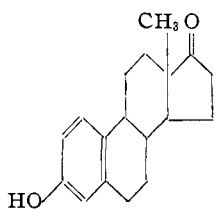
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

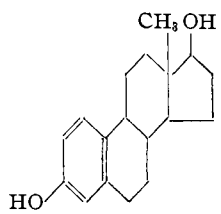
The Total Synthesis of the Sex Hormone Equilenin and Its Stereoisomers

BY W. E. BACHMANN, WAYNE COLE[1] AND A. L. WILDS[1]

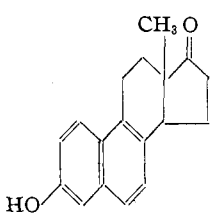
The estrogenic hormone estrone was the first sex hormone to be isolated.[2] Its isolation from pregnancy urine was reported in 1929 by Doisy, Veler and Thayer and by Butenandt. In 1932 Butenandt was able to propose a formula for estrone, which was proved to be correct in all respects by Cook and his associates. The true ovarian hormone appears to be a dihydro derivative of estrone, estradiol, which can be prepared in the laboratory by reduction of estrone. Another estrogenic hormone, equilenin, was isolated by Girard and co-workers[3] in 1932 from the urine of pregnant mares, and the structure which was proposed for it was definitely established by Cook.



Estrone



Estradiol



Equilenin

The synthesis of sex hormones and closely related compounds has engaged the attention of chemists ever since the structures of the natural products were established. One of the features of these compounds, which has been an obstacle in the synthetic path, is the presence of an angular methyl group between the C and D rings. Robinson has devised many ingenious methods for obtaining compounds which may prove useful intermediates for further synthesis. Recently he[4] succeeded in synthesizing a compound possessing the structure of equilenin except for the angular methyl group. Dane[5] has obtained an isomer of estrone by means of the Diels–Alder reaction, although the structure of the compound has not yet been established. Other important advances in the direction of the total synthesis of the sex hormones and related compounds have been made by Bardhan, Chuang, Cook, Hewett, Haberland, Kon, Linstead, Weidlich and others.[6] We have reported the synthesis of 3′-keto-1,2-cyclopentenophenanthrene and of compounds possessing a partially reduced cyclopentenophenanthrene structure.[7]

For some time we have centered our attention on a possible synthesis of equilenin. From the practical standpoint, the synthesis of this hormone possessed the advantage that equilenin contains a naphthalene nucleus and only two asymmetric carbon atoms (four stereoisomers) in contrast to the four asymmetric carbon atoms (sixteen stereoisomers) of estrone. Moreover, since Marker[8] has reported that equilenin can be reduced to estrone and to estradiol, a synthesis of equilenin would represent the synthesis of the other two hormones as well. We have succeeded in accomplishing the total synthesis of the hormone, *d*-equilenin, and also of its three stereoisomers, the antipode, *l*-equilenin, and the diastereoisomers, *d*-isoequilenin and *l*-isoequilenin. A preliminary account of the synthesis of the hormone was reported in a Communication in THIS JOURNAL.[9]

For the synthesis of these compounds we turned to the cyclic ketone, 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene (I), which was first prepared by Butenandt and Schramm[10] from the readily available 1-naphthylamine-6-sulfonic acid (Cleve's acid). We likewise started with the latter compound, but employed some of the procedures of Cohen, Cook, Hewett and Girard[11]

(1) Du Pont Post-doctorate Fellow.

(2) For an excellent review of the sex hormones including an account of the investigations leading toward their synthesis, see Fieser's monograph, "The Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1937, 2nd ed. This book gives references to the original articles up to 1937.

(3) Girard, Sandulesco, Fridenson and Rutgers, *Compt. rend.*, **195**, 981 (1932).

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

(5) Dane and Schmitt, *Ann.*, **536**, 196 (1938); **537**, 246 (1939).

(6) Chuang, Ma, Tien and Huang, *Ber.*, **72**, 949 (1939); Haberland, *ibid.*, **72**, 1215 (1939); Kon, Linstead and Simons, *J. Chem. Soc.*, 814 (1937); Linstead and Millidge, *ibid.*, 478 (1936); Weidlich and Meyer-Delius, *Ber.*, **72** 1941 (1939).

(7) Bachmann and Kloetzel, THIS JOURNAL, **59**, 2207 (1937); **60**, 2204 (1938).

(8) Marker, *ibid.*, **60**, 1997 (1938).

(9) Bachmann, Cole and Wilds, *ibid.*, **61**, 974 (1939).

(10) Butenandt and Schramm, *Ber.*, **68**, 2083 (1935).

(11) Cohen, Cook, Hewett and Girard, *J. Chem. Soc.*, 653 (1934); 445 (1935).

and introduced some modifications of our own in order to obtain the cyclic ketone. We found that the best yields in the final step were obtained by cyclizing the acid chloride of the intermediate γ-(6-methoxy-1-naphthyl)-butyric acid by short treatment with stannic chloride; by this procedure the cyclic ketone was obtained in an average yield of 91%.

From the cyclic ketone it was planned to prepare the 2-methyl-2-carbomethoxy derivative (IV) by the method used to prepare 2-methyl-2-carbethoxycyclohexanone from cyclohexanone,[12] which consisted in forming the glyoxalate of the ketone, converting it to the carbethoxy derivative by pyrolysis and introducing a methyl group between the carbonyl group and ester group by sodium alkoxide and methyl iodide. The prospect of eliminating carbon monoxide successfully from the glyoxalate (II) of 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene did not appear promising in view of Haworth's experience with the corresponding derivative of 1-keto-1,2,3,4-tetrahydrophenanthrene. Eight years ago, Haworth[13] prepared the glyoxalate IIa, but he was unable to eliminate carbon monoxide from the compound to give the 2-carbethoxy derivative; continued heating resulted in extensive decomposition of the glyoxalate.[14] In spite of this result, we ventured to try the reaction on the glyoxalate of the methoxy ketone.

Condensation of 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene with methyl oxalate by means of sodium methoxide in an atmosphere of nitrogen gave the glyoxalate II in 96% yield. When the reaction was carried out in air, the yield was decreased slightly, presumably through oxidation of the sodio derivative of the glyoxalate Like Haworth, we encountered difficulty in eliminating carbon monoxide from the glyoxalate. We were not entirely unsuccessful, for some samples of the compound underwent the reaction and the keto ester was obtained, but the results were erratic. We found, however, that by the simple expedient of adding powdered soft glass to the glyoxalate the latter smoothly lost carbon monoxide at 180°, and the keto ester III was isolated in yields of 90 to 94%.

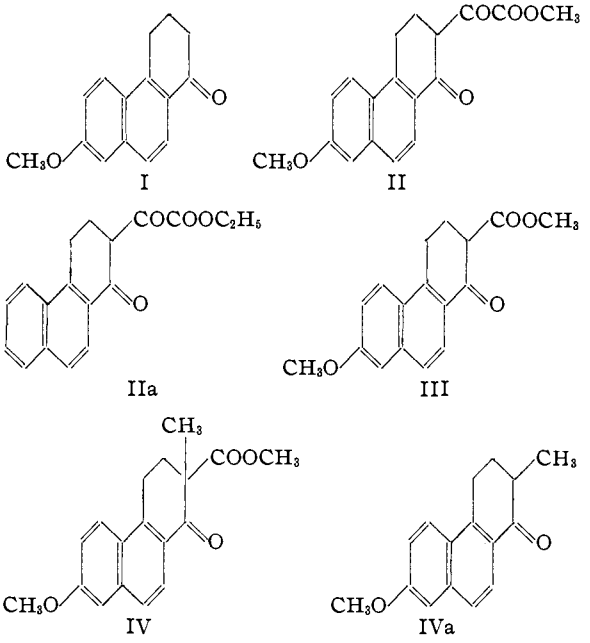
(12) Kötz and Michels, *Ann.*, **350**, 212 (1906).

(13) Haworth, *J. Chem. Soc.*, 1130 (1932).

(14) Robinson and Walker [*ibid.*, 61 (1937)] had a similar experience with a related compound, the 2-glyoxalate of 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene. They state that the carbethoxy group cannot be introduced into this unsaturated ketone by way of the glyoxalate.

This procedure will undoubtedly prove useful with other glyoxalates. We have employed it successfully on the two glyoxalates (of 1-keto- and of 4-keto-1,2,3,4-tetrahydrophenanthrene) from which Haworth was unable to obtain the carboxy derivatives. The procedure can be used to advantage even in those cases where the glyoxalate reacts normally, for in the presence of powdered glass the reaction generally proceeds at a lower temperature and in a shorter time with less resultant decomposition. For example, this has proved to be the case with the glyoxalate of α-tetralone, the yield of carbomethoxy compound (94%) being considerably greater than has been reported previously.[15]

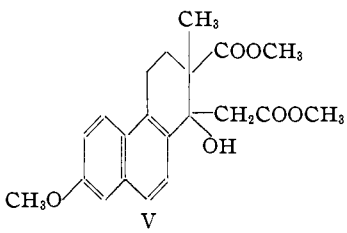
By treatment of the sodio derivative of the 7-methoxy-keto ester III with methyl iodide, 7-methoxy-2-methyl-2-carbomethoxy-1-keto-1,2,-3,4-tetrahydrophenanthrene (IV) was obtained in excellent yield.



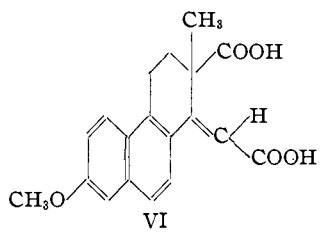
In order to build up the five-membered ring containing the carbonyl group, we proposed to introduce a propionic acid group in the 1-position, and then cyclize the dimethyl ester of the dicarboxylic acid by the Dieckmann method. First of all, conditions were determined so that a Reformatsky reaction on the keto ester IV using methyl bromoacetate gave the dimethyl ester of 7-methoxy-2-methyl-2-carboxy-1-hydroxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (V) in 85

(15) These results will be published in future communications.

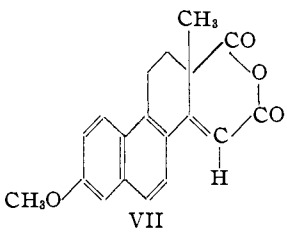
to 90% yields. This compound is susceptible to cleavage by alkali; thus, treatment with hot, concentrated aqueous potassium hydroxide stripped the molecule of its carbomethoxy and acetic ester groups and gave a good yield of 7-methoxy-2-methyl-1-keto-1,2,3,4-tetrahydrophenanthrene (IVa).[16] The same compound resulted by cleavage of IV by alkali. Accordingly dehydration was carried out on the Reformatsky ester (V), itself. This was accomplished by the indirect method, consisting in the replacement of the hydroxyl group by chlorine by means of thionyl chloride, followed by removal of the elements of hydrogen chloride by treatment with alcoholic potassium hydroxide; in this process the two ester groups also were hydrolyzed. Acidification of the alkaline solution yielded a mixture of two compounds: an unsaturated acid and an unsaturated acid anhydride. We consider the free acid and the acid corresponding to the anhydride to be geometrical isomers; to the free acid is assigned the configuration VI (in which the carboxyl group attached to the double bond extends away from the tertiary carboxyl group) and to the anhydride the structure VII.



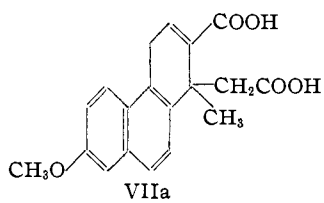
V



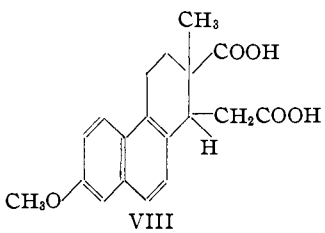
VI



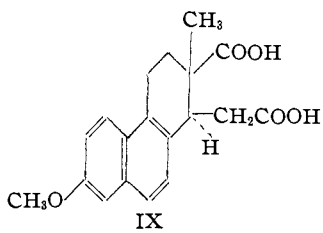
VII



VIIa



VIII



IX

In harmony with the behavior of β-aryl-α,β-unsaturated acids (cinnamic acid type), the potassium salts of the unsaturated acids from VI and VII were rapidly reduced by dilute sodium amalgam and water, and both yielded a mixture of the same two reduced acids, *cis-* (VIII) and *trans*-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (IX). These facts are proof that in the process of dehydration of the Reformatsky ester (V) no rearrangement took place, involving the migration of the methyl group to the 1-position, to form a compound having the formula VIIa, for such a compound could not give rise to an acid and anhydride of an isomeric acid which would yield a mixture of the identical reduced acids. Chuang, Tien and Huang[17] applied the Reformatsky reaction to 2-methyl-2-carbethoxycyclohexanone and converted the product by dehydration and catalytic reduction of the unsaturated compound to 2-methyl-2-carboxycyclohexane-1-acetic acid; it is of interest that they obtained only a single reduced acid.

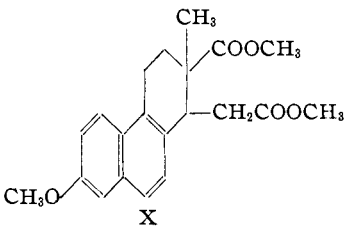
The two isomeric reduced acids, which are actually racemic mixtures, were readily separated and were found to be present in nearly equal amounts. The formation of both acids on reduction was a fortunate circumstance, for it enabled us to synthesize all four stereoisomers possessing the structure of equilenin. Each of the acids was carried through the remaining series of reactions separately, the one eventually yielding racemic equilenin, the other racemic isoequilenin. Since the configuration of the C/D ring fusion of equilenin and the other steroids is still a moot point,[18] although the *trans* arrangement appears to be favored, no definite configuration is assigned to the two acids at this time, and we withdraw the prefixes *cis-* and *trans-* which were given to the two acids in our preliminary communication.[9] Until the configurations are definitely established, the acid from which isoequilenin was finally obtained is designated as the α-acid (m. p. 231–232°), and the one yielding equilenin is called the β-acid (m. p. 213–214°).

(16) Robinson and Walker [*J. Chem. Soc.*, 183 (1938)] submitted the product of the Reformatsky reaction on 7-methoxy-2-methyl-2-carbethoxy-1-keto-octahydrophenanthrene to hydrolysis with hot, concentrated potassium hydroxide. The acidic portion consisted of an intractable oily mixture which showed evidence of containing the desired acid. The principal product (67%) was the 2-methyl-1-keto compound. It occurs to us that this may have been formed by alkaline cleavage of the Reformatsky ester rather than from unreacted starting material.

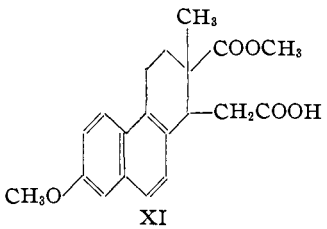
(17) Chuang, Tien and Huang, *Ber.*, **68**, 866 (1935).

(18) Peak, *Nature*, **140**, 280 (1937); Ruzicka, Furter and Goldberg, *Helv. Chim. Acta*, **21**, 507 (1938), footnote 2.

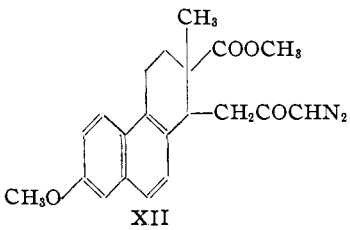
d- and *l*-**Equilenin.**—In order to lengthen the acetic acid side chain to a propionic acid group, we employed the reaction of Arndt and Eistert.[19] The β-acid was converted to its dimethyl ester (X), which was hydrolyzed readily to the acid



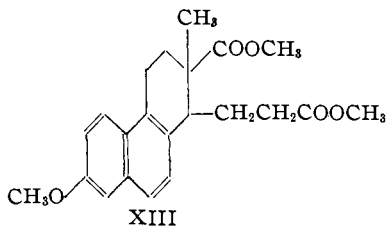
X



XI



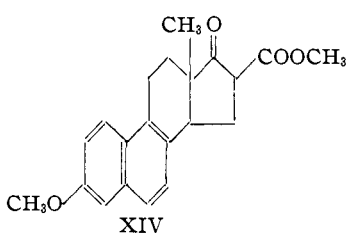
XII



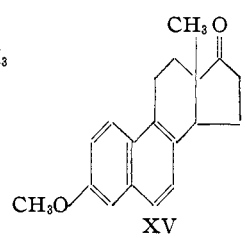
XIII

ester XI. Under the conditions employed, which consisted in the use of one equivalent of sodium hydroxide in the form of a 1% solution in methanol, only the methyl group attached to the acetic acid portion was removed, the ester group of the hindered tertiary carboxyl group being unaffected. Similar instances of partial hydrolysis of esters have been observed by others. The acid chloride, formed by interaction of the acid ester and thionyl chloride, reacted with diazomethane to yield the crystalline diazo ketone XII. When the latter compound was warmed with methanol in the presence of silver oxide, the crystalline dimethyl ester of 7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid (XIII) was obtained in 80–84% yields.[20]

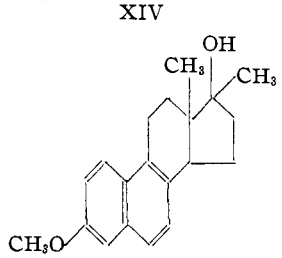
In order to effect the cyclization of the dimethyl ester XIII to XIV, we tried the action of sodium on a benzene solution of the ester containing a trace of methanol. The results by this method proved to be erratic. The powdered sodium became coated with a thin crust which effectively prevented complete reaction. Addition of methanol served to remove the coating, and all of the ester reacted, but the yield of cyclic product was only 40–50%. A thorough investigation of the reaction revealed that sodium methoxide could be used for the cyclization, and, furthermore, that the low yields of product were caused by oxidation of the substance by oxygen of the air. By running the reaction in an atmosphere of nitrogen, it was possible to prepare the methyl ether of 16-carbomethoxy-*dl*-equilenin (XIV) in 95–98% yields. By heating this compound with hydrochloric acid, the ester group was hydrolyzed and the resulting acid was decarboxylated to give the methyl ether of *dl*-equilenin (XV). When a mixture of acetic acid and hydrochloric acid was employed, it was found that even under these mild conditions the ether linkage also was cleaved and the product was *dl*-equilenin. The racemic equilenin melted at 276–278° (natural *d*-equilenin, 250–251°) and like the hormone it gave a deep red liquid when melted in air.



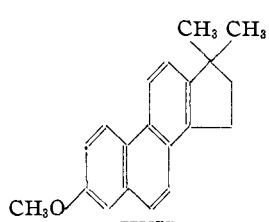
XIV



XV



XVI



XVII

The results of the brilliant investigations of Cook and co-workers[11] on the structures of estrone and equilenin were invaluable to us at this point, for we were enabled to confirm the structure of our racemic equilenin prior to resolution. By treatment with methylmagnesium iodide, the methyl ether of the racemic equilenin was converted to the carbinol XVI, which was dehydrated with migration of the angular methyl group and the dehydration product was dehydrogenated to 3′,3′-dimethyl-7-methoxy-1,2-cyclopentenophenanthrene (XVII), identical with the com-

(19) Arndt and Eistert, *Ber.*, **68**, 200 (1935); Eistert, *ibid.*, **69**, 1074 (1936).

(20) While this work was in progress, Litvan and Robinson [*J. Chem. Soc.*, 1997 (1938)] applied the Arndt-Eistert reaction to a closely related compound, which they obtained by degradation of estrone. They were able to isolate the pure, crystalline propionic acid derivative in about 1% yield.

pound obtained in the same manner from natural equilenin.

The *dl*-equilenin was resolved by converting it to the *l*-menthoxyacetic esters by reaction with *l*-menthoxyacetyl chloride. From the mixture of diastereoisomeric esters was isolated the ester (m. p. 174–174.5°) which on hydrolysis yielded *d*-equilenin.

l-Equilenin, the optical antipode of the natural hormone, was isolated by employing the action of *d*-menthoxyacetyl chloride on the racemic equilenin, or on the mixture obtained after some of the *d*-equilenin had been removed. It possesses the same melting point and specific rotation (opposite in sign) as the natural hormone. Its estrogenic activity is presented in Table III.

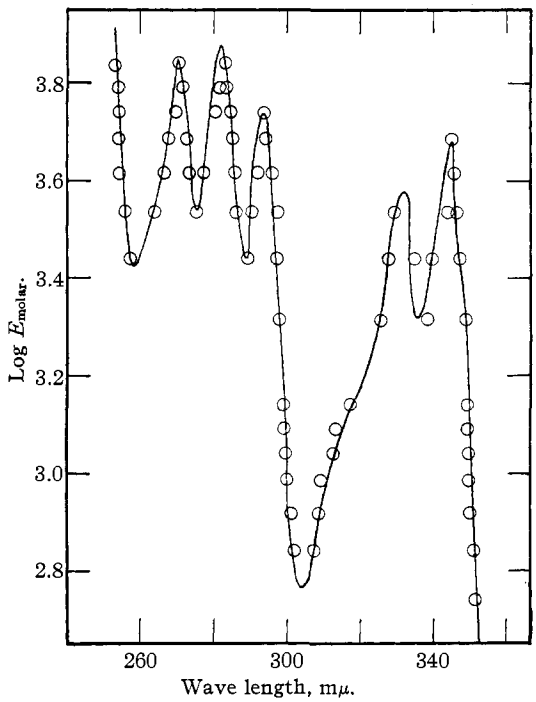


Fig. 1.—Ultraviolet absorption curve of equilenin, showing the logarithm of the extinction coefficient at various wave lengths. The solid line represents the curve for natural equilenin, the circles the values for synthetic *d*-equilenin.

Comparison of Synthetic *d*-Equilenin with the Hormone Equilenin.—The synthetic *d*-equilenin proved to be identical with the natural hormone in all respects. The identity of the two compounds was established by a determination of the melting points and mixed melting points of the hormone and a number of derivatives, by a comparison of the optical rotation, estrogenic activity, absorption spectrum and crystallographic properties. A comparison of the melting points and mixed melting points of the synthetic and natural equilenin and six derivatives is given in Table I.

TABLE I

COMPARISON OF MELTING POINTS[a]

Compound	Melting points, °C. Synthetic	Natural	Mixed
d-Equilenin	250–251	250–251	250–251
Benzoate	222.5–223	222.5–223.5	222.5–223.5
Acetate	156–157	156–156.5	156–157
l-Menthoxyacetic ester	174–174.5	173–173.5	173.5–174.5
Methyl ether	193.5–194	194–194.5	194–194.5
Trinitrobenzene complex	205.5–207	206.5–207.5	206–207
Methyl carbinol of methyl ether (XVI)	132.5–133.5	132–134.5	132.5–134.5

[a] M. p. (uncor.) determined in vacuum. The melting points of equilenin and its derivatives are in general unsatisfactory when determined in open capillary tubes because of the oxidation of the compounds to red products. By determining the melting points in sealed, evacuated (0.2 mm.) tubes, the melts remained colorless; on being cooled, the melts quickly solidified and when heated the solids showed the same melting points as before.

The specific rotation of the synthetic equilenin, $[\alpha]^{30}D$ + 84° (dioxane) agreed with the value reported for natural equilenin, $[\alpha]^{16}D$ + 87° (dioxane).[3] In estrogenic activity the synthetic hormone was indistinguishable from the natural product. In each case a dose of 30 γ produced estrus in 50% of the rats tested (Dr. Bradbury).

A comparison of the ultraviolet absorption spectrum of the synthetic and natural hormones was kindly made by Mr. Nelson V. Seeger. From Fig. 1 and the values for the maxima given in Table II, it can be seen that agreement is satisfactory throughout. This curve for the absorption spectrum in ether agrees with that of natural equilenin in alcohol given by Dirscherl and Hanusch[21] and supplemented by Wintersteiner, *et al.*,[22] in the location of the bands. However, the value of log *E* for the maximum at 282 mμ. was somewhat smaller and that for the maximum at 294 mμ. was somewhat larger than those pre-

TABLE II

COMPARISON OF POSITIONS AND INTENSITIES OF ABSORPTION SPECTRUM MAXIMA

Natural equilenin Wave length, mμ.	Log E_{molar}	Synthetic *d*-equilenin Wave length, mμ.	Log E_{molar}
270	3.85	270	3.84
282	3.87	283	3.84
294	3.74	294	3.74
332	3.58	329	3.54
345	3.68	345	3.68

(21) Dirscherl and Hanusch, *Z. physiol. Chem.*, **233**, 13 (1935).

(22) Wintersteiner, Schwenk, Hirschmann and Whitman, THIS JOURNAL, **58**, 2052 (1936).

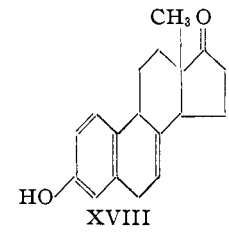
viously reported, while the minima were uniformly lower.

We are indebted to Dr. Chester B. Slawson of the Mineralogy Department for making a comparison of the crystals of the two compounds. He reports that the natural and synthetic equilenin have identical crystallographic properties. When crystallized from dilute alcohol, both formed elongated needles (probably orthorhombic) which are flattened in one direction. In both cases the crystals possessed the following optical properties: biaxial negative; $r > v$; α_D, 1.509 (± 0.001); β_D, 1.718 (± 0.001); γ_D, 1.800 (± 0.010).[23] β may be measured parallel to the elongation and α across the flattened needles. β and γ show very strong dispersion nearly exactly equivalent to that of methylene iodide.

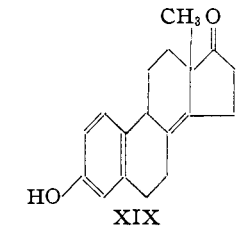
From all of these comparisons it is apparent that there is an exact agreement between the synthetic and natural hormone in all respects. The synthesis completely establishes the correctness of the structural formula which has been proposed for equilenin.

d- and *l*-**Isoequilenin.**—The α-acid (VIII or IX), when carried through the same series of reactions used on the isomeric acid, yielded *dl*-isoequilenin, which has the same structural formula as equilenin but a different spatial configuration. The *dl*-isoequilenin exists in two forms, one melting at 206–206.5°, the other 223–224°. Like the corresponding equilenin derivative, the methyl ether of isoequilenin could be converted to 3′,3′-dimethyl-7-methoxy-1,2-cyclopentenophenanthrene (XVII), although the yield of the product was poor. Attempts to resolve *dl*-isoequilenin by means of *l*-menthoxyacetyl chloride and certain other active compounds were unsuccessful, but resolution of the α-acid was accomplished readily. By reaction of the acid chloride of the α-acid ester (XI) with *l*-menthol, two diastereoisomeric methyl-*l*-menthyl esters were obtained, from which a pure ester was isolated. The pure active *l*-methyl-*l*-menthyl ester was hydrolyzed to the active α-acid, which was then carried through the series of reactions previously described, to yield *d*-isoequilenin. The mixture of methyl-*l*-menthyl esters remaining after removal of the pure individual was hydrolyzed to the dicarboxylic acids and the latter converted to the dimethyl esters (X). It was found possible at this stage to separate nearly completely the *d*-dimethyl ester from the *dl*-dimethyl ester which was present by taking advantage of the great difference in solubility and crystalline forms of the compounds. From the *d*-dimethyl ester was prepared *l*-isoequilenin. Both active forms of isoequilenin melted at the same temperature (257–258°) and possessed equal but opposite specific rotations (Table III).

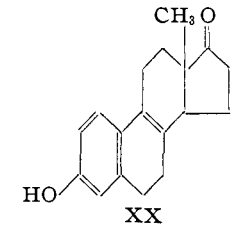
Recently, Hirschmann and Wintersteiner[24] have converted the hormone equilin (XVIII) to an isomer of equilenin which they called 14-*epi*-equilenin. The transformation was accomplished by isomerizing equilin to isoequilin A (XX) by hydrogen chloride in boiling acetic acid. While dehydrogenation of equilin gives equilenin, dehydrogenation of isoequilin A gives the isomer of equilenin, 14-*epi*-equilenin. In the process of isomerization, epimerization at C_{14} takes place, presumably through an intermediate such as XIX. Inasmuch as equilenin can have only one dextrorotatory diastereoisomer, it follows that their 14-*epi*-equilenin (which is dextrorotatory) must be identical with our *d*-isoequilenin. A comparison of the two compounds and their acetates, which was kindly carried out by Dr. Wintersteiner, left little doubt about the identity of the samples of isoequilenin and 14-*epi*-equilenin.



XVIII



XIX



XX

As Hirschmann and Wintersteiner have pointed out, the configuration of the *d*-isoequilenin at C_{13} is the same as that of natural *d*-equilenin. It follows that the configurations of all of the stereoisomers of the natural hormone, which we have prepared, are established with reference to it.

In Table III are summarized some of the chief

(23) Gaudefroy, *Compt. rend.* **195**, 983 (1932), reports the following values for the refractive indices of natural equilenin: α, 1.51; β, 1.718.

(24) Hirschmann and Wintersteiner, *J. Biol. Chem.*, **126**, 747 (1938).

properties of the four stereoisomers and the two racemic compounds which we have prepared; included is a comparison of the estrogenic activities of the optically active compounds. These values are taken from the results of Dr. James T. Bradbury of the Department of Obstetrics and Gynecology.

TABLE III

PROPERTIES OF THE SYNTHETIC COMPOUNDS

Compound	M. p. (vac.), °C.	$[\alpha]_D$ dioxane	Estrogenic activity,[a] γ
d-Equilenin	250–251	+ 84	30
l-Equilenin	250–251	− 85	400
dl-Equilenin	276–278[b]	0	..
d-Isoequilenin	257–258[c]	+147	>500[e]
l-Isoequilenin	257–258[c]	−147	>500[e]
dl-Isoequilenin	223–224[d]	0	..

[a] Amount required to produce estrus in more than 50% of the rats tested. [b] Another form, m. p. 287–288°. [c] Another form, m. p. 272–273°. [d] Another form, m. p. 206–206.5°. [e] A dose of 500 γ produced only pro-estrus in about 25% of the rats, the rest being negative. Larger doses are being tested.

From the table it is apparent that the natural *d*-equilenin is more than thirteen times as active as its antipode, *l*-equilenin, and that both forms of isoequilenin are less potent than the forms of equilenin. It is of interest that here, as in the case of the four known forms of androsterone, the isomer with the greatest physiological activity is the one which occurs naturally.

In this investigation we usually endeavored to determine the conditions for obtaining maximum yields of the intermediates. Frequently this necessitated running a reaction twenty to thirty times under varying conditions before the optimum conditions were discovered. In this way it was sometimes possible to double the yield originally obtained and in nearly all cases we were able to raise the yields to about 90%. As a consequence of this, although numerous steps were involved, ten grams of 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene(I) yielded about two and one-half grams of *dl*-equilenin and the same amount of *dl*-isoequilenin.

Having successfully worked out the experimental conditions for the reactions in this investigation, it appeared of interest to determine whether they could be applied to similar reactions leading to the synthesis of other steroids, such as estrone, vitamin D and related compounds. As a matter of fact, the procedures have already proved successful in the synthesis of desoxyequilenin and desoxyisoequilenin. Moreover, the structural isomer of equilenin with the hydroxyl group in the 6-position has been prepared in both *cis* and *trans* forms by Mr. David W. Holmes in this Laboratory. It has proved a simple matter to introduce other alkyl groups in the position occupied by the angular methyl group, as well as to build up a six-membered D ring. In addition simple analogs of the sex hormones have been synthesized. These compounds should furnish interesting information in regard to the relation between structure and estrogenic activity.

We are extremely grateful to Dr. Oliver Kamm of Parke, Davis and Company for his generosity in supplying us with natural equilenin for purposes of comparison.

Experimental

The melting points of a number of compounds that were found to oxidize in air were determined in sealed, evacuated (0.2 mm.), capillary tubes; these values are indicated by (vac.).

β-(6-Methoxy-1-naphthyl)-ethyl Bromide.—1-Naphthylamine-6-sulfonic acid (Cleve's acid) was fused with alkali and the resulting aminonaphthol was acetylated and methylated according to the procedure of Butenandt and Schramm.[10] Hydrolysis of the 6-methoxy-1-acetylaminonaphthalene was accomplished by refluxing a mixture of 200 g. of the compound, 200 cc. of water and 250 cc. of concentrated hydrochloric acid for fifteen to twenty minutes. All of the compound went into solution and then the hydrochloride of 6-methoxy-1-naphthylamine began to precipitate. The hydrochloride which was filtered from the cooled solution was sufficiently pure for diazotization and conversion to 6-methoxy-1-iodonaphthalene, which was carried out according to the directions of Cohen, Cook, Hewett and Girard.[11]

A solution of 57 g. of 1-iodo-6-methoxynaphthalene and 21 g. of ethyl bromide in 150 cc. of benzene was added in six portions to 9.8 g. of powdered magnesium and 100 cc. of ether in a 1-liter flask. Refluxing was continued for five hours after all of the reagent had been added. The Grignard reagent was diluted with 200 cc. of dry benzene, the solution cooled to 5° and ethylene oxide gas after passing through a tube containing potassium hydroxide was led to within an inch of the surface of the solution. During the addition of 24 g. of ethylene oxide the solution was swirled every few minutes. After standing at room temperature for eight hours, the mixture was warmed to 50–80° for one hour. The mixture was hydrolyzed with ammonium chloride solution and cold 5% hydrochloric acid (about 30 cc.) was added until the emulsion broke. After being washed and dried, the organic layer was distilled; the product boiling at 140–185° at 1 mm. was found to be suitable for conversion to the bromide, although it contained some nerolin; yield, 31–34 g. (76–84%). This method is patterned after that of Cohen, Cook and Hewett.[11]

An ice-cold solution of 40.4 g. of β-(6-methoxy-1-naphthyl)-ethyl alcohol in 125 cc. of dry benzene was treated with a solution of 40 g. of phosphorus tribromide in 50 cc.

of benzene with swirling; the mixture was then kept at 60–75° for three hours. The cooled mixture was poured onto ice and water and worked up according to the procedure of Cohen, Cook and Hewett.[11] The total yield of bromide boiling at 160–175° at 0.6 mm. was 40–42 g. (75–79%).

γ-(6-Methoxy-1-naphthyl)-butyric Acid.—Ten grams of sodium (thin slices) in 25 cc. of benzene was treated with absolute alcohol (about 30 cc.) in portions until all of the sodium had reacted. One hundred grams of malonic ester was introduced and the mixture was warmed with swirling until a clear solution resulted. To the cooled solution was added 79.5 g. of β-(6-methoxy-1-naphthyl)-ethyl bromide in 100 cc. of benzene. After being warmed at 70–80° in a water-bath for eight hours, the mixture was refluxed on a steam-bath for four hours.

The warm solution was poured cautiously into a hot solution of 112 g. of potassium hydroxide in 150 cc. of water and 50 cc. of alcohol (2-l. flask); hydrolysis proceeds rapidly as the solutions mix. The benzene and much of the alcohol were removed in a current of air, more water was added and the turbid solution was heated for two hours on a steam-bath, then cooled and extracted with benzene. The clear aqueous solution was poured with stirring into 275 cc. of concentrated hydrochloric acid. The colorless plates of the substituted malonic acid were filtered from the chilled solution and dried. The product obtained by decarboxylation at 200° was poured while still hot into acetic acid, and the solution diluted with water. The yield of γ-(6-methoxy-1-naphthyl)-butyric acid melting at 149–150° was 55–65 g. (75–89%) depending on the purity of the bromide. Cohen, Cook and Hewett[25] prepared this acid (m. p. 150–151°) by means of potassiomalonic ester in boiling toluene.

7 - Methoxy - 1 - keto - 1,2,3,4 - tetrahydrophenanthrene (I).—Five grams of powdered γ-(6-methoxy-1-naphthyl)-butyric acid was added to a cold solution of 25 cc. of anhydrous ether, 2.4 cc. of thionyl chloride and 2 drops of pyridine. The mixture was allowed to stand at room temperature with occasional swirling until all of the solid had disappeared (about three hours). The mixture was warmed to 35° for ten minutes and the solvent removed under reduced pressure (water pump). Two cc. of benzene was added and then removed by means of a water pump and finally by means of an oil pump in order to remove completely the unreacted thionyl chloride, the acid chloride being warmed finally to 35°. A solution of the acid chloride in 100 cc. of benzene was cooled in a freezing mixture until the benzene began to crystallize, then removed from the cooling bath and treated rapidly with a solution of 5.5 g. of stannic chloride in 20 cc. of benzene, the mixture being swirled until a homogeneous, yellow slurry was obtained. After being kept cold for one minute, the mixture was poured onto ice and 30 cc. of concentrated hydrochloric acid and 30 cc. of ether. When all of the yellow solid had disappeared, more ether was added and the two layers were separated. The ether–benzene solution was washed three times with cold 10% hydrochloric acid, once with water, twice with 10% sodium hydroxide and several times with water. Evaporation of the solvents and the addition of methanol to the residue gave 3.8–4.0 g. of colorless prisms of the cyclic ketone (m. p. 98–100°).[10] From the mother liquors an additional quantity of only slightly less pure ketone was isolated and a further small amount was obtained by sublimation of the remainder at 200° at 0.5 mm. The total yield of ketone was 4.2–4.4 g. (90–95%). The yield was somewhat smaller when larger amounts were cyclized.

Methyl 7 - Methoxy - 1 - keto - 1,2,3,4 - tetrahydrophenanthrene - 2 - glyoxalate (II).—A solution of sodium methoxide prepared from 0.46 g. of sodium and 5 cc. of anhydrous methanol was evaporated to dryness at 100° under reduced pressure. The solid cake was broken up somewhat, 2.36 g. of dimethyl oxalate was added and the flask and condenser were evacuated and then filled with dry nitrogen. Ten cc. of dry, thiophene-free benzene was added and the mixture was refluxed for ten minutes in order to dissolve most of the solid. To the cooled solution was added a solution of 2.26 g. of the aforementioned cyclic ketone in 15 cc. of benzene and the mixture was swirled at room temperature. Within two minutes a clear, light-yellow solution resulted, which soon deposited a light-yellow precipitate of the sodio derivative of the glyoxalate. After four hours at room temperature, the mixture was hydrolyzed with cooling, and a small amount of sodium hydroxide solution was added in order to give two clear layers. After drawing off the aqueous layer, the benzene solution was extracted twice with 2% sodium hydroxide solution and the combined aqueous solution was acidified with cold, dilute hydrochloric acid. The light-yellow crystalline glyoxalate was filtered off and the dried product was digested with a warm mixture of acetone–methanol and cooled. By filtration, 2.95 g. of the glyoxalate (m. p. 133–135°) was obtained; this with an additional 0.06 g. isolated from the filtrate corresponded to a yield of 96%. When the condensation reaction was carried out in an atmosphere of air, using sodium methoxide prepared in benzene with the theoretical amount of methanol, the product was accompanied by varying amounts of a green oxidation product, and the yield of glyoxalate dropped to 88–92%.

The glyoxalate crystallized from methanol–acetone in clusters of long, thin, light-yellow prisms; these melted at 134–135° but the solid formed on cooling the melt showed a melting point of 139–140° with gas. In a Pyrex tube the crystals melted at 138–140°; the solid formed on cooling remelted at 130°; addition of powdered glass to the melt raised the melting point to 138–140° with gas. The glyoxalate gives an intense red-brown color instantly with an alcoholic solution of ferric chloride; it gives a red-brown color with concentrated sulfuric acid.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 69.2; H, 5.2. Found: C, 69.5; H, 5.0.

Methyl Ester of 7-Methoxy-1-keto-1,2,3,4-tetrahydro-2-phenanthroic Acid (III).—The first attempts to prepare this ester by heating the glyoxalate at 180–200° gave low and variable yields of an impure product. Frequently the reaction required more than two hours of heating before the evolution of carbon monoxide ceased. Excellent yields of the product were obtained when powdered glass was added to the glyoxalate, and on small runs the reaction was complete within ten minutes.

Ten grams of the glyoxalate was melted in an 8" (22-cm.) test-tube in an oil-bath (140–150°); 5 g. of finely powdered soft glass was stirred into the melt with a glass rod and the

(25) Cohen, Cook and Hewett, *J. Chem. Soc.*, 52 (1936).

mixture heated to 180°. A vigorous evolution of carbon monoxide took place, all of the gas being evolved in one-half hour. After being cooled, the light-brown semi-solid product was dissolved in benzene and the solution was decanted from the glass. After decolorization with Norite, the solution was evaporated and the residue stirred with methanol, whereupon crystallization took place. The first crop of cream-colored crystals of the keto ester weighed 8.0 g. (m. p. 108–110° with solidification and remelting at 118–120°); the second crop (0.2–0.6 g.) of only slightly less pure product brought the yield to 90–94%. The product so obtained is sufficiently pure to be used in the next step.

A sample of the methyl ester of 7-methoxy-1-keto-1,2,3,4-tetrahydro-2-phenanthroic acid, after sublimation at 220° (0.5 mm.) and recrystallization from acetone–methanol and then from benzene–methanol, was obtained as clusters of colorless prisms. The crystals melted nearly completely at 110–111°; the melt solidified and the solid remelted at 125–126.5°. The keto ester is soluble in benzene and in hot acetone, but is only slightly soluble in methanol. It gives a light orange-yellow color with concentrated sulfuric acid, and slowly develops a deep blue-green color with alcoholic ferric chloride solution (two to ten minutes).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 71.6; H, 5.7.

7 - Methoxy - 2 - methyl - 2 - carbomethoxy - 1 - keto-1,2,3,4-tetrahydrophenanthrene (IV).—To 2.3 g. of sodium dissolved in 45 cc. of anhydrous methanol was added 5.68 g. of the aforementioned keto ester (crude) as a finely divided solid, followed by 25 cc. of dry benzene. As the mixture was refluxed, the solid partially dissolved and then reappeared as the fine, powdery sodio-derivative, which ultimately nearly filled the solution; any lumps which formed were broken up. After thirty minutes of refluxing, the mixture was cooled and treated with 7 cc. of methyl iodide. After forty-five minutes at room temperature, during which time the mixture was swirled occasionally, much of the solid had dissolved. An additional 7 cc. of methyl iodide was added and within thirty minutes all of the solid had reacted. The clear yellow solution was refluxed for forty-five minutes, cooled and neutralized with acetic acid. After being evaporated nearly to dryness, the mixture was treated with benzene and water, and the benzene solution after separating was washed with 5% sodium hydroxide, again with water and dried over sodium sulfate. The solution was decolorized with Norite and evaporated. The residue crystallized from methanol in colorless crystals; yield 5.3–5.5 g. (89–92%); m. p. 84–86°.

After sublimation at 230° (0.2 mm.) and two recrystallizations from methanol, a sample of the 7-methoxy-2-methyl - 2 - carbomethoxy - 1 - keto - 1,2,3,4 - tetrahydrophenanthrene was obtained as colorless, hexagonal plates; m. p. 84.5–85°. The compound gives a light-yellow color with concentrated sulfuric acid, but neither the pure nor the unrecrystallized product gives a color with ferric chloride solution.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 72.3; H, 5.8.

Cleavage of the Keto Methyl Ester (IV) by Alkali.—A mixture of 0.3 g. of the above ester, 3 cc. of 45% aqueous potassium hydroxide and 10 cc. of methanol was refluxed on a steam-bath for two hours, diluted with water and cooled. The resulting crystals were filtered off and recrystallized from methanol; from the solution 0.23 g. (96%) of 7-methoxy-2-methyl-1-keto-1,2,3,4-tetrahydrophenanthrene (IVa) crystallized in thin, colorless plates; m. p. 109–110° (Haberland and Blanke,[26] 108°).

7 - Hydroxy - 2 - methyl - 1 - keto - 1,2,3,4 - tetrahydrophenanthrene was obtained by refluxing 0.2 g. of the methyl ether (IVa) in 12 cc. of 42% aqueous hydrobromic acid for three hours. The residue obtained after removal of the liquids by distillation under reduced pressure was dissolved in aqueous potassium hydroxide, the solution filtered and acidified. The precipitated phenolic ketone (0.17 g.) after sublimation at 180° at 0.01 mm. crystallized from methanol in colorless plates; m. p. 195.5–197.5° (vac.); after cooling the product remelted sharply at 197–197.5° (vac.). In an open tube the compound melted at 193–196° to a brown melt. Haberland and Blanke[26] failed to report the melting point of the compound.

Dimethyl Ester of 7-Methoxy-2-methyl-2-carboxy-1-hydroxy - 1,2,3,4 - tetrahydrophenanthrene - 1 - acetic Acid (V).—To 2.5 g. of granulated zinc (20-mesh, previously washed with dilute hydrochloric acid, water, acetone and dried) and 0.07 g. of iodine in 25 cc. of dry benzene (thiophene-free) and 25 cc. of anhydrous ether was added 1.5 g. of the keto ester IV and 0.75 cc. of methyl bromoacetate. As the mixture was refluxed on a water-bath, the iodine color faded and the solution became cloudy. After five to ten minutes a colorless addition product was deposited. Five additions of 2.5 g. of zinc and a trace of iodine were made at forty-five minute intervals and an additional 0.75 cc. of methyl bromoacetate was introduced after one and one-half hours. The mixture was refluxed for a total of four hours. Frequently the mixture was shaken vigorously in order to free the zinc from the adhering mass of crystals.

The addition product was dissolved by adding a little acetic acid and methanol and the solution was decanted from the zinc into water and the mixture acidified with acetic acid. The ether–benzene layer was separated, the aqueous solution was extracted with benzene and the combined extracts were washed with water and then dilute ammonium hydroxide until no more color was removed. The residue obtained by evaporation of the ether–benzene solution crystallized readily from methanol; yield 1.5–1.6 g. of colorless crystals (m. p. 123–126°). Additional product from the filtrate brought the total yield up to 85–90%. Should the yield fall below this, retreatment of the material in the filtrates with zinc and methyl bromoacetate will give additional product.

The hydroxy ester crystallizes from methanol containing a few drops of acetone in colorless leaflets; m. p. 125–125.5°. With concentrated sulfuric acid the compound gives a blue color which soon changes to a red-brown color and then fades to yellow.

Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.8; H, 6.5. Found: C, 67.8; H, 6.6.

The zinc which is recovered from the reaction may be used over again after being cleaned with acid, washed with water, acetone and dried.

(26) Haberland and Blanke, *Ber.*, **70**, 169 (1937).

Cleavage of the Reformatsky Ester (V) by Alkali.—A mixture of 100 mg. of the ester and 3 cc. of 45% aqueous potassium hydroxide was heated on a steam-bath for forty-five minutes. The solid melted to an oil which later solidified in the hot mixture. The colorless crystals (55 mg. or 85%) of 7-methoxy-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene (IVa) which were filtered off melted at 105–107°; when mixed with authentic ketone (m. p. 109–110°), the melting point was 107–109°. Only a trace of acidic material precipitated when the alkaline filtrate was acidified.

Conversion of the Reformatsky Ester (V) to the Unsaturated Acids.—To a cold mixture of 2 cc. of benzene and 0.6 cc. of pyridine was added 1.2 cc. of pure thionyl chloride. The solution was chilled and 1.65 g. of powdered Reformatsky ester was added. An immediate reaction ensued, and after a few minutes a clear yellow solution resulted. After standing at 25° for one-half hour, the mixture was evaporated under reduced pressure at room temperature and finally at 40°. The crystalline chloride was dissolved in 5 cc. of benzene and decanted from the insoluble pyridine hydrochloride; the latter was digested several times with small portions of benzene and the extracts were added to the main portion. (Alternately, the mixture of ester, thionyl chloride and pyridine in 10 cc. of benzene was allowed to stand at 25° for one-half hour, then chilled and shaken with ice and water; the benzene solution was then separated from the aqueous layer.) To the chilled benzene solution was added a solution of 1.6 g. of potassium hydroxide in 22 cc. of methanol and the mixture was refluxed for fifteen minutes. Four and one-half cc. of 45% aqueous potassium hydroxide was added to the cooled solution and refluxing was continued. After three-quarters of an hour, a large amount of precipitate was present. Sufficient water (20 cc.) was added to dissolve the solid, some of the methanol and benzene were removed in a current of air, and refluxing was continued for four hours.

The excess of alkali was carefully neutralized with 5% hydrochloric acid, and the solution was boiled with Norite and filtered. Acidification of the filtrate precipitated a mixture of unsaturated acid and acid anhydride. The dried product was boiled with 100 cc. of acetone and the insoluble acid anhydride (VII) was filtered from the solution, which contained all of the unsaturated acid (VI) and a small amount of anhydride. The **anhydride of *syn*-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid** (VII) crystallized from acetic acid–xylene in the form of colorless plates; yield, 0.71 g.; m. p. 233–234°. It dissolves only slowly in hot aqueous sodium hydroxide solution.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.0; H, 5.2. Found: C, 73.9; H, 5.2.

The acetone solution was evaporated to dryness and the residue was warmed with a 5% solution of sodium bicarbonate. The solution was filtered from 0.06 g. of the anhydride. Acidification of the aqueous filtrate gave 0.26 g. of the unsaturated acid. From benzene the ***anti*-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrylidene-1-acetic acid** (VI) crystallized in broad, colorless needles; m. p. 216–217° with evolution of gas. When the acid is dissolved in sodium bicarbonate and the solution is acidified, the same acid and no anhydride is precipitated.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.9; H, 5.6. Found: C, 70.2; H, 5.8.

The unsaturated acid reacted immediately with an ether solution of diazomethane while the acid anhydride remained unaffected under the same conditions. The **methyl ester** of the unsaturated acid crystallized from methanol in thin, colorless, nacreous leaflets which melted at 86–87°. The second crop of crystals consisted of stout plates which melted about twenty-five degrees higher. This represented a second form of the ester; when the low-melting product was recrystallized from methanol–petroleum ether and the solution seeded with the high-melting form, stout, colorless plates of the methyl ester were formed; m. p. 113.5–114°.

Anal. Calcd. for $C_{21}H_{22}O_5$: C, 71.2; H, 6.3. Found: C, 70.9; H, 6.2.

Reduction of the Unsaturated Acid (VI).—A warm solution of 120 mg. of the unsaturated acid in 0.12 cc. of 45% potassium hydroxide and 2.4 cc. of water was shaken vigorously with 5 g. of 2% sodium amalgam for fifteen minutes. Acidification of the clarified solution precipitated a mixture of the reduced acids. The dried product was dissolved in a hot mixture of 0.48 cc. of acetic acid and 0.72 cc. of xylene and the solution without filtering was allowed to cool; 55 mg. (45%) of colorless crystals melting at 227–229° precipitated. From xylene–acetic acid the **α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** (VIII or IX) crystallized in colorless rhombic prisms; m. p. 231–232°.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.7; H, 5.8.

The filtrate was evaporated to dryness and the residue was dissolved in a small volume of hot benzene. On cooling, the solution deposited colorless plates (65 mg.). The compound melted slightly at 145°, the melt solidified and the solid melted at 208–210°. It melted completely with bubbling when put into a bath at 150°. It appears that the acid crystallizes with benzene of crystallization. A sample of the pure acid was prepared by hydrolysis of the pure acid ester (XI). From acetone–petroleum ether the **β-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** (VIII or IX) crystallized in colorless prisms; m. p. 213–214°.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.6; H, 6.2.

Reduction of the Acid from the Unsaturated Anhydride (VII).—A mixture of 300 mg. of the acid anhydride, 100 mg. of potassium hydroxide and 10 cc. of methanol was refluxed for one-half hour. The methanol was removed in a current of air and the potassium salt of the unsaturated acid was dissolved in a small amount of water. After being shaken with 12 g. of 2% sodium amalgam for fifteen minutes the solution was acidified and the mixture of reduced acids was separated in the manner already described into 100 mg. (33%) of the α-acid and 130 mg. (43%) of the β-acid. The acids and their methyl esters were identical with the corresponding compounds obtained by reduction of the unsaturated acid.

Direct Preparation of the Reduced Acids, α and β.—Inasmuch as the unsaturated acid and the acid anhydride yielded the same two reduced acids on reduction, it was un-

necessary to isolate the unsaturated compounds. Usually 7.44 g. (0.02 mole) of the Reformatsky ester was converted to the potassium salts of the unsaturated acids as described. The aqueous solution of the salts was then transferred to a strong 500-cc. bottle and shaken vigorously for one-half hour with 150 g. of 2% sodium amalgam; in this process the yellow solution became practically colorless. The dried mixture of reduced acids (6.3–6.4 g.) was dissolved in a hot mixture of 20 cc. of acetic acid and 30 cc. of xylene. Without filtering, the solution is allowed to cool; 3.0–3.1 g. of the α acid crystallized (m. p. 222–225°). By evaporation of the solution and recrystallization of the residue from benzene, the β-acid was obtained; the weight of the latter varied from 2.8–3.5 g., depending on whether benzene of crystallization was present. The yields of the acids formed in the reaction were best obtained from the amount of dimethyl ester produced on treatment with diazomethane. Numerous runs showed that the yield of the α-acid was 44–47%, that of the β-acid 40–43% (total, about 87%) of the theoretical amount based on the Reformatsky ester.

Synthesis of *d*- and *l*-Equilenin

Dimethyl Ester of β-7-Methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid (X).—The ester was prepared from the β-acid by means of diazomethane and recrystallized from acetone–methanol. The yield of the ester varied with the purity of the acid. In a typical run, 0.69 g. of the acid as it was obtained in the reduction process yielded 0.62 g. of the ester melting at 107–109°; this product was found to be sufficiently pure for conversion to the acid ester (XI). Since the acid ester can be obtained more readily in a high state of purity, a pure sample of the dimethyl ester was prepared by reaction of the acid ester with diazomethane. The pure dimethyl ester crystallized from ether in thin, colorless plates; m. p. 114–115.5°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8. Found: C, 70.6; H, 6.7.

β-7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid (XI).—A mixture of the aforementioned dimethyl ester (0.62 g., m. p. 107–109°), 10 cc. of methanol and 1.8 cc. of *N* sodium hydroxide was refluxed for two hours; the solution was clear after a few minutes. After evaporation of the methanol in a current of air, the residue was dissolved in a few cc. of water. About 2 cc. of ethyl acetate was added and the solution was acidified with hydrochloric acid; the precipitated acid went into solution in the ethyl acetate and then reprecipitated in the form of crystals. In the absence of the solvent, the acid usually precipitated in extremely fine crystals which were difficult to filter. The ethyl acetate was removed in a current of air, and the crystals were filtered off; yield, 0.58 g. (97%); m. p. 208–210°. Runs up to 10 g. were carried out in the same manner; two hours was found to be sufficient time for hydrolysis of the one ester group. Ethyl acetate can be used for recrystallization. For 7.2 g. of the acid ester about 400 cc. of boiling ethyl acetate was required to effect solution; the ethyl acetate was then concentrated by distillation until crystals of the acid ester appeared in the hot solution. The pure acid ester crystallizes from ethyl acetate in colorless plates; m. p. 211–212°.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.5; neut. equiv., 342. Found: C, 70.1; H, 6.4; neut. equiv. 339.

A sample of the acid ester (0.15 g.) was hydrolyzed completely to the dicarboxylic acid by heating it with 1.5 cc. of 45% aqueous potassium hydroxide and 3 cc. of methanol for one hour.

Arndt–Eistert Reaction on the β-Acid Ester.—To 4 cc. of ice-cold dry benzene in a 125-cc. suction flask fitted with a drying tube was added 2 drops of pyridine and then 1.5 cc. of pure thionyl chloride. To the cold solution was added 1.71 g. of the aforementioned acid ester (unrecrystallized, m. p. 208–210°) in powdered form. After standing at room temperature for one-half hour, the mixture was warmed to about 40° for ten minutes. The orange-yellow solution containing some pyridine hydrochloride in suspension was evaporated under reduced pressure (water pump); 2 cc. of benzene was added and the solution again evaporated in order to remove traces of thionyl chloride from the crystalline acid chloride. The acid chloride was dissolved in 16 cc. of warm benzene, the solution was cooled somewhat and decanted carefully (through a small plug of cotton in the side-arm of the flask) drop by drop into a cold (5°) solution of diazomethane in ether; during the addition the diazomethane solution was swirled constantly.

Since the acid chloride being used was aliphatic in nature, it was felt desirable to employ a solution of diazomethane which was as free from alcohol as possible; hence, the diazomethane was prepared in *n*-propyl alcohol and ether free from alcohol was used. A solution of 2.8 g. of powdered potassium hydroxide (85%) in 10 cc. of warm *n*-propyl alcohol was prepared in a 125-cc. Claisen flask; 60 cc. of anhydrous ether was added to the solution and the flask was attached to a dry condenser which was attached to a receiver (a suction flask fitted with a drying tube) containing about 10 cc. of pure ether. Through a dropping funnel a solution of 4.5 cc. of nitrosomethylurethan in 10 cc. of anhydrous ether was dropped into the alkaline mixture; the diazomethane was distilled from the mixture as it was formed. The diazomethane solution was poured into a 200-cc. round-bottomed flask which had a ground-glass connection for a reflux condenser. The addition of the acid chloride resulted in the evolution of gas. After fifteen to thirty minutes, the ether and excess of diazomethane were removed under reduced pressure (water pump) at room temperature. The diazo ketone (XII) usually crystallized in the form of cream-colored, elongated, hexagonal plates.

To the diazo ketone was added 35 cc. of dry methanol and to the warm (50°) mixture was added one-half of the finely divided silver oxide obtained from 3.6 cc. of 10% silver nitrate solution (precipitating with alkali, washing well with water, filtering, washing with water and finally methanol, breaking up the silver oxide into a slurry with 1 cc. of methanol). The mixture was warmed on a water-bath at about 60° with frequent swirling of the contents. Nitrogen was evolved and after fifteen to twenty minutes the rather insoluble diazo ketone had gone into solution. At this time a small amount of silver oxide was added and heating was continued; further additions of silver oxide were made every five minutes; after six additions all of the silver oxide had been added. Then the mixture was refluxed for fifteen minutes.

The solution was boiled with Norite, filtered and concentrated to a small volume; on cooling, the product crystallized. Two crops of crystals (1.4–1.48 g.) were isolated; by sublimation of the material in the mother liquor at 240° (0.5 mm.), an additional 0.08 g. of the compound was obtained, making a total yield of 80–84%. The product (m. p. 97–101°) was sufficiently pure for cyclization. Should the crystals darken on exposure to light, the presence of traces of silver compounds is indicated; this impurity can be removed readily by passage of a benzene solution of the ester through a short column of anhydrous alumina. The pure **dimethyl ester of β-7-methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid (XIII)** crystallizes from methanol in glistening, colorless plates; m. p. 101–102°. It is readily soluble in acetone and in benzene, but is little soluble in methanol.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 71.1; H, 6.9.

Cyclization to the Methyl Ether of 16-Carbomethoxy-*dl*-equilenin (XIV).—In the theoretical part mention was made of the difficulty encountered in trying to cyclize the aforementioned ester by the action of sodium on the ester in benzene containing a trace of methanol. Addition of methanol caused the ester to react completely but during the process the mixture became red and a considerable amount of acidic material (extractable by sodium bicarbonate solution) accompanied the cyclic keto ester; as a result the latter was obtained in only 40–50% yields. The observation that the acidic material on esterification did not give back the original ester suggested that oxidation was taking place during the cyclization, and this was found to be the case. By running the reaction in nitrogen and using two moles of sodium methoxide as the condensing agent, the cyclic keto ester was obtained in yields as high as 98%.

A solution of sodium methoxide was prepared from 0.3 g. of clean sodium and 5 cc. of anhydrous methanol; as soon as the reaction was complete, the excess methanol was removed on a steam-bath under reduced pressure. To the solid sodium methoxide, after breaking up the cake, was added 2.0 g. of the ester (XIII) (m. p. 97–101°), and the flask, which was fitted with a condenser, was evacuated and then filled with pure, dry nitrogen. Through the top of the condenser was added 20 cc. of dry benzene and the mixture was refluxed on a water-bath for two hours. The solution was cooled in nitrogen and acidified with acetic acid, and then water containing a little hydrochloric acid. The organic layer was washed with sodium bicarbonate solution to remove a trace of acidic product, the benzene solution was clarified with anhydrous calcium chloride, filtered and evaporated in a current of air. On addition of methanol the product crystallized in colorless plates; yield, 1.77 g. (97%); m. p. 175–180°. By recrystallization from acetone–methanol the methyl ether of 16-carbomethoxy-*dl*-equilenin was obtained in thin, elongated rectangular plates; m. p. 181–182° (vac.) with slight previous softening. It is desirable to recrystallize the compound before converting it to racemic equilenin. The compound gave no color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 75.1; H, 6.5.

***dl*-Equilenin.**—In view of our experiences with oxidation of the cyclic keto ester, subsequent operations were generally carried out in an inert atmosphere. A mixture of 1.56 g. of the methyl ether of 16-carbomethoxy-*dl*-equilenin, 75 cc. of acetic acid, 37 cc. of concentrated hydrochloric acid and 7 cc. of water was refluxed in a nitrogen or carbon dioxide atmosphere. A lively evolution of carbon dioxide took place during the first twenty minutes, corresponding to the formation of the methyl ether of *dl*-equilenin. When the evolution of gas had ceased, a slow stream of nitrogen (or carbon dioxide) was passed through a stopcock attached to the tube leading from the top of the condenser to a mercury trap; in this manner bumping of the boiling solution was prevented. After ten hours of refluxing all of the methyl ether was hydrolyzed, but if heating was discontinued before this time some of the methyl ether of *dl*-equilenin was present. Thus, after eight hours of refluxing, the solution was cooled in order to allow most of the product to precipitate (1.06 g.; m. p. 268–270°); by removal of the solvents under reduced pressure and treatment of the solid residue with sodium bicarbonate solution, an additional 0.11 g. was obtained. In order to separate the racemic equilenin from its methyl ether, the product was heated with 160 cc. of a 2.5% aqueous solution of potassium hydroxide and filtered; there remained 0.06 g. of the methyl ether. After sublimation at 180° (0.01 mm.), the **methyl ether of *dl*-equilenin (XV)** crystallized from acetone–methanol in colorless plates; m. p. 185–186.5° (vac.). The same methyl ether was obtained when the *dl*-equilenin was treated with methyl sulfate in alkaline solution.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.7; H, 7.0.

The *dl*-equilenin obtained by acidification of the alkaline solution was dried and recrystallized from acetone–ethanol. The compound was obtained in at least two forms. In one run the product obtained by one crystallization formed colorless leaflets which melted at 287–288° (vac.). Usually, the racemic equilenin melted at 276–278° (vac.), although sometimes a melting point of 265° was observed; in the latter case the solid formed on cooling remelted at 276–278° (vac.). The yield of purified *dl*-equilenin varied between 90–95%. The *dl*-equilenin crystallized well from benzene, but the crystals were found to contain solvent of crystallization; they melted at about 180° with loss of solvent.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.2; H, 6.8.

The **benzoate** of *dl*-equilenin, prepared by means of benzoyl chloride and pyridine, crystallizes from methanol–ethyl acetate in thin, colorless plates; m. p. 248.5–249.5° (vac.).

Anal. Calcd. for $C_{25}H_{22}O_3$: C, 81.1; H, 6.0. Found: C, 80.7; H, 5.8.

The **acetate** of *dl*-equilenin, prepared by the method described for the active product, crystallizes from methanol in broad, colorless needles, which melted at 153–154° (vac.), solidified and remelted at 159.5–160° (vac.).

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.8; H, 6.5.

Conversion of the Methyl Ether of Equilenin to 3',3'-Dimethyl - 7 - methoxy - 1,2 - cyclopentenophenanthrene (XVII).—Following the procedure of Cohen, Cook and Hewett,[11] 26 mg. of the methyl ether of *dl*-equilenin was converted to the methylcarbinol by means of methylmagnesium iodide. The product (23 mg., m. p. 119–135°) was heated with 100 mg. of powdered potassium acid sulfate (freshly fused) at 160–170° for one hour. The product was extracted with acetone, the solution decolorized with Norite and evaporated, and the residue crystallized from methanol. The thin, colorless plates (5 mg.) proved to be 3',3'-dimethyl-7-methoxy-1,2-cyclopentenophenanthrene rather than the dihydro compound, indicating that dehydrogenation occurred during the process of dehydration. No other products were found in the filtrate. The same action was observed when the carbinol from the natural equilenin was treated in the same manner. The product melted at 162–163.5° (Cohen, Cook and Hewett,[11] 165–165.5°) alone and when mixed with the compound (m. p. 160.5–161.5°) prepared from natural equilenin. Likewise, the trinitrobenzene complexes of the compounds obtained from the two sources melted at 170–171.5° (Cohen, Cook and Hewett, 174–175°) alone and when mixed with each other.

Resolution of *dl*-Equilenin

***d*-Equilenin-*l*-menthoxyacetate.**—Two hundred mg. of *dl*-equilenin was dissolved in 1.5 cc. of dry dioxane and 1 cc. of pyridine by warming. The solution was cooled, the air displaced by nitrogen, and 0.5 cc. of *l*-menthoxyacetyl chloride was added.[27] The flask was stoppered and the mixture was allowed to stand for five hours at room temperature with occasional swirling. The colorless, mobile solution, which may contain crystals of pyridine hydrochloride, was hydrolyzed, the product taken up in benzene and the benzene extract was washed with dilute hydrochloric acid, water, sodium bicarbonate solution and dried with sodium sulfate. The product obtained by evaporation of the benzene crystallized readily from petroleum ether containing a few drops of acetone. Sometimes the crystals consisted nearly entirely of one ester [100 mg., m. p. 160–171° (vac.)]; at other times both esters crystallized out [200 mg., m. p. 135–138° (vac.)]. After two to five recrystallizations from petroleum ether–acetone and finally from acetone alone, pure *d*-equilenin-*l*-menthoxyacetate was obtained as thin, colorless plates; m. p. 174–174.5° (vac.); yield, 85–96 mg. (49–55%). The melting point was 173.5–174.5° when the compound was mixed with the same ester (m. p. 173–173.5°) prepared from natural (*d*-) equilenin.

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.9; H, 8.3. Found: C, 77.6; H, 8.4. *Rotation.* 30.4 mg. made up to 2 cc. in benzene gave a rotation of +0.27° at 30°; *l*, 1; $[\alpha]^{30}D$ +18°.

The remaining crystalline material (about 180 mg.; m. p. 135–140°), which could not be separated further by recrystallization, was hydrolyzed, and the product was used for the isolation of the ester of *l*-equilenin; this is described under the preparation of that compound.

***d*-Equilenin.**—A mixture of 115 mg. of *d*-equilenin-*l*-menthoxyacetate, 2.5 cc. of acetic acid, 1.5 cc. of concentrated hydrochloric acid and 0.3 cc. of water was refluxed in an atmosphere of carbon dioxide (mercury trap) for one hour. The light yellow solution was diluted with water and cooled; from the solution nearly colorless *d*-equilenin precipitated; yield, 57–62 mg. (86–94%); m. p. 246.5–249° (vac.). By recrystallization from dilute alcohol, using Norite, the synthetic hormone was obtained as colorless needles; m. p. 250–251° (vac.); 258–259° (vac., cor.). Mixed with natural equilenin (m. p. 250–251°), the melting point was unchanged. Effective purification also can be obtained by sublimation at 170–180° at 0.01 mm.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.3; H, 6.7. *Rotation.* 12.8 mg. made up to 1.8 cc. in dioxane gave a rotation of +0.60° at 30°; *l*, 1; $[\alpha]^{30}D$ +84°. Girard, *et al.*[3] report 258–259° (cor.) for the melting point and $[\alpha]^{16}D$ +87° (dioxane) for the specific rotation of natural equilenin.

The acetate was prepared by mixing 5 mg. of *d*-equilenin, 2 drops of acetic acid, 1 drop of pyridine and 1 drop of acetyl chloride and allowing the mixture to stand at room temperature for fourteen hours. The product (4 mg.) which was isolated crystallized from methanol in broad, colorless needles; m. p. 156–157° alone, and when mixed with the acetate (m. p. 156–156.5°) of natural equilenin.[3]

The benzoate of *d*-equilenin crystallized from acetone–alcohol in colorless plates; m. p. 222.5–223° (vac.); the mixed melting point with the benzoate (222.5–223.5°) of natural equilenin[3] was 222.5–223.5° (vac.).

The methyl ether was prepared by treating a solution of 10 mg. of *d*-equilenin in 2 cc. of *N* sodium hydroxide and 3 cc. of water with 2 drops of methyl sulfate; the mixture was swirled while being heated on a steam-bath. More methyl sulfate (6 drops) was added until no further precipitate formed, the solution being kept alkaline throughout. By recrystallization from methanol, the methyl ether (6 mg.) was obtained in the form of long, narrow, colorless plates; m. p. 193.5–194° (vac.). Mixed with the methyl ether (m. p. 194–194.5°) of natural equilenin,[28] the melting point was 194–194.5° (vac.).

The **trinitrobenzene complex** of equilenin, which was made because it is more stable than the picrate, was prepared by dissolving 5 mg. of each component in hot absolute ethanol; the first crop of broad, yellow needles melted at 205–207.5° (vac.) and after recrystallization from absolute ethanol melted at 205.5–207° (vac.). When mixed with the same complex (m. p. 206.5–207.5°) of natural equilenin, the melting point was 206–207° (vac.).

Anal. Calcd. for $C_{24}H_{21}O_8N_3$: N, 8.8. Found: N, 9.1.

The methyl carbinol (XVI), prepared from the methyl ether of *d*-equilenin and methylmagnesium iodide according to the procedure of Cohen, Cook and Hewett,[11] crystallized from cyclohexane in colorless needles; m. p. 132.5–133.5° (vac.). The mixed melting point with the same derivative (m. p. 132.0–134.5°) of natural equilenin was 132.5–134.5° (vac.).

***l*-Equilenin.**—*dl*-Menthol[29] was resolved and the *d*-menthol was converted to *d*-menthoxyacetic acid according

(27) Frankland and O'Sullivan, *J. Chem. Soc.*, **99**, 2329 (1911); Read and Grubb, *J. Soc. Chem. Ind.*, **51**, 330T (1932).

(28) Sandulesco, Tchung and Girard, *Compt. rend.*, **196**, 137 (1933).

(29) *dl*-Menthol (Menthol-Y) was purchased from the New York Quiuine and Chemical Works, Inc., New York City.

to the procedure of Read and Grubb.[27] Treatment of the *dl*-equilenin or the mixture of *dl*- and *l*-equilenin recovered after removal of some of the *d*-isomer with *d*-menthoxyacetyl chloride yielded a mixture of esters from which the **l-equilenin-*d*-menthoxyacetate** was isolated in pure form by recrystallization as was done for the antipode. From acetone, the ester was obtained in thin, colorless plates; m. p. 174.5–175° (vac.). A mixture of equal parts of this ester and its antipode (m. p. 174–174.5°) melted at 151–152° (vac.).

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.9; H, 8.3. Found: C, 77.5; H, 8.4. *Rotation.* 30.6 mg. made up to 2 cc. in benzene gave a rotation of −0.25° at 30°; *l*, 1; $[\alpha]^{30}D$ −16°.

Hydrolysis of the aforementioned ester gave *l*-equilenin, which formed colorless needles from acetone–methanol; m. p. 250–251° (vac.), 258–259° (vac., cor.).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.0; H, 7.1. *Rotation.* 20.8 mg. made up to 2 cc. in dioxane gave a rotation of −0.88° at 30°; *l*, 1; $[\alpha]^{30}D$ −85°.

Synthesis of *d*- and *l*-Isoequilenin

Dimethyl Ester of α-7-Methoxy-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid (X).—The α-acid as obtained by separation from its isomer was converted to its dimethyl ester by means of ethereal diazomethane; during the process benzene or acetone was added to dissolve the ester. After decolorization and filtration the solution was concentrated to a small volume and methanol added. From the solution the ester crystallized in large, colorless plates or prisms; yield, practically quantitative. The first time this compound was prepared it was obtained as broad, colorless needles melting at 86–89°; these gradually changed over to the plates which melted at 126–126.5°. In all subsequent runs the higher melting form was always obtained.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8. Found: C, 70.7; H, 6.7.

α-7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid (XI).—A mixture of 10.3 g. of the aforementioned dimethyl ester (powdered), 29.0 cc. of *N* sodium hydroxide and 150 cc. of methanol was refluxed for three hours. After removal of the methanol in a current of air, the residue was digested with 50 cc. of hot water; all but 0.21 g. of unchanged dimethyl ester dissolved. From the filtered solution 9.65 g. (99%, based on the ester used) of the acid ester was obtained on cautious acidification with hydrochloric acid; this product was sufficiently pure for the next step. When recrystallized from acetone–ligroin, it was obtained in fine, colorless needles; these melted at about 110–112° with bubbling; after long standing the melt solidified and the solid then melted at 137–138°. For analysis a sample was fused under reduced pressure.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.5. Found: C, 69.7; H, 6.5.

Arndt–Eistert Reaction on the α-Acid Ester.—The reaction was carried out in essentially the same manner as for the β-acid ester except that anhydrous ether was used in place of benzene in the preparation of the acid chloride. The acid chloride from 1.71 g. of the acid ester was dissolved in 10 cc. of ether and the solution decanted into the ethereal solution of diazomethane. Evaporation of the resulting solution yielded broad, cream-colored needles of the diazo ketone. The latter was warmed with methanol and silver oxide in the manner described for the diazo ketone from the β-acid, and after the reaction was complete, the hot methanol solution was passed through a small column of alumina to remove colloidal silver from the solution. After treatment with Norite and concentration to a small volume, the chilled solution deposited 1.27 g. of the dimethyl ester of **α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid** (XIII). In the filtrate an additional 0.10 g. (determined by cyclization to the cyclic keto ester) of the ester was present, making a total yield of 74%. The compound crystallizes from acetone–methanol in colorless plates; m. p. 89–89.5°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 70.9; H, 7.0.

***dl*-Isoequilenin.**—Cyclization of the aforementioned ester was carried out in nitrogen in the manner described for the isomer. A solution of 1.4 g. of the ester in 14 cc. of benzene refluxed with the dry sodium methoxide from 0.16 g. of sodium for one hour gave 1.115 g. (87%) of the **methyl ether of 16-carbomethoxy-*dl*-isoequilenin.** The compound crystallized from acetone–methanol in colorless plates; m. p. 149–149.5° in an open tube and 152.5–153.5° in a sealed, evacuated tube. The keto ester develops a deep blue-green color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 75.1; H, 6.6.

A mixture of 1.92 g. of the aforementioned cyclic keto ester, 40 cc. of acetic acid, 25 cc. of concentrated hydrochloric acid and 5 cc. of water was refluxed in an atmosphere of nitrogen for ten hours. The product obtained by evaporation of the solution under reduced pressure was digested with 200 cc. of a 2.5% aqueous solution of potassium hydroxide and the solution was filtered from 60 mg. (4%) of the **methyl ether of *dl*-isoequilenin.** After sublimation at 160–180° at 0.01 mm., the methyl ether crystallized from acetone–methanol in colorless prisms; m. p. 127–127.5° (vac.) with solidification and remelting at 130–130.5° (vac.).

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

Acidification of the alkaline solution precipitated the *dl*-isoequilenin (1.42 g., 93%). Recrystallization from acetone–ethanol gave nearly colorless plates (1.27 g.) of ***dl*-isoequilenin**; these melted at 206–206.5°, the melt solidified and the solid remelted at 221–222°. Further recrystallization from benzene–acetone and then from acetic acid containing some water raised the melting point to 223–224° (vac.). Frequently the high-melting form crystallized directly from the solution. By sublimation in a high vacuum (0.01 mm.) the product can be obtained perfectly colorless.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.0; H, 6.8.

The **acetate** of the *dl*-isoequilenin crystallized from acetone–methanol in colorless prisms; m. p. 159–160° (vac.).

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.8; H, 6.7.

The **trinitrobenzene complex** crystallized from absolute ethanol in clumps of long, fine, yellow needles; m. p. 186–187° (vac.).

Anal. Calcd. for $C_{24}H_{21}O_8N_3$: N, 8.8. Found: N, 8.8.

Conversion of *dl*-Isoequilenin to 3′,3′-Dimethyl-7-methoxy-1,2-cyclopentenophenanthrene.—The methyl ether of the racemic isoequilenin (80 mg.) was treated with methylmagnesium iodide to give the corresponding methyl carbinol (63 mg., m. p. 88–92°), which was heated with potassium acid sulfate and worked up in the manner described for the *dl*-equilenin derivative. The product was treated with palladium-charcoal at 360° for one hour, then sublimed and crystallized from methanol. Unlike that from *dl*-equilenin methyl ether, the product was a mixture from which only a small amount (3%) of 3′,3′-dimethyl-7-methoxy-1,2-cyclopentenophenanthrene could be isolated as the trinitrobenzene complex; m. p. 170–171° alone and when mixed with an authentic sample prepared from natural equilenin.

Resolution of α-7-Methoxy-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic Acid.—To an ice-cold mixture of 4 cc. of anhydrous ether, 2 drops of pyridine and 2.2 cc. of thionyl chloride was added 3.38 g. of the acid ester of the α-acid. After forty-five minutes at room temperature, the solution was evaporated under reduced pressure; the acid chloride was dissolved in 2 cc. of benzene and the mixture was again evaporated. To the solution of the acid chloride in 4 cc. of ether 2 g. of *l*-menthol was added. After twenty-four hours at room temperature, the mixture of esters which had precipitated in solid form was filtered off and recrystallized from petroleum ether (60–75°), yielding 1.43 g. of methyl-*l*-menthyl ester melting at 135–138°; from the original filtrate an additional 0.09 g. of the same ester was isolated. The product (1.52 g.) crystallized from acetone–methanol in colorless needles (1.4 g.) which melted at 139–139.5°; this product is sufficiently pure for the next step. In the experiment just described practically only one of the esters came out; if both crystallize, the mixture of esters must be recrystallized several times in order to effect a separation. Further recrystallization of a sample of the *l*-methyl-*l*-menthyl ester of α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid raised the melting point to 139.3–139.8°.

Anal. Calcd. for $C_{30}H_{40}O_5$: C, 75.0; H, 8.4. Found: C, 75.2; H, 8.4. *Rotation.* 30.6 mg. made up to 2 cc. in benzene gave a rotation of −2.31° at 30°; *l*, 1; $[\alpha]^{30}D$ −152°.

***d*-Isoequilenin.**—The aforementioned ester was rather resistant to hydrolysis. A suspension of 1.2 g. of the active ester in a solution of 16 g. of potassium hydroxide (85%) in 40 cc. of methanol was heated on a steam-bath for seven hours. The methanol was removed in a current of air, and the residue was dissolved in water. After the menthol had been extracted by means of benzene, the solution was acidified with hydrochloric acid. The dicarboxylic acid (m. p. 220–224° unrecrystallized) was filtered off, dried and converted to the dimethyl ester by reaction with diazomethane. By recrystallization from methanol 0.82 g. (92%) of the *l*-dimethyl ester of the α-acid was obtained in the form of thin, colorless plates; m. p. 110–110.3°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8. Found: C, 70.7; H, 6.7. *Rotation.* 30.2 mg. made up to 2 cc. in benzene gave a rotation of −2.28°; *l*, 1; temp. 30°; $[\alpha]^{30}D$ −151°.

The dimethyl ester was hydrolyzed to the acid ester in the same manner employed for the racemic ester. From acetone–petroleum ether the active acid ester crystallized in colorless needles; the crystals melt when put into a bath at 130°, the melt solidifies and the solid remelts at 159–160°. The high melting point is observed when the tube is placed into the bath at 90°. The acid ester (0.7 g.) was converted to the propionic acid derivative through the Arndt–Eistert reaction, yielding 0.56 g. in the first crop, which melted at 102–103.5°. From acetone–methanol the ***l*-dimethyl ester of α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid** crystallized in broad, colorless needles; m. p. 103–103.5°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.3; H, 7.1. Found: C, 71.1; H, 6.9. *Rotation.* 12.7 mg. made up to 1.8 cc. in benzene gave a rotation of −0.87° at 28°; *l*, 1; $[\alpha]^{28}D$ −123°.

Cyclization in the manner described for the *dl*-ester gave the active **methyl ether of 16-carbomethoxy-isoequilenin** (0.44 g. from 0.56 g.; after recrystallization, 0.39 g.; m. p. 147–150°); hydrolysis of the latter by refluxing with a mixture of 12 cc. of acetic acid, 8 cc. of concentrated hydrochloric acid and 1.5 cc. of water for ten hours yielded the *d*-isoequilenin, which was isolated in the same manner as the racemic compound. The product dissolved completely in 80 cc. of boiling 1% sodium hydroxide; acidification of the filtered solution precipitated the ***d*-isoequilenin** (0.29 g.). It was recrystallized by dissolving it in acetone, boiling the solution with Norite, filtering, adding alcohol and then concentrating the solution on a steam-bath until crystallization set in. The colorless plates (0.26 g.) melted at 272–273° (vac.). When the compound was recrystallized again, this time by dissolving it in 8 cc. of boiling acetic acid and adding a small amount of water to the solution, colorless leaflets or plates of a second form were obtained; m. p. 257–258° (vac.); 265–266° (vac., cor.).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 80.9; H, 6.7. *Rotation.* 30 mg. made up to 2 cc. in dioxane gave a rotation of +2.20° at 29°; *l*, 1; $[\alpha]^{29}D$ +147°. In absolute alcohol a specific rotation of +173° was observed with a solution of 8.1 mg. in 2 cc. of solution. In view of the higher concentration possible in dioxane, we consider the dioxane value to be the more accurate. Hirschmann and Wintersteiner reported $[\alpha]^{30}D$ +160° (0.4% in ethanol) for the specific rotation of their 14-*epi*-equilenin.[24]

The **methyl ether** of the *d*-isoequilenin, prepared by the action of methyl sulfate on an aqueous solution of the sodium salt, was obtained as thin colorless plates after two recrystallizations from methanol; m. p. 118.5–119.5°.

The **acetate** of *d*-isoequilenin, prepared by means of a mixture of acetic acid, acetyl chloride and pyridine, crystallized from methanol in long, colorless prisms; m. p. 146–147° (vac.).

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.9; H, 6.6.

Comparison of Synthetic *d*-Isoequilenin with 14-*epi*-Equilenin.—Dr. O. Wintersteiner kindly made a comparison of our *d*-isoequilenin and its acetate with his 14-*epi*-equilenin,[24] prepared from equilin, and its acetate. The melting points of the isoequilenin and 14-*epi*-equilenin were taken in capillary tubes evacuated to approximately 0.1 mm. He reported the following melting points: *d*-isoequilenin, 263–264°; 14-*epi*-equilenin, 262–263°; mixed sample 261–264°; all melting points are corrected. In all cases there was previous softening before the melting point was reached.

The acetate of 14-*epi*-equilenin, prepared by Dr. Wintersteiner with acetic anhydride in pyridine at room temperature, had a melting point of 126–127.5°; later it melted fairly sharply at 148–149° (after another recrystallization, 148.5–149.5°) with slight softening around 126°. The higher melting point was observed after the sample had been dried at 100° for analysis (Calcd. for $C_{20}H_{20}O_3$: C, 77.88; H, 6.54. Found: C, 77.63; H, 6.73). Our recrystallized *d*-isoequilenin acetate melted at 149–149.5° with slight softening at 148°. A mixture of the two acetates melted at 149.5° after softening at 148°; the sample resolidified after some time and the solid now melted at 127–128°. From this it is clear that the acetate exists in two forms. The compounds possessed the following specific rotations: 14-*epi*-equilenin acetate, $[\alpha]^{24}D$ +137 ± 7° (0.635% in absolute alcohol); *d*-isoequilenin acetate, $[\alpha]^{22}D$ +129.4° (0.307% in absolute alcohol). The margin of error is probably smaller in the latter case because the readings, which were determined using a 2 dcm. tube, were sharper.

***l*-Isoequilenin.**—The mixture of methyl-*l*-menthyl esters of the α-acid (2.35 g.) which remained after removal of the *l*-methyl-*l*-menthyl ester was hydrolyzed to the dicarboxylic acids by heating with a solution of 24 g. of potassium hydroxide (85%) in 60 cc. of methanol for three hours. After removal of the methanol in a current of air, the product was dissolved in water and the menthol was extracted with benzene. The acid (1.58 g.) which precipitated on acidification of the aqueous solution was converted to the dimethyl ester by means of diazomethane. A benzene solution of the ester was boiled with Norite, the solution was filtered and concentrated to a small volume and the residue was dissolved in hot methanol. On cooling the solution deposited fairly large prisms of the racemic dimethyl ester of the α-acid (0.73 g., m. p. 125.5–126°). With luck these can be filtered from the solution by suction before the active (*d*-) dimethyl ester precipitates. Ordinarily it is safer to decant the clear solution from the heavy crystals. The active ester crystallizes in fine colorless plates which dissolve more rapidly and are more soluble than the coarse prisms of the racemic ester. Even when both crystallize out at the same time, one can effect a separation by warming the mixture to dissolve the fine crystals and decant the solution from the coarse prisms. Still another method, which works well after the bulk of the racemic ester has been removed, is to allow the crystallizing solution to stand for ten hours or longer so that the prisms can grow larger; the latter can then be separated by picking them out of the fine crystals by hand. The ***d*-dimethyl ester of α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid** (0.8 g.) melted at 108–109°, and it was obtained sometimes as high as 110–110.5°. The lower melting point is probably due to a small amount of the racemic ester, but the product is sufficiently pure for the steps which follow. A mixture of equal parts of the *d*-ester (m. p. 110–110.5°) and the *l*-ester (m. p. 110–110.3°) was recrystallized from acetone–methanol; from the solution was obtained prisms of the racemic ester which melted at 126–126.5°, alone and when mixed with the original racemic ester.

The *d*-dimethyl ester was carried through the remaining steps in the manner described for its antipode, the yields of the products being about the same. The product of the Arndt–Eistert reaction, ***d*-dimethyl ester of α-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-propionic acid,** was quite free from its antipode, for it possessed a melting point of 103–103.5° and a specific rotation $[\alpha]^{29}D$ +122° (antipode, m. p. 103–103.5°, $[\alpha]^{28}D$ −123°). A mixture of equal parts of the antipodes recrystallized from methanol yielded crystals of the racemic ester; m. p. 89–89.5°, alone and when mixed with the racemic ester. Cyclization, followed by hydrolysis of the product, yielded the ***l*-isoequilenin.** The latter melted at 272–273° (vac.) when first obtained from its sodium salt by acidification, but after two recrystallizations from acetone–alcohol it formed large colorless plates, which melted at 257–258° (vac.). A mixture of equal parts of the *d*- and *l*-isoequilenin recrystallized from acetic acid yielded the racemic isoequilenin; m. p. 223–224°, alone and when mixed with the original racemic compound.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.2; H, 6.8. Found: C, 81.1; H, 6.9. *Rotation.* 30.7 mg. made up to 2 cc. in dioxane gave a rotation of −2.26°; *l*, 1; $[\alpha]^{28}D$ −147°. In absolute ethanol (7.9 mg. made up to 2 cc.) a specific rotation $[\alpha]^{28}D$ −162° was observed.

Summary

The total synthesis of the sex hormone equilenin and its three stereoisomers is described.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 5, 1940