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.

Acknowledgment.—We wish to thank Mr. George Baral and Dr. Daniel Levy for their assistance in an early phase of these studies, and Varian Associates, Palo Alto, Calif., for the hospitality of their spectroscopy applications laboratory where the ^{13}C and 220-MHz proton measurements were performed. We are also grateful to the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, for a research grant.

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

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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**),

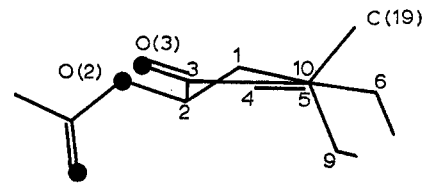
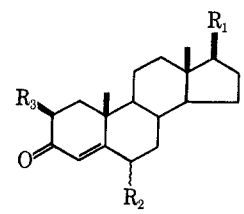


Figure 1.—The A ring structure of **3** computer-projected parallel to C(5)–C(10).

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

(1) (a) This work was supported in part by U. S. Public Health Service Research Grant HD 04945. (b) Faculty Research Awardee, PRA-72, of the American Cancer Society. (c) Postdoctoral Fellow, 1968–1969.

(2) (a) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **75**, 4712 (1953); (b) G. Rosenkranz, O. Mancera, and F. Sondheimer, *ibid.*, **77**, 145 (1955); (c) R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, *ibid.*, **77**, 661 (1955); (d) D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950); (e) L. F. Fieser and M. A. Romero, *J. Amer. Chem. Soc.*, **75**, 4716 (1953); (f) J. Herran, G. Rosenkranz, and F. Sondheimer, *ibid.*, **76**, 5531 (1954); (g) J. S. Baran, *ibid.*, **80**, 1687 (1958); (h) P. N. Rao and L. R. Axelrod, *ibid.*, **82**, 2830 (1960).

(3) It was claimed that the oxidation with manganese oxide at −15° gave 20% yield based on ultraviolet data though it afforded diosphenol both at 0° and at room temperature. We were unable to isolate a crystalline **4** by following the reported procedure.

(4) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Amer. Chem. Soc.*, **72**, 4534 (1950).

(5) H. J. van der Molen, D. Groen, and J. H. van der Maas, *Steroids*, **6**, 195 (1965).

(6) S. L. Patashnik, H. L. Kimball, and S. Burstein, *ibid.*, **2**, 19 (1963).

(7) H. J. Brodie and A. Pillai, 51st Meeting of the Endocrine Society, New York, N. Y., 1969, Program 98.

of the B–C–D rings is compared to those of 157, 128, and 125° of testosterone,[8] 17β-hydroxy-1,4-androstadien-3-one,[9] and methyl 3α,7α-diacetoxy-11α-chloro-12α-nitro-5β-cholaonate,[10] respectively. The A ring of **3** is bent downward extremely so that it is almost identical with that of the 5β steroid. Full details of the structure determination are reported elsewhere[11] with those of another 2β-hydroxytestosterone derivative.

The 2β-acetate 17β-chloroacetate **3** was stirred at room temperature in methanol containing potassium hydroxide under a stream of nitrogen. The oily product was purified through preparative tlc on silica gel to afford 2β-hydroxytestosterone (**4**) in 58% yield, leaflets, mp 127–129°, when crystallized from ethanol–hexanes. The structure was elucidated by spectroscopy (uv, ir, nmr, CD, and ORD; see Experimental Section). When recrystallized from acetone–petroleum ether, the leaflets changed to another polymorphic form, needles, mp 157–159°. The previously reported[2h] crystals are prisms, mp 87–89°, and needles, mp 163–164°. Crystal data on the two forms of **4** (Table II)

TABLE II
CRYSTAL DATA FOR 2β-HYDROXYTESTOSTERONE

	Leaflets	Needles
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions		
a	9.78 ± 0.03 Å	10.237 ± 0.002 Å
b	22.36 ± 0.07 Å	22.318 ± 0.006 Å
c	7.64 ± 0.02 Å	7.203 ± 0.001 Å
Cell volume	1670.3 Å^3	1645.6 Å^3

showed their crystal systems and space groups to be identical. The cell dimensions were equivalent in one direction and varied by approximately $^1/_2$ Å in each of the others, resulting in similar cell volumes. The needles showed very sharp X-ray diffraction spots and sharp extinction of polarized light. However, these parameters were less sharp in the leaflets, indicating some molecular disorder. After standing at room temperature for 10 months, a change in the melting point of the leaflets was observed (sintered at 127–129°, mp 157–159°).

The major problem in previous attempted synthesis of **4** has been that hydrolytic conditions sufficiently vigorous to remove the 17β-acetate function also cause the isomerization of the less stable 2β-hydroxyl group to the more stable 2α configuration. The chloroacetate group, however, appears to have approximately the same lability toward alkaline hydrolysis as a ketol ester and thus can be removed under conditions sufficiently mild to avoid epimerization of the 2β-hydroxyl group.

The close similarity of the CD and ORD curves of **3** and **4** and of the coupling constants of their 2α proton indicates that in solution the A ring of **4** also exists predominantly in the inverted half-chair conformation with the 2β-hydroxyl group in the equatorial position.[12]

(8) A. Cooper, E. M. Gopalakrishna, and D. A. Norton, *Acta Crystallogr., Sect. B*, **24**, 935 (1968).
(9) Y. Osawa and D. G. Spaeth, *Biochemistry*, **10**, 66 (1971).
(10) Y. Komeichi, Y. Osawa, W. L. Duax, and A. Cooper, *Steroids*, **15**, 619 (1970).
(11) W. L. Duax, C. Eger, S. Pokrywiecki, and Y. Osawa, *J. Med. Chem.*, **14**, 295 (1971).

Experimental Section[13]

2β-Acetoxy-17β-chloroacetoxy-4-androsten-3-one (3).—A solution of 1.69 g (0.0046 mol) of testosterone chloracetate (**1**)[4] in 30 ml of CCl_4 was refluxed with 1.8 g (0.010 mol) of *N*-bromosuccinimide and 0.01 g of 2,2′-azobisisobutyronitrile for 75 min. Cooling, filtration, and evaporation of the solvent gave 1.8 g of **2** as a crude oil. Since the product decomposed during attempted purification, the crude oil was used for acetolysis without further handling. The oil was dissolved in 25 ml of acetic acid and refluxed with 4.6 g of potassium acetate for 12 min. The mixture was cooled, diluted with 75 ml of water, and extracted with ether. The ethereal layer was washed with 1 *N* NaOH until the aqueous phase was basic and then with water to neutrality. The organic phase was then dried ($MgSO_4$), concentrated to approximately 25 ml, and stored overnight at −20°. The precipitate was collected and recrystallized from methanol to afford 400 mg (21%) of **3**: mp 190–191°; uv max 244 nm (ε 15,300); ir 1741, 1680, and 1612 cm^{-1}; nmr δ 0.87 (s, 3, 18-CH_3), 1.21 (s, 3, 19-CH_3), 2.13 (s, 3, OAc), 4.05 (s, 2, $COCH_2Cl$), 4.65 (m, 1, 17α H, $W_{1/2}$ = 18 Hz), 5.27 (dd, 1, 2α(a) H, $J_{2\alpha,1\beta}$ = 12.0, $J_{2\alpha,1\alpha}$ = 5.4 Hz), and 5.75 (s, 1, 4-H); ORD (*c* 0.10, dioxane, 25°) $[\alpha]_{700}$ −20°, $[\alpha]_{380}$ −180°, $[\alpha]_{344-354}$ +140°, $[\alpha]_{300}$ −1590°; CD (*c* 0.10, dioxane, 25°), $[\theta]_{386}$ 0°, $[\theta]_{364}$ −330°, $[\theta]_{358}$ 0°, $[\theta]_{332}$ +3350° (sh), $[\theta]_{324}$ +3900°, $[\theta]_{280}$ 0°.

Anal. Calcd for $C_{28}H_{31}O_5Cl$: C, 65.32; H, 7.39. Found: C, 65.11; H, 7.32.

2β,17β-Dihydroxy-4-androsten-3-one (4).—To a suspension of 600 mg (0.00142 mol) of **3** in 40 ml of methanol, under N_2, was added 1.5 ml of 1 *N* potassium hydroxide in methanol, and the mixture stirred at room temperature for 18 min. The reaction mixture was then homogeneous and after 0.2 ml of water had been added, stirring was continued for 2 min, followed by the addition of 2.5 ml of 1 *N* acetic acid. The mixture was concentrated under vacuum and the residue diluted with ether. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to afford 450 mg of an oil. The oil was applied in equal parts to four 20 × 20 cm tlc plates with 1.75-mm layers of silica gel P_{254} and developed three times in ethyl acetate–benzene (35:65). Elution with methanol and crystallization from 95% ethanol–hexanes gave 250 mg (58%) of **4**: mp 127–129° (leaflets); uv max 244 nm (ε 14,600); ir 3420, 1685, 1618 cm^{-1}; nmr δ 0.79 (s, 3, 18-CH_3), 1.19 (s, 3, 19-CH_3), 3.65 (m, 1, 17α H, $W_{1/2}$ = 16 Hz), 4.18 (dd, 1, 2α(a) H, $J_{2\alpha,1\beta}$ = 13.6, $J_{2\alpha,1\alpha}$ = 5.4 Hz), and 5.78 (s, 1, 4 H); ORD (*c* 0.10, dioxane, 25°), $[\alpha]_{700}$ −80°, $[\alpha]_{380}$ −320°, $[\alpha]_{348}$ +60°, $[\alpha]_{320}$ −1700°; CD (*c* 0.10, dioxane, 25°), $[\theta]_{384}$ 0°, $[\alpha]_{370}$ −160°, $[\theta]_{360}$ 0°, $[\theta]_{320}$ +4300°, $[\theta]_{278}$ 0°.

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.88; H, 9.32.

The leaflets **4** were changed to needles, mp 157–159°, by recrystallization from acetone–petroleum ether (bp 36–42°). The needles had the same composition (Found: C, 74.88; H, 9.13) and their CD and ORD curves were identical with those of the leaflets. Acetylation of **4** (120 mg) with pyridine and acetic anhydride afforded the diacetate (125 mg), mp 199–200°, which was identical with authentic 2β-hydroxytestosterone diacetate prepared according to Clarke, *et al.*[2c]

Registry No.—**3**, 31045-19-9; **4**, 10390-14-4.

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(13) Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. The uv spectra were determined in 95% ethanol with a Cary Model 14 spectrophotometer. The ir spectra were determined as KBr micropellets using a Perkin-Elmer Model 421 spectrophotometer. The nmr spectra were recorded in deuteriochloroform on a Varian A-60 spectrometer with a tetramethylsilane internal standard. Optical rotatory dispersion and circular dichroism were recorded on a Jasco optical rotatory dispersion recorder Model ORD/UV-5 with CD attachment.