C-18 Functional Steroids and D-Homo Steroids[1a]

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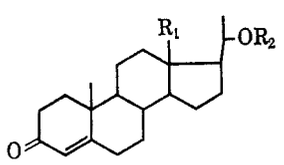
Tosylate esters of 20α-hydroxy- and 20β-hydroxypregnane derivatives gave *trans*-17 olefins and 17aβ-hydroxy-17α-methyl-D-homoandrostane derivatives, respectively, under various conditions. The configurations at C-17 and C-17a of the D-homo steroids were based on nmr spectra. The C-18 and C-21 nmr methyl resonances in the 20-hydroxypregnane derivatives were found to be dependent on side-chain conformations. Related reactions in steroidal 18-nitriles are presented.

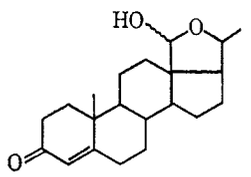
During work directed toward the production of steroid hormone analogs bearing unusual substituents at C-13, a number of D-homo steroids were obtained. These results are now described.

20-Hydroxy steroids for the Barton reaction were formed by reduction of keto steroids. The selective formation of the desirable 20α epimers by this means is only moderately successful; the most satisfactory techniques in our hands consisted of reduction of pregnenolone acetate with sodium and alcohol,[2] acetylation, fractional crystallization, selective hydrolysis at C-3, Oppenauer oxidation, and hydrolysis, giving 20α-hydroxypregn-4-en-3-one in 8% yield. Alternatively, reduction of 3,3-ethylenedioxypregn-5-en-20-one[3] with sodium in isopropyl alcohol, hydrolysis, and recrystallization gave 20α-hydroxypregn-4-en-3-one in 18% yield from progesterone. The 20β epimer was obtained in good yield by reduction of progesterone with lithium tri-*t*-butoxyaluminohydride followed by oxidation of the allylic alcohol with manganese dioxide.[4]

Each of the C-20 epimers was converted into the corresponding 18-oxime **1ab** following the method of Barton.[5,6] The oximes formed the hemiacetals **2ab** on treatment with nitrous acid, whereas the action of acetic anhydride gave the nitriles **3ab**.

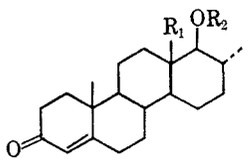
Since the preparation of 20α-hydroxy steroids is difficult, whereas 20β-hydroxy steroids are formed readily, an attempt was made to invert 20β-tosylates by hydroxide displacement on alumina.[7] When **4b**, mp 153–155°, was passed through alumina, an isomeric compound, mp 202–203°, was obtained. The nmr peaks for C-18 and C-21 (Table I) were shifted, showing

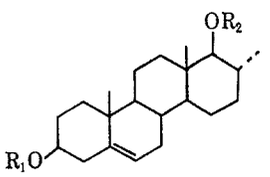




1, R_1 = CHNOH; R_2 = H
3, R_1 = CN; R_2 = Ac
4, R_1 = CH_3; R_2 = Ts
12, R_1 = CH_3; R_2 = Ms
13, R_1 = CN; R_2 = Ts

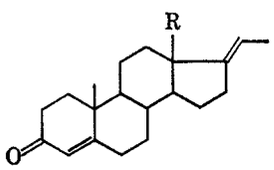
2





5, R_1 = CH_3; R_2 = H
6, R_1 = CH_3; R_2 = Ac
7, R_1 = CH_3; R_2 = Ts
14, R_1 = CN; R_2 = Ts

8, R_1 = Ac; R_2 = Ts
9, R_1 = Ac; R_2 = Ac
10, R_1 = H; R_2 = Ac



11, R = CH_3
15, R = CN

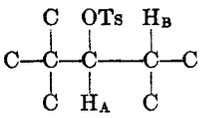
a = 20α series
b = 20β series

TABLE I

NMR SPECTRA OF 17α-METHYL-17aβ-HYDROXY-D-HOMOANDROSTANE DERIVATIVES

Compd	18-H_3, cps	19-H_3, cps	17α-CH_3, cps (J, cps)	17aα-H, cps (J, cps)
5	51.5	70.2	57.4 (5.8)	161.8 (9.5)
6	55.0	70.5	47.5 (6.0)	260.3 (10.5)
7	52.0	68.0	48.5 (6.5)	247.3 (10.5)
8	50.0	57.0	48.0 (6.0)	247.0 (10.0)
9	52.5	59.0	47.8 (6.5)	259.0 (10.0)
10	53.0	59.0	48.0 (6.0)	260.0 (10.5)
14	...	71.0	50.3 (6.0)	250.3 (10.5)

a structural change in the vicinity of the D ring. A doublet (J = 10.5 cps) owing to a proton geminal to a tosyl group in the spectrum, could be satisfied by the partial structure



and the magnitude of the coupling constant indicated a dihedral angle of approximately 180°[8] between H_A and H_B. Only the structure of the D-homo steroid **7** satisfies these conditions. An isomerization of this type had been tentatively proposed by Sarett[9] and

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(2) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(3) A. Ercoli and P. DeRuggieri, *Gazz. Chim. Ital.*, **84**, 312 (1954).

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(7) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

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(9) L. H. Sarett, *ibid.*, **70**, 1690 (1948).

had been implicated in reactions leading to uranediol.[10,11] Until very recently, the exact stereochemistry at C-17a of uranediol had not been specified, although a tentative 17aβ assignment was made on the basis of molecular-rotation differences.[12]

Since uranediol is obtained from 20β-hydroxy steroids by reactions similar to the ones used for the preparation of D-homo steroids in the present case, it is clear that our nmr stereochemical assignment is applicable to uranediol also, and the β configuration at the 17a position is confirmed. After this work was completed, the uranediol rearrangement was discussed by Hirschmann, *et al.*[13] Our results are in accord with the configurational assignments of these workers.

Although it has been reported that 20β-tosylates give 20α-azides on refluxing in lithium azide,[14] **4b** under these conditions gave **7** in yields up to 75%. The action of potassium acetate in acetic acid on **4b** gave the corresponding acetate **6**, which on hydrolysis gave **5**. Compounds **8**, **9**, and **10** were obtained from 3β,20β-dihydroxypregn-5-ene 3-acetate 20-*p*-toluenesulfonate by similar reactions.

All the D-homo compounds are characterized by the presence of doublets (J = 9.5–10.5 cps) corresponding to a single proton. The chemcial shifts of the methyl group and the 17a proton are summarized in Table I.

In the 20α series, **4a** gave the elimination product **11**[15] merely by passage through alumina. The mesylate **12a** behaved similarly.

To investigate the properties of D-homo steroidal 18-nitriles, the 18-nitrile 20-tosylates were subjected to similar conditions, but major differences in their reactivity were observed. In the 20β series **13b** on passage through alumina or heating in pyridine was recovered unchanged. On acetolysis, **13b** gave a gummy mixture from which three major components were isolated: the 20α-acetate **3a**, formed in minor yield by inversion, the D-homo steroid **14** as major product, and an olefinic compound.

Although thin layer chromatography showed only one spot for the olefinic compound, it was in fact two compounds as indicated by two C-18 methyl resonances in benzene solution. It is noteworthy that only one peak was seen in deuteriochloroform solution, which indicates the desirability of obtaining spectra in more than one solvent in cases of this kind. Since the elemental analysis agreed with the elimination product, the product must be a mixture of two isomeric olefins. One is the *trans*-17 olefin **15** as judged from the nmr spectrum, and the other could be a C-20 olefin because in the spectrum a slightly broadened singlet was present at 313 cps in addition to a very broad signal at the same region.

The configuration of **15** was determined on a sample obtained from **13a** and was assigned as *trans* by comparison of the C-20 hydrogen and C-21 methyl resonances of **11** and **15** as summarized in Table II.

On comparison of **11** and **15**, the position of the C-21 methyl group moves downfield by only 4.5 cps. By contrast the C-20 hydrogen resonance is displaced downfield by 25 cps in deuteriochloroform solution. This large difference indicates that in **15** the C-20 hydrogen, and not the C-21 methyl, is close to the nitrile function, and hence the configuration is *trans*.

TABLE II

NMR SPECTRA OF PREGNA-4,17-DIEN-3-ONE DERIVATIVES

Compd	Solvent	18-H$_3$, cps	19-H$_3$, cps	21-H$_3$, cps	20-H, cps
11	$CDCl_3$	48.0	72.5	92.0	302.0
	C_6H_6	44.5	49.5	95.3	308.0
15	$CDCl_3$	...	75.0	96.5	327.5
	C_6H_6	...	51.0	86.3	315.0

In the 20α series **13a** was unchanged by passage through alumina. On refluxing in pyridine, 10% of **15** was formed and much **13a** was recovered.

All of the above reactions of C-20 tosylates are in accord with a mechanism involving ionic species as intermediates.[11,13] The drastic effect of the polar nitrile group on the course of these reactions further supports an ionic mechanism.

Nmr Spectra.— Nmr spectra of 20-epimeric pregnane derivatives have been examined,[16,17] but puzzling phenomena remain. Nmr spectra of several epimeric pairs of 20-oxygenated pregnane derivatives obtained in the present work are summarized in Table III. In all of the compounds studied, except in the 18→20 cyclized derivatives in which the relationship is reversed, the C-21 methyl resonance frequencies of the 20α epimers appear downfield relative to those of the 20β epimers, although not necessarily within the range previously described.[17] Differences in the C-21 methyl resonance frequencies in each 20-epimeric pair parallel changes in $J_{17\alpha\text{-H},20\beta\text{-H}}$, and therefore changes in the conformation of the 17β side chain[18] (Table IV). In the open-chain compounds, the conformation of the 17β side chain in the 20β-oxygenated series varies little with changes in substituents ($J_{17\alpha\text{-H},20\alpha\text{-H}}$ for the 20β epimers is generally constant in the compound studied[18]). Thus, the C-21 methyl group is located in a constant environment. Therefore changes in the differences of C-21 methyl resonance frequencies in each 20-epimeric pair must be due to change in the environment of the C-21 methyl group in the *20α epimers*, relative to the C-16 methylene and/or the C-17α hydrogen. The C-20 epimeric pairs of 18→20 cyclic compounds (*e.g.*, **2ab** and 20α- and -β-hydroxypregn-4-en-3-on-18-oic acid 18→20-lactone) in which the relative position of C-21 is reversed deviate significantly from this trend.

C-18 methyl resonances also vary in a regular manner as long as no shielding groups are introduced at the C-20 oxygen (compounds **1ab**, **2ab**, **12ab**, and 20α- and -β-hydroxypregn-4-en-3-one). Since the C-20β oxygen is nearer to the C-18 methyl group than the C-20α oxygen in the most stable conformations,[18] the C-18 methyl resonance frequencies of 20β epimers are subjected to greater deshielding by the C-20 oxygen and appear at lower field than do the 20α epimers. The reversal of this relationship in acetylated compounds is due to the shielding effect of the carbonyl function

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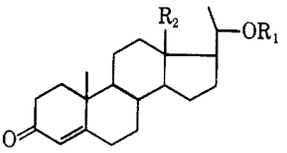
TABLE III

NMR SPECTRA OF EPIMERIC C-20-OXYGENATED PREGNANE DERIVATIVES



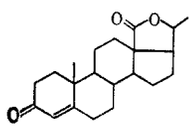
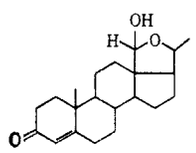
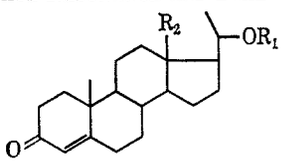
R_1	R_2		18-H_3, cps	19-H_3, cps	21-H_3, cps (J, cps)	20-H, cps (J, cps)
H	CH_3	a	43.0	71.0	73.0 (6.0)	222
		b	48.5	72.0	69.0 (6.0)	224
Ac	CH_3	a	44.0	71.0	73.0 (6.0)	296
		b	41.0	71.0	68.5 (6.0)	288
Ms	CH_3	a	46.5	72.0	88.8 (6.5)	285
		b	50.5	72.0	85.2 (6.3)	290
Ts	CH_3	a	42.3	69.8	78.0 (6.0)	280
		b	46.0	71.0	70.5 (6.0)	288
NO	CH_3	a	48.0	72.0	85.3 (6.5)	328
		b	43.5	71.0	82.3 (6.5)	286
H	NOH ‖ CH	a	446.0	69.0	72.0 (6.0)	235
		b	449.5	68.5	68.5 (6.0)	218
H	CN	a	...	74.0	77.0 (6.0)	240
		b	...	74.5	73.0 (6.0)	240
Ac	CN	a	...	74.0	77.0 (6.0)	313
		b	...	74.0	75.0 (6.0)	300
Ts	CN	a	...	72.0	83.0 (6.0)	288
		b	...	73.0	78.5 (6.0)	294
		a	...	75.5	82.3 (6.5)	279 (4.7)
		b	...	77.5	83.8 (6.5)	264 (0)
		a	306.3	69.6	72.0 (6.0)	260
		b	316.8	75.0	78.0 (6.0)	238

TABLE IV

C-21 METHYL RESONANCE AND DIHEDRAL ANGLES



R_1	R_2	$\Delta\nu_{21\text{-}H_3(\alpha-\beta)}$, cps	$J_{17\alpha\text{-H},20\beta\text{-H}}$,[a] cps	$\Phi_{17\alpha\text{-H},20\beta\text{-H}}$,[a] deg
H	CH_3	4.0	7.5	155
Ac	CH_3	4.5	7.3	153
Ts	CN	4.5	7.0	151
H	NOH ‖ CH	3.5	3.5	129
Ac	CH_3	7.5	8.4	161

[a] Reference 18.

in the 20β epimers. It is noteworthy that this shielding effect is observed only in the 20β series, but not in the 20α series and this is further evidence that the C-20α oxygen is more distant than the C-20β oxygen from the C-18 methyl group. It is now clear that the 17β side chain assumes the same conformation[18] regardless of whether the oxygen function at C-20 is hydroxyl or acetoxyl. Benn's[16] explanation of this reversal on the basis of conformational differences is therefore untenable.

The C-18 methyl resonance positions of the corresponding epimeric 20-mesylate pairs (**12ab**) follow the same pattern as the epimeric 20-hydroxypregnane derivatives. For the corresponding tosylates, a slight shielding effect is observed in both the 20α and 20β isomers because the benzene ring is large enough to exert its effect even though it is distant from the C-18 methyl group in the case of the 20α isomer. The deshielding effect of the sulfonyl group is almost cancelled. The nitrosyl group at C-20 exerts a shielding effect in the 20β isomer but a deshielding effect in the 20α isomer. Since the nitrosyl group can assume both *cis* and *trans* forms, its effect is expected to be different from that of an acetyl group.

Finally, it should be mentioned that the relative chemical shifts of the C-20 hydrogen in the 20α- and 20β-epimeric pairs parallel those of the C-18 methyl resonances. The C-20 hydrogen is, therefore, close to the C-18 methyl group and is subjected to a similar environmental effect (shielding or deshielding).

In summary, all of these chemical shift data are in harmony with the side-chain conformations we have previously proposed.[18] In contrast to the above observations, in the case of Δ^{16}-pregnanes,[16] the C-18 methyl groups are more deshielded in the 20α epimers than in the 20β epimers in both 20-hydroxy and -acetoxy compounds. Furthermore, the acetyl group does not exert any additional effect on C-18 methyl frequencies in either epimer. This indicates that the favored conformation of the side chain not only places the angular C-18 methyl protons closer to the

oxygen function in the 20α epimer than in the 20β compound,[16] but also the oxygen atom in either epimer is distant enough so that the acetyl group does not exert a deshielding effect on the C-18 methyl group.

Experimental Section[19]

20α-Hydroxypregn-4-en-3-one.—A boiling solution of 30.0 g of pregn-5-ene-3,20-dione 3-ethyleneketal[3] in 1500 ml of 2-propanol was treated with 60 g of sodium metal in small pieces during 1–2 hr. The solution was heated under reflux for 18 hr and poured into ice–water while hot. The product was extracted with ether and the combined ether extracts were washed with water, dried over sodium sulfate, and evaporated under vacuum to give 30 g of crystals. This crystalline material was dissolved in a suitable amount of benzene–acetone, containing 10 ml of water. The solution was acidified with *p*-toluenesulfonic acid, heated under reflux for 2 hr, poured into water, and extracted with ether. The combined ether solution was washed with water, dried over sodium sulfate, and evaporated under vacuum. The oily residue was treated with a small amount of benzene, petroleum ether (bp 30–60°), and large amount of ether to give 9.0 g of almost pure product, mp 159.5–161.5°. Recrystallization from hexane–benzene gave 8.0 g of the product: mp 162–163.5° (lit.[2] mp 160.5–161°); nmr 0.72 (18-H_3), 1.18 (19-H_3), 1.22 (21-H_3, doublet, J = 6.0 cps), 3.70 (20β-H), broad, five-line pattern), 5.70 (4-H) ppm.

20β-Hydroxypregn-4-en-3-one.—A solution of 10.0 g of progesterone in 200 ml of tetrahydrofuran was treated with 35.0 g of $LiAlH(t\text{-}BuO)_3$, stirred at 5° for 45 min, and decomposed with 5% acetic acid. The mixture was extracted with ether and the combined ether extracts were washed successively with 5% sodium bicarbonate solution and water, and dried over sodium sulfate. The solvent was removed under reduced pressure leaving a solid which was crystallized from hexane–benzene to give 7.5 g of pregn-4-ene-3β,20β-diol, mp 172–173.5°. To a solution of 2.0 g of this compound in 200 ml of chloroform there was added 20.0 g of MnO_2 and the suspension was stirred magnetically at 27° for 18 hr. The suspension was filtered and the filtrate, after removal of the solvent, gave 2.0 g of product, mp 170–173°.[4]

18-Oxo-20α-hydroxypregn-4-en-3-one 18→20-Hemiacetal (2a).—To a solution of 1.0 g of **1a**[5,6] in 50 ml of glacial acetic acid, there was added 50 ml of 5% sodium nitrite solution. This solution was shaken for 5 min, diluted with water, and extracted with ether. The dried (Na_2SO_4) solution was evaporated under vacuum. The residue solidified on treatment with water and was filtered and dried, giving crystals, mp 143–152°. Recrystallization from benzene–hexane resulted in an analytical sample: mp 160–165°; $[\alpha]^{20}D$ +115° (*c* 1, $CHCl_3$); ν_{max} 3460, 3375, 1670, 1645, 1610 cm^{-1}; nmr 1.16 (19-H_3), 1.20 (21-H_3, doublet, J = 6.0 cps), 4.33 (20β-H, multiplet, broad peak), 5.15 (18-H, doublet, J = 3.5 cps, becoming a singlet on addition of D_2O), 3.79 (18-OH, doublet, J = 3.5 cps, disappeared on addition of D_2O), 5.73 (4-H) ppm.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.53; H, 9.00.

18-Oxo-20β-hydroxypregn-4-en-3-one 18→20-Hemiacetal (2b).—To a solution of 0.5 g of **1b**[5,6] in 20 ml of glacial acetic acid, 15 ml of 5% aqueous sodium nitrite solution was added in the same manner as described for **2a**. The oily, viscous residue obtained after evaporation of ether, was treated with acetone to give 0.2 g of white, crystalline substance, mp 380°. The analytical sample was obtained from acetone–methylene chloride: $[\alpha]^{20}D$ +169°, (*c* 1, $CHCl_3$); ν_{max} 3460, 3375, 1670, 1645, 1610 cm^{-1}; nmr 1.25 (19-H_3), 1.30 (21-H_3, doublet, J = 6.0 cps), 3.97 (20α-H, multiplet), 5.28 (18-H) ppm.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.08; H, 8.95.

3-Oxo-20α-hydroxypregn-4-ene-18-nitrile Acetate (3a).—18-Oximino-20α-hydroxypregn-4-en-3-one (**1a**,[5,6] 3.2 g) was dissolved in 40 ml of acetic anhydride and refluxed for 2 hr. The solvent was evaporated under vacuum and the dry residue was treated with ether to give 3.0 g of crude product, mp 146–147°. Recrystallization from acetone–ether mixture gave the analytical sample: mp 147–148°; $[\alpha]^{20}D$ +120° (*c* 1, $CHCl_3$); nmr 1.23 (19-H_3), 1.28 (21-H_3, doublet, J = 6.0 cps), 2.07 (CH_3CO), 5.22 (20-H, broad peak) ppm.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.82; H, 8.51; N, 3.91.

3-Oxo-20β-hydroxypregn-4-ene-18-nitrile Acetate (3b).—18-Oximino-20β-hydroxypregn-4-en-3-one (**1b**,[5,6] 1.1 g) was dissolved in 25 ml of acetic anhydride and treated in the same manner as described for **3a**. After evaporation of the solvent, 1.0 g of product was obtained, mp 198–199°. Recrystallization furnished the analytical sample: mp 199–200.5°; $[\alpha]^{20}D$ +116° (*c* 1, $CHCl_3$); nmr 1.23 (19-H_3), 1.25 (21-H_3, doublet, J = 6.0 cps), 2.03 (CH_3CO), 5.00 (20-H, multiplet, broad peak) ppm.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.56; H, 8.30; N, 3.56.

20α-Hydroxypregn-4-en-3-one *p*-Toluenesulfonate (4a).—A solution of 1.5 g of 20α-hydroxypregn-4-en-3-one and 1.5 g of *p*-toluenesulfonyl chloride in pyridine was stirred magnetically for 18 hr. The solution was poured into an ice–water mixture and the precipitate was filtered. Recrystallization from methylene chloride–hexane mixture gave 1.4 g of product, mp 145–146°. Further recrystallization from acetone raised the melting point to 152–153°; $[\alpha]^{20}D$ +60° (*c* 1, $CHCl_3$); nmr 0.70 (18-H_3), 1.16 (19-H_3), 1.30 (21-H_3, doublet, J = 6.0 cps), 2.44 (*p*-toluene-CH_3), 4.67 (20β-H, broad peak), 5.70 (4-H) ppm.

Anal. Calcd for $C_{28}H_{38}O_4S$: C, 71.45; H, 8.13; S, 6.81. Found: C, 71.34; H, 7.98; S, 6.66.

20β-Hydroxypregn-4-en-3-one *p*-Toluenesulfonate (4b).—This product was made from 20β-hydroxypregn-4-en-3-one by the same method used for **4a**. Recrystallization from *n*-butyl alcohol–acetone gave the product: mp 153–155°; $[\alpha]^{20}D$ +81° (*c* 1, $CHCl_3$); ν_{max} 1345, 1185, 1170, 1097, 813, 662 cm^{-1}; nmr 0.77 (18-H_3), 1.18 (19-H_3), 1.175 (21-H_3, doublet, J = 6.0 cps), 2.47 (*p*-toluene-CH_3), 4.80 (20-H, octet, $J_{20\text{-H},\ 21\text{-H}_3}$ = 6.0 cps, $J_{17\text{-H},\ 20\text{-H}}$ = 9.5 cps) ppm.

Anal. Calcd for $C_{28}H_{38}O_4S$: C, 71.45; H, 8.13; S, 6.81. Found: C, 71.25; H, 7.98; S, 6.92.

3β,20β-Dihydroxypregn-5-ene 3-Acetate 20-*p*-Toluenesulfonate.—3β,20β-Dihydroxypregn-5-ene 3-acetate was treated with *p*-toluenesulfonyl chloride as described previously for **4a**. The product (90% yield) was recrystallized from ethyl acetate–chloroform and had mp 147–149°; $[\alpha]^{20}D$ −45° (*c* 1, $CHCl_3$); ν_{max} 1362, 1245, 1190, 1177, 1100, 900, 885, 817, 664 cm^{-1}; nmr 0.71 (18-H_3), 1.02 (19-H_3), 1.17 (21-H_3, doublet, J = 6.5 cps), 2.02 (3-CH_3CO), 2.43 (*p*-tosyl-CH_3), 4.68 (overlap of 3α-H and 20α-H, multiplet, broad peak), 5.35 (6-H, multiplet) ppm.

Anal. Calcd for $C_{30}H_{42}O_5S$: C, 70.00; H, 8.22; S, 6.23. Found: C, 69.81; H, 8.43; S, 6.16.

17aβ-Hydroxy-17α-methyl-D-homoandrost-4-en-3-one (5).—A solution of 0.30 g of **6**, 0.15 g of sodium hydroxide, and 10 ml of methanol was boiled under reflux for 10 hr. The reaction mixture was poured onto ice–water and the resulting precipitate, mp 174–175°, was collected. Several recrystallizations from acetone gave colorless crystals: mp 180.5–181.5°; $[\alpha]^{20}D$ +92° (*c* 1, $CHCl_3$); ν_{max} 3540, 1670, 1620 cm^{-1}; nmr 0.85 (18-H_3), 0.96 (17α-CH_3, doublet, J = 5.8 cps), 1.17 (19-H_3), 2.70 (17aα-H, doublet, J = 10.0 cps), 5.72 (4-H) ppm.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.63; H, 9.91.

17aβ-Hydroxy-17α-methyl-D-homoandrost-4-en-3-one Acetate (6).—A solution of 10.0 g of potassium acetate, 10.0 ml of acetic anhydride, 6.0 ml of water, and 3.0 g of **4b** in 150 ml of acetic acid was boiled under reflux for 18 hr, cooled, and concentrated under vacuum. The precipitate which formed after pouring the concentrated reaction mixture onto ice–water was collected and washed with isopropyl alcohol to give almost pure product. The residue obtained from evaporation of the filtrate was passed through alumina to separate additional product, giving altogether 0.80 g, mp 180–182° after recrystallization from hexane: $[\alpha]^{20}D$ +62° (*c* 1, $CHCl_3$); ν_{max} 1728, 1675, 1620 cm^{-1}; nmr 0.92 (18-H_3), 1.18 (19-H_3), 0.79 (17-CH_3, doublet, J = 6.0 cps), 4.34 (17a-H, doublet, J = 10.5 cps), 1.91 (CH_3CO), 5.72 (4-H) ppm.

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.63; H, 9.64.

17aβ-Hydroxy-17α-methyl-D-homoandrost-4-en-3-one *p*-Toluenesulfonate (7). Procedure A.—When 1.1 g of crude **4b** was passed through an alumina column (Merck, acid washed), the

(19) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-8 or Perkin-Elmer 337 instrument. Microanalyses were performed by the Microanalytical Laboratory, University of California at Berkeley, Berkeley, Calif. Optical rotations were obtained in a 0.5-dm tube with a Rudolph photoelectric polarimeter. Nmr spectra were obtained on a Varian A-60 instrument using tetramethylsilane as internal standard.

main fractions, totaling 0.50 g, had melting points ranging from 187–188° to 190.5–191.5°. The rest of the fractions had lower melting points. Recrystallization of the main fractions from *n*-butyl alcohol–benzene gave colorless crystals: mp 202–203°; $[\alpha]^{20}D$ +98° (*c* 1, $CHCl_3$); ν_{max} 1360, 1187, 1175, 1095, 909, 881, 811, 675 cm^{-1}; nmr 0.87 (18-H_3), 1.13 (19-H_3), 0.808 (17-CH_3, doublet, J = 7.0 cps), 4.12 (17aα-H, doublet, J = 10.5 cps), 2.43 (*p*-toluene-CH_3), 5.70 (4-H) ppm.

Anal. Calcd for $C_{28}H_{38}O_4S$: C, 71.45; H, 8.13; S, 6.81. Found: C, 71.69; H, 8.02; S, 6.77.

When neutral alumina was used to pack the column, the same result was observed. In the case of aluminum hydroxide, only a small portion rearranged and was obtained as a mixture with the starting tosylate (**4b**) as seen in the nmr spectrum.

Procedure B.—A solution of 2.0 g of lithium chloride, previously dried at 80° under vacuum, and 4.0 g of sodium azide in 50 ml of absolute methanol was heated to boiling. Compound **4b** (1.5 g) was added, and the solution was boiled under reflux for 5 hr. After cooling, the precipitate was filtered to give 1.0 g of almost pure **7**, mp 190–191°. The filtrate was poured onto an ice–water mixture and the resulting precipitate was filtered. It contained at least five components as shown by thin layer chromatography but these could not be purified even by passage through an alumina column several times.

3β,17aβ-Dihydroxy-17α-methyl-D-homoandrost-5-ene 3-Acetate 17a-*p*-Toluenesulfonate (8).—A solution of lithium azide was prepared as described before for compound **7** (procedure B) by refluxing 6.5 g of dried lithium chloride and 11.0 g of sodium azide in absolute methanol, whereupon 5.2 g of 3β,20β-dihydroxypregn-5-ene 3-acetate 20-*p*-toluenesulfonate was added, and the solution was heated under reflux for 24 hr. After cooling, the precipitate was collected and partitioned between chloroform–water. The chloroform extracts were combined, washed with water, dried over sodium sulfate, and evaporated. The residue solidified on treatment with petroleum ether giving 2.7 g of **8**, mp 165–166°. Recrystallization from chloroform–benzene gave crystals: mp 171–172.5°; $[\alpha]^{20}D$ −53° (*c* 1, $CHCl_3$); ν_{max} 1360, 1250, 1177, 1100, 915, 904, 873, 810, 676 cm^{-1}; nmr 0.83 (18-H_3), 0.95 (19-H_3), 0.80 (17α-CH_3, doublet, J = 6.0 cps), 2.02 (3-CH_3CO), 2.40 (*p*-tosyl-CH_3), 4.12 (17aα-H, doublet, J = 10.0 cps), 4.55 (3α-H, multiplet, broad peak), 5.33 (6-H, multiplet) ppm.

Anal. Calcd for $C_{30}H_{42}O_5S$: C, 70.00; H, 8.22; S, 6.23. Found: C, 69.86; H, 8.48; S, 6.05.

3β,17aβ-Dihydroxy-17α-methyl-D-homoandrost-5-ene Diacetate (9).—A solution containing 2.0 g of 3β,20β-dihydroxypregn-5-ene 3-acetate 20-*p*-toluenesulfonate, 10.0 g of potassium acetate, 10 ml of acetic anhydride, and 150 ml of 96% acetic acid was boiled under reflux for 18 hr. After cooling, the reaction mixture was poured onto ice–water and the precipitate was collected. It was washed with isopropyl alcohol to give 0.50 g of product, mp 209–211°. Further recrystallization gave a sample: mp 210–211°; $[\alpha]^{20}D$ −112° (*c* 1, $CHCl_3$); ν_{max} 1722, 903, 810 cm^{-1}; nmr 0.88 (18-H_3), 0.98 (19-H_3), 0.80 (17α-CH_3, doublet, J = 6.5 cps), 2.02 and 2.06 (3β- and 17a-CH_3CO), 4.32 (17aα-H, doublet, J = 10.0 cps), 4.72 (3α-H, broad peak), 5.32 (6-H, multiplet) ppm.

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.32; H, 9.30.

3β,17aβ-Dihydroxy-17α-methyl-D-homoandrost-5-ene 17a-Acetate (10).—A solution of 0.20 g of **9** and 0.10 g of sodium hydroxide in 10 ml of methanol was boiled under reflux for 1 hr. The reaction mixture was poured onto ice and water and the precipitate was collected and recrystallized to give a small amount of product: mp 172–173°; $[\alpha]^{20}D$ −113° (*c* 1, $CHCl_3$); nmr 0.88 (18-H_3), 0.98 (19-H_3), 0.80 (17α-CH_3, doublet, J = 6.0 cps), 2.07 (17a-CH_3CO), 4.33 (17aα-H, doublet, J = 10.5 cps), 3.50 (3α-H, broad peak), 5.33 (6-H, multiplet) ppm.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.37; H, 10.08.

Pregna-4,17-dien-3-one (11).—When 0.70 g of **4a** was eluted through alumina column as usual, 0.40 g of **11** was obtained, mp 135–137° (lit.[15] mp 142–143°). The rest of the eluents contained a mixture of **11** and the starting **4a**. Nmr showed 0.80 (18-H_3), 1.21 (19-H_3), 1.53 (21-H_3, sextet, $J_{20\text{-H},\ 21\text{-}H_3}$ = 6.5 cps, $J_{16\text{-H},\ 21\text{-}H_3}$ = 1.5 cps), 5.72 (4-H) ppm.

20α-Hydroxypregn-4-en-3-one Methanesulfonate (12a).—A solution of 1.5 g of 20α-hydroxypregn-4-en-3-one and 1.5 ml of methane sulfonyl chloride in pyridine was stirred magnetically for 18 hr. The solution was poured into an ice–water mixture and the precipitate was filtered. Recrystallization from methylene chloride–hexane gave 0.9 g of **12a**: mp 138–140°; $[\alpha]^{20}D$ +62° (*c* 0.5, $CHCl_3$); nmr 0.78 (18-H_3), 1.20 (19-H_3), 1.48 (21-H_3, doublet, J = 6.0 cps), 4.75 (20β-H, multiplet, broad peak), 5.73 (4-H) ppm.

Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.69; S, 8.13. Found: C, 66.72; H, 8.46; S, 8.22.

20β-Hydroxypregn-4-en-3-one Methanesulfonate (12b).—This product was made from 20β-hydroxypregn-4-en-3-one, using the same procedure described for **12a**. Recrystallization gave the analytical sample: mp 158.5–161°; $[\alpha]^{20}D$ +116° (*c* 1, $CHCl_3$); ν_{max} 1417, 1230, 1165, 885, 768 cm^{-1}; nmr 0.83 (18-H_3); 1.30 (19-H_3), 1.42 (21-H_3, doublet, J = 6.3 cps), 3.03 (mesyl-H_3), 4.83 (20α-H, broad peak), 5.75 (4-H) ppm.

Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.69; S, 8.13. Found: C, 66.90; H, 8.39; S, 7.96.

20α-Hydroxypregn-4-en-3-one-18-nitrile *p*-Toluenesulfonate (13a).—A solution of 2.0 g of 20α-hydroxypregn-4-en-3-one-18-nitrile[5,6] and 2.0 g of *p*-toluenesulfonyl chloride in 40 ml of pyridine was stirred magnetically for 18 hr and poured into ice–water. The resulting precipitate was filtered and dried. Chromatography on alumina gave 0.90 g of product: mp 194–196°; $[\alpha]^{20}D$ +99° (*c* 1, $CHCl_3$); nmr 1.18 (19-H_3), 1.38 (21-H_3, doublet, J = 6.5 cps), 2.45 (*p*-toluene-CH_3), 4.78 (20β-H, multiplet, broad peak), 5.67 (4-H) ppm.

Anal. Calcd for $C_{28}H_{35}NO_4S$: C, 69.82; H, 7.33; H, 2.91; S, 6.66. Found: C, 69.64; H, 7.34; N, 3.07; S, 6.58.

20β-Hydroxypregn-4-en-3-one-18-nitrile *p*-Toluenesulfonate (13b).—A solution of 0.80 g of 20β-hydroxypregn-4-en-3-one-18-nitrile and 0.80 g of *p*-toluenesulfonyl chloride in 5 ml of pyridine was stirred for 18 hr, and poured onto ice and water to give a gummy substance which solidified on treatment with ether. The product (0.70 g) had mp 158–164°. When 0.15 g of the crude substance was passed through a neutral alumina column (activity 1), 0.12 g of pure product was recovered unchanged. It was recrystallized from methylene chloride–ether giving crystals: mp 172–173°; $[\alpha]^{20}D$ +93° (*c* 0.6, $CHCl_3$); nmr 1.22 (19-H_3), 1.31 (21-H_3, doublet, J = 6.0 cps), 2.47 (*p*-tolyl-CH_3), 4.90 (20α-H, broad peak), 5.73 (4-H) ppm.

Anal. Calcd for $C_{28}H_{35}NO_4S$: C, 69.82; H, 7.33; N, 2.91; S, 6.66. Found: C, 70.05; H, 7.23; N, 3.10; S, 6.49.

Compound **13b** was refluxed in pyridine for 18 hr and recovered unchanged.

Solvolysis of 3-Oxo-20β-hydroxypregn-4-ene-18-nitrile *p*-Toluenesulfonate (13b).—A solution of 0.80 g of **13b**, 3.0 g of KOAc, 3.0 ml of Ac_2O, and 52 ml of 96% acetic acid was heated under reflux for 18 hr. The mixture, after concentration under vacuum, was poured into an ice–water mixture. The resulting precipitate was filtered and dried. Repeated chromatography on alumina and silica gel (four times) resulted in 0.11 g of elimination product, mp 125–128°. Although thin layer chromatography showed one spot, the nmr spectrum in benzene solution showed two peaks for the C-19 methyl group.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.56; H, 8.66; N, 4.70.

The second component obtained from the column weighed 0.12 g and was shown to be 3-oxo-17α-methyl-17aβ-hydroxy-D-homoandrost-4-ene-18-nitrile *p*-toluenesulfonate (**14**): mp 214–217°; $[\alpha]^{20}D$ +72° (*c* 1, $CHCl_3$); nmr 1.18 (19-H_3), 0.84 (21-H_3, doublet, J = 6.0 cps), 2.45 (*p*-toluene-CH_3), 4.17 (17aα-H, doublet, J = 10.5 cps), 5.71 (4-H) ppm.

Anal. Calcd for $C_{28}H_{35}NO_4S$: C, 69.82; H, 7.33; N, 2.91; S, 6.66. Found: C, 69.62; H, 7.42; N, 3.10; S, 6.65.

The third component was shown to be 3-oxo-20α-hydroxypregn-4-ene-18-nitrile acetate (**3a**).

***trans*-3-Oxopregna-4,17-diene-18-nitrile (15).**—A solution of 0.70 g of **13a** in 2.0 ml of pyridine was heated under reflux for 10 hr. The solution was poured into ice and water, and the precipitate was collected and chromatographed on alumina giving 0.07 g of product: mp 156–158°; $[\alpha]^{20}D$ +78° (*c* 1, $CHCl_3$); nmr 1.27 (19-H_3), 1.63 (21-H_3, sextet, $J_{20\text{-H},\ 21\text{-}H_3}$ = 6.8 cps), 5.34 (20-H, octet, $J_{20\text{-H},\ 21\text{-}H_3}$ = 6.8 cps, $J_{16\text{-H},\ 20\text{-H}}$ = 2.5 cps), 5.79 (4-H) ppm.

Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.30; H, 8.56; N, 4.79.