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The Total Synthesis of Estrone and Three Stereoisomers Including Lumiestrone

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The total synthesis of four of the eight possible racemates having the estrone structure has been described. One of these proved to be the *dl*-form of the natural hormone, and has been resolved. Another has been identified as lumiestrone. The synthetic scheme employed is summarized below. The potassium salt of *m*-methoxyphenylacetylene (prepared from *m*-hydroxyacetophenone) was added to decalin-1,5-dione in a 1:1 molecular ratio. The acetylenic bond of the resulting carbinols α and β VII ($R = OCH_3$) was hydrogenated to give the reduced carbinols α and β VIII ($R = OCH_3$). Direct cyclodehydration of either isomer with aluminum chloride afforded mainly one stereoisomeric form (α) of the tetracyclic ketone X ($R = OCH_3$). Dehydration of the α and/or β reduced carbinols gave the unsaturated ketone IX ($R = OCH_3$), which on cyclization was converted to three (α, β and γ) forms of X ($R = OCH_3$). Each of these was converted to the benzylidene derivatives XI ($R = OCH_3$, $Ar = C_6H_5$) the γ-isomer yielding the same product as the β. Treatment with potassium *t*-butoxide and methyl iodide gave from the α-benzylidene derivative two methylation products XII ($R = OCH_3$, $Ar = C_6H_5$) α^1 and α^2 which were epimeric at the carbon holding the angular methyl group. Similarly the β-benzylidene derivative yielded the epimeric β^1- and β^2-methylated products XII ($R = OCH_3$, $Ar = C_6H_5$). Ozonization of each of the methylation isomers gave the corresponding α^1-, α^2-, β^1- and β^2-homomarrianolic acid methyl ethers XIII ($R = OCH_3$), which on cyclization afforded the α^1-, α^2-, β^1- and β^2-estrone methyl ethers XIV ($R = OCH_3$). Demethylation yielded the α^1-, α^2-, β^1- and β^2-estrones XIV ($R = OH$). The β^2-isomer proved to be the racemic form of the natural product, and the β^1, that of lumiestrone, thus proving that Butenandt's postulated (C_{13} epimeric) configuration for the latter was correct. The relationship of our products to those of Anner and Miescher is discussed. A similar sequence of reactions was studied up through the formation of the tetracyclic ketones X ($R = H$) in the series lacking the methoxyl group. The structures of the cyclization products in both series were established by dehydrogenation experiments. A number of by-products were isolated in the course of the study, and structures for these are postulated. In an attempted estrone synthesis according to a scheme previously used successfully for the synthesis of equilenin, the cyanoketone I ($R = CN$) was prepared. The condensation with succinic ester failed, apparently due to opening of ring C by alcoholysis. Experiments with the analogous cyanoketone containing a double bond between rings B/C also were unpromising.

Introduction.—More than fifteen years ago extensive research programs directed toward the total synthesis of the female sex hormone estrone were already in progress.[6] In the years that followed, studies in this field continued with expanding interest in laboratories all over the world, and several tetracyclic compounds having structures similar to estrone were prepared.[7] The first unequivocal synthesis of the estrone structure was accomplished in 1942 by Bachmann, Kushner and Stevenson,[8] who isolated one of the eight possible *dl*-forms ("estrone a") from the mixture produced by attaching ring D to the keto ester I ($R = COOCH_3$, double bond between rings B/C) according to a method developed in the equilenin synthesis.[9]

In 1948 Anner and Miescher[10] prepared the saturated keto ester I ($R = COOCH_3$) of Bachmann[8] and Robinson[11] in quantity and separated three of the four possible *dl*-modifications in crystalline form. Utilizing the Bachmann method of attaching ring D, they were able to convert these keto esters into five estrones (a, b, d, e and f). The originally reported[10] sixth isomer, "estrone c," was later withdrawn,[12] since it proved to be a degradation product of isomer e. Isomer b was shown to be *dl*-estrone by resolution, and the first total synthesis of the hormone was thus realized. One of the stereoisomers appeared to be identical with that of Bachmann, Kushner and Stevenson[8] and was accordingly labeled "estrone a." Anner and Miescher[12] have also postulated that isomer f is *dl*-lumiestrone.

In the present paper we are reporting the results of our studies of a fundamentally different approach to the estrone structure. This work has culminated in a total synthesis of estrone as well as three of the (*dl*) stereoisomers, including authentic lumiestrone.[13] Some stereochemical considerations and the relationship of our products to those of Anner and Miescher are discussed.

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[1] Watumull Fellow 1947–1949; Wisconsin Alumni Research Foundation Postdoctoral Fellow 1948–1949.

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[3] Wisconsin Alumni Research Foundation Postdoctoral Fellow, summer 1947.

[4] Wisconsin Alumni Research Foundation Postdoctoral Fellow, 1945–1946.

[5] Wisconsin Alumni Research Foundation Research Assistant, 1948–1951; du Pont Grant-in-Aid Research Assistant, summer 1951.

[6] See for example, R. Robinson and E. Schlittler, *J. Chem. Soc.*, 1288 (1935).

[7] *Cf.* for example the products of E. Dane and J. Schmitt, *Ann.*, **537**, 246 (1939), and of S. Breitner, *Med. u. Chem.*, **4**, 317 (1942), which probably are structural isomers of estrone. See J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948).

[8] W. E. Bachmann, S. Kushner and A. C. Stevenson, THIS JOURNAL, **64**, 974 (1942).

[9] W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940).

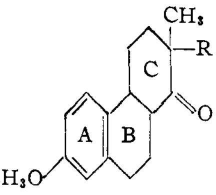
[10] G. Anner and K. Miescher, *Experientia*, **4**, 25 (1948); *Helv. Chim. Acta*, **31**, 2173 (1948); *ibid.*, **32**, 1957 (1949).

[11] The ethyl ester I ($R = COOC_2H_5$) was first prepared by R. Robinson and J. Walker, *J. Chem. Soc.*, 747 (1936); 183 (1938), who also described preliminary experiments on the attachment of ring D.

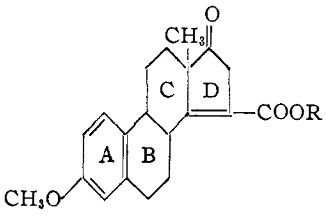
[12] G. Anner and K. Miescher, *Helv. Chim. Acta*, **33**, 1379 (1950).

[13] For a preliminary report of this work see (a) W. S. Johnson, D. K. Banerjee, W. P. Schneider and C. D. Gutsche, THIS JOURNAL, **72**, 1426 (1950); (b) W. S. Johnson and L. J. Chinn, *ibid.*, **73**, 4987 (1951).

Preliminary Studies.[14]—In an earlier publication from this Laboratory[15] we described a total synthesis of the hormone equilenin which involved, as the key step, the condensation of the cyanoketone I (R = CN, ring B aromatic) with succinic ester to produce directly the substance II (ring B aromatic) containing the steroid nucleus. In an effort to synthesize estrone we tried to apply this scheme to the appropriate cyanoketone I (R = CN) with ring B saturated. Two crystalline stereochemical forms of this compound were obtained from the ketone III *via* the isoxazole as in the scheme employed in the equilenin series; however, they failed to condense in the desired manner with succinic ester under a variety of conditions. Instead, ring C of I (R = CN) apparently was opened by the condensing agent in a manner previously observed as a side-reaction in the equilenin series, but with greater ease, which may indeed represent a typical behavior for cyanoketones lacking the aromatic nucleus conjugated with the carbonyl group.[16] In the hope that conjugation of the keto group with the aromatic nucleus as in the ketone IV would inhibit the ring cleavage reaction, the appropriate cyanoketone I (R = CN, double bond between rings B/C) was prepared from IV. An attempt to effect condensation with various alkyl succinates, however, gave such discouraging results that this general approach has been temporarily abandoned in favor of a more promising scheme considered below.



I



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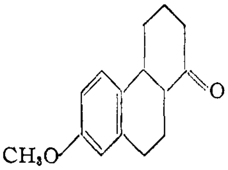

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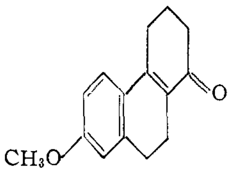
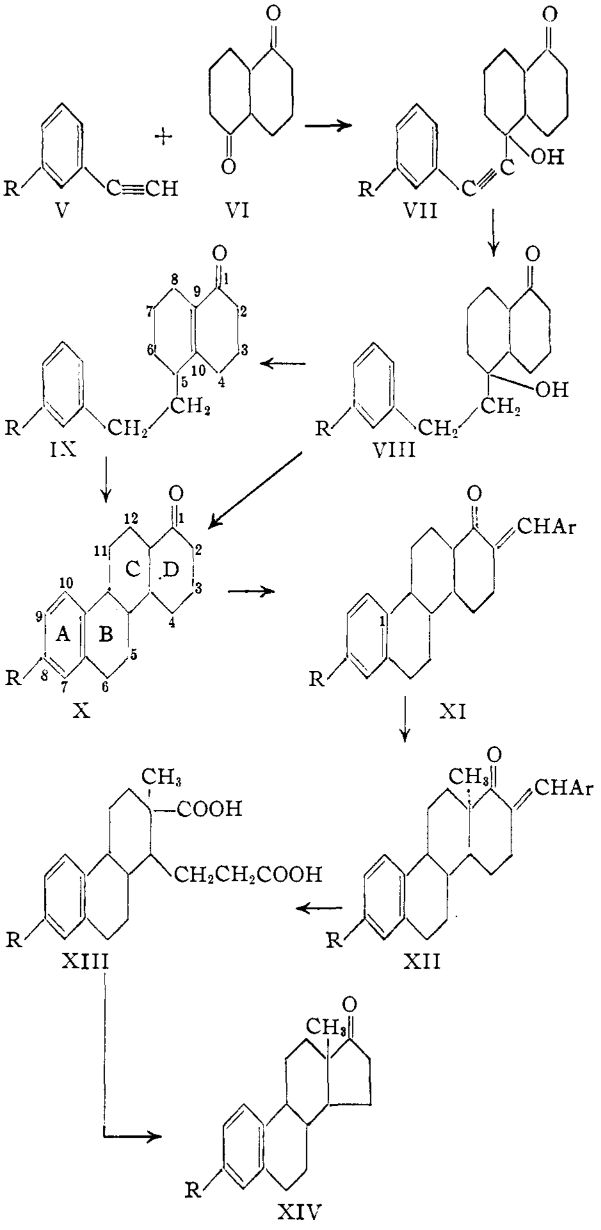


IV

A few years ago we described a four-step synthesis of *cis*- and *trans*-8-methyl-1-hydrindanone from 1-decalone.[17] It was suggested that application of this sequence to the tetracyclic analog X (R = OCH_3) should lead to the estrone methyl ether structure *via* the steps X → XI → XII → XIII → XIV (R = OCH_3). The following sections include a description of such a study as well as the preparation of the chrysenones X (R = H and OCH_3) and their proof of structure.



The Synthesis of 1-Ketododecahydrochrysene X (R = H). Preliminary studies of the proposed reaction scheme for the preparation of the desired chrysenone X (R = OCH_3) were carried out in the series lacking the methoxyl group. The condensation of phenylacetylene (V, R = H) with decalin-1,5-dione (VI)[18] was promoted by potassium *t*-butoxide. By slowly adding a solution of the acetylene in *t*-butyl alcohol containing the butoxide to the dione in a mole to mole ratio, the monocondensation product VII (R = H) was the main product. Either the *cis*- or *trans*-form of the dione or a mixture of these isomers yielded essentially the same product which consisted largely of two stereoisomeric carbinols VII (R = H) (α), m.p. 121°, and (β), m.p. 141°, predominantly the former. These substances are undoubtedly epimeric about the carbon holding the hydroxyl group, and probably have the decalin ring system fused in

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[14] The experiments described in this section were performed by W. E. S.

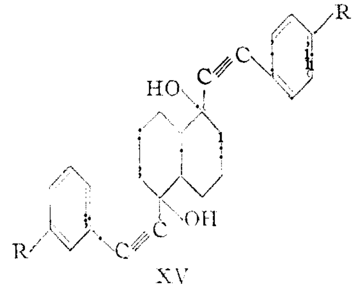
[15] W. S. Johnson, J. W. Petersen and C. D. Gutsche, This Journal, **69**, 2942 (1947).

[16] M. Bumpus has shown in this Laboratory that both 2-cyano-2-methylcyclohexanone and 2-cyano-2-methyl-6-β-phenylethylcyclohexanone are similarly cleaved readily with alkoxide and therefore do not undergo condensation with succinates.

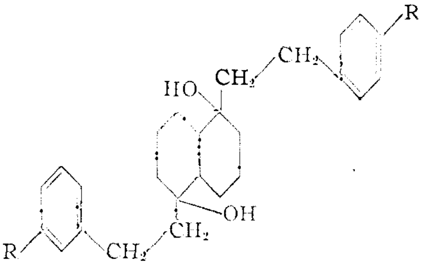
[17] W. S. Johnson, This Journal, **66**, 215 (1944).

[18] W. S. Johnson, C. D. Gutsche and D. K. Banerjee, *ibid.*, **73**, 5464 (1951).

the more stable[19] *trans*-configuration. A third substance, m.p. 212°, was also isolated in very low yield, and this material proved to be the dicondensation product XV (R = H).



XV



XVI

Catalytic hydrogenation of the α- and β-acetylenic carbinols VII (R = H) over palladium-on-carbon gave, respectively, the epimeric reduced carbinols VIII (R = H), (α), m.p. 169° and (β), m.p. 133°. Similarly hydrogenation of the dicondensation product XV (R = H) gave the glycol XVI (R = H), m.p. 232°. For preparing pure materials in quantity it was found expedient not to separate the acetylenic carbinols, but instead to hydrogenate the crude condensation product, and to fractionally crystallize the reduced carbinols. It was thus possible to obtain 65% of VIII (R = H) (α), 10% of VIII (R = H) (β) and 1% of XVI (R = H) based on decalindione.

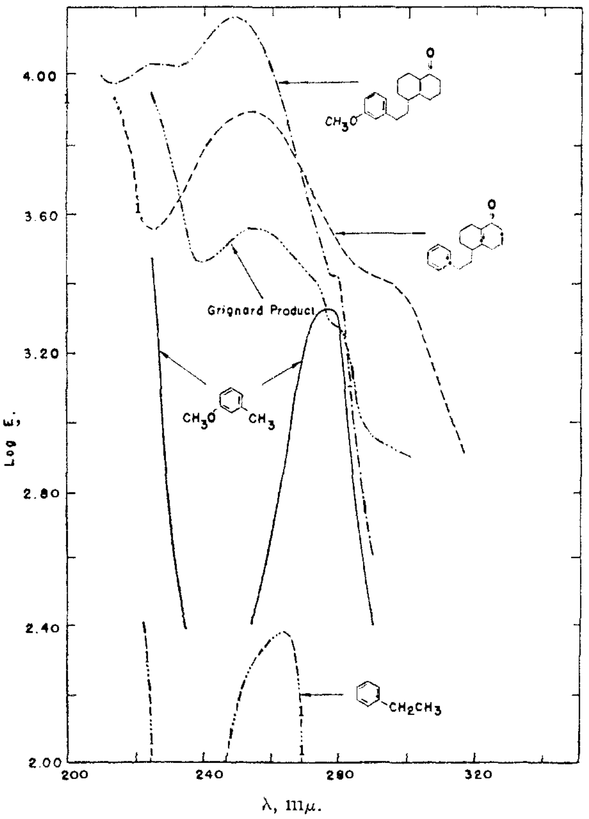
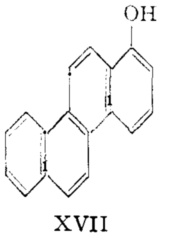


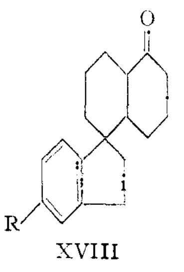
Fig. 1.

Both the α- and β-forms of the reduced carbinol VIII (R = H) gave the same oily unsaturated ketone on dehydration with formic acid. The high absorption at 253 mμ (log E 3.92) in contrast with that of the model compound ethyl benzene (Fig. 1) suggested that the double bond was in conjugation with the carbonyl group. This premise was further supported by the spectrum of the semicarbazone which showed a typical $\lambda_{\max}$ 268.5 (log E 4.14) for α,β-unsaturation, and accordingly the product is formulated as the $\Delta^{9,10}$ compound IX (R = H).[20] A similar (although base- instead of acid-catalyzed) migration of the double bond from the β,γ- to the α,β-position with respect to the keto group has been noted before.[21]

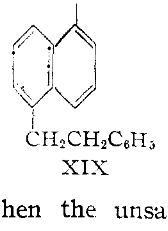
Cyclodehydration of the reduced carbinols VIII (R = H) (α or β) by treatment in benzene with hydrogen chloride followed by aluminum chloride gave three stereoisomeric forms of the keto-dodecahydrochrysene X (R = H): α, m.p. 140° (46% yield); β, m.p. 130° (3% yield); and γ, m.p. 124° (6% yield). Each of these products gave 1-chrysenol (XVII) in good yield on dehydrogenation and thus evidence supporting the structure X (R = H) was provided. The ready dehydrogenation to XVII would not be expected from the alternate spiran structure XVIII (R = H). Similar dehydrogenation of the uncyclized material IX (R = H) did not give 1-chrysenol but instead produced a low-melting phenol which was undoubtedly the phenylethylnaphthol XIX. This fact indicates that cyclization did not occur during the dehydrogenation experiments described above.



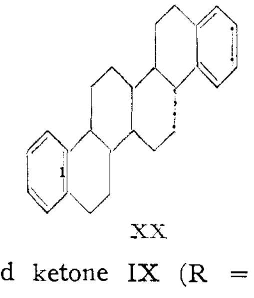
XVII



XVIII



XIX



XX

When the unsaturated ketone IX (R = H)

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[19] W. Hückel and E. Brinkmann, *Ann.*, **441**, 21 (1925); W. Hückel, R. Danneel, A. Gross and H. Naab, *ibid.*, **502**, 99 (1933).

[20] The $\Delta^{8,9}$ structure has not been excluded, but is considered to be less likely. *Cf.* W. P. Campbell and G. C. Harris, This Journal, **63**, 2721 (1941).

[21] *Cf.* W. S. Johnson, J. Szmuszkovicz and M. Miller, *ibid.*, **72**, 3726 (1950).

was submitted to the cyclization conditions, the 130° (β) isomer of X (R = H) was the major product. This reaction represents the intramolecular counterpart of the hydroarylation of 1-acetylcyclohexene with benzene to give 4-phenylhexahydroacetophenone,[22] and therefore would be expected to give the product X (R = H) almost to the exclusion of the spiran XVIII (R = H). The 130° (β) isomer of X (R = H) was shown to be isomerizable into the 140° (α) isomer by potassium *t*-butoxide. This fact suggests that the two forms are epimeric at C_{12a}, and that the rings C/D are *cis* in the former and *trans* in the latter.[23]

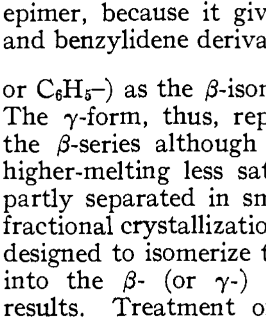
Cyclization of the reduced carbinol XVI arising from dicondensation yielded a hydrocarbon $C_{26}H_{30}$, m.p. 256°, undoubtedly the hydrobenzopicene, XX.

The Synthesis of 1-Keto-8-methoxydodecahydrochrysene X (R = OCH_3).—With the model experiments in the parent series at hand (see above) we directed our attention to a similar study in the methoxy series. *m*-Methoxyphenylacetylene (V, R = OCH_3) was prepared from *m*-hydroxyacetophenone by methylation with dimethyl sulfate and alkali followed by conversion to the α,α-dichloro compound with phosphorus pentachloride and finally dehydrohalogenation with alcoholic potassium hydroxide. The acetylene V (R = OCH_3) was condensed with decalindione VI as described for the parent series to produce a pair of epimeric acetylenic alcohols VII (R = OCH_3) (α), m.p. 100° (85° polymorphic form) and (β), m.p. 116°. In addition some of the product of dicondensation XV (R = OCH_3), m.p. 189° was isolated. Catalytic hydrogenation of the two acetylenic alcohols gave the reduced carbinols VIII (R = OCH_3) (α), m.p. 77° and (β), m.p. 91°, respectively.

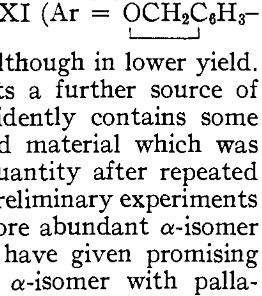
Cyclization of the (α) or (β) form of the reduced carbinol VIII (R = OCH_3) with aluminum chloride in benzene (but without hydrogen chloride) gave largely a single (α) isomer of X (R = OCH_3), m.p. 170°, which was isolated in yields as high as 40%. For the preparation of this isomer in quantity, the crude mixture of acetylenic carbinols was hydrogenated and cyclized directly without separation of isomers, and thus an over-all yield of 25% from decalindione was realized.

Dehydration of the mixture of the α- and β-forms of the reduced carbinol VIII (R = OCH_3) with formic acid gave the oily unsaturated ketone IX (R = OCH_3). As in the parent series the assignment of the position for the ethylenic bond was made on the basis of the ultraviolet absorption spectrum (Fig. 1), λ_{max} 249 (log E 4.18).[20] The semicarbazone likewise showed the typical λ_{max} 269 (log E 4.52) for α,β-unsaturation. For the preparation of the unsaturated ketone IX (R = OCH_3) in quantity it was not necessary to separate isomers at the intermediate stages, and thus an over-all yield of 70% from decalindione was realized. Cyclization of the unsaturated ketone gave a mixture of chrysenones X (R = OCH_3) from which were isolated the α-isomer described above; a β-isomer, m.p. 155°; and a γ-form, m.p. 170°. The last was shown to be different from the α-isomer by mixed m.p. determination and infrared spectroscopy. The total yield of crude solid product was 25% and about 90% of this material was separated into the three forms roughly in the proportion 2:1:1. This distribution, however, appeared to vary and in some experiments the proportion of the α-isomer seemed to be considerably higher.

The α- and β-isomers were recovered unchanged on treatment with potassium *t*-butoxide, and therefore differed in configuration at centers other than C_{12a}. Since as shown below the 155° isomer can be converted into estrone, believed to have the *trans-anti-trans*[24] arrangement, the β-isomer is tentatively assigned this configuration. The γ-form does not depress the m.p. of the β, but they evidently do not represent polymorphic forms because the infrared spectra showed small but distinct differences in the characteristic region (8–15 μ). The γ-form appears to be a fairly sharp melting mixture or molecular compound containing predominantly either the β isomer or the C_{12a} epimer, because it gives the same piperonylidene and benzylidene derivatives XI (Ar = $\underline{OCH_2}C_6H_3$– or C_6H_5–) as the β-isomer, although in lower yield. The γ-form, thus, represents a further source of the β-series although it evidently contains some higher-melting less saturated material which was partly separated in small quantity after repeated fractional crystallization. Preliminary experiments designed to isomerize the more abundant α-isomer into the β- (or γ-) form have given promising results. Treatment of the α-isomer with palladium-on-carbon catalyst at about 250°, conditions used by Bachmann and Dreiding[25] for the isomerization of equilenin methyl ether to isoequilenin methyl ether, resulted in extensive dehydrogenation with the production of a phenolic compound, probably XXI. However, when the reaction temperature was lowered to 183° and the time extended from eight to twenty minutes, very little hydrogen was evolved, 43% of the α-isomer was recovered, and about 3% of what appeared to be the γ-form was isolated. This conversion has not yet been exploited, but obviously provides a po-



XXI



XXII

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[22] C. D. Nenitzescu and I. G. Gavat, *Ann.*, **519**, 260 (1935); W. S. Johnson and R. D. Offenhauer, THIS JOURNAL, **67**, 1045 (1945); W. S. Johnson, *Record of Chemical Progress*, Spring Issue, 1949, p. 53.

[23] This stereochemical argument is sound, except in the event that rings B/C are *trans* and the backbone is *syn* in which case the situation would presumably be reversed with respect to C/D. *Cf.* the case of R. P. Linstead and R. R. Whetstone, *J. Chem. Soc.*, 1428 (1950). See also W. S. Johnson, *Experientia*, **7**, 315 (1951).

[24] The stereochemical representation employed by Linstead in the perhydrophenanthrene ring system (see R. P. Linstead, *Chemistry and Industry*, **15**, 510 (1937) and R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, THIS JOURNAL, **64**, 1985 (1942)) is particularly well adapted to the estrones. The *trans-anti-trans* estrone thus has rings B/C *trans*, the backbone *anti*, and C/D *trans* (formula XXVII).

[25] W. E. Bachmann and A. S. Dreiding, *ibid.*, **72**, 1329 (1950).

tential source of additional material in the natural series.

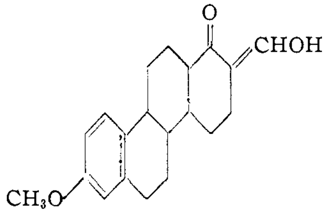
The nuclear structure of the α- and β-isomers of X (R = OCH_3) was confirmed by dehydrogenation experiments. On reduction with lithium aluminum hydride these ketones were converted into crystalline alcohols, m.p. 115° and 141°, respectively, which on dehydration over potassium acid sulfate followed by dehydrogenation with palladium-on-carbon gave 2-methoxychrysene (XXII) in 64 and 75% yields, respectively.

In the cyclization of the mixture of reduced carbinols VIII (R = OCH_3) described above, a new ketone, m.p. 113°, (the δ-isomer) was isolated from the oily residues *via* the semicarbazone. This product was isomeric with the α- and β-forms of X (R = OCH_3), but on treatment by the dehydrogenation sequence described above gave only traces of 2-methoxychrysene. This behavior is consistent with the spiran structure XVIII (R = OCH_3) which is an expected by-product in a Bogart–Cook type of cyclization and could give rise to the chrysene nucleus by rearrangement during dehydrogenation.[26]

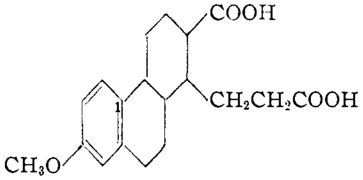
In a preliminary study of the equimolar condensation of β-(*m*-methoxyphenyl)-ethylmagnesium bromide with decalin-1,5-dione the crude reaction product was dehydrated over potassium bisulfate and appeared to contain: decalindione, *m*-ethylanisole, 1,4-di-*m*-methoxyphenylbutane (the coupling product), and a mixture of monocondensation products from which a semicarbazone, m.p. 200°, was obtained in poor yield. This substance was isomeric with the semicarbazone of IX (R = OCH_3), m.p. 193°, and showed a considerably weaker absorption (log *E* 3.76) at 271.5 mμ suggesting that the material was not homogeneous and contained some of the product in which the ethylene bond was not conjugated with the carbonyl group. The oily ketone obtained on hydrolysis of the 200° semicarbazone, absorbed at 254 mμ (log *E* 3.58) and similarly appeared to contain material with the ethylenic bond unconjugated, possibly the $\Delta^{5,6}$-structure. The cyclization has not been studied because of limited amount of this material available.

Demethylation of the α- and β-isomers of X (R = OCH_3) with pyridine hydrochloride gave the phenols X (R = OH) which are isomeric with estrone. The α-phenolic ketone melted at 206° and in preliminary physiological tests by the technique described below showed no estrogenic activity at 100 μg. The β-isomer, m.p. 273°, however, showed weak activity (about 10% response) at this level.[27] It is noteworthy that a small amount of this latter product was isolated from the acidic fraction of the cyclization of IX (R = OCH_3).

The Estrones.—The α- and β-isomers of X (R = OCH_3) underwent condensation with piperonal in dilute alcoholic alkali to give the piperonylidene derivatives XI (R = OCH_3, Ar = $\underline{OCH_2OC_6H_3}$-) α-isomer, m.p. 192°; and β-isomer, m.p. 211°. Methylation of these derivatives with potassium *t*-butoxide and methyl iodide gave in preliminary experiments, complex mixtures from which several compounds of doubtful homogeneity were separated in low yield. One of these substances (in the β-series) melting at 193° appeared to be the desired product of methylation, but was isolated in very low yield. Another melting at 155° was shown to be produced not by methylation but by an alkali-catalyzed isomerization. Oxidation of this isomer with permanganate yielded the β-form of the dibasic acid XXIV, m.p. 222°. The α-isomer of XXIV, m.p. 242°, was obtained by permanganate oxidation of the hydroxymethylene ketone XXIII prepared by the condensation of the α-form of X (R = OCH_3) with ethyl formate.



XXIII



XXIV

Since the difficulties attending the attempted methylation of the piperonylidene derivatives appeared to be due in part to their sparing solubility, attention was turned to the more soluble benzylidene derivatives XI (R = OCH_3, Ar = C_6H_5). Conditions were found for the preparation of the α-isomer in 74% and the β-isomer in 66% yield, the pure substances melting at 176 and 153°, respectively. In the α-series a second form, m.p. 166°, was occasionally encountered, and this was shown to be a product of alkali-catalyzed isomerization of the 176°-derivative (*cf.* the piperonylidene series above). Since the α-ketone X (R = OCH_3) from which the benzylidene derivative was prepared was shown (see above) to be unchanged by *t*-butoxide and therefore must exist in the form with rings C/D in the most stable configuration, this behavior of the derivative probably involves a *cis–trans* isomerization of the benzylidene group. The ultraviolet spectrum of the 166°-isomer was very similar to that of the 176°-form (Fig. 2).

Methylation of the α-benzylidene derivative proceeded smoothly to give the expected mixture of two isomers of XII (R = OCH_3, Ar = C_6H_5), α^1, m.p. 118° (56% yield) and α^2, m.p. 150° (13% yield). By analogy to the established nature of the methylation products of benzylidenedecalone[28] these isomers are undoubtedly epimeric at the carbon (C_{12a}) holding the angular methyl group.

The β-benzylidene derivative similarly gave two additional C_{12a} epimers of XII (R = OCH_3, Ar =

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[26] *Cf.* for example S. C. Sen-Gupta, *J. Indian Chem. Soc.*, **11**, 389 (1934).

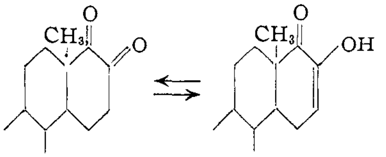
[27] *Cf.* the activity of D-homo-estrone, which is about 1/30 that of estrone. M. W. Goldberg and S. Studer, *Helv. Chim. Acta*, **24**, 478, 295 E (1941).

[28] W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943).

C_6H_5), β^1, m.p. 147° (50% yield) and β^2, m.p. 148° (17% yield). Since the latter was shown to lead to estrone (see below), it therefore undoubtedly has the C/D *trans*-configuration. Accordingly the predominant β^1-isomer is presumed to have rings C/D *cis*. It is interesting to note that the isomer produced in preponderance in the decalone series[28] also undoubtedly belongs to the *cis*-series. It may be suggested, similarly, in the α-series that the preponderant methylation product (α^1) has rings C/D *cis* and the companion isomer (α^2) has C/D *trans*. However, this postulate rests on highly presumptive grounds. The ultraviolet absorption spectra of all four of the methylation isomers were essentially the same and closely resembled that of the unmethylated derivative (Fig. 2).

In the methylation of the β-benzylidene derivative there was also isolated in about 3% yield a third substance, m.p. 157°, which was different from the starting material as well as the two methylation products described above. This material had a typical benzylidene ketone ultraviolet absorption spectrum, and is presumably formed from either the unmethylated or methylated products (C–H analysis does not distinguish between the homologs) by *cis–trans* isomerization of the type noted above with the piperonylidene derivative.

When the methylation of the α-benzylidene ketone was carried out under relatively vigorous (refluxing) conditions, it was difficult to isolate pure products. Oxidation of such a mixture with potassium permanganate in acetone with the view to producing the dibasic acid XIII (R = OCH_3) by analogy to the decalone series,[17] gave only a 38% yield of gummy acidic material. From the neutral fraction, which was resistant to further oxidation with permanganate, was isolated by chromatography a small yield of material, m.p. 113°. The ultraviolet spectrum no longer resembled that of the benzylidene derivatives, but was instead almost identical with that of the product, m.p. 172°, produced by hydrogenation of the ethylenic bond of the α-benzylidene ketone XI (R = OCH_3, Ar = C_6H_5) (see Fig. 2). The 113°-material did not give a semicarbazone under moderate conditions, and a Zeisel determination indicated only one methoxyl group. These results and the carbon–hydrogen values are consistent with a variety of structures in which the benzylidene linkage is reduced. The constitution was not investigated further because of the limited amount of material available. In any case, this experiment clearly demonstrated the importance of carrying out the methylation step under mild conditions.



XXV XXVI

Oxidation of the pure methylated benzylidene derivatives by the permanganate method[17] gave mixtures of dibasic acids which were extremely difficult to purify. Possibly under the alkaline conditions enolization of the probable intermediary α-diketone XXV is promoted, and the tautomer XXVI could easily give rise to a *nor* dibasic acid, just as 1,2-cyclopentadione is partly oxidized under these conditions to succinic acid.[29] Of the oxidation procedures that were investigated ozonization followed by treatment with hydrogen peroxide proved most satisfactory. The α^1-, α^2-, β^1- and β^2-forms of benzylidene-D-homoestrone methyl ether XII (R = OCH_3, Ar = C_6H_5) were each, thus, converted to the corresponding homomarrianolic acid methyl ethers XIII (R = OCH_3) in yields of 72–80%. These dibasic acids were in turn cyclized (in 46–82% yield) by pyrolysis with lead carbonate to the corresponding estrone methyl ethers XIV (R = OCH_3) which were characterized as the 2,4-dinitrophenylhydrazones. Carbon and hydrogen analysis of these derivatives showed conclusively that the molecules contained the additional (angular) methyl group, a distinction which could not be ascertained with the free ketones. Demethylation of each of the estrone methyl ethers with pyridine hydrochloride afforded (in about 90% yield) the α^1-, α^2-, β^1- and β^2-estrones XIV (R = OH), which were characterized as the benzoates. The melting points of all of these products and derivatives are summarized in Table I, which also includes similar data reported by Anner and Miescher[10] for their products.

That the β^2 represents the natural series leading to estrone was established by the following evidence. A mixture of the β^2-dibasic acid (m.p.

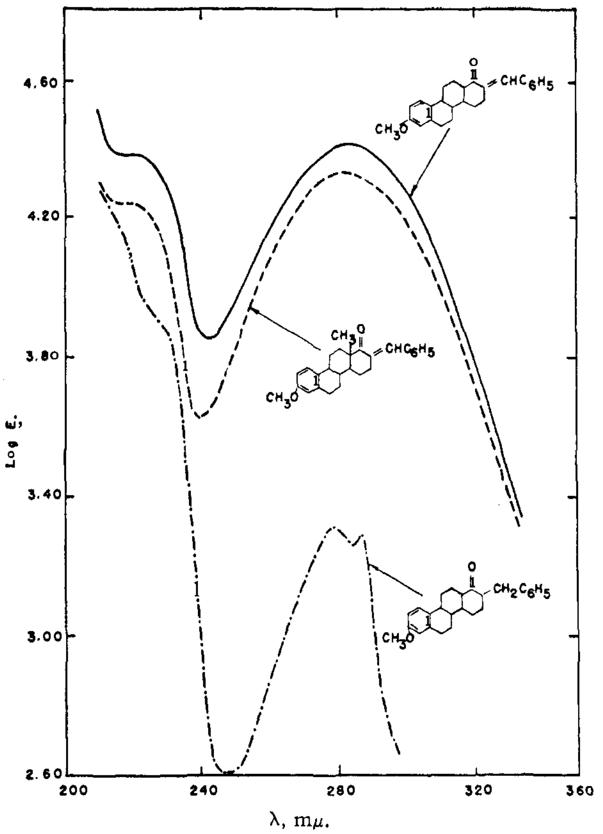


Fig. 2.

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(29) W. Dieckmann, *Ber.*, **35**, 3201 (1902). See also G. Schwarzenbach and Ch. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).

TABLE I

SUMMARY OF MELTING POINTS (°C.) OF THE ESTRONES AND DERIVATIVES

Substance	Present work				Anner and Miescher[10,12]				
	α^1(c)	α^2(h)	β^1(g)	β^2(b)	a	b	d	e	f
Benzylidene-D-homoestrone methyl ether (XII, R = OCH_3, Ar = C_6H_5)	117–118	149–150	146.5–147	147–148					
Homomarrianolic acid methyl ether (XIII, R = OCH_3)	170–170.5	Amorphous	191–192	225–227.5	225–227	225–227	170–171	212–214	Amorphous
Estrone methyl ether (XIV, R = OCH_3)	115–116	67–68	109–110	143–144	114–116	143–144	Oil	162–164	Oil
Estrone methyl ether 2,4-dinitrophenylhydrazone	273–274	209–210	210–211						
Estrone (XIV, R = OH)	180.5–181.5	197–198	238.5–240	253–255	214–216	251–254	184–186[a]	230–232	188–190[a]
Estrone benzoate (XIV, R = $OCOC_6H_5$)	149–151	159.5–161.5	157.5–158.5	184–190	175–176	184–186	150–152	134–136	161–163

[a] In a private communication Drs. Anner and Miescher have recently advised us that the melting points of estrone d and f are now 185–188° and 191–195°, respectively.

227°) XIII (R = OCH_3) with *d*-homomarrianolic acid methyl ether[30] (m.p. 254°) melted at an intermediate range which is characteristic behavior for a mixture of an enantiomorph with the corresponding *dl*-mixture. Similar m.p. behavior was noted on admixture of β^2-estrone methyl ether (m.p. 144°) and *d*-estrone methyl ether (m.p. 169°). The infrared spectra of these last two substances were determined and found to be identical (Fig. 3). Crystallographic comparison of the two materials showed that they are both obtained as tablets and massive prisms from nitrobenzene, belong to the orthorhombic system, have high birefringence, 2 V large, and no dispersion; n_p = 1.518, n_m > 1.64. The identity of these crystallographic properties coupled with the melting point behavior confirms the premise that the synthetic material is a racemic *mixture*. By subcutaneous administration in a total of 40 ovariectomized rats (vaginal smear technique) β^2-estrone gave essentially the same response at 1.04 and 1.66 μg. as U.S.P. estrone at 0.52 and 0.83 μg. levels. Resolution of β^2-estrone was effected *via* the *l*-menthoxyacetate.[9] Synthetic *d*-estrone *l*-menthoxyacetate (m.p. 135°) was isolated by fractional crystallization and showed no depression of the m.p. on admixture with the ester (m.p. 135°) prepared from natural estrone. It is noteworthy that the m.ps. of the compounds in the β^2-series are in excellent agreement with those reported by Anner and Miescher[10] for their b-series (see Table I).

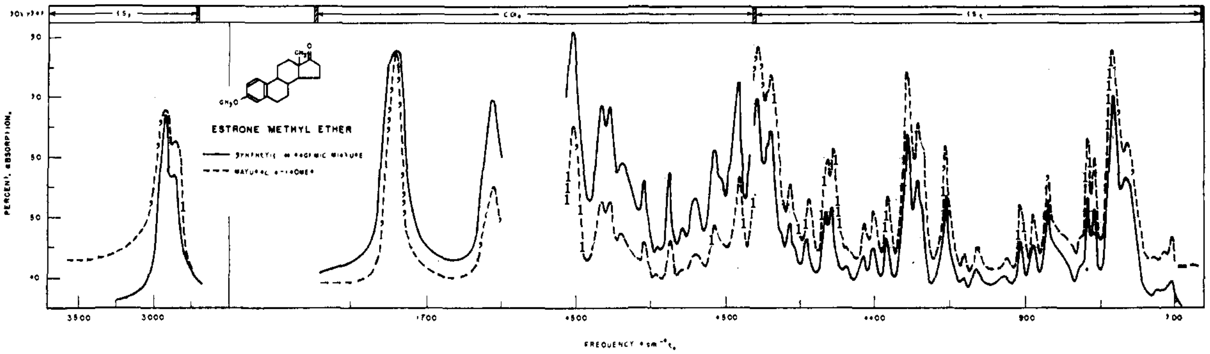
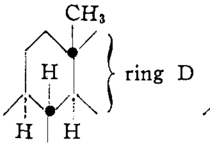
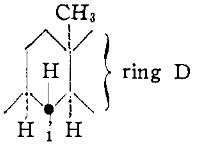


Fig. 3.

Since the β^2-series has been related to natural estrone which most probably has the *trans–anti–trans* configuration (XXVII),[24] the β^1-series which is epimeric with the β^2 at the carbon holding the angular methyl group (see above) may be represented as having the *trans–anti–cis* configuration (XXVIII). The fact alone that β^1-estrone is epimeric with natural estrone at C_{13} establishes it unequivocally as that stereoisomeric form postulated by Butenandt and co-workers[31] for lumiestrone. Anner and Miescher,[12] however, have dismissed our postulate that β^1-estrone is *dl*-lumiestrone, and have proposed instead that their estrone f, which is clearly different from β^1 (see Table I) represents lumiestrone. The arguments which they advanced in support of this premise are, in our opinion, inconclusive for reasons outlined in a previous communication.[13b] That β^1-estrone is indeed *dl*-lumiestrone was demonstrated by the identity of the infrared spectrum (Fig. 4) of the methyl ether with that of lumiestrone methyl ether prepared from estrone by the method of Butenandt.[31] A mixture of β^1-estrone with lumiestrone melted at an intermediate range. Attempts to



XXVII



XXVIII

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[30] Prepared *via* 16-hydroxymethyleneestrone methyl ether according to the method of W. S. Johnson and W. E. Shelberg, THIS JOURNAL, **67**, 1754 (1945).

[31] A. Butenandt, A. Wolff and P. Karlson, *Ber.*, **74**, 1308 (1941); A. Butenandt, *et al.*, *ibid.*, **75**, 1931 (1942); **77**, 392 (1944).

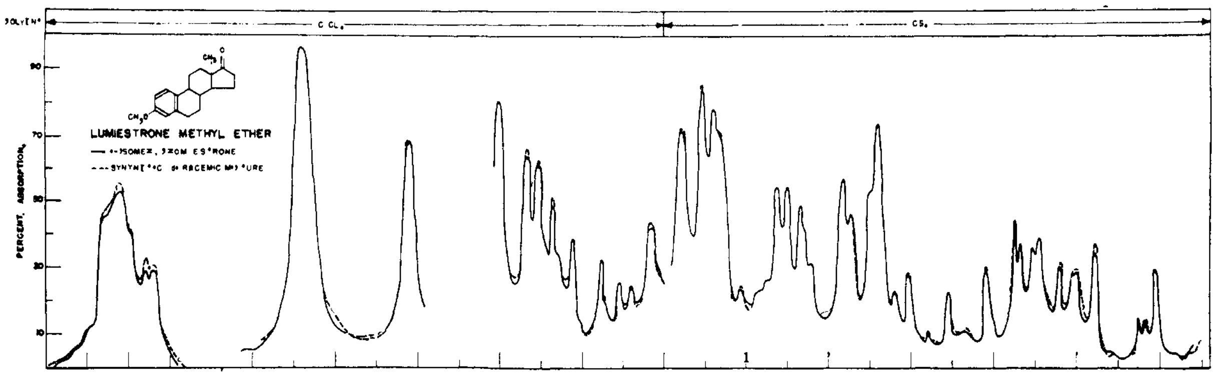

Fig. 4.

resolve the racemic material have not yet been successful.

The fair agreement of the melting points in the d- and the α^1-series (Table I) led us to propose that the two were identical.[13a] Through the courtesy of Drs. Miescher and Anner, who sent us specimens of their products, we have now been able to make a direct comparison of α^1-estrone with estrone d. Mixed melting point determinations with the two estrones and also the two benzoates gave marked depressions, and therefore the non-identity of these products is established. Accordingly our α^1-estrone may now be reassigned the name of the missing[12] estrone c. We have also compared α^2-estrone and the benzoate with the corresponding products in the f-series and have conclusively demonstrated their non-identity. The β^1- and α^2-series accordingly retain the previous[13a] assignments "g" and "h," respectively. If all of the products described in Table I represent different products and actually have the estrone structure,—a point which has not been established unequivocally—then it appears that all eight of the racemates are known.

Acknowledgment.—We wish to thank the agencies mentioned in footnotes 1-5 for generous financial assistance.

We are indebted to Dr. R. N. Jones and his staff of the National Research Council, Canada, for determining infrared spectra and for preparing the curves. We are also grateful to Dr. R. L. Clarke of the Sterling-Winthrop Research Institute for carrying out the crystallographic examinations, and to Drs. R. K. Meyer and E. G. Shipley of the Department of Zoology, University of Wisconsin, for physiological tests.

Experimental[32,33]

Preliminary Experiments[14]

1-Keto-2-hydroxymethylene-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene.—This compound was prepared by Robinson and Walker,[11] but the yield has been improved somewhat by use of a modified procedure for preparing hydroxymethylene ketones.[34] From 9.40 g. of 1-keto-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (m.p. 103.5–106°),[8,35] 6.3 ml. of ethyl formate and sodium methoxide (from 1.86 g. of sodium) there was obtained 9.77 g. (93% yield) of crude cream-colored product, m.p. 134–135° (reported for crude material,[11] 133°) of satisfactory purity for the isoxazole formation. Approximately 180 ml. of benzene and a reaction time of 16 hours were used.

7-Methoxy-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-*d*]-isoxazole.—A mixture of 8.20 g. of the crude hydroxymethylene ketone (see above), 3.34 g. of hydroxylamine hydrochloride and 120 ml. of glacial acetic acid was refluxed for 10 minutes, then cooled and most of the solvent removed in a current of nitrogen on the steam-bath. After dilution with water the organic layer was taken up in ether, washed thoroughly with 5% potassium hydroxide solution, then with water, saturated salt solution and finally dried over anhydrous sodium sulfate. Evaporation of the ether gave 7.8 g. (96% yield) of crude isoxazole, m.p. 105–110°, which, although evidently a mixture of isomers, was suitable for conversion to the cyanoketone. Crystallization from ethanol gave light tan plates, m.p. 112.5–121°. Recrystallization raised the m.p. to 120.8–127.8°. No further effort was made to separate the isomers.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.26; H, 6.72; N, 5.49. Found: C, 75.61; H, 6.86; N, 5.60.

1-Keto-2-cyano-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene.—A solution of 8.60 g. of the crude isoxazole (see above) in 120 ml. of dry benzene was treated with a solution of 1.6 g. of sodium in 45 ml. of anhydrous methanol. After standing for 4 hours at room temperature, water and ether were added, the organic layer was separated and extracted thoroughly with 5% potassium hydroxide. Acidification of the combined alkaline solutions yielded 7.55 g. (88%) of crude, cream-colored cyanoketone, m.p. 143–145.5° (softening at 120°). This product, which was suitable for the methylation step (see below), apparently consisted of a mixture of stereoisomers. A single crystallization from ethanol gave colorless needles, m.p. 158.5–168.5°, and on recrystallization material, m.p. 177–180°, was obtained. A further recrystallization did not raise the m.p., and this specimen may therefore represent one of the pure racemates.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.26; H, 6.72; N, 5.49. Found: C, 75.48; H, 6.87; N, 5.70.

The reddish, semi-solid, alkali-insoluble fraction remaining in the organic layer probably contained some of the isomeric [1,2*c*]isoxazole.

1-Keto-2-cyano-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene.—A solution of 0.39 g. of sodium in 40 ml. of anhydrous methanol was added to a solution of 2.14 g. of crude cyanoketone (described above) in 140 ml. of dry benzene. Twenty milliliters of methyl iodide was then added with shaking and the mixture allowed to remain at room temperature for 30 minutes. An additional 10 ml. of methyl iodide was added and the solution was refluxed for 30 minutes on the steam-bath. After repeating this treatment with another 10-ml. portion of methyl iodide the solvents were largely removed in a current of nitrogen on the steam-bath, water was added, and the organic material extracted with ether. The ether solution was washed thor-

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[32] All melting points are corrected for stem exposure.

[33] The ultraviolet absorption spectra were determined in 95% ethanol solution on a Beckman quartz spectrophotometer.

[34] W. S. Johnson, J. M. Anderson and W. E. Shelberg, THIS JOURNAL, **66**, 218 (1944).

[35] A. L. Wilds and T. L. Johnson, *ibid.*, **70**, 1166 (1948).

oughly with 5% potassium hydroxide, then with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave 2.03 g. of semi-solid product. Acidification of the alkaline solution yielded 0.13 g. of acidic material, m.p. 120–130°. The crude methylated cyanoketone appeared to consist of a mixture of stereoisomers. A single recrystallization from ethanol gave 0.98 g. of a mixture, m.p. 117–126°, from which a pure isomer, m.p. 152.4–153.2°, was obtained as colorless needles by repeated recrystallization.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.80; H, 7.12; N, 5.20. Found: C, 76.14; H, 6.78; N, 5.54.

From the more soluble fraction 0.25 g. of crystals melting at 100–113°, and 0.13 g. melting at 102–119°, were isolated but further purification was not attempted.

A number of attempts to condense the methylated cyanoketone with dimethyl or diethyl succinate failed. Under mild conditions the methylated cyanoketone was largely recovered. The recovered product from such experiments starting with the pure 153°-isomer, however, melted at 117–121° after recrystallization and showed no m.p. depression on admixture with the crude low melting fractions of cyanoketone. This behavior suggests that the 153°-isomer was at least partially isomerized by the potassium *t*-butoxide, possibly at C_{11}. Analyses for ammonia,[15] never gave values over 19%, and in most experiments the value was lower. When more severe conditions were employed for the condensation, more acidic material was formed and this was presumed to be due to ring opening as in the equilenin series.[15]

1-Keto-2-hydroxymethylene-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.—This substance was prepared as described above for the octahydro compound. From 4.22 g. of 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (m.p. 74–76°),[8,11] 3.1 ml. of ethyl formate and sodium methoxide (from 0.87 g. of sodium) there was obtained 3.52 g. of crude, pale yellow hydroxymethylene ketone, m.p. 87–88° (reported for recrystallized material,[11] 90–91°), which gave a dark green color with alcoholic ferric chloride. The neutral fraction, amounting to 0.72 g. was retreated as above with 2 ml. of ethyl formate and sodium methoxide from 0.22 g. of sodium. An additional 0.5 g. of product, m.p. 85–87°, was thus obtained making the total yield 85%.

7-Methoxy-4,5,10,11-tetrahydrophenanthro[2,1-*d*]isoxazole.—This substance was prepared as described above for the hexahydro compound. From 2.89 g. of the crude hydroxymethylene ketone described in the preceding experiment and 1.18 g. of hydroxylamine hydrochloride in 50 ml. of acetic acid, there was obtained 2.45 g. (86% yield) of crude isoxazole, m.p. 99.5–102°. Repeated recrystallization from methanol gave light tan needles, m.p. 103–104.3°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.86; H, 5.98; N, 5.53. Found: C, 75.93; H, 5.90; N, 5.47.

1-Keto-2-cyano-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.—A solution of 2.15 g. of the crude isoxazole described in the preceding experiment in 50 ml. of dry benzene was treated with a solution of 2.0 g. of sodium in 45 ml. of anhydrous methanol. After standing for 24 hours the mixture was worked up as described above for the octahydro compound. The yield of crude light tan cyanoketone was 1.94 g. (90%), m.p. 147–151° (soft at 138°). Repeated recrystallization from methanol gave yellow crystals, m. p. 157.5–159.2°

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.86; H, 5.98; N, 5.53. Found: C, 75.64; H, 5.91; N, 5.38.

1-Keto-2-cyano-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene.—This material was prepared by the procedure described above for the octahydro compound. From 1.63 g. of the crude cyanoketone, described in the preceding experiment, in 70 ml. of benzene, a solution of 0.28 g. of sodium in 20 ml. of methanol, and a total of 65 ml. of methyl iodide (added in successive portions of 15, 20 and 30 ml.), there was obtained 1.61 g. (94% yield) of pale orange crystalline methylated product, m.p. 96–103° (soft at 90°). A single crystallization from ethanol raised the m.p. to 104–106°. Repeated recrystallization gave pale yellow needles, m.p. 108.4–109.2°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.37; H, 6.42; N, 5.24. Found: C, 76.57; H, 6.30; N, 5.30.

Attempts to condense this cyanoketone (m.p. 104–106°) with dimethyl and diethyl succinate failed, the results being similar to those described above for the octahydro compound.

1-Keto-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene

5-Hydroxy-5-phenylethynyl-1-decalone (VII) (R = H).—It was found desirable to carry out the formation of the acetylide and the addition to the dione under strictly anhydrous conditions and in an inert atmosphere. In the procedure described below we generally employed a three-necked flask with rubber-sealed wire stirrer, pressure-equalized dropping funnel and a condenser leading to a system[36] for evacuation and filling with prepurified nitrogen.[37] It was found convenient to incorporate a second dropping funnel (containing the acetylene) in series with the first (containing the *t*-butoxide) so that the acetylide could be formed by dropping the contents of the former into the latter.

Potassium phenylacetylide was prepared by adding 24.6 g. of phenylacetylene[38] ($n^{25}\text{D}$ 1.5459) to a solution of 9.30 g. of potassium in 190 ml. of dry[36] *t*-butyl alcohol. The resulting yellow solution was added slowly to a stirred solution of 40.0 g. of decalin-1,5-dione (mixture of *cis*- and *trans*-forms, m.p. 80–125°)[18] in 160 ml. of *t*-butyl alcohol, which was heated by a bath at 60–70°. The addition was completed in 40 minutes; then the mixture was stirred at room temperature for 3 hours. The clear orange solution was treated with 25 g. of ammonium chloride in 75 ml. of water, and most of the *t*-butyl alcohol was removed by distillation at reduced pressure. The pale yellow residue was taken up in ether, washed with water, saturated salt solution and dried over anhydrous sodium sulfate. The ether solution was concentrated, and petroleum ether (40–60°) was added to incipient cloudiness. On chilling, 16.10 g. of product crystallized, m.p. 116–185°. Trituration with ether left 2.10 g. of crude **1,5-dihydroxy-1,5-di-(phenylethynyl)-decalin (XV)** (R = H), m.p. 197–210°. A single recrystallization from benzene gave 1.63 g., m.p. 210–212°. A sample of such material purified by repeated recrystallization from ether melted at 210.8–212°.

Anal. Calcd. for $C_{26}H_{26}O_2$: C, 84.28; H, 7.07. Found: C, 84.16; H, 7.17.

The ether trituration was concentrated, and on addition of petroleum ether (40–60°), 12.30 g. of the α-isomer of VII (R = H) crystallized, m.p. 118–120°. A sample of such material purified by repeated recrystallization from the same solvent pair was obtained as colorless prisms, m.p. 120.4–121°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.68; H, 7.22.

The **semicarbazone** formed colorless crystals from dilute methanol, m.p. 204–205° dec.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12. Found: C, 69.87; H, 6.86.

Further fractional crystallization of the mother liquors afforded an additional 0.64 g. of the α-isomer, and 0.215 g. of the crude β-isomer of VII (R = H), m.p. 135–139°. Repeated recrystallization of such material from ether–petroleum ether (40–60°) gave colorless needles, m.p. 139.8–141°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.44; H, 7.26.

The **semicarbazone** formed colorless crystals from dilute methanol, m.p. 220–220.4° dec.

Anal. Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12. Found: C, 69.98, 70.07; H, 7.02, 7.35.

In an experiment like that described above in which 20 g. of pure *trans*-decalindione was employed, the first crop of product amounted to 13.9 g. of α-isomer, m.p. 116–117°; the second 3.7 g., m.p. 112–118°; and the third 5.7 g., m.p. 85–112°. Some of the β-isomer was isolated from the gummy residue (8.8 g.) by chromatography.

When the pure *cis*-decalindione was employed in the condensation, some of the dicondensation product was first isolated, and the main ether-soluble material was shown to consist largely of the α-isomer.

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[36] *Org. Syntheses*, **30**, 19 (1950) (see Fig. 1).

[37] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Massachusetts, 1941, p. 395.

[38] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 438.

5-Hydroxy-5-β-phenylethyl-1-decalone (VIII) (R = H) (a) α-Isomer.—A solution of 1.093 g. of the α-acetylenic carbinol, m.p. 116–118° (described above) in 30 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 0.22 g. of 5% palladium-on-carbon.[39] The reaction stopped abruptly after the calculated amount of hydrogen was absorbed (2 hours). The mixture was warmed, filtered, and the filtrate evaporated leaving 1.00 g. of material, m.p. 168.2–169.4°. Recrystallization from ethyl acetate gave colorless needles, m.p. 169–169.4°. Further recrystallization did not raise the m.p.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.17; H, 8.64.

The semicarbazone formed colorless crystals from dilute methanol, m.p. 223° dec.

Anal. Calcd. for $C_{19}H_{27}O_2N_3$: C, 69.27; H, 8.26. Found: C, 69.24; H, 8.06.

(b) **β-Isomer.**—A solution of 0.058 g. of the β-acetylenic-carbinol, m.p. 135–139°, in 10 ml. of ethyl acetate was similarly hydrogenated over 0.013 g. of catalyst as described above. The calculated amount of hydrogen was absorbed in 30 minutes, and the crude colorless product amounted to 0.060 g., m.p. 130–133°. Three recrystallizations from ethyl acetate gave colorless prisms, m.p. 132.5–133.5°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.25; H, 9.06.

(c) **Preparation of α- and β-Isomers without Isolation of Acetylenic Carbinols.**—The condensation of phenylacetylene with decalindione was carried out exactly as described above. The total crude, pale-yellow, oily product (72 g.) obtained after the ether extraction was dissolved in 150 ml. of ethyl acetate and hydrogenated over 2.70 g. of 5% palladium-on-carbon[39] at 2–3 atmospheres. The calculated amount of hydrogen was absorbed in 1.5 hours. The product was isolated as described above, and on fractional crystallization from ethyl acetate yielded a total of 42.0 g. (65% yield) of the α-isomer, m.p. 165–169°; 6.52 g. (10% yield) of the β-isomer, m.p. 129.5–132°; and 0.860 g. (1% yield) of the reduced dicondensation product XVI (R = H) (described below), m.p. 227–230°.

1,5-Dihydroxy-1,5-di-(β-phenylethyl)-decalin (XVI) (R = H).—A solution of 0.146 g. of the dicondensation product XV (R = H), m.p. 209–211°, in 10 ml. of ethyl acetate was hydrogenated over 0.100 g. of 5% palladium-on-carbon.[39] The calculated volume of hydrogen was absorbed in 1 hour. Concentration of the filtered solution and cooling gave 0.095 g. of material, m.p. 228–230°.

Two recrystallizations from ethyl acetate gave flat pointed rods, m.p. 230–232°.

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.30; H, 9.11.

5-β-Phenylethyl-$\Delta^{9,10}$-octalone (IX) (R = H) (a) From the α-Carbinol VIII (R = H).—A solution of 11.05 g. of the reduced carbinol, m.p. 165–167°, in 60 ml. of 88% formic acid was boiled under reflux for 6 hours. The cooled solution was diluted with water, extracted with ether, and the ether solution was washed with water, saturated sodium bicarbonate solution (until free from acid), again with water, and dried over calcium chloride. The ether was evaporated, and the residue submitted to distillation at 0.75 mm. The main fraction came over at about 185° yielding 7.00 g. of a viscous oil.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.53; H, 8.74.

The semicarbazone formed colorless crystals from methanol, m.p. 210–211.5° dec. (with shrinking at 208°).

Anal. Calcd. for $C_{19}H_{25}ON_3$: C, 73.28; H, 8.09. Found: C, 73.31; H, 7.72.

(b) **From the β-Carbinol VIII (R = H).**—A 0.257-g. sample of the reduced carbinol (m.p. 129.5–132°) was treated with 5 ml. of 88% formic acid as described above. Evaporative distillation gave 0.221 g. of pale yellow oil, λ_{max} 253 mμ (log *E* 3.92). The crude semicarbazone was prepared in 96% yield, m.p. 211–212° dec. (introduced in bath at 205°), λ_{max} 268.5 mμ (log *E* 4.14). The m.p. was not depressed on admixture with the semicarbazone of the product obtained by dehydration of the α-isomer (see above).

1-Keto-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (X) (R = H) (a) By Cyclization of the α-Carbinol VIII (R = H).—A solution of 3.00 g. of the α-carbinol, m.p. 167–169°, in 50 ml. of thiophene-free benzene was placed in a 100-ml. flask fitted with a rubber-sealed wire stirrer, a condenser set for distillation, and a gas inlet tube immersed in the solution. The solution was then saturated with anhydrous hydrogen chloride at 6°. The flow of gas was interrupted, and the benzene was distilled off as long as water co-distilled. The hydrogen chloride treatment and distillation was repeated once, and the benzene that distilled was replaced by dry solvent. The gas inlet tube was replaced by a wide-bore addition tube connected by a section of rubber tubing to a 25-ml. erlenmeyer flask containing 3.47 g. of anhydrous aluminum chloride (Baker and Adamson, reagent grade, sublimed). The condenser was placed in reflux position, and the aluminum chloride was added slowly with stirring and cooling to 6°. After the addition was complete the solution was allowed to come slowly to room temperature. The deep red solution was heated at 45° (bath temperature) with stirring for 12 hours, then without stirring for 4 days. The reddish-black mixture was then poured into ice and 25 ml. of concentrated hydrochloric acid and extracted with ether. The organic solution was washed with water, saturated sodium bicarbonate solution, saturated salt solution and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent was crystallized from methanol. The first crop amounted to 1.08 g., m.p. 127–137°, and the second 0.46 g., m.p. 127–135°. Recrystallization of the combined crops from methanol gave a total of 1.29 g. (46% yield) of the α-isomer of X (R = H), m.p. 138–140°. Two more recrystallizations gave colorless plates, m.p. 139–140.5°.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.18; H, 8.88.

In a cyclization like that described above except that the treatment with hydrogen chloride and distillation was carried out repeatedly until no more water was being removed, a small yield (3%) of the β-isomer of X (R = H), m.p. 128–130°, was obtained in addition to 35% yield of the α-form. This β-isomer showed no m.p. depression on admixture with the product prepared by cyclization of the unsaturated ketone IX (R = H) (see below).

Another cyclization was carried out as described in detail above except that the hydrogen chloride treatment was omitted altogether. The orange-red solution resulting after addition of the aluminum chloride (3.50 g.) was stirred at room temperature for 7 hours, then was heated at 47° for 4.5 days. The red solution was worked up as described above. The yield of α-isomer, m.p. 136–139°, was 1.097 g. (39%). The mother liquors, on seeding with a sample of the γ-isomer of X (R = H) described below, yielded 0.153 g. (5% yield) of this isomer, m.p. 121–123.5°, undepressed on admixture with the analytical sample (see below).

(b) **By Cyclization of the β-Carbinol VIII (R = H).**—A solution of 1.995 g. of the β-carbinol, m.p. 129.5–132°, in 25 ml. of benzene was stirred with 1 g. of flake anhydrous calcium chloride while anhydrous hydrogen chloride was passed into the mixture for 1 hour at room temperature. After standing for 6 hours, the solution was decanted from the calcium chloride, and treated with 2.51 g. of aluminum chloride by the technique described in part (a) above. The mixture was stirred at room temperature overnight, then heated at 45° for 3 days. The resulting clear red solution was hydrolyzed and worked up as described above (part a). Crystallization of the crude yellow oil from methanol gave 0.817 g., m.p. 127–134°, and 0.207 g., m.p. 90–112°; recrystallization of the first crop gave 0.710 g. (38% yield) of the α-isomer. From the second crop there was obtained by two recrystallizations from methanol 0.117 g. (6.3% yield) of the γ-isomer of X (R = H), m.p. 122–123.5°. Two more recrystallizations gave colorless rods, m.p. 123–124°.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.16; H, 8.80.

(c) **By Cyclization of the Unsaturated Ketone IX (R = H).**—A solution of 6.33 g. of the unsaturated ketone IX (R = H) in 50 ml. of dry benzene was saturated with anhydrous hydrogen chloride in the cold. By the technique described above (part a) 7 g. of anhydrous aluminum chloride was added with stirring at 3° over a period of 30 minutes. The mixture was allowed to stand at 23° for 2 hours, then was stirred for 15 hours. During this period an oily red complex

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[39] R. Mozingo, *Org. Syntheses*, **26**, 77 (1946), Catalyst B.

separated. The mixture was heated gradually until the temperature was 40°. After 12 hours at this temperature the almost black mixture was hydrolyzed with ice and hydrochloric acid as described in part (a) above. The crude product was obtained as a glass which was submitted to evaporative distillation at 210–230° (0.6–0.8 mm.); yield 5.43 g. Trituration with ether–petroleum ether (40–60°) yielded a solid product, m.p. 125–131°, from which a small fraction, m.p. 140–146°, was separated by repeated recrystallization from ether. The main portion of the product in the mother liquors was obtained after two recrystallizations from ether as colorless crystals, m.p. 128–130.5°. This substance was the β-isomer of X (R = H).

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.60; H, 8.50.

The semicarbazone formed colorless crystals from alcohol, m.p. 255.8–257.4° dec. (with previous shrinking).

Anal. Calcd. for $C_{19}H_{25}ON_3$: C, 73.28; H, 8.09. Found: C, 73.28; H, 8.01

Isomerization Experiments.—The isomerization of the β- to the α-isomer of X (R = H) was carried out as follows: A 0.017-g. sample of the former, m.p. 128–130°, was dissolved in a solution of 0.105 g. of potassium in 2 ml. of *t*-butyl alcohol. After standing at room temperature (nitrogen atmosphere) for 2.5 hours, excess ammonium chloride solution was added, the *t*-butyl alcohol was removed by distillation at reduced pressure, and the organic residue taken up in ether. The ether layer was dried over anhydrous sodium sulfate and evaporated. The residue on crystallization from methanol yielded 0.005 g. of the α-isomer, m.p. 136.5–139°, undepressed on admixture with authentic material. The solid residue from the mother liquor melted at 105–116° and presumably consisted of a mixture of the α- and (unisomerized) β-isomer.

A similar experiment with the α-isomer of X (R = H) gave mainly starting material.

Dehydrogenation Experiments (a) Of 5-β-Phenylethyl-$\Delta^{9,10}$-octalone (IX) (R = H).—A mixture of 0.2276 g. of the unsaturated ketone and 0.112 g. of 30% palladium-on-carbon[40] was heated at 280–300° in the Heymann type of apparatus.[41] Evolution of hydrogen was complete within 1 hour and 90% of the calculated volume of gas was collected. The crystalline material which condensed in the cooler parts of the apparatus was dissolved in ether and combined with the catalyst. The mixture was filtered, the ether evaporated, and the residue evaporatively distilled at 200–205° (0.4 mm.). The crystalline distillate amounted to 0.14 g. (63% yield), m.p. 100–106°. Two recrystallizations from petroleum ether (40–60°) gave colorless needles of 5-β-phenylethyl-1-naphthol (XIX) m.p. 105.6–106.2°.

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 86.46; H, 6.53.

(b) Of the α-Isomer of X (R = H).—A mixture of 0.047 g. of the α-ketone, m.p. 138–140°, and 0.026 g. of catalyst was dehydrogenated at 280–295° as described above (part a). After 30 minutes 85% of the calculated volume of hydrogen was evolved. The crude product was dissolved in benzene, filtered, and on concentration and cooling 0.024 g. of 1-chrysenol crystallized, m.p. 281–282° (vac.) (reported[42] 281–283°). The acetate was prepared with acetic anhydride and pyridine. After recrystallization from benzene it melted at 235–237° (reported[42] 235–236°). The m.p. of this derivative was not depressed on admixture with the analytical specimen obtained by dehydrogenation of the β-isomer (see below).

(c) Of the β-Isomer of X (R = H).—A similar experiment was carried out with 0.0444 g. of the β-ketone, m.p. 128–130.5°, and 0.0305 g. of catalyst. Approximately the calculated volume of hydrogen was evolved in 23 minutes. The product which crystallized amounted to 0.0178 g., m.p. 281.5–283° (vac.). The acetate prepared as described above was obtained as colorless needles, m.p. 240.6–241.2°.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.89; H, 4.93. Found: C, 83.55; H, 5.18.

(d) Of the γ-Isomer of X (R = H).—A similar experiment with 0.040 g. of the γ-ketone, m.p. 122.5–123°, and 0.030 g. of catalyst gave 0.019 g. of 1-chrysenol, m.p. 281–282.5° (vac.). The acetate melted at 234–236° and showed no m.p. depression on admixture with the sample prepared as described above (part b).

(e) Of Oily Residues.—A 0.606-g. sample of the product remaining after all crystalline X (R = H) was separated was dehydrogenated as described above with 0.237 g. of catalyst. After 40 minutes about 46% of the calculated amount of hydrogen was evolved. The total 1-chrysenol obtained amounted to 0.116 g. (20% yield), m.p. 278–281.5°.

Cyclization of 1,5-Dihydroxy-1,5-di-(β-phenylethyl)-decalin (XVI) (R = H).—A suspension of 0.455 g. of XVI (R = H), m.p. 227–230°, in 15 ml. of benzene was stirred with 0.5 g. of anhydrous calcium chloride while the mixture was saturated with dry hydrogen chloride. After standing overnight the lumps of calcium chloride were removed, and the suspension was transferred with the aid of 15 ml. of benzene to an apparatus for conducting the cyclization (see above). Anhydrous aluminum chloride (0.40 g.) was added with stirring at 6°, and the suspension was again saturated with hydrogen chloride. A red complex separated. After heating for 3 days at 45°, the mixture was hydrolyzed and worked up as described above. The crude product was evaporatively distilled at 250° (0.03 mm.) giving 0.371 g. of semi-solid distillate. Crystallization from benzene gave 0.053 g., m.p. 245–247° (soft at 240°), and 0.016 g., m.p. 200–230°. Three recrystallizations of the first crop gave colorless plates, m.p. 254–256°, undoubtedly **4a,5,6,6a,7,8,12b,13,14,14a,14b,15,16-tetradecahydrobenzo[*c*]picene (XX)**.

Anal. Calcd. for $C_{26}H_{30}$: C, 91.17; H, 8.83. Found: C, 90.91; H, 8.87.

1-Keto-2-benzylidene-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XI) (R = H, Ar = C_6H_5).—To a refluxing solution of 2.00 g. of α-isomer of X (R = H), m.p. 139–140°, in 100 ml. of methanol were added 0.95 g. of benzaldehyde and 10 ml. of 33% aqueous sodium hydroxide. A seed crystal of the benzylidene derivative, obtained from previous runs, was added to the cloudy suspension which was heated at 40–45° (bath temperature) for 2 days. The precipitate was filtered, washed with methanol, then with water and dried to yield 1.790 g. of pale yellow crystals, m.p. 148–153°. Water was added to the filtrate to the point of incipient cloudiness, and after 1 day at room temperature an additional 0.306 g. of product, m.p. 145–151° separated. The combined crops were crystallized from ethanol giving 1.929 g. (72% yield) of the α-benzylidene derivative, m.p. 156–159.5°. Repeated recrystallization from ethanol gave colorless flat prisms, m.p. 159.3–160°, λ_{max} 285 mμ (log *E* 4.25).

Anal. Calcd. for $C_{25}H_{26}O$: C, 87.67; H, 7.65. Found: C, 87.85; H, 7.64.

1-Keto-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene

Preliminary Experiments with the Grignard Reaction.—The Grignard reagent was prepared from 50.0 g. of β-*m*-methoxyphenylethyl bromide[43] and 6 g. of magnesium turnings in 130 ml. of ether. Analysis by the method of Gilman, *et al.*,[44] indicated that 80% of the bromide was converted to Grignard reagent.

The solution was transferred, under nitrogen, to a graduated addition funnel of the Hershberg type,[45] diluted with 80 ml. of dry benzene, and added dropwise over a period of 4 hours to a stirred solution of 26.0 g. of decalin-1,5-dione (mixture of *cis*- and *trans*-isomers, m.p. 125–150°) in 300 ml. of dry benzene. After the addition was complete the mixture containing a bright yellow suspension (which had formed after the first 30 minutes) was stirred for 30 minutes at room temperature then for 2 hours at 60°, cooled, and treated with 200 ml. of ice-cold 1:1 hydrochloric acid. The organic layer was washed with 10% sodium hydroxide solution, then concentrated, and the oily residue heated at 175° for 1 hour with 75 g. of powdered, fused potassium bisulfate. The mixture was cooled, diluted with water and extracted

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[40] R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

[41] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Massachusetts, 1941, p. 461.

[42] J. W. Cook and R. Schoental, *J. Chem. Soc.*, 288 (1945).

[43] Prepared by W. E. Shelberg according to the procedure of W. E. Bachmann and D. G. Thomas, THIS JOURNAL, **64**, 94 (1942).

[44] H. Gilman, P. D. Wilkinson, W. P. Fishel and C. H. Meyers, THIS JOURNAL, **45**, 150 (1923).

[45] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Massachusetts, 1941, p. 312.

with benzene. Evaporation of the benzene left an orange oil which was dissolved in a small amount of ether. On standing and cooling, 3.70 g. of decalin-1,5-dione crystallized. The oily residue obtained on evaporation of the mother liquor was distilled through a modified Widmer column and the following fractions were taken: (1) b.p. 50–60° (0.1 mm.), 7.70 g.; (2) b.p. 105–120° (0.4 mm.), 2.00 g.; (3) 165–190° (1.0 mm.), 2.25 g.; (4) 205–210° (1.0 mm.), 14.30 g.; (5) 210–235° (1.3 mm.), 6.10 g.

Redistillation of fraction (1) gave a colorless liquid, b.p. 92–94° (21 mm.), 194° (740 mm.) probably *m*-ethylanisole. Fraction 4 was redistilled and the main portion was obtained as a pale yellow viscous oil, b.p. 180–190° (0.3 mm.).

Anal. Calcd. for $C_{19}H_{24}O_2$ (addition product): C, 80.24; H, 8.51; methoxyl, 10.9. Calcd. for $C_{18}H_{22}O_2$ (coupling product): C, 79.96; H, 8.20; methoxyl, 23.0. Found: C, 80.52; H, 8.20; methoxyl, 16.0, 15.9.

The methoxyl determination indicated that this fraction was a mixture of the addition and coupling products, which was further substantiated by a hydrogenation over 5% palladium-on-carbon[39] in which only 53% of the amount of gas calculated to saturate one ethylenic linkage was absorbed. Semicarbazone formation gave a 43% yield of crude product, m.p. 180–250° dec., which could not be readily purified. A small amount of material, m.p. 191–196° dec., was obtained by recrystallization from ethanol.

Fraction (5) appeared to contain a higher proportion of the addition product. The methoxyl determination was 10.2%, and semicarbazone formation gave a 37% yield of material which on recrystallization melted at 189–195° and showed no m.p. depression on admixture with the product obtained from fraction 4. Comparable material was obtained by semicarbazone formation of material from fraction 5, which was first absorbed on alumina and eluted with benzene. The m.p. continued to rise on successive recrystallizations. Finally colorless plates, m.p. 198.5–200° dec., were obtained.

Anal. Calcd. for $C_{20}H_{27}O_2N_3$: C, 70.35; H, 7.97. Found: C, 70.28; H, 7.73.

A 0.90-g. sample of the semicarbazone (see above), m.p. 195–196.5° dec., was hydrolyzed by refluxing for 1 hour with 5.0 g. of oxalic acid in 50 ml. of water. The ether-soluble material amounted to 0.75 g. of a pale yellow oil which was evaporatively distilled at 180° (0.4 mm.), $\lambda_{\max}$ 254 mμ (log *E* 3.58).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.09; H, 8.27.

A sample of the above unsaturated ketone was reconverted to the semicarbazone in 96% yield, m.p. 189–194° dec.

***m*-Methoxyphenylacetylene.**—*m*-Methoxyacetophenone, was prepared from 102 g. of *m*-hydroxyacetophenone, m.p. 85–89° (Hilton–Davis Chemical Co.), by methylation at 60–65° with a total of 369 ml. of 15% potassium hydroxide and 142 g. of dimethyl sulfate added alternately in several portions with stirring. At the end of the addition, 76 g. of potassium hydroxide in 200 ml. of water was added and the mixture heated for one hour on the steam-bath with stirring. The product was worked up in the usual manner; yield 94 g. (84%), b.p. 130–132° (16 mm.).

To a solution of 175.1 g. of *m*-methoxyacetophenone in 50 ml. of dry benzene was added 250 g. of phosphorus pentachloride in portions with swirling and cooling in an ice–salt-bath. The flask was protected with a calcium chloride drying tube and allowed to stand overnight at room temperature. The dark green solution was poured slowly with stirring into a mixture of about 1 l. of ice and water. The oil was extracted with ether, washed twice with ice-water, then with saturated salt solution and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue treated with a solution of 225 g. of (85%) potassium hydroxide pellets in 280 ml. of 95% alcohol. After refluxing for 10 hours the solution was diluted with water and extracted with ether. The ether solution was washed thoroughly with water, then with saturated salt solution, dried over anhydrous sodium sulfate, and distilled through an 8-inch Vigreux column. The fraction boiling at 94–100° (15 mm.), amounting to 57 g., was collected. The residue was retreated with 120 g. of (85%) potassium hydroxide in 150 ml. of 95% alcohol as described above. A second fraction, b.p. 94–100° (15 mm.) amounting to 21 g. was thus obtained. The two fractions were combined, allowed to stand over solid potassium hydroxide for 1 day, then distilled from a few pellets of potassium hydroxide through an 8-inch Vigreux column. The colorless fraction boiling at 94–98° (15 mm.) amounted to 74.2 g. (48% yield). This material was satisfactory for synthetic purposes. A sample was fractionated through a Fenske column packed with glass helices and about 90% of the material distilled with constant $n^{25}\mathrm{D}$ 1.5560. Material boiling at 85° (13 mm.), $n^{25}\mathrm{D}$ 1.5559, was used for analysis.

Anal. Calcd. for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.71; H, 6.30.

5-Hydroxy-5-*m*-methoxyphenylethynyl-1-decalone (VII) (R = OCH_3).—Potassium *m*-methoxyphenylacetylide was prepared from 0.9 g. of potassium, a total of 45 ml. of *t*-butyl alcohol and 3.4 g. of *m*-methoxyphenylacetylene. This reagent was added to a boiling solution of 4.15 g. of *trans*-decalin-1,5-dione, m.p. 163–165°, in 50 ml. of *t*-butyl alcohol over a period of 1.5 hours, and then the orange solution was allowed to stand at room temperature for 12 hours. These steps, and the subsequent hydrolysis with ammonium chloride, were carried out essentially as described above in detail for the parent series. The isolation of crystalline products was complicated by the occurrence of one substance in two polymorphic modifications in varying amounts. In a typical experiment the crude oily product (6.9 g.) was triturated with ether–petroleum ether (40–60°) and 3.8 g. of solid, m.p. 68–76°, was obtained. The yield of solid material at this stage varied from 50–73% in different runs, and the m.p.'s also varied considerably. The above product after three recrystallizations from ether–petroleum ether (40–60°) yielded the α-isomer of **VII** (R = OCH_3), as colorless plates, m.p. 83.8–84.8°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.43; H, 7.37.

The semicarbazone formed colorless crystals from dilute methanol, m.p. 204.2–205.6° dec.

Anal. Calcd. for $C_{20}H_{25}O_3N_3$: C, 67.58; H, 7.09. Found: C, 67.71; H, 7.10.

From the mother liquors of the α-isomer, a total of 0.2 g. of another product was isolated, m.p. 107–111°. Two recrystallizations from ether–petroleum ether (40–60°) gave the β-isomer of **VII** (R = OCH_3) as colorless prisms, m.p. 116–116.6°.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.49; H, 7.38.

The semicarbazone was obtained as colorless crystals from dilute methanol, m.p. 209–210° dec. Admixture with the semicarbazone of the α-isomer melted at 192–195°.

Anal. Calcd. for $C_{20}H_{25}O_3N_3$: C, 67.58; H, 7.09. Found: C, 67.57; H, 7.13.

The residues from the isolation of the above two isomers gave on trituration with a little cold ether, a small amount of colorless insoluble **1,5-dihydroxy-1,5-di-(*m*-methoxyphenylethynyl)-decalin (XV)** (R = OCH_3), m.p. 182–184°. Recrystallization from benzene–ether gave colorless crystals, m.p. 188.4–189.4°.

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.11; H, 6.98.

The ether-soluble material that remained (about 2 g.) appeared to be essentially one substance, m.p. 92–100°. After three recrystallizations from ether–petroleum ether (40–60°) it was obtained as a colorless, crystalline powder, m.p. 99.4–100.2.

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.55; H, 7.44.

This product proved to be a higher melting (polymorphic) modification of the α-isomer. On seeding a melt of the latter with the 100°-substance, it completely solidified and remelted at 99–100°. Both forms gave identical semicarbazones and identical reduced carbinols on hydrogenation (see below), as ascertained by mixed m.p. determinations.

A similar condensation carried out with *cis*-decalin-1,5-dione (m.p. 79–81°) gave largely the 99–100° form of the α-isomer. A small amount of the high-melting dicondensation product was also isolated.

A similar condensation was carried out with 16.60 g. of the mixture of *cis*- and *trans*-decalin-1,5-dione, m.p. 80–125°, and potassium *m*-methoxyphenylacetylide from 13.21 g. of the acetylene and 3.92 g. of potassium in *t*-butyl alcohol.

The addition step was carried out at 70° (bath temperature) over a period of 1.5 hours. The mixture was then stirred at room temperature for 4.5 hours, and hydrolyzed with 15 g. of ammonium chloride in water and worked up as described above. Trituration of the crude semi-solid product with a 1:1 mixture of ether–petroleum ether (40–60°) gave 20.60 g. of a mixture of carbinols, m.p. 67–123°. Trituration of this product with ether left 0.911 g. of the dicondensation product, m.p. 167–175° (187–189° after recrystallization from benzene). Fractional crystallization of the ether-soluble portion from ether–petroleum ether (40–60°) gave 7.10 g. of the α-isomer, m.p. 96–99°, and 0.265 g. of the β-isomer, m.p. 115–116°. The remaining mixture of isomers was not further separated.

5-Hydroxy-5-β-*m*-methoxyphenylethyl-1-decalone (VIII) (R = OCH_3) (a) **α-Isomer.**—A solution of 0.288 g. of the α-acetylenic carbinol, m.p. 83.8–84.8°, in 20 ml. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 0.103 g. of 5% palladium-on-carbon.[39] The reaction stopped after the absorption of 98% of the calculated volume of hydrogen (19 minutes). Ether was added, the catalyst removed by filtration, and the filtrate evaporated. Trituration of the gummy residue with ether–petroleum ether (40–60°) gave 0.27 g. (92% yield) of colorless crystals, m.p. 76.8–77.6°. Recrystallization from ether–petroleum ether (40–60°) did not raise the m.p.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.55; H, 8.71.

The semicarbazone was obtained as colorless crystals from dilute methanol, m.p. 208.4–209.2° dec. (with shrinking at 206°).

Anal. Calcd. for $C_{20}H_{29}O_3N_3$: C, 66.82; H, 8.13. Found: C, 67.01; H, 8.08.

(b) **β-Isomer.**—A solution of 0.250 g. of the β-acetylenic carbinol, m.p. 115–116°, in 20 ml. of ethyl acetate was similarly hydrogenated over 0.102 g. of catalyst. Reaction ceased in 30 minutes after 98.5% of the calculated amount of hydrogen was absorbed. The product, isolated as above, amounted to 0.232 g. (91% yield), m.p. 87–89°. A sample recrystallized from ether–petroleum ether (40–60°) melted at 89.4–91°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.10; H, 8.63.

The semicarbazone was obtained as colorless crystals from dilute methanol, m.p. 188.4–190.4° dec. The high value for % carbon may be due to partial dehydration during drying for analysis.

Anal. Calcd. for $C_{20}H_{29}O_3N_3$: C, 66.82; H, 8.13. Found: C, 67.58; H, 8.41.

1,5-Dihydroxy-1,5-di-(β-*m*-methoxyphenylethyl)-decalin (XVI) (R = OCH_3) was prepared by hydrogenation of XV (R = OCH_3) as described above for the parent series. After repeated recrystallization from ethyl acetate it was obtained as colorless plates, m.p. 197.8–198.1°. (Experiment performed by H. C. Dehm.)

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 76.66; H, 8.73. Found: C, 76.64; H, 8.84.

5-β-*m*-Methoxyphenylethyl-$\Delta^{9,10}$-octalone (IX) (R = OCH_3) (a) **From the α-Carbinol VIII** (R = OCH_3).—A solution of 0.176 g. of the reduced carbinol in 5 ml. of 88% formic acid was boiled under reflux for 3.5 hours. The product was isolated as described above for the α-isomer in the parent series (R = H). Evaporative distillation at 200–215° (0.4 mm.) gave a colorless oil.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.30; H, 8.32.

The semicarbazone was obtained as colorless crystals from dilute methanol, m.p. 190.8–193° dec.

Anal. Calcd. for $C_{20}H_{27}O_2N_3$: C, 70.35; H, 7.97. Found: C, 70.45; H, 7.98.

(b) **Without Isolation of Intermediary Carbinols.**—The crude mixture of acetylenic carbinols obtained as described above from 95.0 g. of mixture of *cis*- and *trans*-decalindione and potassium *m*-methoxphenylacetylide (from 74.2 g. of the acetylene and 22.1 g. of potassium in *t*-butyl alcohol) was dissolved in about 450 ml. of ethyl acetate and refluxed for 1 hour with about 9 g. of Raney nickel. The catalyst was removed by filtration, and the solution was hydrogenated in a low pressure shaker type of apparatus over 5% palladium-on-carbon.[39] The solution was hydrogenated in three portions, 3.5 g. of catalyst being used for each. The products were combined, filtered to remove catalyst, and the solvent was removed by distillation. The thick oily residue was treated with 1050 ml. of 88% formic acid. After refluxing for 19 hours the solution was diluted with ice-water and extracted with ether. The ether solution was washed twice with water, then thoroughly with saturated sodium bicarbonate solution, followed by saturated salt solution, and dried over anhydrous sodium sulfate. Distillation of the residue obtained on removal of the ether through a 5-inch Vigreux column gave as the major product 104.79 g. (65% yield) of material, b.p. 195–200° (0.1 mm.), $n^{25}D$ 1.5660–1.5665. A sample from a center cut, $n^{25}D$ 1.5663, showed λ_{max} 227.5 mμ (log *E* 4.04), 249 (4.18), 279 (3.44). The semicarbazone, m.p. 190–192° dec., was obtained in 96% yield, λ_{max} 269 mμ (log *E* 4.52).

In another experiment starting with 34.8 g. of decalindione, 42 g. (70% yield) of unsaturated ketone, b.p. 202.5–206° (0.2 mm.) was obtained.

1-Keto-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (X) (R = OCH_3) (a) **By Cyclization of the Unsaturated Ketone IX** (R = OCH_3).—A solution of 20.2 g. of the unsaturated ketone in 200 ml. of dry benzene was saturated with hydrogen chloride and treated with 28 g. of anhydrous aluminum chloride essentially as described above for the preparation of X (R = H). After stirring for 20 hours at 28°, and 72 hours at 40–45°, the dark complex was decomposed with ice and hydrochloric acid and extracted with ether. The organic layer was washed with 1:1 hydrochloric acid, three times with water, three times with dilute sodium hydroxide solution,[46] and finally with water. The residue left on evaporation of the ether was evaporatively distilled at 220–240° (0.2–0.3 mm.). The yellow glassy distillate was dissolved in boiling alcohol, and on cooling 3.85 g. of crystalline material, m.p. 140–156°, separated. Three recrystallizations from alcohol gave 0.6 g. of the **α-isomer** of X (R = OCH_3), m.p. 164–168°. Repeated recrystallization from alcohol gave colorless needles, m.p. 168.4–170°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.60; H, 8.37.

The semicarbazone was obtained as colorless crystals from ethanol, m.p. 237–237.5° dec.

Anal. Calcd. for $C_{20}H_{27}O_2N_3$: C, 70.35; H, 7.97. Found: C, 69.85; H, 7.98.

The 2,4-dinitrophenylhydrazone was obtained from ethyl acetate as yellow needles, m.p. 210.4–211° dec.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.69; H, 6.16.

From the mother liquors of the α-isomer a second product, m.p. about 128–133°, was isolated, which after three recrystallizations from ethanol gave colorless needles of the β-isomer of X (R = OCH_3), m.p. 153.4–154.8° (depressed to 134–150° on admixture with the α-isomer).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.11; H, 8.13.

The semicarbazone was extremely insoluble and could not be recrystallized readily. After purification by trituration with boiling alcohol it melted at 267–269° dec.

Anal. Calcd. for $C_{20}H_{27}O_2N_3$: C, 70.35; H, 7.97. Found: C, 70.35; H, 8.02.

After the β-isomer was separated as above, a further quantity of the α-isomer was obtained by concentration and seeding the mother liquors. The filtrate yielded a third product (the "γ-isomer") which after recrystallization from ethanol melted at 164–166.2°. The m.p. was not depressed on admixture with the β, and was depressed to 137–144° on admix-

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(46) Subsequent experiments indicated that additional washing with Claisen alkali (35 g. of potassium hydroxide in 25 g. of water diluted to 100 ml. with methanol) removed some weakly acidic (phenolic) material which facilitated purification. Acidification of the Claisen alkali extracts yielded a crude oily product which was sparingly soluble in 5% potassium hydroxide. From this oil there was isolated by crystallization from alcohol, sublimation at 218° (0.1 mm.) and recrystallization from acetone, a small yield of colorless plates of the β-phenol, X (R = OH), m.p. 271.2–272.6° (dec.) undepressed on admixture with the authentic specimen described below. The infrared spectra of the two specimens were identical.

ture with the α-isomer. After sublimation at 150° (0.05 mm.) and repeated recrystallization from alcohol, the γ-isomer was obtained as small crystals, m.p. 167.8–169.8°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.18; H, 8.13.

By repeated fractional crystallization of the residues a total of 90% of the 3.85 g. of crude solid product was separated into the α-, β- and γ-forms in a ratio of approximately 2:1:1. Upon long standing the original mother liquor, from which the crude solid was separated, yielded a further 0.60 g. of mixture which could also be separated into the same three isomers.

In another experiment 104.5 g. of the unsaturated ketone in 100 ml. of benzene was added to a stirred suspension of 140 g. of aluminum chloride in 1 l. of benzene at 6°. The mixture was saturated with hydrogen chloride, stirred at room temperature for 8 hours, then at 40° for 3 days. The crude product obtained as described above was distilled through a 2-inch Vigreux column yielding: 4.36 g., b.p. 150–195° (0.2 mm.); 52.0 g., b.p. 215–225° (0.1–0.2 mm.) and 23.5 g., b.p. 225–250° (0.1–0.2 mm.). On standing fraction (1) deposited 0.262 g. of the α-isomer, m.p. 164–167°. On trituration with ethanol fraction (2) yielded 23.30 g. of solid, m.p. 134–167° and fraction (3) afforded 0.810 g., m.p. 160–167°. The total solid amounted to 25.40 g. (24% yield).

Repeated fractional crystallizations of these fractions yielded a total of 15.28 g. (15%) of the α-isomer, m.p. 169–170°, 1.62 g. (1.5%) of the β-isomer, m.p. 150–154°, and 2.06 g. (2%) of the γ-form, m.p. 162–166°. On exhaustive recrystallization of the last product, 0.011 g. of material m.p. 190–196° was separated as colorless plates. The low hydrogen value on analysis suggests the presence of dehydrogenated material.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.50; H, 7.93.

An additional 1.05 g. of the β-isomer, m.p. 152–154°, was isolated *via* the sparingly soluble semicarbazone prepared from the oily residues of fraction (2), making the total amount of this isomer 3.17 g. (3% yield).

(b) **By Cyclization of the α-Carbinol VIII (R = OCH_3).**—A 0.484-g. sample of the α-carbinol, m.p. 75–77°, in 15 ml. of benzene was treated with 0.650 g. of aluminum chloride, and the mixture stirred at 40–45° for 44 hours (*cf.* the detailed procedure described for VIII (R = H) above). After hydrolysis, the crude product was isolated as described above and crystallized from benzene–ether. The yield of solid, m.p. 140–164°, was 0.167 g. (37%). Recrystallization from ethanol gave a total of 0.129 g. (28.5%) of the α-isomer, m.p. 167.5–169.5°.

(c) **By Cyclization of the β-Carbinol VIII (R = OCH_3).**—By the same procedure as outlined in the preceding experiment, 0.160 g. of the β-carbinol, m.p. 87–89°, in 5 ml. of benzene was treated with 0.215 g. of aluminum chloride at 40–45° for 1.75 days. The crude solid amounted to 0.092 g. (61% yield), m.p. 144–161°. Recrystallization gave a total of 0.061 g. (40% yield) of α-isomer, m.p. 168–169.5°.

(d) **By Cyclization of the Crude Mixture of Carbinols. Isolation of the δ-Isomer.**—The crude mixture of reduced carbinols was prepared from 23.41 g. of decalindione (mixture of *cis* and *trans*, m.p. 80–125°), 18.60 g. of *m*-methoxyphenylacetylene and 5.51 g. of potassium in *t*-butyl alcohol just as described above for the preparation of 5-β-*m*-methoxyphenylethyl-$\Delta^{9,10}$-octalone, part b. Instead of dehydrating the product with formic acid, it was dried thoroughly, dissolved in 1400 ml. of benzene and treated with 58.0 g. of aluminum chloride as described in procedures above. After 52 hours at 43–45° the product was hydrolyzed and the crude (undistilled) residue was induced to crystallize by addition of a little ether. The first crop of crystals amounted to 8.90 g. of pure α-isomer, m.p. 168.5–170.5°. Addition of petroleum ether (60–68°) to the filtrate yielded 1.64 g., m.p. 134–155°, which on recrystallization from ethanol gave an additional 1.23 g. of α-isomer, m.p. 167–170° (total yield 25% based on decalindione). A third crop, m.p. 166–167°, proved to be *trans*-decalin-1,5-dione.

The oily residue was distilled from a Claisen flask, and 9.7 g., b.p. 215–225° (0.2 mm.), was collected. This material was converted to 5.3 g. of a semicarbazone, m.p. 187–193°, which was digested with two 100-ml. portions of boiling ethanol. The residue (2.8 g., m.p. 248–250° dec.) was hydrolyzed with oxalic acid solution, and the oily ketone purified by evaporative distillation at 180° (0.05 mm.). Crystallization of the oily distillate from ethanol gave 0.954 g. of very crude δ-isomer, m.p. 97–100°.

Eight recrystallizations from ethanol finally gave constantly melting material, m.p. 112–113.4°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.06; H, 8.38.

Treatment of the α-Isomer X (R = OCH_3) with Palladium-on-Carbon (a) at 250°.—A mixture of 0.420 g. (0.00148 mole) of the α-ketone, m.p. 169.8–170.2°, and 0.420 g. of 5% palladium-on-carbon[39] was heated in the Heymann apparatus[41] for 8 minutes at about 250°; 0.0023 mole of hydrogen was evolved. The residue was extracted with hot alcohol and with hot benzene. Evaporation of the combined extracts gave 0.200 g. of sticky glassy material. Evaporative distillation of 0.150 g. of this product yielded 0.114 g. of an oil coming over at 150° (0.05 mm.) and 0.032 g. of a yellow crystalline product, m.p. 267.8–271° (vac.), coming over at 175° (0.05 mm.). The latter product gave a deep blue color with Folin–Denis reagent. Since it showed a tendency to decompose on recrystallization, it was methylated with potassium hydroxide and dimethyl sulfate and the crude methyl ether (m.p. 165–188°) was sublimed at 150° (0.05 mm.). Repeated recrystallization of the colorless sublimate from ethanol gave colorless plates of **1,8-dimethoxychrysene**, m.p. 198–200.5°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 83.31; H, 5.59. Found: C, 82.98; H, 5.76.

Crystallization of the oily fraction from the evaporative distillation (see above) yielded some starting material, and a small amount (1.7 mg.) of material, m.p. 159–163°, which was undepressed on admixture with the γ-isomer (m.p. 167.8–169.8°).

(b) **At 183°.**—A mixture of 0.300 g. (0.00105 mole) of the α-ketone, m.p. 169.8–170.2°, and 0.670 g. of catalyst[39] was heated at 183° for 20 minutes in the Heymann apparatus[41]; 0.00014 mole of hydrogen was evolved. The residue was extracted with acetone in a Soxhlet apparatus. Evaporation of the solution gave 0.251 g. of residue which on crystallization from alcohol gave 0.131 g. of starting material, m.p. 161–165°, and 0.049 g. of a second crop, m.p. 117–135°. Two recrystallizations of the latter gave 0.010 g. of colorless needles, m.p. 159–163° (soft at 153°). On admixture with the α-isomer, it melted at 142–148°, and on admixture with the γ-isomer of X (R = OCH_3) (m.p. 167.8–169.8°) there was no m.p. depression. One more recrystallization gave material, m.p. 166.4–169.5°, undepressed on admixture with the γ-isomer. The infrared spectrum of this isomerized material closely resembled that of the γ-isomer except for a few minor differences in the characteristic region which may possibly be attributed to the presence of different contaminants in the two specimens.

Dehydrogenation Experiments (a) Of the α-Isomer X (R = OCH_3).—A solution of 0.04 g. of lithium aluminum hydride in 20 ml. of ether was added with stirring to a solution of 0.200 g. of the α-ketone, m.p. 169–170°, in 10 ml. of benzene. After refluxing for 1 hour, the suspension was cooled, 2 ml. of water was added dropwise then 10% sulfuric acid was added until the aqueous layer was clear. The organic layer was washed with water, saturated sodium bicarbonate solution, saturated salt solution and dried over anhydrous sodium sulfate. The oil remaining after evaporation of the solvent amounted to 0.202 g. and largely crystallized on standing. Trituration with a small amount of ether followed by three recrystallizations from ether gave 0.045 g. of colorless **α-isomer of 1-hydroxy-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene**, m.p. 112.5–114°. Further recrystallizations from ether gave small colorless needles, m.p. 114.5–115.5°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.52; H, 9.26.

A 0.157-g. sample of the crude hydroxy compound was dehydrated by heating with 0.250 g. of powdered potassium bisulfate at 200° for 10 minutes in an atmosphere of nitrogen. Evaporative distillation directly from the mixture at 200° (0.05 mm.) gave 0.122 g. of oil which was dehydrogenated with 0.100 g. of 30% palladium-on-carbon[40] at 280–300° for 20 minutes in the Heymann type of apparatus.[41] The product was dissolved in benzene, filtered, and on concentration of the filtrate 0.110 g. of colorless plates crystallized. Recrystallization from benzene gave 0.091 g. (64% yield) of 2-methoxychrysene, m.p. 249.5–250.5° (reported,[42] 250–251°). A 0.025-g. sample of this material was demethylated by refluxing under nitrogen for 4 hours with a mixture of 1 ml. each of acetic acid and 48% hydrobromic acid. The mixture was diluted with water, extracted with ether, and the ether extracts washed thoroughly with 5% sodium hydroxide solution. The phenolic material obtained by acidification of the alkaline solutions was acetylated with pyridine and acetic anhydride. The acetate was obtained from benzene as colorless crystals, m.p. 226–228° (reported[42] 229–230°).

(b) **Of the β-Isomer X** (R = OCH_3).—A 0.106-g. sample of the ketone, m.p. 153.4–154.8°, in 3 ml. of benzene was reduced with 0.06 g. of lithium aluminum hydride in 10 ml. of ether just as described above for that isomer. The crude **β-isomer of 1-hydroxy-8-methoxy-1,2,3,4,4a,4b,5,6,-10b,11,12,12a-docedecahydrochrysene** amounted to 0.108 g., m.p. 127–134°. Repeated recrystallizations from ether gave colorless rods, m.p. 140.3–141°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 80.09; H, 9.14.

A 0.052-g. sample of the crude hydroxy compound was dehydrated with an equal weight of potassium bisulfate just as described above for the α-isomer. Dehydrogenation of the evaporatively distilled product over 0.050 g. of catalyst gave 0.035 g. (75% yield) of recrystallized 2-methoxychrysene, m.p. 248.5–249.5°, undepressed on admixture with the product obtained from the α-isomer.

(c) **Of the δ-Isomer** (probably XVIII, R = OCH_3).—A 0.065-g. sample of the δ-ketone, m.p. 111–112.5°, was reduced, dehydrated and dehydrogenated as described above for the α- and β-isomers. The intermediate hydroxy compound did not crystallize. A total of 0.005 g. (8.5% yield) of 2-methoxychrysene, m.p. 248–250°, was obtained. The m.p. was not depressed on admixture with the product obtained from the α-isomer. The main portion of the material was an uncrystallizable oil.

1-Keto-8-hydroxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (X) (R = OH). **α-Isomer.**—A mixture of 0.200 g. of the α-ketone, m.p. 169–170°, and 2.0 g. of freshly prepared pyridine hydrochloride was heated at 210° for 40 minutes in an atmosphere of nitrogen. Water was added and the product extracted with ether. The ether solution was washed with water, and then extracted with Claisen alkali (see footnote 46). Acidification of the alkaline extracts gave 0.192 g. of crude phenol, m.p. 178–191°. One crystallization from ethyl acetate gave 0.155 g., m.p. 201–203°. Repeated recrystallization afforded colorless plates, m.p. 204.8–206.2°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.57; H, 8.22.

The acetate, prepared with acetic anhydride and pyridine, was obtained from alcohol as colorless plates, m.p. 131.8–132.6°. On admixture with the acetate of the β-phenol (see below) the m.p. was 107–130°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.76; H, 7.92.

β-Isomer.—A 0.10-g. sample of the β-ketone, m.p. 152–153°, was demethylated with 1.0 g. of pyridine hydrochloride just as described above. The crude phenol amounted to 0.061 g., m.p. 254–270° (dec.). Sublimation of 180–190° (0.05 mm.) followed by crystallization from ethanol gave (89% recovery) colorless material, m.p. 267–272° (dec.). Repeated recrystallization from ethanol gave colorless plates, m.p. 271.2–272.6° (dec.).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.69; H, 8.15.

The acetate was obtained from alcohol as elongated colorless plates, m.p. 134.1–137.2°, undepressed on admixture with the acetate of the phenol isolated from the cyclization (footnote 46). The latter melted at 135.7–137.1° and had the following analysis.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.80; H, 7.67.

The Estrones

1-Keto-2-piperonylidene-8-methoxy-1,2,3,4,4a,4b,5,6,-10b,11,12,12a-dodecahydrochrysene (a) **α-Isomer.**—A solution of 1.03 g. of the ketone and 0.65 g. of piperonal in 55 ml. of ethanol was heated to the boiling point, and 6 ml. of 31% potassium hydroxide solution was added. The mixture was then allowed to stand at 42° for 4 days. The yellow crystalline product which separated amounted to 1.16 g., m.p. 179–184°. Crystallization from acetone gave 0.8 g. (53% yield) of pure material, m.p. 190.2–192° (with shrinking at 188°).

Anal. Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.77. Found: C, 78.02; H, 6.89.

(b) **β-Isomer.**—The condensation was carried out exactly as described above with 2.0 g. of the β-ketone, 1.1 g. of piperonal in 75 ml. of ethanol and 12 ml. of 31% potassium hydroxide. The crude yellow crystalline product amounted to 2.16 g., m.p. 199–207°. Recrystallization from benzene gave 1.33 g. (45% yield) of material melting at 206–210°. Repeated recrystallization from benzene raised the m.p. to 209–211.4° (with shrinking at 207°).

Anal. Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.77. Found: C, 77.94, 78.06; H, 6.62, 6.68.

The piperonylidene derivative prepared similarly from the γ-ketone in 40% yield, melted at 207.4–209° after repeated recrystallization and did not depress the m.p. of the β-isomer on admixture.

Preliminary Methylation Experiments.—A solution of 0.1405 g. of the β-piperonylidene derivative described above in 20 ml. of benzene was added to a cold solution of 0.05 g. of potassium in 10 ml. of *t*-butyl alcohol in an atmosphere of nitrogen. Methyl iodide (4 ml.) was added and the mixture was allowed to stand for 12 hours at room temperature. After refluxing for 1.5 hours, the mixture was distilled for a short period under reduced pressure to recover methyl iodide, then retreated with a solution of 0.3 g. of potassium in *t*-butyl alcohol followed by methyl iodide as before. This retreatment was repeated two more times, and the product was isolated in the usual way by dilution with water and extraction. The yellow gummy product was evaporatively distilled at 205° (1×10^{-4} mm.) and the pale yellow distillate was crystallized from acetone–alcohol giving 0.0245 g. of material, m.p. 180–185°. Two recrystallizations from acetone gave 9 mg. of pale yellow crystals, m.p. 191.6–193° (with shrinking at 190°).

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.10; H, 7.04.

In another methylation experiment 0.4378 g. of the β-piperonylidene derivative was added to a solution of 0.45 g. of potassium in 20 ml. of *t*-butyl alcohol. The derivative did not dissolve on stirring at room temperature; so the mixture was refluxed until solution was complete (4 hours). The solution was cooled to 27°, 3 ml. of methyl iodide was added and after standing for 12 hours at room temperature, the mixture was refluxed for 2 hours and worked up in the usual way. The glassy product was dissolved in acetone, and chilled, 0.1 g. of crude product, m.p. 142–148°, crystallized. After four recrystallizations from ethanol 0.026 g. of material, m.p. 148–151.4°, was obtained. Further recrystallization raised the m.p. to 153–154.6°.

Anal. Calcd. for $C_{27}H_{28}O_4$: C, 77.86; H, 6.77. Found: C, 77.61; H, 6.73.

This same product of isomerization was obtained by treatment of the β-piperonylidene derivative (0.167 g.) with a solution of 0.2 g. of potassium in 15 ml. of *t*-butyl alcohol for 6 hours at refluxing temperature. After repeated recrystallization from acetone the product melted at 151–153.6°, undepressed on admixture with the analytical sample.

β-(2-Carboxy-7-methoxy-1,2,3,4,9,10,11,12-octahydro-1-phenanthrene)-propionic Acid (XXIV) (a) **β-Isomer.**—A solution of 0.238 g. of the isomerized β-piperonylidene derivative (m.p. 152–154°) described in the preceding experiment in 25 ml. of acetone was oxidized with 0.27 g. of potassium permanganate at 3° as described previously.[17] The acetone was evaporated, the residue was acidified with dilute sulfuric acid and decolorized with sodium bisulfite. The acidic material, separated by dissolution in sodium carbonate, was treated with diazomethane in ether solution and the ester evaporatively distilled at reduced pressure. Trituration with a small amount of ether gave the dimethyl ester, m.p. 106–107°, which on recrystallization from petroleum ether (40–60°) melted at 110–111°.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.88; H, 7.55.

In another run the acidic fraction was purified by repeated recrystallization from benzene. The sample of acid, m.p. 220.5–222°, was too small for analysis.

(b) α-Isomer.—A solution of 2.00 g. of the α-ketone X (R = OCH_3), m.p. 169–170°, in 120 ml. of dry benzene was added to a cooled suspension of alcohol-free sodium methoxide[30,34] (from 4.0 g. of sodium) in 80 ml. of dry benzene. Dry ethyl formate (36 ml.) was then added and the system was evacuated, filled with nitrogen, and allowed to stand at room temperature for 40 hours with occasional swirling. The yellow solution was treated with ice, and extracted with 5% potassium hydroxide. Acidification of the alkaline solutions gave 2.04 g. (93% yield) of colorless hydroxymethylene ketone, m.p. 139–151°, which gave an intense violet color with alcoholic ferric chloride. Crystallization from carbon tetrachloride yielded 1.83 g. (83% yield) of material, m.p. 156.5–159°. The pure **1-keto-2-hydroxymethylene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXIII)** was obtained by repeated recrystallization from carbon tetrachloride as colorless rods, m.p. 160.2–161.4°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.66; H, 7.37.

To a cooled (ice-bath) and stirred solution of 0.200 g. of the above hydroxymethylene ketone, m.p. 155–157°, in 35 ml. of acetone was added in small portions 0.265 g. of powdered potassium permanganate. The temperature of the reaction mixture was held at 7°, and after the addition, the mixture was allowed to stand for 1.5 hours at ice-bath temperature. The solvent was evaporated in a current of air, excess 1:1 sulfuric acid was added followed by sodium bisulfite, and the colorless mixture was extracted with ether. The ether solution was then extracted with saturated sodium bicarbonate solution, and the alkaline extracts were acidified. The gummy acidic material which precipitated gradually solidified on trituration with water; yield 0.083 g. (39%), m.p. 195–205°. Evaporative distillation at 230–232° (0.01 mm.) followed by repeated recrystallization from alcohol finally gave colorless prisms or rhombs, m.p. 240–241.5° (dec.).

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.61; H, 7.29.

1-Keto-2-benzylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XI) (R = OCH_3, Ar = C_6H_5) **(a) α-Isomer.**—Six grams of the α-ketone X (R = OCH_3), m.p. 160–170°, was dissolved by refluxing in 600 ml. of anhydrous methanol. To the hot solution were added 2.80 g. of freshly purified benzaldehyde, 60 ml. of 33% aqueous sodium hydroxide solution and a few seed crystals of the benzylidene derivative. The cloudy mixture was kept under nitrogen at 40–45° (bath temperature) for 3 days, then at room temperature for 1 day. The pale yellow precipitate amounted to 6.36 g. (81% yield), m.p. 166–170°. Recrystallization from benzene–ether gave 5.81 g. (74% yield) of crystals, m.p. 174–175.9°. Repeated recrystallization from benzene–ether gave colorless needles, m.p. 175–176.5°, $\lambda_{\max}$ 221 mμ (log E 4.39), 283 (4.43); $\lambda_{\min}$ 216 (4.38), 242 (3.85).

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 84.08; H, 7.70.

In another similar experiment, the 176° benzal ketone was isolated in only 51% yield, and, in addition, an isomeric product, m.p. 164–166° was separated by fractional crystallization from benzene–ether in 14% yield. Repeated recrystallization from ethyl acetate gave colorless prisms, m.p. 165.2–166°, $\lambda_{\max}$ 220 mμ (log E 4.29), 285 (4.20); $\lambda_{\min}$ 214 (4.21), 245 (3.04).

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.61; H, 7.61.

The isomerization of the 176° to the 166° isomer was effected as follows. One-tenth of a gram of the former was dissolved in a solution of 0.20 g. of potassium in 5 ml. of dry *t*-butyl alcohol. After standing under nitrogen at 55° for 2 hours, aqueous ammonium chloride was added and 0.096 g. of crude benzylidene derivative, m.p. 120–142°, precipitated. Three recrystallizations from benzene–ether raised the m.p. to 164–165.5° which was not depressed on admixture with the analytical sample described above.

(b) β-Isomer.—A hot solution of 2.585 g. of the β-ketone X (R = OCH_3) in 250 ml. of methanol was treated with 1.20 g. of benzaldehyde and 25 ml. of 33% sodium hydroxide solution as described above for the α-isomer. After 2 days at 40° 2.303 g. (68% yield) of yellow rods separated, m.p. 140–148°. Recrystallization from benzene–ether gave 2.201 g., m.p. 149–151.5°. Repeated recrystallization from benzene–ether gave colorless rods, m.p. 152–153.1°, $\lambda_{\max}$ 219 mμ (log E 4.28), 285 (4.34); $\lambda_{\min}$ 216 (4.26); 241 (3.67).

Anal. Calcd. for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.49; H, 7.66.

The same product, m.p. 151–152° (undepressed on admixture with the sample described above), was obtained in 24% yield by the condensation of benzaldehyde with the γ-form of X (R = OCH_3), m.p. 161–164°.

17-Benzylidene-D-homoestrone Methyl Ether (XII) (R = OCH_3, Ar = C_6H_5) **(a) The α^1- and α^2-Isomers.**—A solution of 16.1 g. of potassium in 320 ml. of dry[36] *t*-butyl alcohol was prepared in a 1-l. flask fitted with a rubber-sealed wire stirrer, a (pressure-equalized) dropping funnel and a reflux condenser. An atmosphere of dry nitrogen was provided while a solution of 5.99 g. of the α-benzylidene ketone, m.p. 174–176°, in 45 ml. of methyl iodide was added over a period of about 20 minutes to the butoxide solution which was maintained in a frozen state by cooling with an ice-bath. The contents of the flask were mixed by swirling until the stirrer could be started, then the mixture was stirred with continued cooling (ice-bath) for 1 hour. A solution of 3.5 g. of potassium in 100 ml. of *t*-butyl alcohol was added, followed by an additional 45 ml. of methyl iodide with cooling as above. Stirring was continued for 12 hours as the temperature was allowed to rise to room temperature. Sufficient water was added to dissolve the potassium iodide and the *t*-butyl alcohol was distilled off at reduced pressure. The residue was diluted with water, taken up in ether, washed with water and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the ether was fractionally crystallized from methanol and from ethanol, the latter solvent being preferred for the higher melting fractions. A total of 3.48 g. (56% yield) of the α^1-isomer, m.p. 116.5–118°, and 0.801 g. (13% yield) of the α^2-isomer, m.p. 147–149°, were thus obtained.

Repeated recrystallization of the α^1-isomer from ethanol gave colorless flat rods, m.p. 117–118°, $\lambda_{\max}$ 221 mμ (log E 4.22), 287.5 (4.32); $\lambda_{\min}$ 217.5 (4.21), 241.5 (3.54).

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 83.65; H, 7.83.

Repeated recrystallization of the α^2-isomer from ethanol gave colorless prisms, m.p. 149.2–150°, $\lambda_{\max}$ 220 mμ (log E 4.21), 286 (4.28); $\lambda_{\min}$ 217.5 (4.21), 241 (3.58).

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 83.69; H, 7.93.

(b) The β^1- and β^2-Isomers.—A solution of 1.537 g. of the β-benzylidene derivative, m.p. 149–151.5°, in 10 ml. of methyl iodide was added to a cold solution of 5.4 g. of potassium in 120 ml. of *t*-butyl alcohol just as described above. After stirring for 1 hour at 0°, a solution of 1.5 g. of potassium in 35 ml. of *t*-butyl alcohol, and 10 ml. of methyl iodide were added. The crude product obtained as described above, amounted to 1.600 g., m.p. 95–123°. Fractional crystallization from ethanol gave a total of 0.790 g. (49.5% yield) of the β^1-isomer, m.p. 145–146.5°, and 0.275 g. (17% yield) of the β^2-isomer, m.p. 146–147.5°. These products gave a depression of the m.p. on admixture with each other, or with the starting benzylidene derivative.

Repeated recrystallization of the β^1-isomer from ethanol gave colorless rods, m.p. 146.6–147.2°, $\lambda_{\max}$ 220.5 mμ (log E 4.20), 286 (4.29); $\lambda_{\min}$ 215 (4.18), 241.5 (3.45).

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 83.88; H, 7.83.

Repeated recrystallization of the β^2-isomer from ethanol gave colorless prisms, m.p. 147–147.8°, $\lambda_{\max}$ 218.5 mμ (log E 4.24), 281 (4.32); $\lambda_{\min}$ 216 (4.23), 241 (3.63).

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 84.01; H, 7.85.

From the mother liquors after separation of the β^1- and β^2-isomers, 0.045 g. (3% yield) of a third substance was isolated, m.p. 151–152.5°. Repeated recrystallization from ethanol gave colorless needles, m.p. 156–157°, $\lambda_{\max}$ 222 mμ (log E 4.24), 287.5 (4.51); $\lambda_{\min}$ 217 (4.18), 242 (3.81). On admixture with the β^1-isomer, the β^2-isomer or the starting benzylidene derivative, this material gave a marked m.p. depression.

Anal. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 84.01; H, 7.82.

Abnormal Product from Methylation of the α-Benzylidene Ketone XI (R = OCH_3, Ar = C_6H_5).—A solution of 0.920 g. of the α-benzylidene ketone, m.p. 175–176° in 25 ml. of *t*-butyl alcohol containing 1.00 g. of dissolved potassium was boiled under reflux for 45 minutes, during which a copious precipitate formed. The mixture was cooled, 0.5 ml. of methyl iodide added and the mixture was stirred for 15 minutes at room temperature then for one hour while refluxing. After cooling, an additional 1.5 ml. of methyl iodide was added, the mixture was refluxed for 1 hour and then allowed to stand at room temperature for 12 hours. The product was isolated as described above giving 0.931 g. of crude oil which could not be induced to crystallize even after chromatography. The eluates were combined and oxidized in 8 ml. of acetone with 1.00 g. of powdered potassium permanganate as described above for the piperonylidene derivative. The acidic material amounted to 0.243 g. of brown intractable resin. The neutral oil (0.567 g.) was treated with another 0.5 g. of permanganate and was largely recovered. Chromatography in carbon tetrachloride solution on acid-washed alumina gave a fraction which could be crystallized from ethanol; yield 0.082 g., m.p. 110–113°. Repeated recrystallization from ethanol gave colorless rods, m.p. 113–113.5°, λ_{max} 279 mμ (log *E* 3.33), 288 (3.30).

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07; $1CH_3O$, 8.3. Calcd. for $C_{27}H_{32}O_2$: C, 83.46; H, 8.30; $1CH_3O$, 7.99. Found: C, 83.63; H, 8.08; CH_3O, 8.3.

This product was largely recovered on attempts to form the semicarbazone, and to effect acetylation.

1-Keto-2-benzyl-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,-12a-dodecahydrochrysene.—A solution of 0.091 g. of the α-benzylidene ketone, m.p. 175–176.5°, in 20 ml. of ethyl acetate was hydrogenated over 0.040 g. of 5% palladium-on-carbon.[39] The reaction became slow after 5 minutes, and 108% of the calculated volume of hydrogen to saturate one double bond was absorbed. The reaction was interrupted, the solution filtered, and the colorless residue obtained upon evaporation of the filtrate melted at 160–165°. Three recrystallizations from alcohol gave colorless needles, m.p. 171–171.7°, λ_{max} 279 mμ (log *E* 3.40), 287.5 (3.35).

Anal. Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.66; H, 8.29.

Homomarrianolic Acid Methyl Ether, XIII (R = OCH_3) (a) **α^1-Isomer.**—A solution of 0.200 g. of the α^1-methylation product, m.p. 117–118°, in 5 ml. each of ethyl acetate and glacial acetic acid was chilled in an ice-salt-bath while sufficient ozonized oxygen (from a calibrated U.S. Ozone Co. ozonizer) was passed through to deliver 25–27 mg. of ozone.

The reaction mixtures of three such ozonizations were combined, 4.5 ml. of water and 1.5 ml. of 30% hydrogen peroxide were added, and the mixture allowed to stand overnight. The ethyl acetate and most of the acetic acid were removed by distillation at reduced pressure, water was added, and the product extracted with ether. The ether solution was washed with water, then extracted thoroughly with saturated sodium bicarbonate solution. The combined bicarbonate solutions were acidified, extracted with ether, and the ether solution was washed with saturated salt solution and dried over anhydrous sodium sulfate. The colorless residue obtained on evaporation of the ether was triturated twice with boiling petroleum ether (60–68°) and then crystallized from a little acetone; yield 0.385 g. (71.5%), m.p. 168–170°. Repeated recrystallization from ethyl acetate gave colorless prisms which crumbled to a powder on drying at 56° under reduced pressure, m.p. 169.8–170.5°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 68.97; H, 7.67.

(b) **The α^2-Isomer.**—The ozonization of the α^2-methylation product, m.p. 148–150°, was carried out exactly as described above for the α^1-isomer.

The reaction mixtures of two 0.200-g. runs were combined and treated with 3 ml. of water and 1 ml. of 30% hydrogen peroxide. The crude acidic oil, isolated as described above, amounted to 0.298 g. After trituration with hot petroleum ether 0.283 g. (79% yield) remained which could be obtained as an amorphous powder, m.p. about 97–120°, by slow acidification of a solution in sodium bicarbonate. This product could not be obtained crystalline but was satisfactory for conversion to the α^2-estrone methyl ether.

(c) **The β^1-Isomer.**—A 0.200-g. sample of the β^1-methylation product, m.p. 146–147°, was ozonized in 5 ml. of ethyl acetate and 5 ml. of glacial acetic acid just as described above. Unlike the previous cases, a colorless precipitate (ozonide) was observed to form and this persisted until treated with 1.5 ml. of water and 0.5 ml. of 30% hydrogen peroxide. The crude product crystallized on acidification of the bicarbonate extracts; yield 0.197 g. (110%, evidently containing some inorganic salts), m.p. 178–183°. Crystallization from benzene gave 0.135 g. (75% yield) of material, m.p. 187–190°. Two recrystallizations from ethyl acetate gave colorless rods, m.p. 191.2–192°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 68.91; H, 7.62.

(d) **The β^2-Isomer.**—A 0.200-g. sample of the β^2-methylation product, m.p. 146–147.5°, was ozonized and worked up exactly as described above for the β^1-isomer. The crude product obtained on acidification of the bicarbonate extracts amounted to 0.138 g. (77% yield), m.p. 218–222°. Two recrystallizations from ethyl acetate and one from acetone gave colorless prisms, m.p. 225.2–227.5° (reported,[50] 225–227°). On admixture with *d*-homomarrianolic acid methyl ether, m.p. 252–256°, prepared as described below, the m.p. was 225–242°.

(e) **By Degradation of *d*-Estrone.**[47]—This degradation was carried out according to the general scheme for opening rings of cyclic ketones,[30] and represents a substantial improvement over the method of Bardhan.[48] *d*-Estrone methyl ether was prepared by a modification of the procedure of Butenandt, *et al.*[49] To a solution of 5.00 g. of *d*-estrone (m.p. 251.7–253.5°) in 40 ml. of methanol and 70 ml. of 17% potassium hydroxide solution, was added slowly with vigorous stirring 30 ml. of dimethyl sulfate. The temperature was maintained at 25–30°, and the solution was kept alkaline (to litmus) by frequent further additions of 17% potassium hydroxide solution (*ca.* 100 ml. altogether). After addition was complete (2.5 hours), 20 ml. of ammonium hydroxide was added and stirring continued for 30 minutes. The finely divided precipitate which separated, amounted to 5.26 g. (quantitative yield), m.p. 162.4–166.8° (reported,[49] 168–169° after recrystallization from ethanol).

The hydroxymethylene derivative was prepared according to a general procedure.[30,34] Crude *d*-estrone methyl ether (5.25 g.) was added to a suspension of dry, alcohol-free sodium methoxide (from 2.00 g. of sodium) in 50 ml. of dry benzene. Dry ethyl formate (22 ml.) was then added, and the mixture allowed to stand overnight in an atmosphere of nitrogen at room temperature. The product was worked up as previously described, and the alkali-soluble material amounted to 5.52 g. (95% yield), m.p. 161.4–164.2° (reported,[48] 170–171° after recrystallization from acetone).

The crude hydroxymethylene ketone was dissolved in 200 ml. of glacial acetic acid and shaken with 2.00 g. of hydroxylamine hydrochloride at room temperature for 48 hours. On dilution with water and cooling, 5.19 g. of colorless material, m.p. 187–192°, was obtained. Analysis indicated that this was the oxime rather than the expected disubstituted hydroxylamine.[50] The oxime was obtained from dilute alcohol in two forms, m.p. 183–184° and 202–204° (presumably polymorphic as the m.p. on admixture was not depressed). The lower melting modification was analyzed.

Anal. Calcd. for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70. Found: C, 72.95; H, 7.32.

The crude oxime (5.19 g.) was refluxed for 41 hours (in a steel flask) with 1 l. of 5% potassium hydroxide solution and 1.3 g. of hydroxylamine hydrochloride. Acidification of the cooled solution gave 4.68 g. (85% yield) of crude *d*-homomarrianolic acid methyl ether, m.p. 241–247.8°. A single recrystallization from dilute (1:1) acetic acid gave material melting at 251–252° in 61% recovery. After repeated recrystallization it melted at 253–254° (reported m.p.,[48] 251–252°).

Estrone Methyl Ether, XIV (R = OCH_3) (a) **The α^1-Isomer.**—A mixture of 0.441 g. of the α^1-dibasic acid, m.p.

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[47] The experiments of this section were performed by J. Szmuszkovicz and H. Wynberg in this Laboratory.

[48] J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

[49] A. Butenandt, I. Stormer and U. Westphal, *Z. physiol. Chem.*, **208**, 149 (1932).

[50] W. S. Johnson and W. E. Shelberg, THIS JOURNAL, **67**, 1745 (1945).

168–170°, and 0.50 g. of lead carbonate was placed in the lower bulb formed in a piece of 10-mm. Pyrex tubing by sealing off one end and forming two constrictions about 5 cm. apart. A small plug of glass wool was placed above the mixture which was then pyrolyzed at 305° (0.05 mm.). Heating was continued until the product had completely distilled beyond the first constriction of the tube (about 20 minutes), then the temperature was lowered to 190°, and the oil was evaporatively distilled beyond the second constriction. The crude oily distillate, amounting to 0.240 g., was crystallized from methanol giving a total of 0.205 g. (57% yield) of crystals, m.p. 113–115.5°. Repeated recrystallization from methanol gave colorless flat rods, m.p. 115–116.2°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.37; H, 8.51.

The 2,4-dinitrophenylhydrazone was obtained as a yellow microcrystalline powder from chloroform–ethyl acetate, m.p. 273–274° dec. (introduced at 260°).

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.65; H, 6.10.

(b) **The α^2-Isomer.**—The amorphous α^2-dibasic acid (0.28 g.) was pyrolyzed with lead carbonate (0.350 g.) just as described in the preceding experiment. The oily distillate, amounting to 0.140 g., was crystallized from methanol (Dry Ice–acetone temperature), giving 0.111 g. (48% yield) of crystals, m.p. 64–68°. Repeated recrystallization from methanol gave colorless rods, m.p. 67–68.3°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.19; H, 8.49.

The 2,4-dinitrophenylhydrazone was obtained as a yellow powder from ethyl acetate, m.p. 209–210° dec. (introduced at 203°).

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.53; H, 6.28.

(c) **The β^1-Isomer (*dl*-Lumiestrone Methyl Ether).**—Pyrolysis of 0.203 g. of the β^1-dibasic acid, m.p. 188.5–190.5°. with 0.230 g. of lead carbonate just as described above gave 0.138 g. (82.5% yield) of colorless solid distillate, m.p, 106.5–107.5°. Recrystallization from methanol gave a total of 0.135 g. (81% yield) of colorless plates, m.p. 109–110°. The m.p. was not raised on further recrystallizations.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.25; H, 8.44.

The 2,4-dinitrophenylhydrazone was obtained as orange prisms from ethyl acetate, m.p. 210–211° dec.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.62; H, 6.03.

(d) **The β^2-Isomer (*dl*-Estrone Methyl Ether).**—Pyrolysis of 0.077 g. of the β^2-dibasic acid, m.p. 223–225°, with 0.080 g. of lead carbonate just as described above gave 0.029 g. (46% yield) of colorless solid distillate, m.p. 139.5–141.5°. Two recrystallizations from methanol gave colorless flat rods, m.p. 143.2–144° (reported,[10] 143–44°). On admixture with authentic *d*-estrone methyl ether (m.p. 168–169°) the m.p. was 143.5–155°.

α^1-Estrone.—A mixture of 0.070 g. of the α^1-methyl ether, m.p. 113–115.5°, and 1.0 g. of freshly prepared dry pyridine hydrochloride was heated at 210° for 40 minutes in an atmosphere of nitrogen.[51] After cooling 3 ml. of 5% hydrochloric acid was added, and the colorless product was taken up in ether, washed with water and extracted thoroughly with 5% potassium hydroxide solution. Acidification of the alkaline solutions gave 0.060 g. (90% yield) of colorless α^1-estrone, m.p. 175–181°. Repeated recrystallization from methanol gave colorless plates, m.p. 180.6–181.4°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.12; H, 8.22.

The benzoate, prepared with benzoyl chloride and pyridine, was obtained from methanol as colorless plates, m.p. 149–151°.

α^2-Estrone.—A 0.040-g. sample of the α^2-methyl ether, m.p. 66–68°, was demethylated with 1 g. of pyridine hydrochloride just as described above for the α^1-isomer. The crude α^2-estrone amounted to 0.032 g. (84% yield) of colorless plates, m.p. 193–196°. Repeated recrystallization from methanol raised the m.p. to 197–198.1°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.14; H, 8.19.

The benzoate was obtained from ethanol as nearly colorless flat rods, m.p. 159.5–161.5°.

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 79.65; H, 6.98.

β^1-Estrone (*dl*-Lumiestrone).—A 0.086-g. sample of the β^1-methyl ether, m.p. 109–110°, was demethylated with 1.5 g. of pyridine hydrochloride as described above for the α^1-isomer. After cooling, 5 ml. of 5% hydrochloric acid was added, and the colorless solid was filtered, washed with water and dried; yield 0.081 g., m.p. 213–223°. Three recrystallizations from acetone gave small colorless prisms, m.p. 238.5–240° (vac.).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.80; H, 8.22.

The benzoate was obtained from ethanol as colorless rods, m.p. 157.5–158.5°.

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.19; H, 6.96.

β^2-Estrone (*dl*-Estrone).—A 0.0153-g. sample of the β^2-methyl ether, m.p. 142.8–144°, was demethylated with 0.5 g. of pyridine hydrochloride as described above for the α^1-isomer. The ether solution of the crude product was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and twice with 0.25-ml. portions of 5% potassium hydroxide which removed most of the color (but not the estrone) from the ether layer. The ether solution was washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the ether gave 0.008 g. of crude *dl*-estrone, m.p. 235–248°. Three recrystallizations from acetone gave nearly colorless flat rods, m.p. 252.8–254.7° (vac.) (reported,[10] 251–254°).

The benzoate was prepared from about 0.005 g. of β^2-estrone, m.p. 252.8–254.7°. After two recrystallizations from ethanol, colorless needles were obtained, m.p. 184.5–190° (reported,[10] 184–186°). Most of the melting occurred between 184.5–187°, a few isolated crystals (on the micro hot-stage) persisting up to 190°. This behavior suggests that the product either was a *dl*-crystalline mixture, or was contaminated with unbenzoylated material.

Resolution of *dl*-Estrone.—The *l*-menthoxyacetate was prepared from 0.013 g. of *dl*-estrone, m.p. 251–254.5° (prepared as described in the preceding experiment) and *l*-menthoxyacetyl chloride (2 drops) in 0.3 ml. of dioxane and 0.2 ml. of pyridine, as described by Bachmann, Cole and Wilds.[9] The crude oily product was crystallized from petroleum ether (60–66°) yielding 0.0015 g., m.p. 127–132° and 0.006 g., m.p. 114–130°. Recrystallization of the second crop gave 0.0035 g., m.p. 128–134°, which was combined with the first crop above, and recrystallized twice from petroleum ether. The *l*-menthoxyacetate was thus obtained as colorless flat rods and plates, m.p. 132–135°. On admixture with a sample of the *l*-menthoxyacetate (m.p. 133.5–135°) of authentic *d*-estrone there was no depression of the melting point.

***l*-Lumiestrone.**—The irradiation of estrone was carried out according to a modification of the procedure of Butenandt, *et al.*[31] A solution of 1.08 g. of *d*-estrone (m.p. 259–261°, $[\alpha]^{25}\text{D}$ +159.7 (dioxane), kindly supplied by Drs. G. Rozenkranz and C. Djerassi, Syntex, S.A.) in 50 ml. of purified dioxane was placed in a 50-ml. long-necked Florence quartz flask which was connected to a mercury trap system and then evacuated and filled with nitrogen. The flask was placed about 20 cm. away from the arc of a Hanovia Alpine Sun Lamp, and the solution was irradiated for 34 hours with occasional swirling. The solution, $[\alpha]^{25}\text{D}$ +24°, was concentrated to about 10 ml. on the steam-bath in a current of nitrogen. The crystals obtained on cooling were recrystallized from alcohol giving 0.269 g. (25% yield) of lumiestrone, m.p. 266–267°, $[\alpha]^{25}\text{D}$ −41 ± 2° (dioxane). The reported m.p. is 268–269°, $[\alpha]^{21}\text{D}$ −43° (dioxane).[31] A mixture of our product with *d*-estrone melted at 223–230°. On admixture with β^1-estrone (described above) the m.p. was 238–270°.

The methyl ether of lumiestrone was prepared according to a previous procedure.[31] After evaporative distillation at 120–130° (0.01 mm.) and repeated recrystallization from alcohol it melted at 130–130.6°, $[\alpha]^{32}\text{D}$ −27° (chloroform) (reported m.p. 129–130°, $[\alpha]^{23}\text{D}$ −28°, chloroform[31]). On admixture with β^1-estrone methyl ether (m.p. 108.3–109.3°), it melted at 106–130°.

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(51) *Cf.* the procedure of A. L. Wilds and W. McCormack, THIS JOURNAL, **70**, 4127 (1948).