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FORMOLYSIS OF 3β-ACETOXY-5α-PREGNAN-20α-YL *p*-TOLUENESULFONATE

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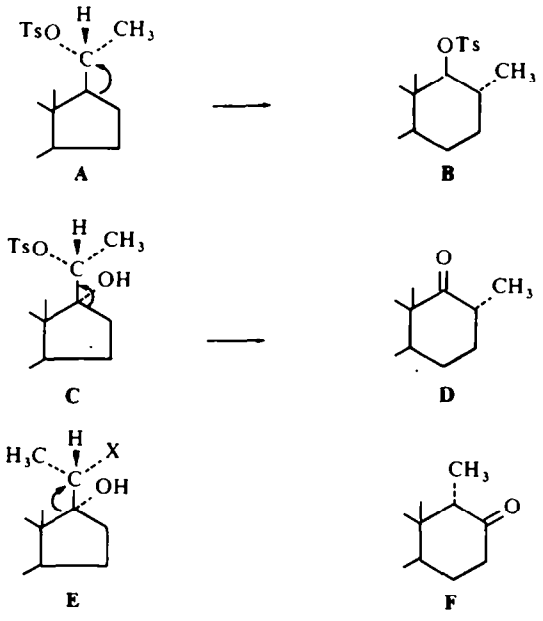
Abstract—In contrast to its 20-epimer, the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate proceeds predominantly without enlargement of the D ring. The products were identified as 17β-methyl-18-nor-5α, 17α-pregn-13-en-3β-yl acetate (**2b**), 3β-acetoxy-5α-pregnan-20α-yl formate (**13**), 3β-acetoxy-17-α-methyl-D-homo-5α-androstan-17αβ-yl formate (**14**). 5α-pregn-20-en-3β-yl acetate (**12b**) and 3β-acetoxy-5α-pregnan-20β-yl formate (**15**). During the degradation of **2b**, two *cis*-13,14 glycols were prepared one of which had an unusually large Δν for the O—H stretching bands of the hydrogens that do and that do not participate in hydrogen bonding. This large value (99 cm^{-1}) is attributed to molecular deformation of the 13α,14α-diol. This configuration and the relative yield of this glycol would indicate that the β face of the 13,14 double bond in **2b** is more accessible to the addition of OsO_4 and probably of other reagents. The catalytic hydrogenation of this double bond is reported. A possible mechanism is suggested for the unexpected formation of the uranediol derivative (**14**).

THE solvolysis of a 5α-pregnan-20β-yl *p*-toluenesulfonate (**A**) gave as the first product the corresponding 17α-methyl-D-homo-5α-androstan-17aβ-yl tosylate (**B**) in high yield and at a rate which suggested that the ionization of the tosyloxy group and the migration of the C-16, C-17 bond towards C-20 occurred in a single step.[1] A sterically analogous reaction was observed with a 17α-hydroxy-20β-tosyloxy steroid (**C**) which gave on solvolysis the 17α-methyl-D-homo-17a-ketone (**D**).[2] Further support for the concerted character of this reaction came from studies of 17α-hydroxy-20α-substituted steroids (**E**), as these gave a different product, the 17aα- methyl-D-homo-17-ketone (**F**). This course was observed for the solvolysis of the 20α-tosylate (**E**. X = OTs)[2] and for the deamination of the 20α-amine (**E**, X = NH_2) with nitrous acid.[3] The difference in the products and the relationship of their structure to the C-20 configuration of the starting material can be rationalized by two basically related explanations: (1) the preferred bridged transition state involves minimal steric strain;[2,3] or (2) as simultaneous bond rupture and bond formation proceed most readily if the bonds involved are antiparallel, the preferred reaction path of analogous reactions is derived from a preferred conformation.[1,4] It seemed reasonable, therefore, to expect that a 20α-tosylate like **1** which lacks a 17α-hydroxy group would undergo D-homoannulation with migration of the C-13, C-17 bond, as was suggested by Wendler.[4] The experiments to be reported were undertaken to test this prediction.

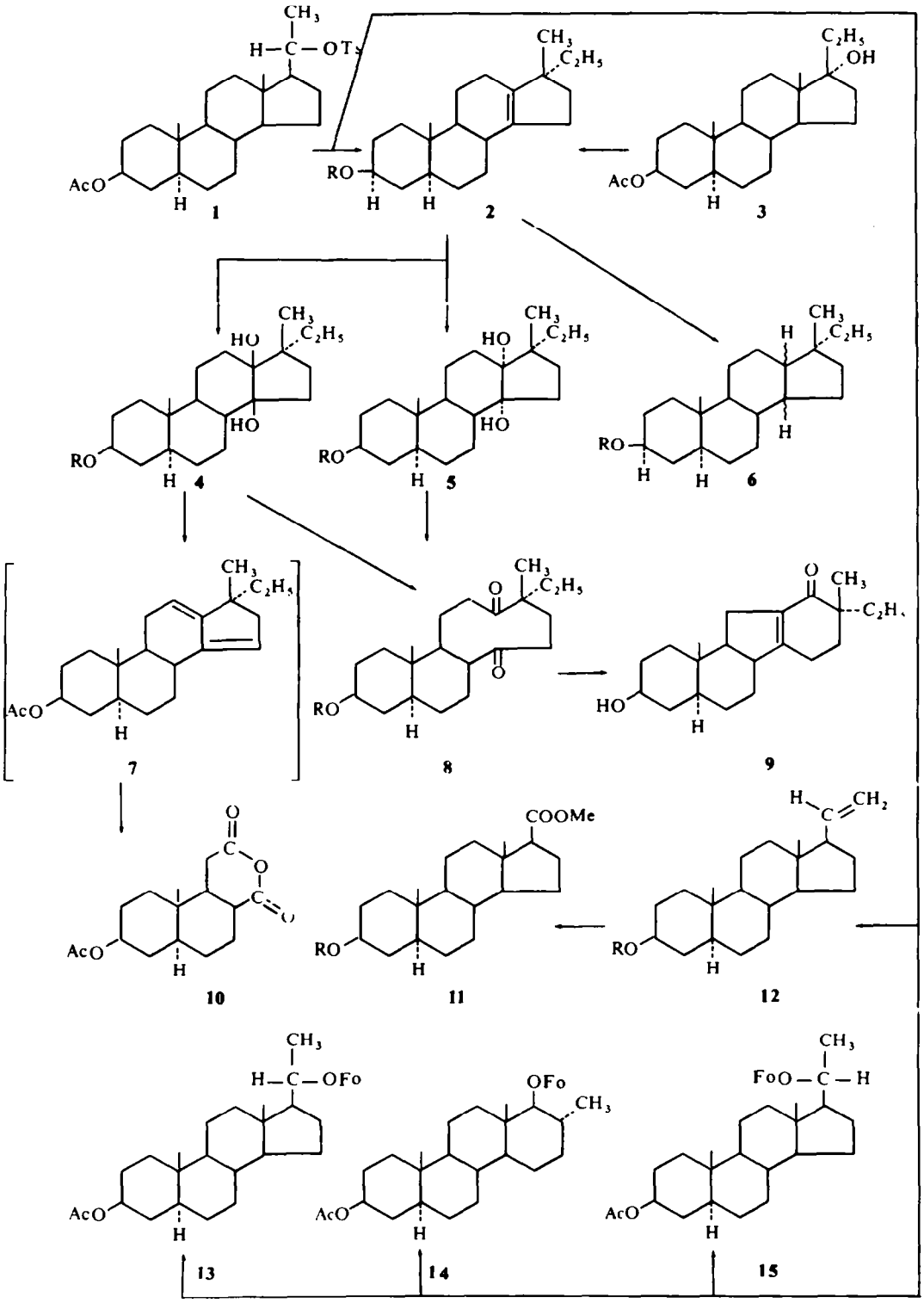
In contrast to the formolysis of 3β-acetoxy-5α-pregnan-20β-yl tosylate (**A**) which after complete ionization of the tosyloxy group gave the 17aβ-formate of uranediol 3-acetate (**14**) in high yield,[1] the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1**) furnished predominantly (75%) elimination products. The main constituent of this fraction was identified as 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**). The presence of a double bond was deduced from addition reactions (yielding

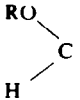


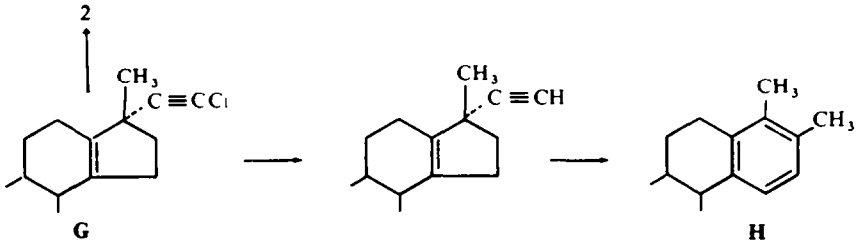
4, **5**, and **6**) and from the UV spectrum of the parent compound (**2a**). The double bond was ditertiary as neither the IR nor the NMR spectra showed the presence of olefinic hydrogens. The melting point and rotation of our alcohol were close to values observed on samples of **2a** that had been prepared by Ouannes *et al.*[5] One of these was obtained from 5α,17α-pregnane-3β,17β-diol by treatment with formic acid and alkaline hydrolysis, another from 21-chloro-17β-methyl-18-nor-5α,17α-pregn-13-en-20-yn-3β-yl acetate (**G**) by catalytic hydrogenation and hydrolysis. These workers provided a persuasive argument for the position of the double bond in **G**, and hence in **2** by showing that **G** contained no olefinic hydrogens and that it could be converted after hydrogenolysis of the chloride to the D-aromatic D-homosteroid **H**.

We did not, at first, suspect the presence of an Et group in our olefin as the NMR spectra of **2b** taken at 60 MHz showed signals at 0·86, 0·76 and 0·63 which seemed inconsistent with the usual triplet pattern. Ultimately, these signals could be attributed to an Et group, because when the curve was measured at 100 MHz, the outer peaks showed equal shifts in opposite directions and the middle peak had a shoulder on the low δ side. This Et group with two diastereotopic[6] hydrogens at C-20, therefore, gives rise to a pair of doublets which were seen particularly well in the spectrum of the ketone (**2c**) since this transformation shifts the 19-H peak[7] from the region of the 21-H signals. This interpretation and the structure assigned to our olefin were confirmed when an identical product was obtained from exposure of 3β-acetoxy-5α-pregnan-17α-ol to formic acid.

Before we realized that the formolysis product of **1** contained a primary rather than a secondary Me and, therefore, could not be a D-homosteroid, we undertook a degradation which gives further support to structure **2**. The acetate (**2b**) was treated with osmium tetroxide. Of the products only the major one could be converted to a glycol (**4**) under the conditions of Baran[8] whereas the cleavage of the other required reduction with LAH.[9] Both glycols (**4b** and **5b**) were oxidized with lead tetraacetate



a. R = H; b. R = CH_3CO—; c. O = C instead of 



G H

to the same 3β-acetoxydiketone (**8b**). Its parent alcohol (**8a**) had an IR peak at 1702 cm^{-1} which indicated that any ring containing a CO group had at least six C atoms. On high resolution mass spectroscopy, all ions that retained all three O atoms contained 15 or more C atoms. This pattern is consistent with the fact that the two CO groups in **8** are joined by a 6 carbon fragment. When exposed to dilute alkali at room temperature, the secodiketone **8a** underwent condensation to two hydroxyketones. These readily dehydrated to an α,β-unsaturated ketone (**9**) which proved to be stable to more vigorous treatment with alkali. This stability is contrary to the findings of Johns[10] who had conducted a similar degradation of 3-methoxy-17β-methyl-18-norestra-1,3,5(10),13-tetraene. He attributed the isomerization of his α,β-unsaturated ketone to inversion at C-8 but was uncertain whether there may not also have been an inversion at C-17. Our results do not seem to be in conflict with this conclusion. Compound **9** lacks an enolizable hydrogen at C-17 but it also differs significantly from Johns' compound in its A ring structure. In our case epimerization at C-8 would lead to serious interaction of the C-19 Me with an upright C ring which might well offset the normally greater stability of the *cis*-hydrindane structure.

Without explaining his reasoning, Johns deduced from the rotations that the more dextrorotatory glycol has the 13β,14β-dihydroxy configuration. Although the presence of the 17α-ethyl side chain might modify the relative ease of approach of osmium tetroxide to the α or β side of the double bond, we too obtained the more dextrorotatory glycol ($[\alpha]_D$ + 11°) in lesser amounts. It showed OH stretching peaks at 3614 and 3515 cm^{-1} in carbon disulfide. As their extinction ratio did not change significantly on dilution, we attribute the peak at the lower frequency to intramolecular H-bonding. Its frequency is unusually low for a vicinal glycol and thus differs from the major reaction product ($[\alpha]_D$ − 10°) which had peaks at 3617 and 3564 cm^{-1}. The feature of the molecular model which seems to account best for this spectral difference is the very short distance of the Me at 17β to the 11β-hydrogen if the OH groups are α and if the C ring is in the chair conformation. The resulting deformation would make the two OH groups more nearly coplanar and thereby lead to a greater Δν for their O—H stretching bands. If the repulsion is great enough to force the C ring into the boat form, the steric situation would be similar to that prevailing in the *endo* or *exo cis*-glycols derived from 2-norbornene where equally large Δν values[11] have been observed.* On these spectrographic grounds we prefer

* This numerical agreement should not be overemphasized because the OH groups of **5** are tertiary and those of norbornanediol secondary and because different solvents, CS_2 and CCl_4, were used for the measurements. No deductions about the precise geometry of **5**, therefore, seem to be warranted.

the 13β,14β configuration for the more levorotatory of our products. If this deduction is correct, the preferred direction of attack of the 13—14 double bond in **2b** by osmium tetroxide is from the β side.

Dehydration studies failed to further clarify this problem since both glycols were converted with $POCl_3$ and pyridine into products with absorption peaks at 246 nm, indicative of a heteroannular diene.* Only the major glycol gave such material in good yield. It proved to be too unstable for purification and was degraded with ruthenium tetroxide[12] and with chromic acid. The resulting acids were chromatographed and the earlier eluates converted to anhydrides. A pure compound (**10**) was isolated but only in low yield although it appeared to be the main constituent of this fraction. It had the infrared peaks of a strainless anhydride[13] and gave IR and NMR evidence that the 3β-OAc group of the starting compound had been retained. It was subjected to high resolution mass spectrometry. The peak with the highest mass could not be the molecular ion since it contained only three of the five oxygen atoms of an acetoxy anhydride. Evidently this highest mass ion had formed from the molecular ion by the loss of acetic acid as has been observed[14] before for a 3β-acetoxy-5α-steroid. The base peak, $C_{11}H_{16}$, would then correspond at least nominally to the loss of acetic acid and of the C ring from the molecular ion, and an analogous elimination of the C ring alone would account for the peak $C_{13}H_{20}O_2$. The other ions in the high mass region also appear to be consistent with the proposed structure (**10**). It received further support from the m.p. which was very close to that reported by Billeter and Miescher[15] for a compound with structure **10** that was obtained by degrading the Koester-Logemann ketone. It is evident that the degradation of the glycol should yield anhydride **10** if olefin **2** had the assigned structure.

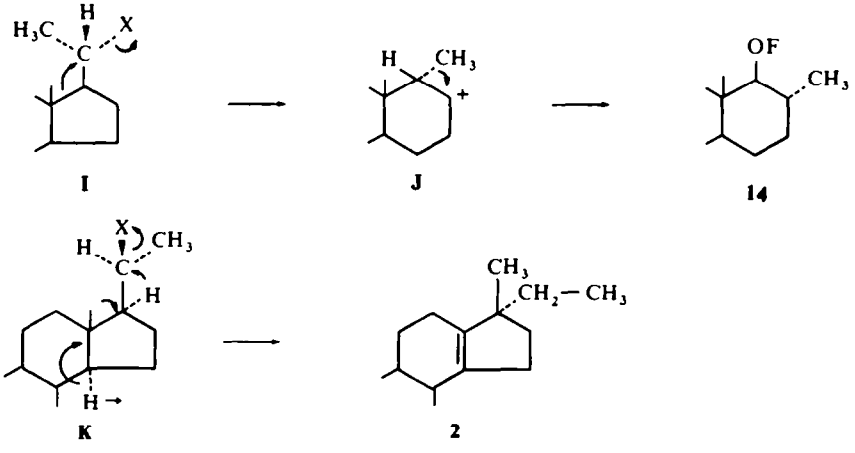
In contrast to Δ^8 and $\Delta^{8(14)}$ olefins, the ditertiary double bond of **2** could be reduced with platinum in acetic acid and more slowly even with palladium-calcium carbonate in alcohol. Usually hydrogenation and osmylation of a double bond proceed preferentially from the same side. We, therefore, favor the 13β,14β configuration for **6**. In an attempt of deducing the configuration from the NMR spectrum we identified[7] the signal of the 19-H by oxidation to **6c**. Unfortunately the shifts of this signal between **2a** and **6a** allowed no conclusions.

The later eluates containing olefin **2b** showed absorption bands indicative of a vinyl group.[13] This second olefin which was obtained in pure form was, therefore, thought to be 5α-pregn-20-en-3β-yl acetate. Its NMR spectrum agreed satisfactorily with the olefinic hydrogen signals calculated according to Pascual *et al.*[16] but differed from the experimental values reported[17] for the parent alcohol (**12a**), which also had a somewhat lower melting point than our preparation. A subsequent paper[18] on the NMR spectrum of 5,20-pregnadien-3β-ol, however, gave values close to ours. To corroborate the structure, compound **12b** was degraded to the etianate (**11**) by hydroxylation with osmium tetroxide, oxidation of the glycols and methylation of the acid. The methyl 3β-acetoxy- and 3β-hydroxy-5α-androstane-17β-carboxylates prepared in this manner were identified by direct comparison with reference specimens[19] obtained from 3β-hydroxy-5-androstene-17β-carboxylic acid.

* The IR spectra indicate that the two preparations of the diene are different. Possibly this is due to stereoisomerism at C-8. The probable configuration of the diene obtained from the predominant glycol (**4**) is 8β as this would account for the apparent identity of the anhydride (**10**) with that obtained by Billeter and Miescher. (See below.)

The remaining formolysis products (25%) were formates. In this fraction four compounds were found of which one was present only in traces and has not been identified. The three others were the formates of 3β-acetoxy-5α-pregnan-20α-ol, of uranediol 3-acetate and of 3β-acetoxy-5α-pregnan-20β-ol. They (**13**, **14**, **15**) were estimated to be present as 60, 34 and 5% of the formate fraction, respectively. Of these products, compound **14** was known,[1] whereas reference samples of the two others were prepared from the corresponding 20-carbinols by interaction with formic acid at room temperature.

The formation of uranediol 3-acetate 17a-formate (**14**) by formolysis of 5α-pregnane-3β,20α-diol 3-acetate 20-tosylate was unexpected. Our isolation of this product could be explained if the starting tosylate in spite of evidence to the contrary had been contaminated with or if during the formolysis it had isomerized to the 20β-tosylate. The conversion of the 20β-tosylate (**A**) to the 17aβ-formate (**14**) proceeds via the 17aβ-tosylate (**B**).[1] The validity of the proposed explanation could be tested if the conversion of **B** to **14** is significantly slower than the formolysis of **1**. This proved to be the case. The formolysis rate of a 17aβ-tosylate[1] was about 20 times slower than that observed for compound **1** (0·06 min^{-1}, Table 1). After tosylate **1** had been formolyzed for nine half lives, the intense absorption bands of tosylates in the IR could no longer be detected although the formolysis of **B** if it were an intermediate would have been less than 30% complete. The absence of **B** confirms the steric homogeneity of the starting tosylate (**1**) and shows further that **1** yields the 17aβ formate by a mechanism different from that of its 20-epimer. The formolyses of the two 20-tosylates follow wholly distinct reaction paths.



The direct formation of **14** from **1** is improbable if this reaction is a concerted process because this would represent a substitution with retention of the configuration. If, however, the ionization of the tosyloxy group precedes the rearrangement, the formation of **14** would be explicable if the intrinsic migratory aptitude of the 16–17 bond were greater than that of the 13–17 bond. As C-13 is more highly substituted this also seems unlikely.[20] Therefore, a further alternative warrants consideration. It involves two rearrangements. The first might consist of a concerted rearrangement analogous to the conversion **E** → **F**, which would lead to the C-17

cation (**J**). If its axial methyl migrates from C-17a to C-17 where it would occupy the equatorial position, the simultaneous reaction of the C-17a cation with solvent would produce **14**. A formolysis of **1** containing isotopic hydrogen at C-17 would afford a test of this mechanism. Such a study is now in progress.

In contrast to the 17α-hydroxy-20-tosyloxypregnanes[2] of either configuration at C-20 and to the 20β-tosyloxypregnanes,[1] which all solvolyzed predominantly with enlargement of the D ring, the 20α-tosylate gave **2b** as the main product. A recent computer analysis of the conformation of the side chain in 20-hydroxypregnanes has shown[21] that the energy difference between that conformation that has the 20-hydroxy *anti* to the 17α-hydrogen (as in **K**, X = OH) and the more stable one with the 20-hydrogen in this position (as in **I**) is much smaller if the configuration is 20α than 20β. A similar relatively favored *anti* orientation of the 17-hydrogen and the tosyloxy group (**K**, X = OTs) therefore should facilitate the elimination of toluenesulfonic acid or the migration of the hydride from C-17 to C-20. Either process might initiate the formation of **2b**. Reactions analogous to a hydride shift can occur also if there is a hydroxyl at C-17 and would result in the formation of epoxides. These have been obtained from 20α- and from 20β-tosylates but only in low yields in aqueous acetone containing an excess of potassium acetate.[2] Two factors are thought to contribute to D-homoannulation as the main path of the solvolysis of the 17α-hydroxy-20-tosylates. As explained above, this path should be favored if the preferred conformations are as shown in **C** and **E**. These allow hydrogen bonding between the 17-OH and the tosylate groups and are thereby stabilized still further relative to the rotamers with the *anti* orientation of these groups. Moreover, as the simultaneous ionization of the tosylate and the ring enlargement proceed, a positive charge develops at C-17 of the pregnane skeleton, which can be delocalized more effectively if this atom carries an OH group rather than a hydrogen. It is, therefore, not unreasonable that *both* epimers (**C** and **E**) show a preference for ring enlargement whereas no such uniformity exists if there is a hydrogen at C-17.

Although the formation of a 17β-methyl-Δ^{13}-olefin has often been demonstrated or postulated for reactions that were initiated by the ionization of a 17α- or 17β-linkage* or that would create a C-17 cation by the protonation of a 17—20 double bond,[5, 23, 24] it has been shown only recently that such an olefin can form also if the reaction is triggered by the ionization of a ligand at C-20.[24, 25,†] It is not known whether any of the latter reactions constitute more than the dehydration of a 20-substituted precursor to the Δ^{17}-olefin which then rearranges after reprotonation. This possibility clearly must be considered in our case as Δ^{17}-olefins with either (*E*) or (*Z*) geometry[27] have been shown to rearrange readily to the Δ^{13}-olefin in formic acid.[5, 24] Nevertheless, an alternative process for the conversion of **1** to **2** in this solvent is attractive, because the *anti* geometries of successive groups consisting of the tosyloxy, the 17-H, 18-Me and 14-H of compound **1** in conformation **K** would allow the facile rearrangement of **1** to **2** in a single step. Rate data (Table 1) gave no decisive support to such a concerted process, as the formolysis was slower than that of a 20β-tosylate[1] but faster than an unassisted process, provided that the formolysis of 3-methylbutan-2-yl tosylate[28] is an adequate model for the latter. Again the experi-

* For an extensive review of the earlier literature see Wendler.[22]

† A reaction studied by Chaudhuri and Gut[26] may provide another example as the product may have a 5- rather than a 6-membered D ring.

TABLE 1. FORMOLYSIS OF 3β-ACETOXY-5α-PREGNAN-20α-YL TOSYLATE (1)

Time	Tosylate concentrations[a]			Rate[b] × 10^3
min	IR	UV	Mean	min^{-1}
5	·762	·693	·728	63·6
10	·561	·561	·561	57·9
22	·276	·269	·273	59·0
50	—	·044	·044	62·6

[a] Expressed as fraction of the concentration at time zero
[b] Mean rate constant k 0·061 min^{-1} = 1·0 × $10^{-3}s^{-1}$ at 25°

ment with 17α-labeled **1** should allow a clear distinction between a process that does and one that does not involve a Δ^{17}-olefin as an intermediate.

The substitution reactions of **1** at C-20 which gave **13** and **15** occur with predominant retention of configuration. Judging from the course of hydride reductions of simple 20-oxosteroids, the energetically favored approach of such a reagent to trigonal C-20 gives the 20β-ol and, therefore, is from the "α" side. The simplest but not the only mechanism which would account for the predominance of **13** over **15**, therefore, appears to be the interaction of the solvent with the C-20 cation after the dissociation of the ion pair.

EXPERIMENTAL

Unless a statement is made to the contrary, the following specifications apply. Rotations were measured on solutions in $CHCl_3$ in a 1 dm tube on a Perkin–Elmer polarimeter (model 141). IR spectra were measured on solns in CS_2 on a Perkin–Elmer grating photometer (model 421). NMR spectra were recorded for solns in $CDCl_3$ containing TMS on Varian instruments (models HA 60 and HA 100). Data are given as shifts in parts per million downfield from TMS. UV spectra were measured in cyclohexane on a Beckman spectrophotometer with photomultiplier or on a recording Perkin–Elmer spectrophotometer (model 350). All m.p.s reported are corrected.

Neutral steroids were usually isolated by extraction with ether, benzene or EtOAc from the diluted reaction mixture. The organic phase was then washed with dil HCl, with Na_2CO_3 and with water and taken to dryness *in vacuo*.

Alumina used for chromatography was Woelm (neutral) hydrated with 6% of water. Silica gel–Celite (2:1) was washed as described.[29] TLC plates (0·5 mm. for preparatory purposes) were made from Adsorbosil 1 (Applied Science Laboratories, State College, Pa.). The formic acid used for preparatory experiments was a commercial product, 97–100%. For the kinetic measurements it was dried over anhydrous copper[II] sulfate and distilled under reduced pressure.

3β-Acetoxy-5α-pregnan-20α-yl p-toluenesulfonate (**1**). 3β-Acetoxy-5α-pregnan-20α-ol was prepared essentially as described.[30] The final product (m.p. 134–136°) was shown to be free of the 20-epimer by subjecting a large aliquot to another chromatogram on alumina and by testing eluates for the constancy of the absorbance ratios of the minima at 977 and 962 cm^{-1}. The tosylate (m.p. 139–141° on fast heating) was prepared as described.[30] To test for the presence of isomeric tosylates in the products of incomplete formolyses the following bands were used: peak at 933 for 3β-acetoxy-5α-pregnan-20β-yl tosylate and peaks at 750 and 931 cm^{-1} for uranediol 3-acetate 17a-tosylate.

Formolysis of 5α-pregnane-3β,20α-diol 3-acetate 20-tosylate (**1**). A soln of **1** (187 mg) in benzene (3·6 ml) was diluted with formic acid (360 ml), kept at 25° for 2 hr and distributed between benzene and water. The benzene phase was washed with water, Na_2CO_3 and water and was taken to dryness *in vacuo*. The residue was chromatographed on a 13 × 165 mm column of silica gel–Celite (11 g). Olefins (93·3 mg of noncrystalline material) were eluted with benzene–light petroleum (1:2 to 2:1) and showed in the later fractions a gradual increase in the IR peak at 3075 cm^{-1}. The isolation of **2** and **12** from such material is given below. The formates (34·8 mg) which were crystalline were obtained with benzene containing 2% ether. This fraction gave [α] at λ in nm: −18° (589), −21° (546), −35° (436) and −57° (365). The respective values calculated for a mixture containing 60% **13**, 34% **14** and 5% **15** were: −15°, −21°, −35° and −57°.

These percentages were based on the weights of separated material (as described below) corrected for minor operative losses. Crude reaction products showed extensive oxidation of olefins on storage.

17β-*Methyl*-18-*nor*-5α,17α-*pregn*-13-*en*-3β-*ol* (**2a**). The early and middle eluates (81 mg) of olefin acetates (from 187 mg of **1**) were hydrolyzed in MeOH containing 2% KOH at room temp for 18 hr. The products after recrystallization from dil MeOH gave **2a** (39 mg, m.p. 128·5–131°) and (20 mg, m.p. 127·5–130°); NMR (60 MHz): 0·94 (Me at C-17) and 0·80 (19-H); $[\alpha]^{26}$ (at λ in nm): −52° (589), −61° (546), −104° (436) and −162° (365); IR: ν_{max} 3609 and 1038 cm^{-1} (3β-OH), very weak band at 1670 cm^{-1} (tetraalkylethylene)[13] and strong peak at 1064 cm^{-1}; UV: plateau between 189 and 194 nm (ε 8000 in methylcyclohexane) (Perkin-Elmer). (Found: C, 83·17; H, 11·36. $C_{21}H_{34}O$ requires: C, 83·38; H, 11·33%).

Acetylation with Ac_2O and pyridine at room temp gave non-crystalline **2b** with 3β-acetoxy bands at 1735, 1241 and 1026 cm^{-1} and with a strong peak at 1063 cm^{-1}; NMR: 2·03 (acetate), 0·92 (Me at C-17), 0·80 (19-H), signals attributed to the Et group at 0·826, 0·755, 0·744 (shoulder) and 0·673 (center 0·750) in the 100 MHz and at 0·863, 0·758 and 0·632 in the 60 MHz spectrum. Both spectra were measured on the same solution.

5α-*Pregn*-20-*en*-3β-*yl acetate* (**12b**). The purification of **12b** required longer columns than the one used above. Another crude formolysis product (185 mg) was chromatographed on a 230 × 15·5 mm column of 20 g silica gel–Celite and gave 22 mg in the late olefin eluates which were rechromatographed. The resulting late eluates (5·9 mg) were recrystallized from MeOH and gave 5α-pregn-20-en-3β-yl acetate (3·8 mg), m.p. 97–98·5°; NMR (100 MHz, 1% in $CDCl_3$): Me singlets at 2·03 (Ac), 0·84 (19-H) and 0·59 (18-H); a complex olefinic hydrogen pattern not adequately analyzable at this dilution with centers approximately at 5·73, 5·02 and 4·88; IR: monoalkylethylene[13] bands at 3075, 2997, 1636, 995 and 909 cm^{-1}, 3β-acetoxy bands at 1733, 1242 and 1024 cm^{-1}.

The acetate **12b** was hydrolyzed as described for **2b** and the product (3·1 mg) recrystallized from dil MeOH, **12a** had m.p. 135–137·5°; IR: monoalkylethylene bands at 3075, 2997, 1636, 995 and 909 (very strong) cm^{-1}, 3β-OH peaks at 3610 and 1038 cm^{-1}. Lit. m.p. 131–133°; NMR: δ 4·95 and 5·54; IR: 3600, 1640 and 912 cm^{-1};[17] and IR: 994 and 906 cm^{-1};[31] NMR: calculated[16] for Δ^{20} 5·72, 5·02 and 4·99; found for 5,20-pregnadien-3β-ol[18] 5·75, 5·03, and 4·90 (Δ^{20}) and 0·60 (18-H).

Separation and identification of formates. The formate fraction (127 mg) from several formolysis runs of **1** was applied to 10 TLC plates of silica gel that had been dried at room temp but were not activated. The plates were developed with benzene containing 0·5% EtOAc and dried. This development was repeated twice. Steroids were then located by spraying with water. Two adjacent bands were seen and eluted by extraction with acetone. The faster moving band gave 67 mg, the other 44 mg of eluate.

The faster moving material was recrystallized from acetone and gave 52 mg of 3β-*acetoxy*-5α-*pregnan*-20α-*yl* formate (**13**) with m.p. 154–155°, raised on further recrystallization to 154·5–155·5° and unchanged on admixture of a reference sample; IR spectra agreed. Identity was confirmed by hydrolysis to the diol (m.p. 218–220°) and acetylation. The product was identified as 5α-pregnane-3β,20α-diol diacetate by m.p. (167·5–169·5°), mixture m.p. and IR comparison with reference sample.

The first mother liquor of **13** showed the stronger of the IR peaks of **15**. This fraction (15 mg) was hydrolyzed with dil KOH in MeOH at room temp and the product (10 mg) was chromatographed on a column of 13 g of silica gel. Development with benzene-EtOAc (3:1) gave unidentified material which after acetylation had a strong peak at 1119 cm^{-1}; 5α-*pregnane*-3β,20β-*diol* identified by its m.p. (194·5°), IR spectrum (KBr) and the IR spectrum of its diacetate. Finally elution with acetone gave 5α-pregnane-3β,20α-diol identified by the IR spectrum of its diacetate.

The eluate of the slower moving band from the original TLC plates was recrystallized from acetone and gave 22 mg of *uranediol* 3-*acetate* 17a-*formate* (**14**). Its m.p. (216–217°) was not depressed by admixture of a reference sample[1] and the IR spectra agreed. A sample was hydrolyzed, acetylated and the product identified as uranediol diacetate by m.p. (159·5–160·5°), mixture m.p. and IR comparison with reference sample.[1] Chromatography of the hydrolyzed mother liquors of **14** gave mainly uranediol and some 5α-pregnane-3β,20α-diol.

17β-*Methyl*-18-*nor*-5α,17α-*pregn*-13-*en*-3-*one* (**2c**). A soln (0·015 ml) of CrO_3-H_2SO_4 reagent[32] was added to **2a** (12·4 mg) in acetone (1 ml). The mixture was kept at 15° for 10 min, diluted with water and extracted with ether. The neutral fraction (12·0 mg) upon recrystallization from MeOH gave 10·7 mg of **2c**, m.p. 100–102°; NMR (100 MHz): 0·99, 0·95 and 0·755 (pair of doublets with apparent J 7·0 and 7·5 Hz and with area ratios of the fully resolved peaks 1:2:1; $[\alpha]^{28}$ (at λ in nm) −24° (589), −25° (546), −21° (436) and +47° (365); IR: 1713 cm^{-1}. (The conspicuous band of **2a** and of **2b** near 1064 cm^{-1} was absent.) (Found C, 84·05; H, 10·79. $C_{21}H_{32}O$ requires C, 83·94; H, 10·74%).

17β-Methyl-18-nor-5α,13ξ,14ξ,17α-pregnan-3β-ol (**6a**). A soln of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-ol (16·5 mg) in glacial acetic acid (9 ml) was shaken with Pt (prepared from 19 mg of the dioxide) in an atmosphere of H_2 for 165 min (60 min beyond the apparent cessation of H_2 uptake). After removal of the catalyst the soln was distributed between benzene and water. The residue of the neutral organic phase was recrystallized from acetone. Cpd. **6a** had m.p. 122–123·5°; NMR (100 MHz): Me signals at 0·735 (19-H) and 0·82 with the latter obscuring the main signal of 21-H which showed a peak at 0·89 and a shoulder at 0·75; 3α-H 6 peaks centered at 3·59; $[\alpha]^{26}$ (at λ in nm): −11° (589), −12° (546), −20° (436), and −31° (365) (*c*, 0·5); IR: 3β-OH at 3609 and 1041 (shoulder on main peak at 1046 cm^{-1}, assignment uncertain); the peak of **2a** at 1064 cm^{-1} was absent; UV: ε at 205 nm 15 (Beckman). (Found: C, 83·33; H, 12·01. $C_{21}H_{36}O$ requires: C, 82·83; H, 11·92%).

The *acetate* (**6b**) prepared with Ac_2O in pyridine at room temp had m.p. 47·5–49° and 3βOAc bands at 1734, 1242 and 1025 cm^{-1}.

17β-Methyl-18-nor-5α,13ξ,14ξ,17α-pregnan-3-one (**6c**). Compound **6a** (10 mg) was oxidized as described for **2a**. The reaction product (ν_{max} 1713 cm^{-1}) upon recrystallization from MeOH gave 7 mg of **6c** with m.p. 80–81°; NMR: (100 MHz): Me's at 0·94, 0·84 and at 0·83, a triplet (*J* 7·3) with the main peak not well resolved. (Found C, 83·69; H, 11·40. $C_{21}H_{34}O$ requires: C, 83·38; H, 11·33%).

Formolysis of 3β-acetoxy-5α-pregnan-17α-ol (**3**). Compound **3** prepared essentially as described,[33] (115 mg) was dissolved in formic acid (270 ml) in 10 min at 23°. After an additional 50 min the soln was distributed between benzene and water. The non-crystalline neutral reaction product (108 mg) was chromatographically and spectrographically pure **2b**. The acetate was hydrolyzed as described above. The m.p. (130·5–132°) of the alcohol was not depressed by admixture of 17β-methyl-5α,17α-pregn-13-en-3β-ol prepared from **1**. The IR spectra agreed. Rotation (*c*, 1·2 in EtOH) $[\alpha]^{22}$ −52° (589), −61° (546), −102° (436) and −157° (365 nm). Identity of both preparations of **2** was confirmed by converting both to the same acetoxyglycols **4b** and **5b**. Lit.[5]: m.p. of **2a** 126–128°; $[\alpha]_D$ −48 ± 6° (dioxan).

Another sample of **2b** was obtained by keeping (*Z*)-5α-pregn-17(20)-en-3β-yl acetate as a soln in formic acid for 2 hr. The product was identified by its IR spectrum and by the IR spectrum and m.p. of the parent alcohol.

3β-Acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13,14-diols (**4b,5b**). A mixture of **2b** (80·9 mg) osmium tetroxide (104 mg) and pyridine (3 ml) was kept at room temp for 67 hr. The product was hydrolyzed according to Baran[8] for 2 hr and extracted with EtOAc which gave 97·9 mg of residue. Upon recrystallization from acetone, 49·2 mg of *3β-acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13β,14β-diol* (**4b**) was obtained, m.p. 179–180°; $[\alpha]^{28}$ −10° (589), −11° (546), −19° (436) and −31° (365); IR: OH peaks at 3617 and 3564 cm^{-1}, 3β-OAc bands at 1733, 1241 and 1025 cm^{-1}. (Found: C, 73·22; H, 10·23. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12%).

The mother liquors were colored and showed an intense peak near 983 cm^{-1}. There was little change in weight, spectrum or appearance when the hydrolysis with bisulfite was repeated. A soln of this material in dry ether was stirred with 120 mg of LAH for 2 hr. The excess reductant was decomposed with HCl and the neutral reaction product acetylated. The acetates (38·6 mg) were adsorbed on 5 g of silica gel–Celite. Elution with benzene containing increasing amounts of EtOAc gave first acetoxyglycol **4b** (24·9 mg of eluate which gave 18·7 mg of crystals with m.p. 179–180°). This fraction was followed by 10·4 mg of eluate which was recrystallized from acetone. These crystals, *3β-acetoxy-17β-methyl-18-nor-5α,17α-pregnane-13α,14α-diol* (**5b**) (8·1 mg) had m.p. 162·5–163·5° and $[\alpha]^{26}$ +11° (589), +12° (546), +18° (436), +25° (365 nm); IR: 3614, 3515, 1733, 1241, 1026 cm^{-1}. (Found: C, 73·19; H, 10·11. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12%).

17β-Methyl-18-nor-5α,17α-pregnane-3β,13β,14β-triol (**4a**). Compound **4b** was kept in methanolic KOH for 21 hr. The product was recrystallized from acetone. Triol **4a** had m.p. 193·5–196·5°. A second modification (m.p. 185°) was observed on resolidification of molten samples. (Found: C, 75·15; H, 10·95. $C_{21}H_{36}O_3$ requires: C, 74·95; H, 10·78%).

3β-Hydroxy-17β-methyl-18-nor-13,14-seco-5α,17α-pregnane-13,14-dione (**8a**). A 0·1 M soln (0·47 ml) of lead tetraacetate in AcOH, dissolved with warming, was added to a soln of **4a** (12·5 mg) in 1·09 ml of a 6:1 mixture of MeOH and *t*-BuOH[34] and kept at 23° for 30 min. The mixture was distributed between ether and HCl. The neutral reaction product (11·9 mg) was recrystallized from acetone–light petroleum to give **8a** (10·8 mg), m.p. 128–130·5°; UV: λ_{max} 294 (ε 53), λ_{min} 242 nm (95% EtOH); IR: 3β-OH peaks at 3610, 1042, ketone peaks at 1702 and 1698,* strong peak at 1075 cm^{-1}. (Found: C, 73·31; H, 10·11. $C_{21}H_{34}O_3$

* 1% solution. This peak changed to a shoulder on dilution.

requires: C, 75·40; H, 10·25. $C_{21}H_{34}O_3 \cdot 0{\cdot}5\,H_2O$ requires: C, 73·43; H, 10·27%). Mass spectrum: molecular ion, found: 334·2505; required: 334·2508. Other prominent peaks with masses greater than 150: $C_{20}H_{34}O_2$, $C_{18}H_{29}O_2$, $C_{16}H_{25}O_3$, $C_{16}H_{24}O_3$, $C_{15}H_{24}O_3$, $C_{15}H_{25}O_2$, $C_{15}H_{24}O_2$, $C_{14}H_{22}O_2$, $C_{14}H_{19}$, $C_{11}H_{17}O$, $C_{12}H_{18}$, $C_{12}H_{17}$, $C_9H_{15}O_2$, $C_{10}H_{15}O$.

When **4a** was oxidized with a larger excess (33%) of $Pb(OAc)_4$ for 90 min, the crude product contained significant amounts of an impurity with acetate absorption bands.

3β-*Acetoxy*-18-*nor*-13,14-*seco*-5α,17α-*pregnane*-13,14-*dione* (**8b**). Identical samples of **8b** were obtained from **4b** and from **5b** by oxidation with lead tetraacetate. Their m.p. after recrystallization from light petroleum was 107–108·5°; IR: 3β-OAc bands at 1735, 1239, 1026 (or 1033, stronger), an asymmetric CO peak at 1702 and a strong peak at 1075 cm^{-1}. (Found: C, 73·39; H, 9·84. $C_{23}H_{36}O_4$ requires: C, 73·36; H, 9·64%).

3β-*Hydroxy*-17α-*ethyl*-17β-*methyl*-*D*-*homo*-18-*nor*-*C*-*nor*-5α-*androst*-13-*en*-17a-*one* (**9**). To a soln of **8a** (13·6 mg) in MeOH (2 ml) was added 1% KOH aq (0·2 ml). The mixture which was kept at 23° for 50 min was extracted with ether. The neutral product had λ_{max} 255 (apparent ε 4500), ν_{max} 1703, 1660 and 1619 cm^{-1}. It was chromatographed on silica gel–Celite with benzene containing increasing amounts of EtOAc. Three elution peaks were obtained. The first 4·5 mg was the α,β-unsaturated ketone **9** with peaks at 1660 and 1619 cm^{-1}, the second and third were both saturated ketones with distinct spectra in KBr (ν_{max} 1698 and 1692, respectively). After acetylation, solution spectra in CS_2 were obtained which reaffirmed the non-identity of these two fractions. Their ketone bands were at 1705 and a triplet at 1703, 1698 and 1695 cm^{-1}, respectively. Each had an OH peak at 3598 cm^{-1}. Hydrolysis of each acetate with 2% methanolic KOH overnight at room temp gave the α,β-unsaturated ketone **9**. The 3 preparations of **9** were combined, chromatographed on silica gel–Celite and recrystallized from dil MeOH and from acetone–light petroleum. The final product had m.p. 57–63°; UV (MeOH) 255 (ε 10,700) and 310 nm (ε 196); IR: 3β-OH 3610 and 1038; unsaturated ketone 1661 and 1621 cm^{-1}. The spectrum remained essentially unchanged when the compound was heated under reflux in 1·5 ml MeOH and 0·15 ml 5% KOH aq for 1 hr under N_2. The peaks (KBr) given by Johns[10] for his less stable α,β-unsaturated ketone (his cpd. **13**) were at 1658 and 1616 cm^{-1} and for the more stable isomer (his cpd. **17**) at 1667 and 1639. He obtained one hydroxyketone intermediate (his cpd. **14**) with λ_{max} at 1698 cm^{-1} (KBr).

Dehydration of acetoxyglycol (**4b**). Phosphorus oxychloride (0·2 ml) was added to a soln of **4b** (17·8 mg) in pyridine (2 ml). The mixture was heated under a reflux in an atmosphere of N_2 on a steam bath for 3 hr. After chilling, water was cautiously added and the product isolated by ether extraction. The neutral material (15·8 mg) had λ_{max} 246 with shoulders near 240 and 256 nm and ν_{max} 3046 (main) and 3091 cm^{-1}. Its IR spectrum differed from that of the product (with ν_{max} 3024) (0·3 mg) obtained in the same manner from 2·1 mg of **5b**. The latter preparation of diene showed three fully resolved peaks at 238, 246 (main) and 255 nm.

Degradation of diene **7**. Acetoxydiene **7** (62 mg, prepared from **4b**) was oxidized with ruthenium tetroxide in dilute acetone for 2 days while the oxidant was periodically reoxidized with $NaIO_4$.[12] Even after this long reaction time a major portion (24 mg) of the product was in the neutral fraction. Both acid and neutral fractions were therefore oxidized further with CrO_3 in 95% AcOH at 50° for 4 hr. The resulting acid fractions were combined (51 mg) and chromatographed on 95 g Celite containing 47·5 ml of 0·2 N H_2SO_4.[35] Elution with chloroform (10 × 150 ml) gave a total of 26 mg of acids. Although some of these eluates contained crystals they were not readily purified by recrystallization. Treatment with Ac_2O in pyridine at room temp gave 13 mg neutral product and another 6 mg on repeating this step. It showed IR peaks of a pentacarbocyclic and of a tetracarbocyclic anhydride.[13] The former was isolated by chromatography from silica gel–Celite by elution with benzene containing 4% ether and recrystallized from acetone–light petroleum to give 1·8 mg of **10**, m.p. 199–201° and prominent IR peaks at 1736, 1235 and 1029 (acetoxy), at 1813, 1766 and 1069 (anhydride)[13] and at 961 cm^{-1}: NMR: Me singlets at 0·83 and 2·00; Mass spectrum: peaks with > 30% intensity of base peak ($C_{11}H_{16}$): C_2H_3O, C_8H_{10}, $C_{10}H_{13}$, $C_{11}H_{16}$, $C_{14}H_{18}O_3$, those with masses between 148 and 234 and intensity > 3% of base peak: $C_{12}H_{18}$, $C_{13}H_{16}O$, $C_{13}H_{18}O$, $C_{12}H_{14}O_2$, $C_{12}H_{16}O_2$, $C_{13}H_{18}O_2$, $C_{13}H_{20}O_2$, $C_{14}H_{16}O_2$ and $C_{13}H_{15}O_3$. Mass peak of olefinic anhydride found: 234·1237, $C_{14}H_{18}O_3$ requires: 234·1256. Lit. m.p. 198–199° (corr.)[15] and 193° (uncorr.)[36]. On the basis of the IR peaks listed, the anhydride **10** was the major component of the neutral fractions described above. Their chromatography was accompanied by partial hydrolysis.

Degradation of olefin **12b**. The total olefin fraction (138 mg) obtained from **1** was converted to glycols as described for **2b** and the triols obtained after LAH reduction were separated by chromatography on silica gel–Celite. The late eluates, (7·1 mg) obtained with benzene-5% EtOH were oxidized with lead tetraacetate (40% excess) as described for **4a** for 1 hr. The product (6·3 mg) which had strong aldehyde peaks at 2705

and 1720 cm^{-1}. in 0·4 ml of acetone was oxidized with 0·1 ml of 5% $KMnO_4$aq for 10 min.[37] The excess oxidant was reduced with sulfurous acid, and the acidic reaction product (4·6 mg) methylated with diazomethane. The IR spectrum with etianate peaks[38] at 1736 and 1157 cm^{-1} agreed with that of a reference sample[19] of *methyl* 3β-*hydroxy*-5α-*androstane*-17β-*carboxylate* (**11a**). The product was acetylated and recrystallized from dil MeOH. The m.p. of *methyl* 3β-*acetoxy*-5α-*androstane*-17β-*carboxylate* (**11b**) (149–151·5°) was not depressed by admixture with a reference sample[19] (m.p. 151·5–153°). The IR spectra with peaks at 1736, 1732, a doublet at 1158 and 1153, and 1024 cm^{-1} agreed. Another sample of **11a** with the same spectrum was prepared from isolated **12b** (3·3 mg) by treatment with OsO_4, cleavage according to Baran[8], oxidation with CrO_3 and methylation.

3β-*Acetoxy*-5α-*pregnan*-20α-*yl formate* (**13**). A soln of 3β-acetoxy-5α-pregnan-20α-ol (30·2 mg) in 5 ml of formic acid was kept at room temp for 4 hr and distributed between benzene and water. The product (32·2 mg) which showed no OH absorption in the IR was recrystallized from acetone, m.p. 155·5–156·5°; [α] −5° (589), −11° (546), −20° (436), −35° (365 nm); IR: formoxy peaks at 3092, 2724, 1723 and 1185 with side peak at 1176 cm^{-1}; 3β-OAc peaks at 1733 (shoulder), 1239 with shoulder at 1245, and 1026 cm^{-1}; prominent peaks for differentiation from the 20-epimer at 1066, 1050 and 944 cm^{-1}. (Found: C, 73·78; H, 9·89. $C_{24}H_{38}O_4$ requires: C, 73·80; H, 9·81%).

3β-*Acetoxy*-5α-*pregnan*-20β-*yl* formate (**15**). This compound was prepared from 3β-acetoxy-5α-pregnan-20β-ol as described for the 20-epimer. Formate **15** had m.p. 148·5–150·5°; $[\alpha]^{28}$ + 33° (589), + 39° (546), +68° (436), and +113° (365 nm); IR: formoxy peaks at 3092, 1724, 1183 cm^{-1}; 3β-acetoxy peaks at 1733 (shoulder), 1240 and 1025 cm^{-1}, peak best suited for differentiation from 20-epimer at 1071 cm^{-1}. (Found: C, 73·91; H, 9·71. $C_{24}H_{38}O_4$ requires: C, 73·80; H, 9·81%).

Kinetic measurements. A solution of **1** (30·3 mg) in 3 ml benzene was diluted at zero time with 122 ml dry formic acid. The soln was maintained at 25°. Samples of 20 ml were withdrawn after 5, 10, 22, 50, 101 and 253 min and were immediately distributed between 150 ml of benzene and 80 ml of water. The products were isolated and dried as previously described for a 20β-tosylate.[1] An aliquot (1/8) of each sample was analyzed in cyclohexane by measuring absorbances at 257, 262, 268, 273 and 285 nm. The last value was used to correct for the non-specific absorption that remained after 101 min. The remainder of each sample was dissolved in CS_2 and absorbances were determined at 813, 781 and 687 cm^{-1}. The relative concentrations of tosylate as determined from measurements at the various wave lengths in the IR or UV agreed with their respective means within 2% for samples taken after 5, 10 and 22 min. Rates were calculated from the averages obtained by the two methods.

The IR spectra taken after reaction times of 101 and 253 min agreed and showed no tosylate absorption.[1] The sole peaks seen after 50 min and absent after 101 min were those attributable to the starting tosylate. Similarly, in the earlier spectra only bands present in the curves of the 20α-tosylate and its final formolysis products were seen. In particular, no indication was found for the presence of either 3β-acetoxy-5α-pregnan-20β-yl tosylate or of uranediol 3-acetate 17a-tosylate in any of these fractions.

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Note added in proof: While this manuscript was in press. we became aware of a report on the cyclization under acid and basic conditions of a 17.17-dimethyl-13.14-secodiketone analogous to **8** (J. Torreilles and A. Crastes de Paulet. *Bull. Soc. Chim. Fr* 4892 (1968)). Our suggestion of the 8β configuration for **9** is consistent with their conclusions. The same workers (*Ibid.* 4112 (1968)) described a diene analogous to **7**. which was obtained from a 13.14-epoxide.