 188.5–190 °C: IR 1733, 1240, 1027 (3β-OAc) and 1075, 898, 794 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.90; H, 10.08.

Hydrogenolysis of 17α,17aα-Epoxy-17-methyl-*D*-homo-5α-androstan-3β-yl Acetate (16a). A solution of epoxide **16a** (9 mg) in 3.2 mL of tetrahydrofuran was heated under reflux for 18 h in the presence of 120 mg of lithium aluminum hydride. The product which was recrystallized from ethyl acetate gave **17α-methyl-*D*-homo-5α-androstane-3β,17aα-diol (17d)** with mp 209.5–211.5 °C. Its acetylation yielded a mixture of the diacetate **17c** and the 3-acetate **17f** which were separated by TLC and identified by their IR spectra. The recrystallized diacetate had mp 133–134 °C (reported[3] 131–132.5 °C). A sample of the crude hydrogenolysis product which was treated with acetic anhydride in pyridine for 7 days[3] gave **17c** but failed to show the presence of a component with the mobility of a monoacetate (such as **15a**) on TLC.

Hydroboration of 17-Methyl-*D*-homo-5α-androst-17-en-3β-yl Acetate (6a). Diborane generated during 70 min from 275 mg of sodium borohydride in 9 mL of diglyme and 2.7 mL of boron trifluoride in 5 mL of diglyme at 15 °C was passed through a solution of 98 mg of **6a** in 6 mL of tetrahydrofuran kept at 20 °C. After 1 h the excess of hydride was hydrolyzed at 0 °C, and the mixture was stirred at this temperature with 3 mL of 10% aqueous sodium carbonate and 2 mL of 30% hydrogen peroxide for 1 h. The reaction product was chromatographed on 100 parts of silica gel–Celite. Elution with benzene gave 3.3 mg of material without a hydroxyl peak but with a spectrum different from that of **6a**. Benzene containing increasing amounts of ether (1 to 4%) eluted in succession:

3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17β-ol (12a): 7.7 mg; mp after recrystallizations from acetone–hexane and from hexane 130–133 °C; IR 3605 (OH, ν_+/ν_- 0.91), 1735, 1241, 1036,[33] and 1027 cm^{-1}. The compound failed to acetylate in pyridine with acetic anhydride (19 h, 24 °C) and gave a product with the IR spectrum of **13a** when dissolved in formic acid (3 h, 25 °C).

This was followed by a fraction (2.3 mg) with the IR spectrum of uranediol 3-acetate (**20a**). The next elution peak (14.8 mg) was recrystallized from acetone–hexane which gave **3β-acetoxy-17β-methyl-*D*-homo-5α-androstan-17aα-ol (11f)** with mp 148–150.5 °C: NMR 0.80 (19-H), 0.86 (18-H), 1.095 (d, J = 7 Hz, 17-Me), 2.01 (Ac), 3.13 (17a-H, poorly resolved d, apparent splitting 1 Hz); IR 3623 (OH, ν_+/ν_- 0.67),[34] 1734, 1240, 1026 cm^{-1} (3β-OAc).

The final eluates containing diol monoacetates (21.2 mg) were not readily purified by recrystallization. This product was acetylated and chromatographed. The crystalline fractions (13 mg) were recrystallized from acetone–hexane to give **3β-acetoxy-17β-methyl-*D*-homo-5α-androstan-17α-ol (15a)** with mp 180–181 °C that was not depressed by admixture of a sample obtained from epoxide **14a** (see below). The IR spectra agreed. The later eluates (diols) were not investigated. The conditions used for the hydroboration–oxidation[1] were chosen to minimize the size of the diol fraction and thus increase the yield of **11f**.

3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aα-yl Formate (11e). A solution of acetoxycarbinol **11f** (6.6 mg) in 2 mL of formic acid was kept at 25 °C for 4 h. The product (**11e**) after recrystallization from methanol had mp 160–161 °C; IR 1733, 1240, 1027 (3β-OAc), 1722, 1185, 1168 cm^{-1} (OFo). The peaks at 980 and at 903 (very strong) cm^{-1} also characterize this formate.

3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-16α-yl Formate (9e). Formic acid (27 mL) was added to a solution of 63 mg of 17-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (**13a**) in 0.1 mL of benzene. The mixture was kept at 25 °C for 8 days and the product was chromatographed. Elution with benzene–hexane 1:1 removed the olefin fraction. Its IR spectrum differed from the starting compound in having a weak extra peak at 1181 cm^{-1}, indicative[36] of a very incomplete ester exchange at C-3. Elution with benzene containing 2% ether gave 13.6 mg of formate which was recrystallized from methanol: mp 98.5–100.5 °C; NMR δ 0.80 (19-H), 0.83 (18-H), 0.845 (d, J = 7 Hz, 17-methyl), 2.01 (Ac), 5.12 (apparent d, splitting 2 Hz, 17-H), 8.11 (Fo); IR 1732, 1241, 1028 (3β-OAc) and 3095, 1722 cm^{-1} (Fo); the following serve to distinguish this formate from others, 1212, 1187, 1165, 984, 961, 950, 906, 900 cm^{-1}.

The product was solvolyzed in 2% methanolic potassium hydroxide (19 h, 23 °C) and then acetylated. The resulting diacetate (**9c**) was recrystallized from methanol: mp 88–91 °C; IR 1734, 1241, 1221, 1210, 1169, 1027, 1016, 985, 968, 906, 900 cm^{-1}. Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.10; H, 9.91.

16α,17α-Epoxy-17-methyl-*D*-homo-5α-androstan-3β-yl Acetate (14a). A solution of 17-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (**13a**) (27.2 mg) and of 30 mg of *m*-chloroperoxybenzoic acid in 2.5 mL of methylene chloride was kept at room temperature for 22 h and distributed between ether and water. The organic phase was washed with sodium carbonate, acidified ferrous sulfate, and water to yield 29.5 mg of product which was recrystallized from methanol: mp 163.5–166 °C; rotation $[\alpha]^{25}_{\lambda}$ −39° (589), −46° (546), −78° (436), and −123° (365 nm); IR 1735, 1241, 1025 (3β-OAc), 1170, 1057, 906, and 788 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 77.04; H, 10.08.

Hydrogenolysis of 16α,17α-Epoxy-17-methyl-*D*-homo-5α-androstan-3β-yl Acetate (14a). Epoxide **14a** (62 mg), an excess of lithium aluminum hydride, and 10 mL of ether were kept at room temperature for 2 days and heated under reflux for 22 h. The remaining hydride was decomposed with water–methanol and the product acetylated and chromatographed. The fastest moving fraction (8.9 mg, eluted with benzene–1% ether) showed the IR spectrum of **9c**. Its mp (89–92 °C, after recrystallization from methanol) was not depressed by admixture with **17α-methyl-*D*-homo-5α-androstane-3β,16α-diol diacetate (9c)** prepared from **13a** via **9e**.

The middle eluates (20.7 mg) were identified as starting material (**14a**) by mp 160–163 °C and the IR spectrum.

Elution with benzene–3% ether gave 29.2 mg of **15a** which was recrystallized from methanol. The mp 179–181 °C was not depressed by admixture with **17β-methyl-*D*-homo-5α-androstane-3β,17α-diol 3-acetate (15a)** obtained from **6a**: IR comparison confirmed the identity, IR 3599 (17-OH; ν_+/ν_- 0.95), 1733, 1242, 1026 (3β-OAc) and 1092, 988, 922, 898 cm^{-1}; NMR* δ 0.81 (19-H), 0.85 (18-H), 1.32 (17-Me), 2.02 (Ac) in $CDCl_3$ and 0.75, 0.88, 1.55, 2.06 in C_5D_5N. Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found C, 76.04; H, 10.61.

3β-Acetoxy-17-methyl-*D*-homo-5α-androstane-16,17-diols (18f and 19f). 17-Methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (**13a**, 17.8 mg) was converted to these glycols according to the procedure of Baran.[37] Adsorption on silica gel–Celite and elution with benzene containing 6% ethyl acetate gave 6.0 mg of **3β-acetoxy-17α-methyl-*D*-homo-5α-androstane-16β,17β-diol (19f)** which was recrystallized from acetone. It had mp 199–200 °C and IR 3614, 3567, 1733, 1242 cm^{-1}. The later eluates (with 9–12% ethyl acetate) gave 12.9 mg of **3β-acetoxy-17β-methyl-*D*-homo-5α-androstane-16α,17α-diol (18f)** with mp 176–177 °C after recrystallization from acetone–hexane: IR 3602, 3562, 1735, 1241, 1059, 1027 cm^{-1}. Both glycols were acetylated and recrystallized from acetone. Diacetate **19c** had mp 248–251 °C; IR 3593, 1741 (main), 1736 (shoulder), 1238, 1121, 1025, and 907 cm^{-1}. Diacetate **18c** had mp 184–187 °C: IR 3596, 1742

(shoulder), 1736 (main), 1239, 1165, 1028, 943, and 900 cm^{-1}. Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.78.

Acetolysis of 3β-Acetoxy-17β-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (8a). The reaction was carried out with 46.3 mg of **8a** for 3 h at 100 °C as described.[12] The product (30.9 mg) which showed no tosylate bands in the IR spectrum was recrystallized, the mother liquors were chromatographed, and the early eluates were again recrystallized. This resulted in a five-fold increase in concentration (in the mother liquor) of **17-methylene-*D*-homo-5α-androstan-3β-yl acetate (7a)** with IR bands at 3067, 1649, and 887 cm^{-1}. A late eluate contained an alcohol (3604 cm^{-1}) with the IR spectrum of **3β-acetoxy-17-methyl-*D*-homo-5α-androstan-17β-ol (12a).** The original crystals were treated with *m*-chloroperoxybenzoic acid and the resulting epoxides (**14a** and **16a**) were chromatographed. By these procedures and IR measurements the yields were estimated as 71% **13a**, 16% **6a**, 10% **7a**, and 1% **12a**. The best preparation of **7a** which contained an equal amount of **13a** was dissolved in formic acid and kept at 24 °C for 3 h. The IR spectrum changed to that of **13a.**

Rate Measurements. The conditions of the formolysis of **8a** were precisely the same as had been used for measuring the rate of solvolysis of 3-oxo-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate ($k_{25.0} = 3.14 \times 10^{-3}$ min^{-1}).[3] Aliquots (13 mL) were withdrawn at 0, 1, 2, 4, and 24 h and prepared for spectrographic analysis as before. Extinctions were measured at 918, 873, and 667 cm^{-1} on solutions in carbon disulfide and used to calculate the mean fraction of tosylate remaining. The first order rates were 6.68, 6.80, and 7.12×10^{-3} min^{-1} with a mean rate of $k_{25.0} = 6.87 \times 10^{-3}$ min^{-1} (1.15×10^{-4} s^{-1}).

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Registry No.—**1a**, 5611-68-7; **4a**, 68151-35-9; **5a**, 68199,19-9; **6a**, 17182-68-2; **8a**, 68151-36-0; **9c**, 68151-37-1; **11e**, 68199-20-2; **11f**, 68151-38-2; **12a**, 68151-39-3; **14a**, 68151-40-6; **15a**, 68151-41-7; **16a**, 68151-42-8; **17c**, 4975-34-2; **17d**, 4975-35-3; **18c**, 68151-43-9; **18f**, 68151-44-0; **19c**, 68151-45-1; **19f**, 68151-46-2; **20a**, 4975-27-3; 3β-acetoxy-17α-hydroxy-5-pregnen-20-one, 1863-39-4.

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