Steroids. III. Transformations of Steroid Ketones Using Phosphonate Carbanions[1]

AJAY K. BOSE AND ROBERT T. DAHILL, JR.

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, New Jersey

Received September 10, 1964

A study of the reaction of phosphonate carbanions with various steroid ketones was made. The carbanion of diethyl ethoxycarbonylmethylphosphonate was very selective in its steric requirements: it reacted only with 3-keto steroids. Diethyl cyanomethylphosphonate, however, led to unsaturated nitriles from steroids with the keto group at C-3, C-17, and C-20. The α,β-unsaturated esters from 3-cholestanone and 3-coprostanone were transformed into steroid derivatives with the cortical side chain at C-3.

Steroids with alcohol groups in different positions are readily available from either chemical or microbiological transformations. Ketones derived from them therefore constitute convenient intermediates for the partial synthesis of various steroid derivatives. In general, the Wittig reaction[2] is a synthetic method of value that has been used widely for ketones. Sondheimer and Mechoulam[3] have shown the utility of this reaction for introducing a methylene group at various positions on the steroid ring, such as C-3 C-7, C-12, and C-20, although in varying yields. We were interested in the preparation of unsaturated steroid esters which could serve as intermediates for the introduction of the cortical side chain at different sites. Since carbomethoxymethylenetriphenylphosphorane (I) failed to react with cholestan-3-one we examined the possibility of using diethyl ethoxycarbonylmethylphosphonate[4] (II) for the preparation of the desired steroid esters. In this paper

$(C_6H_5)_3P{=}CH{-}CO_2CH_3$ (I)

$(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}{-}CH_2{-}CO_2C_2H_5$ (II)

$(C_2H_5O)_2\overset{\overset{O}{\uparrow}}{P}{-}CH_2CN$ (III)

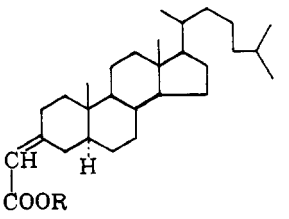
we wish to describe the usefulness of diethyl cyanomethylphosphonate (III) for reaction with various steroid ketones. In addition we give the details of the reaction of diethyl ethoxycarbonylmethylphosphonate with steroid ketones reported briefly in our earlier communication.[5]

The kinetics and mechanism of the Wittig reaction has recently been studied[2] and two alternative mechanisms have been advanced. Which of these mechanisms will predominate in a particular case will apparently depend on the electronic and steric factors. The Wittig reaction has been found, in general, to be nonstereospecific.[6] Steric control of this reaction has, however, been accomplished in some cases.[7] The reaction of a carbonyl compound with a phosphonate carbanion may be expected to be analogous to that with a phosphorane and hence show a lack of stereospecificity. We have found, however, that 3-cholestanone and dihydrotestosterone reacted with the phosphonate II to afford in each case a single isomer of an unsaturated ester IV and VIIa, respectively. The stereochemistry of these esters around the double bond is as yet unknown.

Milas and Priestling[8] had prepared cholestanylidene acetic acid (V) of unknown stereochemistry from 3-cholestanone and ethoxyacetylene. From a comparison of the physical properties of this acid with those of the acid from ethyl cholestanylidene acetate (IV) prepared by us, it appeared that the two different routes had led to the same stereochemistry around the double bond.

The reduction of V in presence of a platinum catalyst led to a mixture of two epimeric acids, one of which could be obtained pure through crystallization. This acid was found on direct comparison to be identical with the 3α-cholestanylacetic acid[9] described by Shoppee.[10]

The reaction of the phosphonate II with 3-coprostanone led to an excellent yield of the desired product VIa which was an oil. Saponification of this oil afforded a crystalline acid VIb which appeared to be sterically homogenous on the basis of its n.m.r. spectrum.



IV, R = C_2H_5
V, R = H
VIa, C-5 epimer of IV
b, C-5 epimer of V

Contrary to the experience of Sondheimer and Mechoulam[3] with methylenetriphenylphosphorane we found that the phosphonate II showed great selectivity in its reaction with steroid ketones. Thus, there was no reaction between II and a 17-ketone such as estrone methyl ether or a 20-ketone such as 5-pregnen-3β-ol-20-one acetate, while 5α-androstane-3,17-dione reacted at only one keto group to afford the keto ester VIIb. That the 17-keto group had failed to react was shown by the presence of a carbonyl band at 5.70 μ in the infrared spectrum of the product and the failure of the C-18

(1) Presented in part at the IUPAC Symposium on the Chemistry of Natural Products, Kyoto, Japan, April 1964. Part II: A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Letters*, 1467 (1963).

(2) For a recent review, see H. O. Huisman, *Chem. Zentr.*, **59**, 133 (1963).

(3) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(4) W. S. Wadsworth and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(5) A. K. Bose and R. T. Dahill, Jr., *Tetrahedron Letters*, 959 (1963).

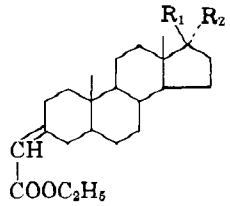
(6) For example, see E. J. Corey and E. Hamanaka, *J. Am. Chem. Soc.*, **86**, 1641 (1964).

(7) L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, 149 (1963).

(8) N. A. Milas and C. P. Priestling, *J. Am. Chem. Soc.*, **80**, 2189 (1958).

(9) Prepared in this laboratory by R. Riddle.

(10) C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.*, 2230 (1954).

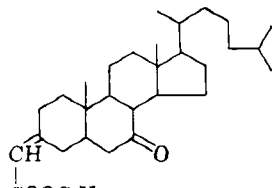


VIIa, $R_1 = OH$; $R_2 = H$

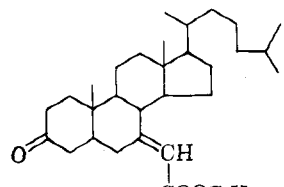
b, $R_1, R_2 = C=O$

methyl protons to be shifted in the n.m.r. spectrum of the product.

Under the usual conditions, no reaction occurred between II and either cholestan-3β-ol-6-one acetate or cholestan-3β-ol-7-one acetate. In view of this, the keto ester obtained from the interaction of II and cholestane-3,7-dione could be expected to have the structure VIII rather than IX.



VIII

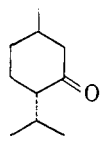


IX

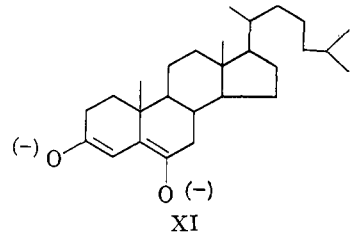
The confirmation of this structure, however, presented a problem since a distinction between the 3- and 7-keto groups is not possible on the basis of the infrared or n.m.r. spectra. One physical method that appeared capable of discrimination between the alternative structures VIII and IX was optical rotary dispersion.

The product from cholestane-3,7-dione and II showed a negative Cotton effect, whereas a positive plain curve was obtained for 3-carboethoxymethylene cholestane (IV). It has been reported[11] that 3-cholestanone shows a strong positive Cotton effect while cholestan-3β-ol-7-one acetate is characterized by a moderately strong negative Cotton effect. It can be concluded, therefore, that in VIII the 3-keto group has been removed and the 7-keto group retained. The sensitivity of II to steric hindrance was further demonstrated by its lack of reaction with menthone (X).

Neither 4-cholesten-3-one nor cholestane-3,6-dione condensed with II under the usual conditions, *e.g.*, in N,N-dimethylformamide in the presence of sodium ethoxide. The lack of reaction at the unhindered 3-position is noteworthy. In the case of the dione it is possible that the formation of the unreactive enolate XI takes place easily and inhibits reaction at C-3 or

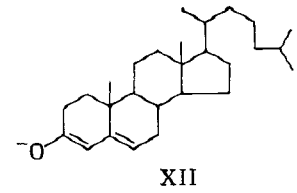


X



XI

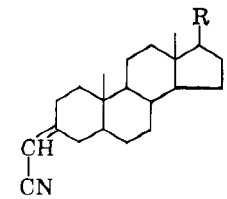
C-6. The enolate ion XII from 4-cholesten-3-one would be unable to react with II *via* the four-centered



XII

mechanism that has been proposed for the Wittig reaction.

In our search for a phosphonate carbanion not so strongly inhibited as II by steric factors, we have studied the reaction between diethyl cyanomethylphosphonate (III) and steroid ketones. Our experimental procedure was modeled after that of Takahashi, Fujiwara, and Ohto.[12] Sodamide was used as the base and dry tetrahydrofuran as the solvent. Cholestan-3-one reacted with diethyl cyanomethylphosphonate at room temperature upon standing 12 hr. to form the α,β-unsaturated nitrile XIIIa in 71% yield. On the



XIIIa, $R = C_8H_{17}$

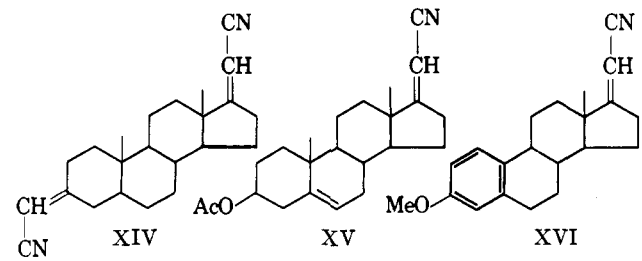
b, R = OH

basis of physical properties and the n.m.r. spectrum the product was found to be homogenous, although the reaction could have been expected to lead to a mixture of *cis* and *trans* isomers.[13] Dihydrotestosterone afforded the analogous nitrile XIIIb.

A difference in the reactivity of this phosphonate from diethyl ethoxycarbonylmethylphosphonate was noticed when 17-ketones were involved. Diethyl cyanomethylphosphonate reacted with 5α-androstane-3,17-dione to form 3,17-dicyanomethylene-5α-androstane (XIV). The structure of the product was confirmed by elemental analysis, infrared spectroscopy (no carbonyl band was observed), and n.m.r. spectroscopy (two signals in the olefinic proton resonance region).

The difference in the reactivity of diethyl cyanomethylphosphonate and diethyl ethoxycarbonylmethylphosphonate can be attributed to the difference in steric requirements of the two reagents. The nitrile group is linear and hence not a very bulky substituent whereas the ethoxycarbonyl group is nonlinear and quite bulky.

Reaction of diethyl cyanomethylphosphonate with 17-keto steroids is interesting because the resulting compound has the same carbon skeleton as the physiologically important steroid hormones, *e.g.*, the progesta-

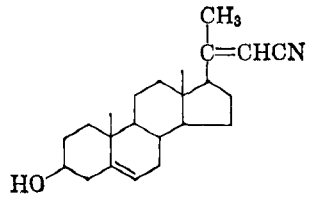


XIV XV XVI

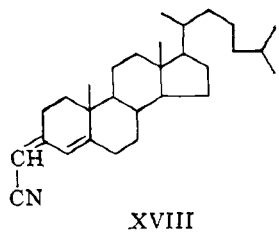
(11) C. Djerassi, "Optical Rotary Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, p. 43.

(12) H. Takahashi, K. Fujiwara, and M. Ohto, *Bull. Chem. Soc. Japan*, **36**, 1498 (1963).

tionals and glucocorticoids. Dehydroepiandrosterone and estrone methyl ether were converted into 17(20)-unsaturated nitriles XV and XVI, respectively. When pregnenolone acetate was treated under these conditions, the 20-ketone reacted and the acetate group was hydrolyzed at the same time to give XVII. This is in contrast with the findings that diethyl ethoxycarbonylmethylphosphonate failed to react with a 20-ketone. Diethyl cyanomethylphosphonate also reacted with 4-cholesten-3-one to form the corresponding unsaturated nitrile XVIII.



XVII

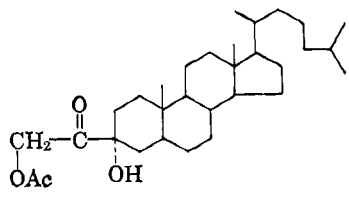


XVIII

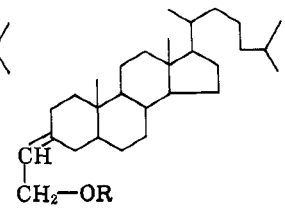
French workers[13] have synthesized a steroid compound with the acetyl side chain in the 3-position and two related steroids with dihydroxyacetone structure at C-3[14].

One of the more successful methods[15] for the elaboration of the cortical side chain involves conversion of the 17-ketone to the 17-carbomethoxymethylene group followed by reduction to the alcohol. The alcohol is acetylated and then treated with a solution of osmium tetraoxide and N-methylmorpholine oxide–hydrogen peroxide complex in *t*-butyl alcohol. The result is a 17β-acetoxyacetyl-17α-hydroxy derivative.

Using this sequence,[15] 3-carboethoxymethylenecholestane was converted to 3-acetoxyacetyl-3-hydroxycholestane XIX *via* the alcohol XX and the acetate XXI.

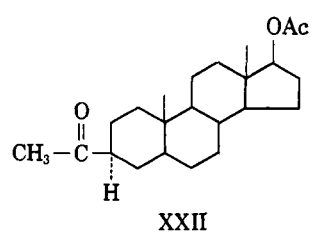


XIX

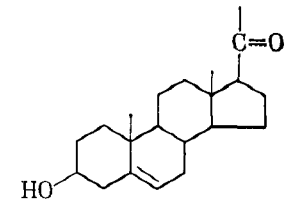


XX, R = H
XXI, R = Ac

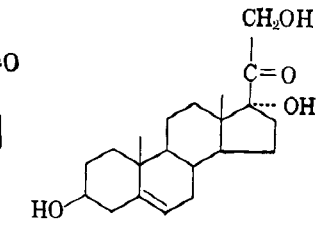
The optical rotary dispersion (O.R.D.) of this compound gave a positive Cotton effect which was in agreement with the published value for 3β-acetyl-17β-acetoxy-5α-androstane XXII.[14a] The two additional hydroxy groups in the cortical side chain compared with the progesterone side chain should not change the sign of the Cotton effect in the O.R.D. curve of these compounds. This can be shown by a comparison of the O.R.D. curves of 3β-hydroxy-5-pregnen-20-one (XXIII) and 3β,17α,21-trihydroxy-5-pregnen-20-one (XXIV).[16] On the basis of this data the configuration



XXII



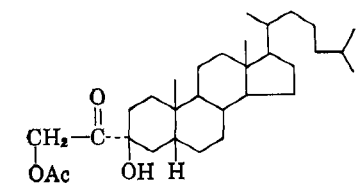
XXIII



XXIV

of the product, XIX, was deduced to be 3α-hydroxy-3β-acetoxyacetylcholestane. This should be the more stable isomer because it has the larger acetoxyacetyl group in the equatorial position.

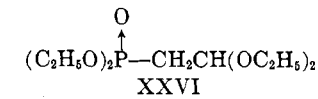
The same sequence of reactions was carried out on 3-carboethoxymethylene-5β-cholestane to give 3-hydroxy-3-acetoxyacetyl-5β-cholestane XXV. The ster-



XXV

eochemistry at the 3-position in this compound could not be determined because no Cotton effect was observed in the optical rotary dispersion curve at wave length above 300 mμ. It can be expected that the more thermodynamically stable product would result in this case as in the cholestane series since the conditions employed were identical. If this be so then the acetoxyacetyl side chain should be in the equatorial position, that is in the 3α-orientation since the A/B ring junction is *cis*.

Another route to the cortical side chain would involve conversion of the steroid ketones to the corresponding α,β-unsaturated aldehyde in one step using diethyl phosphonoacetaldehyde diethyl acetal (XXVI).[13] This reagent has been used on benzalde-



XXVI

hyde to give cinnamaldehyde diethylacetal in 95% yield. However, under the conditions used, it failed to react with cholestan-3-one.

Experimental[17]

Materials.—Diethyl ethoxycarbonylmethylphosphonate was prepared by heating triethyl phosphite and ethyl bromoacetate. Diethyl cyanomethylphosphonate was purchased from Aldrich Chemical Company, Milwaukee, Wis. (diethyl ethoxycarbonylmethylphosphonate is also available from them). The tetrahydrofuran was purified by distillation from lithium aluminum

(13) M. Dvolaitzky, H. B. Kagan, and I. Jacques, *Bull. soc. chim. France*, 598 (1961).

(14) H. B. Kagan, *ibid.*, 1079 (1960).

(15) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2226 (1958).

(16) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(17) Melting points are uncorrected. Microanalysis were performed by Alfred Bernhardt, Mülheim, West Germany. Ultraviolet absorption spectra were measured in ethanol on a Beckman Model DK-2A spectrophotometer. The optical rotary dispersion measurements were made in methanol solution on a Rudolph recording spectropolarimeter using a xenon lamp.

TABLE I

REACTION OF STEROID KETONES WITH DIETHYL ETHOXYCARBONYLMETHYLPHOSPHONATE

Reactant	Product[a]	Formula	$[\alpha]^{26}D$, °	M.p., °C. (recrystn. solvent)	Yield, %	λ_{max}, mμ (ε)	% C Calcd.	% C Found	% H Calcd.	% H Found
Cholestan-3-one	IV	$C_{31}H_{52}O_2$	+30	83–85 (methanol–ethyl acetate)	93	226 (16,500)	81.52	81.24	11.48	11.29
Coprostan-3-one	VI			Noncrystalline	96	...	...	...	...	...
5α-Androstane-3,7-dione	VIIb	$C_{23}H_{34}O_3$	+106	156–157 (methanol)	51	226 (18,600)	77.05	77.18	9.56	9.53
Cholestane-3,7-dione	VIII	$C_{31}H_{50}O_3$	...	93–95 (ethanol)	71	223 (12,500)	79.10	79.40	10.71	10.35
Dihydrotestosterone	VIIa	$C_{23}H_{36}O_3$	+59	77–80 (methanol)	60	226 (16,100)	76.62	76.29 76.49	10.07	9.87 9.87

[a] The n.m.r. spectra show evidence of an olefinic proton.

TABLE II

REACTION OF STEROID KETONES WITH DIETHYL CYANOMETHYLPHOSPHONATE

Reactant	Product[a]	Formula	M.p., °C. (recrystn., solvent)	$[\alpha]^{22}D$, °	Yield, %	λ_{max}, mμ (ε)	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
Cholestan-3-one	XIIIa	$C_{29}H_{47}N$	87–88 (methanol)	+59	71	221 (12,200)	85.02	85.11	11.56	11.06	3.42	3.92
5α-Androstane-3,17-dione	XIV	$C_{23}H_{30}N_2$	202–204 (methanol)	+59	86	219 (23,800)	82.58	82.85	9.04	9.08	8.38	8.31
Dihydrotestosterone	XIIIb	$C_{21}H_{31}NO$	167–168 (methanol)	+11	67	219 (15,600)	80.46	80.73	9.97	9.93	4.47	4.55
Pregnenolone acetate	XVII	$C_{23}H_{33}NO$	186–187 (acetone)	−54	82	222 (11,700)	81.36	81.02	9.80	9.78	4.13	4.40
Dehydroepiandrosterone	XV	$C_{21}H_{29}NO$	184–185 (methanol)	−104	67	219 (15,300)	80.98	80.85	9.39	9.50	4.50	4.38
Estrone methyl ether	XVI	$C_{21}H_{25}NO$	184–185 (methanol)	...	84	219 (11,200)	82.04	82.02	8.20	8.04	4.56	5.28
4-Cholesten-3-one	XVIII	$C_{29}H_{45}N$	147–148 (methanol)	...	20	225 (8140)	85.44	85.14	11.13	11.03	3.44	3.35

[a] The n.m.r. spectra show evidence of an olefinic proton.

hydride. The dimethylformamide was dried over potassium hydroxide. The sodamide was commercial grade.

Reactions with Diethyl Ethoxycarbonylmethylphosphonate.—To a suspension of 1.1 g. (22 mmoles) of sodium ethoxide (prepared by dissolving 0.55 g. of sodium in an excess of absolute ethanol and evaporating off the excess ethanol after the reaction was complete) in 25 ml. of dry dimethylformamide was added dropwise in the cold with stirring 5.0 g. (22 mmoles) of diethyl ethoxycarbonylmethylphosphonate. After the addition was completed the yellow solution was stirred at room temperature for 1 hr. To this solution was added a suspension of 4.6 mmoles of the ketone suspended in dry dimethylformamide in the cold. The mixture was stirred at room temperature for 20 hr. The resulting solution was poured into 1 l. of ice–water and extracted with ether. The ether layer was separated and washed with 3 *N* hydrochloric acid and with water. After drying over magnesium sulfate the solvent was removed under reduced pressure to give the crude product which was purified by crystallization. See Table I for compounds prepared by this general method.

Reaction with Diethyl Cyanomethylphosphonate.—A solution of 3.6 g. (22 mmoles) of diethyl cyanomethylphosphonate in 20 ml. of tetrahydrofuran was added dropwise, with stirring under nitrogen, to 1.1 g. (22 mmoles) of sodium amide in 25 ml. of tetrahydrofuran. The red solution was stirred for 4 hr. with constant nitrogen flushing. To this solution was added 5.2 mmoles of the dry ketone in 100 ml. of tetrahydrofuran. After the addition was complete the solution was stirred at room temperature for 15 hr. The resulting solution was evaporated under reduced pressure. Water was added to the residue and the mixture was extracted with ether. After drying over sodium sulfate, the solvent was removed under reduced pressure giving the crude product which was purified by crystallization. See Table II for compounds prepared by this general method.

2-Cholestanylidenethan-1-ol (XX).—To a well-stirred mixture of 18.0 g. of lithium aluminum hydride in dry ether (1800 ml.) under nitrogen was added dropwise a solution of 12.0 g. (26 mmoles) of 3-carboethoxymethylene cholestane (IV) in 300 ml. of dry ether. After the addition was complete, the mixture was refluxed for 2 hr. The excess lithium aluminum hydride was decomposed with wet ether in the cold. The resulting solution was dried over magnesium sulfate and evaporated to give 10 g. (24 mmoles, 93%) of a colorless solid. One recrystallization from light petroleum ether (b.p. 36–60°) gave an analytical sample: m.p. 96–97°; $[\alpha]^{26}D$ +11.0° (chloroform); λ_{max}^{Nujol} 2.85 μ (–OH); n.m.r. peaks, τ 4.75 (triplet, $HOCH_2$—CH=) and 6.02 (doublet, J = 7.2 c.p.s., –CH_2OH).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.82; H, 12.13.

1-Acetoxy-2-cholestanylidenethane (XXI).—To a solution of 4.1 g. of 2-cholestanylidenethan-1-ol in 30 ml. of pyridine was added dropwise with cooling and stirring 30 ml. of acetic anhydride. After the addition was complete the solution was stirred at room temperature for 4 days. The solution was poured on ice–water, extracted with ether, and the ether solution was washed successively with 3 *N* hydrochloric acid and 10% sodium bicarbonate solution. Evaporation of the solvent produced 3.8 g. of a viscous oil, λ_{max}^{film} 5.75 μ (ester carbonyl).

3α-Hydroxy-3β-(acetoxyacetyl)cholestane (XIX).—To a solution of 1.18 g. (2.59 mmoles) of crude 1-acetoxy-2-cholestanylidenethane in 11 ml. of methylene chloride and 41 ml. of *t*-butyl alcohol was added 1.6 ml. of pyridine followed by 3.2 ml. of N-methylmorpholine oxide–hydrogen peroxide complex in *t*-butyl alcohol (1 ml. requires 25.30 ml. of 0.1023 *N* thiosulfate for neutralization). To this solution was added 4.0 mg. of osmium tetraoxide in 2 ml. of *t*-butyl alcohol. The reaction mixture was stirred at room temperature overnight, then 10 ml. of 0.5% sodium hydrosulfite solution and 0.7 g. of magnesium silicate were added, and stirring was continued for 0.5 hours. The solution was filtered and the residue was washed with 15 ml. of 75% *t*-butyl alcohol in water. The filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in methylene chloride which was then washed with 10% sodium dihydrogen phosphate solution and with water. After drying over sodium sulfate the solvent was removed under reduced pressure and the residue was chromatographed on a Florisil column (80 g.). The column was developed with 1.0 l. of 10% acetone–hexane, 1.0 l. of 20% acetone–hexane, and 0.5 l. of 30% acetone–hexane. The 10% acetone fraction contained the desired material. After two recrystallizations from *n*-hexane there was produced 0.40 g. (0.82 mmoles), 32% yield, of a colorless solid: m.p. 168–169°; λ_{max}^{Nujol} 2.8 (hydroxyl group), 5.7 (ester carbonyl) and 5.8 μ (ketone carbonyl); n.m.r. peak, τ 5.08 (–OCH_2CO).

Anal. Calcd. for $C_{31}H_{52}O_4$: C, 76.18; H, 10.72. Found: C, 75.95; H, 10.95.

5β-Cholestanylidenethan-1-ol.—A solution of 2.0 g. of the oily, unsaturated ester in dry ether and 3.0 g. of lithium aluminum hydride were heated under reflux for 2 hr. The excess lithium aluminum hydride was destroyed with wet ether and the resulting mixture was treated with anhydrous sodium sulfate. After filtration the ether was evaporated under reduced pressure to produce a noncrystalline solid, λ_{max}^{film} 2.85 μ (hydroxyl).

1-Acetoxy-2-(5β-cholestanylidene)ethane.—A solution of 1.2 g. of the noncrystalline alcohol was dissolved in 10 ml. of pyridine and was treated in the cold with 10 ml. of acetic anhydride. After stirring at room temperature for 48 hr. the product was poured on ice–water and extracted with ether. The ether extract was washed successively with 3 *N* hydrochloric acid, 5% aqueous sodium bicarbonate, and water. After drying over magnesium sulfate the solvent was removed under reduced pressure to produce 1.1 g. of an oil, λ_{max}^{film} 5.7 μ (ester carbonyl).

3β-Hydroxy-3α(acetoxyacetyl)-5β-cholestane (XXV).—To a solution of 1.0 g. of 1-acetoxy-2-(5β-cholestanylidene)ethane in 9.3 ml. of methylene chloride and 34.6 ml. of *t*-butyl alcohol was added 1.35 ml. of pyridine followed by 1.76 ml. of N-methylmorpholine oxide–hydrogen peroxide complex in *t*-butyl alcohol (1 ml. requires 38.50 ml. of 0.1008 *N* thiosulfate for neutralization). To this solution was added 4.0 mg. of osmium tetroxide in 2 ml. of *t*-butyl alcohol. The reaction mixture immediately turned red. The red color faded to a yellow color after 2 hr. The solution was stirred at room temperature overnight. After treatment with 10 ml. of 5% aqueous sodium hydrosulfite and magnesium silicate the mixture was stirred for 0.5 hr. The solution was filtered and the residue was washed with 75% *t*-butyl alcohol in water. The filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in methylene chloride, which was then washed with a 10% solution of sodium dihydrogen phosphate and with water. After drying over sodium sulfate the solvent was removed under reduced pressure and the residue was chromatographed on a Florisil column (80 g.). Eluting with 9:1 hexane–acetone mixture produced a colorless solid, m.p. 140–143°. Several recrystallizations from methanol produced colorless plates: m.p. 144–145; λ_{max}^{Nujol} 2.80 (hydroxyl) and 5.70 μ (carbonyl). The product reduces Tollens reagent.

Anal. Calcd. for $C_{31}H_{52}O_4$; C, 76.18; H, 10.72. Found: C, 75.98; H, 10.68.

O.R.D. of 3-Carboethoxymethylenecholestan-7-one.—The optical rotary dispersion curve of this keto ester had a negative Cotton effect: $[\alpha]^{26}_{400}$ + 25, $[\alpha]^{26}_{375}$ + 31, $[\alpha]^{26}_{350}$ + 31, $[\alpha]^{26}_{325}$ +37, $[\alpha]^{26}_{316}$ −76, $[\alpha]^{26}_{310}$ − 53, and $[\alpha]^{26}_{300}$ +166° (*c* 0.065, methanol).

O.R.D. of 3β-Acetoxyacetyl-3α-hydroxycholestane.—The optical rotary dispersion curve of this ketone had a positive Cotton effect: $[\alpha]^{26}_{450}$ +43, $[\alpha]^{26}_{400}$ +60.8, $[\alpha]^{26}_{350}$ +98, $[\alpha]^{26}_{307}$ + 195, and $[\alpha]^{26}_{290}$ + 141° (*c* 0.092, methanol).

3-Carboxymethylene-5β-cholestane.—The noncrystalline unsaturated ester was refluxed with potassium hydroxide and ethanol for 3 hr. The resulting solution was evaporated under reduced pressure and the residual oil was treated with water. The acid was extracted with ether, dried over magnesium sulfate, and evaporated. Repeated recrystallization from ethanol gave an analytical sample, m.p. 162–163°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.62; H, 11.56.

3-Hydroxyethylene-17-hydroxy-5α-androstane.—To a suspension of 3.6 g. of lithium aluminum hydride in 200 ml. of dry ether was added 0.716 g. of the 3-carboethoxymethylene-5α-androstan-17-one (VII) in 50 ml. of dry ether. The resulting mixture was refluxed for 3 hr. Wet ether was added dropwise with cooling. The mixture was allowed to stand 2 days with anhydrous sodium sulfate. Filtration of the mixture and evaporation of the solvent produced a colorless solid. This solid was treated with water and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to produce 0.8 g. of product. One recrystallization from methanol produced small colorless needles, m.p. 193–194°. Recrystallization from benzene–ethyl acetate gave an analytical sample: m.p. 200–201°; $[\alpha]^{26}_{D}$ −16°; λ_{max}^{Nujol} 3.00 μ (hydroxyl).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.16; H, 10.34.

3-Acetoxyethylene-17-acetoxy-5α-androstane.—To a solution of 0.209 g. of 3-hydroxyethylene-17-hydroxy-5α-androstane in 5 ml. of pyridine at 0° was added dropwise with stirring 5 ml. of acetic anhydride. After the addition was complete the solution was stirred at room temperature for 3 days. The solution was poured on ice–water and extracted with 1:3 methylene chloride–ether. The organic layer was washed successively with 3 *N* hydrochloric acid, 10% sodium bicarbonate, and water. After drying over magnesium sulfate, the solvent was removed under vacuum from this solution to produce an oil, λ_{max}^{Nujol} 5.75 μ (carbonyl). The product solidified on standing and was recrystallized from methanol to afford small plates, m.p. 103–104°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.52; H, 9.42.

Acknowledgment.—This research was supported in part by a grant (CA-05079) from the National Institute of Health of the U. S. Public Health Service and fellowships from A. H. Robins and Hoffman-LaRoche, Inc. The authors would like to thank the Upjohn Company and Hoffman-LaRoche, Inc., for generous gifts of steroids and Dr. E. R. Malinowski for some of the n.m.r. data.