with absolute ethyl alcohol. After evaporation of the solvent and recrystallization of the residue from methanol, 56% of the original material was recovered. From the mother liquors a small amount of triphenylcarbinol ethyl ether was isolated.

"Phenyl Cellosolve" Trityl Ether.—This compound was suspended in absolute ethyl alcohol and refluxed for twenty-two hours. After cooling, 78% of the original material was recovered. From the residue obtained from the mother liquor, a trace of triphenylcarbinol ethyl ether was finally isolated.

"Methyl Carbinol" Trityl Ether.—This product was refluxed for twenty-two hours with absolute ethyl alcohol, the solution evaporated to dryness and the residue extracted with 3–4 drops of cold methanol; the residue represented an 81% yield of triphenylcarbinol ethyl ether. However, when a sample of the derivative was refluxed overnight with 95% alcohol, there was fractionally crystallized from the reaction mixture both triphenylcarbinol (39% yield) and triphenylcarbinol ethyl ether (18% yield). Finally, when refluxed for sixteen hours with 65% alcohol, the solution evaporated to dryness and the residue recrystallized, a 47% yield of triphenylcarbinol was obtained.

Summary

1. The trityl ethers of the cellosolves and the ditrityl ethers of the glycols represent easily prepared, nicely crystalline derivatives for their identification.

2. No purification or dehydration of the reactants is necessary in most cases.

CAMBRIDGE, MASSACHUSETTS RECEIVED OCTOBER 7, 1940

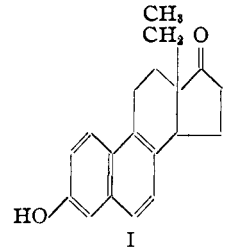
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of Compounds Related to the Sex Hormones. A Homolog of Equilenin Containing an Angular Ethyl Group

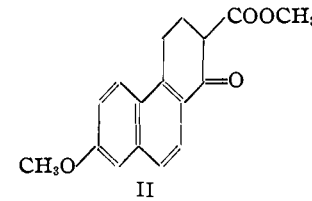
BY W. E. BACHMANN AND D. W. HOLMES

All of the sex hormones and apparently all of the other steroids possess an angular methyl group at C_{13} between the C and D rings. We have now replaced the angular methyl group of the sex hormone equilenin by an angular ethyl group in order to determine what effect such a structural change would have on the estrogenic activity of the molecule. Previous studies have demonstrated that changes in the configuration or structure of the equilenin molecule may result in loss of estrogenic activity. Thus, the diastereoisomers[1] of the hormone possess little activity, and removal[2] of the C_3-OH or shifting[3] it to C_6 is accompanied by loss of the estrogenic property.

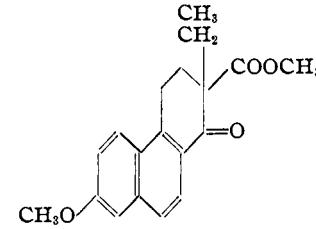
3-Hydroxy-19-methyl-17-equilenone[4] (I), the homolog of equilenin containing an angular ethyl group, was prepared in *cis* and *trans* forms, both of which are racemic mixtures. For the synthesis of these compounds, the methyl ester of 7-methoxy-1-keto-1,2,3,4-tetrahydro-2-phenanthroic acid (II), an intermediate in the synthesis of equilenin, was used as starting material. The sodio derivative of this compound reacted with ethyl iodide to give III, which was allowed to react with zinc and methyl bromoacetate.



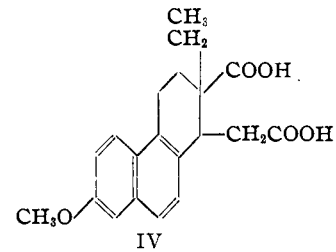
I



II



III



IV

The resulting hydroxy ester was dehydrated and hydrolyzed to give the unsaturated acids which were reduced to a mixture of the *cis* and *trans* forms of 7-methoxy-2-ethyl-2-carboxy-1,2,3,4-tet-

(1) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).
(2) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940).
(3) Bachmann and Holmes, *ibid.*, **62**, 2750 (1940).
(4) For the nomenclature employed for these compounds see Reference (2).

rahydrophenanthrene-1-acetic acid (IV). The two forms of this acid were separated and designated as α and β since it is not known which has the *cis* and which the *trans* configuration. Each acid was then carried through the remaining steps according to the procedures employed in the synthesis of equilenin and isoequilenin.[1] The intermediates and the final product (I) obtained from the α acid were given the prefixes α, while the series of compounds obtained from the β acid were designated as β forms. Inasmuch as the formulas of the intermediates are exactly like those formed in the synthesis of equilenin except for the substitution of an ethyl group for the angular methyl group, the formulas are not repeated here.

The compounds were tested for estrogenic activity by injecting them into ovariectomized rats (Dr. J. T. Bradbury). The α-*dl*-3-hydroxy-19-methyl-17-equilenone failed to induce the estrus response when injected in doses as high as 500 γ. On the other hand, the β racemic mixture proved to be active in 100 γ doses. Inasmuch as *dl*-equilenin required about 60–70 γ to give the response in rats under the same conditions, it is evident that substitution of an ethyl group for the angular methyl group has not resulted in any materially decreased activity. We are now attempting to resolve the β racemic mixture into its optically active forms since in the equilenin series one form (the natural hormone) is thirteen times as active as its antipode.[1]

From a comparison of the biological results we feel justified in assuming that the β-3-hydroxy-19-methyl-17-equilenone possesses the configuration of *dl*-equilenin, the α-form corresponding to *dl*-isoequilenin. This is supported by the relative solubilities of the two forms of the reduced acids (IV) in the two series. In both series one form (the α form) crystallizes readily from xylene–acetic acid, the other form remaining in solution. Both the β-form of I and *dl*-equilenin are derived from the more soluble β forms of the acids.

It will be of interest to determine the effect of introducing other groups at C_{13} and experiments along these lines already have been initiated.

We are grateful to the Horace H. Rackham Fund for a generous grant which made this investigation possible.

Experimental

7 - Methoxy - 2 - ethyl - 2 - carbomethoxy - 1 - keto-1,2,3,4-tetrahydrophenanthrene (III).—To a solution of **sodium methoxide prepared from 1.8 g. of sodium and 30** cc. of anhydrous methanol was added 4.5 g. of the methyl ester of 7-methoxy-1-keto-1,2,3,4-tetrahydro-2-phenanthroic acid[1] (II) and 25 cc. of dry benzene. The mixture was refluxed for thirty minutes, during which time the solid particles dissolved and the sodio derivative appeared as a finely divided powder. Any lumps which formed were pulverized. To the mixture was added 7 cc. of ethyl iodide and the mixture was refluxed for eight hours on a steam-bath; an additional 6 cc. of ethyl iodide was added at the end of four hours. The clear cooled solution was acidified with acetic acid and the solvent was evaporated. The residue was treated with benzene and water, the benzene solution was washed twice with water and then evaporated. Recrystallization of the residue from methanol yielded 4.3 g. (87%) of crystals melting at 99–101°, which were suitable for the next step. After three recrystallizations from methanol a sample formed colorless prisms; m. p. 103–104°. The compound gave no color with alcoholic ferric solution.

Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.1; H, 6.4. Found: C, 73.3; H, 6.2.

Dimethyl Ester of 7-Methoxy-2-ethyl-2-carboxy-1-hydroxy - 1,2,3,4 - tetrahydrophenanthrene - 1 - acetic Acid.—The Reformatsky reaction using the aforementioned ethyl keto ester, zinc and methyl bromoacetate was carried out according to the procedure described.[1] From 4 g. of III 4.32 g. (88%) of the hydroxy ester melting at 145–147° was obtained. After three recrystallizations from methanol a sample formed colorless needles; m. p. 148.5–149.5°.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.4; H, 6.7. Found: C, 68.5; H, 6.5.

Dehydration of the Reformatsky Ester and Reduction of the Unsaturated Acids.—Following the procedure described[1] the hydroxy ester was treated with thionyl chloride and pyridine and the resulting chloride was heated with a methanolic solution of potassium hydroxide to give a mixture of unsaturated acids. The latter were reduced by means of sodium amalgam and water. From 3.75 g. of the hydroxy ester 3.2 g. of the reduced acids (IV) were obtained. The mixture of acids was dissolved in a hot mixture of 15 cc. of xylene and 10 cc. of acetic acid; on being cooled the solution deposited 1.4 g. (44%) of **α - 7 - methoxy - 2 - ethyl - 2 - carboxy - 1,2,3,4 - tetrahydrophenanthrene-1-acetic acid**; m. p. 233–235° d. After two recrystallizations from acetone a sample formed colorless needles; m. p. 234–236° d.

The **β-7-methoxy-2-ethyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** obtained by evaporation of the xylene–acetic acid filtrate was crystallized from chloroform; yield, 1.44 g. (45%); m. p. 206–209°. After four recrystallizations from chloroform, a sample of the acid formed colorless prisms; m. p. 210–213°.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 70.2; H, 6.4. Found: (α-form) C, 70.1; H, 6.5; (β-form) C, 70.2; H, 6.4.

Dimethyl Ester of 7-Methoxy-2-ethyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—Treatment of 1 g. of the α-acid with ethereal diazomethane yielded 1 g. of the dimethyl ester; m. p. 108–109°. After three recrystallizations from methanol a sample of the **α-form** gave colorless needles; m. p. 109.5–110.5°.

In a similar manner the dimethyl ester of the α-acid was prepared in 95% yield. A purified sample of the β-form crystallized from methanol in colorless prisms; m. p. 113–114°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: (α-form) C, 71.4; H, 6.9; (β-form) C, 71.5; H, 7.1.

7 - Methoxy - 2 - ethyl - 2 - carbomethoxy - 1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—A mixture of 1 g. of the aforementioned dimethyl ester, 10 cc. of methanol and 3 cc. of *N* sodium hydroxide solution was refluxed for two hours. After evaporation of the methanol, the residue was dissolved in warm water and the solution was filtered. Acidification of the solution gave the acid ester which was sufficiently pure for the next step.

In this manner 0.95 g. (98%) of the α-form melting at 139–141° was obtained. After two recrystallizations from acetone–petroleum ether a sample formed colorless needles; m. p. 141–142°.

The β-form was obtained in practically quantitative yield; m. p. 184–185°. A sample after three recrystallizations from acetone–petroleum ether formed colorless prisms; m. p. 186–187°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: (α-form) C, 70.6; H, 6.7; (β-form) C, 70.8; H, 6.6.

Arndt-Eistert Reaction on the Acid Esters.—This reaction was carried out in the manner described[1] except that the diazoketone in methanol was refluxed with silver oxide for three hours. From 1.4 g. of the α-acid ester 1.33 g. (88%) of the **α-dimethyl ester of 7-methoxy-2-ethyl-2-carboxy - 1,2,3,4 - tetrahydrophenanthrene - 1 - propionic acid** was obtained; m. p. 83–85°. After three recrystallizations from methanol a sample formed colorless prisms: m. p. 86–87°.

In a similar manner, 1.2 g. of the β-acid ester yielded 0.98 g. (76%) of the **β-dimethyl ester of 7-methoxy-2-ethyl - 2 - carboxy - 1,2,3,4 - tetrahydrophenanthrene - 1-propionic acid**; m. p. 81–83°. After three recrystallizations from methanol, a sample formed colorless prisms; m. p. 83.5–84.5°. A mixture of the α- and β-forms melted at 60–69°. The over-all yield of the product can be raised to the equivalent of 90% by retreating the residual oils with silver oxide in methanol and cyclizing the uncrystallizable product thus obtained by means of sodium methoxide, whereupon a 10–15% yield of the crystalline cyclic ester can be isolated.

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, 72.0; H, 7.3.

3 - Methoxy - 16 - carbomethoxy - 19 - methyl - 17-equilenone.—This compound was obtained by cyclizing the aforementioned esters by means of sodium methoxide in benzene in an atmosphere of nitrogen in the manner described.[1] From 0.4 g. of the α-dimethyl ester 0.32 g. (85%) of the α-form of the cyclized keto ester was obtained; m. p. 134–136°. After three recrystallizations from acetone–methanol a sample formed tiny colorless prisms; m. p. 137–138° (vac.) The compound gave an immediate deep blue color with alcoholic ferric chloride solution.

In like manner 0.5 g. of the β-dimethyl ester yielded 0.37 g. (81%) of the β-form of the cyclized keto ester; m. p. 165–166° (vac.). After three recrystallizations from methanol a sample formed colorless needles; m. p. 167–168.5° (vac.). With ferric chloride solution this form of the cyclized keto ester gave only a faint blue color. By retreating the residual oils the yield of crystalline product can be raised to 90%.

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

3-Hydroxy-19-methyl-17-equilenone (I).—A mixture of 0.3 g. of the aforementioned α-cyclized keto ester, 18 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid and 2 cc. of water was refluxed for twelve hours in a nitrogen atmosphere. The solvents were removed under reduced pressure and the residue was digested with warm dilute aqueous sodium hydroxide. The alkaline solution was decolorized with Norit and acidified and the product was crystallized from ethanol; yield, 0.19 g. (79%); m. p. 217–219° (vac.). After sublimation at 240° at 0.01 mm. and recrystallization from ethanol the α-form gave colorless prisms; m. p. 219–220° (vac.).

In a similar manner 0.5 g. of the β-cyclized keto ester was refluxed for twelve hours with a mixture of 40 cc. of acetic acid, 20 cc. of concentrated hydrochloric acid and 4 cc. of water in a nitrogen atmosphere. Recrystallization of the alkali-soluble portion from ethanol yielded 0.31 g. (78%) of the β-form; m. p. 251–255° (vac.). After sublimation at 250° at 0.01 mm. and two recrystallizations it formed colorless square plates; m. p. 253–255° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: (α-form) C, 81.3; H, 7.0; (β-form) C, 81.5; H, 7.0.

3-Methoxy-19-methyl-17-equilenone.—The methyl ether of the aforementioned α-compound was obtained by employing a shorter time for reaction with the acid mixture. In this manner it was possible to effect hydrolysis and decarboxylation without appreciable demethylation. A mixture of 0.3 g. of the α-cyclized keto ester, 12 cc. of acetic acid and 8 cc. of concentrated hydrochloric acid was refluxed for thirty minutes in a nitrogen atmosphere. The product obtained by evaporation of the solvents was dissolved in benzene and the benzene solution was washed twice with dilute sodium hydroxide solution and then with water. From the benzene solution 0.22 g. (88%) of the α-form was obtained; m. p. 123.5–124.5°. After two recrystallizations from methanol it formed colorless needles; m. p. 124.5–125.5°.

The β-form was best obtained by methylating the β-3-hydroxy-19-methyl-17-equilenone. A solution of 50 mg. of the latter compound in 50 cc. of 1% aqueous sodium hydroxide was shaken with 3 cc. of methyl sulfate. The product was dissolved in benzene, the solution washed with water and evaporated. After sublimation under reduced pressure and recrystallization from methanol the β-form (40 mg. or 76%) formed colorless prisms; m. p. 171–173° (vac.).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: (α-form) C, 81.7; H, 7.6; (β-form) C, 81.5; H, 7.4.

Summary

The synthesis of the *cis* and *trans* forms of a homolog of the sex hormone equilenin is described. The homolog contains an ethyl group

in place of the angular methyl group. The estrogenic activity of one of the racemic forms is of the same order as that of racemic equilenin.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 11, 1940

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

The Synthesis of Analogs of the Sex Hormones. An Analog of Equilenin Lacking the Phenolic A Ring

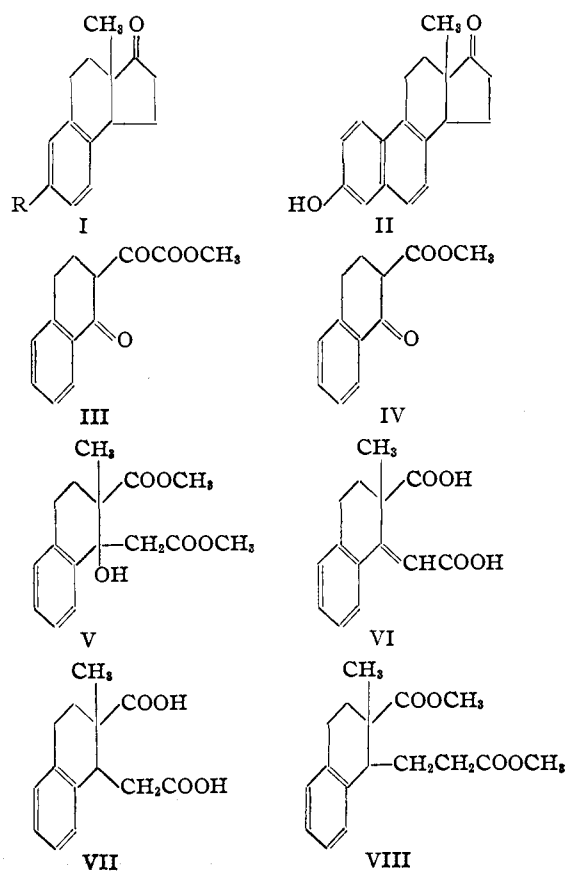
BY W. E. BACHMANN AND DONALD G. THOMAS

As part of a program concerned with the synthesis of sex hormones we have undertaken the preparation of relatively simple analogs of the estrogenic hormones in order to determine the effect of a simplification of structure on the estrogenic activity. We have synthesized 3′-keto-2-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (I, R = H), which possesses the B, C and D rings of the sex hormone equilenin (II) including the angular methyl group but lacks the phenolic A ring.

This compound was synthesized in *cis* and *trans* forms from 1-tetralone by employing the procedures developed in this Laboratory for the synthesis of equilenin.[1] The 2-glyoxalate (III), which was formed by condensation of 1-tetralone with dimethyl oxalate, was decarbonylated smoothly when heated with powdered glass and 2-carbomethoxy-1-tetralone (IV) was obtained in 94% yields. This result is in contrast to that obtained by Hückel and Goth[2] in the pyrolysis of the corresponding ethyl ester without the use of powdered glass. Under their conditions, considerable resinification and decomposition of the glyoxalate occurred which reduced the yield of product to 58%. Methylation of IV followed by a Reformatsky reaction using methyl bromoacetate yielded a hydroxy ester (V) which was dehydrated and hydrolyzed to a mixture of the geometrical isomers of the unsaturated acid (VI). The latter were reduced smoothly by sodium amalgam in alkaline solution to a mixture of the *cis* and *trans* forms of 2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid (VII). The diastereoisomeric forms of the acid were formed in a ratio of about 4:1; this proportion was not appreciably changed when catalytic hydrogenation was employed. Since the configurations of the acids are not known, the prefix α is assigned to one and β to the other, and these prefixes are given to the intermediates and the final products obtained from each of the two forms.

The cyclopentanone ring was constructed by lengthening the acetic acid side chain of VII to a propionic acid group through the Arndt–Eistert reaction, cyclizing the dimethyl ester of the dicarboxylic acid (VIII) and hydrolyzing and decarboxylating the cyclic keto-ester (IX) to I. One of the forms of I is a liquid at ordinary temperature, the other a crystalline solid.

We have also built up a six-membered ring to give 11-methyl-1-keto-octahydrophenanthrene (XI, R = H) by lengthening the propionic



(1) Bachmann, Cole and Wilds, THIS JOURNAL, 62, 824 (1940).
(2) Hückel and Goth, *Ber.*, 57, 1285 (1924).