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

16,17-DIHYDROXYEQUILENANE DERIVATIVES. THE DESOXYEQUILENIN ANALOG OF ESTRIOL[1]

A. L. WILDS, RUTH H. ZEITSCHEL,[2] REID E. SUTTON,[3] AND JAMES A. JOHNSON, JR.[4]

Received September 9, 1953

The three-step process reported by Wilds and Beck in 1944 (1) for preparing 14,15-dehydro-16-equilenone (I) from 2-methyl-1-ketotetrahydrophenanthrene provides the shortest method yet devised for attaching a ring D of the steroids to a tricyclic ketone. The method goes in high over-all yield (70–80% for I) and is applicable to the synthesis either of partially aromatic (*e.g.* 3-methoxy-1,3,5,14-estratetraene-16-one) (2) or non-aromatic steroids (*e.g.* $\Delta^{8\text{-}9,\ 14\text{-}15}$-etiocholadiene-3,16-dione and related compounds) (3). In view of this, it has been attractive to study the introduction of appropriate 17-substituents as a means of synthesizing the ring D structures of the natural steroids. The Δ^{14}-unsaturated 16-ketone structure has provided an unusually versatile intermediate suitable for introduction of the varied C_{17} side chains and substituents found in the natural products. The present paper is concerned with the introduction of 17-oxygen substituents into I and conversion to the 16,17-dihydroxy and 17-hydroxy structures which characterize ring D of the estrogenic hormones. Future papers will report extensions of these reactions to other Δ^{14}-16-ketones and the introduction of 17-carboxyl and other substituents.

Wilds and Beck (1) found that the unsaturated ketone I could be substituted at C_{17} with an oximino group by reaction with butyl nitrite and potassium *tert*-butoxide. Acid hydrolysis of this derivative in the presence of formaldehyde gave the 16,17-diketone II in 80–87% over-all yield. Doban has found that the same diketone may be prepared in yields as high as 93% by selenium dioxide oxidation of I (4).

The diketone II underwent hydrogenation readily to give a single dihydro compound, which proved to be the conjugated ketol III (5). The stereoisomer obtained in as high as 90% yield has now been shown to have the 17β-hydroxy configuration. Reaction of III with ethanedithiol led to the mercaptole VIIIa, which was readily acetylated to the acetoxy derivative VIIIb. Raney nickel desulfuration was accompanied by reduction of the double bond and ring A when the freshly-prepared catalyst was used. With aged Raney nickel, the aromatic ring was not affected and the 17-acetoxy derivative Xb was obtained from VIIIb. This was shown to have the 17β configuration (as well as *trans* C:D rings) by comparison with the ester obtained by lithium aluminum hydride

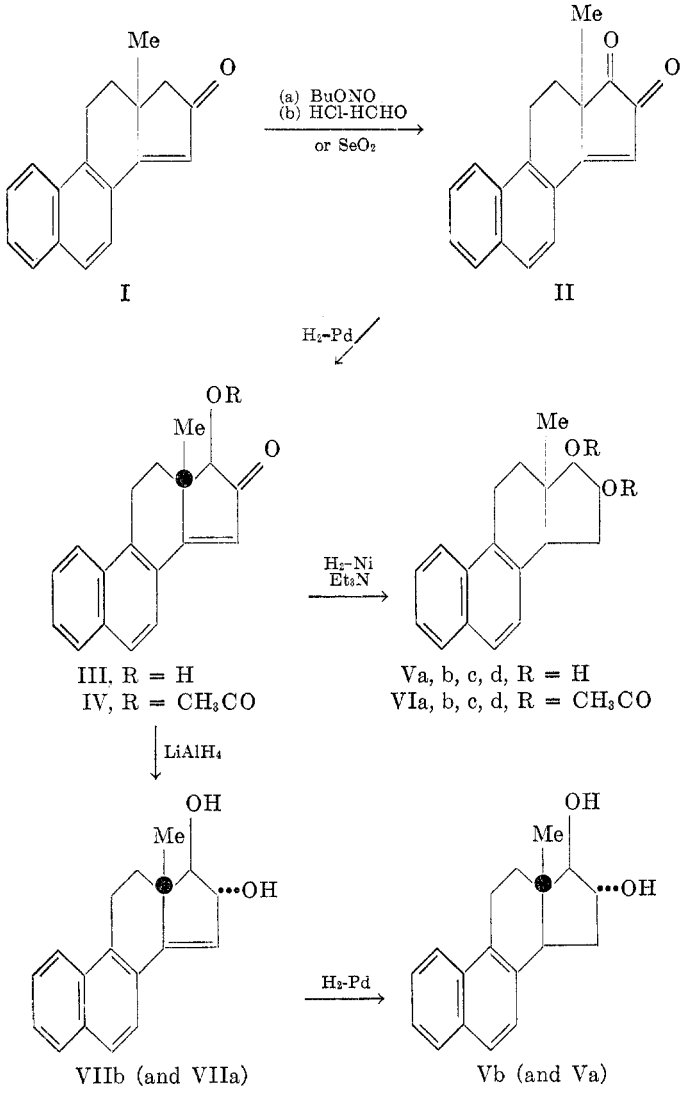
[1] Presented at the W. E. Bachmann Memorial Session, Organic Chemistry Division, American Chemical Society, Chicago Meeting, September 8, 1953.

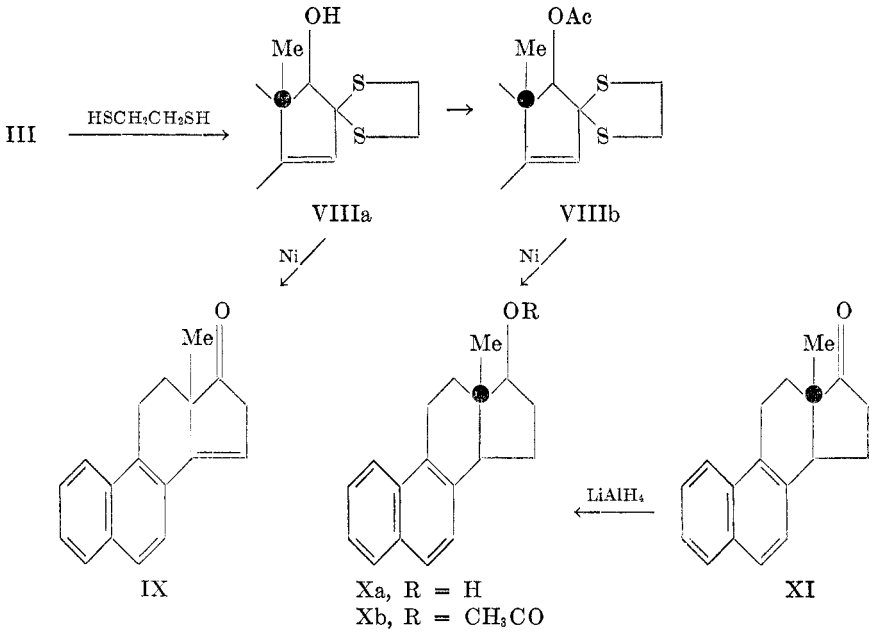
[2] Ph.D. Thesis, 1950. Present address: Rohm and Haas Co., Philadelphia, Pa.

[3] Ph.D. Thesis, 1949. Present address: Shell Oil Co., Wood River, Ill.

[4] Wisconsin Alumni Research Foundation Research Assistant, 1946–1947; Eli Lilly Fellow, 1947–1948. Present address: Southern Research Institute, Birmingham, Ala.

reduction and acetylation of *trans*-17-equilenone (XI). Such reductions of 17-keto steroids having a *trans*-C:D ring are known to give predominately the 17β-configuration (6). Huffman (7) has used a similar mercaptole desulfuration sequence to determine the configuration of a 17-acetoxy-16-ketone in the androstene series. When the hydroxy mercaptole VIIIa was subjected to similar treatment with aged Raney nickel catalyst, desulfuration was accompanied by dehydrogenation to the 17-ketone. About 19% of the 14,15-dehydro-17-equilenone (IX) of Johnson, Petersen, and Gutsche (8) was isolated as well as 3% of the saturated ketone XI. The possibility that such a dehydrogenation could occur, followed by hydrogenation with inversion, requires that the ester

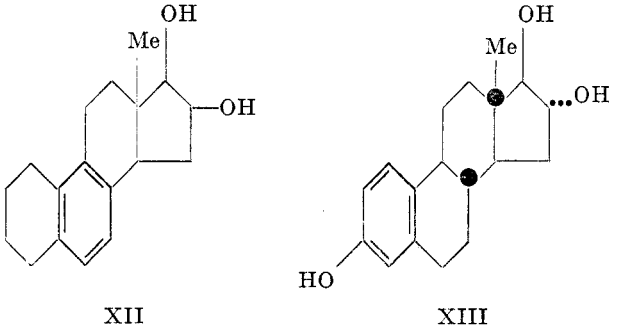




of a hydroxy mercaptole be employed if this type of desulfuration sequence is to lead to an unequivocal stereochemical conclusion.

The unsaturated diketone II was resistant to reduction beyond the dihydro stage (III) with palladium under conditions which give selective reduction of the double bond with I. In acetic acid containing a trace of perchloric acid this catalyst gave further reduction, although it was difficult to control and resulted in a mixture of diols.

More selective hydrogenation could be effected with W-6 Raney nickel (9) at atmospheric pressure. Although a similar catalyst was found earlier (1) to give reduction of one ring forming XII, in the present study triethylamine was added to the solvent to inhibit reduction of the aromatic ring (9) and give the diols of structure V.



XII XIII

The stereochemistry of the nickel reduction, however, was not specific. Although the isomer isolated in largest amount (25–30%) was the 16β,17β-diol with

trans rings (isomer a) the three other isomers possible starting with the 17β-ketol III also were obtained. The *cis*-16β,17β-diol (isomer c) was obtained in smaller amounts (8%) but only traces (1–4%) of the 16α,17β-diols were isolated. The diols themselves were difficult to separate, tending to crystallize as mixtures. The best separation employed chromatography and recrystallization of the diacetates.

Since estriol has been shown by Huffman (7)[5] to have the 16α,17β-configuration XIII, a selective route to this stereoisomer was needed. This was accomplished in a two-step sequence from III. Reduction of this ketol with lithium aluminum hydride gave the unsaturated diol which was largely the 16α,17β isomer VIIb. In contrast to the ketol this diol underwent hydrogenation easily and stereospecifically with a palladium catalyst to give the C:D *trans* rings. The major product was the *trans* 16α,17β-diol Vb, accompanied by lesser amounts of the *trans* 16β,17β-diol Va. This route constitutes a relatively short and stereospecific synthesis of the D ring characteristic of estriol from a tricyclic ketone.

The configurations of the four racemic diols obtained from the ketol III were determined relative to the methyl group at C_{13}. For simplicity we will consider this problem in terms of that enantiomorph having the methyl group projecting above the plane of the ring system, *i.e.* β, although the proof applies equally to the other enantiomer. The C_{14} configuration was determined by heating the diol with potassium bisulfate, the reaction used by Butenandt (10) to show the relationship between estriol and estrone. Such a dehydration with isomer a (m.p. 234°), the major isomer from a nickel reduction of III, gave *trans*-17-equilenone (XI); thus, isomer a has a *trans* C:D ring (14α). Similarly dehydration of isomer b (m.p. 182°) gave *trans*-17-equilenone. Isomer c (m.p. 100.5°), on the other hand, gave *cis*-17-equilenone (19, 11) and must have the 14β (*i.e.* *cis*)-configuration. It is interesting to note that in each case the 16-hydroxyl group was that eliminated, at least in the major product. Presumably, then, relative steric hindrance is the controlling factor here.

Since the diols were obtained from the ketol III which was established to have the 17β-configuration, the only remaining stereochemical point is the configuration at C_{16}. The method of Van Loon, Boeseken, and Derx (12) for establishing the configuration of 1,2-glycols in the cyclopentane and cyclohexane series, the ready formation of an acetone ketal from the *cis*-glycol and failure with the *trans*-glycol, has become standard for this purpose. Huffman and Lott (7) made good use of the method in the case of estriol stereoisomers. Isomer a readily formed the ketal with acetone containing hydrogen chloride; isomer c similarly formed the acetonide. These must be the *cis* diols, and since the 17β-configuration is already established these become the *trans* 16β,17β- and *cis* 16β,17β-diols, respectively. Isomer b, on the other hand, was recovered un-

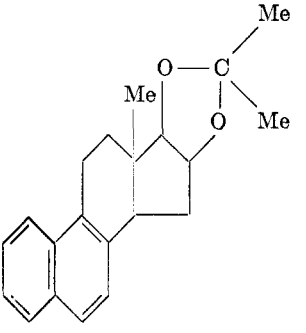
[5] The 16β,17α-configuration given in Ref. 7 is based on the older formulation of natural estradiol as 17α; with the revision of the latter to 17β (see Ref. 6), the estriol configuration became 16α, 17β.

TABLE I

16,17-DIHYDROXYEQUILENANES (V) AND DERIVATIVES

ISOMER	CONFIGURATION		M.P., °C. OF		
	C:D	OH	Diol	Diacetate	Acetonide
a	*trans*	16β,17β	233.5–234	172–174	199–200
b	*trans*	16α,17β	181.2–182	191.6–192.4	—
c	*cis*	16β,17β	99.8–100.4	116.5–118.5	158–159
d	*cis*	16α,17β	126–129	81–82.5	—

changed after similar treatment with acetone; it must, therefore, be the *trans*-16α,17β-diol, identical in configuration at the four asymmetric centers to natural estriol. The fourth diol (isomer d, m.p. 129°) was obtained in quantities too small to test, but it is reasonable to presume it to have the remaining configuration, the *cis*-16α,17β-diol. These results are summarized in Table I.



XIVa, C:D *trans*
XIVb, C:D *cis*

In addition to providing a good route to the 16α,17β-dihydroxy derivative, the Δ^{14}-16-ketone I can be used to prepare the 17β-hydroxy and 17-keto derivatives by selective elimination of the 16-keto group. The first method for accomplishing this was described in 1944 (1), since periodic acid cleavage of the diketone II followed by reduction of the unsaturated dibasic acid gave the same saturated acid used by Bachmann and Wilds (19) in their synthesis of desoxyequilenin (XI). The two methods are comparable in length and yields. In the present study desulfuration of the mercaptole VIIIa to the unsaturated ketone IX provides a shorter approach to the ketone XI, while desulfuration of the acetoxy mercaptole VIIIb leads more directly to the 17-hydroxy function. Since dehydration of both isomers a and b of the diol V gave the *trans*-17-ketone XI, dehydration of the mixture as obtained from III by lithium aluminum hydride reduction and palladium hydrogenation provides still another method. The yield of XI from the ketol III is at least 30%, and this like the yields for the previous methods undoubtedly can be raised appreciably by further study of conditions.

EXPERIMENTAL[6]

β-1-Naphthylethyl bromide. In following the procedure of Newman (13) for converting naphthylethyl alcohol (14) to this bromide using hydrobromic acid, the 80% sulfuric acid wash was found to be unnecessary and it led to lower yields (71–82%). With this operation omitted the yield of bromide was as high as 90% (Calc'd, for $C_{12}H_{10}Br$: Br, 34.0. Found: Br, 33.8).

14,15-Dehydro-16-equilenone (I). Most of the remaining steps in this synthesis were carried out essentially as described by Wilds and Beck (1) with yields at least as high as those reported. The preparation of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetic acid was carried out on a scale up to 30 g. using freshly prepared sodium amide in toluene as indicated by Wilds and T. L. Johnson (15) except heating at 55° for 15–20 hours before adding the bromoester. The yield of recrystallized acid was 76–82%, most melting at 149–151°. The yield of methyl ketone in the next step was as high as 90%, with 5% of recovered acid.

16,17-Diketo-14,15-dehydroequilenone (II). (*a*) The unsaturated ketone I was converted to the oximino derivative and hydrolyzed as described (1), giving the diketone II in 83–87% over-all yield from I.

(*b*) (By Robert C. Doban) (4) A mixture of 245 mg. of the unsaturated ketone I, 110 mg. of freshly sublimed selenium dioxide, and 30 cc. of purified dioxane was heated at reflux under nitrogen for three hours. The cooled mixture was filtered through a short column of Filter-Cel and the crude product was sublimed at 170° (0.01 mm.) giving 240 mg. (93%) of the diketone, m.p. 199–202°. Recrystallization from benzene-ethanol gave a sample, m.p. 204.2–205.4° that did not depress the m.p. of an authentic sample of II.

17β-Hydroxy-14,15-dehydro-16-equilenone (III). The hydrogenation of the above diketone II proceeded better in acetic acid than in dioxane as reported previously. Hydrogenation of 1.0 g. of the diketone with 0.1 g. 30% palladium-on-carbon catalyst (16) in 105 cc. of acetic acid required one to five hours for uptake of one mole of hydrogen. After filtration and concentration under reduced pressure, the product was crystallized from methanol, 871 mg., m.p. 205–209°, and 31 mg., m.p. 197–202°, for a total of 90%. Further recrystallization from acetone gave colorless crystals, m.p. 210–211°.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.10.
Found: C, 81.9; H, 6.26.

The *acetate* was prepared by warming 50 mg. of the ketol, 0.1 ml. of acetyl chloride, and 0.15 ml. of pyridine; 45 mg., m.p. 172–175°. Recrystallization from methanol-acetone gave colorless needles, m.p. 176–176.5°.

Anal. Calc'd for $C_{20}H_{18}O_3$: C, 78.4; H, 5.92.
Found: C, 78.7; H, 6.04.

17β-Hydroxy-14,15-dehydro-16-equilenone 16-ethylene mercaptole (VIIIa). To a suspension of 383 mg. of the hydroxy ketone in 25 cc. dry ether was added 1.33 cc. of ethanedithiol, and a stream of dry hydrogen chloride was passed into the cooled mixture for 15 minutes (17), during which time the ketol dissolved and the product reprecipitated. The crude mercaptole, isolated by filtration and washing with cold ether, amounted to 396 mg. (80%), m.p. 210–217° (vac.). One recrystallization from ethanol-acetone gave 371 mg. (75%) of prismatic needles, m.p. 220.5–222°, raised to 222–223° (vac.) by further recrystallization.

Anal. Calc'd for $C_{20}H_{20}OS_2$: C, 70.5; H, 5.92.
Found: C, 70.3; H, 5.81.

The *acetate* VIIIb was prepared by heating 300 mg. of hydroxy mercaptole with 5 cc. of acetic anhydride at reflux for 2 hours, then removing the solvent *in vacuo*. Recrystallization

---

[6] All melting points are corrected; those designated micro m.p. were taken on a microscope hot stage; vac. m.p.s. were determined in sealed Pyrex capillaries evacuated to 0.5 mm. or lower. Microanalyses for carbon and hydrogen were run by Virginia Miller, Richard Hunt, Bennett Buell, Edward Shiner, John Belew, and Gerald Gilbert. Ultraviolet spectra were determined in 95% alcohol using the Beckman DU instrument.

from ethanol-acetone gave 313 mg., m.p. 187.5–189° and 9 mg., m.p. 185–187° (96% yield); analytical sample, small prisms, m.p. 189.2–189.9° (vac.)

Anal. Calc'd for $C_{22}H_{22}O_2S_2$: C, 69.1; H, 5.80.
Found: C, 69.1; H, 5.92.

Desulfuration of 17β-hydroxy-14,15-dehydro-16-equilenone 16-ethylene mercaptole; 14,15-dehydro-17-equilenone (IX). A solution of 200 mg. of the hydroxy mercaptole VIIIa in 40 cc. of purified dioxane and 1 cc. of water was heated at the reflux with 0.25 teaspoonful of aged Raney nickel catalyst (ten weeks old) (18). After 4½ hours, the test for sulfur in a filtered portion had become negative (following sodium fusion), and the solution was filtered and concentrated to an orange oil. Two recrystallizations from methanol gave 27 mg. (19%) of 14,15-dehydro-17-equilenone, m.p. 132–133.5°, raised to 135–136° by further recrystallization and undepressed in m.p. by admixture with an authentic sample provided by Dr. W. S. Johnson (8).

Anal. Calc'd for $C_{18}H_{16}O$: C, 87.1; H, 6.50.
Found: C, 86.9; H, 6.60.

The material in the filtrate was treated with a total of 200 mg. of 30% palladium-on-carbon catalyst and hydrogen in ethanol, with no measurable uptake of gas, but the material then afforded after several recrystallizations from methanol 4 mg. (3%) of *trans*-17-equilenone, m.p. 190.5–191.5° (vac.), mixture m.p. undepressed (19). An additional 9 mg. of a semicarbazone mixture, m.p. 237–240° (dec.), was obtained from the filtrates, together with 46 mg. of an oil.

Desulfuration of 17β-acetoxy-14,15-dehydro-16-equilenone 16-ethylene mercaptole (VIIIb). A mixture of 50 mg. of the acetoxy mercaptole, 10 cc. of purified dioxane, 0.2 cc. of water, and 0.15 teaspoonful of aged Raney nickel (four weeks old) (18) was heated at gentle reflux with stirring until the test for sulfur was negative (5⅔ hours). Filtration and evaporation left an oil which was recrystallized from methanol and ethanol to give 9 mg. of *trans*-17β-acetoxyequilenane (Xb), m.p. 162–166°. After further recrystallization the material of m.p. 165–168° showed no depression when admixed with the authentic specimen prepared below (m.p. 165.5–167°). The ultraviolet absorption spectrum showed maxima at 230 mμ (log ε 4.99), 286 mμ (3.75), 322 mμ (2.94), and minima at 245 mμ (3.12) and 318 mμ (2.53).

trans-17β-Hydroxyequilenane (Xa). Reduction of 45 mg. of *trans*-17-equilenone (XI) (19) with 23 mg. of lithium aluminum hydride in 50 cc. of ether at reflux for 15 minutes, followed by hydrolysis, extraction with benzene, and crystallization from methanol gave 40 mg. of the impure alcohol, m.p. 113–126°. This was heated with 1.5 cc. of acetic anhydride at reflux for 1 hour, the reagent was removed *in vacuo*, and the residue was crystallized three times from ethanol giving 25 mg. of *trans*-17β-acetoxyequilenane (Xb), m.p. 164–168°. The analytical sample melted at 169.5–170.5°.

Anal. Calc'd for $C_{20}H_{22}O_2$: C, 81.6; H, 7.53.
Found: C, 81.6; H, 7.87.

Hydrolysis of the acetate with 0.05 *N* sodium hydroxide in 85% ethanol (heating 1 hour) and crystallization of the product from methanol gave *trans*-17β-hydroxyequilenane (Xa), m.p. 115.5–116°, (dried 8 hours at 80° and 0.1 mm. to remove solvent of crystallization).

Anal. Calc'd for $C_{18}H_{20}O$: C, 85.7; H, 7.99.
Found: C, 85.8; H, 8.39.

Hydrogenation of 17β-hydroxy-14,15-dehydro-16-equilenone (III). A solution of 1.0 g. of the ketol in 100 cc. of purified dioxane containing 0.7 cc. of triethylamine was stirred with hydrogen and about 200 mg. of W-6 Raney nickel catalyst (three to four days old) (9). During the 9–22 hours required for uptake of 2.0–2.2 moles of hydrogen, three to five 200-mg. portions of catalyst were added. After removing the catalyst and solvent, the residue was crystallized three times to give 207–276 mg. of isomer a (*trans*-16β,17β-dihydroxyequilenane Va), m.p. 225–230°. Acetylation of 40 mg. of this material gave after recrystallization from ethanol 43 mg., m.p. 170–174°. The analytical sample of *isomer a diacetate* (VIa) melted at 172–174°.

Anal. Calc'd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.86.
Found: C, 74.7; H, 6.67.

Recrystallization of the remaining material usually gave diol mixtures, although in one run 10 mg. of isomer b was isolated, m.p. 172–174.5° (mixture m.p. 175–178°; see below). The material in the filtrates was heated with acetic anhydride for 2 hours and the product was crystallized from methanol to give 212 mg. of a mixture, m.p. 132–142°, not adequately separated either by further recrystallizations or by chromatography on alumina. The remaining oily diacetate mixture was chromatographed on 17 g. of alumina. Fractions 1–13, eluted with petroleum ether, gave 90 mg. of oil from which 8 mg., m.p. 145–148°, was crystallized; the ultraviolet spectrum indicated this material to have one ring reduced corresponding to XII (cf. Ref. 1). Fractions 14–26, eluted with petroleum-ether-benzene (10:1) gave 50 mg. of oil from which was crystallized with methanol 36 mg. of the *diacetate of isomer d* (probably *cis*-16α,17β-diacetoxyequilenane, VId), m.p. 81–82.5°.

Anal. Calc'd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.86.
Found: C, 74.7; H, 6.85.

Fractions 27–29, eluted with petroleum ether-benzene (1:1) gave 140 mg. of a mixture from which no pure material was isolated. Fractions 30–34, eluted with benzene, gave 161 mg. of colorless solids, recrystallized from petroleum ether to afford 101 mg. of the *diacetate of isomer c* (*cis*-16β,17β-diacetoxyequilenane), m.p. 113–115°. The analytical sample melted at 116.5–118.5°.

Anal. Calc'd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.86.
Found: C, 74.8; H, 6.94.

From the remaining material a small amount of impure diacetate of isomer a was isolated.

Hydrogenation of 16,17-diketo-14,15-dehydroequilenane (II). From a similar hydrogenation of 1.0 g. of this diketone in dioxane with W-6 Raney nickel (9) and triethylamine (3 moles uptake) 50–127 mg., m.p. 225–229° (vac.) of isomer a (Va) was isolated, together with a mixture of other isomers. From one run 5 mg. of solid, m.p. 141–142.5°, was isolated which corresponded to the decahydro derivative XII of Wilds and Beck (1); the ultraviolet spectrum, maxima at 224 mμ (log ϵ 3.01), 269 mμ (2.84), 278 mμ (2.85), was consistent with this structure.

16,17-Dihydroxy-14,15-dehydroequilenane (VIIb). (*a*) *By lithium aluminum hydride reduction.* A solution of 100 mg. of the 17-hydroxy-16-keto-derivative III in 100 cc. of dry ether was added to 50 mg. of lithium aluminum hydride dissolved in 35 cc. of ether. After heating for 30 minutes, cooling, and adding water, the product was extracted with several portions of ether, 103 mg., m.p. 142–146°. The melting point was not a reliable criterion of purity, fluctuating on repeated recrystallizations from ether or benzene from 151.5–153.5° to 164–167.5°. The sample for analysis, dried at 65° and 0.1 mm. for 15 hours, melted at 164–165.5°.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.81.
Found: C, 80.7; H, 7.11.

(*b*) *By sodium amalgam reduction.* Using a procedure similar to that of Huffman (20), 200 mg. of the ketol III, dissolved in 50 cc. of ethanol and 5 cc. of acetic acid, was maintained at 40° while 100 g. of freshly prepared 2% sodium amalgam was added in small pieces, with swirling, over a period of 80 minutes. After the first 60 minutes, 6 cc. of 50% acetic acid was added to keep sodium acetate in solution. At the end of the reduction water and ether were added, and the extract was washed with water and 0.5 *N* sodium hydroxide and dried over sodium sulfate. The diol was recrystallized from benzene-petroleum ether, giving 65 mg., m.p. 153–155°, and 84 mg. of a different product, m.p. 102–105°. Further recrystallization of the first crop gave material fluctuating in m.p. from 151.5–153.5° to 163–164°. For analysis the material was dried at 80° for 7 hours (m.p. 149–153°).

Anal. Found: C, 81.9; H, 6.7.

The ultraviolet spectrum showed maxima at 254 mμ (log ϵ 4.61), 262 (4.57), 282 (4.08), 292.5 (4.18), 304 (4.10); minima at 258.5 (4.53), 275 (3.96), 286 (4.04), 299 (3.98); and points of inflection at 246 (4.48) and 325 (2.68).

The *diacetate of VIIb*, prepared in low yield by heating with acetic anhydride for one hour, was recrystallized three times from methanol (Norit treatment), m.p. 157.2–157.8°.

Anal. Calc'd for $C_{22}H_{22}O_4$: C, 75.4; H, 6.33.
Found: C, 75.0; H, 6.35.

Hydrogenation of 16,17-dihydroxy-14,15-dehydroequilenane (VII). The crude unsaturated diol isolated from a lithium aluminum hydride reduction of 235 mg. of the ketol III was hydrogenated in 35 cc. of ethanol using 100 mg. of 30% palladium on carbon catalyst (16). After 1½ hours and the uptake of one mole of hydrogen the absorption stopped. Crystallization of the product (230 mg., m.p. 172–180°) from benzene gave 182 mg., m.p. 167–183°, not improved by further recrystallization. Conversion of the recrystallized material to the diacetate and crystallization from cyclohexane gave 128 mg. of the *diacetate of isomer b* (*trans*-16α,17β-diacetoxyequilenane VIb), m.p. 188–191.5°, corresponding to 41% from the ketol. The analytical sample crystallized as platelets, m.p. 191.6–192.4° (vac.).

Anal. Calc'd for $C_{22}H_{24}O_4$: C, 75.0; H, 6.86.
Found: C, 75.3; H, 7.02.

From the filtrates was isolated 67 mg. of the diacetate of isomer a (VIa), m.p. 168–172°, mixture m.p. 170–174°, corresponding to 21% from the ketol.

A similar reduction of the ketol acetate (m.p. 175–176.5°, prepared from 200 mg. of ketol), first with lithium aluminum hydride and then with palladium as described above, gave a mixture which was acetylated and recrystallized from cyclohexane to afford 139 mg. (52%) of the diacetate of isomer b, m.p. 188–191°.

16,17-Dihydroxyequilenane isomers (V). A solution of the diacetate VI was heated with 0.05 to 0.15 *N* sodium hydroxide in 80% ethanol at 60° for 30 to 100 minutes. The diol was isolated by dilution with water and neutralization with acid followed by filtration or extraction. *Isomer a* (*trans*-16β,17β-dihydroxyequilenane) was recrystallized from ethanol, m.p. 233.5–234° (vac.).

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.51.
Found: C, 80.5; H, 7.17.

Isomer b (*trans*-16α,17β-dihydroxyequilenane) was recrystallized from benzene (or cyclohexane-acetone), m.p. 178.6–179.4°. It retained solvent tenaciously in each case, giving analyses for carbon 1 to 2% high (or low) after drying for 9 to 20 hours at 80–100° (0.1 mm.). A sample sublimed at 150° (0.002 mm.) melting at 181.2–182° gave the best results.

Anal. Found: C, 81.1; H, 7.86.

Isomer c (*cis*-16β,17β-dihydroxyequilenane) was recrystallized from petroleum ether-ethanol or cyclohexane-benzene, m.p. 99.8–100.4°.

Anal. Found: C, 80.7; H, 7.63.

Isomer d (probably *cis*-16α,17β-dihydroxyequilenane) was recrystallized from benzene-cyclohexane. It showed evidence of polymorphism, one preparation melting at 65–68° with resolidification and remelting at 126–129°. Usually it was obtained as a powder which changed to needles around 110–115° and melted at 126–129°.

Anal. Found: C, 80.8; H, 7.90.

Dehydration of 16,17-dihydroxyequilenane (V) *to 17-equilenone* (XI). *Isomer a.* The glycol (30 mg.) was ground with 2.0 g. of fused, powdered potassium bisulfate, heated in a sublimation tube at 100° (0.2 mm.) for 2 hours, then at 200° for 3 hours to complete sublimation of the product. Recrystallization of the sublimate from ethanol gave 15 mg. (54%) of *trans*-17-equilenone, m.p. 184–186°, and 2 mg., m.p. 174–180°. Further recrystallization raised the m.p. to 190–191.5° vac., undepressed on admixture with an authentic sample (19).

Isomer b. Similarly 7.5 mg. of this glycol gave 2.5 mg., micro m.p. 105–165°, raised by further recrystallization to 184–187°; mixture m.p. with *trans*-17-equilenone 185–190°.

The crude diol a and b mixture (171 mg.) from hydrogenation of crude 16,17-dihydroxy-14,15-dehydroequilenane gave 71 mg., m.p. 150–168°, and on further recrystallization 45 mg. (28%), m.p. 188.5–192.5°.

Isomer c. From 3 mg. of the diol was obtained about 1 mg. of *cis*-17-equilenone after recrystallization from methanol, micro m.p. 100.5–101.5°; mixture m.p. with an authentic sample m.p. 100–101.5°.

Acetonide formation from 16,17-dihydroxyequilenane. Isomer a. To a solution of 20 mg.

of the diol V in 2 cc. of acetone was added 0.4 cc. of acetone previously saturated at 0° with hydrogen chloride. After 45 minutes at room temperature the solution was poured into dilute potassium carbonate solution and allowed to crystallize in the refrigerator, 18 mg. (78%), m.p. 197–199°. Recrystallization from ethanol gave the acetonide XIVa, m.p. 199–200° (vac.).

Anal. Calc'd for $C_{21}H_{24}O_2$: C, 81.8; H, 7.84.

Found: C, 81.6; H, 7.81.

Isomer b similarly treated gave 97% recovery of the diol, m.p. 176–179°.

Isomer c. A crude sample of diol (18 mg., m.p. 81–90°) gave 15 mg., m.p. 127–151°, which was boiled in petroleum ether with alumina to remove diol. Recrystallization from 80% ethanol gave 5 mg. of acetonide XIVc, micro m.p. 158–159°. Similarly, 1 mg. of pure diol gave about 1 mg. of the acetonide, micro m.p. 158–160°.

Anal. Found: C, 81.6; H, 7.99.

SUMMARY

The readily synthesized 14,15-dehydro-16-equilenone (I) has been used to study the introduction of 17-oxygen substituents, and conversion to the 16,17-dihydroxy analog of estriol, as well as 17-hydroxy and ketone derivatives in the desoxyequilenin series.

The 16,17-diketone (II), prepared by selenium dioxide oxidation or by nitrosation and hydrolysis, was hydrogenated to the 17β-ketol III, the configuration of which was established by desulfuration of the 17-acetoxy-16-ethylene mercaptole.

Raney nickel hydrogenation of the 17β-hydroxy-16-ketone III gave *trans*-16β,17β-dihydroxyequilenane, together with small amounts of the *trans*-16α,17β- and the corresponding *cis*-diols. The best route to the *trans*-16α,17β stereoisomer corresponding to the estriol configuration was lithium aluminum hydride reduction of III followed by palladium hydrogenation.

Dehydration of the diols with potassium bisulfate gave the 17-equilenone (*cis* or *trans*), thereby establishing the C:D ring configurations. The configurations at C_{16} were established relative to that at C_{17} by acetonide formation by the 16β,17β-diols.

These transformations constitute new syntheses of the 17-hydroxy and 17-keto equilenane derivatives from the Δ^{14}-16-keto derivative I.

MADISON 6, WISCONSIN

REFERENCES

(1) WILDS AND BECK, *J. Am. Chem. Soc.*, **66**, 1688 (1944).
(2) WILDS AND T. L. JOHNSON, *J. Am. Chem. Soc.*, **70**, 1166 (1948).
(3) WILDS, RALLS, TYNER, *et al.*, see WILDS, Abstracts, 120th Meeting A.C.S., New York, N. Y., Sept. 4–7, 1951, p. 20M.
(4) ROBERT C. DOBAN, Ph.D. Thesis, Univ. of Wis., 1952.
(5) WILDS, BECK, CLOSE, DJERASSI, J. A. JOHNSON, T. L. JOHNSON, AND SHUNK, *J. Am. Chem. Soc.*, **69**, 1987 (1947).
(6) (a) FIESER AND FIESER, *Natural Products Related to Phenanthrene*. Reinhold Publ. Co., New York, N. Y., 3rd ed., 1949, p. 325 ff. (b) BACHMANN AND DREIDING, *J. Am. Chem. Soc.*, **72**, 1323 (1950).
(7) HUFFMAN AND LOTT, *J. Am. Chem. Soc.*, **69**, 1835 (1947); **71**, 719 (1949).
(8) W. S. JOHNSON, PETERSEN, AND GUTSCHE, *J. Am. Chem. Soc.*, **69**, 2942 (1947).
(9) ADKINS AND BILLICA, *J. Am. Chem. Soc.*, **70**, 695 (1949).

(10) BUTENANDT, *Z. physiol. Chem.*, **191**, 140 (1930); BUTENANDT AND HILDEBRANDT, *Z. physiol. Chem.*, **199**, 243 (1931).
(11) WILDS, J. A. JOHNSON, AND SUTTON, *J. Am. Chem. Soc.*, **72**, 5524 (1950).
(12) VAN LOON, Diss. Univ. Technique Delft, (1919); BOESEKEN AND DERX, *Rec. trav. chim.*, **40**, 519, 529 (1921).
(13) NEWMAN, *J. Org. Chem.*, **9**, 525 (1944).
(14) WILDS, *J. Am. Chem. Soc.*, **64**, 1421 (1942).
(15) WILDS AND T. L. JOHNSON, Ref. 2, footnote 22. See also WILDS AND CLOSE, *J. Am. Chem. Soc.*, **69**, 3081 (1947).
(16) LINSTEAD AND THOMAS, *J. Chem. Soc.*, 1130 (1940).
(17) HAUPTMANN, *J. Am. Chem. Soc.*, **69**, 562 (1947); RALLS, DODSON, AND RIEGEL, *J. Am. Chem. Soc.*, **71**, 3322 (1949).
(18) MOZINGO, *Org. Syntheses*, **21**, 15 (1941).
(19) BACHMANN AND WILDS, *J. Am. Chem. Soc.*, **62**, 2084 (1940).
(20) HUFFMAN, *J. Biol. Chem.*, **169**, 167 (1947).