166.5°; $[\alpha]_{365}$ +104°, $[\alpha]_{436}$ +67.3°, $[\alpha]_{546}$ +39.7°, $[\alpha]_D$ +36.7°; ν_{max} 3050 and 1620 cm^{-1} (C=C).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.03; H, 10.84.

5β-Pregn-16-ene-3α,21-diol Diacetate (27).—Acetylation of 5β-pregn-16-ene-3α,21-diol in the usual fashion gave an amorphous product which was homogeneous (R_f 0.20) by tlc in isooctane–ethyl acetate (6:1): $[\alpha]_{365}$ +144°, $[\alpha]_{436}$ +93.6°, $[\alpha]_{546}$ +55.0°, $[\alpha]_D$ +47.7°.

Hydrogenation of a sample of **27** as in the reduction of **8** to **5** and purification of the product on a small silica gel column afforded prismatic needles from methanol, mp 73–75°. This compound was identical in all respects with the lithium aluminum hydride reduction product (**22**) of the diacetate tosylate **20**.

21-Tosyloxy-5β-pregnan-3α-ol (18) from 21.—A solution of 5β-pregnane-3α,21-diol (100 mg) and tosyl chloride (70 mg) in pyridine (1 ml) stood for 18 hr at room temperature. The crude product was chromatographed on a 20 × 705 mm silica gel column in isooctane–ethyl acetate (3:2). Fractions (3 ml) were collected at 10-min intervals. The residue from fractions 141–180 weighed 39.1 mg and, although homogeneous (R_f 0.14) by tlc in the same system, could not be obtained in crystalline form: ν_{max} 1598, 1493, 1357, 1188, 1173, 1095, 810, 660 (tosylate), and 1035 cm^{-1} (3α-hydroxyl).

Lithium aluminum hyride reduction of the tosylate **28** (23.5 mg) in the usual fashion and crystallization of the product from acetone gave needles (8.8 mg, mp 148.5–150°; 4 mg, mp 144.5–146.5°). On admixture with a sample of **5β-pregnan-3α-ol** derived from **1**, the melting point was unaltered and their infrared spectra were identical. In addition, acetylation afforded a crystalline product which had the same infrared spectrum as that obtained from **6**.

Registry No.—**3**, 16054-71-0; **4**, 16054-58-3; **5**, 4352-07-2; **6**, 16054-60-7; **8**, 16109-75-4; **9**, 16054-61-8; **10**, 16109-76-5; **11**, 16109-77-6; **13**, 16054-62-9; **14**, 16054-63-0; **16**, 16054-64-1; **17**, 16054-65-2; **18**, 16109-78-7; **19**, 16054-66-3; **21**, 16109-79-8; **22**, 16054-67-4; **23**, 16109-80-1; **24**, 16054-68-5; **25**, 16054-69-6; **26**, 16054-70-9.

Studies in the 21-Methyl Steroid Series. Organoborane Rearrangements and a Novel Synthesis of 21-Methyl-19-nor Steroids

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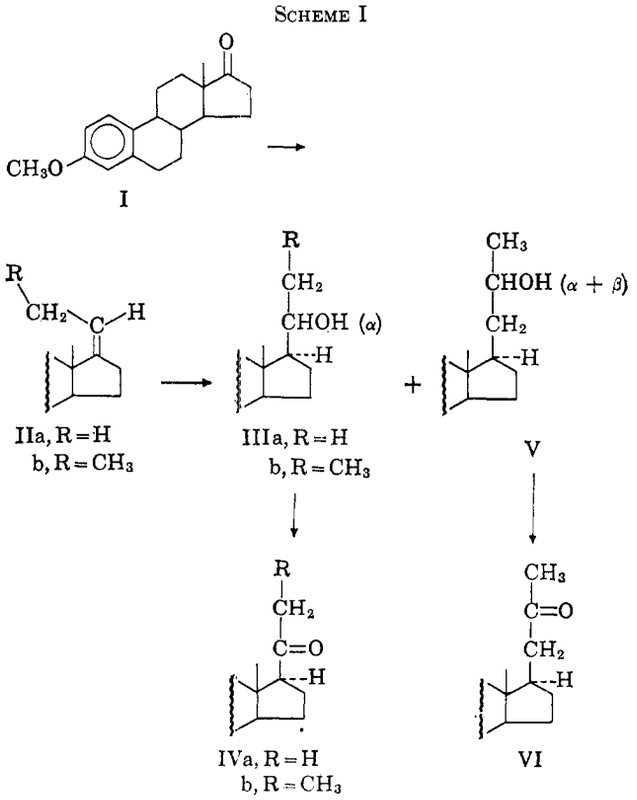
The Wittig reaction of estrone methyl ether (I) with propylidenetriphenylphosphorane gave the 17-propylidene derivative (IIb). Hydroboration at room temperature produced a mixture of C-20 and C-21 alcohols (IIIb and V). At higher temperatures mostly V was formed, whereas at low temperatures predominantly IIIb was obtained. Further conversions into 21-methyl-19-nor steroids X, XI, and XIIIa, b, and c are described.

The addition of a two-carbon pregnane (17β acetyl) side chain to a 17-keto steroid by a Wittig–hydroboration–oxidation sequence (*e.g.* I → IIa → IIIa → IVa) has been previously described[1] (see Scheme I).

Scheme I



We would now like to report the results of our studies directed toward the synthesis of 21-methylpregnanes, *i.e.*, introduction of a three-carbon side chain by the same sequence. Surprisingly, the addition of one more carbon atom to the side chain led us to some fascinating and unexpected new chemistry. For all studies estrone methyl ether (I) was used as a starting 17-keto steroid.

Reaction of I with *n*-propylidenetriphenylphosphorane under identical conditions as those used for the preparation of IIa led to *ca.* 80% of crude, semicrystalline product. This material, when analyzed by vapor phase chromatography (vpc), proved to be a mixture of 90% of the expected geometrically isomeric olefins (ratio 96:4) and 10% of impurities. The major product was obtained pure by recrystallization in an over-all yield of 50–55%. Since the major geometrical isomer (92%) from the two-carbon Wittig reaction (IIa) was shown to be *cis*,[1] we have by analogy assigned the identical configuration to IIb. In addition, the nmr spectra are in agreement. The C-18 methyl resonance of IIa is at δ 0.90 (relative to TMS) and that of its *trans* isomer is at 0.77, consistent with the deshielding effect of the 21-methyl group. The C-18 methyl resonance of IIb also occurred at δ 0.90 being compatible with the above stereochemical assignment. Hydroboration of IIb with excess 1 *M* borane–tetrahydrofuran reagent[2] at room temperature for 2 hr, followed by the usual oxidative work-up, afforded a mixture of alcohols separated by careful column chromatography into two components. The major alcohol isolated in 40% yield after chromatography proved to

(1) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

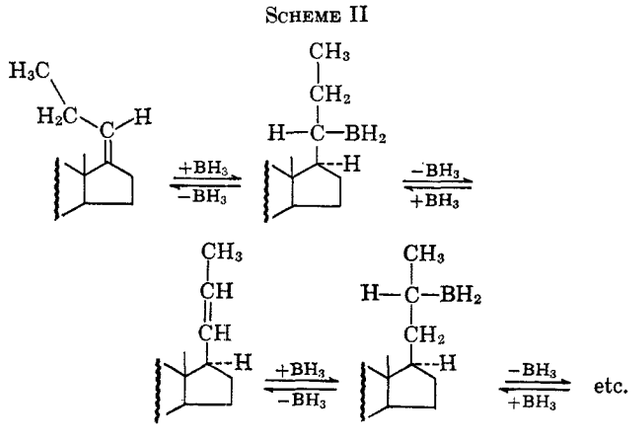
(2) Available from Metal Hydrides, Inc., Beverly, Mass.

be a 20 alcohol. This alcohol most likely had the α configuration (IIIb) based upon our earlier work[1] and the fact that diborane should add from the bottom side, affording a 20α-ol from a *cis*-$\Delta^{17(20)}$ olefin. This material upon chromic oxide oxidation afforded the 20 ketone (IVb), which was clearly characterized from its nmr spectrum (δ 1.03, 3 H, triplet, J = 7 cps; δ 2.41, 2 H, quartet, J = 7 cps). The minor alcohol (V), isolated in 20% yield after chromatography, appeared after closer examination to be a mixture of two components. Chromic oxide oxidation of this mixture afforded one compound easily identified by its distinctive nmr spectrum (δ 2.15, 3 H, singlet) as the 21 ketone (VI). Apparently, the alcohol mixture (V) was composed of the two epimeric 21-ols.

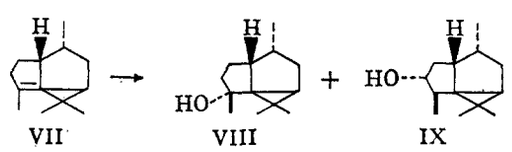
When the hydroboration reaction was repeated, the crude product oxidized to ketone, and this material analyzed by vpc, a C-20/C-21 oxygenation ratio of 3.5:1 was obtained.

At first, we considered it surprising to find that hydroboration of a $\Delta^{17(20)}$ olefin afforded such a substantial amount of C-21 alcohol. However, it is well known that hydroboration of olefins in the presence of excess borane is reversible and that organoborane isomerization can occur to place boron (oxygen precursor) at varying positions of a carbon chain when the reaction is conducted at elevated temperature (usually 160°, refluxing diglyme; 50° is the lowest reported). Indeed, this has been the subject of some intensive investigation by Brown.[3] A possible isomerization sequence of the type discussed by Brown is shown in Scheme II.

SCHEME II



Our reaction was performed at room temperature, and 20–25% isomerization occurred within 2 hr. This was obviously of interest since, as mentioned above, 50° was the lowest temperature reported for such an isomerization. In that case,[3] 15% of terminal alcohol was formed in 2 hr by hydroboration of 2,4,4-trimethyl-2-pentene. There is an example of a possible room temperature organoborane isomerization from some recent work of Ourisson,[4] who observed that equal amounts of tertiary (VIII) and secondary (IX) alcohols were formed from the room temperature hydroboration of the sesquiterpene α-gurjunene (VII).



(3) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **88**, 1433 (1966).
(4) P. Pesnelle and G. Ourisson, *J. Org. Chem.*, **30**, 1744 (1965).

Ourisson suggested that an organoborane isomerization of the type depicted above was occurring, but he could not demonstrate any change in the ratio of alcohols with increasing temperature, even at 160°. He did not try the reaction below room temperature.

We have studied the effect of temperature on the C-20/C-21 oxygenation ratio (ratio of IVb/VI) for the hydroboration–oxidation of IIb. The data are presented in Table I. This reversal, from practically all C-20 oxygenation to almost all C-21 oxygenation within a 65° degree temperature range and at such relatively low temperatures (*i.e.*, close to room temperature), is indeed striking. This is underscored when one realizes the potential synthetic utility (as will be described below) and the possible dangers involved, particularly in using hydroboration as a tool for structural elucidation.

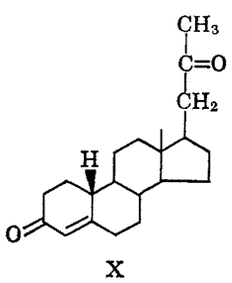
TABLE I

Temp, °C	Ratio of IVb/VI[a]
0	49
25	3.5
65	0.059

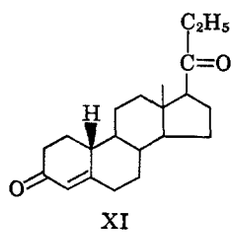
[a] Determined by vpc analysis of crude hydroboration product after Jones oxidation.

We also tried to make boron migrate to the end of the three-carbon side chain by conducting the hydroboration of IIb at higher temperatures, but even reaction at 160° produced no detectable amounts of the C-22 alcohol. It seems likely, therefore, that, in the case of IIb, migration of boron from C-21 to C-22 is an unfavorable process. With IIa, however, terminal (21) alcohol was formed by conducting the reaction at 65°, but at a much slower rate than 21-alcohol formation from IIb.

We have put the above organoborane isomerizations to some synthetic use by preparing novel 21-methyl-19-nor steroids. As previously mentioned, hydroboration of IIb at 65° produces predominantly a mixture of 21-ols (V). These are isolable in 60% yield by direct crystallization of the crude hydroboration product. Subsequent Birch reduction, acid hydrolysis, and Jones oxidation afforded the novel 19-nor steroid (X) in 58% yield from V. In a similar manner the 20α-ol (IIIb) was converted into 21-methyl-19-norprogesterone (XI) in 67% yield.



X



XI

Both X and XI exhibited progestational activity in the Clauberg assay (Table II), X being rather weak when compared with 19-norprogesterone and XI having about the same potency.

It is well known that the introduction of a 17α-acyloxy function in the above type of steroid structure in-

Table II

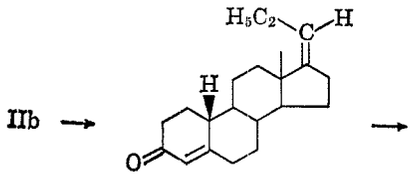
Clauberg Assay

Compd	Active dosage, mcg/kg day^{-1} (s.c.)[a]
X	400
XI	20
XIIIa	200
XIIIb	10
XIIIc	100
19-Norprogesterone	10

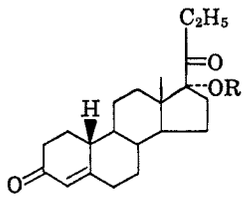
[a] These compounds were inactive orally up to 400 mcg/kg day^{-1}.

creases subcutaneous activity and usually introduces significant oral activity. With this in mind we decided to prepare 17α-hydroxy and acyloxy analogs of XI.

The $\Delta^{17(20)}$-19-nor-3 ketone (XII) was prepared by Birch reduction of IIb, followed by acid hydrolysis. This compound was smoothly converted, in 36% yield, into the ketol (XIIIa) using the Upjohn technique[5] with a catalytic amount of osmium tetroxide and N-methylmorpholine oxide peroxide.



XII



XIIIa, R = H
b, R = $COCH_3$
c, R = $CO(CH_2)_4CH_3$

The corresponding acetate (XIIIb) and caproate (XIIIc) were prepared in the usual manner.

Compounds XIIIa and XIIIc proved to be very weak progestins (see Table II), whereas XIIIb had essentially the same activity as the parent compound XI. All of the above compounds were substantially less active than the more potent progestins presently being marketed. It thus appeared that the addition of a 21-methyl group to a 19-norprogesterone system did not enhance (and in some cases decreased) the progestational activity.

Experimental Section[6]

Preparation of IIb.—Sodium hydride–mineral oil dispersion (34.9 g, 55% NaH) was washed three times with petroleum ether (30–60) and blown dry with nitrogen. Dry dimethyl sulfoxide (DMSO) (1 l.) was added and the mixture was stirred vigorously under nitrogen at 70–75° until hydrogen evolution ceased (30–45 min). The light green solution was cooled to room temperature and a solution of 308 g of *n*-propyltriphenylphosphonium bromide in 1.2 l. of DMSO was rapidly added. To the resulting deep red solution was added a solution of 56.8 g of estrone methyl ether in 650 ml of benzene. The reaction mixture was heated at 60° overnight under nitrogen, cooled, and poured into ice water. After three extractions with petroleum ether, the combined organic extracts were washed three times with water and dried. The solution was evaporated under reduced pressure; the residue was slurried with petroleum ether and filtered through a plug of 100 g of neutral alumina (grade I). Elution with petroleum ether gave a crude crystalline product (vpc analysis: olefin isomers 86%, 4%; impurities, 10%) which was recrystallized from ether–methanol to afford 28.7 g of IIb, mp 72–74°. A second crop, after further purification, afforded an additional 1.47 g: mp 70–71.5°; $[\alpha]^{25}D$ +54.1°.

Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 84.85; H, 9.79.

Room Temperature Hydroboration of IIb.—A solution of 1.8 g of IIb in 75 ml of dry THF was treated at room temperature with 10 ml of 1 *M* BH_3–THF complex for 1.5 hr. After the excess reagent was destroyed by cautious addition of 32 ml of 10% sodium hydroxide solution, the reaction mixture was cooled to 0° and treated with 10 ml of 30% hydrogen peroxide for 45 min. Water and ethyl acetate were added and the organic layer was washed successively with 10% sodium bisulfite solution, water, and saturated brine and dried. The solvent was removed under reduced pressure to afford 2.02 g of crude oil. Tlc analysis indicated two major products were present; this material was chromatographed on 1000 g of silica gel using benzene–ethyl acetate (4:1) as solvent. The two major bands were separated from each other.

The more abundant component (IIIb), 790 mg, was a crystalline solid which, after recrystallization from ether–petroleum ether, had mp 110–114°. Compound III (100 mg) was oxidized with chromic oxide–dimethylformamide reagent[7] in the normal fashion to afford 91 mg of crystalline IVb. The analytical sample had mp 120.5–122.0°, $[\alpha]^{25}D$ +140.2°.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.27. Found: C, 81.19; H, 9.26.

The minor product from chromatography (V), 390 mg, was recrystallized from ether–petroleum ether, mp 127–134°, and appeared to be a mixture of two components by tlc analysis. A portion of this material (50 mg) was oxidized as above to afford 44 mg of an oil which slowly crystallized (VI). An analytical sample was prepared by another method (see below).

Hydroboration of IIb at 65°.—A solution of 4.0 g of IIb in 150 ml of dry THF was treated with 22 ml of 1 *M* BH_3–THF complex. After stirring 0.5 hr at room temperature, the reaction mixture was heated at reflux for 1.5 hr, cooled, and processed as above (71 ml of 10% sodium hydroxide, 22 ml of 30% hydrogen peroxide). The crude crystalline product (4.0 g), which appeared to be mostly V (containing a small amount of III) by tlc analysis, was recrystallized from ether–petroleum ether to afford 1.72 g of V (mixture of epimers), mp 131–134°. A second crop of 864 mg, mp 121–128°, was also obtained.

The above first crop (1.48 g) was treated in the normal fashion with 1.25 ml of 8 *N* chromic acid reagent in acetone at 0°. After work-up, the crude solid was recrystallized from ether–petroleum ether to afford 1.12 g of crystals (VI): mp 92–93°; $[\alpha]^{25}D$ +51.7°.

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.27. Found: C, 80.77; H, 9.27.

A repeat of the above experiment without purification of the alcohol mixture gave a mixture of ketones (VI and IVb) in a ratio of 17:1 (vpc analysis).

Low Temperature Hydroboration of IIb.—A solution of 0.5 g of IIb in 25 ml of dry THF was treated between −10 and 0° (mostly from −5 to 0°) with 5 ml of 1 *M* BH_3–THF complex for 2 hr, then treated with 12.5 ml of 10% sodium hydroxide and 6 ml of 30% H_2O_2. The reaction was then allowed to stir overnight at room temperature and worked up in the normal fashion. Tlc analysis indicated mostly IIIb present, possibly a minor trace of V. Jones oxidation of the material afforded a crystalline solid which appeared to be almost entirely IVb by tlc analysis. Vpc analysis indicated a ratio of IVb to VI of 49:1.

Preparation of X.—To a solution of 3.0 g of V in 250 ml of dry THF was added by distillation 250 ml of ammonia. Lithium metal (3.0 g) was added in small pieces and the reaction vigorously stirred for 45 min. Absolute ethanol (50 ml) was added dropwise over 10 min; the reaction mixture was stirred under

(5) A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *J. Org. Chem.*, **24**, 1517 (1959); Upjohn Co., U. S. Patent 2,769,823.

(6) All melting points are corrected. Infrared spectra and optical rotations (concentration, 1%) were determined in chloroform. Nmr spectra were run in deuteriochloroform using tetramethylsilane as an internal standard. All solutions were dried over sodium sulfate and solvents were evaporated at reduced pressure.

(7) G. Snatzke, *Chem. Ber.*, **94**, 729 (1961).

reflux until the blue coloration disappeared. The ammonia was evaporated by heating with a water bath, and water and ether were added. The ether layer was washed with water, dried, and evaporated. The crude white solid was dissolved in methanol (80 ml) and 2 *N* HCl (30 ml) and heated at reflux for 1.75 hr. After concentration under reduced pressure and extraction with ether, a crude oil (3.6 g) was obtained. This was chromatographed on 100 g of neutral alumina (grade I). Ether–ethyl acetate (9:1 and 8:2) eluted 2.27 g of colorless oil which appeared to be all conjugated ketone by tlc analysis. This material was dissolved in 70 ml of acetone and oxidized at 0° with 2.0 ml of 8 *N* chromic acid reagent. After the usual work-up, 2.3 g of a yellow oil (which slowly solidified) was obtained. Recrystallization from ether–petroleum ether afforded 1.55 g of white needles: mp 93–94°; $[\alpha]^{25}D$ +51.7°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.32; H, 9.77.

Preparation of XI.—IIIb (150 mg) was reduced with lithium (150 mg) in ammonia–THF solution as in the previous example. The crude product was hydrolyzed with refluxing methanolic hydrochloric acid to afford 140 mg of crystalline material. This material was oxidized in acetone solution at 0° by titrating with 8 *N* chromic acid reagent. After the normal work-up, the crude product (125 mg) was chromatographed on 5 of neutral alumina (grade I). A crystalline product (90 mg) was eluted with benzene–ether (1:1) which, after recrystallization from ether–petroleum ether, melted at 98–99°. The analytical sample crystallized as needles and had mp 110–111°, $[\alpha]^{25}D$ +147.0°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.04; H, 9.79.

Preparation of XIIIa.—To a solution of 20.0 g of II in 1800 ml of dry THF was added by distillation 900 ml of ammonia. Lithium wire (20 g) was added with rapid stirring. After 30 min, 270 ml of absolute ethanol was added rapidly. After the blue coloration disappeared the ammonia was evaporated and the product was isolated with ether. This crude material was dissolved in 1 l. of acetone and treated with 330 ml of 2 *N* HCl for 1.5 hr at room temperature. After dilution with water and brine, the product was isolated with ether. The crude oil appeared from tlc analysis to consist of one major spot and a few minor, less polar ones. It was chromatographed on 1000 g of silica gel. Benzene–ethyl acetate (19:1 and 9:1) eluted 18.3 g of oil which appeared homogeneous by tlc analysis (XII). This material was dissolved in a mixture of 830 ml of *t*-butyl alcohol, 100 ml of methylene chloride, and 27.5 ml of pyridine and was treated with 152 ml of N-methylmorpholine oxide peroxide solution in *t*-butyl alcohol[5] and then with 6.7 ml of 3% osmium tetroxide solution in *t*-butyl alcohol. The reaction mixture immediately turned gray-purple in color. After stirring for 69 hr at room temperature, tlc analysis indicated the absence of starting material and the presence of one major new product. The reaction mixture was treated with 150 ml of 5% sodium sulfite solution and then concentrated under reduced pressure. The product was isolated from methylene chloride. The crude, semicrystalline purple material (20.3 g) was chromatographed on 1000 g of silica gel. Benzene–ethyl acetate (4:1) eluted 9.3 g of purple crystals. Recrystallization from methylene chloride–ether afforded 5.47 g of colorless crystals, mp 194–196°. A second crop of light purple product, 1.7 g, mp 193–196°, was also obtained.

The analytical sample was crystallized from methylene chloride–ether: mp 193.5–193.6°; $[\alpha]^{25}D$ +41.8°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.63; H, 9.27.

Preparation of XIIIb.—A solution of 1.5 g of XIIIa in 30 ml of acetic anhydride was treated with 450 mg of *p*-toluenesulfonic acid monohydrate at room temperature for 3.5 hr. Water (65 ml) was then added and stirring was continued for an additional 15 min. The precipitated product was filtered and washed well with water.

This crude material was dissolved in 300 ml of methanol and treated with a solution of 1.35 g of potassium hydroxide in 6 ml of water and 15 ml of methanol for 15 min at room temperature. After neutralization with acetic acid, the reaction mixture was concentrated under reduced pressure, and the product was isolated from benzene to afford 1.59 g of solid, mp 170–173°. Recrystallization from ether–petroleum ether gave 800 mg, mg 176.5–177°. A second crop of 510 mg, mp 175–176°, was also obtained: $[\alpha]^{25}D$ +24.4°.

Anal. Calcd for $C_{27}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.33; H, 8.55.

Preparation of XIIIc.—A solution of 1.375 g of XIIIa in 15 ml of caproic acid was treated with 4 ml of trifluoroacetic anhydride at room temperature for 17 hr. The reaction mixture was treated cautiously with 225 ml of 5% sodium bicarbonate solution and, after CO_2 evolution ceased, the product was extracted into ether. The ether solution was washed twice with cold 2% sodium hydroxide solution and with water and then dried. The crude product was chromatographed on 150 g of silica gel. Benzene–ethyl acetate (9:1) eluted 1.5 g of crystalline material which was recrystallized from ether–petroleum ether, mp 101–107°. One further recrystallization afforded 1.184 g of XIIIc: mp 105–107°; $[\alpha]D^{25}$ +17.3°.

Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.99; H, 9.21.

Registry No.—IIb, 16201-89-1; IIIb, 16240-76-9; IVb, 16201-90-4; α V, 16201-91-5; β V, 16201-71-1; VI, 16201-92-6; X, 16201-93-7; XI, 16201-67-5; XIIIa, 16201-68-6; XIIIb, 16201-69-7; XIIIc, 16201-70-0.

Acknowledgments.—We are indebted to Drs. F. Vane and T. Williams for the nmr spectra, to Drs. A. Steyermark and F. Scheidl for the microanalyses, and to Dr. A. Boris for the endocrinological data. The valuable technical assistance of Mr. Harold Lucas is also greatly appreciated.