Activation energies (E) and frequency factors (A) were calculated from rate data using k-values at 20 and 30°. Although it would have been possible to extrapolate E and A from the individual Arrhenius plots consisting of three points at three different temperatures, this procedure was preferred so as to make our data comparable to that available from Criegee's work.

TABLE V

TYPICAL VARIATIONS OF k

Time, min.	$S_2O_3^=$, ml.	$a-x$	x	k
Compound *cis*-Ib; init. concn. of reagents 0.0025 M at 20° in 2.0 ml. of reacn. mixt.				
0.0	5.00	0.00250	0.00000	...
.4	4.38	.00219	.00031	141
.5	4.24	.00212	.00038	143
1.0	3.72	.00186	.00064	137
2.0	2.96	.00148	.00102	138
3.0	2.50	.00124	.00126	135
			Average	139
Compound *trans*-Ia; init. concn. of reagents 0.0025 M at 30° in 2.0 ml. of reacn. mixt.				
0.0	5.00	0.00250	0.00000	...
.2	4.80	.00240	.00010	83.3
.5	4.54	.00227	.00023	81.5
1.0	4.16	.00208	.00042	80.8
1.5	3.36	.00168	.00082	78.1
3.0	3.12	.00156	.00094	80.3
4.0	2.74	.00137	.00113	82.5
			Average	81.0
Compound *cis*-Ie; init. concn. of reagents 0.00125 M at 40° in 4.0 ml. of reacn. mixt.				
0.0	5.00	0.001250	0.000000	...
.1	4.66	.001165	.000085	299
.2	4.38	.001095	.000155	285
.3	4.12	.001030	.000220	287
.4	3.88	.000970	.000280	293
.5	3.70	.000925	.000325	294
			Average	292

Acknowledgment.—We are indebted to Professor R. C. Fuson, University of Illinois, and Professor R. Criegee, Technische Hochschule, Karlsruhe, Germany, for furnishing some of the diols used in this work. We wish to thank Dr. L. P. Kuhn, Aberdeen Proving Grounds, Aberdeen, Md., for the infrared measurements and Dr. D. J. Hennessy, Fordham University, for many helpful discussions. We also take pleasure in thanking the Research Corporation and the National Science Foundation for grants supporting this work.

NEW YORK 58, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

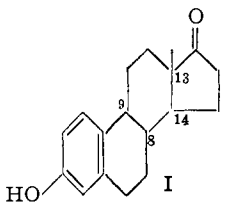
Configuration of the Estrones. Total Synthesis of the Remaining Stereoisomers

BY WILLIAM S. JOHNSON, ISRAEL A. DAVID,[1] HENRY C. DEHM,[2] ROBERT J. HIGHET,[3] E. W. WARNHOFF,[4] W. DAVID WOOD[5] AND E. T. JONES[6]

RECEIVED JULY 24, 1957

Seven of the eight possible racemic forms having the estrone structure have now been synthesized in our laboratory. Five of these, α-1, α-2, β-1, β-2 (*dl*-estrone), and 14-isoestrone, were obtained in former studies and two, γ-1 and γ-2, are described in the present work. Experiments and arguments are presented for the assignments of configurations to each of these products as represented in Chart 4. The interrelationships among our isomers and those of other workers has been considered (see Table II). It has been demonstrated that Anner and Miescher's isomers a, d and f probably correspond to our substances 14-iso-, α-2 and γ-1 estrone, respectively. In addition it appears likely that Bachmann's estrone isomer is identical with estrones f and γ-1. By a process of elimination Anner and Miescher's isomer e accounts for the eighth racemate. A stereochemical rationale is presented for the method by which the isomers of Anner and Miescher and of Bachmann were produced. Independent evidence is presented which establishes the B/C *trans* configuration of estrone in the classical manner through relationship to substances of unequivocal configuration.

The estrone structure (I) contains four dissimilar asymmetric carbon atoms (C_8, C_9, C_{13} and C_{14}); hence there are 16 optical isomers or 8 *dl*-forms theoretically possible. The configurations for one of the enantiomers of each of these 8 *dl*- pairs are depicted in Chart 4.



I

A number of racemic products corresponding to the estrone structure already have been prepared.[7-10] Five different *dl*-forms of estrone, α-1, α-2, β-1, β-2 (natural), and 14-iso, have been produced previously in our own laboratory.[9,10] The present work discloses (a) the synthesis of two additional racemates, γ-1 and γ-2; (b) evidence

(1) Allied Chemical and Dye Corp. (National Aniline Division) Fellow, 1953–1954.

(2) Research Assistant supported by G. D. Searle and Co., 1953; and E. I. du Pont de Nemours and Co., summers 1950–1953.

(3) Research Assistant supported by the Wisconsin Alumni Research Foundation, 1950–1951; Allied Chemical and Dye Corp. Fellow, 1952–1953.

(4) Socony-Vacuum Co. Fellow, 1951–1952; Homer Adkins Fellow, 1952–1953.

(5) Research Assistant supported by grants from the Wisconsin Alumni Research Foundation, The National Science Foundation and G. D. Searle and Co., 1954–1956; and E. I. du Pont de Nemours and Co., summer, 1953.

(6) National Science Foundation Predoctoral Fellow, 1956–1957.

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

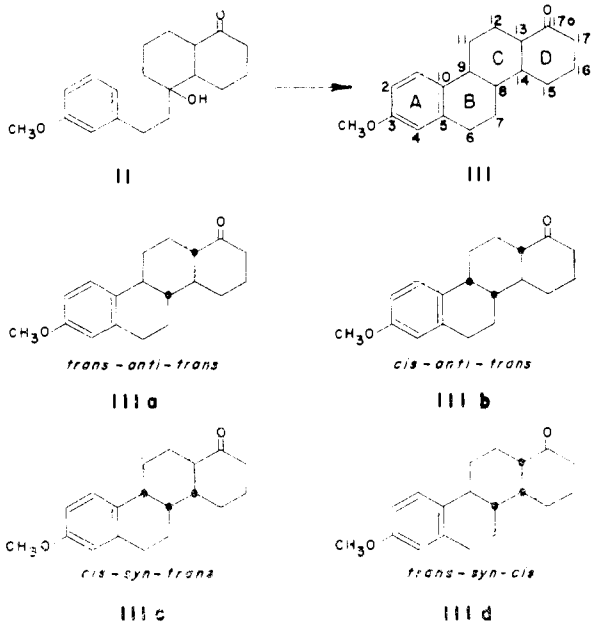
(8) (a) G. Anner and K. Miescher, *Helv. Chim. Acta*, **31**, 2173 (1948); (b) **32**, 1957 (1949).

(9) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, THIS JOURNAL, **74**, 2832 (1952).

(10) (a) W. S. Johnson, R. G. Christiansen and R. F. Ireland, *ibid.*, **79**, 1995 (1957); (b) W. S. Johnson and W. F. Johns, *ibid.*, **79**, 2005 (1957).

that all seven of our products represent distinct molecular species having the estrone structure; (c) arguments and additional experimental evidence permitting assignment of configurations to these seven isomers; and (d) a consideration of the matter of the identity of our products with those of other workers, as the result of which it appears that one isomer, Anner and Miescher's "estrone c,"[8b] is probably different from any of ours; hence all eight possible racemates are accounted for and given configurational assignments.

In previous work[9] we found that aluminum chloride-catalyzed cyclization of the readily available carbinol II (and of the olefin produced upon dehydration) yielded mixtures containing stereoisomeric forms of the methoxyhydrochrysenone III. There are four possible stable[11] (with respect to the readily isomerizable C_{13}-position[12]) racemic forms of this structure (III), and one enantiomer of each is represented by formulas IIIa, IIIb, IIIc and IIId. From the cyclization mixtures two of these, α and β, were isolated.



The β-methoxyhydrochrysenone was shown to have the natural *trans-anti-trans* configuration (formula IIIa) through its conversion to estrone as follows (see Chart 1). Condensation with benzaldehyde afforded the benzylidene derivative IVa which on treatment with potassium *t*-butoxide and methyl iodide, yielded a mixture of two angularly methylated C_{13}-epimers, β-1 and β-2 (formulas Va and VIa). The less preponderant isomer, β-2, on oxidation to the dibasic acid VIIIa followed by ketonic cyclization and demethylation, was transformed into β-2 estrone which proved to be identical with the previously synthesized estrone b of Anner and Miescher[8a] that was resolvable into natural *d*-estrone of known (*trans-anti-trans*) configuration (see below). The configurations of the precursors IVa, VIa and VIIIa are accordingly clearly defined as *trans-anti-trans* (Chart 1). By its mode

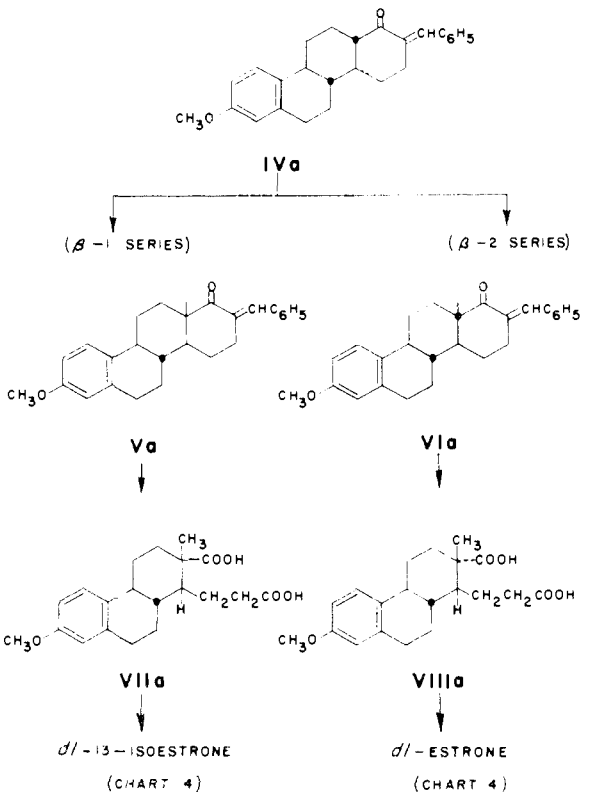


Chart 1.

of formation the preponderant β-1 isomer produced in the methylation step is unequivocally the *trans-anti-cis* isomer Va, leading through the diacid VIIa to β-1 estrone which must, therefore, be *dl*-13-isoestrone, the racemic form of lumiestrone.[9]

Particularly noteworthy features of the angular methylation described above are the facts that (a) the C/D *cis* isomer Va is formed in preponderance over the *trans*-(VIa) by a factor of about 3, and (b) the principal maximum in the ultraviolet spectrum of the *cis* product lies at a significantly longer wave length (286 mμ) than that (281 mμ) of the *trans* product. From various studies in our laboratory[13-20] we have accumulated altogether 14 cases (see Table I) of angular methylation of 2-arylmethylene-1-decalone types in which the configurations of the products are unequivocal. Since, without exception, the *cis* isomer was preponderant and exhibited absorption in the ultraviolet region at a longer wave length than the *trans*, these characteristics may be considered diagnostic and are used in deducing configurations discussed below. It was also noted that the principal maximum in the ultraviolet spectrum of the unmethylated aryl-

(11) *Cf.* W. S. Johnson, *Experientia*, **7**, 315 (1951).

(12) Steroid numbering is used unless otherwise noted.

(13) W. S. Johnson, THIS JOURNAL, **65**, 1317 (1943).

(14) W. S. Johnson, B. Bannister and R. Pappo, *ibid.*, **78**, 6331 (1956).

(15) G. N. Sausen, Ph.D. Dissertation, University of Wisconsin, 1953.

(16) R. R. Hindersinn, Ph.D. Dissertation, University of Wisconsin, 1954.

(17) D. S. Allen, Jr., unpublished work.

(18) W. S. Johnson, R. Pappo and W. F. Johns, THIS JOURNAL, **78**, 6339 (1956).

(19) W. S. Johnson, B. Bannister, R. Pappo and J. B. Pike, *ibid.*, **78**, 6354 (1956).

(20) Present work.

TABLE I

SUMMARY OF SPECTRAL DATA AND RATIOS OF EPIMERIC PRODUCTS FORMED ON ANGULAR METHYLATION OF ARYLMETHYLENE KETONES

Parent arylmethylene ketone	$\lambda_{max}^{95\%}$ EtoH mμ: Parent compound	*cis*-Angular methylation product	*trans*-Angular methylation product	*cis*/*trans* ratio of methylation products	Reference
2-Benzylidenedecalone-1	285	287	283	3[a]	13[b]
2-Furfurylidenedecalone-1	323.5	325	321	3[a]	14[c]
2-*p*-Methoxybenzylidenedecalone-1	313	314	310	2[d]	20[c]
2-*p*-Chlorobenzylidenedecalone-1	289	289.5	286	5[d]	20[c]
2-*p*-Dimethylaminobenzylidenedecalone-1	375	377	369	2[d]	20[c]
2-*p*-Nitrobenzylidenedecalone-1	306	308.5	305.5	2[d]	20[c]
2-α-Naphthylmethylenedecalone-1	310	311	308	2[d]	20[c]
2-Furfurylidene-6-ethylenedioxodecalone-1	324	325.5	322	3.5[a]	15[e]
2-Furfurylidene-4-hydroxydecalone-1	325	325.5	324.5	9[a,f]	16[g]
2-Furfurylidene-3-methyl-4-hydroxydecalone-1	323	317.5	308.5	*ca.* 7[a,f]	17[h]
dl-17-Benzylidene-18-nor-D-homoestrone methyl ether (IVa)	285	286	281	*ca.* 3[a]	9[i]
dl-17-Furfurylidene-18-nor-D-homoepiandrosterone	324.5	326.5	323	2.2[a,f]	14[j]
dl-3β,11β-Dihydroxy-17-furfurylidene-18-nor-D-homoandrostane-17a-one	324	329.5 (diacetate)	322 (diacetate)	2–3[a,f]	18[k]
dl-3-Ethylenedioxy-17-furfurylidene-18-nor-D-homo-5-androstene-17a-one	325	327	323	4[a]	19[l]
dl-17-Benzylidene-18-nor-D-homo-9-isoestrone methyl ether (IVb)	283	287.5	281.5[m]	*ca.* 4[a]	9[n]
dl-17-Furfurylidene-18-nor-D-homo-8-isoestrone methyl ether (IVc)	326.7	326.2	321.9	*ca.* 11[a]	20[n]

[a] This ratio was determined by direct isolation of the products. [b] Each of the methylated products was converted to the corresponding 9-methyl-1-decalones (ref. 13), the configurations of which are well established by much evidence, *e.g.*, the *cis* compound has been prepared by the Diels–Alder reaction of 2-methyl-2-cyclohexenone with 1,3-butadiene, followed by hydrogenation of the ethylenic linkage; A. M. Gaddis and L. W. Butz, THIS JOURNAL, **69**, 117 (1947). [c] The configurations were established by preparation of authentic specimens from the pure 9-methyl-1-decalones, of known (see footnote *b*) configuration, by condensation with the appropriate aldehyde. [d] This ratio was determined by infrared analysis as described in the Experimental part of the present work. [e] The configurations were established by ozonization of the major isomer, followed by hydrolysis of the ketal and Wolff–Kishner reduction to produce *cis*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid which was cyclized to give *cis*-8-methyl-1-hydrindanone, identified with authentic material as its 2,4-dinitrophenylhydrazone, m.p. 140.5–142°. [f] The hydroxyl groups were protected as the tetrahydropyranyl ethers during the methylation. [g] The configurations were established by ozonization of the tosylate of the major isomer which gave a crystalline γ-**lactone of *cis*-β-hydroxy-β-(2-carboxy-2-methylcyclohexyl)-propionic acid**, m.p. 165.5–166.5°. Found: C, 62.4; H, 7.73. Treatment with sodium carbonate solution effected β-elimination—*cf.* R. P. Linstead, L. N. Owen and R. F. Webb, *J. Chem. Soc.*, 1211, 1218 (1953)—to give ***cis*-β-2-carboxy-2-methylcyclohexyl)-acrylic acid**, m.p. 150.5–152.5°, λ_{max} 211 mμ (ε 14,800). Found: C, 62.6; H, 7.70. Catalytic hydrogenation afforded the known saturated *cis*-diacid, m.p. 109.5–111°, undepressed on admixture with authentic material. [h] The hypsochromic shift of the maxima of the two methylation products indicates that these have undergone a geometric isomerization about the furfurylidene group (perhaps due to crowding by the methyl group at C_3) to give the "*cisoid*" system; see W. S. Johnson, E. R. Rogier and J. Ackerman, THIS JOURNAL, **78**, 6322 (1956). It is interesting to note, however, that the rule about the relative positions of the maxima of the epimeric methylation products appears to hold in the *cisoid* as well as the *transoid* systems. [i] See discussion in present paper for assignment of configurations. [j] Configurations established by conversion of minor isomer into *dl*-epiandrosterone. [k] Configurations established by conversion of minor isomer into *dl*-3β,11β-dihydroxyandrostane-17-one. [l] Configurations established by conversion of minor isomer into *dl*-testosterone. [m] Revised value, originally reported as 286 (ref. 9). [n] Configurations deduced—see present work.

methylene ketones generally, but not always, fell between those of the two methylation products.

The α-methoxyhydrochrysenone, accompanying the β-isomer in the cyclization of II, also has been submitted to the angular methylation–ring contraction sequence.[9] The benzylidene derivative (λ_{max} 283 mμ) on methylation afforded a pair of C_{13}-epimers, α-1 (λ_{max} 287.5 mμ) and α-2 (λ_{max} 281 mμ), isolated in a ratio of about 4 to 1 (see Table I). On the basis of the proportion of the isomers and their spectra, these epimers, and in turn their progeny including α-1 and α-2 estrone, may be assigned the C/D *cis* and *trans* configurations, respectively. If the B/C configuration of the α-series were *trans*, the α-1 estrone should correspond to either *dl*-13-iso- or *dl*-14-iso-estrone. Since neither α-1 nor α-2 estrone was identical with *dl*-estrone, *dl*-13-isoestrone or *dl*-14-isoestrone,[10] the α-series clearly has the B/C *cis* configuration. The α-methoxyhydrochrysenone, therefore, is represented by formula IIIb or IIIc and its progeny by the formulas shown in Chart 2 or Chart 3, respectively. Confirmation of this B/C *cis* configuration evolves from (a) the fact that the 13,14-dehydro ketones IX and X derived from the α- and β-ketones were different (see below) and (b) the conversion of the α-ketone into the dimethoxyhexahydrochrysene (XXI, Chart 5) that is known to have the *cis* configuration (see below). The fact that the α-methoxyhydrochrysenone is the major product of the cyclization and is formed apparently to the exclusion of the β-isomer under mild conditions (see Experimental part for new work) is consistent with the known preference for such cyclizations to produce *cis*-fused ring systems, particularly under mild conditions.[21]

(21) R. A. Barnes and M. D. Konort, THIS JOURNAL, **75**, 303 (1953); R. A. Barnes, *ibid.*, **75**, 3004 (1953); R. A. Barnes and M. T. Beachem, *ibid.*, **77**, 5388 (1955).

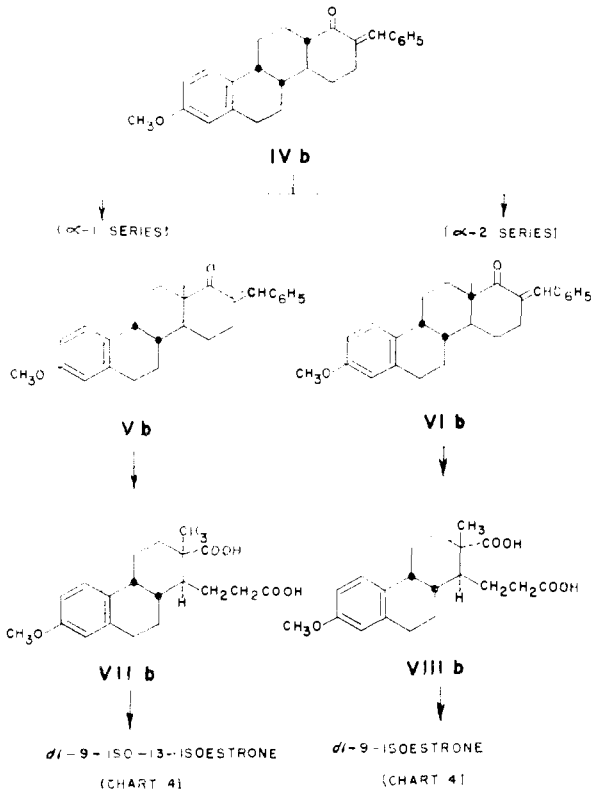


Chart 2.

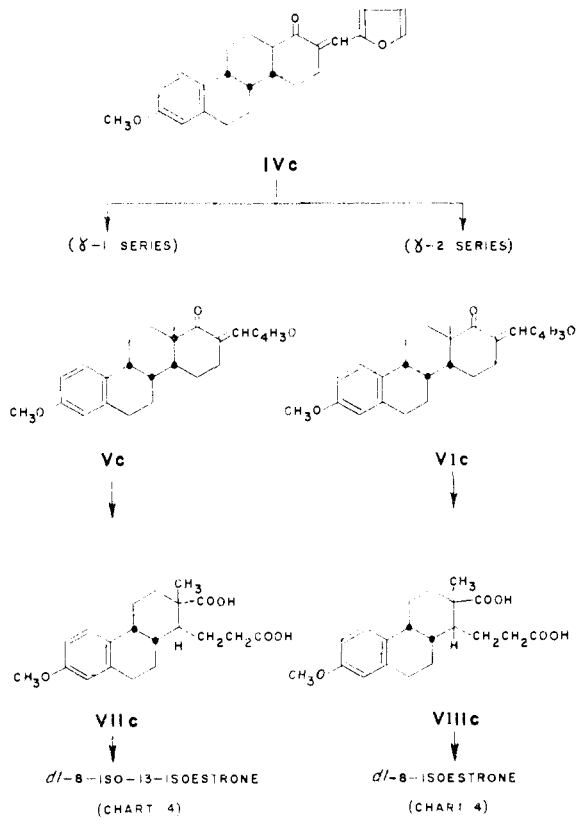
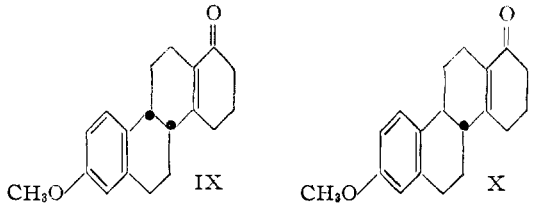


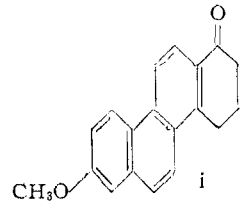
Chart 3.

Preparation of the Third (γ)[22] Stereoisomeric Form of the Methoxyhydrochrysenone III and Its Conversion into the γ-1 and γ-2 Estrones.—With the objective of finding a new stereoisomer of the methoxyhydrochrysenone III, we undertook a study of the preparation of the 13,14-dehydro compounds IX and X from the α- and β-ketones, in the hope that reduction of the double bond might be effected so as to give a different configuration at C_{14}.



Treatment of the α-methoxyhydrochrysenone with sulfuryl chloride afforded a mixture, probably consisting mainly of the angular (C_{13}) chloro epimers[23] which, when heated with collidine, underwent dehydrohalogenation to give an α,β-unsaturated ketone in about 22% yield, melting after purification at 136–137.5°.[24] The olefinic bond was shown to be conjugated with the carbonyl group by the typical unsaturated carbonyl absorption shown at 6.03 μ and 246 mμ. The position of the latter band clearly precludes the 16,17-dehydro structure which would absorb in the 225 mμ region, and the high extinction coefficient (ϵ 15,000) favors the 13,14- over the 12,13-position for the double bond.[25] That this product retained the original B/C *cis* configuration and hence is correctly represented by formula IX was shown by reduction with lithium in ammonia under conditions for selective attack of the olefinic linkage.[26] The only pure product isolated was the original α-methoxyhydrochrysenone.

The 13,14-dehydro ketone IX also could be prepared through the enol acetate XI, m.p. 108–111°, produced from the α-methoxyhydrochrysenone with acetic anhydride and *p*-toluenesulfonic



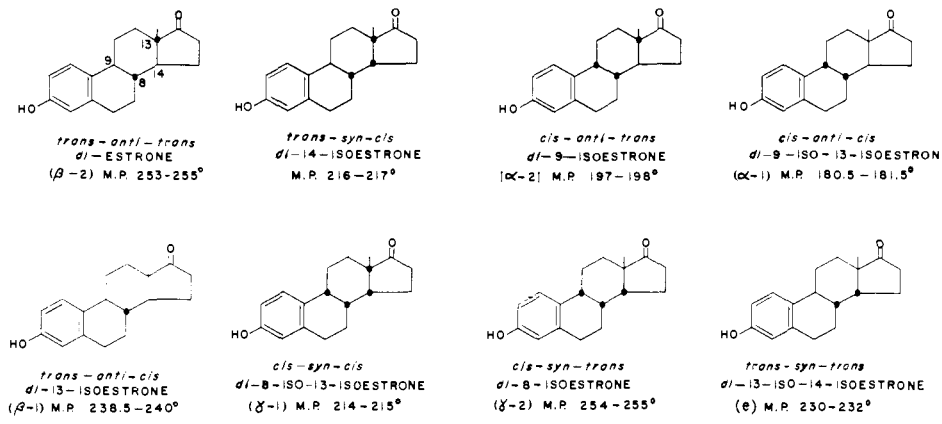
(22) The product previously called the "γ-isomer" was shown to be a complex (or a eutectic mixture) of the α- and β-methoxyhydrochrysenones (ref. 9). The term "γ" is, therefore, reassigned to the new stereoisomeric form of III described in the present work.

(23) Sulfuryl chloride appears to attack a ketone at an α-methylene in preference to an α-methylene hydrogen. *Cf.* the case of 2-methylcyclohexanone which yields the 2-chloro compound, E. W. Warnhoff and W. S. Johnson, THIS JOURNAL, **75**, 494 (1953).

(24) A by-product, m.p. 236–238°, which was estimated to be formed in about 2.8% yield, is formulated as the methoxytetrahydrochrysenone i on the basis of compositional analysis and spectral characteristics described in the Experimental part.

(25) For pure Δ^1-octalone-1 λ_{max} is 246 mμ (ϵ 7300) while for Δ^2-octalone-1 λ_{max} is 215 mμ (ϵ 12,100); E. W. Warnhoff, Ph.D. Dissertation, University of Wisconsin, 1953.

(26) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953).



*ONE ENANTIOMER OF EACH *dl* PAIR IS SHOWN

Chart 4.—The estrones.*

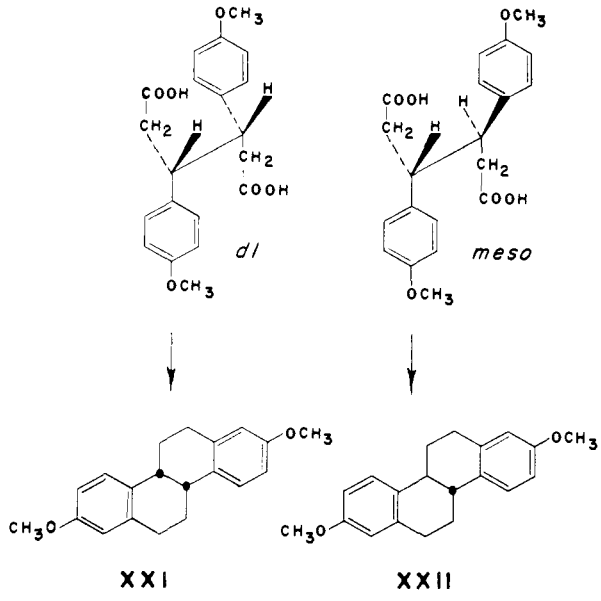
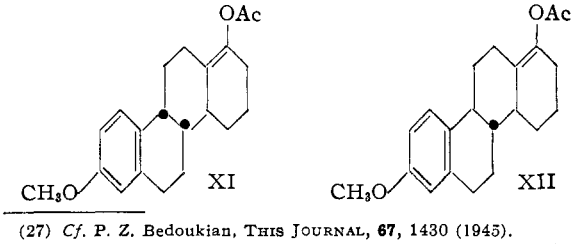


Chart 5.

acid.[27,28] Treatment with bromine,[27] followed by dehydrohalogenation of the resulting bromo ketone with lithium chloride in dimethylformamide,[29] afforded the desired α,β-unsaturated ketone IX in about 40% yield over-all from the α-ketone.



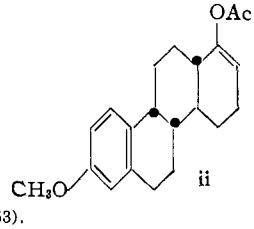
When the β-methoxyhydrochrysenone IIIa was converted to the enol acetate XII, m.p. 122–124°, by the acetic anhydride method,[27,30] brominated, and dehydrohalogenated with collidine, a difficultly separable mixture resulted. The early fractions obtained on chromatography contained considerable saturated ketonic material (exhibiting only the anisole spectrum) possibly arising from some reductive removal of bromine during the collidine treatment.[31] Later fractions showed absorption in the 246 mμ region of increasing intensity—as high as 14,400 for one fraction, m.p. 136–137.5°, which, however, was too small for further characterization. On admixture of this material with the 13,14-dehydro compound IX derived from the α-ketone, the m.p. was depressed.

Treatment of the β-methoxyhydrochrysenone with sulfuryl chloride yielded a mixture from which a monochloro derivative, m.p. 169–170.5°, was isolated in low yield. Dehydrohalogenation of this isomer with collidine gave a chlorine-free mixture, λ_{max} 246 mμ (ϵ 15,600), which melted over a broad range and could not be further purified readily by crystallization or chromatography. Its high extinction coefficient (15,600) at 246 mμ, and its partial isomerization to the dehydro α-ketone IX (see below) indicate that this mixture contained considerable 13,14-dehydro β-ketone X.

Some preliminary experiments were carried out to test the possibility of interconversion of the two 13,14-dehydro ketones IX and X through the potentially labile hydrogen atom at C_8. Boiling methanolic sodium methoxide did not affect the dehydro-α-ketone IX, but transformed the crude dehydro β-ketone X (from the dehydrochlorination described above) partly into the α-isomer IX. It may be concluded that the equilibrium IX $\rightleftarrows$ X

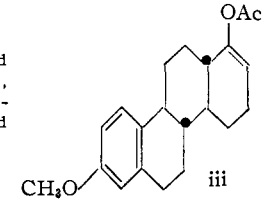
(27) *Cf.* P. Z. Bedoukian, THIS JOURNAL, **67**, 1430 (1945).

(28) It is noteworthy that a different enol acetate, m.p. 122–123°, was produced by the isopropenyl acetate method; H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949). This product is undoubtedly the 17,17a-ene-17a-ol acetate ii; *cf.* Hagemeyer and Hull, *above;* E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, THIS JOURNAL, **74**, 3228 (1952); R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952).



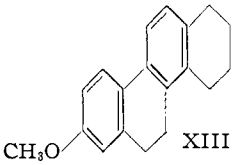
(29) R. P. Holysz, *ibid.*, **75**, 4432 (1953).

(30) The isopropenyl acetate method gave another isomer, m.p. 150.5–152°, presumably the 17,17a-ene-17a-ol acetate iii (see ref. 28) which was isolated in poor yield.



(31) *Cf.* G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

lies largely in favor of the α-isomer IX,[32] or that the conditions were not sufficiently severe to produce, at a reasonable rate, the enolate from the dehydro-α-ketone; hence equilibration was not effected, because of a difference in rates of enolization.[33] Attempts to effect the isomerization by heating with *p*-toluenesulfonic acid in xylene gave, from either IX or X, a product $C_{19}H_{20}O$, m.p. 118–119°, with λ_{max} 280 mμ (ϵ 22,700), λ_{min} 242 (5110); formulated accordingly as the methoxyhexahydrochrysene XIII.



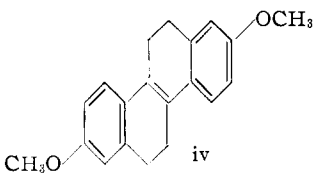
XIII

Catalytic hydrogenation of the 13,14-dehydro-α-methoxyhydrochrysenone IX over palladium-on-carbon proceeded slowly and was attended by considerable reduction of the carbonyl group. In addition to alcoholic material, considerable hydrogenolysis product was formed. The ketonic fraction, obtained in 47% yield, afforded a new stereoisomeric form of the methoxyhydrochrysenone III, namely, the γ-isomer,[22] m.p. 137.5–138°. Side reactions were minimized by hydrogenation in basic solution,[34] and the γ-ketone was isolated in about 60% yield. If the B/C configuration was unaltered during the catalytic hydrogenation—a most reasonable assumption in view of the resistance of IX to base-catalyzed isomerization—then the γ-methoxyhydrochrysenone is clearly epimeric with the α-isomer at C_{14}, and in turn at C_{13}. Conclusive proof of the B/C *cis* configuration in the γ-series followed from the fact that neither γ-1 nor γ-2 estrone (see below) was identical with 14-isoestrone (*cf.* the argument presented above for the B/C *cis* configuration of the α-series). Both of the B/C *cis* isomers were therefore in hand in the form of the α- and γ-ketones, and it remained only to decide which of these corresponded to IIIb and which to IIIc. From molecular models it appears that the 13,14-dehydro-α-ketone IX, in either of its flipped conformations, offers serious hindrance to α-side adsorption on the catalyst; hence the hydrogenation would be expected to occur preferentially on the β-face. On this basis the γ-ketone was considered quite likely to correspond to the *cis-syn-trans* isomer IIIc. The α-ketone accordingly is assigned to the *cis-anti-trans* form IIIb, and its progeny (see above) have the configurations indicated in Chart 2. Further evidence for these configurations was provided by the methylation study described below and by the identity of one of the estrone isomers thus produced with *dl*-8-isoestrone. It should be noted that the results of the lithium-in-ammonia reduction of the dehydro α-ketone (see above) do not provide evidence on this point. The reaction would indeed be expected to favor the more stable isomer,[35] but according to calculations[36] isomers IIIb and IIIc would have the same energy. The product was, in fact, a mixture which probably contained some of the γ- as well as the α-isomer which was isolated.

The application of the angular methylation–ring contraction sequence[13,14] to the new γ-methoxyhydrochrysenone as summarized in Chart 3 is now considered. Condensation with furfuraldehyde afforded the furfurylidene ketone (IVc), m.p. 192–194°, λ_{max} 326.7 mμ, in excellent yield. On methylation this substance was converted into a readily separable mixture of angularly methylated C_{13}-epimers: γ-1, m.p. 166–167.5°, λ_{max} 326.2 mμ; and γ-2, m.p. 149–150.5°, λ_{max} 321.9 mμ; isolated in 78 and 7.4% yields, respectively. In view of the formation of the γ-1 isomer in higher yield and its absorption at longer wave length in the ultraviolet region than the γ-2 epimer, these substances were assigned the C/D *cis* (formula Vc) and *trans* (formula VIc) configurations, respectively. The high ratio (about 11 to 1) of the γ-1 to γ-2 epimers produced in the methylation is consistent with the *cis-syn-trans* assignment for the γ-methoxyhydrochrysenone. It may be seen from a model of the anion of the furfurylidene derivative (IVc) that the methylene at C_7 is involved in a 1,3-diaxial interaction relative to the bond being formed at C_{13} when the methyl group enters from the α (*trans*) side as shown in Fig. 1. The effect would be to decrease the amount of product formed by this approach. The ratio (about 3.5 to 1) of the corresponding α-1 to α-2 epimers was approximately normal as in the model decalone system (see Table I), a fact consistent with the *cis-anti-trans* configuration for the α-methoxyhydrochrysenone. The β-side (*trans*) approach to the anion of the furfurylidene derivative IVb is subject to the same steric effects as in the model compound (see Fig. 1). The axial 9,10-bond is outside of the sphere of influence of the α-side (*cis*) approach which likewise is, therefore, subject to the same steric effects as in the model compound.[37]

The γ-1 and γ-2 methylated furfurylidene derivatives (Vc and VIc), on ozonolysis followed by

(32) The B/C *cis* structure IX might be more stable than the B/C *trans* isomer X- because (a) in the latter there appear to be more serious non-bonded interactions between C_1 and C_{11} and between C_7 and C_{14} than in the former, and (b) in the favored conformation of the former, the two required axial atoms (C_{10} and C_{14}) are occupied by trigonal instead of tetrahedral carbons (*cf.* the arguments presented below for the relative stabilities of the keto esters XVIa, b, c and d). Suggestive evidence that the B/C *cis* configuration of a similar system is at least comparable to the *trans* in stability is afforded by the results of the study of A. J. Birch and H. Smith, *J. Chem. Soc.*, 1882 (1951), on the reduction of the dimethoxytetrahydrochrysene iv with sodium and alcohol in liquid ammonia. These conditions are known to favor thermodynamic product-control—*cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954)—and in the case of compound iv gave rise to the *cis*- and *trans*-dimethoxyhexahydrochrysenes in about equal amounts.



iv

(33) *Cf.* (a) H. E. Zimmerman and H. J. Giallombardo, THIS JOURNAL, **78**, 6259 (1956); (b) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

(34) *Cf.* A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *ibid.*, **72**, 5524 (1950).

(35) *Cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(36) *Cf.* W. S. Johnson, THIS JOURNAL, **75**, 1498 (1953).

(37) That an axial substituent thus located in the decalone ring system does not exert significant influence on the stereochemical course of the methylation was shown by the results with the 6-ethylenedioxy derivative which also gave a *cis* to *trans* ratio of about 3.5 to 1 (see Table I).

TABLE II

RACEMIC ESTRONES AND DERIVATIVES

Stereochemical series	Products from our laboratory (m.p.'s are corrected)						Products of Anner and Miescher					Bachmann's isomer[h]
	α-1	α-2[f]	β-1	β-2[g]	γ-1[h]	γ-2	dl-14-iso[i]	a[i]	b[g]	d[f]	c	f[h]
Reference	9	9	9	9	20	20	10	8	8	8	8	8
M.p., °C., of *dl*-Homonarrianolic acid methyl ethers[a]	170–170.5	Amorphous	191–192	225–227.5	Amorphous	214–217	233.5–234.5	225–227	225–227	170–171	212–214[a]	Amorphous
dl-Estrone methyl ethers	115–116	67–68	109–110	143–144	90.5–91.5, 105–106	152.5–154.5	120.6–121	114–116	143–144	Oil	162–164[a]	Oil
dl-Estrones	180.5–181.5	197–198	238.5–240	253–255	214–215	254–255	216–217	214–216	251–254	184–186	230–232	188–190
										185–188[b]		191–195[b]
										198–200[c]		201–204[c]
dl-Estrone benzoates	149–151	159.5–161.5	157.5–158.5	184–187	172–175	197–198	181–184[d]	175–176	184–186	150–152	134–136	161–163
								179–180[e]		151–155[c]	139–142[e]	

[a] This value was originally assigned to isomer "c" (an artifact), but later reported to belong to the c-series (ref. 42). [b] Revised m.p. private communication from Drs. Anner and Miescher. [c] This is the m.p. (corrected) observed by us of a sample kindly provided by Drs. Miescher and Anner. [d] Present work. [e] See formula VII, Charts 1, 2 and 3. [f] Isomer α-2 and d appear to be identical (present work). [g] Isomer β-2 and b are identical (ref. 9). [h] Bachmann's isomer, γ-1 and f all appear to be identical (present work). [i] Isomer a and *dl*-14-isoestrone are identical (ref. 10 and present work).

Fig. 1.

treatment with alkaline hydrogen peroxide, were transformed, respectively, into the dibasic acids VIIc (amorphous) and VIIIc, m.p. 214–217°. Cyclization of these acids by pyrolysis with lead carbonate[8,9] afforded γ-1 estrone methyl ether, m.p. 90.5–91.5° and 105–106°, and γ-2 estrone methyl ether, m.p. 152.5–154.5°. These ethers, on demethylation by heating with pyridine hydrochloride, were transformed into γ-1 estrone, m.p. 214–215°, and γ-2 estrone, m.p. 254–255°, characterized as the benzoates, melting at 172–175° and at 197–198°, respectively.

Dauben and Ahramjian[38] have reported that the hydrogenation of *d*-equilenin over Raney nickel gives a significant amount of a substance that is most probably 8-isoestradiol. In the present study we applied their procedure to *dl*-equilenin[39] which gave *dl*-8-isoestradiol, m.p. 213.5–214° when pure, as the only isolable product in the phenolic fraction. The 3-benzoate was prepared[40] and oxidized with chromium trioxide in pyridine to give *dl*-8-isoestrone benzoate, m.p. 194.5–197°. Saponification yielded the free phenol, m.p. 254–256° dec., which was converted to the methyl ether, m.p. 152–152.5°. The identity of these last three substances with the corresponding compounds in the γ-2 series was established by mixed m.p. determinations and by infrared comparison of the benzoates and methyl esters.

Confirmatory proof that the products in the α- and the γ-series were truly stereo and not structural isomers of estrone was provided by mild dehydrogenation of the methyl ethers over 5% palladium-on-carbon at 250°—conditions known to convert estrone methyl ether into isoequilenin methyl ether.[41] *dl*-Isoequilenin methyl ether was thus produced in 67% yield from the α-1 isomer and in 75% yield from the γ-1 isomer. The identity of the dehydrogenation products with authentic material[39] was established by mixed m.p. and infrared spectroscopic determinations.

The foregoing considerations permit the following configurations to be assigned with reasonable assurance to the estrones in the α- and γ-series: α-1 = *dl*-9-iso-13-isoestrone; α-2 = *dl*-9-isoestrone; γ-1 = *dl*-8-iso-13-isoestrone; γ-2 = *dl*-8-isoestrone (see Chart 4).

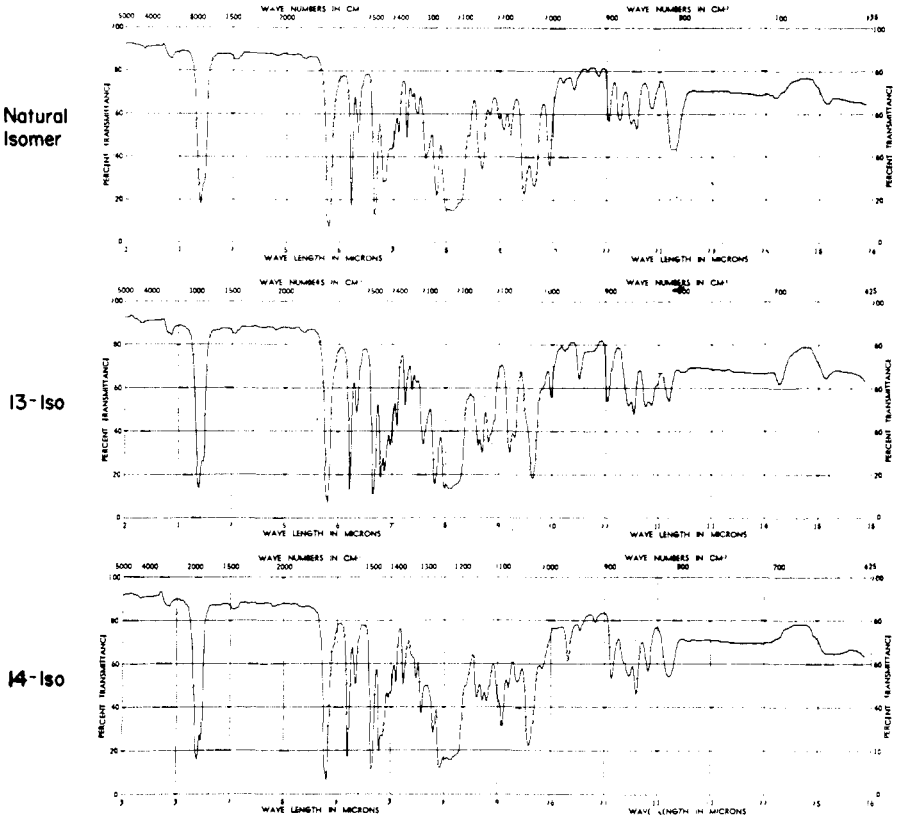
Interrelationships of all of the Synthetic Estrones and Further Configurational Considerations.—As summarized above we have synthesized seven

(38) W. G. Dauben and L. Ahramjian, THIS JOURNAL, **78**, 633 (1956).

(39) W. S. Johnson, J. W. Petersen and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).

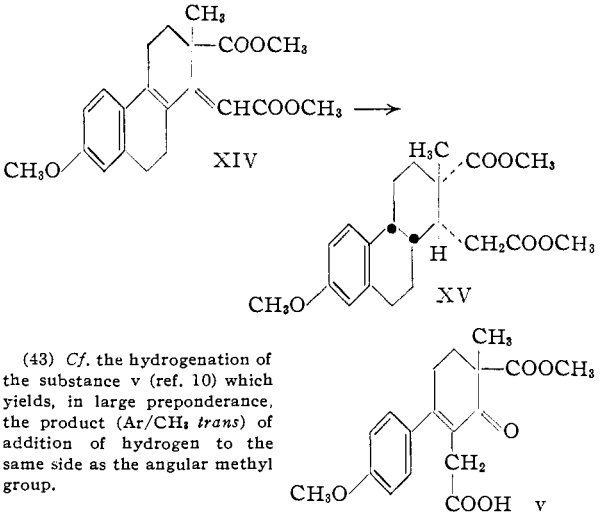
(40) *Cf.* A. Serini and W. Logemann, *Ber.*, **71**, 186 (1938).

(41) W. E. Bachmann and A. S. Dreiding, THIS JOURNAL, **72**, 1323 (1950).



(α-1, α-2, β-1, β-2, γ-1, γ-2 and 14-iso) of the eight possible racemates having the estrone structure. A summary of the properties of these isomers appears in Table II, the configurations are shown in Chart 4, and the infrared spectra of the methyl ethers are reproduced in Fig. 2. Six other products (see Table II) having the estrone structure have been described, namely, estrone a, b, d, e and f[42] of Anner and Miescher,[8] and an isomer of Bachmann, Kushner and Stevenson[7] hereafter referred to as "Bachmann's isomer." Thus a total of 13 racemic products have been described and their properties are summarized in Table II. The matter of the identity of various of these substances is now considered.

The identity of β-2 estrone with isomer b and of 14-isoestrone with isomer a already has been established.[9,10] The latter relationship has been confirmed in the present work by the identity of the infrared spectra of the benzoates. By virtue of the proximity of the melting points of the free hydroxy compounds and of the benzoates, Anner and Miescher proposed tentatively that their estrone a (14-isoestrone) was identical with Bachmann's isomer. The reported physiological activities, however, are not in good agreement[8b] nor are the melting points of the methyl ethers (see particularly the m.p. of 14-isoestrone methyl ether). The melting points of the comparable compounds in the new γ-1 series, on the other hand, appear to be in better agreement with those in the Bachmann series, including the polymorphic nature of the methyl ether. These along with the stereochemical considerations (see below) provide a basis for concluding that γ-1 and Bachmann's estrone are identical. Unfortunately it has not been possible to obtain any of Bachmann's products for a direct comparison. The *cis-syn-cis* configuration is most reasonable for the product of the Bachmann synthesis in which the critical step, stereochemically, was the catalytic hydrogenation of the unsaturated diester XIV. All *cis* addition of hydrogen from that (least hindered) side bearing the angular methyl group[43] would afford the *cis-syn-cis* arrangement XV as, at least, a significant[44] product.



(42) The originally reported (ref. 8) "estrone c" was later withdrawn since it appeared to be a degradation product of isomer e; G. Anner and K. Miescher, *Helv. Chim. Acta*, **33**, 1379 (1950).

(43) *Cf.* the hydrogenation of the substance v (ref. 10) which yields, in large preponderance, the product (Ar/CH_3 *trans*) of addition of hydrogen to the same side as the angular methyl group.

(44) The crude hydrogenation product was not homogeneous, and the remaining steps of the synthesis were carried out on mixtures.

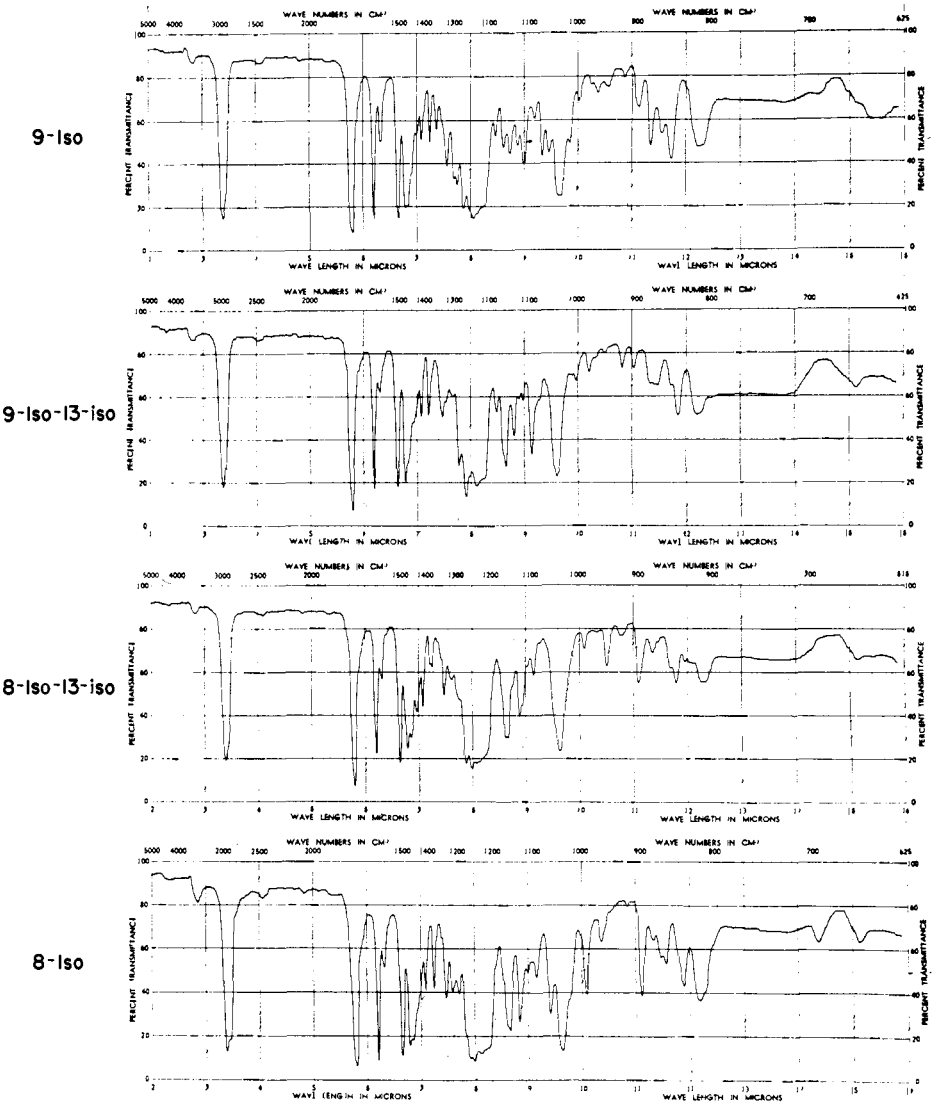
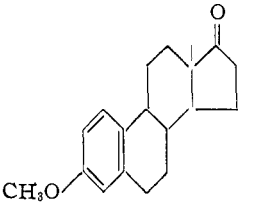


Fig. 2.—Infrared spectra of estrone methyl ethers in chloroform.

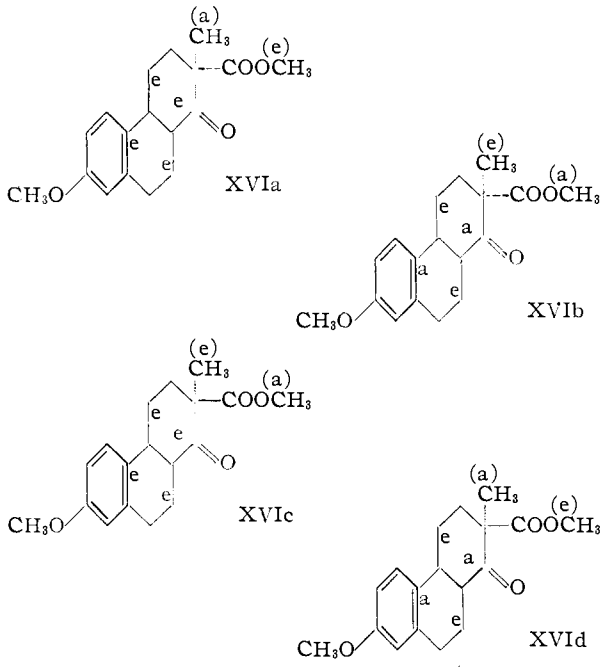


The matter of isomers d, e and f of Anner and Miescher now remains for consideration. From the reported melting points there seemed to be no obvious agreement with any of our products. We elected, therefore, to employ infrared spectroscopy. Although the spectra of the methyl ethers are especially characteristic in the long wave region (see Fig. 2), the benzoates promised to be most suitable for comparison studies from the point of view of availability[45] and apparent purity (note that the d and f methyl ethers, for example, were oils), and complete infrared spectra were determined for all of the benzoates listed in Table II except that of Bachmann which was unavailable. The spectra of the benzoates of estrone d and α-2 estrone were essentially identical and clearly different from any of the others. Similarly the spectra of the benzoates of estrone f and γ-1 estrone were essentially identical and except for that of isomer e (see below), unlike any of the others. Mixed melting point determinations of the following pairs of substances showed no depression[45]: estrone d benzoate and α-2 estrone benzoate; estrone f and γ-1 estrone; estrone f benzoate and γ-1 estrone benzoate. On admixture of estrone d and α-2 estrone, a small (5–8°) depression of the m.p. was observed, pos-

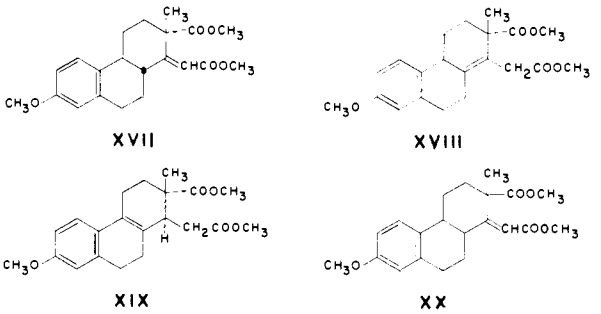
The pure estrone isomer was isolated in low yield only at the last stage (see ref. 7).

(45) We are grateful to Drs. Miescher, Wettstein and Anner for sending us specimens for comparison.

sibly due to the presence of impurities. The balance of the evidence, however, is strongly in favor of the identity of the d and α-2 series, and of the f and γ-1 (and the Bachmann) series. The infrared spectrum of estrone e benzoate was very similar to that of the benzoate of estrone f and of γ-1 estrone. This lack of distinguishing spectral characteristics evidently is fortuitous, for not only is the disagreement in the melting points of the respective series quite significant (see Table II), but the physiological activities are completely different: estrone e, 7–10 γ as compared with estrone f > 1 mg.[8b] Anner and Miescher have described two specimens of estrone e methyl ether, one melting at 146–147° and the other at 162–164°. The latter material, originally called estrone c methyl ether, was later considered to represent a pure specimen of the e series.[42] Only the lower-melting material was available to us for comparison purposes.[45] In our hands it melted at 152–154° and, surprisingly, appeared to be identical with our γ-2 (8-iso) estrone methyl ether, m.p. 152.5–154.5°, as shown by infrared spectroscopic and mixed melting point determinations. Now estrone e benzoate is clearly different from that of γ-2 (see above). It seems probable, therefore, that the specimen of "estrone e" methyl ether, m.p. 146–147°, represents a different molecular species from estrone c methyl ether, m.p. 162–164°, and that the latter is the true progenitor of estrone e, m.p. 230–232°, giving the benzoate, m.p. 134–136°. By a process of elimination, estrone e may accordingly be *tentatively* assigned the *trans-syn-trans* configuration and is thus formulated as *dl*-13-iso-14-isoestrone (Chart 4).



Previous attempts to deduce the configuration of the products of the Anner and Miescher estrone synthesis have proved abortive because of the uncertainty of the stereochemical course of the reactions. Now that the configurations of these isomers are reasonably certain (see above), it is possible to rationalize their formation. The key intermediate in the Anner–Miescher synthesis was a keto ester XVI with three asymmetric centers, capable of existing in four racemic forms XVIa, b, c and d. Three of these, A, B and C were isolated in crystalline form. Keto ester A, on submission to the Reformatsky reaction followed by dehydration, gave as expected a mixture of unsaturated esters. An isomer, m.p. 113–115°, was isolated, and on catalytic hydrogenation it gave predominantly a product which, since it led to *dl*-estrone, possessed the *trans-anti-trans* configuration. Keto ester A was, therefore, properly assigned the configuration XVIa. A by-product of the hydrogenation of the 133–115° ester led to estrone a which, as correctly predicted by Anner and Miescher on the assumption that the olefinic bond of the 113–115° ester was exocyclic (formula XVII), was later shown to be *dl*-14-isoestrone.[10] It has also since been firmly es-



tablished that the 113–115° unsaturated ester is correctly represented by formula XVII.[10] A second unsaturated ester, m.p. 95–97°, isolated from the dehydration mixture, afforded on hydrogenation an oily mixture which led to the d and e series. The geometric isomer of the 113–115° ester is known.[10] It melts at 112–112.2° and on hydrogenation yields the natural (*trans-anti-trans*) series stereospecifically. The 95–97° unsaturated ester, therefore, must be a structural isomer, preferably either XVIII, a likely product of direct dehydration, or its tautomer XIX with the olefinic bond in conjugation with the aromatic nucleus and the two carboxylic ester side-chains oriented in the more stable *trans* manner. The *cis-anti-trans* (d series) product would be produced by a *cis* addition of hydrogen to the β-side of XIX. This isomer XIX could be the immediate precursor of the d series even if the 95–97° ester is correctly represented by formula XVIII, because the olefinic bond in XVIII would be expected to be relatively resistant to hydrogenation,[46] and the reaction conditions—palladium in acetic acid at 60°—might well be expected to promote rearrangement of the double bond prior to reduction.[47] The bond, of course, might also migrate into conjugation with the carbomethoxyl group. Since, by such wanderings of the olefinic bond during hydrogenation, all but one potential asymmetric center can thus become involved, no meaningful *a priori* predictions can be made with respect to the configurations of the prod-

(46) *Cf.* the inertness of the 8,14-bond of steroids to hydrogenation; *e.g.*, Fr. Schenck, K. Buchholz and O. Wiese, *Ber.*, **69**, 2696 (1936).

(47) *Cf.* E. A. Braude and R. P. Linstead, *J. Chem. Soc.*, 3544 (1954); D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **77**, 139 (1955); R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2670 (1956).

ucts. Complex shifts must attend the formation of the e series (if, indeed it is correctly represented as *trans-syn-trans*) conceivably involving migration of the olefinic bond in XIX away from the 9-position[12] leaving the hydrogen there in the β-configuration. Such a shift would have to be followed by an α-side attack of hydrogen while the bond is at 8,14 or in conjugation with the carbomethoxyl group. These last considerations are entirely speculative.

Keto ester A (XVIa) and keto ester C were readily interconvertible under enolizing conditions; therefore the latter is clearly the C_8-epimer XVIb. At equilibrium the A isomer appears to be preponderant, but it is of particular interest that the C form is found in significant amounts, in spite of the fact that the B/C rings are *cis* fused and the carbomethoxy group is probably axially conformed.[48] The reason for this relative stability of the *cis* form is probably, in part, the presence of the two trigonal carbon atoms at the A/B juncture, which are located in such a manner (1,2- relative to the B/C decalin ring system) as to exert a stabilizing influence on the *cis* form.[49]

The keto ester B obviously belongs to the 13-iso series and is evidently the more stable of the two possible epimers XVIc and XVId. The following considerations lead to the conclusion that the latter *cis* form is the more stable. Isomer XVIc is less stable than XVIa, because they differ only in that the carbomethoxyl group is axial in the former and equatorial in the latter. On the other hand, in its preferred conformation[48a] isomer XVId is less stable than XVIb, for similar reasons. If these stability relationships are correct, it follows that the equilibrium XVIc $\rightleftarrows$ XVId must lie further to the right than does XVIa $\rightleftarrows$ XVIb. Since there is a significant amount of XVIb present in the latter equilibrium, there would have to be at least a bit more and possibly very much more of XVId present in the former equilibrium. Therefore since the equilibrium XVIc $\rightleftarrows$ XVId lies essentially completely in the favor of one component, this must be XVId, which is accordingly the preferred configuration for keto ester B. The noted[8b] low reactivity of keto ester B as compared with A in the Reformatsky reaction is consistent with the axial carbonyl group in the former.

Working on the assumption that keto ester B was the B/C *trans* isomer XVIc, Anner and Miescher[50] proposed that estrone f, derived therefrom, was 13-isoestrone (lumiestrone). From the present study it is evident that estrone f is not 13-isoestrone (estrone β-1) but is probably the *cis-syn-cis* isomer, 8-iso-13-isoestrone. This is, indeed, the expected product from the keto ester XVId which should lead to the unsaturated ester XX, and this in turn would be expected to undergo hydrogenation from the less hindered α-side giving the *cis-syn-cis* configuration.

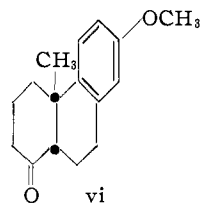
The possibility remains that certain of the above assumptions (*e.g.*, see refs. 48 and 49) are incorrect, or that the analysis is over-simplified since, for example, polar interactions between the keto and carbomethoxyl groups are neglected, in which case keto ester B might indeed be the *trans* isomer XVIc. The formation of estrone f would, in this event, require a less satisfactory rationalization, and the lower reactivity of keto ester B than A would be difficult to explain.

On the Configuration of Estrone.—The arguments presented in the foregoing are predicated on the assumption that the configuration of estrone is *trans-anti-trans* (see Chart 4). While the configurational disposition of the B/C/D rings may be considered unequivocally established for the non-aromatic steroids, the case is not as strong for the estrone series.[51] The evidence that has been cited,[51] coupled with that afforded by total synthesis studies,[52] provides fairly good evidence for the *trans-anti-trans* configuration of estrone.

In this section of the present paper independent evidence is presented which establishes the B/C *trans* configuration of estrone in the classical man-

(48) (a) The conformations shown in formulas XVIb and XVId are preferred to the alternative (flipped) forms because the latter have unfavorable 1,3-diaxial interactions between the 7-methylene and the 18-methyl (see ref. 12) flanking the keto group. While such an interaction is not as severe as in the case without the interposed trigonal atom (E. J. Corey and R. A. Sneen, THIS JOURNAL, **77**, 2505 (1955)), it is considered sufficient to favor the conformations shown. In addition, these conformations allow the ketone carbonyl to occupy the favored axial conformation (*Cf.* W. Klyne, *Experientia*, **12**, 119 (1956)), and models indicate that the aryl group of a *cis*-unsymmetrical octahydrophenanthrene system (as in XVIb and XVId) can also be axially conformed without serious non-bonded interactions, because the aromatic nucleus is frozen in a plane essentially perpendicular to the axial β-hydrogen atom at C_{12}; *cf.* E. Wenkert and T. E. Stevens, THIS JOURNAL, **78**, 2318 (1956). (b) It is assumed that of the two alternative (flipped) conformations of the methyl 2-methylcyclohexanone-2-carboxylate system, that one with the carbomethoxy equatorially conformed is preferred. That the carbomethoxy can be thus accommodated in the axial conformation less readily than the methyl group cannot be supported *a priori*, since the *A*-value (see S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955)), for the former group has not been determined. Support for the premise, however, follows from the rationalization of the formation of estrone f (see below), and from the fact that a system of homologous compounds, *i.e.*, XVIa etc., with an acetic acid residue (*A*-value obviously larger than that for methyl) in place of the carbomethoxy group, appears to exhibit analogous behavior (personal communication from A. L. Wilds and D. Stoutamire).

(49) See Corey and Sneen, and Wenkert and Stevens (ref. 48a). Also note that while 4-ketocholestanone (with A/B *trans*) is clearly the more stable of the two C_8-epimers (see R. Stevenson and L. F. Fieser, THIS JOURNAL, **78**, 1409 (1956)), the related system, with an aromatic ring C, is more stable in the *cis* modification vi as shown by G. Stork and W. H. Reusch (see Ph.D. dissertation of W. H. R., Columbia University, 1957).

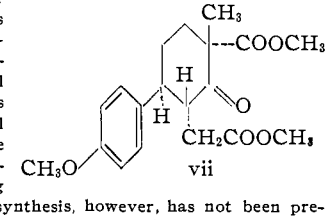


vi

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

(51) R. B. Turner in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 623.

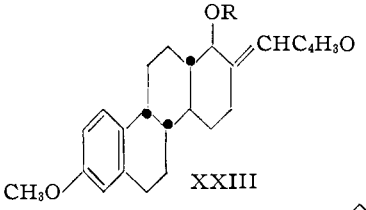
(52) For example: the synthesis of estrone (ref. 9), involving direct introduction of the angular methyl group (see Chart 1), considered in light of the rules evolved in the present study regarding isomer ratio and effects on the ultraviolet spectra, provides strong evidence for the C/D *trans* configuration. The B/C *trans* configuration is supported by the total synthesis (ref. 10) involving the intermediate vii in which the aryl and acetic ester substituents were undoubtedly diequatorial and hence *trans* oriented. The possibility that inversion occurred at C_8 (ref. 12) during some subsequent steps in the synthesis, however, has not been precluded, since it is recognized that once ring B has been completed, the relative stability of the B/C *cis* isomer is probably increased (see the discussion above regarding the relative stabilities of the keto esters XVIa, b, c and d).



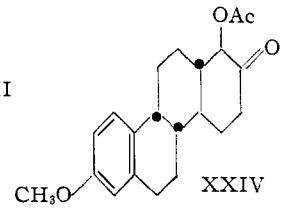
vii

ner through relationships to substances of unequivocal configuration. This work in turn confirms the remaining configurational picture.

Both the *cis*-(XXI) and *trans*-(XXII) forms of 2,8 - dimethoxy - 4b,5,6,10b,11,12 - hexahydrochrysene are known, and their configurations have been established unequivocally by Wilds and Sutton[53] through their preparation, respectively, from the *dl*- and *meso*-forms of β,γ-di-*p*-anisyladipic acid (see Chart 5). The objective of the present investigation was to relate our methoxyhydrochrysenones III, by relocation of the oxygen and aromatization of ring D, to these dimethoxyhexahydrochrysenes. Because of its availability the α-ketone was chosen for the study.

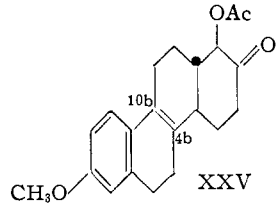


XXIII



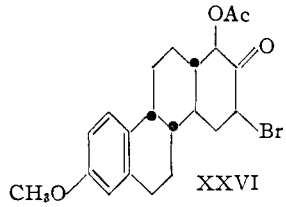
XXIV

Condensation of the α-methoxyhydrochrysenone with furfuraldehyde afforded the furfurylidene derivative, m.p. 181–182°, which on reduction with sodium borohydride was converted mainly into a single hydroxy compound, m.p. 186–188°, probably the 17aβ (equatorial) epimer XXIII (R = H). The conditions for acetylation of this allylic type alcohol were critical because of the competing dehydration reaction. The best procedure found involved heating with pyridine and acetic anhydride for a short period which led to the acetate XXIII (R = Ac), m.p. 133–135° (pure), in about 68% yield.

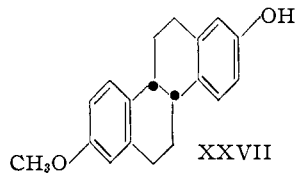


XXV

Treatment of the furfurylidene acetate XXIII (R = Ac) with 1 mole-equivalent of ozone in ethyl acetate containing 1.5 mole-equivalents of pyridine,[54] and then a reductive cleavage with hydrogen in the presence of palladium-on-strontium carbonate, gave the acetoxy ketone XXIV in 29% yield at best. This product, m.p. 172–175°, was almost always accompanied by material absorbing at longer wave lengths in the ultraviolet region. The proportion of this by-product was increased when more than 1 mole-equivalent of ozone was employed. In one such experiment none of the desired acetate was obtained, but instead a compound, m.p. 213–215°, was isolated. The carbon–hydrogen analysis and the ultraviolet spectrum, λ_{max} 273.5 mμ (ϵ 16,700), were compatible with the structure XXV,[55] which is a reasonable product of oxidation of the highly nucleophilic (promoted by the *p*-methoxyl substituent) position C_{10b}[56] (chrysene numbering), followed by elimination of the tertiary heteroatom (also facilitated by the methoxyl group[56]). The possibility of minimizing this oxidative introduction of a double bond at 4b,10b by replacing the methoxy with an electron withdrawing acyloxy group was not investigated.



XXVI



XXVII

A number of unsuccessful attempts were made to eliminate the acetoxy group in XXIV with the view to aromatizing the resulting ketone by dibromination followed by dehydrohalogenation. In connection with some other studies in our laboratory R. Pappo found that the Holysz method[29] for dehydrohalogenation of α-halo ketones was also applicable to the dehydroacetoxylation of α-acetoxy ketones.[57] Thus when the acetoxy ketone XXIV was heated in dimethylformamide saturated with lithium chloride, elimination occurred as evidenced by the appearance of the α,β-unsaturated ketone band at 243 mμ. This product was not isolated because the method promised to be applicable to direct aromatization as follows. The acetoxy ketone XXIV was treated with 1 mole-equivalent of bromine in acetic acid saturated with hydrogen bromide. Alkaline extraction of the crude product afforded a small amount of "acidic" material which, from its typical ultraviolet spectrum, appeared to contain the 1,2-diketo compound arising from some bromination on the carbon atom holding the acetoxyl group followed by hydrolysis. Chromatography of the neutral fraction gave, in about 50% yield, a bromo ketone fraction evidently containing the substance XXVI. After treatment of this material with dimethylformamide saturated with lithium chloride, about 38% of the product was extractable with dilute sodium hydroxide. This extract probably contained some of the sought-for phenol, but the ether prepared on methylation with dimethyl sulfate was not easily purified. Evidently the bulk of the phenol remained in the "neutral" fraction, because further, extraction with Claisen alkali effected a separation in 53% yield, of phenolic material (XXVII) which on methylation with dimethyl sulfate afforded,

(53) A. W. Wilds and R. E. Sutton, *J. Org. Chem.*, **16**, 1371 (1951).

(54) *Cf.* D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, Jr., J. E. Stafford, R. L. Pederson and A. C. Ott, THIS JOURNAL, **77**, 1212 (1955).

(55) *Cf.* the spectrum λ_{max} 275 mμ (ϵ 16,000), 8-dehydroestrone; D. Banes, J. Carol and E. O. Haenni, *J. Biol. Chem.*, **187**, 557 (1950); D. Banes and J. Carol, *ibid.*, **204**, 509 (1953).

(56) *Cf.* the oxidation of comparably activated positions by lead tetraacetate, and also the facile decomposition of the product to produce an olefinic bond; W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman and W. F. Johns, THIS JOURNAL, **78**, 6312 (1956).

(57) For example it was shown, in experiments performed by J. D. Bass, that 2-acetoxy-2-methylcyclohexanone could thus be converted into 2-methylcyclohexenone in about 55% yield. The reaction was slower, requiring higher temperatures and higher concentrations of lithium chloride than with the bromo ketone. It is, of course, possible that the reaction involves an SN2 replacement of acetoxy by chlorine prior to elimination.

after purification, colorless needles, m.p. 146–148°. The identity of this substance with the Wilds–Sutton[53] *cis* compound XXI was established by mixed melting point and infrared spectroscopic determinations.

The reaction product from the aromatization sequence was examined carefully for the presence of the *trans* isomer XXII which, by virtue of its higher melting point (187–188°[53]), should have been readily separated. None could be found. Had the reaction conditions for the aromatization sequence unexpectedly labilized the hydrogens at C_{4b} or C_{10b}, the product undoubtedly would have consisted of a mixture of the *cis*- and *trans* isomers containing a significant proportion of the latter.[32] The facts, therefore, strongly favor the most reasonable assumption that the stereochemical integrity of the B/C ring system was maintained throughout the aromatization sequence, and lead to the conclusion that the α-ketone is indeed the B/C *cis* compound. As a corollary, the β-ketone and, in turn, estrone must have the B/C *trans* configuration. The confirmation of the above experiment, namely, the conversion of the β-ketone into the *trans* compound XXII, has not been carried out.

Experimental[58]

Analysis of Reaction Mixtures by Infrared Spectroscopy.—Infrared spectroscopy was employed for determining the approximate *cis/trans* ratios of methylation products in a number of the cases described below. Characteristic bands were found for the parent arylmethylenedecalone, the *trans*-9-methyl, and the *cis*-9-methyl homolog at approximately 8.45, 9.80 and 10.05 μ, respectively. Specific positions of these bands are recorded below under the preparations of the individual compounds with A-values calculated from the formula $AC = -\log I/I_0$ where C is concentration in moles/kg. of carbon disulfide. Authentic specimens of the *cis* and *trans* forms of the arylmethylene-9-methyldecalones were prepared for spectral examination by condensation of pure *cis*- and *trans*-9-methyldecalone-1 (see below) of known configuration with the aldehyde. The arylmethylenedecalone was prepared by condensation of the aldehyde with 1-decalone. The product was methylated by treatment with potassium *t*-butoxide and methyl iodide in *t*-butyl alcohol according to the procedure already described,[13] and the composition of the mixture calculated from the A-values determined at the characteristic positions in the infrared region (see above). The accuracy of the determination was found to be only about ±10% with known mixtures consisting of benzylidenedecalone and the *cis*- and *trans*-9-methyl homologs. The *cis/trans* ratios thus obtained that are reported in Table I, therefore, are subject to this error.

***cis*-9-Methyldecalone-1** was prepared exactly as described[13] except that a purer specimen was obtained by fractionation of the final product through a 60-cm. Podbielniak wire-spiral column.[59] The fractionated material had $n^{25}D$ 1.4894. d^{25} 0.9918, M_D 48.3 (calcd. 48.6).

***trans*-9-Methyldecalone-1.**—A new preparation of this substance was developed. 2-Furfurylidene-*trans*-9-methyldecalone-1, which is readily separated from the methylation mixture,[14] was heated with aqueous sodium hydroxide in ethylene glycol. The major product was *trans*-9-methyldecalol-1, which evidently was formed by a crossed Cannizzaro reaction of the primary hydrolytic products, *viz.*, *trans*-9-methyldecalone-1 and furfuraldehyde. Oxidation of the alcohol afforded the desired ketone. Although the yield was not good, the sequence is performed readily and provides an easy source of pure material. Details are given below.

A mixture of 120 g. of sodium hydroxide, 600 ml. of ethylene glycol and 60 ml. of water in a stainless steel flask was warmed with an oil-bath at 130°. When the mixture reached about 115°, rapid exothermic dissolution of the sodium hydroxide occurred. Eleven grams of 2-furfurylidene-*trans*-9-methyldecalone-1,[14] m.p. 110.5–111°, was added and the mixture boiled under reflux (bath temperature about 150°) for 7.5 hr. The mixture was then cooled, diluted with water and steam distilled. About 15 l. of distillate was collected and extracted with ether. The combined ether extracts were washed with water, then with saturated brine, and dried over anhydrous magnesium sulfate. Distillation gave 2.33 g., b.p. about 114° (9.5 mm.), of *trans*-9-methyldecalol-1, $n^{25}D$ 1.4990, which was not purified further, but used directly in the oxidation described below. A second fraction from the distillation amounted to 3.13 g., b.p. about 144° (1 mm.), $n^{25}D$ 1.5220, λ_{max} 218 mμ (ϵ ~13,000). After chromatography on Florisil and redistillation, the material was still a liquid, λ_{max} 5.98 μ; C, 78.4; H, 8.52.

A solution of 1.5 g. of sodium dichromate dihydrate in 7 ml. of water, 2 ml. of concentrated sulfuric acid and 1.2 ml. of glacial acetic acid was added slowly with stirring to a chilled solution of 2.17 g. of the aforementioned crude methyldecalol in 10 ml. of benzene. The mixture was stirred for 2 hr. at 0° then for 2 hr. at room temperature. The benzene layer was washed with water, saturated sodium bicarbonate solution and saturated brine. The solvent was removed by distillation and the residue treated with semicarbazide hydrochloride and sodium acetate in aqueous methanol. The semicarbazone that separated amounted to 2.41 g. (83%), m.p. 221.5–222.5° dec. A single recrystallization gave material, m.p. 226–227° dec. (reported[13] 219–220° dec.). Hydrolysis of 3.74 g. of such material by heating with aqueous oxalic acid afforded, after isolation by ether extraction and distillation, 2.38 g., b.p. 104–106° (9.5 mm.), $n^{25}D$ 1.4884, d^{25} 0.9909, M_D 48.3 (calcd. 48.6).

In model hydrolysis experiments with 2-furfurylidenedecalone-1, conducted essentially as described above, it was found that the cleavage was much more rapid than in the case of the 9-methyl homolog, permitting isolation of the ketone before it was appreciably reduced by the Cannizzaro reaction. In one experiment, for example, after a reaction period of only 15 minutes, 1-decalone was isolated from the steam distillate as the 2,4-dinitrophenylhydrazone in 54% yield. With the *trans*-9-methyl homolog, in contrast, appreciable starting furfurylidene derivative was still present after a reaction period of 2.5 hr.

Formation of Arylmethylene Derivatives.—The condensations of the aldehydes with the decalones, summarized below, were carried out essentially as already described,[13] except that methanol, which has been found to be better than ethanol,[9] was employed as the solvent. The condensations with the pure 9-methyldecalones were performed on a small scale (as described in previous work[13]), particular attention being given to preparation of a pure reference specimen rather than to the yield, which is not recorded.

2-*p*-Anisylidene-*cis*-9-methyldecalone-1, after sublimation at 108° (0.02 mm.) and crystallization from methanol, was obtained as colorless prisms, m.p. 110–111°; λ_{max} 229 mμ (ϵ 7,100), 314 (19,400); λ_{min} 253 (2,000); λ_{max} 5.98 and 6.25 μ. For analysis: λ 10.03 μ (A 41.2), 8.50 (25.2), 9.75 (6.5).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.25; H, 8.51. Found: C, 80.0; H, 8.50.

2-*p*-Anisylidene-*trans*-9-methyldecalone-1 was repeatedly recrystallized from methanol to give colorless plates, m.p. 110–111°; λ_{max} 227 mμ (ϵ 7,250), 311 (18,500); λ_{min} 253 (2,000); λ_{max} 5.98 and 6.25 μ. For analysis: λ 9.75 μ (A 32.0), 8.50 (48.1), 10.03 (13.4).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.8; H, 8.50.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow-orange prisms, m.p. 224–225°.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.08. Found: C, 64.2; H, 6.00.

2-*p*-Anisylidenedecalone-1.—From 20 g. of decalone-1 and 18.2 g. of anisaldehyde, treated in 500 ml. of methanol with 200 ml. of 15% sodium hydroxide and 52 ml. of water, there was obtained after 3 days 20.4 g., m.p. 104–106°, and,

(58) Unless otherwise indicated all melting points are corrected for stem exposure. Except where indicated to the contrary, carbon disulfide was employed as the solvent for the infrared, and 95% ethanol for the ultraviolet spectral determinations.

(59) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, pp. 237–243.

after 30 days, an additional 12 g., m.p. 106–107°, of crystalline product. Two crystallizations from methanol afforded colorless crystals, m.p. 107–108°; λ_{max} 228 mμ (ε 7,000), 313 (19,000); λ_{min} 252 (2,200); λ_{max} 5.98 and 6.25 μ. For analysis: λ 8.50 μ (*A* 60.4), 9.75 (4.3), 10.03 (0.8).

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.1; H, 8.16.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as orange prisms, m.p. 223.5–224°. A second form, m.p. 245–246°, was also isolated.

Anal. Calcd. for $C_{24}H_{26}O_5N_4$: C, 63.99; H, 5.82. Found: C, 64.0; H, 5.87.

The methylation product was obtained in 95% yield as a pale yellow solid, m.p. 89–91°; λ 8.50 μ (*A* 34), 9.75 (17), 10.03 (33), *C* = 0.0134, indicating a composition of 0% 9-H, 67% *cis*-9-CH_3 and 40% *trans*-9-CH_3. Fractional crystallization from methanol afforded specimens of pure *cis* and *trans* isomers.

2-*p*-Chlorobenzylidene-*cis*-9-methyldecalone-1, after sublimation at reduced pressure followed by repeated recrystallization from methanol, was obtained as colorless prisms, m.p. 112–112.7°; λ_{max} 222 mμ (ε 7,200), 289.5 (18,400), 6.00 μ, 6.28 μ. For analysis: λ 10.05 μ (*A* 35.8), 8.42 (3.2), 9.77 (4.2).

Anal. Calcd. for $C_{18}H_{21}OCl$: C, 74.86; H, 7.33. Found: C, 74.9; H, 7.33.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as orange prisms, m.p. 184–185°.

Anal. Calcd. for $C_{24}H_{25}O_4ClN_4$: C, 61.46; H, 5.37. Found: C, 61.2; H, 5.13.

2-*p*-Chlorobenzylidene-*trans*-9-methyldecalone-1, after sublimation at reduced pressure followed by repeated recrystallization from methanol, was obtained as colorless rods, m.p. 118.5–119.5°; λ_{max} 221.5 mμ (ε 7,300), 286 (18,400), 5.93 μ. For analysis: λ 9.77 μ (*A* 22.0), 8.42 (3.7), 10.05 (16.1).

Anal. Calcd. for $C_{18}H_{21}OCl$: C, 74.86; H, 7.33. Found: C, 75.0; H, 7.19.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow rods, m.p. 236.5–237.8°.

Anal. Calcd. for $C_{24}H_{25}O_4ClN_4$: C, 61.46; H, 5.37. Found: C, 61.2; H, 5.62.

2-*p*-Chlorobenzylidenedecalone-1.—From 38.3 g. of decalone-1 and 34.4 g. of *p*-chlorobenzaldehyde, condensed as described above, there was obtained, after a reaction period of a few minutes, 39.8 g. of pale yellow crystalline product, m.p. 144–146°. Repeated recrystallization from methanol gave colorless plates, m.p. 152.5–153.5°; λ_{max} 222 mμ (ε 6,800), 289 (17,000), 5.98 μ, 6.25. For analysis: λ 8.42 μ (*A* 26), 9.77 (2.2), 10.05 (2.2).

Anal. Calcd. for $C_{17}H_{19}OCl$: C, 74.31; H, 6.97. Found: C, 74.6; H, 6.94.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow needles, m.p. 217–218°.

Anal. Calcd. for $C_{23}H_{23}O_4ClN_4$: C, 60.72; H, 5.09. Found: C, 60.5; H, 5.07.

The methylation product was obtained in 95% yield as a colorless solid; λ 8.42 μ (*A* 4.8), 9.77 (7.2), 10.05 (33.4), *C* = 0.0128, indicating a composition of 6% 9-H, 86% *cis*-9-CH_3 and 16% *trans*-9-CH_3. Fractional crystallization from methanol afforded a specimen of the pure *cis* isomer. The *trans* epimer was not isolated from the mixture.

2-*p*-Dimethylaminobenzylidene-*cis*-9-methyldecalone-1 was prepared by sodium methoxide-catalyzed condensation of *p*-dimethylaminobenzaldehyde with *cis*-9-methyldecalone-1 according to the procedure described below for the reaction with decalone-1. After sublimation at reduced pressure and repeated recrystallization from chloroform–ethanol it was obtained as pale yellow rods, m.p. 120–120.5°; λ_{max} 248 mμ (ε 9,000), 377 (29,000); λ_{min} 284 (2,200); λ_{max} 6.07 μ, 6.25. For analysis: λ 10.05 μ (*A* 75.2), 8.45 (14.1), 9.78 (4.7).

Anal. Calcd. for $C_{20}H_{27}ON$: C, 80.76; H, 9.15. Found: C, 80.8; H, 9.03.

2-*p*-Dimethylaminobenzylidene-*trans*-9-methyldecalone-1 was also prepared by the sodium methoxide procedure (see below). In order to obtain a satisfactory yield it was necessary to reflux the reaction mixture for 2 hours. After repeated recrystallization from chloroform–ethanol the product was obtained as pale yellow plates, m.p. 154–155°; λ_{max} 248 mμ (ε 9,300), 369 (20,000); λ_{min} 284 (2,200); λ_{max} 6.05 μ, 6.25. For analysis: λ 9.78 μ (*A* 43.2), 8.45 (23.2), 10.05 (26.8).

Anal. Calcd. for $C_{20}H_{27}ON$: C, 80.76; H, 9.15. Found: C, 81.0; H, 9.15.

2-*p*-Dimethylaminobenzylidenedecalone-1.—Attempts to prepare this material by the usual procedure (see above) failed; therefore the following modification was employed. A solution of 0.673 g. of decalone-1 and 0.722 g. of *p*-dimethylaminobenzaldehyde in 4.5 ml. of 5% sodium methoxide in methanol was boiled under reflux for 45 minutes. On cooling, 0.615 g. of yellow plates, m.p. 166–167°, separated. A second crop was obtained by dilution of the filtrate with water. After standing, 0.372 g. of product, m.p. 150–160°, separated. Repeated recrystallization of a specimen of the first crop material from chloroform–ethanol gave pale yellow plates, m.p. 169–170°; λ_{max} 246 mμ (ε 8,600), 375.5 (24,300); λ_{min} 284 (2,400); λ_{max} 6.00 μ. For analysis: λ 8.45 μ (*A* 63.7), 9.78 (3.5), 10.05 (2.4).

Anal. Calcd. for $C_{19}H_{25}ON$: C, 80.52; H, 8.89. Found: C, 80.4, 80.2; H, 8.84, 8.90.

The methylation product, on fractional crystallization, yielded specimens of the *cis* (m.p. 119.8–120.2°) and *trans* (153–154°) isomers. The crude product showed λ8.45 μ (*A* 20.9), 9.78 (15.3), 10.05 (45.3), *C* = 0.0108, indicating a composition of 10% 9-H, 49% *cis*-9-CH_3 and 29% *trans*-9-CH_3.

2-*p*-Nitrobenzylidene-*cis*-9-methyldecalone-1, after sublimation at reduced pressure and repeated recrystallization from chloroform–ethanol, was obtained as colorless plates, m.p. 146–147°; λ_{max} 308.5 mμ (ε 18,200); λ_{min} 248 (4,600); λ_{max} 5.92 μ. For analysis: λ 10.02 μ (*A* 35.6), 8.45 (5.4), 9.75 (4.0).

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 72.3; H, 6.81.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as orange prisms, m.p. 197–198°.

Anal. Calcd. for $C_{24}H_{25}O_6N_5$: C, 60.12; H, 5.26. Found: C, 60.3; H, 5.16.

2-*p*-Nitrobenzylidene-*trans*-9-methyldecalone-1, after sublimation at reduced pressure followed by repeated recrystallization from chloroform–ethanol, was obtained as colorless prisms, m.p. 181–182°; λ_{max} 305.5 mμ (ε 14,000); λ_{min} 249 (3,700); λ_{max} 5.92 μ. For analysis: λ 9.75 μ (*A* 19.3), 8.45 (3.2), 10.02 (10.6).

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07. Found: C, 71.8; H, 7.26.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow prisms, m.p. 223–224°.

Anal. Calcd. for $C_{24}H_{25}O_6N_5$: C, 60.12; H, 5.26. Found: C, 60.1; H, 5.36.

2-*p*-Nitrobenzylidenedecalone-1.—From 15.0 g. of decalone-1 and 15.0 g. of *p*-nitrobenzaldehyde, condensed under conventional conditions (see above), there was obtained, after a 30-hr. reaction period, 12.2 g., m.p. 166–168°, and, after long standing, 8.0 g. (second crop), m.p. 169–173°. A specimen was sublimed at reduced pressure then repeatedly recrystallized from methanol, to give colorless plates, m.p. 171–172°; λ_{max} 306 mμ (ε 19,400); λ_{min} 248 (5,300); λ_{max} 5.92 μ. For analysis: λ 8.45 μ (*A* 29.3), 9.75 (2.4), 10.02 (2.6).

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 71.2; H, 6.62.

The 2,4-dinitrophenylhydrazone was crystallized from chloroform–ethanol as golden needles, m.p. 162–164°, resolidifying and remelting at 198–199°.

Anal. Calcd. for $C_{23}H_{23}O_6N_5$: C, 59.35; H, 4.98. Found: C, 59.3; H, 5.21.

The methylation product was a very dark solid, m.p. 118–150°; λ 8.45 μ (*A* 13.2), 9.75 (6.3), 10.02 (19.4), *C* = 0.0113 indicating a composition of 36% 9-H, 39% *cis*-9-CH_3, and 20% *trans*-9-CH_3.

2-α-Naphthal-*cis*-9-methyldecalone-1, after sublimation at reduced pressure followed by repeated recrystallization from methanol, was obtained as colorless prisms, m.p. 120.5–121°; λ_{max} 223 mμ (ε 23,500), 311 (6,300), 5.98 μ, 6.24 μ. For analysis: λ 10.10 μ (*A* 29.6), 8.45 (2.3), 9.80 (4.3).

Anal. Calcd. for $C_{22}H_{24}O$: C, 86.80; H, 7.95. Found: C, 86.9; H, 7.86.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as orange needles, m.p. 211.5–212.5°.

Anal. Calcd. for $C_{28}H_{28}O_4N_4$: C, 69.40; H, 5.83. Found: C, 69.3; H, 5.61.

2-α-Naphthal-*trans*-9-methyldecalone-1 after sublimation at reduced pressure from methanol, was obtained as colorless needles, m.p. 127–127.5°; λ_{max} 223.5 mμ (ε 40,300), 308 (10,000), 5.95 μ, 6.25. For analysis: λ 9.80 μ (*A* 12.8), 8.45 (4.4), 10.10 (10.8).

Anal. Calcd. for $C_{22}H_{24}O$: C, 86.80; H, 7.95. Found: C, 86.7; H, 8.08.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as golden plates, m.p. 190–191°.

Anal. Calcd. for $C_{28}H_{28}O_4N_4$: C, 69.40; H, 5.83. Found: C, 69.2; H, 5.89.

2-α-Naphthaldecalone-1.—From 15.2 g. of decalone-1 and 15.6 g. of α-naphthaldehyde, condensed under conventional conditions (see above), there was obtained, after two days, 17.3 g., m.p. 97–100°. Repeated crystallization from methanol provided colorless plates, m.p. 107–108°; λ_{max} 223 mμ (ε 42,700), 310 (10,500), 5.92 μ, 6.28. For analysis: λ 8.45 mμ (*A* 20.5), 9.80 (1.9), 10.10 (1.2).

Anal. Calcd. for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.8; H, 7.84.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow-orange prisms, m.p. 197.5–198.5°.

Anal. Calcd. for $C_{27}H_{26}O_4N_4$: C, 68.92; H, 5.57. Found: C, 68.7; H, 5.85.

The methylation product was obtained as a yellow solid, m.p. 94–107°; λ 8.45 μ (*A* 4.3), 9.80 (6.9), 10.10 (21.8), *C* = 0.0098, indicating a composition of 7% 9-H, 62% *cis*-9-CH_3, and 32% *trans*-9-CH_3. Fractional crystallization from methanol gave pure specimens of the *cis* and *trans* isomers.

***dl*-9-Iso-18-nor-D-homoestrone Methyl Ether (the α-Methoxyhydrochrysenone, IIIb).**—A procedure for the preparation of this substance by cyclization of the crude mixture of epimeric carbinols II already has been described.[9] In the present study it was found necessary to decrease the severity of the cyclization conditions from 2 days at 45° to 1.5 hr. at room temperature in order to realize comparable yields. It is suggested that this difference in behavior was due to a difference in the activity of the aluminum chloride employed in the two studies.

The total mixture of hydrogenated carbinols II obtained from 99.2 g. of *m*-methoxyphenylacetylene and 124.5 g. of decalin-1,5-dione,[9] was dissolved in 4 l. of benzene and a total of 310 g. of anhydrous aluminum chloride (Mallinckrodt) was added with stirring at 0°. After addition was complete, the cooling bath was removed and stirring continued at room temperature for 1.5 hr. The product was hydrolyzed and isolated as already described.[9] Crystallization of the total crude product from absolute ethanol containing a little benzene gave 43.5 g. (first crop), m.p. 166–170°, and 7.4 g. (second crop), m.p. 167–170°, corresponding to a yield of 24% from decalindione.

13,17a-Enol Acetate (XI) of *dl*-9-Iso-18-nor-D-homoestrone Methyl Ether.—The aforementioned α-methoxyhydrochrysenone was converted to the 13,17a-enol acetate as follows.[27] A solution of 0.881 g. of the ketone, m.p. 170–171.5°, and 0.118 g. of *p*-toluenesulfonic acid monohydrate in 66.4 ml. of acetic anhydride was concentrated to a volume of about 15 ml. by slow distillation over a period of 5 hr. Most of the remaining acetic anhydride was then removed at reduced pressure, and the residual dark oil dissolved in ether. The solution was chilled, washed in turn with cold sodium bicarbonate solution, cold water, and cold saturated brine. After being dried over anhydrous sodium sulfate, the solution was concentrated and the crude oily residue chromatographed rapidly on 10 g. of Florex. The fraction eluted with 50% benzene in hexane amounted to 0.891 g. of pale yellow crystalline enol acetate, m.p. 93–98° with previous softening. Such material, on repeated recrystallization from methylcyclohexane, gave small colorless platelets, m.p. 108–111°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.1; H, 8.02.

17,17a-Enol Acetate of *dl*-9-Iso-18-nor-D-homoestrone Methyl Ether.—The α-methoxyhydrochrysenone was converted to the 17,17a-enol acetate as follows.[28] A solution of 0.096 g. of the ketone, m.p. 169–171.5°, and 0.06 g. of *p*-toluenesulfonic acid monohydrate in 35 ml. of isopropenyl acetate was concentrated to a volume of about 5 ml. by slow distillation (bath at 130°) over a period of 10 hr. The crude product was isolated as described in the preceding experiment, and, since considerable starting ketone was obtained on crystallization, the total product was re-treated just as above with isopropenyl acetate for another 10-hr. period except that 0.65 g. of *p*-toluenesulfonic acid was used. The crude product could not be crystallized and was chromatographed on 8 g. of Florex. Elution with 33% benzene in hexane gave 0.066 g. of colorless oil which completely solidified. A single crystallization from methylcyclohexane gave 0.042 g. of colorless microprisms, m.p. 102–108°. Repeated recrystallization raised the m.p. to 122–123°. This material apparently was partially converted into the lower melting polymorph on drying at 80° (0.1 mm.) for 6 hr. as indicated by the m.p. 120.5–125° with softening at 118°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.5; H, 8.26.

***dl*-13,14-Dehydro-9-iso-18-nor-D-homoestrone Methyl Ether (IX). (a) Collidine Dehydrohalogenation of the Chloro Ketone.**—A mixture of 0.430 g. of the α-methoxyhydrochrysenone, m.p. 168–170°, and 0.83 g. of sulfuryl chloride in 25 ml. of carbon tetrachloride was allowed to stand at room temperature for 12 hours; then the solvent was evaporated in a current of air. The residue was dissolved in ether and washed in turn with 10% sodium hydroxide solution, water and saturated brine. The ether solution was dried over anhydrous sodium sulfate, then concentrated, and the residual oil dried at reduced pressure and 55°. The analysis (Calcd. for $C_{19}H_{23}O_2Cl$: Cl, 11.1. Found: Cl, 8.5) indicated that this material contained about 76% of the desired chloro ketone.

A solution of 0.389 g. of the above chlorinated ketone in 5 ml. of collidine was boiled under reflux (nitrogen atmosphere) for 0.5 hr. The procedure for isolation was essentially the same as for 2-methyl-2-cyclohexenone.[23] The crude product was chromatographed on 15 g. of alumina. The fraction eluted with benzene amounted to 0.104 g. which crystallized on trituration with 95% ethanol. Recrystallization from 95% ethanol gave material, m.p. 128–133°. Repeated recrystallization raised the m.p. to 134.5–136.5°. In a larger run, starting with crude α-methoxyhydrochrysenone contaminated with the β-isomer,[9] material of comparable quality (m.p. 133.5–137°) was isolated in 22% yield after chromatography and crystallization. Further recrystallization did not improve the m.p., but after rechromatography on alumina followed by two recrystallizations from benzene–hexane the dehydro ketone was obtained as colorless rosettes, m.p. 136–137.5°; λ_{max} 229 mμ (ε 13,400), 246 (15,600), 286 (2,360), 6.03 μ, 6.15.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.5; H, 7.91.

The 2,4-dinitrophenylhydrazone was isolated from chloroform-ethanol in two interchangeable polymorphic forms: red blades, m.p. 194–195.5°, and red needles, m.p. 213.5–214.5°.

Anal. Calcd. for $C_{25}H_{26}O_5N_4$: C, 64.92; H, 5.67. Found: C, 65.2; H, 5.77.

In the first chromatography of the larger scale preparation described above, further elution with 5–100% ether in benzene afforded a crystalline fraction, m.p. 150–196°, which after three recrystallizations from benzene was obtained as colorless plates, m.p. 236–238°; λ_{max} 212 mμ (ε 30,600), 270 (56,000), 280 (75,000), 322 (24,000) and 5.97 μ, indicating that this material was **1-keto-8-methoxy-1,2,3,4-tetrahydrophenanthrene.**

Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.6; H, 6.07.

From the ultraviolet spectrum of the crude dehydrohalogenation product it was estimated that it contained about 80% of α,β-unsaturated ketone and 2.8% of the methoxytetrahydrochrysenone.

(b) By Lithium Chloride Dehydrohalogenation[29] of the Bromo Ketone.—A solution of 5.0 g. of bromine in 400 ml. of carbon tetrachloride was added with stirring over a period of 3.5 hr. to a cooled (ice–salt-bath) solution of 10.2 g.

of crude (chromatographed but not recrystallized) semicrystalline 13,17a-enol acetate XI—prepared in 90% yield from crude α-methoxyhydrochrysenone, m.p. 161–167°—in 450 ml. of carbon tetrachloride. A solution of 20 g. of sodium bisulfite in 100 ml. of water was added, and the organic layer was washed with water followed by saturated brine, and dried over anhydrous sodium sulfate. The red oily residue obtained on evaporation of the solvent was dissolved in 160 ml. of dimethylformamide, 3.97 g. of lithium chloride was added and the mixture heated at 100° under nitrogen for 2 hr. Most of the solvent was removed by distillation at reduced pressure, and the residue dissolved in ether and benzene. The solution was washed with water followed by saturated brine, and dried over anhydrous sodium sulfate. The dark red oil remaining on evaporation of the solvent was crystallized from ethanol to give 3.0 g. of pale tan crystals, m.p. 129–133°. The residue obtained on evaporation of the mother liquor was chromatographed on 100 g. of Fiorisil. The fractions eluted with 60–80% benzene in hexane, benzene and 1–5% ether in benzene were crystalline, and were combined with the 3.0 g. obtained before chromatography (see above) and recrystallized from absolute ethanol to give 4.2 g. of pale tan prisms, m.p. 123–138.5°, sufficiently pure for hydrogenation to the γ-methoxyhydrochrysenone (see below).

Lithium Reduction of *dl*-13,14-Dehydro-9-iso-18-nor-D-homoestrone Methyl Ether.—A mixture of 12 mg. of small pieces of lithium and 15 ml. of liquid ammonia was allowed to stand about 5 minutes, then a solution of 0.150 g. of the 13,14-dehydro-α-ketone, m.p. 133–137°, in 6 ml. of anhydrous ether and 2 ml. of anhydrous dioxane was added. After about one-half of the solution had been added (about 1 minute) the blue color disappeared, and the addition was interrupted until the residual lithium dissolved. The remainder of the ketone solution was added, then by enough lithium to regenerate the blue color; now excess solid ammonium chloride was introduced. The ammonia was evaporated, ether and water added; then the ether layer was washed with water followed by saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the ether yielded a pale amber glassy residue, λ_{max} 246 mμ (ε 460), which, since it could not be crystallized, was chromatographed on 7.5 g. of alumina. All of the fractions were crystalline. A center cut, eluted with benzene and with 1% ether in benzene, amounted to 0.021 g. of colorless crystals, m.p. 160–167°. A single crystallization from absolute ethanol gave colorless needles, m.p. 167.5–169.5°, undepressed on admixture with authentic α-methoxyhydrochrysenone. The infrared spectra of the two specimens were identical.

13,17a-Enol Acetate XII of *dl*-18-nor-D-homoestrone Methyl Ether.—A 0.132-g. sample of the β-methoxyhydrochrysenone IIIa,[9] m.p. 154–156°, was treated with 0.089 g. of *p*-toluenesulfonic acid monohydrate and 50 ml. of acetic anhydride just as described above for the α-isomer. The crude product was chromatographed on 6.5 g. of Florex, and elution with 25–50% benzene in hexane gave 0.117 g. of crystalline material. Crystallization from methylcyclohexane gave 0.073 g. (first crop), m.p. 123.5–125.5°, and 0.025 g. (second crop), m.p. 122–127°. Further recrystallizations gave colorless micro prisms, m.p. 122–124°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.8; H, 8.19.

17,17a-Enol Acetate of *dl*-18-Nor-D-homoestrone Methyl Ether.—A 0.132-g. sample of the β-methoxyhydrochrysenone IIIa, m.p. 154–156°, was treated with 40 ml. of isopropenyl acetate and 0.89 g. of *p*-toluenesulfonic acid monohydrate as described above for the α-isomer. Crystallization of the crude product from methylcyclohexane gave 0.066 g. of colorless crystals, m.p. 136–142°. Four recrystallizations gave 0.013 g. of colorless prisms, m.p. 150.5–152°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.7; H, 8.09.

***dl*-13-Chloro-18-nor-D-homoestrone Methyl Ether.**—A solution of 0.301 g. of the β-methoxyhydrochrysenone,[9] m.p. 155.5–158.5°, and 0.35 ml. of sulfuryl chloride in 10 ml. of carbon tetrachloride was allowed to stand in the dark at room temperature for 15 hr. By successive recrystallizations of the crude product—isolated as described above for the α-isomer—from benzene and then twice from benzene–hexane, 0.042 g. of colorless prisms, m.p. 169–170.5°, was obtained.

Anal. Calcd. for $C_{19}H_{23}O_2Cl$: C, 71.58; H, 7.27. Found: C, 71.2; H, 7.17.

From the mother liquors there was isolated by fractional crystallization 0.029 g. of a second product, m.p. 156–158°. The m.p. was markedly depressed on admixture either with starting material or with the chloro ketone described above. The 156–158° substance may be the C_{13}-epimer of the 169–170.5° chloro ketone, but has not been investigated further.

Dehydrohalogenation Experiments in the β-Series. (a) **With the Chloro Compound.**—A 0.046-g. sample of the 13-chloro ketone, m.p. 164.5–165° (undepressed on admixture with the analytical specimen, m.p. 169–170.5°, described above), was heated under reflux with 0.4 ml. of collidine for 30 minutes. The yield of collidine hydrochloride was 0.022 g. (97%), and the crude product, isolated in the usual manner, was a yellow glass, λ_{max} 229 mμ (ε 13,400), 246 (15,600). The high extinction at 246 mμ indicated the presence of the 13,14-dehydro compound.[25] Trituration with ether gave 0.025 g. of crystals, m.p. 113–123°. Further recrystallizations and chromatography gave only fractions melting over a comparatively broad range. The isomerization of this material to the 13,14-dehydro-α-isomer is described below.

(b) **With the Bromo Compound.**—A 0.619-g. sample of crude 13,17a-enol acetate from the β-ketone (see above) was treated with 3.7 ml. of a solution of 0.818 g. of bromine in 10 ml. of carbon tetrachloride as described above for the α-isomer. The crude bromo ketone was boiled under reflux with 6.8 ml. of collidine for 10 minutes. The yield of crude collidine hydrobromide was 0.420 g. (110%), and the crude unsaturated ketone, isolated as described above, was obtained as a yellow tacky glass, λ_{max} 245 mμ (ε 6,420), corresponding to about 40% of the 13,14-dehydro compound. Trituration with ether gave 0.117 g. of crystals, m.p. 135–153°, λ_{max} 245 mμ (ε 8,500). Recrystallization gave 0.056 g. of material which was chromatographed on 2.5 g. of Florex. The early fractions eluted with benzene exhibited the anisole spectrum, and as the chromatogram was developed, the fractions began to show absorption in the 246 mμ region. A late fraction, eluted with ether, amounted to 0.001 mg., m.p. 136–137.5°; λ_{max} 229 mμ (ε 11,600), 246 (14,400). The m.p. was depressed markedly on admixture with the 13,14-dehydro compound in the α-series.

Isomerization Experiments on the 13,14-Dehydro Ketones. (a) **With Sodium Methoxide.**—A 0.022-g. sample of the chromatographed dehydrochlorination product from the 13-chloro-β-ketone (see above) was dissolved in a solution of 0.08 g. of sodium in 1.6 ml. of absolute methanol. The mixture was refluxed (under nitrogen) for 1.5 hr., concentrated at reduced pressure, and diluted with ether. The ether solution was washed thoroughly with water, dried over anhydrous sodium sulfate and concentrated. The amber glassy residue was treated with Norit in methanol, and the residue obtained by evaporation of the solvent triturated with a little ether which left 0.013 g. of crystals, m.p. 128–135°, undepressed on admixture with the 13,14-dehydro-α-ketone. A single crystallization from methanol gave 0.0075 g., m.p. 135–136.5°, undepressed on admixture with the 13,14-dehydro-α-ketone, m.p. 136–137.5°.

When the 13,14-dehydro-α-methoxyhydrochrysenone, m.p. 132–136°, was treated with methoxide just as described above, about 50% of the starting material, m.p. 132–136°, was recovered. The residues may have contained some of the β-isomer.

(b) **With *p*-Toluenesulfonic Acid.**—A solution of 0.045 g. of the 13,14-dehydro-α-methoxyhydrochrysenone, m.p. 132–136°, and 0.13 g. of *p*-toluenesulfonic acid monohydrate in 1.2 ml. of xylene was refluxed (under nitrogen) for 30 minutes. The dark red solution was cooled, diluted with ether, extracted thoroughly with 10% sodium hydroxide solution; then washed with water followed by saturated brine, and dried over anhydrous sodium sulfate. The dark viscous oily residue obtained upon evaporation of the solvent gave, after a trituration with ether and recrystallization from absolute ethanol, 0.0052 g. of tan prisms, m.p. 116.5–118°. Additional material was obtained by chromatography of the residues on 1 g. of Florex. The first fraction eluted with 50% benzene in hexane amounted to 0.0178 g. of colorless crystals, m.p. 112–118°. Recrystallization from benzene–hexane gave 0.0096 g. of colorless plates, m.p. 118–119°, λ_{max} 280 mμ (ε 22,700), λ_{min} 242 (5110). This spectrum and the analysis reported below are compatible with the formulation of this substance as **8-methoxy-1,2,3,4,5,6-hexahydrochrysene (XIII)**.

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 85.9, 86.2; H, 7.6, 7.6.

Further elution of the column gave intermediate non-homogeneous fractions with increasing absorption in the 245 mμ region. Elution with benzene yielded 0.0036 g. of a fraction with intense absorption in this region. Trituration with ether gave 0.0026 g. of material, m.p. 131–135°, undepressed on admixture with starting material.

When the product of dehydrobromination of the β-bromoketone (see above) was treated with *p*-toluenesulfonic acid in xylene just as described above, the only homogeneous product that was isolated (by crystallization from absolute ethanol) was the methoxyhexahydrochrysene, m.p. 117–119°, undepressed on admixture with the analytical sample described above.

***dl*-8-Iso-18-nor-D-homoestrone Methyl Ether (the γ-Methoxyhydrochrysenone IIIc).**—A solution of 6.74 g. of crude (once-crystallized) *dl*-13,14-dehydro-9-iso-18-nor-D-homoestrone methyl ether, m.p. 125–132°, prepared as described above (procedure b), in 460 ml. of 95% ethanol containing 0.675 g. of sodium hydroxide was hydrogenated over 0.675 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and about 30 p.s.i. Within 8 hr. about 90% of the calculated amount of hydrogen was absorbed and the uptake had ceased. The ultraviolet spectrum (λ_{max} 278 mμ, 286; λ_{min} 245) of the filtered solution indicated complete reduction of the α,β-unsaturated carbonyl system. Most of the solvent was removed by distillation, acetic acid added to neutralize the alkali, and benzene and ether were added. The solution was washed with water then with saturated brine, and dried over anhydrous sodium sulfate. The residual oil obtained on evaporation of the solvent was crystallized from absolute ethanol to give 4.1 g. (60% yield) of prisms, m.p. 128–136°. One recrystallization from absolute ethanol gave 3.6 g., m.p. 134–137°. In comparable runs the residues were shown to contain some of the α-methoxyhydrochrysenone.

A sample of the γ-ketone, after repeated recrystallization from 95% ethanol, was obtained as colorless prisms, m.p. 137.5–138°; λ_{max} 278 mμ (ε 2,270), 287 (2,140), 5.88 μ.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.0; H, 8.75.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as golden needles, m.p. 233–234°.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.08. Found: C, 64.8; H, 5.93.

In an experiment in which a solution of 0.200 g. of the 13,14-dehydro α-ketone in 16 ml. of 95% ethanol was hydrogenated over 0.100 g. of 10% palladium-on-carbon without any added alkali, the reaction was interrupted after the absorption of 1 mole-equivalent of hydrogen, although the uptake had not ceased. Chromatography of the crude product on alumina gave 0.029 g. of a weakly adsorbed fraction which was evidently hydrogenolysis product since it showed no absorption in the carbonyl region in the infrared spectrum. This fraction was followed by the saturated ketone fractions (total weight, 0.094 g.) containing the γ-ketone. The last fraction (0.081 g.) eluted with 1–2% ethanol in ether was hydroxylic material, λ_{max} 2.77 μ. Oxidation of this product with sodium dichromate in acetic acid gave in 50% yield, the 13,14-dehydro α-ketone, m.p. 131–136.5°, undepressed on admixture with authentic material. When the γ-methoxyhydrochrysenone was treated with refluxing sodium methoxide in methanol, it was recovered unchanged.

***dl*-17-Furfurylidene-8-iso-18-nor-D-homoestrone Methyl Ether (IVc).**—A solution of 1.2 g. of furfural in 30 ml. of 33% aqueous methanol containing 9 g. of sodium hydroxide was added to a solution of 1.75 g. of the γ-methoxyhydrochrysenone, m.p. 134–137°, in 200 ml. of methanol, and the mixture allowed to stand overnight at room temperature under nitrogen. The crystals that separated amounted to 2.2 g., m.p. 177–190°, and a single recrystallization from benzene gave 1.7 g., m.p. 191–193.5°. Repeated recrystallization from benzene afforded rectangular prisms, m.p. 192–194°, λ_{max} 326.7 mμ (ε 26,300).

Anal. Calcd. for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.6; H 7.16.

Methylation of IVc.—According to previously described procedures,[9,13] 7.97 g. of the aforementioned furfurylidene ketone, m.p. 190.5–195.5°, followed by 150 g. of methyl iodide, was added (under nitrogen) to a chilled (ice-bath) solution of 20.6 g. of potassium in 700 ml. of anhydrous *t*-butyl alcohol. After the exothermic reaction subsided, the ice-bath was removed and the mixture stirred at room temperature until neutral (about 2 hr.). The crude product, isolated as previously described, amounted to 8.6 g. of an oil. Fractional crystallization from absolute ethanol gave a total of 5.23 g., m.p. 164–167°; and 1.23 g., m.p. 158.5–164°, of the γ-1 isomer; and 0.61 g., m.p. 144–151°, of the γ-2 isomer. One recrystallization of the γ-2 isomer gave 0.49 g., m.p. 152–154°.

From another run a specimen of the γ-1 isomer, ***dl*-17-furfurylidene-8-iso-13-iso-D-homoestrone methyl ether (Vc)**, was obtained, after chromatography and repeated recrystallization from absolute ethanol, as colorless needles, m.p. 166–167.5°, λ_{max} 326.2 mμ (ε 24,600). The analytical specimen was sublimed at reduced pressure.

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.50. Found: C, 79.7; H, 7.43.

The γ-2 isomer ***dl*-17-furfurylidene-8-iso-D-homoestrone methyl ether (VIIIc)**, after similar purification, was obtained as colorless prisms, m.p. 149–150.5°, λ_{max} 321.9 mμ (ε 22,400).

Anal. Calcd. for $C_{25}H_{28}O_3$: C, 79.75; H, 7.50. Found: C, 79.7; H, 7.59.

***dl*-8-Iso-13-isoestrone Methyl Ether (γ-1-Estrone Methyl Ether).**—One mole-equivalent of ozone was passed into a solution of 0.100 g. of the γ-1 furfurylidene ketone, m.p. 164–167°, in 10 ml. of ethyl acetate at −70°. The solvent was removed at reduced pressure and the residue heated with 20 ml. of 5% sodium hydroxide solution and 5 ml. of 30% hydrogen peroxide on the steam-bath for 0.5 hr. The acidic material, isolated essentially as previously described,[9] amounted to 0.087 g. of colorless amorphous solid, λ_{max} 277 mμ (ε 2,250). The quality of this product, as ascertained by the shape of this anisole peak, appeared to vary somewhat from run to run depending, perhaps, on the extent of oxidative attack at C_9 (see below under ozonization of XXIII).

A mixture of 0.115 g. of the amorphous γ-1 diacid and 0.137 g. of lead carbonate was pyrolyzed as previously described.[9] Evaporative distillation at 190° (0.1 mm.) of the pyrolysate gave a yellow oil which was dissolved in ether, washed with 5% sodium bicarbonate solution, water, saturated brine, and dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether was triturated with hexane to give 0.039 g. of crystals, m.p. 103–105° with some previous melting at 73°. The pure material, secured by repeated recrystallization from methanol, was generally obtained as colorless diamond-shaped blades, m.p. 105–106°, but after one of the crystallizations was isolated in a form melting at 90.5–91.5°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.4; H, 8.54.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow prisms, which melted when placed on a hot-stage at 180°, then resolidified to give yellow needles, m.p. 204–206°.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.8; H, 5.83.

***dl*-8-Iso-13-isoestrone (γ-1-Estrone).**—A 0.09-g. sample of once-crystallized γ-1 estrone methyl ether was heated (under nitrogen) at 212–214° with 2 g. of pyridine hydrochloride for 40 minutes. The cooled mass was treated with 5% hydrochloric acid and extracted with chloroform. The chloroform solution was dried by filtration through filter paper, and evaporated to give 0.086 g. of colorless solid, m.p. 210–213°. Repeated recrystallization from acetone gave colorless prisms, m.p. 213.7–215°, with previous sweating at 203°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.1; H, 8.46.

On admixture with a specimen of estrone f,[45] m.p. 195.5–204.5°, there was no depression of the m.p. below 195°.

The benzoate crystallized from ethyl acetate as colorless prisms, m.p. 172–175°, with previous sweating at 170°. On admixture with a specimen of estrone f benzoate,[45] m.p. 162–163°, the m.p. was 163.5–168.5°.

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.0; H, 6.94.

***dl*-8-Isoestrone Methyl Ether (γ-2 Estrone Methyl Ether).**—Ozonization of 0.400 g. of the γ-2-furfurylidene ketone,

m.p. 152–154°, by the procedure described above afforded 0.300 g. of colorless amorphous acid. One crystallization from ethyl acetate gave 0.141 g. of colorless prisms, m.p. 209–216°. **The *dl*-8-isohomomarrianolic acid methyl ether (VIIIc)** was obtained by repeated recrystallization from ethyl acetate as colorless prisms, m.p. 214–217°, with previous sweating at 198°.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.3; H, 7.52.

A 0.234-g. sample of crude oily residue remaining after crystallization of the γ-2 diacid was treated with 0.30 g. of lead carbonate by the pyrolytic procedure (see above). The evaporatively distilled product amounted to 0.081 g. of yellow oil which crystallized on standing, m.p. 149–153.5°. Repeated recrystallization from methanol gave colorless blades, m.p. 152.5–154.5° with previous sweating at 148°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.1; H, 8.54.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as yellow microcrystals, m.p. 261.5–263°, when placed on the hot-stage at 257°.

Anal. Calcd. for $C_{25}H_{28}O_5N_4$: C, 64.64; H, 6.07. Found: C, 64.7; H, 6.18.

***dl*-8-Isoestrone (γ-2 Estrone).**—A 0.050-g. sample of γ-2 estrone methyl ether, m.p. 149–152°, was demethylated with 1 g. of pyridine hydrochloride as described above. Crystallization of the crude product from methanol gave 0.022 g. of prisms, m.p. 239–245°. Repeated recrystallization from methanol gave colorless prisms which sublimed at 240° and melted at 253.6–254.8° in an evacuated capillary.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.2; H, 8.19.

The benzoate, after chromatography, sublimation and recrystallization from methanol was obtained as colorless prisms, m.p. 197–198°.

Anal. Calcd. for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.2; H, 7.10.

Reduction of *dl*-Equilenin.—The procedure of Dauben and Ahramjian[38] for the reduction of *d*-equilenin was followed. A mixture of 6.0 g. of *dl*-equilenin,[39] m.p. 281–283° (vac.), 24 ml. of W-5 Raney nickel and 600 ml. of 2.5% aqueous potassium hydroxide was hydrogenated at 85° and an initial pressure of 2800 p.s.i. (at 25°) for 4 hr. The crude phenolic fraction, isolated essentially as already described,[38] amounted to 1.19 g., m.p. 177–183° dec., λ_{max} 281 mμ (log ε 3.30). This product was chromatographed on 50 g. of Woelm neutral alumina. The fraction eluted with 0.5% methanol in ether amounted to 1.01 g. of colorless ***dl*-8-isoestradiol**, m.p. 205–207° with some previous polymorphic transitions. Repeated recrystallization from dilute methanol afforded small colorless needles, m.p. 213.5–214° with a polymorphic transition at 175–195° followed by softening at 210°, λ_{max} 280 mμ (log ε 3.31).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.1; H, 8.91.

The material isolated from the neutral fraction in the above experiment amounted to 3.45 g., m.p. 155–173°. It was not further purified, but clearly contained the product of reduction of ring A as indicated by the λ_{max} at 269 mμ (log ε 2.58), 278 (2.49).

The 3-benzoate was prepared from crude *dl*-8-isoestradiol, m.p. 175–185°, according to the procedure of Serini and Logemann.[40] Several recrystallizations from ethyl acetate gave a product melting at 179–185°. A solution of 0.169 g. of this material in 4 ml. of pyridine was added to a mixture of 2.5 g. of chromium trioxide in 25 ml. of pyridine,[60] and the mixture allowed to stand overnight. The product, which was isolated by dilution with water and extraction with ether–benzene,[60] was crystallized from ether–benzene. The yield of material, m.p. 190–194°, was 0.104 g. Repeated recrystallization from methanol gave colorless prisms of *dl*-8-isoestrone benzoate, m.p. 194.5–197°, undepressed on admixture with the specimen of γ-2 estrone benzoate described above. The infrared spectra of the two specimens were identical.

A sample of the benzoate, m.p. 190–194°, was saponified by refluxing with 1 *N* methanolic potassium hydroxide for 2 hr. The product was isolated by acidification and extraction with ether. Repeated recrystallization from methanol afforded colorless crystals, m.p. 254–256° dec., undepressed on admixture with the specimen of γ-2 estrone described above.

A specimen of *dl*-8-isoestrone methyl ether was prepared from the phenol according to the modified procedure[9] of Butenandt. Repeated recrystallization of the product from methanol afforded colorless plates, m.p. 152–154.5°, undepressed on admixture with the sample of γ-2 estrone methyl ether described above. The infrared spectra of the two specimens were identical.

Dehydrogenation Experiments. (a) **With γ-1 Estrone Methyl Ether.**—The method of Bachmann and Dreiding[41] was used. A mixture of 16.5 mg. of γ-1 estrone methyl ether, m.p. 101.8–105.5°, and 20 mg. of 5% palladium-on-carbon was heated under nitrogen at 250° for 8 minutes. Benzene was added to the cooled reaction mixture which was then filtered. The colorless oily residue obtained on evaporation of the solvent was triturated with hexane to give 9.5 mg. of colorless crystals, m.p. 122.5–124.5° with previous softening. Several recrystallizations from methanol gave 6.8 mg. of colorless prisms, m.p. 125–128° (reported for *dl*-isoequilenin methyl ether,[61] 127–127.5° and 130–130.5°). On admixture with authentic *dl*-isoequilenin methyl ether,[39] m.p. 129.5–130.5°, there was no depression of the m.p. The infrared spectra of the two specimens were indistinguishable.

(b) **With α-1-Estrone Methyl Ether.**—Dehydrogenation of 12.2 mg. of this isomer over 20 mg. of 5% palladium-on-carbon as described above gave 9 mg. of crude product, m.p. 125–126° with previous softening. After several recrystallizations from methanol there was obtained 6.0 mg. of colorless prisms, m.p. 126–127.3°, undepressed on admixture with authentic *dl*-isoequilenin methyl ether.[39] The infrared spectra of the two specimens were identical.

Conversion of the α-Methoxyhydrochrysenone into *cis*-2,8-Dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene.[62] **1-Keto-2-furfurylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,-12,12a-dodecahydrochrysene.**—The following experiment was performed by Cameron.[63] A 0.05-g. sample of the α-methoxyhydrochrysenone in 12 ml. of methanol was treated with 3 drops of furfural and 0.6 ml. of 33% aqueous sodium hydroxide. After 15 minutes the solution was seeded and allowed to stand for 2 hr. at room temperature. The yield of colorless furfurylidene derivative was 0.063 g., m.p. 179.5–181°. Repeated recrystallization from *n*-butyl alcohol gave colorless needles, m.p. 180.8–181.6°, λ_{max} 324 mμ (ε 22,400).

Anal. Calcd. for $C_{24}H_{26}O_3$: C, 79.53; H, 7.23. Found: C, 79.2; H, 6.98.

In subsequent preparations another form, m.p. 191–192°, was encountered. Such material was generally partly converted into the lower-melting form on recrystallization, resulting in a mixture with an intermediate m.p., *e.g.*, 183–185°. A sample of the lower-melting material, after standing for more than a year, melted at 180–185°.

1-Hydroxy-2-furfurylidene-8-methoxy-1,2,3,4,4a,4b,5,6,-10b,11,12,12a-dodecahydrochrysene (XXIII, R = H).—A suspension of 0.554 g. of the aforementioned furfurylidene α-ketone, m.p. 185–189° (mixture of polymorphs), in 50 ml. of boiling methanol was treated with 0.5 g. of sodium borohydride in 5 ml. of water. Within 1 minute the solution became homogeneous and the strong absorption of the starting material at 324 mμ had disappeared. The hot mixture was diluted with 150 ml. of water, and on cooling 0.540 g. of small colorless needles, m.p. 178–183°, separated. Attempts to improve the m.p. by chromatography, in the hope of separating the presumed mixture of epimeric carbinols, failed. Recrystallizations from ethyl acetate gave material, m.p. 178–185°; λ_{max} 263 mμ (ε 22,700), 269 (25,400), 281 (17,800). Sublimation at 140° (0.015 mm.) gave a mixture of needles melting at 185–186.5° and blades that melted at 186–188°.

(60) *Cf.* G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

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

(62) The new compounds described in this section are racemic, but the prefix "*dl*" has been omitted. Chrysene nomenclature is employed throughout this section.

(63) D. D. Cameron, Ph.D. Dissertation, University of Wisconsin, 1953.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 78.6; H, 7.72.

Conditions for formation of the acetate proved to be critical. Of six different procedures tried, that described below gave the best results with a minimum amount of elimination of the 17a-hydroxyl group.

A mixture of 2.56 g. of the crude carbinol (m.p. 176–183°), 25 ml. of pyridine and 10 ml. of acetic anhydride was boiled under reflux for 15 minutes; then the solution was poured into a mixture of ice and water, and extracted with chloroform. The organic layer was washed with water, thoroughly with dilute hydrochloric acid, then with water followed by saturated brine and finally dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was crystallized from ether to give 1.94 g., m.p. 129–133°. A comparable specimen, recrystallized three times from ether, was obtained as small colorless blades, m.p. 133–135°.

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.82; H, 7.44. Found: C, 76.5; H, 7.45.

Saponification of a specimen of the acetate, m.p. 129–132°, with alcoholic potassium hydroxide gave a crude product in 82% yield, m.p. 180–183°. Sublimation at 145° (0.015 mm.) yielded needles, m.p. 182–185°. This result suggests that the carbinol described above may be a single epimer, undoubtedly 17aβ(equatorial), exhibiting polymorphism.

1-Acetoxy-2-keto-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,-12,12a-dodecahydrochrysene (XXIV).—One mole-equivalent of ozone was passed into a solution of 0.401 g. of the aforementioned acetate, m.p. 128–132°, in 25 ml. of ethyl acetate containing 0.12 ml. of pyridine at −70°. The mixture, which had become cloudy, was hydrogenated over 0.5 g. of 6% palladium-on-strontium carbonate at room temperature and 35 p.s.i. initial pressure. The mixture was filtered and washed with dilute hydrochloric acid, thoroughly with 2% sodium hydroxide solution, water, then saturated brine and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was chromatographed on 25 g. of Merck and Co., Inc., acid-washed alumina. Elution with benzene gave 0.099 g. (29% yield) of crude crystalline acetoxy ketone fraction, λ_{max} 278 and 287 mμ, followed closely by fractions absorbing strongly at 274 mμ and others at 264 mμ undoubtedly containing 8,9- and 9,11-dehydro compounds (see Discussion). The acetoxy ketone fraction from another run was recrystallized three times from acetone to give small colorless plates, m.p. 172–175° with sweating at 169°; λ_{max} 221 mμ (ϵ 8,350), 278 (2,170), 288 (1,990).

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.5; H, 7.75.

Isolation of 1-Acetoxy-2-keto-8-methoxy-1,2,3,4,4a,5,6,-11,12,12a-decahydrochrysene (XXV).—An ozonization of 0.505 g. of the acetoxy furfurylidene derivative, m.p. 129–133°, was carried out just as described above except that excess ozone (1-2 mole-equivalents) was introduced. Chromatography of the product yielded none of the acetoxy ketone. Instead, the benzene eluates yielded fractions with wide melting point ranges (extending as high as 198°) and with intense absorption at 264–270 mμ. These combined fractions (0.136 g.) were recrystallized twice from acetone yielding 0.034 g. of colorless blades, m.p. 213–215°, λ_{max} 273.5 mμ (ϵ 16,700). Repeated recrystallization from acetone raised the m.p. to 216.5–217.5°.

Anal. Calcd. for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.3; H, 7.05.

***cis*-2,8-Dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene (XXI).**—A solution of 30.8 mg. of bromine in 2 ml. of glacial acetic acid was added slowly, over a period of about 20 minutes, to a stirred and cooled (ice-bath) solution of 66.1 mg. of the aforementioned acetoxy ketone, m.p. 164–172° (after two recrystallizations from acetone), in 2 ml. of glacial acetic acid that had been saturated with dry hydrogen bromide. After the bromine was added, the cooling bath was removed and the stirring continued at room temperature for 75 minutes. Ice and water were added, and the mixture extracted with chloroform. The organic layer was washed with water, thoroughly with 2% sodium hydroxide, again with water followed by saturated brine, and dried over anhydrous magnesium sulfate. Since the residue obtained on evaporation of the solvent could not be crystallized, it was chromatographed on 7.3 g. of Merck and Co., Inc., acid-washed alumina. Elution with benzene yielded, after a 1.5-mg. oily fraction that gave no precipitate with alcoholic silver nitrate, 40.4 mg. of oily bromo ketone that gave a precipitate with warm 2% alcoholic silver nitrate solution. This fraction was followed immediately by 8.9 mg. of partially crystalline material, apparently starting acetoxy ketone.

From the sodium hydroxide extracts there was isolated by acidification and extraction, 1.9 mg. of red waxy material; λ_{max} 278 mμ (ϵ *ca.* 3,900), 318 (ϵ *ca.* 1,900); λ_{min} 247 (ϵ *ca.* 2,300). After addition of a drop of 5% sodium hydroxide, the spectral sample exhibited λ_{max} 287 mμ (ϵ *ca.* 3,700); λ_{min} 263 (ϵ *ca.* 2,900).

A solution of 39.7 mg. of the bromo ketone fraction described above and 2 g. of anhydrous lithium chloride in 10 ml. of dry dimethylformamide was boiled under reflux for 10 hr. in an atmosphere of nitrogen. After cooling, the orange solution was diluted with water and extracted with chloroform. When the organic layer was washed with dilute sodium hydroxide solution, only 2.7 mg. of acidic material was extracted. The "neutral" material (34.3 mg.) was, therefore, retreated with 2 g. of lithium chloride in 10 ml. of dimethylformamide for 22 hr. as described above, but this retreatment was evidently unnecessary because only an additional 4.8 mg. of oily material was extracted with sodium hydroxide. The "neutral" fraction remaining (20.3 mg.) was then dissolved in benzene and extracted thoroughly with Claisen alkali. These alkali extracts were acidified, diluted with water, and extracted with benzene. The residue (13.9 mg.) obtained on evaporation of the solvent was treated with 7 ml. of 30% potassium hydroxide solution and 2.5 ml. of dimethyl sulfate. The mixture was heated on the steam-bath for 20 minutes, then an additional 0.1 ml. of dimethyl sulfate was added and the heating continued for 25 minutes. Water was added, the mixture extracted with benzene, and the organic layers washed with saturated brine. The semi-crystalline residue (8.1 mg.) obtained on evaporation of the solvent was chromatographed on 0.8 g. of Alcoa basic alumina. Elution with 50% 60–68° petroleum ether in benzene gave a total of 7.3 mg. which, after crystallization from 60–68° petroleum ether then recrystallization twice from acetone, was obtained as colorless needles, m.p. 146–148°. The m.p. of this material was not depressed on admixture with an authentic specimen (m.p. 146.5–148°) of *cis*-2,8-dimethoxyhexahydrochrysene.[52,64] The infrared spectra (potassium bromide pellet) of the two samples were identical.

Further elution of the column gave only intractable gums (1.1 mg.).

The 7.5 mg. of material that was extracted with alkali from the original reaction mixture (see above) was also methylated with dimethyl sulfate as described above. No homogeneous products could be isolated by chromatography and crystallization. The major fraction (3 mg.) melted at 125–148°.

MADISON, WISCONSIN

(64) We wish to thank Professor A. L. Wilds for providing us with a specimen of this material.