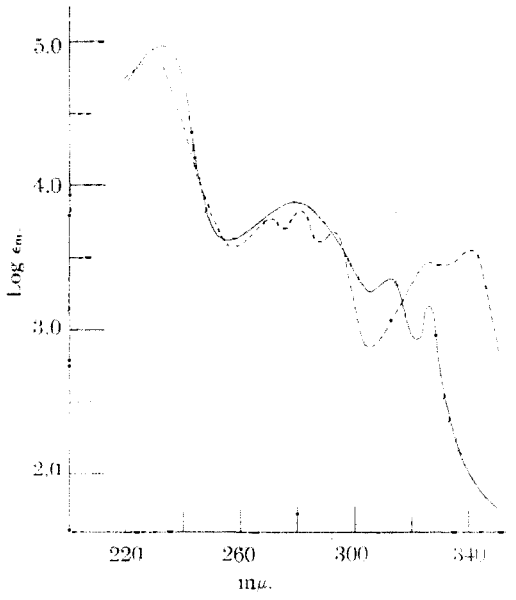

Fig. 2.—Ultraviolet absorption spectra: ——— 17-dihydroequilenin-17β (XVa); - - - 17-dihydroequilenin-17β 3,17-diacetate.

Acetylation produced **17-dihydroequilenin-17β 3,17-diacetate** with m. p. 124–126° (Kofler), $[\alpha]^{20}D$ −12°, u. v. spectrum Fig. 2; reported,[21] m. p. 124°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 75.19; H, 7.04.

B. By Selenium Dioxide Dehydrogenation of Δ⁶-Dehydroestradiol 3,17-Diacetate.—Dehydrogenation of 1 g. of diacetate with 156 mg. of freshly sublimed selenium dioxide in 15 cc. of boiling acetic acid for eight minutes produced 0.81 g. of 17-dihydroequilenin-17β 3,17-diacetate with m. p. 115–118°. Recrystallization from ether-hexane raised the m. p. to 125–127° (Kofler), $[\alpha]^{20}D$ −15°. No depression of the m. p. was observed on mixing with the sample prepared by method A and the ultraviolet absorption spectra proved to be identical.

Alkaline saponification afforded 17-dihydroequilenin-17β with m. p. 246–248° (capillary), undepressed on admixture with a specimen prepared according to method A, $[\alpha]^{20}D$ + 56° (dioxane). The ultraviolet absorption spectrum was practically identical with that depicted in Fig. 2 for material prepared by procedure A.

Summary

A recapitulation of the earlier work of Inhoffen and Butenandt on the bromination of Δ⁴-3-ketosteroids (I), which had led to the conclusion that these ketones could not be employed for the partial synthesis of the estrogens, has demonstrated several inconsistencies. The reinvestigation of the dibromination in ether–acetic acid solution of Δ⁴-3-ketosteroids (I), in particular of the androstane series, has shown that the resulting dibromo derivatives on collidine dehydrobromination produce Δ¹,⁴,⁶-trien-3-ones (XII) in satisfactory overall yield. On the basis of these results, several alternate structures are proposed for the intermediate dibromo compounds, taking into consideration their marked tendency toward rearrangement and their ultraviolet absorption spectra.

Δ¹,⁴,⁶-Androstadiene-3,17-dione (XIIb), thus obtained, has already[1] been converted into Δ⁶-isoequilin, estrone and equilenin, and its corresponding 17-acetoxy derivative on similar treatment has now led to Δ⁶-dehydroestradiol, estradiol and 17-dihydroequilenin-17β. The stereochemistry of the C-17 isomeric dihydroequilenins is discussed.

The present experiments thus constitute a novel, partial synthesis of all of the major, naturally occurring female sex hormones from the potent male hormones testosterone and Δ⁴-androstene-3,17-dione.

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

Steroids. VIII.[1,2] The Dienone–Phenol Rearrangement in the Steroid Series. Synthesis of a New Class of Estrogens

BY CARL DJERASSI, G. ROSENKRANZ, J. ROMO, J. PATAKI AND ST. KAUFMANN

Partial aromatization of a bicyclic ring system possessing an angular methyl group with concomitant migration of the angular substituent was first observed in the santonin (I) series.[3] This rearrangement can be carried out at or near room temperature in acetic anhydride containing a small amount of acid[4] and furnishes the phenol, desmotroposantonin (II), in high yield. Subsequently, Inhoffen and co-workers[5] applied these reaction conditions to analogous steroidal dienones (III) in the hope of preparing members of the female sex hormone series. The resulting products, though insoluble in alkali, were clearly shown to be phenols, and by analogy to the santonin–desmotroposantonin rearrangement they were assigned the 1-methyl-3-hydroxy-1,3,5-triene structure IV. Thus in the case of Δ¹,⁴-androstadien-17-ol-3-one (IIIa), 1-methylestradiol (IVa) was believed to have been obtained. In spite of the comparative non-specificity of estrogenic activity, exhibited by a variety of substances, this close

(1) Presented in part on the program of the Division of Medicinal Chemistry at the Philadelphia, Pa., meeting of the American Chemical Society, April 11, 1950.

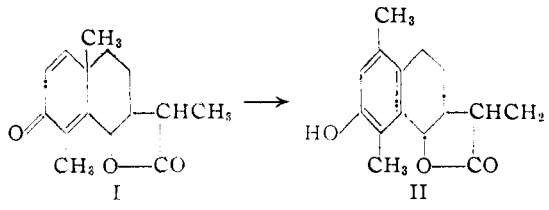
(2) Paper VII, Djerassi, Rosenkranz, Romo, Kaufmann and Pataki, THIS JOURNAL, **72**, 4534 (1950).

(3) Andreocci, *Ber.*, **26**, 1373 (1893); Clemo, Haworth and Walton, *J. Chem. Soc.*, 1110 (1930).

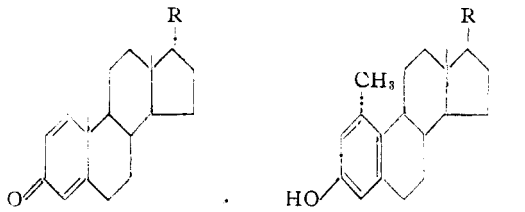
(4) Huang-Minlon, Lo and Cho, THIS JOURNAL, **65**, 1780 (1943).

(5) See Inhoffen, *Angew. Chem.*, **53**, 471 (1940); **59**, 207 (1947); *Ber.*, **563**, 127 (1949).

relative of the potent female sex hormone estradiol was totally devoid of biological activity.

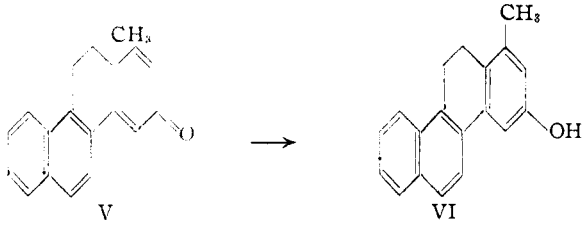


I II



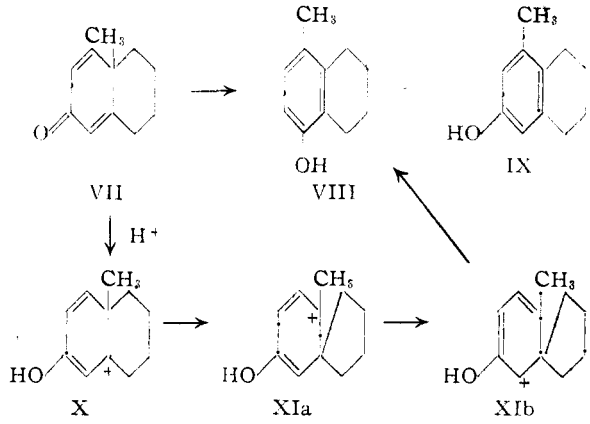
IIIa R = OH IVa R = OH b R = O

In 1946, the generality of this type of rearrangement was emphasized and the term "dienone–phenol rearrangement" was proposed.[6] The preparation[6] of the chrysene dienone V and the proof, by total synthesis, that its rearrangement product possessed the 1-methyl-3-hydroxy structure VI provided considerable, though indirect, support for Inhoffen's structures[5] and the latter were accepted in a considerable number of other rearrangements of steroidal $\Delta^{1,4}$-dien-3-ones (III).[7]



V VI

Recently, however, Woodward and Singh[8] observed that the simple, synthetic dienone VII on rearrangement afforded 1-methyl-4-hydroxy-5,6,-7,8-tetrahydronaphthalene (VIII) rather than the expected 1-methyl-3-hydroxy derivative IX. This reaction was rationalized as proceeding through the carbonium form X which subsequently through spiran structures such as XIa and XIb gave rise to the observed product VIII. As pointed out by Woodward and Singh,[8] if applied to the analogous steroidal $\Delta^{1,4}$-dien-3-ones III, their rearrangement products most likely would possess the 1-methyl-4-hydroxy or 1-hydroxy-4-methyl structure rather than the 1-methyl-3-hydroxy configuration (IV) postulated by Inhoffen.[5] In the case of the chrysene derivative V, where the structure of the rearrangement product VI had been proved,[6] it was suggested[8] that the various carbonium ions (positive charge distributed through the entire naphthalene ring system) would confer considerable double bond character on the 4a-4b (chrysene numbering system) bond, so that conventional methyl migration (as in santonin) by the usual pinacol-type rearrangement[9] prevails.



VII VIII IX

X XIa XIb

The ready availability of the recently described[2,10] steroidal $\Delta^{1,4,6}$-trien-3-ones (XII) prompted us to investigate the dienone-phenol rearrangement of such an unsaturated system. Application of the usual rearrangement conditions (acetic anhydride–*p*-toluenesulfonic acid) [6,7] to the trienones XIIa and XIIb smoothly yielded 1-methyl-Δ^6-dehydroestradiol (XIIIa) ($[\alpha]^{20}D$ $-124°$) and 1-methyl-Δ^6-dehydroestrone (XIIIb) ($[\alpha]^{20}D$ $-77°$), interconvertible through lithium aluminum hydride reduction of the latter. Both phenols were alkali soluble and exhibited a strong maximum at 268 mμ (log *E* 3.90), typical of Δ^6-dehydrophenols of the steroid series.[2,10] Catalytic hydrogenation of 1-methyl-Δ^6-dehydroestrone (XIIIb) proceeded in nearly quantitative yield affording 1-methylestrone (IVb) with m. p. 250–252°, $[\alpha]^{20}D$ + 257°, u. v. maximum at 280 mμ (log *E* 3.26). The substance thus exhibited the characteristic change in the sign of rotation and in the absorption spectrum on hydrogenation of the 6–7 double bond as was found for the estrogens lacking the 1-methyl group.[2,10] Furthermore, *the compound was soluble in dilute, aqueous alkali and possessed approximately one-half the biological activity of estrone in rats.*[10a] In contrast, the so-called "1-methylestrone"[5,7] (with which our product gave a marked melting point depression) is insoluble in alkali and estrogenically inactive in one-thousand times the threshold dose of estrone. Similar experiments with 1-methyl-Δ^6-dehydroes-

(6) Wilds and Djerassi, THIS JOURNAL, **68**, 1715 (1946).

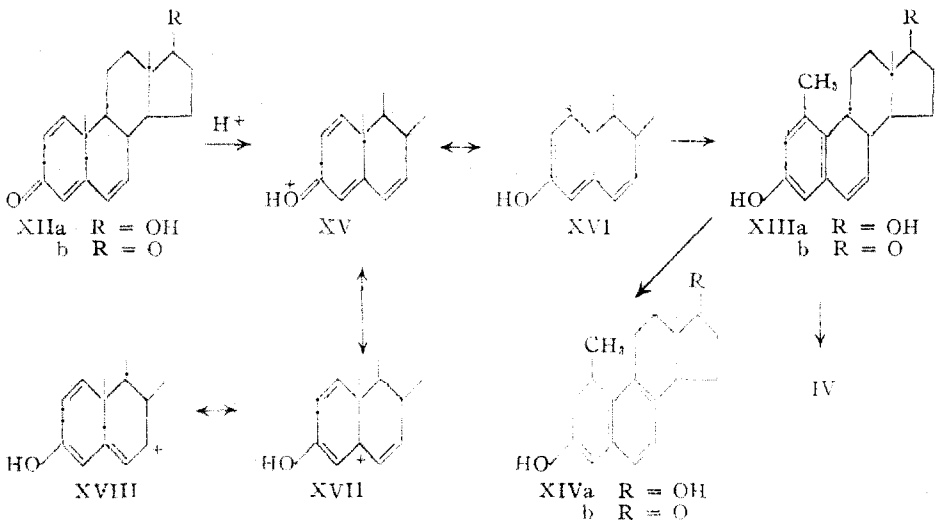
(7) Djerassi, *et al.*, *ibid.*, **68**, 1712, 2125 (1946); **69**, 2404 (1947); **70**, 1911 (1948); *J. Org. Chem.*, **13**, 697, 848 (1948).

(8) Woodward and Singh, THIS JOURNAL, **72**, 494 (1950). We are grateful to Prof. R. B. Woodward, Harvard University, for informing us of his results several months prior to publication.

(9) Arnold, Buckley and Richter, *ibid.*, **69**, 2322 (1948).

(10) Kaufmann, Pataki, Rosenkranz, Romo and Djerassi, *ibid.*, **72**, 4531 (1950).

(10a) The preliminary estrogenic tests were carried out by Dr. Elva G. Shipley, The Endocrine Laboratories, Madison 5, Wisconsin. Subsequent experiments have shown that the estrogenic activity of these 1-methylestrogens (IV) differs considerably, depending on the test method employed. The details will appear elsewhere.



tradiol (XIIIa) gave the same results, our 1-methylestradiol (IVa) (m. p. 116°, $[\alpha]^{20}D$ +146°, dipropionate with four times the biological activity[10a] of estrone) differing completely from the product described in the literature[5] (m. p. 231–232°, $[\alpha]D$ +179.5°).[11] Finally, both 1-methyl-Δ^6-dehydrophenols (XIII) were readily converted into 1-methyl-17-dihydroequilenin (XIVa) and 1-methylequilenin (XIVb) on warming for a few minutes with selenium dioxide in acetic acid or dioxane solution, and exhibited, with minor differences, the same ultraviolet absorption spectrum (Fig. 2) as equilenin.

It is evident that the dienone–phenol rearrangement of the $\Delta^{1,4,6}$-trien-3-ones XII is formally much more closely related to the proved case in the chrysene series (V),[6] because of the additional conjugated double bond, than is that of the $\Delta^{1,4}$-dien-3-ones III, which resemble Woodward's[8] example VII. Three carbonium ions, XVI, XVII and XVIII, are of importance in considering the course of the reaction. Of these XVI would give rise to the 1-methylphenol (XIII) by direct methyl migration[9] while XVII would yield spiran structures (analogous to XI) leading to the "abnormal" products observed by Woodward and Singh[8] and apparently occurring in the steroid series with $\Delta^{1,4}$-dien-3-ones III. It should be noted that the carbonium ion XVII would be in equilibrium with form XVIII, which while probably more stable (conjugated system of double bonds) than XVII could not satisfy the electron deficiency by migration etc. It seems most likely therefore, as demonstrated in the case of the chrysene dienone V, that *the presence of an additional conjugated double bond causes methyl migration to proceed in preference to spiran formation.*[11a] Evidently, lower energy transition states are involved in the methyl migration through the carbonium ion XVI (with its stabilizing feature of a series of conjugated double bonds), than through the equilibrium forms XVII and XVIII, where the partial double bond character of the 5–6 bond may tend to prevent spiran formation.[8]

The substances described earlier in the literature[5,7] as 1-methylphenols of the steroid series must, therefore, possess either the 1-methyl-4-hydroxy or 1-hydroxy-4-methyl structure[12] and it is suggested that until unequivocal proof is forthcoming, these compounds be referred to as "1-methyl*hetero*-phenols."

Experimental[13,14]

Dienone–Phenol Rearrangement of $\Delta^{1,4,6}$-Androstatriene-3,17-dione (XIIb).—A mixture of 15.5 g. of $\Delta^{1,4,6}$-androstatriene-3,17-dione (XIIb),[2,10] 3.90 g. of *p*-toluenesulfonic acid and 600 cc. of acetic anhydride was heated for five hours on the steam-bath. The cooled solution was hydrolyzed by swirling with water, the crystalline product was filtered, dried and recrystallized from methanol; yield, 12.85 g. (72%), m. p. 147–149°. Further recrystallization from the same solvent gave pure **1-methyl-Δ^6-dehydroestrone acetate** with m. p. 152–153° (Kofler), $[\alpha]^{20}D$ −94° (dioxane), u. v. maxima at 222 mμ (log *E* 4.44) and 264 mμ (log *E* 3.93).

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 78.09; H, 7.53.

Saponification of the acetate was accomplished in 97% yield by refluxing with 2% methanolic sodium hydroxide solution for one hour. Two recrystallizations from methanol gave **1-methyl-Δ^6-dehydroestrone** (XIIIb) with m. p. 250–252° (Kofler), $[\alpha]^{20}D$ −87.7°, −76.8° (dioxane), u. v. maxima (Fig. 1) at 228 mμ (log *E* 4.49), 268 mμ (log *E* 3.90) and 306 mμ (log *E* 3.28).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.10; H, 7.54.

(11) The infrared curves of IVa and XIIIa (as their diacetates) showed marked similarities to those of the corresponding estradiol derivatives, but differed completely from that of Inhoffen's 1-methylestradiol.[5] We are indebted to Dr. Konrad Dobriner, Sloan-Kettering Institute for Cancer Research, for this information.

(11a) It has since been possible to prove this unequivocally in the naphthalene series (Sandoval, Miramontes, Rosenkranz and Djerassi, to be submitted for publication).

(12) The isolation of benzene-1,2,3,4-tetracarboxylic acid from the nitric acid oxidation of such a phenol (Wilds and Djerassi, THIS JOURNAL, **68**, 1712 (1946)) affords strong indication that ring B is six-membered.

(13) Melting points marked Kofler were determined on the Kofler block and are corrected; all others were carried out in capillaries and are uncorrected unless noted otherwise. Rotations were determined on *ca.* 60–100 mg. of substance in chloroform solution (unless indicated otherwise) in a 2-dcm. tube of 10-cc. capacity. When two values are given, the first one always refers to chloroform solution. Ultraviolet absorption spectra were measured in 95% ethanol solution with a Beckman Quartz Photoelectric Spectrophotometer.

(14) The microanalyses were carried out in our Microanalytical Department under the direction of Srta. Amparo Barba. The Srtas. Paquita Revaque and Ann Rochman were responsible for all spectra and rotations.

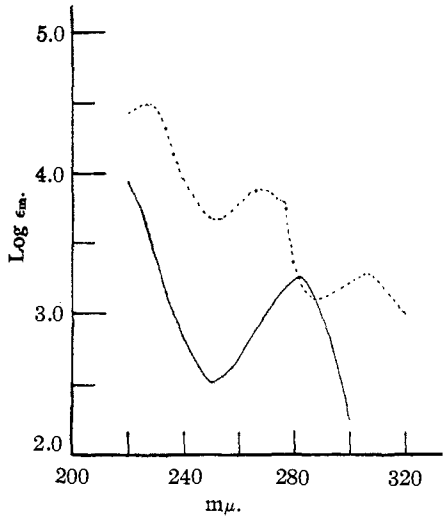


Fig. 1.—Ultraviolet absorption spectra (in 95% ethanol solution): ..... 1-methyl-Δ^6-dehydroestrone (XIIIb); —— 1-methylestrone (IVb).

Hydrogenation of 1-Methyl-Δ^6-dehydroestrone to 1-Methylestrone (IVb).—A solution of 4 g. of 1-methyl-Δ^6-dehydroestrone acetate (m. p. 147–149°) in 60 cc. of ethyl acetate was shaken in the presence of hydrogen with 800 mg. of 10% palladium-on-charcoal catalyst (American Platinum Works) for two hours, at which time the hydrogen up-take corresponded to one mole. After filtration, evaporation and recrystallization from methanol, 3.5 g. (87%) of **1-methylestrone acetate** was obtained with m. p. 157.5–158.5° (Kofler), $[\alpha]^{20}D$ +224°, +219° (dioxane), u. v. maximum at 268 mμ (log *E* 2.52) and minimum at 252 mμ (log *E* 2.31). The so-called 1-methylestrone described in the literature[7] did not form a crystalline acetate.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.02. Found: C, 77.14; H, 8.20.

Alkaline saponification in the usual manner led in quantitative yield after recrystallization from methanol to **1-methylestrone** (IVb), m. p. 250–252° (Kofler), $[\alpha]^{20}D$ +257°, +246° (dioxane), u. v. maximum (Fig. 1) at 282 mμ (log *E* 3.26) and minimum at 250 mμ (log *E* 2.51). The so-called 1-methylestrone, described in the literature,[7] had m. p. 249–251°, $[\alpha]D$ +271.6° and a mixture of the two specimens melted at 212–223°. In contrast to the latter substance, 1-methylestrone dissolved on warming in 5% aqueous alkali and exhibited approximately one-half the estrogenic potency of estrone in rats.[10a]

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.50. Found: C, 80.05; H, 8.50.

Dehydrogenation of 1-Methyl-Δ^6-dehydroestrone (XIIIb) to 1-Methylequilenin (XIVb).—A solution of 1 g. of 1-methyl-Δ^6-dehydroestrone acetate in 20 cc. of glacial acetic acid or dioxane was refluxed for ten minutes with 0.17 g. of freshly sublimed selenium dioxide under nitrogen. After filtration of selenium, the solution was diluted with water, the pink solid (0.90 g., m. p. 160–165°) was filtered and recrystallized from methanol, yielding 0.62 g. of **1-methylequilenin acetate** as colorless crystals with m. p. 171–172.5° (Kofler), $[\alpha]^{20}D$ +113°, u. v. spectrum shown in Fig. 2.

Anal.[15] Calcd. for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.54; H, 6.98.

Alkaline saponification afforded **1-methylequilenin (XIVb)**, which after recrystallization from aqueous methanol had m. p. 215–217° (cor., red melt), $[\alpha]^{20}D$ +138.5° (dioxane). The u. v. spectrum closely resembled that of equilenin[10] and is shown in Fig. 2.

(15) This analysis was carried out by Mr. Joseph F. Alicino, Metuchen, New Jersey.

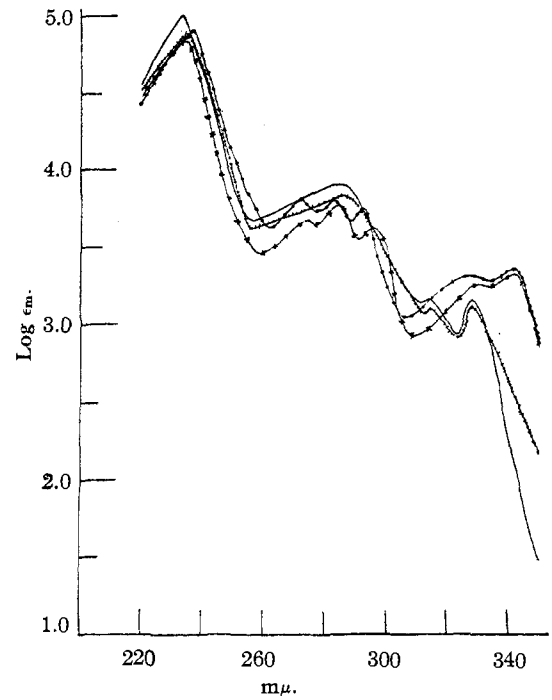


Fig. 2.—Ultraviolet absorption spectra: -•-•-•-•- 1-methyl-17-dihydroequilenin (XIVa); ——— 1-methyl-17-dihydroequilenin 3,17-diacetate; x-x-x-x 1-methylequilenin (XIVb); ++++ 1-methylequilenin acetate.

Anal.[15] Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.65; H, 7.30.

1-Methyl-Δ^6-dehydroestradiol (XIIIa). A. By Dienone–Phenol Rearrangement of $\Delta^{1,4,6}$-Androstatrien-17-ol-3-one 17-acetate (XII, R = OAc).—The rearrangement was carried out in the customary manner with 2.7 g. of androstatrienolone 17-acetate (XII, R = OAc),[2] 100 cc. of acetic anhydride and 1 g. of *p*-toluenesulfonic acid and afforded 2.89 g. (95%) of **1-methyl-Δ^6-dehydroestradiol 3,17-diacetate** with m. p. 110–112°. Recrystallization from hexane gave the analytical sample (71%) with m. p. 116–117° (Kofler), $[\alpha]^{20}D$ −149°, u. v. maxima at 222 mμ (log *E* 4.46) and 264 mμ (log *E* 3.96).

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.65. Found: C, 74.76; H, 7.38.

Saponification led in nearly quantitative yield to **1-methyl-Δ^6-dehydroestradiol (XIIIa)**, which had m. p. 130–133° unchanged after several crystallizations from either hexane–acetone or dilute methanol, $[\alpha]^{20}D$ −124°, −134° (dioxane) u. v. maxima at 226 mμ (log *E* 4.57) and 266 mμ (log *E* 3.95). The compound retained solvent tenaciously and required extensive drying at 78° and 0.002 mm. before correct analytical values were obtained.

Anal.[15] Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.50. Found: C, 80.48; H, 8.50.

The above phenol, which was readily soluble in 2 *N* aqueous sodium hydroxide, was benzoylated by the Schotten–Baumann method and the **1-methyl-Δ^6-dehydroestradiol 3-monobenzoate** was crystallized from hexane–acetone; m. p. 146–147.5° (Kofler), $[\alpha]^{20}D$ −123°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.42; H, 7.27. Found: C, 80.35; H, 7.19.

B. By Lithium Aluminum Hydride Reduction of 1-Methyl-Δ^6-dehydroestrone Acetate.—A solution of 2 g. of 1-methyl-Δ^6-dehydroestrone acetate in 600 cc. of dry ether was refluxed with 1 g. of lithium aluminum hydride

for thirty minutes. After the usual work-up, there was obtained 1.54 g. (88%) of 1-methyl-Δ^6-dehydroestradiol with m. p. 129–132°, which gave no depression on admixture with the sample prepared according to (A) and possessed the same rotation and spectrum.

Hydrogenation of 1-Methyl-Δ^6-dehydroestradiol 3,17-Diacetate to 1-Methylestradiol 3,17-Diacetate.—Hydrogenation of the Δ^6-dehydro diacetate in the usual manner in ethyl acetate solution with 10% palladium-on-charcoal catalyst (barium sulfate supported catalyst was equally satisfactory) afforded 81% of shiny, prismatic blades (from methanol) of **1-methylestradiol 3,17-diacetate** with m. p. 178–180° (Kofler), $[\alpha]^{20}D$ +111°, u. v. maximum at 268 mμ (log E 2.53) and minimum at 252 mμ (log E 2.44). The so-called 1-methylestradiol 3,17-diacetate described in the literature[5,7] had m. p. 138.5–139°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.50; H, 8.19.

1-Methylestradiol (IVa), prepared either by saponification of its diacetate or by hydrogenation of 1-methyl-Δ^6-dehydroestradiol (XIIIa), was obtained from ether–hexane as a microcrystalline powder, which shrank at 95° and melted at 110–116° (Kofler), $[\alpha]^{20}D$ +146°, u. v. maximum at 284 mμ (log E 3.28) and minimum at 250 mμ (log E 2.25). The physical constants of this alkali-soluble phenol are in complete contrast to those reported for the so-called 1-methylestradiol[5,7]: insoluble in alkali, crystallizes readily, m. p. 235.5–236.5°, $[\alpha]D$ +185° (dioxane).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.67; H, 9.14. Found: C, 79.87; H, 9.36.

The **3,17-dipropionate** was isolated in nearly quantitative yield on heating 1-methylestradiol (IVa) for one hour with propionic anhydride and pyridine; colorless plates from methanol, m. p. 125.5–127° (Kofler), $[\alpha]^{20}D$ +101.5°. u. v. maximum at 268 mμ (log E 2.58) and minimum at 254 mμ (log E 2.45).

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.59. Found: C, 75.16; H, 8.63.

1-Methyl-17-dihydroequilenin-17β (XIVa).—This phenol was obtained by both selenium dioxide oxidation of 1-methyl-Δ^6-dehydroestradiol 3,17-diacetate followed by saponification, or by lithium aluminum hydride reduction of 1-methylequilenin acetate exactly as described for the analog lacking the 1-methyl group.[2]

1-Methyl-17-dihydroequilenin-17β crystallized as small, prismatic needles from either aqueous methanol or hexane–acetone, m. p. 225–227° (Kofler), $[\alpha]^{20}D$ +33° (dioxane), u. v. spectrum Fig. 2.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.54; H, 7.65.

The **3,17-diacetate** was obtained as colorless needles from methanol, m. p. 145–147° (Kofler), $[\alpha]^{20}D$ −16°. The u. v. spectrum was very similar to that of 1-methylequilenin acetate and is depicted in Fig. 2.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 75.38; H, 7.15. Found: C, 75.58; H, 7.12.

Summary

The dienone-phenol rearrangement of the recently described[2,10] $\Delta^{1,4,6}$-androstatrien-17-ol-3-one and the corresponding 3,17-dione (XII) produced 1-methyl-Δ^6-dehydroestradiol and 1-methyl-Δ^6-dehydroestrone (XIII). Dehydrogenation led to the corresponding 1-methylequilenin derivatives (XIV), while catalytic hydrogenation afforded 1-methylestradiol and 1-methylestrone, characterized by alkali solubility and high estrogenic potency. A consideration of the reaction mechanism and earlier work on model compounds[6,8] indicates that the present compounds are the true 1-methylestrogens in contrast to the rearrangement products of steroidal $\Delta^{1,4}$-dien-3-ones (III), previously believed to have this structure,[5] which should now be referred to as "x-methyl*hetero*phenols."

The present work, coupled with the results of Woodward and Singh,[8] demonstrates that the dienone-phenol rearrangement in the steroid series proceeds in different directions depending on the presence or absence of an additional, conjugated double bond.

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MEXICO CITY, D. F.

RECEIVED FEBRUARY 20, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Structures of β-Diacetone-D-fructose and β-Monoacetone-D-fructose

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Fischer[2] obtained two crystalline products on treating D-fructose with acetone in the presence of acid and these have come to be designated α-diacetonefructose and β-diacetonefructose wherein the prefixes were assigned in accordance with the order of isolation and bear no anomeric significance. The structure of the former can be considered to be adequately established as 1,2:4,5-diisopropylidene-D-fructopyranose[3,4] while that of the latter cannot.

It is known that C_1 is open in the β-isomer since on oxidation with alkaline permanganate an acid was obtained without acetone removal and this acid on hydrolysis yielded 1-C-carboxy-D-arabinose (2-keto-D-gluconic acid).[5] The main difficulties preventing a solution of this problem have been those encountered in preparing the mono-isopropylidene derivative, essential to the structure determination. Both isopropylidene residues hydrolyze at nearly the same rate and on partial hydrolysis there is obtained a difficultly separable mixture of starting material, D-fructose and a relatively small amount of the sirupy mono-isopropylidene-D-fructose. In the work herein reported the mono derivative has been separated by chroma-

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(2) E. Fischer, *Ber.*, **28**, 1164 (1895); *cf.* H. Ohle and Ilse Koller, *ibid.*, **57**, 1566 (1924).

(3) H. Ohle, *ibid.*, **60**, 1168 (1927).

(4) C. G. Anderson, W. Charlton, W. N. Haworth and V. S. Nicholson, *J. Chem. Soc.*, 1337 (1929).

(5) H. Ohle, *Ber.*, **58**, 2577 (1925); H. Ohle and Gertrud Berend, *ibid.*, **60**, 1159 (1927).