

cence, m.p. 257.5–259° (after drying at 78° (0.5 mm.) for 2 hours), undepressed on admixture with chrysene.

Anal. Calcd. for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.91; H, 5.63.

(c) **Of the Tricyclic Ketone.**—A 0.5-g. sample of the distilled tricyclic ketone was treated with 0.5 g. of lithium aluminum hydride in a total of 150 ml. of anhydrous ether. After refluxing for 15 minutes and standing at room temperature for 1 hour, water was added followed by 70 ml. of 2 *N* sulfuric acid. The product was extracted with ether, the solvent evaporated, and the residual oil dehydrated by heating with 0.5 g. of potassium bisulfate at 160° for 7 minutes under an atmosphere of nitrogen. Evaporative distillation at 140–180° (0.1 mm.) gave 0.45 g. of pale yellow oil which was heated with 0.3 g. of 30% palladium-on-carbon²¹ at 348–352° for 2 hours and 25 minutes. A total of 1.9 moles of gas per mole of compound was evolved. The product was separated from the catalyst by dissolution in ether and filtration. Evaporation of the filtrate gave 0.217 g. of semi-solid material which was treated with 0.223 g. of picric acid in 3 ml. of a saturated solution of picric acid in ethanol. On cooling 0.17 g. of a picrate separated, m.p. 128–132°. Recrystallization from ethanol raised the m.p. to 138–144°. This material (0.1 g.) was dissolved in ethanol and passed through a column of alumina to decompose the picrate. The product was eluted with ethanol, the eluate evaporated, and the residue crystallized from methanol to give 0.025 g. of crystals, m.p. 114–118° (softening at 110°).

Recrystallization from 95% alcohol then again from dilute alcohol raised the m.p. to 119.8–121°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.40; H, 6.54.

The trinitrobenzene complex was obtained as yellow needles from ethanol, m.p. 177.1–178.3°. Kon and Soper¹⁴ report that 1-methoxy-8-methylphenanthrene melts at 121–121.5° and the trinitrobenzene derivative at 177–178°.

The dehydrogenation of 0.300 g. of the distilled tricyclic ketone with 0.0818 g. of sulfur was carried out between 170–215° for 47 minutes, then the temperature was raised to 250° during a 10-minute period and maintained there for 15 minutes. Evaporative distillation of the black product at 180–220° (1–2 mm.) gave 0.12 g. of a viscous oil which solidified immediately, m.p. 60–80°. It was dissolved in 15 ml. of 10% sodium hydroxide, filtered, 3 ml. of dimethyl sulfate was added, and the mixture shaken for 10 minutes, then heated on the steam-bath for 30 minutes. The organic material was taken up in chloroform, dried over calcium chloride and, after evaporation of the solvent, sublimed at 140–160° (0.05 mm.). The sublimate (0.012 g.) was recrystallized twice from alcohol to give 1,7-dimethoxy-8-methylphenanthrene (X, R = CH₃) as colorless rods, m.p. 182–183.2°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.09; H, 6.77.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. III.¹ Reduction of the Olefinic Bonds and of the Carbonyl Group in 1-Methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene

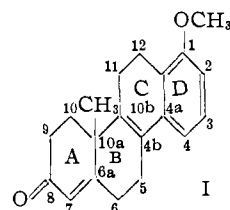
BY WILLIAM S. JOHNSON, E. R. ROGIER,² J. SZMUSZKOVICZ,³ H. I. HADLER,⁴ JAMES ACKERMAN,⁵ B. K. BHATTACHARYYA,⁶ BARRY M. BLOOM,⁷ L. STALMANN,⁸ ROBERT A. CLEMENT,^{9a} BRIAN BANNISTER^{9b} AND HANS WYNBERG¹⁰

RECEIVED MAY 31, 1956

Reduction of the olefinic bonds and the carbonyl group of the tetracyclic ketone I has been studied. Stereoselective reduction of the 6a,7-bond has given the A/B *trans*- and A/B *cis*-dihydro ketones IV and XI. The former on catalytic hydrogenation of the 4b,10b-(styrene) bond gives the *trans-anti-cis* ketone-A, and on lithium-alcohol-ammonia reduction of the corresponding ketal, V affords upon acid hydrolysis the *trans-anti-trans* ketone-B. The alcohol IX derived from ketone-B can be produced in a single step by lithium-alcohol-ammonia reduction of I. Similarly XI has led to the *cis-syn-cis* ketone-C and the *cis-anti-trans* ketone-D. In the reduction of the ketal XII a second isomer (XIV) was produced which afforded on hydrolysis what is probably the *cis-syn-trans* ketone-E. Some other approaches to these tetrahydro ketones or their reduction products are also reported, and the general stereochemical problem is discussed. The present study along with that described in paper IV has thus led to the synthesis and configurational assignment of 6 of the 8 possible 4b,6a,7,10b-tetrahydro derivatives of the tetracyclic ketone I.

In the preceding paper¹ the three-step synthesis (from 1,6-dimethoxynaphthalene) and the proof of structure of the tetracyclic ketone I are described. The present work is a report of a study of the selec-

tive reduction of the double bonds at the 6a,7- and the 4b,10b-position as well as of the carbonyl group at C₈.



The reduction of the 6a,7-bond is first considered. By analogy to the conversion of cholestanone into cholestanone (A/B *trans*),¹¹ the tetracyclic ketone was treated with ethyl orthoformate to produce the crystalline enol ethyl ether II, m.p. 136°, with λ_{\max} 227 $m\mu$ ($\log \epsilon$ 4.58), which is characteristic of the diene structure II and shows that the styrene

(11) H. H. Inhoffen, G. Stoeck, G. Kölling and U. Stoeck, *Ann.*, **568**, 52 (1950).

(1) Paper II, W. S. Johnson, J. Szmuszkovicz, E. R. Rogier, H. I. Hadler and H. Wynberg, *THIS JOURNAL*, **78**, 6285 (1956).

(2) Merck and Co., Inc., Postdoctoral Fellow, 1950–1952.

(3) Sterling-Winthrop Research Institute and Wisconsin Alumni Research Foundation Postdoctoral Fellow, 1948–1949; U. S. National Institutes of Health Postdoctoral Fellow, 1949–1950.

(4) Du Pont Grant-in-Aid Research Assistant, summers 1951 and 1952.

(5) Wisconsin Alumni Research Foundation and Sterling-Winthrop Research Institute Research Assistant, 1952–1954.

(6) Wisconsin Alumni Research Foundation Postdoctoral Project Associate, 1950–1951. On leave of absence from the College of Engineering and Technology, Bengal.

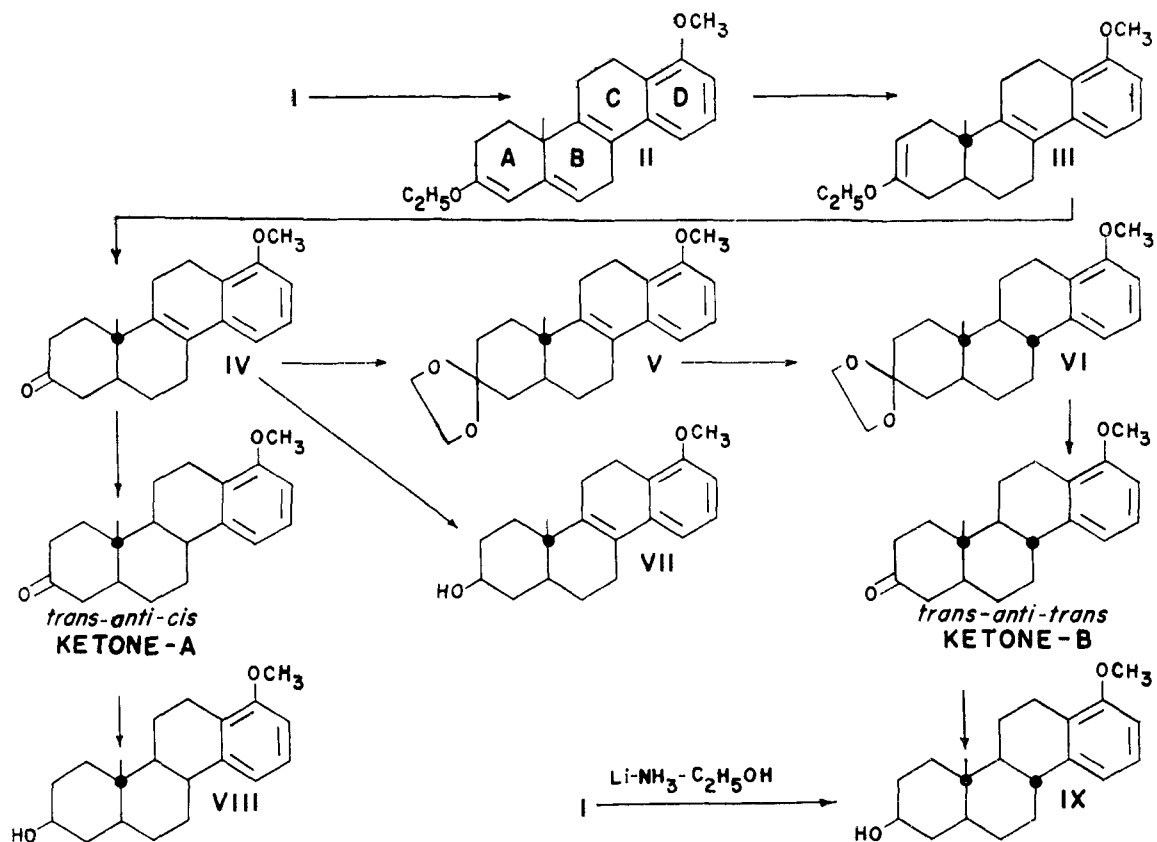
(7) National Research Council Postdoctoral Fellow, 1951–1952.

(8) Wisconsin Alumni Research Foundation Research Assistant, 1951–1952.

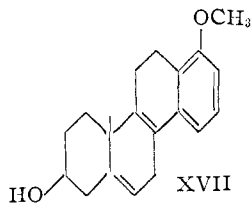
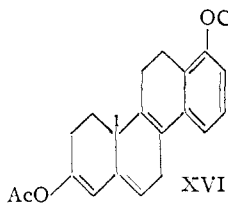
(9) National Science Foundation Postdoctoral Project Associate (a) 1954–1955; (b) 1953–1954.

(10) Sterling-Winthrop Research Fellow, spring 1951; Allied Chemical and Dye Co. Fellow, 1951–1952.

A/B TRANS SERIES

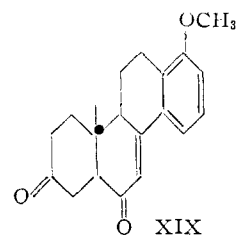
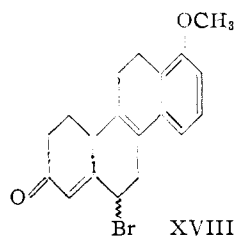


double bond remained at 4b,10b and had not migrated to the conjugated 4b,5-position. The structure was confirmed by hydrolytic regeneration of the tetracyclic ketone I. The 6,6a-double bond of the enol ether was selectively hydrogenated over palladium-on-strontium carbonate giving a product which did not appear to be homogeneous and probably consisted of a mixture of the dihydro enol ether with the double bond at 7,8 and 8,9. The latter (III), which is a rearrangement product of the former, corresponds to the structure that was established for the dihydro enol ether of cholestenone.¹¹ Acid hydrolysis of the dihydro enol ether gave a single product, m.p. 176°, which has been shown to be the expected A/B *trans*-dihydro ketone IV.¹² The ultraviolet spectrum of IV, λ_{\max} 222 and 265.5 $m\mu$, is typical of the *m*-methoxystyrene chromophore. The λ_{\min} at 244 $m\mu$ ($\log \epsilon$ 3.88) as compared with the intense absorption ($\log \epsilon$ about 4.35) for the tetracyclic ketone I clearly shows that the α,β -unsaturated ketone chromophore was



lost and that the 6a,7-double bond was indeed reduced.

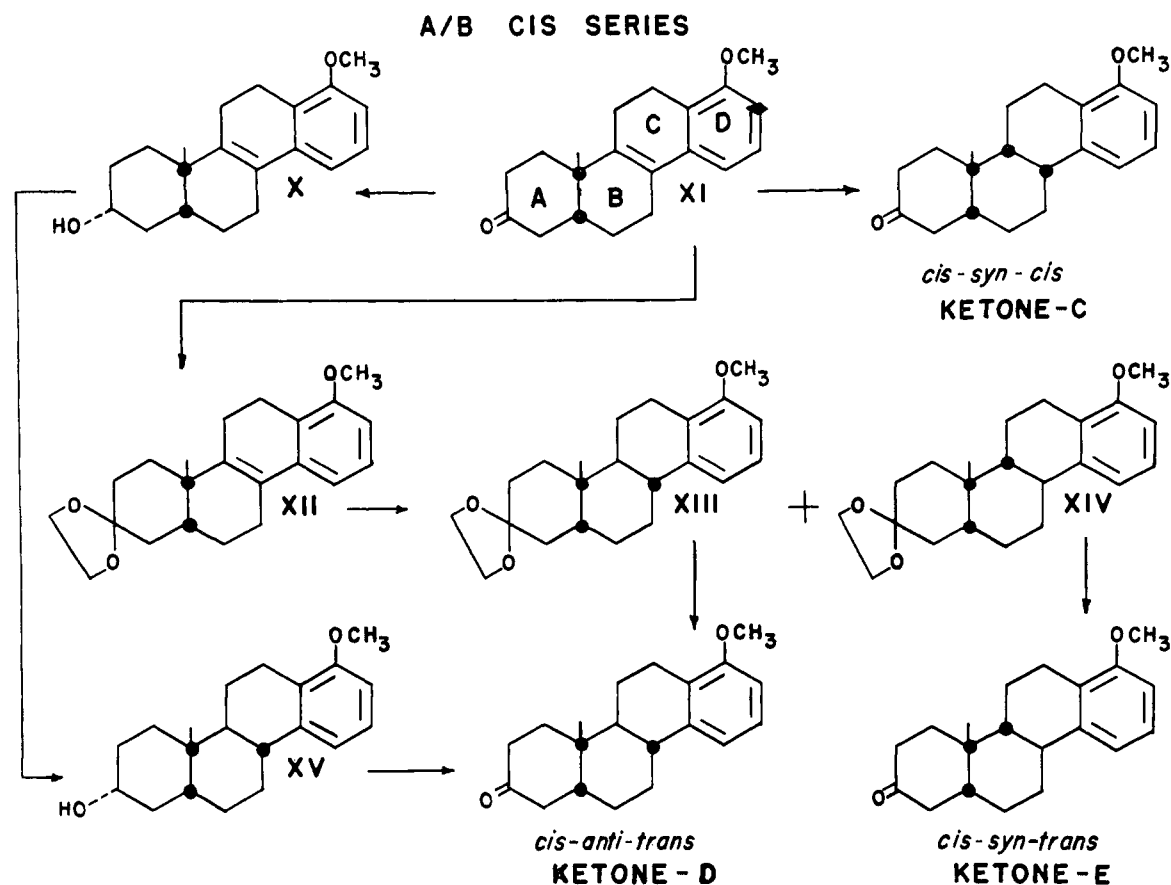
The enol acetate XVI, m.p. 138°, was formed readily from the tetracyclic ketone I. Reduction of XVI with sodium borohydride according to the procedure for the conversion of cholestenone enol acetate to cholesterol,¹³ yielded a dihydro alcohol characterized as the acetate. The structure is undoubtedly correctly represented by formula XVII by analogy to the cholesterol transformation¹³ and because the ultraviolet spectrum exhibits the *m*-methoxystyrene chromophore indicating that the olefinic bonds are unconjugated. It is interesting to note that the maximum in the 265 $m\mu$ region has a double peak at 267 and 272.5 $m\mu$. This change in fine structure presumably is due to a transannular influence of the unsaturation at 6,6a.



Treatment of the enol acetate XVI with N-bromoacetamide gave a monobromo ketone in over 60% yield. The substance was presumed to have

(12) Final confirmation of configuration rests in the ultimate conversion to epiandrosterone, paper VII.

(13) B. Belleau and T. F. Gallagher. *THIS JOURNAL*, **73**, 4458 (1951); W. G. Dauben and J. F. Eastham. *ibid.*, **73**, 4463 (1951).



the structure XVIII by analogy to the formation of 6-bromocholestenone from cholestenone enol acetate.¹⁴ The structure was substantiated by acid-catalyzed hydrolysis of the bromo compound to a diketone XIX, m.p. 215°.¹⁵ The double bond, originally at 4b,10b, evidently migrated into a position (4b,5) of conjugation with the 6-keto group as shown by the appearance of an intense maximum ($\log \epsilon$ 4.4) at 301 $m\mu$ in the ultraviolet spectrum.¹⁶ Although the melting point behavior was suggestive of impurities (perhaps stereoisomers), it is reasonable to assume that the preponderant form was that with the hydrogen atoms at C_{8a} and C_{10b} in the α -configuration thus defining the thermodynamically preferred *trans-anti* form (formula XIX). The diketone readily formed a monoketal, m.p. 222°, with ethylene glycol. As expected, the 8-

keto group was involved in ketal formation for the product still exhibited λ_{\max} at 301 $m\mu$ due to the conjugated system involving the 6-keto group.

Hydrogenation of the tetracyclic ketone I over palladium-on-carbon in the presence of a trace of potassium hydroxide resulted in stereoselective reduction to give a new dihydro ketone, m.p. 121°, in high yield. The ultraviolet spectrum was identical with that of IV showing only the *m*-methoxystyrene chromophore; hence the new stereoisomer must be the A/B *cis*-dihydro ketone XI, an expected product by analogy to the reduction of cholestenone to coprostanone.¹⁷

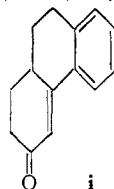
Bromination of the A/B-*cis*-dihydro ketone XI in acetic acid gave a mixture which contained a considerable proportion of the 7-bromo derivative because dehydrobromination by the Mattox-Kendall reaction¹⁸ gave the tetracyclic ketone I. The apparent selective bromination at C₇ is analogous to the preferential attack by this reagent at C₄ of coprostanone (A/B *cis*),¹⁹ and the configurations of the dihydro ketones were thus confirmed.

Both of the dihydro ketones IV and XI were reduced with lithium aluminum hydride. Although there was some doubt about the homogeneity of the crystalline hydroxy compounds produced, the preponderant material was presumed to correspond to VII (hydroxyl 8 β) and X (hydroxyl 8 α), respectively, by analogy to the steric course of

(14) (a) L. Ruzicka, *et al.*, *Helv. Chim. Acta*, **19**, 1147 (1936); (b) E. Dane, Y. Wang and W. Schulte, *Z. physiol. Chem.*, **245**, 80 (1937); (c) H. Reich and A. Lardon, *Helv. Chim. Acta*, **29**, 671 (1946); (d) J. von Euw and T. Reichstein, *ibid.*, **29**, 1913 (1946); (e) N. L. Wender and T. Reichstein, *ibid.*, **31**, 1713 (1948).

(15) Cf. the hydrolysis of 6-bromocholestenone-3 to cholestadiene-3,6, ref. 14c.

(16) Cf. the λ_{\max} at 288 $m\mu$ ($\log \epsilon$ 4.28) exhibited by 3-keto-1,2,3,9-10,10a-hexahydrophenanthrene (i): W. E. Bachmann and G. D. Johnson, *THIS JOURNAL*, **71**, 3463 (1949).



(17) H. Grasshof, *Z. physiol. Chem.*, **223**, 249 (1934).

(18) V. R. Mattox and E. C. Kendall, *THIS JOURNAL*, **72**, 2290 (1950).

(19) A. Butenandt and A. Wolf, *Ber.*, **68**, 2091 (1935).

the comparable reduction of cholestanone and coprostanone²⁰ to give the more stable epimers with an equatorial hydroxyl.²¹ It is noteworthy that the reduction product of IV gave a precipitate with digitonin while that from XI did not, which is consistent with the β - and α -orientation of the hydroxyl groups, respectively.^{20,22}

Of the eight possible stereochemical forms of the 4b,6a,7,10b-tetrahydro derivative of I, namely, ketones A-H, six have been obtained pure and the major portion of the work on the production and proof of configuration of these ketones and derivatives is described in the remainder of the present paper.

Catalytic hydrogenation of the A/B-*trans*-dihydro ketone IV over 30% palladium hydroxide-on-strontium carbonate proceeded stereoselectively to give the *trans-anti-cis* ketone-A, m.p. 187°. A small proportion (3%) of the *trans-anti-trans* ketone-B (described below) was isolated from mother liquors. Ketone-A also could be produced from the enol ether II by allowing the hydrogenation to proceed beyond the dihydro stage to reduce the styrene bond. Acid hydrolysis of the resulting tetrahydro enol ether gave ketone-A. The ultraviolet absorption spectrum of this ketone— λ_{\max} 271.5 μ ($\log \epsilon$ 3.09), 278.5 (3.13); λ_{\min} 243.5 (1.98), 275.5 (3.04)—is practically identical with that of 5-methoxytetralin showing clearly that the styrene bond was indeed reduced.

Reduction of ketone-A either with lithium aluminum hydride or by hydrogenation over platinum oxide proceeded stereoselectively yielding an alcohol, m.p. 134°. Although this substance gave only a trace of a precipitate with digitonin, the hydroxy group is undoubtedly β -oriented,²⁴ and the product is therefore represented by formula VIII. A slightly lower-melting substance which on admixture with VIII showed no m.p. depression was formed directly by palladium-catalyzed hydrogenation of the carbinol, m.p. 147°, obtained by the action of lithium aluminum hydride on the tetracyclic ketone I (see above).

When the A/B-*trans*-dihydro ketone IV was converted to the ethylene ketal V, m.p. 112°, and this derivative treated with lithium and alcohol in ammonia,²⁵ the 4b,10b-(styrene) double bond was reduced stereoselectively to produce VI, m.p. 124°, which on acid hydrolysis yielded a tetrahydro ketone, m.p. 211°, having an ultraviolet spectrum identical with that of ketone-A. This new isomer is the *trans-anti-trans* ketone-B.^{12,23} Ketone-B could also be obtained in somewhat lower yield by the Wilds-Nelson²⁵ lithium-ammonia-alcohol reduction of the dihydro enol ether III followed by acid hydrolysis. In the reduction of the ketal V described above, a small yield (1.3%) of an isomeric tetrahydro ketal, m.p. 138°, was isolated, and this

(20) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(21) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(22) Cf. L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 102.

(23) The arguments leading to the assignment of configuration are set forth in paper I, W. S. Johnson, *THIS JOURNAL*, **78**, 6278 (1956).

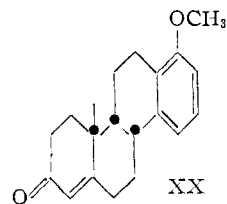
(24) Cf. references 20, 21 and 22.

(25) Following the general procedure of A. L. Wilds and N. A. Nelson, *THIS JOURNAL*, **75**, 5360 (1953).

on acid hydrolysis yielded ketone-A. When the ketal V was treated with lithium in ammonia at 140 p.s.i. and 25°, then with alcohol at atmospheric pressure, extensive demethylation as well as reduction occurred yielding a ketal phenol, m.p. 191°, which on acid hydrolysis afforded the *trans-anti-trans*-phenolic ketone, m.p. 235°, identical with the product produced by demethylation of ketone-B with hydriodic acid.

Lithium aluminum hydride reduction of ketone-B proceeded stereoselectively to give an alcohol, m.p. 124° or 137°, which gave a precipitate with digitonin. This substance is represented by formula IX in which the hydroxyl group is β -oriented.^{12,24} The best method of preparing this alcohol is by a one-step reduction of the tetracyclic ketone I with sodium or lithium and alcohol in ammonia (experiments performed in part by R. Pappo).²⁶ The product was conveniently isolated as the acetate, m.p. 146°, in 37-43% over-all yield from I.

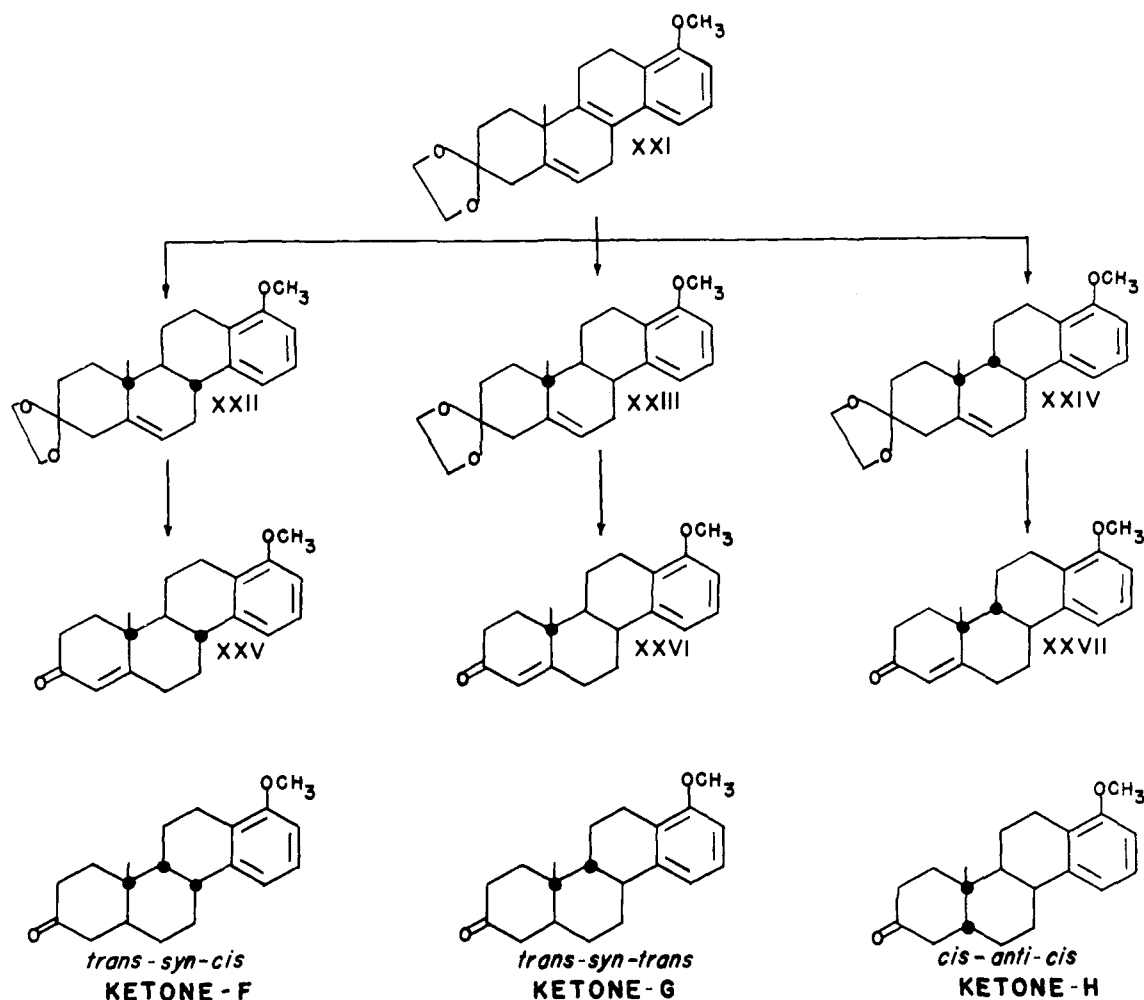
Catalytic hydrogenation of the A/B *cis*-dihydro ketone XI over 30% palladium hydroxide-on-strontium carbonate proceeded stereoselectively to give a new tetrahydro ketone, m.p. 104°, having an ultraviolet spectrum identical with that of ketone-A showing that the 4b,10b-(styrene) bond was reduced. The configuration has been proved²⁷ to be *cis-syn-cis* (ketone-C), which is reasonable *a priori* on the presumption that the absorption of XI on the catalyst surface is more hindered on the rear (α) side by the bending back of ring A than on the front (β) side by the angular methyl which, therefore, is the preferred side for hydrogenation. Ketone-C was also prepared by catalytic hydrogenation of the *syn-cis- α,β* -unsaturated ketone XX and this work is described in a later paper.²⁷ Lithium aluminum hydride reduction of ketone-C gave stereoselectively the corresponding alcohol, m.p. 125°, which failed to give a precipitate with digitonin. It is assigned the $\delta\alpha$ -configuration.²⁴



Conversion of the A/B *cis*-dihydro ketone XI to the ketal XII, followed by treatment with lithium and alcohol in ammonia²⁵ resulted in reduction of the 4b,10b-(styrene) double bond, as shown by ultraviolet spectroscopy, to produce a mixture of tetrahydro ketals, m.p. 110 and 211°. The former (XIII) which was the preponderant isomer, yielded on acid hydrolysis a new tetrahydro ketone, m.p. 136°, which proved (see below) to be the *cis-anti-trans* ketone-D. The 110° ketal is therefore correctly represented by formula XIII. The higher-melting ketal, probably XIV, yielded on hydrolysis

(26) Cf. the reduction of cholestanone to β -cholestanol, O. Diels and E. Abderhalden, *Ber.*, **39**, 884 (1906). We are indebted to Dr. L. H. Sarett for helpful advice in the matter of performing this type of reduction and applying it to the present case.

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



another tetrahydro ketone, m.p. 174°, which is tentatively formulated (see below) as the *cis-syn-trans* ketone-E. The ultraviolet spectra of both ketone-D and -E were identical with that of ketone-A. Reduction of ketone-E with lithium aluminum hydride gave a mixture of C₃-epimeric alcohols, m.p. 181 and 158°. The latter, but not the former, gave a precipitate with digitonin, and the alcohols are accordingly tentatively assigned the 8 β - and 8 α -configurations, respectively.²⁴

An alternate approach to the tetrahydro structure involved conversion of the tetracyclic ketone I to the ketal XXI, m.p. 117°, which like XVII exhibited a double λ_{\max} at 266 and 272 μ . This observation supports the placement of the olefinic bond at the 6,6a-position, which is also preferred by analogy to the established behavior of 3-keto-4-ene steroids on ketal formation.²⁸ Treatment of the ketal XXI with lithium and alcohol in ammonia²⁵ effected reduction of the 4b,10b-(styrene) double bond, as shown by the typical change in the ultraviolet spectrum, yielding a mixture of dihydro ketals from which an isomer, m.p. 150°, could be isolated in 65% yield. This preponderant product was shown to be the *anti-trans* compound XXII by the following transformations: Acid hydrolysis af-

forded an α,β -unsaturated ketone XXV, m.p. 155°, the 6a,7-double bond of which was reduced by hydrogenation over 5% palladium-on-carbon, to produce a mixture of two tetrahydro ketones, m.p. 211 and 137°. The former was identical with ketone-B, the configuration of which has been established unequivocally (see above). The 137° isomer must, therefore, have the *cis-anti-trans* configuration (ketone-D). Since it was identical with the substance produced by hydrolysis of the 110° ketal XIII obtained by lithium reduction of XII (see above), the configuration in the latter series was thus established. A particularly facile route to the *cis-anti-trans* series involves lithium-alcohol ammonia reduction of the carbinol X which gave the tetrahydrocarbinol XV, m.p. 155°, stereoselectively. Even better yields were realized when potassium was substituted for lithium.²⁹ Oppenauer oxidation of XV gave ketone-D.

In the metal-in-ammonia reduction of the ketal XXI described above, besides the major *anti-trans*-dihydro compound XXII, two stereoisomeric dihydro ketals, m.p. 186 and 193°, were isolated as by-products. The higher-melting stereoisomer was obtained from a reduction in which lithium was employed as described above, while the lower-melting

(28) See H. J. Dauben, Jr., B. Löken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954), and references cited therein.

(29) Paper V. W. S. Johnson, A. D. Kemp, R. Pappo, I. Ackerman and W. F. Johns, *ibid.*, **78**, 6312 (1956).

stereoisomer was found as the only by-product from the residues of several combined runs in which mainly sodium and potassium had been used. The factors influencing the preferential formation of one or the other of these by-products have not yet been ascertained, but it has been clearly demonstrated that the two substances are different, as the m.p. of a mixture of the two is depressed well below that of the 186° compound, and on acid hydrolysis they gave different and heretofore unknown α,β -unsaturated ketones melting at 178 and at 101°, respectively.

Since the *anti-trans* (m.p. 155°) and the *syn-cis* (m.p. 151°)²⁷ α,β -unsaturated ketones are known, the two new stereoisomers must represent the only two remaining possible configurations, namely, the *anti-cis* (XXVI) and the *syn-trans* (XXVII) α,β -unsaturated ketones, their ketal precursors being, respectively, XXIII and XXIV. The work with these α,β -unsaturated ketones is not yet complete, and it is therefore not possible to make a definite decision between the two assignments of configuration. The evidence at hand (see below), however, suggests that the 101 and the 178° compounds probably are represented by formulas XXVI and XXVII, respectively. Catalytic hydrogenation of the 178° α,β -unsaturated ketone afforded a mixture from which a tetrahydro ketone, m.p. 174°, was isolated by crystallization. This substance proved to be identical with the 174° ketone (see above) produced as a by-product in the lithium- and alcohol-in-ammonia reduction of the A/B *cis*-dihydro ketal XII. Since the catalytic reduction did not give the *trans-anti-cis*-ketone-A (m.p. 187°), which is the expected product from the *anti-cis*- α,β -unsaturated ketone XXVI, the 178° α,β -unsaturated ketone is tentatively assigned the *syn-trans* configuration XXVII. The ketal precursor (m.p. 186°) and the reduction product (m.p. 174°) accordingly may be provisionally represented as XXIV and ketone-E, respectively. Further work has not yet been carried out with the 101° α,β -unsaturated ketone, which by elimination is herewith tentatively assigned the *anti-cis* configuration (formula XXVI).

Of the eight possible racemic tetrahydro ketones, five (A-E) have been described above. One additional isomer, the *trans-syn-cis*-ketone-F has been prepared and is described in the sequel.²⁷ Future work should determine if the *trans-syn-trans*-ketone-G is present in the mother liquors of the reduction of the 178°, α,β -unsaturated ketone described in the preceding paragraph.

Acknowledgment.—We are grateful to the agencies named in references 2–10 for giving support to this research. We wish particularly to thank Drs. S. Archer, W. B. Dickinson, E. D. Homiller and C. M. Suter of the Sterling-Winthrop Research Institute for supplying us with generous quantities of intermediates.

Experimental^{30,31}

1-Methoxy-8-ethoxy-10a-methyl-5,9,10,10a,11,12-hexahydrochrysenes (II).—The following procedures through to

(30) The new substances described in this section are racemic compounds, but the prefix "dl" has been omitted. Melting points of analytical specimens are corrected for stem exposure. Those fol-

lowed by "(vac.)" were determined in a capillary evacuated to <0.2 mm.

the production of the ketone IV are based on those of Lu-hoffen, *et al.*,¹¹ for the preparation of cholestanone from cholestenone. A solution of 49.2 g. of tetracyclic ketone I, m.p. 173.5–175.5°, in 250 ml. of dry benzene, 25 ml. of absolute ethanol and 49 g. of ethyl orthoformate was confined to an atmosphere of nitrogen; then 4 ml. of a solution of 15% hydrogen chloride in absolute ethanol was added and the mixture heated under reflux. Two additional 1.5-ml. portions of the alcoholic hydrogen chloride solution were added after 3 hr. and then after 8 hr. After refluxing for a total of 22 hr., the mixture was cooled and shaken with 15 g. of sodium hydroxide dissolved in about 60 ml. of dilute alcohol. Water was added (and more benzene if the enol ether began to crystallize), the benzene layer separated and the aqueous layer extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution, water and dried over anhydrous magnesium sulfate. The pale yellow solid obtained on removal of the solvent was crystallized from a mixture of 115 ml. of benzene³² and 790 ml. of absolute ethanol containing 1 ml. of pyridine. The yield of enol ether which crystallized as pale yellow needles was 42.8 g. (80%), m.p. 133–138.5°. This product was satisfactory for the hydrogenation. A sample repeatedly recrystallized from absolute ethanol containing a trace of pyridine was obtained as pale greenish-yellow needles, m.p. 134–136°, λ_{\max} 227 m μ ($\log \epsilon$ 4.58).

Anal. Calcd. for C₂₂H₂₆O₂: C, 81.95; H, 8.13. Found: C, 81.8; H, 8.18.

Hydrolysis of the Enol Ether II.—To a boiling solution of 1.00 g. of the enol ether described above in 28 ml. of 95% ethanol and 2 ml. of benzene was added 0.5 ml. of concentrated hydrochloric acid in 9 ml. of water. After heating for 2 minutes the mixture was allowed to stand for a 2-day period at room temperature during which 0.78 g. (85% yield) of tetracyclic ketone I crystallized, m.p. 175–176°.

The oily residue from the mother liquors of a preparation of enol ether in which the yield was 64% was hydrolyzed as described above. Thus 12% of tetracyclic ketone was recovered. The remaining material was a red oil which may have contained material in which the 4b,10b-bond had migrated to the 4b,5-position.

1-Methoxy-8-ethoxy-10a-methyl-5,6,6a,7,10,10a,11,12-octahydrochrysenes (III).—A solution of 39.52 g. of the enol ether II in 177 ml. of 95% ethanol³² and 354 ml. of benzene³² was hydrogenated over 5.0 g. of 6% palladium-on-strontium carbonate³³ at room temperature and 30–35 (initial) p.s.i. The reaction was interrupted after the calculated amount (for one double bond) of hydrogen was absorbed, the mixture was filtered, and the filtrate evaporated. The oily residue was dissolved in 400 ml. of hot absolute ethanol containing a trace of pyridine, and on cooling 28.07 g. (71% yield) of crystals separated, m.p. 114–120°. This material was satisfactory for the next stage.

Material of comparable quality, m.p. 112–118°, from another run was purified by sublimation at low pressure and two recrystallizations from ethanol, m.p. 100–107°, λ_{\max} 217 m μ ($\log \epsilon$ 4.46), 269 (4.09); λ_{\min} 244 (3.62).

Anal. Calcd. for C₂₂H₂₆O₂: C, 81.44; H, 8.70. Found: C, 81.2; H, 8.69.

In a run in which 0.301 g. of the enol ether II in 5 ml. of methanol and 7 ml. of ether was hydrogenated over 0.20 g.

lowed by "(vac.)" were determined in a capillary evacuated to <0.2 mm.

(31) 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.

(32) Distilled from Raney nickel.

(33) This catalyst was prepared by the following procedure of D. K. Banerjee. A solution of 8.2 g. of palladium chloride in 50 ml. of water containing 8 ml. of concentrated hydrochloric acid was added to a stirred suspension of 77 g. of strontium carbonate (Merck and Co., Inc., U.S.P. grade) in 1.2 l. of water at 60°; then 8 ml. of 37% formaldehyde was added and the solution made strongly alkaline (to litmus) with 30% aqueous sodium hydroxide. The mixture was stirred for 5 minutes, allowed to stand and the supernatant liquid decanted. The catalyst was washed 8 times with distilled water by decantation, then collected on a Büchner funnel, washed well with distilled water and dried at 80°.

of 5% palladium-on-barium sulfate,³⁴ 0.12 g. (40% yield) of crude dihydro enol ether, m.p. 105–113°, was obtained after recrystallization from ethanol.

trans-1-Methoxy-8-keto-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysenes (IV).—To a boiling solution of 7.95 g. of dihydro enol ether III, m.p. 114–119°, in 10 ml. of benzene was added in succession 230 ml. of boiling 95% ethanol, 40 ml. of water, 4.5 ml. of 12 *N* hydrochloric acid and 35 ml. of water. The mixture was allowed to stand at room temperature for 5 hr., then for 2 hr. at 0°. The pale yellow crystals which separated were recrystallized from 40 ml. of *n*-butyl acetate giving 5.95 g. (82% yield) of prisms, m.p. 167–172°. Sublimation at 180–190° (0.05 mm.) gave 5.85 g. of material, m.p. 168–172°, of sufficient purity for hydrogenation to the tetrahydro ketone A (see below). A specimen repeatedly recrystallized from ethyl acetate was obtained as colorless prisms, m.p. 175.5–176°, λ_{max} 222 μ (log ϵ 4.49), 265.5 (4.14); λ_{min} 244 (3.88).

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_2$: C, 81.04; H, 8.16. Found: C, 81.2; H, 8.44.

In another run 21.8 g. of the dihydro enol ether was hydrolyzed as described above to yield 17.5 g. (88%) of crude IV, m.p. 167–174°, which was satisfactory for preparation of the ketal without further purification.

The oxime was obtained from 95% ethanol in the form of clusters of colorless crystals, m.p. 191.5–193° dec. or 208–209° (vac.).

Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{N}$: C, 77.13; H, 8.09. Found: C, 77.4; H, 8.14.

The 2,4-dinitrophenylhydrazone crystallized from *n*-butyl acetate in the form of bright orange platelets, m.p. 231–232° dec. upon insertion at 220°.

Anal. Calcd. for $\text{C}_{26}\text{H}_{28}\text{O}_6\text{N}_4$: C, 65.53; H, 5.92. Found: C, 65.5; H, 5.97.

1-Methoxy-8-acetoxy-10a-methyl-5,9,10,10a,11,12-hexahydrochrysenes (XVI).—This procedure was based on that of Westphal³⁵ for the preparation of cholestenone enol acetate. A solution of 0.84 g. of the tetracyclic ketone I in 2 ml. of acetic anhydride and 3 ml. of acetyl chloride was heated under reflux (nitrogen atmosphere) in an oil-bath at 95–105° for 2 hr. The mixture was cooled, the solvent evaporated at reduced pressure and the residue crystallized from absolute ethanol. The yield of crystals was 0.77 g., m.p. 135–138°. Evaporative distillation at 190° (0.07 mm.) followed by crystallization from absolute ethanol afforded greenish-yellow needles, m.p. 136.5–138.5°, λ_{max} 224 μ (log ϵ 4.61). This material was again evaporatively distilled before analysis.

Anal. Calcd. for $\text{C}_{22}\text{H}_{24}\text{O}_3$: C, 78.54; H, 7.19. Found: C, 78.4; H, 7.12.

1-Methoxy-8 β -hydroxy-10a-methyl-5,7,8,9,10,10a,11,12-octahydrochrysenes (XVII).—The following experiment represents an adaptation of the procedure of Belleau and Gallagher.¹³ A solution of 1.00 g. of the enol acetate XVI, m.p. 136–138°, in 100 ml. of 95% ethanol was cooled to 5° and added slowly to a stirred, cooled (ice-bath) solution of 2.54 g. of sodium borohydride in 65 ml. of 75% aqueous ethanol. After the addition was complete, 32 ml. of 10% sodium hydroxide solution was added, the mixture heated under reflux for about 30 minutes and then most of the solvent was removed at 60° (12 mm.). The product was taken up in ether, washed thoroughly with water and dried over anhydrous sodium sulfate. The oil (0.894 g.) obtained upon evaporation of the solvent was dissolved in 15 ml. of 95% ethanol, 0.3 ml. of concentrated hydrochloric acid was added and the mixture boiled under reflux in an atmosphere of nitrogen for 1 hr. The brown solution was neutralized with solid potassium carbonate, distilled at 80° (10 mm.) to remove alcohol and the residue extracted with ether. The ether solutions were washed thoroughly with water, dried over anhydrous sodium sulfate and concentrated. The yellow-red oily residue (0.890 g.) was crystallized from a concentrated ether solution by cooling in a Dry Ice-acetone-bath. The crystalline product after washing with ether amounted to 0.504 g. (57% yield), m.p. 72–75° with evolution of gas. This material appeared to contain solvent of crystallization. Crystallization from other solvents was not satisfactory.

(34) R. Mozingo, *Org. Syntheses*, **26**, 77 (1946).

(35) U. Westphal, *Ber.*, **70**, 2128 (1937).

The acetate, prepared with isopropenyl acetate and *p*-toluenesulfonic acid, was obtained as a colorless solid, m.p. 136–139°, in 98% yield (from crystalline carbinol) after chromatography on Florex. Three recrystallizations from diisopropyl ether (peroxide-free) gave colorless elongated prisms, m.p. 142–142.5°, λ_{max} 267 μ (log ϵ 3.96), 272.5 (3.98); λ_{min} 246 (3.62).

Anal. Calcd. for $\text{C}_{22}\text{H}_{26}\text{O}_2$: C, 78.07; H, 7.74. Found: C, 78.0; H, 7.72.

cis-1-Methoxy-8-keto-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysenes (XI).—A mixture of 5.00 g. of the tetracyclic ketone I, m.p. 175–176°, 0.10 g. of 10% palladium-on-carbon (American Platinum Works), 5 ml. of 95% ethanol,³² 50 ml. of benzene³² and 1 drop of 10% potassium hydroxide solution was agitated with hydrogen at room temperature and atmospheric pressure. In 1 hr. the absorption of gas ceased with the uptake of one mole equivalent. The mixture was filtered and the filtrate evaporated leaving 4.83 g. (96% yield) of crude *cis*-dihydro ketone, m.p. 117.5–119°. Recrystallization from 95% ethanol gave a product, m.p. 119.5–121°, in 86% recovery. A specimen which was repeatedly recrystallized from methanol was obtained as colorless blades, m.p. 123–124°.

Anal. Calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_2$: C, 81.04; H, 8.16. Found: C, 81.1; H, 8.52.

The 2,4-dinitrophenylhydrazone was obtained from ethyl acetate as small orange rods, m.p. 226.8–227.5° dec.

Anal. Calcd. for $\text{C}_{26}\text{H}_{28}\text{O}_6\text{N}_4$: C, 65.53; H, 5.92. Found: C, 65.2; H, 5.92.

In early experiments the *cis*-dihydro ketone XI was obtained in a less-stable modification, which after repeated recrystallization from petroleum ether (60–68°), melted at 97.6–99.1°, λ_{max} 221.5 μ (log ϵ 4.39), 267.5 (4.07); λ_{min} 243 (3.71). When this material was melted and then seeded with a specimen of the higher-melting form (m.p. 121–121.6°), the melt solidified and remelted at 120–122°.

When the hydrogenation of the 1.00 g. of tetracyclic ketone was carried out as above except that 1 drop of 48% hydrobromic acid was used instead of the potassium hydroxide, the reaction was slower (3 hr.), but the yield of recrystallized material, m.p. 117.5–119°, was comparable (0.89 g. or 88%).

cis-1-Methoxy-7-bromo-8-keto-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysenes.—The procedure of Butenandt and Dannenberg³⁶ for the bromination of androstenedione was used. A solution of 0.10 ml. of bromine in 20 ml. of glacial acetic acid was added over a period of 30 minutes to a solution of 0.594 g. of the *cis*-dihydro ketone XI, m.p. 119.5–120.5°, in 15 ml. of glacial acetic acid containing 4 drops of a 15% solution of hydrogen bromide in acetic acid. During the addition the temperature was maintained just above the solidification point of the reaction mixture. After the addition, the mixture was allowed to stand at room temperature for 2.75 hr., 75 ml. of water was added and the solid extracted with benzene. The organic layer was washed with water, 5% sodium bicarbonate solution, again with water, brine and dried over anhydrous magnesium sulfate. The residue, obtained upon evaporation of the solvent at 50° and reduced pressure, was crystallized from methanol-ethanol to give 0.263 g. of amorphous solid, m.p. 143–162°. Recrystallization gave 0.184 g. (25% yield) of pale yellow needles, m.p. 150–158°. Further recrystallizations did not alter the m.p. significantly. Such material, m.p. 150.4–157°, however, gave satisfactory analytical results.

Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_2\text{Br}$: C, 64.00; H, 6.18. Found: C, 63.8; H, 6.05.

Dehydrobromination.—The general procedure of Djerassi³⁷ was used. A solution of 0.034 g. of 2,4-dinitrophenylhydrazine in 2 ml. of acetic acid was added to a solution of 0.060 g. of the above bromo ketone, m.p. 148–155°, in 2 ml. of acetic acid. An atmosphere of nitrogen was maintained over the mixture by a slow stream of nitrogen. The mixture was heated on the steam-bath for 5 minutes, cooled and the gummy precipitate washed with a 1:5 chloroform-ethanol mixture. The crude 2,4-dinitrophenylhydrazone was dissolved in 3 ml. of chloroform and treated with 4 ml. of pyruvic acid, 1 ml. of water and 0.5 ml. of 15% hydrogen

(36) A. Butenandt and H. Dannenberg, *Ber.*, **69**, 1158 (1936).

(37) C. Djerassi, *This Journal*, **71**, 1003 (1949).

bromide in acetic acid. After standing under nitrogen for 3 hours at 60°, the mixture was diluted with benzene and washed with water, saturated sodium bicarbonate solution, again with water, brine and finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the solvent under a stream of nitrogen was sublimed at 160° (0.05 mm.) to give 0.0345 g. (73% yield) of yellow prisms, m.p. 150–160°. Crystallization from butyl acetate and then from methanol raised the m.p. to 167–168°. On admixture with authentic tetracyclic ketone, m.p. 171–173°, the m.p. was 167–170°.

trans-1-Methoxy-8 β -hydroxy-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysenes (VII).—To an ice-cold solution of 0.500 g. of the *trans*-dihydro ketone IV, m.p. 175–178°, in 20 ml. of dry purified dioxane and 60 ml. of dry ether was added with swirling 15 ml. of a solution of 0.257 M lithium aluminum hydride in ether over a period of 5 minutes. The mixture was boiled under reflux for 1 hr., cooled, 1 ml. of water cautiously added, and the granular precipitate which formed was washed by decantation with ether and benzene. The organic solutions were dried over anhydrous sodium sulfate and evaporated. The residue was crystallized from chilled acetone-ether to give 0.382 g. (76% yield) of colorless prisms, m.p. 86.4–94.8°. Repeated recrystallization of this product, which probably was contaminated with some of the 8 α -hydroxy epimer, did not improve the m.p.

Anal. Calcd. for C₂₀H₂₆O₂: C, 80.49; H, 8.78. Found: C, 80.1; H, 8.43.

The alcohol gave a precipitate with digitonin,³⁸ the crude digitonide melting at 175–225°.

The benzoate of VII prepared from benzoyl chloride and pyridine was crystallized from benzene-petroleum ether (60–68°) giving colorless prisms, m.p. 193.4–201.4° in 80% yield. Sublimation at 160° (0.05 mm.) followed by recrystallization gave material, m.p. 197.2–200.2°, in 63% yield. The purest specimen which was prepared after repeated recrystallization melted at 202.9–203.5°.

Anal. Calcd. for C₂₂H₃₀O₃: C, 80.56; H, 7.51. Found: C, 80.8; H, 7.54.

cis-1-Methoxy-8 α -hydroxy-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysenes (X).—A solution of 2.434 g. of the *cis*-dihydro ketone XI, m.p. 119.5–120.5°, in 20 ml. of dioxane and 70 ml. of ether was reduced with 45 ml. of a solution of 0.402 M lithium aluminum hydride in ether by the procedure described above for the *trans* isomer. The total crude product amounted to 2.45 g., m.p. 147.3–150.8°. Crystallization from benzene-petroleum ether (60–68°) gave 1.850 g. (76% yield) of colorless needles, m.p. 156–158° with previous softening. Repeated recrystallization from petroleum ether (60–68°) raised the m.p. to 158.5–159.1°, λ_{max} 222.5 m μ (log ϵ 4.37), 269 (4.06); λ_{min} 244.5 (3.71). This material failed to give a precipitate with digitonin.

Anal. Calcd. for C₂₀H₂₆O₂: C, 80.49; H, 8.78. Found: C, 80.3; H, 8.81.

The acetate prepared with acetic anhydride and pyridine was obtained in 92% yield after sublimation at 130° (0.05 mm.), m.p. 129–134°. Repeated recrystallization from acetone followed by sublimation at 130° (0.05 mm.) gave small colorless prisms, m.p. 126–126.8°.

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.61; H, 8.29. Found: C, 77.7; H, 8.29.

The benzoate prepared from benzoyl chloride and pyridine was crystallized from acetone-petroleum ether (60–68°) giving colorless prisms, m.p. 174.2–175.7° in 72% yield. Repeated recrystallization followed by sublimation at 160° (0.05 mm.) gave material, m.p. 173.1–173.6°.

Anal. Calcd. for C₂₇H₃₆O₃: C, 80.56; H, 7.51. Found: C, 80.4; H, 7.67.

The *cis*-8 α -hydroxy compound, m.p. 154.3–155.8° with previous softening, was isolated in 36% yield when the *cis*-dihydro ketone XI was hydrogenated over platinum oxide in dioxane containing a trace of concentrated hydrochloric acid.

1-Methoxy-6-bromo-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysenes (XVIII).—A cold solution of 0.495 g. of *N*-bromoacetamide and 0.90 g. of sodium acetate

(38) The procedure of Shoppee and Summers, ref. 20, was employed and the mixture examined for a precipitate after 1 day.

trihydrate in 1 ml. of acetic acid and 20 ml. of water was added dropwise with stirring to a cold (0°) solution of 1.00 g. of the enol acetate XVI, m.p. 134.5–137.5°, in 75 ml. of pure acetone containing one drop of pyridine. After the addition was complete (5 minutes), the mixture was allowed to stand for 40 minutes at 0°, then for 2 hr. at room temperature. The colorless product which separated on dilution with 45 ml. of water and cooling to 0° was washed on the filter with 95% ethanol; yield 0.734 g. (66%), m.p. 134–140° with decomposition and previous darkening. Two recrystallizations from ethyl acetate gave colorless plates, m.p. 135–140° with decomposition and previous darkening (beginning at 122°).

Anal. Calcd. for C₂₀H₂₁O₂Br: C, 64.35; H, 5.67. Found: C, 64.2; H, 5.51.

1-Methoxy-6,8-diketo-10a-methyl-6,6a,7,8,9,10,10a,10b,11,12-decahydrochrysenes (XIX).—A solution of 0.602 g. of the bromo ketone XVIII, m.p. 134–140° dec., in 50 ml. of absolute methanol was treated with 1.3 ml. of concentrated hydrochloric acid, and the mixture was boiled under reflux. After 2 hr., an additional 1.3 ml. of acid was added, and the heating continued for another 2-hr. period. The yellow solution was diluted with water, most of the methanol removed by distillation and the aqueous residue extracted with ether-benzene. The organic layer was washed with water, saturated sodium bicarbonate, again with water and dried over anhydrous magnesium sulfate. The pale orange oil remaining upon evaporation of the ether was triturated with ether-methanol to give 0.100 g. of cream-colored crystals, m.p. 200–205° with previous softening. An additional 0.048 g. of crystals was isolated by retreatment of the mother liquors. Successive recrystallizations from methylene chloride-ethanol and from *n*-butyl acetate, each followed by sublimation at 160° (0.03 mm.), gave colorless plates, m.p. 213–215° with softening at 203°. λ_{max} 241 m μ (log ϵ 4.2), 301 (4.4); λ_{min} 233 (4.1), 260 (3.8).

Anal. Calcd. for C₂₀H₂₂O₃: C, 77.39; H, 7.14. Found: C, 77.2; H, 7.20.

1-Methoxy-6-keto-8-ethylenedioxy-10a-methyl-6,6a,7,8,9,10,10a,10b,11,12-decahydrochrysenes.—A mixture of 0.560 g. of crude diketone XIX (several crops melting in the range of 180–194° were employed), 25 ml. each of benzene and of dioxane, 10 ml. of ethylene glycol and 0.10 g. of *p*-toluenesulfonic acid monohydrate was distilled very slowly in an atmosphere of nitrogen. During 1 hr., 10 ml. of distillate was collected, then 10 ml. of benzene was added and the distillation continued for 15 minutes to give an additional 7 ml. of distillate. The residue was cooled, washed thoroughly with excess 5% potassium carbonate solution, then with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was triturated with ether which effected crystallization. Recrystallization twice from acetone-methanol containing a trace of pyridine gave 0.206 g. of lemon-colored prisms, m.p. 221.5–222° (vac.). λ_{max} 241 m μ (log ϵ 4.1), 301 (4.4); λ_{min} 232 (4.0), 258 (3.6).

Anal. Calcd. for C₂₂H₂₈O₄: C, 74.55; H, 7.39. Found: C, 74.3; H, 7.41.

trans-anti-cis-1-Methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (A).—A suspension of 3.0 g. of 30% palladium hydroxide-on-strontium carbonate³⁹ in 100 ml. of benzene⁴⁰ and 100 ml. of 95% ethanol⁴¹ was shaken with hydrogen at room temperature and 30–40 p.s.i. until no more gas was absorbed (about 12 minutes). A solution of 12.16 g. of sublimed *trans*-dihydro ketone IV, m.p. 168–172°, in 100 ml. of benzene⁴² was then added and the shaking continued at room temperature and 30–40 p.s.i. After 2 hr. the hydrogenation had become very slow and approximately the calculated

(39) This catalyst was prepared by dissolving 3.81 g. of palladium chloride in about 100 ml. of boiling distilled water, then adding this solution to a rapidly stirred suspension of 10 g. of strontium carbonate (Merck and Co., Inc., N. F. grade, twice washed with distilled water) in about 400 ml. of distilled water at 80°. The stirred suspension was maintained at 80° until all of the palladium chloride precipitated as the hydroxide as indicated by a clear supernatant liquid (15 minutes). Stirring was stopped and after the precipitate settled, the supernatant liquid was decanted, and the residue was washed by decantation until free of chloride ion. The catalyst was finally collected on a sintered glass funnel, dried at 95° overnight and powdered in a mortar.

amount (for one double bond) of gas was absorbed. The mixture was filtered, the filtrate evaporated under reduced pressure and the colorless crystalline residue recrystallized from *n*-butyl acetate. The yield of colorless prisms obtained in the first crop was 9.37 g. (77%), m.p. 183.5–186.5° (vac.) with previous shrinking.

A specimen of this ketone A, m.p. 166–174° (in an open tube), obtained by hydrolysis of the ketal (see below) was recrystallized from ethyl acetate and then sublimed at 170° (0.03 mm.), m.p. about 166–174° (in an open tube) or 186.5–187.5° (vac.) with slight previous shrinking, λ_{\max} 271.5 $\mu\mu$ (log ϵ 3.09), 278.5 (3.13); λ_{\min} 243.5 (1.98), 275.5 (3.04). The spectrum of 5-methoxytetralin shows λ_{\max} 270.5 $\mu\mu$ (log ϵ 3.05), 278 (3.07); λ_{\min} 244 (2.99), 275.5 (2.42).⁴⁰

Anal. Calcd. for C₂₀H₂₆O₂: C, 80.49; H, 8.78. Found: C, 80.7; H, 8.77.

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate in the form of yellow micro-prisms, m.p. 215–216.5° with darkening (inserted at 200°).

Anal. Calcd. for C₂₈H₃₀O₅N₄: C, 65.26; H, 6.32. Found: C, 65.3; H, 6.35.

The oxime crystallized from methanol as colorless prisms, m.p. 192–195.5° (vac.). After sublimation at reduced pressure the m.p. was 196–199° (vac.).

Anal. Calcd. for C₂₀H₂₇O₂N: C, 76.64; H, 8.68. Found: C, 76.4; H, 8.32.

After standing for several months the mother liquor from the crystallization of ketone A (see above) deposited a second crop amounting to 0.38 g. (3.1% yield) of crystals, m.p. 195–201.5°. Two recrystallizations from *n*-butyl acetate followed by sublimation at 175° (0.01 mm.) gave material, m.p. 200–205.5°. The infrared spectrum was practically identical with that of the authentic *trans-anti-trans*-ketone B described below.

Ketone A was also produced by allowing the hydrogenation of the enol ether II of the tetracyclic ketone I as described above to proceed further to the tetrahydro stage. Thus from 0.871 g. of enol ether and 0.50 g. of 6% palladium-on-strontium carbonate³³ in 50 ml. of methanol, there was obtained after hydrolysis of the crude product with 20 ml. of ethanol and 16 drops of concentrated hydrochloric acid, 0.5 g. of crude ketone A, m.p. 164–170° (in an open tube), 166–180° after purification.

Hydrogenation of 0.300 g. of the dihydro enol ether III, m.p. 115.5–120°, over 0.1 g. of 30% palladium hydroxide-on-strontium carbonate³⁹ similarly gave after hydrolysis and recrystallization from ethyl acetate, 0.053 g. of ketone A, m.p. 168–178° (open tube). The oxime of this material melted at 194–195.5° (vac.) after recrystallization from methanol.

The ethylene ketal of ketone-A was prepared from 0.72 g. of ketone, 0.04 g. of *p*-toluenesulfonic acid monohydrate in 40 ml. of dry toluene and 6.5 ml. of ethylene glycol. The mixture was heated so that slow distillation occurred over a 7-hr. period during which fresh toluene was added to maintain the original volume. A total of 115 ml. of distillate was collected. The mixture was allowed to cool, washed several times with saturated sodium bicarbonate solution and then with water. The aqueous layers were extracted with ether and the combined organic layers dried over anhydrous magnesium sulfate. The colorless crystalline product remaining after removal of the solvents at reduced pressure was crystallized from methanol-acetone to give 0.61 g. (74% yield) of ketal, m.p. 131–133.5°. Two recrystallizations from methanol-acetone gave long colorless blades, m.p. 135.5–137.5°, λ_{\max} 270.5 $\mu\mu$ (log ϵ 3.12), 278.5 (3.14); λ_{\min} 243.5 (2.19), 275.5 (3.06).

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 76.8; H, 8.71.

To a boiling solution of 0.23 g. of the above ketal, m.p. 136.5–138.5°, in 5 ml. of 95% ethanol, water was added to the point of incipient cloudiness, then 3 drops of concentrated hydrochloric acid. On cooling to room temperature the solution deposited 0.18 g. (90% yield) of ketone-A, m.p. 166–174° (in an open tube). This material was used to prepare the analytical specimen described above.

(40) Private communication from N. A. Nelson; see Ph.D. Thesis, University of Wisconsin, 1952.

trans-anti-cis-1-Methoxy-8 β -hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (VIII).—A mixture of 3.00 g. of the tetrahydro ketone-A, m.p. 181.5–184.5° (vac.), and 30 ml. of dry benzene was warmed to effect dissolution, then 100 ml. of dry purified dioxane and 150 ml. of dry ether were added. A solution of 2.7 g. of lithium aluminum hydride in 100 ml. of dry ether was then added slowly with stirring over a 45-minute period. After the addition, the mixture was heated under reflux for 4.5 hr. and allowed to stand overnight at room temperature. Dilute sulfuric acid (8 ml. of concentrated acid in 200 ml. of water) was added cautiously, the layers separated, the aqueous portion extracted with ether and the combined organic layers dried over anhydrous magnesium sulfate. The oily residue obtained on removal of the solvent at reduced pressure was crystallized from benzene-petroleum ether (100–120°) to yield 2.61 g. (86% yield) of the carbinol, m.p. 132–134°. Repeated recrystallization gave colorless blades, m.p. 130.5–132.5°, λ_{\max} 271 $\mu\mu$ (log ϵ 3.14), 278 (3.15); λ_{\min} 243.5 (2.05), 275 (3.10).

Anal. Calcd. for C₂₀H₂₈O₂: C, 79.95; H, 9.39. Found: C, 80.2; H, 9.44.

This substance gave only a trace of a precipitate with digitonin.

The acetate, prepared with acetic anhydride and potassium acetate in acetic acid, crystallized from dilute ethanol in the form of colorless blades, m.p. 109–109.5° (75° yield). Two additional recrystallizations raised the m.p. to 109.5–110°.

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 77.1; H, 8.83.

Catalytic hydrogenation of 1.00 g. of ketone-A in 20 ml. of 95% ethanol and 40 ml. of benzene³² over 0.20 g. of platinum oxide proceeded to completion (calculated amount of gas absorbed) in 70 minutes at room temperature and 35 (initial) p.s.i. Crystallization of the product from benzene-petroleum ether (100°) gave 0.62 g. (62% yield) of the carbinol VIII, m.p. 135–136°. A second crop of crystals, 0.22 g., melted higher, 141–159°, and was not further investigated.

1-Methoxy-8 β -hydroxy-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysenes.—A solution of 2.00 g. of the tetracyclic ketone I, m.p. 169.7–172.2°, in 40 ml. of dioxane and 150 ml. of ether was reduced with 0.01 mole of lithium aluminum hydride in 25 ml. of ether. The procedure was essentially the same as that described above for the reduction of the *trans*-dihydro ketone IV to VII. After crystallization from acetone-petroleum ether (60–68°) the product amounted to 1.26 g. (63% yield), m.p. 150.4–154.2°, probably a mixture of C₈-epimers. Recrystallization of this material from aqueous ethanol gave plates which melted and resolidified between 100 and 110°, then remelted at 140.5–142.5°. Occasionally a form, m.p. 138–145°, was obtained from acetone-petroleum ether. Repeated recrystallization from aqueous ethanol gave small colorless plates which after drying for 20 hr. at 55° (0.05 mm.) melted at 146.5–147°, λ_{\max} 222 $\mu\mu$ (log ϵ 4.37), 268.5 (4.06); λ_{\min} 244 (3.67).

Anal. Calcd. for C₂₀H₂₄O₂: C, 81.04; H, 8.16. Found: C, 81.0; H, 8.38.

The benzoate, prepared with benzoyl chloride and pyridine, crystallized from acetone-petroleum ether (60–68°) in the form of colorless prisms, m.p. 153.2–154.6°.

Anal. Calcd. for C₂₇H₂₈O₃: C, 80.96; H, 7.05. Found: C, 80.8; H, 7.03.

Hydrogenation of *1-Methoxy-8 β -hydroxy-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysenes*.—A solution of 1.18 g. of the carbinol, m.p. 147.6–151.1°, in 50 ml. of 95% ethanol³² was treated with some 5% palladium-on-carbon catalyst³⁴ and the mixture allowed to stand overnight. The catalyst was removed by filtration and the filtrate shaken with hydrogen at room temperature and atmospheric pressure in the presence of 0.355 g. of 6% palladium-on-strontium carbonate.³³ After 2 hours the calculated (for two double bonds) amount of hydrogen was absorbed, and the reaction was interrupted. The mixture was filtered, the filtrate evaporated and the residue crystallized from chilled acetone-ether to give 0.307 g. (26% yield) of colorless needles, m.p. 125.4–128.8°. Repeated recrystallization from acetone-petroleum ether (60–68°) and sublimation at 130° (0.05 mm.) gave material, m.p. 129.8–132.5°, undepressed

on admixture with the *trans-anti-cis*-tetrahydrocarbinol VIII, m.p. 132–134°, described above. The 129.8–132.5° compound had λ_{max} 270.5 μ ($\log \epsilon$ 3.08), 278 (3.10); λ_{min} 243.5 (2.03).

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{O}_2$: C, 79.95; H, 9.39. Found: C, 79.9; H, 9.32.

A 0.300-g. sample of the 129.8–132.5° carbinol was oxidized by the Oppenauer method according to the procedure described below for the oxidation of XV. After crystallization 0.152 g. (50% yield) of colorless needles, m.p. 147–157° (in an open tube), was obtained. Repeated recrystallization from benzene–petroleum ether (60–68°) gave material m.p. 147–157° or 185.2–187° (vac.), undepressed on admixture with the sample of ketone-A described above.

trans-1-Methoxy-8-ethylenedioxy-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-dodecahydrochrysenes (V).—A solution of 22.7 g. of the *trans*-dihydro ketone IV, m.p. 167–172°, and 1.2 g. of *p*-toluenesulfonic acid monohydrate in 1.2 l. of dry toluene and 200 ml. of ethylene glycol was boiled under reflux with an arrangement for partial take-off. During 4 hr., 400 ml. of distillate was collected, then an additional 50 ml. of ethylene glycol and about 0.4 g. of *p*-toluenesulfonic acid were introduced. Refluxing was continued for 4 hr. more during which 200 ml. of distillate was collected. The product was isolated as described above for the ethylene ketal of ketone A. The crude product was crystallized from a mixture of 15 ml. of acetone and 250 ml. of methanol. The yield of colorless needles, m.p. 110–111°, was 21.0 g. (81%). On repeated recrystallization of a sample from another run, the m.p. was 111.5–112°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_3$: C, 77.61; H, 8.29. Found: C, 77.6; H, 8.09.

The residue obtained from the other liquors of the above crystallization was hydrolyzed at room temperature overnight with dilute ethanolic hydrochloric acid. The product after recrystallization from *n*-butyl acetate amounted to 2.12 g. (9% recovery) of crude starting ketone, m.p. 162–167°.

The ethylene ketal V was also prepared directly from the dihydro enol ether III. Thus from 25.62 g. of the latter, m.p. 116–120°, and 1.60 g. of *p*-toluenesulfonic acid monohydrate in 950 ml. of dry toluene and 200 ml. of ethylene glycol there was obtained, after a total of 21 hr. of refluxing (0.4 g. of additional acid being added after 17 hr.) and crystallization from acetone–methanol, 19.36 g. (72% yield) of ketal, m.p. 105–107.5°. The recovered ketone, m.p. 163–168.5°, amounted to 4.26 g. (18%).

trans-anti-trans-1-Methoxy-8-ethylenedioxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (VI).²⁶—A solution of 3.40 g. of the *trans*-dihydro ketal V, m.p. 110–111°, in 300 ml. of dry ether was placed in a 1-l. three-necked flask equipped with a sealed wire stirrer, a Dry Ice condenser capped with a soda lime drying tube and a stopcock sealed to the bottom for draining the flask. The third neck was kept stoppered except when reagents were added. Liquid ammonia (400 ml.) was added rapidly, stirring was started (cautiously at first) and 3.40 g. of lithium wire cut into small (1–2 cm.) lengths was added to the homogeneous solution. A few pieces were first added; then when the solution became completely blue, the remainder was added as fast as possible without loss of liquid through the condenser. (In order to observe the contents of the flask, a portion of the frost was removed from the outside with acetone.) After the addition was complete, stirring was continued for 15 minutes, then the reaction mixture was drained into a 2-l. beaker containing 33 ml. of absolute ethanol, and the mixture was stirred until all of the blue color disappeared. The ammonia was evaporated by gentle warming on a steam-bath.

The above procedure was repeated 10 times, and the residues remaining after evaporation of the ammonia were combined. Water was added, the ether layer separated and the aqueous layer extracted twice with ether. The combined ether solutions were washed with water until neutral and dried over anhydrous magnesium sulfate. The residue (usually crystalline) obtained upon evaporation of the solvent was recrystallized from a mixture of 375 ml. of acetone and 750 ml. of methanol containing a few drops of pyridine. The first crop amounted to 21.30 g. (62% yield) of colorless blades, m.p. 123–124°. The mother liquor upon chilling deposited a second crop amounting to 6.57 g. (19% yield), m.p. 121.5–122.5°. A third crop obtained by

evaporation and recrystallization of the gummy residue from 150 ml. of methanol amounted to 2.64 g. (8% yield), m.p. 109–119°. Repeated recrystallization of a specimen from another run gave colorless prisms, m.p. 123.5–124.5°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_3$: C, 77.15; H, 8.83. Found: C, 77.2; H, 8.81.

In another run one of the later crops melted at 135.7–137.5°. Recrystallization from acetone–methanol gave (1.3% yield) material, m.p. 136–138°, undepressed on admixture with the ketal of the *trans-anti-cis*-ketone (A), m.p. 135.5–137.5°, described above. Acid hydrolysis of the 136–138° material gave ketone-A, m.p. 187–187.5° (vac.), after recrystallization from ethyl acetate.

In one experiment in which dimethyl Cellosolve was employed instead of ether, the ketal VI was obtained in another modification which melted partially at 121–123°, then resolidified at 125° and remelted completely at 132–133°. Acid hydrolysis of the material yielded ketone-B, m.p. 199.5–204.5°.

trans-anti-trans-1-Methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (B). (a) *From the Ketal VI.*—To a solution of 23.17 g. of the ketal VI, m.p. 123.5–124.5°, in 460 ml. of boiling 95% ethanol was added 38 ml. of water, followed by a solution of 2.6 ml. of concentrated hydrochloric acid in 20 ml. of 95% ethanol, then finally an additional 20 ml. of water. Crystallization began within 1 minute, and the mixture was allowed to stand at room temperature for 5 hr., then at 0° for 3 hr. The yield of ketone B of sufficient purity for reduction to the alcohol was 19.53 g. (97%), m.p. 202–203.5° (inserted at 197°). A specimen, after two recrystallizations from *n*-butyl acetate followed by sublimation at 180° (0.01 mm.), was obtained as colorless prisms. It melted at 211–211.5° (vac.) with previous softening and rehardening at about 207° suggesting the existence of an unstable lower-melting form. Remelting of the same sample showed no previous softening, λ_{max} 271 μ ($\log \epsilon$ 3.13), 278.5 (3.14); λ_{min} 244 (2.10), 275 (3.08).

Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_2$: C, 80.49; H, 8.78. Found: C, 80.1; H, 8.83.

The oxime crystallized from *n*-butyl acetate in the form of colorless elongated prisms, m.p. 234–236° (vac.) with softening and darkening at 228° (tube introduced at 220°).

Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{O}_2\text{N}$: C, 76.64; H, 8.68. Found: C, 76.3; H, 8.34.

The 2,4-dinitrophenylhydrazone was obtained from *n*-butyl acetate in the form of bright orange crystals, m.p. 231–231.5° dec. (inserted at 220°).

Anal. Calcd. for $\text{C}_{26}\text{H}_{30}\text{O}_6\text{N}_4$: C, 65.25; H, 6.32. Found: C, 65.7; H, 6.24.

(b) *From 1-Methoxy-8-ethoxy-10a-methyl-5,6,6a,7,10,10a,11,12-octahydrochrysenes* (III).—The *trans*-dihydro enol ether III was reduced by the method described above. Thus from 3.24 g. of dihydro enol ether, m.p. 114–117°, treated in 240 ml. of dimethyl Cellosolve, 140 ml. of ether and 400 ml. of ammonia with 3.24 g. of lithium and 37 ml. of ethanol, there was obtained upon crystallization of the oily product from absolute ethanol (trace of pyridine), 1.69 g. (52% yield) of the *trans-anti-trans*-tetrahydro enol ether, m.p. 104–108°. This material was employed for the hydrolysis described below. Material of this quality on repeated recrystallization from methanol–benzene (trace of pyridine) melted at 118–119°. When this product was sublimed at 120° (0.04 mm.) the melting point was raised to 141–147°. Further recrystallization gave material, m.p. 152.5–153°. The m.p. on admixture with the 118–119° material was 106–113°, suggesting that migration of the olefinic bond may have occurred during sublimation. A sample of sublimed material, m.p. 149.4–151°, was analyzed.

Anal. Calcd. for $\text{C}_{22}\text{O}_3\text{O}_2$: C, 80.93; H, 9.26. Found: C, 80.8; H, 9.35.

A solution of 1.69 g. of the tetrahydro enol ether, m.p. 104–108°, described above in 45 ml. of boiling 95% ethanol was treated with 5.5 ml. of water followed by 0.9 ml. of concentrated hydrochloric acid. After standing for 3 hours at room temperature and overnight at 0°, the crystalline precipitate amounted to 1.32 g. (86% yield), m.p. 196.5–202.5°. Recrystallization from *n*-butyl acetate gave 1.23 g., m.p. 203.5–206.5°.

trans-anti-trans-1-Hydroxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes. (a) By the Action of Lithium on V.—A mixture of 0.100 g. of the *trans*-dihydro ketal V, m.p. 108–110°, 10 ml. of dimethyl Cellosolve, 25 ml. of liquid ammonia and 0.100 g. of lithium was enclosed in a steel bomb and allowed to stand at room temperature for 2 hr. (pressure *ca.* 140 p.s.i.). The bomb was opened, the ammonia allowed to evaporate, water added and the product extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, concentrated and the residue crystallized from dilute methanol giving 0.04 g. (42% yield), of *trans-anti-trans-1-hydroxy-8-ethylenedioxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes* as a tan solid, m.p. 172–174°. Two recrystallizations raised the m.p. to 173–174.5°. On sublimation at 170–180° (0.04 mm.) the colorless product melted at 190.4–191.8° with softening at 188° (possibly polymorphic with the 174° material).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.1; H, 8.78.

In another run the mother liquors from the first crystallization afforded (22% yield) a second crop of material, m.p. 124–138°, which was probably impure ketal of ketone B.

A specimen of the ketal phenol was hydrolyzed in aqueous methanolic hydrochloric acid to yield the keto phenol as fine needles, m.p. 218–221° dec. Two successive sublimations at 220° (0.1–0.2 mm.) raised the m.p. to 234–235.2 (vac.).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.3; H, 8.61.

(b) By Demethylation of Ketone-B.—A solution of 0.50 g. of ketone-B, m.p. 202.5–206.5°, in 6 ml. of glacial acetic acid and 0.3 ml. of 56% hydriodic acid (freshly distilled from red phosphorus) was heated at reflux in an atmosphere of nitrogen for 30 minutes. The mixture (containing a crystalline precipitate) was cooled, poured into an aqueous solution of sodium bisulfite and the precipitate collected and washed with water. This crude product (0.47 g.) was crystallized from benzene-petroleum ether (90–100°) and then sublimed at 190–200° (0.01 mm.) to give 0.025 g. of phenolic ketone, m.p. 235.5–236.5° (vac.), undepressed on admixture with the analytical specimen described above.

trans-anti-trans-1-Methoxy-8 β -hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (IX). (a) From Ketone-B.—A solution of 25.9 g. of lithium aluminum hydride in 680 ml. of dry ether was added over a 30-minute period to a stirred, refluxing suspension of 25.24 g. of finely powdered ketone-B, m.p. 204.5–206°, in 300 ml. of dry dioxane, 300 ml. of dry ether and 100 ml. of dry benzene. The mixture was heated under reflux for 5 hr., cooled, ethyl acetate added to decompose the excess lithium aluminum hydride, then a solution of 78 ml. of concentrated sulfuric acid in 1 l. of water was cautiously added. The aqueous layer was extracted with ether, and the combined ether solutions were washed with saturated sodium bicarbonate solution, with water and dried over anhydrous magnesium sulfate. The residue remaining upon evaporation of the solvent at reduced pressure was crystallized from 180 ml. of petroleum ether (60–68°) containing a trace of ethyl acetate. The yield of product, m.p. 117.5–122°, was 21.35 g. (84%). This substance exists in two polymorphic forms. Thus when the above material was recrystallized from ethyl acetate-petroleum ether (60–68°) 18.92 g. of material, m.p. 136.3–137°, was obtained. In another similar run a 76% yield of colorless needles, m.p. 123.5–124.5°, was obtained after three recrystallizations from benzene-petroleum ether (60–68°).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.1; H, 9.48.

On standing, the lower-melting form changes over to the higher-melting modifications. Both forms have given the same acetate described below.

The acetate was prepared in 93% yield (m.p. 146–149°) with isopropenyl acetate and a trace of *p*-toluenesulfonic acid in benzene. After repeated recrystallization from ethyl acetate and sublimation at 140° (0.07 mm.), it was obtained as colorless prisms, m.p. 151.3–152.3°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.8; H, 8.82.

(b) Directly from the Tetracyclic Ketone I.⁴¹—A 20.00-g. sample of the tetracyclic ketone, m.p. 175–176.5°, was dissolved in 300 ml. of warm anhydrous dimethyl Cellosolve, and this solution was poured slowly with vigorous stirring into 5 l. of liquid ammonia (du Pont de Nemours and Co.). Absolute ethanol (500 ml.) was then added, followed immediately by 11 g. of cut lithium wire which was introduced over a 2–3 minute period. The ketone, which was partly out of solution at the beginning of the reduction, had completely dissolved by this time. Additional lithium (21 g.) was then added over a 15–20 minute period. As soon as the blue color of the metal in ammonia disappeared, the mixture was warmed on the steam-bath to drive off ammonia, a total of 2.5 l. of ether being added in two portions as the mixture became thick to facilitate removal of ammonia by codistillation. The mixture was cooled, diluted with about 2 l. of water (cautiously) and ether and the aqueous layer extracted with ether. The combined ether layers were washed with water, dried over anhydrous sodium sulfate and concentrated.

The combined oily residue (103 g.) from five runs carried out as described above were crystallized from 1 l. of ether to give 57.2 g. of crude carbinol, m.p. 134–136°. A second and third crop obtained from the mother liquor amounted, respectively, to 20.5 g., m.p. 123–126°, and 2.6 g., m.p. 111–119°. These crops were combined and dissolved in 400 ml. of isopropenyl acetate by refluxing. The mixture was cooled, 4 g. of *p*-toluenesulfonic acid was added and dissolved by swirling, and the slightly cloudy solution was allowed to stand at room temperature overnight, then at 0° for 24 hr. The crystalline precipitate was separated and washed with ether. The yield of the acetate of IX was 42.6 g. (37%), m.p. 145–146°. A small insoluble impurity was removed by adding to a solution of this product in the smallest volume of ethyl acetate, 500 ml. of hot 95% ethanol and filtering the mixture after it cooled to 40°. Concentration and cooling gave 41 g. (35% yield) of acetate, m.p. 146–148°.

In preliminary experiments in which sodium was employed instead of lithium, yields as high as 43% of material, m.p. 148–150°, were realized when the product was isolated by chromatography on Florex. The large-scale procedure has the advantage that no chromatography is required. A sample obtained from a reduction with sodium, after chromatography, sublimation at 136° at high vacuum and recrystallization from ethanol melted at 149–150.5°. The m.p. was not depressed on admixture with the acetate described above (part a).

As expected, the *trans*-dihydro ketone IV, as well as ketone-B, both yielded the 8 β -hydroxy compound IX on reduction with sodium and alcohol in liquid ammonia. The products melted at 126–127° and 127–128°, respectively, and exhibited no depression of the m.p. upon admixture with carbinol prepared as described above (part a).

cis-syn-cis-1-Methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (C).—A solution of 2.25 g. of the *cis*-dihydro ketone XI, m.p. 119.5–121°, in 30 ml. of 95% ethanol³² and 30 ml. of benzene³² was hydrogenated over 0.50 g. of 30% palladium hydroxide-on-strontium carbonate³⁹ at room temperature and atmospheric pressure. The uptake stopped after 2 hr., 96% of the calculated amount of gas being absorbed. The mixture was filtered and the filtrate evaporated to give 2.04 g. of residue, m.p. 76–92°. The remaining material was undoubtedly adsorbed on the catalyst. Recrystallization of 1.16 g. of the material from 95% ethanol gave 0.725 g. of ketone-C, m.p. 97–102°, λ_{max} 271 (log ϵ 3.16), 278 (3.19); λ_{min} 244 (2.37); 275 (3.13). Comparable material from another run was recrystallized from petroleum ether (60–68°), then from methanol to give colorless prisms, m.p. 103–105°. The m.p. was not depressed on admixture with ketone-C prepared *via* reduction of XX²⁷ in which the *syn-cis* configuration has been established.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.2; H, 8.96.

The semicarbazone was obtained from absolute ethanol as colorless microcrystals, m.p. 217–219° dec.

Anal. Calcd. for $C_{21}H_{26}O_2N_3$: C, 70.95; H, 8.22. Found: C, 70.6; H, 8.28.

(41) Procedure from experiments performed in part by R. Pappo.

The crude ketone-C is obviously contaminated with material (stereoisomers) which is difficult to eliminate by recrystallization. Mother liquors from first crop material did not yield more ketone-C, and semicarbazones as well as 2,4-dinitrophenylhydrazones from the residue appeared to be non-homogeneous.

cis-syn-cis-1-Methoxy-8 α -hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes.—A solution of 0.725 g. of ketone-C, m.p. 97–102°, in 25 ml. of dioxane, 10 ml. of benzene and 50 ml. of ether was treated with 10 ml. of 1 *M* lithium aluminum hydride as described above for the preparation of the *trans-anti-trans* 8 β -hydroxy compound IX except that the mixture (which was homogeneous in this case) was refluxed for only 30 minutes. The crude product was chromatographed on 20 g. of F-20 Alcoa activated alumina. Recrystallization of the fraction which was eluted with 2:3 chloroform-benzene, from petroleum ether (60–68°) gave 0.450 g. (62% yield) of the carbinol, m.p. 122–124°, undepressed on admixture with the analytical specimen, m.p. 125–127°, prepared by saponification of the acetate described elsewhere.²⁷ This carbinol failed to give a precipitate with digitonin.³⁸

cis-1-Methoxy-8-ethylenedioxy-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-dodecahydrochrysenes (XII).—A mixture of 1.00 g. of the *cis*-dihydro ketone, m.p. 117–119°, 9 ml. of ethylene glycol, 50 ml. of toluene and 0.04 g. of *p*-toluenesulfonic acid monohydrate was slowly distilled. Each time 10 ml. of distillate was collected, 10 ml. of fresh toluene was added to the reaction mixture, and this process was continued for 4 hr. Then 1 ml. of ethylene glycol and about 10 mg. of acid catalyst were added, and the distillation operations continued for an additional 2 hr. The product was isolated essentially as described above for the ketal of ketone-A. The crude oily product was evaporatively distilled at 0.01 mm. After a forerun of 0.10 g. was collected at 125–130°, there was obtained 1.00 g. (87% yield) at 140–150°. A second evaporative distillation of a portion of this fraction gave a colorless glass.

Anal. Calcd. for C₂₂H₂₈O₃: C, 77.61; H, 8.29. Found: C, 77.9; H, 8.30.

Lithium Reduction²⁵ of the *cis*-Dihydro Ketal XII.—Approximately 220 ml. of ammonia was added carefully to a solution of 2.23 g. of the ketal (produced as described above) in 210 ml. of anhydrous ether. Lithium wire (0.190 g.) was added with stirring, and after dissolution was complete, the dark green-colored solution was stirred for 20 minutes, then an excess of absolute ethanol was added dropwise and the ammonia evaporated by warming. The mixture was diluted with water, the aqueous portion extracted with chloroform and the combined organic layer dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was crystallized from ethyl acetate to give 0.392 g. of *cis-syn-trans*⁴²-1-methoxy-8-ethylenedioxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (XIV), m.p. 209–211°. Recrystallization from ethyl acetate gave colorless blades, m.p. 211.5–212°. This material sublimed readily at 165° (0.01 mm.).

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 77.6; H, 8.87.

The mother liquor from the 209–211° material was evaporated and the residue crystallized from petroleum ether (60–68°) giving 0.793 g. of *cis-anti-trans-1-methoxy-8-ethylenedioxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes* (XIII), m.p. 108–110°. Repeated recrystallization gave colorless prisms, m.p. 110.2–110.8°.

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 77.4; H, 8.78.

In one run the crude ketal, m.p. 110–115°, on four recrystallizations from methanol gave small colorless rods, m.p. 122.8–123.5° with shrinking at 121°. This appeared to be a polymorphic form of the 110° material as on admixture the m.p. was 110.2–123°.

Anal. Calcd. for C₂₂H₃₀O₃: C, 77.15; H, 8.83. Found: C, 76.7; H, 8.74.

*cis-syn-trans*⁴²-1-Methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (E).—A mixture of 0.250 g. of the ketal XIV, m.p. 210–212°, 10 ml. of

dry acetone and a few crystals of *p*-toluenesulfonic acid monohydrate was heated for 4 hr. on the steam-bath. Water was added dropwise to the point of incipient cloudiness. The crystals obtained on cooling amounted to 0.210 g., m.p. 171–173°. A specimen was recrystallized twice from absolute ethanol to give colorless needles, m.p. 173.5–174.5°, λ_{max} 271 m μ (log ϵ 3.20), 278.5 (3.20); λ_{min} , 244 (2.20), 275.5 (3.15).

Anal. Calcd. for C₂₀H₂₆O₂: C, 80.49; H, 8.78. Found: C, 80.5; H, 8.58.

The semicarbazone crystallized from absolute ethanol in the form of fine colorless needles, m.p. 243–244° dec. (introduced at 200°).

Anal. Calcd. for C₂₁H₂₆O₂N₃: C, 70.95; H, 8.22. Found: C, 70.7; H, 8.44.

Hydrolysis of the *cis-anti-trans* Tetrahydro Ketal XIII.—A specimen of the ketal, m.p. 110.2–110.8°, was hydrolyzed under the conditions described above. After recrystallization from benzene-petroleum ether the product melted at 134–136° and gave no depression of the m.p. on admixture with authentic ketone-D, m.p. 134–136.2°, described below.

*cis-syn-trans*⁴²-1-Methoxy-8-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes. —A solution of 0.200 g. of ketone-E, m.p. 173–174°, in 10 ml. of dioxane and 20 ml. of ether was treated with a solution of 0.06 g. of lithium aluminum hydride in 4 ml. of ether. The mixture was heated under reflux for 1 hr. and the product isolated essentially as described above for the *trans*-dihydro compound VII. Repeated recrystallization of the crude product from benzene-petroleum ether (60–68°) and from methanol eventually gave material melting at 176–180°. After sublimation in high vacuum it was obtained as colorless micro crystals, m.p. 178–181°. On treatment with digitonin³⁸ it did not form an appreciable precipitate, and the compound is accordingly tentatively assigned the 8 α -hydroxy configuration.

Anal. Calcd. for C₂₀H₂₈O₂: C, 79.95; H, 9.39. Found: C, 79.7; H, 9.33.

From the more soluble fractions in the crystallization of the 176–180° material, a second isomer was isolated as colorless prisms, m.p. 157.6–158.2°, after repeated recrystallization from benzene-petroleum ether (60–68°). On treatment with digitonin,³⁸ a noticeable precipitate formed. The compound is therefore tentatively assigned the 8 β -hydroxy configuration.

Anal. Calcd. for C₂₀H₂₈O₂: C, 79.95; H, 9.39. Found: C, 79.9; H, 9.45.

When the carbonyl group of ketone-E was reduced with hydrogen over platinum oxide in 95% alcohol containing a trace of acetic acid, a comparable mixture of carbinols was produced.

1-Methoxy-8-ethylenedioxy-10a-methyl-5,7,8,9,10,10a,11,12-octahydrochrysenes (XXI).—A mixture of 1.83 g. of the tetracyclic ketone I, m.p. 173.5–175.5°, 92 ml. of toluene, 0.073 g. of *p*-toluenesulfonic acid monohydrate and 16 ml. of ethylene glycol was very slowly distilled, fresh toluene being added to the reaction mixture at frequent intervals to maintain the starting volume. After 6 hr. a total of 100 ml. of distillate had been collected. The mixture was cooled, washed thoroughly with saturated sodium bicarbonate solution, water, and dried over anhydrous magnesium sulfate. The gummy residue obtained on evaporation of the solvent was crystallized from petroleum ether (60–68°) to give 1.52 g. (72% yield) of ketal, m.p. 117.5–118.5°. Recrystallization from acetone-methanol afforded colorless platelets, m.p. 119–119.7°. In early experiments the ketal was obtained in a colorless microcrystalline form, m.p. 102–103.2°, λ_{max} 220 m μ (log ϵ 4.44), 266 (4.03), 272 (4.04); λ_{min} 245 (3.61), 268 (4.02). Recrystallization of such material gave upon seeding with the higher melting modification a product, m.p. 116.5–117.5°. The lower-melting form was analyzed.

Anal. Calcd. for C₂₂H₂₆O₃: C, 78.07; H, 7.74. Found: C, 78.2; H, 8.17.

Lithium Reduction²⁵ of the Ketal XXI.—A solution of 2.00 g. of the ketal, m.p. 118–119°, in 200 ml. of dry ether was added cautiously to 400 ml. of liquid ammonia contained in a flask equipped with a Dry Ice condenser and wire stirrer. To the stirred solution 2.1 g. of lithium wire (cut into small pieces) was added rapidly, the resulting deep blue

(42) Tentative configuration.

solution stirred 45 minutes, then 20 ml. of absolute ethanol added dropwise with continued stirring. The ammonia was allowed to boil off (steam-bath), 100 ml. of water added to dissolve the ethoxide and the aqueous layer extracted with ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent left a colorless oil (λ_{\max} 271, 278 μ), which crystallized on cooling. Crystallization from diisopropyl ether gave 1.35 g. of material, m.p. 143–148°. Recrystallization gave 0.884 g. (44% yield) of *anti-trans*-1-methoxy-8-ethylenedioxy-10a-methyl-4b,5,7,8,9,10,10a,10b,11,12-decahydrochrysenes (XXII) as colorless prisms, m.p. 148.5–149.5°. A specimen from another run repeatedly recrystallized from benzene-ether melted at 150–150.2°, λ_{\max} 271 μ (log ϵ 3.15), 277.5 (3.18); λ_{\min} 244 (2.20), 275 (3.12).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 77.61; H, 8.29. Found: C, 77.7; H, 8.39.

The residues from the mother liquors were combined and chromatographed on 30 g. of alkaline alumina (Merck and Co., Inc.). Elution with 1:5 benzene-petroleum ether (60–68°) gave 0.261 g. of an isomeric ketal, m.p. 187.5–192.5°. Further elution of the column with the same solvent afforded in a later fraction an additional 0.420 g. of the *anti-trans* isomer XXII, m.p. 146–149°, making the total yield of this isomer 65%.

Recrystallization of the higher-melting isomer from ether and again from diisopropyl ether afforded *anti-cis*⁴²-1-methoxy-8-ethylenedioxy-10a-methyl-4b,5,7,8,9,10,10a,10b,11,12-decahydrochrysenes (XXIII) as colorless plates m.p. 192–193°, λ_{\max} 270 μ (log ϵ 3.12), 277.5 (3.15).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 77.61; H, 8.29. Found: C, 77.5; H, 8.24.

Isolation of *syn-trans*⁴²-1-Methoxy-8-ethylenedioxy-10a-methyl-4b,5,7,8,9,10,10a,10b,11,12-decahydrochrysenes (XXIV).—From a series of metal-ammonia reductions⁴³ the combined residues (7.6 g.), after removal of the preponderant *anti-trans* isomer by crystallization as described above, were chromatographed on 130 g. of Florisil. The early fractions eluted with 40:60 benzene-petroleum ether (60–68°), which appeared to be homogeneous by infrared analyses, were combined and recrystallized three times from absolute ethanol to give 0.271 g. of material, m.p. 179–184°. Repeated recrystallization of a specimen from absolute ethanol-benzene gave colorless blades, m.p. 184–186°, λ_{\max} 271 μ (log ϵ 3.25), 278 (3.28); λ_{\min} 242 (2.29).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 77.61; H, 8.29. Found: C, 77.7; H, 8.25.

Large melting point depressions were observed on admixture of the 186° compound with the 150° and the 193° stereoisomers described above.

*anti-cis*⁴²-1-Methoxy-8-keto-10a-methyl-4b,5,6,8,9,10,10a,10b,11,12-decahydrochrysenes (XXVI).—A 0.151-g. sample of the *anti-cis*⁴²-dihydro ketal, m.p. 191–193°, in 30 ml. of acetone containing 3 drops of concentrated hydrochloric acid was boiled under reflux for 1.75 hr. The solution was concentrated and the pale-yellow gummy residue crystallized with some difficulty from dilute methanol. Recrystallization of this material, m.p. 98–117°, from the same solvent afforded 0.086 g. (65% yield) of colorless leaflets, m.p. 100–101°, λ_{\max} 231 μ (log ϵ 4.21), 241 (4.20), shoulder at 278 (3.28); λ_{\min} 214 (4.09), 237 (4.19).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.9; H, 7.92.

*syn-trans*⁴²-1-Methoxy-8-keto-10a-methyl-4b,5,6,8,9,10,10a,10b,11,12-decahydrochrysenes (XXVII).—A 0.151-g. sample of the *syn-trans*⁴²-dihydro ketal, m.p. 179–184°, was hydrolyzed in the same manner as the 193° stereoisomer except that the heating period was 2 hr. The crystalline residue obtained upon evaporation of the solvent was recrystallized from methanol to give 0.100 g. (76% yield) of material, m.p. 173.5–178°. Recrystallization from methanol afforded colorless blades, m.p. 176–178.5°, λ_{\max} 231 μ (log ϵ 4.21), 243 (4.21), shoulder at 278 (3.31); λ_{\min} 214 (4.08), 237 (4.19).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.0; H, 8.16.

(43) These reductions were carried out essentially as described above, except that in some runs sodium, and in others potassium, was employed instead of lithium.

anti-trans-1-Methoxy-8-keto-10a-methyl-4b,5,6,8,9,10,10a,10b,11,12-decahydrochrysenes (XXV).—A mixture of 0.709 g. of the *anti-trans*-dihydro ketal XXII, m.p. 146–149°, 0.035 g. of *p*-toluenesulfonic acid monohydrate, 20 ml. of acetone and 12 drops of water was heated under reflux for 1 hr. Most of the acetone was evaporated, and the crystals obtained on adding water amounted to 0.583 g., m.p. 144.5–147.5°. Recrystallization from benzene-petroleum ether (60–68°) gave 0.496 g., m.p. 149.5–151°. A sample from another run on repeated recrystallization was obtained as colorless plates, m.p. 154.5–155.5°, λ_{\max} 232 μ (log ϵ 4.32), shoulder at 278 (3.35).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.3; H, 8.19.

Catalytic Hydrogenation of the *anti-trans*-Dihydro Ketone XXV.—A solution of 0.500 g. of the dihydro ketone, m.p. 151–152°, in 125 ml. of ethyl acetate was hydrogenated over 0.300 g. of 5% palladium-on-carbon (Mozingo B⁴⁴) at room temperature and atmospheric pressure. The reaction stopped in 2 hr., after the calculated amount of hydrogen was absorbed for saturation of the olefinic bond. The mixture was filtered and concentrated. On cooling 0.083 g. of colorless rhombs, m.p. 208–212° with softening at 195°, separated. Recrystallization from ethyl acetate, then from acetone-methanol, raised the m.p. to 211–211.7° undepressed on admixture with the *trans-anti-trans*-tetrahydroketone B described above.

Evaporation of the mother liquor remaining from the 208–212° material gave an oily residue which crystallized on standing. Crystallization from absolute ethanol gave 0.335 g. of crude *cis-anti-trans*-1-methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (D), m.p. 131–135°. Repeated recrystallization from ethyl acetate and from benzene-petroleum ether (60–68°) gave colorless blades, m.p. 136–137°, λ_{\max} 271 μ (log ϵ 3.14), 278 (3.15); λ_{\min} 243 (2.19), 274 (3.09).

Anal. Calcd. for $C_{26}H_{36}O_2$: C, 80.49; H, 8.78. Found: C, 80.8; H, 9.00.

The 2,4-dinitrophenylhydrazones crystallized from *n*-butyl acetate as small orange needles, m.p. 221–222°.

Anal. Calcd. for $C_{25}H_{30}O_5N_4$: C, 65.26; H, 6.32. Found: C, 65.3; H, 6.44.

Catalytic Hydrogenation of the *syn-trans*⁴²-Dihydro Ketone (XXVII).—A solution of 0.087 g. of the dihydro ketone, m.p. 173.5–178°, in 30 ml. of 95% ethanol containing one drop of 10% potassium hydroxide was hydrogenated over 0.008 g. of 10% palladium-on-carbon (American Platinum Works) at room temperature and atmospheric pressure. After 30 minutes the absorption of hydrogen was complete. Filtration and evaporation of the filtrate yielded a crystalline residue, which on repeated recrystallization from acetone-petroleum ether (60–68°) afforded 0.015 g. of *cis-syn-trans*⁴²-1-methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (E), m.p. 172–174.2°, undepressed on admixture with the specimen of this substance described above. The infrared spectra of the two specimens were identical.

cis-anti-trans-1-Methoxy-8 α -hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysenes (XV).—To a solution of 1.70 g. of the *cis*-dihydro-8 α -hydroxy compound X, m.p. 156–158°, described above, in 200 ml. of dry ether, was added 256 ml. of liquid ammonia followed by 0.184 g. of lithium wire. The mixture was stirred for 15 minutes, then anhydrous ethanol was added slowly until the blue color had disappeared. The ammonia and ether were evaporated on the steam-bath, ice-water was added and the solid taken up in benzene. The benzene solution was washed with water, 5% hydrochloric acid and saturated brine. The residue obtained on evaporation of the solvent was recrystallized from benzene-petroleum ether (60–68°) to give 1.01 g. (59% yield) of colorless needles, m.p. 150–152°. Repeated recrystallization from benzene-petroleum ether (60–68°) and from acetone-petroleum ether (60–68°) gave colorless needles, m.p. 155.2–155.7°, λ_{\max} 272 μ (log ϵ 3.13), 278 (3.13); λ_{\min} 244.5 (2.20), 275 (3.07).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.62; H, 9.28.

The acetate, prepared with acetic anhydride and pyridine, crystallized from aqueous ethanol as colorless needles, which melted after evaporative distillation at 125° (0.05 mm.) at 113.8–114.5°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.4; H, 9.04.

Oppenauer Oxidation of the *cis-anti-trans*-8 α -Hydroxy Compound XV.—The following is an adaptation of the procedure of Wettstein and Meystre.⁴⁴ A solution of 0.30 g. of aluminum isopropoxide in 10 ml. of dry toluene was added slowly over a period of 30 minutes to a slowly distilling mixture of 0.300 g. of the 8 α -hydroxy compound, m.p. 150–152°, and 3 ml. of cyclohexanone in 20 ml. of toluene (nitrogen atmosphere). The mixture was cooled,

(44) A. Wettstein and Ch. Meystre, *Helv. Chim. Acta*, **30**, 1202 (1947).

4 ml. of a saturated solution of Rochelle salt was added and steam was passed through the mixture for 1 hr. The residue was taken up in benzene, washed with water, then with saturated brine and finally dried over anhydrous sodium sulfate. The residue, m.p. 115–120°, obtained on evaporation of the solvent was crystallized from methanol to yield 0.200 g. of colorless needles, m.p. 131–133° with previous softening. Recrystallization from acetone–petroleum ether (60–68°) gave 0.162 g. (55% yield) of inaterial, m.p. 131–135°, undepressed on admixture with ketone 1) described above.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. IV.¹ 1-Methoxy-6 α -hydroxy-8-keto-10 α -methyl-5,6,6 α ,7,8,9,10,10 α ,11,12-decahydrochrysene and Reduction Products

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The crystalline intermediate produced in the preparation of the tetracyclic ketone IV (from methyl vinyl ketone and the tricyclic ketone I) has been shown to be a mixture of epimeric ketols II and III. Acetylation of the ketols II and III followed by catalytic hydrogenation of the styrene double bond yielded a pair of dihydro compounds V and VI which on treatment with sodium methoxide yielded the same α,β -unsaturated ketone, namely, VII. Reduction of VII gave the *cis-syn-cis* (ketone-C) and the *trans-syn-cis* (ketone-F) isomers. The configuration of the latter has been proved unequivocally (in paper V) by epimerization of the hydrogen at C_{10b} through the agency of an 11-keto group to give the *trans-anti-trans* compound of established (by conversion to a natural product) configuration. The backbone configuration of ketone-C and consequently of the unsaturated ketone and its precursors was thus also established. The structures of some by-products produced in the above reactions have been elucidated and some evidence adduced for the configuration of the hydroxyl group in the ketols. Methods for producing the C- and the F-series stereoselectively from VII have been developed. An air-oxidation product of the enol ether XIV has been shown to have the structure XV or XVI which on treatment with acid or base was isomerized to the diketone XVII. Reduction of the ketol II or of the diol XVIII (obtained from II by the action of lithium aluminum hydride) with lithium and alcohol in ammonia gave the *syn-cis*-diol XIX as the preponderant product. The configuration was established by oxidation with chromium trioxide–pyridine to the dihydroketol (V, H in place of Ac) and by lithium aluminum hydride reduction of the dihydroketol acetate V to XIX. When potassium was employed instead of lithium for the reduction of XVIII, in addition to XIX, a small amount of a stereoisomer, possibly the *anti-trans* compound, was isolated.

The base-catalyzed condensation of methyl vinyl ketone with the tricyclic ketone I to give the tetracyclic compound IV has been described.⁵ When the condensation was carried out under mild conditions, a crystalline intermediate was formed corresponding in composition to a simple adduct without loss of water. This compound, therefore, could be formulated either as the diketone arising from a Michael addition of I to methyl vinyl ketone or as the ketol structure (formulas II or III). In the present paper evidence is provided in favor of the latter formulation, and in addition results are recorded of a study of the reduction of the 4b,10b-(styrene) double bond of the ketol and of its reactions involving β -elimination of the 6 α hydroxyl and reduction of the resulting α,β -unsaturated carbonyl system.

The crystalline intermediate, in fact, proved to be a mixture of the epimeric (at 6 α) ketols II and III which could be separated by fractional crystallization into an isomer-a, m.p. 215°, and an isomer-b, m.p. 188°. The proportion of these isomers

varied somewhat with the concentration of the base employed in the condensation. When the reaction mixture was about 0.14 *N* with respect to sodium methoxide, 77% of isomer-a and 1.3% of isomer-b could be isolated. With a methoxide concentration of approximately 0.03 *N* the yields were 43 and 18%, respectively. An attempt to effect an acid-catalyzed interconversion⁶ of the ketols failed.

The ultraviolet spectra of isomer-a and isomer-b were essentially identical and characteristic of the methoxydihydronaphthalene chromophore (see Fig. 1 in ref. 5). Besides the carbonyl absorption at 5.90 μ in the infrared, strong hydroxyl absorption was observed (null) at 3.01 μ for isomer-a and at 2.82 μ for isomer-b, thus precluding the open diketone structure for either isomer. Isomer-a consumed two mole equivalents of lithium aluminum hydride as determined by the method of Higuchi and Zuck.⁷ In addition, one mole equivalent of hydrogen was liberated in the presence of excess lithium aluminum hydride. These results confirm the presence of one carbonyl and one hydroxyl group.

In the presence of sodium methoxide both the a-

(1) Paper III, W. S. Johnson, E. R. Rogier, J. Szmuszkowicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalman, R. A. Clement, B. Bannister and H. Wynberg, *THIS JOURNAL*, **78**, 6289 (1956).

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(5) Paper II, W. S. Johnson, J. Szmuszkowicz, E. R. Rogier, H. I. Hadler and H. Wynberg, *THIS JOURNAL*, **78**, 6285 (1956).

(6) By an unpublished procedure of A. L. Wilds, *et al.*, for the interconversion of a similar epimeric pair of tricyclic ketols (private communication from Professor Wilds).

(7) T. Higuchi and D. A. Zuck, *THIS JOURNAL*, **73**, 2676 (1951). We are indebted to Drs. Higuchi and R. Kuramoto for performing this experiment.