11-Methoxy-7,12-dimethylbenz[*a*]anthracene (22). The same method as above was applied to 100 mg of **14**, substituting 30 min of reflux for the 30 min that the MeMgI was allowed to react with the dione. Column chromatography of the final product mixture yielded a yellow oil, which crystallized from benzene–ethanol to yield 5 mg (5%) of **22**: mp 121–123 °C (lit.[4] mp 123–124 °C); MS *m/e* 286 (M^+).

Acknowledgments. We thank Dr. D. J. Wilbur for determination of the ^1H NMR spectra and for the many helpful discussions regarding their analysis. We are also grateful to Mr. S. S. Huang for his determination of the mass spectra. This research was supported by the National Cancer Institute under Contract No. N01-CO-75380 with Litton Bionetics, Inc.

Registry No.—1, 481-39-0; **2**, 29263-68-1; **3**, 100-42-5; **4**, 68796-70-3; **5**, 68796-69-0; **6**, 68757-78-8; **7**, 66240-10-6; **13**, 65915-33-5; **14**, 65915-34-6; **15**, 63019-69-2; **16**, 34570-63-3; **17**, 68757-79-9; **18**, 68757-80-2; **19**, 62064-43-1; **20**, 62078-52-8; **21**, 62064-35-1; **22**, 62064-50-0.

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(20) The Prep LC/System 500 preparative LC (Waters Associates, Inc., Milford, Mass.) performed the more difficult separation of **6** and **7** (50 mg total product) without prior cleanup of the reaction mixture. The use of toluene to elute the Porasil columns did not represent an optimization of solvent system. With this optimization and prior purification of the crude reaction mixture, separations should succeed on a larger scale.

Hydroxylation of α,β-Unsaturated Nitriles and Esters in Steroid Systems

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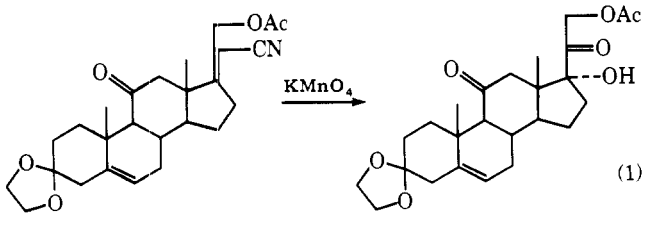
The hydroxylation of α,β-unsaturated nitriles or α,β-unsaturated esters in various steroid systems using stoichiometric amounts of osmium tetroxide furnished α-hydroxy ketones/aldehydes and α,β-dihydroxy esters in moderate yield. The absence of a C-21 acetoxy group in 17(20)-pregnene-20-carbonitriles or 5,17(20)-pregnadiene-20-carbonitriles precluded using potassium permanganate to introduce the 17α-hydroxy 20-ketone synthon. However, the stoichiometric osmium tetroxide oxidation of various 17(20)-pregnene-20-carbonitriles furnished the 17α-hydroxy 20-ketones in moderate yield. α,β-Unsaturated nitriles derived from 3-ketones and 20-ketones were also hydroxylated to give α-hydroxy ketones and aldehydes in moderate yield. No regioselectivity for the $\Delta^{17,20}$-double bond in 5,17(20)-pregnadiene-20-carbonitriles was observed using osmium tetroxide. A catalytic osmium tetroxide–potassium chlorate oxidation of 17(20)-pregnene-20-carbonitriles required zinc nitrate to sequester cyanide ion liberated in the course of the hydroxylation. A brief investigation of osmium tetroxide oxidation of 5,17(20)-pregnadienes bearing withdrawing groups at C-20 other than the nitrile disclosed an interesting hydroxylation of a 17(20)-unsaturated ester in the presence of a nonconjugated Δ^5-double bond.

Sarett[1] employed the hydroxylation of an α,β-unsaturated nitrile using osmium tetroxide in order to introduce the 17α-hydroxy-20-keto synthon found in cortico steroids. Tishler[2] and others[3,4] later modified this procedure by substituting potassium permanganate for osmium tetroxide and recorded regioselective hydroxylation of the $\Delta^{17,20}$-double bond even in the presence of a nonconjugated double bond elsewhere in the steroid as the following example[4] shows (eq 1). In connection with various synthetic interests, we needed to determine: (1) the compatibility of these procedures with other functional groups; (2) the suitability of these procedures for the synthesis of α-hydroxy aldehydes as well as α-hydroxy ketones; and (3) the feasibility of using catalytic procedures to render this reaction economical in the case of osmium tetroxide. In addition, we sought to assess the regioselectivity of attack at the 17(20)-double bond in 5,17(20)-pregnadienes which: (1) lacked a C-21 acetoxy group; and (2) possessed an electron-withdrawing group at C-20 other than a nitrile.



(1)

Results and Discussion

The α,β-unsaturated nitriles **2** and esters **3** used in this study were prepared from various steroidal ketones **1** using the phosphonate Wittig reaction.[5] We have confined our study to the α,β-unsaturated nitriles **2** derived from the condensation of ketones **1** with either diethylphosphonoacetonitrile[6] (**4**) or 2-(diethylphosphono)propionitrile[7] (**5**). As indicated in the Experimental Section, the yields of **2** were moderate to good starting with the sterically hindered C-17 and C-20 ketones. No effort was made to separate the *E*/*Z* isomers. In two cases involving the condensation of **5** with 3β-hydroxy-5α-androstan-17-one tetrahydropyranyl ether or 5-androstene-

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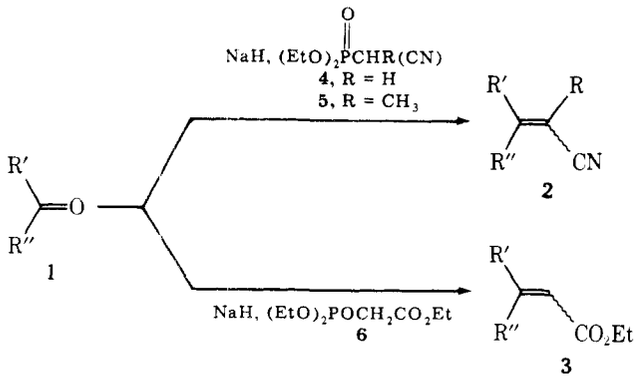


1 2 3

3,17-dione 3-ethylene ketal, the yields were poor for reasons which remain obscure. The α,β-unsaturated esters **3** were prepared from C-17 ketones using ethyl diethylphosphonoacetate (**6**).[8]

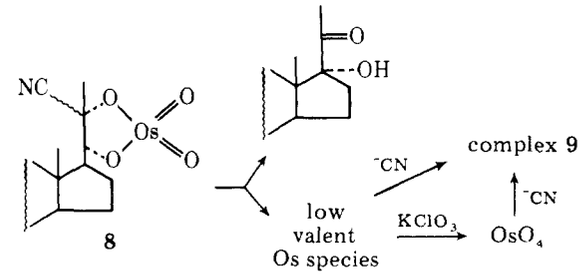
Because of the expense and toxicity of osmium tetroxide, we initially attempted to convert 17(20)-pregnene-20-carbonitriles into 17α-hydroxypregnan-20-ones using potassium permanganate. As shown in Table I, we examined the permanganate oxidation of 3β-*tert*-butoxy-5α-pregn-17(20)-ene-20-carbonitrile (**2c**), 3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraene-20-carbonitrile[9] (**2d**), and 3β-hydroxy-5α-pregn-17(20)-ene-20-carbonitrile acetate (**2i**) under Tishler's carefully defined conditions,[2] but we isolated the corresponding α-hydroxy ketones **7c**, **7d**, and **7i** in only 5, 3, and 7% yields, respectively. The isolation of substantial amounts of unreacted starting material (89, 94, and 87%, respectively) excluded the possibility that the low yield of the 17α-hydroxy 20-ketones was the result of some undesired side reaction consuming the product. These disappointing results then led us to survey a variety of permanganate oxidation procedures. Using **2d**, for example, we were unable to prepare the 17α-hydroxy 20-ketone **7d** in acceptable yield despite extensive variations in experimental conditions. In our best attempt, a combination of potassium permanganate and dicyclohexyl-18-crown-6 in benzene furnished the 17α-hydroxy 20-ketone **7d** in only 16% yield.

These results were somewhat puzzling particularly in view of the regioselective permanganate oxidation shown in eq 1, which afforded the desired product in high yield.[4] To gain a better understanding of this problem, we examined the oxidation of various 5,17(20)-pregnadiene-20-carbonitriles. A compilation of our results and those of others is shown in Table I. It is immediately apparent that the 21-acetoxy group and possibly the C-11 carbonyl group exert a dramatic effect on the regioselective hydroxylation of these systems. In addition, it appears that even in the presence of the C-21 acetoxy group, this regioselectivity is lost unless the enone functionality in the A ring is protected in some fashion.

Exposure of various α,β-unsaturated nitriles **2** to stoichiometric amounts of osmium tetroxide in pyridine followed by sodium bisulfite provided the α-hydroxy ketones and aldehydes **7** shown in Table I. In general, this procedure was compatible with ethers, aromatic rings, and *i*-cyclopropyl ethers, but, as expected, would not accommodate the presence of other carbon–carbon double bonds which are electron-rich relative to the α,β-unsaturated nitrile. For example, the osmylation of **2h**[9] furnished the α-ketol **7h** in only 10% yield and the product of attack on the Δ^5-double bond, 3β-*tert*-butoxy-5α,6α-dihydroxypregn-17(20)-ene-20-carbonitrile, in 22% yield.

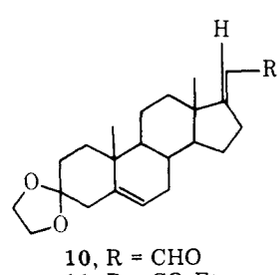
In an effort to render this hydroxylation procedure economical, we examined the catalytic osmium tetroxide oxidations of 17(20)-pregnene-20-carbonitriles. Heer and Miescher[3] noted without comment that such oxidations proved unsuccessful. Initially, our experience was similar in that the oxidation of **2d** (structure in Table I) using 0.3, 0.2, and 0.1 equiv of osmium tetroxide in combination with potassium chlorate[10] furnished the α-hydroxy ketone **7d** in 60, 43, and 7% yield, respectively, as shown in Table II. The use of hydrogen peroxide,[11] *tert*-butyl hydroperoxide,[12] *N*-methylmorpholine oxide,[13] or *N*-methylmorpholine oxide–hydrogen peroxide[14] proved even less effective than potassium chlorate in this connection.

We also found that the addition of 1 equiv of potassium cyanide to an osmium tetroxide catalyzed experiment completely forestalled the reaction (entry 2 vs. entry 1 in Table II). This suggested that the low yield in those experiments using only 0.1 equiv of osmium tetroxide resulted from the fragmentation of the osmate ester **8** and subsequent trapping of regenerated osmium tetroxide or some lower valent osmium species by cyanide ion[15] to give an insoluble, unreactive complex **9**. To circumvent this difficulty, we have explored the

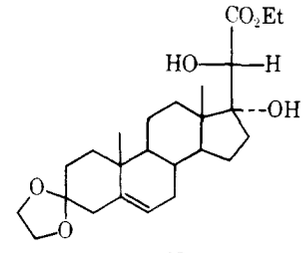


addition of various transition metal ions which would compete effectively with osmium tetroxide for any cyanide ions. Using a table of solubility products as a guide, we explored the use of silver, zinc, and mercury salts and have recorded a moderate degree of success in this regard as shown in Table II.

The addition of zinc nitrate (20 equiv) to an aqueous *tert*-butyl alcohol solution of osmium tetroxide (0.1 equiv) and potassium chlorate (2.5 equiv) provided a reasonably economical alternative to the use of stoichiometric amounts of



10, R = CHO
11, R = CO_2Et



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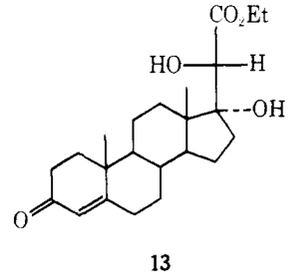

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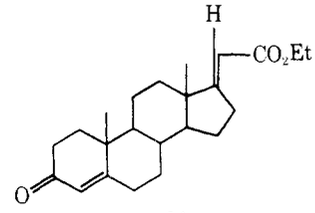

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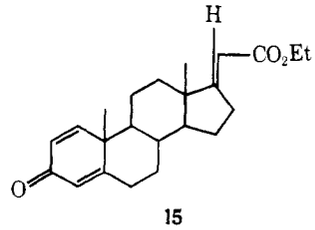

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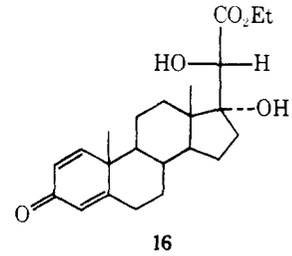

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Table I. A Survey of the Effect of Various Substituents on the Hydroxylation of 17(20)-Pregnene-20-carbonitriles and 5,17(20)-Pregnadiene-20-carbonitriles

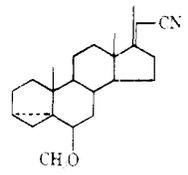
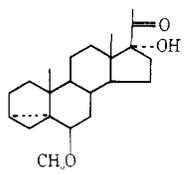
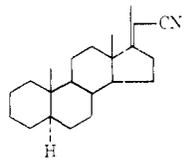
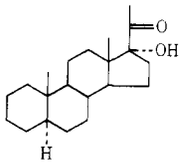
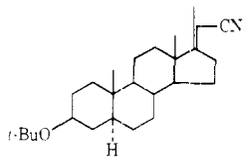
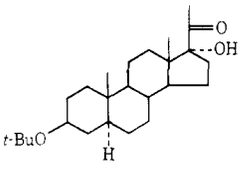
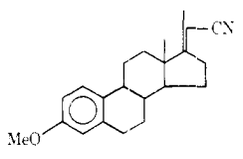
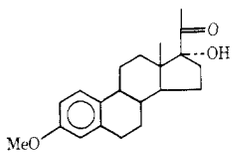
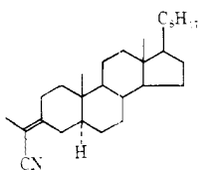
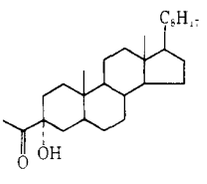
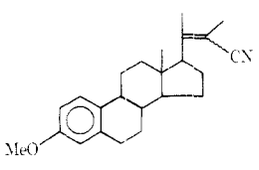
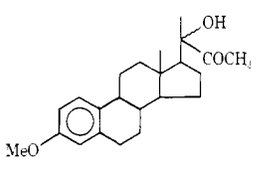
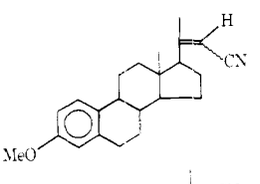
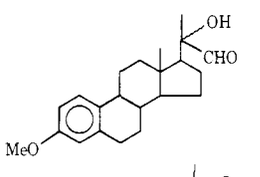
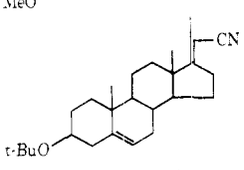
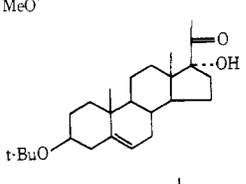
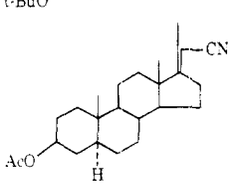
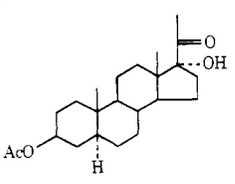
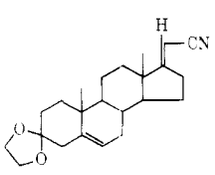
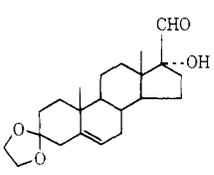
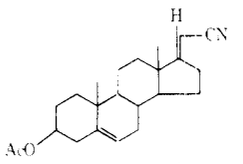
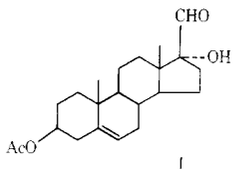
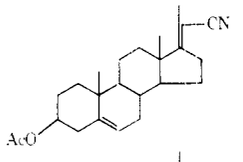
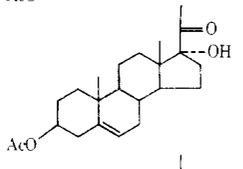
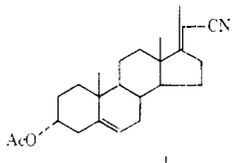
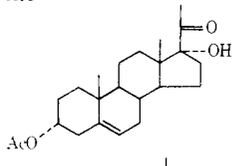
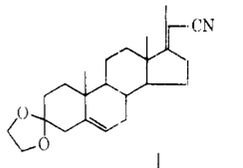
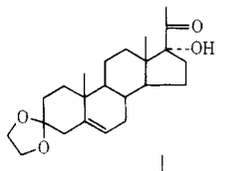
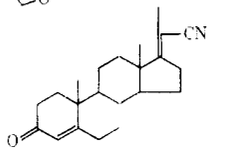
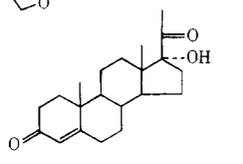
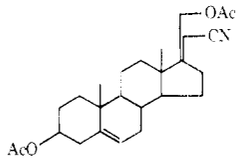
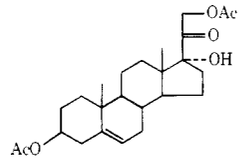
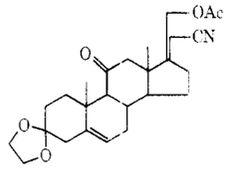
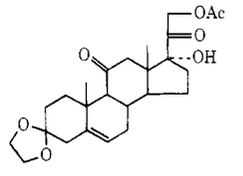
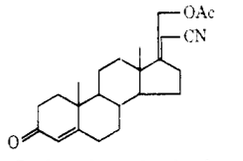
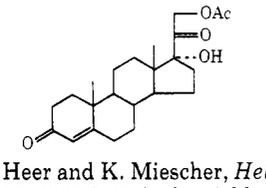
	α,β-unsaturated nitrile **2**	α-hydroxy ketone **7**	oxidant: $KMnO_4$, % yield	oxidant: OsO_4 (stoichiometric), % yield
a				54
b				43
c			5	67
d			3	69
e				34[e]
f				69
g				66
h				10
i			7	52
j				0

Table I (*continued*)

α,β-unsaturated nitrile **2**	α-hydroxy ketone **7**	oxidant: $KMnO_4$, % yield	oxidant: OsO_4 (stoichiometric), % yield
k 			19
l 		1	19
m 		10[d]	
n 		2[a]	26[a]
o 		8	2
p 		45–50[b]	
q 		79–89[c]	
r 		6[b]	

[a] Isolated as 17α-hydroxyprogesterone. [b] J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951). [c] G. I. Poos, R. M. Lukes, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **76**, 5031 (1954); the yield of *d* product was 79% and *dl* product was 89%. [d] R. Tull, R. E. Jones, S. A. Robinson, and M. Tishler, *ibid.*, **77**, 196 (1955). [e] This product was accompanied by another product of uncertain structure.

osmium tetroxide. Four cases contrasting the catalytic and stoichiometric osmium tetroxide oxidations of 17(20)-pregnene-20-carbonitriles are shown in Table III. The catalytic procedure provides the α-hydroxy ketones in comparable yield and if recovered starting material is taken into account in superior yield to the stoichiometric oxidations where only trace amounts of starting material could be recovered. It is interesting that the conditions for the catalytic osmium tetroxide oxidation were sufficiently mild to accommodate the 3β-acetoxy group in **2i** and the *i*-cyclopropyl ether in **2a**.

We did not expect that the substitution of other electron-withdrawing groups for the nitrile group in 5,17(20)-pregnadiene-20-carbonitriles would have any effect on regioselectivity. Like the nitrile **2j** (structure in Table I), the reaction of the aldehyde **10** with osmium tetroxide led to a complex mixture of products. The hydroxylation of the ester **11**, however, provided the 17α,20β-dihydroxy ester[8] **12** in 60% yield, which was further characterized as the enone **13**. The enone ester **14** derived from **11** and the dienone ester **15** again exhibited no regioselectivity in their reactions with osmium tetroxide to give **13** and **16**, respectively.

In summary, the absence of a C-21 acetoxy group in 17(20)-pregnene-20-carbonitriles or 5,17(20)-pregnadiene-20-carbonitriles precluded using potassium permanganate to introduce the 17α-hydroxy 20-ketone synthon. However, the stoichiometric osmium tetroxide oxidation of various

Table II. Catalytic Osmylations of α,β-Unsaturated Nitrile 2d Using Osmium Tetroxide and Potassium Chlorate

OsO_4, equiv	$KClO_3$, equiv	added salt, (equiv)	conditions, h, °C	% isolated yields 7d	2d
0.3	1.34	none	120, 65	60	8
0.3	1.34	KCN (1)	120, 65	0	
0.2	1.34	none	120, 60	43	20
0.1	*1.34*	*none*	*100, 50*	7	*68*
0.1	1.33	$Ag(NO_3)$ (10)	140, 65	49	30
0.1	1.34	$HgCl_2$ (10)	140, 65	50	11
0.1	1.33	$ZnCl_2$ (10)	140, 65	42	43
0.1	1.33	$Zn(OAc)_2$ (10)	140, 65	26	51
0.1	1.33	$Zn(NO_3)_2$ (10)	140, 65	47	49
0.1	2.50	$Zn(NO_3)_2$ (20)	140, 65	52	33

Table III. Contrast between the Catalytic and Stoichiometric Osmium Tetroxide Oxidations of Selected 17(20)-Pregnene-20-carbonitriles

α,β-unsaturated nitrile 2	product 7	% yield of α-hydroxy ketone: OsO_4 (stoichiometric)	OsO_4 (catalytic)	OsO_4 (catalytic) (corrected)[a]
2a	7a	54	50	65
2c	7c	67	52	81
2d	7d	69	52	78
2i	7i	52	61	74

[a] Yield corrected for recovered starting material.

17(20)-pregnene-20-carbonitriles furnished the 17α-hydroxy 20-ketones in moderate yield. α,β-Unsaturated nitriles derived from 3-ketones and 20-ketones were also hydroxylated to give α-hydroxy ketones and aldehydes in moderate yield. No regioselectivity for the $\Delta^{17,20}$-double bond in 5,17(20)-pregnadiene-20-carbonitriles was observed using osmium tetroxide. A catalytic osmium tetroxide–potassium chlorate oxidation of 17(20)-pregnene-20-carbonitriles required zinc nitrate to sequester cyanide ion liberated in the course of the hydroxylation. A brief investigation of osmium tetroxide oxidation of 5,17(20)-pregnadienes bearing withdrawing groups at C-20 other than the nitrile disclosed an interesting hydroxylation of a 17(20)-unsaturated ester in the presence of a nonconjugated Δ^5-double bond.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer infracord spectrophotometer. The abbreviation TF denotes thin film. NMR spectra were determined on a Varian EM390 spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. Osmium tetroxide was purchased in 250-mg ampules from Alfa Inorganics or Stevens Metallurgical Corporation. Anhydrous pyridine was prepared by distillation from calcium hydride. Diethylphosphonoacetonitrile was purchased from Aldrich and distilled prior to use. The following steroids were obtained from G. D. Searle: 3β-hydroxy-5-androsten-17-one, 4-androstene-3,17-dione, 1,4-androstadien-3,17-one, 3β-hydroxy-5α-androstan-17-one, 17α-hydroxyprogesterone, 17α-hydroxypregnenolone, and estrone 3-methyl ether. The remaining 17- or 20-keto steroids used in this study were prepared according to literature procedures and, in the case of new compounds, were fully characterized.

3β-*tert*-Butoxy-5α-androstan-17-one (1c). The procedure of Beyerman and Heiszwolf[16] was modified as follows. To 100 mL of isobutylene in a 500-mL Parr bottle at −78 °C was added 10 g of 3β-hydroxy-5α-androstan-17-one (Searle) in 100 mL of dichloromethane at 0 °C. To this white suspension was cautiously added 2 mL of concentrated sulfuric acid. The heterogeneous mixture was shaken on a Parr shaker for 48 h to obtain a homogeneous solution. The excess isobutylene was allowed to evaporate, and the mixture was diluted with 1 L of ether, washed successively with two 200-mL portions of water and 200 mL of a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The crude product was purified by column (5-cm diameter) chromatography on 250 g of Merck silica gel 60 using an ether–hexane progression (0–50% in 10% steps) and finally by recrystallization from 1:9 dichloromethane–ether to furnish 5.1 g (43%) of **1c:** IR (KBr) 5.79 μm (C=O); NMR ($CDCl_3$) δ 0.82 and 0.85 (two s, 6, C-18 and C-19 angular CH_3), 1.13 (s, 9, $C(CH_3)_3$), and 3.15–3.5 (m, 1, CHO-*t*-Bu); mass spectrum (70 eV) *m/e* (rel intensity) 346 (14), 331 (43), 273 (100), 255 (37), and 233 (30).

An analytical sample was prepared by three recrystallizations from dichloromethane, mp 182–184.5 °C. Anal. ($C_{23}H_{38}O_2$) C, H.

6β-Methoxy-3α,5α-cyclopregn-17(20)-ene-20-carbonitrile (2a). To 4.18 g (99.3 mmol, 5.0 equiv) of 57% sodium hydride (washed with anhydrous hexane to remove mineral oil) in 150 mL of anhydrous THF under a nitrogen atmosphere was added 18.96 g (99.3 mmol, 5.0 equiv) of 2-(diethylphosphono)propionitrile[7] (**5**) in 50 mL of anhydrous THF. The addition was accompanied by vigorous gas evolution and formation of a white precipitate of the sodium salt of **5**. The mixture was refluxed for 1.5 h. To the mixture was added 6.0 g (19.9 mmol) of 6β-methoxy-3α,5α-cycloandrostan-17-one[17] in 75 mL of anhydrous THF. The mixture was refluxed for 6 days, during which time the sodium salt of **5** gradually dissolved. The brown solution was cooled, diluted with 300 mL of ether, washed successively with two 300-mL portions of cold water and 200 mL of brine, and dried over anhydrous magnesium sulfate. The crude product (11.3 g) was purified by column (5-cm diameter) chromatography on 360 g of Merck silica gel 60 using ether–hexane solvent progression (0–45% in 15% steps) to afford 4.2 g (63%) of **2a** as a viscous oil which could not be induced to crystallize: IR (TF) 4.51 (C≡N) and 6.10 μm (C=C); NMR ($CDCl_3$) δ 0.93 and 1.00 (two s, 6, C-18 and C-19 angular CH_3), 1.78 (s, 3, C-21 vinyl CH_3), and 3.30 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 339 (22), 324 (31), 308 (100), 284 (78), and 213 (41).

An analytical sample was prepared by chromatography of 450 mg of **2a** on a preparative silica gel plate in 1:1 ether–hexane and removing the center of the band. Anal. ($C_{23}H_{33}NO$) C, H.

5α-Pregn-17(20)-ene-20-carbonitrile (2b). The procedure described for the preparation of **2a** was repeated using 1.75 g (72.9 mmol, 5.0 equiv) of sodium hydride, 13.9 g (72.9 mmol, 5.0 equiv) of 2-(diethylphosphono)propionitrile[7] (**5**), and 4.0 g (14.6 mmol) of 5α-androstan-17-one[18] in 175 mL of THF (reflux, 7 days) to afford, after column (5-cm diameter) chromatography on 250 g of Merck silica gel 60 using 1:5 ether–hexane, 2.2 g (49%) of **2b:** IR (KBr) 4.55 (C≡N) and 6.12 μm (C=C); NMR ($CDCl_3$) δ 0.78 and 0.87 (two s, 6, C-18 and C-19 angular CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 311 (50), 217 (17), 135 (12), 121 (13), and 105 (100).

An analytical sample was prepared by three recrystallizations from ether, mp 134.5–135 °C. Anal. ($C_{22}H_{33}N$) C, H.

3β-*tert*-Butoxy-5α-pregn-17(20)-ene-20-carbonitrile (2c). The procedure described for the preparation of **2a** was repeated using 1.27 g (52.8 mmol, 5.0 equiv) of sodium hydride, 10.1 g (52.8 mmol, 5.0 equiv) of 2-(diethylphosphono)propionitrile[7] (**5**), and 3.7 g (10.7 mmol) of 3β-*tert*-butoxy-5α-androstan-17-one (**1c**) in 170 mL of 3% HMPA–THF (reflux, 5 days) to afford, after column (5-cm diameter) chromatography on 300 g of Merck silica gel 60 using an ether–hexane progression (0–12% in 4% steps) and finally after recrystallization from ether, 2.4 g (59%) of **2c:** IR (KBr) 4.52 (C≡N) and 6.12 μm (C=C); NMR ($CDCl_3$) δ 0.80 and 0.83 (two s, 6, C-18 and C-19 angular CH_3) and 1.17 (s, 9, $C(CH_3)_3$); mass spectrum (70 eV) *m/e* (rel intensity) 383 (6), 346 (14), 331 (41), 273 (100), 255 (42), and 233 (37).

An analytical sample was prepared by three recrystallizations from ether, mp 170.5–172.5 °C. Anal. ($C_{26}H_{41}NO$) C, H.

3-Methoxy-19-norpregna-1,3,5(10),17(20)-tetraene-20-carbonitrile (2d). The procedure of Watt et al.[9] was repeated.

3-(1′-Cyanoethylidene)-5α-cholestane (2e). The procedure described in the preparation of **2a** was repeated using 1.56 g (65 mmol, 5.0 equiv) of sodium hydride, 12.4 g (65 mmol, 5.0 equiv) of 2-(diethylphosphono)propionitrile[7] (**5**), and 5.0 g (13.0 mmol) of 5α-cholestan-3-one (Sigma) in 225 mL of THF (reflux, 3 days) to afford, after recrystallization from hexane, 3.8 g (69%, first crop) of **2e:** IR (KBr) 4.53 (C≡N) and 6.13 μm (C=C); NMR ($CDCl_3$) δ 0.66 and 0.82 (two s, 6, C-18 and C-19 angular CH_3) and 1.86 (br s, 3, vinyl CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 423 (100), 409 (62), 310 (22), 287 (28), 270 (46), and 268 (86).

An analytical sample was prepared by three recrystallizations from hexane, mp 120–122 °C. Anal. ($C_{30}H_{49}N$) C, H.

20,21-Dimethyl-3-methoxy-19-norpregna-1,3,5(10),20-tetra-

ene-21-carbonitrile (2f). The procedure described in the preparation of **2a** was repeated using 1.53 g (64.1 mmol, 5.0 equiv) of sodium hydride, 12.2 g (64.1 mmol, 5.0 equiv) of 2-(diethylphosphono)propionitrile[7] (5), and 4.0 g (12.8 mmol) of 3-methoxy-19-norpregna-1,3,5(10)-trien-20-one[19] in 330 mL of 3% HMPA–THF (reflux, 4 days) to afford, after a combination of column and preparative layer chromatography on silica gel in dichloromethane, 1.26 g (28%) of **2f:** R_f 0.50; IR (KBr) 4.55 (C≡N) and 6.21 μm (C=C); NMR ($CDCl_3$) δ 0.70 (s, 3, C-18 angular CH_3), 1.80 and 1.93 (two br s, 6, C-20 and C-21 vinyl CH_3), 3.76 (s, 3, OCH_3), and 6.9–7.2 (m, 3, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 349 (27), 227 (82), 202 (23), 158 (21), 145 (24), and 104 (60).

An analytical sample was prepared by four recrystallizations from hexane–ethyl acetate, mp 170–173 °C. Anal. ($C_{24}H_{31}NO$) C, H.

3-Methoxy-20-methyl-19-norpregna-1,3,5(10),20-tetraene-21-carbonitrile (2g). To 60 mg (2.5 mmol, 2.5 equiv) of sodium hydride in 1 mL of anhydrous THF under a nitrogen atmosphere was added 443 mg (2.5 mmol, 2.5 equiv) of diethylphosphonoacetonitrile (4) (Aldrich) in 2 mL of THF dropwise. The solution was refluxed for 1 h, at which time hydrogen gas evolution had ceased. To this solution was added 312 mg (1.0 mmol) of 3-methoxy-19-norpregna-1,3,5(10)-trien-20-one[19] in 2 mL of THF. The solution was refluxed for 16 h, cooled, diluted with 50 mL of ethyl acetate, washed successively with three 25-mL portions of water and 25 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvents afforded 452 mg of crude product which was chromatographed on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in dichloromethane to furnish 258 mg (77%) of **2g:** R_f 0.38; IR (KBr) 4.52 (C≡N) and 6.21 μm (C=C); NMR ($CDCl_3$) δ 0.57 (s, 3, C-18 angular CH_3), 2.08 (s, 3, C-20 vinyl CH_3), 3.72 (s, 3, OCH_3), and 5.12 (s, 1, C-21 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 335 (100), 227 (100), 175 (26), 174 (30), and 147 (26).

An analytical sample was prepared by recrystallization from ether, mp 166–167 °C. Anal. ($C_{23}H_{29}NO$) C, H.

3β-*tert*-Butoxy-5,17(20)-pregnadiene-20-carbonitrile (2h). The procedure of Watt et al.[9] was repeated.

3β-Hydroxy-5α-pregn-17(20)-ene-20-carbonitrile Acetate (2i). The procedure of Ott, Murray, and Pederson[20] was repeated using 20.0 g of 3β-hydroxy-5α-androstan-17-one (Searle), 29 g of dihydropyran, and 10 drops of concentrated hydrochloric acid to afford, after recrystallization from ether–dichloromethane, 22.3 g (86%) of 3β-hydroxy-5α-androstan-17-one tetrahydropyranyl ether: IR (KBr) 5.78 μm (C=O); NMR ($CDCl_3$) δ 0.85 (s, 6, coincident C-18 and C-19 angular CH_3), 3.4–4.2 (m, 3, $CH_2OCHOCH$), and 4.77 (m, 1, $CH_2OCHOCH$); mass spectrum (70 eV) *m/e* (rel intensity) 374 (3), 312 (11), 283 (18), 273 (24), 255 (22), 122 (10), and 84 (100).

An analytical sample was prepared by recrystallization from ether–dichloromethane, mp 186–191 °C. Anal. ($C_{24}H_{38}O_3$) C, H.

The procedure described in the preparation of **2a** was repeated using 120 mg (5.0 mmol, 2.5 equiv) of sodium hydride, 955 mg (5.0 mmol, 2.5 equiv) of 2-(diethylphosphono)propionitrile[7] (5), and 744 mg (2.0 mmol) of 3β-hydroxy-5α-androstan-17-one tetrahydropyranyl ether in 14 mL of 5% HMPA–THF (reflux, 5 days) to afford, after chromatography on three 20 × 20 cm preparative layer (2 mm thick) Merck silica gel F254 plates in 1:1 ether–hexane, 214 mg (26%) of 3β-hydroxy-5α-pregn-17(20)-ene-20-carbonitrile tetrahydropyranyl ether: R_f 0.65; IR (KBr) 4.53 (C≡N) and 6.11 μm (C=C); NMR ($CDCl_3$) δ 0.80 and 0.88 (two s, 6, C-18 and C-19 angular CH_3), 1.80 (br s, 3, C-21 vinyl CH_3), 3.35–4.1 (m, 3, $CH_2OCHOCH$), and 4.70 (m, 1, $CH_2OCHOCH$); mass spectrum (70 eV) *m/e* (rel intensity) 411 (8), 323 (25), 310 (100), and 229 (33).

An analytical sample was prepared by four recrystallizations from hexane: mp 143–145 °C. Anal. ($C_{27}H_{41}NO_2$) C, H.

Methanolysis of 3β-hydroxy-5α-pregn-17(20)-ene-20-carbonitrile tetrahydropyranyl ether (methanol, *p*-toluenesulfonic acid monohydrate, reflux 24 h) and acetylation (acetic anhydride, pyridine, 25 °C, 24 h) afforded, after recrystallization from ether, **2i:** IR (KBr) 4.53 (C≡N), 5.76 (C=O), and 6.10 μm (C=C); NMR ($CDCl_3$) δ 0.83 and 0.90 (two s, 6, C-18 and C-19 angular CH_3), 1.82 (br s, 3, C-21 vinyl CH_3), 2.00 (s, 3, $OCOCH_3$), and 4.69 (m, 1, CHOAc); mass spectrum (70 eV) *m/e* (rel intensity) 369 (58), 309 (100), 295 (23), and 215 (59).

An analytical sample was prepared by two recrystallizations from ether, mp 190–191.5 °C. Anal. ($C_{24}H_{35}NO_2$) C, H.

3-Oxopregna-5,17(20)-diene-21-nitrile Ethylene Ketal (2j). The procedure described for the preparation of **2g** was repeated using 60 mg (2.5 mmol, 2.5 equiv) of sodium hydride, 443 mg (2.5 mmol, 2.5 equiv) of diethylphosphonoacetonitrile (4) (Aldrich), and 330 mg (1.0 mmol) of 5-androstene-3,17-dione 3-ethylene ketal[21] in 7 mL of 7% HMPA–THF (reflux, 33 h) to afford, after chromatography on two 20 × 20 cm preparative layer (2 mm thick) Merck silica gel F254 plates in 1:9 ethyl acetate–dichloromethane, 237 mg (67%) of **2j:** R_f 0.63; IR (KBr) 4.51 (C≡N) and 6.11 μm (C=C); NMR ($CDCl_3$) δ 0.83 and 1.04 (two s, 6, C-18 and C-19 angular CH_3), 3.95 (s, 4, OCH_2CH_2O), 5.00 (m, 1, C-20 vinyl H), and 5.32 (m, 1, C-6 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 353 (16), 178 (6), 133 (7), 119 (7), and 99 (100).

An analytical sample was prepared by four recrystallizations from ethanol, mp 177.5–181.5 °C. Anal. ($C_{23}H_{31}NO_2$) C, H.

3β-Hydroxypregna-5,17(20)-diene-21-nitrile Acetate (2k). The procedure described for the preparation of **2g** was repeated using 1.62 g (67.5 mmol, 2.5 equiv) of sodium hydride, 11.95 g (67.5 mmol, 2.5 equiv) of diethylphosphonoacetonitrile (4) (Aldrich), and 10.0 g (27.0 mmol) of 3β-hydroxy-5-androsten-17-one tetrahydropyranyl ether[20] in 400 mL of THF (reflux, 5 days) to afford, after column (5-cm diameter) chromatography on 400 g of Merck silica gel 60 using 1:1 ether–hexane, 7.8 g (74%) of 3β-hydroxypregna-5,17(20)-diene-21-nitrile tetrahydropyranyl ether as a mixture of diastereomers: IR (KBr) 4.52 (C≡N) and 6.1i μm (C=C); NMR ($CDCl_3$) δ 4.75 (m, 1, $CH_2OCHOCH$), 5.05 (m, 1, C-20 vinyl H), and 5.39 (m, 1, C-6 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 293 (89), 278 (42), 226 (18) and 84 (100).

Analytical sample was prepared by two recrystallizations from dichloromethane–ether, mp 185–199 °C. Anal. ($C_{27}H_{39}NO_2$) C, H.

3β-Hydroxypregna-5,17(20)-diene-21-nitrile tetrahydropyranyl ether (7.6 g) was subjected to methanolysis (50 mL of methanol, 100 mg of *p*-toluenesulfonic acid monohydrate, reflux, 29 h) and acetylation (10 mL of acetic anhydride, 50 mL of pyridine, 25 °C, 28 h) to afford, after recrystallization from ether–dichloromethane, 3.57 g (53%) of **2k:** IR (KBr) 4.52 (C≡N), 5.78 (C=O), and 6.11 μm (C=C); NMR ($CDCl_3$) δ 0.87 and 1.03 (two s, 6, C-18 and C-19 angular CH_3), 2.02 (s, 3, $OCOCH_3$), 4.58 (m, 1, CHOAc), 5.00 (m, 1, C-20 vinyl H) and 5.39 (m, 1, C-6 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 294 (100, $M^+ - OAc$), 278 (23), 145 (18), 121 (25), and 107 (21).

An analytical sample was prepared by two additional recrystallizations from dichloromethane–ether, mp 232–234.5 °C. Anal. ($C_{23}H_{31}NO_2$) C, H.

3β-Hydroxypregna-5,17(20)-diene-20-carbonitrile Acetate (2l). 3β-Hydroxypregna-5,17(20)-diene-20-carbonitrile tetrahydropyranyl ether[7] (7.0 g) was subjected to methanolysis (200 mL of methanol, 250 mg of *p*-toluenesulfonic acid monohydrate, reflux, 16 h) and acetylation (15 mL of acetic anhydride, 75 mL of pyridine, 5 °C, 24 h) to afford after recrystallization from ether–dichloromethane, 2.9 g (46%) of **2l:** IR (KBr) 4.52 (C≡N), 5.75 (C=O), and 6.09 μm (C=C); NMR ($CDCl_3$) δ 0.93 and 1.03 (two s, 6, C-18 and C-19 angular CH_3), 1.80 (m, 3, C-21 vinyl CH_3), 2.00 (s, 3, $OCOCH_3$), 4.60 (m, 1, CHOAc), and 5.36 (m, 1, C-6 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 308 (100, $M^+ - OAc$), 293 (29), 213 (20), 159 (12), 145 (25), 121 (11), and 105 (18).

An analytical sample was prepared by two recrystallizations from ether–dichloromethane, mp 209–214.5 °C. Anal. ($C_{24}H_{33}NO_2$) C, H.

3-Oxopregna-5,17(20)-diene-20-carbonitrile Ethylene Ketal (2n). The procedure described in the preparation of **2a** was repeated using 120 mg (5.0 mmol, 2.5 equiv) of sodium hydride, 955 mg (5.0 mmol, 2.5 equiv) of 2-(diethylphosphono)propionitrile[7] (5), and 660 mg of 5-androstene-3,17-dione 3-ethylene ketal[21] in 14 mL of 5% HMPA–THF (reflux, 3 days) to afford, after chromatography on three 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:9 ethyl acetate–dichloromethane (R_f 0.77) followed by a second chromatography on two plates in dichloromethane (R_f 0.26), 150 mg (20%) of **2n:** IR (KBr) 4.54 (C≡N) and 6.11 μm (C=C); NMR ($CDCl_3$) δ 0.93 and 1.03 (two s, 6, C-18 and C-19 angular CH_3), 1.82 (br s, 3, C-21 vinyl CH_3), 3.94 (s, 4, OCH_2CH_2O), and 5.35 (m, 1 C-6 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 367 (4), 146 (1), and 99 (100).

An analytical sample was prepared by two recrystallizations from absolute ethanol, mp 222.5–226 °C. Anal. ($C_{24}H_{33}NO_2$) C, H.

3-Oxopregna-4,17(20)-diene-20-carbonitrile (2o). 3β-Hydroxypregna-5,17(20)-diene-20-carbonitrile tetrahydropyranyl ether[7] (3.4 g) was subjected to methanolysis (75 mL of methanol, ~100 mg of *p*-toluenesulfonic acid monohydrate, reflux, 18 h) and oxidation (2.55 g of aluminum triisopropoxide, 20 mL of 4-methyl-1-piperidone, 100 mL of toluene, reflux, 12 h) to afford, after chromatography on six 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:3 ethyl acetate–dichloromethane, 1.5 g (56%) of **2o:** R_f 0.6; IR (KBr) 4.53 (C≡N), 5.94 (C=O), 6.09 (C=C), and 6.18 μm (C=C); NMR ($CDCl_3$) δ 0.97 and 1.20 (two s, 6, C-18 and C-19 angular CH_3), 1.82 (br s, 3, C-21 vinyl CH_3), and 5.72 (m, 1, C-4 vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 323 (77), 229 (100), 211 (10), and 124 (13).

An analytical sample was prepared by two recrystallizations from ether–dichloromethane, mp 203–204.5 °C. Anal. ($C_{22}H_{29}NO$) C, H.

The following is a typical experimental procedure for the preparation of α-hydroxy aldehydes and α-hydroxy ketones **7** using osmium tetroxide. All experiments were performed on a 1-mmol scale and the products were purified by preparative layer chromatography (2-mm thick) on Merck silica gel F254. The elution solvent and R_f values are recorded with the summary of spectral data found below.

6β-Methoxy-17α-hydroxy-3α,5α-cyclopregnan-20-one (7a). To 339 mg (1.0 mmol) of 6β-methoxy-3α,5α-cyclopregn-17(20)-ene-20-carbonitrile (**2a**) in 2.5 mL of anhydrous pyridine was added 250 mg of osmium tetroxide in 3 mL of pyridine. The mixture was stirred at 25 °C for 3 days and quenched by stirring with 0.75 g of sodium bisulfite in 7 mL of water for 18 h. The solution was extracted with three 25-mL portions of dichloromethane. The combined organic solutions were washed successively with two 25-mL portions of 2 M hydrochloric acid, two 25-mL portions of water, and 25 mL of brine, and dried over anhydrous magnesium sulfate. The crude product was chromatographed on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:9 ethyl acetate–dichloromethane to afford 185 mg (54%) of **7a**: R_f 0.52; IR (KBr) 2.97 (OH) and 5.89 μm (C=O); NMR ($CDCl_3$) δ 0.76 and 1.02 (two s, 6, C-18 and C-19 angular CH_3), 2.27 (s, 3, $COCH_3$), 3.33 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 346 (74), 321 (100), 314 (32), 271 (84), 227 (49), and 213 (72).

An analytical sample was prepared by three recrystallizations from dichloromethane, mp 210–213 °C. Anal. ($C_{22}H_{34}O_3$) C, H.

Spectral Data for α-Hydroxy Aldehydes and α-Hydroxy Ketones: 17α-Hydroxy-5α-pregnan-20-one (7b): R_f 0.52 in 1:9 ethyl acetate–dichloromethane; mp 170–171 °C; IR (KBr) 2.97 (OH) and 5.91 μm (C=O); NMR ($CDCl_3$) δ 0.68 and 0.78 (two s, C-18 and C-19 angular CH_3), 2.27 (s, 3, $COCH_3$), and 2.73 (s, 1, OH, exchanges with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 318 (100), 275 (45), 257 (91), 230 (19), and 217 (37).

3β-*tert*-Butoxy-17α-hydroxy-5α-pregnan-20-one (7c): R_f 0.40 in 1:9 ethyl acetate–dichloromethane; IR (KBr) 2.94 (OH) and 5.87 μm (C=O); NMR ($CDCl_3$) δ 0.70 and 0.80 (two s, 6, C-18 and C-19 angular CH_3), 1.17 (s, 9, $C(CH_3)_3$), 2.26 (s, 3, $COCH_3$), and 3.2–3.5 (m, 1, CHO-*t*-Bu); mass spectrum (70 eV) *m/e* (rel intensity) 390 (65), 316 (14), 273 (55), 255 (38), 229 (12), and 135 (21).

An analytical sample was prepared by three recrystallizations from anhydrous ether, mp 203–204 °C. Anal. ($C_{25}H_{42}O_3$) C, H.

17α-Hydroxy-3-methoxy-19-norpregna-1,3,5(10)-trien-20-one (7d): R_f 0.39 in 1:9 ethyl acetate–dichloromethane; IR (KBr) 2.89 (OH) and 5.90 μm (C=O); NMR ($CDCl_3$) δ 0.75 (s, 3, C-18 angular CH_3), 2.29 (s, 3, $COCH_3$), 3.76 (s, 3, OCH_3) and 6.5–7.3 (m, 3, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 328 (100), 285 (62), 267 (20), 227 (78), and 147 (23).

An analytical sample was prepared by three recrystallizations from ether–dichloromethane, mp 155–156 °C. Anal. ($C_{21}H_{28}O_3$) C, H.

3β-Acetyl-3α-hydroxy-5α-cholestane (7e): R_f 0.30 in 1:7 ethyl acetate–dichloromethane; IR (KBr) 2.92 (OH) and 5.89 μm (C=O); NMR ($CDCl_3$) δ 2.21 (s, 3, $COCH_3$) and 2.29 (s, 1, OH); mass spectrum (70 eV) *m/e* (rel intensity) 388 (100) and 370 (7).

An analytical sample was prepared by recrystallization from dichloromethane, mp 175–176 °C. Anal. ($C_{29}H_{50}O_2$) C, H.

20-Acetyl-20-hydroxy-3-methoxy-19-norpregna-1,3,5(10)-triene (7f). The diastereomers at C-20 were separable by chromatography in 1:30 ethyl acetate–dichloromethane.

The major band (R_f 0.83) afforded 198 mg (56%) of the 20*R*-diastereomer:[22] IR (KBr) 2.89 (OH), 5.90 (C=O), and 6.19 μm (aromatic); NMR ($CDCl_3$) δ 0.90 (s, 3, C-18 angular CH_3), 1.43 (s, 3, C-21 CH_3), 2.18 (s, 3, $COCH_3$), 3.72 (s, 3, OCH_3), 3.91 (s, 1, OH, exchanges with D_2O), and 6.5–7.3 (m, 3, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 356 (22), 315 (28), 314 (100), 296 (22), 269 (12), 174 (54), and 147 (56).

An analytical sample was prepared by two recrystallizations from hexane, mp 132–133 °C. Anal. ($C_{23}H_{32}O_3$) C, H.

The minor band (R_f 0.77) afforded 48.0 mg (13%) of the 20*S*-diastereomer:[22] IR (KBr) 2.89 (OH), 5.90 (C=O), and 6.19 μm (aromatic); NMR ($CDCl_3$) δ 0.73 (s, 3, C-18 angular CH_3), 1.32 (s, 3, C-21 CH_3), 2.30 (s, 3, $COCH_3$), 3.75 (s, 3, OCH_3), and 6.55–7.2 (m, 3, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 356 (30), 313 (100), 296 (26), 269 (12), 174 (44), and 147 (50).

An analytical sample was prepared by four recrystallizations from absolute ethanol, mp 168–169 °C. Anal. ($C_{23}H_{32}O_3$) C, H.

20-Hydroxy-3-methoxy-19-norpregna-1,3,5(10)-triene-20-carboxaldehyde (7g). In this case, the crude product of the osmylation reaction consisted largely of the cyanohydrin, 20,21-dihydroxy-3-methoxy-20-methyl-19-norpregna-1,3,5(10)-triene-21-carbonitrile. The propensity of this material to lose hydrogen cyanide precluded complete characterization. To the crude cyanohydrin in 30 mL of THF was added 10 mL of 1 M sodium hydroxide. The homogeneous solution was stirred at 25 °C for 16 h, diluted with 30 mL of ethyl acetate, washed successively with two 25-mL portions of water and 25 mL of brine, and dried over anhydrous magnesium sulfate. Evaporation of solvent afforded 364 mg of crude aldehyde, which was chromatographed on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:10 ethyl acetate–dichloromethane to furnish 226 mg (66%) of **7g**: R_f 0.61; IR (KBr) 2.88 (OH) and 5.81 μm (C=O); NMR ($CDCl_3$) δ 0.73 (s, 3, C-18 angular CH_3), 1.29 (s, 3, C-21 CH_3), 3.10 (br s, 1, OH, exchanges with D_2O), 3.77 (s, 3, OCH_3), 6.6–7.2 (m, 3, aromatic H), and 9.67 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 342 (100), 313 (85), 173 (89), and 147 (89).

An analytical sample was prepared by recrystallization from ether, mp 150.5–152 °C. Anal. ($C_{22}H_{30}O_3$) C, H.

3β-*tert*-Butoxy-17α-hydroxypregn-5-en-20-one (7h): R_f 0.54 in 1:9 ethyl acetate–dichloromethane; IR (KBr) 2.95 (OH) and 5.87 μm (C=O); NMR ($CDCl_3$) δ 0.73 and 1.00 (two s, 6, C-18 and C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$), 2.26 (s, 3, $COCH_3$), and 5.20–5.35 (m, 1, vinyl H); mass spectrum (70 eV) *m/e* (rel intensity) 388 (92), 289 (31), 271 (100), 253 (58), and 213 (35).

An analytical sample was prepared by recrystallization from ether, mp 223–224 °C. Anal. ($C_{25}H_{40}O_3$) C, H.

An additional product was also isolated from this osmylation experiment and was identified as **3β-*tert*-butoxy-5α,6α-dihydroxypregn-17(20)-ene-20-carbonitrile:** R_f 0.13 in 1:9 ethyl acetate–dichloromethane, R_f 0.54 in ether; IR (KBr) 2.90 (OH), 4.53 (C≡N), and 6.10 μm (C=C); NMR ($CDCl_3$) δ 0.89 and 0.95 (two s, 6, C-18 and C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$); mass spectrum (70 eV) *m/e* (rel intensity) 415 (3), 359 (40), 323 (100), 306 (33), 229 (17), and 146 (28).

An analytical sample was prepared by recrystallization from ether, mp 227–228 °C. Anal. ($C_{26}H_{41}NO_3$) C, H.

3β,17α-Dihydroxy-5α-pregnan-20-one 3-acetate (7i): R_f 0.69 in 1:3 ethyl acetate–dichloromethane; IR (KBr) 2.98 (OH), 5.76 (C=O), and 5.91 μm (C=O); NMR ($CDCl_3$) δ 0.67 and 0.82 (two s, 6, C-18 and C-19 angular CH_3), 1.98 and 2.21 (two s, 6, $COCH_3$), 2.97 (m, 1, OH, exchanges with D_2O), and 4.66 (m, 1, CHOAc); mass spectrum (70 eV) *m/e* (rel intensity) 376 (19), 332 (34), 254 (100), 228 (43), 215 (33), and 107 (44).

An analytical sample was prepared by two recrystallizations from ether, mp 189.5–191 °C. Anal. ($C_{23}H_{36}O_4$) C, H.

3β,17α-Dihydroxyandrost-5-ene-17β-carboxaldehyde 3-acetate (7k): R_f 0.07 in 1:3 ethyl acetate–dichloromethane; IR (KBr) 2.90 (OH) and 5.83 μm (C=O); NMR ($CDCl_3$) δ 0.97 (br s, 6, C-18 and C-19 angular CH_3), 2.04 (s, 3, $OCOCH_3$), and 9.87 (s, 1, CHO).

3β,17α-Dihydroxypregn-5-en-20-one 3-Acetate (7l). The procedure described in the preparation of **7a** was repeated using 367 mg (1.0 mmol) of **2l** and 250 mg (1.0 mmol, 1.0 equiv) of osmium tetroxide to afford, after chromatography on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:7 ethyl acetate–dichloromethane, 72 mg (19%) of **7l** (R_f 0.45) which was identical with a sample of **7l** prepared by acetylation of 17α-hydroxypregnenolone (Searle). In addition, we recovered 107 mg (29%) of unreacted **2l** (R_f 0.83) and isolated 175 mg (44%) of material tentatively identified as 3β,5α,6α-trihydroxy-17(20)-pregnene-20-carbonitrile 3-acetate (R_f ~0.2).

17α-Hydroxyprogesterone (7o). A. Hydroxylation of 3-Oxo-4,17(20)-pregnadiene-20-carbonitrile (2o). The procedure described in the preparation of **7a** was repeated using 323 mg (1.0 mmol) of **2o** and 250 mg (1.0 mmol, 1.0 equiv) of osmium tetroxide to afford, after chromatography on two 20 × 20 cm preparative layer (2 mm thick) Merck silica gel F254 plates in 1:3 ethyl acetate–dichloromethane, 6 mg (2%) of 17α-hydroxyprogesterone which was identical with an authentic sample.

B. Hydroxylation of 3-Oxo-5,17(20)-pregnadiene-20-carbonitrile Ethylene Ketal (2n). The above procedure was repeated using **2n** and the crude product was hydrolyzed in aqueous acid to furnish a 26% yield of 17-hydroxyprogesterone, which was identical with an authentic sample.

Catalytic Osmylation of 3-Methoxy-19-norpregna-1,3,5(10),-17(20)-tetraene-20-carbonitrile (2d). To 321 mg (1.0 mmol) of **2d** and 5.95 g (20 mmol) of zinc nitrate hexahydrate dissolved in 25 mL of THF was added 305 mg (2.5 mmol) of potassium chlorate in 10 mL of water followed by 5 mL of 0.02 M (0.1 mmol, 0.1 equiv) osmium tetroxide in *tert*-butyl alcohol.[23] The solution was stirred at 65 °C for 6 days. The mixture was filtered through a pad of Celite 545, and the Celite was washed with two 25-mL portions of dichloromethane. The filtrates were shaken with 50 mL of brine and the organic layer was

separated. The aqueous solution was extracted with three additional 50-mL portions of dichloromethane. The combined organic solutions were washed successively with two 100-mL portions of water and 100 mL of brine and dried over anhydrous magnesium sulfate. The crude product (336 mg) was chromatographed on a 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plate in 1:20 ethyl acetate–dichloromethane to afford 170 mg (52%) of **7d** (R_f 0.26) and 106 mg (33%) of unreacted **2d** (R_f 0.62). The yield of **7d** corrected for the recovered starting material was 78%.

3-Oxopregna-5,17(20)-dien-21-al 3-Ethylene Ketal (10). To 2 mL (5 mmol, 2 equiv) of 2.5 M lithium aluminum hydride in THF under a nitrogen atmosphere at 0 °C was added 2.0 g of **11** in 15 mL of THF. The mixture was stirred for 3 h at 0 °C and the product was isolated in the usual fashion. The 1:1 ratio of the integration of the vinyl region and $-CH_2OH$ in the NMR spectrum of the crude product indicated that no reduction of the 17(20)-double bond had occurred. To the crude allylic alcohol in 50 mL of chloroform at 0 °C was added 16 g of manganese dioxide. The mixture was stirred for 90 min at 0 °C and the product was isolated in the usual way to afford, after chromatography on four 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:9 ethyl acetate–dichloromethane, 915 mg (52%) of **10:** R_f 0.36; IR (KBr) 5.95 (C=O) and 6.11 μm (sh) (C=C); NMR ($CDCl_3$) δ 0.87 and 1.08 (two s, 6, C-18 and C-19 angular CH_3), 3.93 (s, 4, OCH_2CH_2O), 5.39 (m, 1, C-6 vinyl H), 5.78 (m, 1, C-20 vinyl H) and 9.88 (d, J = 8 Hz, 1, CHO); mass spectrum (70 eV) m/e (rel intensity) 356 (11) and 99 (100).

Ethyl (*E*)-3-Oxopregna-5,17(20)-dien-21-oate Ethylene Ketal (11). The procedure of Wicha, Bal, and Piekut[8] was repeated using 2.58 g of 5-androstene-3,17-dione 3-ethylene ketal[18] to afford, after recrystallization from absolute ethanol, 2.55 g (82%) of **11:** mp 172–174 °C; IR (KBr) 5.87 (C=O) and 6.08 μm (C=C); NMR ($CDCl_3$) δ 0.83 and 1.04 (two s, 6, C-18 and C-19 angular CH_3), 1.29 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 3.93 (s, 4, OCH_2CH_2O), 4.13 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 5.36 (m, 1, C-6 vinyl H), and 5.53 (m, 1, C-20 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 418 (11), 417 (39), 390 (12), 389 (45), 213 (12), and 99 (100).

An analytical sample was prepared by two recrystallizations from absolute ethanol, mp 177–178.5 °C. Anal. ($C_{25}H_{36}O_4$) C, H.

Ethyl 17α,20β-Dihydroxy-3-oxopregn-5-en-21-oate Ethylene Ketal (12). The procedure described in the preparation of **7a** was repeated using 400 mg (1.0 mmol) of **11** and 250 mg (1.0 mmol, 1.0 equiv) of osmium tetroxide to afford, after chromatography on two 20 × 20 cm preparative layer (2 mm thick) Merck silica gel F254 plates in 1:1 ethyl acetate–dichloromethane, 259 mg (60%) of **12:** R_f 0.60; IR (KBr) 2.88 (OH) and 5.78 μm (C=O); NMR ($CDCl_3$) δ 0.88 and 1.03 (two s, 6, C-18 and C-19 angular CH_3), 1.30 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 2.36 (s, 1, C-17 OH, exchanges with D_2O), 3.48 (d, J = 5 Hz, C-20 OH, exchanges with D_2O), 3.92 (s, 4, OCH_2CH_2O), 4.23 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 4.30 (d, J = 5 Hz, 1, C-20 H) and 5.31 (m, 1, C-6 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 434 (7), 221 (11), 220 (21), 203 (26), and 99 (100).

An analytical sample was prepared by recrystallization from ethyl acetate–hexane, mp 151.5–153 °C. Anal. ($C_{25}H_{38}O_6$) C, H.

Ethyl 17α,20β-Dihydroxy-3-oxopregn-4-en-21-oate (13). A. Hydrolysis of 12. To 248 mg (0.57 mmol) of **12** dissolved in 3 mL of THF was added 2 mL of glacial acetic acid and 1 mL of 1 M hydrochloric acid. The mixture was stirred at 25 °C for 3 h. The solution was diluted with 50 mL of brine and extracted with three 25-mL portions of dichloromethane. The combined extracts were washed with 50 mL of water, 50 mL of saturated sodium carbonate solution, and 50 mL of brine. The solution was dried over anhydrous magnesium sulfate. The crude product (198 mg) was chromatographed on a 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plate in 1:1 ethyl acetate–dichloromethane to afford 187 mg (85%) of **13:** R_f 0.47; IR (KBr) 2.90 (OH), 5.77 (C=O), 6.00 (C=O), and 6.20 μm (C=C); NMR ($CDCl_3$) δ 0.90 and 1.19 (two s, 6, C-18 and C-19 angular CH_3), 1.30 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 2.50 (s, 1, C-17 OH, exchanges with D_2O), 3.33 (d, J = 5 Hz, 1, C-20 OH, exchanges with D_2O), 4.26 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 4.31 (d, J = 5 Hz, 1, C-20 H), and 5.72 (s, 1, C-4 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 390 (23), 372 (10), 354 (6), 299 (22), 287 (100), 269 (36), and 229 (45).

An analytical sample was prepared by two recrystallizations from absolute ethanol, mp 199–200 °C. Anal. ($C_{23}H_{34}O_5$) C, H.

B. Hydroxylation of 14. The procedure described in the preparation of **7a** was repeated using 356 mg (1.0 mmol) of **14** and 250 mg (1.0 mmol, 1.0 equiv) of osmium tetroxide to afford, after chromatography on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:1 ethyl acetate–dichloromethane, 52 mg (13%) of unreacted **14** (R_f 0.83) and 27 mg (7%) of **13** (R_f 0.44) which was identical to **13** obtained in procedure A described above. In addition, the following two products were isolated and tentatively identified: 193 mg (49%) of ethyl (*E*)-4α,5α-dihydroxy-3-oxopregn-17(20)-en-21-oate (R_f 0.68) and 49 mg (12%) of ethyl 3-oxo-4α,5α,17α,20β-tetrahydroxypregnan-21-oate (R_f 0.28).

Ethyl (*E*)-3-Oxopregna-4,17(20)-dien-21-oate (14). To 800 mg (2.0 mmol) of **11** in 30 mL of THF were added 10 mL of glacial acetic acid and 5 mL of 1 M hydrochloric acid. The mixture was stirred at 25 °C for 3.5 h. The solution was diluted with 50 mL of brine and extracted with three 25-mL portions of dichloromethane. The combined extracts were washed successively with two 50-mL portions of water, 50 mL of saturated sodium carbonate solution, and 50 mL of brine. The solution was dried over anhydrous magnesium sulfate. The crude product (688 mg) was chromatographed on two 20 × 20 cm preparative layer (2-mm thick) Merck silica gel F254 plates in 1:9 ethyl acetate–dichloromethane to afford 479 mg (67%) of **14:** R_f 0.44; IR (KBr) 5.86 (C=O), 5.99 (C=O), 6.08 (sh), and 6.20 μm (C=C); NMR ($CDCl_3$) δ 0.86 and 1.20 (two s, 6, C-18 and C-19 angular CH_3), 1.28 (t, J = 7 Hz, 3, $CO_2CH_2CH_3$), 4.15 (q, J = 7 Hz, 2, $CO_2CH_2CH_3$), 5.52 (m, 1, C-20 vinyl H), and 5.72 (s, 1, C-4 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 356 (100), 283 (71), 159 (36), 108 (27), 106 (29), and 99 (20).

Ethyl (*E*)-3-Oxopregna-1,4,17(20)-trien-21-oate (15). The procedure of Wicha, Bal, and Piekut[8] was repeated using 8.52 g (0.03 mol) of 1,4-androstadiene-3,17-dione (Searle) and 33.6 g (0.15 mol, 5.0 equiv) of ethyl diethylphosphonoacetate (**4**) (Aldrich) to afford, after recrystallization from ether, 7.71 g (73%) of **15:** IR (KBr) 5.87 (C=O), 6.01 (C=O), 6.16 (C=C), and 6.24 μm (C=C); NMR ($CDCl_3$) δ 0.90 and 1.25 (two s, 6, C-18 and C-19 angular CH_3), 1.25 (t, J = 7 Hz, 3, OCH_2CH_3), 4.12 (q, J = 7 Hz, 2, OCH_2CH_3), 5.53 (t, J = 2 Hz, 1, C-20 vinyl H), 6.05 (br s, 1, C-4 vinyl H), 6.37 (d of d, J = 2, 10 Hz, 1, C-2 vinyl H), and 7.04 (d, J = 10 Hz, 1, C-1 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 354 (52), 308 (100), 266 (11), 246 (14), 233 (16), and 155 (39).

An analytical sample was prepared by three recrystallizations from ether, mp 151–154 °C. Anal. ($C_{23}H_{30}O_3$) C, H.

Ethyl 17α,20β-Dihydroxy-3-oxopregna-1,4-dien-21-oate (16). The procedure described in the preparation of **7a** was repeated using 354 mg (1.0 mmol) of **15** and 250 mg (1.0 mmol, 1.0 equiv) of osmium tetroxide to afford, after chromatography on a 20 × 20 cm preparative layer (2 mm thick) Merck silica gel F254 plate in 1:3 ethyl acetate–dichloromethane, 107 mg (27%) of **16:** R_f 0.20; IR (KBr) 2.86 (sharp, OH), 2.96 (br, OH), 5.79 (C=O), 6.01 (C=O), 6.18 (C=C), and 6.26 μm (C=C); NMR ($CDCl_3$) δ 0.93 (s, 3, C-18 angular CH_3), 1.2–1.5 (m, 6, C-19 angular CH_3 and OCH_2CH_3), 3.50 (d, J = 6 Hz, 1, C-20 OH), 3.9–4.5 (m, 3, C-20 H and OCH_2CH_3), 6.06 (br s, 1, C-4 vinyl H), 6.29 (d of d, J = 2, 10 Hz, 1, C-2 vinyl H), and 7.06 (d, J = 10 Hz, 1, C-1 vinyl H); mass spectrum (70 eV) m/e (rel intensity) 388 (6), 269 (31), and 268 (100).

An analytical sample was prepared by two recrystallizations from dichloromethane–ether, mp 214.5–216 °C. Anal. ($C_{23}H_{32}O_5$) C, H.

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Registry No.—**1a,** 14425-92-4; **1b,** 963-74-6; **1c,** 18884-29-2; **1e,** 566-88-1; **1f,** 1624-73-3; **1i,** 481-29-8; **1j,** 3754-63-0; **1k,** 19637-35-5; **2a,** 68550-49-2; **2b,** 68550-50-5; **2c,** 68550-51-6; **2d,** 60727-74-4; **2e,** 68550-52-7; **2f,** 68550-53-8; **2g,** 68550-54-9; **2h,** 60727-73-3; **2i,** 31056-35-6; **2j,** 68550-55-0; **2k,** 2312-10-9; **2l,** 68628-67-1; **2m,** 68628-68-2; **2n,** 68550-56-1; **2o,** 68550-57-2; **4,** 2537-48-6; **5,** 29668-61-9; **5** sodium salt, 68550-65-2; **7a,** 68550-58-3; **7b,** 2301-91-9; **7c,** 68550-59-4; **7d,** 1624-58-4; **7e,** 68550-60-7; **7f** isomer 1, 68550-66-3; **7f** isomer 2, 68628-69-3; **7g,** 68550-67-8; **7h,** 68550-62-9; **7i,** 5456-44-0; **7k,** 68550-73-0; **7l,** 1863-39-4; **7m,** 6084-00-0; **7n,** 68550-64-1; **7o,** 68-96-2; **10,** 68628-70-6; **11,** 68628-71-7; **12,** 68550-67-4; **13,** 68550-68-5; **14,** 68679-86-7; **15,** 68550-69-6; **16,** 68582-50-3; 3β-hydroxy-5α-androstan-17-one tetrahydropyranyl ether, 1458-81-7; 3β-hydroxy-5α-pregn-17(20)-ene-20-carbonitrile tetrahydropyranyl ether, 68550-70-9; (*E*)-3β-hydroxypregna-5,17(20)-diene-20-nitrile tetrahydropyranyl ether, 58449-03-9; (*Z*)-3β-hydroxypregna-5,17(20)-diene-20-nitrile tetrahydropyranyl ether, 58449-04-0; 20,21-dihydroxy-3-methoxy-20-methyl-19-norpregna-1,3,5(10)-triene-21-carbonitrile, 68550-71-0; 3β-*tert*-butoxy-5α,6α-dihydroxypregn-17(20)-ene-20-carbonitrile, 68550-72-1; 20-carbonitrile-3β,5α,6α-trihydroxy-

17(20)-pregnene 3-acetate, 68550-73-2; 21-hydroxy-3-oxopregna-5,17(20)-diene 3-ethylene ketal, 68628-72-8; ethyl (*E*)-4α,5α-dihydroxy-3-oxopregn-17(20)-en-21-oate, 68550-74-3; ethyl 3-oxo-4α,5α,17α,20β-tetrahydroxypregnan-21-oate, 68568-35-4; 1,4-androstadiene-3,17-dione, 897-06-3; isobutylene, 115-11-7.

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Aromatic Side Chain Bromination by *N*-Bromosuccinic Imide. 5.[1] Ring Substituents and Selectivity

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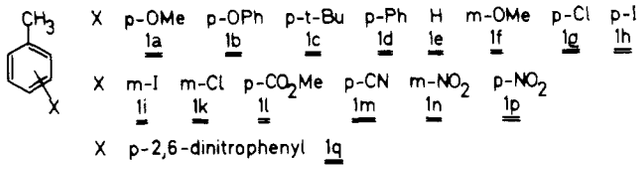
The selectivity (monobromination/dibromination) of *N*-bromosuccinic imide (NBS) toward 15 meta- and para-substituted toluenes was evaluated by ^{1}H NMR integration. Except for two substrates, selectivity and hence maximum yield correlate with Hammett σ^+ parameters. The Hammett ρ value of the reaction $XC_6H_4CH_2Br \rightarrow XC_6H_4CHBr_2$ (dibromination) is −0.88. The results demonstrate that in NBS side chain bromination substrate reactivity parallels selectivity.

Benzylic and allylic bromination, since long achieved by use of NBS,[2] is an important method to functionalize hydrocarbon molecules in phane chemistry[3] as well as in other fields. Although the reaction yields 67% benzylic bromide from toluene,[4] it is, from the angle of phane chemistry, not quite satisfying for two reasons.

(a) In multiple brominations, e.g., of xylenes or mesitylene, yields are reduced according to eq 1 (see Table I), where Y_k is the yield of bromination of a benzene with k methyl groups and Y_1 is the yield of bromination of the corresponding toluene.[5] Equation 1 applies to benzenes where adhering methyl groups are both electronically and sterically independent of one another. As a rule, this condition is met in the case of meta and para substitution.

$$Y_k = Y_1{}^k \quad (1)$$

(b) Electron-withdrawing substituents and heteroatoms affect both yield and reaction time[9] to the worse. For example, 1,3-dimethyl-2-nitrobenzene, which suffers from both restrictions, is brominated to 22% 1,3-bis(bromomethyl)-2-nitrobenzene only.[10] Hence, there is still profit in a general improvement of the preparative NBS side chain bromination method.



Results and Discussion

In order to enlighten the relevant factors, we investigated the NBS bromination of a series of meta- and para-substituted toluenes (**1a–q**).

Product Analysis. In a nonpolar solvent like tetrachloromethane, benzylic bromide **2** formed at first (eq 2) is further converted to dibromide **3** (eq 3). In the ^{1}H NMR spectrum, the benzylic protons show up at ~2.4 (**1**), ~4.5 (**2**), and ~6.6 ppm (**3**). Ring bromination, which would shift these signals by ~0.2 ppm downfield, was not detected. Substantial amounts of unconverted as well as dibrominated side products **1** and **3** indicate that the ratio $\alpha = k_1/k_2$ must be relatively low. For toluene itself (**1e**), Keefer et al.[11] calculated $\alpha = 5.5$ from competition experiments. We determined α by a more convenient method. Each substrate was treated with various amounts of NBS in refluxing CCl_4. The product mixtures were

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