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

The Synthesis of Four Homologs of the Sex Hormone Equilenin

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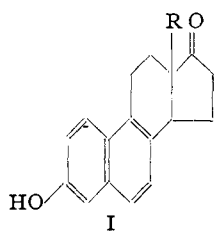
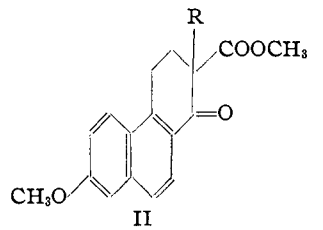
In continuation of our previous studies on the synthesis of sex hormones and related compounds,[1] we have synthesized a number of homologs of equilenin. We were interested in determining the effect on the estrogenic activity of replacing the angular methyl group of equilenin by the *n*-propyl group and the *n*-butyl group, particularly since the estrogenic activity of one of the racemic forms of the homolog containing the angular ethyl group[1d] was found to be of the same order as that of racemic equilenin. Accordingly, we have prepared 3-hydroxy-19-ethyl-17-equilenone[2] (I, R = $CH_2CH_2CH_3$), a homolog containing an angular *n*-propyl group, and 3-hydroxy-19-*n*-propyl-17-equilenone (I, R = $CH_2CH_2CH_2CH_3$), which contains an angular *n*-butyl group.

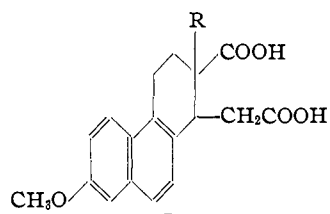


I

The two hormone homologs were synthesized in *cis* and *trans* forms, each of which is a racemic mixture, although one form of the butyl homolog has not yet been obtained crystalline. In both series, the starting material was 7-methoxy-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene, into which the *n*-propyl and *n*-butyl groups were introduced to give II (R = $CH_2CH_2CH_3$ and $CH_2CH_2CH_2CH_3$, respectively). By procedures previously described,[1a] these alkyl keto esters were converted to a mixture of the *cis* and *trans* forms of the dicarboxylic acids III, which were separated into the two racemic forms. The acids were designated as α and β, since it is not known which is the *cis* and which is the *trans* form. Similarly, these prefixes have been assigned to the intermediates and final products which were derived from the acids by the method used to prepare equilenin and related compounds.[1]

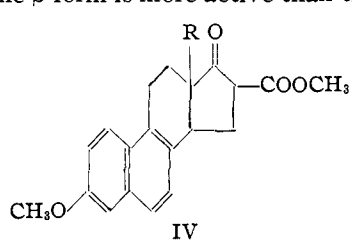


II



III

It seems worth while to mention an observation which we have made on the cyclic keto esters (IV), which are intermediates in the synthesis of the hormone and its homologs, which may have some bearing on the problem of the configuration at the C/D ring fusion. Of the compounds of this series which have been prepared so far (R = methyl, ethyl, *n*-propyl and *n*-butyl), one of the forms (the one we have designated by the prefix α) gives an immediate deep blue color with an alcoholic solution of ferric chloride, while the other form (the β form) with the same reagent gives either no color or only a faint color which develops slowly. Moreover, in the three instances where the estrogenic activities of both forms are known, the β form is more active than the α form.



IV

Tests for estrogenic activity have been carried out on the racemic forms of the products. The results are presented in Table I; included for comparison are the activities of the racemic compounds containing the angular methyl and angular ethyl groups.

(1)(a) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940); (b) Bachmann and Wilds, *ibid.*, **62**, 2084 (1940); (c) Bachmann and Holmes, *ibid.*, **62**, 2750 (1940); (d) *ibid.*, **63**, 595 (1941); (e) Bachmann and Thomas, *ibid.*, **63**, 598 (1941).

(2) For the nomenclature employed for these compounds see reference 1b. It should be noted that the parent substance contains an angular methyl group, the carbon of which is C_{18}. Hence, the homolog containing the angular *n*-propyl group is the 19-ethyl derivative.

TABLE I

ESTROGENIC ACTIVITY OF THE *dl*-FORMS OF I

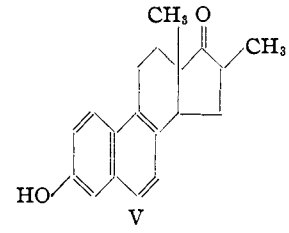
Angular alkyl group R	Estrogenic activity[a] α-Form	β-Form
Methyl	Inactive at 500γ	About 60γ[b]
Ethyl	Inactive at 1000γ	100γ
n-Propyl	250γ	25γ
n-Butyl	*c*	Inactive at 1000γ

[a] The values represent the amounts necessary to produce the estrus response in ovariectomized rats which is given by 1γ of estrone (full response in at least 50% of the animals) under the same conditions. [b] Racemic form of equilenin. This value is estimated from the activity of *d*-equilenin (30γ) and *l*-equilenin (400γ) separately. [c] This form has not yet been obtained crystalline.

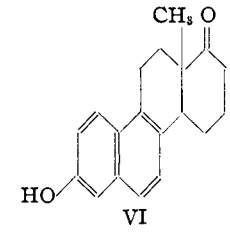
From the table it is apparent that the estrogenic activity of the molecule is retained by replacing the angular methyl group of equilenin by the *n*-propyl group. Even the α-form of the *n*-propyl homolog shows appreciable activity. It probably would be unwise to draw conclusions concerning the relative potencies of the β series of compounds containing the angular methyl, ethyl and *n*-propyl groups, even though the assays were carried out under as similar conditions as possible. The introduction of the angular *n*-butyl group decreased the estrogenic activity, if we are correct in our assumption that the form which was tested has the same configuration as racemic equilenin. We shall be in a better position to judge this point when the other form of this compound has been obtained in crystalline form and tested.

In order to determine the effect of a methyl group adjacent to the carbonyl group, we have prepared *dl*-16-methylequilenin and *dl*-16-methylisoequilenin (both represented by the structural formula V). For their preparation we employed the two forms (*cis* and *trans* with reference to the C/D ring fusion) of the cyclic keto ester (IV, R = CH_3), which were intermediates in the synthesis of *dl*-equilenin and *dl*-isoequilenin.[1a] It is of interest that the isoequilenin derivative after treatment with sodium methoxide reacted readily with methyl iodide to give an excellent yield of the methylated compound, which was then hydrolyzed, decarboxylated and demethylated to give *dl*-16-methylisoequilenin. On the other hand, it proved to be difficult to introduce a methyl group into the equilenin derivative by the same means, and the final *dl*-16-methylequilenin was obtained in poor over-all yield.

In ovariectomized rats 1000γ of *dl*-16-methylisoequilenin failed to induce the estrus response and *dl*-16-methylequilenin was inactive in 500γ doses but gave some indication of activity at 1000γ. This result shows that the introduction of a methyl group next to the carbonyl group markedly decreases the estrogenic activity of the equilenin molecule.



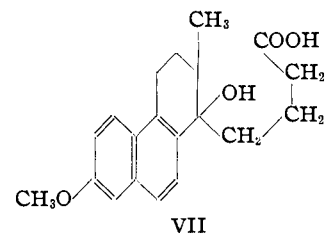
V



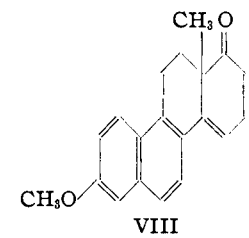
VI

dl-D-Homoequilenin and *dl*-D-homoisoequilenin (both represented by the structural formula VI) have also been synthesized in order to determine the effect on the estrogenic activity of enlarging the five-membered D ring of the hormone to a six-membered ring. These were prepared from the two dicarboxylic acids (III, R = CH_3) which were intermediates in the synthesis of racemic equilenin and isoequilenin. In the preparation of the latter compounds, the acetic acid side chain had been lengthened to a propionic acid group before cyclization; in the present study the propionic acid group was lengthened to a butyric acid group and the resulting product was cyclized to give a six-membered ring. By the usual hydrolysis, decarboxylation and demethylation the desired products were obtained, whose configurations are definitely known with respect to racemic equilenin.

Recently, Burnop, Elliott and Linstead[3] cyclized VII by means of phosphorus pentoxide in benzene to an unsaturated ketone which they believed possessed the structure VIII. According to them, cyclization to the aromatic ring, though considered less likely, could not be excluded entirely. Catalytic reduction of VIII yielded the



VII



VIII

saturated ketone. If the structure proposed by them is correct, then their final product must be the methyl ether of either *dl*-D-homoequilenin or *dl*-D-homoisoequilenin. Through the courtesy of Dr. R. P. Linstead, who kindly furnished us

(3) Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

with a sample of their product, we were enabled to make a direct comparison and found that their compound was identical with our methyl ether of *dl*-D-homoequilenin. This shows that cyclization of VII proceeded as they believed and, furthermore, brings out the interesting point that on reduction of VIII there was produced in the saturated ketone the same configuration at the C/D ring fusion that is present in the natural hormone equilenin.

dl-D-Homoisoequilenin was inactive in doses of 1000γ, but *dl*-D-homoequilenin induced an estrus response at 100γ equivalent to that given by 1γ of estrone. The latter result shows that enlargement of the D ring to a six-membered ring did not materially affect the estrogenic activity of the molecule.

We are grateful to Miss Helen C. McRae of the Department of Gynecology and Obstetrics of this University for carrying out the biological tests and to the Horace H. Rackham School of Graduate Studies for a generous grant which made possible this investigation.

Experimental

3-Hydroxy-19-ethyl-17-equilenone

7-Methoxy-2-*n*-propyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene (II, R = $CH_2CH_2CH_3$).—To a solution of sodium methoxide prepared from 2.3 g. of sodium and 45 cc. of anhydrous methanol was added 5.68 g. of finely powdered 7-methoxy-2-carbomethoxy-1-keto-tetrahydrophenanthrene[1a] and 25 cc. of dry benzene. The reaction with 14 cc. of *n*-propyl iodide was carried out by employing the same procedure and time used for the ethyl derivative.[1d] By recrystallization from acetone, 5.6 g. (86%) of product was obtained, which was sufficiently pure for the next step; m. p. 142.5–144°. A sample after three recrystallizations from acetone formed colorless prisms; m. p. 144–145°. It gave no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.6; H, 5.7. Found: C, 73.7; H, 5.6.

Dimethyl Ester of 7-Methoxy-2-carboxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—A Reformatsky reaction carried out on 4 g. of the aforementioned compound and methyl bromoacetate according to the procedure described[1a] yielded 4.25 g. (86%) of the hydroxy ester; m. p. 109–111°. After four recrystallizations from methanol, a sample formed colorless needles which melted at 112.5–113.5°.

Anal. Calcd. for $C_{28}H_{38}O_6$: C, 69.0; H, 7.0. Found: C, 68.9; H, 7.0.

Dehydration of the Reformatsky Ester and Reduction of the Unsaturated Acids.—Following the procedure described,[1a] the aforementioned hydroxy ester was converted to the chloride by means of thionyl chloride and pyridine, the chloride was treated with alcoholic potassium hydroxide and the resulting salts of the unsaturated acids were reduced with 2% sodium amalgam in water solution. From 4 g. of the hydroxy ester was obtained 3.3 g. of reduced acids (III, R = $CH_2CH_2CH_3$). The mixture of acids was dissolved in a boiling mixture of 8 cc. of xylene and 8 cc. of acetic acid; on cooling the solution deposited 1.1–1.3 g. (31–37%) of **β-7-methoxy-2-*n*-propyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid**; m. p. 245–253°. After three recrystallizations from acetone–chloroform, a sample formed colorless prisms; m. p. 253–255°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: C, 70.7; H, 6.6.

It was difficult to obtain pure α-acid from the acetic acid–xylene filtrate even after repeated recrystallizations of the product from various solvents. The purest α-acid which was obtained melted at 228–230°; a mixture of the α- and β-acids melted at 210–217°. The most practical procedure was to convert the acid obtained by evaporation of the acetic acid–xylene filtrate directly to the dimethyl ester.

Dimethyl Ester of 7-Methoxy-2-*n*-propyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—The esters were prepared by means of diazomethane. The crude **α-form**, obtained from the product mentioned above, melted at 95–105° and was used directly in the next step. A sample after ten recrystallizations from methanol formed clusters of colorless prisms; m. p. 109.5–111°.

The **β-form** of the ester obtained from 2.2 g. of the acid was recrystallized from methanol; yield, 2.23 g. (94%); m. p. 116–118°. After a second recrystallization, a sample was obtained in colorless leaflets; m. p. 118.5–119.5°.

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

7-Methoxy-2-*n*-propyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—A mixture of 1 g. of the dimethyl ester, 10 cc. of methanol and 2.7 cc. of 1.1 *N* sodium hydroxide solution was refluxed for two hours. The methanol was evaporated and the residue was dissolved in warm water. Acidification of the filtered solution yielded the acid ester. The **α-form** was not obtained pure; the crude acid ester (m. p. 110–118°) was used directly in the next step. The **β-form** obtained in this manner melted at 112–114°; yield, 0.94 g. (97%). After three recrystallizations from acetone–petroleum ether, a sample formed colorless rectangular plates; m. p. 116.5–117.5°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: C, 71.1; H, 7.0.

Dimethyl Ester of 7-Methoxy-2-*n*-propyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic Acid.—The acetic acid side chain of the aforementioned acid esters was lengthened by employing the procedure described[1a] with slight modifications. The acid chloride from 0.9 g. of the α-acid ester was added dropwise to a solution of diazomethane, which had been prepared from 4 g. of N-methyl-N-nitrosourea, 5 cc. of 45% potassium hydroxide and 100 cc. of ether and then dried over soda lime. The diazoketone obtained by evaporation of the ether solution was refluxed with silver oxide in methanol for three hours; from the solution 0.39–0.49 g. (40–50%) of the α-form of the desired compound was obtained; m. p. 91–94°. A sample

after four recrystallizations from methanol formed colorless needles; m. p. 96.5–97.5°. The β-form was prepared from the β-acid ester (m. p. 112–114°) in 86% yield; m. p. 81–84°. After three recrystallizations from methanol, a sample was obtained in clusters of colorless prisms; m. p. 86–87°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.4; H, 7.5. Found: (α-form) C, 72.4; H, 7.5; (β-form) C, 72.4; H, 7.5.

3-Methoxy-16-carbomethoxy-19-ethyl-17-equilenone (IV, R = $CH_2CH_2CH_3$).—The aforementioned esters were cyclized by means of sodium methoxide in benzene in an atmosphere of nitrogen in the manner described.[1a] From 0.2 g. of the α-ester, 0.15 g. (84%) of the α-form of the cyclic keto ester was obtained; m. p. 133–135°. In an experiment starting with 1.2 g. of the crude dimethyl ester of the substituted acetic acid (m. p. 95–105°) in which none of the intermediates was purified, there was obtained 0.45 g. (40% over-all yield for the three steps) of product (m. p. 133–135°). A sample after four recrystallizations from methanol formed colorless needles; m. p. 135–136° (vac.). It gave an immediate deep blue color with an alcoholic solution of ferric chloride, which gradually changed to deep purple.

In the best run, a 95% yield of the β-form of the cyclic keto ester was obtained; usually the yields varied from 70–75%; m. p. 170–172° (vac.). After four recrystallizations from methanol, a sample formed colorless needles; m. p. 172.5–173.5° (vac.). It gave no color when first added to an alcoholic ferric chloride solution, but a faint blue color developed gradually.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.4; H, 7.1. Found: (α-form) C, 74.1; H, 7.0; (β-form) C, 75.4; H, 7.1.

3-Hydroxy-19-ethyl-17-equilenone (I, R = $CH_2CH_2CH_3$).—A mixture of 0.3 g. of the aforementioned cyclic keto ester, 15 cc. of acetic acid, 12 cc. of hydrochloric acid and 3 cc. of water was refluxed in a nitrogen atmosphere for eleven hours. After evaporation of the solvents under reduced pressure, the residue was digested with sodium bicarbonate solution, which was removed, and then dissolved in warm dilute sodium hydroxide solution. Acidification of the filtered alkaline solution yielded the desired product. The α-form was evaporatively distilled at 175° and 0.01 mm. and then recrystallized from methanol; yield, 0.2 g. (83%); m. p. 153–154° (vac.). After two more recrystallizations from methanol it formed colorless prisms with the same melting point.

The β-form was recrystallized from alcohol; yield, 0.2 g. (83%); m. p. 234–237° (vac.). After evaporative distillation at 200° and 0.01 mm., it crystallized from alcohol in colorless prisms; m. p. 236–237° (vac.).

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

3-Methoxy-19-ethyl-17-equilenone.—The α-form was obtained by carrying out the hydrolysis experiment mentioned above for only thirty minutes. The residue obtained by evaporation of the solvents was dissolved in benzene, the benzene solution was washed twice with dilute sodium hydroxide solution and twice with water, the benzene was evaporated and the residue was recrystallized from methanol; yield, 77%; m. p. 100–102°. After three recrystallizations from methanol the methyl ether formed colorless prisms; m. p. 103.5–104.5° (vac.).

The β-form was obtained by dissolving 0.1 g. of the phenolic compound in 50 cc. of 10% sodium hydroxide and shaking the solution with 5 cc. of methyl sulfate for fifteen minutes. After the usual purification the methyl ether was recrystallized from methanol; yield, 88%; m. p. 146–148°. After three recrystallizations from methanol it formed colorless prisms; m. p. 148–149.5° (vac.).

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: (α-form) C, 81.7; H, 7.6; (β-form) C, 81.6; H, 7.7.

3-Hydroxy-19-*n*-propyl-17-equilenone

7-Methoxy-2-*n*-butyl-2-carbomethoxy-1-keto-1,2,3,4-tetrahydrophenanthrene (II, R = $CH_2CH_2CH_2CH_3$).—This compound was prepared from the sodio derivative of 7-methoxy-2-carbomethoxy-1-ketotetrahydrophenanthrene and butyl iodide in the manner described; yield, 89%; m. p. 107–109°. A sample after three recrystallizations from methanol formed colorless prisms; m. p. 111–112°. It gave no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.1; H, 7.1. Found: C, 74.3; H, 7.1.

Dimethyl Ester of 7-Methoxy-2-*n*-butyl-2-carboxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—This compound was obtained through the Reformatsky reaction from the aforementioned compound and methyl bromoacetate in 80% yield; m. p. 81–83°. After six recrystallizations from methanol a sample formed colorless rectangular plates; m. p. 84.5–86° with slight previous softening.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.6; H, 7.2. Found: C, 69.4; H, 7.2.

7-Methoxy-2-*n*-butyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid (III, R = $CH_2CH_2CH_2CH_3$).—Four and three-tenths grams of a mixture of the α- and β-forms of this acid was obtained from 5 g. of the aforementioned Reformatsky ester by the procedures employed on analogous compounds.[1] The acids were dissolved in a hot mixture of 6 cc. of xylene and 4 cc. of acetic acid; on standing overnight in a refrigerator the solution deposited 1.1 g. of the β-form; m. p. 223–225°. After three recrystallizations from acetone–chloroform, a sample formed colorless needles; m. p. 224–226°. The residue obtained by evaporation of the solvents from the xylene–acetic acid filtrate was dissolved in 20 cc. of hot benzene; from the solution 1 g. of the α-form of the acid crystallized; m. p. 189–191°. A sample of this α-acid after three recrystallizations from benzene formed colorless needles; m. p. 190.5–191.5°. A mixture of the α- and β-forms melted at 175–185°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.4; H, 7.0. Found: (α-form) C, 71.0; H, 7.0; (β-form) C, 71.5; H, 7.0.

The dimethyl ester of the α-acid was prepared in 93% yield by means of diazomethane; m. p. 74–76°. After three recrystallizations from methanol a sample formed colorless prisms; m. p. 75.5–77°. Similarly, a 94% yield of the dimethyl ester of the β-acid melting at 88–90° was obtained. A sample after three recrystallizations from methanol formed colorless leaflets; m. p. 90–91°.

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.4; H, 7.5. Found: (α-form) C, 72.2; H, 7.4; (β-form) C, 72.6; H, 7.4.

7-Methoxy-2-*n*-butyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—The α-form was prepared

in nearly quantitative yield from the aforementioned dimethyl ester by the procedure employed on the corresponding *n*-propyl derivative; m. p. 124–126°. After three recrystallizations from acetone–petroleum ether, a sample formed colorless needles; m. p. 125–127°.

The β-form was obtained in nearly quantitative yield; m. p. 191–193°. A sample after three recrystallizations from acetone–petroleum ether formed colorless rectangular plates; m. p. 193–194.5°.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.9; H, 7.3. Found: (α-form) C, 72.2; H, 7.3; (β-form) C, 71.6; H, 7.2.

Dimethyl Ester of 7-Methoxy-2-*n*-butyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic Acid.—This product was obtained from the aforementioned acid esters by the procedure employed for the corresponding propyl compound. The α-form was not obtained crystalline. From 1.05 g. of the β-acid ester, 0.95 g. (84%) of the β-form was obtained; m. p. 92–94°. A sample after four recrystallizations from methanol formed colorless leaflets; m. p. 95.5–96.5°.

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.6; H, 7.8. Found: C, 72.8; H, 7.7.

3-Methoxy-16-carbomethoxy-19-*n*-propyl-17-equilenone (IV, R = $CH_2CH_2CH_2CH_3$).—The aforementioned esters were cyclized by sodium methoxide in the manner described.[1a] The α-form was obtained by using a dried benzene solution of the crude reaction product obtained above; it crystallized readily from methanol; m. p. 114–116°; yield, 58% for the two steps from the above α-acid ester. A sample after three recrystallizations from methanol formed colorless needles; m. p. 115.5–116.5°. It gave an immediate deep blue color with an alcoholic solution of ferric chloride.

From 0.5 g. of the β-propionic ester, 0.3 g. (65%) of the β-form of the cyclic keto ester was obtained; m. p. 148–151°. After four recrystallizations from methanol, a sample formed colorless prisms; m. p. 153–154° (vac.). It gave no color with an alcoholic solution of ferric chloride.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.8; H, 7.3. Found: (α-form) C, 75.6; H, 7.2; (β-form) C, 75.6; H, 7.2.

3-Hydroxy-19-*n*-propyl-17-equilenone (I, R = $CH_2CH_2CH_2CH_3$).—The aforementioned cyclic keto esters were hydrolyzed, decarboxylated and demethylated in the same manner as their lower homologs. The α-form has resisted all attempts to crystallize it. From 0.3 g. of the β-cyclic keto ester there was obtained 0.21 g. (86%) of the β-form; m. p. 189–191° (vac.). After evaporative distillation at 200° and 0.01 mm. pressure and two recrystallizations from alcohol it formed colorless prisms; m. p. 191–192° (vac.).

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.8; H, 7.8. Found: (β-form) C, 81.7; H, 7.7.

3-Methoxy-19-*n*-propyl-17-equilenone.—The aforementioned compounds were methylated in alkaline solution by means of methyl sulfate. An 80% yield of the α-form melting at 90–93° was obtained from the liquid phenolic compound. After three recrystallizations from methanol it was obtained in two modifications; both colorless prisms; one melted at 93–94° (vac.) and the other at 104–105° (vac.). Only the latter modification was obtained when the methyl ether was prepared by short treatments (one-half hour) of the cyclic keto ester with the acetic acid–hydrochloric acid mixture.

The β-form from 0.14 g. of the phenolic compound was crystallized from methanol; yield, 0.11 g. (75%); m. p. 140.5–142°. After two recrystallizations from methanol it formed colorless prisms; m. p. 141–142°.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 82.0; H, 8.1. Found: (α-form) C, 81.7; H, 8.0; (β-form) C, 81.9; H, 8.0.

16-Methylisoequilenin and 16-Methylequilenin

***dl*-16-Methylisoequilenin (V).**—To a solution of sodium methoxide prepared from 0.05 g. of sodium, 3 cc. of absolute methanol and 3 cc. of dry benzene was added 0.3 g. of the methyl ether of 16-carbomethoxy-*dl*-isoequilenin,[1a] and the mixture was warmed on a water-bath for one hour. To the cooled solution was added 2 cc. of methyl iodide, the solution was allowed to remain at room temperature for one hour and then warmed on a water-bath for another hour. After acidification of the mixture with acetic acid and evaporation of the solvents, the residue was treated with benzene and water. The benzene layer was washed with sodium bicarbonate solution and with water and then evaporated, and the residue was crystallized from methanol; yield, 0.29 g. (92%); m. p. 144–146°. After three recrystallizations from methanol a sample of the **methyl ether of 16-methyl-16-carbomethoxy-*dl*-isoequilenin** formed colorless leaflets; m. p. 145.5–147° (vac.). A mixture of it and the starting material (m. p. 152.5–153.5°) melted at 131–140°. The compound gave no color with an alcoholic solution of ferric chloride.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 75.2; H, 6.7.

A mixture of 0.2 g. of the compound, 20 cc. of acetic acid, 15 cc. of hydrochloric acid and 2 cc. of water was refluxed in an atmosphere of nitrogen for eleven hours. The alkali-soluble portion after evaporative distillation at 200° and 0.1 mm. pressure was recrystallized from methanol; yield, 0.13 g. (81%); m. p. 182.5–184°. After two more recrystallizations from methanol the ***dl*-16-methylisoequilenin** formed colorless needles; m. p. 183–184° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.6; H, 7.1.

***dl*-16-Methylequilenin (V).**—Treatment of the methyl ether of 16-carbomethoxy-*dl*-equilenin[1a] in the aforementioned manner yielded no methylated product in several runs. A small amount of what appeared to be the desired product was obtained by the following procedure. After 0.2 g. of the β-dimethyl ester of 7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid had been cyclized by refluxing a benzene solution of the ester and sodium methoxide in a nitrogen atmosphere for two hours in the manner described,[1a] 1 cc. of methyl iodide was added to the cooled solution. After thirty minutes the solution was warmed on a water-bath for two hours. When the reaction mixture was worked up in the manner described above, 10–25 mg. of colorless needles was obtained; m. p. 160–163° (vac.). After two recrystallizations from methanol the **methyl ether of 16-methyl-16-carbomethoxy-*dl*-equilenin** melted at 163–164° (vac.). A mixture of this compound and 16-carbomethoxy-*dl*-equilenin (m. p. 181–182°) melted at 148–155°.

Hydrolysis and decarboxylation of 20 mg. of the compound by the procedure employed on the isoequilenin derivative yielded 10 mg. of *dl*-**16-methylequilenin**; m. p. 260–263° (vac.). After sublimation at 200° and 0.01 mm. pressure, it crystallized in colorless prisms; m. p. 261.5–263° (vac.). A mixture of it and *dl*-equilenin (m. p. 276–278°) melted at 240–253° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.1; H, 7.2.

D-Homoisoequilenin and D-Homoequilenin

3'-(7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1)-propanoic Acid.—This acid was prepared in α- and β-forms by refluxing a mixture of the dimethyl ester[1a] (α- and β-forms), 3 cc. of aqueous *N* sodium hydroxide solution and 15 cc. of methanol for two hours. After evaporation of the methanol, the residue was dissolved in hot water and the solution was acidified with dilute hydrochloric acid. The **α-form** was obtained in 98% yield; m. p. 112–117°. After four recrystallizations from acetone–petroleum ether a sample formed colorless needles which melted unsharply at 114–119°. The **β-form** crystallized from acetone–petroleum ether in colorless needles; yield, 97%; m. p. 180–183°. After three recrystallizations a sample melted at 184–185°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: (α-form) C, 70.6; H, 6.5; (β-form) C, 70.8; H, 6.6.

Dimethyl Ester of 4'-(7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1)-butanoic Acid.—The acid chlorides of the aforementioned acid esters were prepared and converted to the corresponding diazoketones by the procedure described for an analogous reaction.[1a] It was found advisable to reflux a methanol solution of the diazoketone with silver oxide for fifteen hours. From 1 g. of the α-acid ester, 0.43 g. (43%) of the **α-form** was obtained; m. p. 62–65°. After four recrystallizations from methanol a sample formed clusters of tiny needles; m. p. 66–67°. If the ester does not crystallize, the crude product can be employed for cyclization.

The β-form, obtained in a similar manner from 1.5 g. of the aforementioned β-acid ester, was sufficiently pure for cyclization after three recrystallizations from methanol; yield, 0.8 g. (49%); m. p. 117–119°. After three more recrystallizations a sample formed colorless prisms; m. p. 119–120.5°.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.9; H, 7.3. Found: (α-form) C, 71.6; H, 7.2; (β-form) C, 71.8; H, 7.2.

Cyclization of the Esters.—This was carried out by means of sodium methoxide in benzene in the manner described.[1a] From 0.2 g. of the aforementioned α-ester, 0.13 g. (71%) of the **methyl ether of *dl*-17-carbomethoxy D-homoisoequilenin** was obtained; m. p. 131–134°. After two recrystallizations from methanol, from which it separates very slowly in ill-defined crystals, a sample melted at 133–135° (vac.). There was no immediate color when the compound was added to an alcoholic solution of ferric chloride, but a reddish-purple color developed gradually.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 75.0; H, 6.7.

In a similar manner, the **methyl ether of *dl*-17-carbomethoxy-D-homoequilenin** was obtained in 76% yield from the β-ester; m. p. 154–156°. After three recrystallizations from methanol, a sample formed colorless prisms; m. p. 158.5–160° (vac.). It gave no immediate color with alcoholic ferric chloride, but a light violet color developed slowly.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.8. Found: C, 74.7; H, 6.7.

***dl*-D-Homoisoequilenin (VI).**—A mixture of 0.3 g. of the methyl ether of *dl*-17-carbomethoxy-D-homoisoequilenin, 15 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid and 2 cc. of water was refluxed for twelve hours in an atmosphere of nitrogen. After evaporation of the liquids under reduced pressure, the residue was treated with 5% sodium bicarbonate solution and then dissolved in 1–2% sodium hydroxide solution. The alkali soluble portion, obtained by acidification, was evaporatively distilled at 240° and 0.01 mm. pressure and then crystallized from alcohol; yield, 0.16 g. (67%); m. p. 236–239° (vac.). Further purification by sublimation under reduced pressure and two recrystallizations from alcohol yielded colorless prisms of the ***dl*-D-homoisoequilenin**; m. p. 239–240° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: C, 81.5; H, 7.0.

The **methyl ether,** prepared by the action of methyl sulfate on a solution of the sodium salt, was recrystallized from methanol; yield, 80%; m. p. 124–126°. After two more recrystallizations, it formed colorless rods; m. p. 125–126°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: C, 81.4; H, 7.4.

***dl*-D-Homoequilenin (VI).**—This was obtained from *dl*-17-carbomethoxy-D-homoequilenin by the procedure employed on the diastereoisomer. After evaporative distillation at 240° and 0.01 mm., it crystallized from methanol in colorless, rectangular plates; yield, 63%; m. p. 231–233° (vac.). After two additional recrystallizations, the ***dl*-D-homoequilenin** melted at 232–233° (vac.). A mixture of this compound and *dl*-D-homoisoequilenin melted at 215–230° (vac.).

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: C, 81.8; H, 7.3.

The **methyl ether was** obtained by refluxing a mixture of 40 mg. of *dl*-17-carbomethoxy-D-homoequilenin, 4 cc. of acetic acid, 1.6 cc. of concentrated hydrochloric acid and 0.2 cc. of water in an atmosphere of nitrogen for one-half hour. Dilution of the solution with water precipitated the desired product. After digestion with warm dilute alkali, it was dissolved in alcohol, the solution was boiled with Norite, filtered, concentrated and treated with water to incipient crystallization. From the solution the methyl ether crystallized in colorless, diamond-shaped plates; m. p. 213–214° (vac.). A mixture of this compound and that of Burnop, Elliott and Linstead,[3] which likewise consisted of diamond-shaped plates (m. p. 212–213°), melted at 212.5–214° (vac.). The semicarbazone of our compound melted at 244–246°; Burnop, Elliott and Linstead reported 245°. Finally, we demethylated a sample of Dr. Linstead's compound by the procedure described just above and obtained colorless plates from methanol; m. p. 232–

233° (vac.) alone and when mixed with our *dl*-D-homoequilenin (m. p. 232–233°).

Summary

The total synthesis of the *cis* and *trans* forms of four homologs of the sex hormone equilenin is described. These include a homolog containing an angular *n*-propyl group, one with an angular *n*-butyl group, a homolog with a methyl group adjacent to the carbonyl group, and one containing a six-membered D ring.

The results of tests on these compounds for estrogenic activity are reported.

ANN ARBOR, MICHIGAN RECEIVED JULY 10, 1941

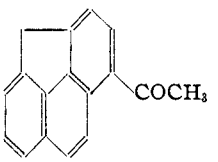
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of 1-Methyl-, 1-Ethyl-, and 3-Ethyl-4,5-methylenephenanthrene[1]

BY W. E. BACHMANN AND JOHN CLARK SHEEHAN[2]

The method which we developed for the synthesis of 4,5-methylenephenanthrene[3] appears to be a general one for the preparation of alkyl derivatives of the hydrocarbon. We have now employed it to prepare 1-ethyl-4,5-methylenephenanthrene (VIII) and 3-ethyl-4,5-methylenephenanthrene (VI) in order to prove the structures of the acetyl compounds formed by acetylation of the parent hydrocarbon.

Fieser and Cason[4] isolated the 1-substituted product from the reaction between 4,5-methylenephenanthrene and succinic anhydride. We have isolated both the 1- (I) and 3-acetyl-4,5-methylenephenanthrene (II) from the acetylation mixture in yields of 30 and 20%, respectively. The structures of the two acetyl derivatives were established by a comparison of the corresponding ethyl derivatives, formed by Clemmensen reduction, with 1- and 3-ethyl-4,5-methylenephenanthrene.



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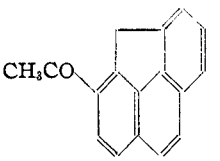
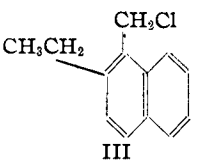


II

For the synthesis of 1-ethyl-4,5-methylenephenanthrene, ethylmagnesium bromide was condensed with 1-keto-4,5-methylenetetrahydrophenanthrene (VII), which has been described previously, and the resulting carbinol was dehydrated and dehydrogenated to the hydrocarbon by the action of palladium on charcoal at 280–300°. 1-Methyl-4,5-methylenephenanthrene was prepared in a similar manner by means of methylmagnesium iodide.

For the synthesis of 3-ethyl-4,5-methylenephenanthrene, 2-ethylnaphthalene was condensed with formaldehyde and hydrochloric acid to give 1-chloromethyl-2-ethylnaphthalene (III). The chloride was converted to the nitrile, which was hydrolyzed to 2-ethyl-1-naphthaleneacetic acid (IV). The structure of this acid was established by decarboxylation of its sodium salt to 2-ethyl-1-methylnaphthalene. Cyclization of the acid through its chloride yielded 1-ethyl-7-acenaphthenone (V), which was reduced by means of aluminum isopropoxide to 1-ethyl-7-acenaphthenol. From the latter 3-ethyl-4,5-methylenephenanthrene was prepared by the same series of steps by which 4,5-methylenephenanthrene had been prepared from 7-acenaphthenol.[3]



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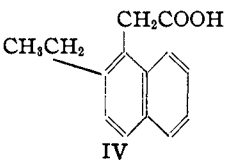

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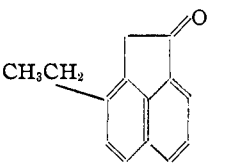

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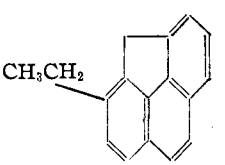

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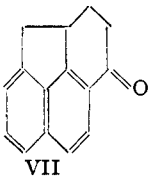

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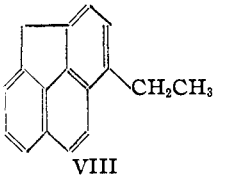

VIII

(1) Presented before the Organic Division at the meeting of the American Chemical Society, St. Louis, Missouri, April 11, 1941.

(2) From the Ph.D. dissertation of John Clark Sheehan.

(3) Bachmann and Sheehan, THIS JOURNAL, **63**, 204 (1941).

(4) Fieser and Cason, *ibid.*, **62**, 1293 (1940).