D-Homosteroids. 6.[1] Diverse Bond Shifts in the Solvolyses of Uranediol 3-Acetate 17a-Tosylate[2]

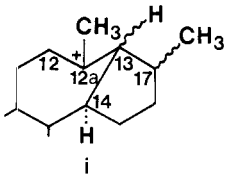
Y. Gopichand and H. Hirschmann*

Department of Medicine, University Hospitals and Case Western Reserve University, Cleveland, Ohio 44106

Received July 5, 1978

The main products of the solvolysis of 3β-acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl tosylate (**1a**) and of 3β-acetoxy-5α-pregnan-20β-yl tosylate (**21a**) in buffered acetic acid have been identified. Those obtained from **1a** include *D*-homosteroids [uranediol diacetate (**2c**), its 17a-epimer (**4c**), 17-methyl-*D*-homo-5α-androst-16-en-3β-yl acetate (**10a**), its 17(17a)-bond isomer (**5a**), and 17α,17a-dimethyl-18-nor-*D*-homo-5α-androst-13(17a)-en-3β-yl acetate (**15a**)], compounds resulting from a migration of the 16,17 bond [(*E*)-5α-pregn-17-en-3β-yl acetate (**16a**), 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**18a**), and both 20-epimers of 5α-pregnane-3β,20-diol diacetate (**26c** and **27c**)], and compounds resulting from a shift of the 13,14 bond [12a,17α-dimethyl-18-nor-*C*-homo-5α-androst-12(12a)-en-3β-yl acetate (**9a**) and its 12a(13)-bond isomer (**6a**)]. Both **6a** and **9a** reverted to *D*-homosteroids in formic acid, yielding uranediol 3-acetate 17a-formate (**2e**) as the major and 3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate (**3e**) as the lesser product. When these reconversions were repeated in HCOOD, varying numbers of ^2H (up to about 15) were taken up. The mole fractions containing any given number of ^2H were compared with those of the same formates that had been obtained by the solvolysis of **1a** in HCOOD. This comparison indicated that the two *C*-homoolefins (**6a** and **9a**) are intermediates in the conversion of **1a** to the isomeric formate (**3e**) and to a small fraction of the normal formate (**2e**). When the two esters were obtained from either olefinic precursor the pattern of isotope incorporation into **2e** differed from that into **3e** in a manner that indicated that the inversion 17α → 17β is not easily reversed during the extensive migrations of the double bond. The main product of a brief acetolysis of the 20β-tosylate **21a** was the 17aβ-tosylate **1a**. As was therefore to be expected, the 20β-tosylate gave all products derived from **1a**. Of these the yields of **18a** and of the compounds with the pregnane skeleton were increased and those of all other products diminished. It further yielded three 5α-pregnen-3β-yl acetates having a 16, 17(*Z*), or 20 double bond (**24a, 22a,** and **23a**). An explanation is offered for the fact that the acetolysis of the 17aβ-tosylate **1a** produced much higher yields of rearranged products than did the formolysis.

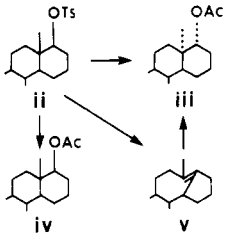
The formolysis of uranediol 3-acetate 17a-tosylate (**1a**) is characterized by a high (~400) ratio of retention (**2e**) to inversion (**4e**) for the substitution of C-17a.[3] This was attributed to the participation of an antiparallel bond (C-13—C-14 or C-16—C-17) in the ionization. Further study of the reaction mechanism received strong impetus with the characterization of a minor side product (**3e**) which was found to differ from **2e** in the configuration at C-13 (as well as C-17a and C-17).[4] The inversion at C-13 must have involved an intermediate possessing only three ligands at this center. We suggested a carbocation (i) formed by migration of the 13,14



i

a, 13α; 17α
b, 13β; 17β
c, 13α; 17β

bond of the *D*-homosteroid to C-17a. This inversion would be followed or preceded (ib) by one at C-17 and the complete reaction was pictured as proceeding through several cationic intermediates. Khattak and co-workers[5] studied the acetolysis of a 17aβ-tosylate lacking the methyl at C-17 (ii) and observed the formation of rather large amounts of the 13α-*D*-homosteroid iii in addition to the main substitution product iv, provided the medium was unbuffered. In the presence of potassium acetate about 60% of the reaction products were a mixture of olefins of which 85% was shown to have the hydroazulenic structure v. In unbuffered acetic acid the initial reaction products showed an even higher proportion of olefins which, judging from the yields given, were slowly being converted to the two major substitution products, iii and iv. The case for an olefinic intermediate in the formation of iii from ii was made even more compelling when it was shown that iii when formed in unbuffered CH_3COOD contained 10–17 atoms of

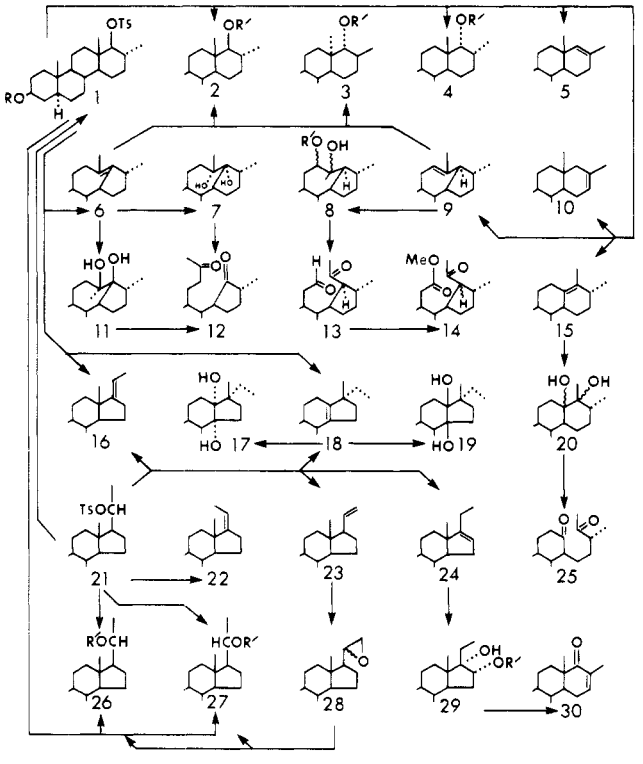


deuterium with the most labeled molecular ion being the dominant one in the mass spectrum. It was suggested that C-7 and all atoms of the C and D rings including the methyl but excluding C-16 had become labeled by migrations of the double bond of v through (and beyond) the hydroazulene system. This process if equally applicable to **1a** would account for the inversion at C-17 by removal of the β-proton and reprotonation from the α side.[5] The British group could detect no uptake of deuterium by acetate iv and deduced that it was formed by a more direct path not involving skeletal rearrangements. We find a complete absence of deuterium hard to reconcile with data (their Table) that show major increases in the yield of iv simultaneously with decreases in the amounts of olefin occurring at a time when the original substrate (ii) must have been consumed.

We have tested the applicability of these mechanistic proposals to the formolysis of uranediol acetate tosylate (**1a**) by conducting the reaction in HCOOD. We observed that the diol (**3d**) derived from the isomeric formate **3e** had become labeled with up to 15 or 16 atoms of deuterium. The NMR spectrum of the diacetate (**3c**) revealed that the hydrogens at C-17a and C-17 were almost completely replaced by the isotope as there was only a weak singlet[6] produced by the 17a-H. All methyl groups appeared as singlets with no apparent differences in their areas. The deduction that little or no deuterium had entered the 13- and 17-methyls is further supported by the mass spectrum of **3d**, if it can be assumed that the fissions of these methyls contribute to the peaks of the $M^+ - 15$ group. The hydrogens at C-16 evidently underwent isotopic ex-

0022-3263/79/1944-0185$01.00/0

Scheme I. Products of the Acetolyses of 3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (1a) and of 3β-Acetoxy-5α-pregnan-20β-yl Tosylate (21a) and Their Identification



a, R = Ac c, R = R′ = Ac e, R = Ac ; R′ = Fo
b, R = H d, R = R′ = H f, R = Ac ; R′ = H

change. This was deduced from the observation of an ion $C_5H_3D_6O^+$. This can arise from a fragment extending from C-15 to C-17a with the loss of one ^1H, if all hydrogens except those of the methyl and of the hydroxyl group are ^2H. This difference from the results obtained in Kirk's laboratory[5] was not unexpected. In iii C-16 can become labeled only by formation of a disecondary olefin[5] whereas in our case a 16,17 double bond is trialkylated.

If all hydrogen atoms attached to C-7 and to all carbon atoms forming the C and D rings can exchange, a total of 15 atoms would be involved. An ion with the composition $C_{13}H_{22}O^+$ was obtained from the unlabeled compound which appears to comprise C-7, the carbons of rings C and D, and their attached methyls because an analogous cleavage has been observed for 5α-cholestane, which was shown to involve at least in part (≥60%) a reciprocal hydrogen transfer between the two fragments.[8] The most labeled species of $C_{13}H_{22}O^+$ in the spectrum of **3d** was found to contain 14 atoms of ^2H. Therefore, except for the differences noted above, the labeling pattern deduced for maximally labeled **3d** is consistent with the one proposed[5] for iii and is quite well supported by our mass spectral data. However, compared to the slow acetolysis of ii at 75 °C, the formolysis of **1a** at room temperature gave such extensively labeled esters with much lower frequency, and most contained fewer ^2H atoms than the minimal number previously observed.

In contrast to iv, uranediol (**2d**) was found to be labeled. As the fraction of molecules containing excess deuterium only amounted to about 6% it seemed important to show that this finding could not have been caused by contamination of the analytical sample with the 13α-stereoisomer. The mass spectra of the unlabeled compounds show a striking difference between the two isomers in the ratios $(M^+ - H_2O) - M^+$, being 0.11 for the 13β and 6.4 for the 13α-compound. Therefore, if the latter were responsible for the ^2H seen in the M^+ region of uranediol, much stronger signals than these should have been observed for the corresponding satellites of $M^+ - 18$. As the reverse was the case, this explanation could be dismissed. We, therefore, conclude that there are two pathways from **1a** to **2e**, of which only the lesser one involves olefinic intermediates.

The isotope incorporation into uranediol was too small to allow us to study the mechanism of the minor pathway. This objective required the preparation of the primary olefinic intermediate. To obtain it we subjected **1a** and the more readily available 3β-acetoxy-5α-pregnan-20β-yl tosylate (**21a**) to solvolysis in buffered acetic acid.[9] Olefins were obtained in good yields (45 and 55%, respectively) but proved to be complex mixtures. We examined these fractions in greater detail than originally planned when it became evident that several novel pathways of these solvolytic reactions were being encountered.

The olefins resulting from the acetolysis of **1a** appeared to be homogeneous on TLC with silica gel, but could be separated into four fractions on silica gel that had been impregnated with silver nitrate. The first of these fractions showed no olefinic hydrogen on IR or NMR examination. On exposure to formic acid it gave a mixture of the formates **2e** and **3e** in which the isomer with the *normal* configuration (**2e**) predominated and a residual olefin which had an IR spectrum that closely resembled that of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**18a**).[10] The presence of this olefin as an original constituent of fraction 1 was firmly established by treating this fraction with osmium tetroxide. Four glycols were observed after cleavage with bisulfite.[11] The fastest moving of these was identical with 3β-acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13β,14β-diol (**19a**)[10] according to IR comparison, mp, and mixture mp and by conversion of the parent triol (**19b**) to the known[10] 13,14-seco diketone for which the presence of an ethyl group was clearly shown by a well resolved triplet at 0.80 ppm. As the glycol with inverted configurations at C-13 and C-14 (**17a**) does not cleave from its osmate[10] under the conditions of Baran,[11] we have searched for and identified this glycol among the complex mixture of additional products that were released from the remaining colored esters with lithium aluminum hydride.

The second and fourth glycols that had been split from their osmates with bisulfite were hydrolyzed to triols (**7b** and **11b**)[12] which gave the same seco compound (**12b**) with lead tetraacetate. It had carbonyl peaks at 1737 and 1719 cm^{-1}. The former signifies a cyclopentanone and the latter must be a methyl ketone to account for the methyl singlet at 2.12 ppm in the NMR spectrum. A doublet at 1.10 ppm suggested a secondary methyl deshielded by a vicinal carbonyl group. The only plausible structure for this diketone is shown in **12b.** It is analogous to the structure that was deduced from similar spectral data for the product of the ozonization of v.[5] We confirmed the assignment for **12b** by its mass spectrum. In contrast to ordinary steroids which require complex processes for the fragmentation of the ring system, only a single bond (8,14) has to be ruptured in the seco compound **12b.** This fission would result from a McLafferty shift of the 9α-hydrogen to the oxygen at C-13 and yield an ion with *m/e* 98. This proved to be the most prominent peak by far of the spectrum above *m/e* 43. The olefin (**6a**) from which **12b** was derived was the major constituent of olefin fraction 1. As such it must be the main or sole source of the two formates that resulted on treating this fraction with formic acid.

The third acetoxy glycol (**20a**) was present only in small amounts. Its degradation with lead tetraacetate gave a product (**25a**) with methyl signals similar to those of **12b** (methyl ketone at 2.15 and a secondary methyl at 1.10 ppm). The IR spectrum showed an acetate peak and a ketone peak at 1711 cm^{-1} which were of comparable intensity. Nevertheless, this

must be an acetoxy seco diketone, as the molecular ion indicated the composition $C_{23}H_{36}O_4$. Absence of ketone absorption in the region of the acetate band was demonstrated by hydrogenolysis of the ester group with lithium aluminum hydride and reoxidation to the triketone. These obervations seemed to be compatible with two plausible structures for the parent olefin. It might be a bond isomer of **6a** with the olefinic link between C-13 and C-17 or it might have structure **15a.** A clear decision in favor of the second alternative could be based on the mass spectra of the degradation products. The removal of the side chain from C-14 by a McLafferty shift to the 13-carbonyl would involve a loss of 98 mass units for **25a** and of 70 for the alternative structure. Only the former was observed and represented the dominant ionic species in the spectrum of **25a** above *m/e* 50.

Olefin fraction 2 was crystalline. It had the IR spectrum of a mixture of 17-methyl-*D*-homo-5α-androst-17-en-3β-yl acetate (**5a**) and of the corresponding 16-ene (**10a**).[1] The mixture could not be separated by crystallization but a single olefin (**10a**) was obtained in formic acid as was to be expected.[1] Fraction 2 was converted into two epoxides which could be separated by chromatography. They were identical with the 17α,17aα- and with the 16α,17α-epoxides that were derived, respectively, from the pure olefins **5a** and **10a.**[1] The 17-olefin is not an intermediate in the formation of its bond isomer because it was stable under the conditions of the acetolysis.

Olefin fraction 3 was small and showed all major IR and NMR peaks of (*E*)-5α-pregn-17-en-3β-yl acetate (**16a**).[13] In addition there were at least two additional olefins with a methyl attached to an unsaturated carbon atom. They were not identified.

Olefin fraction 4 failed to give any crystalline derivative. Nevertheless, it appears to be substantially homogeneous. Its NMR spectrum showed one tertiary (C-19), one secondary, and one olefinic methyl peak besides the one of the acetate group. There was also an olefinic hydrogen which appeared as a triplet at 5.39 ppm. Neither the acetoxy glycol **8f,** prepared with osmium tetroxide, nor its acetyl derivative (**8c**) which had a single hydroxyl peak at 3592 cm^{-1} could be fractionated by chromatography. Their NMR spectra like those of the olefin and of a degradation product (**13b**) showed no more methyl signals than were to be expected for a single structure. When the parent triol **8d** was subjected to bond cleavage with lead tetraacetate, a methyl ketone (δ 2.16) and an aldehyde function (δ 9.76 ppm, pair of doublets) were generated. Further oxidation of this product (**13b**) with permanganate and separation of the acidic material and its methylation with diazomethane gave a methyl ester (**14b**) which showed satellite peaks for the secondary methyl and the methyl ketone. Evidently some isomerization had occurred, presumably when the keto acid was exposed to alkali. The observations indicate as partial structure a ring with five or more carbon atoms with the sequence $C-CH_2-CH{=}C(CH_3)-CH(C)C$. Such a ring could be an enlarged central ring as in **9** or a terminal one as in the bond isomer of **9** that has the olefinic linkage between C-16 and C-17. The presence of the hydroazulene system which is common to both structures was strongly indicated by the reaction of the olefin with formic acid which gave the two formates **2e** and **3e.** As the preponderance of **2e** over **3e** was consistently greater than when the same pair was produced from olefin fraction 1, it was concluded that **6a** was not an obligatory intermediate in the conversion of fraction 4 to the normal formate. This situation clearly exists if fraction 4 has the structure **9a** because its protonation at C-12 would yield the 12a-carbocation ia, the precursor of **2e.** If the double bond were in the D ring, the existence of an important route from the olefin to **2e** that bypasses **6a** seemed far less likely. Moreover, the NMR spectra of the glycol (**8f**) and its acetate (**8c**) showed a significant shift (0.06 ppm) of the signal of the 10-methyl on acetylation which was taken to indicate propinquity between the methyl group and the secondary hydroxyl. Finally strong direct support for structure **9a** was derived from the mass spectrum of the keto ester **14b.** As in the case of **12b,** fragmentation of the ring system can occur by the fission of a single bond. Again the rupture of this bond dominated the spectrum which had the fragment representing the D ring (*m/e* 125) as its base peak.

The olefins derived from 3β-acetoxy-5α-pregnan-20β-yl tosylate (**21a**) showed eight spots in TLC (silica–silver nitrate). The first four fractions contained all the compounds described above. The concentration of (*E*)-5α-pregn-17-en-3β-yl acetate (**16a**) was now much higher and allowed its isolation in pure crystalline form. Fraction 4 contained an additional minor component which was isolated and identified as the 17(*Z*) isomer **22a.**[14] When a portion of fraction 4 containing **22a** was treated with formic acid, the residual olefin, as expected,[15a] had the IR spectrum of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**18a**). Fractions 5, 6, and 8 which were very small were not studied. Fraction 7 was crystalline. It contained a compound with the intense and characteristic IR peaks of the double bond of 5α-pregn-20-en-3β-yl acetate (**23a**)[10] and a second major component with an olefinic C–H stretching band at 3045 cm^{-1}. The two products were separated after epoxidation by chromatography. The faster moving epoxide (**28a**) which was shown to be derived from the 20-ene gave both 20-epimers of 5α-pregnane-3β,20-diol (**27d** and some **26d**) on reduction with lithium aluminum hydride. The second product of the epoxidation reaction unexpectedly showed a hydroxyl peak at 3529 cm^{-1}. Its position suggested hydrogen bonding, probably with an epoxy group. The carbinol carbon was located in a five-membered ring because oxidation with chromic acid gave a ketone absorbing at 1750 cm^{-1}. We suspected the parent olefin to be 5α-pregn-16-en-3β-yl acetate (**24a**)[16] and proved it by subjecting another sample of olefin fraction 7 successively to reaction with osmium tetroxide, to cleavage with bisulfite, and to acetylation. The slower moving component showed a hydroxyl band at 3598 cm^{-1} and had the properties reported[17] for the diacetate of 5α-pregnane-3β,16α,17α-triol (**29c**). The olefin from which this diacetate had been derived was a side product of the reaction of 3β-acetoxy-5α,17α-pregnan-17β-ol with phosphorus oxychloride in pyridine. To corroborate this assignment which had been characterized as being tentative[17] we degraded our parent triol (**29d**) with lead tetraacetate. The expected keto aldehyde appeared to be present in the reaction product, but as the aldehyde bands were quite weak, partial ketalization of this function was suspected. Condensation of the crude product under acid conditions[18] (followed by acetylation) cleanly gave the known[19] ketone **30a** which was identified by direct comparison with an authentic sample.[1]

The diester fraction obtained from either tosylate contained the diacetates of uranediol and of its 17a-epimer (**2c** and **4c**)[3] and of both 20-epimeric 5α-pregnane-3β,20-diols (**26c** and **27c**).[20] As all were known compounds their identification requires no comment. The yields of the various olefins and diacetates are presented in Table I.

The olefins that are formed by migration of the 13,14 bond of **1a** (**6a** and **9a**) presumably are both derived from the ionic precursor ia. The preference (>2:1) for proton removal from the methylene (**9a**) rather than from the methine carbon can probably be ascribed to a wider separation of nonbonded atoms in **9a.** These relationships to **1a** would establish the α configurations at C-13 in **9a** and of both compounds at C-17. They are fully confirmed by the results of isotope incorporation reported below.

As the reversal of the C-homo rearrangement in formic acid was fast[21] compared to the formolysis of **1a** there was no

Table I. Yields of Acetolyses of Tosylates

fraction		registry no.	type[a]	% from **1a**[c]	% from **21a**[d]
			olefins	45.4	54.8
1			tetrasubstituted	13.9	17.5
	18a	33300-00-4	18-abeo-Pr-13(14)-ene	2.1	7.7
	6a	68185-08-0	*C*-homo-An-12a(13)-ene	7.9	5.5
	15a	68185-09-1	*D*-homo-18-abeo-An-13(17a)-ene	*b*	0.7
2	**10a**	68151-33-7	*D*-homo-An-16-ene	3.6	3.1
	5a	17182-68-2	*D*-homo-An-17-ene	2.9	2.1
3	**16a**	16374-33-7	(*E*)-Pr-17(20)-ene	0.7	8.1
			unidentified	1.7	1.3
4	**9a**	68185-10-4	*C*-homo-An-12(12a)-ene	18.4	13.9
	22a	1167-32-4	(*Z*)-Pr-17(20)-ene		1.1
5, 6			unidentified		0.7
7	**23a**	22831-64-7	Pr-20-ene		2.8
	24a	68185-11-5	Pr-16-ene		2.0
8			unidentified		0.7
			diacetates	54.6	46.2
	2c	4975-29-5	*D*-homo-An-17aβ-OAc	51.7	41.3
	4c	4975-34-2	*D*-homo-An-17aα-OAc	1.6	1.4
	26c	6057-94-9	Pr-20β-OAc	*b*	1.4
				0.4[e]	
	27c	6170-08-7	Pr-20α-OAc	*b*	0.4

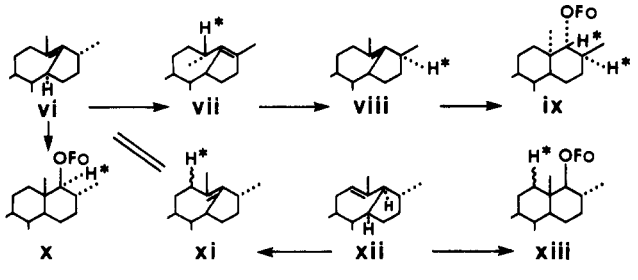
[a] All compunds have a 3β-acetoxy group; An signifies androstane with a 17-methyl, Pr indicates compounds with the pregnane skeleton, *C*-homo compounds show a formal shift of C-18 from C-13 to C-12a. [b] Present, but no adequate measurement available. [c] Registry no. 5611-68-7. [d] Registry no. 38456-46-1. [e] Value for the mixture of **26c** and **27c**.

prospect of demonstrating by isolation that olefins **6a** and **9a** are intermediates when **3e** is formed from **1a** in formic acid. However, we obtained confirmation for this highly probable proposition when we conducted the addition reactions **6a** → **3e** and **9a** → **3e** in HCOOD and compared the isotope distributions (curves E and F, Figure 1) with the distribution observed for **1a** → **3e** (points D). It showed no significant departures from values intermediate between those observed for the two addition reactions.[22]

The schemes presented for the shortest paths of the retro reactions show a minimal uptake of two deuterons for vi → ix, of three for xii → xi → ix, but only one if either olefin is converted to the normal formate (x or xiii). These paths of minimal incorporation of ^2H must be rare events in the formation of the isomeric formate (E and F) but have a high frequency in the formation of the normal ester (B and C) especially if xii is the precursor. The NMR spectra were also consistent with the presence of x or xiii (with H* = ^2H) in our samples. Both preparations of the normal diol (**2d**) showed a large fraction of the 17-methyl signal as a doublet but only the one obtained from olefin **9a** had a doublet representing the 17a-H.

The olefin fraction that escapes an early *D*-homoannulation has an about equal chance of ending up as the formate with the 13β,17α- or with the 13α,17β-methyls. As no other formate could be detected and as the configuration at C-13 is established last, the configuration at C-17 is the one which determines the steric course of the retro reaction. Evidently the migrating double bond has reached the various carbon atoms

Scheme II. Shortest Paths from Olefins 6a and 9a to Formates. Starred Atoms are Expected to be Derived from the Medium



of the C and D rings repeatedly, because both hydrogens of their methylene groups have been exchanged for deuterium in the maximally labeled compounds. We, therefore, expected to find equilibration between the olefins with the 17β and 17α configurations during the later stages of isotope incorporation. This did not seem to be the case because if we compare the mole fractions at the same *d* values, the ratio of measurements E/B or F/C does not approach a constant value but continues to climb with increasing *d* content. Evidently the return from the 17β to the 17α configuration is slow compared to the rates of the retro reactions or perhaps does not occur at all. This interpretation is consistent with the apparent absence of formate **2e** from the products of the formolysis of the isomer of **1a** that has the 17β configuration.[1]

Our results show that the 16,17 bond, which like the 13,14 bond is antiparallel to the C-17a—O bond of the tosylate **1a**, can also migrate during its solvolysis. This is evident from the structures of three compounds with the pregnane skeleton (**16a**, **26c**, and **27c**) and of an 18-norpregnene **18a**, previously obtained by the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate.[10] If both migrations of the antiparallel bonds are irreversible processes under the conditions of the acetolysis, the shift of the 13,14 bond is preferred in a ratio of about 8:1.

The conversion of the 20β-tosylate **21a** to the 17aβ-tosylate **1a** has been observed in several solvents (formic acid, ethanol, pyridine, and aqueous dioxane).[3] It has now been found to proceed also in buffered acetic acid. It represents a major pathway that may well account for all of the products with the C-homo and D-homo structures as these were obtained from the two tosylates in a fairly constant ratio (0.79 ± 0.09 for **21a**/**1a**). However, we also encountered reactions that have been observed with **21a** but not with **1a**, such as the formation of 3β-acetoxy-5α-pregnenes with a 16-, 20-, and 17(*Z*) double bond (**24a**, **23a**, and **22a**). Other products (**16a** and **18a**) were obtained from **21a** in higher yield than from **1a** and in different proportions. Therefore, **21a** cannot be an important intermediate in the formation of the pregnane derivatives from **1a**. We have no analogous data to exclude such a role for the 20α-tosylate but consider it improbable as the latter failed to convert to **1a** in formic acid but gave inter alia the 20-olefin (**23a**)[10] which, therefore, is likely to be produced also by its

acetolysis.

The different relative yields of the pregnane derivatives obtained from **1a** and **21a** may be caused by conformational differences. Tosylate **1a** can be expected to yield a conformationally uniform pregnan-20-yl cation if it rearranges in a concerted process, whereas the greater diversity of the products obtained from **21a** suggests that this tosylate can undergo acetolysis in more than one conformation. These might have different possibilities for participation and different stereoelectronic preferences for proton elimination and they would afford different spatial relationships between the cation and its counterion. As the two 17-olefins (**16a** and **22a**) are stable under the conditions of the acetolysis, the 13-olefin (**18a**) must form by a shift of the 17α-hydrogen. If the 16-olefin (**24a**) is formed by the same mechanism its absence among the products of **1a** seems to require a role of the counterion (derived from **21a**) in the abstraction of a proton from C-16. A conceivable alternative is the shift of the 16β-hydrogen to C-20 because in the most favored conformation of a 20β-oxygenated pregnane[23] this hydride would be rather well placed to participate in the ionization of **21a.** The substitution of **21a** at C-20 showed a preference for retention ($\beta > \alpha$). This outcome is the more remarkable as an inverse proportion of isomers ($\alpha \gg \beta$) resulted from the formolysis of the 20α-tosylate.[10] Obviously these results cannot be attributed simply to steric hindrance to solvation from the rear. Tosylate **1a** like **21a** gave more of the 20-acetate that has the β configuration (**26c**).

A third group of compounds produced from **1a,** which includes the diacetate with inverted configuration at C-17a (**4c**) and the two D-homo olefins (**5a** and **10a**), most likely is derived from the classical 17a-cation. It was to be expected that such an ion would also undergo migration of the 13-methyl.[15b] A product derived from this shift has now been detected and identified as the 13(17a)-olefin **15a.**

To compare these results with observations on the formolysis of **1a,**[3] we have repeated the latter because the resulting olefin fraction had not been examined as promptly as its instability is now known to require. This fraction amounted to 5% and contained besides olefin **18a** and some unidentified material the *D*-homo-16-olefin (**10a**) in a yield of about 1.5%. Evidently the 17a-cation is also formed in formic acid.

This conclusion calls for an examination of the question whether this cation constitutes the primary ionization product from which all others are derived or whether simultaneous with this process there also occurs ionization with anchimeric assistance. In such competitions formic acid has been found to be more favorable to the anchimerically assisted process than acetic acid.[24] The observation of more than fourfold increased yields of the D-homo olefins and of the inverted ester in acetic acid therefore is consistent with having such competing mechanisms of ionization. The most striking difference between the two solvents concerns the ratio of products with retained altered carbon skeletons. Taking into account the amounts of C-homo olefins (**6a** and **9a**) which do not survive in formic acid, we found this ratio to be about 9:1 in formic and 1.5:1 in acetic acid. This result would be most unusual if it represented the partitioning of a classical ion, but not if the alternative hypothesis applied according to which perhaps as much as 98% of the reaction in formic and 91% in acetic acid would involve participation of a carbon–carbon bond. Such participation is supported also by a new interpretation of kinetic measurements.[1] The resulting ionic products might be rearranged ions (ia and 3β-acetoxy-5α-pregnan-20-yl) or the corresponding bridged ions (structures **23** and **24** of ref 4). A preference for the bridged structures can be based on the results of the formolysis of the 17-epimer of **1a.** Its main substitution reaction was sterically analogous to that of **1a** as it proceeded with retention of configuration at all centers.[1] In this case the ionic structure corresponding to ia is ic which would have to assume a prohibitively stressed conformation to return to a *D*-homosteroid with the original 1,3 interaction of methyl groups. Accordingly we suggest that the main initial products of the reaction of **1a** in both solvents are the two bridged ions, of which the one formed by migration of the 13,14 bond is probably much more important. These tight ion pairs are sufficiently stable in formic acid to allow a very large fraction to be converted to the solvent-separated ion pair and from these, in a reversal of the bridging, to the ester with retained configuration (**2e**). The remainder retains the alternative partial bond of the bridged structure to yield the rearranged ions which form olefins (which can undergo further changes in formic acid). In acetic acid both types of bond shift of the bridged ions occur with comparable frequency and thus give the appearance of yielding a larger fraction of rearranged products.

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. 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, occasionally on Model XL-100, or on Model A-60A of Varian. Observations at 60 MHz are marked by an asterisk. Shifts are given in parts per million downfield from Me_4Si.

Olefins were converted to glycols by the method of Baran;[11] glycols in methanol–*tert*-butyl alcohol[25] (6:1) were cleaved with lead tetraacetate in acetic acid (30 min) as described.[10] Alcohols were oxidized to ketones according to the procedure of Bowers[26] and acetylated at room temperature (~16 h) with acetic anhydride in pyridine. Esters were hydrolyzed with 2% potassium hydroxide in methanol at room temperature overnight. Steroids were usually extracted from the diluted reaction mixtures with ether; if the medium was formic or acetic 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. The silica gel used for column chromatography was type 60 (70–230 mesh) of E. Merck, Darmstadt. Its product G was used for TLC plates. These were sprayed with 0.15% vanillin in 42% phosphoric acid for diagnostic runs (0.4 mm thick) and with water for preparatory purposes (0.8 mm thick). Departures from these practices are indicated in the text. References to known compounds are not exhaustive. They usually cite surveys of the literature rather than first descriptions.

Acetolyses. The results presented in Table I are derived from the final acetolyses of the two tosylates (**1a** and **21a**). In each a solution of 950 mg of tosylate and of 2.2 g of potassium acetate in 115 mL of acetic acid was kept at 100 °C for 5 h. The neutral reaction product was chromatographed on 50 g of silica gel from which the olefins were eluted with benzene and the diacetates with benzene containing 10% ethyl acetate. The olefins were separated on 100-g silica gel impregnated with 10% silver nitrate.[27] This adsorbent was packed on top of 10 g of ordinary silica gel. Elution was started with a 1:1 mixture of benzene and hexane. During the later stages the benzene ratio was gradually raised to 3:1 (for olefin 7) and then to pure benzene (olefin 8). Fractions were evaluated by TLC (SiO_2–$AgNO_3$)[27] and IR spectroscopy and as described below by conversion to stable products. The separations were completed and the conversions initiated within 48 h from the start of the acetolysis. Unless these steps are carried out promptly severe losses (50% and more) can be encountered. The acetates, being stable, were fractionated last, as detailed below.

Olefin Fraction 1. A. Conversion to Glycols. This reaction allowed 90 h for the addition of osmium tetroxide to the double bonds and 15 h for the cleavage of the osmates. The products were separated on chromatographic plates (15% ethyl acetate in benzene, two runs) into uncleaved osmates and four glycols which are listed below in the order of their declining mobilities.

3β-Acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13β,14β-diol (19a) was recrystallized from acetone. It had mp 179–180 °C which remained unchanged on admixture of a reference sample:[10] NMR methyl singlets at δ 0.81 (19-H), 1.20 (17-Me), 2.02 (Ac) in $CDCl_3$ and at 0.72, 1.50, and 2.02 in pyridine*. The compound was hydrolyzed and oxidized with lead tetraacetate to yield the 3β-hydroxy-13,14-seco diketone[10] which had mp 128–130 °C (reported 128–130.5 °C):[10] NMR δ 0.84 (19-H), 0.80 (t, J = 7 Hz, 21-H), and 1.04 (17-Me). Its IR spec-

trum and that of **19a** agreed with curves previously recorded.[10]

3β-Acetoxy-12aξ,17α-dimethyl-18-nor-*C*-homo-5α,13ξ-androstane-12aξ_A,13ξ_A-diol (7a or 11a) was recrystallized from acetone. It had mp 157–158 °C; IR 3609 and 3549 (vicinal glycol), 3020, 1732, 1243, 1031, and 1023 cm^{-1}; NMR* δ 0.82 (19-H), 1.22 (d, J = 6.7 Hz, 17-Me), 1.33 (12a-Me), and 2.02 (Ac) in $CDCl_3$ and 0.81, 1.37 (d), 1.49, and 2.04 in pyridine. Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.32; H, 10.15. It was hydrolyzed and degraded with lead tetraacetate to give a diketone with the same IR spectrum as that obtained from the 12a,13-diastereomer described below.

3β-Acetoxy-17α,17a-dimethyl-18-nor-*D*-homo-5α-androstane-13ξ,17aξ-diol (20a): IR 3615, 3557, 1734, 1242, and 1027 cm^{-1}; NMR* δ 0.81 (19-H), 0.90 (d, J = 6.8 Hz, 17-Me), 1.05 (17a-Me), and 2.02 (Ac). Degradation of 4.4 mg of **20a** with lead tetraacetate and recrystallization from hexane gave **25a** with mp 98–99.5 °C: IR 1734, 1241, 1028 (3β-OAc), and 1711 (ketone) cm^{-1}; NMR δ 0.78 (19-H), 1.10 (d, J = 7.0 Hz), 2.02 (Ac), and 2.15 (CO-Me); mass spectrum 376 (M^+), 278 (base peak above m/e 50), 218, 98, 55. Treatment with lithium aluminum hydride in ether (2.5 h) followed by oxidation with chromic acid (4 min, 15 °C) gave the triketone (**25** with oxo group at C-3) with a single unresolved carbonyl peak at 1713 cm^{-1}. The mass spectrum had numerous intense signals in the lower mass region. Above it, 177 and 234 were most prominent. M^+ at 332.

3β-Acetoxy-12aξ,17α-dimethyl-18-nor-*C*-homo-5α,13ξ-androstane-12aξ_B,13ξ_B-diol (7a or 11a) failed to crystallize: IR 3604, 3568, 1736, 1242, 1024 cm^{-1}; NMR δ 0.72 (19-H), 1.00 (d, J = 7 Hz, 17-Me), 1.23 (12a-Me), 2.00 (Ac) in $CDCl_3$ and 0.69, 1.30 (d), 1.43, and 2.03 in pyridine*. The yield ratio of this glycol to its diamer (above) was 2.5. Hydrolysis with methanolic potassium hydroxide gave the parent triol which was recrystallized from acetone–hexane, mp 151–153 °C. Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.87; H, 10.72. Its degradation with lead tetraacetate gave the 3β-hydroxy-12a,13-seco diketone (**12b**) with mp 120.5–121.5 °C: IR 3608, 1737, 1719, 1156, and 1042 cm^{-1}; NMR δ 0.83, 1.10 (d, J = 7 Hz), 2.12. The mass spectrum showed no peak with m/e > 165 which had an intensity > 10% of the base peak (m/e 40). The more prominent of these were at m/e 334 (M^+), 316, 301, 291, 277, 273, 261, 255, 220, 201, 185, 178. The most intense peaks of the spectrum were at 137, 98 (80% of base peak), 55, 43, 41, 40. The peak m/e 125, prominent in the spectrum of **14b**, was very weak.

The colored eluate of the osmate band (22.7 mg) was stirred for 3 h with lithium aluminum hydride in ether as described.[10] The product was acetylated and subjected to TLC (15% ethyl acetate in benzene, two runs). The fraction (6.2 mg) traveling at the same rate as a reference sample of **3β-acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13α,14α-diol (17a)** was eluted and recrystallized from acetone. Its mp (161–163 °C) remained unchanged on admixture of the reference sample.[10] The IR spectra agreed: NMR* δ 0.78 (19-H), 0.90 (17-Me), 0.87 (t, J = 7.3 Hz, 21-H), 2.01 (Ac) in $CDCl_3$ and 0.78, 0.97, 2.05 (the signals of the 21-H were not well resolved) in pyridine. The remainder of this chromatogram was distributed fairly evenly over at least six compounds. In view of the low yields they were not investigated. The entries in Table I are based on the weights of the glycols.

B. By Reaction with Formic Acid. A solution of olefin 1 (9.0 mg) in 0.2 mL of benzene was diluted with 9 mL of formic acid and kept at room temperature overnight. The neutral reaction products were separated by TLC (3% ethyl acetate in benzene, three consecutive runs). The faster moving addition product (2.9 mg) had the same IR spectrum as **3β-acetoxy-17β-methyl-*D*-homo-5α,13α-androstan-17aα-yl formate (3e)**. It melted at 178.5–180 °C after recrystallization from methanol and at 179.5–181 °C after adding a reference sample.[3] The slowest moving fraction (4.3 mg) was identified as **uranediol 3-acetate 17a-formate (2e)** by its IR spectrum, mp (217–218.5 °C, after recrystallization from acetone), and mmp (216.5–217 °C).[3] Further characterization of these formates will be given below for samples obtained in HCOOD.

Olefin Fraction 2. The earlier eluates of this fraction were enriched with a compound characterized by a band at 800 (**10a**) and the later ones at 834 cm^{-1} (**5a**), but no complete separation was achieved. A sample (15.4 mg) of olefin 2 and 31 mg of *m*-chloroperoxybenzoic acid in 1.5 mL of methylene chloride were kept at room temperature overnight. The neutral reaction products were separated on a chromatographic plate (5% ethyl acetate in benzene, two runs). The faster moving component (7 mg) was recrystallized from methanol. Its IR spectrum agreed with that of **17α,17aα-epoxy-17β-methyl-*D*-homo-5α-androstan-3β-yl acetate** and its mp (186.5–188.5 °C) was not depressed by admixture of a reference sample.[1] The second epoxide (4.9 mg) showed the spectrum of **16α,17α-epoxy-17β-methyl-*D*-homo-5α-androstan-3β-yl acetate**[1] and had mp 164–165 °C and mmp 163–164 °C. Another sample of olefin 2 (3 mg) dissolved in 3 drops of benzene and 1.2 mL of formic acid was kept at room temperature for 5 h. The product was freed of a trace of formate[1] by passing a solution in benzene through a short column of silica gel. The reaction caused a change of spectrum from that of a mixture of **5a** and **10a** to that of the 16-olefin (**10a**). There was no spectral change when the pure 17(17a) olefin (4.1 mg) was heated (100 °C) for 5 h in 1 mL of acetic acid containing 15.7 mg of potassium acetate and 2.1 mg of *p*-toluenesulfonic acid. The analyses in Table I are based on the IR bands at 800 (**10a**) and 834 (**5a**) cm^{-1}.

Olefin Fraction 3. The material derived from 17aβ-tosylate (**1a**) was obtained in three eluates which showed in varying intensities absorption bands at 3032 (**16a**) and at 3080 and 1632 (olefin 3–2), and a shoulder near 3055 cm^{-1} (olefin 3–1). Both unknowns were characterized by an NMR signal at δ 1.54 (olefinic methyl). When the precursor was the 20β-tosylate (**21a**), fraction 3 was crystalline. Recrystallization from methanol gave **(*E*)-5α-pregn-17-en-3β-yl acetate (16a)** with mp 122.5–123.5 °C (reported 125.5–126 °C,[13] 120–121.5 °C,[17] and 118–120 °C[28]): NMR* δ 0.73 (18-H) (reported[29] 0.745), 0.84 (19-H), 1.59 (21-H), and 2.00 (Ac); IR spectrum[30] in good accord with that of a reference sample.[13] The IR spectrum of the mother liquor showed the presence of the same components as the material from tosylate **1a.**

Olefin Fraction 4. This fraction when obtained from tosylate **1a** showed no signs of inhomogeneity. Olefin **9a** had IR 3021 cm^{-1} (olefinic H): NMR* δ 0.77 (19-H), 1.04 (d, J = 5.9 Hz, 17-Me), 1.74 (olefinic Me), 2.00 (Ac), 5.39 (t, J = 7.7 Hz, olefinic H, Calcd[31] 5.43). A sample (58 mg) was converted into **3β-acetoxy-12a,17α-dimethyl-18-nor-*C*-homo-5α-androstane-12ξ,12aξ-diol (8f)**. The product on preparative TLC (benzene with 25% hexane and 20% ethyl acetate, four runs) gave essentially one spot which was cut into two zones which were separately eluted (combined yield 49.9 mg). Their IR spectra (3615,-3569, 1733, 1242, 1032 cm^{-1}) were in good agreement. Different solvent systems also failed to effect chromatographic separation of this material: NMR* δ 0.80 (19-H), 1.07 (d, J = 6.3 Hz, 17-Me), 1.16 (12a-Me), 2.00 (Ac), and 3.68 (pair of doublets, 12-H) in $CDCl_3$ and at 0.77, 1.20 (d), 1.33, 2.03, and 3.98 in pyridine. The diacetate (**8c**) [IR 3592 cm^{-1}; NMR* δ 0.74 (19-H), 1.07 (d, J = 6.2), 1.15, 2.01, 2.12 (12-OAc), 4.89 (m, 12-H)] likewise could not be fractionated by chromatography. The acetoxy glycol (**8f**) (32.2 mg) was hydrolyzed to the triol (**8d**) which was also noncrystalline. It was degraded with lead tetraacetate to yield 27.9 mg of a product (**13b**) with IR peaks at 3609 and 1036 (3β-OH), 2807, 2704, and 1726 (aldehyde),[32] 1707 (ketone), and 1048 (strongest peak in the fingerprint region) cm^{-1} and NMR* signals at δ 0.73 (19-H), 0.90 (d, J = 5.6 Hz, 17-Me), 2.16 O=CMe), and 9.76 (pair of doublets, HC=O). A solution of this seco compound in 1.5 mL of acetone was treated with 0.4 mL of 5% aqueous potassium permanganate for 10 min at room temperature. The excess oxidant was reduced with an aqueous solution of SO_2. The product was extracted with ether, washed with hydrochloric acid and with water, and extracted with a 3% solution of sodium hydroxide. This on acidification and extraction yielded 24.8 mg of an oil which was methylated with an ethereal solution of diazomethane. The resulting methyl ester (**14b**) was purified by preparative TLC (15% ethyl acetate in benzene): IR 3608 and 1042 (3β-OH), 1737 and 1165 (ester), 1706 (ketone) cm^{-1}; NMR* main component δ 0.71 (19-H), 0.91 (d, J = 5.6 Hz, 17-Me), 2.18 (methyl ketone), 3.67 (methyl ester), the lesser component had a distinct signal for the methyl ketone (2.13) and presumably for the 17-methyl. Mass spectrum: molecular ion at 364. No peak with mass greater than 160 had intensity >10% of base peak. The more prominent of these were at m/e 346, 332, 291, 290, 273, 272, 255, 247, 232, 219, 175, 173. High peaks at 125 (base peak), 107, 85, 81, 67, 55, 50.

When the olefin 4 was derived from the 20β-tosylate the later fractions contained an impurity with IR peaks consistent with the presence of **(*Z*)-5α-pregn-17-en-3β-yl acetate (22a)**. Such material (8.8 mg) gave 0.6 mg of crystals (**22a**) with mp 105–106.5 °C (reported[14] 107–109 °C and 103 °C) on recrystallization from methanol. The mmp[15b] was 105–107 °C and the IR spectra[30] agreed.

Olefin fraction 4 derived from **1a,** on treatment with formic acid as described for olefin 1, gave the same two formates (13α-isomer, 13.4 mg; 13β, 28.4 mg), which were identified by their IR spectra, and only a trace of olefin. A late eluate of olefin fraction 4 derived from the 20β-tosylate which contained 18% of the (*Z*)-17-pregnene **22a** was exposed to formic acid for only 3 h. This reaction gave 5.5 mg of olefin which was free of starting material and which had the IR spectrum of **17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (18a)**, as well as 8.7 mg of the 13α- (**3e**) and 16.5 mg of the 13β-isomer (**2e**) of the 17a-formates. Hydrolysis of the formates gave **3d** with NMR* δ 0.79 (19-H), 0.94 (18-H), 1.01 (d, J = 6 Hz, 17-Me), and 3.44 (d, J

= 9.6 Hz, 17a-H) and **2d** with 0.80 (18- and 19-H), 0.96 (d, J 5.8 Hz, 17-Me), and 2.71 (d, J = 9.1 Hz, 17a-H).

Olefin Fraction 7. This fraction (like 5, 6, and 8) was obtained only from the 20-β tosylate. It had peaks at 3075 and 3045 cm^{-1}. The former was associated with the strong band of **5α-pregn-20-en-3β-yl acetate (23a)**[10] at 909 cm^{-1} which was used for its quantitation. It moves somewhat faster than the second component. A sample of olefin fraction 7 (22.1 mg) was treated with 45 mg of *m*-chloroperoxybenzoic acid in 2.3 mL of methylene chloride. The product was fractionated by preparative TLC. The faster moving component (12.7 mg) on repeated recrystallization gave 2.5 mg of crystals (mp 125–126 °C) (**28a**) with an IR spectrum (3038 cm^{1}) in essential agreement with that of a less pure sample which could be prepared only on an insufficient scale (3 mg) from authentic 5α-pregn-20-en-3β-yl acetate.[10] A mixture (8.4 mg) of crystals and mother liquors was reduced with lithium aluminum hydride in ether and the product was chromatographed on a plate (20% ethyl acetate in benzene, two runs). The main component (4.3 mg) was recrystallized to yield a product (**27d**) with mp 216–218 °C which remained unchanged after admixture of **5α-pregnane-3β,20α-diol.**[20] The lesser product (0.8 mg) had mp 188–194 °C after recrystallation and an IR spectrum in accord with that of **5α-pregnane-3β,20β-diol (26d).**[20] A third spot on the chromatogram presumably represents 5α-pregnane-3β,21-diol.

The slower moving component obtained by epoxidation of olefin 7 (6.5 mg) showed strong peaks at 3529 (OH) and at 1052, 3β-OAc bands at 1731 and 1240, and a doublet at 1030 and at 1020 cm^{-1}; NMR* methyl singlets δ 0.75 (19-H), 0.85 and 2.00 (Ac). Oxidation with chromic acid (5 °C for 10 min) gave a product without a hydroxyl peak, with ketone at 1750, and acetate bands at 1736 and 1241, and a doublet at 1032 and 1024 cm^{-1}; NMR* methyl singlets at δ 0.79 (19-H), 1.03 and 2.02 (Ac).

Another sample of olefin fraction 7 (24.8 mg) was converted to glycols. These were acetylated and separated by TLC (8% ethyl acetate in benzene, two runs). Two major fractions were obtained. The first (14.8 mg) showed no hydroxyl absorption and undoubtedly represents a mixture of the 20-epimers of 5α-pregnane-3β,20,21-triol triacetate. The second eluate, **5α-pregnane-3β,16α,17α-triol diacetate (29c)**, (11.7 mg) was recrystallized from hexane. It had NMR* δ 0.74 (18-H), 0.83 (19-H), 0.89 (t, J = 7.0 Hz, 21-H), 2.01 (3-OAc), 2.09 (16-OAc), 4.97 (m, 16-H); IR 3598, 1733, 1238, 1039, 1030, 932, and 901 cm^{-1}; mp 159–160 °C (reported[17] 160–161 °C); $[\alpha]_\lambda$ −62° (at 589, reported[17] −60.9°), −65° (578), −74° (546, reported[17] −74.5°), −125° (436), and −195° (365 nm) (acetone, 6 mg/mL, 30 °C). The diacetate (**29c**) on hydrolysis gave **5α-pregnane-3β,16α,17α-triol (29d)** with mp 234–237 °C (reported 234–240 and 240–241 °C).[17] It was degraded with lead tetraacetate to a product with weak aldehyde bands at 1725, 2712, and 2829[32] and a doublet of normal intensity (ketone) at 1699 and 1702 cm^{-1}. Heating of a solution of this in acetic acid containing 1% concentrated hydrochloric acid at 100 °C for 30 min gave a mixture of **30a** and **30b.** This product was acetylated to yield 3β-acetoxy-17-methyl-*D*-homo-5α-androst-16-en-17a-one (**30a**) identified by its IR spectrum [1736, 1240, and 1028 (3β-OAc), 3020, 1673 (α-β unsaturated C=O), 843 cm^{-1}], its mp (206–207 °C), and its mmp (206–208 °C) with a reference sample[1] having mp 205–206 °C. Higher mp's (210–211 °C) were observed on occasion with samples from either preparation.

Fractionation of Diacetates. A preparation (186.5 mg) obtained from the 20β-tosylate was recrystallized from methanol to yield 152 mg of uranediol diacetate (**2c**) with mp 156.5–158.5 °C. The mother liquors (34.6 mg) on layer chromatography (20% hexane in methylene chloride, two runs) were separated into three zones. The slowest moving (14.6 mg) showed the spectrum of uranediol diacetate, the middle zone (5.8 mg) that of 17a-epiuranediol diacetate (**4c**) (mp after recrystallization 133–134 °C), while the first zone (7.7 mg) was a mixture which could be separated after hydrolysis by layer chromatography (20% ethyl acetate in benzene, two runs) into 3.4 mg of **5α-pregnane-3β,20β-diol (26d)** (identified by its IR spectrum in KBr, and after recrystallization by mp 194–195 °C and mmp 195–197 °C),[20] 0.65 mg of **5α-pregnane-3β,20α-diol (27d)** (IR spectrum in KBr; mp after recrystallization 217.5–219 °C and mmp 217.5–218.5 °C),[20] and 1 mg of a mixture containing both isomers in approximately equal proportions (TLC). When the diacetate fraction was obtained from the 17aβ-tosylate, the IR spectrum of the 5α-pregnanediol diacetate fraction (1.4 mg) showed again the presence of both isomers but with a higher proportion of the 20β compound. Hydrolysis and plate chromatography yielded the two spots expected but gave only enough of 5α-pregnane-3β,20β-diol for IR identification.

Brief Acetolysis of 3β-Acetoxy-5α-pregnan-20β-yl Tosylate (21a). A solution of 7.5 mg of tosylate **21a** in 0.2 mL of benzene was added to 4 mL of acetic acid (containing 77 mg of potassium acetate) which was maintained at 100 °C. After 5 min the mixture was chilled and the neutral reaction product (7.0 mg) isolated. Its IR spectrum showed all the bands of the 17a-tosylate **1a** and none that are characteristic only of the starting tosylate.[33] It differed from a reference curve of **1a** mainly in a significantly lower ratio of tosylate to acetate bands (0.77).

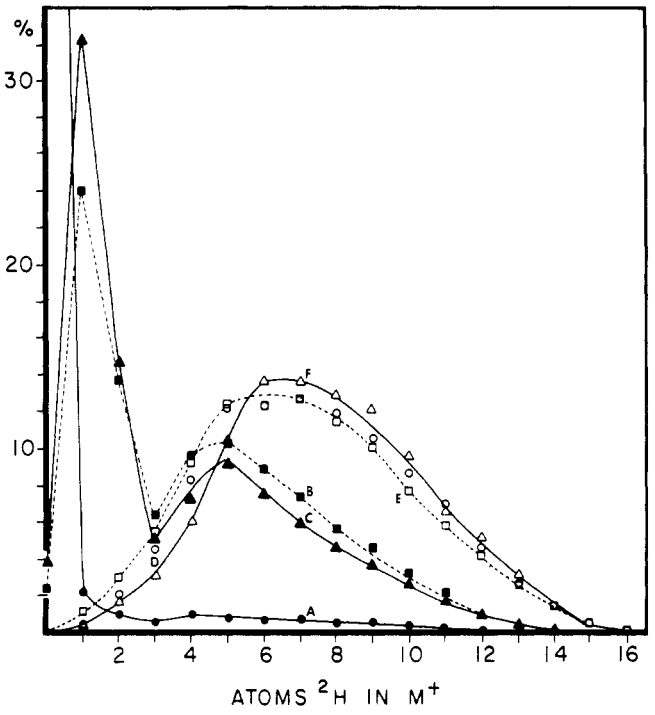


Figure 1. Frequency distributions, corrected for normal abundance of isotopes, of molecular ions with varying deuterium content. Data A–C (solid symbols) are measurements on **2d,** D–F (open symbols) on **3d.** The samples for A and D (circles) were obtained by the ^2H formolysis of **1a,** the others by the addition of this solvent to olefins: B and E (squares) of fraction 1 and C and F (triangles) of fraction 4.

Formolysis of 3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (1a). The reaction was carried out on 212.5 mg of **1a** at 25 °C for 22 h as previously described for **21a.**[3] The product was immediately separated into olefins (6.9 mg) and diesters (153.9 mg) by chromatography on silica. The IR spectrum indicated the presence of **18a** and **10a** in the olefin fraction which was converted to glycols. Separation by TLC gave 1.0 mg of **19a**[10] and 2.1 mg of the two 16,17-cis isomers of 3β-acetoxy-17-methyl-*D*-homo-5α-androstane-16,17-diol[1] and unidentified material. The three compounds were identified by comparison of their chromatographic mobilities and their IR spectra with those of reference samples.

Reactions in HCOOD. A. 3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl Tosylate (1a). A solution of 268 mg of tosylate **1a** in 8.4 mL of benzene was mixed with 100 mL of HCOOD and kept at 24 °C for 27 h.[34] The neutral product (204 mg) was isolated as described.[3] It was free of tosylate[3] and after three recrystallizations from acetone gave 145 mg of uranediol 3-acetate 17a-formate (**2e**) with mp 216–218 °C. It was hydrolyzed to the diol (**2d**) (mp 215–217 °C) for mass spectroscopy (curve A of Figure 1). Chromatography of the mother liquors gave early eluates that had undergone some ester exchange at C-3. These fractions were hydrolyzed, acetylated, and chromatographed on silical gel. The early eluates (5.7 mg) had mp 125.5–126.5 °C after recrystallization: NMR δ 0.83 (6.0 H, 19-H and 17-Me), 0.96 (3.0 H, 18-H), 2.01 (3-OAc), 2.05 (17a-OAc), 4.96 (s, <0.1 H, 17a-H). No signals attributable to **2c** were seen. Hydrogenolysis with lithium aluminum hydride gave diol **3d** with mp 151.5–153.5 °C. In the high resolution mass spectrum the signals for $M^+ - CH_3$ with 9 or more deuterium atoms were resolved from the peaks for $M^+ - H_2O$ with similar mass. Where thus resolved the peak heights of the $M^+ - CH_3$ signals at any given d value had a constant ratio to the corresponding peak heights of M^+. Calcd for $C_5H_3D_6O^+$: 91.1030. Found: 91.1025. Calcd for $C_{13}H_8D_{14}O^+$: 208.2549. Found: 208.2563. The isotope distributions for M^+ for this preparation shown in points D of Figure 1 were measured on a single-focusing spectrometer (like all other data in this figure).

B. Olefin Fraction 1. This reaction was carried out on a sample of 20 mg (derived from **1a**) for 18 h as described for unlabeled formic

acid. It yielded 4.8 mg of olefin, 5.8 mg of **3e**, and 8.6 mg of **2e**. The formates were hydrolyzed to the diols. The 13α-isomer (**3d**) had mp 151.5–153.5 °C: NMR three methyl singlets at δ 0.78 (19-H), 0.92 (18-H), and 1.00 (17-Me). For the M^+ region of mass spectrum see curve E of Figure 1. Uranediol (**2d**) had mp 215–217 °C: NMR δ 0.78 (18- and 19-H), 0.94 (s, 17-Me),[35] 0.95 (d, J = 6 Hz, 17-Me). Mass spectrum, curve B, Figure 1.

C. Olefin Fraction 4. Treatment of 29.7 mg of a fraction 4 derived from **21a** for 18 h gave 3.6 mg of olefin, 9.8 mg of **3e**, and 20.0 mg of **2e**. The formates were hydrolyzed. Diol **3d** had mp 152.5–153.5 °C: NMR (100 MHz, XL) δ 0.784, 0.922, and 1.004 (all methyl singlets), and a weak[6] signal at 3.43 superimposed on the 3α-H multiplet. M^+ signals in curve F, Figure 1. Diol **2d** had mp 216–217 °C; NMR δ 0.787 and 0.791 (18- and 19-H), 0.944 (s, 17-Me),[35] 0.952 (d, J = 6.0 Hz, 17-Me), 2.697 (s, 0.1 H,[6] 17a-H), and 2.698 (d, J = 9.8 Hz, 0.35 H, 17a-H). M^+ in curve C, Figure 1.

Acknowledgement. The authors thank Mr. Nicholas Baldwin for recording the 100 MHz NMR spectra; Dr. Rodger L. Foltz, Batelle High Resolution Mass Spectrometer Center, Columbus, OH, Dr. D. D. Godse, Clarke Institute of Psychiatry, Toronto, and Mr. Fred Dillon, Department of Chemistry, University of Oklahoma, Norman, OK for the mass spectra; Mr. A. W. Spang, Eagle Harbor, Mich., for the microanalyses; and Dr. Miklos Bodanszky for the use of the polarimeter.

Registry No.—**2d**, 516-51-8; **2e**, 4975-26-2; **3d**, 38456-57-4; **3e**, 38456-48-3; **7a**, 68185-12-6; **8c**, 68185-13-7; **8d**, 68185-14-8; **8f**, 68185-15-9; **11a**, 68185-16-0; **12b**, 68185-17-1; **13b**, 68185-18-2; **14b**, 68185-19-3; **14b** acid, 68185-20-6; **17a**, 68185-21-7; **19a**, 33300-10-6; **20a**, 68185-22-8; **25**, 68185-23-9; **25a**, 68201-10-5; **26d**, 516-53-0; **27d**, 566-56-3; **28a**, 68224-79-3; **29c**, 68185-24-0; **29d**, 68185-25-1; **30a**, 53191-38-1; **30b**, 68185-26-2; 12a,17α-dimethyl-18-nor-*C*-homo-5α,13α-androstane-3β,12aα,13-triol, 68185-27-3; 12a,17α-dimethyl-18-nor-*C*-homo-5α-androstane-3β,12aβ,13-triol, 68224-80-6; 17α,17aα-epoxy-17β-methyl-*D*-homo-5α-androstan-3β-yl acetate, 68151-42-8; 16α,17α-epoxy-17β-methyl-*D*-homo-5α-androstan-3β-yl acetate, 68151-40-6; 5α-pregnane-3β,20β-diol diacetate, 6057-94-9; 5α-pregnane-3β,20α-diol diacetate, 6170-08-7.

References and Notes

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