uct. Recrystn from Me_2CO afforded 29.0 g (70%) of **9**, mp 174–176° dec. For instability reasons **9** was not further purified and subjected to elemental analysis.

5α-Cholestane-3β,5α,6β-triol 3-Ethyl Carbonate (10).—Triol 1 (40.0 g, 9.5×10^{-2} mole) in 400 ml of pyridine was cooled on an ice bath. Ethyl chloroformate (88.0 g, 0.81 mole) was added dropwise with stirring. The reaction mixt was allowed to stand at room temp for 6 hr, poured into H_2O, and extd with Et_2O. The dried (Na_2SO_4) Et_2O layer was evapd under reduced pressure. Recrystn from MeOH–Me_2CO (1:1) afforded 40 g (85%) of **10**, mp 185–188°, lit.[23] mp 188°.

5α-Cholestane-3β,6β-diol (11) was prepd according to the method of Plattner and coworkers[11] affording crystals, mp 192–193°, lit.[11] mp 192°.

5α-Stigmastane-3β,5α,6β-triol (13).—β-Sitosterol (**12**) (50 g, 0.124 mole) suspended in 500 ml of 90% HCO_2H was heated on a steam bath with occasional stirring for 1 hr. The mixt was allowed to cool to room temp and 80 ml of 30% H_2O_2 was added. The reaction mixt was stirred for 72 hr at room temp. Boiling H_2O (3 l.) was added with stirring; the mixt was cooled and filtered. The dried filtrate was heated to reflux in 3 l. of MeOH. An aq soln of NaOH (25%, 80 ml) was added and the mixt was refluxed for 1 hr, neutralized with 10% HCl, and allowed to cool to room temp. Compd **13** crystallized affording white needles. Recrystn from MeOH afforded 54 g (94%) of **13**, mp 242–245°, lit.[24] mp 248–250°. *Anal.* ($C_{29}H_{52}O_3$) C, H.

Biological Studies *in Vivo*.—Rabbits were fed Purina rabbit laboratory chow for at least 3 weeks. The rabbits were then fed equal amts of the drug under study and 0.5% cholesterol in 2.5% peanut oil mixed with the same purina chow for 3 weeks. With active compds a final dietary period consisting of only 0.5% cholesterol in 2.5% peanut oil was administered with purina chow for an additional 3 weeks. At the beginning and end of each dietary regimen, body wt of the rabbit was measured and blood samples were collected for serum cholesterol determination which was measured by the method of Abell, *et al.*[25]

Biological studies *in vitro* were carried out according to methods previously reported by Dempsey and coworkers.[13,16–18]

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(23) L. F. Fieser, J. C. Hortz, M. W. Klohs, M. A. Romero, and T. Ulne, *J. Amer. Chem. Soc.*, **74**, 3309 (1952).

(24) D. H. Coffey, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 738 (1936).

(25) L. L. Abell, B. B. Levy, B. B. Brodie, and F. E. Kendell, *J. Biol. Chem.*, **195**, 357 (1952).

Agents for Alkylating Steroid Hormone Receptors. 2. 16α-Substituted Progesterone Derivatives[1]

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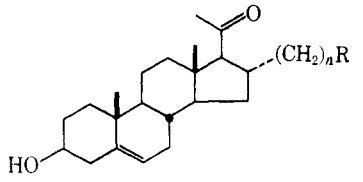
Derivatives of 16α-propyl-, 16α-butyl, and 16α-pentylprogesterone were synthesized and tested for Clauberg activity. Derivatives of the 3-carbon side chain included the ω alcohol, mesylate, tosylate, bromoacetate, and *p*-fluorosulfonylbenzoate. The 4-carbon side chain was derivatized as the ω alcohol, mesylate, and bromoacetate. Derivatives of the *n*-pentyl chain included ω alcohol, mesylate, tosylate, bromoacetate, *p*-fluorosulfonylbenzoate, toluate, and bromide.

In a search for an agent capable of selectively alkylating the Clauberg receptor, we recently investigated a series of diazo ketones derived from esters of 17α-hydroxyprogesterone.[2] In a continuation of that search, we have prepared and had assayed a series of compounds containing functional groups linked by *n*-alkyl side chains to the 16α position of progesterone.

Chemistry.—16-Dehydropregnenolone acetate was treated with the Grignard reagent prepared from 3-*tert*-butoxy-1-bromopropane.[3] Oppenauer oxidation of the resulting 3β-hydroxy-16α-(3-*tert*-butoxypropyl)pregn-5-en-20-one (I) afforded 16α-(3-*tert*-butoxypropyl)-pregn-4-ene-3,20-dione (II). The *tert*-butyl group of II was removed by treatment with CF_3CO_2H to afford alcohol III. The latter compound was converted into mesylate IV, bromoacetate V, tosylate VI, and *p*-fluorosulfonylbenzoate VII by the usual methods.

Grignard reagents prepared from 4-bromobutene and 5-bromopentene reacted with 16-dehydropregnenolone acetate to afford 3β-hydroxy-16α-(3-butenyl)pregn-5-en-20-one (VIII) and 3β-hydroxy-16α-(4-pentenyl)-pregn-5-en-20-one (IX), respectively.[3] Oppenauer oxidation of VIII produced X, and XI was similarly formed from IX. These compounds were each hydroborated and then oxidized by alkaline H_2O_2 to produce 16α-(4-hydroxybutyl)pregn-4-ene-3,20-dione (XII) and 16α-(5-hydroxypentyl)pregn-4-ene-3,20-dione (XIII). Alcohol XII was transformed into mesylate XIV and bromoacetate XV. From XIII were obtained mesylate XV, bromoacetate XVII, tosylate XVIII, *p*-fluorosulfonylbenzoate XIX, toluate XX, and bromide XXI.



I, $n = 3$; R = O-*t*-Bu
VIII, $n = 2$; R = CH = CH_2
IX, $n = 3$; R = CH = CH_2

(1) This investigation was supported, in part, by research grants (AM-006900) from the National Institute of Arthritis and Metabolic Diseases and (CA10116) from the National Cancer Institute and, in part, by a training grant (5-T1-GM-555) from the Division of Medical Sciences, National Institutes of Health, U. S. Public Health Service.

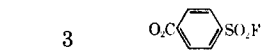
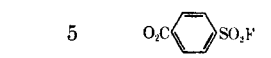
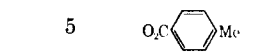
(2) A. J. Solo and J. O. Gardner, *Steroids*, **11**, 37 (1968).

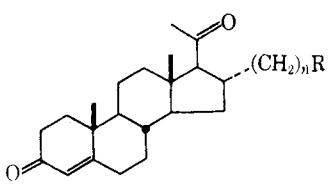
(3) In our hands, the Grignard additions gave cleanest products when run as described by Marker[4] (that is, without catalysis by copper ion).

(4) R. E. Marker and H. M. Crooks, *J. Amer. Chem. Soc.*, **64**, 1280 (1942).

TABLE I

ACTIVITY OF 16α-SUBSTITUTED PROGESTERONES IN A MODIFIED CLAUBERG ASSAY (SUBCUTANEOUS INJECTION)

Compound administered	16α Side chain (CH₂)n	16α Side chain Substituent	Total dose, mg	No. of rabbits	Mean final wt, g	Mean ovarian wt, mg	Mean uterine wt, g	Mean index	Range
Progesterone			0.2	15	1388	50.1	1.25	1.0+	0.0+–2.5+
			0.5	15	1310	38.8	2.11	3.2+	2.5+–4.0+
III	3	OH	10.0	2	1316	52.4	1.60	0.5+	0–1.0+
			20.0	3	1348	29.4	1.40	1.2+	0.5+–2.0+
			40.0	2	1278	45.0	1.22	2.5+	2.0+–3.0+
IV	3	OMs	20.0	2	1200	35.4	1.14	0	0
V	3	O_2CCH_2Br	1.0	2	1760	37.8	0.98	0	0
			20.0	2	1118	29.8	0.95	1.3+	0.5+–2.0+
VI	3	OTs	10.0	2	1128	38.1	0.93	0	0
VII	3		15.0	2	1780	87.0	1.24	0	0
XII	4	OH	5.0	2	1432	62.6	1.08	0.3+	0–0.5+
			18.0	2	1299	28.6	1.56	2.3+	2.0+–2.5+
XIV	4	OMs	2.0	2	1208	40.1	1.20	1.5+	1.0+–2.0+
			10.0	2	1312	33.4	2.55	3.8+	3.5+–4.0+
XV	4	O_2CCH_2Br	0.5	2	1245	33.0	0.88	0	0
			10.0	2	1250	31.1	1.40	3.3+	3.0+–3.5+
XI	5	4-Dehydro	2.0	2	1391	56.8	1.11	0	0
			5.0	2	1462	41.1	2.52	3.5+	3.5+
			10.0	2	1464	80.8	2.28	4.0+	4.0+
			20.0	2	1349	32.8	3.18	4.0+	4.0+
XIII	5	OH	1.0	4	1280	40.6	1.13	0.4+	0.0–1.0+
			2.0	4	1256	49.4	1.43	0.9+	0.0–1.5+
			5.0	4	1393	41.3	1.58	1.8+	1.0+–2.5+
			10.0	4	1254	27.6	2.20	3.3+	3.0+–3.5+
			20.0	2	1414	32.9	2.71	4.0	4.0+
XVI	5	OMs	1.0	4	1316	57.1	1.34	0.6+	0–1.0+
			2	2	1322	30.3	1.60	2.0+	1.5+–2.5+
			5	2	1348	69.4	1.80	2.8+	2.5+–3.0+
			10	2	1360	61.2	3.54	4.0+	4.0+
XVII	5	O_2CCH_2Br	0.2	2	1294	34.8	0.96	0	0
			5.0	2	1344	38.2	1.47	2.8+	2.5+–3.0+
XVIII	5	OTs	2.0	2	1072	47.4	0.95	0	0
			5.0	4	1279	30.3	1.29	0.5+	0–1.0+
			20.0	2	1160	40.7	2.44	3.3+	3.0+–3.5+
XIX	5		5.0	2	1166	33.6	1.76	0	0
			20.0	2	1409	28.2	2.78	4.0+	4.0+
XX	5		5.0	2	1234	32.3	1.10	0	0
			20.0	2	1298	34.5	1.04	0.3+	0–0.5+
XXI	5	Br	5.0	4	1270	40.1	1.12	0.1+	0–0.5+
			10.0	2	1410	24.2	1.68	1.3+	1.0+–1.5+
			20.0	2	1395	22.6	2.38	4.0+	4.0+



II, n = 3; R = O-t-Bu
III, n = 3; R = OH
IV, n = 3; R = OMs
V, n = 3; R = O_2CH_2Br
VI, n = 3; R = OTs
VII, n = 3; R = $O_2CC_6H_4SO_2F$-p
X, n = 2; R = CH = CH_2
XI, n = 3; R = CH = CH_2
XII, n = 4; R = OH
XIII, n = 5; R = OH
XIV, n = 4; R = OMs
XV, n = 4; R = O_2CCH_2Br
XVI, n = 5; R = OMs
XVII, n = 5; R = O_2CCH_2Br
XVIII, n = 5; R = OTs
XIX, n = 5; R = $O_2CC_6H_4SO_2F$-p
XX, n = 5; R = $O_2CC_6H_4CH_3$-p
XXI, n = 5; R = Br

Biological Results.[5]—As shown in Table I, compounds III–VII and XI–XXI were tested for progestational activity by the McPhail modification of the Clauberg assay. Because of the presence of an extra polar group in the ω position of the short 16α-alkyl side chains, it was anticipated that factors which tend to reduce the polarity of the analogs would result in an increase in their Clauberg activity.[2] Such an increase in progestational activity with increasing chain length was observed for the homologous series of alcohols III, XII, and XIII. Similarly, the bromoacetates V, XV, and XVII and the mesylates IV, XIV, and XVI show an increase in activity as the chains are homologated. For the 4-C and 5-C side chains an expected increase in activity was observed when the alcohols XII and XIII

(5) Biological testing was performed at the Endocrine Laboratories, Madison, Wis.

were converted into the corresponding bromoacetates XV and XVII and mesylates XIV and XVI. However, in the case of the 3-C side chain, the alcohol III and the bromoacetate V proved to be comparable in activity; and the mesylate IV, at the highest level tested, proved to be less active than the alcohol. The mesylate IV was also administered with progesterone (in total doses of 10.0 and 0.2 mg, respectively) in a test for antiprogestational activity, but, here also, it proved inactive.

Compounds bearing a substituted Ph group, including tosylates V and XVII, *p*-fluorosulfonylbenzoates VII and XIX, and toluate XX, were all found to have low activity. For the 5-C side chain, the potential alkylating agents XVIII and XIX show significantly higher activity than does toluate XX, thereby demonstrating that the low activity of the series is probably due to the presence of the phenyl group and that it is certainly not solely the result of alkylating extraneous biological material. The higher Clauberg activity of the alkylating agents XVIII and XIX as compared with the toluate XX raises the question of whether one or both of these compounds might be alkylating the Clauberg receptor. The close similarity of the Clauberg activity of these compounds despite the fact that the alkylating site in XIX is 7 atoms removed from the site of reactivity in XVIII makes such a conclusion unlikely. However, unless compounds currently being investigated yield results more promising than these, further investigation of compounds XVIII and XIX may be undertaken.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer Infracord Model 137 or on a Beckman IR-8 spectrophotometer. Nmr spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer and are reported in ppm downfield from a TMS internal standard. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for those elements are within ±0.3% of the theoretical value.

3β-Hydroxy-16α-(3-*tert*-butoxypropyl)pregn-5-en-20-one (I).—To a Grignard reagent prepared from 4 g of 3-*tert*-butoxy-1-bromopropane and 534 mg of Mg in 40 ml of anhyd Et_2O was added a soln of 2 g of 16-dehydropregnenolone acetate in 60 ml of Et_2O. The resulting mixture was stirred at room temp for 30 min. The crude product was hydrolyzed with aq methanolic KOH and was then chromatographed over 60 g of acid-washed Al_2O_3. An oil (2.0 g) was eluted by 25% EtOAc in C_6H_6. The oil was acetylated and then chromatographed on 50 g of acid-washed Al_2O_3. C_6H_6 eluted an oil (900 mg) which was saponified to afford I, as crystals from hexanes, in a yield of 34%: mp 118–120°; nmr, strong singlets at δ 0.61, 1.00, 1.15, and 2.07, a triplet at 3.25, and a multiplet at 5.31 (H on C-18, C-19, *t*-Bu, C-21, C-3′, and C-5, respectively. *Anal.* ($C_{28}H_{44}O_3$) C, H.

16α-(3-*tert*-Butoxypropyl)pregn-4-ene-3,20-dione (II).—A soln of 700 mg of I in 30 ml of PhMe and 4 ml of cyclohexanone was refluxed for 1 hr under a Dean–Stark head. $Al(O\text{-}i\text{-}Pr)_3$ (0.9 g) was then added and reflux was resumed for 2 hr. The crude product was chromatographed on 20 g of acid-washed Al_2O_3, using mixtures of hexanes, C_6H_6, and EtOAc as eluent. II crystd from hexanes in a 75% yield: mp 64–70°; ν^{CCl_4} 1720 and 1680 cm^{-1}; nmr (CCl_4), singlets at δ 0.66, 1.33, 2.06, and 5.58, and a triplet at 3.24 (H at C-18, C-19 and O-*t*-Bu, C-21, C-4, and C-3′, respectively. *Anal.* ($C_{28}H_{44}O_3$), C, H.

16α-(3-Hydroxypropyl)pregn-4-ene-3,20-dione (III).—After II (700 mg) had been treated with CF_3CO_2H, the crude product was chromatographed over 45 g of acid-washed Al_2O_3. EtOAc eluted III which crystd from Et_2O–hexanes, in a yield of 58%: mp 106°; nmr, singlets at δ 0.69, 1.17, 2.12, and 5.72 and a smeared triplet 2.62 (H at C-18, C-19, C-21, C-4, and C-3′, respectively. *Anal.* ($C_{24}H_{36}O_3$) C, H.

16α-(3-Hydroxypropyl)pregn-4-ene-3,20-dione Methanesulfonate (IV).—A soln of 150 mg of III in 5 ml of C_5H_5N was treated with 0.2 ml of $MeSO_2Cl$ for 3 hr at 0°. The excess $MeSO_2Cl$ was decompd by the addition of ice. The reaction mixture was then poured into Et_2O and extd ice-cold, with HCl, H_2O, aq $NaHCO_3$, and H_2O. The org layer was dried ($MgSO_4$) and the solvent distd to afford IV: yield 90%; mp 174–175° dec; nmr, singlets at δ 0.68, 1.18, 2.13, 3.00, and 5.73 and a triplet (J = 5 Hz) at 4.17 (H at C-18, C-19, C-21, OSO_2CH_3, C-4, and C-3′, respectively). *Anal.* ($C_{25}H_{38}O_5S$) C, H.

16α-(3-Hydroxypropyl)pregn-4-ene-3,20-dione Bromoacetate (V).—A soln of 0.2 ml of $BrCH_2COBr$ in 10 ml of EtOAc was refluxed for 10 min and then cooled. After 160 mg of III had been added, refluxing was resumed for 1 hr. The mixture was taken to dryness *in vacuo*. The dark residue was chromatographed on 4 g of acid-washed Al_2O_3. C_6H_6 eluted an oil which crystd from Et_2O–hexanes to give V; in a yield of 24%; mp 88–89°; ν^{CCl_4} 1738, 1703, and 1675 cm^{-1}; nmr, singlets at δ 0.70, 1.21, 2.18, 3.92, and 5.84 and a triplet at 4.24 (H at C-18, C-19, C-21, $COCH_2Br$, C-4, and C-3′, respectively). *Anal.* ($C_{26}H_{37}BrO_4$) C, H.

16α-(3-Hydroxypropyl)pregn-4-ene-3,20-dione *p*-Toluenesulfonate (VI).—A soln of 150 mg of III in 5 ml of cold C_5H_5N was treated with 300 mg of TsCl essentially as described under IV. From Et_2O, VI was obtained as a foam: yield 92%; nmr, singlets at δ 0.65, 1.21, 2.11, 2.45, and 5.75, doublets at δ 7.77 (J = 8 Hz) and 7.34 (J = 8 Hz), and a triplet at 3.96 (J = 5 Hz) (H at C-18, C-19, C-21, $PhCH_3$, C-4, aromatic (both doublets), and C-3′, respectively). *Anal.* ($C_{31}H_{42}O_5S$) C, H.

16α-(3-Hydroxypropyl)pregn-4-ene-3,20-dione *p*-Fluorosulfonylbenzoate (VII).—A soln of 160 mg of III, 100 mg of *p*-fluorosulfonylbenzoyl chloride, and 0.2 ml of C_5H_5N in 2 ml of PhMe was refluxed for 2 hr and then stirred at room temp for 4 hr. The crude product crystd from Et_2O–hexanes to give VII, in an 84% yield: mp 141–142°; ν^{CCl_4} 1725, 1700, and 1670 cm^{-1}; nmr, singlets at δ 0.70, 1.20, 2.16, and 5.17 doublets a 8.17 and 8.37, and a triplet at 4.35 (H on C-18, C-19, C-21, C-4, aromatic H (doublets) and C-3′, respectively). *Anal.* ($C_{31}H_{29}FO_6S$) C, H, S, F.

3β-Hydroxy-16α-(3-butenyl)pregn-5-en-20-one (VIII).—To a Grignard reagent prepared from 15 g of 4-bromo-1-butene and 3.5 g of Mg in 200 mg of Et_2O was added 7 g of 16-dehydropregnenolone acetate in 200 ml of Et_2O. The resulting mixture was refluxed for 15 min. The crude product was refluxed for 30 min in a soln containing 5 g of KOH, 10 ml of H_2O, and 180 ml of MeOH. After having been chromatographed over 200 g of acid-washed alumina, the product (VIII) crystd from hexanes in a yield of 58%: mp 133°; ν^{CCl_4} 3400, 1705, and 1640 cm^{-1}; nmr, singlets at δ 0.65, 1.00, and 2.14 and a multiplet at 5.38 (H at C-18, C-19, C-21, and C-5, respectively[6]). *Anal.* ($C_{25}H_{38}O_2$) C, H.

3β-Hydroxy-16α-(4-pentenyl)pregn-5-en-20-one (IX).—This compd was prepared by addition of the Grignard reagent derived from 5-bromo-1-pentene to 16-dehydropregnenolone acetate under conditions similar to those described for VIII. The product crystd from hexanes in a yield of 64%: mp 90–92°; nmr, singlets at δ 0.65, 1.16, 2.12, and a multiplet at 5.38.[6] *Anal.* ($C_{26}H_{40}O_2$) C, H.

16α-(3-Butenyl)pregn-4-ene-3,20-dione (X).—VIII was oxidized by the procedure described under II to afford in 89% yield an oil which appeared by ir, nmr, and tlc criteria to be slightly impure X. As the oil darkened on handling, it was used in the next step without further purification.

16α-(4-Pentenyl)pregn-4-ene-3,20-dione (XI).—IX was oxidized by a procedure similar to that described under II. After an additional chromatography, XI was obtained as crystals from hexanes; yield 80%; mp 58–59°; ν^{CCl_4} 1710, 1680, and 1640 cm^{-1}; nmr, singlets at δ 0.67, 1.17, 2.12, and 5.73 (H at C-18, C-19, C-21, and C-4, respectively[6]). *Anal.* ($C_{26}H_{38}O_2$) C, H.

3β,4′-Dihydroxy-16α-butylpregn-4-en-20-one.—To a soln of 216 ml of 2-methyl-2-butene in 13 ml of THF, under N_2, was added 13 ml of 1 *M* BH_3 in THF. The temp was maintained at 0–5°, and the mixture was stirred for 1.5 hr. A soln of 3.1 g of X in 2.5 ml of THF was added slowly. The resulting mixture was stirred at 0–5° for 1 hr, and then 10 ml of ice–water, followed by 10

(6) Compounds containing a terminal vinyl group in the side chain possessed a complex nmr pattern appropriate to such groups: see A. A. Bothner-By, C. Naar-Colin, and H. Günther, *J. Amer. Chem. Soc.*, **84**, 2748 (1962).

ml of 3 *N* NaOH, was added. The ice bath was removed and 12 ml of 30% H_2O_2 was added. The product was extd with Et_2O, washed with H_2O, dried ($MgSO_4$), and concd under reduced pressure. Chromatography over 150 g of acid-washed alumina afforded the 3β,4′-dihydroxy-11α-butylpregn-4-en-20-one, as crystals from MeOH, in a yield of 64%: mp 118–120°; nmr, singlets at δ 0.65, 1.04, and 2.04, and multiplets at 3.60 and 5.34 (H at C-18, C-19, C-21, C-4′, and C-4, respectively). *Anal.* ($C_{25}H_{40}O_3$) C, H.

16α-(4′-Hydroxybutyl)pregn-4-ene-3,20-dione (XII).—A soln of 3β,4′-dihydroxy-16α-butylpregn-4-en-20-one in 250 ml of C_6H_6 containing 32 ml of Me_2CO and 7.5 g of $Al(O\text{-}i\text{-}Pr)_3$ was stirred at room temp for 21 hr. The reaction product was chromatographed twice over acid-washed alumina to afford XII as an oil: ν^{CCl_4} 3470, 1703, and 1675 cm^{-1}; nmr, singlets at δ 0.69, 1.20, 2.15, and 5.75, and a multiplet at 3.58 (H at C-18, C-19, C-21, C-4, and C′-4, respectively). *Anal.* ($C_{25}H_{38}O_3$) C, H.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione (XIII).—To a soln of 2.1 ml of 2-methyl-2-butene in 10 ml of THF was added 10 ml of 1 *M* BH_3 in THF. The reaction mixture was stirred under N_2 for 2 hr in an ice bath. A soln of 2.6 g of XI in 20 ml of THF was then added dropwise and stirring in an ice bath was continued for 1 hr. After 10 ml of ice–water, followed by 10 ml of 3 *N* NaOH, had been added, the ice bath was removed, and 9 ml of 30% H_2O_2 was added. The crude product was chromatographed over 150 g of acid-washed alumina. Elution with 20% EtOAc in C_6H_6 afforded 240 mg of unchanged XI. Elution with 90% EtOAc in C_6H_6 gave XIII as an oil which crystd from Et_2O–hexanes, in a 50% yield: mp 107–108°; nmr similar to that of XII. *Anal.* ($C_{26}H_{40}O_3$) C, H.

16α-(4-Hydroxybutyl)pregn-4-ene-3,20-dione Methanesulfonate (XIV).—A procedure similar to that used to form IV converted XII into XIV in a yield of 73%. The compd was an oil and displayed spectroscopic properties similar to those of IV. *Anal.* ($C_{26}H_{40}O_5S$) C, H.

16α-(4-Hydroxybutyl)pregn-4-ene-3,20-dione Bromoacetate (XV).—A soln of 200 mg of XII in 10 ml of EtOAc was cooled in an ice bath and 0.1 ml of $BrCH_2CoBr$ was added. The mixture was stirred in the cold for 30 min and then was poured into Et_2O. The org layer was washed with cold 10% aq HCl, H_2O, satd aq $NaHCO_3$, and H_2O. It was then dried ($MgSO_4$) and the solvent was distd. The residue was chromatographed over 3 g of acid-washed alumina to afford XV, as an oil, in a 74% yield: nmr, singlets at δ 0.69, 1.20, 2.17, 3.87, and 5.78 and a triplet at 4.18 (H at C-18, C-19, C-21, bromoacetate, C-4, and C-4′, respectively). *Anal.* ($C_{28}H_{41}BrO_4$) C, H.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione Methanesulfonate (XVI).—By a procedure similar to that used to form IV, XIII was converted into XVI in a yield of 85%. The compd was an oil which showed spectroscopic properties similar to those of IV. *Anal.* ($C_{27}H_{42}O_5S$) C, H.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione Bromoacetate (XVII).—By a procedure similar to that used to form V, XIII was converted into XVII in a yield of 20%: nmr, singlets at δ 0.69, 1.18, 2.14, 3.83, and 5.71 and a triplet at 4.12 (H at C-18, C-19, C-21, bromoacetate, C-4, and C-5′, respectively). *Anal.* ($C_{28}H_{41}BrO_4$) C, H.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione *p*-Toluenesulfonate (XVIII).—To a soln of 200 mg of XIII in 3 ml of C_5H_5N was added 200 mg of TsCl. The mixture was stirred in an ice bath for 4.5 hr. Several chips of ice were then added and stirring was continued for 20 min. The mixture was diluted with Et_2O and extracted ice cold with 10% aq HCl, H_2O, satd $NaHCO_3$, and H_2O. After drying ($MgSO_4$), the solvent was distilled to leave XVIII as an oil in 68% yield: ν^{CCl_4} 1705 and 1680 cm^{-1}; nmr, singlets at δ 0.68, 1.18, 2.11, 2.45, and 5.74; doublets at 7.35 and 8.01, and a triplet at 4.00 [H at C-18, C-19, C-21, Ar-CH_3, C-4, aromatic (both doublets) and C-5′, respectively]. *Anal.* ($C_{33}H_{46}O_5S$) C, H, S.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione *p*-Fluorosulfonylbenzoate (XIX).—A soln of 200 mg of XIII in 2 ml of PhMe containing 0.2 ml of C_5H_5N and 113 mg of $p\text{-}ClOC_6H_4SO_2F$ was refluxed for 6 hr, diluted with Et_2O, and filtered. The filtrate was washed with 10% aq HCl, satd $NaHCO_3$, and H_2O. After the org phase had been dried ($MgSO_4$) the solvent was distd to leave XIX as an oil, in a yield of 89%; ν^{CCl_4} 1725, 1701, and 1675 cm^{-1}, nmr, singlets at δ 0.69 1.20, 2.16, and 5.74, doublets at 8.17 and 8.76, and a triplet at 4.42 (H at C-18, C-19, C-21, C-4, aromatic (both doublets), and C-5′, respectively). *Anal.* ($C_{33}H_{43}FO_6S$) C, H, S, F.

16α-(5-Hydroxypentyl)pregn-4-ene-3,20-dione *p*-Methylbenzoate (XX).—To a soln of 200 mg of XIII in 5 ml of C_5H_5N was added 1 ml of toluoyl chloride. The mixture was stirred for 4 hr at 0° and then for 20 hr at room temp. After usual work-up, the crude product was chromatographed over 15 g of acid-washed Al_2O_3. Mixture of C_6H_6 and EtOAc were used as eluents to obtain an oil which crystd from Et_2O to give XX in a yield of 35%: mp 170–172°; ν^{CHCl_3} 1720, 1695, and 1660 cm^{-1}; nmr singlets at δ 0.68, 1.18, 2.14, 2.42, and 5.75, doublets at 7.24 and 7.94, and a triplet at 4.28 (H at C-18, C-19, C-21, Ar-CH_3, C-4, aromatic (both doublets), and C-5′, respectively). *Anal.* ($C_{34}H_{46}O_4$) C, H.

16α-(5-Bromopentyl)pregn-4-ene-3,20-dione (XXI).—The crude XVIII, prepared from 400 mg of XIII, was dissolved in 5 ml of freshly distd Me_2CO and 300 mg of anhyd LiBr was added. The reaction mixture was left for 72 hr at room temp and was then filtered. The filtrate was concd and then partitioned between H_2O and Et_2O. The org phase was dried ($MgSO_4$) and distd to leave a residue which crystd from Et_2O–hexanes to afford 390 mg of crude XXI, mp 100–102°. Chromatography over 12 g of acid-washed Al_2O_3 gave an oil which crystd from Et_2O–hexanes to afford XXI, yield 38%: mp 107.5–108°; ν^{CCl_4} 1700 and 1675 cm^{-1}; nmr, singlets at δ 0.68, 1.20, 2.14, and 5.73, and a triplet at 3.40 (H at C-18, C-19, C-21, C-4, and C-5′, respectively). *Anal.* ($C_{26}H_{39}BrO_2$) C, H, Br.

3-*tert*-Butoxy-1-bromopropane.—To 200 ml of CH_2Cl_2 in a hydrogenation bottle was added 25 g of 3-bromopropanol and 0.8 ml of concd H_2SO_4. The mixture was cooled in an ice bath and approximately 200 ml of isobutylene was added. The bottle was sealed, and then shaken at room temp overnight. The reaction mixture was washed with aq $NaHCO_3$ and then with H_2O. After being dried ($MgSO_4$), it was concd and then chromatographed over 200-g of alumina using hexanes as eluent. The 3-*tert*-butoxy-1-bromopropane was isolated in a yield of 15.8 g as in oil. The anal. sample was prepared by distn. *Anal.* ($C_7H_{15}OBr$).

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