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

Steroid Total Synthesis—Hydrochrysene Approach. V.[1] Introduction of Oxygen at the 11-Position

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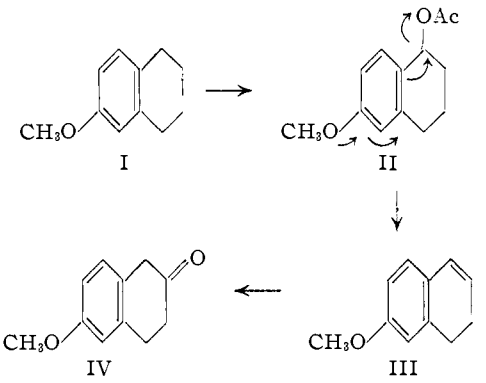
Lead tetraacetate treatment of the acetate VI (readily available from V) gave the 12-acetoxy compound VII which underwent dehydroacetoxylation to give the 11,12-dehydro compound IX. Peracid oxidation of IX yielded mainly hydroxy esters like VIII (R^1 = Ac, R^2 = H, R^3 = acyl) which (a) on pyrolysis gave the 11-keto compound X (R = Ac) or (b) on hydrogenolysis afforded the 11β-hydroxy compound XI. The configuration of XI is certain from its conversion to a natural steroid described in a later paper. Lithium aluminum hydride reduction of the 11-keto compound X yielded the 11α-hydroxy derivative XII. The mode of formation of VIII is discussed, and the application of the scheme to another stereochemical series is described. This series was proved to have the A/B/C *trans-syn-cis* configuration in the course of this study. Thus the acetate XIV was converted to the 12-acetoxy compound XV and this in turn to an 11,12-dehydro compound XVII different from IX. Peracid oxidation followed by pyrolysis or by acid-catalyzed decomposition of the 11,12-disubstitution products XVI gave the *trans-anti-trans* 11-keto compound X. The hydrogen at 10b had thus epimerized in the process. The scheme has been applied also the A/B/C *cis-anti-trans* acetate XIX (R = Ac, R′ = H) and procedures developed for the preparation of the 11β-hydroxy compound XXI in 47% over-all yield. A preliminary study has been made of the application of the scheme to the A/B/C *cis-syn-cis* series (XXII) and to the 6a,8-diacetate XXIV.

This part of the study concerns the problem of the introduction of oxygen at position 11 of some of the dodecahydrochrysene derivatives (like VI) described in previous papers of this series. The realization of this objective provides potential intermediates for the total synthesis of 11-oxygenated steroids like cortisone.

The direct introduction of a substituent at C_{11} in intermediates still retaining the 4b,10b-(styrene) double bond (as in formula V) was considered likely to fail, because a hetero atom in this position would be easily eliminated to give the naphthalenic C/D ring system. The action of selenium dioxide has in fact already been shown to effect such an aromatization.[1] We turned our attention, therefore, to the possible use of compounds like VI. The conception of a scheme for their utilization was



based upon the precedents cited below. In 1944, it was demonstrated in our laboratory[6] that 6-methoxytetralin (I) is selectively attacked by lead tetraacetate at the 1-position to give the acetoxy derivative II. The reaction is evidently directed to that methylene group which, by virtue of its *para* relationship to the methoxy group, has the highest electron density.[7] The acetate II proved to be very susceptible to elimination, particularly in the presence of acid, to give the dihydronaphthalene III. The methoxyl assists the departure of the acetoxyl group by supplying electrons in the manner indicated schematically by the arrows in formula II. Salzer[8] had shown in 1942 that treatment of the olefin III with perbenzoic acid followed by cold dilute mineral acid gave the methoxy-β-tetralone (IV). The sequence I → IV thus served as a model for the introduction of an 11-keto group *via* the steps VI → VII → IX → X.

The *trans-anti-trans*-tetrahydro acetate VI, readily available by reduction of V with lithium and alcohol in ammonia followed by acetylation,[9] was not affected appreciably by lead tetraacetate at room temperature in contrast with the behavior of I. When the temperature was raised to 90°, however, rapid reaction occurred and the 12-acetoxy compound VII (probably a mixture of C_{12}-epimers) was obtained readily. This material was more stable than the model substance II but could be induced to undergo dehydroacetoxylation by heating in acetic acid for several hours. The resulting unsaturated compound melted at 159° and exhibited λ_{max} 268 mμ (log ϵ 3.95), 298 (3.68), 309 (3.65), showing that the newly formed double bond was in conjugation with the aromatic nucleus (*cf.* the spectrum of the saturated compounds like VI[9]). Catalytic hydrogenation regenerated the *trans-anti-trans*-acetate VI proving that no configurational changes were involved in the sequence to introduce the double bond. The structure and configuration of the 159° dehydro compound were

(1) Paper IV, W. S. Johnson, J. Ackerman, J. F. Eastham and H. A. DeWalt, Jr., THIS JOURNAL, **78**, 6302 (1956).

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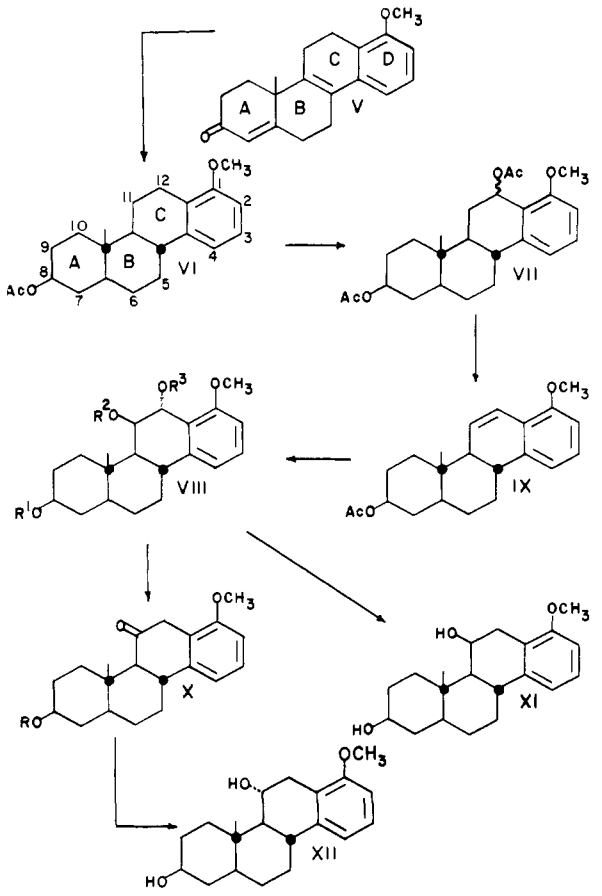
(6) W. S. Johnson, J. M. Anderson and W. E. Shelberg, THIS JOURNAL, **66**, 218 (1944).

(7) *Cf.* G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 3943 (1954).

(8) W. Salzer, *Z. physiol. Chem.*, **274**, 39 (1942); *cf.* J. English and G. Cavaglieri, THIS JOURNAL, **65**, 1085 (1943), and F. L. Weisenborn and D. Taub, *ibid.*, **74**, 1329 (1952).

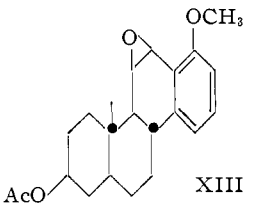
(9) Paper III, W. S. Johnson, E. R. Rogier, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister and H. Wynberg, *ibid.*, **78**, 6289 (1956).



thus conclusively established as represented in formula IX.[10]

For preparative purposes the total crude acetoxylated product could be heated in acetic acid to produce the 11,12-dehydro compound IX in about 70% over-all yield. It consumed one mole-equivalent of perbenzoic acid to give a mixture which was not converted by dilute aqueous hydrochloric acid, as in the Salzer case[8] (see above), into the 11-keto compound. It is noteworthy, however, that this type of conversion was later effected successfully in another stereochemical series by prolonged treatment with methanolic hydrochloric acid (see below).

The perbenzoic acid oxidation product evidently contained appreciable hydroxy benzoate VIII (R^1 = Ac, R^2 = H, R^3 = Bz), although this substance was not actually isolated. When the crude material was washed with alkali to remove benzoic acid, then pyrolyzed at 235°, the product consisted of benzoic acid and a compound which after purification melted at 169° and exhibited ketonic absorption at 5.84 μ. This ketone failed to form a 2,4-dinitrophenylhydrazone (*cf.* the hindrance in 11-keto steroids) but gave a color test with alkali and air typical of β-tetralones.[11] These facts are consistent with the formulation of the 169° substance as the desired 11-keto compound X (R = Ac).



The intermediary epoxide XIII, undoubtedly formed as the primary perbenzoic acid oxidation product of IX described above, evidently is so susceptible to cleavage that the benzoic acid resulting as a by-product reacts to give VIII (R^1 = Ac, R^2 = H, R^3 = Bz). Indeed the best yield (49% over-all from IX) of the 11-keto compound by the pyrolysis method was realized when the peroxidation reaction was carried out in the presence of added benzoic acid in order to facilitate cleavage of the epoxide by this reagent rather than by water (in the work-up). The product of the latter cleavage was, in fact, isolated in another stereochemical series (see below) when an attempt was made to isolate the corresponding epoxide.

When monoperphthalic was employed instead of perbenzoic acid, an appreciable bicarbonate-soluble fraction was isolated, undoubtedly containing the half-ester VIII (R^1 = Ac, R^2 = H, R^3 = $-COC_6H_4COOH$). Pyrolysis of the total crude oxidation product gave the 11-keto compound X (R = Ac) in 17% yield. In an experiment with peracetic acid, the yield was 8.5%. These low yields are probably due to difficulty with the pyrolysis step rather than the oxidation which appeared to proceed satisfactorily.

When the crude perbenzoic acid oxidation product was heated with acetic acid, a small yield (2%) of very impure 11-keto compound, recognized by the strong β-tetralone color test, was isolated by chromatography. Also isolated was a diacetate of questionable stereochemical homogeneity but undoubtedly corresponding in structure to VII (R^1 = R^3 = Ac, R^2 = H). After melting (above 260° with decomposition), it gave the β-tetralone color test. A similarly behaving, but lower-melting, diacetate fraction was isolated from the acetic acid-treated crude monoperphthalic acid oxidation product.

When acetic acid-treated perbenzoic acid oxidation product (see above) was saponified, the trihydroxy compound VIII (R^1 = R^2 = R^3 = H), m.p. 207°, was obtained in yields as high as 40% over-all from IX. The configuration of this triol as well as of the major constituent of the other 11,12-disubstitution products, described above, follows from the hydrogenolysis experiments described below, the α-configuration of the C_{12}-substituent being presumed on the basis of a *trans* opening of the oxide.[12]

The C_{12}-substituent of the products of peracid oxidations (see above) could be selectively sub-

(10) If the 159° compound had the alternative (and unlikely, considering the mode of formation) 4b,10b-dehydrostructure, the spectrum would be different (see ref. 9) and the catalytic hydrogenation would be expected to yield the *trans-anti-cis* configuration (see ref. 9).

(11) See J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

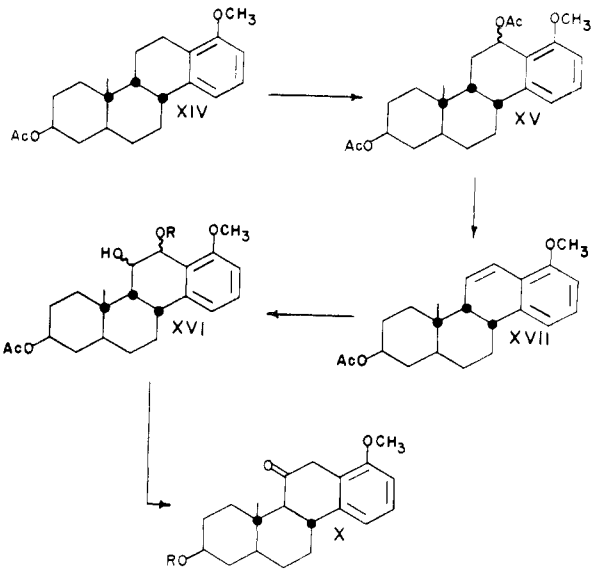
(12) It is possible, however, that the 12-hydroxyl group isomerized to the more stable β configuration, because benzylic alcohols are known to be susceptible to acid-catalyzed epimerization. See, for example, E. D. Bergmann, R. Pappo and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950).

stituted by hydrogen. The hydrogenolysis could be effected either by catalytic hydrogenation over palladium in acetic acid with a trace of perchloric acid[13] or with sodium in liquid ammonia. In all experiments the major product was the 8β,11β-dihydroxy compound XI, m.p. 241°, isolated sometimes as its diacetate, m.p. 199°. The structure and configuration of this diol follows unequivocally from its conversion to the natural product 3β,11β-dihydroxyandrostane-17-one.[14] The hydrogenation studies were carried out on the pure trihydroxy compound VIII ($R^1 = R^2 = R^3 = H$) and on the crude perbenzoic acid oxidation product, but the yields were low. The best method tried for obtaining the diol XI was to treat the crude product from performic acid oxidation of the 11,12-dehydro compound with sodium and alcohol in liquid ammonia, which afforded 31% of the 8β,11β-diol XI and 11% of the epimeric 8β,11α-diol XII, m.p. 183°. The latter compound was identical with material produced by lithium aluminum hydride reduction of the 11-keto compound X (R = H).[15]

The stereochemical results described above indicate that one of the major primary products of peracid oxidation of IX is the 11,12β-epoxide XIII which through the influence of the methoxyl group, would be expected to be very susceptible to nucleophilic attack at C_{12} to give axial-axial[16] 11β,12α-substituents. The isolation of some 11α-hydroxy compound XII in the sodium reduction is of special interest. It might arise from a sterically abnormal opening of the α-epoxide—a hypothesis presupposing that the reactivity at C_{12} toward nucleophilic attack is great enough to overcome the normal tendency of an oxide ring to open to give axial-axial substituents.[16] An alternative possibility is that the 11α-hydroxy compound is derived from some 11-keto compound (*cf.* the lithium aluminum hydride reduction above) promoted by acid during the oxidation step.

Treatment of the 11,12-dehydro compound IX with osmium tetroxide gave an 11,12-dihydroxy derivative, m.p. 214°, in which the vicinal hydroxyl groups undoubtedly are oriented *cis* to each other. In another experiment the crude osmate ester was treated directly with lithium and alcohol in ammonia, and the 11β-hydroxy compound XI was isolated in 16% yield, thus indicating that the hydroxyls at C_{11} and C_{12} of the 214° compound are probably both oriented in the β-configuration.

In the previous paper of this series,[1] we described the ready preparation of a tetrahydro acetate, m.p. 135°, presumed to have the *trans-syn-cis* configuration XIV. In order to establish this point, we undertook the introduction of the 11-keto group into this substance in order to labilize the hydrogen atom at C_{10b} thus permitting isomerization to the *trans-anti-trans* series of established configuration (see above). An account of this study follows.



Treatment with lead tetraacetate converted the acetate XIV into the diacetate XV in over 60% yield. Heating the diacetate in acetic acid effected dehydroacetoxylation giving the 11,12-dehydro compound XVII, m.p. 144°, with an ultraviolet spectrum essentially the same as that of the *trans-anti-trans* isomer IX. The two 11,12-dehydro compounds were obviously different as shown by depression of the m.p. on admixture. The 144° compound XVII was oxidized with perbenzoic acid and an attempt made to isolate the epoxide by direct chromatography. However, the fractions consisted of 4.5% of starting material XVII, 43% of which was apparently a mixture of hydroxy benzoates XVI (R = Bz) from which one form, m.p. 200°, was separated by crystallization in 17% yield, and 28% of a dihydroxy compound XVI (R = H), m.p. 172°. The 200° benzoate could be isolated directly in 24% yield from the crude reaction mixture by crystallization. Pyrolysis of this material, followed by chromatography, gave a crude ketonic fraction from which a pure ketone, m.p. 169°, was crystallized in 14% yield. The substance proved to be identical (mixed m.p. and infrared comparison) with the *trans-anti-trans*-11-keto compound X (R = Ac) described above. Attempts to isolate the epimeric *trans-syn-cis* precursor failed, although it appeared to be present in non-crystalline residues which gave the β-tetralone color test. The unlikely (on theoretical grounds) possibility that the 169° keto compound has the *trans-syn-cis* rather than the *trans-anti-trans* configuration was eliminated by the isolation on lithium aluminum hydride reduction (giving mainly XII) of the *trans-anti-trans*-11β-hydroxy compound XI of established configuration as the sole by-product. It is unlikely that the formation of this substance was preceded by an epimerization during

(13) The method of K. Kindler; see K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1850 (1942).

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

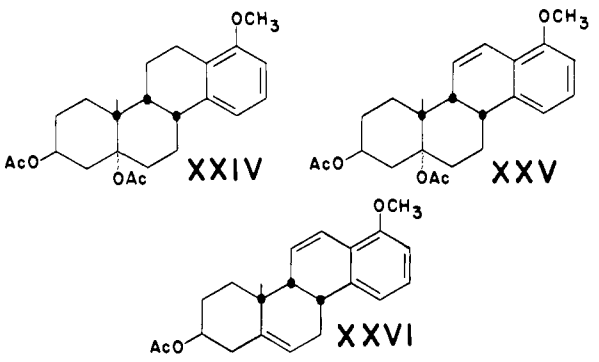
(15) The lithium aluminum hydride reduction of the 11-keto group of X (R = H) to give the 11α-hydroxyl group follows the general expectation for such conditions to give the more stable (equatorial) epimer. This behavior is in contrast to that of the exceptional 11-keto steroids, which, due to steric hindrance, give under these conditions the 11β-(axial) hydroxyl. The major factor which is responsible for this difference is the absence in X (R = H) of the β-oriented (axial to ring C) angular methyl group between rings C and D which hinders approach of the reagent from the β-side in the steroids.

(16) L. F. Fieser, *Experientia*, **6**, 312 (1950); D. H. R. Barton, E. Miller and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

reduction, for lithium aluminum hydride would not be expected to effect such an isomerization.[17]

The products from the perbenzoic acid oxidation of the 11,12-dehydro compound XVII could be converted to the hydroxy ketone X (R = H) by the prolonged action of methanolic hydrochloric acid. The crystalline 200° benzoate, the oily benzoate fraction and the 172° dihydroxy compound (all described above) thus gave X (R = H) in 54, 65 and 30% yields, respectively. For preparative purposes the crude perbenzoic acid oxidation product could be used directly to give X (R = H) in 52% yield. The pure hydroxy ketone X (R = H) melted at 184° and on acetylation gave material identical with the acetate X (R = Ac) produced by the pyrolytic method as described above.

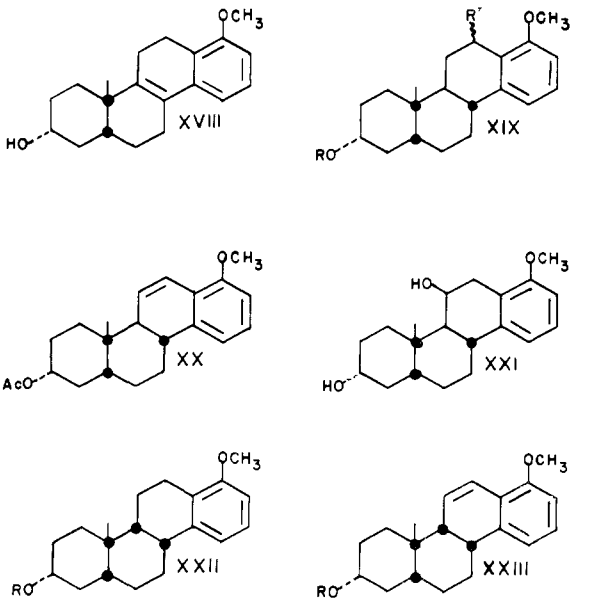
In part III[9] we described the stereoselective catalytic hydrogenation of the 6a,7-double bond of the tetracyclic ketone V and the lithium aluminum hydride reduction of the resulting *cis*-dihydro ketone to give the *cis*-8α-hydroxy compound XVIII. The reduction of the 4b,10b-(styrene) double bond of XVIII with lithium and alcohol in ammonia[18] to give the *cis-anti-trans*-tetrahydro alcohol XIX (R = R′ = H) was also described. In the present work it was shown that this last step was accompanied by appreciable reduction of the aromatic nucleus involving hydrogenolysis of the 1-methoxy group. When potassium was used instead of lithium in the Wilds–Nelson procedure,[18] attack of the aromatic nucleus was eliminated and the yield of XIX (R = R′ = H) was thus raised from 59 to 81%.



Acetoxylation of the acetate XIX (R = Ac, R′ = H) with lead tetraacetate afforded the 8α,12-diacetoxy compound XIX (R = Ac, R′ = OAc), m.p. 166°, which on dehydroacetoxylation as described above gave the 11,12-dehydro compound XX, m.p. 146°. The latter substance was prepared in 80% over-all yield directly from XIX (R = Ac, R′ = H) without purification of the intermediate. Oxidation of XX with perbenzoic acid, followed by treatment with benzoic acid, then with lithium and alcohol in ammonia (to effect hydrogenolysis) afforded the 8α,11β-dihydroxy compound XXI, m.p. 193°, in 47% over-all yield. A small amount (9% yield) of the 11α-epimer, m.p. 221°, was also isolated. The proof of configuration of the 11-hydroxyl group follows from a study of the reduction of the aromatic nucleus of XXI.[14]

Preliminary studies have been made on the acetoxylation of the *cis-syn-cis*-acetoxy compound XXII (R = Ac) which is particularly readily available directly from the tetracyclic ketone V by catalytic hydrogenation followed by reduction of the carbonyl group and acetylation.[1] In this series a 12-acetoxy compound (m.p. 131°) was isolated in poor yield because it was exceedingly unstable, undergoing dehydroacetoxylation during the treatment with lead tetraacetate. The principal product of the reaction was therefore the 11,12-dehydroacetate XXIII (R = Ac), m.p. 143°.

Since the *cis-syn-cis*-acetoxy compound XXII (R = Ac) was an oil and therefore did not lend itself readily to purification, the benzoate XXII (R = C_6H_5CO) was investigated. This derivative, which was nicely crystalline, m.p. 154°, could be prepared directly from the mixture of epimeric alcohols produced on reduction of the ketonic precursor. When this reduction was carried out with lithium aluminum hydride, the benzoate was isolated in 63% yield. Hydrogenation of the ketone over platinum oxide gave the benzoate in 68% yield, and reduction with lithium and alcohol in ammonia afforded the derivative in only 46% yield. Attempted acetoxylation of the benzoate gave the 11,12-dehydro compound XXIII (R = C_6H_5CO), m.p. 99°, in low yield.



Preliminary experiments, carried out by Jerome F. Eastham and Robert A. Clement, on the acetoxylation of the 6a,8-diacetate XXIV[1] showed that this reaction was also complicated by the ready elimination of the 12-acetoxy group to give some 11,12-dehydro compound XXV, m.p. 183°, which moreover appeared to be susceptible in turn to further attack by the lead tetraacetate (perhaps to aromatize ring C). In addition, when the crude product was heated with acetic acid to complete

(17) See, for example, G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953)—reduction of their compound "XIV"; and R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952)—reduction of their "VII" and "IX."

(18) The method of A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5360 (1953).

the dehydroacetoxylation, the 6a-acetoxy group was eliminated at about the same rate as the 12-substituent to produce a diene, m.p. 153°, perhaps XXVI. Although in one run (see experimental) XXV and XXVI were isolated in 25 and 52% yields, respectively, the yields were capricious in other runs, and a good preparative method has not yet been evolved.

The striking susceptibility of the 12-acetoxyl group to undergo elimination in the B/C *cis* series (as compared with the B/C *trans*) suggests that this group may be in the axially conformed 12β-configuration, in position for concerted elimination with the $C_{11\alpha}$-hydrogen atom. The corresponding elimination reaction in the B/C *trans* series may be slower either because the 12-acetoxyl group is equatorial (β), or because of steric hindrance about the $C_{11\beta}$-hydrogen which would inhibit a concerted process if the 12-acetoxyl is α-(axially) oriented.

Acknowledgment.—The generous assistance of the agencies mentioned in refs. 2–5 is acknowledged. We are deeply indebted to Professor Gilbert Stork of Columbia University for encouraging us to exploit and helping us to apply the scheme for introducing the 11-oxygen *via* the 11,12-dehydro compound. We thank him particularly for supplying us with unpublished information from his laboratory on methods of oxidizing the methoxydihydronaphthalene system.

Experimental[19]

trans-anti-trans-1-Methoxy-8β,12-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (VII).—A mixture of 0.404 g. of *trans-anti-trans*-1-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene[9] (VI), m.p. 149–150°, 0.668 g. of lead tetraacetate and 1 ml. of glacial acetic acid was heated on the steam-bath with stirring. After 5–10 minutes the mixture became homogeneous and soon crystals of the diacetate began to separate. After a total heating period of 20 minutes the mixture was cooled, sufficient glycerol introduced to destroy excess lead tetraacetate (as shown by the starch–iodide test) and 1 ml. of water was added. The solid was separated and washed thoroughly with water on the filter to give in 96% yield crude material suitable for the next stage of the synthesis (see below).

A sample was purified by chromatography on activated alumina and elution with benzene. After repeated recrystallization from 95% ethanol containing a few drops of benzene, it was obtained as colorless elongated plates, m.p. 205.5–211.7°, with slight decomposition and previous softening, λ_{max} 275 mμ (log ϵ 3.38), 281 (3.38); λ_{min} 244 (2.13).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.9; H, 8.04.

trans-anti-trans-1-Methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (IX).—A mixture of 3.40 g. of the acetate VI,[9] m.p. 148–149°, 5.52 g. of lead tetraacetate and 8.3 ml. of glacial acetic acid was heated with stirring as described above for the preparation of VII, except that the reaction was conducted in an atmosphere of nitrogen and the total heating period was 27 minutes. Glycerol (2 drops) and water (8 ml.) were added, and the solid product separated and washed well with water on the filter. The crude wet diacetate was dissolved in 60 ml. of glacial acetic acid and heated under nitrogen at 90–100° for 14 hr. The solvent was removed by distillation at reduced pressure, and the pale brown residue crystallized from 75 ml. of 95% ethanol; yield 2.26 g., m.p. 151.5–157.5°. Two recrystallizations from 95% ethanol, followed by sublimation at 152° (0.06 mm.) and a final crystallization from 95% ethanol gave colorless rods, m.p. 157.2–159°, λ_{max} 268 mμ (log ϵ 3.95), 298 (3.68), 309 (3.65); λ_{min} 243 (3.55), 291 (3.60), 305 (3.62).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.4; H, 8.36.

The mother liquor from the first crystallization of the crude 11,12-dehydro compound, upon evaporation and chromatography on activated alumina, yielded on elution with 1:3 benzene–petroleum ether (60–68°); 0.07 g. of starting acetic VI, m.p. 147–150°, undepressed on admixture with authentic material; and in later fractions a total of 0.247 g. of what evidently was a mixture of the acetate VI and 11,12-dehydro compound. This mixture melted at 131–133° and exhibited absorption at λ_{max} 268 mμ (log ϵ 3.74), 298 (3.42), 309 (3.39), consistent with an approximate composition of 50% of each component.

Hydrogenation of the 11,12-Dehydro Compound IX.—This experiment was performed by J. C. Collins and C. I. Judd. A 0.011-g. sample of the 11,12-dehydro compound, m.p. 155.5–156.5°, was hydrogenated in 10 ml. of ethyl acetate over 0.015 g. of 10% palladium-on-carbon[20] at atmospheric pressure and room temperature. Within 5 minutes one mole-equivalent of hydrogen was absorbed and reaction had ceased. The mixture was filtered, evaporated and the residue crystallized from ether to give 0.009 g. of colorless prisms, m.p. 150–152°. Recrystallization raised the m.p. to 151–152.1°, undepressed on admixture with the analytical specimen of authentic acetate VI described above. The infrared spectra of the two specimens were identical.

trans-anti-trans-1-Methoxy-8β-acetoxy-10a-methyl-11-keto-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (X, R = Ac). (a) Perbenzoic Acid Method.—One milliliter of 0.652 *M* perbenzoic acid[21] in chloroform was added slowly with stirring to a mixture of 0.340 g. of the 11,12-dehydro compound IX, m.p. 150.5–152°, and 0.61 g. of benzoic acid in 5 ml. of chloroform. The temperature of the reaction mixture was maintained at −3° during the addition (13 minutes) and at −3 to −1° for a subsequent 5-hr. stirring period, during which the perbenzoic acid had been consumed as indicated by a negative starch–iodide test. An additional 0.3 ml. of the perbenzoic acid solution was added at −3° over a 25-minute period and the mixture allowed to stand overnight in the refrigerator at 1°. A final 0.245 ml. of the oxidizing solution was then added at −3° over a 20-minute period, and after 24 hours at 1°, the mixture was washed well with saturated sodium bicarbonate solution, then with water. The residue (0.435 g.) obtained upon removal of the solvent at reduced pressure and drying exhibited λ_{max} 224 mμ (log ϵ 4.05), 274 (3.38) and only slight absorption in the 300 mμ region indicating the presence of not more than 5% of starting 11,12-dehydro compound.

A 0.211-g. sample of this crude oxidation product contained in a Pyrex tube 9 mm. in diameter was heated at 235° at a pressure of about 150 mm. Rapid decomposition ensued and benzoic acid (m.p. 122–123°, undepressed on admixture with authentic material) condensed in the cold part of the tube. After 1 hour the distillate consisting of benzoic acid and some oily liquid was all washed back into the bottom of the cooled tube with ether, the ether evaporated, and the residue evaporatively distilled at 135° (15 mm.) for 4 hours to separate the benzoic acid (0.024 g.). The distillation was then continued at 168–180° (0.06 mm.) for 14 hours to give 0.132 g. of an almost colorless oil which was crystallized from about 6 ml. of methanol to give 0.080 g. (first crop), m.p. 156–163° with softening at 151°, and 0.005 g. (second crop), m.p. 149–160° with softening at 140°. Two recrystallizations from methanol gave colorless needles which melted at 161–163.5° after drying at 100° and reduced pressure for 5 hr. Further drying for

(19) The new substances described in this section are racemic compounds, but the prefix "*dl*" has generally been omitted.

Unless otherwise indicated, melting points of analytical specimens are corrected for stem exposure; those followed by "(vac.)" were determined in a capillary evacuated <0.3 mm. Ultraviolet absorption spectra were determined on either a Beckman model DU quartz spectrophotometer or a Cary recording spectrophotometer (model 11 MS), 95% alcohol being employed as the solvent. Infrared spectra were determined on a Baird double beam infrared recording spectrophotometer, model B. Unless otherwise specified, carbon disulfide was used as the solvent.

(20) American Platinum Works.

(21) Freshly prepared according to "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

12 hr. raised the m.p. to 163.5–165°,[22] λ_{max} 272 mμ (log ε 3.23), 279 (3.24); λ_{min} 251 (2.68); λ_{max} 5.84 μ.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.9; H, 8.12.

A solution of a small amount of the 11-keto compound in methanolic sodium methoxide slowly developed a deep yellow color on shaking in the presence of air. The color changed to blue upon addition of concentrated hydrochloric acid.

(b) **Perphthalic Acid Method.**—A total of 2.1 ml. of 0.66 *M* monoperphthalic acid[23] in ether was added quickly to a solution of 0.056 g. of the 11,12-dehydro compound, m.p. 150–152°, in 1 ml. of methylene chloride and the reaction mixture maintained at 10° during the addition and also for 28 hr. thereafter. The solvent was evaporated at reduced pressure[24] and the residue (0.160 g.) pyrolyzed as described in above in part (a). Evaporative distillation at 105–110° (0.08 mm.) for 3 hr. gave 0.054 g. of forerun (probably phthalic acid or anhydride). Further distillation at 125–225° (0.08 mm.) for 3 hr. gave 0.046 g. of distillate which on crystallization from methanol yielded 0.010 g. of crude 11-keto compound, m.p. 155–160.5°, giving the characteristic color test described above.

trans-anti-trans-1-**Methoxy-8β,12-diacetoxy-10a-methyl-11-hydroxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene.**—Two different specimens corresponding to this structure were isolated as described below. They both melted broadly with decomposition and hence their homogeneity is in question. However, both specimens undoubtedly contained appreciable amounts of the 11β,12α-epimer (formula VIII, $R^1 = R^3 = Ac$, $R^2 = H$).

(a) A 0.039-g. sample of the neutral fraction from the perphthalic acid oxidation[24] was heated in 10 ml. of acetic acid at 100° for 9 hr. The residue obtained on evaporation of the solvent at reduced pressure was chromatographed on Merck and Co., Inc., acid-washed activated alumina (grade II to III). After elution with benzene there was obtained from chloroform eluates an oily fraction which on crystallization from methanol–chloroform gave 0.004 g. of crude material, m.p. 252–257.5° dec. Further recrystallization from *n*-butyl acetate gave material, m.p. 250–255° dec. It was noted that this material gave a positive β-tetralone color test after, but not before, melting.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.1; H, 8.16.

(b) A perbenzoic acid oxidation of 0.116 g. of the 11,12-dehydro compound, m.p. 150–152°, was carried out essentially as described above except that no benzoic acid was employed, the reaction temperature was 10–12° and the total reaction period was 22 hr. The crude product isolated as described above was dissolved in 10 ml. of acetic acid containing 10 drops of water and the solution was heated at 90–100° in an atmosphere of nitrogen for 6 hr. Evaporation of the solvent under reduced pressure left 0.152 g. of crude oily product. One-half (0.076 g.) of this material was reserved for the saponification experiment to produce trihydroxy compound VIII ($R^1 = R^2 = R^3 = H$) described below. The other half of this crude material was chromatographed on a 16 × 1.5-cm. column of Merck and Co., Inc., acid-washed activated alumina. Elution with 1:1 benzene–chloroform (25-ml. fractions were collected) gave 0.002 g. (fraction 1) of oil which did not crystallize from methanol but did give a strong color test (see above) indicating the presence of the 11-keto compound. Fractions 2 and 3 contained no material. Fractions 5 and 6 contained 0.010 and 0.014 g., respectively, of solid crude hydroxy diacetate. Crystallization of fraction 6 from ethyl acetate gave 0.005 g. of material, m.p. 250–260° dec. Recrystallization from *n*-butyl acetate gave material, m.p. 260–268° dec. As with the specimen described above, the β-tetralone color test was positive only after melting.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.9; H, 8.07.

trans-anti-trans-1-**Methoxy-8β,11β,12α-trihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (VIII, $R^1 = R^2 = R^3 = H$).**—The 0.076-g. portion of the perbenzoic acid oxidation experiment described above under part (b) of the preparation of the hydroxy diacetate was dissolved in 10 ml. of 4% potassium hydroxide in methanol, and the mixture was boiled under reflux (atmosphere of nitrogen) for 2 hr. Most of the methanol was removed at reduced pressure, water was added and the mixture extracted three times with *n*-butyl alcohol and once with benzene. The combined organic layers were washed once with water, then with 3% hydrochloric acid, again with water and finally dried over anhydrous magnesium sulfate. The residue obtained upon evaporation of the solvent at reduced pressure was crystallized from chloroform–benzene to give 0.022 g. of colorless microcrystalline triol, m.p. 206–207°. A specimen from another comparable run was prepared for analysis by repeated recrystallization from chloroform–benzene, m.p. 203–204°, λ_{max} 3.0 μ (OH).

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.5; H, 8.76.

trans-anti-trans-1-**Methoxy-8β,11β-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (Diacetate of XI).**—A mixture of 0.022 g. of the triol, m.p. 206–207°, described above, 2.5 ml. of glacial acetic acid, 0.08 ml. of 60% perchloric acid[13] and 0.01 g. of 30% palladium-on-carbon[20] was agitated at 26° with hydrogen at atmospheric pressure for 24 hr. The mixture was filtered, potassium acetate added to the filtrate and the mixture again filtered to remove precipitated potassium perchlorate. The filtrate was evaporated at 90° (30 mm.) and the colorless residue treated with dilute potassium hydroxide and extracted with ether. The ether layers were washed with water and dried by azeotropic distillation with benzene. The residue obtained on evaporation of the solvent was crystallized from methanol to give 0.0074 g. of crude diacetate, m.p. 180–193°, probably contaminated with some incompletely acetylated product. Three recrystallizations from 95% ethanol gave 0.0031 g. of colorless needles, m.p. 197.5–199°, λ_{max} 5.8 μ (ester C=O), no absorption in the OH region.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 71.97; H, 8.05. Found: C, 72.3; H, 8.44.

This diacetate was also isolated in poor (3%) yield by chromatography of the material obtained by hydrogenolysis, according to the above procedure, of crude perbenzoic acid oxidation product (see above). When a similar reaction was carried out except that the perchloric acid was omitted, and the acetylation was completed with pyridine and acetic anhydride, the crude diacetate was isolated by chromatography in 20% yield. In both of these experiments small amounts of the 8-acetoxy compound VI were also isolated.

Saponification of the diacetate with dilute methanolic sodium hydroxide gave the diol which, after crystallization from 95% ethanol, melted at 240–242° alone or on admixture with the analytical specimen described in the following experiment.

trans-anti-trans-1-**Methoxy-8β,11β-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XI) by Performic Acid Oxidation of IX Followed by Sodium Reduction.**—To a cooled suspension of 1.166 g. of the 11,12-dehydro compound IX, m.p. 151.5–157.5°, in 20 ml. of 100% formic acid, 0.41 ml. of 30% hydrogen peroxide was added with stirring. The stirred reaction mixture was maintained at 17–22°. After about 1 hr. the mixture had become completely homogeneous, and after a total of 4.3 hours, the solvent was removed by distillation at 20–30° under reduced pressure. The gummy residue was dissolved in benzene–ether and washed well with water, once with 5% sodium hydroxide solution, then thoroughly with 20% potassium bicarbonate solution and finally again with water. The solution was dried over anhydrous sodium sulfate and evaporated.

The gummy residue was dissolved in 30 ml. of absolute ethanol and poured into 300 ml. of liquid ammonia contained in a 1-l., 3-necked flask fitted with a Hershberg stirrer and a Dry Ice-cooled reflux condenser. With continued stirring a total of 8.4 g. of sodium was added in seven portions over a 1-hr. period. After the last of the sodium reacted as indicated by the disappearance of the blue color, most of the ammonia was allowed to evaporate, then the remainder removed by codistillation with ether. Cold water and

(22) In later work the m.p. was raised to 168–169° by elution of the analytical sample from a column of Florisil with 1:100 ether–benzene.

(23) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 619.

(24) In another run using 0.124 g. of the 11,12-dehydro compound, bicarbonate treatment at this stage, as described in part (a), gave approximately equal amounts (about 0.045 g.) of acidic and neutral fractions.

ether were added, the aqueous layer extracted with ether and the combined ether layers were washed thoroughly with water and dried over anhydrous sodium sulfate. The gummy residue obtained on evaporation of the ether partially crystallized. After boiling with 4 ml. of methyl ethyl ketone and cooling, the solid was separated and washed with cold methyl ethyl ketone and then with ether. The yield of diol was 0.338 g., m.p. 238–241°. Recrystallization from 95% ethanol and again from methyl ethyl ketone gave colorless micro-prisms, m.p. 240–241°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.4; H, 8.88.

The mother liquor yielded on evaporation 0.533 g. of gummy residue which was dissolved in 1:1 ether–benzene and chromatographed on 35 g. of Florisil. Gradual elution with petroleum ether–benzene, benzene, benzene–ether and ether afforded, in order, a total of 0.253 g. of the 8β-hydroxy compound (formula VI with H in place of Ac), m.p. 132–135°; 0.120 g. of the 8β,11α-dihydroxy compound XII, m.p. 149–154° resolidifying and remelting at 180°, undepressed on admixture with material prepared by lithium aluminum hydride reduction of the 11-keto compound (see below); and an additional 0.063 g. of the 8β,11β-dihydroxy compound, m.p. 236–240°. The diacetate, prepared with isopropenyl acetate and *p*-toluenesulfonic acid, after crystallization from 95% ethanol, melted at 195–198° alone or on admixture with material obtained by catalytic hydrogenolysis (see preceding experiment).

Lithium Aluminum Hydride Reduction of the Hydroxy Ketone X (R = H).[25]—A solution of 0.329 g. of the hydroxy ketone X (R = H), m.p. 181.4–182.6°, which is described below, in 25 ml. of purified (by distillation from lithium aluminum hydride) tetrahydrofuran was added slowly over a period of 1.75 hr. to a solution of 0.396 g. of lithium aluminum hydride in 25 ml. of purified tetrahydrofuran. This addition as well as a subsequent 2-hr. period of refluxing was conducted in an atmosphere of nitrogen. Ethyl acetate (5 ml.) was added to decompose the excess hydride, then 50 ml. of 2 *N* sulfuric acid was added and the aqueous layer extracted with ether. The combined organic layers were washed thoroughly with water until the washings were neutral to litmus. Ten milliliters of ethanol was added and the solution evaporated under reduced pressure. The residual yellow solid was chromatographed on 15 g. of Florisil. After elution in the usual manner, the early fractions of the 1:9 ether–benzene eluate yielded, after recrystallization from methyl ethyl ketone, a total of 0.0312 g. (9% yield) of the 8β,11β-dihydroxy compound, m.p. 241–243°, undepressed on admixture with the specimen of XI described above. Acetylation of a specimen with acetic anhydride and pyridine gave, after two recrystallizations from methanol, the diacetate, m.p. 193–197°, undepressed on admixture with, and having an infrared spectrum identical with that of, authentic material (see above).

The later 1:9 ether–benzene eluates yielded, after crystallization from ethyl acetate, a total of 0.274 g. (83%) of colorless needles of *trans-anti-trans*-1-methoxy-8β,11α-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XII), m.p. 179.5–183°. Repeated recrystallization of a specimen from another run (starting with the 3-acetoxy-11-keto compound X, R = Ac) gave material melting at 183–183.9°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.6; H, 9.02.

The diacetate of XII was prepared with acetic anhydride and pyridine at room temperature overnight. It was finally obtained from methanol as colorless needles, m.p. 179.5–180.7°, λ_{max} 5.8 μ (ester C=O).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.9; H, 8.23.

Osmium Tetroxide Oxidation of the 11,12-Dehydro Compound IX.—A solution of 0.075 g. of osmium tetroxide and 5 drops of pyridine in 1.5 ml. of dry methylene chloride was added to 0.047 g. of the 11,12-dehydro compound, m.p. 152–157°, in 3 ml. of methylene chloride. After 6 days at room temperature, the solvent was evaporated, and 5 ml. of water, 7 ml. of absolute ethanol, 1 ml. of benzene and 1 g. of sodium sulfite were added to the residue. The mixture was boiled under reflux for 4 hr., the black osmium precipitate separated by filtration and extracted with absolute ethanol. The combined filtrate and extracts were evaporated to dryness under reduced pressure. The residue was taken up in *n*-butyl alcohol and washed thoroughly with water until neutral to litmus. Evaporation of the solvent left a glassy residue probably consisting of a mixture of *trans-anti-trans*-1-methoxy-8β-acetoxy-10a-methyl-11β,12β-dihydroxy-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene and the free trihydroxy compound. Some of the former was eventually isolated as colorless needles by crystallization from methanol; yield 0.0082 g., m.p. 195–207°. After two recrystallizations from absolute ethanol, the m.p. was 211.5–214.5°.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.8; H, 8.29.

In another experiment a mixture of 0.340 g. of the 11,12-dehydroacetate IX, 50 ml. of absolute ether and 0.250 g. of osmium tetroxide was allowed to stand at room temperature. After 2 days the dark mixture was evaporated to dryness in a stream of nitrogen, the residue was dissolved in 10 ml. of absolute ethanol and poured into 100 ml. of liquid ammonia, then a total of 2.8 g. of lithium wire was added in portions over a 30-minute period. The crude product was isolated as described above for the preparation of XI (sodium reduction step). The ether extracts contained suspended osmium metal and were filtered carefully before drying over anhydrous sodium sulfate. The dark oily residue obtained upon evaporation of the ether deposited 0.100 g. of crude crystalline diol. Recrystallization from methyl ethyl ketone gave 0.050 g. of the 3β,11β-diol, m.p. 238–240°, undepressed on admixture with the authentic sample (see above).

***trans-syn-cis*-1-Methoxy-8β-12-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XV).**—A mixture of 1.05 g. of the *trans-syn-cis*-tetrahydro acetate XIV,[1] m.p. 130–132°, and 2.10 g. of lead tetraacetate in 1.0 ml. of acetic acid was heated on the steam-bath with occasional swirling for 35 minutes. At the end of this period, only a few crystals of lead tetraacetate remained undissolved, and a few drops of glycerol was added to consume the excess of the oxidizing agent. Water and ether were added, and the aqueous layer extracted with ether. The combined ether layers were washed with saturated sodium bicarbonate, then with saturated brine and finally dried over anhydrous sodium sulfate. The residue (1.28 g., m.p. 158–175°) obtained upon evaporation of the ether was crystallized from 95% ethanol to give 0.670 g. (first crop), m.p. 178–185°, and 0.078 g. (second crop), m.p. 172–184°, making the total yield 61%. Repeated recrystallization from 95% ethanol gave colorless prisms, m.p. 179–184° dec. (on the hot-stage) or 187–189° dec. (in an evacuated capillary), λ_{max} 275 mμ (log ε 3.44), 282 (3.45); λ_{min} 251 (2.76), 278 (3.43); λ_{max} 5.80 μ (ester C=O).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.9; H, 8.11.

In an experiment similar to that described directly above, 0.200 g. of the acetate XIV, m.p. 132–134°, was treated with 0.400 g. of lead tetraacetate in 0.5 ml. of acetic acid. The crude product (0.218 g., m.p. 150–154°) was chromatographed on 10 g. of Florisil. Elution with benzene gave 0.036 g. (18%) of starting material, m.p. 126–132°, which on recrystallization from 95% ethanol melted at 130–133° (undepressed on admixture with authentic XIV). Elution with 1:4 ether–benzene gave 0.156 g. (67%) of crude diacetate, m.p. 155–168°. The conversion of this material as well as the purer specimen (described above) to the 11,12-dehydro compound is described below.

***trans-syn-cis*-1-Methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (XVII).**—The first (0.670 g.) and second (0.078 g.) crops of the diacetate XV described in the first part of the preceding experiment were combined and dissolved in 10 ml. of acetic acid. The solution was heated for 2 hr. at 120°, the solvent evaporated in a current of air (steam-bath temperature) and the residue crystallized from 95% ethanol to give 0.520 g. (first crop), m.p. 138–140°, and 0.047 g. (second crop), m.p. 136–139°. The total yield was thus 89%, or 55% over-all from XIV. Repeated recrystallization from 95% ethanol gave small colorless needles, m.p. 143.5–144.5°, λ_{max} 269 mμ (log ε 4.01), 298 (3.75), 309 (3.71); λ_{min} 243 (3.52), 293 (3.67), 305 (3.67); λ_{max} 5.79 μ (ester C=O).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.5; H, 8.42.

(25) This experiment was carried out in part by Gerhard J. Fonken.

Occasionally a polymorphic form was encountered which melted at 120–121°, then resolidified and remelted at 137–140°.

When the 0.156-g. sample of the diacetate obtained by chromatography (see above) was heated in 3 ml. of acetic acid for 2 hr. at 120°, there was obtained (by the procedure just described) 0.083 g. (62% yield or 43% over-all from XIV) of the 11,12-dehydro compound, m.p. 139–143°.

Perbenzoic Acid Oxidation of the 11,12-Dehydro Compound XVII.—The following is a slight modification of a general procedure.[26] To a solution of 0.200 g. of the *trans-syn-cis*-11,12-dehydro compound, m.p. 139–142°, in 2 ml. of chloroform was added 1.4 ml. of 0.45 *M* perbenzoic acid in benzene. After standing at 0° for 25 hr., the mixture no longer contained peracid (starch–iodide test negative). Ether was added, the solution was washed twice with 10% potassium hydroxide solution, then with saturated brine and finally dried over anhydrous sodium sulfate. The colorless oily residue (0.26 g.) obtained upon evaporation of the solvent was chromatographed on 12 g. of Florisil. Elution with benzene gave 0.009 g. (4.5%) of starting material, m.p. 138–141°, undepressed on admixture with the 11,12-dehydro compound XVII. Elution with 1:12 ether–benzene gave 0.087 g. (31%) of crude benzoate, m.p. 165–192°. Crystallization from 95% ethanol gave 0.049 g. (17%) of *trans-syn-cis*-1-**methoxy-8β-acetoxy-10a-methyl-11-hydroxy - 12 - benzoyloxy - 4b,5,6,6a,7,8,9,10,10a,10b,11,-12-dodecahydrochrysene** (XVI, R = COC_6H_5), m.p. 198–200°. Repeated recrystallization from 95% ethanol gave small elongated plates, m.p. 198–200°, λ_{max} 226 mμ (log ε 4.31), 274 (3.58), 281 (3.56); λ_{min} 256 (3.20), 278 (3.55); λ_{max} 2.82 μ (OH), 5.80 (acetate C=O), 5.90 (benzoate C=O).

Anal. Calcd. for $C_{29}H_{34}O_6$: C, 72.78; H, 7.16. Found: C, 72.6; H, 7.27.

Further elution of the column (see above) with 1:3 ether–benzene gave 0.036 g. of colorless oil which was assumed to be impure (stereoisomeric ?) acetate benzoate and was combined with the oily residue from the mother liquors of the crystalline isomer described above.

Elution of the column with isopropyl alcohol gave 0.062 g. (28% yield) of crystalline *trans-syn-cis*-1-**methoxy-8β-acetoxy - 10a - methyl - 11,12 - dihydroxy - 4b,5,6,6a,7,8,9,-10,10a,10b,11,12-dodecahydrochrysene (XVI, R = H)**, m.p. 169–171°. Repeated recrystallization from benzene–petroleum ether (60–68°) gave small colorless elongated prisms, m.p. 170–172°, λ_{max} 272 mμ (log ε 3.24), 279 (3.29); λ_{min} 242 (2.71), 276 (3.15); λ_{max} 2.80 μ (free OH), 3.08 (bonded OH), 5.80 (C=O).

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.3; H, 8.05.

In another oxidation experiment the crystalline benzoate XVI (R = COC_6H_5) was isolated directly without chromatography as follows.

A mixture of 0.600 g. of the 11,12-dehydro compound, m.p. 138–140°, in 8 ml. of benzene and 5.0 ml. of 0.39 *M* perbenzoic acid in benzene was allowed to stand at 0° for 60 hr. The crude oily product (0.896 g.) isolated as described above was dissolved in 95% ethanol and seeded with the crystalline benzoate. On cooling 0.207 g. (24.5% yield) of this product crystallized, m.p. 198–200°, undepressed on admixture with the analytical specimen. The yield in another experiment was not improved by the addition of benzoic acid to the reaction mixture.

Formation of the *trans-anti-trans*-11-Keto Compound. (a) From the *trans-syn-cis*-Benzoates.—A 0.040-g. sample of the oily (*trans-syn-cis*) benzoate fraction from the perbenzoic acid oxidation described above was dissolved in 3 ml. of methanol, 10 ml. of concentrated hydrochloric acid was added and the mixture allowed to stand at room temperature for 1 day. Excess solid sodium bicarbonate was added to the blue solution, followed by water and ether. The aqueous layer was extracted with ether, and the combined ether layers were washed with saturated brine and dried over anhydrous sodium sulfate. The yellow oily residue obtained on evaporation of the solvent was chromatographed on 2.5 g. of Florisil. Elution with 1:9 and 1:4 ether–benzene gave a total of 0.017 g. (65% yield) of the crystalline *trans-anti-trans*-1-**methoxy-8β-hydroxy-10a - methyl - 11 - keto - 4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (X, R = H)**, m.p. 178–181°, giving a strong β-tetralone color test. Repeated recrystallization from 95% ethanol gave colorless prisms, m.p. 183–184°, λ_{max} 273 mμ (log ε 3.24), 279 (3.26); λ_{min} 253 (2.72), 276 (3.21); λ_{max} 2.86 μ (OH), 5.87 (C=O).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.2; H, 8.23.

This material appeared to separate with solvent of crystallization which was lost on warming at about 90°. Acetylation of a specimen of the hydroxy ketone with acetic anhydride and pyridine gave the acetate, m.p. 164–167°, in 80% yield. Recrystallization from methanol gave material, m.p. 166–168°, undepressed on admixture and having an identical infrared spectrum with the authentic *trans-anti-trans*-keto acetate described above. This keto acetate was obtained directly in 14% yield by pyrolysis of the benzoate XVI (R = COC_6H_5), m.p. 198–200°, as described above for the *trans-anti-trans* series. The chromatography also yielded some oily, less readily adsorbed, fractions that gave a strong β-tetralone color test, due possibly to some of the *trans-syn-cis*-ketone. In one pyrolysis experiment on total crude benzoate a small amount of material, m.p. 120–124°, giving the color test was isolated, but has not been examined further.

In another experiment a solution of 0.200 g. of the benzoate, m.p. 198–200° (see above), in 25 ml. of methanol was treated with 25 ml. of concentrated hydrochloric acid, and the mixture allowed to stand at room temperature for 60 hr. The product was isolated as described above, and the crude oily material was crystallized directly, without chromatography, from 95% ethanol to give 0.059 g. (first crop), m.p. 181–183°, and 0.012 g. (second crop), m.p. 180–182°. The total yield was thus 54%. The m.p. of the first crop material was not depressed on admixture with the authentic *trans-anti-trans*-hydroxy ketone (see above).

For the over-all preparation a mixture of 0.600 g. of the *trans-syn-cis*-11,12-dehydro compound, m.p. 137–140°, 8 ml. of chloroform and 6.0 ml. of 0.311 *M* perbenzoic acid in chloroform was allowed to stand at 0° for 48 hr. The solvent was evaporated in a current of air, the residue dissolved in 25 ml. of methanol and 25 ml. of concentrated hydrochloric acid was added slowly enough (15 minutes) so that the solution remained essentially homogeneous. After 6 days at room temperature, the black solution was treated as described above, to give 0.628 g. of crude brown semi-solid product. Recrystallization (without chromatography) from 95% ethanol gave 0.253 g. (first crop), m.p. 181–182°, and 0.012 g. (second crop), m.p. 180–182°. An additional 0.024 g. of hydroxy ketone, m.p. 179–181°, was obtained from the residues by chromatography on 15 g. of Florisil as described above. The total yield was thus 52%. The m.p. of the first crop material was not depressed on admixture with authentic *trans-anti-trans*-hydroxy ketone.

From the Dihydroxy Acetate XVI (R = H).—A solution of 0.016 g. of the dihydroxy acetate, m.p. 170–172° (see above), in 2 ml. of methanol was treated with 10 ml. of concentrated hydrochloric acid for 22 hr. at room temperature. The product was isolated as described above and chromatographed on 1 g. of Florisil. Elution with 1:4 ether–benzene gave 0.006 g. (46% yield) of material, m.p. 169–178°. Recrystallization from 95% ethanol gave 0.004 g. of *trans-anti-trans*-hydroxy ketone, m.p. 180–182°, undepressed on admixture with authentic material.

cis-anti-trans-1-**Methoxy-8α-hydroxy-10a-methyl-4b,5,6,-6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XIX, R = R′ = H). Potassium Reduction.**—This is essentially the procedure of Wilds and Nelson.[18] The *cis*-dihydro-8α-hydroxy compound XVIII[9] (30.50 g., m.p. 157–159°) was dissolved by warming in 100 ml. of dry tetrahydrofuran; then 450 ml. of anhydrous ether was added followed by 1 l. of liquid ammonia. While the homogeneous solution was stirred, a total of 36 g. of potassium was added in 8-g. pieces over a 5-minute period. The mixture was stirred for 20 minutes, then 90 ml. of absolute ethanol in 70 ml. of anhydrous ether was added dropwise over another 20-minute period. As soon as the blue color disappeared, most of the ammonia was evaporated (see above), benzene and ice-water were added and the aqueous layer extracted with benzene. The organic layers were washed with water, then combined and dried over anhydrous sodium sulfate. The

(26) D. Swern in R. Adams, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 396.

residue obtained upon evaporation of the solvents was crystallized from acetone–petroleum ether (32–35°) to give 23.11 g. of the tetrahydro alcohol, m.p. 154–157°.[9] A second crop amounting to 1.67 g., m.p. 154–156°, was obtained by crystallization of the mother liquor residues from a small volume of acetone. The same total yield (81%) was realized when the reaction was carried out on 105 g. of XVIII. In a 2-g. run in which the tetrahydrofuran was replaced by additional ether, the reduction product amounted to 1.46 g. (first crop), m.p. 148–153°, and 0.08 g. (second crop), m.p. 142–149°, or a total yield of 77%.

cis-anti-trans-**1-Methoxy-8α,12-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XIX, R = Ac, R′ = OAc).**—A solution of 1.60 g. of the *cis-anti-trans*-tetrahydro acetate XIX (R = Ac, R′ = H),[9] m.p. 113–115°, in 1.5 ml. of acetic acid was heated to 105°, the heating bath removed, 2.93 g. of lead tetraacetate added all at once and the exothermic reaction resulting in gentle boiling allowed to continue. The tetraacetate was consumed within 4 minutes as shown by the starch–iodide test. The solution was immediately cooled, diluted with water, extracted with ether and the ether layers washed thoroughly with water, then dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was chromatographed on 80 g. of Florisil. The fraction eluted with 1:9 ether–petroleum ether (65–68°) amounted to 0.305 g. of starting material, m.p. 104–110°. Elution with 2:8 ether–petroleum ether (65–68) gave 1.225 g. (66% yield) of crude diacetate, m.p. 140–155°, suitable for use in the next step. Recrystallization of the material from acetone and again from ether–petroleum ether (65–68°) gave colorless prisms, m.p. 164–166°, λ_{max} 274 mμ (log ε 3.39), 282 (3.38); λ_{min} 242 (2.20), 278 (3.36).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.3; H, 8.19.

cis-anti-trans-**1-Methoxy-8α-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (XX).** (a) **From the Diacetate XIX (R = Ac, R′ = OAc).**—A solution of 1.12 g. of the crude diacetate, m.p. 140–155° (see above), in 20 ml. of acetic acid was heated at reflux under nitrogen. After 16 hr., most of the solvent was evaporated under reduced pressure. On addition of methanol to the concentrate, 0.860 g. (first crop) of material, m.p. 143–146°, crystallized. A second crop amounting to 0.030 g., m.p. 135–144°, was obtained from the mother liquors. A specimen repeatedly recrystallized from absolute ethanol was obtained as colorless rods, m.p. 145–146°, λ_{max} 214 mμ (log ε 4.22), 225 (4.19), 268 (3.97), 298 (3.71), 308 (3.67); λ_{min} 222 (4.18), 242 (3.59), 291 (3.63), 305 (3.65).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.6; H, 8.27.

(b) **From XIX (R = Ac, R′ = H).**—A solution of 20.00 g. of crude acetate,[9] m.p. 111–114° (prepared by the acetic anhydride–pyridine method in 99% yield from the hydroxy compound, m.p. 153–156°, described above), in 50 ml. of glacial acetic acid was heated to 95°; then 34.0 g. of lead tetraacetate was added with vigorous stirring while the temperature was maintained below 110°. The addition required 5 minutes, and after an additional 10 minutes the lead tetraacetate had been completely consumed (negative starch–iodide test). Benzene was added and the solution washed thoroughly with water and dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was dissolved in 300 ml. of glacial acetic acid and heated on the steam-bath for 17 hr. under nitrogen. The solution was concentrated under reduced pressure to a volume of about 80 ml. On cooling, 13.89 g. of the 11,12-dehydro compound XX crystallized, m.p. 143–145°. Concentration of the mother liquors under reduced pressure and crystallization of the residue from methanol gave a second crop amounting to 2.06 g., m.p. 134–140°. The total yield was thus 80%.

cis-anti-trans-**1-Methoxy-8α,11β-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XXI).**—Fourteen milliliters (1.2 mole equivalents) of 0.209 *M* perbenzoic acid[26] in benzene was added to a solution of 0.835 g. of the 11,12-dehydro compound, m.p. 143–146°, in 10 ml. of benzene at 5°. After standing for 24 hr. at 5°, 0.7 g. of benzoic acid was added and the mixture kept at 5° for an additional 24 hr. The crude amorphous product, which was isolated as described above for the oxidation of XVII, amounted to 1.11 g. and exhibited log ε of 4.27 at 226 mμ (*cf.* the log ε of 4.31 at 226 mμ for pure monobenzoate (described above)).

The total crude monobenzoate was dissolved in 18 ml. of absolute ethanol and added to a solution of 1 g. of lithium in 350 ml. of liquid ammonia; then an additional 1.8 g. of lithium was added over a 30-minute period. The crude product which was isolated as described above in the preparation of XI (sodium reduction), amounted to 0.700 g. of an oil which crystallized on trituration with ether. In this way 0.470 g. of crude material, m.p. 181–184°, was obtained. Repeated recrystallization from acetone gave 0.170 g. of colorless plates, m.p. 192–193°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.9; H, 8.80.

The combined residues from the trituration and crystallizations amounting to 0.530 g. were chromatographed on 20 g. of Florisil. The fraction eluted with 2:8 ether–petroleum ether (65–68°) amounted to 0.130 g. of the hydroxy compound XIX (R = R′ = H), m.p. 153–158°. Elution with 3:7 ether–petroleum ether (65–68°) afforded an additional 0.235 g. of crude 11β-hydroxy compound, which on crystallization from acetone yielded 0.190 g. of fairly pure material, m.p. 189–191°.

Elution with 6:4 ether–petroleum ether (65–68°) gave 0.090 g. of crude *cis-anti-trans*-**1-methoxy-8α,11α-dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene**, which on recrystallization from acetone afforded 0.070 g. of colorless rods, m.p. 212–217°. Two additional crystallizations from acetone raised the m.p. to 220–221°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.9; H, 9.11.

Acetoxylation of *cis-syn-cis*-1-Methoxy-8α-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XXII, R = Ac).—One gram of the hydroxy compound XXII (R = H),[9] m.p. 124–126°, was dissolved in 20 ml. of pyridine, 10 ml. of acetic anhydride added and the solution heated on the steam-bath. After 10 minutes, the solution was cooled, poured onto ice and aqueous sodium bicarbonate and extracted with ether. The extracts were combined, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was adsorbed on 40 g. of Florisil and eluted with 3:7 ether–petroleum ether (65–68°) to give 1.02 g. of oil which showed no hydroxyl absorption in the infrared. This acetate was not obtained crystalline.

The 1.02 g. of oily acetate was dissolved in 1 ml. of acetic acid and acetoxylated with 2 g. of lead tetraacetate at steam-bath temperature. Heating was continued for 35 minutes until all of the reagent dissolved, a few drops of glycerol added, the solution cooled, water added and the mixture extracted with ether. The extracts were washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The pale yellow oil obtained upon evaporation of the solvent under reduced pressure was chromatographed on 40 g. of Florisil. Elution with 1:19 ether–petroleum ether (65–68°) gave 0.175 g. of oil (probably starting material), recognized by its identical ultraviolet absorption spectrum. Elution with 1:9 ether–petroleum ether (65–68°) gave 0.150 g. of 11,12-dehydro acetate XXIII (R = Ac) fraction. Crystallization from methanol yielded 0.060 g., m.p. 106–112°. Repeated recrystallization from methanol gave *cis-syn-cis*-**1-methoxy-8α-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (XXIII, R = Ac)** as large colorless prisms, m.p. 112–114°. In later runs a higher melting polymorphic modification was encountered, m.p. 143–143.5°, λ_{max} 221 mμ (log ε 4.25), 227 (4.25), 271 (3.91), 300 (3.65), 312 (3.62); λ_{min} 225 (4.24), 245 (3.47), 294 (3.60), 307 (3.58).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 77.61; H, 8.29. Found: C, 77.8; H, 8.48.

Further elution with 1:9 ether–petroleum ether (65–68°) gave 0.365 g. of crude 8,12-diacetoxy compound. Crystallization from petroleum ether (32–35°) yielded 0.240 g. of *cis-syn-cis*-**1-methoxy-8α,12-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene**, m.p. 123–126° dec. Several recrystallizations from the same solvent gave colorless platelets, m.p. 128–131° dec.

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.35; H, 8.12.

Preparation of the 11,12-Dehydro Compound XXIII (R = Ac) from the Diacetate.—A solution of 0.100 g. of the diacetate, m.p. 128–131°, described in the preceding experiment, in 2 ml. of acetic acid was heated at 110° for 70 minutes. The solvent was evaporated under reduced pressure and the residue crystallized from a small volume of methanol to give 0.077 g. of colorless prisms, m.p. 140–142°. Recrystallization from methanol yielded pure material melting at 143–143.5° alone or on admixture with the analytical specimen described above.

***cis-syn-cis*-1-Methoxy-8α-benzoyloxy-10a-methyl-4b,5,6,-6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XXII, R = C_6H_5CO).**—A 14.4-g. sample of the crude oily product containing the alcohol XXII (R = H), as obtained directly by lithium aluminum hydride reduction of the corresponding ketone,[9] was dissolved in 50 ml. of pyridine, the solution cooled to 5°, 21 g. of benzoyl chloride added with swirling and the mixture heated on the steam-bath. After 15 minutes the solution was cooled, and 50 ml. of pyridine was added followed by careful addition of 50 ml. of water. The mixture was heated on the steam-bath for another 30-minute period, an additional 50 ml. of water added and the solution concentrated to about 30 ml. at reduced pressure. The mixture was extracted with ether–benzene and the organic layers washed with dilute hydrochloric acid, water, saturated sodium bicarbonate, then dried over anhydrous sodium sulfate. The oily residue obtained upon evaporation of the solvent was crystallized from absolute ethanol to give 11.35 g. (first crop), m.p. 148–151°, and 0.81 g. (second crop), m.p. 144–148°, a total yield of 63%. A specimen repeatedly recrystallized from absolute ethanol was obtained as colorless prisms, m.p. 153–154°.

Anal. Calcd. for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 79.9; H, 7.78.

The ready separation of the benzoate (described above) from the C_8-epimeric mixture encouraged examination of other methods of reducing the ketone precursor of XXII (R = H). When the reduction was carried out by catalytic hydrogenation over platinum oxide, the benzoate, m.p. at least 144–150°, was isolated in 68% over-all yield. Reduction of the ketone by lithium and alcohol in ammonia afforded the benzoate, m.p. 145–149°, in 46% over-all yield. The benzoate, m.p. 145–149°, was prepared in 95% yield from pure alcohol XXII (R = H), m.p. 124–126°.

***cis-syn-cis*-1-Methoxy-8α-benzoyloxy-10a-methyl-4b,5,6,-6a,7,8,9,10,10a,10b-decahydrochrysene (XXIII, R = C_6H_5CO).**—A solution of 0.975 g. of the benzoate XXII (R = C_6H_5CO), m.p. 145–152°, in 1 ml. of acetic acid was treated with 1.34 g. of lead tetraacetate at 100° as described above for the *cis-anti-trans*-acetate. The reaction was complete in 5 minutes and the crude product isolated also as described above. Chromatography on 40 g. of Florisil gave on elution with 2% ether in petroleum ether (65–68°) 0.280 g. of starting material, m.p. 145–150°. Elution with 5% ether in petroleum ether (65–68°) afforded 0.420 g. of crude product which was crystallized from methanol to give 0.345 g. (36% yield) of 11,12-dehydrobenzoate, m.p. 93–98°. Repeated recrystallization from methanol gave colorless prisms, m.p. 98–99°.

Anal. Calcd. for $C_{27}H_{30}O_3$: C, 80.56; H, 7.51. Found: C, 80.3; H, 7.61.

Treatment of the Diacetate XXIV with Lead Tetraacetate.—A mixture of 0.395 g. of XXIV,[1] m.p. 172–178°, 0.590 g. of lead tetraacetate and 1 ml. of glacial acetic acid was stirred to effect solution and maintained at 70° for 20 minutes. The hot solution, which gave a negative starch–iodide test, was treated with 4 drops of ethylene glycol, cooled and diluted with water and ether. The ether layer was washed with water and evaporated. The residue (0.428 g.) was dissolved in 5 ml. of acetic acid and heated on the steam-bath for 6 hr. The residue obtained upon evaporation of the solvent was chromatographed on 20 g. of Florisil. The benzene eluate yielded after recrystallization from ether–petroleum ether (60–68°), 0.175 g. of colorless plates, m.p. 148–153°, λ_{max} 268 mμ (log ε 3.79), 298 (3.54), 308 (3.50). The spectrum and analysis indicate that this compound may be *syn-cis*-1-methoxy-8β-acetoxy-10a-methyl-4b,5,7,8,9,10,10a,10b-octahydrochrysene (XXVI).

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 77.8; H, 7.93.

Elution with 4:1 benzene–ether yielded, after recrystallization from ether–petroleum ether (60–68°), 0.100 g. of colorless needles, m.p. 178–183°, λ_{max} 268 mμ (log ε 3.99), 298 (3.75), 308 (3.70). This substance was probably *trans-syn-cis*-1-methoxy-6aα,8β-diacetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (XXV).

Anal. Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.05; H, 7.96.

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