Excess hydride was destroyed by treatment with a saturated ammonium chloride solution. Ether was removed and the residue was reacetylated with pyridine and acetic anhydride. The reaction mixture was diluted with water and extracted with ether. The ether was dried and removed. The residue was crystallized from benzene–petroleum ether yielding 5.8 g (85%) of the diene **5b**: mp 160°; nmr ($CDCl_3$) τ 4.7–4.9 (4, complex, vinyl), 7.90 (6, s, $OCOCH_3$), 7.93 (6, s, $OCOCH_3$), 8.50 (6, s, CCH_3), 8.64 (18, s, CCH_3).

Anal. Calcd for $C_{36}H_{54}O_{16}$: C, 58.21; H, 7.33. Found: C, 58.32; H, 7.27.

Hexadeca-*O*-acetylhexadecitol (6a).—A solution of 1.0 g of diene **5b** and 2.5 g of *m*-chlorobenzoic acid in 25 ml of chloroform was kept 2 days at 2°. Then 50 ml of 10% acetic acid was added and the solution was warmed for 0.5 hr. The cooled solution was extracted with ether. Evaporation of water from the aqueous layer gave crude hexadecitol which was acetylated in 30 ml of pyridine and 15 ml of acetic anhydride. The acetylation product was extracted into ether and crystallized from benzene–petroleum ether to give 0.5 g (32%) of hexadeca-*O*-acetylhexadecitol **6a**: mp 110–112°; $[\alpha]^{23}_{589}$ +2.8 ± 1°, $[\alpha]^{23}_{320}$ 15.7° (*c* 0.6, MeOH); nmr ($CDCl_3$) τ 7.9 (unresolved $OCOCH_3$).

Anal. Calcd for $C_{48}H_{66}O_{32}$: C, 49.91; H, 5.71. Found: C, 49.73; H, 5.52.

7,8,9,10-Tetradeoxy-D-*erythro*-L-*gluco*-D-*manno*-hexadecitol (6b).—Catalytic hydrogenation of 450 mg of diene **5a** in ethanol over palladium on charcoal followed by removal of catalyst and solvent gave tetradeoxytetra-*O*-isopropylidenehexadecitol which was recrystallized from benzene–petroleum ether: mp 137–138°; nmr (CCl_4) τ 8.5–8.7 (unresolved CCH_3); *m/e* 561 (M − 17). A mixture of 300 mg of tetradeoxytetra-*O*-isopropylidenehexadecitol and 10 ml of 10% acetic acid was warmed for 15 min until solution was obtained. The cooled solution was extracted with ether, and the aqueous layer was concentrated to yield 230 mg of tetradeoxyhexadecitol **6b**. The tetradeoxyhexadecitol was recrystallized from ethanol: mp 160–163°; $[\alpha]^{25}_{589}$ 11° (*c* 1, water); R_f 0.80 (water–isopropyl alcohol 1:4).

Anal. Calcd for $C_{16}H_{34}O_{12}$: C, 45.93; H, 8.19. Found: C, 45.74; H, 7.95.

7,8,9,10-Tetradeoxydecitol (3c or C-6 Epimer).—A solution of 6.0 g of di-*O*-isopropylidene mannose in 50 ml of ether and 150 ml of 1 *M* tetramethylenedimagnesium bromide in ether (Peninsular ChemResearch) was heated at reflux overnight. The cooled solution was extracted with saturated ammonium chloride solution. The ether layer was dried ($MgSO_4$) and condensed. The 8-g residue was eluted from alumina to give a colorless syrup. The syrup (1.5 g) was hydrolyzed by heating with 50 ml of 10% acetic acid for 40 min. The cooled solution was extracted with ether and the aqueous layer was evaporated. The residue was crystallized from ethanol giving 1.0 g of tetradeoxydecitol: mp 218–220°; $[\alpha]^{23}_{589}$ −2°, $[\alpha]^{23}_{300}$ −11° (*c* 0.6, water); nmr (D_2O) τ 8.6–8.9 (6 complex, CH_2), *ca.* 9.1 (3, virtually coupled CH_3).

Anal. Calcd for $C_{10}H_{22}O_6$: C, 50.80; H, 9.34. Found: C, 50.42; H, 9.24.

1-Octyne-D-*glycero*-D-*galacto*-3,4,5,6,7,8-hexol (3b).—A solution of 800 mg of the octyne derivative **2a** in 30 ml of acetic acid was warmed until a clear solution was obtained. The cooled solution was extracted with ether and the aqueous layer was concentrated. The white residue was crystallized from ethanol to give 450 mg of octynitol **3b**: mp 175°; $[\alpha]^{23}_{589}$ 0°, $[\alpha]^{23}_{250}$ −31° (*c* 0.3, water); R_f 0.47 (water–isopropyl alcohol 1:4); nmr (D_2O) τ 6.0–6.2 (complex, CHOH), 7.00 (1, m, propargyl H), 7.68 (1, broad, acetylenic H).

Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.79. Found: C, 46.49; H, 6.79.

7,8-Dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol.—A solution of 150 ml of 2 *M* ethylmagnesium bromide in ether (Peninsular ChemResearch) and 8.0 g of di-*O*-isopropylidene mannose in 100 ml of ether was heated at reflux 12 hr. The cooled solution was extracted with saturated ammonium chloride solution. The ether layer was dried, and the ether was removed. The residue was crystallized from benzene–petroleum ether giving 3.5 g (40%) of dideoxydiisopropylideneoctitol: mp 78°; $[\alpha]^{23}_{589}$ −17.7°, $[\alpha]^{23}_{300}$ −87° (*c* 3, methanol).

Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.89; H, 9.02. Found: C, 57.83; H, 8.83.

7,8-Dideoxy-D-*glycero*-D-*manno*-octitol.—A mixture of 1.8 g of 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol and 45 ml of 10% acetic acid was heated until solution occurred. Removal of water and crystallization of the residue from ethanol gave 1.2 g (92%) of dideoxyoctitol: mp 215°; $[\alpha]^{23}_{589}$ −4.7° (*c* 1.3, water); R_f 0.60 (water–isopropyl alcohol 1:4); tri-*O*-isopropylidene derivative mp 71°.

Anal. Calcd for $C_8H_{18}O_6$: C, 45.71; H, 8.63. Found: C, 45.86; H, 8.33.

7,8-Dideoxy-L-*glycero*-D-*manno*-octitol (3a).—Catalytic hydrogenation of 1.0 g of octene **2c** in 50 ml of ethanol over palladium on charcoal followed by concentration of the solution gave 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene octitol, mp 75–78°. Hydrolysis of this compound in aqueous acetic acid gave crystalline 7,8-dideoxyoctitol: mp 158–159°; $[\alpha]^{23}_{589}$ 0°, $[\alpha]^{23}_{300}$ 11.6° (*c* 0.7, water); R_f 0.65 (water–isopropyl alcohol 1:4).

Anal. Calcd for $C_8H_{18}O_6$: C, 45.92; H, 8.63. Found: C, 45.92; H, 8.27.

Registry No.—**3a**, 31129-32-5; **3b**, 31119-93-4; **3c**, 31119-94-5; **3c** C-6 epimer, 31119-95-6; **4b**, 31081-95-5; **5b**, 31081-96-6; **6a**, 31119-96-7; **6b**, 31119-97-8; 7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-octitol, 31119-98-9; 7,8-dideoxy-D-*glycero*-D-*manno*-octitol, 31119-99-0.

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The Action of Triphenylphosphine Dibromide on Cholest-5-ene-3β,4β-diol, an Unexpected Vilsmeier Reaction

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Since the introduction by Horner and his colleagues[1] of triphenylphosphine dihalides for the preparation of alkyl and aryl halides from alcohols and phenols, these reagents have been finding increasing use as reagents in organic synthesis. Wiley and coworkers[2] have emphasized advantages of these reagents over phosphorus pentahalides, particularly with alcohols which are readily dehydrated or undergo rearrangement, and have discussed a mechanism.[3] The action of triphenylphosphine dibromide on a variety of steroids,[4] triterpenoids,[5] and norbornanols[6] has also been investigated and the stereochemical consequences of conversion of optically active alcohols to halides have been outlined.[1-7] The phosphine dihalides have also been used to prepare acid halides from carboxylic acids[1,8] and anhydrides,[8]

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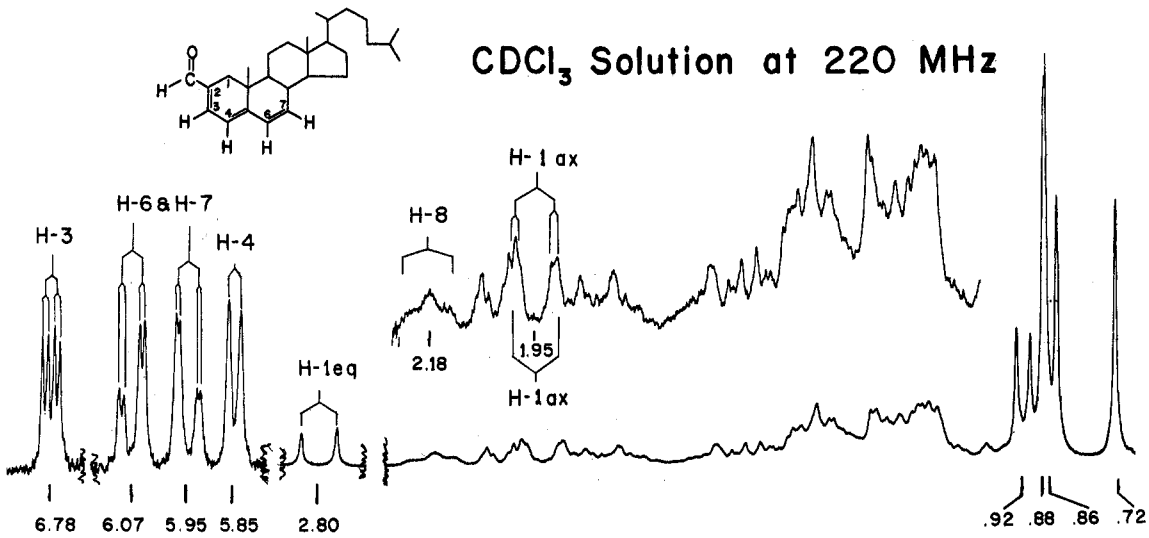
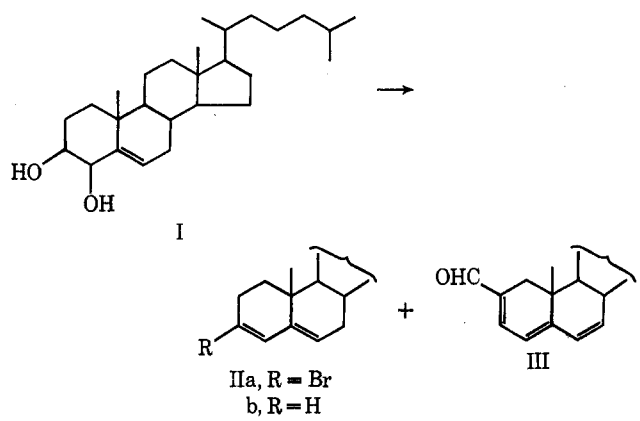


Figure 1.

gem dihalides and vinyl halides from aldehydes and ketones,[1] and nitriles from amides and oximes.[1] A modification of this last reaction also permits the conversion of ketoximes to ketenimines.[9] Triphenylphosphine dibromide also reacts with hydrazine or 1,1-disubstituted hydrazines to give hydrazinotriphenylphosphonium bromides[10] and has been used for the cleavage of ethers under mild conditions.[11]

In seeking to extend the scope of triphenylphosphine dibromide as a reagent for conversion of alcohols to alkyl halides, we wished to examine the reaction with a vicinal diol and chose as a substrate, cholest-5-ene-3β,4β-diol (I), readily obtained from cholesterol by selenium dioxide oxidation.[12] When I was heated with triphenylphosphine dibromide in dimethylformamide solution, conditions hitherto used routinely, two products readily separated by chromatography on alumina were isolated. The first was a conjugated bromodiene, $C_{27}H_{43}Br$, with constants in agreement with those reported for 3-bromocholesta-3,5-diene (IIa), previously obtained[13] by treatment of cholest-4-en-3-one with phosphorus tribromide. In agreement with this formulation, the bromodiene was converted to cholesta-3,5-diene (IIb) with lithium in tetrahydrofuran–*tert*-butyl alcohol solution. The second product, isolated as yellow needles, was shown by the infrared spectrum to be a conjugated unsaturated aldehyde and the ultraviolet absorption maximum (λ 360 mμ) indicated the probability that the conjugated trienaldehyde incorporated a homoannular diene chromophore moiety. It was characterized by formation of a very dark red 2,4-dinitrophenylhydrazone derivative. Difficulties in deriving an adequate structure for this aldehyde, based on the C_{27} content of the diol precursor and apparently conflicting elemental analysis data, were resolved on examination of the proton noise decoupled ^{13}C nmr spectrum. This clearly showed that the compound contained 28 carbon atoms, one of which could be attributed to an aldehydic carbon atom and six to olefinic carbon atoms. This permitted the formulation of the aldehyde as $C_{28}H_{42}O$, the additional unexpected carbon atom being derived from the dimethylformamide solvent as an aldehyde function in a Vilsmeier type reaction.[14] The constitution, 2-formylcholesta-2,4,6-triene (III), is accordingly proposed for the yellow aldehyde.



The proton magnetic resonance spectrum, being extremely complex at 100 MHz, notably in the vinyl region, was measured at 220 MHz (see Figure 1) and uniquely supports this structure. The chemical shift assignments, supported where appropriate with spin decoupling and nuclear Overhauser effect[15] experiments, are summarized for brevity in Table I.

As a probable pathway of I to III, it is suggested that the Vilsmeier reagent, $(CH_3)_2N^+{=}CHBr$, is formed by interaction of dimethylformamide with triphenylphosphine dibromide and reacts with cholesta-2,4,6-triene, a dehydration product of I in a Vilsmeier reaction, mechanisms for which have been proposed.[16] In this connection, it has recently been shown[17] that androsta-2,4,6-triene derivatives react with phosphorus oxychloride and dimethylformamide to form the analogous 2-formyl products.

Cholest-5-ene-3β,4β-diol (I) provides an interesting example of a steroid alcohol from which useful struc-

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TABLE I

PROTON MAGNETIC RESONANCE DATA (220 MHz) OF 2-FORMYLCHOLESTA-2,4,6-TRIENE

Assignment	Chemical shift, δ	Appearance of signal	Coupling constants, Hz	Other observations
C-2 formyl proton	9.47	Sharp singlet		Signal enhancement (25%) when H-3 irradiated under NOE conditions
H-3	6.78	Pair of doublets	$J_{3,4}$ = 5.5 (vicinal) $J_{3,1\alpha}$ = 3.0 (allylic)	Confirmed by irradiating H-4 resonance Confirmed by irradiating resonance at δ 1.95
H-6 (or 7)	6.07	Pair of doublets	$J_{6,7}$ = 10.5 (cis olefin) $J_{6 \text{ or } 7,8}$ = 2.5	Small coupling of 2.5 Hz disappears on irradiation of H-8
H-7 (or 6)	5.95	Pair of doublets	$J_{6,7}$ = 10.5 (cis olefin) $J_{6 \text{ or } 7,8}$ = 1.5	Small coupling of 1.5 Hz disappears on irradiation of H-8
H-4	5.85	Broad doublet (half line width ~3 Hz)	$J_{3,4}$ = 5.5 (vicinal)	Half line width reduced to ~1 Hz on irradiation of H-1α; broad singlet on irradiation of H-3
H-1β	2.80	Doublet	$J_{1\beta,1\alpha}$ = 17 (geminal)	Singlet on irradiation of H-1α
H-8β	2.18	Smeared triplet	$J_{8,9} + J_{8,14} \sim 20$	Broadening due to unequal coupling to H-6 and H-7
H-1α	1.95	Broad doublet (half line width ~7 Hz)	$J_{3,1\alpha}$ = 3.0 (allylic)	Narrower doublet (half line width ~3 Hz) on irradiation of H-3, indicating *W* type of long-range coupling to C-19 methyl
C-21 methyl	0.92	Doublet	J = 6.0	
C-19 methyl	0.88	Shoulder on lower field signal of C-26,27 doublet		Sharpens on irradiation of H-1α
C-26,27 methyls	0.86	Doublet	J = 5.5	
C-18 Methyl	0.72	Singlet		

tural information is readily available by examination of its nmr spectrum before and after addition of trichloroacetyl isocyanate.[18] As expected from the work of Bose and coworkers,[19] the secondary nature of both hydroxyl groups is shown by the large downfield shifts (1.32 and 1.51 ppm) of the carbinol protons and the presence of a vinyl proton β to a hydroxyl group, *i.e.*, the fragment C(OH)C=CH is indicated by a downfield shift of 0.30 ppm.

Experimental Section

Melting points are uncorrected. Rotations were measured in chloroform solution and nuclear magnetic resonance spectra in deuteriochloroform solution with tetramethylsilane as an internal standard.

Cholest-5-ene-3β,4β-diol, prepared by selenium dioxide oxidation of cholesterol, had mp 174–175° (reported[12] mp 176–177°); nmr δ 0.70 (s, C-18), 1.20 (s, C-19), 3.58 (br m, H-3), 4.17 (d, J = 3.5 Hz, H-4), 5.70 (m, H-6). After addition of trichloroacetyl isocyanate, significant downfield shifts resulted in signals at δ 4.90 (br m, H-3), 5.68 (d, J = 3.5 Hz, H-4), 6.00 (m, H-6), and 8.40 (br s, hydroxyl groups).

Action of Triphenylphosphine Dibromide–Dimethylformamide on Cholest-5-ene-3β,4β-diol.—Triphenylphosphine (24.85 g) and bromine (15.2 g) were added to dry dimethylformamide (*ca.* 100 ml). A solution of cholestenediol (2.0 g) in the same solvent was then added, and the mixture was heated on the steam bath under nitrogen for 16 hr, diluted with water, and extracted with ether. The extract was washed with water, dried, and evaporated and the residual solid was washed and digested with cold petroleum ether (bp 30–60°). The petroleum soluble extract was concentrated and chromatographed on alumina (Merck, acid washed). Elution with this solvent (250 ml) gave a colorless oil (300–600 mg), which on crystallization from ether–methanol yielded **3-bromocholesta-3,5-diene** as plates: mp 63–66°; $[\alpha]$D −121° (*c* 1.0); λ (isooctane) 236 nm (ϵ 23,300), 243 (23,300), and 252 (16,000); nmr δ 0.71 (s, C-18), 0.83 (s, C-19), 5.57 (m, H-6), and 5.98 (s, H-4) (lit.[13] mp 65–72°, $[\alpha]$D −115°).

Anal. Calcd for $C_{27}H_{43}Br$: C, 72.46; H, 9.68; Br, 17.85. Found: C, 72.65; H, 9.58; Br, 17.68.

Continued elution with petroleum ether–benzene and benzene gave a yellow solid (230 mg) which crystallized from ether–methanol to give **2-formylcholesta-2,4,6-triene** as bright yellow needles: mp 157–158°; $[\alpha]$D −117° (*c* 1.0); λ (C_2H_5OH) 360 nm (ϵ 17,000); ν (KBr) 2778 and 2703 (aldehyde CH), 1656 (conjugated CO), and 1530 cm^{-1} (unsaturation).

Anal. Calcd for $C_{28}H_{42}O$: C, 85.22; H, 10.73. Found: C, 85.28; H, 10.82.

It gives a deep orange color with tetranitromethane in chloroform. The nmr spectroscopic data (220 MHz) is reported in Table I.

Debromination of 3-Bromocholesta-3,5-diene.—*tert*-Butyl alcohol (178 mg) and lithium (100 mg) were added to a soltuion of the bromodiene (105 mg), and the mixture was heated under reflux for 80 hr in an atmosphere of nitrogen. After cooling, water was added and the product extracted with ether in the usual way. Evaporation gave a colorless oil which crystallized from ether–methanol yielding **cholesta-3,5-diene** as needles: mp 78–80°; $[\alpha]$D −97° (*c* 2.1); λ (cyclohexane) 228 nm (ϵ 16,000), 236 (17,500), and 244 (11,100) (reported[20] mp 78–79°, $[\alpha]$D −114°).

2-Formylcholesta-2,4,6-triene 2,4-Dinitrophenylhydrazone.—A solution of 2,4-dinitrophenylhydrazine (140 mg) in acetic acid (20 ml) was added to a solution of the aldehyde (476 mg) in the same solvent (8 ml). The mixture was boiled for 10 min, cooled, diluted with water, and extracted with ether, and the washed ($NaHCO_3$ and H_2O) and dried extract was chromatographed on alumina. Elution with petroleum ether–benzene (1:1) gave a dark red residue, which on crystallization from ether–methanol gave the 2,4-dinitrophenylhydrazone derivative as a dark red solid (230 mg): mp 217–220° dec; nmr δ 0.78 (s, C-18), 0.88 (d, J = 5.5 Hz, C-26,27), 0.97 (s, C-19), 3.02 (d, J = 17 Hz, H-1β), 5.77–6.22 (complex m, H-4,6,7), 6.38 (d d, J = 5, 2.5 Hz, H-3), 7.82 (s, CH=N), 7.93 (d, J = 10 Hz, H-6′), 8.36 (q, J = 10, 3 Hz, H-5′), 9.14 (d, J = 3 Hz, H-3′), 11.20 (br s, NH).

Anal. Calcd for $C_{34}H_{46}O_4N_4$: C, 71.05; H, 8.07; N, 9.75. Found: C, 71.53; H, 8.00; N, 9.56.

Proton Decoupled ^{13}C Nmr Spectrum of 2-Formylcholesta-2,4,6-triene.—This was obtained on a Varian HA-100 spectrometer operating at 25.1 MHz with a V-350 RF/AF sweep unit and a V-4335-1 8-mm probe. Proton decoupling was effected by a Varian V-3512-1 Heteronuclear Noise decoupler and time-averaged on a Varian C-1024 computer. The sample was run as a 0.25 molar dioxane solution with the ^{13}C resonance of dioxane carbon atoms acting as an internal lock. The ^{13}C chemical shifts are measured relative to external CS_2, those located at higher fields than the reference (CS_2 = 0) being considered positive. The accuracy of the chemical shift measurement was ±0.1 ppm.

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The spectrum consisted of 28 singlets, one of which could be ascribed to the aldehyde carbon atom (δ 1.2), six to the olefinic carbon atoms (δ 40.4, 50.8, 55.3, 56.5, 65.2, 73.7), and 21 to the saturated carbon atoms (δ 136.6, 138.5, 141.3, 149.5, 152.8, 153.1, 155.1, 156.1, 156.4, 156.7, 161.1, 164.6, 164.7, 168.8, 169.0, 170.0, 170.2, 171.8, 174.0, 177.1, 180.9).

Registry No.—I, 17320-10-4; IIa, 31382-63-5; IIb, 747-90-0; III, 31382-65-7; III 2,4-DNPH, 31382-66-8; triphenylphosphine dibromide, 1034-39-5.

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Synthesis and Conformation of 2β-Hydroxytestosterone[1a]

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Received September 11, 1970

Although 2β,17β-diacetoxy-4-androsten-3-one is readily synthesized,[2] the hydrolysis of both ester groups to obtain 2β,17β-dihydroxy-4-androsten-3-one (2β-hydroxytestosterone **4**) has been unsuccessful,[2a,2b,2h] resulting in partial hydrolysis, isomerization, or oxidation. The original synthesis[2h] involved lithium aluminum hydride reduction of the diacetate of **4** to a mixture of isomeric allyl alcohols followed by reoxidation of the alcohols with manganese dioxide to give the α,β-unsaturated ketone in poor yield.[3] A facile synthesis of **4** was desired for biochemical studies since it is a natural metabolite of androgens and may be an important precursor in estrogen biosynthesis. A novel preparation was devised in which direct hydrolysis of a mixed ester gave **4** in a good yield.

The bromination procedure of Djerassi, *et al.*,[4] was applied to testosterone chloroacetate (**1**)[5] to afford 6-bromotestosterone chloroacetate (**2**). Acetolysis[2h] of crude **2** with potassium acetate in acetic acid afforded 2β-acetoxy-17β-chloroacetoxy-4-androsten-3-one (**3**),

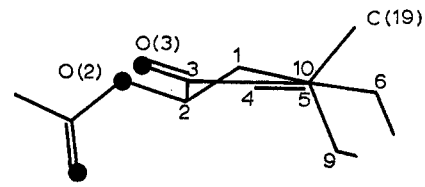
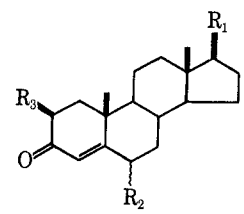


Figure 1.—The A ring structure of **3** computer-projected parallel to C(5)–C(10).

mp 190–191°. The structure was elucidated by spectroscopy (uv, ir, nmr, CD, and ORD) as described in the Experimental Section. The crystal and molecular structure have also been determined by single-



1, $R_1 = OCOCH_2Cl$; $R_2 = R_3 = H$
2, $R_1 = OCOCH_2Cl$; $R_2 = Br$; $R_3 = H$
3, $R_1 = OCOCH_2Cl$; $R_2 = H$; $R_3 = OAc$
4, $R_1 = R_3 = OH$; $R_2 = H$

crystal X-ray diffraction techniques. The structure was refined to reliability index (R) of 8.3% for 1874 observed reflections. The average standard deviations in nonhydrogen bond distances and angles are ±0.01 Å and ±0.8°, respectively. The A ring is in an inverted half-chair conformation with the 2β oxygen at the equatorial position as shown in Figure 1. The torsional angles related to the A ring are in Table I.

TABLE I
TORISONAL ANGLES OF THE A-RING REGION OF **3**

O(2)-C(2)-C(3)-O(3)	16.8[a]
C(1)-C(2)-C(3)-C(4)	−45.8
C(2)-C(3)-C(4)-C(5)	17.7
C(3)-C(4)-C(5)-C(6)	−172.9
C(3)-C(4)-C(5)-C(10)	−0.4
C(4)-C(5)-C(10)-C(1)	11.6
C(5)-C(10)-C(1)-C(2)	−42.1
C(10)-C(1)-C(2)-C(3)	60.3
O(3)-C(3)-C(4)-C(5)	−161.0

[a] In degrees.

Atoms C(3), C(4), C(5), C(10), and C(1) reside in a nearly coplanar arrangement as do atoms O(2), C(2), C(3), and O(3). The torsional angle of −161° for the α,β-unsaturated ketone O(3)–C(3)–C(4)–C(5) indicates a slight disruption of the conjugate system in the crystal. The O(2)–O(3) interatomic distance is 2.72 Å which is of a hydrogen bonding order. An intramolecular hydrogen bond between O(2) and O(3) has been postulated as a possible stabilizing factor of the "twist" and half-boat conformations of the A rings of 2β-hydroxy-Δ[4]-3-keto steroids.[6,7] However, the required C(2)–O(2)–H(02) bond angle of approximately 109° would eliminate the possibility of hydrogen bonding. The dihedral angle of 127° between the least-squares plane of the A ring and the least-squares

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