minutes, with ammonium chloride and water, the ether extract gave 90% yields of the carbinol (IX).

Other analytical data on this compound are contained in the earlier paper[2] (in which this compound was numbered VIII).

4 - Oxy - 2,3 - dimethyl - 1,1,4 - triphenyldihydronaphthalene, IX, m. p. 154°.—This carbinol was formed in 90% yields by the addition of phenylmagnesium bromide to VIII. It is very unstable in the presence of acid and when an alcohol solution of the carbinol was treated with hydrochloric acid, a molecule of water was lost with the formation of the hydrocarbon (IV). IX melts at 154° with the loss of a molecule of water and the formation of the hydrocarbon (IV). Warming with zinc chloride and concd. hydrochloric acid in benzene also converted IX to the hydrocarbon (IV). The Grignard machine showed one active hydrogen. Boiling for one hour with potassium permanganate and potassium hydroxide gave 90% of unchanged material. Boiling for one hour with potassium dichromate in glacial acetic acid gave a solid from which, after many recrystallizations from alcohol and ethyl acetate, it was possible to isolate a small amount of the 235° hydrocarbon. Ozonization of IX in chloroform gave the ketone (V), so dehydration to the hydrocarbon (IV) probably occurred before the reaction with ozone.

Anal. Calcd. for $C_{30}H_{26}O$: C, 89.51; H, 6.51. Found: C, 89.31, 88.95; H, 6.80, 6.75.

The 235° Hydrocarbon.—This compound, isomeric with the 189° hydrocarbon (IV), was formed in small amounts in many attempts to oxidize the hydrocarbon (IV) with potassium dichromate or potassium permanganate in glacial acetic acid or with ozone, and to oxidize the carbinol (IX) with potassium dichromate in glacial acetic acid.

Heating the hydrocarbon (IV) with acetic acid alone or with iodine in acetic acid did not convert it into the high melting isomer. Ozone converted 0.4 g. of the 235° compound into an oil from which no solid material could be obtained. The 235° compound was only slightly soluble in alcohol and in ethyl acetate, but could be crystallized from benzene.

Anal. Calcd. for $C_{30}H_{24}$ (384.2): C, 93.71; H, 6.29. Found: C, 93.84, 93.23; H, 6.29, 6.07; mol. wt. (camphor), 360.

The author wishes to thank the University of Minnesota for the courtesy shown her as an Honorary Fellow of the University while on leave from Vassar College in the spring of 1938.

Summary

Starting with the two di-addition products from the reaction between phenylmagnesium bromide and 2,3-dimethyl-1,4-naphthoquinone, parallel series of reactions lead to the same product, a hydrocarbon.

Structures have been assigned to these two di-addition products, to the two compounds resulting from the dehydration and rearrangement of these compounds, and to four new compounds obtained in these series of reactions.

POUGHKEEPSIE, N. Y. RECEIVED AUGUST 24, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXVI. Oxidation and Reduction Products of Equilenin

BY RUSSELL E. MARKER AND EWALD ROHRMANN

In previous work[1] from this Laboratory it was observed that equilenin when reduced with Adams catalyst in acidic ethanol gave approximately a 70% yield of 5,7,9-estratrienol-17. No other reduction products were isolated. Ruzicka, Müller and Mörgeli[2] in a somewhat similar reduction obtained this same product in addition to some α-dihydroequilenin. By modifying the reduction technique these workers were able to obtain a 5,7,9-estratrienediol-3,17 which was identical with one of the diols obtained by the reduction of equilenin with sodium.[2,3,4]

When the hydrogenation of equilenin is carried out in a neutral medium with Adams catalyst, the essential product is α-dihydroequilenin, a product first isolated from the phenolic fraction of mares pregnancy urine by Wintersteiner and co-workers[5] and later prepared by Marker and co-workers[1] by the reduction of equilenin with aluminum isopropylate. The hydrogenation of α-dihydroequilenin in acidic ethanol yields the same 5,7,9-estratrienol-17 as was obtained from equilenin, indicating that the hydroxyl group at C-17 is of the α-configuration.

In a previous comprehensive investigation of the carbinol fraction of mares pregnancy urine[6] we reported the isolation (from the chromic anhy-

(1) Marker, Kamm, Oakwood and Tendick, THIS JOURNAL, **59**, 768 (1937).

(2) Ruzicka, Müller and Mörgeli, *Helv. Chim. Acta.*, **21**, 1394 (1938).

(3) Marker, Rohrmann, Wittle and Tendick, THIS JOURNAL, **60**, 2440 (1938).

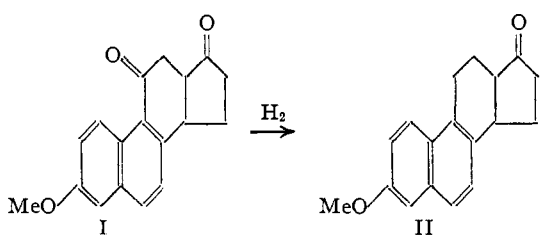
(4) David, *Acta Brevia Neerland Physiol. Pharmacol. Microbiol.*, **8**, 211 (1938).

(5) Wintersteiner, Schwenk, Wirschmann and Whitman, THIS JOURNAL, **58**, 2652 (1936).

(6) Marker and Rohrmann, THIS JOURNAL, **61**, 2537 (1939).

dride oxidation products of a crude carbinol fraction) of a diketone of the composition $C_{18}H_{16}O_2$. This substance formed a mono-semicarbazone, which suggested the presence of a hindered carbonyl group. We now have strong indications that this product is 3-desoxy-11-keto-equilenin. On catalytic hydrogenation in acidic ethanol, it gave a good yield of 5,7,9-estratrienol-17(α) identical with that obtained from equilenin. The fact that the reduction in acidic medium removes the carbonyl group at C-11 is in accordance with the fact that carbonyl groups adjacent to benzenoid ring systems are usually removed on hydrogenation under the proper conditions.

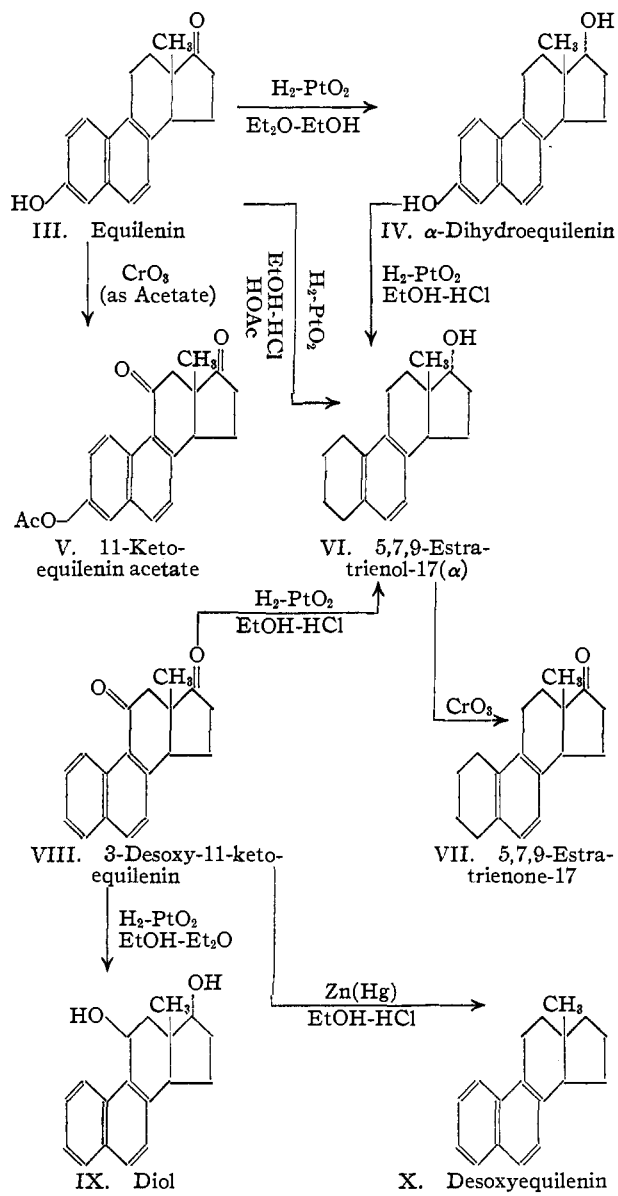
The properties of 3-desoxy-11-ketoequilenin resemble those of the methyl ether of 11-keto-*nor*-equilenin (I) prepared synthetically by Koebner and Robinson.[7] This product (I) formed only a mono-carbonyl derivative and on reduction with a platinum–charcoal catalyst in the presence of palladium chloride yielded the methyl ether of *nor*-equilenin (II).



When the hydrogenation of 3-desoxy-11-keto-equilenin was carried out in a neutral medium the product appeared to be a compound in which the two carbonyl groups were reduced to hydroxyl groups. A mild Clemmensen reduction (unamalgamated zinc) of 3-desoxy-11-keto-equilenin yielded a mono-keto derivative while more vigorous reduction (amalgamated zinc) gave desoxyequilenin.

Inasmuch as the 3-desoxy-11-keto-equilenin was obtained from the oxidation of a ketone free (*i. e.*, non-hindered ketones) carbinol fraction, some question might be raised concerning the nature of the compound before oxidation. It now seems highly probable that the carbonyl group at C-11 was introduced during the chromic anhydride oxidation of the carbinol fraction, inasmuch as equilenin acetate upon oxidation with chromic anhydride yields a product which appears to be 11-keto-equilenin acetate. The substance forms only a mono-semicarbazone. The 11-keto-equilenin acetate was obtained in rather poor yields apparently due to the lability of the product to further oxidation under the conditions used.

The introduction of a carbonyl group into the C-11 position by oxidation of equilenin derivatives with chromic anhydride strongly suggests that the 3-desoxy-11-keto-equilenin obtained from the oxidation of the mares urine carbinol fraction was actually formed by the oxidation of 3-desoxy-dihydroequilenin, thus indicating the presence of this substance in mares pregnancy urine.



Equilenin resembles estrone in that it reacts

(7) Koebner and Robinson, *J. Chem. Soc.*, 1994 (1938).

readily with ethyl chloroacetate and sodium ethylate to yield the acetic acid derivative.[8] Catalytic hydrogenation of equilenin-3-oxy-acetic acid in acidic ethanol yielded largely 5,7,9-estratrienol-17(α) and very little acidic material was obtained.

This investigation was supported by a grant from the Committee for Research in Problems of Sex, National Research Council. We also wish to thank Parke, Davis and Company for the supply of urine concentrate and equilenin and for their generous assistance in various phases of this work.

Experimental Part

Hydrogenation of Equilenin and α-Dihydroequilenin.—A mixture of 500 mg. of equilenin, 500 mg. of Adams catalyst, 300 cc. of ether and 10 cc. of absolute ethanol was shaken with hydrogen at three atm. and 25° for fifteen hours. The product was crystallized from 80% ethanol to give compact white crystals, m. p. 245–247°. This gave no depression with an authentic sample of α-dihydroequilenin. It gave a 30° depression with a sample of equilenin of m. p. 257–258°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.5. Found: C, 80.8; H, 7.6.

A mixture of 250 mg. of α-dihydroequilenin, 120 cc. of absolute ethanol, 2 cc. of hydrochloric acid and 200 mg. of Adams catalyst was shaken with hydrogen at three atm. for twelve hours at 25°. The product was crystallized from ether–pentane as white needles, m. p. 144–146°. This gave no depression with a sample of 5,7,9-estratrienol-17(α), m. p. 144–146°, obtained from equilenin.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.0; H, 9.5.

5,7,9-Estratrienone-17.—To a solution of 300 mg. of 5,7,9-estratrienol-17(α) in 30 cc. of acetic acid was added a solution of 300 mg. of chromic anhydride in 20 cc. of 80% acetic acid. After standing for one hour at 25°, the mixture was diluted with water and extracted with ether. The ethereal solution was washed with sodium carbonate solution and the ether removed. The residue was crystallized from aqueous methanol as thick white needles, m. p. 107–109°.

Anal. Calcd. for $C_{18}H_{22}O$: C, 85.0; H, 8.7. Found: C, 84.7; H, 8.8.

With hydroxylamine hydrochloride the product yielded an **oxime** which crystallized from acetone as white needles, m. p. 203–205° dec.

Anal. Calcd. for $C_{18}H_{23}ON$: C, 80.25; H, 8.6. Found: C, 80.5; H, 8.3.

Reduction of 3-Desoxy-11-keto-equilenin. (a) By Catalytic Hydrogenation in Acidic Medium.—A mixture of 250 mg. of 3-desoxy-11-keto-equilenin, 120 cc. of absolute ethanol, 200 mg. of Adams catalyst and 2 cc. of concentrated hydrochloric acid was shaken with hydrogen at two atm. for five hours at room temperature. After treatment with Norite the product was crystallized from ether–pentane to give 150 mg. of white needles, m. p. 144–146°. This gave no depression with a sample of 5,7,9-estratrienol-17(α), m. p. 144–146°, prepared by a similar reduction of equilenin.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.2; H, 9.5.

When refluxed for thirty minutes with an excess of acetic anhydride the reduction product yielded an **acetate** which crystallized from methanol as white needles, m. p. 101.5–102.5°. This gave no depression with a sample of the acetate of 5,7,9-estratrienol-17(α), m. p. 102–103°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.5; H, 8.9.

(b) **By Catalytic Hydrogenation in Neutral Medium.**—A mixture of 200 mg. of 3-desoxy-11-keto-equilenin, 60 cc. of ether, 60 cc. of absolute ethanol and 200 mg. of Adams catalyst was shaken with hydrogen at three atm. at room temperature for four and one-half hours. The product was crystallized from ether–acetone as white needles, m. p. 209–212°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.55; H, 7.5. Found: C, 80.5; H, 7.7.

(c) **By Clemmensen Reduction with Unamalgamated Zinc.**—A mixture of 250 mg. of the 11-keto compound, 40 cc. of 95% ethanol and 10 g. of 20-mesh zinc was refluxed for three and one-half hours during which time 7 cc. of hydrochloric acid was added. The solution was decanted into water and the resulting mixture extracted with ether. The reaction product was sublimed in high vacuum at 130–140° to give a product which crystallized from ether–pentane as needles, m. p. 156–158°.

Anal. Calcd. for $C_{18}H_{18}O$: C, 86.35; H, 7.25. Found: C, 86.3; H, 7.3.

(d) **Clemmensen Reduction with Amalgamated Zinc.**—To a boiling mixture of 100 mg. of the ketone, 25 cc. of ethanol and 5 g. of amalgamated zinc (20-mesh) was added 15 cc. of hydrochloric acid over a period of two hours. The product was sublimed in high vacuum at 60–65° and the sublimate crystallized from methanol and acetone to give white crystals, m. p. 73–75°.

Anal. Calcd. for $C_{18}H_{26}$: C, 91.5; H, 8.5. Found: C, 91.2; H, 8.5.

11-Keto-equilenin Acetate.—To a solution of 2 g. of equilenin acetate (m. p. 158–160°) in 75 cc. of acetic acid was added a solution of 2.5 g. of chromic anhydride in 40 cc. of 80% acetic acid. The mixture was allowed to stand at 25° for five hours, when it was diluted with water and extracted with ether. The ethereal extract was washed well with water and sodium carbonate solution and the ether evaporated. The residual sirup was crystallized first from ether–pentane and then from ether to give compact white crystals, m. p. 195–197°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.7; H, 5.7.

With semicarbazide acetate under the usual conditions the substance yielded a **mono-semicarbazone** which crystallized from aqueous methanol, m. p. 238–241° decomp.

Anal. Calcd. for $C_{21}H_{21}O_4N_3$: C, 66.5; H, 5.6. Found: C, 66.3; H, 5.8.

(8) Marker and Rohrmann, THIS JOURNAL, **61**, 2974 (1939).

Equilenin-3-oxyacetic Acid.—To a mixture of 1 g. of equilenin, 50 cc. of absolute ethanol and 3.5 cc. of ethyl chloroacetate was added a solution of 600 mg. of sodium in 20 cc. of ethanol. The mixture was refluxed for sixteen hours, when 1 g. of potassium hydroxide was added and the mixture refluxed for an additional hour. Upon dilution with water a white precipitate separated which was taken up in ether.

The water layer was acidified with hydrochloric acid and the white solid taken up in a large volume of ether. The ethereal extract was washed twice with sodium carbonate solution. Evaporation of the ether yielded about 200 mg. of unreacted equilenin. The sodium carbonate washings were acidified with hydrochloric acid and the precipitated solid collected and crystallized from acetone–ether as white needles, m. p. 233–236°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.2. Found: C, 73.7; H, 6.3.

The neutral fraction which separated upon first dilution of the reaction mixture with water was crystallized from aqueous acetone to give white crystals, m. p. 141.5–143°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 75.4; H, 7.1.

Hydrolysis of this neutral material with an excess of ethanolic potassium hydroxide yielded an acid which when crystallized from acetone–ether, m. p. 232–235°, gave no depression with equilenin-3-oxyacetic acid. The neutral product was very probably the ethyl ester.

With diazomethane equilenin-3-oxyacetic acid yielded a **methyl ester** which crystallized from acetone–methanol as white plates, m. p. 180–182°.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 74.4; H, 6.5.

Hydrogenation of Equilenin-3-oxyacetic Acid.—A mixture of 800 mg. of equilenin-3-oxyacetic acid, 120 cc. of absolute ethanol, 500 mg. of Adams catalyst and 2 cc. of hydrochloric acid was shaken with hydrogen at two atm. at room temperature for five hours. The reaction products contained no appreciable acidic material. Crystallization from ether–pentane gave white needles, m. p. 144–146°, which gave no depression with a sample of 5,7,9-estratrienol-17(α), m. p. 144–146°.

Anal. Calcd. for $C_{18}H_{24}O$: C, 84.3; H, 9.4. Found: C, 84.0; H, 9.5.

Summary

Equilenin derivatives upon mild oxidation with chromic anhydride yield 11-keto derivatives.

Catalytic hydrogenation of equilenin derivatives in acidic medium gives 5,7,9-estratrienol-17(α).

STATE COLLEGE, PENNA. RECEIVED SEPTEMBER 25, 1939

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXVII. The Oxidation of Pregnanetriol-3,4,20(α) and of Coprostanediol-3,4

BY RUSSELL E. MARKER, EUGENE L. WITTLE, LOUIS PLAMBECK, JR., EWALD ROHRMANN, JOHN KRUEGER AND PAUL R. ULSHAFER

Gardner and Godden[1] oxidized coprosterol and coprostanone with cleavage of the 2,3-bond to a dicarboxylic acid of m. p. 247°. Windaus[2] confirmed Gardner and Godden's work and also oxidized *epi*-coprostanol with chromic oxide to the same acid. Windaus and Riemann[3] oxidized this dibasic acid to isolithobilianic acid which has been proved to have the carboxyl groups in the 2- and 3-positions. We have repeated the oxidation of coprostanone and obtained an acid of m. p. 247°, which appears to be the acid described above. The major oxidation product in the coprostane series, coprostane-2,3-dicarboxylic acid, is therefore formed by cleavage of the 2,3-bond.

On the other hand, oxidative degradations of compounds with the coprostane configuration in the bile acid series result in cleavage of the 3,4-bond as the major reaction. Wieland, Dane and Scholz[4] found that the oxidation of lithocholic acid proceeded with the formation of a 50% yield of lithobilianic acid and a 15% yield of isolithobilianic acid. Thus the oxidative cleavage in this compound took place chiefly at the 3,4-bond, and the substance formed by cleavage of the 2,3-bond was a by-product. Also J. Sawlewicz and T. Reichstein[5] obtained deoxybilianic acid as the major product in the oxidation of α-3-hydroxy-12-keto-cholanic acid. The same is true in the oxidation of other cholic acid derivatives.

Because the major oxidative cleavage in the bile acids of coprostane configuration is at the 3,4-bond, whereas the bile acids of the *allo* series are attacked at the 2,3-bond, it has been generally assumed that all coprostane and cholestane derivatives will behave in the same way. Confusion has resulted in the literature because of this

(1) Gardner and Godden, *Biochem. J.*, **7**, 588–595 (1913).
(2) Windaus, *Ber.*, **49**, 1724–1734 (1916).
(3) Windaus and Riemann, *Z. physiol. Chem.*, **126**, 277 (1923).
(4) Wieland, Dane and Scholz, *Z. physiol. Chem.*, **211**, 261–274 (1932).
(5) Sawlewicz and Reichstein, *Helv. Chim. Acta*, **20**, 992 (1937).