Steroids of Unnatural Configuration. Synthesis and Properties of Ring B Modified 17α-20-Ketopregnanes

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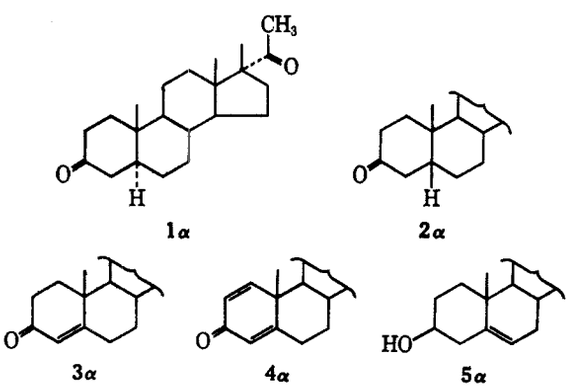
17α-Pregnenolone acetate served as starting material for synthesis of a series of 17α-6,20- and 17α-7,20-diketopregnanes. The corresponding 17β compounds were also prepared. The effect of C-17 configuration on optical rotation and nmr and mass spectra has been investigated.

The synthesis and properties of the following 17α-20-ketopregnanes,[2] 5α,17α-pregnane-3,20-dione (**1α**), 5β,17α-pregnane-3,20-dione (**2α**), 17α-Δ⁴-pregnene-3,-20-dione (17α-progesterone, **3α**), 17α-Δ¹,⁴-pregnadiene-3,20-dione (**4α**), and 17α-Δ⁴-pregnene-3β-ol-20-one (17α-pregnenolone, **5α**), have previously been reported.[3] Base-catalyzed reaction of such compounds leads, through a common enol or enolate ion, to an equilibrium mixture of both C-17 epimers; in the case of the above compounds mixtures containing 73 ± 2% of 17β resulted, irrespective of the variation in functionality of ring A. Compounds **1–5** exhibited another constant property, namely a 17.5-Hz downfield shift of the resonance of the C-18 methyl protons in the 17α isomer compared with the 17β although the absolute value of the chemical shifts varied from compound to compound. These results led to the conclusion that no significant conformational transmission or other long-range effect is operative from ring A to ring D. The synthesis of the ring B modified steroids described in the present work was undertaken to examine the possibility that structural changes closer to ring D might lead to observable long-range effects.



The starting material for synthesis of compounds in the 17α series was 17α-pregnenolone acetate (**6α**) which could be prepared[4] in 58–66% over-all yield from commercially available 16α,17α-oxidopregnenolone acetate *via* lithium aluminum hydride reduction, acetylation, and Serini–Logemann reaction. Syntheses starting from pregnenolone acetate (**6β**) provided the corresponding 17β isomers and also served to elaborate some of the appropriate experimental conditions for work in the 17α series. (See Scheme I.)

Oxidation of **6β** with *t*-butyl chromate solution[5] afforded 7-ketopregnenolone acetate (**7β**) in 50–60% yield and this, in turn, was converted in 53% yield into Δ³,⁵-pregnadiene-7,20-dione (**8β**) by treatment with mineral acid.[6] Hydrogenation of **8β** over palladium on charcoal was allowed to proceed until 1 equiv of hydrogen was absorbed. The resulting mixture of starting material and di- and tetrahydro products afforded 61% of the dihydro product, Δ⁵-pregnene-7,20-dione (**9β**), upon chromatography. The tetrahydro product, 5α-pregnane-7,20-dione (**10β**), could be obtained by hydrogenation of either **8β** or **9β**. The stereochemistry of **10β** at C-5 was assigned on the basis of analogy with results observed in the cholestane series[7] and the ORD results presented below.

When the *t*-butyl chromate oxidation procedure was applied in the less readily available 17α series, the yield of 17α-7-ketopregnenolone acetate (**7α**) from **6α** was a disappointing 40%. A second product not observed in the 17β series, 17α,5β,6β-oxidopregnan-3β-ol-20-one acetate (**11α**, 15%) could be isolated by chromatography of the mother liquors on silica gel. Assignment of the structure of **11α** is based on its independent synthesis from **6α** with *m*-chloroperbenzoic acid (*vide infra*). In the hope of improving the yield of **7α**, reaction time, temperature, and concentration of reactants were varied without success. However, when a more concentrated *t*-butyl chromate solution was used, a third product,[8] 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**12α**), was isolated in 14% yield in addition to 40% **7α** and 14% **11α**. Epimerization of **12α** in alkaline solution followed by reacetylation of the 3-hydroxyl group afforded the known[9] 17β isomer, pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**). The structure of **12α** was further established by independent synthesis (*vide infra*).

The acid-catalyzed conversion employed in the 17β series could not be used for synthesis of 17α-Δ³,⁵-pregnadiene-7,20-dione (**8α**) from **7α** since appreciable epimerization at C-17 would be anticipated.[10] Attempted elimination of acetic acid from **7α** by heating in aqueous acetic acid alone or in the presence of *p*-toluenesulfonic acid did not yield appreciable quantities of **8α**. The elimination could be effected in 37%

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(2) For convenience and in order to emphasize their structural relationship, each pair of C-17 isomers has been designated by a numeral followed by α or β to indicate the stereochemistry at C-17.

(3) M. B. Rubin and E. C. Blossey, *J. Org. Chem.*, **29**, 1932 (1964).

(4) M. B. Rubin and E. C. Blossey, *Steroids*, **1**, 453 (1963).

(5) W. Logemann and P. Giraldi, *Gazz. Chim. Ital.*, **81**, 548 (1951).

(6) (a) C. W. Marshall, R. C. Ray, J. Laos, and B. Riegel, *J. Amer. Chem. Soc.*, **79**, 6308 (1957); (b) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

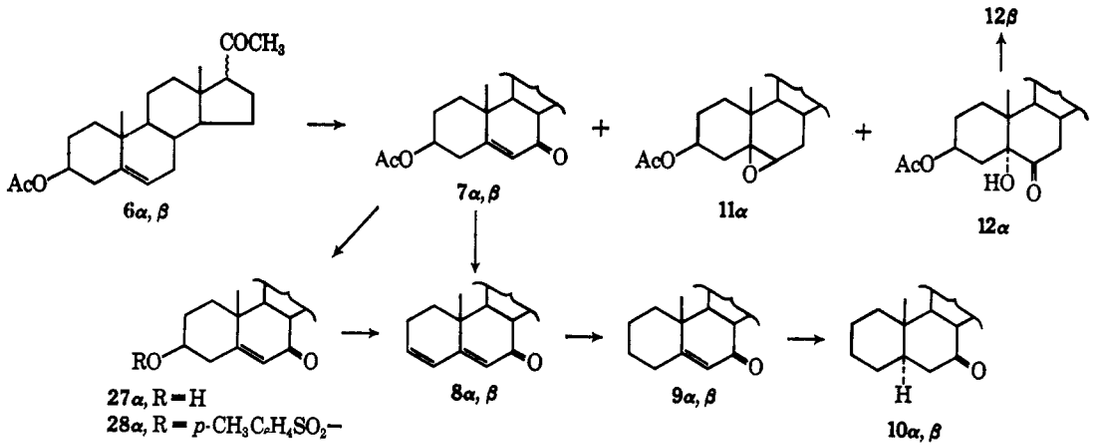
(7) I. M. Heilbron, W. Shaw, and F. S. Spring, *Rec. Trav. Chim. Pays-Bas*, **57**, 529 (1938).

(8) Reaction of the 5α,6α-oxide **19α** with *t*-butyl chromate under similar conditions resulted in conversion into **12α** while **11α** was recovered largely unchanged suggesting that epoxidation by *t*-butyl chromate proceeds to the extent of at least 28%. Failure to isolate epoxides from the reaction of **6β** may have been due to solubility factors.

(9) L. Knof, *Ann. Chem.*, **657**, 171 (1962).

(10) M. B. Rubin, *Steroids*, **2**, 561 (1963), and references contained therein.

SCHEME I



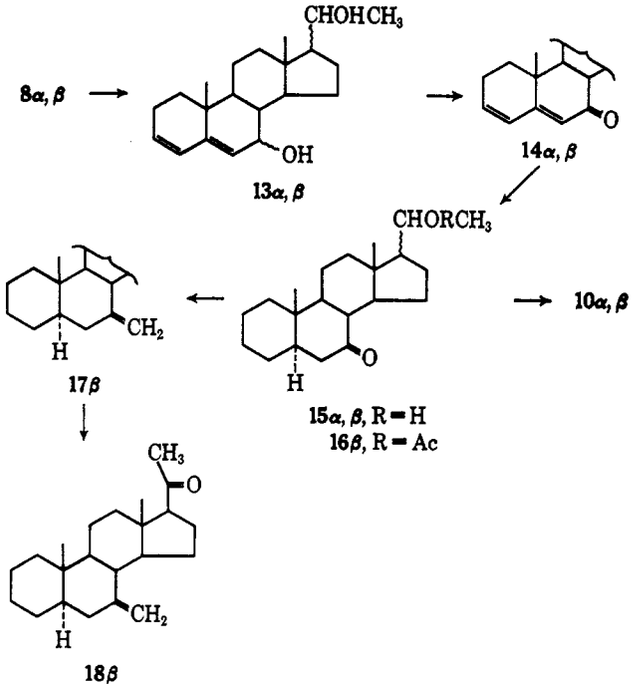
yield by allowing **7α** to stand for several hours on a column of neutral alumina.[11] Alternatively, **7α** could be converted quantitatively into the free alcohol (**27α**) with sodium carbonate in aqueous alcohol. Attempted dehydration of the alcohol was not successful. However, tosylation of **27α**, followed by heating with dimethyl sulfoxide in the presence of excess lithium carbonate, afforded **8α** in 52% over-all yield from **7α**.

Hydrogenation of **8α** was allowed to proceed until 1.15 equiv of hydrogen were absorbed[12] and afforded 39% 17α-Δ^5-pregnene-7,20-dione (**9α**). Complete hydrogenation of either **8α** or **9α** yielded 68 or 81%, respectively, 5α,17α-pregnane-7,20-dione (**10α**).

Each Δ^5-7-ketone (**9α**, **9β**) afforded a single product (**10α**, **10β**) upon catalytic hydrogenation. As noted above, it has been shown in the cholestane series that such reductions afforded products having the **5α** configuration. To establish the stereochemistry of **10α** and **10β** unequivocally, their ORD curves were examined. These showed the strong positive (**10β**) and negative (**10α**) Cotton effects characteristic of 20-keto steroids[10] but allowed no conclusions concerning C-5 stereochemistry. The 20-ketone function was, therefore, removed in the following way. Reduction of **8α** or **8β** with lithium aluminum hydride afforded mixtures of $\Delta^{3,5}$-diene-7,20-diol (**13α,β**) which were oxidized to the corresponding $\Delta^{3,5}$-dien-20-ol-7-ones (**14α,β**) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone or activated manganese dioxide. Hydrogenation of these afforded the corresponding 5α-20-ol-7-ones (**15α,β**) which could be oxidized to **10α** or **10β**. The structure of **15β** was further confirmed by acetylation to give known[13] 5α-pregnane-20β-ol-7-one acetate (**16β**) (Scheme II). The ORD curves of **15α** and **15β** were almost superposable and exhibited low-intensity, negative Cotton effect curves characteristic[14] of 5α-7-keto steroids.

The availability of **15β** allowed synthesis of 7-methylene-5α-pregnan-20-one (**18β**). Reaction of **15β** with

SCHEME II



methyl triphenylphosphorane according to the procedure of Sondheimer and Mechoulam[15] afforded 7-methylene-5α-pregnan-20β-ol (**17β**) in 32% yield. This was oxidized with chromium trioxide–pyridine to **18β**.[16] Attempted preparation of 7-methylene-$\Delta^{3,5}$-pregnadien-20-one from **14β** by the same sequence was unsuccessful.

Pregnenolone acetate (**6β**) and 17α-pregnenolone acetate (**6α**) also served as starting materials for synthesis of a series of 6,20-diketones. The known 5α,6α-oxidopregnan-3β-ol-20-one acetate (**19β**) was conveniently prepared from **6β** using *m*-chloroperbenzoic acid[17] and was converted with chromic acid[9] into **12β**, identical with the material obtained by base-catalyzed isomerization of **12α**. Similar epoxidation of **6α** furnished a mixture of oxides from which were isolated the 5β,6β-oxide (**11α**), previously obtained from the *t*-butyl chromate oxidation of **6α**, in 30% yield, and the

(11) Alkaline alumina, which might be more effective in promoting the conversion of **7α** into **8α** has been found to cause appreciable isomerization of 17α to 17β epimers. No such isomerization was observed in this work with neutral alumina.

(12) The use of an excess over 1 equiv of hydrogen was necessary because the separation of **9α** from **8α** proved difficult. The low yield of **9α** is partly due to this overreduction.

(13) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1413 (1952).

(14) C. Djerassi and R. Ehrlich, *J. Amer. Chem. Soc.*, **78**, 440 (1956); C. Djerassi, W. Closson, and A. E. Lippman, *ibid.*, **78**, 3163 (1956); C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956).

(15) F. Sondheimer and R. Mechoulam, *ibid.*, **79**, 5029 (1957).

(16) This scheme was not applied in the 17α series because of the small amount of **15α** available.

(17) This reaction afforded a mixture of oxides from which the pure isomers could be isolated.

TABLE I
NMR AND MOLECULAR ROTATION DATA

20-Ketopregnane	Chemical shifts[a] of methyl protons, Hz: C-18 17β	C-18 17α	C-18 ΔC-18[b]	C-19 17β	C-19 17α	C-21 17β	C-21 17α	Molecular rotation,[c] deg: 17β	17α	ΔMD[d]
1. 3β-Acetoxy, 5α,6α-oxide (19)	34.5	52.0	17.5	64.8	64.6	127.2	126.9	+54	−483	+537
2. 3β-Acetoxy, 5β,6β-oxide (11)	36.0	53.6	17.6	61.0	60.5	127.2	127.5	+209	−318	+527
3. Δ⁴-6-Keto (24)	39.5	57.0	17.5	58.0	57.0	127.5	127.0	+320	−154	+474
4. Δ²,⁴-6-Keto (25)	39.0	56.6	17.6	60.0	59.5	127.0	128.6	+303	−203	+506
5. 5α-Hydroxy-6-keto (23)	35.5	45.5	10.0	46.5	53.2	126.5	128.0		−508	
6. 3β-Acetoxy-5α-hydroxy-6-keto (12)	36.5	48.2	11.7	48.8	54.0	127.7	129.2	−58	−505	+447
7. Δ³,⁵-7-Keto (8)	41.6	56.8	15.2	68.0	66.4	127.0	127.0	−837	−1410	+573
8. 3β-Acetoxy-Δ⁵-7-keto (7)	40.2	54.7	14.5	73.4	71.6	128.4	127.7	−253	−709	+456
9. Δ⁵-7-Keto (9)	39.7	54.5	14.8	71.3	69.7	127.0	126.0	−377	−801	+424
10. 5α-7-Keto (10)	37.6	53.4	15.8	63.0	62.2	126.0	126.0	−16	−417	+401

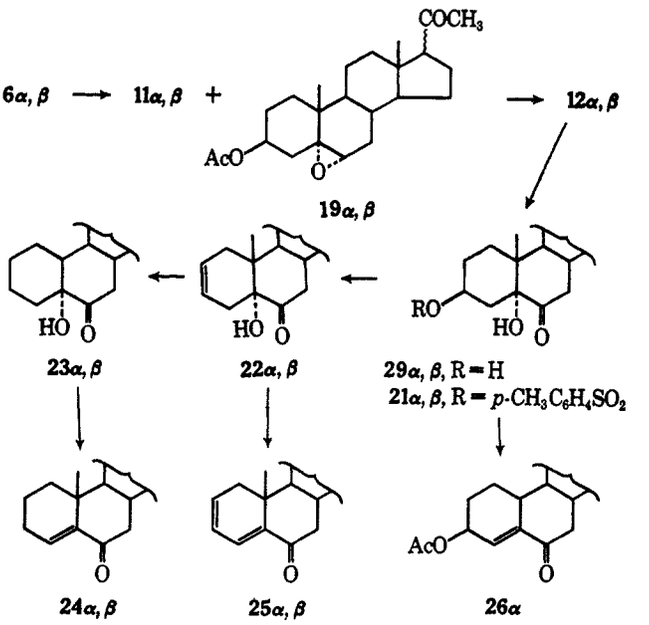
[a] In hertz from tetramethylsilane. Spectra were determined on 0.3 *M* solutions in deuteriochloroform containing tetramethylsilane using a Varian Associates A-60 spectrometer. [b] Chemical shift (hertz) of 17α isomer minus shift of 17β. [c] Rotations were measured using 1% solutions in chloroform at the sodium D line. [d] MD of 17β minus 17α.

5α,6α-oxide, **19**α, in 50% yield. Chromic acid oxidation of **19**α afforded 89% **12**α identical with the material obtained previously. The configurations assigned to **11**α and **19**α are consistent with the nmr spectra of these compounds. It has been shown[18] with a variety of steroid 5,6-epoxides that the magnitude of the coupling constant between C-6 and C-7 protons depends on configuration. For α-epoxides, the 6β-proton resonance appears as a doublet with J = 3.3–4.1 Hz whereas the 6α proton of β-epoxides also appears as a doublet but with J = 2.1–2.7 Hz. The spectrum of **19**α exhibited a doublet at τ 7.06 with J = 3.8 while **11**α exhibited a doublet at τ 6.95 with J = 2.5.

Hydrolysis of the ester group of the hydroxy ketones **12**α and **12**β afforded the corresponding free alcohols **29**α and **29**β which were converted into the tosylates **21**α and **21**β. Heating each tosylates in dimethyl sulfoxide yielded 17α- or 17β-Δ²-pregnen-5α-ol-6,20-dione (**22**α and **22**β). The position of the double bond in these compounds was assigned by analogy with the reaction of cholestane-3β,5α-diol 3-tosylate.[19] Catalytic hydrogenation of each isomer to the saturated 5α-hydroxy-6,20-dione (**23**α and **23**β) and then dehydration with thionyl chloride pyridine gave 17α-Δ⁴-pregnene-6,20-dione (**24**α) and its 17β isomer (**24**β). Similarly, dehydration of **22**α and **22**β afforded 17α- and 17β-Δ²,⁴-pregnadiene-6,20-dione (**25**α and **25**β) and dehydration of **20**α afforded 17α-Δ⁴-pregnene-3β-ol-6,20-dione 3-acetate (**26**α) (Scheme III). The yields obtained in both the 17α and 17β series were comparable.

No attempt was made to prepare 6,20-diketones unsubstituted at C-5 since epimerization could then occur[20] at both C-5 and C-17 in the projected equilibration studies. The results of these studies will be published in the future together with the results obtained with various ring C and ring D modified 20-ketopregnanes. It is noteworthy that no gross differences were observed in the reactivity of compounds in the 17α or 17β series. However, optical rotations and nmr and mass spectra of isomeric 20-ketones merit discussion.[21]

SCHEME III



Examination of the optical rotation data summarized in Table I shows that in every case the 17α isomer is the more levorotatory of the two, the molecular rotation differences ($M^{17\beta}D - M^{17\alpha}D$) ranging from 401 to 573°. This is in accord with previous observations and provides a confirmation of the assigned stereochemistry. However, as noted in our previous work,[4] the constant value of ΔMD = 550 ± 20 assigned by earlier workers[22] applies only to a limited number of cases involving changes in functionality of ring A.

The distinguishing features of the nmr spectra of ring A modified 20-ketones were (1) a nearly constant value (127.8 ± 0.5 Hz) for the chemical shift of the C-21 protons, (2) a slight (0.5–1.0 Hz) upfield shift of the C-19 protons in 17α isomers relative to 17β, and (3) a pronounced, constant downfield shift of C-18 protons in 17α isomers (ΔC-18 = 17.5 ± 0.2 Hz). The nmr results obtained in the present work are summarized in Table I. The C-21 protons fall in the range 126–129 Hz for the 20 compounds examined in good agreement with the earlier results. The C-19 protons of 17α isomers were shifted to higher field by 0.2–1.6 Hz with the exception of no.

(18) A. D. Cross, *J. Amer. Chem. Soc.*, **84**, 3206 (1962).
(19) H. Reich, F. E. Walker, and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1951).
(20) In the case of 6-ketocholestanone, it has been shown that 12% of the 5β isomer is present at equilibrium: N. L. Allinger, M. A. Darooge, and R. B. Hermann, *ibid.*, **26**, 3626 (1961).
(21) Results of an investigation of the gas chromatographic behavior of a large number of 20-keto steroids including the compounds obtained in this work are being published separately: M. B. Rubin and A. P. Brown, *J. Gas Chromat.*, in press.
(22) (a) C. W. Marshall and T. F. Gallagher, *J. Biol. Chem.*, **179**, 1265 (1949); (b) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

5 and 6, the 5α-hydroxy 6-ketones **23** and **22** where the C-19 protons of the 17β isomer appear at 6.7 and 5.2 Hz higher field, respectively, than those of the 17α isomers. The 5α-hydroxy 6-ketones also show unusually small values for ΔC-18 of 10.0 and 11.7 Hz, respectively.[23] Examination of ΔC-18 for the remaining compounds shows that the constants downfield shift of 17.5 Hz for the C-18 protons of 17α isomers is also observed with the 5,6-oxides (**19**, **11**) and the unsaturated 6-ketones (**24**, **25**). However, all of the 7-ketones (**7**–**10**) exhibit lower values of ΔC-18 ranging from 14.5–15.8 Hz. These results might suggest a change of the spatial relationship between C-17 substituent and the neighboring angular methyl group in 7-ketones. Such a change is not apparent from examination of models nor is it supported by the results of equilibration studies with these compounds. In fact, equilibrated mixtures[24] of **8**, **9**, and **10** contained 18–20% 17α isomer in reasonably close agreement with the value of 23 ± 2% observed previously[4] with compounds **1**–**5**.

It has recently been reported[25] that significant differences are observed at *m/e* 71, 124, 229, 244, and 272 in the mass spectra of the epimeric progesterones **3**α and **3**β. These differences were attributed in part (*m/e* 71 and 244 peaks) to intensive rupture of the 15–16 and 13–17 bonds caused by the presence of the 17α-acetyl group. It seemed of interest to examine the generality of this behavior and, accordingly, mass spectra of the Δ⁴-pregnene-6,20-diones (**24**α and **24**β) and 5α-pregnane-7,20-diones (**10**α and **10**β) were determined. The intensities of those peaks where significant differences between the two isomers were observed are presented in Table II. It is immediately apparent that

TABLE II

INTENSITIES[a] OF CHARACTERISTIC PEAKS IN MASS SPECTRA[b]

		m/e						
Compound	M⁺	71	79	85	136	229	233	234
24α (Δ⁴-6-one)	9.6 (314)	1.6	0.7	1.3	0.7	5.9	2.1	3.3
24β	7.3	0.7	3.3	3.5	2.3	1.2	0.2	
		178	202	231	246	298		
10α (5α-7-one)	3.5 (316)	...	2.4	1.5	15.3	0.9		
10β	4.4	3.7	0.3	2.6	2.1	2.3		

[a] $\%\Sigma_{40}$. [b] Mass spectra were determined on an Atlas CH-4 instrument: ionizing voltage 70 eV; ion source temperature 150°.

there are considerable differences between the two isomers in both cases. The very pronounced difference at *m/e* 244 (9.4% in **3**α, 1.2% in **3**β) observed with the progesterones is also evident with the 5α-7-ones **10**α and **10**β, shifted to *m/e* 246 as expected. However, no such difference is observed with the Δ⁴-6-ones **24**α and **24**β. Instead, a pronounced difference is observed 15 mass units lower at *m/e* 229. The variations in the peak at *m/e* 71, assigned to the fragment formed by rupture of the 13–17 and 15–16 bonds accompanied by hydrogen migration in the case of **3** (3.4% in **3**α, 1.0% in **3**β), were also observed in the spectra of **24**α and **24**β but not at *m/e* 71 or 73 in the case of **10**α and **10**β. These results support the conclusion that the configuration of the acetyl group at C-17 plays a role in determining the relative importance of various fragmentations, but further investigation is required to provide a rational interpretation of the results.

(23) It has been suggested [A. I. Cohen, B. T. Keller, E. J. Becker, and P. A. Diassi, *J. Org. Chem.*, **30**, 2175 (1965)] that certain steroidal α-hydroxy ketones exist in solution in the form of hydrogen-bonded dimers. The possibility that the anomalous results observed in the nmr spectra (deuteriochloroform) of **23** and **12** might be due to such a phenomenon is supported by infrared studies. Both **12**α and **12**β exhibit free hydroxyl absorption at 3580 cm^{-1} and bonded, concentration-dependent absorption at 3460 cm^{-1} in chloroform solution.

(24) A. P. Brown, unpublished results.

(25) V. I. Zaretskii, N. S. Wulfson, and V. G. Zaikin, *Tetrahedron*, **23**, 3683 (1967).

Experimental Section[26]

Δ⁵-Pregnene-7,20-dione (9β).—A solution of 5.0 g (16.0 mmol) of Δ³,⁵-pregnadiene-7,20-dione[6a,b] (**8**β) in 250 ml of ethyl acetate with 0.50 g of 10% palladium on charcoal was hydrogenated at 27° and atmospheric pressure (738 mm). After 33 min, 407 cc (16.0 mmol) of hydrogen were absorbed, and the reaction was terminated. The catalyst was removed by filtration through a Celite filter cake and washed with ethyl acetate. Evaporation of the combined solvents gave 5 g of solid: λ_{max} (EtOH) 238 mμ (ε 10,000) (74% **9**β) and 279 (750) (3% **8**β). Thin layer chromatography of the crude product on silica gel with 1:4 diethyl ether–benzene as the eluent and iodine as the indicator indicated the presence of a third component, presumably 5α-pregnane-7,20-dione (**10**β). Chromatography of the product on 250 g of Florisil with benzene–ethyl acetate (99:1–95:5; 17 1-l. portions) afforded 3.7 g of impure **9**β. Crystallization alternately from benzene–hexane and ethanol–water gave 3.0 g (60%) of Δ⁵-pregnene-7,20-dione (**9**β), mp 160–161°.

Crystallization from ethanol afforded the analytical sample: mp 163–164°; $\alpha^{30}D$ −120°; λ_{max} 237 mμ (ε 13,500); 5.87, 6.04, 6.13 (sh) μ; nmr τ 4.40 (1 H), 7.91 (3 H), 8.81 (3 H), 9.33 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.90.

5α-Pregnane-7,20-dione (10β). **A. From Δ³,⁵-Pregnadiene-7,20-dione** (**8**β).—A 5.0-g (16.0 mmol) sample of **8**β in 250 ml of ethyl acetate with 0.50 g of 10% palladium on charcoal was hydrogenated at 26° and atmospheric pressure (736 mm). After 70 min, uptake of hydrogen ceased with the absorption of 826 ml of hydrogen (32.7 mmol). The catalyst was removed by filtration and washed with ethyl acetate. The combined solvents were evaporated to give 5.1 g of white solid which was chromatographed on 250 g of Florisil. Elution with pure benzene and benzene–ethyl acetate (99:1; 14 × 1 l.) gave 3.8 g of material. One crystallization from ethanol afforded 3.0 g of 5α-pregnane-7,20-dione (**10**β), mp 148–149°. An additional 0.37 g (total yield 67%) of **10**β was obtained from the mother liquor.

Crystallization from ethanol–water gave the analytical sample: mp 148–149°; $\alpha^{30}D$ −4.8°; λ_{max} 5.89 μ; nmr τ 7.91 (3 H), 8.95 (3 H), 9.38 (3 H) ppm.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.60; H, 10.30.

B. From Δ⁵-Pregnene-7,20-dione (9β).—A 180-mg (0.57 mmol) sample of **9**β in 15 ml of ethyl acetate with 18 mg of 10% palladium on charcoal was hydrogenated at 28° and atmospheric pressure (741 mm). A total of 10.1 cc of hydrogen (0.4 mmol) was absorbed after 15 min. Filtration and removal of the solvent gave a white solid. One crystallization from methanol gave 126 mg (70%) of **10**β, mp 147°, identical with the **10**β described above.

C. From 5α-Pregnan-20β-ol-7-one (**15**β).—Nitrogen was bubbled through a solution of 100 mg of **15**β in 13 ml of acetone distilled from potassium permanganate for 30 min. The stirred solution was cooled to 10°, and 0.20 ml of Jones reagent,[27] similarly flushed with nitrogen, was rapidly added. After 6–7 min at 10° the reaction mixture was diluted with 100 ml of water. Filtration of the crystalline precipitate afforded 86 mg (86%) of **10**β, mp 147–149°, identical in all respects with the material described above.

***t*-Butyl Chromate Oxidation of 17α-Pregnenolone Acetate.**—A 1.10-g sample of **6**α in 5 ml of dry carbon tetrachloride was oxidized with 30 ml of *t*-butyl chromate solution prepared by the procedure of Logemann and Giraldi.[5] The reaction mixture was maintained at 50–60°. After 2 hr, 4 ml of acetic anhydride

(26) Melting points are corrected. Ultraviolet spectra were determined in ethanol solution, infrared spectra in potassium bromide pellets except where noted otherwise, optical rotations in 1% chloroform solutions, and nmr spectra in deuteriochloroform solution containing tetramethylsilane. Hexane refers to a commercial petroleum fraction of bp 60–67°.

(27) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

were added, and after an additional 2 hr, 6 ml of acetic acid were added over a 90-min period. The reaction was maintained at 50–60° for 6 hr after the addition of the acetic acid, and then allowed to stand at room temperature overnight. The excess chromate was reduced by the portionwise addition of 100 ml of 10% aqueous oxalic acid solution. The carbon tetrachloride solution was washed with 10% sodium carbonate solution which was back-washed with fresh carbon tetrachloride. The combined organic phases were washed with water and dried. Evaporation of the solvent afforded 1.18 g of a yellow solid: λ_{max} 236 mμ (ε 4900, 37% **7α**).

Two crystallizations of the crude product from ethyl acetate–hexane afforded 284 mg of 17α-Δ⁵-pregnene-3β-ol-7,20-dione acetate (**7α**), mp 214–216°. The mother liquors were chromatographed on 35 g of silica gel with 5% diethyl ether in benzene as the eluent; 35-ml fractions were collected. Fractions 3–5 afforded 353 mg of impure starting material which was crystallized from acetone–water to give 290 mg of **6α**, mp 170°. Fractions 17–19 afforded 151 mg of **7α** which were crystallized from ethyl acetate–hexane to give an additional 55 mg (40% total yield) of **7α**.

Crystallization from methanol afforded a sample of **7α** for analysis: mp 217–218°; $\alpha^{25}D$ −190°; λ_{max} 236 mμ (ε 13,200); ($CHCl_3$) 5.78, 5.88, 5.99, 6.12, 8.10 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.57.

Fractions 6–14 (9 × 35 ml) afforded 129 mg (15%) of 17α-5β,6β-oxidopregnan-3β-ol-20-one acetate (**11α**).

Crystallization from methanol–water afforded an analytical sample: mp 126–126.5°; $\alpha^{27}D$ −85°; λ_{max} ($CHCl_3$) 5.78, 5.88, 8.15 μ; nmr τ 5.07–5.50 (1 H, complex), 6.95 (1 H, d, J = 2.5 Hz), 7.90 (3 H), 7.99 (3 H), 9.00 (3 H), 9.10 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.75; H, 9.17. Found: C, 73.87; H, 9.06.

***m*-Chloroperbenzoic Acid Oxidation of 17α-Pregnenolone Acetate.**—To a 5.0-g sample of **6α** in 20 ml of chloroform at 25° was added a solution of 3.5 g of *m*-chloroperbenzoic acid (technical) in 30 ml of chloroform. The addition was carried out over a 10-min period. After an additional 25 min the excess peracid was reduced by the slow addition of a 10% sodium sulfite solution. The organic layer was separated, washed with sodium bicarbonate solution and water, and then dried. Evaporation of the solvent gave 5.43 g of the mixed α- and β-oxides which were chromatographed on silica gel with 6–8% ether in benzene. Fractions 5–8 (four-250 ml portions) contained 2.3 g (44%) of 17α-5β,6β-oxidopregnan-3β-ol-20-one acetate (**11α**) identical with the material obtained in the *t*-butyl chromate oxidation of **6α**.

Continued chromatography of the above sample (nine 250-ml fractions) gave a total of 2.6 g of 17α-5α,6α-oxidopregnan-3β-ol-20-one acetate (**19α**), mp 216–219°. This material was used without further purification.

Crystallization of a sample from methylene chloride–isopropyl ether furnished the analytical sample: mp 221.5–223°; $\alpha^{27}D$ −129°; λ_{max} (CH_2Cl_2) 5.78, 5.87, 8.12 μ; nmr τ 4.75–5.25 (1 H, complex), 7.06 (1 H, d, J = 3.8 cps), 7.86 (3 H), 7.98 (3 H), 8.91 (3 H), 9.12 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.75; H, 9.17. Found: C, 73.93; H, 9.26.

17α-Pregnane-3β,5α-diol-6,20-dione 3-Acetate (12α). A. From 17α-Pregnenolone Acetate (6α).—A portion of the *t*-butyl chromate solution prepared according to the procedure of Logemann and Giraldi[5] was concentrated below 40° under reduced pressure to half of its original volume. A 30-ml portion of this concentrated chromate solution was used for the oxidation of 2.2 g of 17α-pregnenolone acetate (**6α**). The reaction procedure was identical with that described above. The crude product, λ_{max} 234 mμ (ε 5900, 45% **7α**), was crystallized from ethyl acetate–hexane to give 1.07 g of solid, mp 197–205°. Chromatography of this mixture with 5% ether in benzene, followed by crystallization from chloroform–hexane gave 282 mg (15%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**12α**) identical with the material described below.

B. From 17α-5α,6α-Oxidopregnan-3β-ol-20-one Acetate (19α).—To a 2.6-g sample of **19α** in 20 ml of acetone at 10° was added 0.7 ml of 75% chromic acid solution.[9] After 1 min an additional 0.7 ml of the chromic acid solution was added, followed after 30 min by the addition of another 0.35 ml. After a total reaction time of 1 hr the reaction mixture was diluted with water, and the precipitated product was taken up in ethyl acetate. The ethyl acetate was washed with water, dried, and evaporated to give 2.7 g of impure product, mp 255–259°. Crystallization from chloroform–hexane gave 2.4 g (89%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**12α**), mp 258–260°.

An analytical sample was prepared by crystallization from chloroform–hexane: mp 259–261°; $\alpha^{27}D$ −129°; λ_{max} (CH_2Cl_2) 2.83; 5.81 (sh), 5.85, 8.08 μ; nmr τ 4.75–5.10 (1 H, complex), 6.07 (1 H), 7.89 (3 H), 8.04 (3 H), 9.11 (3 H), 9.21 (3 H) ppm.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.76. Found: C, 70.83; H, 8.80.

17α-Δ⁵-Pregnene-3β-7,20-dione (27α).—To an ice-cold solution of 4.2 g of **7α** in 380 ml of methanol were added 190 ml of water containing 17.5 g of potassium carbonate. After stirring at room temperature for 2 hr, the solution was neutralized with concentrated hydrochloric acid. The methanol was removed under reduced pressure on the steam bath, and the resulting aqueous suspension was extracted three times with ethyl acetate which was washed with water and dried. Removal of the solvent afforded 3.8 g (98%) of 17α-Δ⁵-pregnen-3β-ol-7,20-dione (**27α**), mp 177–179°.

Crystallization from methanol afforded an analytical sample: mp 182–183°; $\alpha^{25}D$ −191°; λ_{max} 237 mμ (ε 13,200); ($CHCl_3$) 2.67, 2.80 (br), 5.87, 5.98, 6.11 μ.

Anal. Calcd for $C_{21}H_{30}O_3 \cdot H_2O$: C, 72.38; H, 9.26. Found: C, 72.46; H, 9.26.

17α-Δ⁵-Pregnen-3β-ol-7,20-dione Tosylate (28α).—A mixture of 3.59 g of crude **27α** and 3.6 g of *p*-toluenesulfonyl chloride in 11 ml of pyridine was kept at room temperature for 2 hr and then at 0° overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with 5% sulfuric acid, 10% sodium bicarbonate, and water and dried. Removal of the solvent *in vacuo* at room temperature gave 5.3 g (100%) of 17α-Δ⁵-pregnen-3β-ol-7,20-dione tosylate (**28α**) as an oil which gradually solidified. The crude tosylate was used without further purification for the preparation of the 17α-dienone **8β**. Both the crude and purified tosylates were unstable and had to be used shortly after their preparation.

Crystallization of the tosylate from methylene chloride–isopropyl ether afforded an analytical sample: mp 129.5°; $\alpha^{30}D$ −131°; λ_{max} 224 mμ (ε 23,700); ($CHCl_3$) 5.99, 6.10, 6.25, 6.37, 8.63, 10.33, 10.60, 11.20, 11.51, 11.94 μ.

Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.38; H, 7.49; S, 6.62. Found: C, 69.18; H, 7.51; S, 6.42.

17α-Δ³·⁵-Pregnadiene-7,20-dione (8α). A. From 17α-Δ⁵-Pregnen-3β-ol-7,20-dione Tosylate (28α).—A solution of 5.2 g of **28α** in 300 ml of anhydrous dimethyl sulfoxide (DMSO) containing 20 g of lithium carbonate was heated at 100° under nitrogen for 3.5 hr. Approximately 80% of the DMSO was removed by vacuum distillation at 100°. The residue was taken up in ethyl acetate and the lithium carbonate removed by filtration. The ethyl acetate was washed with water and dried. Evaporation of the solvent left 3.1 g of a reddish brown oil: λ_{max} 278 mμ (ε 16,000, 76% **8α**). Chromatography of the oil on 155 g of silica gel with 5% diethyl ether in benzene (eight 125-ml portions) afforded 2.1 g of solid from which 1.77 g (52%) of 17α-Δ³·⁵-pregnadiene-7,20-dione (**8α**), mp 126–127°, were obtained in two crops from isopropyl ether–hexane.

Crystallization of **8α** from ethanol–water provided the analytical sample: mp 130–131.5°; $\alpha^{30}D$ −452°; λ_{max} 278 mμ (ε 23,400); 5.90, 6.01, 6.14, 6.26 μ; nmr τ 3.95 (2 H), 4.45 (1 H), 7.91 (3 H), 8.90 (3 H), 9.07 (3 H) ppm.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.82; H, 8.82.

B. From 17α-Δ⁵-Pregnen-3β-ol-7,20-dione Acetate (7α).—A 2.46-g sample of **7α** was placed on a column of 70 g of neutral alumina using 5% diethyl ether in benzene as the solvent. After 2.5 hr the column was washed with 2 l. of ethyl acetate. Evaporation of the ethyl acetate afforded 1.67 g of solid: λ_{max} 278 mμ. Chromatography of the crude product on 85 g of silica gel with 4% diethyl ether in benzene gave 990 mg of impure **8α** and 386 mg of starting material. The 17α-dienone was treated with activated charcoal and crystallized from acetone–hexane to give 645 mg (37%) of **8α**, mp 130–131°, which was identical with that obtained from **28α**.

17α-Δ⁵-Pregnene-7,20-dione (9α).—A solution of 824 mg (2.63 mmol) of **8α** in 60 ml of ethyl acetate with 80 mg of 10% palladium on charcoal was hydrogenated at 30° and atmospheric

pressure (744 mm). After the uptake of 77.5 ml (3.08 mmol) of hydrogen, the reaction was terminated. The catalyst was removed by filtration and washed, and the solvent was evaporated to give 799 mg of white solid: λ_{max} 237 mμ (ε 9400, 71% 9α). Chromatography of the sample on 40 g of silica gel with 1–1.5% diethyl ether in benzene (19 × 40 ml) afforded 481 mg of impure 9α. Crystallization from methylene chloride–hexane afforded 323 mg (39%) of 17α-Δ⁵-pregnene-7,20-dione (9α), mp 133–134.5°.

An analytical sample was obtained by crystallization from methylene chloride–hexane: mp 134–134.5°; $\alpha^{30}D$ −255°; λ_{max} 236 mμ (ε 12,600); 5.88, 6.00, 6.14 μ; nmr τ 4.40 (1 H), 7.91 (3 H), 8.85 (3 H), 9.11 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.92; H, 9.86.

17α-5α-Pregnane-7,20-dione (10α). A. From 17α-Δ³,⁵-Pregnadiene-7,20-dione (8α).—A 251-mg sample of 8α in 25 ml of ethyl acetate with 25 mg of 10% palladium on charcoal was hydrogenated at atmospheric pressure. After the absorption of hydrogen ceased, the catalyst was removed by filtration and evaporation of the solvent gave a white solid which was chromatographed on 20 g of silica gel. Elution with 5% diethyl ether in benzene (four 100-ml portions) gave 171 mg (68%) of 17α-5α-pregnane-7,20-dione (10α), mp 127–130°.

Crystallization of 10α from ethanol–water afforded the analytical sample: mp 130.5–131.5°; $\alpha^{30}D$ −132°; λ_{max} 5.88 μ; nmr τ 7.90 (3 H), 8.98 (3 H), 9.11 (3 H) ppm.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.86; H, 9.79.

B. From 17α-Δ⁵-Pregnene-7,20-dione (9α).—A 100-mg sample of 9α in 15 ml of ethyl acetate with 11 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. After the absorption of hydrogen ceased, the reaction was worked up as described above to give 99 mg of white solid. One crystallization from methanol–water gave 81 mg (81%) of 10α, mp 129–130.5°, identical with a sample prepared from 8α.

C. From 17α-5α-Pregnan-20ε-ol-7-one (15α).—A solution of 39 mg of the mixed C-20 alcohols 15α in 5 ml of acetone was flushed with nitrogen and oxidized as described above for 15β. Thin-layer and gas chromatography of the crude product showed it to be a single compound with an R_f value and retention time identical with those of an authentic sample of 10α. Crystallization from methanol–water afforded, in two crops, 20 mg (50%) of 10α, mp 130–131°, identical with an authentic sample.

Δ³,⁵-Pregnadiene-7ε,20ε-diol (13β).—To an ice-cold solution of 5.5 g of 8β in 200 ml of tetrahydrofuran (THF), 2 g of lithium-aluminum hydride was slowly added. The stirred reaction mixture was heated to reflux for 1 hr and then cooled in an ice bath. The excess $LiAlH_4$ was destroyed by the slow addition of aqueous THF. The precipitated aluminum hydroxide was removed by filtration through a Celite filter cake and washed with ethyl acetate. The combined solvents were evaporated to give 5.9 g (107%) of the mixed alcohols of Δ³,⁵-pregnadiene-7ε,20ε-diol (13β) as a white foam which was used without further purification: λ_{max} 235 mμ (ε 17,500); (CH_2Cl_2) 2.69, 2.82 μ.

Δ³,⁵-Pregnadien-20β-ol-7-one (14β).—A 5.5-g sample of crude 13β in 460 ml of dry chloroform was treated with 39 g of activated manganese dioxide (Beacon Chemical Co.) under nitrogen. The stirred solution was kept at room temperature for 36 hr. The manganese dioxide was removed by filtration through a Celite filter cake and washed with chloroform. Evaporation of the solvent left 5.3 g of a yellow glass: λ_{max} 278 mμ (ε 16,700, 78% 14β). Chromatography of the glass on 170 g of neutral alumina gave 1.7 g (31%) of Δ³,⁵-pregnadien-20β-ol-7-one (14β) used without further purification in the next step: mp 151.5–154.5°; λ_{max} 273 mμ (ε 20,600); (CH_2Cl_2) 2.72, 6.03, 6.15, 6.28 μ.

The remainder of the material contained 14β mixed with starting material which could be recycled.

5α-Pregnan-20β-ol-7-one (15β).—A 1.55-g (4.86 mmol) sample of 14β in 75 ml of ethyl acetate with 0.16 g of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. The uptake of hydrogen ceased with the absorption of 254 ml (theoretical: 248 ml) of hydrogen. Removal of the catalyst by filtration and evaporation of the solvent gave 1.6 g of white solid which was crystallized alternately from benzene–hexane and methanol to give 700 mg of 5α-pregnan-20β-ol-7-one (15β): mp 155–156°; λ_{max} (CH_2Cl_2) 2.66, 5.90 μ; ORD (dioxane, c 0.1), $[\alpha]_{400}$ −220°, $[\alpha]_{350}$ −350°, $[\alpha]_{318}$ −760°, $[\alpha]_{285}$ 0°, $[\alpha]_{257}$ +150°. By concentration of the mother liquor an additional 530 mg (79% total yield) of 15β were obtained mp 150–152°. The acetate, prepared in the usual way, had mp 198–199° and $\alpha^{30}D$ −45° (lit.[13] mp 202–203°, $\alpha^{30}D$ −33°).

17α-Δ³,⁵-Pregnadiene-7ε,20ε-diol (13α).—A 421-mg sample of 8α in 50 ml of ice-cold tetrahydrofuran was treated with 0.40 g of lithium aluminum hydride. The reaction mixture was heated to reflux for 1 hr and cooled, and the excess $LiAlH_4$ was destroyed. After filtration through a Celite filter cake, the solvent was removed to give 406 mg (96%) of the mixed alcohols of 17α-Δ³,⁵-pregnadiene-7ε,20ε-diol (13α) as a colorless oil. The crude diol was used directly without further purification.

17α-Δ³,⁵-Pregnadien-20ε-ol-7-one (14α).—To a solution of 406 mg of 13α in 5 ml of dioxane were added 355 mg of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ). After standing at room temperature for 28 hr the reaction mixture was filtered to remove the precipitated hydroquinone. The hydroquinone was washed with 20 ml of methylene chloride, and the combined filtrate and washings were evaporated. The residue was taken up in methylene chloride which was washed with a total of 90 ml of 10% sodium hydroxide and 70 ml of water and dried. Removal of the solvent left 301 mg of a red oil: λ_{max} 278 mμ (ε 18,400, 87% 14α). Chromatography of the oil on 9 g of neutral alumina with 8% diethyl ether in benzene (139-ml portions) gave a total of 195 mg (55%) of the mixed C-20 alcohols of 17α-Δ³,⁵-pregnadien-20ε-ol-7-one (14α) as an oil: λ_{max} ($CHCl_3$) 2.68, 6.06, 7.16, 6.28 μ. A second chromatography of the mixed alcohols failed to bring about their separation.

17α-5α-Pregnan-20ε-ol-7-one (15α).—An 84-mg (0.27 mmol) sample of 14α in 10 ml of ethyl acetate with 20 mg of 10% palladium on charcoal was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake ceased with the absorption of 7.5 ml of hydrogen. Removal of the catalyst by filtration and evaporation of the solvent left an oil which was chromatographed on 3 g of silica gel with 10% diethyl ether in benzene; 3-ml fractions were collected. A total of 43 mg of the mixed alcohols of 17α-5α-pregnan-20ε-ol-7-one (15α) were obtained as an oil: λ_{max} ($CHCl_3$) 2.69, 5.89 μ; ORD (dioxane, c 0.1), $[\alpha]_{400}$ −180°, $[\alpha]_{350}$ −285°, $[\alpha]_{318}$ −640°, $[\alpha]_{275}$ +260°.

7-Methylene-5α-pregnan-20-one (18β).—A five-necked round-bottomed flask was fitted with a nitrogen inlet, a thermometer well, an addition funnel, a rubber septum, and a partial take-off head. To 1.9 g (5.4 mmol) of methyltriphenylphosphonium bromide suspended in 30 ml of anhydrous ether, under nitrogen, was added 3.3 ml (5.4 mmol) of 1.6 *N* *n*-butyl lithium in *n*-hexane (Foote Mineral Co.). After the mixture was stirred for 2 hr, a solution of 343 mg (1.08 mmol) of 5α-pregnan-20β-ol-7-one (15β) in 70 ml of ether was added. The mixture was stirred at room temperature an additional 4 hr and allowed to stand overnight.

The ether was removed by distillation while being replaced with anhydrous tetrahydrofuran until the temperature of the reaction mixture reached 60–65°. The mixture was heated to reflux for 7.5 hr, cooled, and diluted with water. The crude product was extracted into ether which was washed with water and saturated sodium chloride and dried. Evaporation of the solvent yielded 1.13 g of a red solid which was chromatographed on silica gel with benzene. A total of 210 mg of material was obtained which was crystallized from methylene chloride–hexane to give 110 mg (32%) of 7-methylene-5α-pregnan-20β-ol (17β): mp 132–133°; λ_{max} 2.84, 6.10, 11.39 μ.

A 200-mg sample of crude 7-methylen-20β-ol was added to the reagent prepared from 2.5 ml of pyridine and 190 mg of chromic acid.[28] The reaction mixture was stirred for 30 min and allowed to stand at room temperature overnight. It was then poured into water and the crude product was collected by filtration. The filtrate was extracted with ether and the residue was taken up in the same solvent. The combined ether fractions were washed with water and saturated sodium chloride and dried to give 120 mg of crude product which was treated with Norit A and crystallized from aqueous methanol to yield 93 mg (47%) of 7-methylene-5α-pregnan-20-one (18β), mp 109–112°.

Crystallization from methylene chloride–hexane afforded the analytical sample: mp 111–111.5°; $\alpha^{27}D$ −1°; λ_{max} (CH_2Cl_2) 5.88, 6.09, 11.30 μ.

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.95; H, 10.42.

(28) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 722 (1953).

Pregnane-3β,5α-diol-6,20-dione 3-Acetate (12β).—A 177-mg sample of **12α** in 18 ml of 1:1 dioxane–2 *N* methanolic potassium hydroxide was allowed to stand under nitrogen for 48 hr. The potassium hydroxide was neutralized with acetic acid, and the solvent was removed under reduced pressure at room temperature. The residue was taken up in ethyl acetate which was washed with water and dried. Removal of the solvent afforded a white solid which was acetylated overnight with a few drops of acetic anhydride in pyridine. The excess reagents were removed *in vacuo* at room temperature, and the residue chromatographed on silica gel with 20% ether in benzene. The appropriately combined fractions (determined by tlc) were crystallized alternately from methanol and chloroform–hexane to give 37 mg (21%) of pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**), mp 223–224.5°, identical with an authentic sample.[5]

Pregnane-3β,5α-diol-6,20-dione 3-Tosylate (21β).—To a 4.5-g sample of pregnane-3β,5α-diol-6,20-dione 3-acetate (**12β**) in 480 ml of ice-cooled methanol was added a solution of 22 g of potassium carbonate in 242 ml of water. The reaction mixture was stirred for 2 hr at room temperature. The potassium carbonate was neutralized with concentrated hydrochloric acid and the methanol removed under reduced pressure on the steam bath. The product was recovered by extraction into ethyl acetate which was evaporated to give 4.4 g (110%) of crude pregnane-3β,5α-diol-6,20-dione (**29β**) used without further purification.

The crude diol (4.4 g) was treated with 4.4 g of *p*-toluenesulfonyl chloride in 35 ml of pyridine. After standing at room temperature for 1 hr, the reaction mixture was kept at 0° overnight. The mixture was poured into water, and the crude product was taken up in ethyl acetate which was washed with dilute acid and water and dried. Removal of the solvent gave a solid which was crystallized from methylene chloride–isopropyl ether to give a total of 5.8 g (100%) of pregnane-3β,5α-diol-6,20-dione 3-tosylate (**21β**), mp 166–167°.

Crystallization from isopropyl ether afforded the analytical sample: mp 166–166.5° dec; $\alpha^{30}D$ −22°; λ_{max} ($CHCl_3$) 2.85, 5.85, 6.26, 8.55, 10.66, 11.61 μ.

Anal. Calcd for $C_{28}H_{38}O_6S$: C, 66.90; H, 7.62; S, 6.38. Found: C, 67.21; H, 7.77; S, 6.15.

Δ²-Pregnen-5α-ol-6,20-dione (22β).—A 4.0-g sample of the tosylate **21β** together with 10 g of Li_2CO_3 was heated for 2 hr under nitrogen in 200 ml of dimethyl sulfoxide. The dimethyl sulfoxide was removed by vacuum distillation, and the residue was taken up in ethyl acetate. The ethyl acetate was washed with water, dried, and evaporated to give 2.42 g of solid. This crude product was chromatographed on silica gel with 10% ether in benzene. A total of 1.29 g (49%) of Δ²-pregnen-5α-ol-6,20-dione (**22β**), mp 180–190° dec, was obtained which was used without further purification: λ_{max} (KBr), 2.86, 5.85, 5.92 μ.

Pregnan-5α-ol-6,20-dione (23β).—A solution of 454 mg (1.34 mmol) of **22β** in 65 ml of ethyl acetate with 45 mg of 10% palladium on charcoal was hydrogenated at 27° and atmospheric pressure (734 mm). After 1 hr 35.1 ml (theoretical, 34.3 ml) of hydrogen were absorbed. Filtration of the reaction mixture to remove the catalyst, and evaporation of the solvent gave 424 mg of solid. Crystallization from methanol yielded 344 mg (76%) of pregnan-5α-ol-6,20-dione (**23β**) used without further purification: mp 215–223° dec; λ_{max} 2.86, 5.86 (sh), 5.91 μ.

Δ²,⁴-Pregnadiene-6,20-dione (25β).—To a solution of 690 mg of **22β** in 4.5 ml of pyridine at 0° was added 0.25 ml of thionyl chloride. After 20 min the reaction mixture was diluted with water. The product was taken up in ethyl acetate which was washed with dilute acid and water and dried. Evaporation of the solvent gave 561 mg of a sticky, yellow solid: λ_{max} 315 mμ (ε 3260, 39% **25β**). Chromatography on silica gel with 4% ether in benzene afforded 227 mg of material. Treatment with decolorizing charcoal and crystallization from methylene chloride–hexane yielded 118 mg (18%) of Δ²,⁴-pregnadiene-6,20-dione (**25β**), mp 137.5–141°.

Crystallization from isopropyl ether gave the analytical sample: mp 142.5–144°; $\alpha^{27}D$ +97°; λ_{max} 313 mμ (ε 8400); 5.89, 6.01, 6.19, 6.52 μ.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.34; H, 8.87.

Δ⁴-Pregnene-6,20-dione (24β).—A 275-mg sample of **23β** in 5 ml of pyridine at 0° was treated with 0.5 ml of thionyl chloride. After 25 min the reaction mixture was treated as described in the preparation of **25β** above. Evaporation of the solvent gave 222 mg of a sticky, yellow solid: λ_{max} 241 mμ (ε 5600); 82% (**24β**). Chromatography on silica gel with 3% ether, followed by treatment with decolorizing charcoal and crystallization from methanol–water furnished 129 mg (50%) of Δ⁴-pregnene-6,20-dione (**24β**), mp 112.5–114°.

An analytical sample was obtained by crystallization from methanol–water: mp 116–117°; $\alpha^{27}D$ +102°; λ_{max} 239 mμ (ε 6800); 5.87, 5.92, 6.19 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80,20; H, 9.67.

17α-Pregnane-3β,5α-diol-6,20-dione (29α).—To a solution of 2.5 g of **20α** in 220 ml of ice-cold methanol was added a solution of 1.9 g of potassium carbonate in 110 ml of water. After standing at room temperature for 2 hr, the reaction mixture was made neutral to litmus with concentrated hydrochloric acid and the methanol was removed under reduced pressure on the steam bath. The precipitated diol was taken up in ethyl acetate which was washed with water, dried, and evaporated to give 2.15 g (97%) of 17α-pregnane-3β,5α-diol-6,20-dione (**29α**), mp 262–272°. This impure diol was used without additional purification.

The analytical sample was prepared by crystallization from methanol and drying at the reflux temperature of toluene: mp 288–289.5°; $\alpha^{27}D$ −121°; λ_{max} 2.82, 2.94, 5.87 μ.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.62; H, 9.15.

17α-Pregnane-3β,5α-diol-6,20-dione 3-Tosylate (21α).—A mixture of 1.22 g of **29α** and 1.22 g of *p*-toluenesulfonyl chloride in 4.5 ml of pyridine was kept at room temperature for 2 hr and then at 0° overnight. Dilution of the reaction mixture with water followed by extraction with ethyl acetate which was washed with dilute acid, water, dried, and evaporated afforded 1.73 g (98%) of 17α-pregnane-3β,5α-diol-6,20-dione 3-tosylate (**21α**) as a tacky solid. The tosylate was used directly without purification.

Crystallization from isopropyl ether furnished an analytical sample: mp 169° dec; $\alpha^{27}D$ −112°; λ_{max} ($CHCl_3$) 2.84, 5.85, 6.25, 8.56, 10.67, 11.59 μ.

Anal. Calcd for $C_{28}H_{38}O_6S$: C, 66.90; H, 7.62; S, 6.38. Found: C, 66.59; H, 7.11; S, 6.07.

17α-Δ²-Pregnen-5α-ol-6,20-dione (22α).—A 1.63-g sample of the crude tosylate (**21α**) in 80 ml of DMSO containing lithium carbonate was heated under nitrogen at 100° for 5 hr. The DMSO was removed by vacuum distillation and the residue was taken up in ethyl acetate. The lithium carbonate was removed by filtration. The ethyl acetate was washed with water and dried. Evaporation of the solvent gave 1.14 g of a yellow solid. Chromatography on silica gel with 5% ether in benzene gave a total of 433 mg (40%) of 17α-Δ²-pregnen-5α-ol-6,20-dione (**22α**), mp 225–230°, used without further purification.

Crystallization from methylene chloride–isopropyl ether afforded an analytical sample: mp 231–233°; $\alpha^{30}D$ −117°; λ_{max} ($CHCl_3$) 2.70, 5.85, 6.03 μ; nmr τ 4.38 (2 H, br), 7.89 (3 H), 9.10 (3 H) 9.30 (3 H) ppm.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.13.

17α-Pregnen-5α-ol-6,20-dione (23α).—A solution of 361 mg of **22α** in 50 ml of ethyl acetate with 40 mg of palladium on charcoal was hydrogenated at 22° and atmospheric pressure (744 mm). After 35 min, 33.9 ml of hydrogen were absorbed. The catalyst was removed by filtration through a Celite filter cake and washed with ethyl acetate. Evaporation of the combined filtrate and washings gave 371 mg (103%) of 17α-pregnan-5α-ol-6,20-dione (**23α**), mp 193–198°.

Crystallization from methylene chloride–isopropyl ether afforded the analytical sample: mp 208–209.5°; $\alpha^{27}D$ −153°; λ_{max} ($CHCl_3$) 2.84, 5.86 μ.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.83; H, 9.57.

17α-Δ²,⁴-Pregnadiene-6,20-dione (25α).—Thionyl chloride (0.35 ml) was added to a solution of 303 mg of 17α-Δ²-pregnen-5α-ol-6,20-dione (**22α**) in 4 ml of pyridine at 0°. After 20 min the reaction mixture was diluted with water. The product was taken up in ethyl acetate which was washed with dilute acid, dilute bicarbonate solution, water, and saturated sodium chloride solution and dried. Evaporation of the solvent yielded 274 mg of solid: λ_{max} 314 mμ (ε 3700), 48% **25α**. Chromatography on silica gel with 4% ether in benzene gave a total of 120 mg of material which was treated with Norit A and crystallized from methanol–water to give 75 mg (26%) of 17α-Δ²,⁴-pregnadiene-6,20-dione (**25α**), mp 144–147°.

The analytical sample was prepared by crystallization from methanol–water: mp 144.5–147.5°; $\alpha^{27}D$ −65°; λ_{max} 315 mμ (ε 7700); 5.89, 5.95, 6.15, 6.40 μ.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.45; H, 9.08.

17α-Δ⁴-Pregnene-6,20-dione (24α).—To a 366-mg sample of 17α-pregnan-5α-ol-6,20-dione (**23α**) in 3.3 ml of pyridine at 0° was added 0.5 ml of thionyl chloride. After 20 min the reaction mixture was diluted and treated as described above for the preparation of **25α** to give 266 mg of a yellow solid: λ_{max} 241 mμ (ε 5400, 80% **24α**). Chromatography on silica gel with 4% ether gave 193 mg of material which was crystallized from isopropyl ether–hexane to give 134 mg (42%) of 17α-Δ⁴-pregnene-6,20-dione (**24α**), mp 134–136°.

Crystallization from methylene chloride–hexane furnished the analytical sample: mp 134.5–136°; $\alpha^{30}D$ −49°; λ_{max} 240 mμ (ε 6800); 5.87, 5.96, 6.18 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.10; H, 9.62.

17α-Δ⁴-Pregnen-3β-ol-6,20-dione Acetate (26α).—A 117-mg sample of 17α-pregnane-3β,5α-diol-6,20-dione 3-acetate (**20α**) in 0.5 ml of pyridine at 0° was treated with 0.02 ml of thionyl chloride as described above. Work-up gave 109 mg of a white solid: λ_{max} 234 mμ (ε 4200, 60% **26α**). Chromatography on neutral alumina with 10% ether in benzene followed by crystallization gave 48 mg (43%) of 17α-Δ⁴-pregnen-3β-ol-6,20-dione acetate (**26α**), mp 198–202°.

Crystallization from isopropyl ether afforded the analytical sample: mp 207–208°; λ_{max} 233 mμ (ε 7000); ($CHCl_3$) 5.76, 5.88, 6.10 μ.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.34; H, 8.74.

Registry Nos.—**7α**, 16649-44-8; **8α**, 16649-22-2; **9α**, 16703-88-1; **9β**, 16649-23-3; **10α**, 16649-24-4; **10β**, 16703-89-2; **11α**, 16649-45-9; **12α**, 16649-25-5; **12β**, 2723-04-8; **13β**, 16649-46-0; **14α**, 16649-27-7; **14β**, 16649-28-8; **15α**, 16649-29-9; **15β**, 16649-30-2; **17β**, 16649-31-3; **18β**, 16649-32-4; **19α**, 16720-14-2; **21α**, 16649-33-5; **21β**, 16703-90-5; **22α**, 16649-47-1; **22β**, 16649-34-6; **23α**, 16649-35-7; **23β**, 16649-36-8; **24α**, 16649-37-9; **24β**, 16703-91-6; **25α**, 16649-38-0; **25β**, 16649-39-1; **26α**, 16649-40-4; **27α**, 16649-41-5; **28α**, 16649-42-6; **29α**, 16649-43-7.

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C-18-Functional Steroids. V.[1a] Synthesis of Androstane Derivatives[1b]

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Methods for the preparation of C-18 functional androstane and androstene derivatives from pregnane compounds are described. C-20-hydroxy steroidal 18-nitriles are dehydrated to give the Δ^17,20^-olefins. Hydroxylation with osmic acid followed by periodate cleavage gives the corresponding 17β-alcohols. Less successful is the Beckmann rearrangement of 20-oximes derived from 18-nitriles which gives rise to 17β-amines. Degradation of these amines gives rise to mixtures of alcohols and olefins.

In continuing our study of C-18-substituted steroids, the preparation of C-18-substituted androstane derivatives was required. Some of these compounds have been obtained by total synthesis,[2,3] by microbiological conversions,[4] from conessine,[5–7] from iodine–lead tetraacetate treatment of C-20 carboxamides followed by removal of C-20,[8] and from C-18-functional pregn-20-ones *via* a Baeyer–Villiger degradation.[9] The present compounds were made by application of the Barton reaction to pregnane derivatives. A few of the substances obtained recently have been prepared from conessine.[10]

The synthetic problem involved was that a side chain is needed for the functionalization step[11] but its removal is necessary to obtain the final product. Since a method applicable to 3-keto-Δ⁴ analogs was sought, the use of ozonolysis, etc., for side-chain oxidation was contraindicated. A mild method, involving elimination, osmylation, and periodate cleavage was therefore employed. Although the 3-keto-Δ⁴ system is capable of reacting with OsO_4,[12] the side chain was attacked selectively under the conditions we employed.

Treatment of 20α-hydroxy-5α-pregnane with nitrosyl chloride in pyridine solution gave the corresponding nitrite ester which on photolysis furnished the 18-oxime **1**.[10a] Dehydration with acetic anhydride afforded the nitrile **2**[10a] (Scheme I). Saponification of the ester followed by treatment with *p*-toluenesulfonyl chloride produced the tosylate **4**. Elimination formed the *trans*-olefin **5**, the stereochemistry of which was assigned on the basis of the nmr spectrum as in our previous work.[1a] Hydroxylation with OsO_4 furnished one predominant diol, presumably the 20β-hydroxy compound

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