B. Potassium acetate method. A mixture of 1.049 g. of 22-ketocholesteryl tosylate (VII), 1.5 g. of fused potassium acetate and 50 ml. of methanol was heated under reflux for 4.5 hr. After working up as described for procedure *A*, above, the crude oil was chromatographed on alumina. Elution with 1:4 benzene–hexane furnished 605 mg. (77%) of the *i*-ether as an oil, $[\alpha]_D$ +26° to +30° (chloroform). Further elution with 1:1 benzene–hexane and benzene gave 128 mg. of oil that was probably the normal ether, $[\alpha]_D$ −29° (chloroform).

22-Ketocholestery acetate (IX). A sample of 6β-methoxy-3,5-cyclocholestan-22-one (107 mg., $[\alpha]_D$ +26°) and 10 ml. of glacial acetic acid were heated under reflux for 5 hr. The mixture was diluted with water to give 108 mg. of material having m.p. 144–150°. Crystallization from ethanol gave 71 mg.; m.p. 150.5–152.5°; $[\alpha]_D^{31}$ −61° (chloroform). There was no depression upon mixing with an authentic sample of 22-ketocholesteryl acetate.

Attempted conversion of 6β-methoxy-3,5-cyclocholestan-22-one to 6β-methoxy-3,5-cyclocholestane. Two grams of sodium was dissolved in 10 ml. of methanol and 15 ml. of 85% hydrazine hydrate and 1.041 g. of the keto *i*-ether ($[\alpha]_D^{21}$ +30.1°) in 20 ml. of methanol were sealed in a tube.[8] The mixture was heated at 200° ± 10° for 12 hr. The product was extracted with ether-hexane, the solvent was removed, and the resulting oil was chromatographed on alumina. Elution with hexane gave 167 mg. of oil, $[\alpha]_D^{21}$ +43° (chloroform). (An additional 812 mg. of oil was obtained in subsequent elutions.)

The first eluate (167 mg., above) was heated under reflux for 5 hr. with 15 ml. of acetic acid. The 156 mg. of precipitate recovered was chromatographed on alumina and eluted with hexane. One fraction of 91 mg. had a specific rotation, $[\alpha]_D^{27}$ −52° (chloroform) and a following fraction of 36 mg. had a rotation of $[\alpha]_D^{25}$ −47°. Both fractions were oils and their structure is uncertain, since cholesteryl acetate has the m.p. 115–116° and $[\alpha]_D$ −47.4°.[12]

Essentially the same results were obtained when the Huang-Minlon procedure was used.[7]

Stability of the *i*-ether structure was shown by subjecting 1.0 g. of 6β-methoxy-3,5-cyclocholestane to the reduction conditions of Huang-Minlon.[7] Chromatography and crystallization from acetone-methanol furnished 485 mg. of purified starting material, m.p. 78–79°, $[\alpha]_D^{30}$ +54.0° (chloroform). Stoll[6] reported m.p. 79°, $[\alpha]_D$ +51.8°.

Acknowledgment. The authors wish to thank Drs. Wayne Cole and Byron Riegel for their helpful suggestions given during the course of this work.

CHICAGO 14, ILL.

(12) I. H. Page and H. Rudy, *Biochem. Z.*, **220**, 304 (1930).

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

Steroids. CXIII.[1] 6-Methyl Estrogens

ESPERANZA VELARDE,[2] J. IRIARTE, H. J. RINGOLD, AND CARL DJERASSI

Received October 15, 1958

17-Ethylenedioxy-6α,7α-oxidoestrone acetate (IV) was transformed into 6β-methyl-7α-hydroxyestrone (VI) and thence by collidine treatment of its 3-benzoate-7-mesylate (VIII) into 6-methyl-6-dehydroestrone (X). Catalytic hydrogenation provided 6β-methylestrone (XIII) while reduction with sodium borohydride led to 6β-methylestradiol (XV). Introduction of a 6β-methyl group into estrone or estradiol was found to be associated with a drastic decrease in estrogenic activity.

Introduction of a methyl group in position 6 of steroids belonging to the androgenic, progestational, and cortical hormone series[3] usually results in an increase in biological activity. The only group of hormones which have so far not been investigated in this respect are the estrogens and the present paper deals with the preparation of some 6-methylated estrogenic hormones.

The most commonly employed route to 6-methyl steroids has been the conversion of a Δ^5-olefin to the corresponding 5α,6α-epoxide followed by opening with a methylmagnesium Grignard reagent.[3,4] The ready availability of 6-dehydroestrone (I)[5] and 6-dehydroestradiol (II)[6] led us to employ the same path, the key intermediate being, 17-ethylenedioxy-6α,7α-oxidoestrone 3-acetate (IV); its preparation (I→II→III→IV) and stereochemistry (by transformation to 7α-hydroxyestrone) have already been reported in an earlier paper from this Laboratory.[7] Treatment of the ketal-epoxide IV with methylmagnesium bromide provided 17-ethylenedioxy-6β-methyl-7α-hydroxyestrone (V),[8] while cleavage of the ketal to 6β-methyl-7α-hydroxyestrone (VI) was accomplished

(1) Paper CXII, J. A. Zderic, D. Chávez, H. J. Ringold, and C. Djerassi, in press.

(2) This material represents part of the professional thesis submitted by Srta. Esperanza Velarde to the Facultad de Química, Universidad Motolinia.

(3) For leading references see: (a) H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); A. Bowers and H. J. Ringold, *J. Am. Chem. Soc.*, **80**, 3091 (1958). (b) G. Cooley, B. Ellis, D. N. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957) and earlier papers. (c) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 4717 (1958) and earlier papers.

(4) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939); L. F. Fieser and J. Rigaudy, *J. Am. Chem. Soc.*, **73**, 4660 (1951); R. B. Turner, *J. Am. Chem. Soc.*, **74**, 5362 (1952).

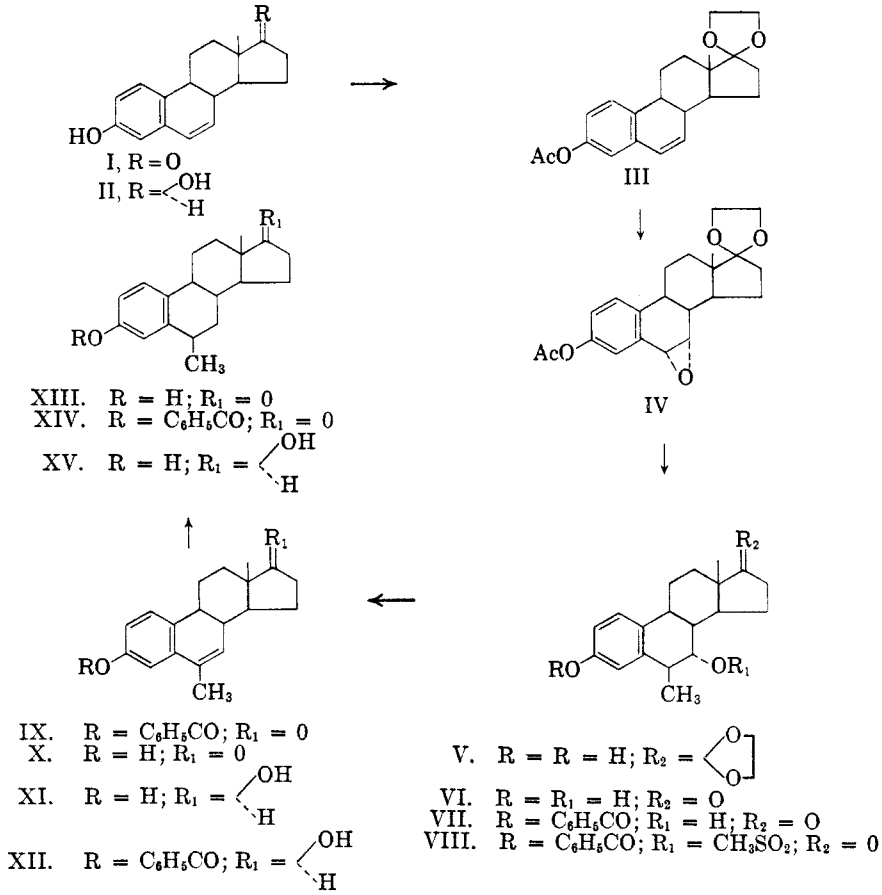
(5) S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4531 (1950).

(6) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(7) J. Iriarte, H. J. Ringold and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6105 (1958).

(8) The product of normal diaxial opening (see A. Fürst and P. Plattner, 12th Internat. Congress Pure and Appl. Chem., New York 1951, Abstracts, p. 405), which is still further favored because of benzylic activation.

with *p*-toluenesulfonic acid in acetone solution.[9] The 7α-hydroxy group was removed by converting 6β-methyl-7α-hydroxyestrone (VI) *via* its 3-benzoate VII to the 3-benzoate-7-mesylate VIII and heating the latter with γ-collidine. The resulting 6-methyl-6-dehydroestrone benzoate (IX) was saponified to 6-methyl-6-dehydroestrone (X), which exhibited the characteristic triple ultraviolet absorption maxima at 222, 262, and 305 mμ associated with the 6-dehydroestrogen chromophore.[5,6,10] Reduction of X with sodium borohydride provided 6-methyl-6-dehydroestradiol (XI) which was characterized further as the 3-monobenzoate XII.



Hydrogenation of 6-methyl-6-dehydroestrone (X) proceeded smoothly to yield 6β-methylestrone (XIII), the β-orientation being assigned to the methyl group by assuming hydrogenation from the less hindered α-side,[11] while further reduction with sodium borohydride led to 6β-methylestradiol (XV). Estrogenic assay[12] (by injection) in mice using uterine weight increase as the criterion and estrone as the standard indicated that XIII and XV possessed only about $\frac{1}{500}$ the estrogenic activity of estrone.

EXPERIMENTAL[13]

17-Ethylenedioxy-6β-methyl-7α-hydroxyestrone (V). To a solution of 2.0 g. of 17-ethylenedioxy-6α,7α-oxidoestrone 3-acetate (IV)[7] in 200 cc. of dry ether and 10 cc. of dry benzene was added 20 cc. of an ethereal solution of methylmagnesium bromide (Arapahoe Chemicals, Inc., Boulder, Colo.) and the mixture was heated under reflux for 30 min. After pouring into dilute hydrochloric acid solution, the organic solution was dried, evaporated, and the residue recrystallized from ethyl acetate to give an average yield of 60% of satisfactory material, m.p. 226–229°. The analytical sample of V crystallized from ethyl acetate as colorless crystals, m.p. 235–237°, $[\alpha]_D$ ±0°, λ_{max}^{EtOH} 280 mμ, log ϵ 3.32.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19; O, 18.58. Found: C, 72.62; H, 8.11; O, 18.64.

6β-Methyl-7α-hydroxyestrone (VI) and derivatives. A solution of 1.38 g. of the ketal V and 100 mg. of *p*-toluenesulfonic acid in 100 cc. of acetone and 30 cc. of water was heated under reflux for 30 min. and then poured into aqueous so-

(9) G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.*, **17**, 290 (1952).

(10) It is interesting to note that the methyl substituent had essentially no effect upon the position of the three maxima.

(11) That this assumption is also valid in the presence of an aromatic ring A is evidenced by the course of the hydrogenation of 7-ketoestrone enol acetate [ref. 7 and W. H. Pearlman and O. Wintersteiner, *J. Biol. Chem.*, **132**, 605 (1940)].

(12) We are indebted to Dr. R. I. Dorfman, Worcester Foundation for Experimental Biology, Shrewsbury, Mass., for the bioassays.

(13) Melting points are uncorrected. Unless noted otherwise all rotations were measured in dioxane solution. We are indebted to Dr. L. Throop and staff for all rotation and spectral measurements.

dium bicarbonate solution. Extraction with ethyl acetate and concentration afforded 1.22 g. of crystals, m.p. 206–208°, raised upon further recrystallization to m.p. 218–220°, $[\alpha]_D$ +110°, λ_{max}^{EtOH} 280 mμ, log ε 3.41.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.17; H, 7.85.

The *3-monobenzoate VII* was prepared by adding dropwise 0.6 cc. of benzoyl chloride to 0.38 g. of 6β-methyl-7α-hydroxyestrone (VI) in 30 cc. of cold 5% aqueous potassium hydroxide and shaking vigorously. Extraction with ethyl acetate, thorough washing with sodium bicarbonate solution and water, drying, and concentration yielded the monobenzoate (0.37 g.) m.p. 220–223°, which was used in the next step. The analytical sample exhibited m.p. 230–232°, $[\alpha]_D$ +101°.

Anal. Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.28; H, 6.91; O, 15.88.

To a solution of 0.36 g. of the benzoate VII in 10 cc. of pyridine was added dropwise at 0° 1 cc. of methanesulfonyl chloride and 10 cc. of pyridine and after standing at room temperature overnight, the mixture was diluted with ether and washed well with dilute sulfuric acid, bicarbonate solution, and water. The dry ether solution was concentrated to incipient crystallization and after chilling, 0.20 g. of *6β-methyl-7α-hydroxyestrone 3-benzoate 7-mesylate* (VIII), m.p. 148–150° (dec.), was collected. Decolorization with Norit in hexane–benzene solution followed by recrystallization from chloroform furnished the analytical specimen, m.p. 156–158° (dec.), $[\alpha]_D$ +79° (chloroform).

Anal. Calcd. for $C_{27}H_{30}O_6S$: C, 67.20; H, 6.27; O, 19.89; S, 6.64. Found: C, 67.68; H, 6.40; O, 19.61; S, 6.32.

6-Methyl-6-dehydroestrone (X). A solution of 0.77 g. of the 3-benzoate-7-mesylate VIII in 50 cc. of γ-collidine was heated under reflux for 1 hr., cooled, diluted with ether, and washed well with dilute hydrochloric acid and water. Evaporation of the dried ether solution, decolorization with Norit in hexane–benzene solution and recrystallization from methanol led to 0.48 g. of *6-methyl-6-dehydroestrone 3-benzoate* (IX), m.p. 142–145°. The analytical sample, prepared from the same solvent, showed m.p. 153–156°, $[\alpha]_D$ −57°.

Anal. Calcd. for $C_{26}H_{26}O_3$: C, 80.80; H, 6.78. Found: C, 80.89; H, 7.16.

Saponification of the benzoate IX was performed by heating it under reflux for 1 hr. with 1% methanolic potassium hydroxide solution and recrystallization from ether. The analytical specimen of *6-methyl-6-dehydroestrone* (X) exhibited m.p. 218–220°, $[\alpha]_D$ −67°, λ_{max}^{EtOH} 222, 262, and 305 mμ, log ε 4.37, 3.83 and 3.42 mμ.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.30; H, 7.84.

6-Methyl-6-dehydroestradiol (XI). To a solution of 0.6 g. of 6-methyl-6-dehydroestrone (X) in 50 cc. of methanol was added 0.7 g. of sodium borohydride dissolved in 50 cc. of water. After standing for 3 hr., acetic acid was added to neutrality, the mixture was concentrated, extracted with ethyl acetate, and the crude product chromatographed on 30 g. of silica gel. Elution with benzene–ether (4:1) and recrystallization from ether–hexane gave 0.40 g. of colorless crystals, m.p. 197–199°, $[\alpha]_D$ −135°, λ_{max}^{EtOH} 221, 262, and 304 mμ, log ε 4.35, 3.86, and 3.45.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.85; H, 8.32.

Schotten-Baumann benzoylation (as described above for VI) and recrystallization from ether provided *6-methyl-6-dehydroestradiol 3-monobenzoate* (XII), m.p. 169–170°, $[\alpha]_D$ −98°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26; O, 12.36. Found: C, 79.81; H, 7.22; O, 12.64.

6β-Methylestrone (XIII). The hydrogenation of 0.86 g. of 6-methyl-6-dehydroestrone (X) in 80 cc. of ethyl acetate was conducted at room temperature and atmospheric pressure in the presence of an equal weight of pre-reduced 10% palladized charcoal catalyst. Hydrogen up-take (corresponding to one equivalent) ceased within 30 min. and filtration of the catalyst, evaporation of the solvent, and recrystallization from ethyl acetate provided 0.84 g. of 6β-methylestrone (XIII), m.p. 219–222°. Repeated recrystallization furnished the analytical specimen, m.p. 225–226°, $[\alpha]_D$ +121°, λ_{max}^{EtOH} 281 mμ, log ε 3.32.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; O, 11.25. Found: C, 79.94; H, 8.51; O, 11.27.

6β-Methylestrone benzoate (XIV) was obtained by heating a sample of XIII with benzoyl chloride in pyridine solution for 30 min. on the steam bath and recrystallization from ether; m.p. 146–150°, $[\alpha]_D$ +98°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26; O, 12.36. Found: C, 80.01; H, 7.14; O, 12.58.

6β-Methylestradiol (XV). The reduction of 6β-methylestrone with sodium borohydride was performed exactly as described above for X and after recrystallization from ether–hexane yielded 78% of pure 6β-methylestradiol, m.p. 174–176°, $[\alpha]_D$ +50°, λ_{max}^{EtOH} 281 mμ, log ε 3.29.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.20; H, 9.44; O, 11.59.

APT. POSTAL 2679
MEXICO, D. F.