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

Steroid Total Synthesis—Hydrochrysene Approach. VI.[1] Catalytic Hydrogenation of the Aromatic Nucleus. Synthesis of *dl*-3β-Acetoxy-14-*iso*-etioallohomobilianic Acid

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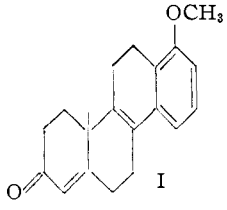
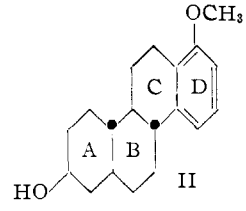
The *trans-anti-trans*-methoxy alcohol II (described in a previous paper) has been demethylated with methylmagnesium iodide to give the diol III (R = H), which in turn has been selectively acetylated to the half-acetate III (R = Ac). Both the diol and the half-acetate have been hydrogenated over platinum to give mixtures of the two stereoisomeric perhydro compounds IV and V. The latter (preponderant isomer) was oxidized in the form of the half-acetate to the stable ketone VII (R = Ac) and in the form of the diol to the diketone IX. Oxidation of IV (R = Ac) gave a labile acetoxy ketone VI (R = Ac) which could be isomerized to the stable *trans-anti-trans-anti-trans* form VIII (R = Ac or H). The 17α-hydroxyl of IV was found to be very susceptible to oxidation, and not only was IV (R = Ac) oxidized much more rapidly than V (R = Ac), but it was possible to selectively oxidize the diol IV (R = H) at C_{17a}. Condensation of the acetoxy ketone VII (R = Ac) with benzaldehyde in the presence of sodium hydroxide yielded the hydroxybenzylidene ketone X (R = H). This substance was converted to the tetrahydropyranyl ether, methylated with methyl iodide and potassium *t*-butoxide, then hydrolyzed with acid to give XI (R = H) isolated in two forms isomeric about the ethylenic bond. Acetylation followed by ozonization yielded *dl*-3β-acetoxy-14-iso-etioallohomobilianic acid (XIII, R = Ac). The infrared spectrum of the dimethyl ester XIV was identical with authentic material prepared by partial synthesis. The 18-nor acid XII (R = Ac) was also prepared by oxidation of X (R = Ac). Further hydrogenation studies were made in the *trans-anti-cis* series. The diol XVI (R = H), prepared from XV, and the half-acetate XVI (R = Ac) were both very susceptible to hydrogenolysis. When platinum catalyst was used, the only products isolated corresponded to the structure XVIII (R = Ac or H), the latter giving XXI on oxidation. Hydrogenolysis was inhibited by use of Raney nickel in the presence of alkali which yielded a mixture of diols XIX (R = H) and XVII most easily separated by oxidation and isolation of the diketones XXIII and XX. Hydrogenation of the half-acetate XVI (R = Ac) in the presence of ruthenium oxide gave the highest stereoselectivity without hydrogenolysis. The only product isolated was the half-acetate XIX (R = Ac) which on oxidation afforded the acetoxy ketone XXII (R = Ac). Saponification followed by oxidation yielded the same diketone (XXIII) that was produced as the preponderant product in the Raney nickel study. The configurations of the products obtained in the A/B/C *trans-anti-cis* series are assigned tentatively.

In paper III[4] of this series the conversion of the tetracyclic ketone I into what was presumed to be the *trans-anti-trans* tetrahydro alcohol II is described. In the present study the results are disclosed of a study of the catalytic hydrogenation of ring D of this substance as well as of the *trans-anti-cis* isomer XV. Also reported herein is the conversion of the major hydrogenation product in the former series to a substance recognized as *dl*-3β-acetoxy-14-iso-etioallohomobilianic acid XIII (R = Ac)—a transformation which serves to establish the configuration of II as well as of the subsequent hydrogenation products.



I



II

Preliminary attempts to effect demethylation of the methoxy alcohol II by conventional acid-catalyzed conditions were unpromising. On pyrolysis of II with methylmagnesium iodide[5] smooth cleavage was effected and the phenolic alcohol III (R = H), m.p. 209°, was produced in excellent yield. The alcoholic hydroxyl of this product could be selectively acetylated with acetic anhydride and potassium acetate in acetic acid according to the method of Cornforth and Robinson[6] to give the acetoxy phenol II (R = Ac), m.p. 161°. The yield was improved somewhat by omission of the potassium acetate, but the best yields were obtained by a new method consisting of an ester-exchange with ethyl acetate in the presence of *p*-toluenesulfonic acid (study made by H. Lemaire). Under these conditions the phenolic hydroxyl does not participate significantly in ester-exchange. Attempts to selectively saponify the diacetate, m.p. 145°, with potassium bicarbonate gave an unpromising mixture. Apparently the two acetoxy groups were cleaved at comparable rates.

Catalytic hydrogenation of the phenolic alcohol III (R = H) over platinum oxide in acetic acid gave, in addition to some (*ca.* 30%) material in which the hydroxyl at C_1 was lost by hydrogenolysis, a mixture of two diols, m.p. 186° and 243°, isolated in about 9 and 21% yields, respectively. In work presented below and in subsequent papers, these diols have been shown to have the configurations represented by formulas IV (R = H) and V (R = H), respectively.

The acetoxy phenol III (R = Ac) resisted hydrogenation under the conditions used for the diol. However, when platinum oxide prepared according to the method of Frampton, Edwards and Henze[7] was employed, reduction proceeded readily.[8] About 18% of the product corresponded to hydrogenolyzed material from which a pure isomer, m.p. 105°, was easily isolated by crystallization.

(1) Paper V, W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman and W. F. Johns, THIS JOURNAL, **78**, 6312 (1956).

(2) Merck and Co., Inc., Postdoctoral Fellow, 1951–1953.

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

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

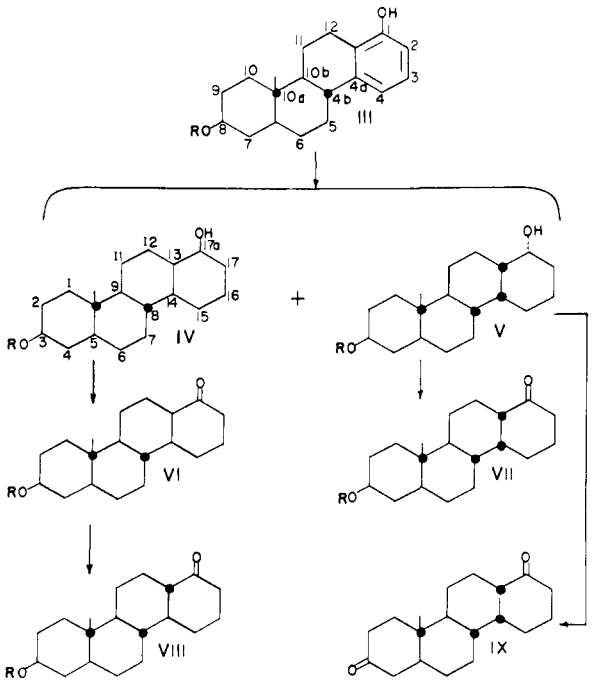
(5) (a) E. Spath, *Monatsh.*, **35**, 319 (1914); (b) A. L. Wilds and W. B. McCormack, THIS JOURNAL, **70**, 4127 (1948).

(6) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946); 1855 (1949).

(7) V. L. Frampton, J. D. Edwards, Jr., and H. P. Henze, THIS JOURNAL, **73**, 4432 (1951).

(8) In later preliminary experiments performed by H. Lemaire, the use of ruthenium oxide catalyst appeared to inhibit hydrogenolysis almost completely (*cf.* the use of this catalyst in the *trans-anti-cis* series described below).

The major portion of the product consisted of a mixture (obtained in about 40% yield) of hydroxy acetates, from which only the preponderant isomer V (R = Ac), m.p. 151°, was obtained pure. A second lower-melting crude product, which was shown by its reactions to consist largely of the hydroxy acetate IV (R = Ac), was also isolated. In addition, a product, m.p. 134°, was isolated in small yield and shown to be a diacetoxymethylperhydrochrysene produced, obviously, by acetylation of one of the hydroxy acetates during the hydrogenation in acetic acid.



Oxidation of the hydroxy acetates IV (R = Ac) and V (R = Ac) with potassium chromate in acetic acid led to the corresponding acetoxy ketones VI (R = Ac), m.p. 112°, and VII (R = Ac), m.p. 173°. The oxidation proceeded much more rapidly with the former than the latter isomer as indicated qualitatively by the rate of darkening of the reaction mixtures. The former, but not the latter, was readily isomerized; thus on heating in acetic acid it was converted to a stable isomer VIII (R = Ac), m.p. 152°, saponification of which yielded the hydroxy ketone VIII (R = H), m.p. 162°. The 173° acetoxy ketone, in contrast, was not isomerized even upon heating with ethanolic potassium hydroxide which gave the hydroxy ketone VII (R = H), m.p. 167°. Acetylation of this material regenerated the 173° acetoxy ketone.

The experiments described above on the relative reactivity of the pair of hydrogenation products toward oxidation and on the relative stability of the resulting products have been rationalized on conformational grounds and thus provided the basis for preliminary assignments of configuration of the products described above as well as their precursors.[9] Proof that these assignments are correct follows from the work discussed below and in subsequent papers.

(9) See paper I, W. S. Johnson, THIS JOURNAL, **78**, 6278 (1955).

The relative susceptibility to oxidation of the hydroxyl group at C_{17a}[10] in the hydroxy acetate IV (R = Ac), which is a reflection of the axial conformation,[9] carried over to the diol IV (R = H) which accordingly could be selectively oxidized to a hydroxy ketone VI (R = H). Treatment with ethanolic potassium hydroxide effected epimerization at C_{13} converting this hydroxy ketone into the stable 162° isomer obtained (see above) by saponification of the acetoxy ketone VIII (R = Ac). The selective oxidation provides a potential method of separating the mixture of isomers obtained on hydrogenation, but this study has not been completed.

The method for transforming the α-decalone ring system into the C/D ring moiety of a 17-keto steroid[11] was applied to the acetoxy ketone VII (R = Ac). It may be noted in passing that the supply of materials derived from the other stereochemical series IV was insufficient for such studies in the present work. Condensation of VII (R = Ac) with benzaldehyde in the presence of methanolic sodium hydroxide yielded the hydroxybenzylidene ketone X (R = H), m.p. 157°. A freshly prepared solution of this material exhibited λ_{max} 222 mμ (log ε 3.86), 292 (4.24), but after standing in light the spectrum changed to λ_{max} 221 mμ (log ε 4.12), 278 (3.91). This behavior is undoubtedly due to a geometric isomerization of the benzylidene group from the transoid to the cisoid configuration.[12] In incidental work, the acetoxy derivative X (R = Ac), m.p. 185°, was ozonized to give the acetoxy acid XII (R = Ac), m.p. 232°.

The hydroxybenzylidene ketone X (R = H) was treated with dihydropyran[13] and the resulting tetrahydropyranyl ether X (R = $-\underline{CHCH_2CH_2CH_2CH_2O}$), m.p. 144°, methylated with methyl iodide and potassium *t*-butoxide. After acid hydrolysis to remove the tetrahydropyranyl (blocking) group, two isomers, m.p. 147 and 189°, were separated by fractional crystallization. The former exhibited the transoid spectral characteristics changing over into those of the cisoid form on irradiation. The higher-melting isomer, on the other hand, exhibited typical cisoid absorption on immediate dissolution. Acetylation of the 147° isomer gave in high yield a single acetate, m.p. 184°, having the same (transoid) spectral characteristics. Acetylation of the 189° isomer, in contrast, gave a mixture, from which an acetate, m.p.

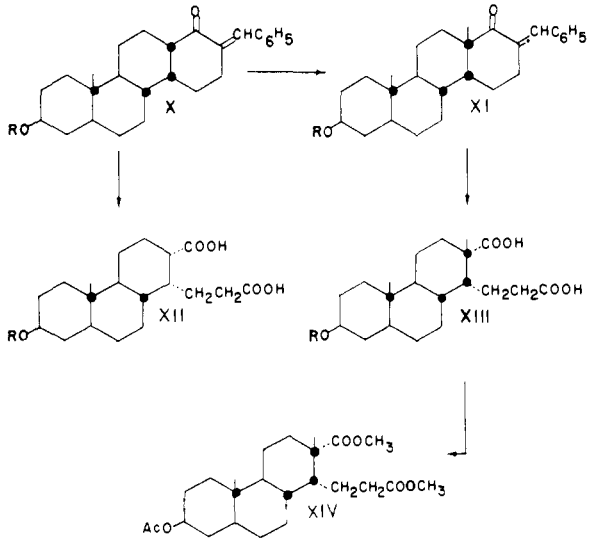
(10) An arbitrary change from chrysene (see formula III) to steroid (see formula IV) nomenclature has been invoked when ring D becomes hydroaromatic.

(11) (a) W. S. Johnson, THIS JOURNAL, **66**, 215 (1944); (b) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(12) The terms *cisoid* and *transoid* are used here to denote a *cis* and *trans* relationship, respectively, of the aryl with respect to the carbonyl group. A number of arylmethylene ketones have been found in our laboratory to be susceptible to this type of light-catalyzed isomerization with attendant spectral shifts (see, for example, H. C. Dehm, Ph.D. thesis, University of Wisconsin, 1954). The phenomenon is typified by the thoroughly studied case of benzalacetophenone, R. E. Lutz and R. H. Jordan, THIS JOURNAL, **72**, 4090 (1950), and L. P. Kuhn, R. E. Lutz and C. R. Bauer, *ibid.*, **72**, 5058 (1950).

(13) G. F. Woods and D. N. Kramer, *ibid.*, **69**, 2246 (1947); W. E. Parham and E. L. Anderson, *ibid.*, **70**, 4187 (1948); C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

155° (with cisoid absorption in the ultraviolet), was isolated in poor yield. A crude, higher-melting fraction appeared to contain some of the 189° transoid isomer, suggesting that partial isomerization occurred during the acetylation.[14] Conclu-



sive evidence that the 147 and 189° isomers differed only in the configuration of the benzylidene group was provided by ozonization of the acetates. Both substances yielded the same product, m.p. 266°, namely, *dl*-3β-acetoxy-14-iso-etioallohomobilianic acid (XIII, R = Ac). The infrared spectrum of the dimethyl ester XIV, m.p. 100°, was different from that of naturally derived *d*-dimethyl 3-acetoxyetioallohomobilianate but identical with that of authentic *d*-14-iso compound prepared by partial synthesis.[15]

No further substances were isolated from the methylation product described above. It is likely that the residues contained some of the epimeric 13-isobenzylidene compound by analogy to previous cases.[11]

Further studies of the hydrogenation of the aromatic nucleus have been made with the *trans-anti-cis*-tetrahydro alcohol XV.[4] Demethylation as in the case of II gave a diol XVI (R = H), m.p. 211°, which on remethylation gave back the starting methyl ether XV showing that no isomerization had occurred during the demethylation. In incidental work the diol was oxidized by the Oppenauer method to give a phenolic ketone, m.p. 199°. Selective acetylation of XVI (R = H) with acetic anhydride in acetic acid afforded the acetoxy phenol XVI (R = Ac), m.p. 161°. An attempt to effect selective acetylation by ester-exchange with phenyl acetate in the presence of sodium hydride[15] gave a mixture of diacetate, half-acetate and phenolic alcohol.

Hydrogenation of the phenolic alcohol XVI (R = H) or the half-acetate XVI (R = Ac) over platinum oxide resulted in extensive hydrogenolysis and the only products isolated were oily desoxy compounds, presumably consisting mainly of XVIII (R = H and R = Ac). Oxidation of the oily hydroxy compound XVIII (R = H) yielded an oily ketone XXI which gave a semicarbazone, m.p. 217°.

When the phenolic alcohol XVI (R = H) was hydrogenated at high pressure over Raney nickel in the presence of potassium hydroxide to inhibit hydrogenolysis,[16] a complex mixture was produced which could not be separated readily by crystallization or chromatography. Oxidation with potassium chromate yielded mono- and diketonic fractions separable by chromatography. The latter consisted largely of two isomeric crystalline diketones, m.p. 126° (preponderant isomer) and 151°, which were separated by fractional crystallization. Both isomers were stable to acid or basic treatment and are assigned the tentative configurations represented in formulas XXIII and XX, respectively, for the reasons set forth below.

While the hydrogenation studies described above were in progress, it was brought to our attention[17] that ruthenium oxide, as a hydrogenation catalyst, was particularly effective in inhibiting hydrogenolysis and in promoting stereoselective reaction. The case at hand afforded a particularly good test for such a catalyst. Hydrogenation of the acetoxy phenol XVI (R = Ac) over ruthenium oxide at 1500 p.s.i. and 50° gave practically no hydrogenolysis, and a single crystalline hydroxy acetate, m.p. 142°, was isolated in over 50% yield. Since approach by the catalyst to the front (β) side of the aromatic nucleus is seriously hindered by the concave bending of the molecule at the B/C ring juncture, it is reasonable to predict that hydrogenation would occur preferentially on the back (α) unhindered side of the nucleus. The 142° hydroxy acetate accordingly is presumed to have the *trans-anti-cis-syn-cis* configuration (formula XIX, R = Ac). Oxidation with potassium chromate yielded an acetoxy ketone, m.p. 168° (formulated as XXII, R = Ac), which on saponification afforded the hydroxy ketone XXII (R = H), m.p. 130°. Oxidation of the hydroxy ketone with potassium chromate gave a diketone (XXIII), m.p. 125°, identical with the preponderant diketone obtained on oxidation of the Raney nickel hydrogenation product (see above). In view of its stereoselective formation *via* the ruthenium oxide hydrogenation, the 125° diketone probably has the *trans-anti-cis-syn-cis* configuration (formula XXIII) with the labile hydrogen at C_{13} oriented in the more stable[17a] α-configuration. The 151° diketone, obtained as the minor product in the Raney nickel study is presumed, therefore, to have the *trans-anti-cis-anti-trans* configuration (formula XX), because it is probably derived from the diol XVII formed by

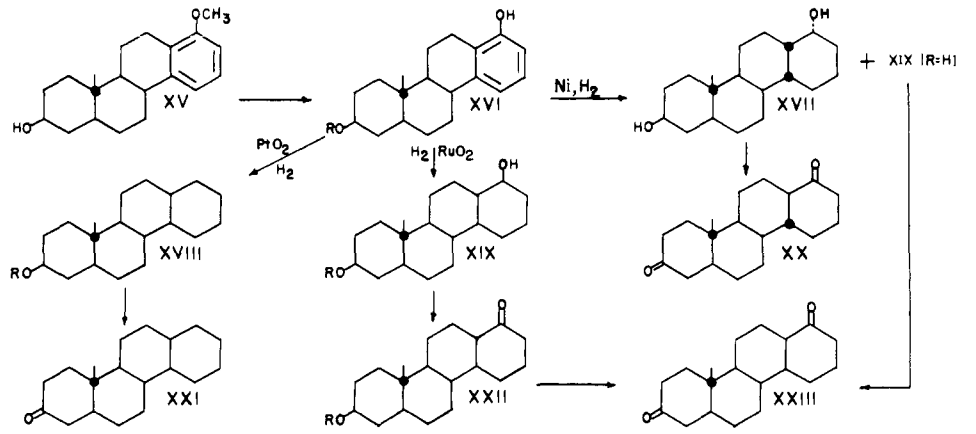
(14) Note that Lutz, *et al.* (see ref. 12), have described the acid-catalyzed cisoid to transoid isomerization with benzalacetophenone.

(15) Paper IX, R. Pappo, B. M. Bloom and W. S. Johnson, *ibid.*, **78**, 6347 (1956).

(16) *Cf.* H. E. Ungnade and A. D. McLaren, *ibid.*, **66**, 118 (1944); H. E. Ungnade and D. V. Nightingale, *ibid.*, **66**, 1218 (1944); W. S. Johnson, C. D. Gutsche and D. K. Banerjee, *ibid.*, **73**, 5464 (1951).

(17) We are indebted to Dr. B. W. Howk of the Chemical Department, E. I. du Pont de Nemours and Co., for telling us of the special catalytic properties of ruthenium oxide and for suggesting its use in the present case.

(17a) For the C_{13}-hydrogen to be β-oriented, it is necessary for either ring B or C to assume the less stable boat conformation. Hence it is estimated that the C/D *cis* arrangement is preferred over the C/D *trans*, as in the case of the B/C rings of *trans-syn-cis*-perhydrophenanthrene—W. S. Johnson, *Experientia*, **8**, 315 (1951); THIS JOURNAL, **75**, 1498 (1953).



some addition of hydrogen to the more hindered front (α) face of the aromatic nucleus of XVI (R = H). The epimerization at C_{13} presumably occurred during the oxidation of XVII or, more likely, during the chromatography of the product.

Acknowledgment.—We are indebted to the agencies mentioned in footnotes 2 and 3 for supporting this work.

Experimental[10,18]

trans-anti-trans-1,8β-**Dihydroxy-10a-methyl-4b,5,6,6a,7-8,9,10,10a,10b,11,12-dodecahydrochrysene (III, R = H).**—According to previous procedures,[5] 10.18 g. of the *trans-anti-trans*-tetrahydrohydroxy compound II,[4] m.p. 136.3–137°, was added in portions to 162 ml. of 0.67 *M* ethereal methylmagnesium iodide. There was immediate evolution of methane. The ether was removed under reduced pressure, and the residue was warmed at 100° (bath temperature) for 30 minutes at the reduced pressure of an oil-pump. Nitrogen was admitted to the flask which was then connected to an eudiometer and immediately plunged into a bath maintained at 175°. The evolution of gas ceased in 43 minutes, 1120 ml. being collected (theory at conditions used required 914 ml. calculated as ethane). The mixture was cooled in an ice-bath, 80 ml. of petroleum ether (40–60°) added, followed by an excess of ethyl acetate which was introduced cautiously to decompose the excess Grignard reagent. Cold, dilute sulfuric acid was added slowly and the mixture shaken thoroughly to dissolve the magnesium salts. The remaining precipitate was separated by filtration and amounted to 9.63 g., m.p. 200–200.8° (vac.). For subsequent reactions this material was sublimed at 200° (0.03 mm.), m.p. 196–200° (vac.) (recovery 94%). Crystallization of the crude material from dilute ethanol gave in 90% recovery material melting (vac.) at 200.5–202°, resolidifying and remelting at 204–205°. A specimen of such material after recrystallization followed by sublimation was obtained as colorless prisms, which melted (vac.) at 204–209.5° with softening at 200°. After cooling, this material remelted at 208–209.5°.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.9; H, 9.40.

trans-anti-trans-1-**Hydroxy-8β-acetoxy-10a-methyl-4b,5,6,-6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (III, R = Ac).** (a) **Acetic Acid–Anhydride Method.**—A solution of 2.02 g. of sublimed dihydroxy compound, m.p. 195–202°, in 3.5 ml. of glacial acetic acid and 0.9 ml. of acetic anhydride was boiled under reflux for 2 hr. Water was added to the warm solution to the point of incipient cloudiness, and on cooling (and seeding) 1.64 g. of crude half-acetate crystallized. This material was chromatographed on 50 g. of acid-washed alumina (grade I–II). Elution with benzene, then with 9:1 followed by 4:1 benzene–chloroform gave a small amount of gummy material. Further elution with lower ratios of benzene–chloroform through to pure chloroform yielded a total of 1.46 g. (63% yield) of crystalline half-acetate in fractions varying in melting point from 149.5–153° to 169.5–170.5° depending upon the polymorphic form obtained (see below). Recrystallization of material of this quality from dilute acetic acid gave pale gray crystals, m.p. 173–174.5° (vac.), in about 85% recovery. Sublimation at 180–190° (0.01 mm.) yielded colorless prisms, m.p. 158.5–161°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.6; H, 8.76.

The low-melting polymorphic modification (see above) was occasionally obtained on evaporating solutions of the half-acetate in benzene and chloroform or on recrystallization from petroleum ether. On warming at 100° this lower-melting form was gradually converted into material, m.p. 170.5–172° (vac.).

(b) **Acid-catalyzed Ester Exchange Method.**—A solution of 0.199 g. of the dihydroxy compound, m.p. 201–205°, in 40 ml. of ethyl acetate containing 0.25 g. of *p*-toluenesulfonic acid monohydrate was boiled under reflux for 4.25 hours, an additional 0.25 g. of sulfonic acid being added after the first 2.5 hours. The solution, which was almost colorless, was cooled, washed with water, saturated sodium bicarbonate solution, again with water and dried over anhydrous sodium sulfate. The residue obtained upon evaporation of the solvent was recrystallized from methylcyclohexane to give 0.178 g. (78% yield) of almost colorless microcrystals, m.p. 157–159° (vac.). A second crop amounted to 0.018 g., m.p. 154–158° (vac.). The infrared spectrum of the first crop material in chloroform was identical with that of the analytical specimen described above.

trans-anti-trans-1,8β-**Diacetoxy-10a-methyl-4b,5,6,6a,7,-8,9,10,10a,10b,11,12-dodecahydrochrysene.**—A solution of 0.544 g. of the phenolic alcohol in 4.1 ml. of isopropenyl acetate containing 0.027 g. of *p*-toluenesulfonic acid monohydrate was distilled very slowly so that the volume was reduced to about 2 ml. in 15 minutes. The remaining isopropenyl acetate was then evaporated at reduced pressure, benzene added to the residue and the solution washed with saturated sodium bicarbonate solution, then dried over anhydrous magnesium sulfate. The residue obtained upon evaporation of the benzene at reduced pressure was crystallized from dilute ethanol to give 0.586 g. (83% yield) of crystals, m.p. 144–146.5°. Recrystallization from dilute acetic acid, followed by evaporative distillation at 160–170° (0.01 mm.) gave colorless micro-crystals, m.p. 144.5–145.5°, λ_{max} 261 mμ (log ε 2.45), λ_{min} 246 (2.25).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.2; H, 8.19.

Attempts to selectively hydrolyze the diacetate with potassium bicarbonate in methanol were unpromising. When an excess of reagent was employed, only the dihydroxy compound was isolated. With one mole-equivalent

(18) The new substances described in this section are racemic compounds, but the prefix "*dl*" has generally been omitted. Unless otherwise indicated, melting points of analytical specimens are corrected for stem exposure; those followed by "(vac.)" were determined in a capillary evacuated to <0.2 mm. Ultraviolet absorption spectra were determined on either a Beckman model DU quartz spectrophotometer or a Cary recording spectrophotometer (model 11 MS), 95% alcohol being employed as the solvent. Infrared spectra were determined on a Baird double beam infrared recording spectrophotometer, model B. Unless otherwise specified, carbon disulfide was used as the solvent. Nujol was used for mulls.

an unpromising mixture, m.p. 165.5–187°, was isolated but not investigated further.

Catalytic Hydrogenation of *trans-anti-trans*-1,8β-Dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (III, R = H).—A solution of 0.427 g. of the diol, m.p. 201–203°, in 25 ml. of glacial acetic acid (distilled from potassium permanganate, then from Raney nickel) was hydrogenated over 0.200 g. of platinum oxide[19] at room temperature and atmospheric pressure. The gas uptake ceased after 23 hr., an additional 0.200 g. of catalyst was introduced and the reduction continued for 6 hr. during which period only a little additional hydrogen was absorbed. The mixture was filtered, the filtrate evaporated and the gummy residue triturated with ether to leave 0.124 g. of crude crystalline perhydro diol, m.p. 217.5–232°, which was transparent between 216–278 mμ. Recrystallization from *n*-butyl acetate afforded 0.09 g. (21% yield) of ***dl*-3β,17aα-dihydroxy-14-iso-18-nor-D-homoandrostane (V, R = H)**, m.p. 236–238°. A comparable specimen was purified by repeated recrystallization from *n*-butyl acetate–petroleum ether (90–100°) followed by sublimation at 200° (0.01 mm.), giving colorless crystals, m.p. 244–246°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.3; H, 11.12.

All of the mother liquors from the triturations and the recrystallization described above were combined with the comparable mother liquors from another run in which 0.168 g. of the phenolic alcohol III (R = H) was reduced and 0.033 g. (19% yield) of the perhydro product V (R = H) was isolated. The solvents were evaporated from these mother liquors and the gummy residue chromatographed on 15 g. of activated alumina (Merck and Co. reagent quality, grade II–III). After elution of 13 mg. of gummy material with benzene–petroleum ether (60–68°), a further 0.110 g. of comparable material was eluted with benzene. This fraction undoubtedly corresponded to material in which the hydroxy group of ring D was lost by hydrogenolysis. Three later fractions eluted with benzene–chloroform amounted to a total of 0.079 g. of crystalline material melting from 166–183° to 182–186°. These fractions were combined and recrystallized from *n*-butyl acetate–petroleum ether (90–100°) to give 0.053 g. of ***dl*-3β,17aβ-dihydroxy-13-iso-18-nor-D-homoandrostane (IV, R = H)** as colorless rods, m.p. 185–187°. Recrystallization from the same solvent pair afforded 0.049 g. as colorless plates, m.p. 185.5–186.5°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.65; H, 11.08.

Later fractions eluted with chloroform amounted to 0.1 g. of crystalline mixtures melting between 176° and 241–249°, probably containing additional amounts of IV (R = H) and V (R = H).

In another experiment in which 0.147 g. of the phenolic alcohol was hydrogenated as described above, the crude solid obtained on trituration with ether–petroleum ether amounted to 0.071 g., m.p. 175–210° with softening at 150°. The carbon–hydrogen analysis was in good agreement with the calculated value for the perhydro diol. The triturate was concentrated and the gummy residue evaporatively distilled at 150–170° (0.01 mm.). The oily distillate amounted to 0.06 g.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. For $C_{19}H_{32}O$ (hydrogenolysis product): C, 82.54; H, 11.66. Found: C, 80.1; H, 11.42.

The analytical data indicated the presence of about 46% of the hydrogenolysis material in the gummy residue, or 21% in the total hydrogenation product isolated.

Catalytic Hydrogenation of *trans-anti-trans*-1-Hydroxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (III, R = Ac).—A solution of 4.065 g. of sublimed half-acetate III (R = Ac), m.p. 173–174.5° (vac.), in 180 ml. of purified (see above) glacial acetic acid was hydrogenated over 1.50 g. of freshly prepared platinum oxide[7] at room temperature and atmospheric pressure. Gas was no longer being absorbed after 17 hr. An additional 0.60 g. of catalyst was introduced and the hydrogenation continued until reaction ceased (6 hr.). The mixture was filtered, the filtrate evaporated and the gummy residue triturated with ether–ethyl acetate–petroleum ether (60–68°) to give 1.01 g. (24% yield) of crude ***dl*-3β-acetoxy-17aα-hydroxy-14-iso-18-nor-D-homoandrostane (V, R = Ac)**, which melted at 150–151° except for a trace of solid (inorganic?) which failed to melt at 250°. Recrystallization from petroleum ether (90–100°) gave 0.876 g., m.p. 150–150.5°. A comparable specimen from another run was recrystallized twice from petroleum ether (90–100°) to give small colorless needles, m.p. 151.4–151.7°, λ_{max} 2.78 μ (OH), 5.8 (C=O).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.2; H, 10.23.

Saponification of a specimen of the above acetate with 5% methanolic potassium hydroxide yielded the diol, which after crystallization from *n*-butyl acetate followed by sublimation at 190° (0.01 mm.), melted at 244–246°.

The mother liquor from the trituration described above was evaporated under reduced pressure and the gummy solid residue chromatographed on 100 g. of acid-washed activated alumina (grade I). The major fractions eluted with benzene–petroleum ether (60–68°) were mostly solid and amounted to 0.702 g. (18% yield) of crude hydrogenolysis product. Recrystallization of such material from methanol gave, in about 55% recovery, colorless needles, m.p. 94–102.5°. Recrystallization afforded an apparently pure stereoisomeric form of 8-acetoxy-10a-methylperhydrochrysene, m.p. 104.5–105°, λ_{max} 5.8 μ (C=O).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.2; H, 10.91.

The later fractions (total of 2.4 g.) which were eluted with benzene and with benzene–ethyl acetate could not be readily purified by recrystallization or rechromatography. The presence of acetate of both perhydro diols was demonstrated by saponification of various fractions which led after purification to materials recognized as IV (R = H) and V (R = H), the latter obviously being preponderant.

Rechromatography of the benzene eluates and first 9:1 benzene–ethyl acetate eluate (total weight 0.79 g.) on 24 g. of acid-washed alumina (grade I) yielded upon elution with benzene, 0.123 g. of a crude fraction which after crystallization from dilute ethanol gave 0.075 g. of colorless plates, m.p. 132–134.5°. The analysis and infrared spectrum demonstrated that this was one of the stereoisomers of 1,8-diacetoxy-10a-methylperhydrochrysene. A specimen, twice recrystallized from dilute ethanol, then sublimed, melted at 133–135°, λ_{max} 5.81 μ (C=O).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.41; H, 9.79.

Later eluates from the rechromatography gave mixtures from which no homogeneous products were separated.

In another hydrogenation experiment, the fraction corresponding to the 0.79-g. benzene and benzene–ethyl acetate eluate described above amounted to 0.41 g. The latter was recrystallized from petroleum ether (90–100°) giving 0.185 g. of ***dl*-3β-acetoxy-17aβ-hydroxy-13-iso-18-nor-D-homoandrostane (IV, R = Ac)**, m.p. 131.5–134°. Another sample similarly prepared was obtained as irregular colorless platelets, m.p. 131–133.5°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.5; H, 10.34.

Saponification of a sample of the 131.5–134° material afforded the diol, m.p. 188–189.5°.

***dl*-3β-Acetoxy-14-iso-18-nor-D-homoandrostane-17a-one (VII, R = Ac).**[20]—A solution of 1.09 g. of potassium chromate in 2.2 ml. of water was added drop by drop with swirling over a 15–20 minute period to a solution of 1.09 g. of the perhydro half-acetate V (R = Ac), m.p. 150–150.5°, in 28 ml. of glacial acetic acid. After the addition, a portion of the yellow chromate precipitated, but most of it dissolved gradually as the oxidation proceeded with concomitant darkening of the reaction mixture which was allowed to stand for 22.5 hr. with occasional swirling. Water was

(19) This catalyst was freshly prepared according to the procedure in "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 463, except that potassium nitrate was used in place of sodium nitrate following A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 946 (1934), and the final fusion temperature was 550–560° following L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 447.

(20) An adaptation of the procedure of L. F. Fieser and S. Rajagopalan, THIS JOURNAL, **72**, 5530 (1950).

added, and the crystals which precipitated were separated by filtration and washed with water. This product amounted to 1.00 g. (91% yield), m.p. 166–169.5° (vac.). A specimen of such material was recrystallized from dilute alcohol to give colorless plates, m.p. 171–173.5° (vac.). Sublimation at 160–170° (0.01 mm.) did not alter the m.p., λ_{max} 5.79 μ (C=O), 5.85 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.65; H, 9.86.

Oxidation of 0.020 g. of the half-acetate V (R = Ac) in 0.8 ml. of acetone, 0.2 ml. of water and a trace of methanol, with 0.014 g. of N-bromosuccinimide was carried out according to the method of Fieser and Rajagopalan.[21] The mixture was allowed to stand at room temperature for 28 hr., water was added and the precipitate separated by centrifugation. Recrystallization from dilute alcohol gave 0.010 g. of crude keto acetate, m.p. 164–169° (vac.).

dl-3β-Hydroxy-14-iso-18-nor-D-homoandrostane-17a-one (VII, R = H).—Saponification of 0.048 g. of the keto acetate VII (R = Ac), m.p. 166–173° (vac.), in 1.0 ml. of 0.4 *N* ethanolic potassium hydroxide was effected by heating at reflux for 2 hr. The mixture was neutralized with acetic acid, water added to incipient cloudiness, and the material which crystallized was separated by centrifugation and washed with water. The yield of crude hydroxy ketone was 0.038 g. (91%), m.p. 162–166°. Recrystallization from dilute alcohol gave 0.032 g. of small colorless prisms, m.p. 162–168°. Another recrystallization from ethyl acetate–petroleum ether (60–68°) afforded 0.025 g., m.p. 165–167.5°, λ_{max} 2.79 μ (OH), 5.85 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.4; H, 10.54.

Reacetylation of a sample of the hydroxy ketone with pyridine and acetic anhydride gave a product which after recrystallization from dilute alcohol melted at 172.5–174° (vac.). There was no depression of the m.p. upon admixture with the authentic acetoxy ketone. The identity of these two specimens proved that no isomerization occurred (at C_{13}) during the alkaline treatment.

dl-3β-Acetoxy-13-iso-18-nor-D-homoandrostane-17a-one (VI, R = Ac).[20]—A solution of 0.052 g. of potassium chromate in 0.12 ml. of water was added slowly to a solution of 0.052 g. of crude monoacetate, m.p. 131.5–134°, in 1.35 ml. of acetic acid. The solution began to darken within 35 seconds after the addition of the first portion of the chromate solution. After 7.3 hr. at room temperature, water was added slowly until crystallization was complete. The precipitate was collected, washed with water and dried; yield 0.045 g., m.p. 109–111°. Recrystallization of a 16-mg. portion from petroleum ether (60–68°) gave 15 mg. of colorless crystals which partially melted at 104–106°, then resolidified at 107° to give a polymorphic form, m.p. 111.5–112.5°, λ_{max} 5.80 μ (C=O), 5.85 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.1; H, 9.94.

dl-3β-Acetoxy-18-nor-D-homoandrostane-17a-one (VIII, R = Ac).—An attempt to recrystallize a specimen of the material, prepared as described in the preceding section, from hot acetic acid resulted in isomerization. The residue obtained on removal of the solvent was crystallized from dilute methanol to give in about 40% recovery material melting at 145–151° (vac.). Recrystallization from the same solvent afforded colorless prisms, m.p. 151–152.5° (vac.). After evaporative distillation at 180° (0.01 mm.), the m.p. was broadened, due perhaps to the formation of some lower-melting polymorphic material or to partial isomerization. In any case the infrared spectrum was distinctly different in the characteristic region from that of the 111.5–112.5° isomer described above, proving that these forms were indeed stereoisomeric and not dimorphic. In the short wave length region, the sublimed material exhibited λ_{max} 5.80 μ (C=O), 5.85 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.0; H, 9.54.

dl-3β-Hydroxy-18-nor-D-homoandrostane-17a-one (VIII, R = H). (a) By Saponification of the Acetoxy Ketone VIII (R = Ac).—A solution of 0.048 g. of the acetoxy ketone in 1.0 ml. of 0.4 *N* ethanolic (95%) potassium hydroxide was heated at reflux for 15 hr. The product was isolated as described above for the 14-iso series to give 0.035 g. (81% yield) of crude hydroxy ketone, m.p. 144.5–155°. Recrystallization from dilute ethanol gave 0.029 g. of colorless, thin, flat blades, m.p. 158–161°. Further recrystallization from petroleum ether (90–100°) afforded small colorless prisms, m.p. 159–162.5°, λ_{max} 2.75 μ (OH), 5.85 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.5; H, 10.43.

(b) By Selective Oxidation and Isomerization of the Diol IV (R = H).—A 0.071-g. specimen of the diol, m.p. 173–182°, in 1.84 ml. of acetic acid was oxidized[20] with 0.071 g. of potassium chromate in 0.15 ml. of water. After 5.5 hr. at room temperature, water was added, and the product which crystallized amounted to 0.050 g., m.p. 125.5–141°. Recrystallization from ethyl acetate–petroleum ether (60–68°) yielded 0.030 g., m.p. 146–151°. On admixture with the analytical specimen described above, the m.p. was depressed to 120–133°, suggesting that the 146–151° material was largely the 13-isohydroxy ketone VI (R = H).

A solution of 0.005 g. of the 146–151° material in 0.5 ml. of 0.4 *N* ethanolic (95%) potassium hydroxide was heated at reflux for 2 hr. The product was isolated as described above (part a) and recrystallized from dilute ethanol to yield 0.003 g. of material, m.p. 158–161°, undepressed on admixture with the analytical specimen described above. The infrared spectra of the two specimens were identical.

dl-3β-Hydroxy-17-benzylidene-14-iso-18-nor-D-homoandrostane-17a-one (X, R = H).[22]—A solution of 0.49 g. of pure benzaldehyde in 8.3 ml. of methanol was added to a solution of 1.20 g. of the crude acetoxy ketone VII (R = Ac), m.p. 166–169.5° (vac.); 10.2 ml. of 33% sodium hydroxide solution was then added followed by a few seed crystals of the benzylidene derivative X (R = H). The cloudy mixture was placed under an atmosphere of nitrogen and warmed to 40° (bath temperature). The system was allowed to stand for 30 hr. while the bath was allowed to cool to room temperature. The crystalline precipitate was separated, washed with dilute methanol and dried; yield, 0.94 g. (69%), m.p. 155.5–156.5° (vac.). Recrystallization of such material from dilute methanol yielded a product which appeared to contain solvent of crystallization since it partially melted and resolidified at about 101–103°. A specimen was purified by chromatography on alumina followed by two recrystallizations from ethyl acetate–petroleum ether (60–68°). This product was obtained as almost colorless blades, m.p. 156.5–157.5°, λ_{max} (within 30 minutes after dissolution) 222 mμ (log ε 3.86), 292 (4.24), λ_{max} 239 (3.37). After standing 9 days as mentioned above: λ_{max} 221 mμ (log ε 4.12); 278 (3.91); λ_{max} 247 (3.69).[12]

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.4; H, 9.19.

The mother liquor from the condensation described above was neutralized with acetic acid, water was added and the solid precipitate combined with comparable material obtained from another run in which 0.232 g. of acetoxy ketone was employed and 0.170 g. (64%) of the benzylidene derivative was isolated directly. The combined solid residues (0.452 g.) were chromatographed on 15 g. of acid-washed alumina (grade I). The center fractions that were eluted with 9:1 benzene–ethyl acetate amounted to 0.262 g. of solid material which on crystallization from ethyl acetate–petroleum ether (60–68°) afforded 0.177 g. (11% yield) of additional benzylidene derivative, m.p. 152.5–158°. Recrystallization from the same solvent pair raised the m.p. to 156.5–157.5°. This material gave no m.p. depression on admixture with the first crop of material described above, and the infrared spectra of the two specimens were essentially identical. From the later 1:1 benzene–ethyl acetate eluates there was isolated 0.098 g. of solid which on recrystallization from *n*-butyl acetate gave 0.043 g. of diol IV (R = H), m.p. 244–46°, which probably arose from an impurity in the original acetoxy ketone.

dl-3β-Hydroxy-17-benzylidene-18-nor-D-homoandrostane-17a-one.[22]—A solution of 0.029 g. of the 13-isoacetoxy ketone VI (R = Ac), m.p. 109–111°, in 1.2 ml. of methanol was treated with a solution of 0.0115 g. of benzaldehyde in 0.42 ml. of methanol followed by 0.24 ml. of 33% sodium hydroxide solution, just as described for the 14-iso compound above. After 48 hr. at room temperature no crystals

(21) Fieser and Rajagopalan, *ibid.*, **71**, 3935 (1949).

(22) An adaptation of the procedure described in reference 11b.

had separated; therefore the mixture was placed in the refrigerator for several days. The crystals which separated amounted to 0.010 g., m.p. 162–164.5°. Recrystallization from dilute methanol gave small colorless plates, m.p. 163.5–165.5°, λ_{max} (within 30 minutes after dissolution) 222 mμ (log ε 3.77), 286.5 (4.20); λ_{min} 238 (3.40). After 18 days (see above): λ_{max} 220 mμ (log ε 4.06), 269 (3.93); λ_{min} 247 (3.81).[12]

Anal. Calcd. for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.5; H, 8.5.

dl-**3β-Acetoxy-17-benzylidene-14-iso-18-nor-D-homoandrostane-17a-one (X, R = Ac)** was prepared from the hydroxy compound X (R = H), m.p. 156–157°, by the pyridine–acetic anhydride method in quantitative yield. The crude material melted at 186.5–187.5° (vac.). Two recrystallizations from methanol gave colorless blades, m.p. 184.5–185.5°.

Anal. Calcd. for $C_{28}H_{36}O_3$: C, 79.96; H, 8.63. Found: C, 80.3; H, 8.73.

dl-**3β-Acetoxy-14-iso-18-noretioallohomobilianic Acid (XII, R = Ac).**—An excess of ozone was passed through a solution of 0.057 g. of the acetoxybenzylidine ketone X (R = Ac), m.p. 181.5–184°, in 7 ml. of ethyl acetate at −15 to −20°; then 2 ml. of acetic acid, 0.5 ml. of water and 0.2 ml. of 30% hydrogen peroxide were added. After standing at room temperature for 20 hr., the mixture was evaporated to dryness, the solid residue dissolved in chloroform, and the solution extracted with a saturated solution of sodium bicarbonate. The bicarbonate extracts were combined, washed with ether and acidified. The solid acid which precipitated was extracted with chloroform–ether. The organic solution was washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent was crystallized from acetone to give 0.022 g. of colorless micro-crystals, m.p. 231–233°. Recrystallization from ethyl acetate raised the m.p. to 231.8–232.5°, λ_{max}^{mull} 5.81 μ (C=O), 5.94 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_6$: C, 66.30; H, 8.48. Found: C, 66.1; H, 8.58.

dl-**3β-2′-Tetrahydropyranyloxy-17-benzylidene-14-iso-18-nor-D-homoandrostane-17a-one (X, R = $-\overline{CHCH_2CH_2-CH_2CH_2O}$).**—According to the established method,[13] a solution of 0.028 g. of *p*-toluenesulfonic acid monohydrate in 1.6 ml. of benzene was added with swirling to a solution of 0.907 g. of the hydroxy benzylidene ketone X (R = H), m.p. 155.5–156.5° (vac.), in 5.5 ml. of dihydropyran. After 2.75 hr. at room temperature, the mixture was neutralized with methanolic sodium hydroxide, and water (along with some additional methanol) was added until crystallization was complete. The product was separated, washed with dilute methanol and dried; yield 0.978 g. (88%), m.p. 146–147° (vac.). Recrystallization from dilute methanol gave small colorless plates, m.p. 143–144°.

Anal. Calcd. for $C_{31}H_{42}O_3$: C, 80.47; H, 9.15. Found: C, 80.4; H, 9.43.

dl-**17-Benzylidene-14-iso-D-homoepiandrosterone (XI, R = H).**—The conditions used for the methylation step were essentially those previously described.[11b] To a cold (frozen) solution of 8.07 ml. of 1.28 *M* potassium *t*-butoxide in anhydrous *t*-butyl alcohol was added over a 20-minute period with stirring a solution of 0.186 g. of the tetrahydropyranyl ether, m.p. 142.5–144.5° (prepared as described in the preceding experiment) in 1.12 ml. of methyl iodide. After the addition was complete stirring was continued for 2 hr. The mixture was then allowed to stand as the ice in the cooling bath was permitted to melt. After 12 hr. the reaction mixture, which was neutral, was concentrated to dryness under reduced pressure. Methanol was added, the mixture filtered from insoluble potassium iodide, and a trace (0.3 ml.) of concentrated hydrochloric acid was introduced.

The mixture was warmed to 50° for 5–10 minutes, then neutralized with sodium bicarbonate and concentrated under reduced pressure until crystallization commenced. Water was added to effect complete crystallization. The crude product thus obtained amounted to 0.151 g., m.p. about 130–140°. Fractional crystallization yielded a total of 0.050 g. of the transoid isomer in two fractions: 0.042 g., m.p. 148–153°, with partial melting and resolidification at 95–100°, and 0.008 g., m.p. 145.5–149°. Recrystallization of the latter from dilute methanol gave long colorless needles, m.p. 146.5–147.5°, λ_{max} (within 30 minutes after dissolution) 222 mμ (log ε 3.90), 290 (4.19); λ_{min} 239 (3.47). After long standing: λ_{max} 220 mμ (log ε 4.03), 274 (3.94); λ_{min} 252 (3.83).[12]

Anal. Calcd. for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.6; H, 9.36.

In later crops a total of 0.044 g. of the cisoid isomer was separated in three fractions: 0.020 g., m.p. 183–186.5°; 0.010 g., m.p. 185–188.5°; and 0.014 g., m.p. 188.5–190.5° (from dilute ethanol). Recrystallization of the last fraction from dilute ethanol gave colorless needles, m.p. 188–189.5°, λ_{max} (within 30 minutes of dissolution, as well as after long standing) 219 mμ (log ε 4.08), 274 (3.95); λ_{min} 252 (3.85).

Anal. Calcd. for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.2; H, 9.38.

In another run in which 0.827 g. of crude tetrahydropyranyl ether, m.p. 134–141°, was methylated, there was separated a total of 0.419 g. (60%) of the transoid and 0.188 g. (27%) of the cisoid isomer.

A 0.419-g. sample of the transoid isomer, m.p. 146.5–148.5°, was converted to the **transoid acetate** by the pyridine–acetic anhydride method. The yield of crude product, m.p. 180.5–181.5°, was 0.460 g. (99%). Two recrystallizations from methanol–ethyl acetate gave colorless blades, m.p. 182–184°, λ_{max} (within 1 hour after dissolution) 222 mμ (log ε 3.82), 292 (4.22); λ_{min} 239 (3.34).

Anal. Calcd. for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found: C, 80.1; H, 8.86.

Acetylation of 0.052 g. of the cisoid isomer, m.p. 190–191°, as above with 0.175 ml. of acetic anhydride and 0.35 ml. of pyridine for 17 hr. at room temperature gave a mixture which was chromatographed on 1.8 g. of acid-washed activated alumina (grade I). Recrystallization of the main benzene eluate from dilute methanol gave 0.028 g. of the **cisoid acetate**, m.p. 154–155°, λ_{max} (within 1 hour of dissolution) 220 mμ (log ε 4.08), 275 (3.89); λ_{min} 252 (3.75).

Anal. Calcd. for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found: C, 79.9; H, 8.89.

From another run a higher-melting form of the cisoid acetate was isolated. It was not obtained pure, m.p. 166.5–171°, but on admixture of this material with the lower-melting form, the m.p. was 168.5–171.5°. A small higher melting (149–174°) fraction eluted from the column with 3:1 benzene–ethyl acetate exhibited an infrared spectrum very similar to that of the pure transoid isomer indicating that some isomerization occurred during the acetylation.

dl-**3β-Acetoxy-14-iso-etioallohomobilianic Acid (XIII, R = Ac).** (a) **From the Transoid Acetate.**—A solution of 0.050 g. of the transoid acetate, m.p. 181–183°, prepared as described above, in 5 ml. of ethyl acetate was ozonized as described above for the 18-nor compound. The yield of crude acid, after drying at 100° (0.1 mm.), was 0.041 g. (91%), m.p. 257–261°. Crystallization from dilute methanol, which was not very satisfactory, gave 0.032 g., m.p. 260–264°. Two recrystallizations from ethyl acetate gave small needles, m.p. 263.5–266°, λ_{max}^{mull} 5.79 μ (C=O), 5.85 (C=O).

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.0; H, 8.87.

(b) **From the Cisoid Acetate.**—A solution of a mixture of 0.050 g. of the two polymorphic forms of this isomer (see above) in 5 ml. of ethyl acetate was ozonized as described above for the 18-nor compound. The yield of crude acid, m.p. 250–262°, was 0.032 g. (71%). Recrystallization from ethyl acetate yielded 0.017 g., m.p. 262–266°, undepressed on admixture with the analytical specimen described above. The infrared spectra of the two samples were identical.

dl-**Dimethyl 3β-Acetoxy-14-iso-etioallohomobilianate (XIV).**—A crude specimen (0.042 g.) of the above acid, m.p. 257–261°, was methylated with diazomethane in ether. After evaporative distillation at reduced pressure and recrystallization from petroleum ether (90–100°), the ester was obtained as small, flat, colorless prisms, m.p. 98.5–100°.

Anal. Calcd. for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 68.5; H, 9.16.

trans-anti-cis-1,8β-Dihydroxy-10a-methyl-4b,5,6,6a,7,8,9,-10,10a,10b,11,12-dodecahydrochrysene (XVI, R = H).—Three grams of the methoxy compound XV, m.p. 132.5–133.5°, was added to 90 ml. of 0.5 *M* ethereal methylmagnesium iodide and the pyrolysis step carried out essentially as described above for the *trans-anti-trans* isomer. The reaction mixture was cooled, water added cautiously, followed by ether and dilute sulfuric acid. The aqueous layer was extracted with benzene and the combined organic layers dried over anhydrous magnesium sulfate. The gray solid residue obtained upon removal of the solvent under reduced pressure was crystallized from *n*-butyl acetate to yield 2.24 g. (78%) of dihydroxy compound, m.p. 204.5–206.5°, with darkening. A sample from another run, after two recrystallizations from benzene–*n*-butyl acetate followed by sublimation at 190–195° (0.05 mm.) was obtained as colorless prisms, m.p. 208.5–211.5° (vac.), λ_{max} 273 mμ (log ε 3.16), 279 (3.15); λ_{min} 244 (2.01), 276 (3.14).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.9; H, 8.92.

Methylation of a specimen of the dihydroxy compound with dimethyl sulfate and aqueous potassium hydroxide gave after recrystallization a 67% yield of material, m.p. 128.5–131°, undepressed on admixture with authentic XV. It was thus demonstrated that the methylmagnesium iodide treatment described above had not been accompanied by isomerization.

The diacetate was prepared by the isopropenyl acetate–*p*-toluenesulfonic acid method. It was not obtained crystalline even after chromatography on alumina, followed by evaporative distillation at 150° (0.02 mm.).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.1; H, 8.23.

trans-anti-cis-1-Hydroxy-8-keto-10a-methyl-4b,5,6,6a,7,-8,9,10,10a,10b,11,12-dodecahydrochrysene.—A 0.220-g. sample of the diol XVI (R = H), m.p. 200–204°, was oxidized by a modification of a general procedure for the Oppenauer oxidation.[23] The diol was dissolved in 100 ml. of toluene, 20 ml. of cyclohexanone and 1.0 g. of aluminum isopropoxide were added and the mixture heated at reflux for 16 hr. The mixture was acidified (to litmus) with dilute sulfuric acid, the aqueous layer extracted with ether and the combined organic layers washed with saturated sodium bicarbonate solution. The solvent was removed under reduced pressure and a little 95% ethanol added to the partly crystalline residue. The crystalline material amounted to 0.067 g., m.p. 185–192°. An additional 0.062 g. of product, m.p. 170–177°, was obtained by chromatography of the residues on 5 g. of acid-washed activated alumina and elution with 2:3 chloroform–benzene.

Repeated recrystallization of the 185–192° material from benzene afforded colorless blades, m.p. 198–199° (vac.), λ_{max} 2.93 μ (OH), 5.83 (C=O).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.45; H, 8.52.

The acetate was prepared with acetic anhydride in acetic acid by heating at reflux for 3 hr. After chromatography on alumina (elution with 1:99 ethyl acetate–benzene) and repeated recrystallization from methanol, it was obtained as colorless elongated prisms, m.p. 129–137° in an open capillary, or 138–139.5° (dec.) in an evacuated capillary, λ_{max} 262 mμ (log ε 2.85); λ_{min} 244 (2.70); λ_{max} 5.68 μ (C=O), 5.84 (C=O).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.2; H, 8.08.

trans-anti-cis-1-Hydroxy-8β-acetoxy-10a-methyl-4b,5,6,-6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (XVI, R = Ac). (a) By the Acetic Anhydride Method.—A solution of 1.00 g. of the diol, m.p. 200–204°, in 2 ml. of glacial acetic acid and 0.5 ml. of acetic anhydride was heated at reflux for 3 hr. The oily residue obtained on evaporation of the solvent was chromatographed on 30 g. of acid-washed activated alumina. Elution with 2:3 chloroform–benzene yielded 0.69 g. (60%) of crude crystalline half-acetate, m.p. 151–156°. Crystallization from 95% ethanol gave 0.17 g. (first crop), m.p. 160–162°, and 0.33 g. (second crop, from dilute ethanol), m.p. 157–159°. (Further elution of the column with isopropyl alcohol gave 0.14 g. of starting diol, m.p. 194–200°.)

Another specimen, prepared by the method of Cornforth and Robinson,[6] was obtained as flat colorless prisms, m.p. 158.5–161°, after recrystallization from acetic acid, then from petroleum ether (60–68°), again from acetic acid and evaporative distillation at 175° (0.01 mm.).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.8; H, 8.54.

(b) By Base-catalyzed Ester-exchange.—This procedure was based on that described for the acetylation of *d*-3β-hydroxy-14-iso-etiohomoallobilianic acid.[15] A mixture of 0.100 g. of the diol, m.p. 200–204°, 1 ml. of phenyl acetate, 10 ml. of xylene and 0.040 g. of sodium hydride was stirred at room temperature for 30 minutes. Water, ether and dilute sulfuric acid were added and the aqueous layer extracted with ether. The combined organic layers were washed with water, evaporated at reduced pressure and the residue chromatographed on 5 g. of acid-washed activated alumina. Elution with benzene yielded 0.017 g. of oily material, undoubtedly the diacetate. Elution with 1:5 ethyl acetate–benzene afforded 0.060 g. (52% yield) of very crude half-acetate, m.p. 135–140°. Further elution with 1:1 ethyl acetate–benzene gave 0.026 g. (26%) of starting diol, m.p. 198–204°.

Hydrogenation of the Diol XVI (R = H) over Platinum Oxide.—A solution of 1.00 g. of sublimed diol, m.p. 204–206°, in 50 ml. of purified (see above) glacial acetic acid was hydrogenated over 0.20 g. of platinum oxide at room temperature and atmospheric pressure. Gas absorption was very slow and, after 3 hours, an additional 0.10 g. of catalyst was introduced and the reduction continued at 50°. After 41 hr. gas absorption had ceased, the mixture was filtered and the filtrate concentrated.

The gummy residue could not be crystallized, so it was dissolved in 15 ml. of acetic acid and treated with a solution of 0.52 g. of chromium trioxide dissolved in a few drops of water and 10 ml. of acetic acid. After 2.5 days at room temperature, the mixture was diluted with water and extracted with ether, then with benzene. The combined extracts were washed thoroughly with saturated sodium bicarbonate solution, then evaporated leaving a gummy residue which did not crystallize. Treatment of this residue with 0.80 g. of semicarbazide hydrochloride and 1.2 g. of sodium acetate trihydrate in 12 ml. of 95% ethanol afforded 0.35 g. of light tan powdery **semicarbazone of XXI**, m.p. about 214° dec. Two recrystallizations from absolute ethanol gave colorless micro-crystals, m.p. 217–217.5° dec.

Anal. Calcd. for $C_{20}H_{33}ON_3$: C, 72.46; H, 10.03. Found: C, 72.3; H, 9.79.

Hydrogenation of the Half-acetate XVI (R = Ac) over Platinum Oxide.—A solution of 1.97 g. of sublimed half-acetate, m.p. 160.5–162.5°, in 90 ml. of purified (see above) acetic acid was hydrogenated over 0.75 g. of platinum oxide[7] at 2–3 atmospheres. After 16 hr. an additional 0.25 g. of catalyst was introduced and the reaction continued. After 7 hr. gas absorption had ceased, the mixture was filtered and the filtrate evaporated under reduced pressure. The oily residue exhibited λ_{max} 280 mμ (log ε 2.65) which indicated that about 30% of the material still retained the aromatic nucleus. The pure starting material exhibits λ_{max} 279 mμ (log ε 3.15).

The oily residue was chromatographed on 60 g. of acid-washed activated alumina. Elution with 1:4 benzene–petroleum ether (60–68°) yielded 0.60 g. (31%) of oily hydrogenolysis product, probably XVIII (R = Ac). The oil was evaporatively distilled at 150° (0.02 mm.) before analysis.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.4; H, 10.66.

Further elution of the column with 1:1 chloroform–benzene afforded 0.45 g. (27%) of oily material which was evaporatively distilled at 160° (0.02 mm.). This substance absorbed only slightly (log ε 1.6) at 279 mμ indicating that there was little if any starting material present. The carbon–hydrogen analysis and infrared spectrum, λ_{max} 2.78 μ (OH), suggested that this was largely hydroxy methyl perhydrochrysene, probably mainly XVIII (R = H) produced by hydrolysis of the acetate.

(23) C. Djerassi, in R. Adams, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 235.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66. Found: C, 81.5; H, 11.38.

Further elution with chloroform and with methanol gave 0.36 g. of a crude crystalline fraction with λ_{max} 280 mμ (log ε 3.21) corresponding to material in which the aromatic nucleus had not been reduced.

Hydrogenation of the Diol XVI (R = H) over Raney Nickel.—A mixture of 2.01 g. of the diol XVI (R = H), m.p. 200–204°, 60 ml. of methanol, 2 ml. of 10% potassium hydroxide solution and 8 g. of W-7 Raney nickel[24] was rocked in a bomb under 3000 p.s.i. of hydrogen at 150° for 12 hr. The mixture was then filtered and the filtrate evaporated in a current of air leaving 2.20 g. of oily residue, λ_{max} 279 mμ (log ε 1.6). Chromatography of a portion on acid-washed activated alumina gave no clear separation of fractions, some of which, however, could be induced to crystallize slowly. They melted over a wide range, *e.g.*, 150–180°, and could not be purified satisfactorily by recrystallization.

To a solution of 2.20 g. of the crude oily hydrogenation product in 60 ml. of acetic acid was added drop by drop a solution of 3.50 g. of potassium chromate in 8 ml. of water.[20] Some of the chromate crystallized from solution and the mixture darkened in a few minutes. After 2 days at room temperature (occasional swirling) most of the chromate had dissolved. Water and chloroform were added, the aqueous layer extracted with chloroform and the combined organic layers were washed with saturated sodium bicarbonate solution, saturated brine and finally dried over anhydrous magnesium sulfate. The orange oily residue obtained on evaporation of the solvent was chromatographed on 50 g. of acid-washed activated alumina. Two distinct major fractions were obtained: 0.669 g. of a crystalline mixture containing the diketones XX and XXIII (see below), and 0.753 g. (more strongly adsorbed) of an oily mixture, which gave a positive reaction with 2,4-dinitrophenylhydrazine reagent and therefore presumably contained partial oxidation products (hydroxy ketones). The first portion (0.22 g.) of the diketone fraction, namely, that eluted with benzene and in part with 1:99 ethyl acetate–benzene, was repeatedly recrystallized from petroleum ether (60–68°) to give a specimen of what is presumed (see Discussion) to be ***dl*-8-iso-13-iso-18-nor-D-homoandrostane-3,17a-dione (XXIII)** as colorless leaflets, m.p. 124.5–126°, λ_{max} 5.86 μ (C=O).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.45; H, 10.06.

The remainder (0.449 g.) of the diketone fraction, eluted with increasing proportions (1:99 to 1:19) of ethyl acetate–benzene, was repeatedly recrystallized from petroleum ether (90–100°) to give a specimen of what is presumably ***dl*-8-iso-13-iso-14-iso-18-nor-D-homoandrostane-3,17a-dione (XX)**, as colorless prisms, m.p. 149–151°, λ_{max} 5.85 μ (C=O).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.8; H, 9.89.

By careful fractional crystallization of the diketone fractions there was isolated a total of 0.259 g. of the lower-melting isomer, the least pure portion of which melted at 122–125°, and 0.105 g. of the higher-melting isomer, m.p. at least 143–146°.

The 126° diketone (0.05 g., m.p. 123–125°) was recovered unchanged after treatment for 7 hr. with a refluxing mixture of 20 ml. of methanol and 4 ml. of 20% potassium hydroxide. No change was observed either when 0.05 g., m.p. 123–125°, was heated in 20 ml. of methanol containing 0.1 g. of *p*-toluenesulfonic acid monohydrate for 6 hr.

When the 151° diketone (0.05 g., m.p. 145–149°) was heated for 3 hr. in 25 ml. of ethanol containing 2 ml. of 20% potassium hydroxide, only starting material could be recovered.

The diketal of the 126° diketone was prepared from a 0.102-g. specimen, m.p. 122–125°, by treatment with 70 ml. of toluene, 3 ml. of ethylene glycol and 0.03 g. of *p*-toluenesulfonic acid monohydrate. The mixture was slowly distilled over a 5-hr. period, 40 ml. of distillate being collected; then the mixture was heated at reflux for 12 hr. The mixture was cooled, washed with saturated sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure left 0.157 g. of colorless crystals, m.p. 120–165°, which were chromatographed on 6 g. of acid-washed activated alumina. Elution with 2:3 and 1:1 benzene–petroleum ether (60–68°) gave 0.078 g. of the diketal, m.p. 172.5–175.5°. Repeated recrystallization from petroleum ether (60–68°) gave colorless clusters of elongated prisms, m.p. 176.5–178.5°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 73.36; H, 9.64. Found: C, 73.4; H, 9.87.

Acid hydrolysis of the diketal regenerated the pure diketone, m.p. 124–126°, in quantitative yield.

Hydrogenation of the Half-acetate XVI (R = Ac) over Ruthenium Oxide.[17]—A solution of 0.284 g. of the half-acetate, m.p. 158–160°, in 10 ml. of absolute ethanol was hydrogenated over 0.02 g. of ruthenium oxide (procured from Baker and Co., Inc.) at 1500 p.s.i. and 50°. After 10 hr. the bomb was opened, the mixture filtered and the filtrate evaporated in a current of nitrogen. The oily residue exhibited only low absorption (log ε 1.2) in the 250–280 mμ region. Comparable material from another run was evaporatively distilled at 150° (0.02 mm.). The distillate exhibited λ_{max} 2.78 μ (OH) and 5.80 (C=O). The carbon–hydrogen analysis showed that this material contained very little, if any, hydrogenolysis product.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 74.6; H, 10.26.

The oily residue described above was chromatographed on 6 g. of acid-washed activated alumina. Elution with 2:3 chloroform–benzene gave 0.263 g. of crystalline material, m.p. 107–120°. Recrystallization from petroleum ether (60–68°) gave 0.082 g. (first crop), m.p. 115–120°, and 0.075 g. (second crop), m.p. 132–135°. These two crops behaved as though they represented mainly different polymorphic modifications of the same material. A mixture of the two melted partly at 115–121° and completely at 127–133°. Recrystallization of the combined crops gave 0.100 g. of the higher-melting form, m.p. 136–138°. Repeated recrystallization from petroleum ether (60–68°) gave what is presumed to be ***dl*-3β-acetoxy-17aβ-hydroxy-8-iso-13-iso-18-nor-D-homoandrostane (XIX, R = Ac)** as colorless elongated prisms, m.p. 140–142.5°, λ_{max} 2.78 μ (OH), 5.80 (C=O).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.3; H, 10.26.

***dl*-3β-Hydroxy-8-iso-13-iso-18-nor-D-homoandrostane-17a-one (XXII, R = H).**—A total of 0.128 g. (0.088 g., m.p. 134–136°, and 0.040 g., m.p. 116–118°) of the crude half-acetate in 4 ml. of glacial acetic acid was oxidized[20] with 0.125 g. of potassium chromate in 0.25 ml. of water. After 23 hr. at room temperature (occasional shaking), water and ether were added and the aqueous layer extracted with ether. The combined organic layers were washed with saturated sodium bicarbonate solution, then with saturated brine and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the solvent at reduced pressure was chromatographed on 4 g. of acid-washed activated alumina. Elution with benzene gave 0.075 g. of crystalline material which was recrystallized from petroleum ether (60–68°) to give 0.049 g. of the **acetoxy ketone XXII (R = Ac)**, m.p. 168–168.5°. Repeated recrystallization from petroleum ether gave colorless clusters of small blades, m.p. 167–168.5°, λ_{max} 5.80 μ (C=O), 5.85 (C=O).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.1; H, 9.75.

A solution of 0.073 g. (0.049 g., m.p. 168–168.5°, and 0.024 g., m.p. 166–168°) of the above acetoxy ketone in 20 ml. of methanol and 2 ml. of saturated potassium carbonate was heated at reflux for 3 hr. Acetic acid was added until the mixture was acidic, the solvent was evaporated, water and benzene were added and the aqueous layer extracted with ether. The combined organic layers were dried over anhydrous magnesium sulfate, then the solvent was evaporated in a current of air. The crystalline residue was recrystallized from petroleum ether (60–68°) to give 0.050 g. (78% yield) of hydroxy ketone, m.p. 128–130°. Repeated recrystallization from the same solvent gave colorless prisms, m.p. 129–130.5°, λ_{max} 2.75 μ (OH), 5.85 (C=O).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.7; H, 10.76.

Oxidation of the Hydroxy Ketone XXII (R = H).—A solution of 0.022 g. of the hydroxy ketone, m.p. 129–

(24) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 176 (Note 1).

130.5°, in 1 ml. of glacial acetic acid was oxidized[20] with 0.022 g. of potassium chromate in 0.1 ml. of water. After 22 hr. at room temperature (occasional shaking), the mixture was treated as described above. The crude, partly crystalline residue obtained on evaporation of the extraction solvents, was chromatographed on 2 g. of acid-washed activated alumina. Elution with 1:99 ethyl acetate–benzene gave 0.012 g. of diketone, m.p. 123.5–125.5°, undepressed on admixture with the sample of XXIII obtained from the Raney nickel hydrogenation experiment described above.

MADISON, WISCONSIN

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

Steroid Total Synthesis—Hydrochrysene Approach. VII.[1] Metal-in-Ammonia Reduction of the Aromatic Nucleus. *dl*-Epiandrosterone and the Lumi Epimer

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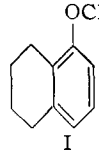
A composite utilization of established metal-in-ammonia reduction procedures has made possible the successful reduction of the aromatic nucleus of the dodecahydrochrysene derivative II. After acid hydrolysis of the resulting enol ether and isomerization of the olefinic bond, both possible α,β-unsaturated ketones III and IV were produced. The latter on catalytic hydrogenation gave *dl*-18-nor-D-homoepiandrosterone (VI) which had been obtained as a minor product from the catalytic hydrogenation study reported in the previous paper of this series. Catalytic reduction of III gave the unstable 13-iso-hydroxy ketone V which is easily isomerized with alkali to VI. To prepare VI, the mixture of III and IV could be hydrogenated in the presence of alkali. The new reduction procedure was applied directly to the tetracyclic ketone XI, to give directly the unsaturated ketones III and IV. The combination of two reduction steps thus has led to a stereoselective synthesis of VI from XI involving the introduction of no less than 6 new asymmetric centers. The angular methylation–ring contraction sequence for converting the α-decalone system to the 17-keto C/D steroid moiety has been improved by use of the furfurylidine blocking group. Application to the hydroxy ketone VI (by the steps indicated in chart 2) led to *dl*-epiandrosterone (XVIII) and the 13-iso epimer XVII. The identity of these substances as well as some of the precursors was established by infrared comparison with naturally derived substances. The preparation of some additional *dl*-18-nor-D-homo steroids (XIX, R = H and R = Ac, and XX) for physiological examination is described.

This paper contains a report of exploratory studies of the metal-in-ammonia reduction[4] of the aromatic nucleus of the dodecahydrochrysene derivative II which, as already described,[5] is easily obtained by a one-step reduction of the readily accessible tetracyclic ketone XI. It was hoped that the reduction would proceed according to established precedents[4] to give, *via* the intermediates expressed in sequence a of Chart 1, the unsaturated ketone III. In the event of success we expected to be able to reduce III further to *dl*-18-nor-D-homoepiandrosterone (VI), which had already been obtained—in amounts sufficient only for characterization, but by a route establishing configuration—as a minor product in the study of the reduction of the aromatic nucleus by catalytic hydrogenation.[1] We hoped, then, to employ the hydroxy ketone in the angular methylation–ring contraction sequence[6] to produce the natural steroid epiandrosterone (XVIII). All of these objectives have been realized and the details are reported below.[7]



I

The sodium–ammonia–alcohol reduction of 1-methoxy-5,6,7,8-tetrahydronaphthalene (I), which serves as a model of the C/D ring system of II, has been examined by Birch[8] who obtained $\Delta^{9,10}$-1-octalone (as the 2,4-dinitrophenylhydrazone) in "trace" yield, formed undoubtedly according to the steps indicated by sequence a in Chart 1. We confirmed the results of Birch. At the time we were making this study, the excellent modification of Wilds and Nelson[9] involving the use of lithium in ammonia followed by alcohol was brought to our attention.[10] Application of this procedure to the methoxytetralin I gave the octalone, isolated as the 2,4-dinitrophenylhydrazone, in 42% yield. The details of this experiment are not described here, because further study[10] has resulted in improved yields of 55–58%, and these results are already recorded.[9] Much to our surprise the new reduction procedure failed completely with the tetracyclic compound II. After numerous unsuccessful attempts this approach was abandoned temporarily, until a modification in the metal–ammonia reduction procedure discovered by Short came to our attention.[11] The modification involves the use of approximately 40% (instead of 10%) of alcohol

(1) Paper VI, W. S. Johnson, E. R. Rogier and J. Ackerman, THIS JOURNAL, **78**, 6322 (1956).

(2) Postdoctoral Project Associate supported by the Wisconsin Alumni Research Foundation, 1952–1953, and the the National Science Foundation, 1953–1954.

(3) Merck and Co., Inc., Postdoctoral Fellow, 1952–1953. On leave of absence from the Weizmann Institute, Israel.

(4) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).

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

(6) (a) W. S. Johnson, *ibid.*, **65**, 1317 (1943); **66**, 215 (1944); (b) W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, *ibid.*, **74**, 2832 (1952).

(7) A preliminary report of this and some earlier work has appeared: W. S. Johnson, B. Bannister, B. M. Bloom, A. D. Kemp, R. Pappo, E. R. Rogier and J. Szmuszkovicz, *ibid.*, **75**, 2275 (1953).

(8) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(9) A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5360 (1953).

(10) We are indebted to Prof. A. L. Wilds for informing us of his discoveries prior to publication (ref. 9) and for urging us to use his procedures in the present study. We also thank him for allowing E. R Rogier of our laboratory to carry out the preliminary examination of the applicaion of the new method to the methoxytetralin I which was one of the substances scheduled for study by Prof. Wilds. It should be emphasized that while the Wilds–Nelson procedure in its original form failed to reduce the tetracyclic compound (see below), the success of the procedure which finally evolved may be attributed in large measure to the discovery of Wilds and Nelson of the special reducing properties of lithium.

(11) Personal communication of unpublished results to one of us (B.B.) *via* Sir Robert Robinson from Dr. W. F. Short of Messrs. Boots Pure Drug Co., Ltd.