3-Butyl-3,6-dihydroxy-1-(*p*-nitrobenzoxy)-2-heptanone (IIb).—To 0.1 mole of potassium *p*-nitrobenzoate in 400 ml of dry acetone (see Vb), was added 50 ml of an acetone solution of the crude α-bromo-α′-hydroxy ketone, prepared from 4.04 g (0.02 mole) of XIa and 4.00 g (0.025 mole) of bromine. The resulting mixture was heated under reflux for 20 hr with stirring and then allowed to stand for an additional 20 hr at room temperature. After work-up and solvent removal, the residue was crystallized from benzene–petroleum ether (bp 60–110°) (1:1), which afforded 1.5 g (20%) of colorless crystals of IIb: mp 109–110°; ν_{max} (cm^{-1}) 3450(s) (O–H), 1350(m), 1130(m), (*t*-OH), 1725(s) (C=O), 1530 (s) (NO_2).

Anal. Calcd. for $C_{18}H_{25}NO_7$: C, 58.83; H, 6.87; N, 3.82. Found: C, 58.67; H, 7.01; N, 4.10.

A sample of 200 mg (0.54 mmole) of IIb in 30 ml of methanol was stirred with 1.5 ml of 0.54 *M* periodic acid solution for 12 hr. The solution was diluted with 30 ml of water, and the methanol was evaporated *in vacuo*. The residue was extracted with ether, and the ethereal extract was shaken vigorously with sodium bicarbonate solution and separated. The organic phase was washed with water and dried over anhydrous sodium sulfate. After solvent removal, the residue was taken up in 20 ml of ethanol and treated with 2,4-dinitrophenylhydrazine. The resulting crystalline precipitate was recrystallized from ethanol, affording 2,5-nonanedione (XII) as the 2,4-dinitrophenylhydrazone, mp 184–186° (lit.[17] mp 186°).

(17) K. Alder and C. H. Schmidt, *Ber.*, **76**, 187, 193 (1943).

The sodium bicarbonate extract was acidified with hydrochloric acid and extracted with ether, and the extract washed with water, and dried. After evaporation of the solvent, O-*p*-nitrobenzoylglycolic acid (XIIIb), mp 146–147°, was obtained which, on admixture with an authentic sample, showed no depression, mp 146–174°.[4]

3-Butyl-3,6-dihydroxy-1-(*p*-hydroxybenzoxy)-2-heptanone (IIc).—To a refluxing solution of potassium *p*-hydroxybenzoate [from 10.0 g (0.10 mole) of potassium bicarbonate and 13.8 g (0.10 mole) of *p*-hydroxybenzoic acid in 400 ml of dry acetone] was added dropwise the crude α-bromo-α′-hydroxy ketone intermediate [from 4.04 g (0.02 mole) of XIa and 4.0 g (0.025 mole) of bromine in 50 ml of dry acetone]. After continued heating for 20 hr and the usual work-up, the crude product was crystallized from benzene–petroleum ether (1:1) to give 1.43 g (21%) of colorless crystals IIc, mp 117–118°.

Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.88; H, 7.75. Found: C, 63.95; H, 7.90.

Acknowledgment.—This investigation was supported by a research grant (A-253, C5-C8) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. For biological evaluations, we wish to thank the National Service Center, U. S. Public Health Service, Bethesda, Md.

Steroids. CCLXXXVII.[1] A Synthetic Route to 19-Substituted 10α-Steroids

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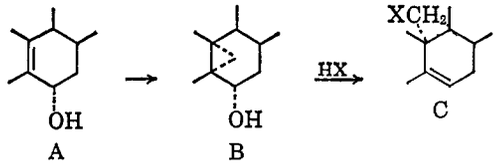
Simmons–Smith methylenations of estr-5(10)-en-6-ols have been studied. 3β-(Tetrahydropyran-2-yl)oxy-5α,19-cyclo-10α-androsta-6α,17β-diol (VIa) undergoes ring opening with ethanolic hydrochloric acid–lithium chloride to furnish 19-chloro-10α-androst-5-ene-3β,17β-diol (VII).

General acceptance of fertility control through the estrogen–progestagen oral contraceptive pill approach provided added impetus to the search for progestational agents of increased potency. Among the more remarkable findings was the observation by Dutch workers that certain 9β,10α- (retro) steroids display progestational activity.[4] Some results of our broad program aimed at developing new synthetic routes to steroids of abnormal configuration have already been disclosed.[5,6] This present communication describes a novel approach to 19-disubstituted 10α-androstanes which is considerably shorter than that previously described by Sondheimer and his colleagues.[7,8] The method chosen involves a stereospecifically controlled Simmons–Smith methylenation[9] of a $\Delta^{5(10)}$-steroid, a reaction used earlier in the synthesis of 10α-androstanes.[6] A study of molecular models[10] suggested no steric difficulties would be encountered in the realization of the sequence A → B → C.



3β,19-Dihydroxyandrost-5-en-17-one (Ia)[11] was oxidized with lead tetraacetate to afford 6β-acetoxy-3β-hydroxyestr-5(10)-en-17-one (IIa), the β configuration at C-6 becoming apparent from subsequent experiments (*vide infra*).[12] The acetate group in the derived 3β-(tetrahydropyran-2-yl) ether IIIa was hydrolyzed to afford the corresponding allylic alcohol IIIb. (See Chart I.) Simmons–Smith methylenation under normal conditions of ether reflux[9] converted this allylic alcohol IIIb into the cyclopropane IV. β-Face ad-

(1) Steroids. CCLXXXVI: J. A. Edwards, M. C. Calzada, L. Cuellar, and A. Bowers, submitted for publication.

(2) Syntex Postdoctoral Research Fellow, Mexico, 1963–1964.

(3) To whom correspondence should be addressed: Syntex Research Center, Palo Alto, Calif.

(4) E. H. Reerink, H. F. L. Schöler, P. Westerhof, A. Querido, A. A. H. Kessenaar, E. Diczfalusy, and K. C. Tillinger, *Nature*, **186**, 168 (1960); P. Westerhof and E. H. Reerink, *Rec. Trav. Chim.*, **79**, 771, 794 (1960).

(5) J. A. Edwards, P. Crabbé, and A. Bowers, *J. Am. Chem. Soc.*, **85**, 3313 (1963); J. A. Edwards, H. Carpio, and A. D. Cross, *Tetrahedron Letters*, 3299 (1964).

(6) R. Ginsig and A. D. Cross, *J. Am. Chem. Soc.*, **87**, 4629 (1965).

(7) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron Letters*, 38 (1960).

(8) M. Torigoe and J. Fishman [*ibid.*, 1251 (1963)] reported syntheses of 19-substituted 3-desoxy-10α-steroids.

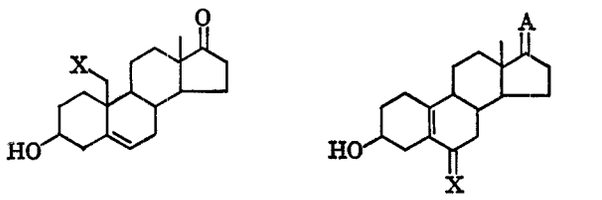
(9) Collected references to the Simmons–Smith reaction, methodology, applications, and stereochemical control appear in ref 3–6 and 16, of our earlier publication.[6]

(10) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(11) J. S. Mihina, U. S. Patent 2,856,415 (1958); K. Tanabe, R. Takahashi, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962).

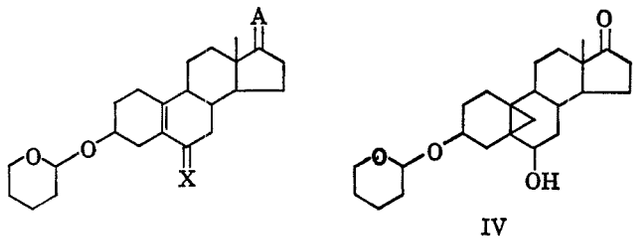
(12) D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner, and O. Jeger [*Helv. Chim. Acta*, **47**, 1961 (1964)] have established the configuration at C-6 by an elegant method. Their results became known after completion of our studies. The lead tetraacetate oxidation employed in this work follows an experiment procedure developed by Drs. O. Halpern and A. Bowers, manuscript in preparation. *Cf.* also R. M. Moriarty and K. Kapadia, *Tetrahedron Letters*, 1165 (1964).

CHART I



Ia, X = OH
b, X = Cl

IIa, A = O; X = α-H, β-OAc
b, A = O; X = α-H, β-OH
c, A = X = α-H, β-OH
d, A = X = O
e, A = α-H, β-OH; X = α-OH, β-H



IV

IIIa, A = O; X = α-H, β-OAc
b, A = O; X = α-H, β-OH
c, A = X = O
d, A = α-H, β-OH; X = α-OH, β-H

dition of "methylene" was proven by treatment of the 5β,19 cyclo compound IV with hydrochloric acid–boron trifluoride in tetrahydrofuran when 19-chloro-3β-hydroxyandrost-5-en-17-one (Ib) was formed and identified by comparison with an authentic sample.[13] A characteristic of the change from the allylic alcohol IIIb to the cyclopropane IV was an upfield shift of the C-18 proton resonance from 55.5 to 51.5 cps. The C-19 geminal methylene protons in IV resonated as an AB four-line pattern (18.5 and 23, 49 cps, and an obscured peak, J_{HH} = 4.5 cps[14]).

Saponification of the 6β-acetate IIa furnished the corresponding diol IIb which was reduced by lithium aluminum hydride to the triol IIc. Allylic oxidation of the alcohol IIb with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[15] gave the conjugated ketone IId [λ_{max} 250 mμ (log ϵ_{max} 4.06)]. When the latter was similarly reduced with lithium aluminum hydride there was obtained a new triol, which from the nature of the transformations carried out can only differ from IIc in the configuration at C-6. Accordingly, this second triol is considered to be estr-5-(10)-ene-3β,6α,17β-triol (IIe). Chemical evidence for stereochemical identity of the triols IIc and IIe except at C-6 was provided by the acid-catalyzed dehydration of both triols to the same diene, V.[16] (See Chart II.) Application of the Mills' rule[17] to the two triols was also in full accord with the assigned configurations, the 5(10)-en-6β-ol (IIc, [α]D 96°) being more powerfully dextrorotatory than the 6α epimer (IIe, [α]D 71°).[18]

Prior to attempting Simmons–Smith methylenation of the 5(10)-en-6α-ol system it was considered desirable to block the 3β-hydroxyl function to eliminate any possibility of the homoallylic hydroxyl exerting stereochemical control during "methylene" addition. Accordingly, 3-(tetrahydropyran-2-yl)oxy-6β-hydroxyestr-5(10)-en-17-one (IIIb) was oxidized with DDQ to the conjugated ketone (IIIc), and the latter was reduced to the allylic 5(10)-ene-6α,17β-diol IIId with lithium aluminum hydride. A Simmons–Smith reaction upon the allylic alcohol IIId gave 3β-(tetrahydropyran-2-yl)oxy-5α,19-cyclo-10α-androstane-6α,17β-diol (VIa). In this series of reactions both the product VIa and the intermediate 3-(tetrahydropyran-2-yl) ether IIId showed a wide melting point range.[19] In view of this, the desired 5α,19 cyclo compound VIa was synthesized by an alternative route in which the 3β-hydroxyl blocking group was introduced later in the reaction sequence.

3β-Hydroxyestr-5(10)-ene-6,17-dione (IId), obtained as outlined above, was converted to the 3β-(tetrahydropyran-2-yl) ether IIIc, and the ether was reduced with lithium aluminum hydride to afford the corresponding 5(10)-ene-6α,17β-diol IIId. In contrast to the earlier sample (*vide supra*) the diol IIId prepared by this second route showed a sharp melting point. A Simmons–Smith reaction then led to the cyclopropane VIa in easily purified form. In the nmr spectrum the geminal C-19 methylene protons resonated as a two-proton singlet at 27 cps, indicative of accidental chemical equivalence.

For the final step in the reaction sequence A → C, it was hoped that acid-catalyzed cleavage of the cyclopropylcarbinol system in VIa would proceed in an analogous manner to that experienced with the 5β,19-cycloandrostan-6β-ol derivative IV, with concomitant hydrolysis of the 3β-(tetrahydropyran-2-yl) ether function.[20] However, when the cyclopropylcarbinol VIa was treated with ethanolic hydrochloric acid or hydrogen chloride–boron trifluoride etherate, only multicomponent mixtures resulted. Oxidation of the diol VIa with chromium trioxide–pyridine[21] furnished the corresponding diketone VIb. When the latter was exposed to ethanolic hydrochloric acid containing added chloride ion (LiCl) equal amounts of two crystalline products were isolated, neither of which showed physical constants and elemental analysis data consistent with 5α,19- or 5β,19-chloro-3β-hydroxy-10α-

(13) O. Halpern, R. Villotti, and A. Bowers, *Chem. Ind.* (London), 116 (1963).

(14) This *J* value is in good agreement with previously published values for 5β,19 cyclo steroids: O. Halpern, P. Crabbé, A. D. Cross, I. Delfín, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(15) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, 14 (1960).

(16) Prepared earlier in these laboratories by Dr. O. Halpern, manuscript in preparation.

(17) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

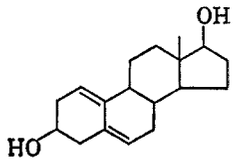
(18) In view of the relatively small differences in optical rotation at the sodium D-line wavelength, rotations were also recorded at lower wave lengths. At 295 mμ specific rotations recorded were $[\alpha]_{295}$ 590°, IIc, and $[\alpha]_{295}$ 340°, IIe, thus confirming the original conclusions.

(19) In spite of heterogeneity indicated by wide melting point ranges for products IIId and VIa prepared by this route, both substances showed chromatographic behavior and spectral characteristics very closely resembling those of the pure specimens prepared subsequently.

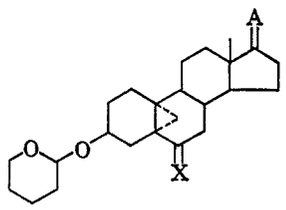
(20) Formation of a 10α,19-chloromethylandrost-5-ene derivative was not a predictable certainty. Existing knowledge concerning the mode of ring cleavage of cyclopropylcarbinols and ketones under the influence of acid catalysis presents a complex picture; *cf.* R. Breslow in "Molecular Rearrangements," Vol. I, P. De Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 254–276. S. Julia, M. Julia, and C. Huynh [*Bull. Soc. Chim. France*, 174 (1960)] have given examples which underline the need for separate consideration of individual cyclopropanes and the conditions of the reaction. It appears reasonable that in concerted reactions that C–C bond of the cyclopropane ring will break which is *trans* to and axially disposed relative to the C–X bond where X is the protonated leaving group. For nonconcerted reactions, carbonium ion stability factors are expected to be a dominating influence determining which cyclopropane C–C bond is ruptured. Breslow noted the propensity for chloride ion nucleophile to give chloromethylated products.

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and C. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

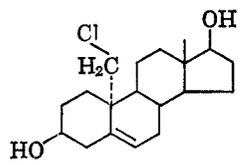
CHART II



V



VIa, A = α-H, β-OH; X = α-OH, β-H
b, A = X = O



VII

androstane-6,17-dione.[22] The diol VIa was next exposed to ethanolic hydrochloric acid–lithium chloride whereby the desired 19-chloro-10α-androst-5-ene-3β,17β-diol (VII) was secured. Nmr olefinic proton resonance at 326 cps, half-band width 10 cps, and a four-line AB resonance pattern at 201, 213, 225, and 237 cps, J_{gem} = 12 cps, for angular CH_2Cl are in agreement with the assigned structure as are other physical data (see Experimental Section).

Experimental Section[23]

6β-Hydroxy-3β-(tetrahydropyran-2-yl)oxyestr-5(10)-en-17-one (IIIb).—6β-Acetoxy-3β-hydroxyestr-5(10)-en-17-one (IIa,[12] 1 g) was added to 100 ml of benzene containing 2 ml of dihydropyran and the whole was dried by azeotropic distillation. A similarly dried solution of 20 mg of *p*-toluenesulfonic acid in 50 ml of benzene was then added at room temperature. After 0.5 hr the reaction solution was washed with aqueous sodium bicarbonate and sodium chloride solutions, filtered, dried over sodium sulfate, and evaporated. The oily 6β-acetate IIIa was promptly hydrolyzed by addition of an ethanolic solution of potassium hydroxide (1 g in 25 ml). After being kept 0.75 hr at room temperature, this mixture was poured into 50 ml of concentrated sodium chloride solution, and a little solid carbon dioxide was added. Extraction with ethyl acetate and evaporation of the washed (aqueous NaCl) and dried (Na_2SO_4) extracts afforded a solid residue. Recrystallization of the latter from benzene–hexane furnished 520 mg of the title 3β-(tetrahydropyran-2-yl) ether IIIb: mp 202–204°; $[\alpha]_D$ 113°; ν_{max} 1720 and 3390 cm^{-1}; nmr, 55.5 (18-H), *ca.* 235 (6α-H), and 286.5 cps (OCHO).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.19; O, 17.09. Found: C, 73.73; H, 9.02; O, 17.18.

3β-(Tetrahydropyran-2-yl)oxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IV).—A solution of 1 g of the 6β-alcohol IIIb in 40 ml of dry tetrahydrofuran was added over 0.5 hr to a stirred solution of Simmons–Smith reagent[9] (prepared from 3 g of zinc–copper couple, 1.15 g of methylene diiodide, and 25 ml of ether) maintained under reflux. The majority of the ether was then removed by distillation and the remaining solution was boiled under reflux a further hour. The reaction mixture was then cooled to 0°, 100 ml of saturated aqueous sodium chloride was added, and the mixture was extracted with ethyl acetate. Combined extracts were washed (aqueous Na_2CO_3), dried (Na_2SO_4), and evaporated, and the solid residue was crystallized from benzene–hexane. Recrystallization from ethyl acetate afforded 467 mg of 3β-(tetrahydropyran-2-yl)oxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IV): mp 192–193°; $[\alpha]_D$ 42°; ν_{max} 1740 and 3480 cm^{-1}; nmr, see discussion section.

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.44; H, 9.34; O, 16.70.

19-Chloro-3β-hydroxyandrost-5-en-17-one (Ib).—The 5β,19 cyclo derivative IV (50 mg) was dissolved in 2.5 ml of tetrahydrofuran. The resulting solution was cooled to 0°, 0.25 ml of 36% hydrochloric acid and 0.11 ml of boron trifluoride etherate were added, and the whole was then kept overnight at room temperature, before dilution with 30 ml of ethyl acetate. The washed (aqueous $NaHCO_3$) solution was dried (Na_2SO_4) and evaporated under reduced pressure to furnish a crude solid which was purified by recrystallization from benzene–hexane. Thereby was obtained 21 mg of 19-chloro-3β-hydroxyandrost-5-en-17-one, mp 189–191° (undepressed in admixture with an authentic sample[13]), indistinguishable by infrared spectroscopy from the reference sample.

Estr-5(10)-ene-3β,6β,17β-triol (IIc).—6β-Acetoxy-3β-hydroxyestr-5(10)-en-17-one (IIa,[12] 20 g) was dissolved in 300 ml of methanol, and 12 g of potassium hydroxide was added. After being kept 2 hr at room temperature, 200 ml of saturated sodium chloride was added and the whole was extracted with ethyl acetate. Evaporation of the dried (Na_2SO_4) extracts afforded 13.9 g of crude 3β,6β-dihydroxyestr-5(10)-en-17-one (IIb), mp 100–110°.

To a solution of 500 mg of crude 3β,6β-dihydroxyestr-5(10)-en-17-one (IIb) in 50 ml of dry tetrahydrofuran was added 1 g of lithium aluminum hydride. After being maintained 3 hr at reflux, the reaction mixture was worked up in the usual way and the product was recrystallized from acetone and methanol to give 150 mg of estr-5(10)-ene-3β,6β,17β-triol (IIc): mp 215–217°; $[\alpha]_D$ 96°; ORD $[\alpha]_{295}$ 590°; ν_{max} 3290 cm^{-1}; nmr, 54.5 cps (18-H).

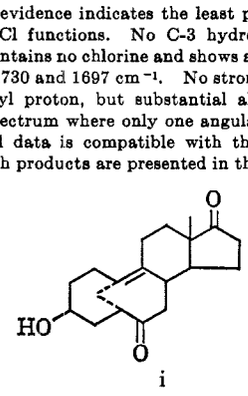
Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.78; H, 9.71; O, 17.04.

3β-Hydroxyestr-5(10)-ene-6,17-dione (IId).—The lead tetraacetate reaction on 40 g of 3β,19-dihydroxyandrost-5-en-17-one (Ia) and base-catalyzed hydrolysis of the resultant crude 6β-acetoxy-3β-hydroxyestr-5(10)-en-17-one (IIa) were carried out as described above to obtain crude 3β,6β-dihydroxyestr-5(10)-en-17-one (IIb). The latter was dissolved, without prior purification, in 600 ml of dioxane containing 40 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; the mixture was kept 3 days at room temperature. Following filtration the majority of the solvent was removed *in vacuo* at room temperature and the residual solution was diluted with 100 ml of 1:1 benzene–methylene dichloride and filtered through a short column composing 500 g of acid-washed alumina. Evaporation of the filtrate and recrystallization of the residue from methylene dichloride yielded 15.2 g of 3β-hydroxyestr-5(10)-ene-6,17-dione (IId): mp 220–225°; $[\alpha]_D$ 161°; λ_{max} 250 mμ (log ε 4.06); ν_{max} 1655, 1750, and 3500 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.84; H, 8.51; O, 16.84.

Estr-5(10)-ene-3β,6α,17β-triol (IIe).—A mixture of 150 mg of the conjugated ketone (IId) and 300 mg of lithium aluminum hydride in 30 ml of dry tetrahydrofuran was boiled under reflux during 3 hr, and the reaction was worked up in the normal manner. Recrystallization of the product from acetone–methanol

(22) The available evidence indicates the least polar product to contain both CHCl and CH_2Cl functions. No C-3 hydroxyl could be detected. The second product contains no chlorine and shows absorptions for hydroxyl, and for carbonyls, at 1730 and 1697 cm^{-1}. No strong ultraviolet absorption is observed. No vinyl proton, but substantial allylic proton resonance, appears in the nmr spectrum where only one angular methyl (C-18) proton signal is present. All data is compatible with the tentative structure i. Complete data for both products are presented in the Experimental Section.



i

(23) Melting points were recorded on the Fisher-Johns block and are corrected. Rotations were determined at room temperature in chloroform solution. Ultraviolet absorption spectra were determined using potassium bromide pellets and a Perkin-Elmer Model 21 spectrophotometer. Microanalyses were performed by Mid-West Microlaboratories, Indianapolis 20, Ind., or by A. Bernhardt, Mülheim (Ruhr), West Germany. Nmr spectra were recorded for 8–10% solutions in deuteriochloroform containing a little tetramethylsilane as an internal reference (0.0 cps). Chemical shifts are quoted as cycles per second downfield from the reference signal and are accurate to ±1 cps. Coupling constants and half-band widths are also quoted in cycles per second. The former have an accuracy of ±0.5 cps. Spectra were measured on a Varian A-60 spectrometer in collaboration with Mr. E. Diaz, Universidad Nacional Autónoma de México, and Mr. J. W. Murphy, Syntex Research, Palo Alto, Calif.

gave 80 mg of the triol (IIe): mp 205–212°, $[\alpha]_D$ 71°, ORD $[\alpha]_{295}$ 340°, ν_{max} 3270 cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65; O, 16.42. Found: C, 73.72; H, 9.76; O, 16.66.

Conversion of the Triols (IIc and IIe) to Estra-1(10),5-diene-3β,17β-diol (V).—A solution of 1 g of estr-5(10)-ene-3β,6β,17β-triol (IIc) in 10 ml of ethanol containing 0.5 ml of 36% hydrochloric acid was boiled under reflux for 30 min and then diluted with 10 ml of water. The solid which separated was collected at the filter and crystallized twice from aqueous ethanol and from acetone to afford 620 mg of a pure sample of estra-1(10),5-diene-3β,17β-diol (V): mp 159–160°; $[\alpha]_D$ −110°; ν_{max} 3500–3100 (br), 1640 (w), 800, and 765 cm^{-1}; λ_{max} 242 mμ (log ε 4.18).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55; O, 11.66. Found: C, 78.55; H, 9.57; O, 11.79.

By an identical experimental procedure 1 g of the epimeric triol IIe was converted to 480 mg of the diene V, purified by the above method to furnish a sample identical by infrared, melting point, and mixture melting point with the sample made from IIc.

3β-(Tetrahydropyran-2-yl)oxyestr-5(10)-ene-6,17-dione (IIIc).—A solution of 1 g of the allylic alcohol IIIb in 5 ml of dioxane was added to 1.5 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 5 ml of the same solvent at room temperature. After 3 days the solvent was removed by distillation *in vacuo* and the remaining solid was taken up in 1:1 methylene chloride–benzene. Chromatography of this solution over 50 g of acid-washed alumina yielded in ether–hexane eluates 430 mg of 3β-(tetrahydropyran-2-yl)oxyestr-5(10)-ene-6,17-dione (IIIc): mp 185–187°, $[\alpha]_D$ 117°, λ_{max} 249 mμ (log ε 4.05), ν_{max} 1670 and 1740 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66; O, 17.18. Found: C, 74.24; H, 8.52; O, 17.02.

3β-(Tetrahydropyran-2-yl)oxyestr-5(10)-ene-6α,17β-diol (IIId).

A. From 3β-(Tetrahydropyran-2-yl)oxyestr-5(10)-ene-6,17-dione (IIIc).—Lithium aluminum hydride (2 g) was added to a solution of the conjugated ketone IIIc (2 g) in 150 ml of dry tetrahydrofuran and the mixture was boiled under reflux for 3 hr, cooled, and worked up with 10% aqueous sodium hydroxide. Thereby was obtained 1.91 g of crude allylic 6α alcohol IIId, mp 150–156° after crystallization from methylene chloride–hexane. Three further crystallizations from acetone furnished a product, homogeneous by thin layer chromatography (tlc): mp 162–190°, $[\alpha]_D$ +17°; ν_{max} 3280 cm^{-1}.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.53; H, 9.72; O, 17.65.

B. From 3β-Hydroxyestr-5(10)-ene-6,17-dione (IId).—Azeotropically dried solutions of 5 g of the enedione IId in 750 ml of benzene and 10 mg of *p*-toluenesulfonic acid in 15 ml of the same solvent were mixed, and 60 ml of dihydropyran was added. After 30 min the solution was neutralized with 100 mg of sodium bicarbonate and reduced to dryness at room temperature *in vacuo*. A solution of the crude residual tetrahydropyran-2-yl ether IIIc in 400 ml of tetrahydrofuran was treated with 4 g of lithium aluminum hydride and the mixture was heated to reflux during 3 hr. Work-up in the usual way gave 6.4 g of 3β-(tetrahydropyran-2-yl)oxyestr-5(10)-ene-6α,17β-diol (IIId). A homogeneous sample recrystallized from acetone showed mp 163–165°; $[\alpha]_D$ +50°; infrared spectrum very similar to the sample described above; nmr, 47.5 cps (18-H). A sample admixed with that prepared above gave a single spot on tlc.

3β-(Tetrahydropyran-2-yl)oxy-5α,19-cyclo-10α-androstane-6α,-17β-diol (VIa).—The homogeneous allylic alcohol IIId (3 g, mp 163–165°) was added in portions over 0.5 hr to a refluxing solution of Simmons–Smith reagent (prepared[9] from 20 g of zinc–copper couple, 48 g of methylene diiodide, and 150 ml of ether mixture held 1 hr under reflux). Approximately 50% of the solvent was removed by slow distillation over 2 hr and the reaction was then worked up in the manner described earlier (*vide supra*). Recrystallization of the crude reaction product from ether–methylene chloride afforded 1.95 g of the cyclopropane VIa: mp 187–190°; $[\alpha]_D$ ±0°; ν_{max} 3260 cm^{-1}; nmr, 27 (two-proton singlet, 19-H), 44.5 (18-H), and 282 cps (O–CHO multiplet).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81; O, 16.39. Found: C, 73.97; H, 9.85; O, 15.89.

A similar experiment conducted with allylic alcohol IIId of wide melting point (*vide supra*) furnished the cyclopropyl compound VIa as an heterogeneous product, mp 110–140°.

Reaction of 3β-(Tetrahydropyran-2-yl)oxy-5α,19-cyclo-10α-androstane-6,17-dione (VIb) with Lithium Chloride–Hydrochloric Acid.—The allylic alcohol VIa (1 g) was oxidized with 2 g of chromium trioxide in 100 ml of pyridine at room temperature overnight[21] and then diluted with ice–water. Ether extracts were washed to neutrality, dried (Na_2SO_4), and evaporated. The colorless oily product VIb (ν_{max} 1675 and 1730 cm^{-1}, homogeneous by thin layer chromatography) was dissolved in 75 ml of ethanol containing 7.5 g of lithium chloride and 5 ml of 36% hydrochloric acid; the mixture was boiled under reflux for 2 hr, poured into ice water, and extracted with ether. These extracts, after being washed to neutrality, were evaporated and the residue was separated into two products by fractional crystallization. The least polar component (320 mg) was recrystallized from ether–hexane and showed mp 208–210°; $[\alpha]_D$ +45°; ν_{max} 1705 and 1745 cm^{-1}; nmr, 52 (18-H), 211, 223.5, 241, 253.5 (CH_2Cl, J_{gem} 12.5 cps), and 230–267 cps (CHCl, half-band width 23 cps); CD (*c* 0.1, dioxane), $[\theta]_{260}$ 0°, $[\theta]_{324}$ 4560°, $[\theta]_{306}$ 5750°, $[\theta]_{296}$ 4360°, and $[\theta]_{330}$ 0°.

Anal. Found: C, 64.34; H, 7.53; Cl, 18.22; O, 9.51.

The more polar product (310 mg) crystallized from ether–hexane as prisms: mp 230–232°; $[\alpha]_D$ +6°; ν_{max} 1730 and 1697 cm^{-1}; nmr, 53.5 (18-H) and 248 cps (3α-H), and no vinylic proton resonance. A tentative structure for this product has been postulated.[22]

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; O, 15.87. Found: C, 75.17; H, 8.82; O, 16.16.

19-Chloro-10α-androst-5-ene-3β,17β-diol (VII).—A mixture of 500 mg of the cyclopropyl carbinol VIa, 7 g of lithium chloride, 3 ml of 36% hydrochloric acid, and 70 ml of ethanol was maintained under reflux for 1 hr and then poured onto ice. Ethereal extracts were washed thoroughly with aqueous sodium chloride, dried (Na_2SO_4), and evaporated. Chromatography of the residue over 50 g of silica gel and elution with 1:1 hexane–ethyl acetate gave 250 mg of 19-chloro-10α-androst-5-ene-3β,17β-diol (VII). A sample recrystallized from methylene chloride–ether showed mp 120–122°; $[\alpha]_D$ +25°; ν_{max} 3260 cm^{-1}; nmr, 45 (18-H) cps and see discussion.

Anal. Calcd for $C_{19}H_{29}ClO_2$: C, 70.25; H, 9.00. Found: C, 69.85; H, 9.36.

Oily fractions were also obtained from the chromatogram but could not be crystallized.