Stereochemistry of the Addition of Metalated Carboxylic Acids to Steroids[1]

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The stereochemistry of the addition of dilithiopropionate and α-halopropionate to dehydroisoandrosterone (**1a**) was studied. The stereochemistry at C_{17} and C_{20} of 17-hydroxybisnorcholanic acids previously determined was reassigned on the basis of new chemical and nmr spectroscopic evidence. The stereochemistry at C_{17} of 3β,17β-dihydroxy-20β-bisnorchol-5-enic acid (**3a**) and its 17α-hydroxy isomer **2a** was determined. Reduction with lithium aluminum hydride of **2a** and **3a** followed by tosylation of the alcohol **8a** and **9a**, which were again reduced by lithium aluminum hydride, yielded two isomeric C_{17} isopropyl compounds, **10** and **11**. Nmr characterization of **10** and **11** indicated that the expected major product resulted from α-side attack at the C_{17} ketone. Compound **11** was also prepared by Grignard reaction of 2-bromopropene and **1b**. The stereochemistry at C_{20} was determined by β-lactonization of acids **2a** and **3a** followed by decarboxylation to cis and trans olefins **6** and **7**.

The metalation of aliphatic carboxylic acids with lithium diisopropyl amide and the reaction of the dimetalated acids with alkylating agents have been reported.[2] We report on a study of the stereochemistry of the addition of dilithiopropionate to dehydroisoandrosterone (**1a**), since the equivalent Reformatsky reaction with α-bromopropionate has been studied in detail and all four compounds isomeric about C_{17} and C_{20} have apparently been isolated and characterized.[3,4]

Reaction of propionic acid with lithium diisopropylamide proceeded smoothly in tetrahydrofuran–hexane, and the dimetalated acid reacted with dehydroisoandrosterone **1a** to give acidic material in a yield of 50% (Scheme I). The nmr spectrum of the acidic fraction showed multiple C_{18} and C_{21} methyl resonances in a ratio of 4:1, indicating the formation of two isomers. The isomers were separated by fractional crystalization from acetone.

The major acidic isomer **3a** was esterified and acetylated to yield a methyl ester 3-acetate, mp 153–154°, $[\alpha]^{24}D$ −49° (acetone). These physical properties are in apparent accord with the isomer designated by Hey, *et al.*,[4] as methyl 3β-acetoxy-17α-hydroxy-20α-bisnorchol-5-en-21-oate, which was isolated as a minor Reformatsky reaction product.

If the previously assigned 17α-hydroxy stereochemistry is valid, this would indicate that the principal product resulted from attack at the more hindered β face of the C_{17} ketone by the dimetalated acid. This result is contrary to all previous addition reactions at C_{17} and suggested that the stereochemical assignment of the bisnorcholenic acids from the Reformatsky reaction should be reinvestigated.

The Reformatsky reaction of dehydroisoandrosterone **1a** with zinc and methyl α-bromopropionate in benzene gave the methyl esters, which were isolated in a 70% yield by a modified method compared to 26% when the products were isolated as acids.[4] Nmr inspection of the C_{18} angular methyl resonances revealed an approximately 3:2 mixture of the esters **3b** and **2b**. Saponification of the mixture of these methyl esters **3b** and **2b** yielded acid **2a** and only traces of acid **3a** along with the neutral ketone **1a**.

The low yield of the acid **3a** recovered under the saponification conditions indicates that retroaldolization of **3b** to starting ketone and propionic acid occurs. Since the retroaldol process changes the product distribution of the isomeric acids, owing to the disappearance of acid **3a** during saponification of its methyl ester **3b**, stereochemical assignments based solely on the relative distribution of acid isomers in the Reformatsky reaction are invalid.

To establish the stereochemistry of the acids **2a** and **3a**, the following series of transformations were conducted. Each acid was reduced with lithium aluminum hydride to afford the corresponding bisnorcholanetriols **8a** and **9a**. Reduction of the respective tosylates **8b** and **9a** with lithium aluminum hydride gave a pair of isomeric 17-hydroxy-3,5-cyclodinorcholanes, **10** and **11**, which had different physical properties and were different by thin layer chromatographic (tlc) behavior.

Since the transformation of **2a** to **10** and **3a** to **11** occurs with destruction of the asymmetric center at C_{20}, the nonidentity of **10** and **11** is evidence for a difference in their stereochemistry at C_{17}. For isomer **3a**, the major isomer formed by the reaction with dilithiopropionate, the nmr of its 17β-hydroxy-17α-isopropyl conversion product **11** shows an equivalence of the isopropyl methyl groups at τ 8.99 (J = 6.6 Hz) and the C_{18} angular methyl resonance appears at τ 9.06. In the nmr of the isopropyl derivative **10** derived from **2a**, which has the 17α-hydroxy-17β-isopropyl grouping, C_{18} angular methyl resonance now experiences greater shielding and resonates at higher fields at τ 9.20 and the isopropyl methyls show nonequivalence at τ 9.08 (J = 6.6 Hz), and τ 9.10 (J = 6.6 Hz). The 17β-isopropyl group is expected to show a greater nonequivalence of the isopropyl groups because of the severe nonbonded interactions with the β-oriented C_{18} angular methyl groups. The nmr data of **10** and **11** are consistent with the stereochemistry of acid **2a** as the 17α-hydroxy derivative and acid **3a** as the isomeric 17β-hydroxy compound.

The stereochemical assignments are in accord with the nmr pyridine solvent shifts of the C_{18} methyl resonance in **2a**, **3a**, **10** and **11**, Table I. The observed shift difference of 10 Hz is in agreement with previously observed values for vicinal deshielding by the 17β-hydroxy group.[5] Our assignment is also in accord with the observation that 17α-hydroxyl compounds

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(1) This work was supported by the Public Health Service under Grant AI 07397 from the National Institute of Allergy and Infectious Diseases.

(2) (a) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); (b) P. L. Creger, *ibid.*, **92**, 1396 (1970); (c) P. E. Pfeffer and L. S. Silbert, *Tetrahedron Lett.*, 699 (1970).

(3) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **24**, 1127 (1941).

(4) D. H. Hey, J. Honeyman, and W. J. Peal, *J. Chem. Soc.*, 185 (1954).

(5) P. Demarco, E. Farkas, D. Doddrell, B. Mylari, and E. Wenkert *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

SCHEME I

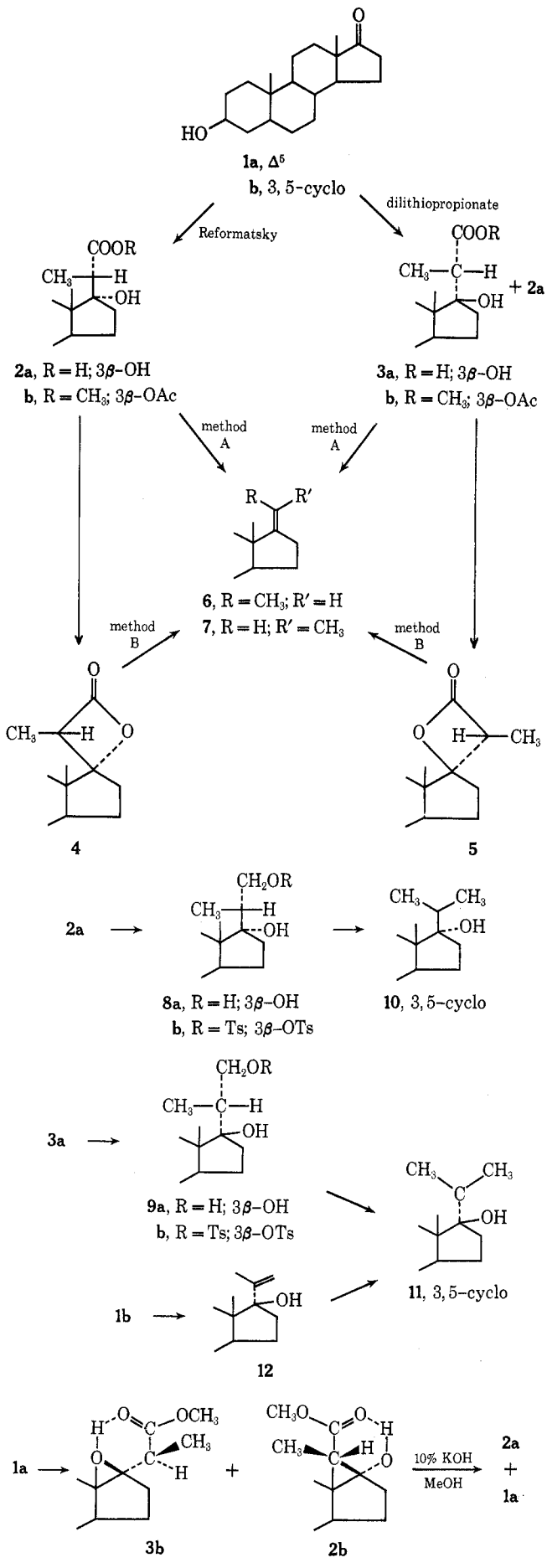
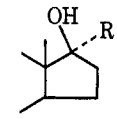
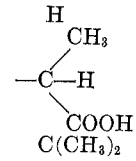


TABLE I

PYRIDINE SOLVENT SHIFTS



R	$\Delta_{18\text{-}CH_3}$[a]
H	10.0
	10.5
$C(CH_3)_2$	10.0

[a] $\Delta_{18\text{-}CH_3} = Hz_{CD_3N} - Hz_{1:1CDCl_3\text{-}CD_3OD}$. The $\Delta_{18\text{-}CH_3}$ pyridine solvent shifts for the corresponding isomeric 17α-hydroxy compounds were not detectable.

have a more negative rotation value than the 17β isomer.[6]

An alternate synthesis of **11** was achieved by the addition of isopropenylmagnesium bromide to 3α,5β-cycloandrostan-17-one **1b**. Catalytic reduction of the intermediate 17-isopropenyl compound yielded material identical in all respects with **11**. This method of synthesis also supports the 17α-isopropyl stereochemistry for **11**, since all known Grignard additions to C_{17} ketones occur predominantly from the α side.[7]

With the C_{17} configuration firmly established, we determined the C_{20} stereochemistry of **2a** and **3a**. Advantage was taken of a recent observation[8] that a 17-hydroxybisnorcholanic acid decarboxylates with boiling acetic anhydride to yield *cis*-pregn-17(20)-ene, which was formed by decarboxylation of an intermediate β-lactone (5.48 μ). Iwasaki[8] provided conclusive chemical evidence for the 17(20) double bond stereochemistry by osmium tetroxide hydroxylation of 3β-hydroxy-5α-pregn-*cis*-17(20)-ene to yield 3β,20α-dihydroxy-5α-pregnane. Nmr studies[9] have also shown that, in 17(20)-enes with a *cis*-oriented ethylidene side chain, deshielding of the C_{18} angular methyl group occurs in contrast to the trans ethylidene side chain relative to the corresponding C_{17} ketone in the nmr. This spectral correlation is a useful method for establishing the geometry of the 17(20) double bond (Table II).

For rigid stereochemical correlation, the conclusion that a 17α-hydroxy-20β-bisnorcholanic acid will yield pregn-*cis*-17(20)-ene and the 17β-hydroxy-20β epimer will yield pregn-*trans*-17(20)-enes proceeding *via* a β-lactone is valid if isomerization does not occur during this transformation. A recent study[10] shows that the decarboxylation of β-lactones to olefins proceed as a stereospecific cis-elimination reaction.

Application of this β-lactone to olefin conversion for the establishment of C_{20} stereochemistry in bisnorcholanic acids was studied with the acid **3a** obtained from dilithiopropionate. Isolation of β-lactone **5** was achieved by reaction of the acid **3a** with ethyl chloro-

(6) L. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 179.

(7) (a) L. Fieser and M. Fieser, ref 6, p 467; (b) S. Pines, R. Firesteone, L. Re, M. Kozlowski, and M. Sletzinger, *Steroids*, **8**, 877 (1966).

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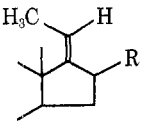
(9) (a) W. R. Benn and R. M. Dodson, *J. Org. Chem.*, **29**, 1142 (1964); (b) M. Leboeuf, A. Cave, and R. Goutarel, *Compt. Rend.*, **264**, 1090 (1967); (c) F. A. MacKeller and G. Slomp, *Steroids*, **11**, 787 (1968).

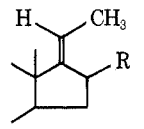
(10) D. S. Noyce and E. H. Baniff, *J. Org. Chem.*, **31**, 4043 (1966).

TABLE II

CIS–TRANS DESHIELDING EFFECTS



cis olefin



trans olefin

Compd	Cis 18-CH_3[a]	Cis $\Delta_{18\text{-}CH_3}$[b]	Trans 18-CH_3[a]	Trans $\Delta_{18\text{-}CH_3}$[b]
3β,16β-Diacetoxy-5α-pregn-17(20)-ene (R = OAc)	55.0[c]	+0.5	47.0[c]	−7.5
3β-Acetoxy-pregn-5,17(20)-diene (R = H)	54.5	+0.5	46.0	−7.0
3β-Acetoxy-5α-pregn-17(20)-ene (R = H)	52.5	+0.5	44.7	−7.3

[a] Values of chemical shifts in hertz downfield from TMS. [b] $\Delta_{18\text{-}CH_3}$ = [18-CH_3 of olefin] − [18-CH_3 of corresponding C_{17} ketone]. [c] These values are from ref 9a.

formate in the presence of triethylamine. The crystalline β-lactone exhibited a characteristic ir band at 5.46 μ. On treatment with *p*-toluenesulfonic acid in boiling xylene, decarboxylation occurred to give only 3β-hydroxy-pregna-5-*trans*-17(20)-diene, isolated as the acetate **7**.

A similar sequence of reactions on the acid **2a**, the major acidic product of the Reformatsky reaction, afforded the β-lactone **4**, which was decarboxylated to 3β-hydroxypregna-5-*cis*-17(20)-diene, then acetylated to give **6**, which had different physical properties and tlc mobility from **7**. The assignment of the C_{20} configuration in **6** and **7** is based on nmr data and is presented in Table I.

The retroaldozation of **3b** can now be rationalized on the basis of steric effects. Examination of models of a hydrogen-bonded form of the methyl ester **3a** [ν_{max} 3510 cm^{-1} (bonded OH)] shows the C_{20} methyl and the C_{12} methylene groups hinder attack of base at the C_{20} carbonyl group, whereas similar considerations with the ester **2b** shows the absence of steric encumbrance at the C_{20} carbonyl.

The addition of dianions of acids offers a convenient alternative to the Reformatsky reaction for the synthesis of β-hydroxy acids.[11,12]

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord instrument from Nujol mulls. Infrared spectra of **3b** in carbon disulfide solution were obtained on a Beckman infrared 7. Proton nmr spectra were obtained on a Varian A-60A instrument, using deuteriochloroform as a solvent and tetramethylsilane as an internal standard unless otherwise stated. Optical rotations were measured in 0.1–0.2% chloroform solutions at 24° unless stated differently. Melting points were taken with a Fisher-Johns hot-stage apparatus and are essentially uncorrected. Reagents were freshly distilled and all glassware was flame-dried. All extracts were dried over anhydrous sodium sulfate and evaporated at reduced pressure.

3β,17β-Dihydroxy-20β-bisnorchol-5-enoic acid (3a).—To a solution containing 12.6 ml of diisopropyl amine in 350 ml of tetrahydrofuran at 0–5° was added, dropwise, 56.5 ml of 1.6 *M* *n*-butyllithium in hexane. After the mixture was stirred for 0.5 hr, 3.4 ml of propionic acid in 60 ml of tetrahydrofuran was added dropwise and stirring was continued for 3.5 hr. To the slightly cloudy suspension, 6.49 g of **1a** in 60 ml of tetrahydrofuran was added. Stirring was continued at 0–5° for 2 hr and then at room temperature for 14 hr. Water (50 ml) was added, and the tetrahydrofuran was evaporated. Ethyl acetate was added and extracted with 4% NaOH. The neutral phase was evaporated to yield 3.08 g of starting ketone **1a**. The basic phase was acidified with 18% HCl and extracted with ethyl acetate. The ethyl acetate was evaporated to yield 4.05 g of acid.

Composition of the acid mixture as determined by nmr indicated an 18-CH_3 ratio of 4:1 for the 17β- to 17α-hydroxy isomers **3a** and **2a**, respectively. The crude acid was recrystallized from acetone to give 1.05 g of **3a**: mp 244–250°; $[\alpha]_D$ −11° (dioxane); ir λ_{max} 3.0 (broad, OH), 5.92 μ (C=O); nmr (CD_3OD–$CDCl_3$, 1:1) τ 9.06 (18-CH_3), 8.96 (19-CH_3), 8.64 (d, *J* = 7 Hz, 21-CH_3).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.94; H, 9.57.

Methyl 3β-Acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate (3b).—To a solution of 0.25 g of **3a** in 50 ml of methanol was added an ethereal solution of diazomethane. After 1 hr, the reaction was quenched with acetic acid and evaporated. The residue was dissolved in ether, washed with saturated sodium bicarbonate and water, dried, and evaporated. The residue was acetylated and then recrystallized from ether–petroleum ether to give **3b**: mp 153–154° (lit.[4] mp 154–155°); $[\alpha]_D$ −49° (acetone) ir λ_{max} 2.85 (OH), 5.75, 8.00 (acetate), 5.87 μ (C=O, methyl ester); nmr τ 9.10 (18-CH_3), 8.98 (19-CH_3), 8.71 (d, *J* = 7 Hz, 21-CH_3), 7.98 ($OCOCH_3$), 6.33 ($COOCH_3$).

3β,17α-Dihydroxy-20β-bisnorchol-5-enoic Acid (2a).—To a solution of 17.30 g of dehydroisoandrosterone acetate in 100 ml of dry benzene were added 20.0 g of activated zinc and 54.0 g of ethyl 2-bromopropionate. The reaction mixture was heated to slightly below reflux temperature until the reaction became exothermic; the external heating was withdrawn until the reaction subsided (15 min). The mixture was heated to reflux for 1.5 hr and, after cooling, 60 ml of 10% sulfuric acid and 60 ml of ether were added with vigorous stirring. The benzene–ether layer was separated and the water was extracted with additional ether. The combined benzene–ether solutions were washed with water, dried, and evaporated. The residue was dissolved in 200 ml of methanol containing 10% potassium hydroxide and was refluxed for 0.5 hr. The solution was cooled; 100 ml of water was added and concentrated to approximately 125 ml. The resulting suspension was extracted with ether; the ether was dried and evaporated to yield 11.4 g of **1a**. The aqueous phase was treated with 18% HCl until the solution's pH was approximately 3 and then extracted with ether. After evaporation, the residue was recrystallized from acetone to give 1.72 g of **2a**: mp 225–231° (lit.[4] mp 229–232°); ir λ_{max} 2.70 (OH), 2.90 (OH), 5.40 μ (C=O, acid); nmr ($CDCl_3$–CD_3OD, 1:1) τ 9.18 (18-CH_3), 8.95 (19-CH_3), 8.77 (d, *J* = 7 Hz, 21-CH_3).

Saponification of 3b.—A solution of 0.10 g of **3b** in 50 ml of a 10% potassium hydroxide–methanol solution was refluxed for 1.0 hr. After cooling, the methanol was evaporated and the residue was taken up in water and ether. The ether solution afforded 0.07 g of **1a**. The basic phase was acidified with 18% HCl and extracted with ether. The ether solution after evaporation gave 6 mg identical in all respects with **3a**.

Methyl 3β-Acetoxy-17α-hydroxy-20β-bisnorchol-5-enoate (2b) and Methyl 3β-Acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate (3b).—The Reformatsky reaction was carried out essentially as described previously, but with the use of 4.0 g of dehydroisoandrosterone acetate, 32.2 g of methyl α-bromopropionate, 8.0 g of activated zinc, and 120 ml of benzene. The resulting crude mixture was acetylated with acetic anhydride in pyridine to give a residue weighing 5.80 g. To a solution of 1.04 g of the residue in 125 ml of methanol were added 0.35 g of hydroxylamine hydrochloride and 0.42 g of sodium acetate. The solution was heated to reflux for 0.25 hr, cooled, and evaporated. The resulting residue was heated to boiling in chloroform and the insoluble oxime was collected by filtration. The chloroform solution was washed with water, dried, and evaporated to give 0.73 g of a white solid. An nmr spectra indicated that only esters were present and only two isomers were detectable. The composition, using C_{18} methyl chemical shifts was 65% methyl 3β-acetoxy-17β-hydroxy-20β-bisnorchol-5-enoate [nmr ($CDCl_3$) τ 9.10 (18-CH_3), 8.98 (19-CH_3), 8.71 (d, *J* = 7 Hz, 21-CH_3)] and 35% methyl 3β-acetoxy-17α-hydroxy-20β-bisnorchol-5-enoate [τ 9.23 (18-CH_3), 8.95 (19-CH_3), 8.76 (d, *J* = 7 Hz, 21-CH_3)].

(11) A. E. Opara and G. Read, *Chem. Commun.*, 679 (1969).

(12) D. A. Cornforth, A. E. Opara, and G. Read, *J. Chem. Soc.*, 2799 (1969).

20β-Bisnorchol-5-ene-3β,17β,22-triol (9a).—To a solution of 1.3 g of lithium aluminum hydride in 80 ml of tetrahydrofuran was added 0.65 g of **3a** in 80 ml of tetrahydrofuran. The suspension was refluxed for 96 hr, cooled, and quenched with saturated sodium sulfate. The tetrahydrofuran was evaporated; ether and 10% sulfuric acid were added. The ether solution was washed with saturated sodium bicarbonate, 3% hydrochloric acid, and water, and then dried and evaporated to yield 0.90 g of **9a**. An analytical sample was recrystallized from acetone: mp 214–217°; $[\alpha]_D$ −53° (MeOH); ir λ_{max} 2.95 μ (OH, broad).

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.44; H, 10.45.

20β-Bisnorchol-5-ene-3β,17α,22-triol (8a).—The lithium aluminum hydride reduction of **2a** was carried out as previously described for **3a**, but with the use of 0.50 g of **2a** in 60 ml of tetrahydrofuran, and 1.0 g of lithium aluminum hydride in 60 ml of tetrahydrofuran. The resulting residue **8a** weighed 0.43 g, which afforded an analytical sample upon recrystallization from methanol, mp 201–202° (lit.[4] mp 200–208°).

20β-Bisnorchol-5-ene-3β,17β,22-triol 3,22-Ditosylate (9b) and 17β-Hydroxy-3α,5-cyclo-5α-dinorcholane (11).—A solution of 0.45 g of **9a** and 4.50 g of *p*-toluenesulfonyl chloride in 75 ml of pyridine was stirred for 24 hr at room temperature. The solution was poured into water and extracted with ether. The ether solution was washed with water, 3% HCl, and water. The ether solution after evaporation afforded 0.51 g of ditosylate (**9b**): ir λ_{max}^{film} 2.75 (OH), 6.22, 7.45, 8.50 μ (tosylate).

To a solution of 2.0 g of lithium aluminum hydride in 100 ml of tetrahydrofuran was added 0.1 g of **9b** in 50 ml of tetrahydrofuran. After stirring at room temperature for 48 hr, the reaction mixture was quenched by the slow addition of saturated sodium sulfate. The tetrahydrofuran was evaporated; ether and 10% sulfuric acid were added. The ether solution was separated, washed with 10% sulfuric acid and water, dried, and evaporated to afford 0.29 g of an oil. The oil (0.29 g) and 0.25 g of *m*-chloroperbenzoic acid[13] (78%) in 25 ml of methylene chloride were stirred at room temperature in the dark for 96 hr and then washed with saturated sodium bicarbonate, dried, and evaporated. Preparative thin layer chromatography, using a SiGF plate, developed in benzene–10% ether gave **11** as an oil: $[\alpha]_D$ +38°; ir λ_{max}^{film} 2.90 μ (OH); mass spectrum mol wt 316 (calcd for $C_{22}H_{36}O$), 316 (found); nmr τ 9.06 (18-CH_3, 19-CH_3), 8.99 (d, J = 6.6 Hz, isopropyl methyls, equivalent).

20β-Bisnorchol-5-ene-3β,17α,22-triol 3,22-Ditosylate (8b) and 17α-Hydroxy-3α,5-cyclo-5α-dinorcholane (10).—A solution of 0.23 g of **8a** and 0.33 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine was stirred for 16 hr at room temperature. The workup was as previously described. The resulting gum weighed 0.16 g: ir λ_{max}^{film} 2.75 (OH), 6.22, 7.45, 8.50 μ (tosylate).

The reduction of **8a** was essentially as previously described but with the use of 0.16 g of **8b**, 0.64 g of lithium aluminum hydride, and 50 ml of tetrahydrofuran. The resulting residue weighed 0.068 g. An analytical sample was obtained by sublimation: $[\alpha]^{25}_D$ +24°; ir λ_{max}^{film} 2.75 μ (OH); mass spectrum mol wt 316 (calcd for $C_{22}H_{36}O$), 316 (found); nmr ($CDCl_3$) τ 9.20 (18-CH_3), 9.06 (19-CH_3), 9.08 (d, J = 6.6 Hz, isopropyl methyl), 9.10 (d, J = 6.6 Hz, isopropyl methyl).

Addition of Isopropenylmagnesium Bromide to 3α-5-Cyclo-5α-androstane (1b).—To 300 ml of tetrahydrofuran containing 3.6 g of magnesium turnings was initially added 6.5 g of 2-bromopropene followed by dropwise addition of 7.0 g of 2-bromopropene. To the solution of 11.7 g of anhydrous lithium perchlorate was added portionwise and stirring was continued for 20 min at room temperature. A solution of 9.2 g of **1b** in 100 ml of tetrahydrofuran was added and stirred for 18 hr. The reaction mixture was poured into 3% hydrochloric acid and extracted with ether. The ether solution was washed with water, dried, and evaporated to yield 8.4 g of a mixture. Crystallization from methanol yielded 3.61 g of **1b** and after evaporation 5.2 g of an oil. A solution of 150 ml of methanol containing 4.2 g of the filtrate of the oil residue, 2.1 g of hydroxylamine hydrochloride, and 2.1 g of sodium acetate was refluxed for 1 hr and then cooled. After evaporation, the residue was taken up in chloroform and washed with 3% hydrochloric acid and water, dried, and evaporated to yield a 5.1-g mixture of oxime and **11**. The mixture (5.0 g) was chromatographed on 500 g of SiGF and the fraction eluted with 2% ether–benzene was put on a SiGF thick plate and developed in benzene–5% ether to afford 0.02 g of **12**: ir λ_{max}^{film} 2.90 μ (OH); nmr τ 9.08 (18-CH_3), 9.06 (19-CH_3), 8.17 (21-CH_3), 5.32, 4.97 (22-=CH_2).

A suspension of 0.02 g of ruthenium in 10 ml of ethanol containing 0.02 g of **12** and 2 drops of 0.1 *N* NaOH was hydrogenated over a period of 3.0 hr. The reaction was filtered through Celite and the ethanol was evaporated. The residue in chloroform was washed with water and evaporated to yield 0.02 g of **11**.

3β-Acetoxypregna-5-*trans*-17(20)-diene (7). Method A.—A solution of 0.25 g of **3a** in 15 ml of acetic anhydride was heated to reflux. After 2 hr, the reaction mixture was cooled and the acetic anhydride was evaporated. To the residue were added 5 ml of pyridine and ice. After the mixture was allowed to stand for 0.5 hr, water was added and the suspension was extracted with ether. The ether extract was washed with 10% sulfuric acid, 5% sodium bicarbonate, and water, dried, and evaporated to yield 0.20 g of **7**. The nmr of the residue indicated only trans olefin. Preparative chromatography using SiGF thick plates, developed in benzene–ether (1:1), followed by recrystallization from methanol yielded an analytical sample: mp 143.0–143.5°; $[\alpha]_D$ −72°; ir λ_{max} 5.75, 8.00 μ (acetate); nmr ($CDCl_3$) τ 9.24 (18-CH_3), 8.95 (19-CH_3), 8.46 (doublet of triplets, $J_{H_{21},H_{20}}$ = 7 Hz, $J_{H_{20},H_{16}}$ = 1.5 Hz), 7.97 (3, $OCOCH_3$), 4.94 (m, 20-H).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.33; H, 10.02.

3β-Acetoxypregna-5-*cis*-17(20)-diene (6). Method A.—The same procedure was followed as previously described, with the use of 0.18 g of **2a**. The residue obtained weighed 0.15 g. An nmr spectra of the crude residue indicated only cis olefin. The residue was sublimed to give an analytical sample: mp 73–77°; $[\alpha]^{22}_D$ −63°; ir λ_{max} 5.75 8.00 μ (acetate); nmr ($CDCl_3$) τ 9.08 (18-CH_3), 8.95 (19-CH_3), 8.33 (doublet of triplets, $J_{H_{21},H_{20}}$ = 7 Hz, $J_{H_{20},H_{16}}$ = 1.9 Hz), 7.97 ($OCOCH_3$), 4.87 (m, 20-H).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.92; H, 10.28.

3β,17β-Dihydroxy-20β-bisnorchol-5-enic Acid 22,17-Lactone (5).—To a solution of 0.25 g of **3a** in 10 ml of methylene chloride and 10 ml of triethylamine at 0.5° was added, dropwise, 0.2 ml of ethyl chloroformate. After stirring for 1.0 hr, the reaction mixture was warmed to room temperature for 2.0 hr and then added to water. The methylene chloride was separated and washed with 3% HCl, saturated sodium bicarbonate, and water. The methylene chloride was dried and evaporated to yield 0.28 g. Recrystallization from acetone gave 0.08 g of **5**: mp 137–140°; $[\alpha]^{20.5}_D$ −119°; ir λ_{max} 3.0 (OH), 5.50 μ (β-lactone carbonyl); nmr ($CDCl_3$–DMSO-d_6, 1:1) τ 9.05 (18-CH_3), 8.98 (19-CH_3), 7.77 (d, J = 8 Hz, 21-CH_3).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.58; H, 9.34.

3β-Acetoxypregna-5-*trans*-17(20)-diene (7). Method B.—To a solution of 0.25 g of **5** in 20 ml of xylene was added 1 mg of *p*-toluenesulfonic acid. After refluxing for 3 hr, the solution was diluted with ether and washed with 3% HCl, saturated sodium bicarbonate, and water. The ether solution was dried and evaporated to yield a residue of 0.5 g. The 3-acetate was identical with **7** synthesized by method A.

3β,17α-Dihydroxy-20β-bisnorchol-5-enic Acid 22,17-Lactone (4) and 3β-Acetoxypregna-5-*cis*-17(20)-diene (6). Method B.—The same procedure was followed as previously described for 0.25 g of **2a** to yield a residue of 0.23 g: ir λ_{max} 2.8 (OH), 5.50 μ (β-lactone carbonyl); nmr ($CDCl_3$–DMSO-d_6, 1:1); τ 9.08 (18-CH_3), 9.00 (19-CH_3), 8.65 (d, J = 8 Hz, 21-CH_3). The residue **4** was treated with xylene and *p*-toluenesulfonic acid as described previously. Only cis olefin was obtained. The acetate was identical with **6**. There was no depression of the melting point upon admixture.

Registry No.—**2a**, 29842-77-1; **2b**, 29842-78-2; **3a**, 29842-79-3; **3b**, 29842-80-6; **4**, 29842-81-7; **5**, 29842-82-8; **6**, 1167-32-4; **7**, 16374-33-7; **8b**, 29842-85-1; **9a**, 29842-86-2; **9b**, 29842-87-3; **10**, 29842-88-4; **11**, 29936-65-0; **12**, 29842-89-5; *cis*-3β,16β-diacetoxy-5α-pregn-17(20)-ene, 29842-90-8; *trans*-3β,16β-diacetoxy-5α-pregn-17(20)-ene, 29842-91-9; *cis*-3β-acetoxypregn-5,17(20)-diene, 1167-33-5; *trans*-3β-acetoxypregn-5,17(20)-diene, 29842-93-1.

(13) Impurities of 17β-hydroxydinorchol-5-ene were removed as the 5,6-epoxide.