nium chloride solution, the product (1.16 g.) was isolated by ether extraction and then dehydrogenated by treating with an equal amount of 5% palladium-on-carbon at 300–325° for 8 hr. The dehydrogenated product was isolated by an ether extraction and then chromatographed through a silica gel column with hexane to give 273 mg. of pure pimanthrene, m.p. 84–85° (lit.[14] m.p. 86°). The trinitrobenzene derivative was prepared, m.p. 160–160.5° (lit.[15] m.p. 161–162°); and the picric acid derivative was also prepared, m.p. 130–131° (lit. m.p. 132°).[16] Melting points of mixtures of these derivatives with authentic samples were not depressed below their individual melting points. X-Ray diffraction patterns of the hydrocarbon and its derivatives were identical to those of authentic samples. The authentic sample of pimanthrene was obtained from the dehydrogenation of dihydrodextropimaric acid (m.p. 241–243°, $[\alpha]_D$ +19.2°).[17]

(14) R. D. Haworth, B. M. Letsky and C. R. Mavin, *J. Chem Soc.*, 1789 (1932).

(15) L. C. Craig and W. A. Jacobs, *J. Biol. Chem.*, **152**, 648 (1944).

(16) W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 200 (1947).

(17) T. Hasselstrom and B. L. Hampton, THIS JOURNAL, **61**, 967 (1939).

Dehydration and Ozonization of IV.—A 3.2-g. sample of the hydroxy lactone IV was fused with potassium hydrogen sulfate for 30 min. at 190°. Extraction with methylene chloride yielded an oil which crystallized upon standing, m.p. 80–85°. This was dissolved in methylene chloride and then treated with an excess of ozone at −70° for 12 min. The ozonide was decomposed with zinc and acetic acid at 50°, the evolved gases aided by a nitrogen sparge being passed through a 2,4-dinitrophenylhydrazine hydrochloride solution. The resulting orange precipitate was purified by chromatography, m.p. 124–125°, and identified as the 2,4-dinitrophenylhydrazone of acetone.[13] No evidence for the corresponding formaldehyde derivative was obtained.

Conversion of V to IV.—A 500-mg. sample of the 7-acetyl compound V was stirred at room temperature for 18 hr. with a Grignard solution prepared from 160 mg. of magnesium, 940 mg. of methyl iodide and 25 cc. of ether. After isolation, the product (470 mg.) was twice recrystallized from acetone to give 90 mg. of a material which melted at 178–179°. An X-ray diffraction pattern comparison showed this to be identical to the 14-hydroxy compound IV obtained by the catalytic autoxidation of the original lactone I.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA, BERKELEY]

The Hydrogenation of Equilenin to an Isoestradiol

BY WILLIAM G. DAUBEN AND LEO AHRAMJIAN

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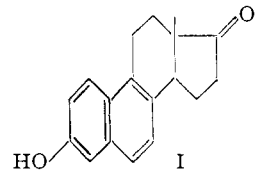
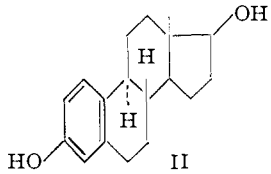
When equilenin is hydrogenated over Raney nickel in alkaline solution a mixture consisting of 20% of an isoestradiol and 50% of $\Delta^{5,7,9}$-estratriene-3β,17β-diol is formed. Under acidic conditions, no phenolic product is obtained. This formation of an estradiol isomer represents the first conversion of equilenin to an estradiol-type of structure by catalytic hydrogenation. The stereochemistry of the products and the effect of *p*H on the course of hydrogenation is discussed.

Since the isolation and determination of the structure of the estrogens,[1] many investigators have tried to convert the relatively inactive compound equilenin (I) to the naturally occurring hormone 17β-estradiol (II). In hydrogenation studies, for

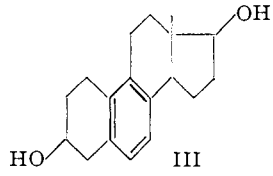


I

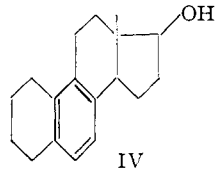


II

example, it has been found that the reaction over a platinum catalyst in acidic solution proceeds by either reducing the phenolic ring A to yield $\Delta^{5,7,9}$-estratriene-3β,17β-diol (III)[2] or by reducing the phenolic ring with concomitant hydrogenolysis to form $\Delta^{5,7,9}$-estratriene-17β-ol (IV).[2–4]



III



IV

With a chemical reducing agent, the reduction of the isomeric 17-dihydroequilenins by sodium and amyl alcohol has yielded the four isomeric $\Delta^{5,7,9}$-estratriene-3,17-diols (III).[2,5–8] In addition, Marker[5] has reported that besides these neutral products, a small yield of the phenolic 17β-estradiol (II) can be isolated (from 1.0 g. of the 17β-dihydroequilenin, 194 mg. of crude phenolic material was received which was converted into 41 mg. of the 3-monobenzoate). This same reduction was studied by Ruzicka, Müller and Morgeli,[2] however, and in their hands no pure phenolic material was obtained. In a similar vein, Marker and his colleagues[9] also reported a reduction of dehydroergosterol to a ring A phenolic material and this again was not able to be repeated by Windaus and Deppe.[10]

During the past decade, the importance of the acidity and the basicity of the media in a catalytic hydrogenation over Raney nickel of a phenol has been established[11–15] as being an important factor

(1) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 306.

(2) L. Ruzicka, P. Müller and E. Morgeli, *Helv. Chim. Acta*, **21**, 1934 (1938).

(3) R. E. Marker, O. Kamm, T. S. Oakwood and F. H. Tendick, THIS JOURNAL, **59**, 769 (1937).

(4) W. E. Bachmann, A. S. Dreiding and E. F. M. Stephenson, *ibid.*, **73**, 2765 (1951).

(5) R. E. Marker, *ibid.*, **60**, 1897 (1938).

(6) R. E. Marker, E. Rohrmann, E. L. Little and F. H. Tendick, *ibid.*, **60**, 2440 (1938).

(7) K. David, *Brevia Neerland. Physiol. Pharmacol. Microbiol.*, **8**, 211 (1938); *C. A.*, **33**, 2528 (1939).

(8) R. D. H. Heard and M. M. Hoffman, *J. Biol. Chem.*, **138**, 651 (1941).

(9) R. E. Marker, O. Kamm, T. S. Oakwood and J. F. Laucius, THIS JOURNAL, **58**, 1503 (1936).

(10) A. Windaus and M. Deppe, *Ber.*, **70**, 76 (1937).

(11) H. E. Ungnade and A. D. McLaren, THIS JOURNAL, **66**, 1181 (1944); H. E. Ungnade and F. V. Morriss, *ibid.*, **70**, 1898 (1948); **72**, 2112 (1950).

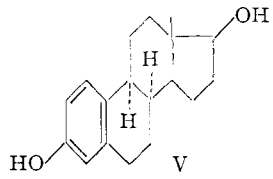
(12) G. Stork, *ibid.*, **69**, 576 (1947).

(13) W. G. Dauben and R. E. Adams, *ibid.*, **70**, 1759 (1948).

(14) L. F. Fieser and M. Leffler, *ibid.*, **70**, 3196 (1948).

(15) W. G. Dauben, C. F. Hiskey and A. H. Markhart, Jr., *ibid.*, **73**, 1393 (1951).

not only in the control of hydrogenolysis but also in the control of the course of the partial hydrogenation of a compound. Utilizing these new techniques for control of the reaction, the hydrogenation of equilenin has been reinvestigated. It was found that when the reaction was conducted in alkaline solution over W-5 Raney nickel at 2800 p.s.i. and 115°, the non-phenolic isomer III was formed in 50% yield. In addition, 24% of a crystalline phenolic fraction was isolated which after extensive purification amounted to 14%. The compound analyzed for a hexahydroequilenin, *i.e.*, a compound formed by reduction of the 17-keto group and ring B. Confirming this phenolic tetrahydronaphthol structure was the ultraviolet spectrum which showed a maximum at 280 mμ (log ε 3.5), characteristic of an estradiol system[16] and in contrast to the maximum at 269 mμ (log ε 2.57) possessed by the non-phenolic isomer III. The properties of this new phenol as well as those of 17β-estadiol II and an isoestradiol V, a compound previously prepared by the hydrogenation of



V

equilin[17] and thought to differ from II by having an 8α-hydrogen atom (*cis* B/C ring juncture), are listed in Table I.[18]

TABLE I

PHYSICAL PROPERTIES OF THE PHENOLIC TETRAHYDRO-17-DIHYDROEQUILENINS

	Phenolic redn. product	"8-Isoestradiol"[17]	β-Estradiol[19,20]
Diol, m.p., °C.	181	181	178
$[\alpha]_D$	+28° (alc.) +17° (diox.)	+18° (diox.)	+81° (alc.)
3-Benzoate, m.p., °C.	186.5	190	195
$[\alpha]_D$	+10° (diox.)	+9.5° (diox.)	+60° (diox.)
Diacetate, m.p., °C.	80	.....	127
Diol pptn. by digitonin	Negative	Negative	Positive

It is seen that the equilenin hydrogenation product appears to be identical with the isoestradiol obtained from equilin, but a direct comparison with an authentic sample was not possible. It is interesting to note that the isoestradiols and 17β-estradiol melt in the same range and it was found that the phenolic material from equilenin hydrogenation did not depress the melting point of 17β-estradiol upon admixture. Thus, the present experiments represent the first transformation of equilenin to an estradiol-type structure, albeit to the unnatural isomer, by catalytic hydrogenation.

Since the hydrogenation of 2-naphthol under acidic conditions has been reported to occur preferentially in the non-hydroxylated ring,[12] equilenin also was studied under these conditions. It was found, however, that the major product (70%) was the non-phenolic isomer III. A 12% yield of a phenolic fraction was obtained, but the material could not be obtained in crystalline form and could not be shown to be homogeneous.

It has also been reported by Stork[12] that when the methyl ether of 2-naphthol is reduced under acidic conditions, the predominant product formed is the *ar*-isomer, 6-methoxy-1,2,3,4-tetrahydronaphthalene. When equilenin methyl ether was hydrogenated under these conditions, a single tetrahydro-3-methoxy-17-dihydroequilenin derivative was formed. The ultraviolet spectrum of the material (λ_{max} 269 mμ, log ε 2.66) was almost identical with that of $\Delta^{5,7,9}$-estratriene-3,17-diol (III) and clearly established the material as the undesirable 1,2,3,4-tetrahydro isomer.

In view of the foregoing results, one can evaluate the effect of the medium on the course of hydrogenation of substituted naphthols. It is seen that in the free phenol, equilenin, the preferred attack, irrespective of acidity or basicity, is on the hydroxylated ring. With the methyl ether of this steroid, hydrogenation under acidic conditions goes exclusively in the hydroxylated ring. These results are to be compared with those of Stork[12] in which it was found that with 2-naphthol preferential attack of one ring or the other could be obtained, the phenolic ring being attacked under basic conditions and the non-substituted ring under acidic conditions. Furthermore, with 2-naphthyl methyl ether, hydrogenation occurred exclusively in the unsubstituted ring. It is apparent from the results in the present study that no correlation of acid–base effects exists between the phenolic sterols and the parent 2-naphthol. In addition, if one compares the results obtained previously in this Laboratory with 6-hydroxy-1(and 2)-naphthoic acid,[15] it would appear that the generalized theory of acidity control of catalytic hydrogenation developed by Stork[12] finds application only in the specific case of 2-naphthol.

Returning to the stereochemical considerations of the estradiol isomers formed by hydrogenation, the 17β-configuration can be assigned to the 8-isoestradiol since the molecular rotational difference, [M-17-ol] − [M-17-one], is +187° as compared to 169° for 17β-estradiol and estrone.[21] As for the $\Delta^{5,7,9}$-estratriene-3,17-diols, if it be assumed that in the reduction by sodium and amyl alcohol of the 17α- and 17β-dihydroequilenins[22] the 17-position re-

TABLE II

CONFIGURATION AND PROPERTIES OF $\Delta^{5,7,9}$-ESTRATRIENE-3,17-DIOL

Configuration	Diol M.p., °C.	Diol $[\alpha]_D$	Diacetate
3β,17β	168	0 (±5)	117
3α,17β	193	+68°	128
3β,17α	171	−49	147
3α,17α	181	+31	91

(16) W. V. Mayneord and E. M. F. Roe, *Proc. Roy. Soc.* (*London*), **A158**, 634 (1937).

(17) A. Serini and W. Logemann, *Ber.*, **71**, 186 (1938).

(18) The 17α-estradiol is not considered since it possesses a m.p. of 223° and an $[\alpha]$ +54°.[19]

(19) B. Whitman, O. Wintersteiner and E. Schwenk, *J. Biol. Chem.*, 118 (1937).

(20) O. Wintersteiner, THIS JOURNAL, **59**, 765 (1937).

(21) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 206.

(22) These configurations are opposite to those used by the earlier worker,[2-8] see C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

tains its original configuration and since a 3α-compound has a more positive rotation than its 3β-isomer, the four epimers[7] can be assigned the configurations listed in Table II. On the basis of these configurations, the product formed in the hydrogenation in the present work is the 3β,17β-isomer.

Acknowledgment.—The authors are indebted to the Parke–Davis Co. for their generous supply of the equilenin used in this study.

Experimental[23]

Hydrogenation of Equilenin. (a) Basic Solution.—A mixture of equilenin (1.0 g., m.p. 258–259° with development of equilenin red color in open capillary, m.p. 271–272° in evac. capillary), 4 ml. of W-5 Raney nickel[24] and 135 ml. of 2.5% potassium hydroxide solution was hydrogenated at 85° and an initial pressure of 2800 p.s.i. (25°). After two hours, the reaction was complete and the cooled mixture diluted with 2% potassium hydroxide and benzene. The two-phase mixture was warmed, with stirring, until all organic material dissolved and then was filtered through Super-cel. The benzene layer was separated and the alkaline layer extracted with benzene. The combined benzene solutions were reëxtracted with 2% potassium hydroxide.

The alkaline solution was acidified, and, after digestion, the solid was filtered, yield 250 mg. (25%), m.p. 160–173°, $[\alpha]^{25}D$ +20° (alc.). The material was chromatographed on neutral alumina and the ether eluate yielded 188 mg. of solid. Crystallization of the material afforded colorless needles, m.p. 180.5–181.5°, $[\alpha]^{21}D$ +28° (alc.), $[\alpha]^{27}D$ +17° (diox.).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.14; H, 8.93.

The reported values for 8-isoestradiol[17] are m.p. 181°, $[\alpha]$ +18° (diox.). The 3-benzoate was prepared according to the procedure of Serini and Logemann[17] and recrystallized from dilute ethanol, m.p. 183–186°, $[\alpha]^{21}D$ +10° (diox.). The reported values[17] are m.p. 190°, $[\alpha]$ +9.5° (diox.).

A diacetate was prepared following the procedure employed by Whitman, Wintersteiner and Schwenk[19] with 17β-estradiol, m.p. 79.6–80.6° (reported[18] for 17β-estradiol diacetate, m.p. 126–127°).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.12; H, 7.92. Found: C, 73.66; H, 9.72.

The neutral fraction in benzene solution was isolated by evaporation of the solvent and then recrystallized from dilute acetone, yield 513 mg. (50%), m.p. 160–168°, $[\alpha]^{26}D$ +5.6° (alc.). The material was chromatographed on neutral alumina and only one fraction was eluted and that with ether. The $\Delta^{5,7,9}$-estratriene-3β,17β-diol was recrystallized from dilute methanol, m.p. 165–167.5°, $[\alpha]^{23}D$ +1° (±2) (alc.) (reported[8] m.p. 168°, $[\alpha]$ −5° (±4) (alc.)).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.24; H, 9.01.

The diacetate was prepared according to the procedure of Heard and Hoffman[8] and recrystallized from dilute ethanol, m.p. 111–113° (lit.[8] 115°).

(b) **Acidic Solution.**—A mixture of equilenin (1.0 g.) in 70 ml. of absolute ethanol, 0.6 ml. of glacial acetic acid and one teaspoon of W-5 Raney nickel[24] was hydrogenated at 115° and initial pressure of 2700 p.s.i. (25°). After two hours, the uptake of hydrogen had ceased. The reaction was cooled and the catalyst filtered. After evaporation of the solvent, the residue was dissolved in ether and the ethereal solution extracted with 2% potassium hydroxide solution to afford 130 mg. of a crude phenolic material which failed to crystallize.

The neutral fraction was isolated and purified as described above and 740 mg. of $\Delta^{5,7,9}$-estratriene-3β,17β-diol, m.p. 158–160°, was obtained.

Hydrogenation of Equilenin Methyl Ether.—A solution of equilenin methyl ether (757 mg., m.p. 196.0–196.5°) in 75 ml. of methanol, 0.5 ml. of glacial acetic acid and 1 teaspoon of W-5 Raney nickel[24] was hydrogenated at 100° and an initial pressure of 2800 p.s.i. (25°). After one hour, the reaction had stopped and the catalyst was filtered from the cooled mixture. The solvent was removed under reduced pressure and the residue chromatographed on neutral alumina. The only material obtained was eluted with ether–benzene (2:1), yield 650 mg. (84%), m.p. 142–149°. The material was recrystallized from dilute ethanol, yield 377 mg., m.p. 150–154°, $[\alpha]^{25}D$ 0 (±3°) (MeOH), λ_{max} 269 mμ, log ε 2.7.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.77; H, 9.30.

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(23) All analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

(24) H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

Acid Catalysis in the Isomerization of 5α,6β-Dibromocholestane

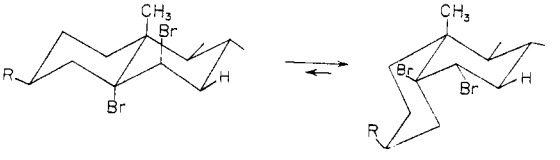
BY HAROLD KWART AND LEWIS B. WEISFELD

RECEIVED JUNE 28, 1955

General acid catalysis has been shown to occur in the isomerization of 5α,6β-dibromocholestane. The significance of this observation in the light of the most recent suggestions for the mechanism of the fundamental mutarotation reaction is discussed. The dependence of the rate on acid concentration is correlated with molecularity in acid. Mechanisms for the acid-catalyzed reaction are considered which correlate both with these rate results and the results of experiments using mixed acid catalysts. Some consideration is given to the question of general acid catalysis in media of very low polarity.

Introduction

Barton and co-workers[1,2] have shown that the dibromide resulting from addition to cholesterol possesses the 5α,6β-configuration (I) and may be readily isomerized to the 5β,6α-configuration (II) Thus when the 3β-substituent (R) is hydrogen, as in the dibromocholestane, the transition of "labile" to "stable" is essentially complete and as the size of this substituent is increased the equilibrium



I (labile) II (stable)

constant becomes progressively smaller.[3] Barton and Miller[1] proposed that isomerization proceeded through the β-bromonium ion III and the reverse process through the α-bromonium ion IV

(1) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(2) D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

(3) C. A. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952).