The Uranediol Rearrangement[1]

H. HIRSCHMANN, FRIEDA B. HIRSCHMANN, AND ANTONIA P. ZALA

The Department of Medicine, Western Reserve University, and the University Hospitals, Cleveland, Ohio

Received September 14, 1965

Uranediol (17α-methyl-D-homo-5α-androstane-3β,17aβ-diol) 3-acetate 17a-formate (**2**) was obtained in high yield when 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate (**1a**) was treated with formic acid. The 17aβ configuration for uranediol (**3b**) was deduced by synthesis of and comparison with the 17a epimer (**9b**) of uranediol. The 17aα isomer did not form in significant amounts on reduction of the 17a-ketone with sodium and propanol but was obtained in the highest yield on hydrogenation with platinum in an acid medium. Compared with its epimer, the 17aα (axial) alcohol was more hindered in the formation of esters and showed a much smaller splitting of the magnetic resonance signals of the proton at C-17a. The uranediol rearrangement which was observed in various solvents was fastest in formic acid. It occurred in two stages. The first, a fast conversion of the 20β-tosylate to the 17aβ-tosylate, was followed by a much slower solvolytic displacement at C-17a with retention of configuration and preservation of the carbon skeleton in the main product. Although the second stage was not appreciably faster than the formolysis of simpler equatorial tosylates, the reaction path may be through a nonclassical carbonium ion. This would explain the unusual behavior of a tosylate with a neopentyl-like structure. In contrast to the formolysis of the equatorial 17aβ-tosylate, the axial isomer gave an olefin as the main product. Correlations of structure with infrared and proton magnetic spectra and with rotations are presented.

An earlier report from this laboratory[2] described the formation of uranediol (17α-methyl-D-homo-5α-androstane-3β,17aβ-diol) (**3b**) by acid hydrolysis of 5α-pregnane-3β,20β-diol 20-sulfate and provided an explanation for the presence of the D-homosteroid in the hydrolyzed urine of pregnant mares. The occurrence of such a rearrangement was first observed with a 20β-hydroxy steroid *p*-toluenesulfonate.[3] It is the purpose of this communication to describe the solvolytic reactions of 20β-tosylates in detail, to establish the structures of the rearrangement products, to provide new evidence for the configuration of uranediol at C-17a, and to describe the course of the rearrangement which proceeds in two stages: the first, a conversion of the original 20β-tosylate to the rearranged 17aβ-tosylate, and the second, a solvolytic displacement of the tosyloxy group with retention of the configuration at C-17a.

The structure of uranediol (**3b**) was established by Klyne[4] who noted the identity of its partial oxidation product, uranol-17a-one (3β-hydroxy-17α-methyl-D-homo-5α-androstan-17a-one) (**6b**) with the deamination product of 17β-amino-17aα-methyl-D-homo-5α-androstane-3β,17aβ-diol. The structure of **6** was confirmed by independent syntheses of its acetate (**6a**).[5,6] The equatorial orientation of its 17-methyl group which had been proposed by Klyne[4] received strong support from further arguments by Klyne and Shoppee[7] and from the demonstration that the 17 epimer of uranol-17a-one acetate is unstable to acid and alkali and yields uranol-17a-one acetate either directly or after acetylation.[6]

The only structural feature not elucidated by these studies of uranol-17a-one is the configuration of uranediol at C-17a. The 17aβ orientation of the hydroxyl group was considered most probable by Brooks, *et al.*,[8] who based this assignment on the assumption that the presence or absence of the 17α-methyl group would not affect the sign of the molecular rotation difference between a 17a-carbinol and its benzoate. The correctness of this assignment is affirmed by our observations which are summarized in Scheme I.

Treatment of 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate (**1a**) with formic acid gave an acetate formate (**2**) in 86% yield.[9] The free diol **3b** and its diacetate **3a** were shown to be identical with reference samples[10] of uranediol and its diacetate, respectively, by determination of melting points, mixture melting points, rotations, and infrared spectra. Although the formate group of **2** was hydrolyzed much more slowly with alkali than were 3- or 16α-formates,[11a-c] conversion of **2** to the 3-acetate of uranediol could be effected in 58% yield. This monoester (**5**) was used for the preparation of the 17a epimer **9c**.

The availability of newer techniques[12,13] for the displacement of a tosylate with inversion which had been successful even with an ester of the neopentyl type[13] prompted us to attempt the preparation of **9e** from the 17a-tosylate (**4a**).[14a] This sulfonate was readily obtained from **5** by reaction with tosyl chloride in pyridine, but **4a** failed to give significant amounts of the desired product. The tosylate in N,N-dimethylformamide at the usual reaction temperatures[12] remained unchanged and at higher temperatures gave complex mixtures which, according to their infrared spectra, contained only small amounts of formates or alcohols. The use of tetramethylammonium formate in N-methylpyrollidone[13] gave similarly unsatisfactory re-

(1) Supported by U. S. Public Health Service Grants CA-01679 and AM-09105 and a Research Career Program Award, K6-AM-14367.

(2) H. Hirschmann and J. S. Williams, *J. Biol. Chem.*, **238**, 2305 (1963).

(3) D. M. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962).

(4) W. Klyne, *Nature*, **166**, 559 (1950).

(5) R. S. Rosenfeld, *J. Am. Chem. Soc.*, **79**, 5540 (1957).

(6) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

(7) W. Klyne and C. W. Shoppee, *Chem. Ind.* (London), 470 (1952).

(8) R. V. Brooks, W. Klyne, E. Miller, and J. Y. F. Paterson, *Biochem. J.*, **51**, 694 (1952).

(9) This yield is considerably higher than the one obtained by Glick and Hirschmann.[3] Under the conditions then used, extensive ester exchange occurred at C-3.

(10) We are greatly indebted to Professor Klyne for providing us with these reference compounds.

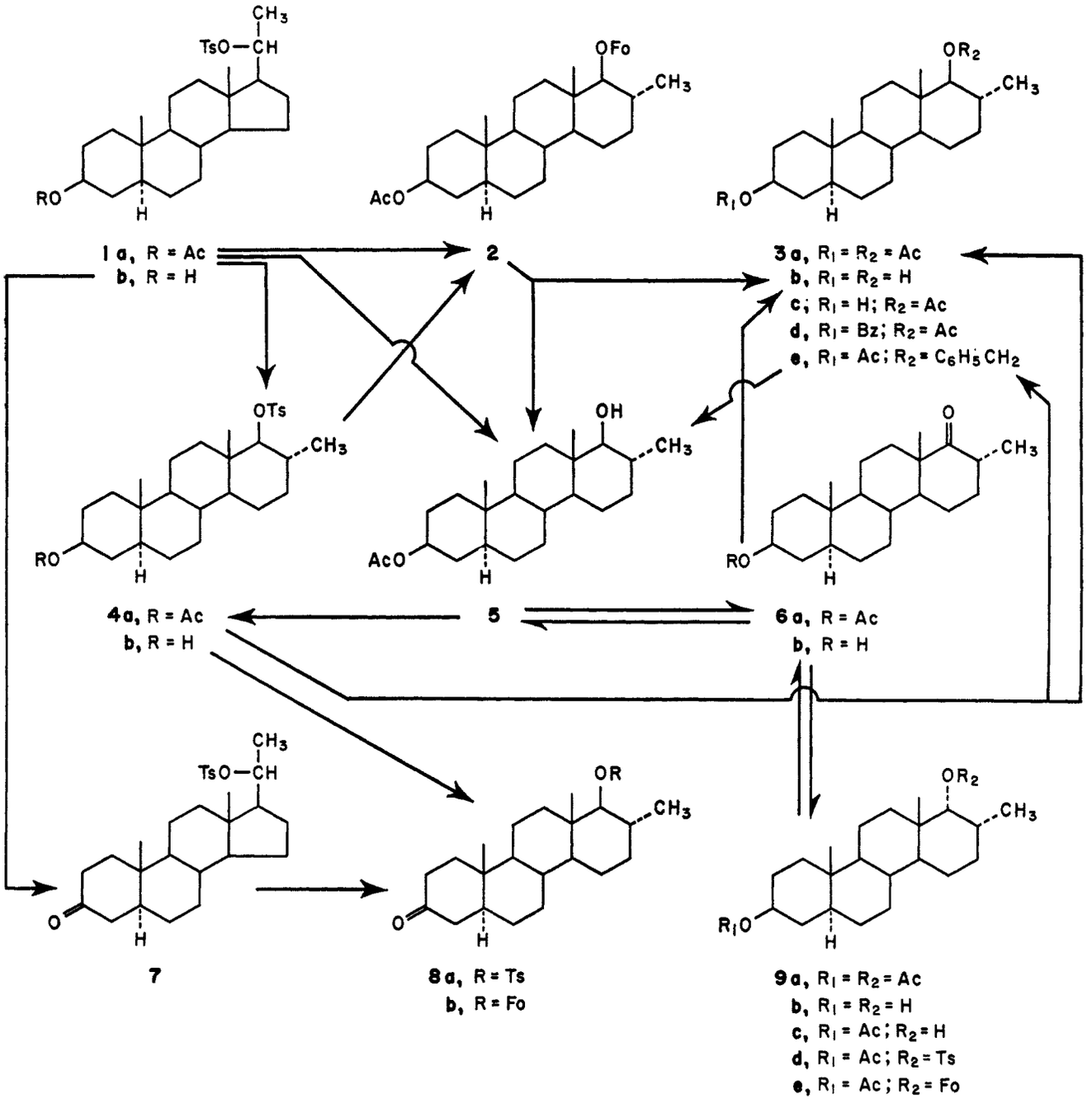
(11) (a) H. Hirschmann and M. A. Daus, *J. Org. Chem.*, **24**, 1114 (1959); (b) H. Hirschmann, F. B. Hirschmann, and J. W. Corcoran, *ibid.*, **20**, 572 (1955); (c) H. Hirschmann and F. B. Hirschmann, *J. Am. Chem. Soc.*, **78**, 3755 (1956); (d) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Biol. Chem.*, **236**, 3141 (1961).

(12) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(13) H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962).

(14) (a) A 17aβ-tosylate without a methyl group at C-17 was reported to give "very small amounts" of the 17aα-ol by reaction with potassium acetate in boiling acetic acid after saponification.[14b] (b) R. O. Clinton, R. G. Christiansen, H. C. Neumann, and S. C. Laskowski, *J. Am. Chem. Soc.*, **79**, 6475 (1957).

SCHEME I



Ac = CH_3CO-, Fo = $HCO-$, Bz = C_6H_5CO-, Ts = p-$CH_3C_6H_4SO_2-$

sults. The largest yield of formate was observed when the tosylate was heated in dimethylformamide in the presence of sodium formate at 130°. The product was chromatographed and the small formate fraction—rather unexpectedly—was found to consist mainly of the 17a-formate 2 with retained configuration.

The route to 17a-epiuranediol (17α-methyl-D-homo-5α-androstane-3β,17aα-diol) (**9b**) *via* the 17a ketone **6a** was, therefore, examined.[15] Reduction with sodium and propanol yielded uranediol (**3b**). The carbinol with the same (β) configuration at C-17a was also the main product on reduction with sodium borohydride in methanol or hydrogenation with nickel in alcohol or with platinum in acetic acid. However, with these procedures, spectrographic and chromatographic evidence for the formation of an isomer could be obtained. The isomer ratio became approximately 1 when hydrochloric acid[16] was added to the medium of the platinum reduction. We were able to get good separations of the resulting mixture of monoacetates only by thin layer chromatography and, therefore, found it laborious to prepare large amounts of the new compound. Its structure as the 17a epimer of urane-

(15) (a) R. E. Marker and E. Rohrmann [*J. Am. Chem. Soc.*, **61**, 2719 (1939)] found that the 17a-keto group of related compounds was resistant to reduction with aluminum isopropoxide and hydrogenation with platinum in alcohol but obtained an alcohol of unknown configuration on hydrogenation in acetic acid. For reduction of 17a ketones without a 17-methyl group, see (b) M. W. Goldberg and E. Wydler, *Helv. Chim. Acta*, **26**, 1142 (1943); (c) M. W. Goldberg, J. Sicé, H. Robert, and P. A. Plattner, *ibid.*, **30**, 1441 (1947); (d) H. Heusser, P. T. Herzig, A. Fürst, and P. A. Plattner, *ibid.*, **33**, 1093 (1950); (e) ref. 14b.

(16) M. G. Vavon and B. Jakubowicz, *Bull. soc. chim. France*, [4] **53**, 581 (1933).

diol 3-acetate (**9c**), which was strongly indicated by this synthesis, was confirmed by oxidation with chromium trioxide in acetone[17,18] which gave uranol-17a-one acetate (**6a**). This structural relationship between **5** and **9c** is further supported by their n.m.r. spectra. According to the generalizations of Trenner, *et al.*,[19] the signals of the C-18 methyl should be identical if the two reduction products differed only in their configuration at C-17a, but should show a major shift (0.13 p.p.m.) if **5** and **9c** differed in their configuration at C-17. Since no difference was observed (Table I) and since the frequency of this resonance signal agreed precisely with the value predicted by Trenner, *et al.*, for these 17α-methyl compounds, we conclude that **9c** is the 17a epimer of uranediol 3-acetate. The newly formed hydroxyl group of **9** was significantly less reactive than the 17a-hydroxyl group of uranediol in acylations in pyridine (with acetic anhydride or with tosyl chloride) and gave a lower yield of formate on treatment with formic acid at room temperature.

TABLE I

N.M.R. SIGNALS[a]

5	**9c**	**3a**	**9a**	
		Substituent at C-17a		
β-OH	α-OH	β-OAc	α-OAc	Assignment
0.81[b]	0.81[b]	0.85	0.89	18-H
0.81	0.81	0.79	0.81	19-H
0.94 D (5)	0.92 D (7)	~0.79 D (6)	~0.77 D (5)	17-CH_3[c]
2.00	2.00	2.00	2.01	3-OAc[d]
...	...	2.05	2.10	17a-OAc
2.70 D (9)	3.04[e]	4.33 D (10)	4.63[e]	17a-H

[a] Signals (δ) in parts per million downfield from tetramethylsilane; D = center of doublet, figures in parentheses give the splitting in cycles per second. [b] Expected value, 0.81.[19] [c] Expected value, splitting of 6–8 c.p.s. (N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p. 34). [d] Expected value, 2.03 ± 0.05 p.p.m.[29] [e] Somewhat broadened peaks with half-intensity band width of 5 (**9c**) and 6 c.p.s. (**9a**).

If these differences between the epimers are to be used for the determination of their configurations, the possible effects of additional substituents on the behavior of axial and equatorial groups of typical cyclohexane derivatives should be considered. This seems the more necessary as observations[20,21] about C-12 carbinols (with certain side chains at C-17) have been interpreted[21] to signify a reversal of the usual stability order at this similarly situated center. In the pair **3** and **9** the presence of the C-12 methylene group causes one additional 1,3 interaction for both the axial and the equatorial group at C-17a (**10**). This should not alter the normal differences in the stability of axial and equatorial substituents. There are, however, two skewed interactions with vicinal methyl groups if the C-17a substituent is equatorial but only one if the substituent is axial. The reference data available[22,23a] suggest that the resulting destabilization of this equatorial alcohol is only about half the usual energy difference between the axial and the equatorial conformations of cyclohexanol (best value,[23b] 700 cal.). There is, therefore, no reason to question that the usual rules about the behavior of axial and equatorial alcohols[24] would be applicable. They yield a consistent assignment. The 17a-carbinol that formed with sodium and alcohol[25] showed less steric hindrance on acylation. Furthermore, on catalytic hydrogenation of the ketone, the yield of this epimer decreased as the acidity of the reaction medium was raised.

The assignment of the 17aβ configuration for uranediol **3b**, which was deduced from these results, was strongly supported by measurements of n.m.r. (Table I). The only signal besides the broad hump of the 3α-proton which appears above 2.5 p.p.m. is attributed to the proton at C-17a. It is more shielded[26] in **5** and in **3a** than in their epimers. This indicates[27a,28,29] an axial proton at C-17a for uranediol. The somewhat greater shielding of the acetate methyl group at C-17a of **3a** is also consistent with the equatorial orientation of the ester.[28] The most decisive test comes from consideration of the fine structure of the signals of the protons at C-17a. In the 3-monoacetate and in the 3,17-diacetate of uranediol there were two distinct peaks, separated by 9 or 10 c.p.s., respectively, whereas the epimers showed only a broadened single peak with a half-intensity band width of 5 or 6 c.p.s., respectively. The behavior of uranediol 3-monoacetate and diacetate is typical of the spin–spin coupling of an equatorial alcohol or ester if its axial carbon-bound proton is adjacent to an axial proton[27b] as is the case in structure

(17) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953).

(18) A. I. Laskin, P. Grabowich, B. Junta, C. de Lisle Meyers, and J. Fried [*J. Org. Chem.*, **29**, 1333 (1964)] reported the inversion of an adjacent tertiary center during such an oxidation and inferred that different conditions (chromium trioxide–pyridine) apparently caused the same change with their type of substrate (a 15-hydroxy-17-oxo steroid). A product, evidently identical with that obtained by the latter procedure, resulted also from oxidation with chromium trioxide in acetic acid [K. Tori and E. Kondo, *Steroids*, **4**, 713 (1964)]. To increase the probability of preserving an unstable configuration at C-17 in the unlikely event that inversion at this center had occurred during the hydrogenation that produced **9c**, we conducted the oxidation at a lower temperature and for a much shorter period than Laskin, *et al.* Fukushima, *et al.*,[6] observed no inversion of C-17 when the 17 epimer of **6b** was oxidized with chromium trioxide in acetic acid.

(19) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

(20) J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **27**, 3381 (1962); J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *ibid.*, **29**, 2963 (1964).

(21) M. Alauddin and M. Martin-Smith, *ibid.*, **28**, 886 (1963).

(22) D. S. Noyce and L. J. Dolby, *ibid.*, **26**, 3619 (1961).

(23) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965: (a) p. 356; (b) pp. 44, 434.

(24) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(25) If the proportion of epimers that result from the reduction of ketones with alkali metals reflects their difference in free energy,[24] the virtually exclusive formation of a single isomer from **6a** with sodium and propanol would seem surprising. Although no claim is made for the reliability of the calculation given above, it should be noted that, in some cases at least, the proportion of epimers can vary widely with reaction conditions and can even be the reverse of that predicted from the relative stability of the reduction products (for references, see those quoted by Huffman, *et al.*[20]).

(26) The magnitude of this shift is similar for the pair of alcohols (δ_{e-a} 0.34) and of acetates (δ_{e-a} 0.30) and falls into the range observed with other steroids.[27a] The signals of the C-17a protons in the acetates **3a** and **9a** also appear to be quite typical,[27a] but the chemical shift of this proton on acetylation of the parent alcohol [δ (**3a** − **5**) 1.63, δ (**9a** − **9c**) 1.59] is much larger than the values cited by Bhacca and Williams[27a] (1.01 to 1.10 p.p.m. for six-membered rings). Clearly, factors besides ring size must affect this shift. The signals of the two alcohols are close to the values predicted by the rule of E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962) (calcd.: **5**, δ 2.67; **9c**, δ 3.00 for solutions in carbon tetrachloride).

(27) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964: (a) p. 83; (b) p. 51.

(28) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(29) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

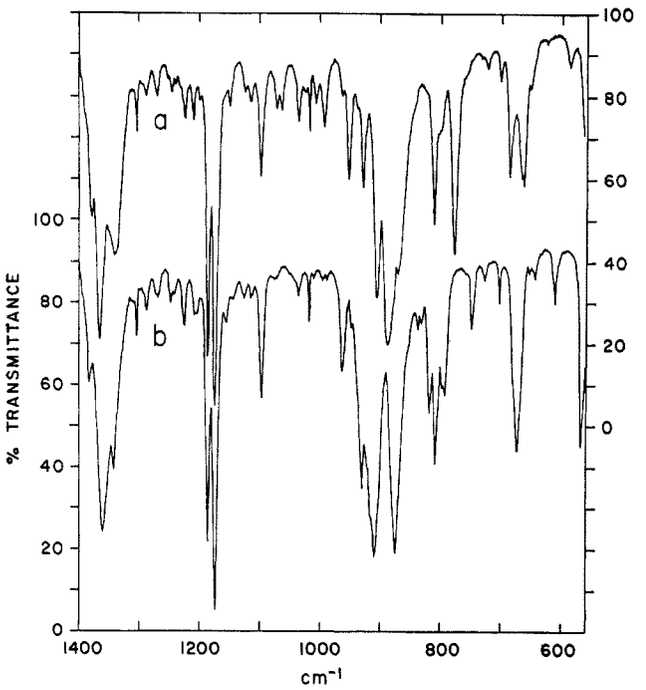


Figure 1.—Infrared spectra of (a) 20β-hydroxy-5α-pregnan-3-one tosylate (**7**) and (b) uranol-3-one (17aβ-hydroxy-17α-methyl-D-homo-5α-androstan-3-one) tosylate (**8a**), 0.012 *M* solutions in carbon disulfide. The bands at or near 1187, 1175, 1099 (*cf.* Jones and Herling[54a]), 1305, and 1020 cm.$^{-1}$ are found generally in steroid tosylates; those common to 20β-tosyloxy and 17aβ-tosyloxy compounds, respectively, regardless of the substituent at C-3 (oxo, 3β-hydroxy,3β-acetoxy) are listed with compounds **1b, 4a**, and **4b**, in the Experimental Section. Curve a is drawn with reference to the ordinate at the right, b at the left.

3. If the 17a proton is equatorial as in **9**, only a much smaller coupling constant (3 c.p.s. or less)[30] is to be expected.

The molecular rotations of **5** and of **9c** and of their acetates (Table II) are of interest since Klyne and Stokes,[31] in their survey of carbinol rotations, included only one pair of secondary carbinols which was substituted by a tertiary and a quaternary carbon atom. The difference between the two epimeric alcohols **5** and **9c** (+13°) is very small, especially if compared with a pair of 17a alcohols which lacks the 17-methyl group ($\Delta[M]D_{\beta-\alpha}$ +128°).[31] As was already pointed out by Klyne and Stokes, the effect of acetylating the 17aβ-hydroxy group of uranediol is similar to the anomalous[31] change observed with a 17aβ alcohol without the methyl at C-17. In the 17aα series no reference data for acetates without a 17-methyl appear to be available. Acetylation of **9c** caused a shift in the opposite direction from that observed with **5**.

TABLE II

MOLECULAR ROTATIONS OF 17a ALCOHOLS AND ACETATES

Compd.	C-17a substituent	C-17a configuration	[M]D, deg.	Δ[M]D, deg. (β − α)	Δ[M]D, deg. (OAc − OH)
5	OH	β	−6		
3a	OAc	β	−118		−112
9c	OH	α	−19	+13	
9a	OAc	α	+70	−188	+89

As one might expect, the tosylate **9d** showed a greater propensity toward elimination reactions than the equatorial tosylate **4b**. The latter showed no spectrographically observable change when kept for 2 hr. in boiling pyridine, whereas tosylate **9d** underwent almost complete elimination of the tosylate group under these conditions. The main product, which requires study on a larger scale, appears to be neither the Δ^{17} nor the Δ^{16} olefin because the spectrum failed to show absorption characteristic of an olefinic hydrogen above 3000 cm.$^{-1}$.[32] However, a compound with the spectrographic characteristics of an olefin substituted with a hydrogen and a methyl group was obtained when **9d** was treated with formic acid. Again, the identification of the unsaturated product will require the accumulation of larger amounts of material. In contrast, the equatorial tosylate **4a** reacted almost entirely by substitution as will be discussed below.

The reactions of the 20β-tosylate **1** in alcohol also support the equatorial orientation of the tosylate group of **4**. At room temperature, the side-chain structure of **1a** is quite stable, and removal of the acetate group at C-3 with alkali can be achieved with little rearrangement. At higher temperatures, rearrangement occurred. In boiling ethanol in the absence of alkali, the main product was the rearranged tosylate **4a**. The parent tosylate **4b** was formed in about 50% yield even when an 0.0016 *M* solution of the 20β-tosylate **1a** was treated with 1.2 *N* alcoholic potassium hydroxide (3 hr. at 60°). Clearly, the much stronger nucleophilic hydroxide and ethoxide ions do not compete very effectively with the tosylate group. This is explicable if the conversion of the 20β- to the 17aβ-tosylate involves either simultaneous rupture and formation of the C–O bonds of the tosylates or the internal return from an ion pair. In either case, the initial location of the tosylate group on the β side of ring D may be expected to lead to preferential β substitution of the rearranged structure.

Although the principal reaction products obtained with formic acid and with alcohol do not appear to be analogous, there is no intrinsic difference between the two processes. When the reaction time of the formolysis was shortened, the rearranged tosylate **4a** was obtained in high yield, and this compound on continued formolysis yielded in a much slower reaction uranediol 3-acetate 17a-formate (**2**). The rates of the two processes were measured with the corresponding 3 ketones **7, 8a,** and **8b,** since these were more soluble in carbon disulfide, the solvent of choice if the ratio of the two tosylates in the product was to be measured by infrared analysis. The wide differences in the spectra are shown in Figure 1. The bands at 780 and 673 cm.$^{-1}$ were used for measurement. The first stage, 20-β-tosylate (**7**) to 17aβ-tosylate (**8a**), had a half-life of about 2 min. (Table III); the solvolysis of the rearranged tosylate was about 100 times as slow. Although acetone (2.5%) was used as a cosolvent to effect prompt solution at the start of the reaction, the rate of the first step was appreciably faster than the solvolysis[33] of 3-methylbutan-2-yl tosylate, which had

(30) D. H. Williams and N. S. Bhacca, *J. Am. Chem. Soc.*, **86**, 2742 (1964).

(31) W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954).

(32) Possible structures include $\Delta^{13(14)}$ and $\Delta^{13(17a)}$ olefins with migration of C-18 to C-17a. Eliminations with rearrangements have been observed for other axial groups with comparable location under similar conditions by F. C. Chang [*Tetrahedron Letters*, 2057 (1963)] (12α-mesylate with collidine) and by K. Waisser, M. Krumpolc, J. Klinot, and A. Vystrcil, [*Z. Chem.*, **4**, 349 (1964), *Chem. Abstr.*, **61**, 16103 (1964)] (1α-ol with phosphorus oxychloride and pyridine).

(33) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952).

a half-life of 46 min. in pure formic acid at 24.5°. This indicates that the heterolysis of the 20β-tosylate is anchimerically assisted by the migration of the 16,17 bond to C-20.[34] This inference had been drawn previously[2] from the stereospecificity of the rearrangement and confirms the conformation assigned[3] to the 20β-tosylate on independent grounds. It provides an additional argument for the α configuration of the methyl at C-17 in uranediol.

TABLE III

FORMOLYSIS OF 20β-HYDROXY-5α-PREGNAN-3-ONE TOSYLATE (7)[a]

Time, min.	Amount in sample, mg. 7	8a	Rates × 10³ k_r, min.⁻¹	k_t, min.⁻¹
0	2.13	...		
2	1.20	1.10	287	
10	0.12	2.02	285	
120		1.43		3.32
250		0.98		3.10
370		0.67		3.12
490		0.49		3.00

[a] k_r is the rate of disappearance of **7**; k_t is the rate of removal of tosylate group. Both were calculated as first-order rates. For details, see the Experimental Section.

The second stage of the reaction proceeds in an unexpected manner. The structural relationship between the 17a-tosylate and the 17a-formate is unambiguous because the formolysis product (**2**) has been reconverted to the tosylate **4a** by hydrolysis of the formate and reaction of the alcohol (**5**) with tosyl chloride. The formolysis reaction, therefore, proceeds with retention of configuration. The stereospecificity of this replacement is very high. The yield of the 17a-α-formate (**9e**) was too small to allow its isolation and definite identification. The spectrographic data indicate that the formolysis of **1a** which had given 86% of **2** had also produced 0.2% of the 17aα-formate (**9e**).[35] Results analogous to the main course of the reaction were obtained with solvents which are more nucleophilic than formic acid. In aqueous dioxane the 20β-tosylate was again isomerized to the 17aβ-tosylate, and on prolonged heating uranediol 3-acetate (**5**) was formed. When the 17aβ-tosylate **4a** was heated with benzyl alcohol, a benzyl ether (**3e**) was obtained which was shown to have the 17aβ configuration when hydrogenolysis gave uranediol 3-acetate (**5**). These findings are in striking contrast to the usual results of solvolysis of equatorial cyclohexyl tosylates. The formolysis of *trans*-4-*t*-butylcyclohexyl tosylate[36] or of 2α-hydroxy-5α-androstan-17-one tosylate,[37] and the methanolysis of 5α-cholestan-3β-ol tosylate[38] proceed predominantly, if not exclusively, by inversion. In the acetolysis of optically active 2-octyl tosylate,[39] a diminished optical purity of the inverted product could be traced to inversion of the original tosylate by substitution with toluenesulfonic acid or tosylate ion. Such a mechanism for over-all retention cannot explain our results. It seemed improbable because our solvolyses were conducted at great dilution (usually 0.5 to 2 m*M*) and because the 17aβ-tosylate is extremely resistant to replacement even by powerful nucleophiles. It was definitely excluded when we failed to obtain the 17aβ-formate on formolysis of the 17aα-tosylate **9d**.

Retention of configuration has been observed in solvolyses of an equatorial 11α-tosylate which gave the corresponding 11α-carbinol although in rather low yield.[40] The phenomenon was explained by steric hindrance to replacement from the axial (β) side. Although the slower esterifications of the axial carbinol **9c** demonstrate greater crowding on the α than on the β side of C-17a, this crowding is not severe enough to prevent other addition reactions to a trigonal C-17a from proceeding from the α side. This is demonstrated by the predominant α (axial) addition of hydride or hydrogen in the reduction of **6a** with sodium borohydride or with nickel. In contrast, sodium borohydride causes equatorial hydride addition to C-11 ketones almost exclusively.[41] At C-2, where steric hindrance is less than at C-11, the hydride still adds preferentially from the equatorial side,[42] but the formolysis of a representative 2α-tosylate proceeded with inversion.[37] It seems doubtful, therefore, that steric hindrance to attack from the axial side is an adequate explanation for the virtually complete retention of configuration in our case. This explanation also would not account for a second unusual feature of the solvolysis of the 17aβ-tosylate. Although the compound **4** is a substituted neopentyl derivative, its conversion to its main formolysis product (**2**) involves no change in the carbon skeleton. Recent steroid examples for the very extensive rearrangement which usually results from the solvolysis of such sulfonates were given by Hirschmann, *et al.*,[43] in their studies of a 12β-mesylate and by Shoppee and Johnston and by Bancroft, *et al.*,[44] of 4,4-dimethyl-3-tosylates. Two mechanisms would explain the retention both of configuration and of the carbon skeleton of our main products. The first is an attack on sulfur rather than on carbon during solvolysis as was suggested (but not proven) for the hydrolysis of a 3-tosylate by Moriarty and Wallis.[45] To our knowledge, the process is without precedent if the ionizing power of the solvent is as great as that of formic acid. An attack of formic acid on sulfur, if it occurs at all, therefore, must be slower than the usual formolyses which rupture C–O bonds. The formolysis of **8a** does not have this characteristic since it was somewhat faster than that

(34) M. Uskokovíc, M. Gut, and R. I. Dorfman [*J. Am. Chem. Soc.*, **82**, 3668 (1960)] found no indication of anchimeric assistance in their studies of the D-homo rearrangement of 20-hydroxybisnor-5α-cholanes.

(35) It remains to be determined whether this small amount is also formed *via* **4a** or by some other route.

(36) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(37) J. Ramseyer and H. Hirschmann, *Federation Proc.*, **24**, 534 (1965).

(38) N. Pappas, J. A. Meschino, A. A. Fournier, and H. R. Nace, *J. Am. Chem. Soc.*, **78**, 1907 (1956).

(39) A. Streitwieser, Jr., and T. D. Walsh, *Tetrahedron Letters*, 27 (1963).

(40) S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(41) W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

(42) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *ibid.*, **78**, 3752 (1956). J.-C. Richer [*ibid.*, **30**, 324 (1965)] and J. A. Marshall and R. D. Carroll [*ibid.*, **30**, 2748 (1965)] have explained the steric course of hydride reductions solely by operation of steric approach control.

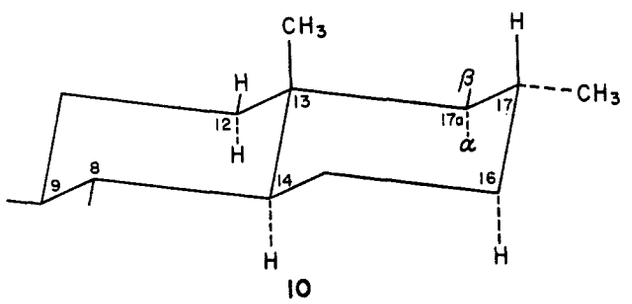
(43) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey, and N. L. Wendler, *ibid.*, **76**, 4013 (1954).

(44) (a) C. W. Shoppee and G. A. R. Johnston, *J. Chem. Soc.*, 3261 (1961); (b) G. Bancroft, Y. M. Y. Haddad, and H. G. R. Summers, *ibid.*, 3295 (1961).

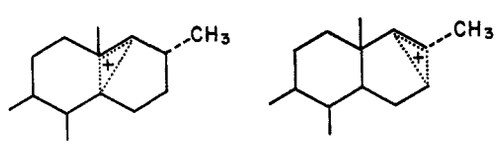
(45) (a) R. M. Moriarty and E. S. Wallis, *J. Org. Chem.*, **24**, 1274 (1959). (b) Cleavage of the sulfur–oxygen bond evidently can occur under the rather different conditions (*t*-butoxide in dimethyl sulfoxide) used by F. C. Chang [*Tetrahedron Letters*, 305 (1964)], who also cites earlier examples of sulfur–oxygen cleavage. For a subsequent report, see F. C. Chang and N. F. Wood, *Steroids*, **4**, 55 (1964).

of *trans*-4-*t*-butylcyclohexyl tosylate,[36] 3.14×10^{-3} and 2.11×10^{-3} min.$^{-1}$, respectively. The nature of the products[44] (formate, benzyl ether) would exclude an attack on sulfur if their formation from **5** by secondary reactions can be excluded. This cannot be claimed for the formolysis because the formation of **2** from the carbinol **5** is appreciably faster than from the tosylate **4a**. However, the situation is reversed for acetolysis. In a medium of acetic acid containing 0.02 *M* sodium acetate the tosylate **4a** yielded the diacetate **3a** but no detectable amount of the alcohol after 2 hr. at 100° (about three half-lives), whereas compound **5** was recovered virtually unchanged after exposure to the same conditions. The acetate **3a**, therefore, was formed by rupture of the C–O bond of **4a** at C-17a.

The second mechanism which would explain retention of configuration and of the carbon skeleton is the formation of a nonclassical carbonium ion such as **11** or **12** which on subsequent reaction with solvent would



10



11 **12**

be expected to yield uranediol derivatives with retained configuration. The main objection which can be raised against this pathway is the observation that the rate of formolysis of **8a** (which was measured in the presence of a small amount of a retarding cosolvent, acetone) is only a little faster than those of other cyclohexyl tosylates that receive no anchimeric assistance from the participation of neighboring atoms. However, a similar lack of major acceleration relative to simpler cyclohexyl tosylates was observed in the acetolyses of 4,4-dimethyl-5α-cholestan-3-ol tosylates, although in these cases the formation of nonclassical carbonium ions was indicated by the structure of the rearrangement products.[44] Further exploration of the reaction mechanism in our case must await a study of the as yet very minor amounts of unidentified substitution or elimination products that were detected in the mother liquors.

Our observations on the origin of urinary uranediol and our failure to find more than a trace of 17a-epiuranediol derivatives among the solvolysis products of 20β-tosylates focus attention on the report by Brooks, *et al.*,[8] who suggested that they may have isolated a compound (designated as MW) with the structure of 17a-epiuranediol as the diacetate from the hydrolyzed urine of pregnant mares. This diacetate had a higher melting point and was much more levorotatory than uranediol diacetate. It gave a compound, presumed to be a monoacetate, on boiling with potassium carbonate in aqueous methanol and uranediol on heating with potassium hydroxide in the same solvent. It was suggested that the more vigorous treatment with alkali during the second hydrolysis might have caused inversion at C-17a. The 17a-epiuranediol diacetate described in the present report differs from the isolated diacetate in its melting point, rotation, and in its configurational stability towards strong alkali. In view of the evidence which we have presented for our product, we regard it as the authentic preparation of **9a**.[46]

The availability of the tosylate **4a** allowed the identification of the tosylate[3] which remained after heating the 20β-tosylate **1a** with pyridine for 2 hr. It proved to be a mixture mainly of **4a** with some unchanged starting material (**1a**). The slowness of the elimination reaction of **1a** compared with those of the three stereoisomers studied by Glick,[3] therefore, is only in part due to its rearrangement to the much more stable 17aβ-tosylate. It is probable that the unidentified tosylate encountered by Sarett[47a] as a by-product in a similar elimination reaction of a 20β-tosylate has a D-ring structure identical with that of **4a**.

Although D-homo compounds form very readily from 20β-tosylates even under conditions which are not particularly favorable to solvolyses, intervention of this process does not preclude substitution of a tosylate without rearrangement. 20α-Substituted pregnanes have been obtained from 20β-tosylates not only in reactions with intramolecular nucleophiles as in the formation of a 20α,21-epoxide from a 20β-tosyloxy-21-acetoxy steroid with methanolic alkali[47b] but also with an external reagent as in the formation of a 20α-azide by substitution with lithium azide in methanol.[48]

Spectrographic Characterization.—The infrared spectra of uranediol 3-acetate (**5**) and of its 17a epimer **9c** possess some noteworthy features. Both compounds show a hydroxyl peak which differs from that of a 3β hydroxyl as in **3c**, not only in its wavenumber which is about 20 cm.$^{-1}$ higher but also in its contour (Figure 2). The equatorial 17a-carbinol, especially, showed a shoulder at lower frequencies. Since the absorbance of this shoulder did not diminish relative to that of the

(46) If the findings of Brooks, *et al.*, signify an alkali-catalyzed isomerization of a carbinol, the mechanism proposed for such reactions by W. Hückel and H. Naab [*Ber.*, **64**, 2137 (1931)] would accommodate not only inversion of an unstable configuration at C-17a but also at C-17. Since such an isomerization of an isolated carbinol usually requires much higher temperatures, a different interpretation was considered. Possibly the diacetate of Brooks, *et al.*, was a molecular compound or a hard-to-separate mixture which contained uranediol diacetate as one component. Subsequent chemical reactions did not cause an inversion at C-17a but merely facilitated fractionation. The following observations support this explanation. On treatment with potassium carbonate under the conditions of Brooks, uranediol diacetate (**3a**) gave uranediol 17a-acetate (**3c**) in good yield, which melted 11° higher than the presumed MW monoacetate. Uranediol 3-benzoate 17a-acetate (**3d**) which was prepared from **3c** melted only a little higher than the corresponding derivative that had been prepared from the mother liquors of MW diacetate by hydrolysis with carbonate and benzoylation. The rotations also agree fairly well, whereas the molecular rotation difference, 102°,[8] between MW acetate benzoate and MW diacetate shows a much larger discrepancy from the value computed, 34°, for the substitution of a benzoate for a 3β-acetate in a 5α-steroid: D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

(47) (a) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1690 (1948); (b) *ibid.*, **71**, 1175 (1949).

(48) D. H. R. Barton and L. R. Morgan, Jr., *J. Chem. Soc.*, 622 (1962).

main peak on fourfold dilution to 0.007 M, it is probably not caused by hydrogen bonding but by the existence of different conformational forms. As this extra absorption is too weak and too distant, this asymmetry of the peak is not revealed by measurements of the ratio of the segments of the half-absorbance band width at the high and the low frequency side of the maximum (ν_+/ν_-). This ratio was proposed by Aaron and Rader[49] as a quantitative measure for band asymmetry in the differentiation of the relatively symmetric bands of axial alcohols from the less symmetric bands of their equatorial epimers. They regarded a ratio which deviated from unity by less than 10% as a firm indication of an axial hydroxyl but anticipated the occurrence of less symmetric bands for vicinally substituted axial alcohols. The ratio obtained with **5** (0.98) which did not differ significantly from that of **9c** (1.02) shows that atypical values can also be obtained with vicinally substituted equatorial alcohols. The frequency difference in the peaks of **9c** and **5** is small but conforms to the rule[50] that the axial alcohol absorbs at the higher wavenumber.

A peculiarity of the 3-acetate band of **5** and other 3β-acetoxy steroids was revealed, we believe, by the relatively high resolution of the spectrometer in the 6-μ region. At 1% concentration (~0.03 M), two closely spaced peaks were seen (Figure 2) which coalesced on fourfold dilution into a single peak of intermediate wavenumber. If the phenomenon signifies association of two moledules at higher concen tration, it probably involves two acetate groups, since the double peak did not depend on the nature of the second functional group of the molecule. Moreover, as mentioned above, if this second group was a 17a alcohol, there was no concomitant change in the spectrum of the hydroxyl region near 2.8 μ on dilution.

All formates showed a rather weak maximum near 3100 cm.$^{-1}$. A peak at 3107 cm.$^{-1}$ has been reported for a solution of methyl formate in carbon tetrachloride and identified as a combination band of the carbonyl stretching and the in-plane C–H bending frequency of the formate group.[51] The origin of this band should be recognized in order to avoid possible confusion with an olefinic hydrogen. The main ester band of the equatorial formates **2** and **8b** was at 1175 and 1174 cm.$^{-1}$, respectively, that of **9e** at 1182 cm.$^{-1}$. This difference is close to those reported for equatorial and axial formates at C-3.[11a,d]

Other bands useful for the detection of reaction products are given in the Experimental Section. The formation of the tosylate derivative appears to be of particular value for the distinction of isomeric alcohols since the bands which change with changes in the molecular environment of the tosyloxy group are of unusual intensity. This is illustrated in Figure 1.

Experimental Section

General Procedures.—Rotations were measured in a 2-dm. tube on solutions in 95% ethanol unless another solvent is specified. All melting points reported are corrected. The melting points of tosylates, all of which melted with decomposition, varied considerably with the rate of heating. With these compounds, samples were introduced into the bath about 10° below the melting point. The purity of tosylates was always determined by infrared spectroscopy. Infrared spectra were measured with a Perkin-Elmer double-beam grating spectrometer (Model 421) which was calibrated with the fully resolved atmospheric and ammonia bands listed by the Commission on Molecular Structure and Spectroscopy.[52] The solvent was carbon disulfide for all compounds except uranediol (**3b**) and 17a-epiuranediol (**9b**) which were examined as KBr pressings. The absorption maxima reported (except the strongest ones) were usually measured on 1% solutions, those of the acetate band in the 6-μ region are for a 0.25% solution unless a more concentrated solution is specified. N.m.r. spectra were measured in a microcell on solutions (~10%) in deuteriochloroform and are reported as shifts in parts per million from tetramethylsilane. The instrument was Model A-60 of Varian Associates.

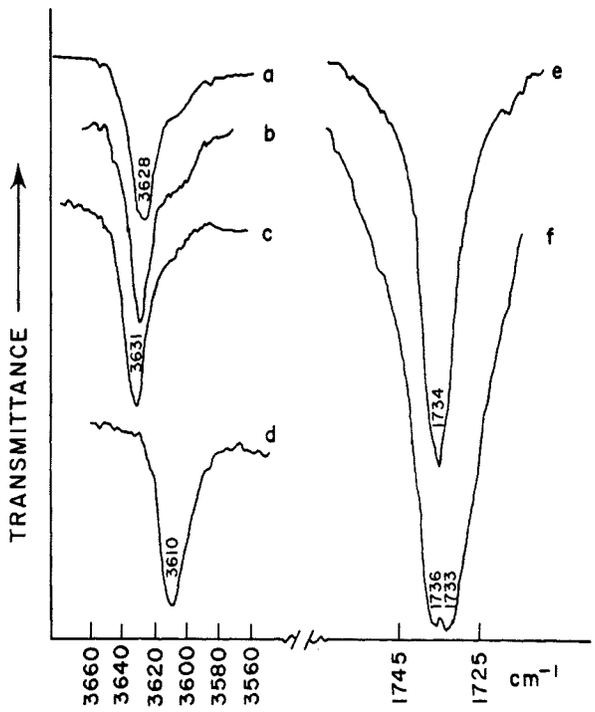


Figure 2.—Infrared spectra of diol monoacetates in carbon disulfide. Curves a, b, e, and f are of uranediol 3-acetate (**5**); curve c, 17a-epiuranediol 3-acetate (**9c**); curve d, uranediol 17a-acetate (**3c**). All solutions were 1% except b and e which were 0.25%. The ordinate of b was expanded five times.

Unless specified otherwise, steroids were isolated from reaction mixtures by extraction with ether or benzene, which was then washed with dilute hydrochloric acid, with sodium carbonate, and with water, and was taken to dryness either under a current of nitrogen or by distillation *in vacuo*. The formic acid used for preparative purposes was a commercial product (97–100%). For the kinetic run it was dried over anhydrous copper sulfate and distilled under reduced pressure.

The alumina used for chromatography was the more acidic preparation described previously[3]; the silica gel–Celite mixture (2:1) was washed as reported.[11d] In paper chromatography, steroids were made visible with phosphomolybdic acid.[3] Thin layer plates of silica gel–calcium sulfate were usually made with the preparation Adsorbosil 1 (Applied Science Laboratories, State College, Pa.). Plates were activated by heating (110° for 30 min.). Those used for analysis had a layer of 0.25 mm. Zones containing steroids were detected by spraying the plates with water[53] after the solvents used for developing had evaporated. The boundary between **5** and **9c** was clearly visible

(49) H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85**, 3046 (1963). These workers used the symbol α/β (which could be confusing with steroids) and studied solutions in carbon tetrachloride. Our experience with carbon disulfide although still limited to 2- and 3-hydroxy steroids has shown this solvent to be equally suitable for the test.

(50) A. R. H. Cole, G. T. A. Müller, D. W. Thornton, and R. L. S. Willix, *J. Chem. Soc.*, 1218 (1959).

(51) J. K. Wilmshurst, *J. Mol. Spectry.*, **1**, 201 (1957).

(52) International Union of Pure and Applied Chemistry, *Pure Appl. Chem.*, **1**, 603 (1960).

(53) B. Samuelsson, *J. Biol. Chem.*, **238**, 3229 (1963).

because the two compounds gave rise to different degrees of opacity.

Uranediol 3-Acetate 17a-Formate (2).—A solution of 205 mg. of 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate (**1a**)[3] in 8.2 ml. of benzene and 12.3 ml. of acetone was diluted with 184.5 ml. of formic acid and kept at 23° for 24 hr. Sodium bicarbonate (400 mg.) and toluene (300 ml.) were added to the chilled reaction mixture which was then concentrated *in vacuo* at a bath temperature below 23°. The two phases which remained were distributed between benzene and water. The benzene phase was washed with sodium bicarbonate and water and was taken to dryness. The product (156 mg.) on recrystallization from acetone gave 116 mg. of **2** melting at 216–218°. The analytical sample had m.p. 217–220°; $[\alpha]^{23}D$ −41° (*c* 0.7, chloroform); ν_{max} 1732, 1241, 1027 (acetate),[54a,b] 1726, 1175 cm.$^{-1}$ (formate).[54a,c,11a] The latter peak showed side bands[54d] at 1197, 1188, and 1159 cm.$^{-1}$. N.m.r. signals were at 0.79 (19-H), 0.87 (18-H), 2.00 (acetate), 4.42 doublet (J = 11 c.p.s., 17a-H), and 8.18 p.p.m. (formate). Signals assignable to the methyl at C-17 were not resolved from those of the angular methyl groups.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.91; H, 10.01.

Recrystallization of the mother liquors gave more **2**. The resulting mother liquors (26.6 mg.) were chromatographed on 1.35 g. of silica gel–Celite. The early eluates [with benzene–petroleum ether (b.p. 60–70°) 1:1] gave material (1 mg.) with infrared peaks indicative of olefinic hydrogens and of the 3β-acetoxy group. The fractions containing **2** (6.5 mg.) were preceded by 3.0 mg. of a different acetate formate, which is characterized below, and were followed by several spectrographically distinct fractions (10.6 mg.) which showed both hydroxyl and 3β-acetoxy absorption. These may have contained **5** but gave no indication for the presence of **9c**. The main formate fraction was recrystallized and the mother liquor (2.2 mg.) was chromatographed on a thin layer of silica (ethyl acetate–petroleum ether, 1:9, v./v.). This gave a fraction containing **2** which also showed the stronger infrared peaks characteristic of **9e** in an amount estimated as 0.3 mg. The total yield of spectrographically pure **2** was 133 mg.

Compound **2** was obtained more rapidly but in lower yield (64%) when a solution of 290 mg. of tosylate **1a** in 290 ml of formic acid was kept boiling under a reflux for 20 min. and the product was isolated as described above. Chromatography of the mother liquors gave the isomeric formate mentioned above, in comparable yield. After recrystallization from methanol this formate melted at 179.5–181° and had δ 0.85, 1.00, and 2.01 (methyl singlets) and a methyl doublet centered at 0.87 p.p.m. (splitting 6 c.p.s.). The formate proton was at 8.18 and a proton doublet (splitting 10 c.p.s.) was centered at 5.09 p.p.m. The infrared spectrum showed formate peaks at 3095, 1723, and 1180 (with side bands at 1199 and 1161) cm.$^{-1}$. Acetate peaks were at 1732, 1242, and 1023 or 1033 cm.$^{-1}$. The latter peak was the stronger but lay somewhat outside the usual range for a 3β-acetoxy group.[54b] Later eluates of the chromatogram contained uranediol 3-acetate (**5**). The olefin fractions were larger than those obtained by solvolysis at room temperature.

Partial Solvolysis of Uranediol 3-Acetate 17a-Formate (2).—A mixture of ester **2** (225 mg., 0.575 mmole) and of an equimolar amount of potassium hydroxide in 337 ml. of methanol was kept at 23° for 20 hr., was neutralized with 5.78 ml. of 0.1 *N* hydrochloric acid, and was taken to dryness *in vacuo*. The residue was distributed between ether and water. The organic phase gave 205.6 mg. of residue which was extracted with benzene. The insoluble portion (22.6 mg.) gave 18.3 mg. of uranediol (**3b**). The solution was chromatographed on 10.2 g. of alumina. Elution with petroleum ether containing 10–75% of benzene gave first starting material (5 mg.) and then 3-acetate. Uranediol was eluted with benzene containing 5% ether.

Uranediol 3-Acetate (5).—The eluates derived from the solvolysis of **2** that showed acetate but no formate absorption in the infrared spectrum (129 mg.) gave 121 mg. of 3-acetate on recrystallization from acetone. The compound usually had a double melting point, 162.5–164.5° and 168.5–169.5°. It had $[\alpha]D$ −2° (*c* 0.6) and ν_{max} 3628 (OH), 1734, and 1030 cm.$^{-1}$ (3β-acetate). The nearly equal intensity of the twin peaks at 1132 and 1153 (3β-acetoxy[54b]) and the presence of absorption maxima at 1041 (C-17a-O stretching?) and 1001 and of a minimum at 988 cm.$^{-1}$ serve particularly to distinguish **5** from its 17a epimer.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.66; H, 10.51.

The same compound was obtained in a single step when 57 mg. of **1a** in 57 ml. of dioxane and 38 ml. of water was heated under a reflux for 200 min. The reaction was essentially complete, but the yield (13.2 mg.) and purity (m.p. 159–162° and 163.5–166° after resolidification) of **5** were inferior to the results obtained by the two-step procedure. No **9c** could be detected by thin layer chromatography, but a small amount (0.4 mg.) of **5α-pregnane-3β,20β-diol 3-acetate** was identified by infrared spectroscopy. The presence of a similar amount of its 20 epimer was also indicated but could not be verified by isolation of the compound in spectrographically pure form. The product of an incomplete solvolysis (130 min.) gave spectrographic evidence for the absence of the 20β-tosylate **1a** and the presence of the 17aβ-tosylate **4a**.

When a solution of 4 mg. of compound **5** in 0.2 ml. of acetone and 4.8 ml. of formic acid was kept at 25° for 2 hr., the product showed the infrared spectrum of **uranediol 3-acetate 17a-formate (2)**. The residual hydroxyl absorption of **5** was too weak to be measured.

Uranediol (3b).—The late eluates (44 mg.) derived from the solvolysis of the acetate formate **2** were recrystallized from methanol. The product (37 mg.) melted at 215–216°. More extensively purified uranediol had $[\alpha]^{23}D$ +5° (*c* 0.6) and showed no depression of its melting point (216.5–217°) when mixed with a reference sample.[10] The infrared spectra agreed. The main absorptions in the 10-μ region were at 1049 and 1041 cm.$^{-1}$. Previously recorded constants for this compound were m.p. 210°,[55] 211–213°,[56] 216–219°,[8] and 216–217°[2]; $[\alpha]D$ +3.7° (alcohol),[56] +2.1, +3.7° (chloroform).[8]

Uranediol Diacetate (3a).—A mixture of 18.2 mg. of uranediol (**3b**), 2 ml. of pyridine, and 1 ml. of acetic anhydride was kept at room temperature for 20 hr. when the excess of anhydride was hydrolyzed by the addition of water. The product, which showed no absorption near 2.8 μ, was recrystallized from methanol to give 15.7 mg. of uranediol diacetate with m.p. 160.5–161.5°, $[\alpha]^{22}D$ −29° (*c* 0.6) [lit. m.p. 160°,[55] 159.5–160.5°,[56] 157.5–159.5°[2]; $[\alpha]D$ −29.6° (alcohol), −30.4° (chloroform)[56]]. The infrared spectrum had ν_{max} 1735, 1733 (main), 1240, and 1026 cm.$^{-1}$ (acetoxy); the fairly strong peaks at 978 and 907 cm.$^{-1}$ were also seen in the spectrum of **9a**, whereas the one at 1153 cm.$^{-1}$ was not. The curve agreed with that of a reference sample.[10] The mixture melting point showed no depression.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.18; H, 9.84.

Uranediol diacetate was obtained also when 24.6 mg. of uranediol 3-acetate 17a-tosylate (**4a**) in 8.6 ml. of anhydrous acetic acid containing 0.02 *M* sodium acetate was heated at 100° for 4 hr. The product (17.6 mg.) appeared to be free of starting material (infrared spectrum) and was recrystallized from methanol. Uranediol diacetate was identified by melting point (156–158.5°), mixture melting point, and infrared spectrum. The crude reaction products after 2 and 4 hr. showed no hydroxyl absorption in the 2.8-μ region.

Uranediol 3-Acetate 17a-Benzyl Ether (3e).—A solution of 109 mg. of uranediol 3-acetate 17a-tosylate (**4a**) in 96 ml. of benzyl alcohol was kept at 100° for 4 hr. and was then distributed between ether and water. The organic phase was washed with sodium carbonate and with water and was concentrated *in vacuo*. The residue was dissolved in petroleum ether and chromatographed on silica gel–Celite. The crystalline eluates (30 mg.) obtained with benzene were recrystallized from acetone to give **3e** melting at 174–176.5°. The spectrum showed benzyloxy bands at 3109, 3087, 3063, 3028, 730 (with side bands at 756 and 745), and 694 cm.$^{-1}$ [11c] and acetate bands at 1735, 1732 (1% solution), 1242, and 1028 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{44}O_3$: C, 79.60; H, 9.80. Found: C, 79.91; H, 9.84.

(54) (a) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954); (b) *J. Am. Chem. Soc.*, **78**, 1152 (1956); (c) H. W. Thompson and P. Torkington, *J. Chem. Soc.*, 640 (1945); (d) R. A. Russell and H. W. Thompson, *ibid.*, 479 (1955).

(55) R. E. Marker, E. Rohrmann, and E. L. Wittle, *J. Am. Chem. Soc.*, **60**, 1561 (1938).

(56) W. Klyne, *Biochem. J.*, **43**, 611 (1948).

A solution of 7.1 mg. of benzyl ether **3e** in 19 ml. of 95% ethanol and 70 mg. of freshly reduced and washed palladium on carbon[11b] was shaken in an atmosphere of hydrogen. The product (4.0 mg.) was recrystallized from acetone and identified as **uranediol 3-acetate** (**5**) by its infrared spectrum and its melting point (166–168.5°).

Uranediol 17a-Acetate (**3c**).—A solution of 44 mg. of potassium carbonate in 0.44 ml. of water was added to a solution of 34.8 mg. of uranediol diacetate (**3a**) in 2.2 ml. of methanol. The mixture was heated under reflux for 1 hr. The neutral reaction product (32.5 mg.) was recrystallized from methanol and gave 25.5 mg. of monoacetate melting at 165–167° with $[\alpha]^{23}D$ −29° (*c* 0.6). Hydroxyl bands were at 3610 (ν_+/ν_- 0.69)[49] and 1037 cm.$^{-1}$,[54a] acetate bands at 1733 and 1240 cm.$^{-1}$. The peaks at 1022, 978, and 905 cm.$^{-1}$ may be associated with an acetate at C-17aβ as peaks with similar frequencies were also seen in **3a** and **3d**.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.30; H, 10.61.

A solution of 0.6 mg. of monoacetate **3c** in 0.9 ml. of 90% alcohol remained clear for about 45 min. after mixing with an equal volume of a 1% solution of digitonin in the same solvent but then yielded a precipitate. The partial hydrolysis product of MW was reported[8] to melt at 152–156° and not to precipitate with digitonin in 90% alcohol.

Uranediol 3-Benzoate 17a-Acetate (**3d**).—A mixture of 16.6 mg. of uranediol 17a-acetate (**3c**), 0.5 ml. of pyridine, and 0.03 ml. of benzoyl chloride was kept at room temperature for 17 hr. After the hydrolysis of the excess of the acid chloride, the product (20.7 mg.) was isolated by ether extraction and recrystallized from acetone. The benzoate **3d** had m.p. 221–223°; $[\alpha]D$ −22° (*c* 0.4, chloroform); and ν_{max} 1732, 1237, 1026, 979, 906 (17aβ-acetate), 1715,[54a] 1273,[54a] 1112, and 710[54a] (3β-benzoate) cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07. Found: C, 77.24; H, 9.20.

The acetate benzoate derived from the mother liquors of MW was reported[8] to have m.p. 214–218° and $[\alpha]D$ −24.9° (chloroform).

Uranediol 3-Acetate 17a-Tosylate (**4a**) **A. From Uranediol 3-Acetate** (**5**).—A mixture of 10 mg. of **5**, 103 mg. of *p*-toluenesulfonyl chloride, and 0.5 ml. of pyridine was kept at room temperature for 24 hr. when it was diluted with pyridine, treated with 0.1 ml. of water, and distributed between benzene and water. The organic phase was washed with hydrochloric acid, sodium bicarbonate, and water and gave on distillation *in vacuo* a product which showed no hydroxyl band in the infrared. After recrystallization from acetone, the tosylate **4a** melted at 170–172° and had ν_{max} 1305, 1187, 1176, 1099, 1020, 966, 931, 913, 877, 821, 810, 801, 795, 750, 728, 704, 673, 569 (17aβ-tosylate), 1735, 1732 (saturated solution), 1242, and 1028 (3β-acetate) cm.$^{-1}$.

B. From 5α-Pregnane-3β,20β-diol 3-Acetate 20β-Tosylate (**1a**).—A solution of 107 mg. of the 20β-tosylate **1a** in 85 ml. of ethanol was heated under a reflux for 3 hr. The product on recrystallization from acetone gave 34 mg. of uranediol 3-acetate 17a-tosylate (**4a**) which melted at 172–173° and showed the same infrared spectrum as the preparation described above.

Anal. Calcd. for $C_{30}H_{44}O_5S$: C, 69.73; H, 8.58. Found: C, 69.73; H, 8.64.

The compound was obtained in 79% yield when a solution of 100 mg. of **1a** in 4 ml. of benzene, 6 ml. of acetone, and 90 ml. of formic acid was kept at 24° for 15 min. The product was recrystallized from acetone: m.p. 171–173°. The only impurity which could be detected in the mother liquor was the formate **2**.

Tosylate **4a** gave no depression of its melting point when mixed with a previously described[3] tosylate which was obtained by heating **1a** with pyridine. The latter tosylate showed all the infrared maxima of **4a** and weak additional peaks near 780, 957, and 1068 cm.$^{-1}$ which indicated the presence of unchanged starting material in the product of the pyridine reaction.

Uranol-17a-one Acetate (**6a**). **A. From Uranediol 3-Acetate** (**5**).—A solution of 19.6 mg. of chromium trioxide in 0.78 ml. of 90% acetic acid was added to a solution of 71.1 mg. of **5** in 2.84 ml. of glacial acetic acid. The mixture was kept at 23° for 2 hr. when 0.5 ml. of methanol was added. The neutral steroid reaction product (69.3 mg.), which was isolated by ether extraction, was recrystallized twice from methanol to yield compound **6a**, m.p. 172.5–173°. The infrared spectrum showed 1704 (17a-ketone) 1732, 1241, and 1026 (3β-acetate) cm.$^{-1}$. The crude oxidation product can be used for reduction without recrystallization. The compound has been reported to melt at 170.5–172°[6,15a] 171°,[57] 170–171°,[5] 174–174.5°,[58] 171.5–172°.[59]

B. From 17a-Epiuranediol 3-Acetate (**9c**).—A solution of 2.5 mg. of **9c** in 0.3 ml. of acetone was maintained at 15°. The CrO_3–H_2SO_4 reagent[17b] (4 μl.) was added. After 5 min. the product (2.5 mg.) was isolated as above. The infrared spectra were in agreement. The melting point after recrystallization from methanol was 171–173.5°.

17a-Epiuranediol 3-Acetate (**9c**).—A mixture of 52 mg. of uranol-17a-one acetate (**6a**), platinum (from 22 mg. of the dioxide), 11.94 ml. of acetic acid, and 0.06 ml. of concentrated hydrochloric acid was shaken with hydrogen which was taken up for 60 min. The mixture was freed of platinum, diluted with water, and extracted with ether, which was washed with sodium hydroxide and with water. A solution of the product in chloroform was applied to eight thin layer (0.5 mm. of silica gel) plates (20 cm.^{2}) which were developed with a 4% solution (v./v.) of ethanol in benzene. Three zones formed, which were removed from each plate and eluted with methanol. The slowest moving, very narrow band with R_f 0.20 (0.3 mg.) probably contained uranediol. The middle zone (R_f 0.37) gave 24.3 mg. of eluate which had the infrared spectrum of uranediol 3-acetate containing a small amount of the 17a epimer, which is difficult to remove by recrystallization. Usually the crude eluate was oxidized and reduced as described above without purification of **6a** to yield additional amounts of **9c**.

The eluate from the zone with R_f 0.40 (27.9 mg.) was recrystallized from acetone and gave 17a-epiuranediol 3-acetate: m.p. 197.5–199.5°; $[\alpha]^{22}D$ −5° (*c* 0.4); ν_{max} 3631, 1732, 1239, 1026 cm.$^{-1}$. The much greater intensity of the peak at 1132 than at 1152 cm.$^{-1}$ and the presence of an absorption maximum at 988 and of a minimum at 1000 cm.$^{-1}$ are of particular help in the differentiation of **9c** from **5**.

The mother liquors contained some of the 17a epimer **5**, which is removed more efficiently by thin layer chromatography than by direct crystallization. This chromatographic technique was also far more effective in fractionating the crude reaction product than was column chromatography on silica gel–Celite. The addition of sulfuric to acetic acid (1:300 v./v.) was less effective than an equimolar amount of hydrochloric acid in raising the proportion of the 17aα isomer in the hydrogenation product.

Other Reductions of Uranol-17a-one Acetate (**6a**). **A. With Sodium.**—A solution of 3.5 mg. of **6a** in 3 ml. of 1-propanol was kept boiling while 193 mg. of sodium was added in portions during 17 min. The product had the same R_f as uranediol on analytical thin layer chromatography (benzene–ethyl acetate, 1:1, v./v.) and after acetylation showed the spectrum of uranediol diacetate (**3a**). The acetylation (with acetic anhydride and pyridine for 16 hr. at room temperature) appeared to be complete (*cf.* **9a**).

B. With Sodium Borohydride.—A solution of 10 mg. of sodium borohydride in 0.2 ml. of water was added to a solution of 3 mg. of **6a** in 0.8 ml. of methanol. The mixture was kept at room temperature for 18 hr. and the product, which showed some deacylation at C-3, was acetylated for 16 hr. The infrared spectrum of the resulting material showed still weak hydroxyl absorption and indicated a mixture of mainly **3a** with small amounts of **9a** and **9c**.

C. Nickel and Hydrogen.—A mixture of 3.1 mg. of **6a**, 5.5 ml. of 95% ethanol, and 0.2 ml. of a suspension of Raney nickel was shaken with hydrogen for 105 min. According to thin layer chromatography and infrared spectroscopy, the product was a mixture mainly of **5** with about 12% of **9c**.

17a-Epiuranediol Diacetate (**9a**).—A solution of 15.2 mg. of 17a-epiuranediol 3-acetate (**9c**) in equal volumes of pyridine and acetic anhydride was kept at room temperature for 80 hr. The product (17.0 mg.) on recrystallization from methanol gave 14 mg. of the diacetate, m.p. 131–132.5°, $[\alpha]^{23}D$ +17° (*c* 0.5). The infrared spectrum showed the usual peaks of acetates and no hydroxyl absorption. The maxima at 1125 and 959 cm.$^{-1}$ are most useful for distinction from the 17a epimer **3a**. The high peak at 1017 cm.$^{-1}$ may be the C-17aα–O stretching vibration.

---

(57) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(58) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

(59) K. I. H. Williams, M. Smulowitz, and D. K. Fukushima, *ibid.*, **30**, 1447 (1965).

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.30; H, 9.97.

When the acetylation of **9c** was done with our usual 2:1 mixture of pyridine and acetic anhydride for 15 hr., the reaction was only about 54% complete and starting material was isolated by recrystallization.

The constants of a compound tentatively assigned the structure **9a** (MW diacetate[8]) were m.p. 175.5–178° and $[\alpha]_D$ −54° (chloroform).

17a-Epiuranediol (9b).—17a-Epiuranediol diacetate (**9a**, 7.4 mg.), 160 mg. of lithium aluminum hydride, and 15 ml. of anhydrous ether were stirred for 2 hr. The excess of hydride was decomposed with methanol–ether (1:1), and the product was distributed between ether and dilute hydrochloric acid. The ether was washed with water and gave 6.1 mg. of product, which was recrystallized. When dilute methanol was the solvent, the melting point was 211–215°, whereas acetone gave crystals melting at 256–257° and at 212° after resolidification of the melt. The main infrared absorption peaks in the 10-μ region were at 1041 and 994 and 991 (doublet) cm.$^{-1}$. As in the monoacetate **9c** there was a prominent peak at 1133 cm.$^{-1}$.

When 2.6 mg. of the diacetate **9a**, 32 mg. of sodium hydroxide, and 5 ml. of 80% ethanol were heated under a reflux for 1 hr., the product showed the spectrum of a monoacetate with a 3β-hydroxy group. On paper chromatography (toluene–isooctane–methanol–water, 15:5:16:4, v./v.) two spots were detected. The stronger had R_f 0.92, the other R_f 0.78. The mobility of the weaker spot agreed with that of 17a-epiuranediol but differed from that of uranediol (**3b**) (R_f 0.71). [Although this procedure of hydrolysis has been adequate with the steroidal secondary acetates studied in this laboratory, it also failed to give a complete reaction with uranediol diacetate (**3a**).]

17a-Epiuranediol 3-Acetate 17a-Tosylate (9d).—17a-Epiuranediol 3-acetate (5 mg.) in 1 ml. of pyridine was allowed to react with 300 mg. of *p*-toluenesulfonyl chloride for 140 hr. at room temperature when the excess reagent was hydrolyzed with 0.5 ml. of a 2:1 (v./v.) mixture of pyridine and water. The reaction product, which was isolated by extraction with benzene, failed to crystallize. It showed no hydroxyl absorption near 3630 cm.$^{-1}$ and had the following maxima characteristic of steroidal tosylates 1305, 1187, 1176, 1098, 1021 cm.$^{-1}$ and of a 3β-acetoxy group 1732, 1241, and 1027 cm.$^{-1}$. The peaks at 908, 813, 808, 794, 674, and 562 cm.$^{-1}$ are also near frequencies of peaks observed for the 17a epimer **4a**. The curve lacks the maxima of the latter at 877 and 931 cm.$^{-1}$, but has maxima at 894, 884, and 842 cm.$^{-1}$ which further aid in the differentiation from **4a**.

Tosylation of **9c** under the conditions used for **5** left about 55% of the starting compound unchanged. The long time needed for the complete reaction evidently caused some secondary changes. These can be minimized by using a still higher concentration of tosyl chloride (0.85 g./ml. of pyridine) which gave about 93% reaction in 49 hr.

Formolysis of 17a-Epiuranediol 3-Acetate 17a-Tosylate (9d).—A solution of 30 mg. of a preparation of **9d** which still contained 7% of **9c** in 1.2 ml. of acetone was diluted with 28.8 ml. of formic acid and was kept at 25° for 90 min. The mixture was distributed between benzene and water and gave 22.5 mg. of residue which was recrystallized from methanol. The product (8.3 mg.) melted at 113–116°. The infrared curve showed acetate bands at 1733, 1242, and 1026 cm.$^{-1}$ and gave no evidence for other functional groups besides a double bond (olefinic hydrogen stretching band at 3041 cm.$^{-1}$ and perhaps bending at 799 cm.$^{-1}$). The proton magnetic resonance peak at 1.62 p.p.m. (half-intensity band width 5.5 c.p.s.), which is attributed to an olefin-bound methyl group,[60] was much broader than the other methyl signals (2.01, acetate; 0.81, C-19; and 0.77). The olefinic proton resonance[60] at 5.32 p.p.m. had a half-intensity band width of 10 c.p.s.

Chromatography of the mother liquors on alumina gave additional amounts of this olefin, 2.7 mg. of not quite pure **9c**, and diol monoacetates distinct from **5**.

17a-Epiuranediol 3-Acetate 17a-Formate (9e).—A solution of 4.4 mg. of 17a-epiuranediol 3-acetate (**9c**) in 0.2 ml. of acetone and 4.8 ml. of formic acid was kept at 25° for 2 hr. The product showed 9% of the original hydroxyl absorbance. This impurity was removed by thin layer chromatography (petroleum ether–ethyl acetate, 9:1, v./v.). The infrared spectrum showed the main formate peak at 1182 cm.$^{-1}$ with a side band at 1165 cm.$^{-1}$. Other peaks useful for the detection of **9e** in mixtures with **2** were at 1123, 1114, 904, and 883 cm.$^{-1}$.

5α-Pregnane-3β,20β-diol 20-Tosylate (1b).—A solution of 104.7 mg. (0.203 mmole) of 5α-pregnane-3β,20β-diol 3-acetate 20-tosylate (**1a**) in 10.1 ml. of benzene was diluted with 81.3 ml. of ethanol and 10.1 ml. of 0.4 *N* ethanolic potassium hydroxide. The mixture was kept at 23° for 25 hr., concentrated under reduced pressure at a bath temperature below 20°, and distributed between benzene and water. The reaction product showed bands characteristic of the 3β-hydroxy group [3609 (ν_+/ν_- 0.58),[49] 1038 cm.$^{-1}$], barely perceptible absorption at 750 cm.$^{-1}$ (**4b**), and no acetate bands. Solutions evaporated from benzene or acetone retained solvent. Recrystallization from benzene–petroleum ether gave nonsolvated crystals in 89% yield. These melted at 156–157.5° and were free of **4b** in spectrographically detectable amounts. General tosylate bands were at 1304, 1186, 1175, 1099, and 1020 cm.$^{-1}$; other bands common to 20β-tosylates were at 1209, 1117, 955, 932, 907, 892, 814, 780, 725-704, 688, 668, 662, 589, 564, and 556 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{42}O_4S$: C, 70.84; H, 8.92. Calcd. for $C_{28}H_{42}O_4S \cdot 0.5(C_3H_6O)$: C, 70.34; H, 9.00. Found: C, 70.80; H, 9.02. Found for a sample recrystallized from acetone: C, 70.30; H, 8.86.

The rearrangement product **4b** was formed in much larger amounts when the hydrolysis was done in 0.086 *N* alcoholic potassium hydroxide at 60° for 1.5 hr.

20β-Hydroxy-5α-pregnan-3-one Tosylate (7).—A mixture of 55 mg. of 5α-pregnane-3β,20β-diol 20-tosylate (**1b**) in 8 ml. of acetone and of 0.05 ml. of the CrO_3–H_2SO_4 reagent[17b] was kept at 15° for 10 min. The neutral product was isolated by benzene extraction and was recrystallized from acetone. 20β-Hydroxy-5α-pregnan-3-one tosylate melted at 160–162°, showed no hydroxyl peaks or absorption at 750 cm.$^{-1}$, and had ν_{max} 1714 cm.$^{-1}$ (3-ketone).[54a] The curve below 1400 cm.$^{-1}$ is shown in Figure 1.

Anal. Calcd. for $C_{28}H_{40}O_4S$: C, 71.15; H, 8.53. Found: C, 71.20; H, 8.75.

When starting material was used which was not free of **4b**, recrystallization of the oxidation product from acetone or from benzene–petroleum ether gave crystals which had a higher concentration of **8a** than the mother liquors.

Uranediol 17a-Tosylate (4b).—Uranediol 3-acetate 17a-tosylate (35.1 mg.) was dissolved at 60° in 59 ml. of 0.086 *N* ethanolic potassium hydroxide. The solution was kept at this temperature for 1 hr. and then distributed between benzene and water. The neutral reaction product was recrystallized from methanol and from benzene–petroleum ether: m.p. 184–185°; ν_{max} 1305, 1187, 1175, 1098, 1020, 965, 928, 912, 877, 820, 810, 800, 795, 750, 728, 705, 674, 569 cm.$^{-1}$. The hydroxyl peak at 3610 showed ν_+/ν_- [49] 0.67; the C-3–O stretching band[54a] was at 1037 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{42}O_4S$: C, 70.84; H, 8.92. Found: C, 71.24; H, 8.93.

Uranol-3-one (17aβ-Hydroxy-17aα-methyl-D-homo-5α-androstan-3-one) Tosylate (8a).—Uranediol 17a-tosylate (**4b**, 12.6 mg.) in 2.5 ml. of acetone was oxidized with 0.02 ml. of chromic acid solution[17b] for 10 min. at 15°. The product, which was recrystallized from acetone, had m.p. 177–178.5°. The carbonyl peak was at 1715 cm.$^{-1}$; other peaks are shown in Figure 1 (p. 378).

Anal. Calcd. for $C_{28}H_{40}O_4S$: C, 71.15; H, 8.53. Found: C, 71.28; H, 8.65.

Uranol-3-one Formate (8b).—This compound was prepared from 20β-hydroxy-5α-pregnan-3-one tosylate (**7**) in the manner described in the kinetic run (27 hr.). The product, which was recrystallized from dilute acetone, melted at 160.5–162° after sintering at 156°. The keto group absorbed at 1715 cm.$^{-1}$; formate bands were at 3100, 1726, and 1174 cm.$^{-1}$ with side bands at 1201, 1188, 1184, and 1156 cm.$^{-1}$. A maximum at 1751 cm.$^{-1}$ showed constant absorptivity relative to the stronger carbonyl peaks during purification. Compound **2** had a less well-resolved peak at 1749 cm.$^{-1}$. The strongest peak in the 10-μ region of **8b** (967 cm.$^{-1}$) corresponds to one at 968 cm.$^{-1}$ of **2**.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.84, 76.74; H, 9.99, 10.07.

Kinetic Measurements.—20β-Hydroxy-5α-pregnan-3-one tosylate (**7**, 23.7 mg.) was dissolved in 2.5 ml. of acetone and diluted at zero time with 97.5 ml. of dry formic acid. The

(60) G. V. Smith and P. J. Trotter, *J. Org. Chem.*, **28**, 2450 (1963).

mixture was maintained at 25.0°. Samples (9 ml.) were withdrawn at the intervals stated in Table III and immediately distributed between 75 ml. of benzene and 40 ml. of water. The organic phase was washed three times with sodium carbonate (5%) and five times with water and taken to dryness *in vacuo*. To complete the removal of water, acetone was added, and the distillation was repeated. To free the residue of acetone, the crystals were suspended twice in warm petroleum ether which was evaporated each time. The adequacy of this procedure for terminating the first stage of the reaction was tested by adding compound **7** in 0.7 ml. of benzene to a separatory funnel containing 75 ml. of benzene, 40 ml. of water, and 9 ml. of formic acid. The product isolated as above showed no change in spectrum. The residues from the first two samples were dissolved in carbon disulfide and analyzed by absorbance measurements at 780 and 673 cm.$^{-1}$. The later samples were dissolved in dioxane and their absorbances were measured at 263, 268, 274, and 300 mμ. A_{300} values served to correct for nonspecific absorption on the basis of the spectrum of a sample withdrawn after 26 hr. The weights entered in Table III represent the means calculated from the measurements at the three other wavelengths and the absorptivities of **8a**. The maximum difference between the mean and the individual values was less than 1.5% except at 8 hr. (3%). The infrared spectrum of the sample taken after 26 hr. agreed closely with that of purified **8b**.

Acknowledgment.—The authors wish to express their indebtedness to Mr. Howard Gerlach of the Department of Chemistry, Western Reserve University, and to Mr. Herbert Grossman of the Research Department, Standard Oil Company of Ohio, for the recording of the n.m.r. spectra and to Mr. A. W. Spang, Ann Arbor, Michigan, for the microanalyses reported in this paper.

Reactions with Base of 2-Propargylthioethanol and the 2-(2-Haloallylthio)ethanols[1]

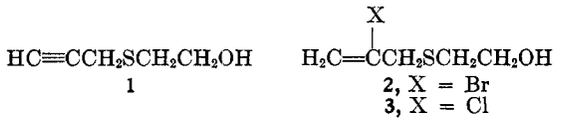
ALBERT T. BOTTINI AND ERNST F. BÖTTNER

Chemistry Department, University of California, Davis, California 95616

Received August 9, 1965

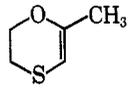
Treatment of 2-propargylthioethanol (**1**) or a 2-(2-haloallylthio)ethanol (**2** or **3**) with sodium hydroxide in water, toluene, or dimethyl sulfoxide, or with sodium amide in ether, gave 2-methyl-1,4-oxathiene (**4**) as the only cyclic product. Further study of the reactions carried out in water and in ether showed that 2-allenylthioethanol (**5**) and 2-(1-propynylthio)ethanol (**6**) were also formed. **4** was prepared from **2** and **3** in deuterium oxide. The amount and location of deuterium in **4** from 2-(2-bromoallylthio)ethanol (**2**) were consistent with the hypothesis that **4** results from cyclization of **6**, which is formed exclusively by prototropic rearrangement of **1**, the dehydrohalogenation product of **2**. The amount and location of deuterium in **4** from 2-(2-chloroallylthio)ethanol (**3**) indicated that a significant amount of **6** was formed by dehydrochlorination of 2-(*trans*-2-chloropropenylthio)-ethanol (**8**), which was formed together with its *cis* isomer (**7**), by prototropic rearrangement of **3** at a rate competitive with dehydrochlorination of **3** to **1**.

Previous work has shown that the mode of base-induced cyclization of propargylaminoethanols,[2] propargyloxyethanol,[3] and their 2-haloallyl analogs is markedly dependent on solvent. In aprotic solvents, the principal cyclization products are formed by nucleophilic addition of alkoxide to the allene or internal acetylene formed by prototropic rearrangement of the propargyl compound. In water, wherein prototropic rearrangements occur relatively slowly, most of the cyclization products result from nucleophilic addition of alkoxide to the acetylenic carbons of the propargyl compound. Continuing work directed toward determining the scope and limitations of base-induced cyclization reactions of propargyl and 2-haloallyl compounds, we have examined reactions of 2-propargylthioethanol (**1**) and the 2-(2-haloallylthio)ethanols (**2** and **3**) with base in various solvents.

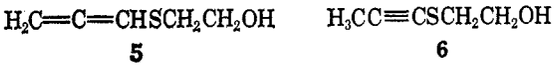


1 **2**, X = Br; **3**, X = Cl

When the sulfides **1–3** were subjected to a variety of conditions similar to those used to effect cyclization of their amine[2] and ether[3] analogs, *i.e.*, sodium hydroxide in water, toluene, and dimethyl sulfoxide, and sodium amide in ether, only one cyclic product, **4**, was obtained. The infrared and nmr spectra of **4** clearly indicated that it was 2-methyl-1,4-oxathiene, and comparison of **4** with 2-methyl-1,4-oxathiene prepared from mercaptoethanol and chloroacetone[4] confirmed the structural assignment.



4



5 **6**

Further examination of the aqueous and ethereal reaction mixtures[5] revealed that, in addition to 2-methyl-1,4-oxathiene (**4**), 2-propargylthioethanol (**1**) and 2-(2-bromoallylthio)ethanol (**2**) were converted to 2-allenylthioethanol (**5**) and 2-(1-propynylthio)ethanol (**6**) in varying amounts, depending on the conditions. Pure **6**, which was readily characterized by spectral means, was isolated from reaction mixtures that contained excess base. The presence of **5** in products isolated after a short reaction time or from mixtures that were deficient in base was indicated by the appearance in the infrared spectrum of a band at

(1) Presented in part at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963. This research was supported by Grant GM-10606 from the National Institute of General Medical Sciences of the U. S. Public Health Service.

(2) (a) W. J. Croxall and J. H. Mellema, U. S. Patent 2,960,508 (Nov 15, 1960); *Chem. Abstr.*, **55**, 14482 (1961); (b) A. T. Bottini, J. A. Mullikin, and C. J. Morris, *J. Org. Chem.*, **29**, 373 (1964).

(3) A. T. Bottini, F. P. Corson, and E. F. Böttner, *ibid.*, **30**, 2988 (1965).

(4) I. R. Marshall and H. A. Stevenson, *J. Chem. Soc.*, 2360 (1959).

(5) Reactions of 2-haloallylaminoethanols and propargyloxyethanol carried out in water and ethers gave the greatest differences in product compositions.