was removed at ~1 mm, H_2O was added, and the resultant solid was filtered and washed well with H_2O. The solid was dissolved in CH_2Cl_2, dried, and concentrated *in vacuo* to afford a yellow solid. Crystallization from CH_2Cl_2–Et_2O gave 0.323 g of 9, mp 198–206°. The filtrate was concentrated to dryness and chromatographed on 25 g of alumina (activity III). Elution with C_6H_6 and with 10% EtOAc–C_6H_6 gave, on crystallization from CH_2Cl_2–Et_2O, 0.241 g of 9: mp 200–211°; [α]D −1.5°; ir showed no carbonyl absorption; nmr δ 3.90 (m, 8, ethylenedioxy), 3.45 (m, 3, C-6 and C-8 H's). *Anal.* ($C_{24}H_{38}O_6$) C, H.

17α-Hydroxy-7-oxa-5α-pregnane-3,20-dione (10a). Deketalization of 9 (6.68 g) was accomplished by refluxing with 500 ml of 8% H_2SO_4 in 500 ml of dioxane under N_2 for 2.5 hr. The solution was concentrated *in vacuo* to remove the dioxane, H_2O was added, and the product was extracted with CH_2Cl_2. After washing the extract with 5% $NaHCO_3$, it was dried and concentrated to yield a yellow solid. Crystallization from CH_2Cl_2–Et_2O gave 4.01 g of **10a**: mp 249–264°; [α]D +32.9°; ir (KBr) 1700 cm^{-1}; nmr δ 3.46 (m, 3, C-6 and C-8 H's). An additional 1.17 g of **10a** was obtained from the filtrate to give a total yield of 98%. *Anal.* ($C_{20}H_{30}O_4$) C, H.

17α-Hydroxy-7-oxa-5α-pregnane-3,20-dione Acetate (10b). To 1.50 g of **10a** dissolved in 75 ml of anhydrous EtOAc was added 0.03 ml of 70% $HClO_4$ and 15 ml of Ac_2O in 60 ml of EtOAc.[11] After stirring for 7 min at room temperature, the solution was washed with 5% $NaHCO_3$, dried, and concentrated to dryness. The solid mixture of 3-ketone and 3-enol acetate was dissolved in 300 ml of hot MeOH; 15 ml of 1 *M* $NaHCO_3$ was added and refluxed for 30 min. The solvent was removed *in vacuo*, H_2O was added, and the product was extracted with EtOAc. Chromatography of the crude product on 40 g of silica gel and elution with 10% EtOAc–C_6H_6 gave pure **14**. Crystallization of the combined fractions from CH_2Cl_2–Et_2O gave 0.91 g (53% yield) of **10b**: mp 237–244°; [α]D +29.4°; ir 1738 and 1720 cm^{-1}; nmr δ 3.50 (m, 3, C-6 and C-8 H's), 2.03 and 2.07 (s, 3, C-21 Me and C-17 OAc). *Anal.* ($C_{22}H_{32}O_5$) C, H.

17α-Hydroxy-7-oxapregna-1,4-diene-3,20-dione Acetate (11). A solution of 2.32 g (6.16 mmol) of **10b** and 3.92 g (17.25 mmol) of DDQ in 75 ml of anhydrous dioxane containing 15 mg of TsOH was refluxed under N_2 with stirring for 24 hr. An additional 0.136 g (0.6 mmol) of DDQ was added and reflux was continued for 4 hr. CH_2Cl_2 (100 ml) was added and the precipitated solids were removed by filtration. The filtrate was washed with five portions of 3 *N* NaOH and with saturated brine, dried, and concentrated to an oil. Preparative tlc on silica gel served to purify the product which was crystallized from CH_2Cl_2–Et_2O to give 0.71 g of **11**: mp 223–228°; [α]D +30.1°; λ_{max} 240 nm (ε 16,000); ir 1733, 1718, 1670, 1633, and 1610 cm^{-1}; nmr δ 7.04 (d, 1, J = 11 Hz, C-1 H), 6.29 (d of d, $J_{2\text{-}1}$ = 11 Hz, $J_{2\text{-}4}$ = 2 Hz, C-2 H), and 6.15 (broad s, 1, C-4 H). *Anal.* ($C_{22}H_{28}O_5$) C, H. A second crop (0.33 g) was obtained from the filtrate making the total yield 44%.

17α-Hydroxy-7-oxapregn-4-ene-3,20-dione Acetate (12). Reduction of the Δ^1 double bond was achieved by stirring a solution of 1.10 g of **11** and 0.55 g of $[(C_6H_5)_3P]_3RhCl$ in 220 ml of C_6H_6–EtOH (5:1) under an H_2 atmosphere for 3 hr at room temperature.[12] The solvents were removed *in vacuo* and the residue was dissolved in C_6H_6 and passed through a column of 22 g of neutral alumina. Elution with 500 ml of C_6H_6 and concentration of the eluent gave a dark foam. Preparative tlc on silica gel gave material (0.72 g) which was homogeneous by tlc but was shown by nmr analysis to contain the desired compound **12**, contaminated by about 30% of the fully saturated 3-ketone. Attempted purification by recrystallization was unsuccessful. The above mixture (0.72 g) dissolved in 30 ml of anhydrous THF was reduced by dropwise addition to 1.44 g of $LiAlH[OC(CH_3)_3]_3$ in 10 ml of THF over a 30-min period at room temperature. After stirring the reaction mixture for 1.5 hr, 10 ml of Me_2CO was added and the solvent was removed *in vacuo*. $CHCl_3$ was added followed by 10% AcOH to acidify the aqueous layer. The extract was washed with 5% $NaHCO_3$, dried, and concentrated to dryness. The mixture of 3β-hydroxy-Δ^4 and 3β-hydroxy-5α compounds was dissolved in 30 ml of $CHCl_3$, treated with 5 g of activated MnO_2, and stirred at 25° for 1 hr. The mixture was filtered through Celite and the filtrate was concentrated to dryness and purified by preparative tlc on silica gel. The purified product was crystallized from CH_2Cl_2–Et_2O to yield 0.18 g of **12**: mp 190–195°; $[\alpha]^{25}D$ +62.1°; λ_{max} 232 nm (ε 15,800); ir 1735, 1720, 1680, and 1630 cm^{-1}; nmr δ 5.75 (s, 1, C-4 H).

The analytical sample was obtained from EtOAc–C_6H_{14}. It melted at 192–198°, resolidified, and remelted at 207–209°. *Anal.* ($C_{22}H_{30}O_5$) C, H.

Acknowledgment. We wish to thank the following members of our physical chemistry department: Dr. W. Benz, Dr. V. Toome, Mr. S. Traiman, and Dr. T. Williams for the mass, ultraviolet, infrared, and nmr spectra, respectively. Thanks are also due Dr. F. Scheidl for the microanalyses.

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19-Norprogestins. Synthesis and Biological Activity of 6-Chloro-16-methylene-17α-hydroxy-19-nor-4,6-pregnadiene-3,20-dione 17-Acetate

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Two chemical syntheses of 6-chloro-16-methylene-17α-hydroxy-19-nor-4,6-pregnadiene-3,20-dione 17-acetate (**1a**), starting respectively from 19-norpregnane and from pregnane substrates, are presented. In rabbits and rats, **1a** is among the most active members of the 16-methylene-17α-acetoxy-20-keto steroid family but superior in neither Clauberg assay nor antiandrogenic activity to its 10-methyl homolog.

The pharmacology and chemistry of 16-alkylideneprogestins have been of interest to us for some time.[1,2] More recently we have been particularly interested in 6-chloro-Δ^6 members of the 16-alkylidene family[3–7] as exemplified by **1b** (Scheme II). With the findings of enhanced progestational activity (compared to the 19-methyl-containing counterpart) for a modified 19-norprogesterone[8] and for 19-norprogesterone,[9] there resulted an interest, which is still continuing, in the synthesis of 19-norprogestins.#

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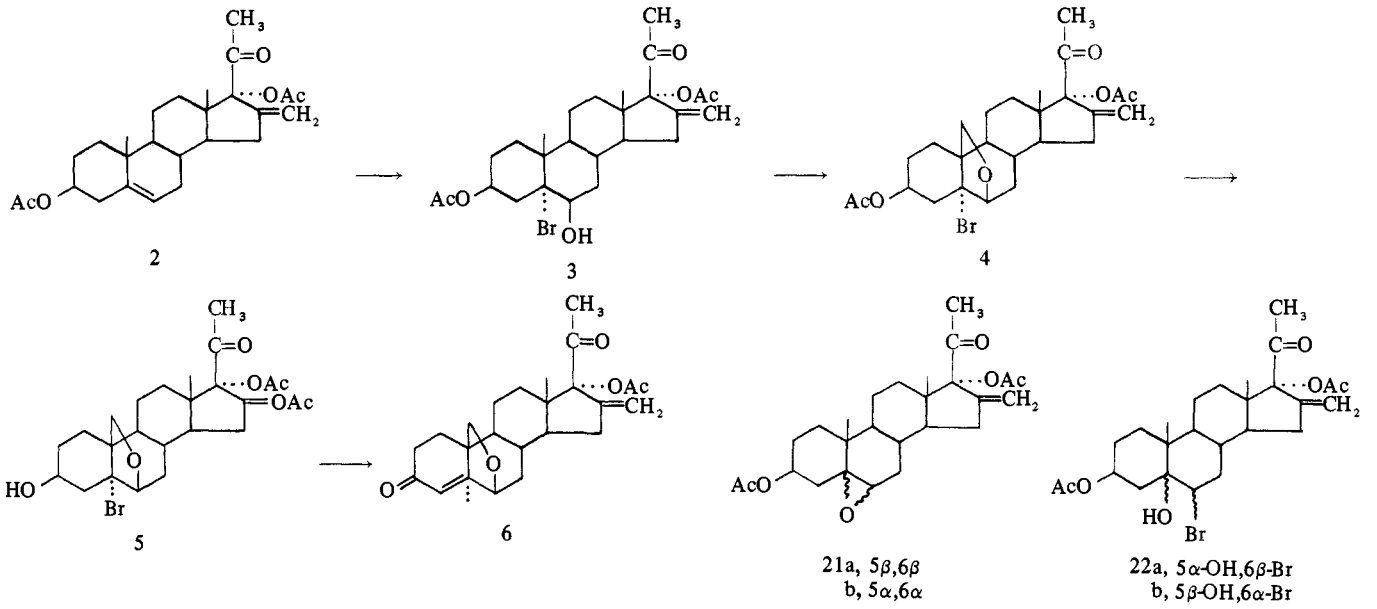
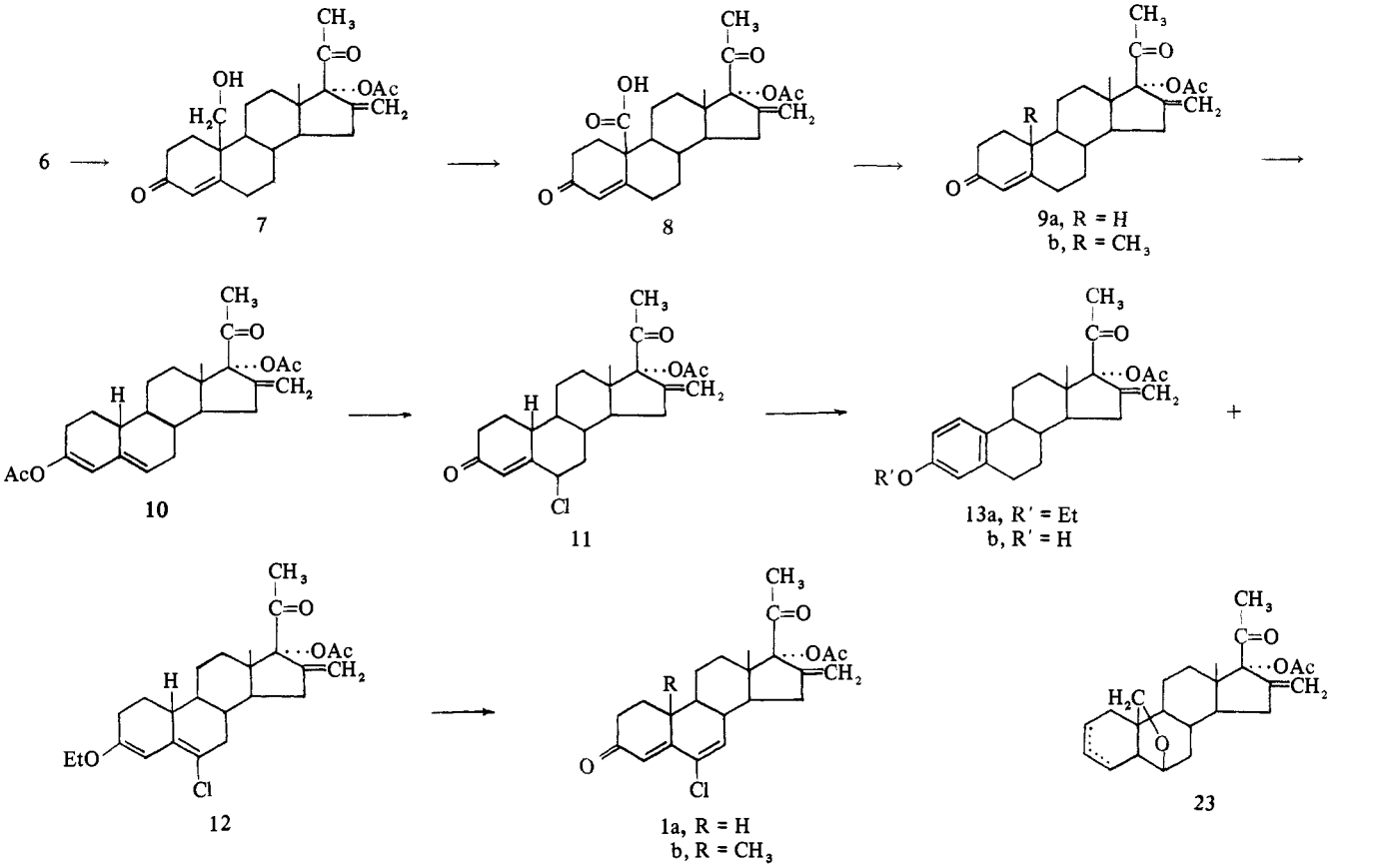
§ Physiology and Biochemistry Department.

Relevant to our publications may be cited ref 10–13.

Scheme I



Scheme II



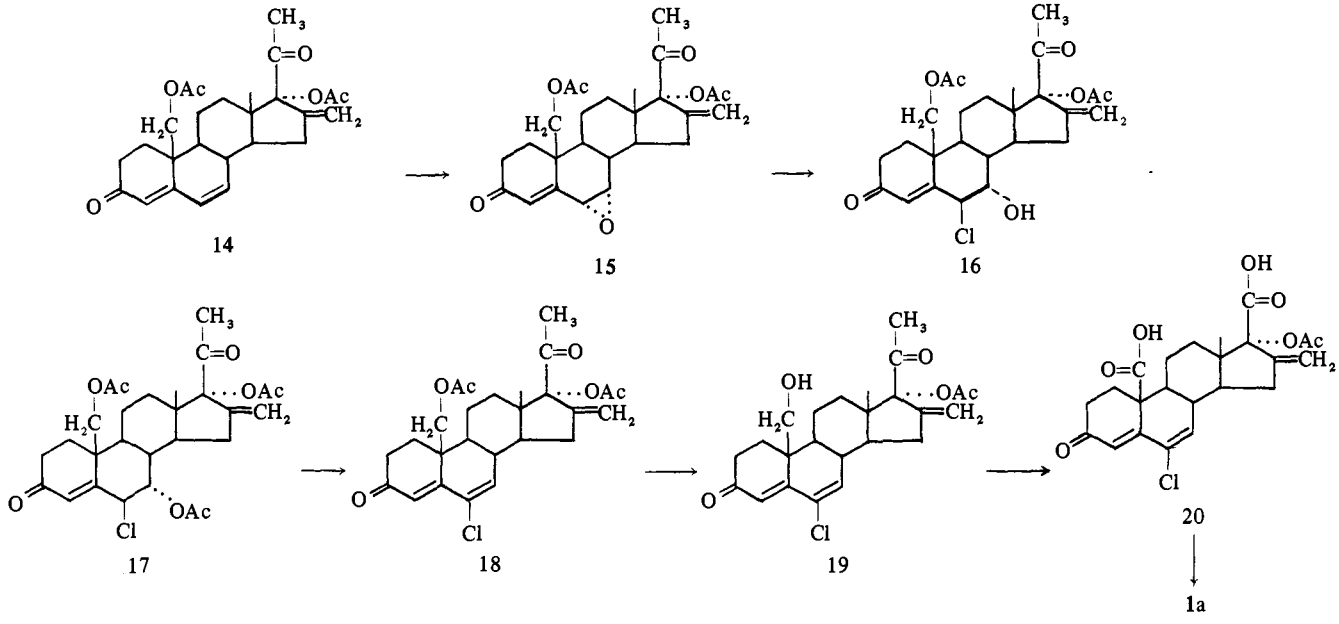
It seemed worthwile to us, in the light of potency enhancement associated with demethylation at 10, to modify the already potent progestin **1b** by removal of the 10-methyl function, with the reasonable expectation of additional potency enhancement. We report now our synthetic approaches directed to the preparation of 6-chloro-16-methylene-17α-hydroxy-19-nor-4,6-pregnadiene-3,20-dione 17-acetate (**1a**),** as well as some of our biological findings with **1a** and related compounds.

Our preparation of **1a** was achieved *via* two routes (outlined in Schemes II and III), although the latter scheme was by far the more efficient. The common starting material for both schemes was the 6,19-oxide **6**. As outlined in Scheme I, **6** was obtained from the readily available **2**[15,16] in five steps. Exposure of **2** to *N*-bromoacetamide (NBA) in aqueous dioxane with $HClO_4$ gave principally the 5α-bromo-6β-hydroxy (**3**),†† our results being comparable to Mehrhof and coworkers[11] in that essentially there was no

The preparation of **1a by a scheme which utilizes **18** as an intermediate has been described by Schwarz, *et al.*[14] One of our two schemes describing the preparation of **1a** converges with their scheme at **18**.

†† Consistent with the findings reported by Syhora, *et al.*, in ref 15, although with a different substrate, we also observed "α" and "β" attack. We obtained directly the 5,6α-oxido (**21b**), presumably arising from the 5α-hydroxy-6β-bromo (**22**). In addition, we unex-

Scheme III



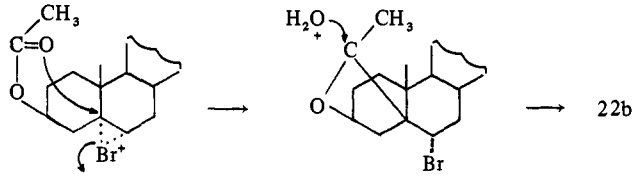
reaction with the 16-methylene. Functionalization of the 10-methyl group was achieved by formation of the 6,19-oxide **4** in 64% yield by exposure of **3** to lead tetraacetate[18] and iodine. Transformation to **6**‡‡ was effected by hydrolysis of the 3-acetate in **4**, followed by oxidation of the resulting 3-hydroxyl in **5** and dehydrobromination.

In Scheme II we outline the first sequence which led to the synthesis of **1a**. The conversion of the 6,19-oxide **6** to the 19-hydroxy **7**§§ was effected with zinc in acetic acid in yields as high as 63%.##

Chromic acid in acetone oxidation of **7** gave the crude 10-carboxyl (**8**), which with HCl gave the 19-nor (**9a**).*** The yield of **9a** from **7** was 32%. Enol acetylation of **9a** with Ac_2O and *p*-toluenesulfonic acid (pTSA)††† gave **10** which was chlorinated to give the 6β-chloro (**11**). The yield of **11** from **9a** was 60%.

Conversion of **11** with ethyl orthoformate to the enol ether **12** resulted also in substantial aromatization‡‡‡ of ring **A**, with the formation of both the 3-ethyl ether **13a** and the 3-hydroxy (**13b**).[19] In order to maximize the yield of **1a** and because of the difficulty in separation of **13a** from **12**, the crude reacton product of enol etherification was exposed directly to dehydrogenation. Initial attempts at de-

pectedly obtained approximately 3% of the 5β-hydroxy-6α-bromo (**22**), possibly formed *via* the transient 5,6α-cyclobromonium ion, which species gives principally the expected 6β-hydroxy (**3**) (see ref 17, particularly p 95 with reference to the usual formation of the 5α-bromo-6β-hydroxy). For the formation of **22b**, the 3β-acetoxy may be participating in ring opening of the cyclobromonium species, as depicted, followed by intervention of water.



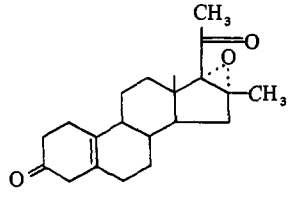
‡‡ The 17-hydroxy analog of **6** is reported in ref 14.

§§ Reference 13 reports the 17-hydroxy parent of **7**, with no constants cited.

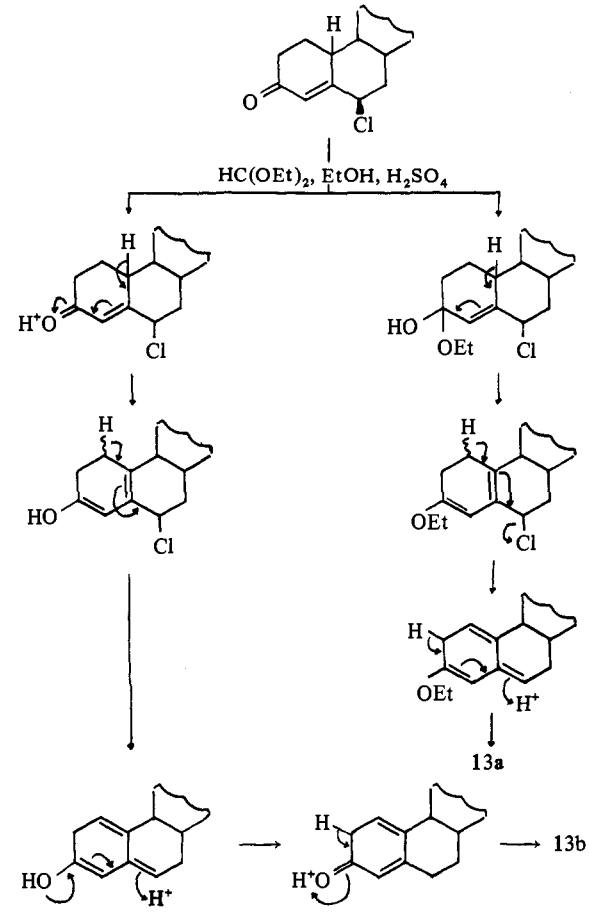
##: In one experiment **7** was obtained in lower yield, with 3-desoxy **23** being formed in 35% yield. The assignment of the general features of **23** was based principally on nmr, with, however, the location of the double bond not defined but considered to be at 2 or 3.

*** References 10, 11, and 13 describe the preparation of **9a** by other methods.

††† Reference 14 reports failure to prepare **10** and **9a** with Ac_2O and sulfosalicyclic acid and ref 13 reports formation of **10** from



‡‡‡ The conversion of **11** to **13a** and **13b** may be depicted as occurring as follows.



hydrogenation with DDQ failed. However, dehydrogenation with MnO_2[20-22] was successful, although the yield from **11** was only 3%. This result may be contrasted with results in the 10-methyl series where conversion of the 6β-chloro analog of **11** to the enol ether corresponding to **12** occurred in 90% yield and formation then of **1b** was effected in about 38% yield with DDQ and about 20% yield with MnO_2.§§§

Our more successful sequence for the preparation of **1a** is outlined in Scheme III. In the manner of Kalvoda and Anner,[12] but using Ac_2O, trifluoroacetic anhydride (TFAA), and pTSA, **6** was converted to the triene **14**[12,14] in 51% yield. Epoxidation of **14** with *m*-chloroperbenzoic acid proceeded with sufficient selectivity so that the desired 6α,7α-monoxide was obtained in approximately 45% yield, although some bisoxide (5-10%) was obtained as a result of epoxidation of the 16-methylene function. A small amount of starting material was also recovered. The chlorohydrin **16**, which was formed from **15** with dimethylacetamide-HCl in $CHCl_3$, was exposed to Ac_2O in pyridine to give the 7,17-diacetate **17**. Deacetoxylation of the 7-acetoxy moiety with HCl in $CHCl_3$, or better, tetramethylammonium fluoride (TMAF)[23] in acetonitrile, gave the $\Delta^{4,6}$-6-chloro (**18**)[14] in 74% yield after crystallization. After selective hydrolysis of the 19-acetate in **18** with perchloric acid to give the 19-hydroxy, the conversion to **1a** was carried out by oxidation of **19** to **20** followed by decarboxylation[14] to yield **1a**.

A comparison of the yield of **1a** from **6** *via* Scheme II and Scheme III reveals a 0.2% yield for the seven-step process in Scheme II and a 2.5% yield for the eight-step process in Scheme III.

Biology. The concept[24] that 19-norprogestins may display greater progestogenic activity than their 10-methylated counterparts has been established for the pairs progesterone-19-norprogesterone[9] and ethisterone-19-norethisterone.[25] However, results set out in Table I illustrate that potentiation of progestational activity is not invariably associated with this structural change. Thus, substitution of progesterone with 17α-acetoxyl and 16-methylene enhances the progestational activity of the resulting product but abolishes the potentiation heretofore associated with removal of the 10-methyl (*viz.* **9b** *vs.* **9a**). The same results are also found (with respect to both progestational and antiandrogenic activity) for the 6-chloro-6-dehydro members of the 16,17-disubstituted progesterone family. It seems clear that for this limited series of compounds, substitution at 16 and 17 dominates and overrides any effect of demethylation at 10.

Table I. Progestational and Antiandrogenic Activity

Compd	Progestational[a] im	Progestational[a] po	Antiandrogenic[b,c] (as % of control)[d] SV	VP	LA
9b	32				
9a	14.6				
1b	77	55[e]	36	46	42
1a	78	15	38	65	101

[a]Progesterone = 1 (im); 19-norethisterone = 2.8 (po). Progestational activity was determined in immature rabbits by the method of M. K. McPhail, *J. Physiol. (London)*, 83, 145 (1934). For procedures and reference to statistical method cited, see E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, *J. Med. Chem.*, 12, 631 (1969). [b]Daily dose, 10 mg/kg, for 3 weeks. [c]Male rats (Charles River CD strain) 21-28 days old and weighing approximately 60 g were used to assess the ability of these compounds to inhibit endogenous androgens. The compound was suspended in an aqueous suspending vehicle (0.9 NaCl, 0.5 carboxymethylcellulose, 0.4% polysorbate 80, and 0.9% benzyl alcohol) and injected sc each day for 3 weeks. Twenty-four hours following the last drug treatment, the seminal vesicles (SV), ventral prostates (VP), and levator ani (LA) muscle were removed, freed of extraneous tissue, and weighed. [d]Controls taked as 100 with decreasing value signifying greater activity. [e]Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, 8, 205 (1966), reports activity of 75.

Experimental Section###

5α-Bromo-16-methylene-3β,6β,17α-trihydroxypregnan-20-one 3,17-Diacetate (3). A solution of 21.4 g (0.05 mol) of 3β,17α-dihydroxy-16-methylene-5-pregnen-20-one 3,17-diacetate (**2**) and 50 ml of 10% aqueous $HClO_4$ (0.05 mol) in 430 ml of dioxane was cooled to 15° with stirring. To this was added 7.24 g (0.0525 mol) of NBA and the reaction was stored in the dark for 15 min at 25°. It was then added to 5 l. of salt water; the solids were collected and crystallized (Et_2O) to give 16.5 g of about 80% **3**, by Br and nmr analysis, and about 15% of 5α,6α-oxido (**21b**). This material was used for the preparation of **4**. Crystallization (twice, EtOAc) gave the analytical sample **3**: mp 175° dec; [α]D −126°; nmr 1.35 (10-CH_3), 2.35 (6-OH), 4.25 (6-H), 5.43 and 5.58 (16-CH_2). *Anal.* ($C_{26}H_{37}O_6Br$) C, H, Br; *m/e* 524.

5β-Hydroxy-6α-bromo (22b). In another preparation of **3**, and after column chromatography (silica gel, Et_2O–hexane), about 3% of 5β-hydroxy-6α-bromo (**22b**) was obtained: mp 242-244°; [α]D +88°; nmr 0.68 (13-CH_3), 1.02 (10-CH_3), 2.10 (3- and 17-$OCOCH_3$), 2.13 (20-CH_3), 3.00 (5-OH), 4.53 (broad, 3-H), 5.32 (6-H), 5.45 and 5.60 (16-CH_2). *Anal.* ($C_{26}H_{37}O_6Br$) C, H, Br; *m/e* 524. See below for conversion to **21a**.

5α,6α-Oxido (21b). Also obtained by column chromatography (silica gel, Et_2O–hexane) was **21b** in about 10–15% yield. Because its R_f was approximately that of the 5,6β-oxido isomer (formed during silica gel chromatography from **3**), it was not obtained pure, and the constants for **21b** were taken on a sample containing about 15–20% of **21a**: [α]D −139°; nmr 2.92 (d, J = 3.5 Hz, 6β-H). *Anal.* ($C_{26}H_{36}O_6$) C, H.

5β,6β-Oxido (21a). (a) **From 5β-Hydroxy-6α-bromo (22b).** Compound **22b** (100 mg), KOAc (1 g), and DMF (2 ml) at 100° for 6 hr and then usual work-up gave **21a**: mp 124-127°; [α]D −109°; nmr 3.11 (d, J = 2.0 Hz, 6α-H). *Anal.* ($C_{26}H_{36}O_6$) *m/e* 444.

Attempted preparation using 50 mg of **22b**, 500 mg of KOAc, and 50 ml of Me_2CO and refluxing for 4 hr failed to give any significant amount of **21a**; mainly recovered starting material was obtained.

(b) **From 5α-Bromo-6β-hydroxy (3).** Using **3** (50 mg), KOAc (50 mg) and Me_2CO (5 ml) at reflux for 2 hr gave complete conversion to **21a**. After 1 hr, an aliquot by tlc indicated almost complete conversion.

5α-Bromo-16-methylene-6β,19-oxido-3β,17α-dihydroxypregnan-20-one 3,17-Diacetate (4). To a mixture of 30.2 g (0.32 mol) of $CaCO_3$ and 66.1 g (0.148 mol) of $Pb(OAc)_4$ in 1350 ml of cyclohexane, stirred and illuminated (photoflood lamp, 375 W) at 65°, was added 16.3 g (0.0642 mol) of I_2 and 15.0 g (0.0285 mol) of **3** (of about 85% purity). The reaction was refluxed with stirring and illumination for 1 hr. After cooling to room temperature and separation of insolubles, the filtrate was evaporated *in vacuo* to a residue which was dissolved in CH_2Cl_2 and the solution washed with $Na_2S_2O_3$ solution and then water. Work-up and crystallization from Et_2O gave 8.44 g of **4**. An additional 1.79 g was obtained from the mother liquor by chromatography over 600 g of silica gel and elution with Et_2O–C_6H_{14} (3:2). The total of 10.23 g contained between 20 and 25% of 5,6-oxides. Thus, the yield of the 6,19-oxide was approximately 64%. An analytical sample of **4** was preferably obtained by reesterifying (Ac_2O–pyridine) purified 3-hydroxy (**5**) (free of 5,6-oxides, see below) and crystallizing from Et_2O: mp 203° dec; [α]D −86°; nmr 3.72 (d, J = 8.5 Hz) and 3.98 (d, J = 8.5 Hz, 10-CH_2),

§§§Private communication from E. L. Shapiro and L. Weber.

###All melting points were determined on a Kofler hot-stage microscope and are uncorrected. Optical rotations are in dioxane at 25° at about 1% concentration; uv spectra are in MeOH solution; ir spectra are in Nujol, and nmr spectra are measured on a Varian A-60A spectrometer in $CDCl_3$ with chemical shift given in parts per million on the δ scale (TMS = 0) unless otherwise stated. Mass spectra were determined on a Varian-Mat CH5 spectrometer using an electron impact source at 70 eV with direct probe inlet. Analyses were determined by the Physical Organic Chemistry Department of Schering Corp. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

4.10 (br, 6-H). *Anal.* ($C_{26}H_{35}O_6Br$) H, Br; C: calcd, 59.05; found, 59.53.

5α-Bromo-16-methylene-6β,19-oxido-3β,17α-dihydroxypregnan-20-one 17-Acetate (5). To a solution of 12.60 g of 4 (of about 80% purity) in 63 ml of CH_2Cl_2 and 441 ml of MeOH at 15° was added 25.2 ml of 70% $HClO_4$. The reaction mixture was allowed to stand at 25° for 4.75 hr and then added to 3.2 l. of water. Gaseous N_2 was passed through the mixture (to remove CH_2Cl_2), and the resulting solids were collected by filtration to yield 10.50 g. Crystallization (EtOAc) gave 8.29 g (71.5%) of 5: mp 220° dec; [α]D −99°; nmr (DMSO-d_6) 3.65 (d, J = 9 Hz) and 3.76 (d, J = 9 Hz, 10-CH_2), 3.87 (br, 3-H), 4.05 (br, 6-H), 4.68 (d, J = 5 Hz, 3-OH). *Anal.* ($C_{24}H_{33}O_5Br$) C, H, Br.

16-Methylene-6β,19-oxido-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate (6). A solution of 9.03 g (0.0188 mol) of 5 in 1355 ml of Me_2CO was cooled to 5° with stirring under N_2. To this was added 18.1 ml (0.0474 mol) of a prepared Jones reagent solution.[26] After 1.5 hr at 5°, the mixture was added to water and extracted into CH_2Cl_2 which was washed three times with water, dried with $MgSO_4$, and filtered, and the filtrate was evaporated to a residue *in vacuo*. To this was added 270 ml of MeOH and 18.1 g of anhydrous KOAc, and the mixture maintained at 60° for 24 hr. Then 270 ml of water was added and the MeOH removed by distillation *in vacuo*. Extraction into CH_2Cl_2 afforded 6, crystallization (EtOAc) yielding 5.89 g (78.8%): mp 247–250°; [α]D −225°; λ_{max} 237 nm (ε 13,510); nmr 3.52 (d, J = 8 Hz) and 4.21 (d, J = 8 Hz, 10-CH_2), 4.71 (d, J = 4.5 Hz, 6-H), 5.87 (4-H). *Anal.* ($C_{24}H_{30}O_5$) C, H.

16-Methylene-17α,19-dihydroxy-4-pregnene-3,20-dione 17-Acetate (7). Zinc dust (47 g) was added portionwise over a period of 30 min to an agitated solution of 4.66 g of 6 in 135 ml of HOAc and 5 ml of water at 60°. After 4 hr the insolubles were removed by filtration, and the filtrate was added to 500 ml of water. The mixture was evaporated to a residue *in vacuo* and then dissolved in CH_2Cl_2 and the resulting solution was washed with dilute NaOH and then water until neutral, dried with $MgSO_4$, and, after removal of the salts, evaporated to a residue. Crystallization (EtOAc) yielded 1.66 g; chromatography over silica gel of the mother liquor afforded an additional 1.30 g (total of 63%): mp 223–226°; [α]D −48°; λ_{max} 241 nm (ε 14,900); nmr 1.90 (19-OH), 3.93 (d, J = 10.5 Hz), and 4.08 (d, J = 10.5 Hz, 19-CH_2), 5.97 (4-H). *Anal.* ($C_{24}H_{32}O_5$) C, H.

Also isolated from one experiment was a 3-desoxy compound designated as 16-methylene-6β,19-oxido-17α-hydroxy-2- (or 3-) pregnen-20-one 17-acetate (23) in approximately 35% yield. Crystallization (Et_2O) gave mp 213–216°; [α]D −109°; λ_{max} 5.75, 5.85, 6.05 μ (vw); nmr 3.68 (19-CH_2), 4.10 (d, J = 4.5 Hz, 6-H), about 5.65 (2- and 3-H, or 3- and 4-H). *Anal.* ($C_{24}H_{32}O_4$) H; C: calcd, 74.97; found, 74.53; *m/e* 384.

16-Methylene-17α-hydroxy-19-nor-4-pregnene-3,20-dione 17-Acetate (9a). To a solution of 2.90 g (0.0072 mol) of 7 in 116 ml of Me_2CO under N_2 at 5° with stirring was added 8.7 ml (0.23 mol) of a prepared solution of Jones reagent. After 30 min at 5°, the solution was allowed to stand at room temperature for 90 min. Following the usual work-up of dilution with water, CH_2Cl_2 extraction, and evaporation, a residue of crude acid 8 of wt 2.68 (89.6%) was obtained, nmr 8.48 (10-COOH).

A solution of 2.60 g of crude 8 in 260 ml of $CHCl_3$, 20 ml of MeOH, and 6.5 ml of concentrated HCl was refluxed for 1.5 hr. It was then cooled to 25°, washed neutral with water, dried with $MgSO_4$, and filtered, and the filtrate was evaporated to a residue, 2.39 g. Chromatography on 240 g of silica gel (Et_2O–hexane, 7:3–4:1) gave 1.40 g, substantially 9a. Crystallization (Et_2O) gave 850 mg (36.6%) of 9a:[10,13] mp 160–162°; [α]D −106°; λ_{max} 240 nm (ε 17,500); nmr 5.87 (br, 4-H). *Anal.* ($C_{23}H_{30}O_4$) C, H.

16-Methylene-3,17α-dihydroxy-19-nor-3,5-pregnadien-20-one 3,-17-Diacetate (10). A solution of 2.00 g of 9a and 800 mg of pTSA·H_2O in 60 ml of Ac_2O was kept at 25° for 6.5 hr and then added to 600 ml of salt water. Extraction with CH_2Cl_2 in the usual way gave after crystallization (EtOAc) 1.48 g (66.7%): mp 205–208°; [α]D −217°; λ_{max} 235 nm (ε 19,948); nmr 2.13 and 2.15 (20-CH_3 and 3-$OCOCH_3$), about 5.55 (6-H), 5.80 (4-H). *Anal.* ($C_{25}H_{32}O_5$) C, H.

6β-Chloro-16-methylene-17α-hydroxy-19-nor-4-pregnene-3,20-dione 17-Acetate (11). A solution of 1.24 g (0.003 mol) of 10 in 25 ml of CH_2Cl_2 was cooled to 5° with stirring, and 5.58 ml (0.073 mol) of Et_3N was added over a period of 3 min, and then finally a solution of Cl_2 (0.0054 mol) in 5.82 ml of CCl_4 was added rapidly.**** After 30 sec, the reaction solution was negative to starch iodide paper. After 1 min, the reaction was diluted to 150 ml with CH_2Cl_2, washed with water, evaporated to a residue which was dissolved in 7.5 ml of HOAc, and heated on steam bath for 30 min. The solution was added to water, extracted with CH_2Cl_2 and alkali (NaOH), then water washed, and evaporated to a solid (1.28 g) although not crystallized: tlc (silica gel, CH_2Cl_2–EtOAc, 9:1, and H_2SO_4–MeOH spray) indicated one spot (effectively); mp 165° dec; [α]D −139°; λ_{max} 238 nm (ε 14,297); nmr 4.80 (t, J = 2.5 Hz, 6-H), 5.97 (d, $J_{4,10}$ = 1.8 Hz, 4-H). Assignment as 6β-chloro was made also by comparison with nmr of 6β- and 6α-chloro analogs in the 10-methyl series. *Anal.* Calcd for $C_{23}H_{29}O_4Cl$: Cl, 8.76. Found: C, 9.28. Mass spectrum, no *m/e* at 404, but *m/e* 368 (M − HCl).

3-Ethoxy-6-chloro-16-methylene-17-hydroxy-19-nor-3,5-pregnadien-20-one 17-Acetate (12). A solution of 1.20 g (0.003 mol) of 11 in 25 ml of dioxane, 0.375 ml of EtOH, and 3.75 ml of $(EtO)_3CH$ was stirred under N_2 at 25°. To this was added 0.20 ml (0.00375 mol) of concentrated H_2SO_4 and the mixture was stirred at 25° for 1 hr. Then 2 ml of pyridine was added, and the reaction was added to 250 ml of Et_2O. The mixture was washed with water, then the solution was dried with $MgSO_4$ and filtered, and the filtrate was evaporated to a residue of 1.20 g: λ_{max} 251 nm ($E^{1}_{1\%}$ 220); λ_{max} 5.72, 5.81 5.92 (w), 6.08, 6.18 μ. Nmr analysis indicated, by aromatic hydrogens at 6.6–7.2, that the residue consisted of at least 1/3 aromatic **13a** and **13b**. Chromatography on 100 g of silica gel yielded 456 mg of a mixture (used as a mixture in the following preparation of **1a**; see also for constants for **13a**) of **13a** and 12 from Et_2O–C_6H_{14} (2:3), 144 mg of impure 13b from Et_2O–hexane (3:2), and 235 mg of impure starting material **11** from Et_2O–hexane (4:1) and Et_2O. Purification of 13b by a silica gel preparative plate, $CHCl_3$–EtOAc (9:1), gave 60 mg (5%): λ_{max} 3.00, 5.75, 5.90, 6.20 μ; nmr 5.35 (3-OH), 6.62 (br, 4-H), 6.69 (2-H, d of d, $J_{1,2}$ = 9, $J_{2,4}$ = 2.5 Hz), 7.19 (d, $J_{1,2}$ = 9 Hz). Identity was obtained also by comparison of tlc, ir, and nmr with an authentic sample.[19]

6-Chloro-16-methylene-17α-hydroxy-19-nor-4,6-pregnadien-20-one 17-Acetate (1a). **(a) From 12.** To freshly prepared and dried MnO_2[20] (2.3 g) was added 18.6 ml of CH_2Cl_2; then 37.1 ml of CH_3CN†††† was added. The mixture was cooled to 0° and 450 mg of the mixture of 12 and **13a,b** was added. The reaction was stirred at 0° with N_2 for 3.5 hr; then 2 ml of water and 600 mg of Super Cel was added, and the insolubles were separated by filtration. The filtrate was evaporated to a residue of 342 mg. A silica gel preparative plate, $CHCl_3$–EtOAc (9:1), gave 20 mg of **1a** (of about 75% purity, as judged by λ_{max} 282 nm (ε 17,440)) and 162 mg of 16-methylene-17α-hydroxy-19-nor-1,3,5(10)-pregnatriene-3-ethyl ether 17-acetate (**13a**). Identity of **1a** was by tlc, ir, uv, and nmr with **1a** obtained *via* Scheme III from **20**. An analytical sample of **13a** (EtOH) had mp 157–159°; [α]D −68°; λ_{max} 278, 288 nm (ε 2274, 1900); λ_{max} 5.70, 5.80, 6.20, 6.35 μ; nmr 0.72 (13-CH_3), 1.40 (t, J = 7.5 Hz, 3-CH_3CH_2O), 2.08 (17-$OCOCH_3$), 2.17 (20-CH_3), 3.90 (d, J = 7 Hz), and 4.14 (d, J = 7 Hz, 3-CH_3CH_2O), 5.48 and 5.62 (16-CH_2), 6.66 (br, 4-H), 6.72 (d of d, $J_{1,2}$ = 9, $J_{2,4}$ = 2.5 Hz, 2-H), 7.2 (d, J = 9 Hz, 1-H). *Anal.* ($C_{25}H_{32}O_4$) C, H; *m/e* 396.

(b) From 20. Using the method described for the preparation of **9a**, 1.03 g of impure acid **20** (see below) was converted into impure **1a**. Preparative plate silica gel chromatography [$CHCl_3$–EtOAc (9:1)] and crystallization from MeOH gave 339 mg (36.5%) of 1a:[10] mp 175° dec; [α]D −155°; λ_{max} 282 nm (ε 23,449); nmr 0.78 (13-CH_3), 2.06 (17-$OCOCH_3$), 2.18 (20-CH_3), 5.50 and 5.65 (16-CH_2), 6.43–6.45 (br, 4-H and 7-H). *Anal.* ($C_{23}H_{27}O_4Cl$), C, H, Cl.

16-Methylene-17α,19-dihydroxy-4,6-pregnadiene-3,20-dione 17,19-Diacetate (14). To a solution of 25.0 g of 6 and 2.5 g of pTSA-H_2O in 250 ml of HOAc, at 15° with stirring, was added 100 ml of TFAA over 20 min. The solution was then allowed to stand at ambient temperature for 27.5 hr and then added to 3.5 l. of water. Work-up in the usual way afforded a residue which was chromatographed on 1.5 kg of silica gel and eluted with Et_2O–hexane mixture to yield 14.2 g (51%) of 14.[14] Analytical sample, crystallized from MeOH, had mp 166–168°; [α]D −102°; λ_{max} 282 nm (ε 26,078); nmr 2.04 (19-$OCOCH_3$), 4.26 (d, J = 11.5 Hz) and 4.34 (d, J = 11.5 Hz, 19-CH_2), 5.86 (4-H), 6.13 (d, J = 10 Hz) and 6.18 (d, J = 10 Hz, 6-H and 7-H). *Anal.* ($C_{26}H_{32}O_6$) C, H.

16-Methylene-6α,7α-oxido-17α,19-dihydroxy-4-pregnene-3,20-dione 17,19-Diacetate (15). To a solution of 10.65 g (0.0242 mol) of 14 in 213 ml of *tert*-BuOH just under reflux, with stirring, was added 10.71 g of 78% *m*-chloroperbenzoic acid (0.0484 mol). The reaction mixture was refluxed, with stirring, for 1 hr, cooled,

****The procedure is a modification of a related process used by Syhora, *et al.*[27]

††††We thank Drs. B. A. Hems and T. Walker of Glaxo Research, Ltd., Greenford, Middlesex, England, for informing us of the utility of CH_3CN in MnO_2 dehydrogenation, as well as of the pyrophoricity of CH_3CN with dry MnO_2.

and added to 1.7 l. of water. The resulting mixture was extracted with CH_2Cl_2 and worked up in the usual way to afford a residue of 11.23 g which was chromoatographed over silica gel (Me_2CO–hexane, 1:4) to afford approximately 5.2 g of 15, 1.4 g of 6,7α-oxido-16ξ-oxirano-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (bisoxide), and 500 mg of starting material. Both 15 and the bisoxide had minor impurities each of the other and also of 14. An analytical sample of 15 (estimated impurities of 3% by uv), crystallized (*i*-Pr_2O), had mp 177–179°; $[\alpha]D$ −68°; λ_{max} 238 nm (ε 13,527) with impurity as indicated by λ_{max} 280 nm (ε 880); nmr 3.39 (d, J = 3 Hz, 7-H), and 3.50 (d, J = 3 Hz, 6-H), 4.10 and 4.44 (19-CH_2), 5.50 and 5.62 (16-CH_2), 6.30 (4-H). *Anal.* ($C_{26}H_{32}O_7$) C, H.

The bisoxide after crystallization from MeOH still had impurity of 5–10%, by nmr, of **15**, and exhibited the following: λ_{max} 238 nm ($E^{1\%}$ 309); nmr 2.94 (d, J = 5 Hz), and 3.21 (d, J = 5 Hz, 16-epoxy H_2), 3.32 (d, J = 3 Hz, 7-H), 3.51 (d, J = 3 Hz, 6-H). *Anal.* ($C_{26}H_{32}O_8$) C, H; *m/e* 4.72.

6β-Chloro-16-methylene-7α,17α,19-trihydroxy-4-pregnene-3,20-dione 17,19-Diacetate (16). A solution of 5.20 g of **15** in 104 ml of $CHCl_3$ to which had been added 2.60 g of $MeCONMe_2$–HCl was kept at 25° for 35 min. The mixture was diluted to 700 ml with CH_2Cl_2, washed with salt water and then water, and evaporated to give a residue of 5.67 g consisting principally of 16, which was used in the preparation of 17: nmr 3.94 (7-H), 4.47 (6-H), 6.14 (4-H); calcd for $C_{26}H_{33}O_7Cl$, *m/e* 492.

6β-Chloro-16-methylene-7α,17α,19-trihydroxy-4-pregnene-3,20-dione 7,17,19-Triacetate (17). A solution of 5.60 g of **16** in 56 ml of pyridine and 28 ml of Ac_2O was allowed to remain at 25° for 19 hr. Work-up gave 5.46 g which was crystallized from MeOH yielding 3.1 g (as 0.5 mol equiv of MeOH of solvate). Purification of the mother liquor (2.1 g) by a silica gel preparative plate ($CHCl_3$–EtOAc, 9:1) gave an additional 1 g of 17. Analytical sample of 17, as MeOH solvate, had mp 175–177°; $[\alpha]D$ −44°; λ_{max} 235 nm (ε 15,042); nmr 2.00, 2.02, 2.09 (7-,17-, and 19-$OCOCH_3$), 3.39 (CH_3OH), 4.50 (6-H), 5.04 (br, 7-H), 6.10 (4-H). *Anal.* ($C_{28}H_{35}O_8Cl$, 0.5 mol of MeOH) C, H, Cl; *m/e* 534.

6-Chloro-16-methylene-17α,19-dihydroxy-4,6-pregnadiene-3,20-dione 17,19-Diacetate (18). (a) TMAF·$5H_2O$ (3.41 g, 0.0186 mol) was dissolved with warming in CH_3CN (250 ml); then the solvent was removed *in vacuo* to a residue. This process was repeated two additional times. Then, to the residue was added 3.41 g (0.00637 mol) of 17 in 700 ml of CH_3CN and the reaction was stirred at 25° for 18 hr. An equal volume of water was added, and the liquid phase then evaporated to a residue which was dissolved in CH_2Cl_2 and washed with dilute NaOH and then water. Evaporation gave a residue which after chromoatography on 300 g of silica gel (Me_2CO–hexane, 1:4) gave 1.74 g (57.4%) of the $\Delta^{4,6}$ 18.[14] Analytical sample, crystallized (MeOH), had mp 221–223°; $[\alpha]D$ −100°; λ_{max} 285 nm (ε 21,000); nmr 6.30 (d, J = 2 Hz, 7-H), 6.48 (4-H). *Anal.* ($C_{26}H_{31}O_6Cl$) C, H, Cl.

(b) A solution of 1.00 of **17**, in 20 ml of $CHCl_3$, was saturated with HCl (g) at 25° and then let stand at 25° for 91 hr. CH_2Cl_2 (280 ml) was then added, and the solution was washed three times with water, dried with $MgSO_4$, and filtered and the filtrate evaporated to a residue which was chromatographed on silica gel preparative plates ($CHCl_3$–EtOAc, 9:1) to yield 397 mg (44.7%) of 18.

6-Chloro-16-methylene-17α,19-dihydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (19). A solution consisting of 1.75 g of 18, 8.8 ml of CH_2Cl_2, 61 ml of MeOH, and 4.4 ml of 70% $HClO_4$ was allowed to remain at 25° for 24 hr. Addition into water and extraction of the mixture with CH_2Cl_2 afforded a residue of 1.55 g. Crystallization (MeOH) gave 1.26 g of 19[14] (73.7%, calcd as 1 mol of solvate): mp 156°, resolidified, 185° dec; $[\alpha]D$ −116°; λ_{max} 285 nm (ε 22,373); nmr 2.07 (17-$OCOCH_3$), 3.49 (CH_3OH), 3.87 (10-CH_2), 6.45 (4-H). *Anal.* ($C_{24}H_{29}O_5Cl$·1 mol equiv of MeOH) C, H, Cl; *m/e* 432.

Preparation of the 10-Carboxylic Acid 20. Using the method described in the preparation of **8**, 1.27 g of 19 gave 1.15 g of impure acid 20 (used for the preparation of 1a); nmr 6.76 (10-COOH).

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