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D-Homo Steroids. Effects of Methyl Substitutions on the Formolysis of an Axial Cyclohexyl Tosylate[1]

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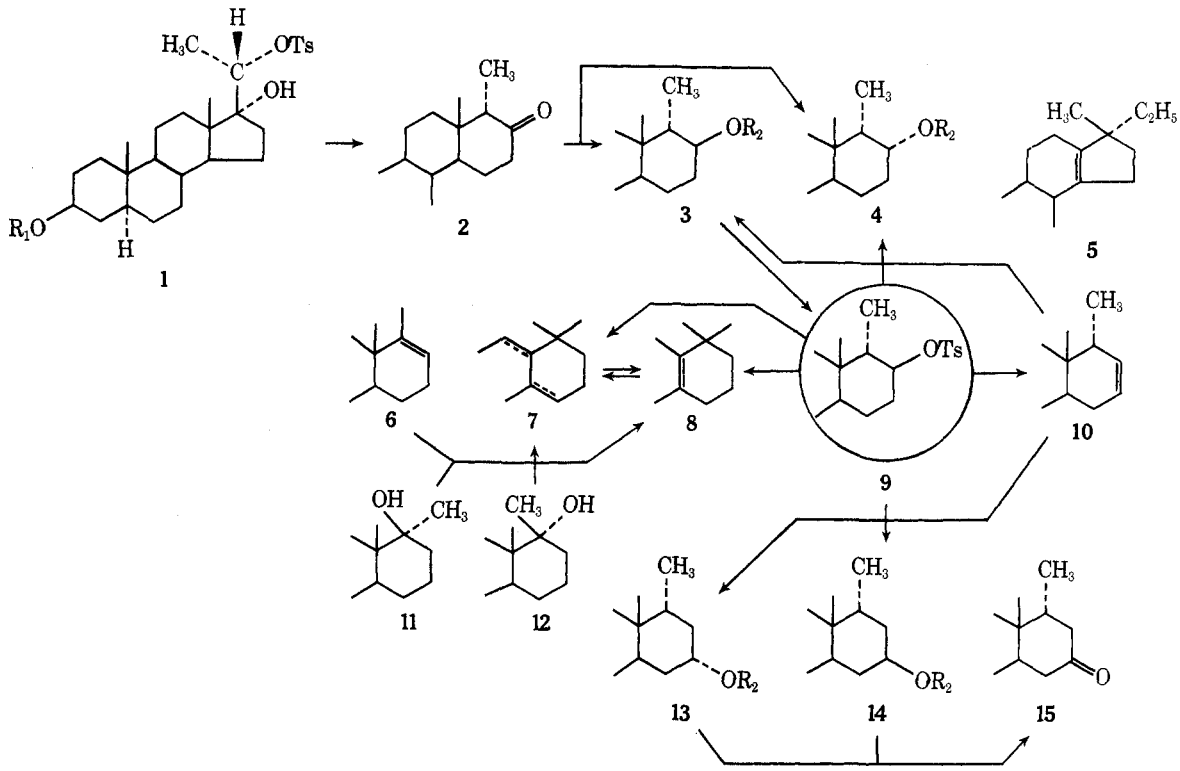
The main products (representing 95% of the material) of the formolysis of 3β-acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl tosylate (**9b**) were identified. The reaction gave the 16-olefin **10b** in 76% yield and only 7% of products that formed by shift or elimination of hydrogen from the more highly substituted C-17a. At C-17 retention was strongly favored over inversion, although this resulted in the unfavorable syn-diaxial interaction of the formoxy with a methyl group. Various explanations for this unusual result were examined. Addition of formic acid to the 16-olefin was negligible during the time required for the formolysis of the tosylate. The hydroboration of the 16-olefin showed only a minor effect of the 17a-methyl on the distribution of the four isomers. This is consistent with the published suggestion that the reaction has an early transition state.

There is a wide divergence of products in the formolyses of the 17a-epimeric 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17a-yl tosylates[2] that has not been plausibly explained by the differing positions of the departed tosylate ions. It seemed that the nature of the cationic species involved might be further clarified if new pathways to such 17a cations could be found. With this objective we investigated the solvolysis of a 17aα-methyl-*D*-homo-17β-tosylate (**9b**) because it contains an axial methyl antiparallel to the departing group, an arrangement which might be expected to stabilize itself by a methyl shift to C-17 in concert with the ionization. This migration did not occur. We observed instead the formation of a tertiary C-17a cation which reacted quite unlike the 17a-cationic intermediates which we had studied before.[2-4]

The 17β-hydroxy D-homo steroid (**3e**) required for this investigation was prepared from the known[5,6] 17-ketone **2b.** When we repeated the synthesis of the latter from 3β-acetoxy-17α-hydroxy-5α-pregnan-20α-yl tosylate (**1b**)[6] under the original conditions (potassium acetate in aqueous acetone), we obtained over 40% of the reaction product as the 17α,20β-epoxide,[7] but could suppress its formation by solvolyzing in formic acid. As formolysis gave the desired 17-ketone **2b** in nearly quantitative yield, it follows that the different course of D-homoannulation reported for **1b** and its 17-deoxy analog[4] results from this structural difference and not from the different conditions of solvolysis that had been used heretofore. Reduction of **2b** with lithium tri-*tert*-butoxyaluminohydride gave a single alcohol (**3e**) which was shown to have the 17β configuration by the symmetry[8] of the O–H stretching band at 3611 cm^{-1}; by the narrow NMR signal of the equatorial 17-hydrogen;[9] and by the shifts of ^1H NMR signals on changing the solvent from $CDCl_3$ to C_5D_5N. These changes were large (0.33 ppm downfield) for the 13-methyl but small (0.05 ppm in the same direction) for the 17a-methyl. Comparison of these shifts with those reported by Demarco et al.[10] shows that both the hydroxyl and the 17a-methyl must be axial. This confirms the α configuration of the latter and establishes the chair conformation of the ring. When the reduction was carried out with lithium aluminum hydride both 17-epimeric diols (**3d** and some **4d**) were obtained.

Formolysis of the axial tosylate **9b** gave 85% olefins and a polar fraction which showed strong formate bands. It was hydrogenolized with lithium aluminum hydride and gave six diols on chromatography. Two minor constituents of this fraction had tertiary hydroxyl groups. They may be artifacts resulting from the autoxidation of an olefin and have not been identified. The four other diols could also be obtained by hydroboration of **10b,** the principal olefin derived from **9b.** Two of these diols were identical with **3d** and **4d,** the reduction products of **2.** The two others must also be secondary alcohols because the oxidation of their 3-monoacetates (**13e** and **14e**)[11] gave a common acetoxy ketone (**15b**). We conclude from these observations that C-17 is unsaturated in **10b,** that this olefin has formed from **9b** without rearrangement or configurational change, and that the double bond extends to C-16. The axial isomer (**13e**) of the two 3β-acetoxy-16-hydroxy compounds was identified by the greater symmetry of the O–H stretching frequency; by the lower frequency of the probable stretching band of the C-16–O bond;[12] and by a much greater rate of oxidation with chromic acid.[13] The four 16- and 17-formates derived from **9b** must have arisen by a process of substitution rather than of addition to **10b** because no addition to the double bond was detected during the time required for "complete" solvolysis (9 half-lives). When **10b** was kept in formic acid containing 1 molar equiv of *p*-toluenesulfonic acid for 370 half-lives of the formolysis of **9b,** 12% was recovered as a formate fraction which consisted primarily of the two axial isomers (16α and 17β). This corresponds to 0.3% addition during the formolysis of **9b.**[14]



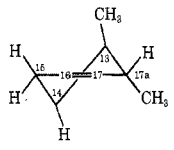
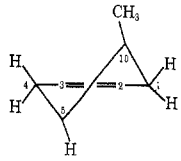
a, R_1 = H c, C=O instead of $CHOR_1$ e, R_1 = Ac; R_2 = H g, R_1 = Ac; R_2 = HCO
b, R_1 = Ac d, R_1 = R_2 = H f, R_1 = R_2 = Ac

Olefin **10b** comprised 90% of the unsaturated compounds that were derived from tosylate **9b**. Two additional products were isolated from the mother liquors. The major one had no olefinic hydrogen. Its ^1H NMR spectrum showed three methyl singlets with the frequencies to be expected from observations[16] on 17a-dimethyl-18-nor-*D*-homo-5α-androst-13-en-3-one (**8c**) (if the published assignments for the 10- and for one of the 17a-methyls are reversed). As in Monneret's[16] work on the 3-ketone, the strongest argument for the 13(14) position of the tetrasubstituted double bond in **8a** lies in the intensity of the $M^+ - CH_3$ peak of the mass spectrum [46% of the base peak (M^+) in our case]. The following observations lend further support to structure **8**. The mass spectrum shows a peak at $M^+ - C_2H_5$ as is to be expected from the work of Aplin et al.[17] Like another 13(14) olefin, **5a** and its acetate **5b**,[18] compounds **8a** and **8b** showed a very intense maximum near 1063 cm^{-1} which in both series disappeared on converting the 3β-ol to the ketone (**5c** and **8c**). As in **5**, the NMR signal of the 19-hydrogens of **8** appears to be essentially unperturbed by the unsaturation. This is not to be expected[19] if the tetrasubstituted double bond occupied the 8(9) position. Because of molecular distortions it may not be justified to exclude the remaining 8(14) location on analogous grounds. However, this position of the double bond is improbable, as it would cause in D-homo steroids a severe interaction between hydrogens at C-7 and C-15.

The French workers[16] obtained the 17a-dimethyl-*D*-homo-13-ene (**8c**) from 17aβ-hydroxy-17a-methyl-*D*-homo-5α-androstan-3-one (**11c**) or from 17a-methyl-*D*-homo-5α-androst-17-en-3-one (**6c**) on treatment with formic acid. When we subjected the corresponding acetoxy compounds **11b** and **6b** as well as **12b** to the conditions of our solvolysis we observed in every instance the formation of **8b** and of the third olefin (**7b**) that we had obtained from the tosylate **9b**. The ir and NMR spectra of **7** showed the presence of olefinic hydrogen. Whereas the C–O stretching frequencies were as expected, the ^1H NMR spectrum of **7a** was most unusual as it showed five methyl signals. Four of these had only 1.5 times the area of the olefinic proton or of the one at C-3, while the fifth had three times the area of a single proton. This could signify two magnetically equivalent ethyl groups (J = 6.9 Hz) and one methyl coupled to a single vicinal hydrogen (J = 6.1 Hz). If, however, the strongest signal (0.81 ppm) results from an accidental coincidence of two lines, the spectrum could be consistent with the presence of three $CHCH_3$ groups. Oxidation of the alcohol **7a** to the ketone **7c** eliminated the first of these possibilities, because the assumed coupling pattern did not persist. There were now six peaks of approximately equal intensity, four very close to signals observed for the alcohol (with downfield shifts of 0.01–0.02 ppm) and two displaced downfield by 0.20 or 0.21 ppm. This large shift is consistently observed for the methyl at C-10 in 5α-steroids.[19] As the spatial relationship between C-3 and C-10 is not duplicated for any other position of the methyl group, a rearrangement involving C-10 and leading to a secondary methyl is as improbable on spectrographic as it is on mechanistic grounds. Accordingly we conclude that olefin **7a** in spite of its sharp melting point and its apparent homogeneity on chromatography, is a 1:1 mixture of two secondary–tertiary olefins, each with three tertiary methyl groups. According to ir evidence, **7** also formed when **8** was dissolved in formic acid and this conversion was reversible. This suggests that each one of the three compounds has the 17a-dimethyl group and that they differ in the position of the double bond (13, 14, and 12).[20] Although no isomers could be detected when **5b** was kept in the medium of the formolysis reaction, similar reversible shifts of the double bond must have occurred as a large uptake of isotopic hydrogen was observed.[4]

In Table I the proportions of the four alcohols (**3, 4, 13,** and **14**) that resulted from the hydroboration of **10** are compared with those of the alcohols obtained from another steroidal olefin which has its double bond similarly placed in a terminal ring.[21] In both experiments we observe strong steric hindrance at that facet of an olefinic carbon (17β in i

Table I
Percentages of Alcohols Obtained by Hydroboration

Of 10b			Of 17,17-ethylenedioxy-5α-androst-2-ene[21]		
 i			 ii		
Atom	Config	%	Atom	Config	%
C-17	β ax	11	C-2	β ax	10
	α eq	21		α eq	26
C-16	α ax	47	C-3	α ax	39
	β eq	21		β eq	24

and 2β in ii) where the C–B bond would create a syn-diaxial interaction with an angular methyl group. The additional methyl at C-17aα which is present in **10**, although likewise axially oriented in the products, has no inhibitory effect on the α-attack at C-16. This is to be expected if the geometry of the transition state resembles the half-chair conformation of the starting compound as has been deduced for hydroboration by Pasto et al.[22] Only the angular methyls in i and ii have nearly true axial orientations whereas the 17a-methyl shows a major *outward* deflection. This would move the 17a-methyl away from C-16 but would allow it to retard an α-attack on the adjacent C-17 position. The apparently somewhat lower yield of the 17α- than of the 2α-ol suggests the operation of such a vicinal effect.

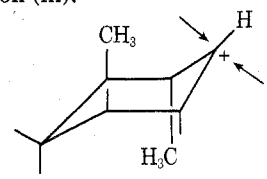
The interpretation of the formolysis of **9b** presents more of a challenge. Pánková et al. explored the acetolysis of a simpler analog, 2β-methyl-4α-*tert*-butylcyclohex-1α-yl tosylate,[23] and observed that the 2β-methyl caused only a minor acceleration but had a major effect on the distribution of the products. The olefins with a vinylic methyl predominated over the one with an allylic methyl, while the esters were confined to substitution products at the site of the tosyloxy group and of the methyl-bearing carbon. In contrast, in the formolysis of **9b** the shift or elimination of a hydrogen from C-16 greatly predominated over the corresponding reactions of the hydrogen at the more highly substituted C-17a (Table II). Our most striking result was an about 5:1 preference for retention over inversion at C-17.

Table II
Solvolyses of Axial Cyclohexyl Tosylates[a]

Products		Substrates			Product
Shifted	Orient	4-BuCy	A-3α	9b	from 9b
		1. Substitution			
−	Axial	0.8	1.2	4.3	3
−	Equat	7.9	4.0	0.9	4
+	Axial	4.3	3.5	6.4	13
+	Equat	0.4	0.1	0.6	14
Unidentified				2.0	
		2. Elimination			
Total		86.5	90.7	84.8	
−		83.5	90.7[b]	76.0	10
+		3.0		7.2	7 + 8

[a] 4-BuCy signifies 4-*cis*-*tert*-butylcyclohexyl tosylate (acetolysis),[24] A-3α, androsterone tosylate (formolysis, corrected for addition).[15] Products are marked shifted (+) if neither the substituted nor either of the unsaturated carbon atoms coincides with the original site of the tosyloxy group. [b] This was a mixture of olefins consisting of the 2-ene and 3-ene in the ratio 9:1.[15]

This may be compared with the 1:8 ratio observed for the cyclohexyl case studied by the Czech workers[23] or the 1:10 ratio obtained for the acetolysis of 4-*cis*-*tert*-butylcyclohexyl tosylate[24] (Table II). This reversal is not simply a solvent effect (cf. the formolysis of androsterone tosylate,[15] Table II) and seems the more remarkable as retention in the substitution of **9b** reintroduces a 1,3-diaxial interaction between the entering ligand and the angular methyl, a feature which is absent in the three other cases. If one postulated that an ion pair in the congested space on the β side of C-17 would dissociate very rapidly, a major obstacle toward retention would be removed. Nevertheless, this would explain the high ratio of **3** to **4** only if one makes the further assumption that a β-attack by the solvent on the C-17 cation would be favored over one from the less hindered α side. This seems most improbable if the ion has the chair conformation (iii).[25]



iii

The interaction between the methyl at C-13 and the ester group would be avoided if the intermediate cation had a nonchair conformation. The spectrum of shapes which this flexible form could assume represents a path of pseudo-rotation between only two boat forms. The first lacks the bow–stern interaction but shows eclipsing effects involving large groups: the 17a-methyl and a methylene (C-12) as well as the 13-methyl and the 17a-hydrogen. In the second boat the 13-methyl causes a particularly severe bow–stern interaction. Both types of destabilizing effects are reduced in the twist form but we still measure distances between nonbonded atoms that are shorter than any found in the chair. It seems hardly possible, therefore, that the transition state of a flexible form of the cation leading to **3g** could have a lower energy than the transition state between the chair conformation of this cation and the equatorial isomer **4g**.

A different mechanism was suggested by Winstein and Holness,[26] who derived the two axial substitution products of 4-*cis*-*tert*-butylcyclohexyl tosylate, the 4-*cis*-*tert*-butyl- and 3-*trans*-*tert*-butylcyclohexyl acetates (or formates) from a hydrogen-bridged cation. Two factors might make such a process more important in our case. The formation of a bridged ion from **9b** would involve the outward and upward movement of the 16α-hydrogen, which can be expected to be favored as it would reduce the 1,3 interaction of this hydrogen with the 17aα-methyl. Moreover, bridging could compensate for any steric hindrance to solvation of a 17-cation that might be caused by the methyl substituents. Actually, the reaction was quite fast, more than ten times faster than the formolysis of androsterone tosylate.[15,27] If a pathway through a bridged ion would indeed have greater importance in the formolysis of **9b** than in the solvolyses of other axial tosylates, this should manifest itself also in a higher yield of the rearranged substitution products. This was the case as our yield of secondary ester formed by hydride shift was exceptionally high.[28]

Olefins **7b** and **8b** must have formed via the tertiary 17a-methyl-17a-cation. This in turn may have formed from the classical C-17 cation or possibly from the 16α-hydrogen-bridged 17-cation by hydride shift. Another conceivable route to the tertiary ion is through protonation of the olefin **6b** which could have formed from **9b** and which was found to be completely isomerized under the conditions of

the solvolysis. Even if all of 7 and 8 were so derived, the total amount of 6 that would have formed in the course of the reaction could not have significantly exceeded the yield of that formolysis product of androsterone tosylate that has a double bond in the corresponding position relative to the ring junctions (5α-androst-3-en-17-one). Therefore the extra methyl at C-17a does not seem to promote the removal of the hydrogen from this site. This too can be rationalized if in a large fraction of the 17-cations the charge was delocalized by a 16α-hydrogen bridge.

Regardless of its origin (**6b, 9b, 11b,** or **12b**), the tertiary cation reacts exclusively by migration of the 13-methyl to C-17a. This distinguishes it from the ion that is generated in the same solvent from uranediol 3-acetate 17a-tosylate. In the latter case, methyl migration, if it occurs at all, still remains to be demonstrated.

Experimental Section

General Procedures. Melting points are corrected. Rotations were measured by means of a Perkin-Elmer polarimeter (Model 141) on solutions in $CHCl_3$, and ir spectra by means of a Perkin-Elmer grating photometer (Model 421) on solutions in CS_2, except the diols which were examined as pressings in KBr. The peaks listed are those characteristic of functional groups and other prominent bands. NMR spectra were recorded for solutions in $CDCl_3$ containing Me_4Si on Model HA-100 or, if the steroid concentrations were low, on Model XL-100 of Varian. Shifts are given in parts per million downfield from Me_4Si. For uv spectra a Beckman spectrophotometer with photomultiplier was used.

Steroids were usually extracted from the diluted reaction mixture with ether; if the medium was formic acid, distribution between benzene and water was used. These organic phases were washed (when appropriate) with dilute hydrochloric acid, sodium carbonate, and water and were taken to dryness under reduced pressure. Chromatography was done on silica gel. Departures from these procedures are indicated in the text.

The homogeneity of the various compounds was deduced from the observation that they and their derivatives gave single spots on TLC and from the constancy of their ir spectra when the purified samples were obtained from different starting materials and when they were subjected to further attempts at fractionation. Yields were determined by the weight of pure material. For this purpose each component that had been separated by chromatography was purified by recrystallization. The mother liquors were fractionated by chromatography on longer columns. The purity of the ensuing fractions was ascertained by ir comparison with the recrystallized reference samples and by TLC. Occasionally very minor fractions were encountered which were still mixtures. Their weight was allotted to their respective components in accordance with the intensity of the spots on TLC.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17-one (2b). 5α-Pregn-(*Z*)-17(20)-en-3β-yl acetate[29] was converted to the 17α,20α-glycol[6] (mp 190.5–192.5°) according to the procedure of Baran[30] and then to its 20-tosylate[6] (**1b,** mp 138–140°). After solvolysis of 82 mg as described by Williams et al.[6] (method A), the product (57 mg) was chromatographed on silica gel which had been deactivated with water and dried by exposure to air. Elution with benzene–hexane (1:1) and with benzene gave 25 mg of **17α,20β-epoxy-5α-pregnan-3β-yl acetate,** mp 172–175° after recrystallization from dilute acetone (reported[6] mp 153–170°).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.83; H, 10.24.

The later eluates (32 mg, obtained with benzene) contained ketone **2b.** An identical product was obtained by keeping a solution of 100 mg of **1b** in 2 ml of benzene and 100 ml of formic acid at 25° for 170 min. The neutral product (71 mg) when chromatographed on deactivated silica gel (see above) gave two unidentified nonketonic products followed by 68 mg of ketone **2b** which was recrystallized from acetone–petroleum ether. Two crystal modifications (mp 120–122.5° and 131.5–132.5°) were observed, $[\alpha]^{30}D$ −27° (reported[5,6] mp 127–129° and 125–129°, $[\alpha]D$ −49°).[31]

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.62; H, 10.13.

Reduction of 3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17-one (2b). A mixture of **2b** (166 mg), 333 mg of lithium tri-*tert*-butoxyaluminohydride, and 9 ml of dry tetrahydrofuran was kept at room temperature for 17 hr, diluted with solvent, chilled, and treated dropwise with 1 *N* HCl. The neutral reaction product, which was homogeneous on chromatography, was recrystallized from hexane-benzene. **3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-ol (3e)** had mp 167–168°; $[\alpha]^{24}D$ −31°; ^1H NMR ($CDCl_3$) 0.81 (19-H), 0.87 (d, J = 7.4 Hz, 17a-methyl), 1.13 (18-H), 2.01 (H_{OAc}), 3.82 ppm (17-H, m with half-intensity band width 5 Hz as compared to 22 Hz for 3α-H); ^1H NMR (C_5D_5N) 0.74,[32] 0.92 (d, 7.5 Hz), 1.46 (18-H), 2.04, 4.06 ppm (17-H);[10] ir, OH, 3611 (ν_+/ν_- 0.96),[2,8] 985; 3β-OAc, 1736, 1028 cm^{-1}.[33]

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.55; H, 10.81.

When the reduction of **2b** was carried out with lithium aluminum hydride in ether, recrystallization of the reaction product from acetone–methanol gave **17aα-methyl-*D*-homo-5α-androstane-3β,17β-diol (3d):** mp 198–200°; ir 1035 (3β-OH)[33] and 987 cm^{-1}. The mother liquors on TLC yielded, in addition to **3d, 3e, 4d,** and **4e.** (This unusual but to us useful preservation of an ester group evidently was caused by the great age of our preparation of the hydride.) Of the total reaction products 80% had the 17β configuration.

Hydroboration of 17aα-Methyl-*D*-homo-5α-androst-16-en-3β-yl Acetate (10b). Diborane was generated slowly and without heating from $NaBH_4$ and BF_3·Et_2O. It was passed during 55 min through a solution of 52 mg of **10b** in 4 ml of tetrahydrofuran maintained at 20°. After an additional 1 hr the mixture was diluted with solvent and kept at 1 ± 1° with stirring while 0.7 ml of ice water and then a chilled 3:2 mixture (2.8 ml) of 10% sodium carbonate and 30% H_2O_2 were added dropwise. After 1 hr at this temperature the neutral reaction product was isolated, adsorbed from benzene on silica gel, and eluted with 4% ethyl acetate in benzene to yield material without a hydroxyl group (5%), the four 3β-acetoxy 16- and 17-carbinols (68%) and with 40% ethyl acetate the combined diols (26%). The products are listed in their order of elution.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-ol (3e): for characterization see above.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17α-ol (4e) was recrystallized from 95% methanol: mp 172–173.5°; ir 3612 (ν_+/ν_- 0.72), 1733 and 1027 (3β-OAc), 1015 cm^{-1}.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-16α-ol (13e) was recrystallized from 95% methanol: mp 156.5–158°; ir 3612 (ν_+/ν_- 1.04), 1732 and 1031 (3β-OAc), 1019 cm^{-1}.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-16β-ol (14e) was recrystallized from 90% acetone: mp 162.5–163°; ir 3608 (ν_+/ν_- 0.67), 1732 and 1025 (3β-OAc), 1036 cm^{-1}.

The diol fraction was again adsorbed and fractionated by elution with 20% ethyl acetate in benzene into **3d** (see above), **4d** [mp 201.5–202°; ir 1035 (3β-OH) and 1018 cm^{-1}], **13d** [ir 1039 (3β-OH) and 1021 cm^{-1}], and **14d.** They were identified by converting them and the corresponding monoacetates to the common diacetates. The combined percentages of the four stereoisomeric forms, obtained by hydroboration as diols and monoacetates, are given in Table I. The properties of the diacetates were as follows.

17aα-Methyl-*D*-homo-5α-androstane-3β,17β-diol diacetate (3f) was amorphous: ir 1029 (3β-OAc) and 1013 cm^{-1}.

17aα-Methyl-*D*-homo-5α-androstane-3β,17α-diol diacetate (4f) was recrystallized from methanol: mp 207.5–209°; ir 1027 (3β-OAc) and ~1019 cm^{-1} (shoulder).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.21; H, 10.18.

17aα-Methyl-*D*-homo-5α-androstane-3β,16α-diol diacetate (13f) was recrystallized from dilute methanol: mp 136–138°; ir 1031 (3β-OAc) and 1019 cm^{-1}.

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.37; H, 9.91.

17aα-Methyl-*D*-homo-5α-androstane-3β,16β-diol diacetate (14f) was recrystallized from methanol: mp 174.5–175.5°; ir 1030 (3β-OAc) and ~1021 cm^{-1} (shoulder).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.27; H, 10.16.

3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl Tosylate (9b). Acetoxycarbinol **3e** (105 mg) and 1.2 g of *p*-toluenesulfonyl chloride were kept in 1.5 ml of pyridine for 3 hr. The neutral reaction product was recrystallized from 96% acetone: mp 135–137°; ir, OAc bands 1734, 1240, 1029; general tosylate bands[2] 1306, 1188, 1177, 1098, 1020; specific tosylate bands 924, 913, 900, 827, 812, 683, 659, 582 cm^{-1}.

Formolysis of 3β-Acetoxy-17aα-methyl-*D*-homo-5α-androstan-17β-yl Tosylate (9b). A solution of 100 mg of **9b** in 4 ml of benzene was diluted with 200 ml of dry formic acid and kept at 23°

for 70 min. The neutral reaction product (68.8 mg), which showed no tosylate absorption, was adsorbed on deactivated silica gel. Elution with benzene–hexane (1:1) gave 57.6 mg of olefins, with benzene 0.0 mg, and with 12% acetone in benzene 11.7 mg of formates.

The formate fractions from two such runs were hydrogenolized[26] with lithium aluminum hydride to the diols which on recrystallization from acetone–methanol gave **13d** (mp 208–210°). The mother liquors were chromatographed as described for the diols obtained by hydroboration. An incompletely fractionated mixture of **4d** and **13d** was separated by preparative TLC (25% ethyl acetate in benzene). The mother liquors of **3d** and **13d** each contained at least one additional diol which readily separated by acetylation and chromatography because these side products gave monoacetates. They were not identical with **11b** or **12b** or any of the other monoacetates described in this paper.

Diols **3d, 4d, 13d,** and **14d** and their diacetates were identified by comparisons (TLC, ir, melting point) with the reduction products of **2b** and the hydroboration products of **10b.** Uranediol and its diacetate, which could not be separated by chromatography from **3d** and **3f,** respectively, were not detected in the mother liquors of **3d** and **3f** by ir spectroscopy.

The olefin fraction (57.6 mg obtained from the formolysis of **9b**) on recrystallization from 95% acetone gave 44.2 mg of **17aα-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (10b):** mp 104–106°; $[\alpha]^{28}D$ −139°; ir, olefinic frequencies 3061, 3014 (strong), 1656, 717 (very strong); 3β-acetoxy 1737, 1242, 1029 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.67; H, 10.85.

Another 7.4 mg of **10b** was obtained by chromatographing the mother liquors on silica gel–silver nitrate (prepared by stirring 1.4 g of $AgNO_3$ in 2 ml of water and 12 ml of acetone with 10 g of silica gel, filtering, washing with acetone, and drying at 75° for 4 hr).

On this column **8b** (3.0 mg) and product **7b** (1.9 mg) were eluted ahead of **10b** with benzene–hexane (1:1). The sample of **8b** which was not crystalline had the same ir spectrum as the ones obtained from **6b, 11b,** and **12b.** It was hydrolyzed with methanolic potassium hydroxide and recrystallized from dilute acetone. **17a-Dimethyl-18-nor-*D*-homo-5α-androst-13-en-3β-ol (8a)** had mp 154.5–155.5°; ^1H NMR 0.76 (19-H), 0.94 and 0.98 ppm (17a-methyls). (A further prominent signal at 1.46 ppm disappeared on adding D_2O.) The ir spectrum agreed with that of the higher melting sample described below.

The next eluate (**7b**) had ^1H NMR peaks at 0.76, 0.83, 0.89, 0.98, 1.05 and 2.03 (very weak curve). Its ir spectrum (3β-OAc, 1026 cm^{-1}) agreed with those of the preparations obtained from **6b, 11b,** and **12b.** (The relatively high ratio **7:8** observed in the formolysis of **9b** may have been caused by autoxidation of **8b** during the isolation which was much more protracted than the fractionations reported below.)

17a-Methyl-*D*-homo-5α-androst-17-en-3β-yl Acetate (6b). 3β,17aβ-Dihydroxy-17a-methyl-*D*-homo-5α-androstan-17-one (mp 199–201°, reported[34] 200–200.5°) was prepared from 3β-acetoxy-17α-hydroxy-5α-pregnan-20-one by method d (15 min, base 0.2 *N*) of Kirk and Mudd.[35] It was subjected to the Wolff–Kishner reaction under the conditions described by Turner et al.[36] The product gave on chromatography in the early eluates **17a-methyl-*D*-homo-5α-androst-17-en-3β-ol (6a)** (mp 159–161°, reported[37] 159–160°). Its acetate (**6b**) after recrystallization from methanol had mp 131–132°; $[\alpha]^{25}D$ + 48°; ir, 3β-acetoxy 1736, 1241, 1028; =CH 3023, 794; other 1054 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.15; H, 10.52.

3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aβ-ol (11b). The later eluates of the chromatogram of the Wolff–Kishner products contained an impurity with absorption near 3020 cm^{-1} suspected to be the 16,17-dehydro analog of **11a.** It was removed after acetylation by repeated chromatography. Recrystallization of the somewhat less mobile material from methanol gave **11b:** mp 187–188°; $[\alpha]^{24}D$ −15°; ir, 3β-acetoxy 1735, 1244, 1025; 17a-OH 3610 and on the basis of its intensity 1049 cm^{-1}; the band at 1060 cm^{-1} serves best to distinguish **11b** from **12b.**

Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.04; H, 10.81.

3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aα-ol (12b). Compound **6b** (20 mg) was treated with 20 mg of *m*-chloroperoxybenzoic acid in 0.6 ml of methylene chloride for 140 min. The resulting **17α,17aα-epoxy-17a-methyl-*D*-homo-5α-androstan-3β-yl acetate** was recrystallized from acetone: mp 157–159° (reported[38] 158–160°, see also ref 39); $[\alpha]^{24}D$ +22°;[40] ir, 3β-acetoxy 1733, 1242, 1027; others 1053, 1042 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.40; H, 10.04.

This epoxide was treated with lithium aluminum hydride under the conditions reported by Ruzicka et al.[41] The product was acetylated and although essentially homogeneous (TLC) was chromatographed. 3β-Acetoxy-17a-methyl-*D*-homo-5α-androstan-17aα-ol (**12b**) had mp 159.5–160° (reported[42] 152.5–154 or 117–118°); $[\alpha]^{24}D$ −25° ($CHCl_3$ or dioxane) (reported[42] −40°, dioxane; for reference data on analogs in $CHCl_3$ see ref 41); ir, 3β-acetoxy 1732, 1244, 1028; 17a-OH 3617, 1019 cm^{-1}. On TLC [SiO_2–$CaSO_4$ dried for 7 hr at room temperature, benzene–ethyl acetate (85:15)] **12b** and **11b** each traveled as a single spot, clearly separated from the other (R_f 0.59 and 0.52, respectively).

Alternative Sources of 7 and 8. Compounds **6b, 11b,** and **12b** (0.04 mmol) were each dissolved in 0.8 ml of benzene and diluted with 41 ml of formic acid containing 0.04 mmol of *p*-toluenesulfonic acid monohydrate and kept at room temperature for 70 min. The reaction products, which had very similar ir spectra, were adsorbed on silica–silver nitrate. Elution was completed within 2 hr and gave in each case **8b** and **7b.** Product **7b** comprised 20 ± 2% of the total. (This ratio was not altered when **6b** was kept in the formic acid medium for 69 hr.) The fractions with identical ir spectra were combined, hydrolyzed, and recrystallized. **17a-Dimethyl-18-nor-*D*-homo-5α-androst-13-en-3β-ol (8a)** had mp 165–167°; ir, 3β-OH 3610, 1039; 1064 cm^{-1} (equally strong); $[\alpha]^{26}D$ −104°; mass spectrum M^+ (base peak, 24% of intensity sum of spectrum) calcd for $C_{21}H_{34}O$, 302.2610; found, 302.2580; signals with mass >150 and intensity >5% of base peak (except isotopic satellites) $C_{21}H_{33}O$, $C_{20}H_{31}O$, $C_{21}H_{33}$, $C_{20}H_{29}$, $C_{16}H_{23}$, $C_{13}H_{20}$, $C_{13}H_{19}$, $C_{12}H_{17}$; uv in cyclohexane, only end absorption down to 200 nm.

The hydroxy olefins derived from the later eluates gave **7a** with mp 121.5–123.5°; ir, 3β-OH 3612, 1040; =CH 3051, 829; others 1051 cm^{-1}; ^1H NMR 0.74 (19-H), 0.81 (19-H and 17a-methyl), 0.88, 0.98, and 1.04 ppm.

The appearance of the ir bands of **7a** could also be demonstrated after **8a** had been exposed to the formic acid medium (70 min) and the resulting mixture of the 3-formates of **7** and **8** had been hydrolyzed.

Oxidation of Hydroxyolefins 7a and 8a to 3-Ketones. A sample of **8a** (2.8 mg) in 0.5 ml of acetone was stirred at 12° for 1 min after the addition of 5 μl of the CrO_3–H_2SO_4 reagent of Bowers et al.[43] The neutral product (**8c**) [ir 1713 cm^{-1} (C=O) (reported 1720 cm^{-1}),[16] no hydroxyl, other peaks 1215 and 1167 cm^{-1}] was recrystallized from dilute methanol, mp 143–145° [reported 140° (uncorrected)].[16]

Preparation **7a** (3.4 mg) was oxidized under the same conditions. The product contained unwanted absorption near 1670 cm^{-1}. This contaminant was removed by chromatography and recrystallization. Preparation **7c** had ir, C=O 1712; =CH 3052 and 829; other 1223 cm^{-1}; ^1H NMR 0.83, 0.90, 0.95 (19-H), 0.99, 1.01 (19-H), 1.05 ppm.

After exposure of **7c** to the formic acid medium, the ir spectrum changed to that of a mixture of predominantly **8c** with **7c.** On reduction with lithium tri-*tert*-butoxyaluminohydride the strong peak of **8a** at 1064 cm^{-1} appeared.

Oxidations of 13e and 14e. Solutions of 800 μg of 3β-acetoxy-17aα-methyl-*D*-homo-5α-androstan-16α-ol (**13e**) and of its 16-epimer (**14e**) in 1.7 ml of 90% acetic acid were each mixed at zero time with an equal volume of 90% acetic acid containing 323 μg of chromium trioxide. The mixture was maintained at 20.6° while its extinction at 350 nm was measured. The constants (k) of the rates of oxidation follow: **13e,** 2.07; **14e,** 0.112 M^{-1} sec^{-1}[$k = [1.535/(a - b)t] \log[b(a - x)/a(b - x)]$, where a, $a - x$ represent the molar concentrations of CrO_3 at times zero and t, respectively, and b represents ⅔ of the molar concentration of the alcohol at time zero.] The rate ratios **13e/14e:** found, 18.5; expected 15.4 from the structural factors given by Schreiber and Eschenmoser.[13] At the end of each run the reaction product (**15b**) was isolated. The ir spectra agreed and showed ν_{max} at 1736, 1711, and 1028 cm^{-1}.

Rate of Formolysis of Tosylate 9b. This process was measured under the same conditions as were specified for the preparative run, but was terminated by distribution between benzene and water after 5 and 10 min, respectively. The fraction of tosylate remaining was determined from the extinctions at 1098 and 683 cm^{-1}. The first-order rate constant was 1.48×10^{-3} sec^{-1}, corresponding to a half-life of 7.8 min. The ir curves after 5, 10, and 70 min showed no bands attributable to an isomeric tosylate.

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Registry No.—**1b,** 1914-30-3; **2b,** 2270-04-4; **3d,** 56665-84-0; **3e,** 56665-85-1; **3f,** 56665-86-2; **4d,** 56665-87-3; **4e,** 56665-88-4; **4f,** 56665-89-5; **6b,** 56665-90-8; **7a** isomer 1, 56665-91-9; **7a** isomer 2, 56665-92-0; **7b** isomer 1, 56665-93-1; **7b** isomer 2, 56665-94-2; **7c** isomer 1, 56665-95-3; **7c** isomer 2, 56665-96-4; **8a,** 56665-97-5; **8c,** 31751-19-6; **9b,** 56665-98-6; **10b,** 56665-99-7; **11b,** 56666-00-3; **12b,** 56666-01-4; **13d,** 56666-02-5; **13e,** 56666-03-6; **13f,** 56666-04-7; **14e,** 56666-05-8; **14f,** 56666-06-9; **15b,** 56666-07-0; 17α,20β-epoxy-5α-pregnan-3β-yl acetate, 56666-08-1; diborane, 18099-45-1; *p*-toluenesulfonyl chloride, 98-59-9; 3β,17aβ-dihydroxy-17a-methyl-*D*-homo-5α-androstan-17-one, 3751-01-7; *m*-chloroperbenzoic acid, 937-14-4; 17α,17aα-epoxy-17a-methyl-*D*-homo-5α-androstan-3β-yl acetate, 56666-09-2.

References and Notes

(1) Supported by Grants AM 9105 and K6-AM-14367 of the National Institutes of Health.
(2) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31,** 375 (1966).
(3) F. B. Hirschmann and H. Hirschmann, *J. Org. Chem.*, **38,** 1270 (1973).
(4) S. S. Deshmane and H. Hirschmann, *J. Org. Chem.*, **38,** 748 (1973).
(5) F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.*, **77,** 134 (1955); **78,** 644 (1956).
(6) K. I. H. Williams, M. Smulowitz, and D. K. Fukushima, *J. Org. Chem.*, **30,** 1447 (1965).
(7) Williams et al.[6] isolated 3% of this epoxide but accounted only for 53% of their product. They used alumina for its separation which at least in our hands caused some destruction of the epoxide.
(8) H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85,** 3046 (1963).
(9) D. H. Williams and N. S. Bhacca, *J. Am. Chem. Soc.*, **86,** 2742 (1964).
(10) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90,** 5480 (1968).
(11) To permit these and other studies of the 3-monoacetates, the conditions of hydroboration were modified for an improved preservation of the ester group of **10b.**
(12) For references see J. E. Page, *J. Chem. Soc.*, 2017 (1955).
(13) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta,* **38,** 1529 (1955).
(14) As a result, the formolysis of **9b** would be a far more suitable object than that of androsterone tosylate[15] for the precise determination of the effect of isotopic substitution of a neighboring hydrogen on the rate of formation of the individual formolysis products.
(15) J. Ramseyer and H. Hirschmann, *J. Org. Chem.*, **32,** 1850 (1967).
(16) C. Monneret and Q. Khuong-Huu, *Bull. Soc. Chim. Fr.*, 623 (1971).
(17) R. T. Aplin, H. E. Browning, and P. Chamberlain, *Chem. Commun.*, 1071 (1967).
(18) F. B. Hirschmann, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron,* **27,** 2041 (1971).
(19) R. F. Zuercher, *Helv. Chim. Acta,* **46,** 2054 (1963).
(20) As the prototropic shifts are reversible the reaction seems to be under thermodynamic control. Judging from models, the more stable structures have the 13β-H in the 14-ene and the 14α-H in the 12-ene.
(21) J. Ramseyer, J. S. Williams, and H. Hirschmann, *Steroids,* **9,** 347 (1967).
(22) D. J. Pasto and F. M. Klein, *J. Org. Chem.,* **33,** 1468 (1968); D. J. Pasto, B. Lepeska, and T.-C. Cheng, *J. Am. Chem. Soc.,* **94,** 6083 (1972).
(23) M. Pánková, J. Sicher, M. Tichý and M. C. Whiting, *J. Chem. Soc. B,* 365 (1968). Their compound is named according to rule d: *Chemical Abstracts,* **76,** Index Guide, Section IV, 86l (left column) (1972).
(24) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B,* 355 (1968).
(25) This is borne out by measurements analogous to those reported by J. A. Marshall and R. D. Carroll, *J. Org. Chem.,* **30,** 2748 (1965), for axial hydrogens. At *any* fixed C-17–O distance assumed for the transition state, the oxygen would be closer to a methyl group if it is on the β rather than on the α side.
(26) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.,* **77,** 5562 (1955).
(27) As this axial tosylate lacks a 1,3 interaction between the tosyloxy and a methyl group, some but possibly not all of the acceleration is to be attributed to the lessened strain between these groups in the transition state. For the probable magnitude of this effect in acetic acid see S. Nishida, *J. Am. Chem. Soc.,* **82,** 4290 (1960).
(28) The high yield of the 16α isomer also argues against the possibility that the steric preference at C-17 could have been caused by a rapid equilibration between C-17 and C-16 open cations. If the "windshield wiper effect" [H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Am. Chem. Soc.,* **87,** 2137 (1965)] of the 16α-hydrogen were operative in our case we would expect it to block α-attack about as effectively at C-16 as at C-17.
(29) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.,* **98,** 604 (1965).
(30) J. S. Baran, *J. Org. Chem.,* **25,** 257 (1960).
(31) This value is disconcertingly close to the one reported for the more stable 17a epimer (−51°)[5] and not in good accord with those reported by the same authors for **2a** and **2c.**
(32) This upfield shift for the 19-H agrees with observations on 3β-acetoxy-5α-steroids made by von Bruno Hampel and J. M. Kraemer, *Tetrahedron,* **22,** 1601 (1966).
(33) R. N. Jones and F. Herling, *J. Org. Chem.,* **19,** 1252 (1954); *J. Am. Chem. Soc.,* **78,** 1152 (1956).
(34) D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Am. Chem. Soc.,* **77,** 6585 (1955).
(35) D. N. Kirk and A. Mudd, *J. Chem. Soc. C,* **2045** (1970).
(36) R. B. Turner, R. Anliker, R. Helbling, J. Meier, and H. Heusser, *Helv. Chim. Acta,* **38,** 411 (1955).
(37) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta,* **26,** 185 (1943).
(38) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta,* **24,** 1321 (1941).
(39) R. J. W. Cremlyn, D. L. Garmaise, and C. W. Shoppee, *J. Chem. Soc.,* 1847 (1953).
(40) There is a wide discrepancy between the differences in molecular rotations of various 17a-methyl-*D*-homo-17α,17aα-epoxides[39,41] and the standard values for transformations in the A and B rings of steroids as given by D. H. R. Barton and W. Klyne, *Chem. Ind. (London),* 755 (1948). Our measurement is in reasonable accord with the rotation reported by Ruzicka et al.[41]
(41) L. Ruzicka, N. Wahba, P. T. Herzig, and H. Heusser, *Chem. Ber.,* **85,** 491 (1952).
(42) E. Hardegger and C. Scholz, *Helv. Chim. Acta,* **28,** 1355 (1945).
(43) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.,* 2548 (1953).

Synthesis of α-Methylene Lactones by Reductive Amination of α-Formyl Lactones. Scope and Limitations

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The synthesis of α-methylene lactones by reductive amination of α-formyl lactones with sodium cyanoborohydride and dimethylamine is described with regard to its scope and limitations. The α-methylene lactones α-methylene-δ-valerolactone (**10**), α-methylene-*trans*-2-hydroxycyclohexaneacetic acid γ-lactone (**13**), α-methylene-*cis*-2-hydroxycyclohexaneacetic acid γ-lactone (**16**), and 3-methylene-3,4-dihydrocoumarin (**23**) are prepared from their α-formyl lactones. The α-methylene lactone of 2-coumaranone could not be synthesized by this procedure.

As a counterpart to our development of a synthesis of α-methylene-γ- or -δ-lactones by reductive amination of the corresponding α-formyl lactones,[3a] which enabled an efficient synthesis of tulipalin A and pentaacetyl tuliposide A,[3b] we decided to examine the scope and limitations of this method. In view of the continued great interest in synthetic methods for construction of α-methylene-γ- and -δ-lactone units,[4] which are found in a variety of biologically active natural products,[5] such a study was felt to be necessary to truly define the generality of our synthetic approach. We now report the successes and failures of our investigation.