(57%). The acid fraction yielded a trace of IIa when recrystallized from alcohol.

Summary

1. The action of two moles of phenylmagnesium bromide on dimethylmaleic anhydride yields a mixture of two stereoisomeric acids, which have been shown to be 2-phenyl-2-methyl-3-benzoylbutyric acids.

2. The probable mechanism of their formation involves a splitting of the anhydride ring by one mole of phenylmagnesium bromide, followed by 1,4 addition of a second mole to the unsaturated keto acid formed. Evidence to support this mechanism is presented.

3. Phenylzinc chloride reacts with dimethylmaleic anhydride to give a high yield of β-benzoyltiglic acid, but shows no tendency to add a second mole.

4. Phenyllithium gives 2,3-dimethyl-4,4-diphenylcrotonolactone, which probably results from 1,2 addition of a second mole of organometallic compound to the intermediate unsaturated keto acid. Only a small amount of material resulting from 1,4 addition is formed.

5. Phenylzinc chloride and succinic anhydride give a 40% yield of β-benzoylpropionic acid.

ROCHESTER, NEW YORK RECEIVED JULY 8, 1940

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of 6-Hydroxy-17-equilenone (an Isomer of Equilenin) and Two of its Homologs

BY W. E. BACHMANN AND D. W. HOLMES[1]

Inasmuch as the procedures worked out for the synthesis of equilenin[2] appeared applicable to the preparation of homologs and isomers of the sex hormone, we were in a position of being able to secure information in regard to the effect of varying the structure of the molecule on the estrogenic activity. As part of this program, we prepared desoxyequilenin and desoxyisoequilenin,[3] which possess the same structure as equilenin except for the hydroxyl group. The method has been extended now to the synthesis of an isomer of equilenin which differs from the sex hormone only in having the hydroxyl group on C_6 instead of on C_3. According to the nomenclature proposed by us recently,[3] the compound is called 6-hydroxy-17-equilenone (I). In virtue of the asymmetric carbon atoms C_{13} and C_{14}, the compound can exist in *cis* and *trans* forms, both of which are racemic mixtures. We have synthesized the *cis dl* and *trans dl* forms of 6-hydroxy-17-equilenone, but have made no attempt to resolve them at this time.

As starting material for the synthesis, we employed the 1-keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene (II) of Kon and Ruzicka,[4] which can be prepared readily from the methyl ether of α-naphthol. The steps involved in the synthesis are exactly analogous to those employed in the preparation of equilenin, and consist in the introduction of a carbomethoxy group in position 2 through the glyoxalate reaction, the introduction of a methyl group to give III, the reaction of this compound with zinc and methyl bromoacetate, the dehydration of the Reformatsky ester and the reduction of the unsaturated acids to the reduced acids (VI), which were separated into the *cis* and *trans* forms. Since the configurations of these acids are not yet known, they are distinguished by the prefixes α and β, and the compounds synthesized from them are known as α- and β-6-hydroxy-17-equilenone, respectively, it being understood that one of them is the *cis* and the other the *trans* form. The formation of the latter compounds was accomplished by lengthening the acetic acid side-chain of the reduced acids to the propionic acid group by means of the Arndt–Eistert reaction, cyclizing the product and hydrolyzing, decarboxylating and demethylating the cyclic compound. Inasmuch as the formulas of the intermediates are exactly like those of the equilenin synthesis except for the position of the hydroxyl group, the formulas are not reproduced here with the exception of a few that require further mention.

It is of interest that hot methanolic potassium hydroxide strips the carbomethoxy group from

(1) From the Ph.D. dissertation of D. W. Holmes.

(2) Bachmann, Cole and Wilds, THIS JOURNAL, **61**, 974 (1939); **62**, 824 (1940).

(3) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940).

(4) Kon and Ruzicka, *J. Chem. Soc.*, 187 (1936).

III to form IV, the ring remaining intact. Confirmation of the structure of the unsaturated acids formed by dehydration of the Reformatsky ester obtained from III was obtained by oxidation of the acid ester V. This reaction yielded III, an indication that no rearrangement had taken place in the process of dehydration.

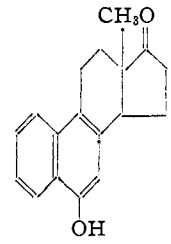
Reduction of the unsaturated acids in the form of their sodium salts in aqueous solution by means of sodium amalgam yielded the α and β acids in a ratio of 1:2, respectively. A 1:6 ratio of the α and β acids resulted on catalytic reduction in an acid medium.

Hydrolysis, decarboxylation and demethylation of the 6-methoxy-16-carbomethoxy-17-equilenone was accomplished by heating the compound with a mixture of hydrochloric and acetic acid. The methyl ether of the hormone isomer is an intermediate in these steps and can be isolated when the mixture is heated for a short time only, although it is accompanied by some of the phenolic compound. There is a considerable difference in the rates of demethylation of the α- and β-6-methoxy-17-equilenone. The β-form is demethylated completely in about one-fifth the time required for demethylation of the α-form under the same conditions.

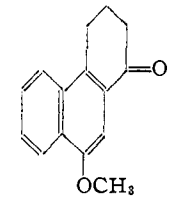
In addition to varying the structure of the equilenin molecule by shifting the hydroxyl group to a different position, we have introduced an additional methylene group into the molecule in two different positions. In one of the homologs, 6-hydroxy-19-methyl-17-equilenone (VII), which was obtained in *cis* and *trans* forms, an ethyl group has been substituted for the angular methyl group. This was accomplished by ethylating the 2-carbomethoxy derivative of II and carrying the resulting compound through the same series of reactions employed on the methyl derivative.

In the second homolog, the D ring of 6-hydroxy-17-equilenone has been enlarged to a six-membered ring, the resulting 6-hydroxy-D-homo-17a-equilenone[5] (X) being obtained in both *cis* and *trans* forms. In this synthesis, the propionic acid side-chain of the compound previously obtained was lengthened to a butyric acid group to give VIII. Cyclization of this compound yielded IX, which was converted to X by refluxing it with a mixture of acetic and hydrochloric acids.

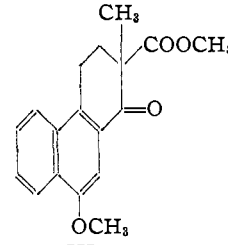
(5) We have employed the nomenclature proposed by Ruzicka and Meldahl [*Helv. Chim. Acta*, **23**, 364 (1940)] for the steroids containing a six-membered D ring.



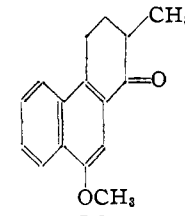
I. 6-Hydroxy-17-equilenone



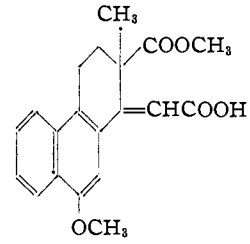
II



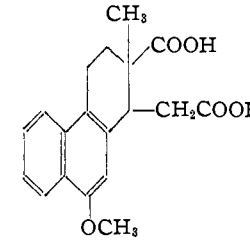
III



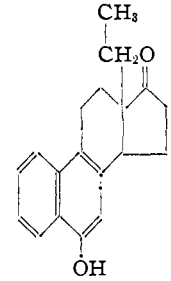
IV



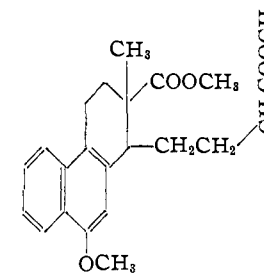
V



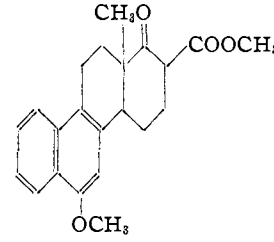
VI



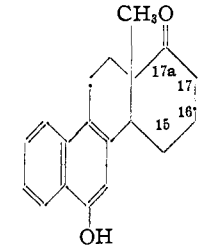
VII. 6-Hydroxy-19-methyl-17-equilenone



VIII



IX



X. 6-Hydroxy-D-homo-17a-equilenone

The six compounds, *cis* and *trans* 6-hydroxy-17-equilenone, *cis* and *trans* 6-hydroxy-19-methyl-17-equilenone and *cis* and *trans* 6-hydroxy-D-homo-17a-equilenone, have been tested for estrogenic activity by injecting them into ovariectomized rats (Dr. J. T. Bradbury). The first

two compounds proved to be inactive when injected in amounts up to 500 γ; the other four compounds showed no activity even in 1000 γ doses. Since the racemic mixtures were inactive in the amounts indicated, it follows that none of the optically active forms of 6-hydroxy-17-equilenone can be active in amounts less than 250 γ, and that none of the optically active forms of the other four compounds can be active in amounts less than 500 γ. These results indicate that shifting the hydroxyl group from C_8 to C_6 has resulted in loss of estrogenic activity, which was not restored by substituting an ethyl group for the angular methyl group or by enlarging the D ring to a six-membered ring.

Experimental

1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene (II).—For the preparation of β-(4-methoxy-1-naphthoyl)-propionic acid we employed nitrobenzene as a solvent in the Friedel–Crafts reaction instead of carbon disulfide[6] or tetrachloroethane.[7] To a cooled stirred solution of 246 g. of aluminum chloride, 600 cc. of nitrobenzene and 93 g. of succinic anhydride was added 147.3 g. of α-methoxynaphthalene at such a rate that the temperature of the mixture remained below 10°. After the addition was complete, the ice-bath was removed and the mixture was stirred for four hours and then hydrolyzed. The product remaining after steam distillation was purified through its sodium salt and the acid recrystallized from acetic acid; yield, 200 g. (83%); m. p. 172–174°.

The keto acid was reduced by Martin's procedure[8] except that a different proportion of solvents was employed and the time was decreased. A mixture of 25 g. of the keto acid, 100 g. of amalgamated zinc, 100 cc. of concentrated hydrochloric acid, 50 cc. of acetic acid and 25 cc. of toluene was refluxed for five hours, an additional 50 cc. of hydrochloric acid being added after the first two hours. The product after treatment with 12 cc. of methyl sulfate in alkaline solution was recrystallized from alcohol, yielding 12.5 g. (53%) of acid melting at 127–129°. By retreating the mother liquors the yield was raised to 60%.

To a mixture of 10 g. of γ-(4-methoxy-1-naphthyl)-butyric acid in 50 cc. of dry ether and 4 drops of pyridine was added 7 cc. of thionyl chloride. After the acid had dissolved, the mixture was allowed to stand at room temperature for one-half hour. After removal of the ether and excess of reagent under reduced pressure, 2 cc. of benzene was added and this removed under reduced pressure finally at 35–40°. A solution of the acid chloride in 100 cc. of benzene was chilled until the solvent began to freeze, when 8 cc. of stannic chloride was added. After being swirled for one minute, the mixture was hydrolyzed with ice and 50 cc. of hydrochloric acid. Some ether was added and the organic layer was separated, washed with concentrated hydrochloric acid, with water and with concentrated ammonium hydroxide. The ketone obtained by removal of the solvent was recrystallized from dilute alcohol; yield 8.45 g. (92%); m. p. 99–100° (reported, 98°[4]).

Methyl 1-Keto-9-methoxy-1,2,3,4-tetrahydrophenanthrene-2-glyoxalate.—The condensation of II with methyl oxalate was carried out in the manner described for the 7-methoxy derivative,[2] 22.6 g. of the ketone being used in a run. Recrystallization of the glyoxalate from acetone–methanol gave 29.8 g. (95%) of lemon-yellow needles; m. p. 123–124°. A sample after three more recrystallizations melted at 124–124.5°. It gives a deep red-brown color with alcoholic ferric chloride.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 69.2; H, 5.1. Found: C, 69.5; H, 5.1.

1-Keto-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene.—Following the procedure described[2] 11.6 g. of the glyoxalate and 6 g. of powdered soft glass were heated at 180° until evolution of carbon monoxide ceased (one-half to one hour). The product, separated from the glass by hot acetone, was recrystallized from acetone–methanol; yield, 9.61 g.; m. p. 118–121°. This was suitable for the next step. A sample after three more recrystallizations formed fine colorless needles which melted at 120.5–121°. With alcoholic ferric chloride a light blue-green color develops slowly.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.6. Found: C, 71.5; H, 5.6.

1-Keto-2-methyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene (III).—A solution of 9 g. of the aforementioned keto ester in 10 cc. of dry benzene was added to a solution of sodium methoxide prepared from 3.6 g. of sodium and 60 cc. of absolute methanol. After being warmed for one hour and then cooled, the mixture was treated with 9 cc. of methyl iodide and kept between 30 and 40° until nearly all of the sodio derivative had disappeared; the mixture was then refluxed on a steam-bath for one-half hour. An additional 3 cc. of methyl iodide was added and refluxing continued for an hour. The chilled mixture was acidified with acetic acid, evaporated nearly to dryness and the residue treated with benzene and water. The product obtained from the benzene solution crystallized from acetone–methanol in colorless needles; yield, 8.66 g. (92%); m. p. 136–137°. After two recrystallizations a sample had a m. p. 137–137.5°. It gave no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.0. Found: C, 72.8; H, 6.1.

To a solution of 1 g. of the compound in 35 cc. of methanol was added 6 cc. of 45% aqueous potassium hydroxide solution and the mixture was refluxed for two hours. The product obtained from the mixture was sublimed at 200° at 0.4 mm. and recrystallized from dilute alcohol from which 0.73 g. (91%) of **1-keto-2-methyl-9-methoxy-1,2,3,4-tetrahydrophenanthrene** (IV) was obtained; m. p. 81–83°. After passage of a benzene solution of the compound through alumina, the ketone formed colorless prisms melting at 82–83°.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 80.0; H. 6.7. Found: C, 79.7; H, 6.8.

Dimethyl Ester of 1-Hydroxy-2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic

(6) Ruzicka and Waldman, *Helv. Chim. Acta*, **15**, 914 (1932).
(7) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).
(8) Martin, *ibid.*, **58**, 1438 (1936).

Acid.—The Reformatsky reaction between III and zinc and methyl bromoacetate was carried out as described for the 7-methoxy isomer.[2] The product from 5 g. of III crystallized from methanol in colorless cubes; yield, 5.46 g. (87%); m. p. 127–129°. By re-treating the residual oil in the mother liquor, an additional 5% of crystalline product was obtained. A sample after three more recrystallizations melted at 130–131°.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.7; H, 6.5. Found: C, 67.2; H, 6.3.

Conversion of the Reformatsky Ester to the Unsaturated Acids.—This was carried out on 2.24 g. of the ester in the manner described.[2] The mixture of the sodium salts of the unsaturated acids was acidified and the precipitate (1.5 g.) was digested with 50 cc. of 10% sodium bicarbonate solution for thirty minutes and filtered. The insoluble solid on recrystallization from acetic acid gave 0.45 g. of the **anhydride of *syn*-2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid;** m. p. 238–240°. After sublimation at 220° at 0.4 mm. and recrystallization from acetic acid, it formed yellowish prisms with a m. p. 239–240.5°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 74.0; H, 5.2. Found: C, 73.8; H, 5.2.

Acidification of the sodium bicarbonate solution yielded a solid which on recrystallization from acetone–benzene gave 1.1 g. of ***anti*-2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid.** After three more recrystallizations, the acid formed yellowish plates with a m. p. 224 5–226°, dec., when placed in a bath preheated to 215°.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 70.0; H, 5.5. Found: C, 69.8; H, 5.5.

The **methyl ester** of the *anti*-acid, prepared by means of diazomethane, crystallized from methanol in colorless prisms; m. p. 104.5–105°.

Anal. Calcd. for $C_{21}H_{22}O_5$: C, 71.2; H, 6.2. Found: C, 71.0; H, 6.0.

Oxidation of the Half Ester of the *anti*-Acid (V).—The half ester was prepared by refluxing a mixture of 0.37 g. of the dimethyl ester and 1.12 cc. of *N* sodium hydroxide in 10 cc. of methanol for two hours. After removal of the methanol, the product was dissolved in water and the solution acidified. The ***anti*-2-methyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid** (0.35 g.) crystallized from acetone–petroleum ether in yellowish prisms; m. p. 197.5–199°, dec.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 70.6; H, 5.9. Found: C, 70.4; H, 6.0.

To a cooled solution of the potassium salt of 0.30 g. of the half ester in 30 cc. of water was added 10 cc. of benzene and 2 cc. of a solution of 0.32 g. of potassium permanganate in 15 cc. of water. When the color had disappeared, the remaining permanganate solution was added in portions. From the benzene solution 0.04 g. of III was isolated.

Preparation of the α- and β-Reduced Acids (VI).—To an ice-cold solution of 7 cc. of dry benzene, 5 cc. of thionyl chloride and 2.5 cc. of pyridine was added 7.44 g. of the Reformatsky ester. After the mixture had stood at room temperature for fifteen minutes and at 40° for the same length of time, the solvent was removed under reduced pressure. The residue was extracted from the pyridine hydrochloride by three 7-cc. portions of benzene and the combined extracts added to an ice-cold solution of 6 g. of potassium hydroxide in 50 cc. of methanol. The mixture was refluxed for twenty minutes, the methanol was evaporated, 20 cc. of 45% aqueous potassium hydroxide was added and heating continued on a steam-bath for fifteen minutes. Warm water (200 cc.) was added to dissolve the precipitate and the warm solution was transferred to a strong 500-cc. bottle where it was shaken vigorously for thirty minutes with 250 g. of 2% sodium amalgam.

In some runs a precipitate of the sodium salt of the β-acid formed during the reduction. It was filtered from the chilled solution, redissolved in warm water, 10 cc. of 45% aqueous potassium hydroxide added to the solution, and the mixture refluxed for four hours to ensure hydrolysis of the tertiary ester group. The β-acid (4 g.) obtained on acidification was recrystallized from acetone; yield, 3.38 g.; m. p. 227–229°. If no precipitate of the sodium salt formed on cooling, the solution was heated for four hours and then acidified. The mixture of acids was dissolved in a solution of 20 cc. of 45% aqueous potassium hydroxide in 200 cc. of water and treated with 4 g. of sodium hydroxide. The insoluble sodium salt of the β-acid precipitated immediately; after one hour it was filtered off, dissolved in water and the free acid obtained by acidification. A sample of the **β-2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** after three recrystallizations formed colorless needles with a m. p. 228.5–230°, dec.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.3; H, 6.0.

The filtrate obtained after removal of the sodium salt of the β-acid was heated for four hours (this heating was omitted if the second procedure described above had to be used) and then acidified. By recrystallization of the product (2.24 g.) from acetone, 1.8 g. of **α-2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** was obtained with a m. p. 222–224°. This acid although not quite pure was used to make the dimethyl ester. A sample of the acid after five recrystallizations from acetone formed colorless prisms melting at 233–235° (when placed in a bath at 220°). A mixture of the α- and β-acids melted at 208–215°. On an average, a 28% yield of the α-acid and a 51% yield of the β-acid were obtained.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.1; H, 6.1.

Reduction by sodium amalgam of 0.2 g. of the *anti* unsaturated acid in the form of its potassium salt yielded 0.06 g. of the α-acid and 0.12 g. of the β-acid. Similarly, reduction of the potassium salt obtained from 0.1 g. of the anhydride of the *syn* acid yielded 0.025 g. of the α-acid and 0.052 g. of the β-acid. In both cases, the acids were separated by making use of the insolubility of the sodium salt of the β-acid in aqueous sodium hydroxide. The identity of the acids was established by mixed melting point determinations of the acids and their dimethyl esters.

Catalytic reduction of the *anti* unsaturated acid was carried out by shaking a mixture of 0.5 g. of the acid in 30 cc. of acetic acid in a hydrogen atmosphere with 10 mg. of

Adams catalyst. After thirty minutes an additional 50 mg. of catalyst was added and shaking continued for two hours. From the mixture 0.05 g. of the α-acid and 0.33 g. of the β-acid were isolated.

α- and β-6-Hydroxy-17-equilenone

Dimethyl Ester of 2-Methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid.—The **α-form** of this compound prepared in 98% yield from the α-acid by means of diazomethane, crystallized from methanol in colorless prisms; m. p. 106–107°. A sample after two more recrystallizations had a m. p. 107–108°.

The **β-form,** prepared from 2.9 g. of the β-acid and diazomethane, crystallized from methanol in colorless prisms; yield, 2.84 g. (97%); m. p. 94–96°. After two more recrystallizations a sample melted at 96–97°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: (α-form) C, 70.8; H, 6.7; (β-form) C, 70.4; H, 6.8.

2 - Methyl - 2 - carbomethoxy - 9 - methoxy - 1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—A mixture of 1 g. of the dimethyl ester, 20 cc. of methanol and 3 cc. of *N* sodium hydroxide was refluxed for two hours, the methanol was removed and the product dissolved in about 10 cc. of warm water. Acidification of the solution gave the acid ester, which was sufficiently pure for the next step.

In this manner 0.96 g. (99%) of the **α-form** melting at 195–198° was obtained. A sample after three recrystallizations from acetone–petroleum ether formed fine, colorless needles; m. p. 198.5–200°.

The **β-form** was obtained in quantitative yield; m. p. 185–198°. From acetone–petroleum ether it crystallized in two forms: clusters of colorless needles (m. p. 190–192°) and colorless prisms (m. p. 202.5–204°).

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.4. Found: (α-form) C, 70.1; H, 6.3; (β-form) C, 69.8; H, 6.5.

Arndt-Eistert Reaction on the Acid Esters.—This was carried out on 1.7 g. of the acid esters as described for the 7-methoxy isomer.[2] The solution of the product obtained by the action of silver oxide on the crystalline diazoketone from the α-acid ester in methanol was filtered and passed through a column of alumina. The **α-dimethyl ester of 3′-(2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1)-propanoic acid** crystallized from methanol in colorless prisms; yield, 1.51 g. (82%); m. p. 150–152°. A sample after sublimation at 200° at 0.4 mm. and two recrystallizations melted at 152.5–153.5°.

Recrystallization from methanol of the product obtained from the β-acid ester gave 1.36 g. (74%) of the **β-dimethyl ester of 3′-(2-methyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1)-propanoic acid;** m. p. 73–75°. A sample purified by sublimation and recrystallization from methanol formed colorless rod-like prisms; m. p. 75.5–76.5°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.1. Found: (α-form) C, 71.4; H, 7.1; (β-form) C, 71.3; H, 7.1.

6 - Methoxy - 16 - carbomethoxy - 17 - equilenone.—Cyclization of 1 g. of the aforementioned esters was accomplished by sodium methoxide by the procedure described.[2] The **α-form** crystallized from methanol in colorless rod-like prisms; yield, 0.8 g. (86%); m. p. 149–151° (vac.). A sample after three recrystallizations melted at 151–152° (vac.). A light yellowish-green color develops slowly when the compound is treated with alcoholic ferric chloride.

By recrystallization from methanol the **β-form** was obtained as colorless prisms; yield, 0.82 g. (90%); m. p. 139–141° (vac.). After three recrystallizations a sample melted at 140–141° (vac.). The compound gives an immediate dark blue color with alcoholic ferric chloride.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.5. Found: (α-form) C, 74.5; H, 6.5; (β-form) C, 74.3; H, 6.4.

6-Methoxy-17-equilenone.—A mixture of 0.4 g. of the 16-carbomethoxy derivative, 12 cc. of acetic acid, 8 cc. of concentrated hydrochloric acid and 1.5 cc. of water was refluxed for one-half hour in an atmosphere of nitrogen. The residue remaining after removal of the solvents under reduced pressure was dissolved in benzene and the solution was washed three times with 1% sodium hydroxide and twice with water in order to remove demethylated product. The product obtained from the benzene solution was sublimed at 200° at 0.01 mm. and recrystallized from methanol.

The **α-form** crystallized in colorless slender prisms; yield, 0.18 g.; m. p. 147.5–148.5°. After two more recrystallizations it melted at 147.5–149° (vac.). From the alkaline washings 0.08 g. of the corresponding demethylated product was isolated.

The **β-form** crystallized in colorless needles; yield, 0.1 g.; m. p. 112–113° (vac.). From the alkaline washings 0.17 g. of the demethylated product was isolated.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: (α-form) C, 81.1; H, 7.0; (β-form) C, 81.3; H, 7.0.

6-Hydroxy-17-equilenone (I).—A mixture of 0.6 g. of the α-6-methoxy-16-carbomethoxy-17-equilenone, 30 cc. of acetic acid, 20 cc. of concentrated hydrochloric acid and 2 cc. of water was refluxed in an atmosphere of nitrogen for ten hours and then worked up in the manner described for equilenin.[2] By recrystallization from dilute alcohol, the **α-form** was obtained as colorless prisms; yield, 0.35 g. (74%); m. p. 238–240° (vac.). After sublimation at 200° at 0.01 mm. and two recrystallizations it melted at 240–242° (vac.), when placed in a bath at 220°.

The β-form was obtained by refluxing a mixture of 0.5 g. of the β cyclized ester, 12 cc. of acetic acid, 8 cc. of concentrated hydrochloric acid and 1.5 cc. of water for two hours. The product crystallized from dilute alcohol in colorless needles; yield, 0.35 g. (87%); m. p. 170–172° (vac.). After sublimation and two recrystallizations the β-form melted at 171.5–172.5° (vac.). From benzene–petroleum ether it crystallized with solvent of crystallization; m. p. 101–102° with evolution of gas.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: (α-form) C, 80.9; H, 6.7; (β-form) C, 80.9; H, 6.8.

α- and β-6-Hydroxy-19-methyl-17-equilenone

1 - Keto - 2 - ethyl - 2 - carbomethoxy - 9 - methoxy-1,2,3,4-tetrahydrophenanthrene.—This compound was prepared from 9 g. of 1-keto-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene by the procedure employed for the methyl derivative. After the addition of 8 cc. of ethyl bromide to the sodio derivative, the mixture was refluxed for seven hours. To ensure complete ethylation, a

solution of sodium methoxide from 2 g. of sodium and 20 cc. of methanol was added to the cooled mixture; after ten minutes 3 cc. of ethyl bromide was added and refluxing was continued for three hours. The product obtained in the usual manner crystallized from acetone–alcohol in colorless leaflets; yield, 9.23 g. (92%); m. p. 109–112°. After three recrystallizations a sample melted at 113–114°. In two early runs the compound was obtained in colorless prisms melting at 95.5–97°; this lower-melting form was converted readily to the higher-melting form. The compound gave no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.1; H, 6.5.

Dimethyl Ester of 1-Hydroxy-2-ethyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—Following the procedure used to prepare the Reformatsky ester from the methyl homolog, 4.65 g. (75%) of this compound was obtained from 5 g. of the aforementioned keto ester. By re-treating the material in the mother liquors with zinc and methyl bromoacetate, the yield of crystalline Reformatsky ester was raised to 88%. The product crystallized from methanol in colorless plates melting at 98–101°, which were sufficiently pure for the next step. After three more recrystallizations a sample melted at 103.5–104.5°.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.4; H, 6.7. Found: C, 68.6; H, 6.9.

Preparation of the Unsaturated Acid and Anhydride.—The product (2.8 g.) obtained by dehydration of 3.22 g. of the Reformatsky ester by the procedure employed on the methyl homolog was digested with sodium bicarbonate solution and the insoluble residue was recrystallized from acetone, yielding 0.25 g. of the **anhydride of *syn*-2-ethyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid.** After sublimation at 250° at 0.4 mm. and recrystallization from acetone the compound was obtained as yellow needles; m. p. 228.5–229.5°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.2; H, 5.6.

The ***anti*-2-ethyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid** (2.2 g.) obtained from the sodium bicarbonate solution crystallized from acetone–benzene in slender yellow prisms; m. p. 203.5–205° with evolution of gas.

Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.6; H, 5.9. Found: C, 70.1; H, 6.0.

Preparation of the α- and β-Reduced Acids.—In order to obtain samples of the pure acids, 3.22 g. of the Reformatsky ester was dehydrated in the manner described, the unsaturated compounds were reduced by 2% sodium amalgam and the alkaline solution was refluxed for four hours to ensure complete hydrolysis. The mixture of acids (2.7 g.) obtained on acidification was dissolved in hot acetone, the solution boiled with Norit, filtered and put in a refrigerator for two days. The α-acid which precipitated was filtered off; weight, 0.4 g. From the filtrate 1.6 g. of the β-acid crystallized. After three recrystallizations from acetone–benzene the **α-2-ethyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** melted at 230.5–232.5°. The **β-acid** was purified by recrystallization from acetone–benzene; the crystals melted at 155° with evolution of gas, solidified and melted at 223–225°. The crystals contain benzene of crystallization which can be removed by heating the solid at 180° at 0.4 mm. for one hour; about 0.8 g. of the acid was obtained from 1 g. of the crystals. The product so obtained melted at 223–225°. A mixture of the α- and β-acids melted at 208–215°.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.4. Found: (α-form) C, 69.9; H, 6.4; (β-form) C, 69.8; H, 6.3.

Usually 7.5 g. of the Reformatsky ester was converted to the mixture of the reduced acids, the latter (6.5 g.) dissolved in acetone–benzene and the solution seeded with the β-acid. The β-acid (3.15 g.) which precipitated melted at 155°, solidified and melted at 219–223° was sufficiently pure to be used for the next step. Although the α-acid could be obtained from the filtrate it was found best to convert the product in the mother liquors to the dimethyl esters by means of diazomethane. The dimethyl ester of the α-acid was obtained by recrystallization from methanol; yield, 2.51 g.; m. p. 130–133°. By seeding the methanol filtrate with the dimethyl ester of the β-acid 0.5 g. of the β-ester was obtained (m. p. 96–99°). By this procedure a total yield of 34% of the α-acid and 44.5% of the β-acid was isolated.

The same α- and β-acids were obtained by reduction by sodium amalgam of the potassium salts of the *anti*-unsaturated acid and the *syn*-unsaturated acid obtained from the anhydride.

Dimethyl Ester of 2-Ethyl-2-carboxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—The **α-form** prepared in 95% yield from the α-acid by means of diazomethane crystallized from methanol in colorless hexagonal plate-like prisms; m. p. 133.5–134.5°, not raised by further recrystallization.

By treatment of 2.6 g. of the β-acid (containing benzene of crystallization) with diazomethane, there was obtained 2.08 g. of the **β-form** of the dimethyl ester which crystallized from methanol in colorless rod-like prisms; m. p. 97–99°. A sample after three recrystallizations melted at 99.5–100.5°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: (α-form) C, 71.7; H, 7.0; (β-form) C, 71.0; H, 7.0.

2-Ethyl-2-carbomethoxy-9-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—Partial hydrolysis of the dimethyl ester was carried out as described for the methyl homolog. The acid esters obtained by acidification of the aqueous solutions of the salts were sufficiently pure for the next step. From 2 g. of the α-dimethyl ester 1.92 g. (m. p. 195–197°) of the **α-form** of the acid ester was obtained. A sample after three recrystallizations from acetone–petroleum ether formed colorless needles; m. p. 198.5–199.5°.

In a similar manner 1.93 g. of the **β-form** of the acid ester (m. p. 158–160°) was obtained. After three recrystallizations from acetone–petroleum ether it formed colorless needles; m. p. 160–161°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: (α-form) C, 70.4; H, 6.7; (β-form) C, 70.7; H, 6.7.

Arndt–Eistert Reaction on the Acid Esters.—This reaction was carried out on 1 g. of the α-acid ester in the manner described except that the diazoketone in methanol was refluxed with silver oxide for three hours. The **α-dimethyl ester of 3'-(2-ethyl-2-carboxy-9-methoxy-1,2,3,4-tetra-**

hydrophenanthrene-1)-propanoic acid crystallized from methanol in colorless hexagonal prisms; yield, 0.84 g. (81%); m. p. 126–128°. After two more recrystallizations a sample melted at 129–130°.

The **β-form**, obtained in 77% yield from 1.9 g. of the β-acid ester, crystallized from methanol in colorless needles melting at 69–71°. A sample after four more recrystallizations melted at 73–74°.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.9; H, 7.3. Found: (α-form) C, 71.7; H, 7.2; (β-form) C, 71.8; H, 7.1.

6 - Methoxy - 16 - carbomethoxy - 19 - methyl - 17-equilenone.—Cyclization of the aforementioned esters was accomplished by means of sodium methoxide by the procedure described. For the α-compound two hours of refluxing was employed for the reaction. In this manner an 80% yield of the **α-form** was obtained which crystallized from methanol in colorless prisms; m. p. 159–161°. After three more recrystallizations a sample melted at 161–162° (vac.). A light greenish-yellow color develops slowly when the compound is mixed with alcoholic ferric chloride.

Cyclization of 0.87 g. of the β-ester yielded 0.67 g. (84%) of the **β-form** melting at 117–120° after recrystallization from methanol. This cyclized product crystallized slowly; for best results the methanol solution should be allowed to stand for two or three days. A sample after three more recrystallizations formed colorless prisms; m. p. 118–120° (vac.). It gives no immediate color with ferric chloride but in time a very light reddish-purple color forms.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: (α-form) C, 74.8; H, 6.7; (β-form) C, 74.5; H. 6.6.

6-Methoxy-19-methyl-17-equilenone.—Hydrolysis and decarboxylation of the aforementioned cyclized products was accomplished in the manner described for the homolog, thirty minutes being allowed for the reaction. The product purified as described was recrystallized from methanol. From 0.5 g. of the α-cyclized compound there was obtained 0.25 g. of the **α-form** as colorless needles melting at 141.5–142.5°. After another recrystallization it melted at 142–142.5°. From the alkaline washings 0.07 g. of the demethylated compound was isolated.

The **β-form** crystallized from methanol in colorless needles; yield, 0.12 g.; m. p. 75–76°. From the alkaline washings 0.22 g. of the demethylated product was isolated.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: (α-form) C, 81.3; H, 7.3; (β-form) C, 81.3; H, 7.5.

6-Hydroxy-19-methyl-17-equilenone (VII).—The **α-form** was obtained by refluxing a mixture of 0.37 g. of the α - 6 - methoxy - 16 - carbomethoxy - 19 - methyl - 17-equilenone, 12 cc. of acetic acid, 8 cc. of concentrated hydrochloric acid and 1 cc. of water in a nitrogen atmosphere for ten hours. After purification through its water-soluble salt and recrystallization from acetone–petroleum ether the compound formed yellowish prisms; yield, 0.22 g. (75%); m. p. 203–206° (vac.). After sublimation at 200° at 0.01 mm. and three recrystallizations it formed colorless rhombic prisms which melted at 206–208° (vac.).

In a similar manner an 80% yield of the β-form was obtained as colorless needles from dilute alcohol melting at 121.5–123°. This compound crystallized from acetone–petroleum ether with solvent of crystallization, the crystals melting at 109–110° with evolution of gas.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: (α-form) C, 81.3; H, 7.1; (β-form) C, 81.1; H, 7.1.

α- and β-6-Hydroxy-D-homo-17a-equilenone

3′ - (2 - Methyl - 2 - carbomethoxy - 9 - methoxy - 1,2,3,4-tetrahydrophenanthrene-1)-propanoic Acid.—Partial hydrolysis of 1 g. of the dimethyl ester was accomplished by the procedure employed on the homolog. The **α-form** crystallized from acetone–petroleum ether in colorless needles; yield, 0.92 g. (96%); m. p. 166–168°. A sample after two more recrystallizations melted at 167.5–168.5°.

The corresponding **β-form**, obtained in 94% yield, crystallized from acetone–petroleum ether in colorless needles; m. p. 133–135°. After two more recrystallizations a sample melted at 135.5–137°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: (α-form) C, 70.4; H, 6.7; (β-form) C, 70.5; H, 6.6.

Arndt–Eistert Reaction on the Acid Esters.—The **α-dimethyl ester of 4′-(2-methyl-2-carboxy-9-methoxy-1,-2,3,4-tetrahydrophenanthrene-1)-butanoic acid (VIII)** obtained from 0.92 g. of the α-acid ester was sublimed at 200° at 0.4 mm. and recrystallized from methanol, from which it was obtained as colorless needles; yield, 0.47 g. (48%); m. p. 92.5–93.5°. After two more recrystallizations a sample melted at 94.5–95.5°.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.9; H, 7.3. Found: C, 71.8; H, 7.3.

The **β-form** was obtained as an uncrystallizable oil which was purified by sublimation at 200° at 0.4 mm. and used directly for cyclization.

6 - Methoxy - D - homo - 17 - carbomethoxy - 17a-equilenone (IX).—Cyclization of 0.15 g. of the α-compound by sodium methoxide in benzene followed by purification of the product in the manner described yielded 0.12 g. (86%) of the **α-form** as cream-colored prisms (from methanol); m. p. 151–154°. After two recrystallizations a sample melted at 152–154° (vac.). No immediate color was formed with alcoholic ferric chloride, but a light greenish-yellow color developed slowly.

The **β-form** obtained in a 41% yield (based on the acid ester) crystallized from methanol in colorless plates; m. p. 142–147°. After three more recrystallizations a sample melted at 150–151° (vac.). A light reddish-purple color developed slowly when the compound was mixed with alcoholic ferric chloride.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: (α-form) C, 75.0; H, 6.7; (β-form) C, 74.5; H, 6.6.

6-Methoxy-D-homo-17a-equilenone.—The **α-form** was obtained by refluxing 0.3 g. of the α-cyclized product with the usual acid mixture for one-half hour. After separation from phenolic material by means of alkali and sublimation at 200° at 0.01 mm. it crystallized from methanol in colorless needles; yield, 0.12 g.; m. p. 130.5–132°. After another recrystallization it melted at 131–132.5° (vac.). From the alkaline washings 0.08 g. of the demethylated product was isolated.

The **β-form** was best obtained by methylating the β-6-hydroxy-D-homo-17a-equilenone. A solution of 60 mg. of the latter compound in 130 cc. of 0.5% sodium hydroxide and 5 cc. of methyl sulfate was shaken for thirty minutes.

The solution was then warmed to decompose the excess of reagent and extracted with benzene. The product after sublimation and recrystallization from methanol formed colorless prisms; yield, 55 mg. (87%); m. p. 142–143°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: (α-form) C, 81.3; H, 7.3; (β-form) C, 81.2; H, 7.5.

6-Hydroxy-D-homo-17a-equilenone (X).—The **α-form** obtained by refluxing a mixture of 0.12 g. of the α-cyclized product and acetic and hydrochloric acid for ten hours was purified in the manner described. After sublimation at 200° at 0.01 mm. it crystallized from dilute alcohol in colorless triangular plates; yield, 0.08 g. (84%); m. p. 226–229° (vac.). After another recrystallization it melted at 227–229° (vac.).

The **β-form** obtained in 84% yield in the same manner was recrystallized from dilute alcohol; m. p. 223–224.5°. After sublimation at 200° at 0.01 mm. it crystallized in colorless prisms; m. p. 223–225° (vac.). A mixture of the α- and β-forms melted at 193–202° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: (α-form) C, 81.1; H, 7.1; (β-form) C, 81.3; H, 7.0.

Summary

An isomer of the sex hormone equilenin in which the hydroxyl group is at C_6 has been synthesized. In addition there is described the synthesis of two homologs of this isomer, one of which contains an angular ethyl group and the other a six-membered D ring. All of the compounds have been tested for estrogenic activity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

Rearrangement of the Triphenylmethyl Ether of Ortho Cresol: Direct Synthesis of 3-Methyl-4-methoxyphenyltriphenylmethane

BY H. A. IDDLES AND H. L MINCKLER

The rearrangement of the triphenylmethyl ether of *o*-cresol, when heated with various rearranging agents, has been interpreted by Schorigin[1] and other investigators[2,3] as a migration of the triphenylmethyl group to the side chain. However, the work of Boyd and Hardy[4] indicated that the migration of the triphenylmethyl group in the triphenylmethyl ethers of phenol and the three cresols led to the same type of rearrangement product in each case. Each product was distilled with soda-lime, yielding triphenylmethane, and with sulfuric acid, producing triphenylcarbinol. Consequently, from this evidence it was concluded that the rearrangement products were tetraphenylmethane derivatives in each case.

In previous work from this Laboratory[5] the methylated cryptophenol of Schorigin, m. p. 162–163°, was compared with the synthetic α-2-methoxyphenyl-β,β,β-triphenylethane, m. p. 142–143°. The non-identity of the two products supported the interpretation that the triphenylmethyl group had not migrated to the side-chain of *o*-cresol. From another angle it has been possible to obtain positive evidence that migration involves a ring position[6] by comparing the condensation product obtained by direct condensation of 6-bromo-*o*-cresol and triphenylcarbinol in acid medium on the one hand with the product obtained by bromination of the simple cryptophenol under consideration. By this indirect procedure the triphenylmethyl group was shown to occupy the para position in the cryptophenol.

In this paper, a direct synthesis of 3-methyl-4-methoxyphenyltriphenylmethane has been realized. The agreement in melting points for the synthetic material and the methylated rearranged product offers further confirmation for interpreting this rearrangement as one in which the triphenylmethyl group has migrated to the para ring position.

For use in the synthetic steps, shown in the accompanying schematic set, *o*-methoxytoluene was treated with benzoyl chloride and stannic chloride to yield I, which in turn was converted into the carbinol II by use of phenylmagnesium bromide. The same carbinol II was also produced when benzophenone was treated with the Grignard reagent prepared from the methyl ether of 4-bromo-*o*-cresol. Treatment of II with acetyl bromide formed the bromide III, which was coupled with phenylmagnesium bromide to form the desired product IV. The synthetic product IV melted at 162° and a mixed melting point with the methylated rearranged product gave no depres-

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(6) Iddles, Miller and Powers, *ibid.*, **62**, 71 (1940).