the side band technique of Arnold and Packard.[20] The positions of the remaining signals were measured by interpolation on the record chart. The sample contained in a 5 mm. (diam.) spinning tube, was usually a nearly saturated solution of the compound in chloroform or dioxane (see figures of spectra for the solvent used). The signal for the hydrogens of the solvent was in each case used as an internal standard for establishing the positions of the signals in the magnetic field. In several instances the spectra were determined in carbon tetrachloride and in the liquid state and the separation of the signals was found to be nearly the same as those obtained in chloroform or dioxane.

The acetates of the *cis*- and *trans*-4-*t*-butylcyclohexyl alcohols ($n^{24.5}$D 1.4491 and $n^{23.5}$D 1.4512, respectively) were prepared by heating the alcohols with acetic anhydride and sodium acetate. The products, isolated in the usual fashion, were purified by distillation *in vacuo* and possessed the expected saponification equivalents.

All the other compounds are reported in the literature references cited in the text. In all cases, the compounds were of high purity as gauged from the reported physical constants.

Acknowledgments.—The authors wish to thank E. L. Eliel for samples of the isomeric 4-*t*-butylcyclohexyl alcohols; H. G. Fletcher, Jr., for several rare sugars; A. Novak and E. Whalley for the isomeric 2,4,6-trichloromethyltrioxanes; J. M. Winchester for the isomeric 1,2,3,4,5,6-hexachlorocyclohexanes; S. J. Angyal for the *cis*-inositol hexaacetate; N. K. Richtmyer for the 1,6-anhydrohexopyranose triacetates; E. G. Horswill for *l*-inositol hexaacetate; and P. Chu for samples of the α- and β-1-deuterated D-glucose pentaacetates.

(20) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. XCIX. Synthesis of Ring B Oxygenated Estrogens[1]

BY J. IRIARTE, H. J. RINGOLD AND CARL DJERASSI

RECEIVED MAY 1, 1958

Osmium tetroxide oxidation of 6-dehydroestrone or estradiol derivatives gave the corresponding 6α,7α-glycols which on treatment with acid were inverted to the 6β,7α-glycols. Peracid oxidation of the Δ^6-compounds yielded the 6α,7α-oxides which underwent acid opening to the 6β,7α-glycols or hydride reduction to the 7α-alcohols. Oxidation of 7α-hydroxyestrone furnished 7-ketoestrone which was converted to the 7β-alcohol by catalytic reduction of the 7-enol acetate. Elimination reactions of the 7α and 7β alcohols led only to the Δ^6-compound rather than to equilin.

Of all the naturally occurring biologically active steroid hormones only equilin (7-dehydroestrone), which was first isolated by Girard, *et al.*,[2] from mare's urine, had resisted both partial and total synthesis at the time this work was initiated.[3] The work described herein, aimed at the synthesis of this hormone, basically involved the introduction of a hydroxyl function at the 7-position of an estrone or estradiol derivative followed by the elimination of this group with the hope that a new double bond could be introduced between carbon atoms 7 and 8. In particular, the possibility existed that pyrolysis of a 7-ester group would lead, as in the cholestane[4] and sapogenin[5] series, to the Δ^7-compound although it was recognized that conjugation of the newly introduced double bond with the benzene ring was more likely. This latter path, leading to 6-dehydroestrone, indeed was the only recognizable reaction in various eliminations of both 7α- and 7β-hydroxy estrogens.

However, it should be noted that almost all of the oxygenated estrogens herein described are new compounds. Their essential inactivity as estrogens offer valuable structure–activity relationships and even a possible utility as so-called "non-estrogenic" estrogens which are of potential interest in the treatment of certain hormone dependent tumors and in atherosclerosis.

7-Monohydroxy Estrogens.—Introduction of a C-7 oxygen function was accomplished starting with the readily available 6-dehydroestrone (Ia).[6] The 17-cycloethylene ketal (Id) of this compound on treatment with monoperphthalic acid at low temperature led to the 6α,7α-oxido compound IIb which after lithium aluminum hydride reduction and acid hydrolysis gave 7α-hydroxyestrone (IIIa). That the alcohol thus obtained was the C-7 alcohol was proved by the direct oxidation of IIIa with the Jones reagent[7] to the known 7-ketoestrone IIIf, a compound first prepared by Pearlman and Wintersteiner[8] from equilin. These workers also prepared a 7-hydroxyestrone by the catalytic hydrogenation in acetic acid, of the enol acetate of 7-ketoestrone (IV).[8] Repetition of Pearlman and Wintersteiner's[8] sequence gave a compound (IIIh) whose constants agreed with the reported ones, but which was different from IIIa. On steric considerations we assign the 7β-configuration to the alcohol derived from the hydrogenation of the enol acetate and conversely the compound from hydride reduction of the epoxide is 7α-hydroxyestrone and the starting epoxide II must be the α-epoxide. Thus, cleavage of the epoxide follows the normal stereochemical course[9] with axial hydride attack and axial alcohol formation, a reaction even more favored in this case since the cleaved bond is benzylic.

(1) Paper XCVIII, J. Pérez, J. Iriarte, F. Kincl and C. Djerassi, *J. Org. Chem.* **23**, 1744 (1958).

(2) A. Girard, G. Sandulesco, A. Fridenson and J. J. Rutgers, *Compt. rend.*, **194**, 909 (1932).

(3) The synthesis of this hormone has just been accomplished in these laboratories by J. A. Zderic, A. Bowers, H. Carpio and C. Djerassi, THIS JOURNAL, **80**, 2596 (1958).

(4) For leading references see L. F. Fieser, M. Fieser and R. N. Chakravarty, *ibid.*, **71**, 2226 (1949).

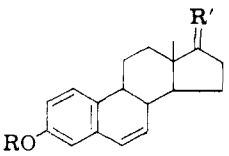
(5) H. J. Ringold, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3318 (1952).

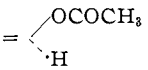
(6) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, *ibid.*, **72**, 4531 (1950).

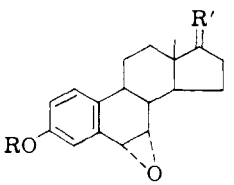
(7) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946), and later papers by E. R. H. Jones and collaborators.

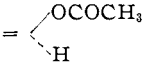
(8) W. H. Pearlman and O. Wintersteiner, *J. Biol. Chem.*, **130**, 35 (1939); **132**, 605 (1940).

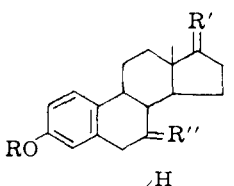
(9) A. Fürst and P. Plattner, 12th Intern. Congress Pure and Applied Chem., New York, 1951, Abstracts, p. 405.

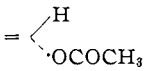
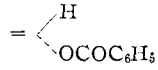
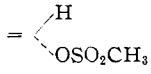
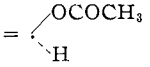
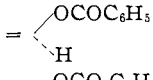
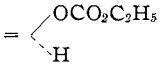


Ia, R = CH_3CO; R′ = O
b, R = H; R′ = O
c, R = CH_3CO; R′ = 
d, R = H; R′ = 
e, R = CH_3CO; R′ = 

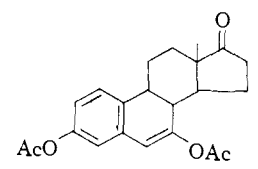


IIa, R = CH_3CO; R′ = 
b, R = H; R′ = 
c, R = CH_3CO; R′ = 

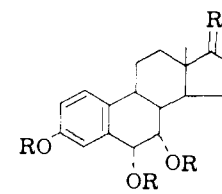


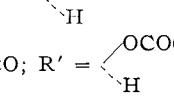
IIIa, R = H; R′ = O; R″ = 
b, R = CH_3CO; R′ = O; R″ = 
c, R = C_6H_5CO; R′ = O; R″ = 
d, R = C_6H_5CO; R′ = O; R″ = 
e, R = C_6H_5CO; R′ = O; R″ = 
f, R = H; R′ = O; R″ = O
g, R = C_6H_5CO; R′ = O; R″ = O
h, R = H; R′ = O; R″ = 
i, R = CH_3CO; R′ = O; R″ = 
j, R = C_6H_5CO; R′ = O; R″ = 
k, R = C_6H_5CO; R′ = O; R″ = 
l, R = C_6H_5CO; R′ = O; R″ = 

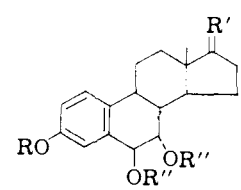
m, R = H; R′ =  ; R″ = 
n, R = CH_3CO; R′ =  ; R″ = 
o, R = H; R′ =  ; R″ = 
p, R = C_6H_5CO; R′ =  ; R″ = 

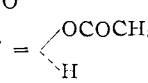


IV



Va, R = H; R′ = O
b, R = CH_3CO; R′ = O
c, R = H; R′ = 
d, R = CH_3CO; R′ = 



VIa, R = R″ = H; R′ = O
b, R = R″ = CH_3CO; R′ = O
c, R = CH_3CO; R″ = H; R′ = 

6-Dehydroestradiol diacetate (Ie)[10] was similarly epoxidized and the α-oxide IIc on lithium aluminum hydride reduction gave 7α-hydroxyestradiol (IIIm), identical with the sodium borohydride reduction product of IIIa.

Although yields of the α-epoxides IIa and IIc were satisfactory, the benzylic 6,7-oxides were extremely labile and if the peracid oxidations were carried out at a temperature higher than 10°, acid-catalyzed hydrolysis of the oxide occurred. Similar results have been reported by Johnson and collaborators[11] in the case of a ring D aromatic 9,11-benzylic epoxide.

The oxidation of 7α-hydroxyestradiol (IIIm) warrants additional comment. The 3-monobenzoate IIIp of this compound on oxidation with an excess of pyridinium–chromate complex was only oxidized at C-17 while the 7α-hydroxyl was not

(10) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).
(11) W. S. Johnson, A. D. Kemp, R. Pepps, J. Ackerman and W. F. Johns, *ibid.*, **78**, 6312 (1956).

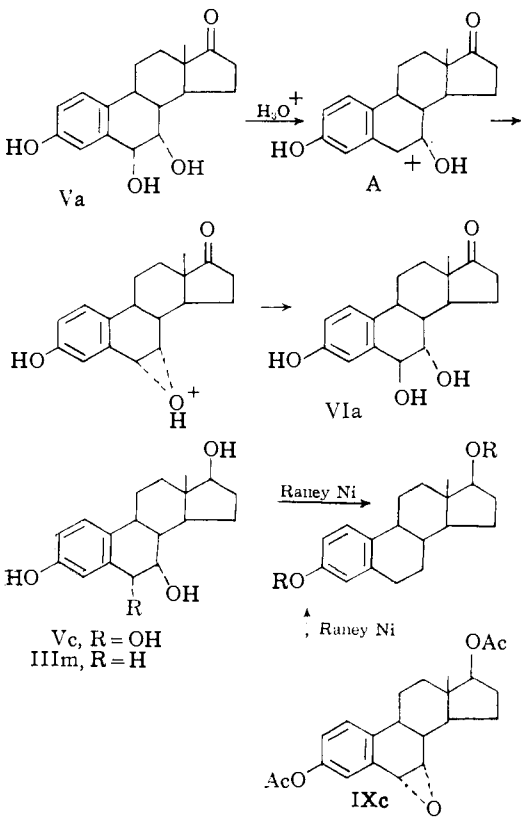
attacked. However, oxidation of the free phenol IIIa with chromic acid in acetone–sulfuric acid[7] at 0° rapidly gave, in 60% yield, the 7,17-diketone IIIf without any oxidation of the phenolic A ring.

Discussion of elimination reactions of 7α-(IIIa) and 7β-hydroxyestrone (IIIh) are deferred until the final section.

6,7-Dihydroxy Estrogens.—6α,7α-Dihydroxyestrone acetate (Vb) and 6α,7α-dihydroxyestradiol 3,17-diacetate (Vd) were prepared readily in high yield by osmium tetroxide oxidation of the corresponding Δ^6-compounds (Ia, Ie) and were interrelated by hydride reduction of Va to Vc.

In the estrone series the *trans*-6β,7α-glycol VIa was prepared by acid hydrolysis of the 17-ketal-6α,7α-oxide IIb in aqueous acetone containing a few drops of perchloric acid, cleavage of both the ketal and oxide proceeding rapidly. The estradiol diacetate *trans*-glycol VIc was isolated by chromatography of mother liquors as a by-product in the preparation of 6α,7α-oxido-estradiol diacetate (IIc).

Unexpectedly, treatment of the *cis*-glycol Va with methanolic hydrochloric acid, a reaction expected to result in dehydration of the C-6 benzylic alcohol and concomitant formation of the 7-ketone, gave instead an isomeric glycol VIa which proved



to be identical with the epoxide hydrolysis product. *This inversion of an equatorial 7α-hydroxyl group to the axial 7β-orientation* may be best formulated by assuming that initially dehydration at C-6 occurred with formation of a carbonium intermediate A. Stabilization of A by participation of the 7α-hydroxyl function yielded the oxonium intermediate B which then underwent attack at C-6 from the β-side, the net effect being inversion of the 6α-hydroxyl group.

The reaction of 6α,7α-oxidoestradiol diacetate (IIc) and of 6α,7α-dihydroxyestradiol (XIIa) with Raney nickel was investigated with the hope that this would lead to hydrogenolysis at the benzylic position and formation of the 7α-monohydroxy compound. Surprisingly, treatment of these compounds with nickel in boiling ethanol gave estradiol diacetate and estradiol, respectively. It is probable that the initial product formed in both cases was 7α-hydroxyestradiol (Vc) which then underwent further hydrogenolysis since 7α-hydroxyestradiol yielded estradiol under these conditions. While the nickel elimination of a hydroxyl group β to a benzene ring has been described,[12] no mechanism has yet been postulated for this reaction.

As indicated earlier, elimination reactions of the 7-oxygenated estrogens led to the 6-dehydro compound Ib. Thus treatment of 7α-hydroxyestrone in aqueous alkali with benzoyl chloride gave the 3-monobenzoate IIIc which on dehydration with phosphorus oxychloride–pyridine followed by hydrolysis gave Ib. The monobenzoate (IIIc) was converted to the 3-benzoate-7-mesylate (IIIe) by treatment with mesyl chloride–pyridine, and this latter derivative on elimination with γ-collidine, alcoholic potassium hydroxide, potassium acetate or potassium benzoate again furnished the 6-dehydro compound as the only identified product. Similarly, pyrolysis of the 3,7α-dibenzoate at 280–300° or of the 3-benzoate-7α-ethyl carbonate (IIII)[13] at 250–260° and reduced pressure, with subsequent alkaline hydrolysis, led only to 6-dehydroestrone (Ib).

Oxygenation at positions 6 and 7 markedly decreased estrogenic activity.[14] In the mouse uterotrophic assay, 6α,7α-oxido-estradiol diacetate (IIc) exhibited, by the subcutaneous route, approximately 1% of the estrogenic activity of estrone, while the *cis*-glycols Va and Vc and the *trans*-glycol VIa were less than $^1/_{2000}$ as active as the reference compound.

Experimental[15]

17-Ethylenedioxy-6-dehydroestrone 3-Acetate (Ic) and 17-ethylenedioxy-6-dehydroestrone (Id).—A mixture of 6-dehydroestrone acetate[6] (2.35 g.), ethylene glycol (17 cc.), benzene (180 cc.) and *p*-toluenesulfonic acid monohydrate (100 mg.) was boiled for 20 hours with continuous separation of water. The cooled mixture was poured into an aqueous sodium bicarbonate solution and the product extracted with ether. Evaporation of the extract and chromatography of the residue over 100 g. of neutral alumina gave, in the hexane–benzene 4:1 eluate, 1.5 g. of ketal acetate, m.p. 98–102°. Recrystallization from methanol gave 1.0 g. of Ic, m.p. 107–109°. The analytical specimen from the same solvent exhibited m.p. 111–112°, $[\alpha]_D$ −205° (dioxane), λ_{max} 220 and 262 mμ, log ε 4.40 and 3.94.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; O, 18.06. Found: C, 74.33; H, 7.58; O, 18.03.

(12) J. A. Zderic, W. A. Bonner and T. W. Greenlee, THIS JOURNAL, **79**, 1696 (1957).

(13) For pyrolysis of steroid ethyl carbonates see G. L. O'Connor and H. R. Nace, *ibid.*, **75**, 2118 (1953).

(14) Bioassays were carried out at the Worcester Foundation for Exptl. Biology under the direction of Dr. Ralph Dorfman.

(15) Melting points are uncorrected. Rotations were determined at 20° and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srita. E. Velarde for technical assistance and to Dr. L. Throop and staff for rotation and ultraviolet spectral data.

Elution of the column with benzene–ether 4:1 and ether crystallization gave 0.68 g. of the free phenol ketal Id, m.p. 183–184°, $[\alpha]D$ −199° (dioxane) (λ_{max} 222, 263, 272 and 305 mμ; log ε 4.40, 3.87, 3.80 and 3.40) identical with the product obtained by potassium hydroxide–methanol saponification of Ic.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.59; H, 7.47.

17-Ethylenedioxy-6α,7α-oxidoestrone (IIb) and 17 Ethylenedioxy-6α,7α-oxidoestrone Acetate (IIa).—A solution of Ic (2.5 g.) in 100 cc. of ether was cooled to 0° and treated with 35 cc. of a 0.7 *N* solution of monoperphthalic acid in ether. The mixture, after standing for 65 hours at 10°, was poured into cold bicarbonate solution and the product extracted with benzene. Evaporation of the solvent followed by fractional crystallization from ether gave as the most insoluble fraction, 1.1 g. of the free phenol IIb, m.p. 220–221°, $[\alpha]D$ −81° (dioxane), λ_{max} 229 and 284 mμ, log ε 3.80 and 3.24. The analytical sample, from methanol, melted at 224–225°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37; O, 19.49. Found: C, 72.82; H, 7.58; O, 19.76.

Concentration of the ether mother liquors gave the epoxide acetate IIa (0.87 g.), m.p. 160–162°, $[\alpha]D$ −68° (dioxane), λ_{max} 269 and 276 mμ, log ε 2.69 and 2.64.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; O, 21.59. Found: C, 70.90; H, 7.50; O, 21.59.

When the epoxidation was allowed to proceed at room temperature the yield of epoxide was considerably lower, the major product being the *trans*-glycol VI.

6α,7α-Oxidoestradiol Diacetate (IIc).—The diacetate of 6-dehydroestradiol (Ie)[6] (12.4 g.) in a mixture of anhydrous tetrahydrofuran (150 cc.) and ether (200 cc.) was treated at 0° with a solution of 150 cc. of 0.7 *N* monoperphthalic acid in ether. The mixture, after standing for 40 hours at 10°, indicated the uptake of one equivalent of peracid and then was poured into aqueous bicarbonate solution. Extraction with ether, evaporation of the washed and dried extract and crystallization of the residue from methanol gave 8.5 g. of epoxide IIc, m.p. 167–169°, $[\alpha]D$ −47° (chloroform), λ_{max} 269 and 276 mμ, log ε 2.84 and 2.84.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07; O, 21.60. Found: C, 70.67; H, 7.35; O, 21.83.

7α-Hydroxyestrone (IIIa).—A solution of 0.87 g. of ketal epoxide IIa in 50 cc. of anhydrous tetrahydrofuran was added slowly to a suspension of 2 g. of lithium aluminum hydride in 200 cc. of dry tetrahydrofuran and the mixture boiled under reflux for 15 hours. The cooled mixture was then cautiously treated dropwise with water, acidified with dilute hydrochloric acid and extracted with ethyl acetate. The washed extract, on concentration, gave 0.51 g. of 7α-hydroxyestrone (IIIa), m.p. 258–262°. The analytical sample from the same solvent melted at 260–262°, $[\alpha]D$ +124° (dioxane), λ_{max} 281 mμ, log ε 3.35.

Similarly, reduction of the free phenol ketal epoxide IIb gave a high yield of IIIa.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75; O, 16.76. Found: C, 75.53; H, 7.93; O, 17.01.

7α-Hydroxyestrone Diacetate (IIIb).—Treatment of IVa with excess acetic anhydride–pyridine for 18 hours at room temperature and methanol crystallization of the water precipitated product gave the diacetate IVb, m.p. 140–141°, $[\alpha]D$ +65° (chloroform), λ_{max} 268 and 274 mμ, log ε 2.82 and 2.80.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.48; H, 7.17.

7α-Hydroxyestrone 3-Monobenzoate (IIIc). (a) **By Schotten–Baumann Benzoylation of IIIa.**—Solution of 170 mg. of IIIa in 40 cc. of 5% aqueous potassium hydroxide and treatment with excess benzoyl chloride at 10° followed by ethyl acetate extraction and crystallization gave 185 mg. (80%) of IIIc, m.p. 239–242°, $[\alpha]D$ +96° (dioxane), λ_{max} 232 mμ, log ε 4.29.

Anal. Calcd. for $C_{25}H_{26}O_4$: C, 76.90; H, 6.73; O, 16.39. Found: C, 76.97; H, 6.78; O, 16.48.

(b) **By Partial Oxidation of IIIp.**—7α-Hydroxyestradiol 3-benzoate (IIIp) (400 mg.) in pyridine (10 cc.) was added to the chromium trioxide–pyridine complex prepared from 400 mg. of chromic anhydride and 15 cc. of pyridine. The mixture, after standing for 18 hours at 25°, was diluted with 100 ml. of ethyl acetate, the dark precipitate filtered and washed with hot ethyl acetate and the combined solutions washed with dilute hydrochloric acid and then water. Evaporation of the solvent and crystallization of the residue from acetone gave 100 mg. of IIIc, m.p. 237–239°.

7α-Hydroxyestrone Dibenzoate (IIId).—The free phenol IIIa or the monobenzoate IIIc was converted to the dibenzoate IIId by heating for one hour at 90° with excess benzoyl chloride in pyridine. After pouring the reaction mixture into water, the product was extracted with, and crystallized from, ethyl acetate whereupon it exhibited m.p. 213–215°, $[\alpha]D$ +51° (dioxane).

Anal. Calcd. for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.32; H, 6.46.

7α-Hydroxyestrone 3-Benzoate-7-mesylate (IIIe).—A solution of 180 mg. of the monobenzoate IIIc in 10 cc. of pyridine was cooled to −15° and treated dropwise with a cold solution of 1 cc. of methanesulfonyl chloride in 3.5 cc. of pyridine. The solution was allowed to stand for one hour at 0° and for 2 hours at 25° and then diluted with ether and water. The organic layer was separated and washed successively with dilute sulfuric acid, water, bicarbonate solution and water and finally dried (sodium sulfate) and evaporated. The residue, which crystallized from ether–hexane, was purified by recrystallization from ether containing a few drops of acetone, yielding 100 mg. (46%) of IIIe, m.p. 155–157°, $[\alpha]D$ +74° (chloroform), λ_{max} 232 mμ, log ε 4.28.

Anal. Calcd. for $C_{26}H_{28}O_6S$: C, 66.65; H, 6.02; S, 6.84. Found: C, 66.24; H, 6.39; S, 6.73.

7α-Hydroxyestradiol (IIIm) (a). By Reduction of IX.—Lithium aluminum hydride reduction of 2 g. of 6α,7α-oxidoestradiol diacetate (IIc) was carried out exactly as described for the preparation of IIIa, and yielded, by ethyl acetate crystallization, 1.22 g. of pure IIIm, m.p. 259–260°, $[\alpha]D$ +42° (dioxane), λ_{max} 282 mμ, log ε 3.23, and a second crop of 0.21 g., m.p. 249–255°.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.56; H, 8.43; O, 17.07.

(b) **By Reduction of IIIa.**—A solution of 100 mg. of 7α-hydroxyestrone (IIIa) in methanol (30 cc.) was treated with 200 mg. of sodium borohydride in 10 cc. of water and allowed to stand for 3 hours at 25°. Acetic acid was added to decompose the excess borohydride, the solution was poured into water and the product which was isolated by ethyl acetate extraction proved to be identical with that obtained in (a) above.

7α-Hydroxyestradiol Triacetate (IIIn).—Treatment of the free triol IIIm with excess acetic anhydride–pyridine for one hour at 90° and then methanol crystallization of the water precipitated product yielded the triacetate IIIn, m.p. 155–156°, $[\alpha]D$ −17° (chloroform), λ_{max} 268 mμ, log ε 2.86.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30; O, 23.16. Found: C, 69.24; H, 7.51; O, 23.08.

7α-Hydroxyestradiol 7,17-Diacetate (IIIo).—A solution of 0.6 g. of triacetate IIIn in 100 cc. of ethanol was boiled under reflux for 18 hours with 2 g. of sodium sulfite in 100 cc. of water. The solution was concentrated *in vacuo*, water was added and the product, after extraction with ethyl acetate, was crystallized from methanol furnishing 0.2 g. of 7,17-diacetate (IIIo), m.p. 225–226°, $[\alpha]D$ −22° (chloroform), λ_{max} 282 mμ, log ε 3.29. The same product was obtained by selective hydrolysis of the triacetate with 1% methanolic potassium hydroxide for one hour at 0°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.97; H, 7.58; O, 21.45. Found: C, 71.16; H, 7.52; O, 21.31.

7α-Hydroxyestradiol 3-Monobenzoate (IIIp).—7α-Hydroxyestradiol (IIIm) (600 mg.) was dissolved in 60 cc. of 3% potassium hydroxide solution and the solution after cooling to 0° was treated dropwise and with vigorous stirring with 3 cc. of benzoyl chloride. The separated solid was filtered, washed and crystallized from acetone yielding 540 mg. of 3-monobenzoate IIIp, m.p. 256–260°, $[\alpha]D$ +39° (dioxane), λ_{max} 231 mμ, log ε 4.28.

Anal. Calcd. for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.30; H, 7.35.

7-Ketoestrone (IIIf).—A stirred solution of 300 mg. of 7α-hydroxyestrone (IIIa) in 40 cc. of acetone (previously distilled from potassium permanganate) was cooled to 0–5° and treated dropwise over a few minutes period with a

solution of 8 *N* chromic acid, in sulfuric acid,[7] until the yellow color persisted. The mixture was poured into water, extracted with ethyl acetate and the extract washed with bicarbonate, dried (sodium sulfate) and evaporated. Methanol crystallization of the residue yielded 175 mg. of 7-ketoestrone (IIIf) of m.p. 207–209°. The analytical specimen exhibited m.p. 212–213°, $[\alpha]_D$ +166° (dioxane), λ_{max} 282 mμ, log ε 3.32 (reported[8] m.p. 212–212.5°, $[\alpha]_D$ +167° (dioxane), λ_{max} 283 mμ, log ε 3.33).

Similarly, oxidation of 7α-hydroxyestradiol (IIIm) with excess Jones reagent furnished IIIf but in only 10% yield.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.55; H, 7.08.

7-Ketoestrone Benzoate (IIIg).—A solution of 90 mg. of the 3-monobenzoate of 7α-hydroxyestrone (IIIc) in 60 cc. of acetone was treated at room temperature with 1 cc. of 8 *N* chromic acid in sulfuric acid and the mixture allowed to stand for 5 minutes before pouring into water. The resultant precipitate was filtered, washed and crystallized from methanol, yielding pure IIIg, m.p. 202–203°, λ_{max} 232 mμ, log ε 4.27.

Anal. Calcd. for $C_{25}H_{24}O_4$: C, 77.30; H, 6.23; O, 16.47. Found: C, 76.98; H, 6.33; O, 16.86.

7-Hydroxy-6-dehydroestrone 3,7-Diacetate (Enol Acetate of 7-Ketoestrone) (IV).—A mixture of 1 g. of 7-ketoestrone (IIIf), 0.5 g. of anhydrous sodium acetate and 5 cc. of acetic anhydride was boiled for one hour and then cooled and poured into water. The product was extracted with ether, the extract washed with dilute bicarbonate and water and evaporated to dryness. The residue was purified by chromatography on 20 g. of silica gel, the benzene–ether (4:1) fractions after recrystallization from methanol, yielding pure IV (1.1 g.), m.p. 172–173°, $[\alpha]_D$ +104° (dioxane), λ_{max} 266 mμ, log ε 4.02 (reported[8] m.p. 171–171.5°, λ_{max} 268 mμ, log ε 3.99).

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57; O, 21.71. Found: C, 72.12; H, 6.75; O, 21.30.

7β-Hydroxyestrone (IIIh).—The enol acetate IV (1.05 g.) in 80 cc. of glacial acetic acid was hydrogenated over 200 mg. of 10% palladium–carbon catalyst at 20° and 587 mm. Hydrogen uptake stopped after 30 min. with the absorption of 1.07 molar equivalents. The filtered solution was evaporated *in vacuo* and the residue chromatographed over 40 g. of silica gel. The benzene–ether (9:1) fractions gave 50 mg. of estrone acetate, m.p. 125–127°, while the benzene–ether 4:1 and 2:1 fractions gave crude 7β-hydroxyestrone diacetate which was saponified directly by a one hour treatment with boiling 1% methanolic potassium hydroxide. Ethyl acetate extraction and crystallization of the neutralized saponification mixture yielded 0.65 g. of crude 7β-hydroxyestrone (IIIh), which, on recrystallization from methanol, gave 320 mg. of pure IIIh, m.p. 264–265°, $[\alpha]_D$ +149° (dioxane), λ_{max} 280 mμ, log ε 3.37 (reported[8] m.p. 265–267°, $[\alpha]_D$ +134.5° (dioxane)). This product, admixed with 7α-hydroxyestrone (IIIa) of m.p. 260–262°, melted at 235–240°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.75; O, 16.76. Found: C, 75.27; H, 7.51; O. 16.92.

The diacetate (IIIi), an analytical sample from aqueous methanol, gave m.p. 123–124°, $[\alpha]_D$ +153° (dioxane), λ_{max} 268 and 276 mμ, log ε 2.96 and 2.94 (reported[8] m.p. 122–123° or 131–131.5°, λ_{max} 269 mμ, log ε 2.82).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; O, 21.59. Found: C, 71.60; H, 7.13; O, 21.46.

3-Monobenzoate (IIIj).—Benzoylation by the Schotten–Baumann technique and crystallization of the product from methanol gave IIIj, m.p. 182–184° (reported[8] m.p. 181°).

Anal. Calcd. for $C_{25}H_{26}O_4$: C, 76.91; H, 6.71. Found: C, 76.22; H, 6.61.

The 3,7-dibenzoate (IIIk) was prepared from IIIh by treatment with benzoyl chloride-pyridine and crystallization from methanol, m.p. 179–180°, $[\alpha]_D$ +120° (dioxane).

Anal. Calcd. for $C_{32}H_{30}O_5$: C, 76.57; H, 6.43. Found: C, 76.77; H, 6.37.

3-Benzoate-7-ethylcarbonate (IIIl).—7β-Hydroxyestrone 3-benzoate (IIIj) (50 mg.) was added to a cold solution of pyridine (5 cc.) and ethyl chlorocarbonate (2 cc.) and the mixture allowed to stand for 60 hours at room temperature. Precipitation with water followed by ether extraction and crystallization gave IIIl, m.p. 160–164°.

Anal. Calcd. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54; O, 20.75. Found: C, 72.93; H, 6.60; O, 20.52.

6α,7α-Dihydroxyestrone (Va).—A solution of 6-dehydroestrone acetate (Ia) (1.24 g., 0.004 mole) in 200 cc. of anhydrous ether containing three drops of pyridine was allowed to react for 4 days with 1 g. (0.004 mole) of osmium tetroxide dissolved in 150 cc. of dry ether. The black osmate complex which had formed was filtered, washed with ether, suspended in 300 cc. of alcohol, treated with a solution of 7 g. of sodium sulfite in 50 cc. of water and the mixture boiled for 16 hours under reflux. The remaining inorganic precipitate was filtered and the solution concentrated to a volume of *ca.* 50 cc. and water (200 cc.) added precipitating 0.43 g. of crystalline *cis*-glycol, m.p. 130°, resolidification at 150° and m.p. 197–198°. Extraction of the mother liquors with ethyl acetate gave an additional 0.47 g. of material of the same constants raising the total yield to 74%.

The analytical specimen of Va (a monohydrate) from ethyl acetate exhibited m.p. 202–203°, $[\alpha]_D$ +129° (dioxane), λ_{max} 282 mμ, log ε 3.29.

Anal. Calcd. for $C_{18}H_{22}O_4.H_2O$: C, 67.48; H, 7.55. Found: C, 67.86; H, 7.55.

A sample dried at 90° for 40 hours *in vacuo* lost 4.2% water.

6α,7α-Dihydroxyestrone Triacetate (Vb) was prepared by acetic anhydride–pyridine (one hour, 90°) treatment of Va and crystallized from ethyl acetate–ether, m.p. 188–189°, $[\alpha]_D$ +107° (chloroform), λ_{max} 267 and 275 mμ, log ε 2.86 and 2.81.

Anal. Calcd. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59. Found: C, 67.24; H, 6.67.

6α,7α-Dihydroxyestradiol (Vc). (a) **By Osmium Tetroxide Oxidation of Ie.**—Oxidation of Δ^6-dehydroestradiol diacetate (Ie) was carried out as described for the preparation of Va with the exception that the alcohol–water–bisulfite mixture was extracted with ethyl acetate after concentration and addition of water. The residue from evaporation of the ethyl acetate was then saponified by one hour heating with 1% methanolic potassium hydroxide, the solution neutralized with dilute hydrochloric acid, poured into water and the product extracted with ethyl acetate. Crystallization from this solvent gave Vc as the monohydrate, double m.p. 150–155° and 228–230°, $[\alpha]_D$ +56° (dioxane), λ_{max} 282 mμ, log ε 3.28.

Anal. Calcd. for $C_{18}H_{24}O_4.H_2O$: C, 67.06; H, 8.13. Found: C, 67.48; H, 8.16.

(b) **By Reduction of Va.**—A solution of 240 mg. of 6α,7α-dihydroxyestrone (Va) in 40 cc. of methanol was treated at 20° with 300 mg. of sodium borohydride in 5 cc. of water, and the solution allowed to stand for one hour at this temperature. Acetic acid was added to decompose the excess hydride, the solution was concentrated *in vacuo*, water was added and the product, which was extracted and crystallized from ethyl acetate, was identical with that obtained above.

6α,7α-Dihydroxyestradiol Tetraacetate (Vd).—Treatment of Vc with acetic anhydride-pyridine in the usual manner and ethyl acetate crystallization of the acetylated product gave the tetraacetate Vd, m.p. 228–229°, $[\alpha]_D$ +17° (dioxane), λ_{max} 268 and 274 mμ, log ε 2.81 and 2.76.

Anal. Calcd. for $C_{26}H_{32}O_8$: C, 66.09; H, 6.83; O, 27.09. Found: C, 66.53; H, 7.02; O, 26.63.

6β,7α-Dihydroxyestrone (VIa). (a) **By Inversion of the *cis*-Glycol Va.**—A solution of 250 mg. of 6α,7α-dihydroxyestrone in a mixture of 10 cc. of ethanol and 10 cc. of concentrated hydrochloric acid was boiled under reflux for one hour and then allowed to stand at 25° for 18 hours. Water was added and the product extracted with, and crystallized from, ethyl acetate, m.p. 285–290°, $[\alpha]_D$ +147° (dioxane).

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.04; H, 7.55.

(b) **By Hydrolysis of the Epoxide** IIb.—17-Ethylenedioxy-6α,7α-oxidoestrone (IIb) (30 mg.) was dissolved in 20 cc. of 50% aqueous acetone, one drop of 70% aqueous perchloric acid was added and the solution boiled for 15 minutes. Water was added, the product extracted with ethyl acetate, the extract washed with dilute bicarbonate and concentrated yielding VIa, m.p. 283–290°.

6β,7α-Dihydroxyestrone Triacetate (VIb) was prepared by acetic anhydride–pyridine (90°, one hour) treatment o

VIa, crystallization from methanol, m.p. 201–202°, $[\alpha]_D$ +168° (dioxane), λ_{max} 268 and 276 mμ, log ε 2.81 and 2.81.

Anal. Calcd. for $C_{24}H_{28}O_7$: C, 67.27; H, 6.59; O, 26.14. Found: C, 67.18; H, 6.82; O, 26.07.

6β,7α-Dihydroxyestradiol 3,17-Diacetate (VIc).—Silica gel chromatography of the mother liquors from the preparation of 6α,7α-oxidoestradiol diacetate (IIc), gave a very low yield of VIc, m.p. 86–88° (ether–hexane crystallization), $(\alpha)_D$ +17° (dioxane), λ_{max} 268 and 276 mμ, log ε 2.75 and 2.71.

Anal. Calcd. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26; O, 24.72. Found: C, 67.52; H, 7.77; O, 25.00.

Raney Nickel Hydrogenolysis. (a) **Of 6α,7α-Oxidoestradiol (IIc).**—A solution of 200 mg. of epoxide IIc in 50 cc. of 96% ethanol was boiled for 10 hours with 2 g. of freshly prepared W-4 Raney nickel catalyst. The filtered solution was concentrated to dryness, the residue acetylated with acetic anhydride–pyridine (four hours, 25°) and the acetylated product crystallized from hexane to yield 100 mg. of estradiol diacetate (m.p. 125–126°) identical with an authentic sample.

(b) **Of 6α,7α-Dihydroxyestradiol (Vc).**—Treatment of 300 mg. of glycol Vc in 50 cc. of 96% ethanol with 3 g. of W-4 Raney nickel for 15 hours under reflux followed by evaporation of the filtered solution and crystallization of the residue from ethyl acetate–ether gave 200 mg. of estradiol (m.p. 175–176°) identical with an authentic sample.

(c) **Of 7α-Hydroxyestradiol (IIIm).**—Treatment of 300 mg. of 7α-hydroxyestradiol with Raney nickel, exactly as described in b, gave 100 mg. of estradiol, m.p. 171–173°.

Elimination Reactions of 7α-Hydroxyestrone. (a) **Treatment of 7α-Hydroxyestrone 3-Benzoate (IIIc) with Phosphorus Oxychloride.**—A solution of IIIc (220 mg.) in dry pyridine (4 cc.) and freshly distilled phosphorus oxychloride (3.5 cc.) was boiled for 1.5 hours under anhydrous conditions. The cooled mixture was poured into ice-water, the product extracted with ethyl acetate and the extract washed with dilute bicarbonate. Evaporation of solvent and crystallization of the residue from methanol gave 80 mg. of material, m.p. 170–175°, λ_{max} 230 mμ, log ε 4.41, which was then saponified with methanolic potassium hydroxide, and crystallized to give authentic 6-dehydroestrone, m.p. 259–262°. The mother liquors of the methanol crystallization were shown by chromatographic analysis to consist primarily of starting material and of 6-dehydroestrone benzoate.

(b) **Treatment of 7α-Hydroxyestrone 3-Benzoate, 7-Mesylate (IIIe) with Collidine.**—A solution of the mesylate IIIe (50 mg.) in 3 cc. of collidine was boiled for one hour and then diluted with ethyl acetate. After washing with dilute hydrochloric acid, the solvent was evaporated and the residue saponified by one hour reflux with 1% methanolic potassium hydroxide. Crystallization from methanol gave slightly impure 6-dehydroestrone of m.p. 255–257°.

(c) **Treatment of IIIe with Potassium Hydroxide.**—The mesylate IIIe (200 mg.) was heated for one hour in 30 cc. of boiling 2% methanolic potassium hydroxide. The cooled solution was acidified, diluted with water, the precipitate extracted with ethyl acetate and the residue twice recrystallized from methanol yielding 55 mg. of 6-dehydroestrone, m.p. 259–262°, $[\alpha]_D$ −100° (dioxane).

(d) **Treatment of IIIe with Potassium Acetate.**—A solution of 100 mg. of 7α-mesylate IIIe and 200 mg. of anhydrous potassium acetate in 40 cc. of absolute ethanol was boiled for one hour. Water was added, the product isolated by ethyl acetate extraction and then saponified by treatment with 1% methanolic potassium hydroxide. Chromatography of the saponified product on silica gel, gave, in the benzene–ether (9:1) fractions, 20 mg. of 6-dehydroestrone, m.p. 258–260°.

(e) **Treatment of IIIe with Potassium Benzoate.**—A solution of 300 mg. of IIIe, 1 g. of potassium benzoate and 50 cc. of absolute ethanol was boiled, under reflux, for 60 hours. After the addition of water the product was extracted, saponified and chromatographed on 30 g. of silica gel. Benzene–ether (95:5) eluted 140 mg. of crude 6-dehydroestrone which was recrystallized from ethyl acetate to yield 100 mg. of product of m.p. 258–260°, $[\alpha]_D$ −110°.

Elimination Reactions of 7β-Hydroxyestrone, (a) **Pyrolysis of 7β-Hydroxyestrone Dibenzoate (IIIk).**—In a sublimation tube, 520 mg. of IIIk was heated for four hours at 280–300° under reduced pressure (20 mm.), whereupon 115 mg. (93%) of benzoic acid sublimed. The residue was saponified in the usual manner with 1% methanolic potassium hydroxide and crystallized from methanol to yield 210 mg. of somewhat impure 6-dehydroestrone, m.p. 252–257°. $[\alpha]_D$ −61° (dioxane); λ_{max} 226, 262 and 306 mμ; log ε 4.40, 3.80 and 3.30. Chromatography of the mother liquors gave additional quantities of the same product, containing some dextrorotatory contaminant, but no equilin could be detected.

(b) **Pyrolysis of 7β-Hydroxyestrone 3-Benzoate-7-ethylcarbonate (IIIj).**—Forty mg. of IIIj was pyrolyzed at 250–260° (20 mm. pressure) for two hours. Saponification and crystallization from methanol again gave 6-dehydroestrone of m.p. 253–257°.

APDO. POSTAL 2679
MEXICO, D. F.

[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY]

Steroids. C.[1] Synthesis of 19-Nor-Δ⁴-pregnene-11β,17α,21-triol-3,20-dione (19-Norhydrocortisone) and Related 19-Nor-adrenal Hormones

BY A. ZAFFARONI,[2a] H. J. RINGOLD,[2a] G. ROSENKRANZ,[2a] FRANZ SONDHEIMER,[2a,3a] G. H. THOMAS[2b,3b] AND CARL DJERASSI[2b]

RECEIVED MAY 1, 1958

19-Nor-Δ[1,3,5(10),16]-pregnatetraen-3-ol-20-one (I) is converted by a seven-step sequence to 19-nor-17α-hydroxyprogesterone (VII), which on treatment first with iodine and then with potassium acetate yields 19-nor-Substance S 21-acetate (Xa). Adrenal incubation of 19-nor-17α-hydroxyprogesterone (VII) or of 19-nor-Substance S (Xb) leads to 19-norhydrocortisone (XIa) which can be oxidized to 19-norcortisone (XII). Similarly, adrenal incubation of the previously described 19-norprogesterone (XVa) or 19-nordesoxycorticosterone (XVb) yields 19-norcorticosterone (XVI). The biological activities of the various hormone analogs are reported and discussed.

It has been shown that the 19-nor analogs of progesterone,[4a] 17α-ethinyltestosterone[4b] and desoxycorticosterone[4c] are considerably more potent hormones than the corresponding 19-methyl compounds. It was therefore of interest to prepare the corresponding analogs of the 11-oxygenated adrenal hormones. This objective was achieved by use of

(1) Paper IC, J. Iriarte, H. J. Ringold and C. Djerassi, THIS JOURNAL, **80**, 6105 (1958)..

(2) (a) Synthex, S. A., (b) Wayne State University.

(3) (a) The Weizmann Institute of Science, Rehovoth, Israel; (b) University of Birmingham, Birmingham, England.

(4) (a) C. Djerassi, L. Miramontes and G. Rosenkranz, THIS JOURNAL, **75**, 4440 (1953); (b) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954); (c) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **77**, 148 (1955).