45. *A Stereoselective Total Synthesis of Œstrone, and Related Studies.**

By J. Elton Cole, jun., William S. Johnson, P. A. Robins, and James Walker.

A stereoselective total synthesis of œstrone (1) has been effected starting with 6-methoxy-1-tetralone (25) and proceeding *via* *cis-syn*-1,4,4a,4b,5,6,12,12a-octahydro-8-methoxy-1,4-dioxochrysene (23) and *cis-syn*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1,4-dioxochrysene (16). Protection of the 1-carbonyl group in the latter compound, epimerisation at $C_{(4a)}$, removal of the 4-carbonyl group, and regeneration of the 1-carbonyl group afforded *trans-anti*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1-oxochrysene (14). The furfurylidene derivative of the latter ketone gave on methylation a preponderance of the *trans-anti*-methylated furfurylidene-ketone (62), which was oxidised with alkaline hydrogen peroxide. Reduction of the resulting acidic product (65) with sodium in liquid ammonia afforded the known homomarrianolic acid methyl ether (2), in an overall yield of 5·3% from 6-methoxy-1-tetralone; the conversion of this dibasic acid into œstrone has already been described.

In order to study the effect of a double bond in the 4b,10b-position on the stereochemical course of angular methylation, the furfurylidene derivative (39) of *cis*-1,2,3,4,4a,5,6,11,12,12a-decahydro-8-methoxy-1-oxochrysene (13) was methylated; it gave exclusively the *cis*-stereoisomer (41).

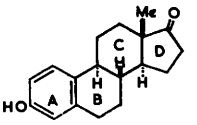
Reduction of the trimethylene ketals of the preceding *cis*-ketone (13) and its *trans*-stereoisomer (37) gave access to four racemates of 1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene. The hitherto unknown *cis-syn-trans*-stereoisomer ("δ-methoxyhydrochrysenone") (79) was methylated, after protection of the 2-position, to give exclusively the CD-*cis*-derivative (84), a precursor of 14-iso-œstrone methyl ether (86).

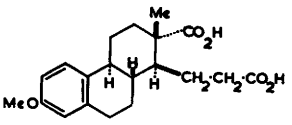
The structure of œstrone (1) was established in 1932,[1] and its synthesis was first accomplished in 1948 by Anner and Miescher,[2] following a route previously adumbrated by Robinson and Walker.[3] In the interval two other successful syntheses of œstrone have been effected by Johnson and his collaborators,[4,5] and all of the eight possible racemic forms of the œstrone structure have now been obtained synthetically.[2,6,7] None of these syntheses, however, has possessed the desirable feature of stereoselectivity at every step, and the present communication describes a total synthesis of œstrone from 6-methoxy-1-tetralone, which is stereoselective throughout and affords the precursor of œstrone, homomarrianolic acid methyl ether (2), in 5·3% overall yield; the last stage, conversion of homomarrianolic acid methyl ether into œstrone, has been described in the course of previous syntheses.[2,4,5a] A preliminary account of the present work has already been

* In this paper structural formulæ are shown depicting one diastereoisomeric series, and, although the prefix (±)- is consistently omitted, it is to be understood that reference in the text is to racemic forms throughout. Stereochemical configurations of hydrochrysenes at points of ring fusion are given in the order 4a,12a; 4a,4b; 4b,10b. The lettering of rings follows the steroid sequence, as in (1).

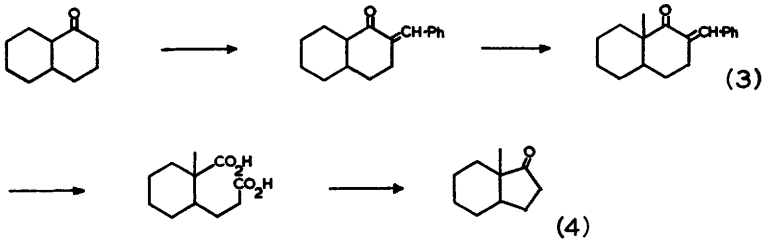
[1] Butenandt, *Nature*, 1932, **130**, 238; Marrian and Haslewood, *Biochem. J.*, 1932, **26**, 25.
[2] Anner and Miescher, *Helv. Chim. Acta*, 1948, **31**, 2173; 1949, **32**, 1957; 1950, **33**, 1379.
[3] Robinson and Walker, *J.*, 1936, 747; 1938, 183.
[4] (*a*) Johnson, Banerjee, Schneider, and Gutsche, *J. Amer. Chem. Soc.*, 1950, **72**, 1426; (*b*) Johnson, Banerjee, Schneider, Gutsche, Shelberg, and Chinn, *ibid.*, 1952, **74**, 2832.
[5] (*a*) Johnson and Christiansen, *J. Amer. Chem. Soc.*, 1951, **73**, 5511; (*b*) Johnson, Christiansen, and Ireland, *ibid.*, 1957, **79**, 1995.
[6] Johnson, David, Dehm, Highet, Warnhoff, Wood, and Jones, *J. Amer. Chem. Soc.*, 1958, **80** 661.
[7] Bachmann, Kushner, and Stevenson, *J. Amer. Chem. Soc.*, 1942, **64**, 974.

given,[8] and, since then, the outlines of other stereoselective total syntheses of œstrone have appeared.[9,10]

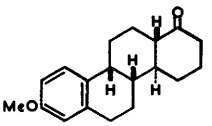
(1) 

 (2)

An essential procedure in the total synthesis of the œstrone structure consists of the introduction at a suitable stage of the methyl group rendering $C_{(13)}$ quaternary. A method used in a number of total steroid syntheses [4,6,11] for this purpose, and for the construction of the five-membered D-ring, has involved angular methylation and ring-contraction of appropriate nor-D-homo-compounds. This sequence has been based on the observation [12] that protection of the 2-position in 1-decalone by an arylmethylene residue forced subsequent methylation to occur in the angular position, and oxidation of the product (3) then afforded a dibasic acid that could be converted into perhydro-7-methylindan-1-one (4). Unfortunately, in the cases of 1-decalone [12] and of substituted 1-decalones,[4,6,11] while yields for the angular methylation–ring contraction sequence were generally satisfactory, the stereochemical course of the methylation stage was always unfavourable and resulted in the production of a preponderance of the less desirable stereoisomer with *cis*-fusion of the two rings. In the case of 1-decalone [12] itself, for example, the ratio *cis* : *trans*-2-benzylidene-9-methyl-1-decalone (3) observed was 3 : 1, while, in the most versatile approach yet developed [4,6] to the various stereoisomeric œstrone structures the *trans-anti-cis-* (" α- ") (5), *trans-anti-trans-* (" β- ") (6), and *trans-syn-cis*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene (" γ-methoxy-hydrochrysenone ") (7), afforded, on analogous treatment, CD-*cis*- and CD-*trans*-fused methylated products in the ratios 4 : 1, 3 : 1, and 11 : 1, respectively.[6,11]



(3) (4)



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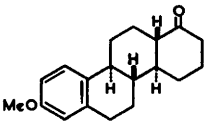
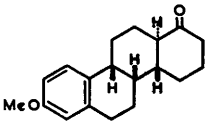


(6)

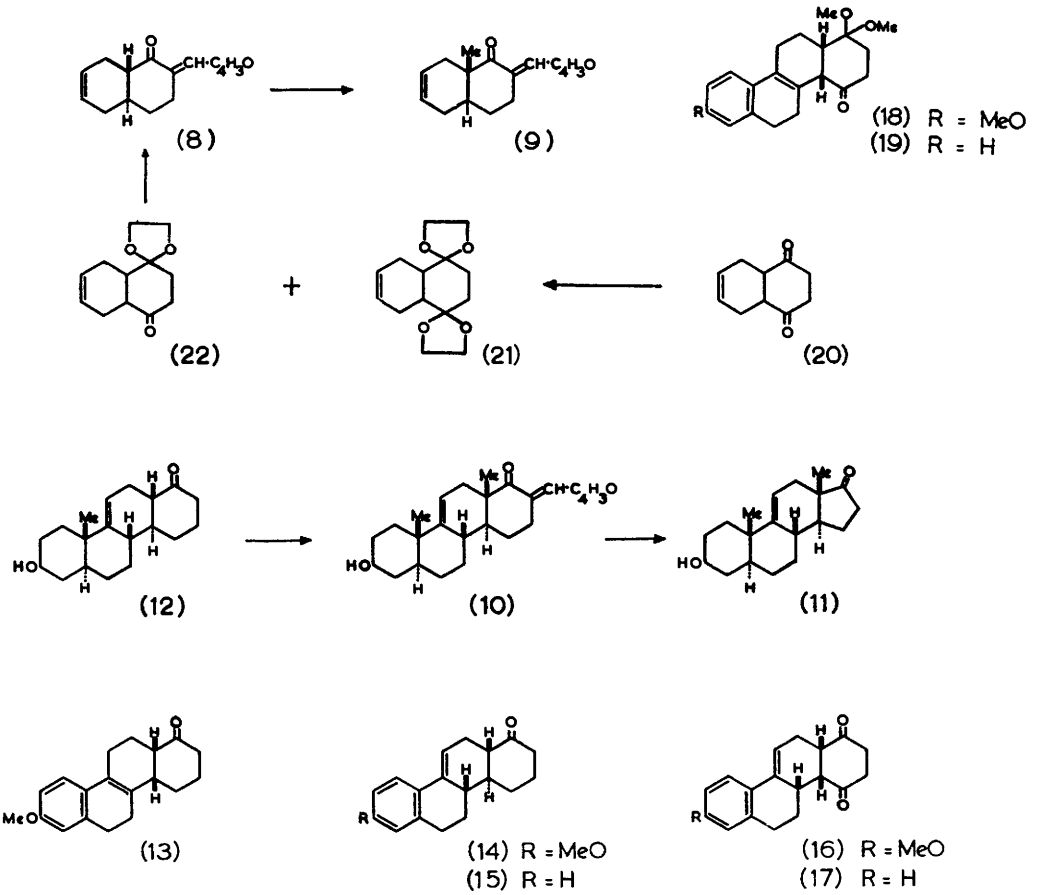


(7)

Although the unfavourable stereochemical course of the alkylation could be circumvented by an elaborate procedure,[13] a simpler solution was reached by Johnson and

[8] Cole, Johnson, Robins, and Walker, *Proc. Chem. Soc.*, 1958, 114.
[9] Hughes and Smith, *Proc. Chem. Soc.*, 1960, 74; *Chem. and Ind.*, 1960, 1022.
[10] Velluz, Nominé, Mathieu, Toromanoff, Bertin, Vignau, and Tessier, *Compt. rend.*, 1960, **250**, 1510; Velluz, Nominé, and Mathieu, *Angew. Chemie*, 1960, **72**, 725.
[11] (*a*) Johnson, Bannister, and Pappo, *J. Amer. Chem. Soc.*, 1956, **78**, 6331; (*b*) Johnson, Pappo, and Johns, *ibid.*, p. 6339; (*c*) Johnson, Bannister, Pappo, and Pike, *ibid.*, p. 6354; (*d*) Johnson, Vredenburgh, and Pike, *ibid.*, 1960, **82**, 3409.
[12] Johnson, *J. Amer. Chem. Soc.*, 1943, **65**, 1317; 1944, **66**, 215.
[13] Johnson, Martin, Pappo, Darling, and Clement, *Proc. Chem. Soc.*, 1957, 58.

Allen,[14] who showed that predominantly the *trans*-compound was formed on alkylation of a system in which steric hindrance to the *trans*-approach of the electrophilic alkylating agent to the keto-carbanion was reduced by the introduction of a double bond into the 1-decalone ring, so as to eliminate one of the axial hydrogen atoms (the one attached at position 7) appearing from models to oppose such *trans*-approach. Thus, 2-furfurylidene-Δ^6-octal-1-one (8) gave as major product the *trans*-9-methyl derivative (9); and the *trans*-product (10), leading to 9,11-dehydro-3β-hydroxyandrostan-17-one (11), was the major product on angular methylation of the corresponding nor-D-homo-compound (12). As an axial hydrogen atom attached to $C_{(5)}$ in the 1-decalone derivative is also responsible for some of the presumed steric hindrance to the *trans*-approach of the alkylating agent, the introduction of a trigonal carbon atom at position 5 (*i.e.*, a double bond in the 5,6-position) would be expected to have a similar steric effect on angular methylation, but



that was not conveniently amenable to study in the hydronaphthalene series. It was, however, capable of examination in the course of the present work in the hydrochrysene series, in which the angular methylation–ring contraction process has been applied to *cis*-1,2,3,4,4a,5,6,11,12,12a-decahydro-8-methoxy-1-oxochrysene (13), *trans-anti*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1-oxochrysene (14), and the demethoxy-derivative (15) of the latter.

[14] Johnson and Allen, *J. Amer. Chem. Soc.*, 1957, **79**, 1261.

Access to these substances (13)—(15) was obtained *via* the 1,4-diketones (16) [15,16] (17),[17] which are now readily available, and it was necessary for this purpose to eliminate the 4-oxygen function in the latter. It has previously been shown [17,18] that the 1-carbonyl group in these diketones participates very readily in ketal formation with methanol in the presence of a trace of mineral acid, but the lability towards acid of their 10b,11-double bond resulted in simultaneous migration of the double bond to the 4b,10b-position under the conditions then used, with formation of the $\Delta^{4b,10b}$-*cis*-dimethyl ketals (18) and (19), respectively. At the outset, moreover, it was not known whether or not a ketal group would be stable under the Huang-Minlon conditions for the Wolff–Kishner reduction, which was the method envisaged for elimination of the unwanted 4-carbonyl group in $C_{(1)}$-ketals derived from the diketones (16) and (17). A preliminary model study was therefore undertaken. Reaction between *cis*-Δ^6-1,4-dioxo-octalin (20) and ethylene glycol under Salmi's conditions [19] for cyclic ketal formation gave after separation by chromatography a solid bisethylene ketal (21) and an oily monoethylene ketal mixture (22). Careful fractional crystallisation of the latter afforded one fairly pure crystalline stereoisomer, reverting, apparently, to the original mixture on chromatography. It was assumed that the ketalisation proceeded with retention of the *cis*-configuration to give the *cis*-bisethylene ketal (21) and the *cis*-monoethylene ketal (22), and that equilibration of the latter had occurred during isolation. No evidence is available to show whether the crystalline monoethylene ketal (22) is the *cis*- or the *trans*-form. Huang-Minlon Wolff–Kishner reduction of the monoketal (22) mixture afforded an oil, showing no carbonyl absorption in its infrared spectrum, which, on acid hydrolysis, gave crude Δ^6-octal-1-one, characterised as the *trans*-furfurylidene derivative (8). The stability of a ketal to the Huang-Minlon conditions for the Wolff–Kishner reduction was thus demonstrated. Further proof was obtained when the bisethylene ketal (21) was recovered unchanged after similar Wolff–Kishner treatment. Since the completion of these exploratory experiments, other workers [20] have likewise demonstrated the stability of a ketal function to the conditions of this reduction. With this assurance the way was clear to attempt the preparation of the monoketones (13) and (14) from the diketone (16).

The Diels–Alder adduct, *cis-syn*-1,4,4a,4b,5,6,12,12a-octahydro-8-methoxy-1,4-dioxochrysene (23), obtained from 3,4-dihydro-6-methoxy-1-vinylnaphthalene (24) and benzoquinone, became readily available when it was found that lithium acetylide and 6-methoxy-1-tetralone (25) afforded the ethynyl-carbinol in good yield,[15,21] and conditions were carefully selected for conversion of the latter into the vinyl-carbinol (26) and diene (24) for direct reaction with benzoquinone.[15] A considerable improvement reported later,[16] however, consisting of the application of the Normant vinylmagnesium bromide reagent [22] to 6-methoxy-1-tetralone (25), led to the vinyl-carbinol (26) directly in very high yield, and by a combination of the best available conditions for each of the necessary steps we have obtained the *cis-syn*-diketone (23) from 6-methoxy-1-tetralone (25) in an overall yield of 75%, as compared with 42% [15] and 35% [16] reported previously. Migration of the 10b,11-double bond in the *cis-syn*-diketone (23) to the 4b,10b-position was observed on concentration of a benzene solution on the water-bath, affording *cis*-1,4,4a,5,6,11,12,12a-octahydro-8-methoxy-1,4-dioxochrysene (27); mild treatment with acid would normally be expected to cause this double-bond migration, but such treatment in the case of the *cis-syn*-diketone (23) resulted in simultaneous aromatisation of ring D with formation of

[15] Robins and Walker, *J.*, 1956, **3249**.
[16] Nazarov, Torgov, and Verkholetova, *Doklady Akad. Nauk S.S.S.R.*, 1957, **112**, 1067.
[17] Robins and Walker, *J.*, 1957, 177.
[18] Robins and Walker, *J.*, 1956, **3260**.
[19] Salmi, *Ber.*, 1938, **71**, 1803.
[20] Gerber, Division of Org. Chemistry, Amer. Chem. Soc., Abs. Papers, Sept. 7—12, 1958, p. 62; Fried, Arth, and Sarett, *J. Amer. Chem. Soc.*, 1959, **81**, 1235.
[21] Goldberg and Scott, U.S.P. 2,524,787.
[22] Normant, *Compt. rend.*, 1954, **239**, 1510, and later papers.

the corresponding quinol.[15] As demonstrated previously,[15] however, reduction of the 2,3-double bond in the *cis-syn*-octahydro-diketone (23) with zinc and acetic acid takes place readily without migration of the double bond, to give the polymorphic *cis-syn*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1,4-dioxochrysene (16), and similar reduction of the *cis*-octahydro-diketone (27) afforded *cis*-1,2,3,4,4a,5,6,11,12,12a-decahydro-8-methoxy-1,4-dioxochrysene (28), which is also readily obtained by isomerisation of the *cis-syn*-decahydro-diketone (16) in the presence of a trace of mineral acid.[15] Equilibration of the *cis-syn*-decahydro-diketone (16) on alumina gave, as before,[23] the *trans-anti*-form (29), and treatment of both of these stereoisomers (16) and (29) with toluene-*p*-sulphonic acid in benzene gave a new polymorphic form of the $\Delta^{4b,10b}$-*cis*-diketone (28). The alternative positions of the double bond in these structures are, of course, readily distinguished [15] by the position of the maximum due to the methoxystyrene chromophore in the ultraviolet absorption spectrum; thus, a 4b,10b-double bond results in maximum absorption at 273 ± 2 mμ, and a 10b,11-double bond in maximum absorption at 263 ± 2 mμ.* A 10b,11-double bond is also characterised by an infrared absorption band at 6·1 μ.

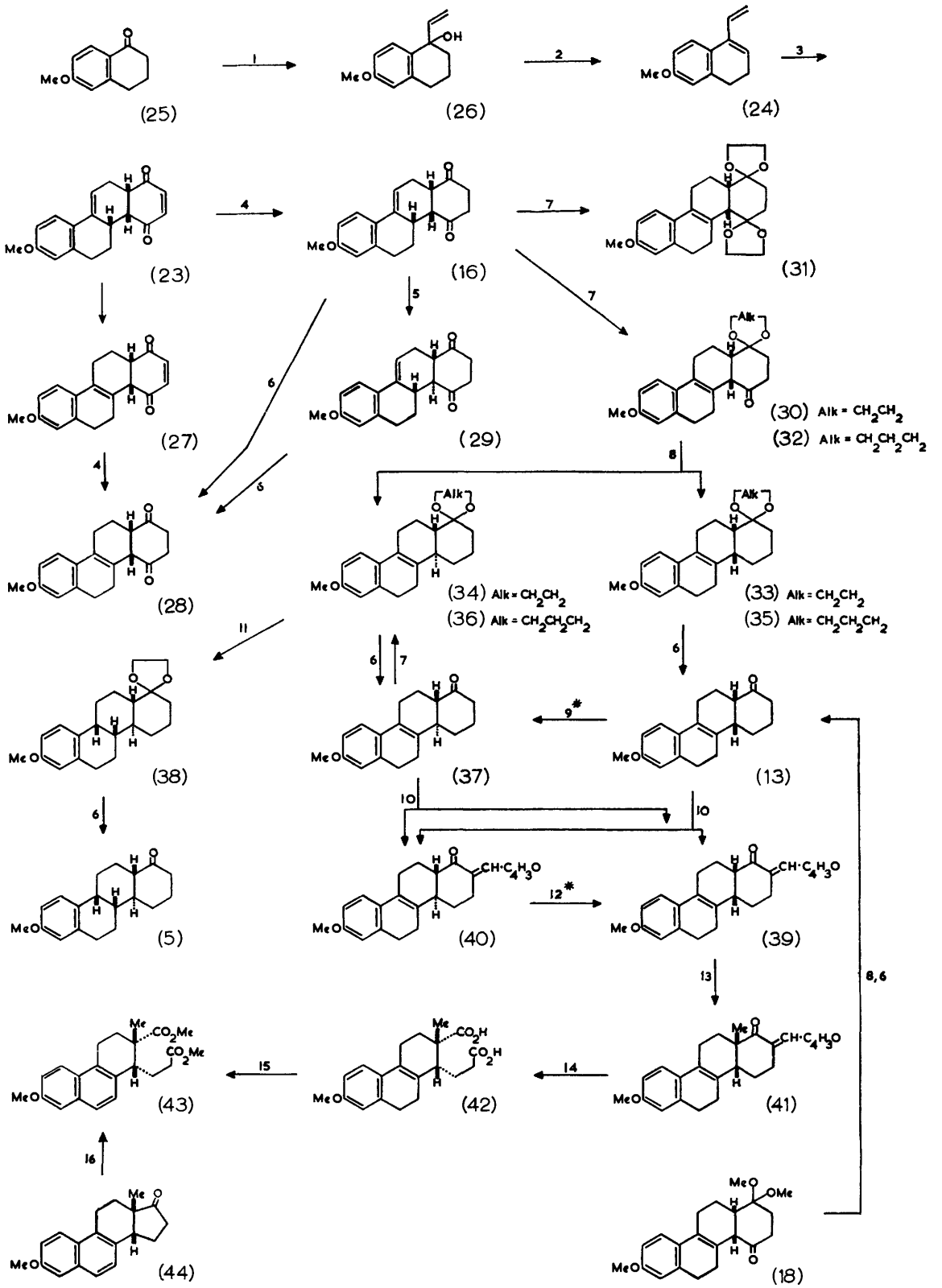
Application of the Salmi procedure [19] to the *cis-syn*-diketone (16) resulted in migration of the double bond and afforded the *cis*-1-monoethylene ketal (30) as major product, together with a small proportion of the *cis*-bisethylene ketal (31), traces of the *cis*-diketone (28), and unidentified material, when very careful attention was paid to the concentration of glycol and toluene-*p*-sulphonic acid. The *cis*-bisethylene ketal (31) was the sole product formed when a 20-molar excess of glycol was used, showing that the 5-methylene group did not offer as marked steric hindrance to ketal formation by the 4-carbonyl group with ethylene glycol as had been expected. An examination of molecular models indicated that the 5-methylene group would possibly offer substantially greater steric hindrance to the formation of a cyclic ketal if the ketal ring to be formed were larger than a five-membered one. This prediction was borne out by the fact that the *cis*-1-monotrimethylene ketal (32) was obtained in good yield from the *cis-syn*-diketone (16) and trimethylene glycol, and the bistrimethylene ketal could not be obtained. Proof that ketal formation occurs preferentially at the 1-carbonyl group has already been given in the case of the *cis*-dimethyl ketal (18),[23] and it follows (below) for the *cis*-monoethylene ketal (30) by its conversion by a series of stages into *trans-anti-cis*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene (" α-methoxyhydrochrysenone ") [6] (5).

Treatment of the *cis*-monoethylene ketal (30) under the Huang-Minlon conditions [24] for the Wolff–Kishner reduction gave a mixture of *cis*- (33) (43%) and *trans*-deoxo-ketal (34) (28%). These two ketals (33) and (34) were assumed to be stereoisomeric at $C_{(4a)}$, as the result of epimerisation at this position of the parent *cis*-monoethylene ketal (30) under the basic conditions of the reaction before formation of the hydrazone. If this were the case, and if further epimerisation could not take place after formation of the hydrazone, then it would be expected that stereochemical control in this Wolff–Kishner reduction could be obtained by selective addition of the reagents. This expectation was realised and confirmed the stereochemical assignments made to the two deoxo-ketals (33) and (34). The *cis*-deoxo-ketal (33) was the only product isolated (65·5%) when the *cis*-monoethylene ketal (30) was treated with hydrazine hydrate, to effect complete conversion into the hydrazone, before it was heated with potassium hydroxide in the normal way. If, however, potassium hydroxide was added to the *cis*-monoethylene ketal (30) to effect epimerisation at $C_{(4a)}$ before the addition of hydrazine hydrate then the only product isolated (49·5%) was the *trans*-deoxo-ketal (34). Additional evidence for the *cis*- and *trans*-configurations of these deoxo-ketals (33) and (34) follows from their subsequent conversions (below) into substances of established configuration. The *cis*-monotrimethylene ketal (32) was similarly converted on Huang-Minlon Wolff–Kishner reduction

* In the demethoxy-series these ranges are *ca.* 263—265 and 254—258 mμ, respectively.

[23] Robins and Walker, *J.*, 1959, 237.

[24] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.



* In these conversions substances (13) and (40) undergo epimerisation at $C_{(12a)}$ to give what should be shown as the enantiomorphs of compounds (37) and (39), but there is no inconsistency here as racemic forms are concerned.

Reagents: 1, CH_2:CH·MgBr. 2, Iodine. 3, Benzoquinone. 4, Zn–AcOH. 5, Al_2O_3. 6, H^+. 7, Glycol–H^+. 8, Huang-Minlon Wolff–Kishner redn. 9, OH^-. 10, Furfuraldehyde–OH^-. 11, H_2–Pd. 12, Florisil. 13, KOBu^t–MeI. 14, H_2O_2–NaOMe. 15, (i) CH_2N_2, (ii) Pd–C. 16, (i) H·CO_2Et, (ii) NH_2·OH, (iii) OH^-, (iv) CH_2N_2.

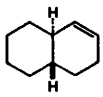
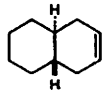
into a mixture of *cis*- (35) and *trans*-deoxo-ketal (36), the former being the major product. In contrast to the behaviour shown by the *cis*-monoethylene ketal (30), no appreciable change in the ratio of *cis*- (35) to *trans*-deoxo-ketal (36) was observed when the order of the addition of the reagents in the reduction was varied. Mild acid hydrolysis of the *cis*-deoxo-ketals (33) and (35) afforded *cis*-1,2,3,4,4a,5,6,11,12,12a-decahydro-8-methoxy-1-oxochrysene (13), which was also obtained by Huang-Minlon Wolff–Kishner reduction of the *cis*-dimethyl ketal (18) and subsequent hydrolysis. Similar acidic treatment of the *trans*-deoxo-ketals (34) and (36) afforded the *trans*-ketone (37), which also resulted from treatment of the *cis*-ketone (13) with 5% methanolic sodium hydroxide. Partial conversion of the *cis*- (13) into the *trans*-ketone (37) also occurred on crystallisation of the former from hot solvents but the latter was recovered unchanged after treatment with base or with hot solvents, indicating the greater stability of the CD-*trans*-form of the 4-deoxo-compound. This is in contrast to the apparently greater stereochemical stability of $\Delta^{4b,10b}$-CD-*cis*-4-oxo-compounds, which has been discussed previously.[23] As expected from a consideration of molecular models and the concept of *cis*-addition of hydrogen to that side of the molecule most readily adsorbed on to the surface of the catalyst,[25] catalytic hydrogenation of the *trans*-ethylene ketal (34) in ethanol over palladised strontium carbonate gave stereospecifically the known saturated ethylene ketal (38), identical with an authentic specimen [26] and affording *trans-anti-cis*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene ("α-methoxy-hydrochrysenone") (5) of unequivocal configuration [6] on mild acid hydrolysis. This conversion, besides giving proof that the ketal residue in the *cis*-monoethylene ketal (30) was situated at position 1, established the stereochemistry of the decahydro-ketones (13) and (37) and of the intermediate ethylene ketals (33) and (34) and trimethylene ketals (35) and (36).

The two decahydro-ketones (13) and (37) were thus available for a study of their angular methylation, and, in contrast with other known cases which afforded only one derivative, treatment of the *trans*-ketone (37) with furfuraldehyde in the usual way [11a] gave a mixture of two furfurylidene derivatives, arbitrarily assigned the *cis*- (39) and *trans*-structure (40), in approximately 75% and 7% yield, respectively. It should be pointed out that this ratio of yields did not necessarily represent the equilibrium mixture as the stereoisomer formed in greater proportion separated from the reaction mixture, thus probably affecting the result. In fact a 70 : 30 *cis* : *trans*-ratio was approached by equilibration on a column of Florisil. While the formation of the two products under basic conditions indicated that they were of comparable relative stereochemical stability, it was observed that treatment of the supposed *trans*-form (40) with base converted it into the supposed *cis*-stereoisomer (39) to the extent of at least 75%. As indicated already, the assignments of stereochemistry to these derivatives were arbitrary, but it was considered a reasonable assumption that the presence of two trigonal carbon atoms in the D-ring of a $\Delta^{4b,10b}$-system would favour a *cis*-locking at the CD-ring juncture. The *cis*-ketone (13) on similar treatment with furfuraldehyde also afforded the supposed *cis*- (39) and *trans*-furfurylidene derivative (40) in approximately 80% and 5% yield, respectively. Methylation of the supposed *cis*-form (39) with methyl iodide and potassium t-butoxide in the usual manner afforded the pure *cis*-methylated furfurylidene-ketone (41) in 91·5% yield. The stereochemistry of this product was proved as shown below, although, in the light of previous work,[6,11a] the small bathochromic shift in the maximum of the ultraviolet absorption spectrum of the methylation product strongly indicated the *cis*-assignment; exceptions to this rule have now, however, been found and are noted below. An exhaustive search among the residues of this methylation reaction gave no evidence of the presence of further material containing a furfurylidene ketone chromophore, indicating that the *trans*-methylated furfurylidene-ketone had not been formed.

[25] Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[26] Chinn, Ph.D. Thesis, University of Wisconsin, 1951.

Oxidation of the *cis*-methylated furfurylidene-ketone (41) with alkaline hydrogen peroxide afforded dehydroisohomomarrianolic acid methyl ether (42), and the dimethyl ester was dehydrogenated over 10% palladised charcoal to give the known methyl *cis*-β-(2-methoxycarbonyl-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenanthryl)-propionate (43). An authentic specimen of the latter was obtained by applying to the methyl ether of isoequilenin (44) the ring-cleavage procedure that has previously been applied to œstrone methyl ether for the opening of ring D and addition of a carbon atom,[4b,27] namely, treatment of the hydroxymethylene derivative with hydroxylamine and hydrolysis of the resulting α-cyano-ketone with alkali; esterification of the resulting acid with diazomethane gave the dimethyl ester (43), identical with that obtained from the methylated furfurylidene-ketone (41), thus confirming the *cis*-configuration of the latter.

The exclusive production of the *cis*-methylated product (41) in the methylation of the furfurylidene-$\Delta^{4b,10b}$-ketone (39) seems inconsistent with the qualitative considerations of Johnson and Allen,[14] but an explanation may be found in the vector concept discussed by Corey and Sneen.[28] These authors pointed out, on the basis of accurate calculations of molecular geometry, that in the *trans*-Δ^1-octalin system (45) the 1,3-interaction between the 8- and the 10-axial hydrogen atoms becomes acute owing to distortion of the molecule by the 1,2-double bond; in *trans*-Δ^2-octalin (46), however, the same non-bonded inter-

(45)   (46)

action is scarcely affected and distortion of the saturated ring is negligible. If it is assumed that the 4b,10b-double bond in the furfurylidene-ketone (39) affects the C/D-ring geometry in this system in the same way that the 1,2-double bond affects the geometry of the octalin system, then any favourable effect of removing obstruction by a 4b-axial hydrogen atom to *trans*-approach to $C_{(12a)}$ during the methylation of the furfurylidene-ketone (39) is more than off-set by increased steric hindrance due to the 4-axial hydrogen atom, caused by torsional strain in the system. It is, of course, realised that, in order to draw any analogies with the treatment of the octalins by Corey and Sneen,[28] it must be assumed that the effect of the 4b,10b-double bond on the 4-axial hydrogen atom is not off-set by alterations in the geometry of the C/D-ring system due to the 1-carbonyl group, the 2-furfurylidene group, and the A/B fused ring system in the furfurylidene-ketone (39). It is not easy to demonstrate *a priori* that this assumption is correct since adequate vector-analysis treatment in the present instance offers formidable mathematical difficulties. The greater stability of *trans*-Δ^2-octalin (46) than that of *trans*-Δ^1-octalin (45) is also reflected in the heat of hydrogenation [29] and infrared absorption spectrum [30] of cholest-2-ene as compared with those of other cholestenes.[29,30]

Although migration of the double bond from the 10b,11- to the 4b,10b-position took place in the formation of the ketals described above, its mobility has been found to be considerably less [31] in *cis-syn*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-1,4-dioxochrysene (17). In fact, the use of a sufficiently low concentration of hydrogen chloride in methanol resulted in 90% conversion of the diketone (17) into the *cis-syn*-1-dimethyl ketal (47), without any concomitant shift of the double bond. The same conditions, however, failed to retain the double bond in the 10b,11-position when applied to the 8-methoxy-compound (16), but the use of methanol containing 10% by weight of glacial acetic acid afforded an acceptable (up to 48%) conversion of the ketone (16) into the *cis-syn*-1-dimethyl ketal (48). Though by no means perfect these conditions achieved a reasonable balance

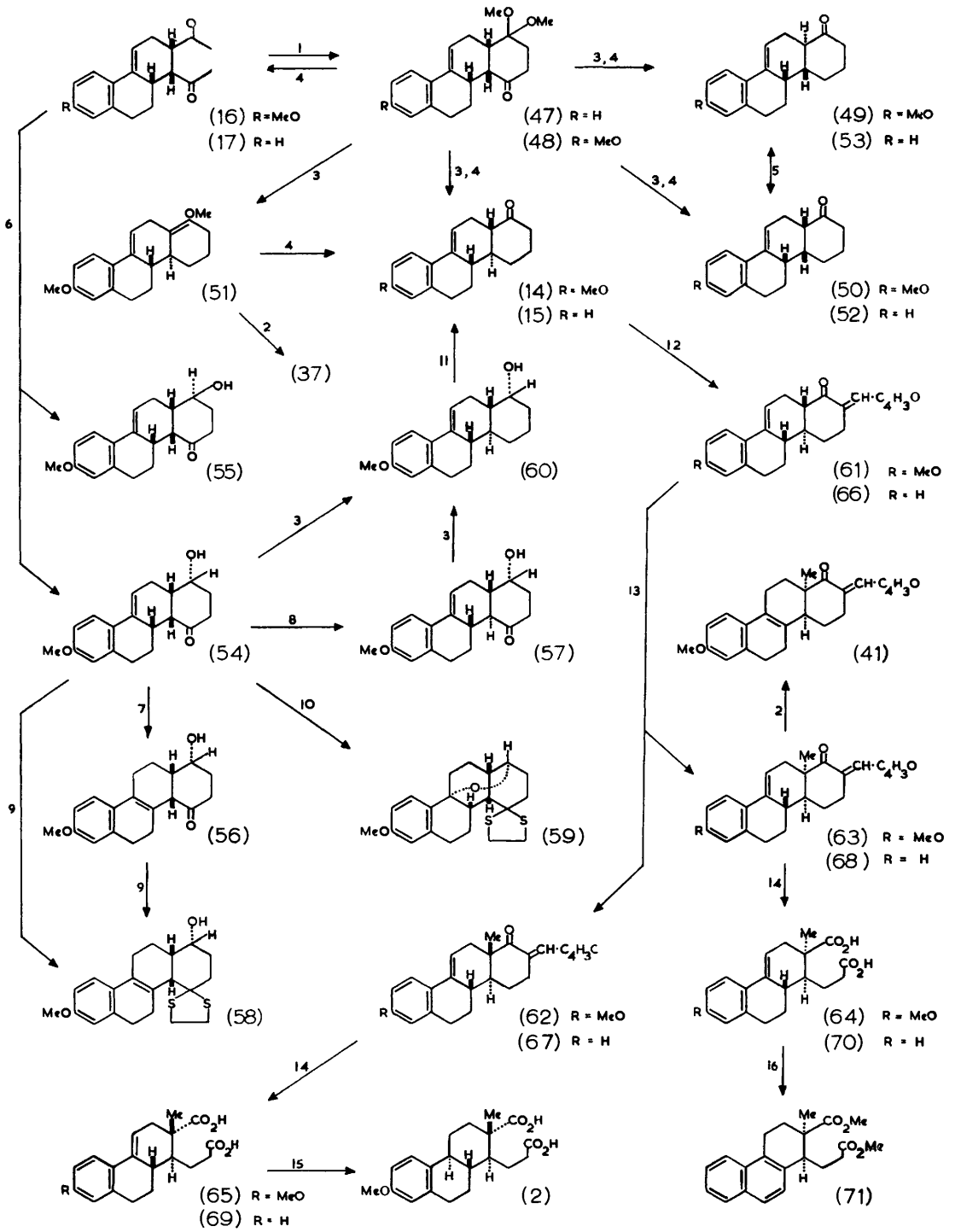
[27] Cf. Bardhan, *J.*, 1936, 1848.
[28] Corey and Sneen, *J. Amer. Chem. Soc.*, 1955, **77**, 2505.
[29] Turner, Meador, and Winkler, *J. Amer. Chem. Soc.*, 1957, **79**, 4122.
[30] Henbest, Meakins, and Wood, *J.*, 1954, 800.
[31] Robins and Walker, *J.*, 1958, 409.

between the rate of ketal formation and the rate of double-bond shift after ketal formation, and gave a mixture of the desired product (48), unchanged starting material (16), and some *cis*-1-dimethyl ketal (18). The *cis*-dimethyl ketal (18) was readily separated, but the *cis-syn*-dimethyl ketal (48) could not be freed completely from starting material (16) by fractional crystallisation. The latter, however, could be removed as its sparingly soluble 1-monosemicarbazone, or by treatment of the crude reaction mixture with alkali, which converted it into soluble decomposition products. Neither method of separation, unfortunately, permitted re-use of unchanged starting material (16), and it was advantageous to omit purification routinely, since the diketone (16) was destroyed and the resulting product easily eliminated in the next stage, the Huang-Minlon Wolff–Kishner reduction. It is of interest to note that the *trans-anti*-diketone (29) failed to form a dimethyl ketal under the conditions that proved effective for the *cis-syn*-diketone (16), and attempts to prepare the diethyl ketal corresponding to the *cis-syn*-dimethyl ketal by using ethanol and acetic acid in a similar manner afforded only unchanged starting material (16). These observations further illustrate the critical steric requirements for acetal formation in this series, to which attention has already been directed above.

Huang-Minlon Wolff–Kishner reduction of the *cis-syn*-dimethyl ketal (48) presented a number of difficulties, and a noteworthy point was that if 100% hydrazine hydrate was used, instead of 60% hydrazine hydrate, the yield of useful product was greatly reduced by the formation of substantial amounts of demethylated phenolic material. In the $\Delta^{4b,10b}$-series remethylation by methyl iodide and potassium carbonate in acetone was effective in utilizing this phenolic by-product, but in the $\Delta^{10b,11}$-series remethylation was extremely slow and was accompanied by migration of the double bond. Demethylation under the Huang-Minlon conditions for the Wolff–Kishner reduction has been observed previously and even used deliberately by others.[32] Treatment of the *cis-syn*-dimethyl ketal (48) with 60% hydrazine hydrate and alkali effected stereochemical equilibration at $C_{(4a)}$, and preferential hydrazone formation by the *trans-anti*-form ensured that the major isolable product in the Wolff–Kishner reduction under normal Huang-Minlon conditions was, after mild acid hydrolysis of the ketal group, *trans-anti*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1-oxochrysene (14). The immediate product of the reaction, however, was a complex mixture, and, after treatment of the crude product with acetic acid, there were isolated, in addition to the *trans-anti*-ketone (14), the *trans-syn*-stereoisomer (49) and *trans-anti*(?)-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxychrysene [*i.e.*, dideoxo-(29)]. Chromatography of the crude reaction product before treatment with acetic acid gave, in addition to the decahydromethoxychrysene [dideoxo-(29)] and the *trans-anti*-ketone (14), the dimethyl ketal of the *cis-syn*-ketone (50) and an impure precursor of the *trans-anti*-ketone (14). The *cis-syn*-ketone (50), obtained by hydrolysis of its dimethyl ketal, underwent partial conversion into the *trans-syn*-form (49) on treatment with alcoholic alkali. In a number of experiments a crystalline product isolated in small amount (*ca.* 2%) was diagnosed by its nuclear magnetic resonance spectrum, which showed only two methoxyl peaks and no enol ether hydrogen absorption, to be the *anti*-enol ether (51); it was converted on treatment with alcoholic mineral acid into the *trans*-ketone (37), and partially by hot acetic acid into the *trans-anti*-ketone (14). The loss of methanol from dimethyl ketals on heating to give enol ethers is known,[33] and we have found that heating the dimethyl ketal of 1-decalone in boiling ethylene glycol for 1½ hours gave a 1 : 1 mixture of 1-methoxy-Δ^1-octalin and starting material. In these experiments an overall yield of about 22% of the *trans-anti*-ketone (14) could be obtained from the *cis-syn*-diketone (16) if isolation of the intermediate *cis-syn*-dimethyl ketal (48) was omitted.

In a similar manner Huang-Minlon Wolff–Kishner reduction of the *cis-syn*-dimethyl

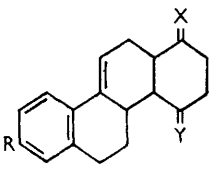
[32] Cf. Gates and Tschudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380; Gates and Webb, *ibid.*, 1958, **80**, 1186.
[33] Alder and Niklas, *Annalen*, 1954, **585**, 97; Grob and Jundt, *Helv. Chim. Acta*, 1952, **35**, 2111.



Reagents: 1, MeOH–H^+. 2, H^+. 3, Huang-Minlon Wolff–Kishner redn. 4, AcOH. 5, NaOMe. 6, Ponndorf redn. 7, Al_2O_3. 8, OH^-. 9, $HS{\cdot}CH_2{\cdot}CH_2{\cdot}SH$–$BF_3$–$Et_2O$. 10, $HS{\cdot}CH_2{\cdot}CH_2{\cdot}SH$–$ZnCl_2$. 11, Oppenauer oxidn. 12, Furfuraldehyde–OH^-. 13, KOBu^t–MeI. 14, H_2O_2–NaOMe. 15, Na–NH_3. 16, (i) CH_2N_2, (ii) Pd–C.

ketal (47) afforded *trans-anti-* (15), *cis-syn-* (52), and *trans-syn*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-1-oxochrysene (53). The assignments of stereochemical configuration to the ketonic products (14), (49), (50) and (15), (52), (53) of these Huang-Minlon Wolff–Kishner reductions were made in the first instance largely on the basis of ultraviolet-light absorption evidence as described below. Further correlations, whenever possible, with compounds of established configuration have corroborated these assignments. It has been found in a large number of cases that, when the *cis-syn*-configuration of any of the $\Delta^{10b,11}$-structures now under consideration is altered to the *trans-anti-* or to the *trans-syn*-configuration, a slight, but definite, shift in the positions of the two maxima (at *ca.* 264—266 and 299—302 mμ) takes place to shorter wavelength (*ca.* 262 and 294—296 mμ), *irrespective* of the groups present as substituents in positions 1 and 4. The data

Ultraviolet absorption of compounds of the type



Formula	Compound R	X	Y	Stereochemistry	*K* band $\lambda_{max.}$ (mμ) (log ε)	*B* band $\lambda_{max.}$ (mμ) (log ε)	Ref.
(16)	MeO	O	O	*cis-syn*	264 (4·23)	299 (3·60)	15
	MeO	O	H,OH	*cis-syn*	265 (4·28)	300 (3·58)	15
(54)	MeO	H,α-OH	O	*cis-syn*	265·2 (4·24)	300 (3·51)	
(55)	MeO	H,β-OH	O	*cis-syn*	265·5 (4·24)	302 (3·54)	
	MeO	H,OH	H,OH	*cis-syn*	265 (4·28)	300 (3·54)	15
(48)	MeO	$(MeO)_2$	O	*cis-syn*	266 (4·29)	300·5 (3·62)	
	MeO	$(MeO)_2$	H,OH	*cis-syn*	266 (4·32)	300 (3·59)	23
	MeO	$(MeO)_2$	H_2	*cis-syn*	265 (4·29)	300·5 (3·54)	
(50)	MeO	O	H_2	*cis-syn*	265 (4·32)	300 (3·59)	
(29)	MeO	O	O	*trans-anti*	262 (4·28)	294 (3·50)	23
(57)	MeO	H,α-OH	O	*trans-anti*	261·2 (4·26)	295 (3·42)	
(14)	MeO	O	H_2	*trans-anti*	263 (4·25)	296·5 (3·44)	
(60)	MeO	H,α-OH	H_2	*trans-anti*	262·5 (4·33)	298 (3·49)	
	MeO	H,OH	H,OH [b]	*trans-anti*	262 (4·27)	296 (3·50)	
	MeO	H_2	H_2	*trans-anti* [a]	262 (4·27)	297 (3·41)	
	MeO	O	O	*trans-syn* [a]	262 (4·28)	295 (3·50)	23
(49)	MeO	O	H_2	*trans-syn*	259 (4·28)	292 (3·48)	
(17)	H	O	O	*cis-syn*	260 (4·13)	290 (3·47), 300 (3·36)	17
(47)	H	$(MeO)_2$	O	*cis-syn*	261 (4·18)	290 (3·51), 301 (3·40)	
(52)	H	O	H_2	*cis-syn* [a]	260 (4·26)	289 (3·62), 300 (3·48)	
(15)	H	O	H_2	*trans-anti*	256 (4·14)	288 (3·36), 297 (infl.) (3·22)	
(53)	H	O	H_2	*trans-syn* [a]	253 (4·20)	284 (infl.) (3·31)	

[a] Stereochemistry not rigidly proved by further correlation with substance(s) of established configuration. [b] Mixed stereoisomeric diols from reduction of the *trans-anti*-diketone (29) with lithium aluminium hydride.

are recorded in the Table, and these effects are, of course, comparable in magnitude with the effects of stereochemistry on the position of maximum absorption by the arylmethylene ketone chromophore,[6,11a] noted above.

Since the above scheme for the conversion of the *cis-syn*-diketone (16) into the *trans-anti*-monoketone (14) *via* the *cis-syn*-dimethyl ketal (48) proceeded so poorly (22% overall yield), an alternative method for the protection of the 1-carbonyl group was sought and its temporary reduction to a secondary alcohol group proved satisfactory. Although it is well known that the related Oppenauer oxidation is susceptible to steric effects and can be used for the selective oxidation of particular secondary alcohol functions in polyols,[15,34] little in the way of precedent has been found [35] for the selective Ponndorf

[34] (*a*) Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422; (*b*) Robins and Walker, *J.*, 1954, 3960.
[35] Wilds, *Organic Reactions*, 1949, **2**, 178.

reduction of only one carbonyl group in a molecule containing two or more such functions. A case is known in which a saturated ketone group was selectively reduced in a molecule containing also an αβ-unsaturated ketone function.[36] It may also be noted that forcing conditions were required[37] for reduction of the carbonyl group in 1,2,3,4-tetrahydro-4-oxochrysene, which presents some analogy with the 4-carbonyl group in the *cis-syn*-diketone (16). Under appropriate conditions, Ponndorf reduction of the *cis-syn*-diketone (16) afforded two main products in nearly 90% total yield, together with a small amount of the *trans-anti*-diketone (29), resulting from equilibration of unchanged *cis-syn*-diketone (16) during chromatography of the crude product. It is known that this method of reduction of unhindered ketones gives both possible epimeric alcohols, with the equatorial form predominating.[38] Since, as shown below, the stereochemistry at the CD-ring junction was unchanged during the reaction, the equatorial (α) hydroxyl structure (54) was assigned to the predominant stereoisomer and the axial (β) hydroxyl structure (55) to the minor product. Migration of the double bond in the former (54) to the 4b,10b-position under the influence of acid afforded the *cis*-1-hydroxy-4-ketone (56), previously obtained[15] by catalytic hydrogenation of the *cis*-diketone (28) over platinum oxide; the latter mode of preparation strongly pointed to the α- or equatorial configuration for the 1-hydroxyl group, since the catalyst must have approached the *cis*-diketone (28) from the less hindered β-side. As the locations of the hydroxyl and carbonyl functions in the *cis*-keto-alcohol (56), as well as the *cis*-configuration, have been proved conclusively,[15] the locations of the hydroxyl and carbonyl groups in the keto-alcohol (54) were confirmed. Evidence for the *cis-syn*-configuration in the keto-alcohols (54) and (55) was obtained by treatment of the former (54) with alkali; this gave in excellent yield a new keto-alcohol, to which the *trans-anti*-structure (57) was assigned. All three keto-alcohols (54), (55), and (57) were stable on a column of Florisil. It should be pointed out that the *trans-anti*-diketone (29) was recovered unchanged when treated under a wide variety of Ponndorf reduction conditions; this also shows that the *trans-anti*-diketone (29) could not have been concerned in the above reduction, and further confirmed the assumption that the stereochemistry at the ring-junction remained unchanged during the reaction.

As a method for the elimination of the unwanted 4-carbonyl group from the keto-alcohols (54) and (55), attempts were made to prepare 4-ethylene thioketals with a view to their desulphurisation. Products (58) lacking carbonyl absorption in the infrared region were obtained but migration of the double bond to the 4b,10b-position also took place. Application of Hauptmann's method[39] for thioketal formation to the keto-alcohol (54) gave in high yield a crystalline product which had no infrared hydroxyl, carbonyl, or trisubstituted double-bond absorption, and it was assigned the bridged ether structure (59).* This assignment of structure was supported by cleavage of the substance by the boron trifluoride–ether complex to material shown by its ultraviolet absorption spectrum to contain a 10b,11-double bond. The conversion of the keto-alcohol (54) into this bridged-ether structure (59) conclusively proved the *cis-syn*-stereochemistry and α-hydroxyl orientation of the keto-alcohol (54), since no other stereochemical arrangement would permit such a 1,10b-ether linkage.

The unwanted 4-carbonyl group in the keto-alcohol (54) was successfully removed as follows. Alkaline epimerisation at $C_{(4a)}$ in the *cis-syn*-keto-alcohol (54) and Huang-Minlon Wolff–Kishner reduction of the resulting *trans-anti*-keto-alcohol (57) afforded, in

* This structure contains a boat ring C. An analogous oxide structure is found in 3α,9α-oxidocholl-11-enic acid (Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall, *J. Biol. Chem.*, 1946, **164**, 569), and transannular epoxide formation has also been observed with $\Delta^{8(14)}$-dehydro-17α-hydroxycorticosterone (Bollinger and Wendler, *Chem. and Ind.*, 1960, 1022).

[36] Miescher and Fischer, *Helv. Chim. Acta*, 1939, **22**, 158.
[37] Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 456.
[38] Dauben, Fonken, and Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579; Dauben, Blanz, Jiu, and Micheli, *ibid.*, p. 3752; Wheeler and Mateos, *Canad. J. Chem.*, 1958, **36**, 1431.
[39] Hauptmann, *J. Amer. Chem. Soc.*, 1947, **69**, 562.

nearly 80% yield, the *trans-anti*-alcohol (60), but the temperature for the latter reaction was unusually critical and the use of triethylene glycol proved advantageous. The *trans-anti*-alcohol (60) was smoothly oxidised by the Oppenauer method and gave the *trans-anti*-ketone (14) in nearly 90% yield. It was then found possible to carry the *cis-syn*-diketone (16) through the Ponndorf reduction, alkaline epimerisation, Huang-Minlon Wolff–Kishner reduction, and Oppenauer oxidation without isolation of the intermediates, to give the pure *trans-anti*-monoketone (14) in 48·5% overall yield, since it was extremely easily separated from the reaction mixture by crystallisation. This yield is possible only if both keto-alcohols (54) and (55) are converted into the *trans-anti*-monoketone (14), and thus the structure of the keto-alcohol (55) is proved.

Once *trans-anti*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1-oxochrysene (14) was readily available, the angular methylation sequence was pursued. Condensation with furfuraldehyde was nearly quantitative and methylation of the resulting derivative (61) with methyl iodide and potassium t-butoxide in the usual way gave a mixture of methylated 12a-epimers, which was separated with difficulty by fractional crystallisation into the *trans-anti*- (62) (55·8%) and *cis-anti*-2-furfurylidene-12a-methyl derivative (63) (33·2%). On account of the sensitivity of the furfurylidene-ketone (61) to potassium t-butoxide, it was necessary to modify the methylation procedure so that an excess of that reagent was never present; even so about 7% of the product was a red tar which showed no furfurylidene ketone absorption in the ultraviolet spectrum. The configuration of the *trans-anti*-methylated furfurylidene-ketone (62) was established by its subsequent conversion into homomarrianolic acid methyl ether (2), and that of the *cis-anti*-stereoisomer (63) by its treatment with toluene-*p*-sulphonic acid, under conditions known to effect migration of the 10b,11-double bond, to give the $\Delta^{4b,10b}$-*cis*-methylated furfurylidene-ketone (41), whose configuration is known unequivocally (see above).

Nuclear magnetic resonance spectroscopy at either 40 or 60 Mc./sec. has provided a very accurate means of determining the ratios (by area under the curve) of angular methylation products, as the resonance due to the methyl group of the *cis*-stereoisomer is down-field with respect to, and clearly separated from, that of the *trans*-stereoisomer by as much as 10 c./sec. This effect has been observed in a number of cases and may thus possibly be the best analytical method available for the diagnosis of the stereochemistry of methylation products. The total crude methylation mixture from the *trans-anti*-furfurylidene-ketone (61) was shown in this way to contain the *trans*- (62) and *cis*-methylated product (63) in a ratio of 60 : 40. Thus methylation of the *trans-anti*-ketone (14), as its furfurylidene derivative (61), did indeed give a preponderance of the CD-*trans*-methylated stereoisomer (62), and demonstrated, in accordance with the Johnson and Allen hypothesis,[14] the use of the 10b,11-double bond for obtaining stereochemical control during angular methylation. The degree of stereoselectivity obtained, however, was not as great as that observed by Johnson and Allen [14] in their model experiments, and the smaller difference observed in the present case may have been due to conformational transmission effects arising in ring A.[40] It was also significant that the ultraviolet absorption maxima observed for these two stereoisomers (62) and (63) did not conform to the trend previously noted,[6,11c] that in all *cis*- and *trans*-pairs of methylated arylmethylene-ketones studied (14 cases) the *cis*-stereoisomer absorbed at longer wavelengths than the *trans*-form; in fact this trend has been considered diagnostic and has been used in assigning configurations to methylation products.[6,11c]

Oxidation of the *cis-anti*- (63) and *trans-anti*-methylated furfurylidene-ketone (62) with alkaline hydrogen peroxide afforded, respectively, *cis-anti*- (64) (38·7%) and *trans-anti*-β-(2-carboxy-1,2,3,9,10,10a-hexahydro-7-methoxy-2-methyl-1-phenanthryl)propionic acid (65) (35·6%). Finally, reduction of the crude *trans-anti*-dicarboxylic acid (65) with

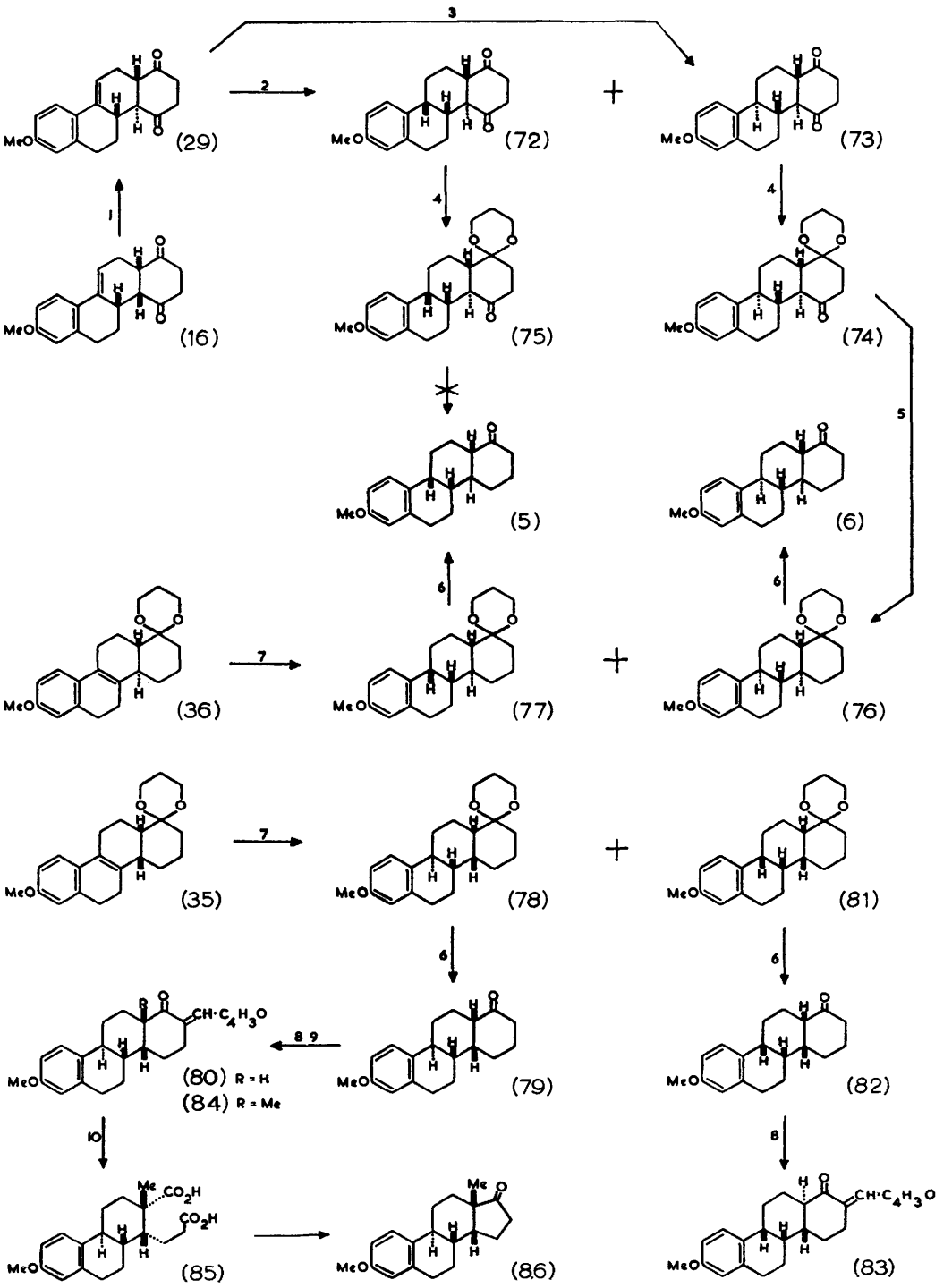
[40] Barton, Head, and May, *J.*, 1959, 935; Barton, in " Theoretical Organic Chemistry " (Kekulé Symposium), Butterworths, London, 1959, p. 127.

sodium in liquid ammonia gave the known *trans-anti-trans*-dicarboxylic acid (homomarrianolic acid methyl ether) (2) in 31·5% yield from the *trans-anti*-methylated furfurylidene-ketone (62). Since homomarrianolic acid methyl ether (2) has previously been transformed [2,4,5a] into the racemate of natural œstrone (1), the present stereoselective preparation of this dibasic acid (2) constitutes a stereoselective total synthesis of œstrone. In this synthesis the overall yield of the *trans-anti-trans*-homomarrianolic acid methyl ether (2) from 6-methoxy-1-tetralone (25) in six steps [(25) $\xrightarrow{74\cdot8\%}$ (23) $\xrightarrow{86\cdot0\%}$ (16) $\xrightarrow{48\cdot5\%}$ (14) $\xrightarrow{96\cdot5\%}$ (61) $\xrightarrow{55\cdot8\%}$ (62) $\xrightarrow{31\cdot5\%}$ (2)] was thus 5·3%.

As the demethoxy-*trans-anti*-ketone (15) became available in the present work its angular methylation was undertaken as a further test of the Johnson and Allen hypothesis.[14] Methylation of the derived polymorphic furfurylidene derivative (66) in the usual manner gave a mixture of 12a-methylated epimers, which was shown by nuclear magnetic resonance spectroscopy to contain 40 $\pm$ 5% of the *trans-anti-* (67) and 60 $\mp$ 5% of the *cis-anti*-form (68). These yields were determined spectroscopically, since complete separation by chromatography and crystallisation was not possible in the classical manner, although some concentration of the *cis-anti*-form (68) was obtained in the early fractions on chromatography. The stereochemical assignments were made on the basis of nuclear magnetic resonance spectroscopy, and are proved below; they were also indicated by the chromatographic behaviour,[41] the less symmetrical (*cis*-)form (68) being the less strongly adsorbed, but they are, again, contrary to the assignments that would have been made on the basis of ultraviolet absorption observations.[6,11c] As seen above, however, stereochemical assignments based on such ultraviolet absorption data can no longer be considered valid. The *trans-anti*-methylated furfurylidene-ketone (67) was cleaved with alkaline hydrogen peroxide to give the *trans-anti*-dibasic acid (69), and the dimethyl ester on rearrangement and dehydrogenation on palladised charcoal gave oily methyl *trans*-β-(1,2,3,4-tetrahydro-2-methoxycarbonyl-2-methyl-1-phenanthryl)propionate. In a similar manner, oxidation of the *cis-anti*-methylated furfurylidene-ketone (68) gave the *cis-anti*-dicarboxylic acid (70), and rearrangement and dehydrogenation of its dimethyl ester over palladised charcoal gave the known dimethyl ester [42] (71) of *cis*-β-(2-carboxy-1,2,3,4,-tetrahydro-2-methyl-1-phenanthryl)propionic acid, whose infrared spectrum was rich in detail and superposable on that of the authentic material. The above configurational assignments were thus established. While the 3 : 2 CD-*cis*- : CD-*trans*-methylation ratio was an improvement over the normal 3 : 1 order for this ratio, this methylation did not afford the stereochemical control observed in the cases studied by Johnson and Allen,[14] and contrasts with the favourable 2 : 3 ratio observed in the present 8-methoxyhydrochrysene (61) series. It is obvious that all the factors governing the angular methylation of these arylmethylene-ketones are not yet fully appreciated, and conformational transmission [40] no doubt plays a significant part. Conformational effects, however, would be expected to be the same in the furfurylidene-8-methoxy-ketone (61) and the 8-unsubstituted furfurylidene-ketone (66) and in their respective mesomeric anions participating in the methylation, yet they afford on methylation CD-*cis*- : CD-*trans*-products in the ratios 2 : 3 and 3 : 2, respectively.

The availability of a number of unsaturated ketones in the work described above has made possible an extension of previous studies [6] in the methoxyhydrochrysenone series, in which three [designated in the order of their isolation the α- (5), β- (6), and γ-methoxyhydrochrysenone (7)] out of the eight possible racemic forms of 1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene have given rise to six out of the eight possible racemates of the œstrone methyl ether structure. In the work now to be described the three forms already known, [(5)—(7)] and a fourth, which may be termed δ-methoxyhydrochrysenone, were encountered.

[41] Barton, *J.*, 1953, 1027.
[42] Bachmann and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 2085.



Reagents: 1, Al_2O_3. 2, H_2–Pd–C. 3, (i) Na–NH_3, (ii) CrO_3–C_5H_5N. 4, Glycol–H^+. 5, Huang-Minlon Wolff–Kishner redn. 6, H^+. 7, Li–NH_3. 8, Furfuraldehyde–OH^-. 9, $KOBu^t$–MeI. 10, H_2O_2–NaOMe.

As shown previously,[23] catalytic hydrogenation of the *trans-anti*-decahydro-diketone (29) gave access to *trans-anti-cis-* (72) and *trans-anti-trans*-dodecahydro-diketone (73), and improved conditions have now led directly and quantitatively to a difficultly separable ~2 : 1 mixture of these two ketones. The configurations previously assigned[23] to these substances were confirmed by the conversion (see below) of the latter (73) into the *trans-anti-trans*-(" β- ")methoxyhydrochrysenone (6). In contrast also with the stereochemical instability of the *trans-anti-cis*-compound (72),[23] the *trans-anti-trans*-diketone (73) was recovered unchanged after adsorption on alumina. Since carbanion reductions appear to be thermodynamically controlled and usually give the stereochemically favoured products when the creation of new asymmetric centres is involved,[43] reduction of the *trans-anti*-diketone (29) with sodium in liquid ammonia was undertaken. The initial product was a diol, and oxidation with the chromium trioxide–pyridine reagent[34] gave, as expected,[44] the *trans-anti-trans*-diketone (73) as sole identifiable product. The *trans-anti-trans*-assignment was also proved by conversion of the diketone into *trans-anti-trans*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene (" β-methoxyhydrochrysenone ") (6) by the method repeatedly used in the present work. Reaction of the *trans-anti-trans*-diketone (73) with trimethylene glycol gave a monotrimethylene ketal (74), which afforded on Huang-Minlon Wolff–Kishner reduction the *trans-anti-trans*-trimethylene ketal (76), further described below. Acid hydrolysis of this ketal (76) gave the known *trans-anti-trans*-monoketone (" β-methoxyhydrochrysenone ") (6) of unequivocal configuration; a more convenient route to this substance is given below. The *trans-anti-cis*-diketone (72) was similarly converted smoothly into a monotrimethylene ketal (75) but stereochemical instability at $C_{(4a)}$ resulted in the production of an intractable product when the Huang-Minlon Wolff–Kishner reduction was applied to this ketal.

By extrapolation from the energy relationships in the analogous phenanthrene series,[44] it was expected that thermodynamic control of stereochemistry offered by carbanion reduction would lead to results of interest on application to the trimethylene ketals (36) and (35) of the *trans-* (37) and *cis*-decahydro-ketones (13). It could be predicted that the major product from the former (36) would be the *trans-anti-trans*-trimethylene ketal (76) and that minor products would be the *trans-syn-cis-* or the *trans-anti-cis*-trimethylene ketal (77), but formation of the energetically least favoured *trans-syn-trans*-form would be highly improbable. In the case of the *cis*-trimethylene ketal (35) the least likely product would be the *cis-anti-trans*-form as it would have the bulky 1-trimethylene ketal group as an axial substituent of ring c, and the major product expected would be the *cis-syn-trans*-trimethylene ketal (78), leading to the hitherto unknown *cis-syn-trans*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysene (79) (δ-methoxyhydrochrysenone). It was found that neither sodium nor lithium in completely anhydrous ammonia reduced the ketal (35) or (36), but sodium in moist liquid ammonia reduced the *cis*-trimethylene ketal (35) and lithium in moist liquid ammonia reduced both ketals. The *trans*-trimethylene ketal (36) afforded two products; as expected the major product (80%) was the polymorphic *trans-anti-trans*-trimethylene ketal (76) and the minor product (15%) was the *trans-anti-cis*-trimethylene ketal (77). Acid hydrolysis of the former (76) gave the known *trans-anti-trans*-(" β ")-methoxyhydrochrysenone (6), and the latter gave similarly the known *trans-anti-cis*-(" α ")-methoxyhydrochrysenone (5), confirming the expected course of the reduction. Reduction of the *cis*-trimethylene ketal (35) gave, as expected, the *cis-syn-trans*-trimethylene ketal (78) as the major product (74%), affording, on acid hydrolysis, the previously unknown *cis-syn-trans*-(" δ ")-methoxyhydrochrysenone (79). This ketone was stable to methanolic sodium methoxide as the possible product of epimerisation at $C_{(12a)}$ was the energetically less favoured *trans-syn-trans*-form requiring a boat c-ring.[44] The uniqueness of this new ketone (79) was confirmed by comparison

[43] Barton and Robinson, *J.*, 1954, 3045.
[44] Johnson, *Experientia*, 1951, **7**, 315; *J. Amer. Chem. Soc.*, 1953, **75**, 1498.

of the infrared spectrum of its furfurylidene derivative (80) with those of the furfurylidene derivatives of the three previously known stereoisomers. The residue from the reduction of the *cis*-ketal (35), after removal of the *cis-syn-trans*-trimethylene ketal (78), must have contained a substantial proportion of the *cis-syn-cis*-trimethylene ketal (81); it was hydrolysed with acid and, without purification, the crude *cis-syn-cis*-ketone (82) was condensed with furfuraldehyde to give, with inversion at $C_{(12a)}$, the known furfurylidene derivative (83) of the *trans-syn-cis*-("γ")-methoxyhydrochrysenone in amount indicating the presence of at least 17·2% of the *cis-syn-cis*-trimethylene ketal (81) in the original reduced product.

If one includes the *cis-syn-cis*-dodecahydro-ketone (82), which was not isolated in the pure state, metal–ammonia reduction of the *trans*- (37) and *cis*-decahydro-ketone (13) as their trimethylene ketals, gave access to five out of the eight possible stereoisomeric 1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1-oxochrysenes, of which three, (5), (6), and (7), have already been used [4,6] for the synthesis of six out of the eight possible racemates of the œstrone structure by the angular methylation–ring contraction sequence. It was therefore of interest to apply the same procedure to the new *cis-syn-trans*-dodecahydro-ketone (δ-methoxyhydrochrysenone) (79). Methylation of the furfurylidene derivative (80) afforded the *cis-syn-trans*-methylated furfurylidene-ketone (84) as the sole product, and examination by ultraviolet and nuclear magnetic resonance spectroscopy failed to show the presence of a stereoisomer, which would, of course, have been a derivative of the energetically less favoured *trans-syn-trans*-ketone. The stereochemical assignment was proved by cleavage of the methylated furfurylidene-ketone (84) with alkaline hydrogen peroxide to the known *cis-syn-trans*-dicarboxylic acid (85),[5b] which has previously been converted into 14-iso-œstrone methyl ether (86).

Experimental

M. p.s were observed on a microscope hot stage. Ultraviolet-light absorptions were measured for 95% ethanol solutions. Nuclear magnetic resonance spectra were determined at 40 or 60 Mc./sec. with a Varian Associates V-4300-B high resolution spectrometer with associated 12 in. magnet system equipped with a V-K3506 flux stabiliser; $CDCl_3$ or CCl_4 was used as solvent; benzene, contained in a small internal capillary, was used for reference, and chemical shifts are reported in c./sec. (estimated accuracy ±2 c./sec.) relative to benzene (=0 c./sec.). Infrared bands are characterised as strong (s), medium (m), weak (w), very weak (vw), sharp (sh), broad (br).

cis- *and* trans-4,4-*Ethylenedioxy*-Δ[6]-*octal*-1-*one* (22) *and* cis-1,1:4,4-*Bisethylenedioxy*-Δ[6]-*octalin* (21).—A modification of Salmi's ketalisation procedure [19] was employed. A solution of *cis*-Δ[6]-1,4-dioxo-octalin [45] (20) (4·0 g.) in benzene (50 c.c.) was boiled under reflux with toluene-*p*-sulphonic acid monohydrate (100 mg.) and redistilled ethylene glycol (1·7 c.c.), the refluxing benzene being returned *via* a conventional water separator; reaction was effectively complete in 4½ hr. (Found: H_2O, 0·40 c.c.; 91%). The hot mixture was treated with pyridine (0·3 c.c.) and diluted with benzene (30 c.c.), and water (50 c.c.) was added. The aqueous phase was washed with benzene, and the combined benzene extracts were washed with water, dried, and evaporated under reduced pressure to give a yellow oil (4·9 g.), which was chromatographed on Florisil (200 g.) in the usual way. Benzene (2—50%) in light petroleum eluted cis-1,1:4,4-*bisethylenedioxy*-Δ[6]-*octalin* (21), which separated from methanol in colourless crystals (1·35 g., 22%), m. p. 116·5—117°, showing no infrared carbonyl absorption (Found: C, 66·6; H, 7·9. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%). Benzene eluted a colourless oil (1·8 g., 35·4%), which, on repeated recrystallisation from pentane or ether, gave colourless crystals of either the *cis*- or the *trans*-monoketal (22), m. p. 52—54°, $\lambda_{max.}$ (in $CHCl_3$) 5·88s μ (C=O). The oily residue was rechromatographed on Florisil; each fraction partially crystallised when seeded with the material of m. p. 52—54°. All fractions were combined to give a semi-solid oil (a), part of which was characterised as a *semicarbazone*, which was repeatedly recrystallised from ethyl acetate–light petroleum to give needles, m. p. 182·5—184° (Found: C, 59·1; H, 7·0. $C_{13}H_{19}N_3O_3$ requires C, 58·9; H, 7·2%).

Ether (2—10%) in benzene eluted unchanged starting material (20) (750 mg., 19%) from

[45] Alder and Stein, *Annalen*, 1933, **501**, 247.

the original Florisil column. Material not accounted for in the three main fractions was eluted as indeterminate intermediate fractions and was not further investigated.

trans-2-*Furfurylidene*-Δ^6-*octal*-1-*one* (8).—The technique used was essentially that described by Huang-Minlon.[24] The above semi-solid oil (a) (331 mg.), 99—100% hydrazine hydrate (0·25 c.c.), and triethylene glycol (5 c.c.) were heated together under total reflux with powdered 85% potassium hydroxide (360 mg.) (bath 150—155°) for 1½ hr. The excess of hydrazine and water were then distilled off, and after 4 hr. at 195—210° the light brown solution was diluted with water (25 c.c.) and extracted with ether. Concentration, under nitrogen, of the washed and dried ethereal solution afforded a reddish oil (167 mg., 54%), showing no infrared carbonyl absorption. A solution of this oil (126 mg.) in methanol (4 c.c.), water (2 c.c.), and hydrochloric acid (0·2 c.c.) was heated under reflux for 1 hr. and then neutralised with 5% aqueous sodium hydroxide. The product (60 mg., 97%), recovered in ether, was a sweet-smelling semi-solid red oil, showing a strong carbonyl band at $\lambda_{max.}$ (film) 5·88 μ. The crude Δ^6-octal-1-one (60 mg.) in ethanol (0·46 c.c.) and 20% aqueous sodium hydroxide (0·17 c.c.) were stirred, with exclusion of light, with redistilled furfuraldehyde (0·042 c.c.) and water (0·46 c.c.). After 1 hour's stirring, the yellow crystalline product (81 mg., 90%), m. p. 128—135°, was collected and washed free from alkali with 40% ethanol. Recrystallisation from methanol and sublimation at 117°/0·3—0·5 mm. afforded *trans*-2-furfurylidene-Δ^6-octal-1-one [14] (8) as pale yellow needles, m. p. and mixed m. p. 135—135·6°.

cis-1,1:4,4-Bisethylenedioxy-Δ^6-octalin (21) was unaffected by the conditions of the Huang-Minlon procedure.

cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (16).—This substance was prepared by the following composite route. (i) 6-Methoxy-1-tetralone (25) (12 g.) was condensed with vinylmagnesium bromide (from 6 g. of magnesium and 33·0 g. of vinyl bromide), essentially by the method of Nazarov, Torgov, and Verkholetova,[16] affording crude 1-hydroxy-6-methoxy-1-vinyltetralin (26) as a light brown oil (17·0 g.), $\lambda_{max.}$ (film) 2·9s (OH) and 11·2s μ (=CH_2). (ii) The crude alcohol (26) was dehydrated by heating it with iodine as described by Robins and Walker.[15] (iii) The resulting crude diene (24) was allowed to react in benzene with *p*-benzoquinone (9·6 g.) as already described,[15] affording *cis-syn*-1,4,4a,4b,5,6,12,12a-octahydro-8-methoxy-1,4-dioxochrysene (23) as light yellow needles (15·0 g., 74·8% based on 6-methoxy-1-tetralone), m. p. 157·5—161° (decomp.). It is important that the adduct (23) should start to crystallise after the first 20 min.; if it has not, a seed must be added. (iv) The adduct was reduced with zinc and acetic acid as before,[15] yielding the *cis-syn*-decahydrodiketone (16) as colourless needles (86%), m. p. 201—201·5° (cf. 194—196° recorded previously [15]) In later work a new polymorphic form, m. p. 184—186°, was frequently encountered; the two modifications gave identical infrared spectra in solution.

cis-1,4,4a,5,6,11,12,12a-*Octahydro*-8-*methoxy*-1,4-*dioxochrysene* (27).—A solution of the *cis-syn*-isomer (23) (10·4 g.) in benzene (100 c.c.) was concentrated on the steam-bath to a volume of about one-half (15—20 min.). Dilution of the hot solution with light petroleum (200 c.c.) and cooling afforded yellow plates (8·5 g., 81·5%), m. p. 155—162·5° (decomp.); further concentration gave a second crop (1·8 g.), m. p. 150—160° (decomp.). Repeated crystallisation of the first crop from ethyl acetate improved the m. p. only slightly, giving cis-1,4,4a,5,6,11,12,12a-*octahydro*-8-*methoxy*-1,4-*dioxochrysene* (27) as yellow plates, m. p. 155·5—160° (decomp.), $\lambda_{max.}$ 276 mμ ($\Delta^{4b,10b}$) (log ε 4·18) (Found: C, 77·6; H, 6·0. $C_{19}H_{18}O_3$ requires C, 77·5; H, 6·2%).

Stereoisomerisation of cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (16): trans-anti-*Isomer* (29).—The following modification of the conditions previously employed [23] afforded slightly better conversion. A concentrated solution of the *cis-syn*-stereoisomer (16) (1·0 g.) in benzene was placed on a column of activated alumina (30 g.) and left overnight. Elution with ether then afforded a white solid (736 mg.), and elution with ethyl acetate gave a discoloured yellow solid (239 mg.). Recrystallisation of the former fraction from methanol gave colourless needles (533 mg.), m. p. 173—175·5°. The material left in the mother liquors and that eluted with ethyl acetate contained both stereoisomers (16) and (29), as shown by the infrared spectrum, and these fractions were again treated on the alumina column. Recrystallisation from methanol of the material eluted with ether gave a further crop of colourless needles (210 mg.), m. p. 174—176°. Further recrystallisation afforded the pure *trans-anti*-stereoisomer (29), m. p. 175·5—176° (lit.,[15,16] m. p. 172—174°, 174—175°), $\lambda_{max.}$ 261·5 ($\Delta^{10b,11}$), 295 mμ (log ε 4·30 and 3·51, respectively).

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (28).—(A) *From* cis-1,4,4a,5,6,11,12,12a-*octahydro*-8-*methoxy*-1,4-*dioxochrysene* (27). The rearranged adduct (27) (1·0 g.) was reduced with zinc dust (2·0 g.) and glacial acetic acid (100 c.c.) in the usual way. The product (28) separated from methanol–methylene chloride in yellow plates (790 mg., 79%), m. p. 154—157° (decomp.), as previously reported.[15]

(B) *From* cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1,4-*dioxochrysene* (16). A solution of the *cis-syn*-isomer (16) (70 mg.) in benzene (80 c.c.) containing toluene-*p*-sulphonic acid monohydrate (32 mg.) was boiled under reflux for 3 hr. and poured hot into 5% aqueous sodium hydrogen carbonate solution (50 c.c.). The washed benzene layer was taken to dryness under reduced pressure, giving a yellow oil which, on crystallisation from methanol, gave yellow needles (45 mg., 64%), m. p. 140—142°, raised on further crystallisation to 141·5—142·5°; a mixed m. p. with material of m. p. 154—157°, prepared as in (A), was 148—154°.

(C) *From* trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1,4-*dioxochrysene* (29). As in the preceding experiment, the *trans-anti*-isomer (29) (102 mg.) was heated in benzene (80 c.c.) with toluene-*p*-sulphonic acid monohydrate (30 mg.) for 3 hr. Crystallisation of the crude oil from methanol gave the *cis*-isomer (28) as yellow plates (62 mg., 62%), m. p. 148—152°, raised by further recrystallisation to 153·5—154·5° (decomp.); the infrared spectrum was identical with that of the substance, m. p. 154—157°, prepared as in (A) (above).

cis-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-4-*oxochrysene* (30).—Salmi's method [19] for cyclic ketal formation was followed essentially. A mixture of the *cis-syn*-diketone (16) (900 mg.) and ethylene glycol (0·4 c.c.) in benzene (300 c.c.) containing toluene-*p*-sulphonic acid monohydrate (75 mg.) was boiled under reflux for 35 min., water being segregated in the usual way. The mixture was then poured into 5% aqueous sodium hydrogen carbonate (100 c.c.), and the benzene layer, washed and dried, afforded on evaporation a yellow oil, further purified by either (*a*) chromatography or (*b*) crystallisation.

(*a*) The crude product was chromatographed on Florisil (50 g.), and the material eluted with 10—90% benzene in light petroleum separated from methanol in colourless crystals (165 mg., 14%), m. p. 163—167° (plates) or 132—133° (needles). This material showed no infrared carbonyl absorption, and the melting behaviour and infrared spectrum were identical with those of the diketal (31) described below. Benzene eluted a purple oil (526 mg.), affording on crystallisation from methanol, colourless diamond-shaped crystals (410 mg., 40%) of the cis-*monoketal* (30), m. p. 137—137·5°, $\lambda_{max.}$ 273 mμ ($\Delta^{4b,10b}$) (log ε 4·17), $\lambda_{max.}$ (in $CHCl_3$) 5·88s (C=O), 8·98s μ (ketal) (Found: C, 74·4; H, 7·1. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%).

(*b*) Crystallisation of the crude product from methanol gave several crops, and these, on recrystallisation, gave the *cis*-monoketal (30) (482 mg., 46·5%), m. p. 133—137°, of adequate purity for subsequent use.

cis-1,1:4,4-*Bisethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (31).—In a similar manner, the *cis-syn*-diketone (16) (300 mg.) and ethylene glycol (1·0 c.c.) in benzene (100 c.c.) containing toluene-*p*-sulphonic acid monohydrate (30 mg.) gave a crude product, affording, after one crystallisation from methanol, colourless crystals (330 mg., 84·6%), m. p. 131—133°. Three further recrystallisations gave the cis-*diketal* (31) as colourless needles, m. p. 132·5—133°, and plates, m. p. 172—172·5°, $\lambda_{max.}$ 274 mμ ($\Delta^{4b,10b}$) (log ε 4·43), $\lambda_{max.}$ (in $CHCl_3$) 8·98s μ (ketal; no carbonyl absorption) (Found: C, 71·9; H, 7·4. $C_{23}H_{28}O_5$ requires C, 71·9; H, 7·3%). The modification of m. p. 172—172·5° was that most frequently encountered.

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-4-*oxo*-1,1-*trimethylenedioxychrysene* (32).—Analogously, the *cis-syn*-diketone (16) (2·0 g.) and trimethylene glycol (0·80 c.c.) in benzene (300 c.c.) containing toluene-*p*-sulphonic acid (75 mg.) afforded, as crude product, a viscous oil. Crystallisation from methanol gave yellow crystals (1·46 g., 61·5%), m. p. 135—140°; further recrystallisation afforded the pure cis(?)-*monotrimethylene ketal* (32) as colourless diamond-shaped crystals, m. p. 143·5—145°, $\lambda_{max.}$ 272·8 mμ ($\Delta^{4b,10b}$) (log ε 4·15), $\lambda_{max.}$ (in $CHCl_3$) 5·84s (C=O), 8·99s μ (ketal) (Found: C, 74·5; H, 7·3. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%).

cis-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (33) *and* trans-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (34).—A mixture of the *cis*-monoethylene ketal (30) (200 mg.), 99—100% hydrazine hydrate (0·49 c.c.), and powdered 85% potassium hydroxide (640 mg.) in triethylene glycol (15 c.c.) was heated under nitrogen at 150° for 1 hr. The temperature was raised during 15 min. to 195° and kept at 195—200° for 1½ hr. in the usual way.[24] The crude oily product (194 mg.), isolated in the normal manner, afforded two colourless crystalline compounds on fractional crystallisation from methanol:

(i) needles (82 mg., 42·6%), m. p. 141—144°, and (ii) plates (54 mg., 28·2%), m. p. 130—132°. Three further recrystallisations of fraction (i) from methanol gave the cis-*ethylene ketal* (33) as needles, m. p. 143—143·5°, $\lambda_{max.}$ 272·5 mμ ($\Delta^{4b,10b}$) (log ε 4·25), $\lambda_{max.}$ (in $CHCl_3$) 8·98s μ (ketal) (Found: C, 77·3; H, 8·0. $C_{21}H_{26}O_3$ requires C, 77·3; H, 8·0%). Five further recrystallisations of fraction (ii) from methanol afforded the trans-*ethylene ketal* (34) as plates, m. p. 135·5—136°, $\lambda_{max.}$ 272·8 mμ ($\Delta^{4b,10b}$) (log ε 4·25), $\lambda_{max.}$ (in $CHCl_3$) 8·98s μ (ketal) (Found: C, 77·1; H, 8·2%).

cis-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (33).—The following modification of the Huang-Minlon procedure [24] gave only the *cis*-ethylene ketal (33). A mixture of the *cis*-monoethylene ketal (30) (197 mg.), 99—100% hydrazine hydrate (1·0 c.c.), and triethylene glycol (15 c.c.) was stirred under nitrogen at room temperature to effect solution (3½ hr.), after which powdered 85% potassium hydroxide (480 mg.) was added under nitrogen. The mixture was then heated to 190° (20 min.) and maintained at 190—195° for 1½ hr., before being poured into water. The crude brown oil (192 mg.), recovered by ether extraction, was filtered through a column of Florisil (10 g.) in 20—50% benzene in light petroleum. The material passing through the column gave, on crystallisation from methanol, colourless crystals (126 mg., 65·5%) of the *cis*-ethylene ketal (33), m. p. 140—144°, showing an infrared absorption spectrum (in $CHCl_3$) identical with that of the above *cis*-ketal (33). This was the only product isolated, and no evidence for the presence of the *trans*-stereoisomer (34) was found; the remaining material was not eluted from the Florisil column.

trans-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (34).—The following modification of the preceding experiments gave only the *trans*-ethylene ketal (34). A mixture of the *cis*-monoethylene ketal (30) (200 mg.), triethylene glycol (15 c.c.), and powdered 85% potassium hydroxide (480 mg.) under nitrogen was heated at 95—100° for 1 hr., after which 99—100% hydrazine hydrate (0·5 c.c.) was added under nitrogen. The mixture was then heated at 150° ± 5° for 70 min., and the temperature was raised to 190° (30 min.) and maintained at 185—195° for 1½ hr. The product was recovered as in the preceding experiment and crystallisation from methanol gave colourless crystals (97 mg., 49·5%) of the *trans*-ethylene ketal (34), m. p. 132—134°, showing an infrared absorption spectrum (in $CHCl_3$) identical with that of the above *trans*-ketal (34). This was the only product isolated, as the remainder was retained as a brown tar on the Florisil column; no evidence for the presence of the *cis*-ketal (33) was found.

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (35) *and* trans-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (36).—Conditions analogous with those of the preceding experiment were used. In a typical run the *cis*-monoketal (32) (1·0 g.) and powdered 85% potassium hydroxide (480 mg.) were heated together under nitrogen in triethylene glycol (15 c.c.) to 110° (1 hr.). 99—100% Hydrazine hydrate (1·5 c.c.) was then added and the temperature was kept at 105—110° for 1 hr., then raised during 30 min. to 190° and kept there for 1½ hr., during which water and excess of hydrazine hydrate were removed in a current of nitrogen. The crude product, isolated in the usual way, was applied to a column of Florisil (50 g.) in light petroleum (20 c.c.). Fractions eluted with 20—25% benzene in light petroleum afforded, on crystallisation from methanol, colourless crystals (218 mg., 22·7%), m. p. 141—144°. Fractions eluted with 30—50% benzene in light petroleum gave similarly colourless crystals (490 mg., 51·2%), m. p. 123—127°. Elution with benzene and ether in benzene afforded only traces of yellowish brown tars, which were not further studied.

Further recrystallisation of the substance, m. p. 123—127°, from methanol gave the cis-*trimethylene ketal* (35) as colourless plates, m. p. 124·8—126°, $\lambda_{max.}$ 272·5 mμ ($\Delta^{4b,10b}$) (log ε 4·28), $\lambda_{max.}$ (in $CHCl_3$) 8·98s μ (ketal) (Found: C, 77·9; H, 8·5. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%). Further recrystallisation of the material, m. p. 141—144°, from methanol afforded the trans-*trimethylene ketal* (36) as colourless needles, m. p. 142—144°, $\lambda_{max.}$ 273 ($\Delta^{4b,10b}$) (log ε 4·20), $\lambda_{max.}$ (in $CHCl_3$) 8·98s μ (ketal) (Found: C, 77·3; H, 8·4%). Similar results were obtained when the hydrazine hydrate was added before or with the potassium hydroxide.

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (13).—(*A*) A solution of the preceding *cis*-trimethylene ketal (35) (346 mg.) in the minimum volume of acetone was treated with 1% hydrochloric acid in 50% methanol (8 c.c.), and the mixture was kept overnight under nitrogen at room temperature. Acetone was removed in a current of nitrogen at room temperature and the resulting crystalline product was collected and washed with 50% methanol until neutral. The crude product (277 mg., 98·5%), m. p. 111—115°, was recrystallised from

cold methanol, affording the cis-*ketone* (13) as colourless needles, m. p. 117·5—118°, $\lambda_{max.}$ 275 mμ ($\Delta^{4b,10b}$) (log ε 4·25), $\lambda_{max.}$ (in $CHCl_3$) 5·92s μ (C=O) (Found: C, 81·2; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·9%).

Similar treatment of the *cis*-ethylene ketal (33) also gave the *cis*-ketone (13). Recrystallisation from hot methanol effected partial equilibration at $C_{(12a)}$ and raised the m. p. into the range 120—135°.

(*B*) The *cis*-dimethyl ketal [18] (18) (2·4 g.) was reduced by the modified Huang-Minlon Wolff–Kishner technique with 60% hydrazine hydrate as described below for the *cis-syn*-$\Delta^{10b,11}$-isomer (48). The crude product crystallised spontaneously and recrystallisation from methanol–chloroform afforded cis-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-1,1,8-*trimethoxychrysene* as colourless leaflets (1·40 g.), m. p. 141—144°, $\lambda_{max.}$ 273 mμ ($\Delta^{4b,10b}$) (log ε 4·26) (Found: C, 76·9; H, 8·4; MeO, 28·2. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6; 3MeO, 28·4%). The mother liquors contained phenolic material which was not further investigated.

The preceding *cis*-deoxo-dimethyl ketal (500 mg.) was dissolved in warm acetic acid (5 c.c.). After 15 min. water was added and the precipitated solid, on recrystallisation from methanol, afforded the *cis*-monoketone (13), m. p. 116—120°, $\lambda_{max.}$ 274·5 mμ (log ε 4·23) (Found: C, 80·7; H, 7·7%).

trans-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (37).—(*A*) In a similar manner hydrolysis of the *trans*-trimethylene ketal (36) (310 mg.) with aqueous-methanolic hydrochloric acid (20 c.c.) and crystallisation of the crude product (249 mg., 97%), m. p. 141—145°, from methanol afforded the trans-*ketone* (37) as colourless needles, m. p. 147·5—149°, $\lambda_{max.}$ 275·5 mμ ($\Delta^{4b,10b}$) (log ε 4·26), $\lambda_{max.}$ (in $CHCl_3$) 5·86s μ (C=O) (Found: C, 80·6; H, 7·5. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·9%). Similar treatment of the *trans*-ethylene ketal (34) also gave the *trans*-ketone (37).

(*B*) The *cis*-ketone (13) (100 mg.) was heated under reflux for 3 hr. in 1% ethanolic potassium hydroxide (20 c.c.). After dilution with water, crystallisation of the precipitated solid from methanol gave the *trans*-stereoisomer (37), m. p. 149—152°. Similar conversion of the *cis*-(13) into the *trans*-ketone (37) occurred in 5·8% methanolic potassium hydroxide overnight. The pure *trans*-ketone (37) was recovered quantitatively from similar treatment with methanolic potassium hydroxide.

trans-anti-cis-1,1-*Ethylenedioxy*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*dodecahydro*-8-*methoxy*-*chrysene* (38).—A solution of the *trans*-ethylene ketal (34) (49 mg.) in absolute ethanol (5 c.c.) was stirred in hydrogen at atmospheric pressure in presence of 6% palladised strontium carbonate (54 mg.). One mol. of hydrogen (Found: 4·15. Calc.: 4·07 c.c.) was absorbed in 5 min. and there was no further uptake in 30 min. The product was recovered in the usual way and recrystallisation from methanol afforded the *trans-anti-cis*-ethylene ketal (38) as colourless rectangular crystals (46 mg., 94%), m. p. 134·5—135°, alone and in admixture with an authentic specimen; [26] the infrared spectrum in chloroform solution was also identical with that of the authentic specimen.

trans-anti-cis-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1-*oxochrysene* ("α-*Methoxyhydrochrysenone*") (5).—The *trans-anti-cis*-ethylene ketal (38) (9·4 mg.) in methanol (3 c.c.) and acetone (2 c.c.) was hydrolysed with 1% hydrochloric acid in 50% aqueous methanol (1 c.c.) at room temperature under nitrogen overnight, and the product (9 mg., 98%) was recovered in the usual way. Recrystallisation from methanol and from ethanol afforded the *trans-anti-cis*-ketone (5) as colourless needles, m. p. 163·5—166°, not depressed on admixture with an authentic specimen,[4b] m. p. 169—170·4°; the infrared spectrum in chloroform was also identical with that of the authentic specimen.

trans-1,1-*Ethylenedioxy*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxychrysene* (34).—A mixture of the *trans*-ketone (37) (60 mg.) and ethylene glycol (0·50 c.c.) in benzene (100 c.c.) containing toluene-*p*-sulphonic acid monohydrate (25 mg.) was heated under reflux for 3 hr. with segregation of the water formed. The product, isolated in the usual way, afforded the *trans*-ethylene ketal (34) on crystallisation from methanol as colourless crystals (63 mg., 91%), m. p. 134—136°, alone and in admixture with the *trans*-ketal (34) (above) obtained from the *cis*-monoethylene ketal (30).

trans- (40) *and* cis-2-*Furfurylidene*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (39).—(A) *From* cis-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (13). The *cis*-ketone (13) (115 mg.) was warmed with methanol (20 c.c.) and 20% aqueous sodium hydroxide (1 c.c.) under nitrogen with exclusion of light until dissolution was complete. The

mixture was then cooled to room temperature, treated with freshly distilled furfuraldehyde (0·1 c.c.), and left overnight. The yellow solid which separated was collected and washed with 50% aqueous methanol until neutral. Fractional crystallisation of the crude product (140 mg., 96%), m. p. 155—168°, from methanol–methylene chloride afforded (i) the cis-*furfurylidene-ketone* (39) (116 mg., 79·5%), m. p. 172—175°, raised on further recrystallisation to 178—179·5°, $\lambda_{max.}$ 275 ($\Delta^{4b,10b}$), 324·2 mμ (furfurylidene-ketone) (log ε 4·21 and 4·43, respectively) (Found: C, 79·9; H, 6·4. $C_{24}H_{24}O_3$ requires C, 80·0; H, 6·7%), and (ii) the trans-*furfurylidene-ketone* (40) (7·3 mg., 5%), m. p. 130—131·5°, raised on further recrystallisation from methanol to 132—133·5°, $\lambda_{max.}$ 271·8 ($\Delta^{4b,10b}$), 331 mμ (furfurylidene-ketone) (log ε 4·24 and 4·40, respectively) (Found: C, 80·1; H, 6·7%).

(B) *From* trans-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (37).—In a similar manner, the *trans*-ketone (37) (106 mg.) afforded a crude furfurylidene derivative (130 mg., 96·8%), m. p. 158—170·5°, giving on fractional crystallisation the *cis*-furfurylidene-ketone (39) (102 mg., 75·5%), m. p. 173—175·5°, and the *trans*-furfurylidene-ketone (40) (9·4 mg., 7%), m. p. 121—132°.

(C) *From* cis-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-4-*oxo*-1,1-*trimethylenedioxy*-*chrysene* (32). The procedures described above were employed for this three-stage conversion without purification of intermediates. The *cis*-monotrimethylene ketal (32) (1·0 g.) thus afforded (i) *cis*-furfurylidene-ketone (39) (381 mg., 37·5%), m. p. 171—174°, (ii) a fraction (187 mg.), m. p. 129—165°, and (iii) *trans*-furfurylidene-ketone (40) (47 mg., 4·6%), m. p. 130—133°. Further treatment of fraction (ii) with sodium methoxide (25 mg.) in methanol (30 c.c.) for 30 min. and recovery in the usual manner gave, after crystallisation from methanol, the *cis*-furfurylidene-ketone (39) (158 mg., 15·6%), m. p. 168·5—174°.

(D) *By equilibration of* trans-2-*furfurylidene*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (40). The *trans*-furfurylidene-ketone (40) (10 mg.), m. p. 128—130·5°, was placed on a column of Florisil (500 mg.). Rapid (10—30 min.) elution with benzene (100 c.c.) afforded, after crystallisation from methanol, the *cis*-furfurylidene-ketone (39) (7·1 mg., 71%), m. p. 174—176°. The fraction eluted with 5% ether in benzene gave, after crystallisation from methanol, the *trans*-furfurylidene-ketone (40) (3·0 mg., 30%), m. p. 129—130·5°. This order of elution from the column [41] supports the *cis*- and *trans*-assignments to the respective furfurylidene derivatives.

cis-2-*Furfurylidene*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (41).—In a dried vessel, clean potassium (815 mg.) was allowed to dissolve in t-butyl alcohol (50 c.c., distilled from calcium hydride) by overnight stirring under nitrogen. A solution of the *cis*-furfurylidene-ketone (39) (498 mg.), m. p. 172—175°, in dry benzene (20 c.c.) was then added under nitrogen, and the mixture was cooled with stirring to 3°. Methyl iodide (2·6 c.c.) was added under nitrogen, and the mixture, which became cloudy in 5 min., was allowed to come to room temperature and was stirred for 24 hr., at the end of which it was neutral to litmus. The solvent was removed at 35° under reduced pressure and the residue was distributed between benzene and water. Evaporation of the washed and dried organic phase under reduced pressure gave a yellow oil (544 mg.), and crystallisation from methanol afforded (on nucleation with crystals obtained after chromatography in a previous smaller run) light yellow crystals (458 mg.), m. p. 127—130°. Recrystallisation from methanol gave colourless crystals (450 mg., two crops), m. p. 129—130·5°. Material contained in the entire combined mother liquors was chromatographed on a Florisil (4·0 g.) column, wrapped in tin foil. Elution with benzene and crystallisation from methanol gave yellow crystals (22 mg.; total, 472 mg., 91·5%), m. p. 127—129°; the remaining material, eluted with varying concentrations of ether in benzene, showed no furfurylidene-ketone absorption in the ultraviolet spectrum and was discarded. Further recrystallisation from methanol–methylene chloride afforded the *cis*-12a-methylated *furfurylidene-ketone* (41) as colourless prisms, m. p. 131—131·5°, $\lambda_{max.}$ 273·5 ($\Delta^{4b,10b}$), 328 mμ (furfurylidene-ketone) (log ε 4·25 and 4·40, respectively) (Found: C, 80·4; H, 6·8. $C_{25}H_{26}O_3$ requires C, 80·2; H, 7·0%).

cis-β-(2-*Carboxy*-1,2,3,4,9,10-*hexahydro*-7-*methoxy*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (*Dehydroisohomomarrianolic Acid Methyl Ether*) (42).—Oxidation of the preceding methylated furfurylidene-ketone (41) was carried out by a modification of a known procedure.[11c] Solid sodium methoxide (1·8 g.), followed by 30% hydrogen peroxide (10 c.c.), was added to a stirred solution of the ketone (41) (80 mg.) in methanol (35 c.c.). The resulting suspension was stirred under reflux for 6½ hr. (total), further additions (each 10 c.c.) of 30% hydrogen

peroxide being made after 1¾, 4, and 5½ hr.; the solution became clear after the second of these additions. The methanol was removed with slight warming under nitrogen and the residue was distributed between benzene and water. The aqueous phase was washed with benzene; the combined benzene layers, washed, dried, and evaporated, gave a neutral oil (12·2 mg.). The combined aqueous layers were chilled, acidified to Congo Red with concentrated hydrochloric acid, and thoroughly extracted with ethyl acetate. The combined extracts, when washed with brine, dried, and evaporated under reduced pressure, gave a partially crystalline brown oil (95 mg.) that was chromatographed in chloroform on silicic acid (2·0 g.). Serial fractions (5 × 15 c.c.) were collected, affording: (i) + (ii) (chloroform), an oil (21·1 mg.), not further investigated; (iii) + (iv) (2% methanol in chloroform), a white solid (70·5 mg.), m. p. 185—190°; (v) (2% methanol in chloroform), an oil (3 mg.), not further investigated. Recrystallisation of the solid fractions from ethyl acetate–benzene gave three crops (35 mg., 47·5%, m. p. 192—194·5°; 3 mg., 4·0%, m. p. 194—197°; 5·7 mg., m. p. <180°). Further recrystallisation from the same solvent mixture afforded *dehydroisohomomarrianolic acid methyl ether* (42) as colourless needles, m. p. 196—197·5°, $\lambda_{max.}$ 272·6 mμ ($\Delta^{4a,10a}$) (log ε 3·88) (Found: C, 70·1; H, 7·0. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%).

Methyl cis-β-(1,2,3,4-*Tetrahydro-7-methoxy-2-methoxycarbonyl-2-methyl-1-phenanthryl)propionate* (43).—(A) *From dehydroisohomomarrianolic acid methyl ether* (42). The procedure used was essentially that of Bachmann and Dreiding.[46] The acid methyl ether (42) (54 mg.) was esterified with ethereal diazomethane in the usual way, and the oily ester (71 mg.) was chromatographed on Florisil (2·5 g.). The colourless oils (16·1, 22·0, 10·0 mg.; 82%) eluted with increasing concentrations of benzene in light petroleum had identical infrared spectra. The dimethyl ester (11·5 mg.) and 10% palladium–charcoal (9 mg.) were heated together under nitrogen at 235—241° (metal bath) for 8 min., and the product (10 mg., 87%), recovered with the aid of benzene, was filtered through Florisil (200 mg.) in ether (2 × 2 c.c.). Evaporation of these two fractions gave a white solid (3·0 mg., 7·0 mg.). Recrystallisation of the second fraction from cold methanol afforded the dimethyl ester (43) (3·4 mg.), m. p. 91·0—92·5° (lit.,[47] m. p. 89·0—89·5°), not depressed on admixture with the authentic substance, m. p. 91·5—93·0°, prepared as described below. The infrared spectra in chloroform of the two specimens were identical.

(B) *From isoequilenin methyl ether* (44). (i) Dry benzene (25 c.c.) containing isoequilenin methyl ether (2·0 g.) and ethyl formate (8·0 c.c.) was added under nitrogen to sodium ethoxide (2·20 g.), freshly prepared and dried at 200°/0·1 mm. After being kept overnight the dark brown solution was treated with water (30 c.c.) and worked up in the usual way. Acidification of the combined aqueous alkaline layer and washings afforded a red gum, which was recovered by ether extraction. (ii) The oil was shaken with acetic acid (25 c.c.) and hydroxylamine hydrochloride (750 mg.) at room temperature for 46 hr. On dilution with water a yellow solid, assumed to be the oxime, separated and was collected. (iii) The preceding yellow solid was treated with 5% aqueous potassium hydroxide solution (300 c.c.) and hydroxylamine hydrochloride (500 mg.) at the b. p. in a stainless-steel flask for 46 hr. Acidification of the cooled solution with hydrochloric acid gave a yellow solid (1·96 g.), assumed to be the *cis*-β-(2-carboxy-1,2,3,4-tetrahydro-7-methoxy-2-methyl-1-phenanthryl)propionic acid; recrystallisation from ethyl acetate afforded crops (*a*) (769 mg.), m. p. 214—217°, and (*b*) (73 mg.), m. p. 211—217°. (iv) Treatment of part (97 mg.) of crop (*a*) with diazomethane in the usual way gave a yellow oil, which was chromatographed on Florisil. Crystallisation from methanol of the fraction eluted with 50% benzene in light petroleum afforded the dimethyl ester (43) as colourless needles, m. p. 91·5—93·0°.

cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro-1,1-dimethoxy-4-oxochrysene* (47).—*cis-syn*-1,2,3,4,4a,4b,5,6,12,12a-Decahydro-1,4-dioxochrysene [17] (17) (5·0 g.) was suspended in boiling methanol (70 c.c.) and treated with methanolic 1·39N-hydrogen chloride (0·2 c.c.), giving a final acid concentration of 0·004N. After 2 min. at the b. p. the slightly cloudy solution was filtered and cooled. The crystals (4·40 g.), m. p. 128—130°, were collected and cautious evaporation of the mother liquors afforded a further quantity (890 mg.; total 90%). Recrystallisation from methanol afforded the cis-syn-*dimethyl ketal* (47) as colourless lozenges, m. p. 128—131°, $\lambda_{max.}$ 261, 290, 301 mμ (log ε 4·18, 3·51, and 3·40, respectively) (Found: C, 76·8; H, 7·9; MeO, 20·6. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7; 2MeO, 19·8%).

[46] Bachmann and Dreiding, *J. Amer. Chem. Soc.*, 1950, **72**, 1323.
[47] Bachmann, Cole, and Wilds, *J. Amer. Chem. Soc.*, 1940, **62**, 824.

With increasing concentrations of hydrogen chloride the isomeric *cis*-$\Delta^{4b,10b}$-dimethyl ketal [17] (19) was formed in progressively increasing proportion.

trans-anti- (15), cis-syn- (52), *and* trans-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1-*oxochrysene* (53).—The preceding *cis-syn*-dimethyl ketal (47) (2·13 g.) was heated under reflux in ethylene glycol (90 c.c.) containing potassium hydroxide (9 g.) and 60% hydrazine hydrate (9 c.c.) for 1 hr., after which the mixture was distilled until the still-head temperature reached 193°, and the residue was maintained under reflux for a further 1 hr. The mixture was worked up in the usual way, and a solution of the resulting crude brown oil in warm acetic acid (30 c.c.) was diluted to cloudiness with water and set aside overnight. The brownish leaflets (1·0 g.) which separated were collected and washed with methanol; two recrystallisations from ethanol then afforded the trans-anti-*decahydro*-1-*oxochrysene* (15) as colourless plates, m. p. 168—170°, $\lambda_{max.}$ 256, 288, 297 (infl.) mμ (log ε 4·14, 3·36, and 3·22, respectively) (Found: C, 85·8; H, 7·9. $C_{18}H_{20}O$ requires C, 85·7; H, 8·0%). The acetic acid mother liquors, poured into water and extracted with ether, afforded a brown oil (750 mg.) which, after repeated crystallisation from methanol with hand-sorting of the crystals where possible, gave a small quantity of the cis-syn-*stereoisomer* (52), as colourless leaflets, m. p. 133—136°, $\lambda_{max.}$ 260, 289, 300 mμ (log ε 4·26, 3·62, and 3·48, respectively) (Found: C, 85·4; H, 8·1%).

The material (4·0 g.) from the combined mother liquors from several experiments was chromatographed on alumina (100 g.), affording a single main fraction (1·44 g.), eluted by benzene–light petroleum (1 : 1); this, on crystallisation from methanol, gave the trans-syn-*stereoisomer* (53) as needles or plates (the former changing into the latter in contact with the solution), m. p. 158—160°, $\lambda_{max.}$ 253, 284 (infl.) mμ (log ε 4·20 and 3·31, respectively) (Found: C, 85·5; H, 7·9%).

cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1,1,8-*trimethoxy*-4-*oxochrysene* (48).—A suspension of *cis-syn*-1,2,3,4,4a,4b,5,6,12,12a-decahydro-8-methoxy-1,4-dioxochrysene (16) (10 g.) in methanol (720 c.c.) and glacial acetic acid (80 c.c.) was heated under reflux for 8 hr., during which the solid slowly dissolved. The solution was cooled rapidly and concentrated somewhat by the application of a water-pump vacuum, whereupon crystallisation commenced. After storage overnight at 2°, filtration afforded crude ketal (7·15 g.), m. p. 145—160°, raised to 156—170° on crystallisation from benzene–methanol, but sufficiently pure for subsequent stages. [On a smaller scale it was found that better conversion was obtained at this stage in greater dilution (1 g. of diketone in 150 c.c. of methanol and 15 c.c. of acetic acid gave 989 mg. of crude ketal, suitable for further use without purification).]

The methanol–acetic acid mother liquors, on addition to much water, gave a flocculent solid (3·25 g.), which consisted mainly of *cis*-1,2,3,4,4a,5,6,11,12,12a-decahydro-1,1,8-trimethoxy-4-oxochrysene (18), and could be used as a source of the latter by dissolution in boiling methanol containing a trace of hydrogen chloride: the pure *cis*-$\Delta^{4b,10b}$-isomer (18) crystallised.

Crude *cis-syn*-dimethyl ketal (48) could not be purified by crystallisation alone owing to the presence of a small proportion of the less soluble starting material (16), and advantage was taken of the reactivity of the 1-oxo-group in the latter towards semicarbazide. Crude *cis-syn*-dimethyl ketal (48) (2·45 g.) and potassium acetate (0·98 g.) were dissolved in warm ethanol (110 c.c.), and a concentrated solution of semicarbazide hydrochloride (1·11 g.) in water was added. Next morning the solution and precipitated solid were poured into water, and the crude product was collected, washed with water and methanol, and dried (2·30 g.). Crystallisation from methanol–chloroform, or from ethyl acetate, afforded, after rejection of a higher-melting insoluble fraction (0·54 g.), pure cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-1,1,8-*trimethoxy*-4-*oxochrysene* (48) as colourless needles (1·31 g.), m. p. 161—163°, $\lambda_{max.}$ 266 ($\Delta^{10b,11}$), 300·5 mμ (log ε 4·29 and 3·62, respectively) (Found: C, 73·3; H, 7·7; MeO, 27·9. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7; 3MeO, 27·2%). Solution of a sample of this substance (48) in a small volume of warm acetic acid followed by addition of water regenerated the *cis-syn*-1,4-diketone (16).

The higher-melting insoluble solid, on recrystallisation from methoxyethanol, afforded the 1-*monosemicarbazone* of the *cis-syn*-1,4-diketone (16) as leaflets, m. p. 231—235°, identical with an authentic specimen prepared directly (Found: C, 68·0; H, 6·8; N, 11·7. $C_{20}H_{23}N_3O_3$ requires C, 68·0; H, 6·5; N, 11·9%).

An alternative method for the isolation of the *cis-syn*-dimethyl ketal (48) was based on the conversion of unchanged *cis-syn*-diketone (16) by alkali into a brown decomposition product,

readily soluble in methanol, in the following way. Potassium hydroxide pellets were slowly added with stirring to the still hot ketalisation mixture from *cis-syn*-diketone (16) (1·0 g.), methanol (150 c.c.), and glacial acetic acid (15 c.c.) until the solution showed an apparently neutral reaction to indicator paper. Solid immediately began to separate from the dark yellow solution. After cooling in an ice-bath, the cream-coloured solid (630 mg.) was collected; the dark brown filtrate was discarded. Recrystallisation from methanol–methylene chloride afforded the *cis-syn*-dimethyl ketal (48) as colourless crystals (550 mg., 48%), m. p. 160—162°.

The following observations summarise experience gained in a considerable number of experiments: (i) less than 10% of acetic acid resulted in very slow conversion of *cis-syn*-diketone (16) into *cis-syn*-dimethyl ketal (48); (ii) more than 10% of acetic acid resulted in excessive formation of the isomeric *cis*-dimethyl ketal (18); (iii) reaction periods shorter than 5—8 hr. resulted in recovery of excessive amounts of starting material (16); (iv) longer reaction times afforded increasing amounts of the isomeric dimethyl ketal (18); (v) higher concentrations of starting material (16) gave increasing amounts of the unwanted *cis*-dimethyl ketal (18); (vi) treatment of the *cis-syn*-dimethyl ketal (48) with 10% acetic acid in methanol at the b. p. for 2 hr. afforded material exhibiting ultraviolet absorption indicative of partial conversion into the *cis*-dimethyl ketal (18).

Attempts to prepare analogous *cis-syn*-cyclic ketals from the diketone (16) with ethylene glycol, 2,2-dimethyldioxolan, or trimethylene glycol, in the presence of acetic acid or cation-exchange resins were abortive.

Application (5 hr.) of the above successful methanol (90 c.c.)–acetic acid (10 c.c.) ketalisation procedure to the *trans-anti*-diketone (29) (65 mg.) afforded unchanged starting material (59 mg., 91%), as shown by m. p. 174—175·5° and infrared spectrum.

Huang-Minlon Wolff–Kishner Reduction of cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1,1,8-*trimethoxy*-4-*oxochrysene* (48): trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (14).—The crude *cis-syn*-dimethyl ketal (48) (4·95 g.) was added to ethylene glycol (200 c.c.) containing potassium hydroxide (20 g.) and 60% aqueous hydrazine hydrate (20 c.c.), and the mixture was heated under reflux for 4 hr., a further quantity (8 c.c.) of 60% hydrazine hydrate being added at the end of 2 hr. The reaction mixture was then distilled until the still-head temperature reached 195°, and the residual solution was heated under reflux for ½ hr. After cooling, the mixture was poured into water containing a slight excess (24 c.c.) of acetic acid and extracted several times with ether. The washed and dried extracts were evaporated *in vacuo* with minimum application of heat. The oily residue, which failed to crystallise, was taken up in warm acetic acid (30 c.c.); crystals separated. After overnight storage, the solid (2·45 g.) was collected and washed with methanol. Two recrystallisations from methanol–chloroform afforded trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (14) as colourless leaflets (1·20 g.), m. p. 203—204°, $\lambda_{max.}$ 263 ($\Delta^{10b,11}$) 296·5 mμ (log ε 4·25 and 3·44, respectively) (Found: C, 81·0; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·9%).

The combined material recovered from the mother liquors of two experiments (total 3·58 g.) was chromatographed on activated alumina (80 g.) in benzene–light petroleum (1 : 4) after rejection of an insoluble resin (620 mg.), and gave three main fractions, described in the order of elution, (i) (?)trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxychrysene* [dideoxo-(29)] (560 mg.), separating from methanol as needles, m. p. 120—123°, $\lambda_{max.}$ 262 ($\Delta^{10b,11}$), 292 mμ (log ε 4·27 and 3·41, respectively), no bands attributable to carbonyl or hydroxyl in the infrared spectrum (Found: C, 84·7; H, 8·9. $C_{19}H_{24}O$ requires C, 85·0; H, 9·0%); (ii) a further quantity of the *trans-anti*-ketone (14) (270 mg.); (iii) trans-syn-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (49) (590 mg.) separating from methanol as colourless leaflets, m. p. 163—165°, $\lambda_{max.}$ 259 ($\Delta^{10b,11}$), 292 mμ (log ε 4·28 and 3·48, respectively) (Found: C, 80·7; H, 7·9. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·9%).

In another experiment the precursor of the *trans-syn*-ketone (14) was isolated by chromatography on alumina of the crude Wolff–Kishner reduction product without prior reaction with acetic acid; two intermediate fractions were obtained between the decahydromethoxychrysene [dideoxo-(29)], described in (i) (above), and the *trans-anti*-ketone (14), first a precursor of the *trans-anti*-ketone (14) (not obtained pure; it gave the free ketone on crystallisation from methanol), and secondly cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-1,1,8-*trimethoxychrysene*, separating from methanol as leaflets, m. p. 96—99°, $\lambda_{max.}$ 265 ($\Delta^{10b,11}$), 300·5 mμ (log ε 4·29 and 3·54, respectively) (Found: C, 76·7; H, 8·5; MeO, 28·0. $C_{21}H_{28}O_3$ requires C, 76·9;

H, 8·4; 3MeO, 28·4%). Treatment of this ketal with warm acetic acid gave cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (50), separating from methanol–chloroform in colourless laths, m. p. 145—148°, $\lambda_{max.}$ 265 ($\Delta^{10b,11}$), 300 mμ (log ε 4·32 and 3·59, respectively) (Found: C, 80·6; H, 7·8. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·9%). Some strongly adsorbed phenolic material was eluted from the alumina by chloroform–methanol but was not further investigated.

In a number of experiments, material (0·2—0·5%) eluted from Florisil as a colourless oil immediately after the decahydromethoxychrysene [dideoxo-(29)], afforded, on crystallisation from methanol, (probably) *anti*-2,3,4,4a,4b,5,6,12-octahydro-1,8-dimethoxychrysene (51), colourless plates, m. p. 147—148·5°, $\lambda_{max.}$ 262 ($\Delta^{10b,11}$), 297 mμ (log ε 4·26 and 3·46, respectively), $\lambda_{max.}$ 6·05vw μ (double bond), n.m.r.$_{40}$ (in CCl_4) + 104 (aromatic OMe) and +111 c./sec. (vinyl-OMe). The substance (12 mg.) was unaffected by treatment in glacial acetic acid (3 c.c.) and acetone (3 c.c.) at the b. p. (30 min.). It (6 mg.) was converted on treatment in acetone (1 c.c.) with 1% hydrochloric acid in 50% aqueous methanol (1 c.c.) overnight into the $\Delta^{4b,10b}$-*trans*-ketone (37) (5·5 mg., 92%). On treatment at the b. p. (15 min.) in glacial acetic acid (20 c.c.), it (10·1 mg.) afforded, on filtration of the product through Florisil in benzene, a colourless solid (10·4 mg.), exhibiting an infrared spectrum showing the presence of unchanged material (51) and the *trans-anti*-ketone (14); crystallisation from methanol–methylene chloride then afforded impure *trans-anti*-ketone (14) as needles (3·3 mg., 33%), m. p. 188—194°, having an infrared spectrum in chloroform identical with that of the *trans-anti*-ketone (14), m. p. 203—204°.

Equilibration of cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (50): trans-syn-*Isomer* (49).—The *cis-syn*-ketone (50) (11 mg.) in methanol (5 c.c.) was treated with sodium methoxide (11 mg.) and kept at room temperature overnight. Isolation in the usual way gave a cream-coloured solid (12 mg.), shown by its infrared spectrum to contain both the *cis-syn-* (50) and the *trans-syn*-ketone (49). Crystallisation from methanol afforded the *trans-syn*-ketone (49) as needles (3·1 mg., 28·2%), m. p. 159—161°, $\lambda_{max.}$ 259·4 mμ.

Ponndorf Reduction of cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (16): cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1α- (54) *and* -1β-*hydroxy*-8-*methoxy*-4-*oxochrysene* (55).—A mixture of the *cis-syn*-diketone (16) (1·0 g.), propan-2-ol (150 c.c.), and a propan-2-ol solution (25 c.c.) of freshly distilled aluminium isopropoxide (775 mg.) was heated to the b. p. in 7 min. and boiled under reflux for 15 min. The suspended solid dissolved after 7 min. at the b. p. The hot reaction mixture was poured into a mixture of benzene (300 c.c.) and saturated aqueous potassium sodium tartrate solution (300 c.c.), and the organic phase was washed, dried, and concentrated under reduced pressure to *ca.* 100 c.c. with slight warming to remove the propan-2-ol. The residue was diluted to its original volume with benzene, again washed with Rochelle salt solution and with brine, dried, and evaporated under reduced pressure to give a semi-solid product (1·0 g.). Crystallisation from ethyl acetate afforded (*a*) crystals (439 mg., 44%), m. p. 168—171°, $\lambda_{max.}$ 265 mμ. The material in the mother liquors was chromatographed on Florisil (25 g.) in the usual way. Crystallisation from methanol of the material eluted with 80% benzene in light petroleum gave light yellow crystals (65 mg., 6·5%) shown by the infrared spectrum to be the *trans-anti*-diketone (29). Elution with benzene afforded in succession (*b*) a substance (148 mg., 15%), m. p. 152—159° (from ethyl acetate–light petroleum), $\lambda_{max.}$ 265 mμ, and (*c*) white crystals (100 mg., 10%), $\lambda_{max.}$ 265 mμ. Finally elution with 10% ethyl acetate in benzene gave, after crystallisation from ethyl acetate–light petroleum, (*d*) a substance (194 mg., 19·4%), m. p. 167—170°. Infrared spectroscopy showed these fractions (*a*)—(*d*) to exhibit both hydroxyl and carbonyl absorption; furthermore the spectra also showed (*a*) and (*d*) to be identical and (*c*) to be a mixture of (*b*) and (*d*). Fraction (*c*) was not further studied.

Further recrystallisation of fractions (*a*) and (*d*) (63·4%) from ethyl acetate–light petroleum afforded the cis-syn-1α-*hydroxy-ketone* (54) as colourless needles, m. p. 169·5—171°, $\lambda_{max.}$ 265·2 ($\Delta^{10b,11}$), 274 (infl.), 300 mμ (log ε 4·24, —, and 3·51, respectively), $\lambda_{max.}$ (in $CHCl_3$) 2·9w (OH), 5·88s (C=O), 6·1w (trisubstituted double bond), 9·12, 9·25, 9·6, 9·9 μ (Found: C, 76·2; H, 7·6. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

Further recrystallisation of fraction (*b*) (14·8%) in the same way gave the cis-syn-1β-*hydroxy-ketone* (55) as colourless needles, m. p. 163—164°, $\lambda_{max.}$ 265·5 ($\Delta^{10b,11}$), 274 (infl.), 302 mμ (log ε 4·24, —, and 3·54, respectively), $\lambda_{max.}$ (in $CHCl_3$) 2·9br (OH), 5·88s (C=O), 6·1w (trisubstituted double bond), 9·0, 9·35, 9·6 μ (Found: C, 76·7; H, 7·5%).

The following observations summarise experience gained in a number of experiments: (i)

the reaction times are critical—7 min. to the b. p. and 15 min. at the b. p.; shorter periods afford unchanged starting material and longer periods give the isomeric *cis*-1α-hydroxy-ketone (56) and the corresponding 1,4-diol; (ii) failure to remove the propan-2-ol in the extraction procedure led mainly to the *cis*-1α-hydroxy-ketone (56); (iii) normal Ponndorf conditions (prolonged refluxing) gave material showing no infrared carbonyl absorption; (iv) larger quantities of aluminium isopropoxide had a similar effect; (v) smaller quantities of aluminium isopropoxide required longer reaction times and afforded more of the isomeric *cis*-1α-hydroxy-ketone (56).

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-1α-*hydroxy*-8-*methoxy*-4-*oxochrysene* (56).—The above *cis-syn*-isomer (54) (201 mg.) was dissolved in hot ethyl acetate, aluminium hydroxide (15 mg.) was added, and the solution was concentrated on the water-bath for 15 min. Filtration and cooling afforded a solid (187 mg., 93·5%), m. p. 161—163°. Recrystallisation from ethyl acetate gave the $\Delta^{4b,10b}$-*cis*-hydroxy-ketone (56), m. p. 165—167°, not depressed on admixture with the specimen, m. p. 167—168°, previously described.[15]

trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1α-*hydroxy*-8-*methoxy*-4-*oxochrysene* (57).—A suspension of the *cis-syn*-1α-hydroxy-ketone (54) (183 mg.) in ethylene glycol (10 c.c.) was warmed on the water-bath to 60° with powdered 85% potassium hydroxide (61 mg.) until dissolution took place (12 min.) and then kept at 60° for ½ hr. The warm solution was poured into water and extracted with ethyl acetate. Crystallisation of the product from ethyl acetate–light petroleum afforded two crops (181 mg., 99%), m. p. 157—160°. Further crystallisation from ethyl acetate–light petroleum afforded the trans-anti-1α-*hydroxy-ketone* (57) as colourless needles, m. p. 164·5—166°, $\lambda_{max.}$ 261·2 ($\Delta^{10b,11}$), 295 mμ (log ε 4·26 and 3·42, respectively), $\lambda_{max.}$ (in $CHCl_3$) 2·9w (OH), 5·88s (C=O), 6·1w (trisubstituted double bond), 9·0, 9·2, 9·6, 9·88 μ (Found: C, 76·3; H, 7·5. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

Attempted Ponndorf Reduction of trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (29).—Conditions known to convert the *cis-syn*-diketone (16) into the *cis-syn*-ketol (54) (55) were employed. The *trans-anti*-diketone (29) (50 mg.) was recovered quantitatively after treatment with a propan-2-ol solution (3 c.c.) of freshly distilled aluminium isopropoxide (33 mg.) in propan-2-ol (15 c.c.) at 50° for 3 hr.; a similar result was obtained when a large excess (150 mg.) of catalyst was used (50°, 2 hr.).

cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-1α-*hydroxy*-8-*methoxy*-4-*oxochrysene Ethylene Thioketal* (58).—(A) *From the* cis-syn-1α-*hydroxy-ketone* (54). The technique described by Fieser [48] was employed. A mixture of the *cis-syn*-ketol (54) (89 mg.) and ethanedithiol (0·5 c.c.) was treated with the boron fluoride–ether complex (0·5 c.c.) and kept at room temperature for 1 hr. Removal of the ether left a bright red oil, and the colour was discharged on dilution with ethyl acetate and water. The oil left on evaporation of the washed and dried organic phase was chromatographed on Florisil in the usual way. Light petroleum and light petroleum–benzene (1 : 1) eluted an oil (17·5 mg.) with the odour of ethanedithiol. Benzene eluted an oil (80 mg.) which readily crystallised (m. p. 104—115°). Repeated recrystallisation from light petroleum, ether, and ethyl acetate–ether raised but failed to sharpen the m. p., and gave the $\Delta^{4b,10b}$-*cis*-ethylene-thioketal (58) as colourless needles, m. p. 115—122°, $\lambda_{max.}$ 278 mμ (broad; $\Delta^{4b,10b}$) (log ε 4·24), $\lambda_{max.}$ (in $CHCl_3$) 2·85m μ (OH), no carbonyl absorption.

(B) *From the* cis-1α-*hydroxy-ketone* (56). The same procedure was applied to the *cis*-1α-hydroxy-ketone (56) (32 mg.) and elution of the column with benzene afforded a colourless solid (31 mg., 77·5%). Recrystallisation from ether gave the $\Delta^{4b,10b}$-*cis*-ethylene thioketal (58) as needles, m. p. 121—127°, showing an infrared spectrum identical with that of the material prepared as in (A) (above).

cis-syn-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1α,10bα-*oxido*-4-*oxochrysene Ethylene Thioketal* (59).—The technique described by Hauptmann [39] was employed. A mixture of the *cis-syn*-1α-hydroxy-ketone (54) (70 mg.), freshly fused and powdered zinc chloride (90 mg.), and powdered anhydrous sodium sulphate (150 mg.) was treated with stirring at −70° with ethanedithiol (0·2 c.c.), stirred, and allowed to come to room temperature. After 5 days the mixture was distributed between ether and water, and the organic phase, washed and dried, gave, on evaporation, a yellow oil (120 mg.), which was chromatographed on Florisil in the usual way. Light petroleum and benzene–light petroleum (1 : 4) eluted an oil (24·7 mg.) with the odour of ethanedithiol. Benzene–light petroleum (1 : 1) eluted a white solid (73·1 mg., 83%), m. p. 147—149°. Benzene eluted a colourless oil (16·6 mg.), and 1—50% ether in

[48] Fieser, *J. Amer. Chem. Soc.*, 1954, **76**, 1945.

benzene eluted a brown oil (6·6 mg.); these oils were discarded. Sublimation of the solid at 0·01 mm./130° and crystallisation from methylene chloride–methanol afforded a substance considered to be the 1α.10bα-*oxide* (59) as colourless prisms, m. p. 149·5—150°, $\lambda_{max.}$ 275 and 283 mμ (log ε 3·51 and 3·43, respectively), no infrared hydroxyl or carbonyl absorption (Found: C, 67·4; H, 6·7. $C_{21}H_{26}O_2S_2$ requires C, 67·3; H, 7·0%).

Treatment of this substance (2·2 mg.) with the boron fluoride–ether complex (0·4 c.c.) for ½ hr. and then distribution between water and ethyl acetate afforded, on evaporation of the washed and dried organic phase, a yellow oil, $\lambda_{max.}$ 262 mμ ($\Delta^{10b,11}$) (log ε 4·39).

trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-1α-*hydroxy*-8-*methoxychrysene* (60).—The *cis-syn*-1α-hydroxy-ketone (54) (290 mg.) and powdered 85% potassium hydroxide (240 ± 10 mg.) were dissolved under nitrogen in triethylene glycol (15 c.c.) by warming at 70° ± 5°, and the mixture was held at this temperature for ½ hr. to effect stereoisomerisation to the *trans-anti*-form (57). 99—100% Hydrazine hydrate (1·2 c.c.) was added and the temperature was maintained at 70° for a further ½ hr. The temperature was then raised in ½ hr. to 120° and held there for 1 hr., then again raised under nitrogen to 200° in 1 hr. and maintained at 200° ± 5° for 1 hr. The crude product, a semi-solid brown oil (283 mg.), was extracted with ethyl acetate and chromatographed on Florisil in the usual way. Benzene–light petroleum (1 : 1) eluted a white solid (216 mg., 78·3%), and benzene and benzene–ether subsequently eluted a brown oil (60 mg.) which was discarded. Crystallisation of the solid from light petroleum afforded two crops (193 mg., 70%), m. p. 143—146°, and further recrystallisation from ethyl acetate–light petroleum gave the trans-anti-1α-*hydroxy*-8-*methoxyhydrochrysene* (60) as colourless crystals, m. p. 145—146·5°, $\lambda_{max.}$ 262·5 ($\Delta^{10b,11}$), 298 mμ (log ε 4·33 and 3·49, respectively) (Found: C, 80·1; H, 8·6. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%). The infrared spectrum of this substance was kindly studied by Dr. Robert West, University of Wisconsin, who reported that it exhibited unassociated hydroxyl absorption but lacked the normally observed associated hydrogen-bonded absorption.

trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (14).—The technique previously described [15] for Oppenauer oxidations was followed. The preceding *trans-anti*-1α-hydroxy-hydrochrysene (60) (95 mg.) was treated under nitrogen in benzene (15 c.c.) and cyclohexanone (5 c.c.) with a benzene solution (5 c.c.) of distilled aluminium isopropoxide (320 mg., large excess). The mixture was boiled under reflux overnight and then distributed between benzene and saturated sodium potassium tartrate solution. Evaporation of the washed and dried organic phase gave a suspension (1·10 g.) of colourless crystals in a yellow oil. The slurry was diluted 10-fold with light petroleum, and the suspended solid was collected, washed free from cyclohexanone with light petroleum, and applied to a Florisil column. Traces of oil eluted with light petroleum and benzene–light petroleum (1 : 1) were discarded. Benzene eluted a white solid, affording on crystallisation from methanol–methylene chloride successive crops of the same material: (i) (35 mg.), m. p. 203—204°; (ii) (31·8 mg.), m. p. 202—204°; (iii) (16·3 mg.), m. p. 198—202° (total, 83·1 mg.; 88·2%), shown by infrared spectra to be identical with the *trans-anti*-ketone (14), m. p. 203—204°, described above.

Conversion of cis-syn-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (16) *into* trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1-*oxochrysene* (14) *without Isolation of Intermediates*.—(i) The *cis-syn*-diketone (16) (1·0 g.) was reduced by the Ponndorf reaction in propan-2-ol with aluminium isopropoxide (1·11 g.) as described above, affording a crude cream-coloured solid. (ii) This was submitted directly to the Huang-Minlon Wolff–Kishner reduction in triethylene glycol (15 c.c.) with 85% potassium hydroxide (320 mg.), and, after ½ hr. at 75° ± 4°, 99—100% hydrazine hydrate (3·6 c.c.). The crude dark brown product, isolated as before, was filtered in benzene through Florisil (50 g.) and recovered as a cream-coloured solid (631 mg.). (iii) This (621 mg.) was dissolved in benzene (75 c.c.), part (15 c.c.) of which was distilled off to ensure dryness, and cyclohexanone (20 c.c.) was added, followed by freshly distilled aluminium isopropoxide (1·28 g.). The crude product was obtained as a slurry of colourless needles in the excess of cyclohexanone. Most of the latter was removed by distillation with slight warming under reduced pressure, and the resulting colourless solid cake was freed from the last traces by washing it with light petroleum; crystallisation as before from methanol–methylene chloride gave material (*a*) (323 mg.), m. p. 199—202°, (*b*) (129 mg.), m. p. 198—202°, and (*c*) (9 mg.), m. p. 201—203°. The total yield of the *trans-anti*-ketone (14) (461 mg.) from the *cis-syn*-diketone (16) *via* these three stages was thus 48·5%.

trans-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (61).—

The usual procedure [12] was modified. The preceding *trans-anti*-ketone (14) (607 mg.) was dissolved under nitrogen with warming in tetrahydrofuran (50 c.c., distilled from lithium aluminium hydride) and methanol (150 c.c.). To the resulting warm solution 20% aqueous sodium hydroxide (2·5 c.c.) and freshly distilled furfuraldehyde (3·5 c.c.) were added, and the mixture was set aside in the dark overnight. The resulting suspension was reduced to *ca.* 25 c.c. with slight warming under nitrogen, and the solid was collected and washed with 50% aqueous methanol until neutral, affording bright yellow needles (768 mg., 99%). Crystallisation from methanol–methylene chloride afforded three crops (total, 746 mg., 96·8%), m. p. 176·5—179·5° to 170—175°. Filtration through Florisil in benzene and further recrystallisation afforded the *furfurylidene-ketone* (61) as colourless needles, m. p. 179·5—180·5°, $\lambda_{max.}$ 261·9 ($\Delta^{10b,11}$), 327 mμ (furfurylidene-ketone) (log ε 4·34 and 4·43, respectively) (Found: C, 80·3; H, 6·9. $C_{24}H_{24}O_3$ requires C, 80·0; H, 6·7%).

Methylation of trans-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-1-*oxochrysene* (61): trans-anti- (62) *and* cis-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (63).—The usual methylation procedure [12] was modified. A solution of the preceding *trans-anti*-furfurylidene-ketone (61) (1·31 g.) in tetrahydrofuran (25 c.c., distilled from lithium aluminium hydride) and methyl iodide (50 c.c.) was stirred under nitrogen and protected from light, while a solution of potassium t-butoxide (from 3·0 g. of clean potassium, wet with benzene) in t-butyl alcohol (150 c.c., distilled from calcium hydride) was added at room temperature in 1½ hr. (at a rate such that the solution remained basic to moist litmus paper throughout the addition). After a further ½ hr., the solution, which contained precipitated potassium iodide, had become neutral, and solvent was removed under nitrogen at 40° ± 5°. The residue was distributed between benzene and water, and evaporation of the organic phase (washed and dried) gave a light yellow solid. An aliquot part (45 mg.) was removed, $n.m.r._{60}$ (in $CDCl_3$) +309 (12a-methyl; 301 units = 39·9% yield), +320 c./sec. (12a-methyl; 456 units = 60·3% yield). The remainder (1·315 g.) was fractionally crystallised from methanol–methylene chloride affording: (A) a solid (556 mg.), m. p. 192·5—194·5°; (B) a yellow solid (571 mg.); (C) a semi-solid oil (188 mg.). Crop (B) was further fractionated to give: (B1) (229 mg.), m. p. 173·5—175°; (B2) (70 mg.), m. p. 191·5—194°; (B3) (113 mg.), m. p. 173—174·5°; (B4) (67 mg., after a recrystallisation), m. p. 193—194·5°; (B5) (37 mg., after two recrystallisations), m. p. 173·5—175°; (B6) an orange semi-solid oil (46·4 mg.). Crops (C) and (B6) were applied to Florisil columns, and four fractions were eluted with benzene, benzene, ether, and ethyl acetate, respectively. Fractional crystallisation of the material eluted with benzene gave materials, (i) (16 mg.) m. p. 191—193·5°, (ii) (6·1 mg.) m. p. 170·5—173°, (iii) (24 mg.) m. p. 169—173°, and (iv) (5·8 mg.) m. p. 191—193·5°. The ether filtrate afforded a light yellow semi-solid oil (69·5 mg., 5·1%), which resisted further separation by crystallisation, $n.m.r._{60}$ (in $CDCl_3$) +309 (12a-methyl; 23 units = 50%), +320 c./sec. (12a-methyl; 23 units = 50%). The ethyl acetate filtrate afforded a red oil (97 mg.), which exhibited no furfurylidene-ketone absorption in the ultraviolet and no methyl resonance in the nuclear magnetic resonance spectrum.

The material (740 mg., 53·8%, or 56·3% after allowance for material in the above ether filtrate), m. p. 190—194°, was trans-anti-2-*furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (62), separating from methanol–methylene chloride in colourless prisms, m. p. 193·5—194·5°, $\lambda_{max.}$ 261·4 ($\Delta^{10b,11}$), 326·5 mμ (furfurylidene-ketone) (log ε 4·28 and 4·40, respectively), $n.m.r._{60}$ (in $CDCl_3$) +320 c./sec. (12a-methyl) (Found: C, 80·2; H, 6·8. $C_{25}H_{26}O_3$ requires C, 80·2; H, 7·0%).

The material (422 mg., 31·2%, or 33·7% after allowance for material in the ether filtrate), m. p. 170—174°, was cis-anti-2-*furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (63), separating from methanol–methylene chloride in colourless plates, m. p. 173·5—174·5°, $\lambda_{max.}$ 261 ($\Delta^{10b,11}$), 324·7 mμ (furfurylidene-ketone) (log ε 4·33 and 4·41 respectively), $n.m.r_{60}$ (in $CDCl_3$) +309 c./sec. (12a-methyl) (Found: C, 80·1; H, 7·0%).

cis-2-*Furfurylidene*-1,2,3,4,4a,5,6,11,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (41) *from* cis-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (63).—A solution of the above *cis-anti*-ketone (63) (11·5 mg.) in benzene (5 c.c.) was boiled under reflux with toluene-*p*-sulphonic acid monohydrate (2 mg.) for 1½ hr., then cooled and poured into saturated aqueous potassium hydrogen carbonate. The washed and dried organic phase gave a yellow oil (12 mg.), affording, on crystallisation from methanol, the

cis-ketone (41), m. p. 129—131°, not depressed on admixture with the substance (41), m. p. 131—131·5°, described above; the infrared spectra of the two specimens were identical.

cis-anti-β-(2-*Carboxy*-1,2,3,9,10,10a-*hexahydro*-7-*methoxy*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (64).—The technique previously described [11c] was modified. A solution of the methylated *cis-anti*-furfurylidene-ketone (63) (118 mg.) and sodium methoxide (17·0 g.) in methanol (90 c.c.) was stirred vigorously under reflux for 3¼ hr., during which 30% hydrogen peroxide was added in portions (each 25 c.c.) at 0, ¾, 2¼, and 3 hr. Each addition caused the separation of a heavy white precipitate which almost disappeared before the next addition. The last two additions were accompanied by considerable foaming. Methanol was removed under reduced pressure and the resulting aqueous solution was extracted with benzene. The organic phase yielded only a trace of a light brown neutral oil (8 mg.). The aqueous phase was made acid to Congo Red and extracted with ethyl acetate. Evaporation of the washed and dried extract gave an acidic brown oil (88·2 mg.), which was chromatographed on silicic acid (1 g.), five fractions (each 10 c.c.) being collected. The first two fractions (chloroform) gave a brown oil (11·4 mg.) with the odour of 2-furoic acid. The following three fractions (2—5% methanol in chloroform) afforded a colourless solid (74·1 mg.). Crystallisation from ethyl acetate gave the cis-anti-*dicarboxylic acid* (64) as colourless crystals (42·4 mg., 38·7%), m. p. 181·5—183°, $\lambda_{max.}$ 261·2 ($\Delta^{4,4a}$), 295 mμ (log ε 4·24 and 3·40, respectively) (Found: C, 69·2; H, 7·0. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%).

trans-anti-β-(2-*Carboxy*-1,2,3,9,10,10a-*hexahydro*-7-*methoxy*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (65).—In similar fashion a solution of the methylated *trans-anti*-furfurylidene-ketone (62) (85 mg.) in methanol (200 c.c.) containing sodium methoxide (12·0 g.) was heated under reflux and vigorously stirred for 4½ hr. during oxidation with 30% hydrogen peroxide (3 × 30 c.c.) added at 0, 1½, and 3¼ hr. The neutral product (13 mg.) was discarded, and the acidic product (80 mg.) was chromatographed on silicic acid (1·0 g.), six fractions (each 10 c.c.) being collected. The first two fractions (chloroform) gave a yellow oil (31·9 mg.) with a furoic acid-like odour, but it did not crystallise. The third fraction gave a trace of oil (<1·0 mg.). The next two fractions (2—4% methanol in chloroform) gave a semi-solid brown oil (45 mg.), and the last fraction (5% methanol in chloroform) contained no involatile material. On crystallisation from ethyl acetate the brown oil afforded the trans-anti-*dicarboxylic acid* (65) as colourless prisms (27·8 mg., 35%), m. p. 189—190·5°, $\lambda_{max.}$ 261·8 ($\Delta^{4,4a}$), 297 mμ (log ε 4·21 and 3·36, respectively) (Found: C, 69·7; H, 7·1%).

trans-anti-trans-β-(2-*Carboxy*-1,2,3,4,4a,9,10,10a-*octahydro*-7-*methoxy*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (*Homomarrianolic Acid Methyl Ether*) (2) *from* trans-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (62).—(i) The methylated *trans-anti*-furfurylidene-ketone (62) (45 mg.) was oxidised (6 hr.), as described above, with 30% hydrogen peroxide (3 × 15 c.c.) in methanol (50 c.c.) containing sodium methoxide (4·0 g.), affording a neutral oil (<1·0 mg.) and an acidic semi-solid brown oil (54 mg.). (ii) This was dissolved in tetrahydrofuran (6·0 c.c.) and added to liquid anhydrous ammonia (50 c.c.). To this colourless solution there was added under nitrogen distilled water (50 ± 5 mg.), to give a cloudy solution, and enough sodium (350 mg.) to give a permanent blue colour to the solution, which was stirred at the b. p. (−33°) for 1½ hr. (Additional sodium should be added if needed to maintain the blue colour during this time.) Ammonium chloride (total, 1·0 g.) was slowly added to discharge the blue colour, and the solvent was removed in a stream of nitrogen at room temperature. The residual colourless solid was distributed between water and benzene. The organic phase, washed and dried, gave on evaporation a pale brown neutral oil (14 mg.), which was not investigated. The aqueous phase, cooled to 0° and rendered acid to Congo Red with hydrochloric acid, was extracted with ethyl acetate, affording, in the usual way, a pale yellow acidic oil (38·4 mg.), which was chromatographed on silicic acid (0·4 g.), ten fractions (each 2 c.c.) being collected. Fractions 1—3 (chloroform) contained no material of interest (*ca.* 1·0 mg.); fractions 4 and 5 (1% methanol in chloroform) afforded colourless crystals (13·1 mg., 31·5% overall), m. p. 221·5—225°; fractions 6 and 7 (1% methanol in chloroform) gave a colourless oil (7·1 mg.), which failed to crystallise on nucleation with the preceding crystalline material; fraction 8, nil; fractions 9 and 10 (5—90% methanol in chloroform) gave a non-crystallising oil (8 mg.). Crystallisation of the solid fraction from ethyl acetate afforded the *trans-anti-trans*-dicarboxylic acid (2), m. p. 226—228°, alone and in admixture with an authentic specimen,[4a] m. p. 225—227·5°; the infrared spectra (potassium bromide discs) of the two specimens were identical.

trans-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-1-*oxochrysene* (66).—The *trans-anti*-ketone (15) (177 mg.) was warmed to effect solution in ethanol (40 c.c.) containing 20% sodium hydroxide solution (1·0 c.c.), and the mixture was stirred under nitrogen with exclusion of light with freshly distilled furfuraldehyde (0·15 c.c.) for 2 hr., and left overnight. The crystalline product was washed with 50% aqueous methanol and dried (yield, 209 mg., 90%; m. p. 168—175°). Crystallisation from methanol–methylene chloride afforded the *furfurylidene derivative* (66) as pale yellow needles, m. p. 167—168° and 175—176·5°; the latter polymorph was the form usually obtained; it had $\lambda_{max.}$ 255 ($\Delta^{10b,11}$), 328·2 mμ (furfurylidene-ketone) (log ε 3·98 and 4·27, respectively) (Found: C, 83·3; H, 6·6. $C_{23}H_{22}O_2$ requires C, 83·6; H, 6·7%).

trans-anti- (67) *and* cis-anti-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,12,12a-*decahydro*-12a-*methyl*-1-*oxochrysene* (68).—A solution of the preceding *trans-anti*-furfurylidene-ketone (66) (190 mg.) in benzene (5 c.c.) and methyl iodide (6·0 c.c.) was treated at 5° under nitrogen with stirring and exclusion of light with a solution of potassium t-butoxide (from 360 mg. of clean potassium) in t-butyl alcohol (20 c.c.), added during 1¾ hr. After being stirred for a further 1½ hr. the solution was neutral and was worked up as already described, affording a yellow oil (193 mg., 97·5%), $n.m.r._{40}$ (in $CDCl_3$) +206 (12a-methyl; about 15 units), +214 c./sec. (12a-methyl; about 10 units).

Repeated fractional crystallisation from methanol–methylene chloride afforded two substances, m. p. 141—143° and m. p. 168—170°, respectively. Repeated chromatography on Florisil resulted in concentration of the higher-melting substance in the first fractions eluted with 10% benzene in light petroleum but did not afford effective separation.

Further recrystallisation of the lower-melting substance from methanol–methylene chloride afforded the methylated trans-anti-*furfurylidene-ketone* (67) as colourless plates, m. p. 143—143·8°, $\lambda_{max.}$ 254·5 ($\Delta^{10b,11}$), 327·4 mμ (furfurylidene-ketone) (log ε 4·11 and 4·32, respectively) $n.m.r._{40}$ (in $CDCl_3$) +214 c./sec. (12a-methyl) (Found: C, 83·9; H, 7·2. $C_{24}H_{24}O_2$ requires C, 83·7; H, 7·0%).

Further recrystallisation of the higher-melting substance similarly afforded the methylated cis-anti-*furfurylidene-ketone* (68) as colourless plates, m. p. 170—171·5°, $\lambda_{max.}$ 254 ($\Delta^{10b,11}$), 325·2 mμ (furfurylidene-ketone) (log ε 4·19 and 4·38, respectively); $n.m.r._{40}$ (in $CDCl_3$) +206 c./sec. (12a-methyl) (Found: C, 84·0; H, 7·0%).

trans-anti-β-(2-*Carboxy*-1,2,3,9,10,10a-*hexahydro*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (69).—The preceding ketone (67) (170 mg.) in methanol (150 c.c.) containing sodium methoxide (12·0 g.) was heated under reflux and vigorously stirred for 5¾ hr. during oxidation with 30% hydrogen peroxide (4 × 30 c.c.), added at 0, 2, 4, and 4¾ hr. The neutral product (7 mg.) was discarded, and the brown oily acid (184 mg.) was chromatographed on silicic acid (1·5 g.), nine fractions (each 6 c.c.) being collected. Fractions 1—2 (chloroform) gave an oil (77 mg.; discarded). Fractions 3—5 (chloroform) gave a white solid (44 mg.), and fractions 6—8 (2% methanol in chloroform) gave a white solid (53 mg.). Fraction 9 gave a colourless oil (2 mg.; discarded). Recrystallisation of the solid product from ethyl acetate–light petroleum afforded the trans-anti-*dicarboxylic acid* (69) as prisms (73 mg., 47%), m. p. 215—215·5°, $\lambda_{max.}$ 226, 255, ($\Delta^{4,4a}$), 287 mμ (log ε 4·03, 4·19, and 3·29, respectively) (Found: C, 72·5; H, 7·0. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·0%).

The dimethyl ester (25 mg.) [$\lambda_{max.}$ 254·5 mμ ($\Delta^{4,4a}$) (log ε 4·04)], prepared with the aid of diazomethane, was an oil. It was heated with 10% palladium–charcoal (26 mg.) for 12 min. at 240° ± 5° and filtration of the crude product through Florisil in ether and evaporation gave a colourless oil (26 mg.), which did not crystallise, $\lambda_{max.}$ 258, 274, 283 mμ (log ε 3·77, 3·79, and 3·81, respectively); authentic methyl *trans*-β-(1,2,3,4-tetrahydro-2-methoxycarbonyl-2-methyl-1-phenanthryl)propionate has been reported [42] to be an oil.

cis-anti-β-(2-*Carboxy*-1,2,3,9,10,10a-*hexahydro*-2-*methyl*-1-*phenanthryl*)*propionic Acid* (70).—In similar fashion the methylated *cis-anti*-furfurylidene-ketone (68) (108 mg.) was oxidised with 30% hydrogen peroxide (4 × 17 c.c.) in methanol (90 c.c.) containing sodium methoxide (7·0 g.), affording a neutral oil (10 mg.) and a semi-solid acidic fraction (116 mg.). Chromatography of the latter on silicic acid (1 g.) gave in the intermediate fractions (eluted with 5% methanol in chloroform) a white solid (85 mg.), affording crystals (60 mg., 61%), m. p. 221—223° (from ethyl acetate). Further recrystallisation yielded the cis-anti-*dicarboxylic acid* (70) as prisms, m. p. 222·5—224°, $\lambda_{max.}$ 225, 253·8 mμ ($\Delta^{4,4a}$) (log ε 4·00 and 4·14, respectively) (Found: C, 72·9; H, 7·0%).

This acid (70) (12·0 mg.) with diazomethane afforded the dimethyl ester (14 mg.), which

crystallised from methanol in long colourless prisms, m. p. 100—100·5°, $\lambda_{max.}$ 225, 254 mμ ($\Delta^{4,4a}$) (log ε 4·03 and 4·18, respectively). The entire product was mixed with 10% palladium–charcoal (17 mg.) and heated at 247° ± 3° for 10 min. The crude dehydrogenated ester was chromatographed on Florisil (700 mg.). Benzene eluted a colourless oil (5·3 mg., 40·5%), which was not further investigated. Ether (50%) in benzene eluted, in the first fraction, a colourless oil (8·4 mg., 64·5%), which crystallised on trituration with low-boiling light petroleum, giving colourless crystals (m. p. 69—71°), $\lambda_{max.}$ 265 (infl.), 274, 284, 291 (infl.) mμ (log ε–, 3·70, 3·74, and – respectively). The infrared spectrum was identical with that of the authentic *cis*-dimethyl ester (71), m. p. 71—73°, kindly supplied by Dr. A. L. Wilds.

Catalytic Hydrogenation of trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (29).—The following procedure afforded more ready access to the *trans-anti-trans*-dodecahydro-diketone (73) than the method previously used.[23] The *trans-anti*-decahydro-diketone (29) (1·0 g.) in glacial acetic acid (100 c.c.) and ether (50 c.c.) was stirred in hydrogen at atmospheric pressure and room temperature in the presence of 30% palladium–carbon (75 mg.). Absorption of hydrogen was complete (1 mol.) in 1½ hr. Repeated fractional crystallisation of the crude product (1·0 g.), m. p. 151—173°, from methanol–methylene chloride afforded: (a) the *trans-anti-cis*-dodecahydro-diketone (72) as colourless needles (387 mg., 38·7%), m. p. 171—173·5°; (b) the *trans-anti-trans*-dodecahydro-diketone (73) as colourless needles (102 mg., 10·2%), m. p. 187—191°; (c) a mixture (507 mg., 50·7%), m. p. 155—173°, of (a) and (b), as shown by the infrared spectrum.

Comparison of the infrared spectra in chloroform of the *trans-anti-trans*-stereoisomer (73), [$\lambda_{max.}$ (in $CHCl_3$) 6·85sh,w, 6·95s μ], of the *trans-anti-cis*-form (72) (6·83sh,s, 6·90sh,w μ), of mixtures of the two of known composition, of the crude hydrogenation product, and of fraction (c) showed the crude hydrogenation product to contain 65 ± 5% of the *trans-anti-cis*-form and 35 ∓ 5% of the *trans-anti-trans*-form, while fraction (c) contained 40 ± 5% of the former and 60 ∓ 5% of the latter.

Further recrystallisation of the *trans-anti-cis*-diketone (72) from methanol–methylene chloride afforded colourless needles, m. p. 173—173·5°, $\lambda_{max.}$ 278, 287 mμ (log ε 3·32 and 3·29) [lit.,[23] m. p. 171—174°; $\lambda_{max.}$ 280 mμ (log ε 3·34)] (Found: C, 76·3; H, 7·5. Calc. for $C_{19}H_{22}O_3$: C, 76·5; H, 7·4%).

Further recrystallisation of the *trans-anti-trans*-diketone (73) gave a specimen, m. p. 189·5—190·5°, $\lambda_{max.}$ 278, 287 mμ (log ε 3·32 and 3·26) (lit.,[23] m. p. 181—184°) (Found: C, 76·8; H, 7·5%).

When these two substances were left overnight on a column of alumina and then eluted with benzene, a substance differing from the starting material (infrared spectrum) was obtained from the *trans-anti-cis*-compound (72), as previously reported,[23] but the *trans-anti-trans*-diketone (73) was recovered unchanged (infrared spectrum).

Reduction of trans-anti-1,2,3,4,4a,4b,5,6,12,12a-*Decahydro*-8-*methoxy*-1,4-*dioxochrysene* (29) *with Sodium in Moist Ammonia:* trans-anti-trans-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1,4-*dioxochrysene* (73).—(i) A solution of the *trans-anti*-diketone (29) (895 mg.) in tetrahydrofuran (25 c.c.) was mixed with anhydrous liquid ammonia (100 c.c.), and water (3 drops; 7·0 ± 1·0 mg.) was added to the clear light yellow solution, causing cloudiness. Sodium (1·0—1·5 g.) was then added to impart a permanent dark blue colour to the solution. After stirring at the b. p. (−33°) under reflux for 1½ hr., ammonium chloride (6·0 g.) was added to discharge the blue colour, leaving a milky suspension. The product, isolated in the usual way with the aid of ethyl acetate, was a dark brown oil (917 mg.), $\lambda_{max.}$ 278, 287 mμ (log ε 3·41 and 3·36), $\lambda_{max.}$ (in $CHCl_3$) 2·75m,sh (OH) and 2·88br,m μ (OH), no carbonyl absorption.

(ii) The preceding crude diol (917 mg.) in anhydrous pyridine (20 c.c.) was added (3 min.) to the complex [34a] from chromium trioxide (1·0 g., dried in a desiccator over lithium aluminium hydride) and anhydrous pyridine (distilled from barium oxide) (10 c.c.) under nitrogen with vigorous stirring. The mixture was stirred at room temperature for 4½ hr. and then distributed between ethyl acetate (100 c.c.) and water (50 c.c.). The organic phase, appropriately washed and dried, afforded a dark brown semi-solid oil (903 mg.), exhibiting slight hydroxyl and strong carbonyl absorption in its infrared spectrum. Crystallisation from methanol–methylene chloride afforded the *trans-anti-trans*-diketone (73) as pale yellow needles (270 mg., 30·1% overall), m. p. 188—191°, identical (infrared spectrum) with the *trans-anti-trans*-diketone (73) described above. The material in the mother liquors was filtered through a Florisil column with benzene and benzene–ether (9 : 1), affording, on evaporation of solvent, a cream-coloured solid (598 mg., 66·8%), which was not further studied.

trans-anti-trans-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1-*oxochrysene* (" β-*Methoxyhydrochrysenone* ") (6) *from* trans-anti-trans-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1,4-*dioxochrysene* (73).—(i) A solution of the *trans-anti-trans*-diketone (73) (240 mg.) in benzene (300 c.c.) containing trimethylene glycol (1·0 c.c.) and toluene-*p*-sulphonic acid monohydrate (75 mg.) was boiled under reflux, in the manner previously described, for 4½ hr. and the crude product, isolated in the usual way, was a dark brown oil, which was chromatographed on Florisil (15·0 g.). Benzene–light petroleum (1 : 1) eluted an oil (197 mg.), $\lambda_{max.}$ (in $CHCl_3$) 5·85m (C=O), 9·1s μ (ketal), which did not crystallise. Benzene eluted unchanged diketone (93 mg.). The oily product was taken to be a mixture of *trans-anti-trans*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-4-oxo-1,1-trimethylenedioxychrysene (74) and trimethylene glycol.

(ii) The preceding oil (110 mg.) and 99—100% hydrazine hydrate (0·5 c.c.) were heated together under nitrogen in triethylene glycol (15·0 c.c.) at 115° for 1 hr. Powdered 85% potassium hydroxide (93 mg.) was then added, and the temperature was raised during 1 hr. to 195° ± 5°, being maintained there for 1½ hr. The crude yellow oil (108 mg.), isolated in the usual way, was chromatographed on Florisil (5·0 g.), and two middle fractions, eluted with benzene–light petroleum (1 : 4 and 1 : 1), afforded colourless crystals (36 mg.), m. p. 113—126°, $\lambda_{max.}$ (in $CHCl_3$) 9·1s μ (ketal) which showed no carbonyl absorption; the substance was shown (infrared spectrum) to be *trans-anti-trans*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydro-8-methoxy-1,1-trimethylenedioxychrysene (76), m. p. 115·5—116·5°, described below. Acid hydrolysis by the method already described converted the substance, m. p. 113—126°, into the *trans-anti-trans*-ketone (" β-methoxyhydrochrysenone ") (6), m. p. 154·5—156°, alone and in admixture with an authentic specimen.[4b]

trans-anti-cis-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-4-*oxo*-1,1-*trimethylenedioxychrysene* (75).—In a similar manner the *trans-anti-cis*-diketone (72) (330 mg.) and trimethylene glycol (0·6 c.c.) afforded, on working up of the ketalisation mixture, a slurry (610 mg.) of crystals in an excess of glycol, which was chromatographed on Florisil (30 g.). The material in middle fractions, eluted with benzene–light petroleum (1 : 1) and benzene, solidified completely and crystallisation from methanol–methylene chloride gave colourless crystals (283 mg., 71·6%), m. p. 211—216°. Further recrystallisation afforded the pure trans-anti-cis-*monotrimethylene ketal* (75) as prisms, m. p. 217—218°, $\lambda_{max.}$ 277·3, 286·7 mμ (log ε 3·15 and 3·13), $\lambda_{max.}$ (in $CHCl_3$) 5·88m (C=O), 9·0s μ (ketal) (Found: C, 74·4; H, 7·9. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·9%).

Huang-Minlon Wolff–Kishner reduction of this monoketal (87 mg.) in the usual way proceeded in an anomalous fashion and the product could not be identified.

Reduction of trans-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (36) *with Lithium in Moist Ammonia:* trans-anti-trans- (76) *and* trans-anti-cis-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (77).—Stoutamire's method [49] was modified. A solution of the *trans*-trimethylene ketal (36) (190 mg.) in tetrahydrofuran (40 c.c.) was added under nitrogen to anhydrous liquid ammonia (90 c.c.), followed by water (3 drops; 70 ± 10 mg.). Lithium wire (*ca.* 40 mg.) was added to the slightly cloudy solution, giving a dark blue colour. The solution was allowed to boil (−33°) under reflux for 10 min., and ammonium chloride (2·0 g.) was then slowly added, giving a milky suspension. The crude product, isolated in the usual way, was a colourless oil (211 mg.), $\lambda_{max.}$ 278, 287 mμ (log ε 3·32 and 3·28), which was chromatographed on Florisil (10 g.). Light petroleum and benzene–light petroleum (1 : 9) eluted traces of oil which were discarded. Fractions eluted with benzene–light petroleum (1 : 4) up to benzene (100%) afforded colourless crystals (187 mg., 98·5%), and ether eluted an oil (17 mg.) (discarded).

Crystallisation of the solid from methanol–methylene chloride gave two crystalline compounds (needles, m. p. 114—115°, and prisms, m. p. 170—172°), which were hand-sorted to obtain pure seeds. Fractional crystallisation from methanol–methylene chloride then readily separated these two substances, yielding colourless needles (152 mg., 80·3%), m. p. 112·5—115°, and colourless prisms (29 mg., 15·2%), m. p. 169—171°.

Further recrystallisation of the lower-melting product afforded the trans-anti-trans-*trimethylene ketal* (76) as colourless needles, m. p. 115·5—116·5°, $\lambda_{max.}$ 278·4, 287 mμ (log ε 3·29 and 3·24) (Found: C, 77·1; H, 8·6. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%). Recrystallisation of material recovered from the mother liquors of the specimen, m. p. 115·5—116·5°, gave plates,

[49] Stoutamire, Ph.D. Thesis, University of Wisconsin, 1957.

m. p. 119—119·5°; a mixture of these two specimens showed no m. p. depression (m. p. 115·5—119°). Cooling, to solidification, of the mixed melt and re-heating resulted in partial melting at 119°, complete re-solidification at 119·5—121°, and complete melting at 126—127°. This material. m. p. 115·5—116·5°. 119—119·5°/126—127°, was taken to be *trans-anti-trans*-trimethylene ketal (76), as it (10·1 mg.; m. p. 119—119·5°) afforded the *trans-anti-trans*-ketone (" β-methoxyhydrochrysenone ") (6) (8·5 mg.), m. p. 154—155°, on acid hydrolysis in the manner already described; there was no depression of m. p. on admixture with an authentic specimen,[4b] m. p. 153—158°, and the infrared spectra of the two specimens were identical. The modification, m. p. 115—116·5°, behaved similarly.

Further recrystallisation of the higher-melting product, m. p. 169—171°, gave the trans-anti-cis-*trimethylene ketal* (77) as colourless prisms, m. p. 170·5—171·5°, $\lambda_{max.}$ 279·4, 288·2 mμ (log ε 3·26 and 3·22) (Found: C, 77·1; H, 8·7%). This (5·1 mg.) afforded on acid hydrolysis the *trans-anti-cis*-ketone (" α-methoxyhydrochrysenone ") (5) (4·1 mg.), m. p. 167—168·5°, exhibiting an infrared spectrum identical with that of an authentic specimen,[4b] m. p. 169—170·4°.

Reduction of cis-1,2,3,4,4a,5,6,11,12,12a-*Decahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (35) *with Lithium in Moist Ammonia:* cis-syn-trans-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1,1-*trimethylenedioxychrysene* (78).—In a similar manner the *cis*-trimethylene ketal (35) (500 mg.) in tetrahydrofuran (40 c.c.) was added to anhydrous liquid ammonia (200 c.c.); water (10 drops; 250—350 mg.) was added and then lithium wire (50 mg.). The dark blue solution was kept (−33°) for 10 min., then treated slowly with solid ammonium chloride (2·0 g.). The crude oily product (508 mg.) afforded, from methanol, colourless crystals (299 mg.), m. p. 140—141·5°. Material contained in the mother liquors was chromatographed on Florisil (20 g.). Intermediate fractions (total, 202 mg.), eluted with benzene–light petroleum (1 : 1) and benzene, partly crystallised on being seeded with the above solid, and crystallisation from methanol afforded a further quantity (73 mg.), m. p. 139·5—140·5°. The mother liquors afforded an oil (a) (127 mg., 25·2%) on evaporation. The solid product (372 mg., 74%) afforded, on recrystallisation from methanol–methylene chloride, the cis-syn-trans-*trimethylene ketal* (78) as colourless flakes, m. p. 139·5—140°, $\lambda_{max.}$ 278·5, 287·8 mμ (log ε 3·30 and 3·27) (Found: C, 76·8; H, 8·7%).

It was shown (following experiment) that at least 68·5% of the above oil (a), or 17·2% of the lithium–ammonia reduction product, had consisted of the *cis-syn-cis*-trimethylene ketal (81); no further attempts were made to crystallise this form.

trans-syn-cis-*Furfurylidene*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*dodecahydro*-8-*methoxy*-1-*oxochrysene* (83).—(i) The oil (a) [*cis-syn-cis*-trimethylene ketal (81)] (111 mg.) was hydrolysed with 1% aqueous-methanolic hydrochloric acid as already described, affording a yellow oil, assumed to be crude *cis-syn-cis*-ketone (82). (ii) This crude ketone was treated in methanol (25 c.c.) with 20% aqueous sodium hydroxide (1·0 c.c.), and freshly distilled furfuraldehyde (0·15 c.c.) under nitrogen and protected from light. The product was collected after 3 days in the dark at room temperature and washed until neutral with 50% aqueous methanol, affording yellow crystals [95 mg.; 81% based on the oil (a)], m. p. 182—188°; benzene extraction of the filtrate gave a yellow oil (23 mg.), which was discarded. Recrystallisation of the solid from methanol–methylene chloride afforded the *trans-syn-cis*-furfurylidene-ketone (83) [80 mg., 68·5% based on the oil (a)], m. p. 193—194·5°, not depressed on admixture with an authentic specimen,[6] m. p. 193·5—195·5°.

cis-syn-trans-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*Dodecahydro*-8-*methoxy*-1-*oxochrysene* (" δ-*Methoxyhydrochrysenone* ") (79).—The *cis-syn-trans*-trimethylene ketal (78) (240 mg.) in acetone (30 c.c.) was hydrolysed with 1% hydrochloric acid in 50% aqueous methanol (20 c.c.) in the usual way overnight, and organic solvents were removed at room temperature in a current of nitrogen. The colourless crystalline product (193 mg., 96·8%), m. p. 140·5—142·5°, was collected and washed, and recrystallisation from methanol afforded the cis-syn-trans-*ketone* (" δ-methoxyhydrochrysenone ") (79) as plates, m. p. 144—145°, $\lambda_{max.}$ 278·2, 286·8 mμ (log ε 3·29 and 3·27) (Found: C, 80·1; H, 8·3. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%).

The substance (6·2 mg.) was recovered unchanged after treatment with sodium methoxide (1 mg.) in methanol (5 c.c.) at the b. p. for 1 hr., and also when an ethereal solution (10·3 mg. in 12 c.c.) was shaken overnight with 2% aqueous potassium hydroxide (10 c.c.).

cis-syn-trans-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*dodecahydro*-8-*methoxy*-1-*oxochrysene* (80).—The *cis-syn-trans*-ketone (79) (150 mg.) was allowed to react under nitrogen in the dark for 24 hr. with furfuraldehyde (0·15 c.c.) in methanol (25 c.c.) containing 20%

aqueous sodium hydroxide (1·0 c.c.). The product, isolated in the usual way, consisted of yellow plates (180 mg., 94·5%), m. p. 159—162°. Recrystallisation from methanol–methylene chloride afforded the cis-syn-trans-*furfurylidene-ketone* (80) as colourless rectangular plates, m. p. 165·5—166°, $\lambda_{max.}$ 288 (infl.), 330·5 mμ (furfurylidene-ketone) (log ε – and 4·43) (Found: C, 79·6; H, 7·5. $C_{24}H_{26}O_3$ requires C, 79·5; H, 7·2%). Infrared spectra in chloroform solution showed this substance to be distinct from the furfurylidene derivatives of the *trans-anti-cis-*(" α- ")[6] (5), *trans-anti-trans-*(" β- ")[6] (6), and *trans-syn-cis-*(" γ- ")*methoxy-hydrochrysenone*[6] (7).

cis-syn-trans-2-*Furfurylidene*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*dodecahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (84).—The preceding *cis-syn-trans*-furfurylidene-ketone (80) (116 mg.) in benzene (7·0 c.c.) was added to potassium t-butoxide (from 242 mg. of clean potassium) in t-butyl alcohol (15 c.c.), and the mixture was treated at 5° with methyl iodide (0·7 c.c.). The solution became turbid in 15 min. and was kept at room temperature overnight. Isolation in the usual way gave a cream-coloured solid (130 mg.), affording, on crystallisation from methanol–methylene chloride, colourless crystals (88·1 mg., 72·8%), m. p. 169—170·5°, $n.m.r._{60}$ (in $CDCl_3$) +159 (aromatic OMe), +307 c./sec. (12a-methyl); the material in the mother liquors showed only one 12a-methyl peak in the nuclear magnetic resonance spectrum [(in $CDCl_3$) +159 (aromatic OMe), +308 c./sec. (12a-methyl)] and was not further fractionated.

Further recrystallisation from methanol–methylene chloride afforded cis-syn-trans-2-*furfurylidene*-1,2,3,4,4a,4b,5,6,10b,11,12,12a-*dodecahydro*-8-*methoxy*-12a-*methyl*-1-*oxochrysene* (84) as prisms, m. p. 171—172°, $\lambda_{max.}$ 287, 328·5 mμ (furfurylidene-ketone) (log ε 3·83 and 4·35) (Found: C, 79·9; H, 7·4. $C_{25}H_{28}O_3$ requires C, 79·8; H, 7·5%).

cis-syn-trans-β-(2-*Carboxy*-1,2,3,4,4a,9,10,10a-*octahydro*-7-*methoxy*-2-*methyl*-1-*phenanthryl*)-*propionic Acid* (85).—The preceding methylated *cis-syn-trans*-furfurylidene-ketone (84) (41 mg.) in methanol (90 c.c.) containing sodium methoxide (7·0 g.) was oxidised during 4 hr. with 30% hydrogen peroxide (3 × 17 c.c.) in the usual way, affording a neutral oil (7·5 mg.) and semi-solid acid (42 mg.). The latter was chromatographed on silicic acid (1·0 g.), and eight fractions (each 10 c.c.) were collected. The first four fractions (chloroform) gave a colourless oil (16·8 mg.), which was not investigated, and the fifth (chloroform) was devoid of solute. The next two fractions (5% methanol in chloroform) gave a colourless solid (27·2 mg.), and the last fraction (10% methanol in chloroform) gave a trace of brown oil. Recrystallisation of the solid from ethyl acetate afforded the *cis-syn-trans*-dicarboxylic acid (85) as needles (22·4 mg., 59·5%), m. p. 236—237°, alone and in admixture with an authentic specimen,[5b] m. p. 235·5—237°.

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[*Received, June 29th,* 1961.]