Normal Ester (XVI).—Onto a suspension of 400 mg. of the 137° acid in ether diazomethane is distilled; the mixture is permitted to stand in ice until the evolution of nitrogen ceases. Removal of most of the ether on the steam-bath followed by cooling in ice results in the formation of 300 mg. of solid ester. Recrystallization from ether containing a little methanol produces clusters of transparent needles, m. p. 57° (dec.). This ester is estremely unstable, decomposing slowly in the cold room (5°) and very rapidly at room temperature (about an hour).

Anal. Calcd. for $C_{10}H_{13}O_6Br$: C, 38.9; H, 4.21; Br, 25.9. Found: C, 38.9; H, 4.43; Br, 26.3.

The Schiff test on this ester is negative but positive Fehling and Tollens tests are very readily obtained on only slight warming. Silver nitrate in alcoholic solution reacts slowly in the cold but rapidly on warming to produce a copious quantity of silver bromide.

Acid potassium permanganate does not effect a rapid oxidation but in an alkaline solution this reagent is instantly decolorized.

Summary

The reaction between furan and maleic acid in water, and that between furan and maleic anhydride in ether, take different stereochemical courses. In the former case, an *endo–cis* adduct is formed, while in the latter, an *exo–cis* product is obtained.

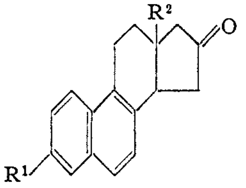
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 23, 1947

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

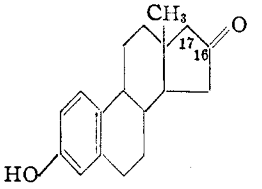
The Synthesis of 1,3,5-Estratrien-3-ol-16-one, A Structural Isomer of Estrone[1]

BY A. L. WILDS AND THOMAS L. JOHNSON[2,3]

Several years ago[4] a method of synthesis was developed for the ketone Ia, which possesses the basic ring system of the female sex hormones but with the ketone group at the 16 rather than the 17-position, and lacking the angular methyl and 3-hydroxyl groups. More recently[5] this synthetic approach was modified to permit incorporation of the angular methyl group as in Ib, and extended[6] to the synthesis of Ic, a structural isomer of equilenin. The present paper is concerned with the synthesis of 1,3,5-estratrien-3-ol-16-one (II), which is a structural isomer of estrone having the carbonyl group shifted to the 16-position.



Ia, $R^1 = R^2 = H$
Ib, $R^1 = H$; $R^2 = CH_3$
Ic, $R^1 = OH$; $R^2 = CH_3$



II

For this extension to compounds having ring B hydrogenated the key intermediate was the ketone VII,[7] for which an improved synthesis was developed by Bachmann, Kushner and Stevenson.[8]

In the present work the over-all yield in the conversion of the substituted malonic ester III to V could be raised from 28 to 45% by eliminating distillation of the intermediate keto ester IV and carrying out the cyclization with anhydrous hydrogen fluoride.[9] The remaining steps involving reduction of the dibasic acid to VI, conversion to the methyl ester, Dieckmann cyclization and methylation of the cyclic β-keto ester, followed by hydrolysis and decarboxylation, proceeded well to give mainly the crystalline isomeride of the octahydro ketone VII. Similar treatment of V led to the related hexahydro ketone VIII.[8] In each case the over-all yield of ketone from dibasic acid was 75–78%, or about 6.5 and 7.4%, respectively, for the 14–15 step synthesis from *m*-aminophenol.

In the earlier synthesis of the desoxy tetracyclic ketone Ib,[5] an acetic acid residue was introduced into the 2-position of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene by preparing the sodium enolate of the ketone with sodium amide and alkylating with methyl bromoacetate. Preliminary attempts to apply this procedure to the methoxy ketones VII or VIII (on a 0.5 g. scale) led to oily acidic mixtures after hydrolysis, from which no pure crystalline products could be isolated. Further work in the tetrahydro desoxy series showed that the original procedure, although quite satisfactory on a moderately large scale (71% yield on a 20 g. scale) was poor for small scale experiments (35–39% on a 0.5 g. scale). Triphenylmethylsodium, however, proved to be satisfactory as an enolizing agent even on a small scale, and when the optimum conditions for the reaction were developed it was possible to prepare the crystalline acetic acid derivatives IXa and Xa in 55–59% yields from the methoxy ketones VII and VIII.

With the hexahydroketone VIII the most probable position of alkylation was the 2-position.

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[1] Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

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[3] Present address: Sterling-Winthrop Research Institute, Rensselaer, N. Y.

[4] Wilds, THIS JOURNAL, 64, 1421 (1942).

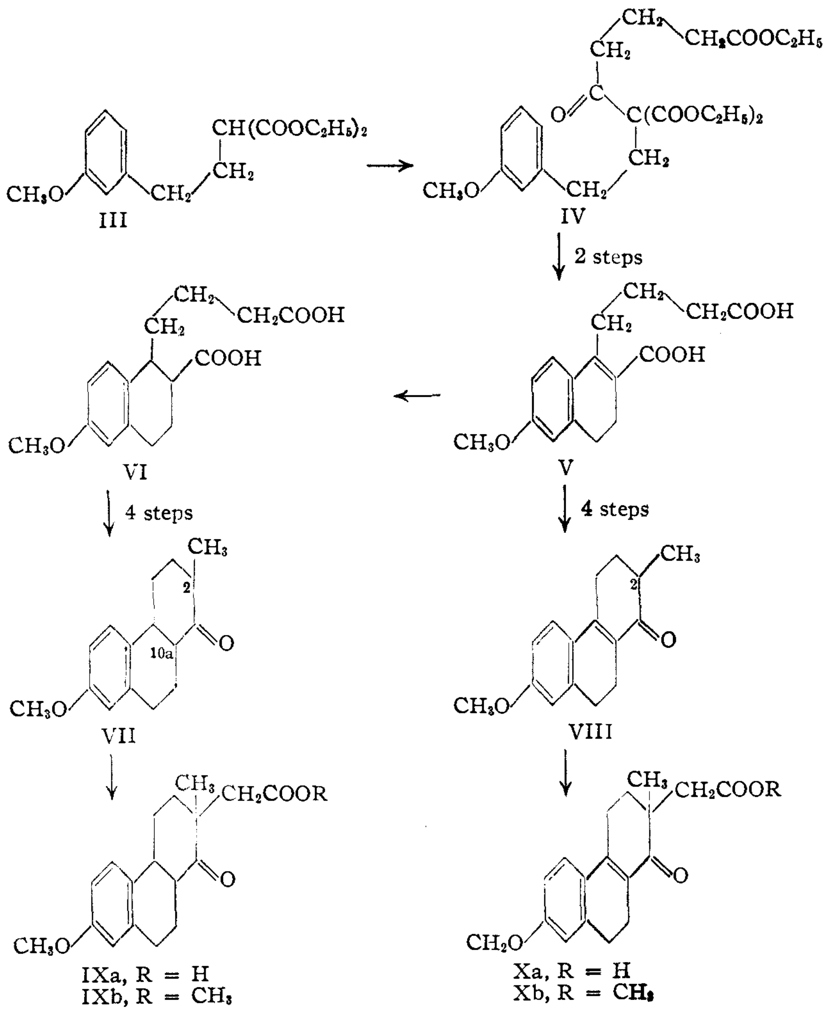
[5] Wilds and Beck, *ibid.*, 66, 1688 (1944).

[6] Wilds and Close, *ibid.*, 69, 3079 (1947).

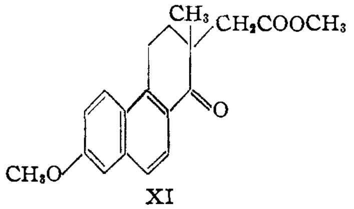
[7] Robinson and Walker, *J. Chem. Soc.*, 183 (1938).

[8] Bachmann, Kushner and Stevenson, THIS JOURNAL, 64, 974 (1942).

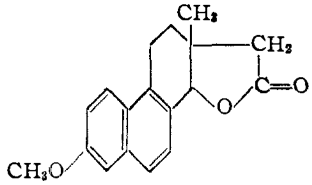
[9] Adkins and Hager have found this to be an excellent reagent for effecting the cyclization of somewhat analogous β-keto esters; Glenn F. Hager, Ph.D. Thesis, University of Wisconsin, 1943.



This structure for the acid Xa was proved by selective dehydrogenation of the methyl ester at 150° to the tetrahydro ester XI, which has been prepared[6] by a similar alkylation of the tetrahydro analog of VIII. The structure Xa for the acid also was supported by the ultraviolet absorption spectrum of the ester Xb, which was almost identical with that of the ketone VIII.



XI

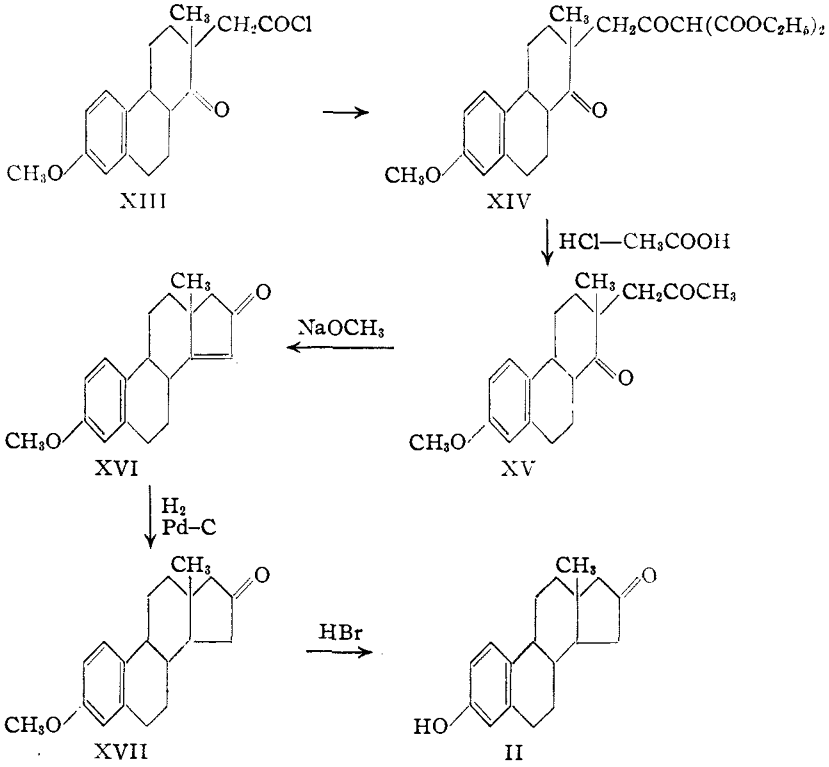


XII

In the case of the octahydro ketone VII not only the 2-position but also the angular 10a-position is available for alkylation. The results of dehydrogenation of the octahydro ester IXb were not so definitive as those for the hexahydro ester. The product after hydrolysis of the dehydrogenated ester contained considerable lactonic as well as acidic material. A small amount (5%) of the tetrahydro ester XI could, however, be isolated from the acidic product. The crystalline lactone, surprisingly enough, had the composition $C_{18}H_{20}O_3$ and thus apparently contained two hydrogen atoms more than the tetrahydro lactone XII, which was prepared by aluminum isopropoxide reduction of the ester XI. On the other hand, the ultraviolet absorption spectrum which closely resembled that of the tetrahydro lactone XII would indicate the presence of a naphthalene nucleus. Further work will be necessary to establish its structure.

Regardless of its own structure, however, the lactone obtained from the octahydro ester furnishes additional support for structure IXb, since a small amount of the same lactone was obtained by dehydrogenation of the hexahydro ester Xb at 225°. And finally, the hexahydro and octahydro series were linked by hydrogenation of the ester Xb. While the reaction was complex, it was possible to isolate a small amount (3%) of the crystalline octahydro ester IXb. Another product was the tetrahydro lactone XII, identical with that obtained from XI. Although in each of these reactions to establish the structure of IXa the yield of the critical derivative was low, the combined evidence affords reasonably good proof for the formula assigned.

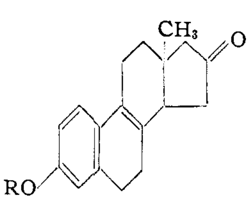
The next step of the synthesis involved converting the substituted acetic acids (IXa and Xa) into the corresponding methyl ketones. The reactions,[5] which involved formation of the acid chloride, condensation with sodiomalonic ester and acid hydrolysis of this intermediate to the diketone, proceeded well (78–83% yield) in the tetrahydro desoxy series regardless of the scale of the run (0.15 g. to 24 g.). Initial experiments in both the hexahydro and octahydro methoxy series, however, were unsuccessful and no crystalline products could be isolated. In the hexahydro series, starting with Xa, a large amount of *acidic* oil was obtained at the stage of the acyl malonic ester derivative. Part of the difficulty can be attributed to the step involving formation of the supposed acid chloride, for after hydrolysis of the latter, prepared with thionyl chloride or oxalyl chloride, only a small fraction of the starting acid could be recovered.



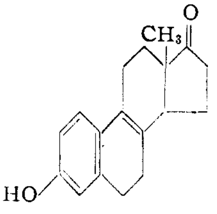
Early experiments with the octahydro acid IXa, using thionyl chloride to prepare the acid chloride, likewise led to an oily product at the diketone stage. However, in one run employing oxalyl chloride, 20% of the crystalline diketone XV was obtained. Here, too, the major difficulty consisted in forming the acid chloride. When the supposed acid chloride was hydrolyzed with water most of the product was a *neutral* oil, from which some of the starting acid could be obtained by alkaline hydrolysis. This indicated that the major product of this step was the *enol* lactone of IXa, rather than the acid chloride. By employing the sodium salt of the acid with oxalyl chloride,[10] the reaction was improved and the yield of the diketone increased to 42%. The sodium salt method, however, was unsuccessful in the hexahydro series, as were attempts to block the carbonyl group of IXb by conversion to a ketal with ethyl orthoformate or ethylene glycol.[11,12]

The cyclization of the diketone XV to the unsaturated ketone XVI was markedly influenced by the reaction conditions. The yield of the crystalline product was 90% using sodium methoxide in methanol as the condensing agent and heating for two and three-quarters hours. With shorter or longer times the yield was markedly decreased, in the latter case probably through isomerization of the crystalline ketone XVI. The ultraviolet absorption spectrum of the ketone (Fig. 1) showed bands typical for an α,β-unsaturated ketone (max. 227 mμ)[13] and for a phenol ether (max. 280 mμ).

Demethylation of the methoxy ketone XVI with hydrobromic and acetic acids gave a mixture from which a crystalline phenolic ketone could be isolated in 37% yield. The ultraviolet absorption spectrum of the latter (Fig. 1, max. at 273 mμ), different from that of the original methyl ether, indicated that the double bond had shifted from ring D into conjugation with ring A, most probably as shown in XVIIIa. This compound is then the 16-keto isomer (*dl*) of Hirschmann and Wintersteiner's isoequilin A (XIX, max. at 273 mμ)[14] which was prepared by a similar acid isomerization of the 7–8 double bond of equilenin to the 8–9 position.



XVIIIa, R = H
XVIIIb, R = CH_3



XIX

By hydrogenation with a palladium-on-carbon catalyst the unsaturated methoxy ketone XVI was converted into one of the isomeric forms of the reduced ketone XVII in 90% yield. Demethylation of this compound gave one of the eight possible racemic forms of the phenolic ketone II, m.p. 177.5–178°. The ultraviolet absorption

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(10) *Cf.* Adams and Ulich, This Journal, **42**, 599 (1920).

(11) Salmi, *Ber.*, **71**, 1803 (1938).

(12) Serini and Köster, *ibid.*, **71**, 1766 (1938).

(13) The predicted value for a five-membered ring ketone having two β-substituents and an exocyclic double bond is about 229 mμ [*cf.* Woodward, This Journal, **64**, 76 (1942) and Gillam and West, *J. Chem. Soc.*, 486 (1942)].

(14) Hirschmann and Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938).

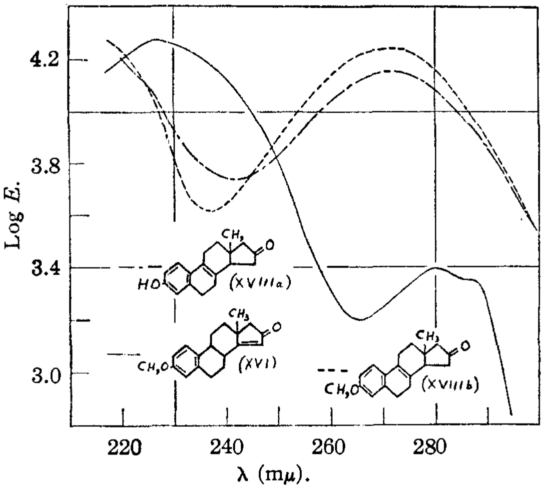

Fig. 1.

spectrum of the reduced phenolic ketone was in reasonably good agreement with that for estrone as can be seen from Fig. 2.

Tests for estrogenic activity, for which we are indebted to Drs. J. A. Leighty and E. D. Campbell of Eli Lilly and Co., indicated that this isomer of the phenolic ketone II possesses a low order of activity in ovariectomized mice. When injected as a solution in cottonseed oil, about 500 γ was equivalent to one mouse unit of estrone (0.066 γ). Since in the case of the analogous structural isomer of equilenin, reported recently,[6] the decrease in activity was much less (to about one-third that of *dl*-equilenin), it seems apparent that the present isomer of II does not possess the same stereochemical configuration as estrone. The unsaturated phenolic ketone XVIIIa was considerably more active, with one mouse unit equal to about 30 γ. This activity is the same as that for one of the isomers of Ic,[6] but is much lower (of the order of one-hundredth) than that for isoequilin A, which was reported[14] to be about one-fifth as active as estrone. Further work is in progress to prepare other stereoisomers of II by isomerization at various stages of the synthesis and by other suitable variations. The introduction of a keto group at C-17[5] in XVI with the goal of synthesizing the structures of estriol and estrone also is being investigated.

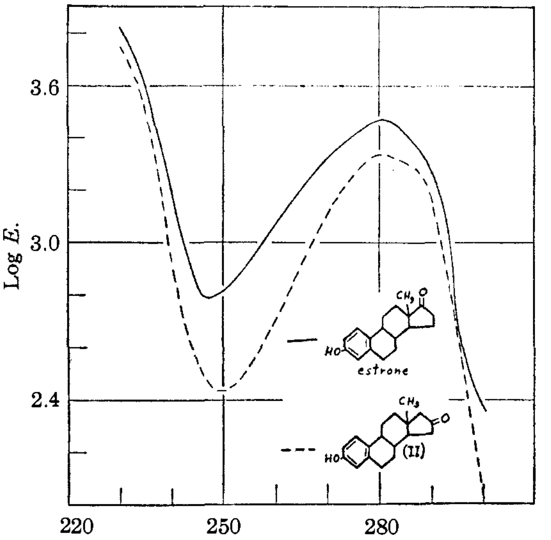

Fig. 2.

In view of the low yield at the stage of converting the acetic acid derivative IXa to the diketone XV, and the failure of the reaction in the hexahydro series, other approaches to the diketone and cyclic ketone which did not involve formation of the acid chloride, were investigated. Trial experiments were carried out first with the more readily available tetrahydro desoxy derivatives. Attempts to prepare the diketone directly from the ketone (corresponding to VII) by alkylation of the enolate with chloroacetone or iodoacetone were unsuccessful. Another route which appeared to offer considerable promise was the acetoacetic ester type of condensation between the keto ester XX and esters of acetic acid. Condensation reactions with ethyl acetate or acetonitrile, using sodium methoxide as the condensing agent, gave no positive results. Consequently the stronger base triphenylmethylsodium was used to prepare the enolate of the ester XX which was then condensed with phenyl acetate, a method employed with considerable success by Hauser and co-workers.[15] This led to an initial alkali-soluble product which underwent hydrolysis and decarboxylation with acid to give the cyclic ketone XXIIIa (in 23% yield) instead of the diketone. The yield could be raised by a retreatment of the neutral fraction to 37% (or 52% when corrected for recovered starting acid). The intermediate alkali-soluble material appears to be the cyclic keto ester XXII, previously prepared by Wilds and Beck[5] from XXIIIa through the glyoxalate reaction. The ultraviolet absorption spectrum of the compound closely resembled that of XXIIIa and other compounds having the same ring and conjugated double bond system.[16] The reaction of acetyl chloride with the enolate of the ester XX also was investigated. In this case the product (presumably XXI) was neutral, and after acid hydrolysis and decarboxylation the diketone corresponding to this was isolated in 19% yield using Girard's reagent P.

Application of the triphenylmethylsodium–phenyl acetate reaction to the methoxy hexahydro ester Xb gave an initial alkali-soluble product which led to a neutral oil upon hydrolysis and decarboxylation. Apparently this product unlike that in the tetrahydro desoxy series was not completely cyclized (if at all); upon heating with

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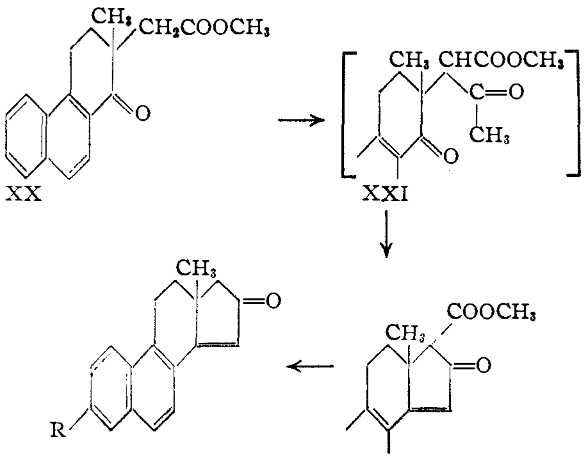
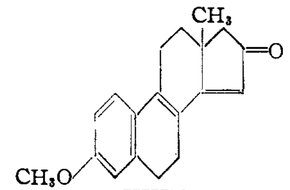
[15] Reviewed by Hauser and Hudson in "Organic Reactions," John Wiley and Sons, Vol. 1, New York, N. Y., 1942, pp. 266–302.

[16] See Wilds, Beck, Close, Djerassi, J. A. Johnson, T. L. Johnson and Shunk, THIS JOURNAL, **69**, 1985 (1947).


XX XXI XXII

XXIIIa, R = H
(XXIIIb, R = CH_3O)

alkali, however, it gave the crystalline cyclic ketone XXIV in 11% yield. This material, a yellow solid, was not obtained entirely pure, judging from the melting point range, but the ultraviolet absorption spectrum, with the main maximum at 360 mμ, supports the structure with the double bonds as shown. Upon standing the filtrate from this ketone slowly deposited a small amount of a higher melting ketone which proved to be the dehydrogenated naphthalenic analog XXIIIb.[6] The reaction of acetyl chloride with the enolate of Xb gave after hydrolysis and cyclization about 2% of the same ketone XXIV as obtained from the phenyl acetate reaction.


XXIV

In the octahydro series the yields were even lower. In one run the reaction of phenyl acetate with the enolate of IXb gave after hydrolysis and decarboxylation 6% of the crystalline diketone XV, identical with that from the acid chloride–malonic ester procedure. In another run no crystalline diketone could be isolated, but after cyclization the crystalline compound obtained was similar in melting point and analysis to the cyclic ketone XVI; the mixed melting point, however, showed a 25° depression. The ultraviolet absorption spectrum (Fig. 1) indicated that in this isomer the double bond had shifted away from the carbonyl group and into conjugation with the aromatic ring as shown in XVIIIb.

Experimental[17]

Preparation of 1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene and 1-Keto-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene.[18]—The method of Bachmann, Kushner and Stevenson[8] was employed for preparing these ketones with some modification in certain of the steps.

Ethyl 5-Keto-6,6-dicarbethoxy-8-*m*-anisyloctanoate (IV).—To 7.85 g. of powdered sodium in 230 cc. of dry, thiophene-free benzene was added 100 g. of diethyl β-*m*-anisylethylmalonate (III)[8] and the mixture was stirred and refluxed for twenty hours. Then the solution was cooled in an ice-bath and 76 g. of the acid chloride of ethyl hydrogen glutarate[8] was added. After four hours at room temperature and one hour at reflux the mixture was cooled and water added. The benzene layer and the ether extract of the aqueous layer were combined, washed with sodium bicarbonate solution and dried over sodium sulfate. Then the solvents and low boiling material were removed *as rapidly as possible* under reduced pressure (25 mm.), warming the residue finally to 100° in an oil bath. The residual yellow oil (134 g. corresponding to an apparent yield of 91%) was used in the next step without further treatment.[19]

γ-(6-Methoxy-2-carboxy-3,4-dihydro-1-naphthyl)-butyric Acid (V).[8]—To 25 g. of the crude undistilled keto ester (from the above procedure) in a 500-cc. platinum beaker cooled in an ice–salt mixture to −10°, was added approximately 150 g. of anhydrous, liquid hydrogen fluoride.[9] The mixture was kept in the bath at −10° for five hours, then the hydrogen fluoride was removed in a stream of air. Ice was added, most of the residual acid was neutralized with solid sodium bicarbonate, and the mixture was extracted twice with ether, washing the latter with water and evaporating. The residual triester was refluxed for three hours with 100 cc. of 45% potassium hydroxide and 100 cc. of methanol, most of the methanol was evaporated in a stream of air and the diluted mixture extracted with ether. The alkaline layer was acidified by pouring onto a mixture of ice and 110 cc. of concentrated hydrochloric acid and the tribasic acid was extracted with three portions of ether. Following removal of the ether the residue was heated with 250 cc. of water on the steam-bath for twelve hours. After cooling, the oily solid was filtered, triturated with about 30 cc. of ether, refiltered and washed with cold benzene, giving 8.15 g. of the dibasic acid, m. p. 185–187.5° (d.). A second crop of 0.10 g., m. p. 175–182°, brought the total yield to 50%, based upon the crude keto-ester, or an over-all yield of 45%, based on the diethyl β-*m*-anisylethylmalonate.

A third crop of 0.85 g., m. p. 135–143° (d.), proved to be β-*m*-anisylmalonic acid. After recrystallization from dioxane–benzene the compound melted at 143–144° (d.) and showed no m. p. depression when mixed with an authentic sample.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9. Found: C, 60.5; H, 6.0.

The above conditions represent the optimum determined from a number of cyclizations in which the time of standing with hydrogen fluoride and the temperature were varied.

1-Keto-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.[8]—The dibasic acid (20 g., m. p. 185–188°) was converted to the dimethyl ester with diazomethane in ether (prepared from 30 g. of N-nitroso-N-methylurea), the ether was removed by distillation and the absence of water insured by adding dry benzene and again distilling the solvent. Meanwhile

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(17) All melting points are corrected unless otherwise indicated; those marked "vac." were determined in sealed Pyrex melting point tubes evacuated to at least 0.5 mm.

(18) Some of the early experiments in this section were carried out by Dr. Lloyd W. Beck.

(19) The earlier procedure[8] for this reaction included further purification by flash distillation at 340° (0.05 mm.) followed by fractional distillation. We have observed that this purification results in lower and more variable over-all yields of the dibasic acid V after cyclization, as indicated by the following example: crude keto ester obtained in 86% apparent yield gave a 43% over-all (from III) yield of the acid V; after the flash distillation the over-all yield of V dropped to 38%, after the fractional distillation to 16%, and after a second fractional distillation to 7%.

sodium methoxide was prepared from 3.2 g. of sodium and 70 cc. of anhydrous methanol, removing the excess solvent under reduced pressure at 100°. Dry benzene was added to the solid and again removed. The cake of sodium methoxide was broken up, the system filled with nitrogen, and the dimethyl ester was added in 250 cc. of dry benzene. The suspension was refluxed with occasional vigorous swirling; in one hour the sodio derivative of the cyclic keto ester began to separate as a voluminous precipitate. After eighteen hours at reflux, the mixture was cooled and 25 cc. of methyl iodide in 25 cc. of anhydrous methanol was added. After twenty-four hours at room temperature, the solid had completely dissolved, and an additional 10 cc. of methyl iodide and 10 cc. of methanol were added and the solution refluxed for one hour. The mixture was acidified with acetic acid, water and ether added and the organic layer was washed with sodium bicarbonate solution, dried and evaporated. The residue readily crystallized from methanol giving 15.6 g. of the keto ester, m. p. 96–97.5° and an additional 1.85 g., m. p. 90–96.5°, for a total yield of 84%. The pure compound is reported[8] to melt at 98–100°.

1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VIII).—A mixture of 20.1 g. of the above keto ester, 200 cc. of acetic acid, 200 cc. of hydrochloric acid and 100 cc. of water was refluxed under nitrogen for two hours, then cooled, diluted and extracted twice with ether, washing with water, dilute potassium hydroxide and acid. From the ether extract by recrystallization from petroleum ether (b. p. 60–68°) was obtained 14.8 g. (91%) of the ketone, m. p. 67–69°. Further recrystallization gave material melting at 68–69° (reported 66–67°[8] and 67–68°[7]). The ultraviolet absorption spectrum was reported earlier.[18]

From the potassium hydroxide washings was obtained 0.52 g. of phenolic material, m. p. 183–189°. Two recrystallizations from methanol gave colorless prisms of what appears to be 1-keto-2-methyl-7-hydroxy-1,2,3,4,-9,10-hexahydrophenanthrene, m. p. 187–189°.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1. Found: C, 78.8; H, 7.0.

γ-(6-Methoxy-2-carboxy-1,2,3,4-tetrahydro-1-naphthyl)-butyric Acid (VI).—Reduction of the recrystallized unsaturated dibasic acid (5.03 g.) was carried out as described by Bachmann, Kushner and Stevenson,[8] with palladium-on-carbon catalyst.[20] A total of 4.64 g. (92%), m. p. 155–157.5°, of the reduced acid was obtained by crystallization from benzene (reported,[8] m. p. 156–157.5°).

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VII).—The Dieckmann reaction was carried out on the dimethyl ester of the reduced dibasic acid (from 12.4 g. of acid and diazomethane) as described for the unsaturated analog, allowing twenty-one hours at reflux and using 25 cc. of methyl iodide in 50 cc. of methanol for the first addition and 10 cc. of methyl iodide in 25 cc. of methanol for the second. The mixture was allowed to stand for another twenty hours, followed by three hours at reflux, and the intermediate keto ester was isolated as an oil.[21] It was hydrolyzed and decarboxylated by refluxing with 120 cc. of acetic acid, 120 cc. of hydrochloric acid and 60 cc. of water for one and one-half hours under a nitrogen atmosphere. The cooled mixture, which showed an intense green fluorescence, was worked up as described for the hexahydro ketone. The product crystallized from methanol giving 5.74 g. of colorless ketone, m. p. 107–114°. The filtrate contained a preponderance of oily diastereoisomers which were partially converted to the crystalline isomeride by a repetition of the acid treatment for one and one-half hours using one-half the original quantity of reagents. In this manner an additional 1.71 g. of the crystalline ketone, m. p. 114–116°, was obtained, and from a third acid treatment another 0.26 g., m. p. 102–112°, for a total crude yield of 74%. Two recrystallizations of this material from methanol gave 5.1 g. of ketone, m. p. 116–118°, which was used in the subsequent reactions. By further recrystallization material of m. p. 118.5–119° was obtained (reported 116–117.5°[8] and 119–120°[7]).

Syntheses in the Desoxy Series (with 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene)

1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetic Acid.—For the preliminary experiments in the methoxy series it was essential to have a procedure suitable for small-scale runs. The procedure previously described by Wilds and Beck,[5] in which sodium amide was used in ether[22] suspension to enolize the ketone, gave considerably lower yields (35–39%) when the amount of ketone was reduced to 0.5 g.; with potassium amide (and allowing only 0.75 hour for enolization) the yield was slightly improved (49%). Triphenylmethylsodium[15] proved to be a suitable reagent for runs on a small scale, giving 74% yield of the acid in 0.5 g. runs (by a procedure similar to that described below in the octahydro series).

Condensation of Methyl 1-Keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetate with Phenyl Acetate.—To a solution of 1 g. of the methyl ester XX (m. p. 72–73.5°) in 10 cc. of dry ether was added triphenylmethylsodium solution[25] in slight excess (11 cc. of 0.4 *M*) under nitrogen followed by 0.5 cc. of phenyl acetate.[23] The mixture was allowed to stand at room temperature for four hours with occasional swirling. Dilute acetic acid and ether were then added and the ether solution was washed with water and three times with 10% potassium hydroxide solution (the latter constitutes fraction a). The ether solution was evaporated and a crop of triphenylmethane (0.5 g., m. p. 91–93°) was crystallized from benzene. The filtrate was dried by repeated addition of dry benzene and distillation under reduced pressure, then the residue was treated again with the triphenylmethylsodium solution until a permanent red color remained (9 cc.). Phenyl acetate (0.5 cc.) was added and the above procedure repeated, giving a second portion of material in the alkaline extract (fraction b). Both fractions were worked up separately. The potassium hydroxide solution containing fraction a was acidified, extracted with ether and the latter washed with sodium bicarbonate solution. Evaporation of the ether left 0.48 g. of oil which was refluxed for two hours with 10 cc. of acetic acid, 10 cc. of hydrochloric acid and 4 cc. of water. After cooling, extracting with ether and washing with alkali and water, 0.23 g. of a yellow oil was obtained which crystallized immediately when stirred with petroleum ether, giving 0.203 g., m. p. 142.5–148°.

Fraction b gave in a similar manner an additional 0.120 g., m. p. 133–144°. This material proved to be $\Delta^{1,1'}$-2'-keto-2-methyl-3,4-dihydro-1,2-cyclopentenophenanthrene (XXIIIa); a recrystallized sample had the m. p. 148–150° alone and when mixed with a known sample.[5] From the neutral fraction after the second treatment was obtained 0.283 g. (30%), m. p. 148–151.5°, of the starting acid by alkaline hydrolysis and recrystallization of the bicarbonate-soluble fraction. The yield of the cyclic ketone corresponded to 37%, or 52% taking into account the recovered acid.

In another run, starting with 2 g. of the methyl ester, the intermediate alkali-soluble product was investigated. This material (950 mg. of oil which contained phenol)

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[20] Linstead and Thomas, *J. Chem. Soc.*, 1130 (1940).

[21] Recently Anner and Miescher [*Helv. Chim. Acta*, **30**, 1427 (1947)] have reported isolation of three of the four possible crystalline *dl*-forms of this compound.

[22] Subsequent work has indicated toluene to be a more suitable solvent than ether for this reaction on a large scale, and in this case also the size of run can be reduced to at least 2 g. without lowering of yield. Using toluene at 55° for seven hours for the enolization of the ketone with sodium amide, the yield of crystallized acid (m. p. 148–150.5°) amounted to 71%; 5% of the starting ketone was recovered and none of the high melting by-product (m. p. 255–256°) was formed.

[23] Ethyl acetate was much less satisfactory, resulting in a lower yield of cyclic ketone, a trace of the uncyclized diketone and an appreciable amount of lactonic material.

would not crystallize until seeded in methanol with methyl $\Delta^{1,1'}$-2'-keto-2-methyl-3,4-dihydro-1,2-cyclopentenophenanthrene-3'-carboxylate (XXII, m. p. 148–154°) prepared earlier.[5] A total of 0.30 g. of yellow solid was obtained, m. p. 141–150°, which gave a green color with alcoholic ferric chloride. Repeated recrystallization from methanol gave a sample with the m. p. 149.5–158°. This material apparently retained solvent of crystallization since the analysis showed a low carbon value (76.4%). After drying at 80° and 0.1 mm. for forty hours, satisfactory analytical values were obtained.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.3; H, 5.9.

The ultraviolet absorption spectrum[24] was very similar to that of the cyclic ketone XXIIIa[16] and showed maxima at 219 mμ (log E = 4.33), 238.5 mμ (4.10), 267 mμ (4.48), 276 mμ (4.56) and 315.5 mμ (4.40); minima at 230.5 mμ (4.05), 249 mμ (4.08), 270 mμ (4.45) and 287.5 mμ (4.06); and points of inflection at 245 mμ (4.09) and 360 mμ (3.75).

Syntheses in the Hexahydro Series (with 1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene)

1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-acetic Acid (Xa).—The hexahydro ketone VIII (5.04 g.) was alkylated using triphenylmethyl sodium and methyl bromoacetate following the same procedure as described below for the octahydro ketone VII, except that ten minutes was allowed between the addition of the base and the bromo ester. The acid was crystallized from benzene to give 3.40 g. of acid (m. p. about 90–100°) containing benzene of crystallization. An additional 0.26 g. of crystalline material was obtained by chromatographic fractionation of the remaining acidic oil as the methyl ester (see below). The solvent of crystallization could be removed only by heating for one to two days at 70° and 0.2 mm., then giving a product melting at 105.5–106.5°. The loss in weight (10.4%) corresponded approximately to one-half molecule of benzene of crystallization (calcd. 11.5%). The yield of product, corrected for the benzene of crystallization, was 52%. Recrystallization of the combined acid from carbon tetrachloride (which is not suitable for crystallizing the crude product) gave 2.82 g. (45%) of nearly colorless, solvent-free material, m. p. 105.5–106.5° with slight softening at 104°. The purest sample was obtained from methanol as colorless clumps of prisms, m. p. 106.5–107.5°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.9; H, 6.9.

The **methyl ester Xb**, prepared with an ethereal solution of diazomethane, was obtained in practically quantitative yield as colorless blades from methanol, m. p. 66.5–68°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1. Found: C, 72.3; H, 6.9.

The ultraviolet absorption spectrum[24] of the ester showed maxima at 240 mμ (log E = 4.04) and 329 mμ (4.34) and a minimum of 262.5 mμ (3.04).

In addition to the acid some phenolic material also was obtained which crystallized when stirred with benzene, 360 mg. (7%), m. p. 119–125°. Repeated recrystallization from benzene raised the m. p. of the product to 124–126.5°; from the analytical values this material appears to be **2-methyl-7-methoxy-9,10-dihydro-1-phenanthrol**.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.8; H, 6.6.

Chromatographic fractionation of the residual oily acid (as the methyl ester) was carried out on alumina. Elution with 60% benzene (in petroleum ether) gave 430 mg. of a nearly colorless oil which crystallized when stirred with petroleum ether; 204 mg., m. p. 140–160°. After two recrystallizations from methanol a compound, isomeric with the desired methyl ester, was obtained as colorless prisms, m. p. 161.5–163°.

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1. Found: C, 72.5; H, 7.0.

The ultraviolet absorption spectrum[24] of this ester was quite different from that of the methyl ester Xb, showing a maximum at 261 mμ (log E = 4.23), a minimum at 233 mμ (3.63) and a point of inflection at 292 mμ (3.51).

Subsequent eluates of the chromatogram, finally using pure benzene, gave material which upon saponification yielded 0.26 g. of the acetic acid derivative Xa mentioned above.

Dehydrogenation of the Hexahydro Methyl Ester Xb.—The ester (100 mg., m. p. 64–66°) and 100 mg. of palladium-on-carbon catalyst[20] were heated under nitrogen at 130–150° for a total of twenty minutes. The product was crystallized from methanol to give a total of 54 mg. of solid, m. p. 94–96°; after a second recrystallization the product melted at 97.5–99° alone and when mixed with a sample of the tetrahydro methyl ester XI (m. p. 98.5–99.5°).[6] Saponification gave the corresponding acid, m. p. 145–147° alone and when mixed with an authentic sample.[6]

In another run the same quantities of the methyl ester and catalyst were heated for five minutes in a bath preheated to 225°. The crude product gave 46 mg. of the tetrahydro ester, m. p. 94.5–97.5°. The material in the filtrate was hydrolyzed with 5% potassium hydroxide, extracted with ether and acidified. After warming the suspension of acid for one-half hour on the steam-bath it was taken up in ether and washed with sodium bicarbonate solution. The latter gave 22 mg. of acidic material and from the ether was obtained 16 mg. of neutral, lactonic material. Crystallization gave 11 mg. of a mixture, m. p. 123–133.5° (softening at 117°), from which a small amount of material, m. p. 131.5–134°, was obtained after five recrystallizations from benzene–petroleum ether. This showed no depression in m. p. when mixed with the lactone obtained below by dehydrogenation of the methyl ester of the octahydro acid.

$\Delta^{1,1'}$-2'-Keto-2-methyl-7-methoxy-3,4,9,10-tetrahydro-1,2-cyclopentenophenanthrene (XXIV).—To a solution of 634 mg. of the hexahydro methyl ester Xb (m. p. 64–66°) in 10 cc. of dry, thiophene-free benzene was added 1.4 equivalents of triphenylmethylsodium solution[25] (9 cc. of 0.3 M) under nitrogen; the red color of the reagent did not persist. Phenyl acetate (0.4 cc.) was added and the mixture allowed to stand for eighteen hours. Then it was worked up as described above for the desoxy series and the potassium hydroxide-soluble portion isolated. A retreatment of the neutral fraction (5 cc. of triphenylmethylsodium and 0.4 cc. of phenyl acetate) gave additional alkali-soluble material. These were hydrolyzed in a nitrogen atmosphere with acid; as the neutral fraction was not crystalline it was heated for fifteen hours under nitrogen with 2 cc. of 45% potassium hydroxide and 8 cc. of methanol, and the neutral portion was evaporatively distilled at 180–200° (0.1 mm.). The yellow distillate (105 mg.) was crystallized from methanol yielding 50 mg., m. p. 120–127°, and 14 mg., m. p. 116–127°, corresponding to an 11% yield. A sample with a sharp melting point could not be obtained. Repeated recrystallization of the cyclic ketone from methanol gave yellow prisms, m. p. 122.5–128° with a small residue remaining to 135°.

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

The ultraviolet absorption spectrum[24] showed maxima at 257.5 mμ (log E = 4.03) and 360 mμ (4.44); minima at 230 mμ (3.74) and 293 mμ (3.53); and an inflection at 280 mμ (3.70).

The methanol filtrate from which the ketone XXIV had crystallized slowly deposited a small amount of solid which was filtered after five months. This material, which melted at 120–130° but with a residue up to 185°, gave after two recrystallizations from methanol a small sample of cream colored solid, m. p. 202–203°, which gave

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[24] The ultraviolet absorption spectra were all determined in absolute alcohol solution using a Beckman quartz photoelectric spectrophotometer; $E = (1/c) \log (I_0/I)$ for a 1-cm. cell, where c = concentration in moles per liter.

no melting point depression (m. p. 202–204°) when mixed with $\Delta^{1,1'}$-2'-keto-2-methyl-7-methoxy-3,4-dihydro-1,2-cyclopentenophenanthrene (XXIIIb).[6]

Basic hydrolysis of the initial neutral material containing triphenylmethane gave 272 mg. of acidic oil from which 71 mg. of the starting acid could be crystallized using benzene.

Synthesis in the Octahydro Series (with 1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene)

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetic Acid (IXa).—The following procedure represents the best of a number of runs in which the conditions were varied. To a solution of 5.47 g. of the octahydro ketone VII in 50 cc. of dry, thiophene-free benzene was added[25] at room temperature under nitrogen a 10% excess of triphenylmethylsodium[15] in ether (61 cc. of 0.4 *M*). After twenty minutes the reaction flask was cooled in ice, transferred to a nitrogen-filled condenser attached to a mercury trap and 10 cc. of methyl bromoacetate was added *all at once* through the condenser with swirling. The mixture was refluxed for one and one-half hours, then the ether and benzene were evaporated and the residue was saponified by refluxing for twelve hours with 75 cc. of 45% potassium hydroxide and 75 cc. of methanol. After evaporating most of the methanol, the alkaline solution was washed twice with ether and acidified. The product was extracted with ether and crystallized from carbon tetrachloride to give 4.96 g. of the acid containing solvent of crystallization; the latter was removed by heating at 65° for twelve hours, giving 3.40 g. of acid, m. p. 132.5–138°. The mother liquors were evaporated and the residue was treated with 25 cc. of saturated sodium bicarbonate solution and allowed to stand; more of the acid separated as the insoluble sodium salt from which, after acidifying and extracting with ether, an additional 0.41 g. of the crystalline acid, m. p. 136.5–140°, was obtained. By a second treatment with a smaller volume of bicarbonate solution another 0.15 g. of the acid, m. p. 127–135°, was obtained, bringing the total yield to 59%. The ether washings contained 0.18 g. of phenolic oil which could not be crystallized. The purest sample of the acid was obtained by recrystallization from methanol, giving clumps of colorless prisms, m. p. 139.5–140.5°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: C, 72.0; H, 7.5.

The methyl **ester IXb**, obtained in 91% yield with diazomethane, crystallized from methanol as colorless leaflets, m. p. 97–97.5°.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.1; H, 7.6. Found: C, 72.0; H, 7.6.

Dehydrogenation of the Octahydro Methyl Ester IXb.—A mixture of 100 mg. of the ester (m. p. 94–96°) and 100 mg. of palladium-on-carbon catalyst[20] was heated at 200–205° for twenty-five minutes. Crystallization of the product from benzene–petroleum ether (b. p. 60–68°) gave 46 mg., m. p. 110–128°; after four recrystallizations was obtained 12 mg. of material, m. p. 133.5–134.5°, which proved to be a lactone. It gave no depression in m. p. when mixed with the lactone obtained by dehydrogenation of the hexahydro ester (see above), but showed depression to 110–120° with the tetrahydro lactone XII (m. p. 145–145.5°).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.0; H, 7.1; for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4; for $C_{18}H_{22}O_3$: C, 75.5; H, 7.8. Found: C, 76.1, 75.9; H, 7.1, 7.1.

The ultraviolet absorption spectrum[24] showed maxima at 229 mμ (log E = 4.66), 265 mμ (3.70), 274 mμ (3.71), 320 mμ (3.29), and 334 mμ (3.39); minima at 252–258 mμ (3.60), 269 mμ (3.66), 298 mμ (2.81) and 324 mμ (3.21); and inflections at 284 mμ (3.54), 308 mμ (3.01) and 329 mμ (3.26).

In another experiment 100 mg. of the ester was heated with the catalyst for ten minutes at 250°. A total of 37 mg. of the crude lactone and 32 mg. of acid, m. p. 125–131°, were obtained. The acid was treated with diazomethane and recrystallized five times from methanol to give about 5 mg. of the methyl ester of the tetrahydro acid XI, m. p. 95.5–96°. The mixed m. p. with an authentic sample[6] was 95.5–98.5°, while with the octahydro ester IXb (m. p. 94–96°) the m. p. was depressed to 72–96°.

Hydrogenation of the Hexahydro Methyl Ester Xb.—A solution of 489 mg. of the hexahydro ester Xb (m. p. 64–66°) in 16 cc. of purified dioxane was stirred with 200 mg. of palladium-on-charcoal catalyst[20] and hydrogen at atmospheric pressure and room temperature. After seven hours, when 1.1 mole-equivalents of hydrogen had been absorbed, reduction was still taking place at a steady rate and the reaction was stopped. The catalyst and solvent were removed, the residue hydrolyzed with 5 cc. of 45% potassium hydroxide and 20 cc. of methanol and separated into acidic (250 mg.) and lactonic (210 mg.) material as described above. A small portion (50 mg.) of the lactone crystallized from methanol, m. p. 114–138°. Recrystallization from benzene–petroleum ether gave a mixture of needles and clumps of microscopic crystals which were separated by hand. The former had the m. p. 162–171°, the latter 143–145°. A mixture of the latter with the lactone of 1-hydroxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid (XII; see below) gave no m. p. depression. Apparently this lactone was formed by disproportionation.[26] The higher melting material was not investigated further.

The acidic fraction was dissolved in 5 cc. of hot sodium bicarbonate solution (saturated at room temperature) cooled and seeded with a trace of the sodium salt of the octahydro acid. After two days at 0° a small amount of precipitate had formed from which was obtained 15 mg. of acid which readily crystallized, m. p. 118–130°. The melting point was raised to 125–138° when the crude sample was mixed with the octahydro acid IXa. The crude acid was converted to the methyl ester (diazomethane) and recrystallized twice from methanol giving material melting at 95–97°. A mixture with the methyl ester of the octahydro acid IXb (m. p. 95.5–97°) showed no m. p. depression, while with the tetrahydro methyl ester XI (m. p. 98.5–99.5°)[6] the m. p. was depressed to 76–90°.

Aluminum Isopropoxide Reduction of the Tetrahydro Methyl Ester XI.—A solution of 100 mg. of the methyl ester[6] (m. p. 97.5–98.5°), and 300 mg. of aluminum isopropoxide in 5 cc. of anhydrous isopropyl alcohol was refluxed for sixteen hours. The solution was cooled, dilute acid added and the product was extracted with ether. The residue after evaporating the solvent was heated for two hours with 1 cc. of 45% potassium hydroxide and 4 cc. of methanol, diluted, acidified and warmed on the steam-bath for one-half hour. The product was extracted with ether, washed with bicarbonate solution (only 5 mg. of acidic material obtained) and crystallized from alcohol, giving 63 mg. of lactone, m. p. 144.5–145.5°, and an additional 11 mg., m. p. 142–144°, for a yield of 82%. The melting point of the pure lactone XII was 145–145.5°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.3; H, 6.4.

The ultraviolet absorption spectrum[24] showed maxima at 236 mμ (log E = 4.84), 266.5 mμ (3.75), 275.5 mμ (3.77), 314 mμ (3.21), and 329 mμ (3.27); minima at 253.5 mμ (3.63), 270.5 mμ (3.73), 306 mμ (3.05) and 324

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[25] The apparatus, designed by Dr. C. David Gutsche, was a convenient modification of that described by Baumgarten and Hauser [This Journal, **66**, 1039 (1944)], which permitted the reagent reservoir and buret to be closed off from the rest of the system while this and the reaction flask were evacuated and filled with nitrogen. Measured amounts of the reagent solution were then added to the reaction flask from the buret.

[26] Disproportionation accompanying hydrogenation of somewhat related compounds has been observed before with equilin by Dirscherl and Hanusch, *Z. physiol. Chem.*, **233**, 13 (1935); **236**, 131 (1935), and with dihydroequilin by Serini and Logemann, *Ber.*, **71**, 186 (1938); for a recent example see Anner and Miescher, *Helv. Chim. Acta*, **29**, 1889 (1946).

mμ (3.08); and inflections at 285 mμ (3.62), 308 mμ (3.07), and 321 mμ (3.11).

1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetone (XV).—The octahydro acid IXa (1.34 g.) was converted to the sodium salt by means of 0.374 g. of sodium bicarbonate in 5 cc. of water, the water was evaporated in a stream of air and the solid residue was powdered and dried in an oven at 100° for twelve hours. Dry benzene (15 cc.), a drop of pyridine and 4 cc. of oxalyl chloride (b. p. 63–64°) were added to the sodium salt[10] at 0°. Immediate reaction took place and after standing at room temperature for two and one-half hours, the solvent was removed under reduced pressure without heating, and an additional 10 cc. of benzene was added and removed as before. The acid chloride was dissolved in 30 cc. of dry benzene and filtered through a plug of cotton into a suspension of sodiomalonic ester (from 0.5 g. of sodium powder and 5 cc. of diethyl malonate in 50 cc. of dry ether). After stirring at room temperature for fifteen hours and at reflux for two, the mixture was acidified with dilute acetic acid, extracted with ether, the ether removed and the residue heated for one and one-half hours under nitrogen with 10 cc. of water, 25 cc. of acetic acid and 25 cc. of hydrochloric acid. The cooled mixture, which showed an intense green fluorescence, was diluted, extracted with ether and washed with water, 10% potassium hydroxide and dilute acid. From the ether was obtained 1.02 g. of brown oil which crystallized from methanol to give 471 mg. of the diketone, m. p. 115–122°. Evaporative distillation of the material in the filtrate at 170–190° (0.05 mm.) and recrystallization from methanol gave an additional 76 mg., m. p. 114–117.5° and 18 mg., m. p. 107–117° for a total yield of 42%. One recrystallization of the combined material gave 422 mg. of the diketone, m. p. 121–122.5°. The pure compound crystallized from methanol as colorless blades, m. p. 122–122.5°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.1. Found: C, 75.9; H, 8.1.

Acidification of the potassium hydroxide extracts gave 410 mg. of oil, from which 282 mg. of starting acid, m. p. 131–136°, was recovered through the insoluble sodium salt. The yield of crude diketone corrected for this recovered acid was 54%. When the acid chloride was prepared from the free acid, rather than the salt, the yield of crude diketone was only 20%.[27]

Condensation of Methyl 1-Keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetate with Phenyl Acetate.—This reaction was carried out with 750 mg. of the octahydro ester IXb (m. p. 95–97°) in the same manner as described above for the hexahydro ester Xb, except that ether was used instead of benzene to dissolve the ester originally, and the reaction mixture was allowed to stand for six hours. After hydrolysis and decarboxylation of the potassium hydroxide-soluble material, the neutral oil was evaporatively distilled at 185–200° (0.1–0.4 mm.) giving 130 mg. of oil from which 41 mg. (6%) of solid diketone, m. p. 105–118°, could be crystallized using methanol. Recrystallization from methanol gave 19 mg. of material, m. p. 121.5–122.5°, which showed no depression in m. p. when mixed with the diketone XV prepared by the malonic ester procedure.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 76.0; H, 8.1. Found: C, 75.5; H, 8.0.

A retreatment of the initial neutral fraction with triphenylmethylsodium and phenyl acetate gave only 7 mg. more of the crystalline diketone, m. p. 113–120.5°.

From another run starting with 700 mg. of the ester, the only variations being that benzene was used as the initial solvent and the reaction time was sixteen hours instead of six, no crystalline diketone was obtained. The oily diketone (135 mg., after evaporative distillation) was cyclized by heating with 1 cc. of 45% potassium hydroxide and 5 cc. of methanol for fifteen hours under nitrogen; 95 mg. of neutral oil was obtained which crystallized from methanol upon cooling to Dry Ice temperature, giving 26 mg. of solid, m. p. 103–109°. Recrystallization from methanol gave 7 mg., m. p. 108–111°. A mixture of this material with the cyclic ketone XVI (m. p. 110–111°) prepared by cyclization of the crystalline diketone XV (see below) gave a depression in melting point to 84–95°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.3; H, 7.7.

The ultraviolet absorption spectrum[24] of this substance (Fig. 1), which supported the structure XVIIIb as a result of a shift of the double bond, showed a maximum at 273 mμ (log E = 4.25) and a minimum at 237.5 mμ (3.62); a lower maximum and minimum in the region 320–370 mμ (log E = 2.7–2.9) were indicated but were not measured accurately.

3-Methoxy-1,3,5,14-estratetraen-16-one (XVI).—The optimum conditions for cyclizing the diketone XV were as follows: To a solution of 0.7 g. of sodium in 14 cc. of absolute methanol was added 284 mg. of the diketone (m. p. 120.5–122.5°) and the mixture was refluxed on the steam-bath in a nitrogen atmosphere for exactly two and three-quarters hours. The cooled mixture was diluted and extracted twice with ether and the extracts washed with water and dilute acid. After evaporating the ether the residue was stirred with petroleum ether (b. p. 60–68°), giving 239 mg. (90%) of solid, m. p. 107.5–111°. Recrystallization from alcohol gave 195 mg. of colorless blades, m. p. 110–111°, and 39 mg., m. p. 106.5–109°. The melting point of the first crop was not raised by further recrystallization.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.8; H, 7.8.

The ultraviolet absorption spectrum[24] (Fig. 1) showed maxima at 227 mμ (log E = 4.27) and 280 mμ (3.40); a minimum at 265 mμ (3.21); and an inflection at 287 mμ (3.36).

The great importance of time in the above procedure was demonstrated by the following experiments, using the same concentration of sodium methoxide in methanol and starting with 100 mg. of diketone: two hours, 54% yield of crystalline cyclic ketone; two and three-quarters hours (above run on 284 mg.), 90%; three hours, 71%; four hours, 48%; and eight hours, no crystalline cyclic ketone isolated. In the last case the oily product was refluxed under nitrogen with 2 cc. of water, 5 cc. of acetic acid and 5 cc. by hydrochloric acid for one and one-half hours in order to effect isomerization if possible. When the neutral fraction was evaporatively distilled at 180–200° (0.05 mm.) and stirred with petroleum ether, it partially crystallized giving 22 mg. of an impure yellow solid, m. p. 110–145°. Further recrystallization from methanol gave material, m. p. 145–165°, which was still impure (*Anal.* Found: C, 79.1; H, 6.5); the ultraviolet absorption spectra suggested that it contains some of the methyl ether XXIIIb.

1,3,5,8(9)-Estratetraen-3-ol-16-one (XVIIIa).—A mixture of 75 mg. of the methoxy cyclic ketone XVI (m. p. 110–11°), 2.5 cc. of acetic acid and 2.5 cc. of 42% hydrobromic acid was refluxed under nitrogen for two and one-half hours. The cooled mixture, which exhibited a bright blue fluorescence, was diluted and made distinctly basic with 45% potassium hydroxide solution. Extraction with ether removed 12 mg. of oily neutral material. From the alkaline solution was obtained 60 mg. of phenolic oil which crystallized when stirred with a small amount of methanol yielding 26 mg. (37%) of a gray solid, m. p. 182–186°. Two recrystallizations from methanol gave the sample used for analysis which still melted over the range 188–193.5° (vac.).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.3; H, 7.5.

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[27] Hydrolysis of the acid chloride prepared from the free acid gave only 17% of acidic material and 82% of a neutral oil, from which 24% of the solid starting acid was recovered by alkaline hydrolysis. When acid chloride prepared from the sodium salt was hydrolyzed, the acidic fraction was 40% and the neutral 56%. The latter probably is the enol lactone of the keto acid.

The ultraviolet absorption spectrum[24] (Fig. 1) showed maxima at 273 mμ (log E = 4.16), 336 mμ (2.36) and 362.5 mμ (2.22) and minima at 241.5 mμ (3.73), 332 mμ (2.35) and 355 mμ (2.20). The non-crystalline phenolic material, evidently a mixture, did not give crystalline material when converted to the benzoate.

3-Methoxy-1,3,5-estratrien-16-one (XVII).—A suspension of 200 mg. of palladium-on-carbon catalyst[20] in 10 cc. of purified dioxane was saturated with hydrogen at room temperature and atmospheric pressure, then 192 mg. of the methoxy ketone XVI, dissolved in 6 cc. of dioxane, was introduced and stirring continued for twenty hours until one mole-equivalent of hydrogen was absorbed. After removal of the catalyst and solvent, the product crystallized readily upon stirring with petroleum ether to give 168 mg. of colorless solid, m. p. 146–148°. An additional 6 mg., m. p. 143–148°, from the filtrate brought the yield to 90%. The pure material crystallized from absolute alcohol as colorless blades, m. p. 147.5–148°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.2; H, 8.5. Found: C, 80.3; H, 8.4.

The compound was shown to be a ketone by reaction with Girard reagent P; 48 mg. (from 50 mg.) was recovered from the water-soluble fraction, m. p. 144–147.5°.

1,3,5-Estratrien-3-ol-16-one (II).—A mixture of 62 mg. of the saturated methoxy ketone XVII (m. p. 147–148°), 2 cc. of acetic acid and 2 cc. of 42% hydrobromic acid was refluxed under nitrogen for three hours. The cooled mixture (intense blue fluorescence) was diluted, extracted twice with ether, and the latter washed with water and three times with 10% potassium hydroxide; acidification of the alkaline layers and extraction with ether gave 52 mg. of phenolic product which crystallized upon stirring with petroleum ether to give 41 mg. (70%) of gray solid, m. p. 166–174.5°. An additional 2 mg., m. p. 158–170°, was obtained from the filtrate. Two recrystallizations of the material in the first crop from methanol gave the phenol II as colorless, irregular blades, m. p. 177.5–178°. Indications of polymorphism were obtained for this substance. When one sample was introduced in a bath preheated to 140°, it melted and immediately resolidified to melt again at 174–176°. If inserted at 100° and heated rather rapidly, the solid partially melted at 166–168°, followed by resolidification and remelting at 174–177°; if this melt was allowed to resolidify it remelted at 174–176.5° with no apparent change at the lower temperature.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.7; H, 8.1.

The ultraviolet absorption spectrum[24] (Fig. 2) showed a maximum at 280.5 mμ (log E = 3.34) and a minimum at 249.5 mμ (2.43). For estrone the maximum was found at 279.5 mμ (3.48) and the minimum 247 mμ (2.79). The values for the extinction coefficient were somewhat higher than those found by Mayneord and Roe[28] and Dannenberg[29]—maximum at 280 mμ (log E = 3.3 and 3.36 respectively) and minimum at 248 mμ (2.5 and 2.58).

Digestion of the residue from the original ether extracts with 10% potassium hydroxide gave an additional 5 mg. of solid phenolic material, m. p. 135–150°, and 8 mg. of neutral oil.

The **benzoate** was prepared from the total crude phenolic material from demethylation of 50 mg. of the methyl ether by refluxing for three hours under nitrogen with a mixture of 0.25 cc. of benzoyl chloride and three drops of pyridine in 5 cc. of dioxane. After cooling and allowing to stand for several hours, the semi-solid material was filtered and washed well with water and alcohol, giving 43 mg. of nearly colorless benzoate, m. p. 213–225° (vac.). An additional 8 mg., m. p. 218–226° (vac.) was obtained from the filtrate for a total yield of 77% (from the methoxy ketone). Recrystallization of the material from acetone gave 32 mg., m. p. 227–229° (vac.). Another recrystallization gave the benzoate as colorless leaflets, m. p. 228–229.5° (vac.).

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.2; H, 7.0. Found: C, 79.8; H, 7.0.

Summary

A twenty-step total synthesis of an isomer (II) of estrone having the keto group at C-16 instead of C-17 has been accomplished. Several alternative routes to 3-methoxy-1,3,5,14-estratetraene-16-one (XVI) from 1-keto-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a - octahydrophenanthrene - 2 - acetic acid (IXa) were explored. Hydrogenation and demethylation of XVI gave one of the eight possible isomers of II. Demethylation of the unsaturated ketone XVI resulted in a shift of the double bond to the 8–9 position, giving the 16-keto isomer (XVIIIa) of isoequilin A. The estrogenic activity of II was low (about 1/7600th that of estrone) indicating it to differ from estrone stereochemically as well as in the position of the keto group. XVIIIa was about 1/450th as active as estrone. The preparation of other stereoisomers is being investigated.

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[28] Mayneord and Roe, *Proc. Roy. Soc. (London)*, **A158**, 634 (1937).

[29] Dannenberg, *Abhandl. preuss. Akad. Wiss., Math.-nat. Klasse*, No. 21 (1939).