

was 17 g. of material melting at 53–55° after crystallization from petroleum ether, using decolorizing carbon.

*Anal.* Calcd. for  $C_{17}H_{15}NCl$ : C, 75.68; H, 5.98; N, 5.19. Found: C, 75.70; H, 6.08; N, 5.22.

**4-Dimethylamino-2,2-diphenylpentanenitrile (IV) A.**—A mixture of 11 g. of the bromonitrile (II), 20 ml. of alcohol and 20 g. of dimethylamine was heated in a sealed tube at 94° for fourteen hours. After opening the tube, the contents were evaporated to dryness under reduced pressure. After adding 20% hydrochloric acid to the residue, the mixture was extracted with ether. The aqueous layer was separated and made alkaline with 50% sodium hydroxide. It was then extracted with ether, the ether solution dried over magnesium sulfate and evaporated to dryness. On cooling and scratching, the oily residue crystallized. The crystals melted at 89–91° and the melting point was not depressed by the additions of 4-dimethylamino-2,2-diphenylpentanenitrile prepared by the German process.<sup>2</sup> Crystallization from Skellysolve did not change the melting point.

*Anal.* Calcd. for  $C_{19}H_{21}N_2$ : N, 10.06. Found: N, 10.06, 10.05.

The material recovered from the first ether extraction agreed in all of its properties with 2,2-diphenyl-4-pentenenitrile (VI), the preparation of which is described below, except in refractive dispersion, and was therefore probably 2,2-diphenyl-3-pentenenitrile (V) or a mixture of the two: b. p. 133–136° under 2 mm.;  $n_D$  1.5748,  $n_F - n_C$  0.0286. For 2,2-diphenyl-4-pentenenitrile, b. p. 134–136° under 2 mm.;  $n_D$  1.5747,  $n_F - n_C$  + 0.0183. All refractive index data were at 22.4°.

*Anal.* Calcd. for  $C_{17}H_{15}N$ : N, 6.00. Found: N, 6.04, 6.01.

**B.**—The procedure was repeated using the chloronitrile (III), except that the mixture was heated at 150°. The products were identical.

**Amidone.**—Amidone prepared from 4-dimethylamino-2,2-diphenylpentanenitrile obtained by either of the procedures above was identical with that obtained by the German process.<sup>2</sup> The yield was about 85%.

**Exhaustive Methylation of 4-Dimethylamino-2,2-diphenylpentanenitrile.**—The methiodide of this compound was decomposed in the usual way, to yield an oily product which, without purification, was hydrolyzed by heating on the steam-bath with 90% sulfuric acid. After crystallization from Skellysolve C, the white product melted at 112–113°. There was no depression in melting point after mixing with the lactone of 2,2-diphenyl-4-hydroxypentanoic acid prepared from 2,2-diphenyl-4-pentanenitrile.

*Anal.* Calcd. for  $C_{17}H_{15}O_2$ : C, 80.92; H, 6.39. Found: C, 81.00; H, 6.40.

**2,2-Diphenyl-4-pentenenitrile (VI).**—To a suspension of 39 g. of sodium amide in 180 ml. of dry benzene, there was added 173.4 g. of diphenylacetone during fifteen minutes, with efficient stirring. The mixture was heated to 40–45° for one and a half hours and then cooled to 25°. Then, 78 ml. of allyl chloride was added during thirty minutes, with cooling. The mixture was refluxed for thirty minutes and then poured into water. The benzene layer was separated, dried over magnesium sulfate and filtered. The residue, after evaporation of the solvent, was distilled under reduced pressure. The yield of material boiling at 134–136° under 2 mm. pressure was 159 g. (76%).

*Anal.* Calcd. for  $C_{17}H_{15}N$ : C, 87.51; H, 6.48; N, 6.00. Found: C, 87.60; H, 6.33; N, 6.05.

**Lactone of 2,2-Diphenyl-4-hydroxypentanoic Acid (VII)**—A mixture of 2,2-diphenyl-4-pentenenitrile (VI) and 90% sulfuric acid was heated on a steam-bath for two hours. The solution was poured into water and allowed to stand overnight. The solid which separated was crystallized from Skellysolve C. The white product melted at 112–113°.

*Anal.* Calcd. for  $C_{17}H_{15}O_2$ : C, 80.92; H, 6.39. Found: C, 80.90; H, 6.34.

**Hydrolysis of 3,3-Diphenyl-5-methyltetrahydrofuranone-2-imine Hydrochloride (I).**—An aqueous solution of the hydrochloride was allowed to stand overnight. The precipitate was collected and melted at 112–113° after crystallization from methylcyclohexane. Mixed melting points with samples of the lactone (VII) prepared by each of the methods described above gave no depression.

*Anal.* Calcd. for  $C_{17}H_{15}O_2$ : C, 80.92; H, 6.39. Found: C, 80.95; H, 6.28.

**Acknowledgment.**—We wish to express our appreciation to Dr. V. B. Fish for the analyses, to Dr. E. C. Larsen for the refractive index data and to Miss Mary L. Evanick for technical assistance.

### Summary

1. A new synthesis of amidone has been developed.
2. A confirmation of the structure of amidone has been presented.

PHILLIPSBURG, N. J.

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

## A New Synthesis of Fused Ring Structures Related to the Steroids. The 17-Equilenones. A Total Synthesis of Equilenin<sup>1,2</sup>

BY WILLIAM S. JOHNSON, JACK W. PETERSEN<sup>3</sup> AND C. DAVID GUTSCHE<sup>4</sup>

In the course of studies of the synthesis of steroid-like structures we endeavored to effect a Stobbe condensation with the keto ester I in the hope that by procedures already described,<sup>5</sup> a

(1) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

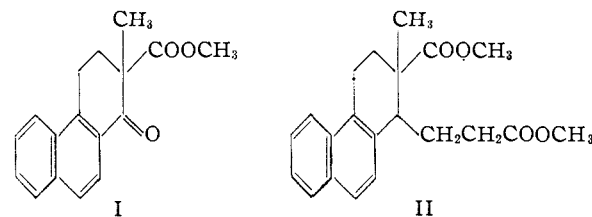
(2) A preliminary announcement of this work was reported in a communication to the Editor, *THIS JOURNAL*, **67**, 2274 (1945).

(3) W. A. R. F. Research Assistant, 1943–1945. Present address: Department of Chemistry, University of California, Berkeley, California.

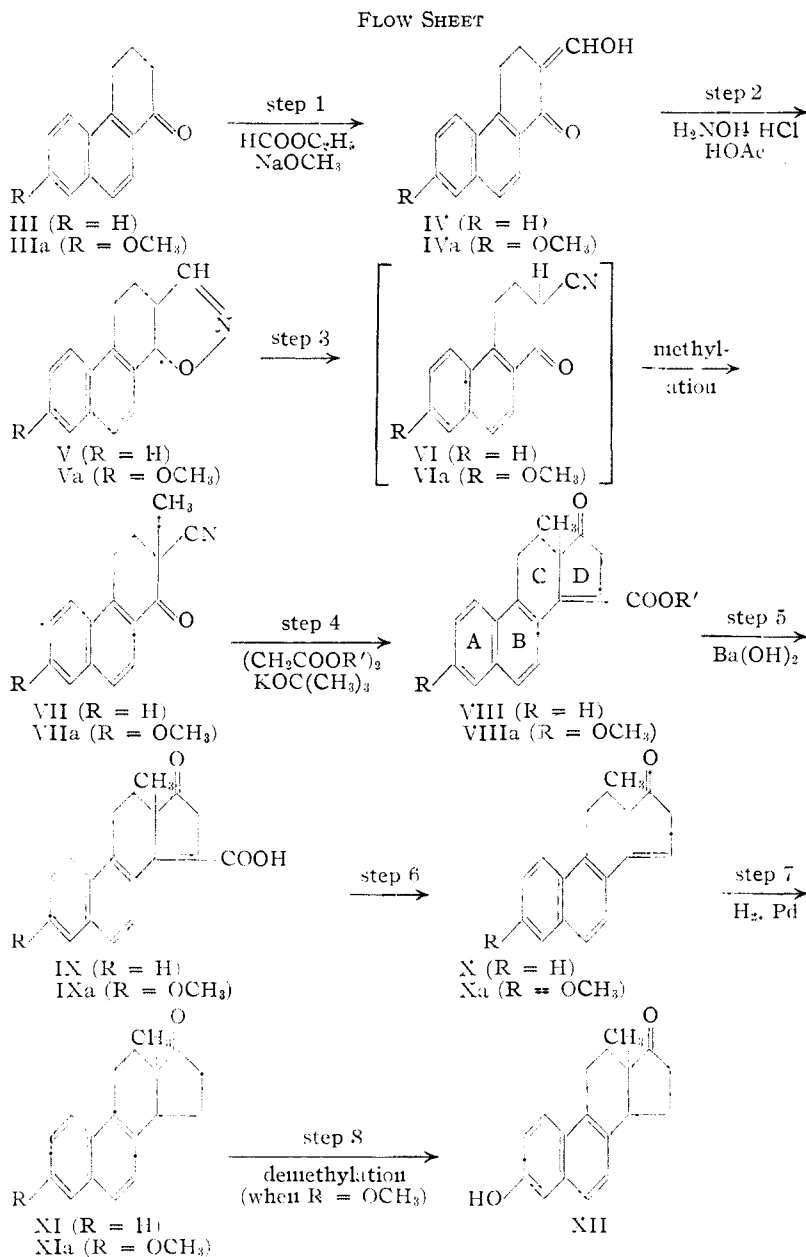
(4) du Pont fellow, September 1946–March 1947; Wisconsin Alumni Research Foundation Post-doctorate fellow March 1947–

(5) Johnson, Goldman and Schneider, *THIS JOURNAL*, **67**, 1357 (1945); Johnson, Johnson and Petersen, *ibid.*, **67**, 1360 (1945); Johnson and Petersen, *ibid.*, **67**, 1366 (1945).

propionic acid side-chain could be introduced at the site of the keto group to form a product II, known to be convertible to 17-equilenone (3-desoxyequilenin), XI.<sup>6</sup> Preliminary experiments,



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

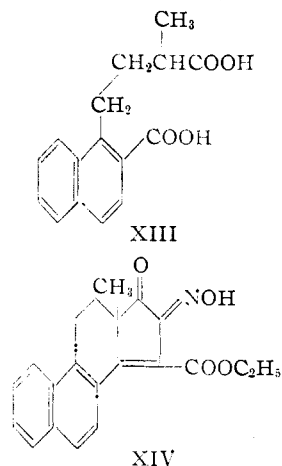


however, were unpromising, as the carbomethoxy group was largely eliminated during the reaction.

In the hope that the cyano group would be less susceptible to cleavage, the reaction of the  $\beta$ -keto nitrile VII with diethyl succinate and potassium *t*-butoxide was investigated. Instead of the expected Stobbe condensation product, a nitrogen-free ester was produced, which proved to have the structure VIII ( $R' = C_2H_5$ ) with the five-membered ring D already completely formed as shown by its ready conversion to the two isomeric 17-equilenones, XI. The discovery of this new keto ester and the proof of structure is described directly below.

The desired  $\beta$ -keto nitrile VII was obtained by

methylation (with sodium methoxide and methyl iodide) of 2-cyano-1-keto-1,2,3,4-tetrahydrophenanthrene, VI, which was readily available from 1-keto-1,2,3,4-tetrahydrophenanthrene, III, via the hydroxymethylene ketone IV and the isoxazole V.<sup>7</sup> That the methylation took place at the carbon rather than the oxygen<sup>8</sup> was proved by exhaustive alkaline hydrolysis, which gave a dibasic acid XIII different from that produced



by the hydrolysis of VI.<sup>9</sup> In addition, a Zeisel determination indicated that the methylated cyano ketone contained no methoxyl group. For the preparation of VII, it was found unnecessary to isolate the cyano ketone VI, since sodium methoxide converts the isoxazole V into the sodio derivative of VI<sup>7</sup> which on treatment with methyl iodide gives VII directly in 91% over-all yield.

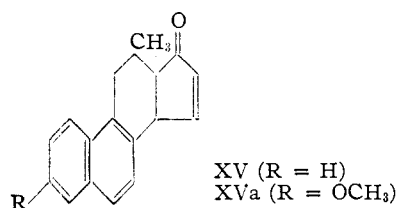
The reaction of VII with diethyl succinate in the presence of potassium *t*-butoxide and *t*-butyl alcohol produced a yellow intermediate which on treatment with mineral acid was decomposed, with the liberation of carbon dioxide, to give the crystalline 15-carbomethoxy-14,15-dehydro-17-equilenone, VIII ( $R' = C_2H_5$ ), in 60% yield. Except for the position of the ethylenic bond which might alternately be located at the 15,16-position, the structure was proved beyond doubt. The new product formed a semicarbazone and an oxime,

(7) Johnson and Shelberg, *ibid.*, **67**, 1745 (1945).

(8) Cf. the behavior of other  $\beta$ -keto nitriles on methylation; for example von Auwers and Enbergs, *Ber.*, **65**, 828 (1932), and Fuson and Wolf, *THIS JOURNAL*, **61**, 1940 (1939).

(9) Johnson and Shelberg, *THIS JOURNAL*, **67**, 1754 (1945).

was saponified to yield a monobasic acid (IX), and on nitrosation afforded an alkali-soluble derivative, undoubtedly XIV, indicating the presence of a reactive methylene group.<sup>10</sup> When the new keto ester was heated with hydrochloric and acetic acid, simultaneous hydrolysis and decarboxylation took place, a behavior that is also compatible with the formula VIII ( $R' = C_2H_5$ ) since it not only has a cinnamic acid structure, but is related (by vinylogy) to a  $\beta$ -keto ester. Two dehydro-17-equilenones were isolated from the product of decarboxylation, one melting at  $138^\circ$  (the less soluble isomer) and the other at  $102^\circ$ . Catalytic hydrogenation gave respectively  $\beta$ - and  $\alpha$ -17-equilenone which were identified by mixed melting point comparisons of the ketones and semicarbazones with authentic specimens prepared by the method of Bachmann and Wilds.<sup>6,11</sup>



Since the  $138^\circ$  and the  $102^\circ$  dehydro-17-equilenones described above appeared to be inter-

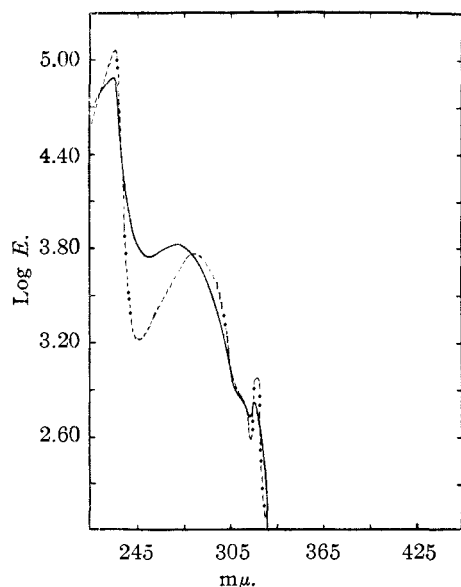
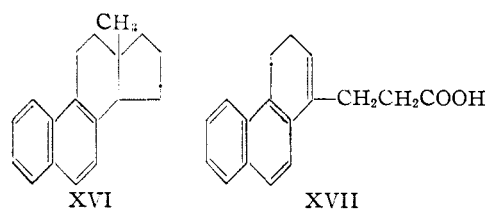


Fig. 1.— — 15,16-Dehydro-17-equilenone (XV);  
----- $\beta$ -*dl*-equilenane (XVI).

(10) The nitrosation reaction does not constitute proof of the position of the ethylenic linkage in the keto ester, because the behavior could be explained equally well with the double bond at the 15,16-position provided the reasonable assumption is made that the latter is convertible to the 14,15-isomer *via* a 3-carbon tautomerism catalyzed by the reagent.

(11) These ketones have added interest in view of the recent report of Prelog and Führer, *Helv. Chim. Acta*, **28**, 583 (1945), of the isolation of one of the enantiomorphs (*d*-3-desoxyequilenin) from pregnant mares' urine. The identity with synthetic material must await resolution of the *dl*-17-equilenones.

convertible (probably *via* a 3-carbon tautomerism), it did not appear expedient to attempt to decide on chemical grounds whether they represented *cis* and *trans* (at rings C/D) forms of the  $\alpha,\beta$ -unsaturated ketone XV, or if they were indeed 3-carbon tautomers, X and XV. That the latter was the case was shown by the fact that the ultraviolet absorption spectra (Figs. 1 and 2), were definitely dissimilar. In addition it was possible to identify the  $102^\circ$  isomer as XV and the  $138^\circ$  isomer as X, since the spectrum of the former was very similar to that of  $\beta$ -equilenane,<sup>12</sup> XVI (Fig. 1). This similarity was expected, since the principal maximum due to the  $\alpha,\beta$ -unsaturated ketone grouping in XV would be predicted to lie in the unexamined region of shorter wave lengths.<sup>13</sup> The spectrum of the  $138^\circ$  isomer, on the other hand, was found to resemble that of  $\beta$ -(3,4-dihydro-1-phenanthryl)-propionic acid,<sup>14</sup> XVII



(Fig. 2), which like formula X is a 1-alkyl-2-vinylnaphthalene. Independent confirmation of the position of the ethylenic bonds in the two de-

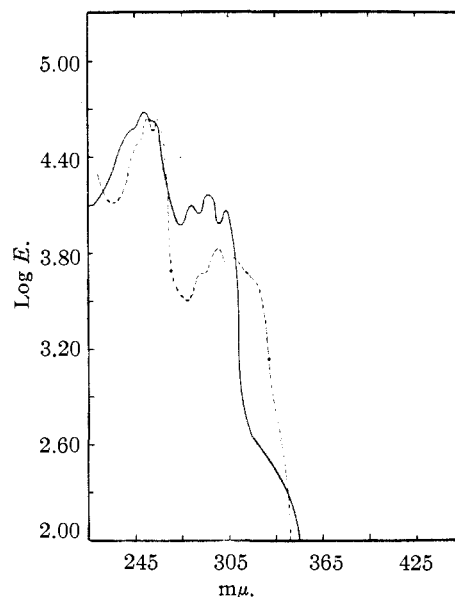


Fig. 2.— — 14,15-Dehydro-17-equilenone (X);  
----- $\beta$ -(3,4-dihydro-1-phenanthryl)-propionic acid (XVII).

(12) Wilds, Beck and Johnson, *THIS JOURNAL*, **68**, 2161 (1946).

(13) An  $\alpha,\beta$ -unsaturated cyclopentanone derivative with one  $\beta$ -substituent would be expected to have  $\lambda$  max. = ca. 215 m $\mu$  according to an estimation made on the basis of the work of Gillam and West, *J. Chem. Soc.*, 486 (1942), and of Woodward, *THIS JOURNAL*, **64**, 76 (1942).

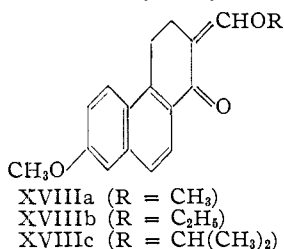
(14) Johnson and Petersen, *ibid.*, **67**, 1366 (1945).

hydro-17-equilenones has been obtained by infrared spectrographic analysis.<sup>15</sup>

### Synthesis of Equilenin

Having successfully synthesized the 17-equilenones as described above we turned our attention to the synthesis of equilenin, XII, from 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene,<sup>16</sup> IIIa, which is the same starting material that was used by Bachmann, Cole and Wilds<sup>17</sup> in their classical synthesis of the hormone. The steps in the new synthesis are outlined in the accompanying flow sheet. The procedures have been developed so that according to the best yields which have been realized for each step it is possible to prepare 3.3 g. of *dl*-equilenin from 10 g. of the starting ketone IIIa in seven operations (steps 3 and 4 being combined). This represents a 28% over-all yield. The manipulations are for the most part relatively easy and promise to be adaptable to large-scale operation. The production of a steroid by total synthesis, therefore, now appears to be well within the realm of practicability, particularly since the starting ketone IIIa promises to be readily available.<sup>18</sup>

**Step 1.**—2-Hydroxymethylene-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, IVa, was prepared in 97–98% yield by the interaction of ethyl formate and IIIa, in the presence of sodium methoxide. Experimentation with IVa revealed the fact that the substance reacts rapidly with methanol in the presence of a trace of acid catalyst to give the crystalline enol methyl ether XVIIa.<sup>19</sup> The reaction is so rapid that it may take place during attempts to recrystallize the hydroxymethylene ketone from methanol unless special precautions are taken to free the reagents and glassware from traces of acid. The ethyl, XVIIIb, and isopropyl derivative, XVIIIc, were similarly prepared from the corresponding alcohols, although the reaction was not so rapid. *t*-Butyl alcohol failed to react with the hydroxymethylene ketone.



**Step 2.**—Conversion of the hydroxymethylene ketone IVa into the beautifully crystalline 10,11-

(15) We are indebted to Dr. R. N. Jones and to Dr. K. Dobriner for making this study on our compounds. The details of their work will appear in the near future in *THIS JOURNAL*.

(16) First prepared by Butenandt and Schramm, *Ber.*, **68**, 2083 (1935).

(17) Bachmann, Cole and Wilds, *THIS JOURNAL*, **62**, 824 (1940).

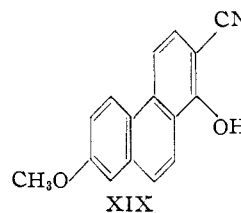
(18) See Stork, *THIS JOURNAL*, **69**, 2936 (1947). In addition other methods are being developed at the University of Wisconsin.

(19) This substance is particularly interesting because it has certain structural features which are similar to the Windaus structure for colchicine.

dihydro-7-methoxyphenanthro[2,1-*d*]isoxazole, Va, was effected in 96% yield simply by heating the former with hydroxylamine hydrochloride in acetic acid for ten minutes. The isoxazole could be produced also by previously described procedures<sup>7</sup> but in somewhat lower yield.

**Step 3.**—The best method developed for producing 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, VIIa, consisted in treatment of the isoxazole with potassium *t*-butoxide in *t*-butyl alcohol to form the potassio derivative of VIa, followed by methylation with methyl iodide. The crystalline cyano ketone VIIa thus was obtained in yields as high as 92%.

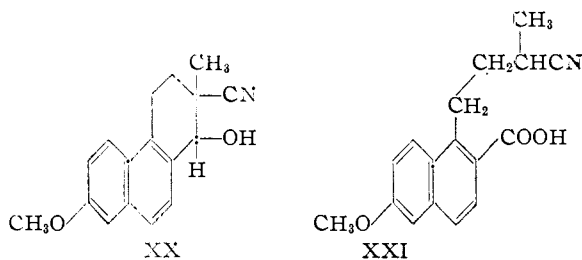
In earlier studies the intermediate 2-cyano-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, VIa, was first prepared by alkoxide-catalyzed isomerization of the isoxazole according to procedures already described.<sup>7</sup> Methylation with sodium methoxide and methyl iodide gave fairly good yields of the desired product, but an insoluble by-product also was formed in about 4–5% yield. This substance probably is 2-cyano-1-hydroxy-7-methoxyphenanthrene, XIX, as indicated by its analysis, phenolic properties, and reaction with acetic anhydride to form an acetate. The production of XIX by aromatization of VIa resembles the formation of 1-hydroxy-2-phenanthraldehyde under similar conditions from IV, noted by Wilds and Djerassi.<sup>20</sup>



**Step 4.**—Considerable study was made of the key reaction of the synthesis, namely, the condensation of the cyano ketone VIIa with a succinic ester. In the earlier work, diethyl succinate was used, but the best conditions found afforded the keto ester VIIIa (R' = C<sub>2</sub>H<sub>5</sub>) in only about 50% yield. The nitrogen lost during the formation of the keto ester appeared as ammonium salts in amount approximately equivalent to the yield of keto ester. The determination of ammonia thus provided a rapid and reliable estimation of the extent of the condensation, and therefore afforded a valuable tool in pilot experiments performed for the purpose of finding the best conditions for the condensation. An effort to ascertain the fate of the remaining cyano ketone which did not react in the desired manner led to the isolation of two side-products in addition to some unchanged cyano ketone. One of these was obtained in low yield by chromatographic adsorption as a colorless crystalline material melting at 203°. The analysis was compatible with the formula C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>, but the structure is not known. An

(20) Wilds and Djerassi, *THIS JOURNAL*, **68**, 1715 (1946).

analogous product,  $C_{17}H_{16}O_2$ , was also found in the desoxyequilenin series. A second side-product was isolated by crystallization directly from the reaction mixture in yields as high as 10%. This substance was shown to be one of the two possible stereoisomeric forms of 2-cyano-1-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene, XX, by comparison with material produced by reduction of VIIa with aluminum isopropoxide. The formation of XX during the reaction with diethyl succinate may be explained as the result of a Meerwein-Ponndorf type of reduction by the potassium ethoxide which is formed as a by-product of the normal condensation reaction and also of ester condensation of diethyl succinate with itself. A similar behavior has already been noted in the *t*-butoxide-catalyzed Stobbe condensation of diethyl succinate with benzophenone which was partially reduced to benzhydrol.<sup>21</sup>



In an effort to avoid reagents with potential reducing action, di-*t*-butyl succinate was tried in place of the diethyl ester. Although there was no evident reduction of the cyano ketone VIIa, the desired condensation proceeded so slowly that other competing reactions took precedence, and the *t*-butyl keto ester VIIIa ( $R' = C(CH_3)_3$ ) was isolated in only 13% yield. An ammonia determination indicated that not more than 23% of the cyano ketone was involved in the desired condensation. The low yield was not surprising in view of the discovery that potassium *t*-butoxide alone slowly acts on the cyano ketone VIIa to open the alicyclic ring. Thus after four hours at  $55^\circ$  (conditions which were too mild to give any of the desired condensation with *t*-butyl succinate) more than 20% of VIIa was cleaved, the product being isolated from the alkali-soluble fraction as the crystalline  $\alpha$ -methyl- $\gamma$ -(2-carboxy-7-methoxy-1-naphthyl)-butyronitrile, XXI.

Since metal methoxides have been shown to be weaker reducing agents than ethoxides,<sup>22</sup> it seemed probable that there would be less tendency toward reduction of VIIa to XX with dimethyl succinate than with the diethyl ester. This indeed proved to be the case, as none of the carbinol XX was found when dimethyl succinate was employed in the condensation. Our attention was, therefore, centered on the use of this ester in the condensation, and eventually conditions were worked

out whereby the crystalline 15-carbomethoxy-14,15-dehydroequilenin methyl ether,<sup>23</sup> VIIIa ( $R' = CH_3$ ), was obtained in yields as high as 83%. A further refinement in the synthesis was effected on realization that it was unnecessary to isolate the cyano ketone VIIa for use in the condensation; thus the reaction mixture from the methylation step was simply evaporated, and the residue containing a mixture of cyano ketone and potassium iodide was treated with dimethyl succinate and potassium *t*-butoxide as described above. In this way the keto ester VIIIa was obtained directly from the isoxazole Va (steps 3 and 4 combined) in 77–80% yield.

One of several possible mechanisms for the complex condensation reaction described above is suggested in the accompanying flow sheet, formulas A  $\rightarrow$  F. The first step, A  $\rightarrow$  B, is represented as a Thorpe type of addition of the active methylene to the cyanide group.<sup>24</sup> The resulting ketimine B is a monosubstituted keto succinic ester, and thus could conceivably undergo an intramolecular Stobbe condensation, B  $\rightarrow$  E. The intermediary hydroxy ester C and paraconic ester D simply represent the counterparts of the intermediates probably involved in a normal intermolecular Stobbe condensation.<sup>25</sup> The substance E being the imino derivative of a  $\beta$ -keto acid would be expected to undergo hydrolysis and decarboxylation readily to give the keto ester F, along with carbon dioxide and ammonium chloride, all of which were actually recognized as products of hydrochloric acid hydrolysis. The existence of an intermediate imino compound such as E (possibly lacking the 16-carboxyl group) was indicated experimentally by the fact that small amounts of acid-soluble material were frequently found, particularly in small-scale runs, in the course of working up the reaction mixtures. On standing in acid solution this basic material hydrolyzed to the neutral keto ester F. This phenomenon was observed in both the equilenin and the desoxyequilenin series.

An equally satisfactory mechanism may be postulated in which the first step is a Stobbe condensation. The intermediary paraconic ester G<sup>26</sup> thus could be envisaged as undergoing an intramolecular Thorpe reaction. Since in any mechanism all of the steps up to the alkoxide cleavage of the paraconic ester type D<sup>27</sup> would probably be

(23) The position of the ethylenic bond has not yet been established, but is formulated in the 14,15- rather than the 15,16-position as the more probable structure.

(24) The reactions of all of the intermediates A  $\rightarrow$  E would undoubtedly involve anions produced by the strong basic catalyst. All of the structures may thus be revised according to the conventional electronic interpretation for base-catalyzed reactions. Such a treatment, however, adds little to the present argument.

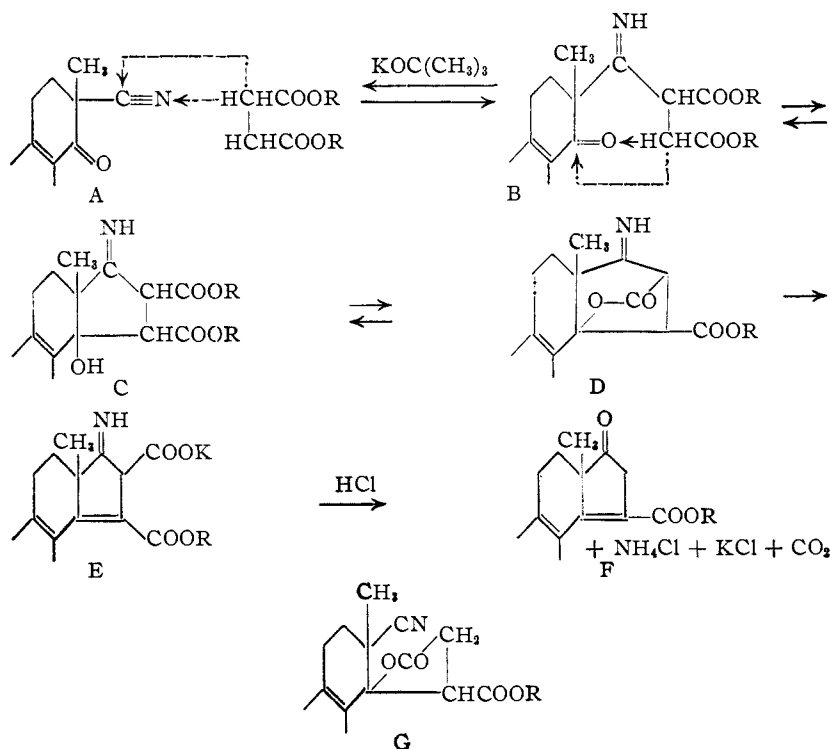
(25) The mechanism as originally proposed by Stobbe, *Ann.*, **282**, 280 (1894), has received substantial support by subsequent developments which will be discussed in future publications.

(26) Note (ref. 25) that in some instances it has been possible to stop the Stobbe condensation at the paraconic ester stage.

(27) Cf. the cleavage of paraconic esters to unsaturated acid esters: Fittig, *Ann.*, **256**, 50 (1890).

(21) Johnson, Petersen and Schneider, *THIS JOURNAL*, **69**, 74 (1947).

(22) Adkins and Eloffson, unpublished observation.



reversible, the transient existence of a variety of intermediates may be reasonably postulated.

**Steps 5-8.**—Attempts to effect simultaneous hydrolysis and decarboxylation of the keto ester VIIIa ( $\text{R}' = \text{C}_2\text{H}_5$ ) with acetic and hydrochloric acid—the method that was used successfully in the desoxyequilenin series (see above)—indicated that decarboxylation proceeded, but that partial demethylation also occurred producing phenolic material which was difficult to purify. However, when the free keto acid IXa was treated with this reagent, the rate of decarboxylation was so much more rapid than with the ester,<sup>28</sup> that essentially complete decarboxylation was realized before appreciable demethylation occurred, and 14,15-dehydroequilenin methyl ether, Xa, thus was obtained. The proof of the position of the ethylenic linkage in this product, m. p.  $162^\circ$ , is considered below.

The most successful method for effecting the decarboxylation involved first saponification of the keto ester with barium hydroxide (step 5) which afforded 15-carboxy-14,15-dehydroequilenin methyl ether, IXa, in 98% yield. The latter was then decarboxylated (step 6) with a boiling mixture of pyridine hydrochloride and hydrochloric acid. Carbon dioxide was evolved rapidly and 14,15-dehydroequilenin methyl ether, Xa, was separated by crystallization in 56% yield. Retreatment of the residues with pyridine hydrochloride and hydrochloric acid gave additional material raising the yield to 66%. Since no car-

(28) Similar comparative behavior has been noted in other decarboxylation studies; see ref. 21.

bon dioxide was evolved, this treatment probably involved isomerization of some 15,16-dehydroequilenin methyl ether (XVa) to the 14,15-compound (see below). A study of the effect of other amines (see experimental part) indicated that the function of the amine hydrochloride was to partially solubilize the large molecule, thus bringing the latter in contact with the acid reagent.

Catalytic hydrogenation of Xa over palladium-on-charcoal catalyst (step 7) proceeded rapidly and quantitatively to give a mixture of *dl*-equilenin methyl ether, XIa (ring C/D probably *trans*) and the stereoisomer *dl*-isoequilenin methyl ether, XIa (ring C/D probably *cis*) in a ratio of approximately 2 to 1. The former, being much less soluble, was separated almost completely by a

single crystallization which gave material of good purity in 63% yield. The isoequilenin derivative was isolated from the mother liquor in 32% yield. Demethylation of *dl*-equilenin methyl ether with hydrochloric and acetic acid (step 8) afforded *dl*-equilenin, XII, of fair purity in 98% yield. Resolution was easily effected *via* the *l*-menthoxyacetic ester according to the excellent procedure of Bachmann, Cole and Wilds.<sup>17</sup> The identity was established by comparison with natural equilenin<sup>29</sup>: mixed melting point determinations were performed with the hormone, the acetate and the *l*-menthoxyacetate.

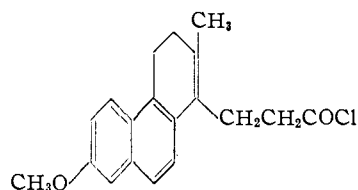
In addition to the methods described above for step 6 it was found possible to effect thermal decarboxylation of the keto acid IXa under reduced pressure, which gave in addition to the dehydroequilenin methyl ether melting at  $162^\circ$ , an isomeric substance melting at  $106^\circ$ . That these were 14,15- (Xa), and 15,16-dehydroequilenin methyl ether (XVa), respectively,<sup>30</sup> was suggested by the fact that hydrogenation of the  $162^\circ$  isomer gave a mixture of equilenin and isoequilenin methyl ether, while the  $106^\circ$  isomer gave exclusively isoequilenin methyl ether. If it is assumed that no shifting of bonds occurred during hydrogenation, the ethylenic linkage in that substance which gave rise to both possible configurations on hydrogenation, namely, the  $162^\circ$  isomer, must involve that carbon atom (at the 14 position) which becomes

(29) We are indebted to Dr. Oliver Kamm of Parke, Davis and Company for supplying this material.

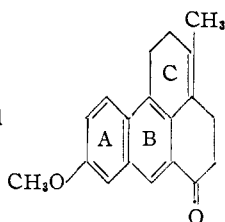
(30) Independent evidence for assigning these structures has been obtained by infrared adsorption data; see ref. 15.

asymmetric on reduction. Since the 162° isomer was recovered completely unchanged after treatment with the hydrogenation catalyst in the absence of any hydrogen, it seemed unlikely that the isoequilenin methyl ether produced on hydrogenation of the 162° isomer was formed by hydrogenation of some 106° isomer arising from partial isomerization of the 162° isomer under the influence of the catalyst. Such a mechanism, however, may possibly explain the behavior of the 162° isomer on hydrogenation in the presence of a base (known to catalyze 3-carbon tautomerism), which gave preponderantly isoequilenin methyl ether, isolated in yields as high as 57%. The course of the hydrogenation of Xa appeared to be unaffected by mild acid catalyst. The above argument could not be applied to the proof of structure of the two corresponding dehydro isomers X and XV in the desoxyequilenin series considered at the beginning of this paper, because in this case the hydrogenation was essentially stereospecific.

The 3-carbon tautomeric relationship between the two dehydroequilenin methyl ethers, Xa and XVa, was established by their interconversion. When the 106° isomer was heated with pyridine hydrochloride and hydrochloric acid, the 162° isomer was isolated from the resulting mixture in 44% yield. On the other hand, when the pure 162° isomer was similarly treated, it was recovered only in 65% yield. Although the 106° isomer was not isolated from the oily residues, its presence was indicated by the fact that retreatment with the reagent gave additional 162° isomer. Since the isomerizations were not effected under homogeneous conditions, it is not possible to draw any significant conclusions regarding the true position of the equilibrium in the 3-carbon tautomerism,  $Xa \rightleftharpoons XVa$ .



XXII



XXIII

In connection with the cyclization of the acid chloride XXII which was studied by Haberland<sup>31</sup> it is interesting to note that if the ring had closed into the 2-position of the phenanthrene nucleus, the product would have had the structure Xa or XVa. Since these substances are now known to melt at 162 and 106°, respectively, and since the ketone isolated by Haberland melted at 205–207°, it seems probable that his product had the structure XXIII resulting from cyclization into the aromatic ring. The susceptibility of his ketone to dehydrogenation is also compatible with

(31) Haberland, *Ber.*, **72**, 1215 (1939); **76**, 621 (1943).

this structure which would be expected to aromatize readily by loss of two hydrogen atoms from ring C.

**Acknowledgment.**—We wish to thank Drs. A. L. Wilds and Warren Close for supplying intermediates for the preparation of the ketone IIIa which was used in our preliminary studies. We are also indebted to Mr. Merlin Bumpus for his assistance in the preparation of starting materials.

### Experimental<sup>32</sup>

#### Part I. The 17-Equilenone (3-Desoxyequilenin) Series

**2-Cyano-1-keto-1,2,3,4-tetrahydrophenanthrene (VI)** was prepared in improved yield by a modification of the method already described.<sup>7</sup> A solution of 20 g. of V, m. p. 104–107°, in 250 ml. of benzene was added to a cooled solution of 3.2 g. of sodium in 40 ml. of methanol. A yellow precipitate of the sodio derivative of the cyano ketone separated immediately. After standing for thirty minutes at room temperature, the mixture was treated with water and extracted thoroughly with 0.5% potassium hydroxide solution. About 4 liters in all was required to dissolve the sparingly soluble potassium derivative. Acidification of the combined aqueous solutions gave 18.8 g. (94% yield) of light tan cyano ketone, m. p. 125–126.5°. An 85% yield of material melting at 125–126° was previously reported.<sup>7</sup>

**2-Cyano-1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene (VII).** (a) *From 2-Cyano-1-keto-1,2,3,4-tetrahydrophenanthrene.*—A solution of 18.8 g. of VI in 67 ml. of warm benzene was added to a solution of 7.3 g. of sodium in 110 ml. of methanol. The mixture was then refluxed for fifteen minutes to insure complete conversion to the sodio derivative. After cooling, the mixture was treated with 11 ml. of methyl iodide and allowed to stir at room temperature for forty-five minutes. An additional 11 ml. of methyl iodide was then added, and after thirty minutes a third portion (5 ml.) of methyl iodide was introduced and the mixture was refluxed for one and one-half hours. All moisture was excluded up to this point. The solvents were largely removed at reduced pressure, the residue taken up in benzene and extracted with 0.5% potassium hydroxide solution. Acidification of these extracts gave 1.2 g. of unchanged starting material, m. p. 125.5–127°. The benzene solution was washed with water, dried, treated with decolorizing charcoal and evaporated. Crystallization of the residue from methanol afforded 15.0 g. of methylation product, m. p. 125.5–127°. An additional 1.7 g. of material melting at 121–124° was obtained from the residues by evaporative distillation under reduced pressure followed by recrystallization. The total yield thus was 84%, or 89% accounting for recovered starting material.

An analytical specimen was obtained by repeated recrystallization from alcohol as colorless plates, m. p. 126–127.2°.

*Anal.* Calcd. for  $C_{15}H_{13}ON$ : C, 81.67; H, 5.57. Found: C, 81.70; H, 5.58. A Zeisel determination for methoxyl was negative.<sup>33</sup>

(b) *Directly from the Isoxazole V.*—A solution of 4.7 g. of V (m. p. 105–108°) in 17 ml. of benzene was added to a solution of 0.6 g. of sodium in 28 ml. of methanol. After standing for thirty minutes at room temperature, the mixture was refluxed for ten minutes and cooled. Methyl iodide (3 ml.) was added, the solution was shaken and allowed to stand for one hour. An additional 2 ml. of methyl iodide was added, and after two hours at room temperature the mixture was refluxed for four hours. The product was isolated as described above: yield 4.55 g.

(32) All melting points are corrected unless otherwise indicated. Those designated "vac." were determined in sealed Pyrex melting point tubes evacuated below 0.5 mm.

(33) Kindly performed by Dr. Gilbert Stork

(91%); m. p. 124.5–126°. No unmethylated cyano ketone was recovered from the alkaline washings.

$\alpha$ -Methyl- $\gamma$ -(2-carboxy-1-naphthyl)-butyric acid (XIII) was obtained by hydrolysis of 0.230 g. of VII with 0.5 g. of potassium hydroxide in 15 ml. of dilute alcohol (80%). After refluxing until no more ammonia was given off (six days), the alcohol was evaporated, the mixture acidified and extracted with ether. The ether solution was washed with sodium bicarbonate solution which on acidification gave 0.050 g. of colorless dibasic acid, m. p. 157–158.5°. Sublimation under reduced pressure, and recrystallization from methanol gave colorless needles, m. p. 160–161°.

*Anal.* Calcd. for  $C_{15}H_{15}O_4$ : C, 70.57; H, 5.92; neut. equiv., 136.1. Found: C, 70.81; H, 5.83; neut. equiv., 139.4, 139.1.

$\gamma$ -(2-Carboxy-1-naphthyl)-butyric acid, which is the product that would be expected on hydrolysis of the O-methylation product of VI, is known to melt at 174.5–176°.<sup>9</sup>

**Ethyl 14,15-Dehydro-17-equilenone-15-carboxylate (VIII, R' = C<sub>2</sub>H<sub>5</sub>).**—To a cold solution of 0.74 g. of potassium in 30 ml. of dry *t*-butyl alcohol was added 6.6 ml. of diethyl succinate followed by 2.00 g. of VII (m. p. 124.5–126°). The system was evacuated and filled with nitrogen, then sealed and allowed to shake mechanically. After three hours the cyano ketone had completely dissolved to give a deep red solution, and after four additional hours a yellow precipitate had formed. The mixture was acidified carefully with dilute hydrochloric acid; a gas was evolved and recognized as carbon dioxide. After evaporation of most of the alcohol under reduced pressure, the insoluble residue was taken up in benzene and ether, washed with water, then three times with 5% potassium hydroxide solution, again with water and dried. The solvent was removed under reduced pressure, and the pale red oily residue dissolved in hot methanol. On cooling the keto ester separated in pale pink crystals; yield 1.50 g.; m. p. 151–153.5°. An additional 0.15 g. of material melting at 145–151° was crystallized from the mother liquor, making the total yield 60%. A sample purified by repeated recrystallization from methanol was obtained as almost colorless, lozenge-shaped crystals, m. p. 152.5–153.5°.

*Anal.* Calcd. for  $C_{21}H_{20}O_3$ : C, 78.72; H, 6.29. Found: C, 78.55, 78.49; H, 6.23, 6.22.

The yellow acidic aqueous solution and first aqueous washing which remained from the extraction step on standing deposited a total of 0.04 g. of material melting at 120–140°. Recrystallization from methanol gave 0.02 g. of crystals, m. p. 151–153°, not depressed on admixture with the above keto ester.

The oxime of VIII (R' = C<sub>2</sub>H<sub>5</sub>) was prepared in ethyl alcohol with hydroxylamine hydrochloride and pyridine. Recrystallization from dilute alcohol gave almost colorless felted needles, m. p. 198–200° (dec.) when introduced at 195°.

*Anal.* Calcd. for  $C_{21}H_{21}O_3N$ : C, 75.20; H, 6.31. Found: C, 75.49; H, 6.43.

The semicarbazone was similarly prepared with semicarbazide hydrochloride. Recrystallization from alcohol gave pale orange plates, m. p. 230–232° (dec.) when introduced at 225°.

*Anal.* Calcd. for  $C_{22}H_{23}O_3N_3$ : C, 70.01; H, 6.14. Found: C, 69.55; H, 6.20.

A side-product of unknown structure from the condensation of the cyano ketone VII with diethyl succinate was isolated from reactions which were carried out at the boiling point. The crude product, m. p. 205–210°, crystallized in low yield from the mother liquors remaining after separation of the keto ester. Repeated recrystallization from butyl acetate gave colorless needles, m. p. 229–230°.

*Anal.* Calcd. for  $C_{17}H_{15}O_2$ : C, 80.92; H, 6.39; mol. wt., 252.3. Found: C, 80.74; H, 6.29; mol. wt. (Ras):<sup>34</sup> 240.3, 247.6.

(34) Determination by Oakwold Laboratories, Alexandria, Virginia.

A micro Dumas determination<sup>34</sup> indicated that no nitrogen was present.

**14,15-Dehydro-17-equilenone-15-carboxylic Acid (IX).**—The saponification of 1.00 g. of the keto ester VIII (R' = C<sub>2</sub>H<sub>5</sub>) was effected with a solution of 1 g. of barium hydroxide octahydrate in 25 ml. of dilute alcohol (80%). After refluxing for one and one-half hours in an atmosphere of nitrogen, the mixture was concentrated under reduced pressure to remove most of the alcohol, and acidified with hydrochloric acid. The oil which separated was taken up in ether, and extracted with saturated sodium bicarbonate solution. Acidification of the bicarbonate solution afforded 0.88 g. (97% yield) of pale yellow keto acid, m. p. 228–231° (dec.) when introduced at 225°. Repeated recrystallization from methanol gave pale yellow blades, m. p. 236–239° (dec.) when introduced at 230°.

*Anal.* Calcd. for  $C_{19}H_{18}O_3$ : C, 78.06; H, 5.52; neut. equiv., 292.3. Found: C, 77.76; H, 5.44; neut. equiv., 293.8, 293.8.

**Ethyl 16-Oximino-14,15-dehydro-17-equilenone-15-carboxylate XIV.**—Ethyl 14,15-dehydro-17-equilenone-15-carboxylate was nitrosated according to the procedure of Chakravarti and Swaminathan for the nitrosation of hydrindones.<sup>35</sup> To a mixture of 0.500 g. of the keto ester and 10 ml. of methanol was added 1 ml. of freshly distilled butyl nitrite and 0.5 ml. of concentrated hydrochloric acid. While the mixture was heated with stirring at 50–60° for thirty minutes, the solid gradually dissolved. The solvent was evaporated in a current of air on the steam-bath, and the residue was taken up in ether. The ethereal solution was extracted with 5% potassium hydroxide which on acidification yielded a dark red oil which soon solidified; yield 0.470 g.; m. p. 192–195°. This material was insoluble in sodium bicarbonate solution. A sample was purified by repeated recrystallization from alcohol; pale orange needles; m. p. 210–212° (dec.) when introduced at 202°.

*Anal.* Calcd. for  $C_{21}H_{19}O_4N$ : C, 72.19; H, 5.48. Found: C, 72.17; H, 5.38.

**14,15-Dehydro-17-equilenone (X).**—A mixture of 2.00 g. of VIII (R' = C<sub>2</sub>H<sub>5</sub>), 25 ml. of acetic acid, 18.5 ml. of water and 12.5 ml. of concentrated hydrochloric acid was refluxed in an atmosphere of nitrogen for ten and one-half hours. The acetic acid was removed under reduced pressure, and the light red oily residue was extracted with ether. The ether solution was washed twice with 3% potassium hydroxide solution, then with dilute hydrochloric acid and finally with saturated salt solution. Evaporation gave a red-orange oil which was evaporatively distilled at 150° (0.1 mm.) giving an almost colorless partially crystalline oil. Crystallization from alcohol gave a total of 0.55 g. (35% yield) of X as colorless needles, m. p. 134–136°. The 15,16-isomer (XV) was isolated from the mother liquors (see below). A sample purified by a second evaporative distillation as above and recrystallization from alcohol melted at 136.8–138°.

*Anal.* Calcd. for  $C_{18}H_{16}O$ : C, 87.06; H, 6.50. Found: C, 86.81; H, 6.21.

**15,16-Dehydro-17-equilenone (XV).**—The mother liquor from the crystallization of crude X described above was evaporated to dryness, and the residue crystallized from ether-petroleum ether. From this solution a total of 0.62 g. (40% yield) of tan prisms was obtained; m. p. 100–102°. A sample purified by evaporative distillation under reduced pressure followed by recrystallization from ether-petroleum ether was obtained as heavy colorless prisms, m. p. 100.5–102°.

*Anal.* Calcd. for  $C_{18}H_{16}O$ : C, 87.06; H, 6.50. Found: C, 87.05; H, 6.46.

**Conversion of 15,16- into 14,15-Dehydro-17-equilenone.**—A mixture of 0.200 g. of XV (m. p. 100–102°), 3 ml. of acetic acid, 1.5 ml. of concentrated hydrochloric acid and 2.3 ml. of water was refluxed in an atmosphere of nitrogen for eighteen hours. The product was worked up as de-

(35) Chakravarti and Swaminathan, *J. Ind. Chem. Soc.*, **11**, 101 (1934).



scribed above for the preparation of 14,15-dehydro-17-equiolenone, to give 0.030 g. of this substance; m. p. 132–134°. The main portion of the organic material did not volatilize in the evaporative distillation and had probably polymerized.

**$\beta$ -17-Equiolenone (XI).**—A solution of 0.200 g. of 14,15-dehydro-17-equiolenone (m. p. 136–138°) in 15 ml. of ethyl acetate was hydrogenated over 0.05 g. of 30% palladium-charcoal catalyst.<sup>36</sup> The calculated amount of hydrogen (for one double bond) was absorbed in two hours. The filtered solution was evaporated, and the solid residue crystallized from acetone-alcohol to give 0.165 g. of material melting at 183–188° (vac.). An additional 0.020 g. of crude material, m. p. 176–180° (vac.), was obtained from the mother liquor. Recrystallization of the first crop gave 0.140 g. of colorless crystals; m. p. 189–191° (vac.). The melting point was not depressed on admixture with an authentic sample of  $\beta$ -17-equiolenone, m. p. 189–191° (vac.).<sup>37</sup> Attempts to isolate any  $\alpha$ -17-equiolenone from the mother liquors failed. The low melting points of the later fractions, however, may possibly have been due to the presence of small amounts of this isomer.

The semicarbazone of the material prepared above melted at 259.5–261.5° (dec.) either alone or when mixed with an authentic specimen of  $\beta$ -17-equiolenone semicarbazone, m. p. 260.5–261.5° (dec.).<sup>37</sup>

**$\alpha$ -17-Equiolenone (XI)** was prepared by hydrogenation of 0.200 g. of 15,16-dehydro-17-equiolenone (m. p. 100–102°) just as described above for the 14,15-isomer. The calculated amount of hydrogen was absorbed in one and one-half hours, and a total of 0.190 g. of colorless crystals was obtained from acetone-methanol; m. p. 100–102° (depressed to 92–98° on admixture with the starting material). The melting point was not depressed on admixture with an authentic sample of  $\alpha$ -17-equiolenone, m. p. 100–102°.<sup>37</sup> The semicarbazone melted at 261–264° (dec.) when introduced at 255°, either alone or on admixture with an authentic specimen of  $\alpha$ -17-equiolenone semicarbazone, m. p. 262–264° (dec.).<sup>37</sup>

**Absorption Spectra.**—The determinations were performed in absolute alcohol solution with a Beckman ultraviolet spectrophotometer. The principal absorption maxima are recorded below.

**14,15-Dehydro-17-equiolenone (X).**— $\lambda_{\max}$ . 251 (log  $E$  4.69), 281 (4.09), 292 (4.16), 303 (4.06).

**$\beta$ -(3,4-Dihydro-1-phenanthryl)-propionic Acid (XVII).**<sup>14</sup> — $\lambda_{\max}$ . 253 (log  $E$  4.64), 260 (4.67), 297 (3.82), 308 (3.77).

**15,16-Dehydro-17-equiolenone (XV).**— $\lambda_{\max}$ . 230 (log  $E$  4.89), 270 (3.83), 321 (2.82).

**$\beta$ -dl-Equiolenane (XVI).**<sup>12</sup>— $\lambda_{\max}$ . 230.5 (log  $E$  4.97), 282 (3.76), 321.5 (2.96).<sup>38</sup>

## Part II. Synthesis of Equilenin

This part contains only selected procedures which are best adapted for the synthesis of the hormone. The experiments involving side-reactions, isolation of by-products, proof of structure, etc., are recorded below under part III.

**Step 1. 2-Hydroxymethylene-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (IVa)** was prepared from IIIa<sup>39</sup> (m. p. 101–102°) and ethyl formate according to a procedure already described for the preparation of III.<sup>7</sup> Numerous runs were made with as much as 20 g. of starting material, and consistent yields were realized varying between 97 and 99% of yellow material melting at 129–131°, which was entirely suitable for conversion to the isoxazole. A sample recrystallized several times from alcohol was obtained as yellow crystals, m. p. 130–130.6°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>14</sub>O<sub>3</sub>: C, 75.57; H, 5.55. Found: C, 75.37; H, 5.68.

(36) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

(37) Material described in ref. 12 and kindly supplied by the authors.

(38) We are indebted to Eugene Woroch for this determination.

(39) Prepared according to procedures of Wilds and Close, *THIS JOURNAL*, in 69, 3079 (1947).

**Step 2. 10,11-Dihydro-7-methoxyphenanthro[2,1-d]-isoxazole (Va).**—In a typical run a solution of 27.8 g. (0.109 mole) of IVa (m. p. 129–131°) in 600 ml. of glacial acetic acid was treated with 11.4 g. (0.164 mole) of dry powdered hydroxylamine hydrochloride, and the mixture was quickly heated to boiling (three minutes) in an oil-bath maintained at 170°. Refluxing was continued for seven minutes, and then hot water (about 600 ml.) was added until the light red solution was definitely turbid. Crystallization began immediately and after chilling several hours at 0°, 26.5 g. (96% yield) of almost colorless, glistening plates was collected; m. p. 137–138°. This material was entirely satisfactory for the subsequent step. A sample of the isoxazole was purified for analysis by evaporative distillation at 150° (0.5–1 mm.), followed by recrystallization from methanol-ethyl acetate which gave colorless needles, m. p. 139.5–140°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>16</sub>O<sub>2</sub>N: C, 76.47; H, 5.21. Found: C, 76.71; H, 5.07.

**Step 3. 2-Cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene (VIIa).**—To a solution of 1.0 g. (0.026 mole) of potassium in 25 ml. of *t*-butyl alcohol<sup>40</sup> was added 2.00 g. (0.008 mole) of the above isoxazole (m. p. 137–138°), whereupon the yellow potassium derivative of VIa began to precipitate immediately. The mixture was heated with stirring at 75–80° (bath temperature) for ten minutes, and then 8 ml. (0.13 mole) of methyl iodide was added dropwise over a period of ten minutes with continued stirring and refluxing. Heating was continued for an additional twenty minutes, until the originally yellow precipitate was completely replaced by a colorless suspension of potassium iodide. Care was taken to exclude all moisture up to this point. Most of the solvent was evaporated on the steam-bath in a current of air, water was added, and the organic material extracted with benzene. The benzene layer was washed successively with water, dilute potassium hydroxide solution, and again with water. Evaporation of the benzene and recrystallization of the residue from alcohol gave 1.94 g. (92% yield) of almost colorless crystals, m. p. 135–136°. A sample was purified by evaporative distillation at 150° (0.5–1 mm.) followed by recrystallization from ethyl acetate which gave colorless needles, m. p. 135–137.5°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>N: C, 76.96; H, 5.70. Found: C, 77.10; H, 5.90.

When the methylation was carried out on a larger scale, a somewhat longer reaction period was required. Thus a mixture of 5.0 g. of potassium dissolved in 125 ml. of *t*-butyl alcohol and 10.0 g. of isoxazole (m. p. 136–138°) was stirred for fifteen minutes in a bath at 90° and then treated with 35 ml. of methyl iodide over a period of twenty minutes. After an additional twenty-five minutes of refluxing the product was isolated as above. The yield was 9.30 g. (88%) of light tan needles, m. p. 135–136.5°.

The 2,4-dinitrophenylhydrazone was prepared by the hydrochloric-acid method. The yield of crude product was poor (34%) even after heating the reaction mixture for almost two hours. A homogeneous sample was isolated by trituration with methanol followed by several crystallizations from ethyl acetate; light orange needles; m. p. 231–233° (dec.) with slight previous softening.

*Anal.* Calcd. for C<sub>23</sub>H<sub>16</sub>O<sub>4</sub>N<sub>2</sub>: C, 62.02; H, 4.30. Found: C, 62.26; H, 4.50.

**Step 4. 15-Carbomethoxy-14,15-dehydroequilenin Methyl Ether (VIIIa, R' = CH<sub>3</sub>).**—Since the conditions for the preparation of this keto ester in good yield proved to be quite critical, the procedure is described in considerable detail.

(a) *From 2-Cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene.*—A 500-ml., three-necked flask with ground glass joints was fitted with a Hershberg dropping funnel<sup>41</sup> and a Hershberg wire stirrer with a special

(40) Dried by twice refluxing over and distilling from sodium.

(41) "Organic Syntheses," Coll. Vol. II, 129 (1943); see also Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 312.

seal designed to withstand reduced pressure. The third neck of the flask was connected with pressure tubing to a T-tube leading to the top of the dropping funnel and to a 3-way stopcock which was connected to a source of nitrogen and vacuum. The apparatus was flame-dried, and 4.00 g. (0.0151 mole) of dry cyano ketone VIIa (m. p. 134–136°) was placed in the flask. The dropping funnel was charged with a mixture prepared by adding 15 ml. (0.115 mole) of dimethyl succinate (b. p. 194.5–195° at 740 mm.) to a solution of 4.0 g. (0.102 mole) of potassium in 100 ml. of *t*-butyl alcohol.<sup>40</sup> The air in the system was then completely replaced by nitrogen by alternately evacuating the system and admitting nitrogen. The system was protected from the atmosphere by a mercury trap, and 20 ml. (400 drops) of the reagent in the funnel was admitted to the flask. Stirring was started (260 r. p. m.) and the flask was immersed in an oil-bath maintained at 53–55° throughout the reaction. Stirring was continued for one hour, the mixture gradually turning bright orange; then the remainder of the reagent was added dropwise at such a rate that 10 ml. was introduced during the second hour, 15–20 ml. during the third, 30–35 ml. during the fourth, and 35 ml. during the fifth hour. By the end of the third hour the mixture had become very viscous, almost pasty, and remained in this condition to the end of the reaction as the color again gradually changed from orange to bright yellow. (In condensations where this viscosity appeared at a later point or not at all, the yields were lower, 60–75%.) After the addition was complete the mixture was stirred for an additional hour making the total reaction time six hours. The mixture was cooled and 100 ml. of dilute (1 to 1) hydrochloric acid was added carefully with stirring as considerable carbon dioxide was evolved. This gave a clear orange solution from which most of the *t*-butyl alcohol was removed at the steam-bath in a stream of nitrogen. Water was added, and the suspension of yellow solid was taken up in benzene and washed successively with dilute (1 to 4) hydrochloric acid, water, 10% potassium hydroxide, and finally several times with water. The benzene solution was concentrated on the steam-bath in a stream of nitrogen, and the pale yellow solid residue was triturated with about 50 ml. of petroleum ether (b. p. 60–68°) at room temperature. 15-Carbomethoxy-14,15-dehydroequilenin methyl ether remained as an almost colorless to pink crystalline solid; yield 3.94–4.21 g. (77.5–83%); m. p. 164–167 to 161–164° with dec. and slight previous softening. Material of this purity was used in the next step of the synthesis.

An ammonia determination<sup>42</sup> on an aliquot taken from a combination of all water and acid washings up to (but not including) that with 10% potassium hydroxide indicated that about 83–88% of the nitrogen in the starting material was converted to ammonia.

A sample of the keto ester purified by sublimation under reduced pressure and repeated recrystallization from methanol was obtained as colorless needles; m. p. 169.5–171° (dec.), 170–171° (vac.) with slight dec.

*Anal.* Calcd. for  $C_{21}H_{20}O_4$ : C, 74.98; H, 5.99. Found: C, 74.72; H, 6.04.

The semicarbazone was prepared in methanol with semicarbazide hydrochloride and pyridine by refluxing for two hours. Several recrystallizations from methanol gave colorless plates, m. p. 238–239° (dec.).

*Anal.* Calcd. for  $C_{22}H_{23}O_4N_3$ : C, 67.16; H, 5.89. Found: C, 66.96; H, 5.98.

(b) From 10,11-Dihydro-7-methoxyphenanthro[2,1-*d*]-isoxazole (Steps 3 and 4 combined).—Four grams (0.016 mole) of the isoxazole (m. p. 135–136.5°) was isomerized and methylated using 0.75 g. (0.019 mole) of potassium in 40 ml. of *t*-butyl alcohol<sup>40</sup> and 15 ml. (0.24 mole) of methyl iodide according to the procedure described above for the preparation of VIIa. After all of the methyl iodide was added (fifteen minutes) and the reaction was complete (thirty minutes, refluxing) the mixture was evaporated practically to dryness in a current of dry nitrogen. The

flask was then equipped with a Hershberg dropping funnel containing 15 ml. (0.115 mole) of dimethyl succinate dissolved in a solution of 4.00 g. (0.102 mole) of potassium in 100 ml. of *t*-butyl alcohol,<sup>40</sup> and the condensation step was carried out exactly as described in the preceding section (part a). The yield of pale pink crystalline keto ester was 4.10–4.30 g. or 77–80%; m. p. 162–166° (dec.) with slight previous softening. An ammonia determination on the wash waters gave values corresponding to about 83% yield. A 10.0-g. sample of the isoxazole submitted to the above reaction using proportionate amounts of reagents yielded 10.6 g. (79%) of the keto ester; m. p. 161–167° (dec.) with slight previous softening.

**Step 5. 15-Carboxy-14,15-dehydroequilenin Methyl Ether (IXa).**—A suspension of 4.06 g. (0.0121 mole) of crude VIIIa,  $R' = CH_3$  (m. p. 164–167°) in 46 ml. of water and 60 ml. of alcohol was treated with 4.06 g. (0.013 mole) of barium hydroxide octahydrate, and the mixture refluxed in an atmosphere of nitrogen for one hour. While still at refluxing temperature the alcohol was removed by gradually reducing the pressure until the barium salt precipitated as a thick crystalline mass. After cooling (in the absence of air) the mixture was treated with 600 ml. of dilute (1 to 2) hydrochloric acid, and the suspension was warmed on the steam-bath for one and one-half hours to complete the decomposition of the sparingly soluble barium salt. The orange, crystalline keto acid obtained on cooling amounted to 3.90 g. (100% yield); m. p. 180–190° (dec.). Recrystallization from benzene gave 3.77–3.83 g. (97–98.5% yield) of pale orange needles, m. p. 193–195° (dec.) with slight previous softening. It was necessary to dry the product several hours at 100° in order to remove all of the solvent. A sample twice recrystallized from benzene and dried at 55–60° (0.5 mm.) for twenty hours was obtained as pale yellow crystals, m. p. 196.5–197.5°. A solution of the keto acid in aqueous sodium bicarbonate at room temperature slowly turns purple on exposure to air. This sensitivity to alkali and air makes it necessary to exclude air throughout the above saponification of the keto ester.

*Anal.* Calcd. for  $C_{20}H_{18}O_4$ : C, 74.52; H, 5.63. Found: C, 75.01; H, 5.49.

The yield in the saponification step is dependent somewhat upon the purity of the starting material; thus from 13.0 g. of crude keto ester, m. p. 159–165°, there was obtained 12.35 g. (99% yield) of crude acid, but only 11.3 g. (91% yield) of recrystallized material, m. p. 194–196° (dec.).

**Step 6. 14,15-Dehydroequilenin Methyl Ether (Xa).**—A solution of 1.00 g. (0.0031 mole) of IXa (m. p. 193–195°, dec.) in 7.5 ml. of pyridine was treated with 15 ml. of concentrated hydrochloric acid. The suspension was refluxed (under an initial atmosphere of nitrogen) until the evolution of carbon dioxide had ceased (about thirty minutes), and by this time the product had usually crystallized from the boiling mixture. After cooling, the mixture was diluted with water and extracted with benzene. The benzene solution was washed successively with dilute hydrochloric acid, water, sodium bicarbonate solution, and finally with water. Evaporation of the benzene in a stream of nitrogen gave 0.795 g. (a 92% yield) of crude decarboxylation product, m. p. about 140–154°. The 14,15-isomer was isolated by crystallization from methanol which gave in the first crop 0.484 g. (56% yield) of pale orange plates, m. p. 159–161°. The mother liquors, from which no more of this material could be crystallized, were concentrated and retreated with pyridine (5 ml.) and hydrochloric acid (10 ml.) by refluxing for ten minutes, to isomerize the 15,16- to the 14,15-isomer. The latter was then isolated as described above and amounted to 0.085 g. of orange plates, m. p. 158–161°, making the total yield 66% of material suitable for the next step.

A sample of Xa purified by sublimation at 140° (0.5–1 mm.) followed by recrystallization from acetone-methanol was obtained as colorless plates, m. p. 161.5–162.5°.

*Anal.* Calcd. for  $C_{19}H_{18}O_2$ : C, 81.99; H, 6.52. Found: C, 82.01; H, 6.36.

(42) Ma and Zuazaga, *Ind. Eng. Chem., Anal. Ed.*, **14**, 280 (1942).

**Step 7. *dl*-Equilenin Methyl Ether (XIa).**—A solution of 1.93 g. of Xa (m. p. 159–161°) in 65 ml. of ethyl acetate was hydrogenated over 0.140 g. of 30% palladium-charcoal catalyst<sup>16</sup> at room temperature and atmospheric pressure. After two and one-half hours the calculated amount of hydrogen (for one double bond) was absorbed. The crystalline residue obtained on evaporation of the filtered solution was crystallized from acetone-methanol. The first crop invariably consisted of fairly pure *dl*-equilenin methyl ether; in this case there was obtained 1.23 g. (63% yield) of colorless, diamond-shaped plates, m. p. 183–187° (dec.). This material was satisfactory for the demethylation step described below. A sample of the methyl ether twice recrystallized from acetone-methanol melted at 189–190.5° (reported m. p. 185–186.5° (vac.) uncor.<sup>17</sup>). The m. p. of a sample of *dl*-equilenin methyl ether prepared by the Bachmann, Cole and Wilds synthesis<sup>17</sup> and kindly furnished by Dr. Bachmann for comparison was not depressed on admixture with the material described above.

The second crop of crystals obtained after concentration of the mother liquors consisted largely of *dl*-isoequilenin methyl ether; yield 0.525 g. (27%); m. p. 124–130°. An additional 0.10 g. (5%) of the same material. m. p. 126–128°, was isolated as a third crop. Recrystallization from acetone-methanol gave colorless prisms, m. p. 128–130°. *dl*-Isoequilenin methyl ether is reported to crystallize from this solvent in colorless prisms; m. p. 127–127.5° (vac.) with solidification and remelting at 130–130.5° (vac.).<sup>17</sup>

**Step 8. Equilenin (XII).**—Demethylation of 1.10 g. of *dl*-equilenin methyl ether (m. p. 185–188° with slight previous softening) was effected with a mixture of 71 ml. of acetic acid, 33 ml. of concentrated hydrochloric acid and 8 ml. of water. After refluxing for thirteen hours in an atmosphere of nitrogen, the pale yellow solution was cooled and diluted with water giving 1.03 g. (98% yield) of colorless *dl*-equilenin of fair purity; m. p. 272–277° (vac., uncor., previous softening). A single recrystallization from acetone-methanol gave colorless leaflets, m. p. 279–280.5° (vac., uncor.); the reported m. p. for the most frequently encountered form is 276–278° (vac., uncor.).<sup>17</sup>

The resolution of *dl*-equilenin was carried out according to the procedure of Bachmann, Cole and Wilds.<sup>17</sup> Practically pure *d*-equilenin *l*-menthoxyacetate, m. p. 175–178° (vac.), was obtained easily in 48% yield after a single recrystallization of the first crop of material from the crystallization of the crude derivative. A second recrystallization from acetone alone gave plates melting at 177.2–177.8° (vac.). A mixture with natural equilenin *l*-menthoxyacetate, m. p. 177.0–177.8° (vac.), melted at 177.0–177.8° (vac.).

The hydrolysis of the *l*-menthoxyacetate proceeded in 91% yield. A sample of *d*-equilenin after sublimation under reduced pressure, and recrystallization from dilute methanol, was obtained in the form of small, colorless needles, m. p. 257.5–258° (vac.). A mixture with natural equilenin, m. p. 258–259° (vac.), melted at 257–258° (vac.).

The acetate of synthetic *d*-equilenin was prepared<sup>17</sup> and crystallized from methanol in colorless blades, m. p. 155.5–156.5°. A mixture with the natural equilenin acetate, m. p. 156–157°, melted at 155–156.5° (with slight previous softening).

### Part III. Other Experiments Pertaining to the Synthesis of Equilenin.

The procedures described below are arranged in the order of the steps of the synthesis (1–7) to which they pertain.

**2-Methoxymethylene-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XVIIIa).**—A boiling mixture of 1.00 g. of IVa (m. p. 129–131°) and 45 ml. of methanol was treated with one drop of concentrated sulfuric acid. A heavy precipitate of colorless needles formed almost immediately. The refluxing was continued for one to two minutes, and on cooling 0.71 g. (67% yield) of enol ether, m. p. 168–170°, was obtained. The crude product turned

yellow on exposure to air. Two recrystallizations from methanol afforded colorless needles, stable to air; m. p. 171.8–172.6°. This material gave a slowly developing dark-brown-purple color with alcoholic ferric chloride.

*Anal.* Calcd. for C<sub>17</sub>H<sub>16</sub>O<sub>3</sub>: C, 76.10; H, 6.01. Found: C, 76.06; H, 5.94.

**2-Ethoxymethylene-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XVIIIb)** was prepared as described above. From 0.400 g. of IVa and 10 ml. of ethanol containing one drop of concentrated sulfuric acid there was obtained after cooling 0.249 g. (56% yield) of colorless needles, m. p. 126–127° (dec.). The analytical sample obtained by two recrystallizations from alcohol melted at 128.8–129.6° with slight previous softening. It gave a slowly developing dark-brown-purple color with alcoholic ferric chloride.

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>O<sub>3</sub>: C, 76.57; H, 6.43. Found: C, 76.59; H, 6.76.

**2-Isopropoxymethylene-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XVIIIc)** was prepared from 0.400 g. of IVa, 10 ml. of isopropyl alcohol and one drop of sulfuric acid as described above. The yield of colorless needles which crystallized on cooling amounted to 0.343 g. (74%); m. p. 132–134° (dec.). Two recrystallizations from isopropyl alcohol gave material melting at 134.5–135.5° with slight previous softening. The color with ferric chloride was the same as described above for the lower homologs, but developed more rapidly.

*Anal.* Calcd. for C<sub>19</sub>H<sub>20</sub>O<sub>3</sub>: C, 77.00; H, 6.80. Found: C, 76.74; H, 6.94.

**2-Cyano-1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (VIa).**—The isoxazole Va (6.66 g.) was isomerized with sodium methoxide (from 0.9 g. of sodium and 11 ml. of methanol) in benzene (80 ml.) according to procedures already described for this type of reaction. The sodio derivative of the cyano ketone was sparingly soluble and about 1.5 liters of dilute alkali in all was required for its extraction. The crude product amounted to 6.23 g. (94% yield); m. p. 164–168.5°. A sample was purified by vacuum sublimation followed by recrystallization from alcohol which gave pale yellow plates, m. p. 169.5–171°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>N: C, 76.47; H, 5.21. Found: C, 76.28; H, 5.38.

The sodium methoxide-catalyzed methylation of VIa according to the procedure described above (Part I) for the preparation of VII gave VIIa in 80% yield. A similar procedure was worked out for the direct methylation of the isoxazole Va, and it was found that the yields of VIIa were increased to about 90% (on a 2-g. scale) when the proportionate amount of sodium methoxide was doubled. On a 10-g. scale, however, the yields were somewhat lower and variable, 82–87%.

**A By-Product of the Methylation with Sodium Methoxide.**—In the experiments described directly above a product was usually encountered which was insoluble in both benzene and water. This proved to be a salt which could be dissolved in a large volume of boiling water. Acidification of such a solution gave a flocculent precipitate of what was probably 2-cyano-1-hydroxy-7-methoxyphenanthrene (XIX); yield usually about 4–5%. Recrystallization from ether-benzene or, preferably, ethanol gave colorless felted needles: m. p. 256–257° (uncor.), resolidifying at 261° and sintering with dec. at about 310°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>11</sub>O<sub>2</sub>N: C, 77.09; H, 4.45. Found: C, 77.01, 77.18; H, 4.52, 4.41.

This substance had properties resembling those reported for 10-cyano-9-hydroxy-1,2,3,4-tetrahydrophenanthrene.<sup>48</sup> It was soluble in a large volume of hot sodium bicarbonate solution—an acidic behavior characteristic of a negatively substituted phenol—and it did not give a color reaction with ferric chloride. A qualitative test indicated the presence of nitrogen. The presence of an acetyltable hydrogen was shown by the preparation of the acetate

(43) Linstead, Whetstone and Levine, *THIS JOURNAL*, **64**, 2014 (1942).

which crystallized from ethanol in the form of almost colorless blades, m. p. 182.5–183°.

*Anal.* Calcd. for  $C_{18}H_{18}O_3N$ : C, 74.22; H, 4.50. Found: C, 73.86; H, 4.56.

**15-Carboethoxy-14,15-dehydroequilenin Methyl Ether (VIIIa,  $R' = C_2H_5$ ).**—To a cold solution of 0.13 g. of potassium in 9 ml. of *t*-butyl alcohol was added 0.80 ml. of diethyl succinate and 0.500 g. of the cyano ketone VIIa (m. p. 134–136°). The system was evacuated and filled with nitrogen; then the mixture was heated in an oil-bath at 55–57° for six and one-half hours with continuous stirring (Hershberg wire stirrer). During this period the pale yellow suspension of cyano ketone gradually changed to orange-yellow during the first hour and then to bright yellow after three hours. The cooled mixture was treated with 50 ml. of dilute (1 to 4) hydrochloric acid, and worked up as described for the methyl keto ester (see Part II, step 4), except that the final benzene solution was not evaporated to dryness, but was concentrated to a small volume and then treated with hot methanol. On cooling 0.330 g. (50% yield) of 15-carboethoxy-14,15-dehydroequilenin methyl ether crystallized; pink needles, m. p. 175–178° (dec.). A sample was purified for analysis by sublimation at 160° (0.5–1 mm.), followed by recrystallization from ethyl acetate which gave colorless, felted needles, m. p. 183.6–184.2°.

*Anal.* Calcd. for  $C_{22}H_{22}O_4$ : C, 75.41; H, 6.33. Found: C, 75.64; H, 6.47.

The semicarbazone was prepared in methanol with semicarbazide hydrochloride and pyridine by refluxing for one hour. Several recrystallizations from methanol gave colorless, felted needles, m. p. 224–226° (dec.).

*Anal.* Calcd. for  $C_{23}H_{26}O_4N_3$ : C, 67.79; H, 6.18. Found: C, 67.49; H, 6.14.

**By-Products from the Condensation with Diethyl Succinate.** (a) *Reduction Product.*—Upon standing several weeks the mother liquor from the crystallization of the crude keto ester described in the preceding experiment deposited a crop of large red prisms. In one run this product amounted to 10% of the weight of starting cyano ketone. Recrystallization from methanol and then from ethyl acetate gave colorless, diamond-shaped prisms, m. p. 194–195°. The melting point was not depressed on admixture with a specimen of 2-cyano-1-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene prepared by reduction of the cyano ketone (see below).

(b) *A Product Isolated by Chromatographic Adsorption.*—The oily residues obtained by evaporation of the mother liquor from the initial crystallization of the crude 15-carboethoxy-14,15-dehydroequilenin methyl ether, were combined from several experiments, so as to represent the product from a total of 3.00 g. of starting cyano ketone. This material was dissolved in 70 ml. of dry benzene and 20 ml. of dry petroleum ether (b. p. 40–60°) and submitted to a flowing chromatographic analysis with benzene, ether and acetone in a column of 100 g. of activated alumina (marius-80 mesh from the Aluminum Ore Co.). The benzene-petroleum ether eluates contained 0.78 g. of a fragrant liquid which was not further investigated. The benzene and ether eluates contained 0.77 g. of crude recovered cyano ketone identified by mixed melting point determinations. The first acetone eluate contained 0.08 g. of red crystals, m. p. 75–115°; and the second, 0.14 g. of orange material, m. p. 184–190°. Purification of the latter by repeated recrystallization from benzene gave small, almost colorless prisms, m. p. 201–203° (dec.). Mixed melting point determinations with 2-cyano-1-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene and with 15-carbo-*t*-butoxy-14,15-dehydroequilenin methyl ether (see below) showed a marked depression in each case. A qualitative test indicated the absence of nitrogen.

*Anal.* Calcd. for  $C_{18}H_{18}O_3$ : C, 76.57; H, 6.43. Found: C, 76.34; H, 6.41.

**2-Cyano-1-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene (XX).**—The reduction of VIIa was

carried out according to directions given by Wilds.<sup>44</sup> A suspension of 1.00 g. of the cyano ketone and 2.28 g. of freshly distilled aluminum isopropoxide in 20 ml. of dry isopropyl alcohol was distilled slowly so that 15 ml. of distillate was collected over a period of fifteen hours. An additional 10 ml. of isopropyl alcohol was added and the distillation continued for two hours, until the distillate no longer gave a test for acetone. The alcohol was then removed under reduced pressure and the residue treated with dilute hydrochloric acid. The precipitate was collected, washed thoroughly with dilute hydrochloric acid and then water; yield 0.99 g.; m. p. about 171–173° (not clear until 183°). This product consisted of a mixture, probably containing the two expected stereoisomers, epimeric at C-1. Crystallization from methanol effected a separation of one of the epimers; yield 0.195 g. (19%) of colorless, diamond-shaped prisms, m. p. 180–195°. Recrystallization from ethyl acetate gave 0.118 g. (12% yield) of prisms melting at 194–195.5°. Two more recrystallizations raised the melting point to 194.5–195.5°.

*Anal.* Calcd. for  $C_{17}H_{17}O_3N$ : C, 76.38; H, 6.41; N, 5.24. Found: C, 76.05; H, 6.34; N, 5.45, 5.50.

**15-Carbo-*t*-butoxy-14,15-dehydroequilenin Methyl Ether (VIIIa,  $R' = C(CH_3)_3$ ).**—To a solution of 0.16 g. of potassium in 6 ml. of *t*-butyl alcohol was added a solution of 1.4 g. of di-*t*-butyl succinate<sup>45</sup> in benzene. The resulting red solution was treated with 0.500 g. of 2-cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene (m. p. 134–136°) and the system was evacuated and filled with nitrogen. The mixture was refluxed for one and three-quarters hours, and then worked up essentially as already described for the methyl ester (see Part II, step 4). Evaporation of the benzene solution afforded an orange-red oil which was dissolved in 15 ml. of hot methanol. On cooling, the crude ester crystallized in the form of red blades; yield 0.094 g. (13%); m. p. about 177–187° (dec.). The only additional material which could be obtained crystalline in further crops was starting cyano ketone. The ammonia analysis indicated that the condensation had proceeded to the extent of 23%.

An analytical sample was obtained by sublimation under reduced pressure followed by several recrystallizations from methanol; colorless needles; m. p. 191.5–193° (dec.).

*Anal.* Calcd. for  $C_{24}H_{26}O_4$ : C, 76.16; H, 6.93. Found: C, 75.60; H, 6.97.

**Behavior of 2-Cyano-1-keto-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene toward Potassium *t*-Butoxide.**—A 0.500-g. sample of the cyano ketone (m. p. 134–136°) was treated with a solution of 0.5 g. of potassium in 12.5 ml. of *t*-butyl alcohol, and the mixture was stirred at 55° for four hours. The mixture was worked up like that from the condensation with dimethyl succinate (see Part II, step 4). Unreacted cyano ketone 0.388 g., m. p. 131–134°, was isolated from the neutral benzene solution. Acidification of the potassium hydroxide wash solutions gave 0.126 g. of brown acidic material, m. p. 168–171°. It was purified by dissolution in sodium bicarbonate solution, filtration, and reprecipitation with acid. Several recrystallizations from benzene gave colorless needles of what is probably  $\alpha$ -methyl- $\gamma$ -(2-carboxy-7-methoxy-1-naphthyl)-butyronitrile (XXI); m. p. 172.5–173.5°.

*Anal.* Calcd. for  $C_{17}H_{17}O_3N$ : C, 72.06; H, 6.05. Found: C, 71.84; H, 6.04.

**15-Carbomethoxy-14,15-dehydroequilenin Methyl Ether: Small-Scale Preparation and Discovery of an Acid-Soluble Intermediate.**—The preliminary studies of the condensation of the cyano ketone VIIa with dimethyl succinate were carried out according to the procedure already described (see Part II, step 4), but on a 0.400-g. scale in a proportionately small apparatus (50-ml. capacity). The yields were somewhat lower, usually about 73% and the ammonia analysis was likewise lower (about 80%). In these small-

(44) Wilds, "Organic Reactions," Vol. II, p. 203 (1944).

(45) Prepared by Chester E. Davis according to the method of Backer and Homan, *Rec. trav. chim.*, **66**, 1048 (1939).

scale experiments it was noted that the acidic washings were bright yellow and on standing, deposited a yellow solid, m. p. 149–159° (dec.) in about 2% yield. Purification by recrystallization from methanol gave material melting at 168–170° (dec.) and showing no depression of the melting point on admixture with pure 15-carbomethoxy-14,15-dehydroequilenin methyl ether.

**Decarboxylation Studies with 15-Carboxy-14,15-dehydroequilenin Methyl Ether.** (a) *Pyrolytic Decarboxylation and the Isolation of 15,16-Dehydroequilenin Methyl Ether (XVa).*—A 2.00-g. sample of the keto acid (m. p. 193–195° with dec.) was placed in the bottom of an 8-inch test tube and covered with a tightly fitting wad of Pyrex glass wool. The tube was evacuated to a pressure of 23 mm. and heated to 200 ± 5° while supported at a 45° angle. The evolution of carbon dioxide which was steady at first slackened off after about seventy minutes, and some colorless oil condensed in the cool part of the tube. The pressure was then lowered to 0.5–1 mm. and the heating continued for one and one-half hours to complete the evaporative distillation. The distillate which was almost colorless and semi-crystalline was washed out of the tube with acetone, the solution was concentrated and the residue crystallized from methanol. The first crop consisted mainly of 14,15-dehydroequilenin methyl ether (Xa); yield 0.72 g. (42%) colorless plates; m. p. 150–159°. Several recrystallizations raised the melting point to 162–163°.

The second crop amounted to 0.40 g. of pink crystals, m. p. 104–114°. Recrystallization gave a small amount of additional crude 14,15-isomer (m. p. 146–155°), followed by material melting at 99–103° which was purified by repeated recrystallization from isopropyl ether. A sample of XVa thus was obtained as colorless blades, m. p. 104.5–106°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>15</sub>O<sub>2</sub>: C, 81.99; H, 6.52. Found: C, 81.65; H, 6.73.

(b) *Hydrochloric-Acetic Acid Decarboxylation.*—A mixture of 0.400 g. of the keto acid, 5.0 ml. of acetic acid, 3.7 ml. of water and 2.5 ml. of concentrated hydrochloric acid was refluxed (under an initial atmosphere of nitrogen) for fifteen minutes, 81% of the calculated amount of gas being evolved. After cooling, the mixture was evaporated in a stream of nitrogen to remove most of the acetic acid, and the residue extracted with benzene. The benzene solution was washed with sodium bicarbonate solution, with water, and evaporated in a stream of nitrogen. Crystallization of the oily residue from methanol gave 0.116 g. (33.5% yield) of 14,15-dehydroequilenin methyl ether, m. p. 156–160°.

(c) *Decarboxylation with Various Amines and Hydrochloric Acid.*—Two-tenth-gram samples of the keto acid were treated with 2.5 ml. of the amine listed in Table I, followed by 5.0 ml. of concentrated hydrochloric acid. The mixture was heated until the evolution of gas ceased (time indicated in Table I), and the product was isolated according to the procedure already described (see Part II, step 6). Since the decarboxylation product is sensitive to acids, in order to realize good yields it is important to

have conditions such that the dehydroequilenin methyl ether precipitates out of solution as it is formed. With the higher molecular weight amines,  $\gamma$ -collidine and quinoline, the decarboxylation was very rapid, but the reaction mixture was homogeneous due to the greater solubilizing effect of these amines, and none of the desired product was isolated. With lower molecular weight amines such as diethylamine and ethanalamine, the keto acid was so sparingly soluble that the decarboxylation was slow and incomplete, and the yields were poor. Without any amine, the keto acid was insoluble in the hydrochloric acid, and no reaction was observed.

**Hydrogenation of 15,16-Dehydroequilenin Methyl Ether to *dl*-Isoequilenin Methyl Ether.**—A solution of 0.155 g. of XVa (m. p. 103–105°) in 20 ml. of ethyl acetate was hydrogenated in the presence of 0.035 g. of 30% palladium-charcoal catalyst.<sup>36</sup> The calculated volume of hydrogen (for one double bond) was absorbed in twenty-five minutes. Evaporation of the filtered solution gave 0.150 g. (96% yield) of almost pure colorless isoequilenin methyl ether; m. p. 127–130°. Recrystallization from methanol gave colorless prisms; m. p. 129–130°, not depressed on admixture with the isomer of this melting point isolated from the hydrogenation of Xa described above (Part II).

A sample of the methyl ether was demethylated according to the procedure already described for the isomer (see Part II, step 8). After crystallization, sublimation under reduced pressure and recrystallization the product was obtained as small colorless plates, m. p. 221–222° (vac.) (reported,<sup>17</sup> 206–206.5°, resolidifying and remelting at 221–222°).

**Effect of Acid and Base on the Hydrogenation of 14,15-Dehydroequilenin Methyl Ether.**—Two-tenth-gram samples of Xa (m. p. 160–162°) were hydrogenated over 0.040 g. of 30% palladium-charcoal catalyst<sup>36</sup> as described above. The rate of reaction was more rapid in ethyl acetate than in ethyl alcohol solvent, but the proportion of isomers was approximately the same. The addition of a trace of concentrated hydrochloric acid (0.0062–0.0124 mole) had no significant effect on the rate of hydrogenation or on the proportion of products. The addition of a drop of piperidine to the reaction mixture (alcohol solvent) also had little effect on the rate of hydrogenation, but the crude product melted at 124–144° (instead of 155–167°) indicating a higher proportion of the lower melting isomer, isoequilenin methyl ether. Hydrogenation in alcohol solution containing 0.00072 mole of potassium hydroxide proceeded much more rapidly and the crude product was a semi-solid. Recrystallization from acetone-methanol gave from the more soluble fraction 0.115 g. (57% yield) of isoequilenin methyl ether; m. p. 127–128°.

**Isomerization of the Dehydroequilenin Methyl Ethers.** (a) *Conversion of the 15,16- to the 14,15-isomer.*—When 0.070 g. of the 15,16-isomer (m. p. 104.5–106°) was treated with 2 ml. of pyridine and 4 ml. of concentrated hydrochloric acid according to the procedure described above (Part II, step 6) for decarboxylation of the keto acid, 0.031 g. (44% yield) of the 14,15-dehydroequilenin methyl ether was isolated as pale orange plates; m. p. 158–160.5°.

(b) *Isomerization of pure 14,15-dehydroequilenin methyl ether* (0.100 g.) was similarly effected with 2.5 ml. of pyridine and 5 ml. of concentrated hydrochloric acid. After heating for twelve minutes it was possible to recover only 0.065 g. (65%) of the starting material, m. p. 159–161°. The remaining material was an oil, presumably containing the 15,16-isomer, as further treatment with pyridine hydrochloride and hydrochloric acid gave additional Xa.

### Summary

It has been discovered that a cyano ketone such as VII or VIIa may condense with a succinic ester in the presence of an alkoxide catalyst to give a keto ester (VIII or VIIIa) having a new fused five-membered ring. This reaction has been employed in a synthesis of the 17-equilenones (3-desoxyequil-

TABLE I

DECARBOXYLATION STUDIES WITH VARIOUS AMINES

| Amine                     | Reaction time in minutes | % Carbon dioxide evolved | % Yield of Xa (14,15-isomer)    | M. p., °C.  |
|---------------------------|--------------------------|--------------------------|---------------------------------|-------------|
| Pyridine                  | 15                       | 103                      | 57                              | 159–161     |
| $\alpha$ -Picoline        | 15                       | 98                       | 50                              | 158–161     |
| 2,6-Lutidine              | 15                       | 101                      | 47                              | 158.5–160.5 |
| $\gamma$ -Collidine       | 12                       | 98                       | (Failed to give crystalline Xa) |             |
| Quinoline                 | 15                       | 97                       |                                 |             |
| Tri- <i>n</i> -butylamine | 17                       | ...                      | 23                              | 152–158     |
| Diethylamine              | 40                       | ...                      | 25                              | 157.5–161   |
| Ethanalamine              | 60                       | 54                       | (Failed to give crystalline Xa) |             |

enins), XI, and in a total synthesis of the sex hormone equilenin, XII. In the latter case the procedures have been refined so that the racemic form of the hormone can be prepared in about 28% over-all yield in eight steps from 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene, IIIa. The steps involve formylation (step 1) followed by treatment with hydroxylamine (step 2) to produce an isoxazole Va, which is isomerized with alkoxide and methylated (step 3) to give the cyano ketone VIIa. Condensation of VIIa with dimethyl suc-

cinatate in the presence of potassium *t*-butoxide (step 4) affords, in one operation, 15-carbomethoxy-14,15-dehydroequilenin methyl ether, VIIIa ( $R' = CH_3$ ), which is hydrolyzed (step 5) to the free acid IXa, and decarboxylated (step 6) to give 14,15-dehydroequilenin methyl ether, Xa. Hydrogenation of Xa (step 7) followed by demethylation (step 8) gives *dl*-equilenin XII, which on resolution affords *d*-equilenin, identical with the natural product.

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### Some Reactions of Butadiene Monochlorohydrin, 1-Chloro-3-buten-2-ol

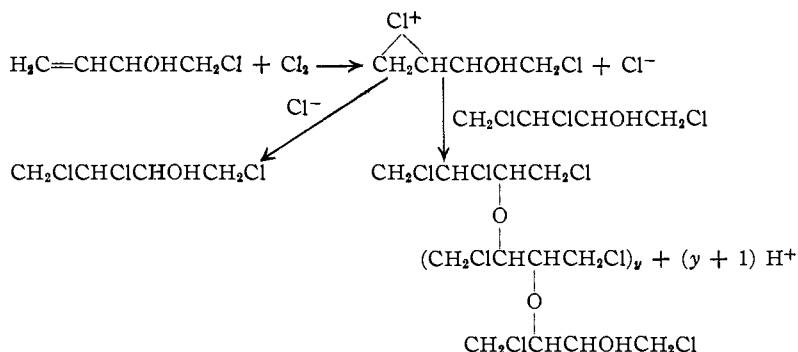
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The recent availability of 1-chloro-3-buten-2-ol (I) from the hypochlorination of butadiene<sup>3,4</sup> prompted us to investigate some of the typical reactions associated with the functional groups in this compound. Our studies have involved (1) chlorination of the double bond to form a trichlorobutanol and dehydrohalogenation of the latter to a dichloroepoxybutane, (2) conversion of the chlorohydrin to chloromethylvinyl ketone, (3) hydrolysis of the chlorohydrin to erythrol, 2-butene-1,4-diol and aldehydic products, (4) reaction of the chlorohydrin with sodium cyanide to form a butadiene cyanohydrin and dehydration of the cyanohydrin to cyanobutadiene, (5) hydrogenation of the butadiene cyanohydrin to butylene cyanohydrin and its hydrolysis and dehydration, (6) reaction of the chlorohydrin with formaldehyde to produce a formal and attempted reaction of this formal with metal cyanides and magnesium, and (7) phosgenation of the chlorohydrin to chloroformate and carbonate esters.

#### Discussion

**Chlorination of 1-Chloro-3-buten-2-ol (I).**— We have observed the addition of chlorine to 1-chloro-3-buten-2-ol (I) to be complicated considerably by side reactions, as is also apparently the case with allyl alcohol.<sup>5</sup> In our experiments polymeric ethers were obtained along with the expected 1,3,4-trichlorobutan-2-ol (II). This is understandable on the basis of a two-stage mech-

anism for halogen addition such as the one suggested by Bartlett and Tarbell<sup>6</sup> for bromine addition to stilbene in methyl alcohol. For the present case the reactions may be formulated as



Chlorine and hydroxyl analyses of the viscous polyether fraction indicated an average value of  $y$  of about 0.21.

As expected from the formulated mechanism, increase in the chloride ion concentration prevailing during the chlorine addition increased the yield of the trichlorobutanol and decreased the formation of ether. Thus, direct chlorination of I in carbon tetrachloride gave a 47% yield of 1,3,4-trichlorobutan-2-ol with approximately 43% of polyether. Saturation of the carbon tetrachloride with hydrogen chloride increased the yield of trichlorobutanol to 63%, while chlorination in concentrated hydrochloric acid gave this product in 77% yield. In the latter preparations polyether formation was correspondingly reduced (see Experimental section).

Dehydrochlorination of II using sodium hydroxide proceeded easily, giving practically quantitative yields of dichloroepoxybutane (III) probably consisting of a mixture of the two possible iso-

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