Material represented by the first peak of the chromatogram contained unchanged (−)-equilenin acetate.

(+)-11-Oxoequilenin Acetate.—The fractions represented by the first half of the second peak were combined and recrystallized from methanol giving 0.078 g. (6% yield) of acicular crystals, m.p. 198–200°, $[\alpha]^{24}D$ +31°.

(−)-14ξ-Hydroxyequilenin-3-acetate.—The second lot of material from the second peak was recrystallized from methanol giving 0.11 g. (8% yield) of white crystals, m.p. 177–177.5°, $[\alpha]^{25}D$ −104°.

Acknowledgment.—The receipt of a generous gift of (±)-equilenin methyl ether from Professor W. S. Johnson through the Research Committee of the Graduate School of the University of Wisconsin is gratefully acknowledged. The author is indebted to Dr. R. P. Jacobsen for valuable suggestions during the course of this work and to Dr. Harris Rosenkrantz for interpreting the infrared data.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Cholesterol and Companions. IX. Oxidation of Δ^5-Cholestene-3-one with Lead Tetraacetate

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Oxidation of Δ^5-cholestene-3-one with lead tetraacetate at 15–25° gives Δ^5-cholestene-4α-ol-3-one acetate (VI) as the major crystalline product. The structure and configuration were established by reduction to Δ^5-cholestene-3β,4α-diol (VII) and cholestane-3β,4α-diol (XI), oxidation of these diols to Diels acid and dihydro-Diels acid, respectively, and characterization of VII as a digitonin-precipitated *trans* diol isomeric with the 3α,4β-diol. Δ^5-Cholestene-4α-ol-3-one acetate (VI) on contact with alumina undergoes acyl migration to the known Δ^5-cholestene-3β-ol-4-one acetate (XIII); on acid hydrolysis VI yields the known Δ^4-cholestene-4-ol-3-one (XV). The carbonyl group of VI is unusually reactive since the substance can be converted under mild conditions to a dimethyl ketal and a dimethylene ketal; the former derivative was converted by saponification, oxidation and acid hydrolysis to diosterol-I(IV). Condensation of VI with phenylhydrazines affords derivatives of $\Delta^{4,6}$-cholestadiene-3-one; condensation with ethanedithiol gives the bis-ethylenethioketal of cholestane-3,6-dione.

Since oxidation of cholesterol with sodium dichromate in benzene–acetic acid has been shown to afford Δ^5-cholestene-3-one as the major primary product,[2] a study of the action on this substance of the milder agent lead tetraacetate was undertaken in the hope of clarifying the further oxidation of Δ^5-cholestene-3-one by dichromate to Δ^4-cholestene-6β-ol-3-one. In contrast to the behavior of Δ^4-cholestene-3-one,[3] which reacts with lead tetraacetate in acetic acid–acetic anhydride at 70° to give the 2α-acetoxy derivative[3,4] in 13% yield, the non-conjugated ketone is oxidized at a lower temperature (15–20°) and gives a crystalline product in higher yield (30–40%).

The easily isolated product has the composition of a monoacetoxy derivative of the starting ketone V, the infrared spectrum is that of a non-conjugated ketone acetate, the substance is unsaturated to tetranitromethane and is levorotatory, as expected for a Δ^5-ene; these observations suggest that the substance is the product of acetoxylation at the doubly activated 4-position. Confirmatory evidence of structure is afforded by transformations, discussed below, to three different substances known to have oxygen functions at C_3 and C_4, but another proof of structure that also affords evidence that the acetoxyl group is α-oriented (VI) was obtained by characterization of a cholestenediol (VII) that resulted in high yield on lithium aluminum hydride reduction of the oxidation product; the diacetate of VII also resulted on hydrogenation of VI with Raney nickel in benzene and acetylation. Cleavage of the diol with periodic acid, followed by oxidation with hydrogen peroxide in acetic acid, gave the Diels acid (VIII), and hence the two hydroxyl groups are located at positions 3 and 4. The unsaturated diol differs from the well-characterized Δ^5-cholestene-3β,4β-diol[5,6] (m.p. 177°, αD −96°) but, like this substance, is precipitated by digitonin. The inference that the hydroxyl groups are in the 3β,4α-orientation is supported by the following independent evidence. Unlike Δ^5-cholestene-3β,4β-diol, which readily loses water and affords Δ^4-cholestene-3-one,[5] the new diol is stable to mineral acid in boiling methanol and hence is a *trans* diol, 3β,4α- or 3α,4β-. On hydrogenation it yields a saturated diol that on oxidative cleavage as above gives dihydro-Diels acid (XII) and therefore belongs to the cholestanol series; since it differs from the known cholestane-3α,4β-diol[7] (m.p. 236°, αD +16°; diacetate, m.p. 133°, αD −10°), it must be the alternative *trans*-glycol cholestane-3β,4α-diol.

Ruzicka, Plattner and Furrer,[8] on hydrogenating material later characterized[4] as a mixture of the acetates of cholestane-2α-ol-3-one and cholestane-4α-ol-3-one and acetylating the product, isolated a substance that corresponds well in properties (m.p. 162°, αD +33°) with our cholestane-3β,4α-diol diacetate (see chart). Thus in this instance as well as in the reduction of Δ^5-cholestene-4α-ol-3-one acetate (VI) opening of the 3-keto group proceeds by attack from the rear with production of the more stable, equatorially oriented 3β-alcohol. Brown[9] has described two substances that he suggests may be "the unknown Δ^5-cholestene-3,4-diols," but neither substance resembles Δ^5-cholestene-3β,4α-diol (VII).

(1) Merck International Fellow, 1952–1953.

(2) L. F. Fieser, THIS JOURNAL, **75**, 4377 (1953).

(3) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944).

(4) L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953).

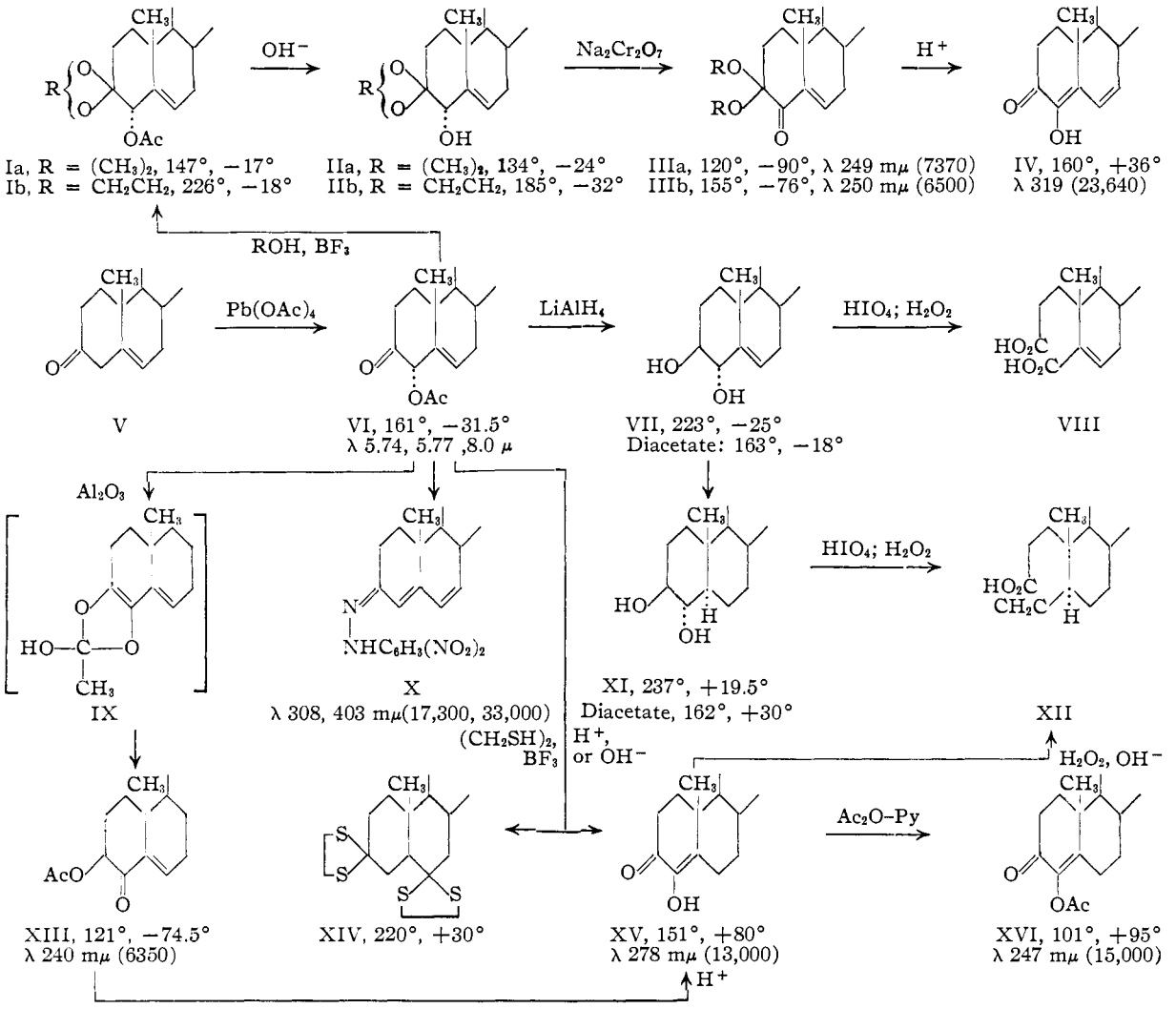
(5) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937).

(6) A. Butenandt and E. Hausmann, *Ber.*, **70**, 1154 (1937).

(7) P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(8) L. Ruzicka, P. A. Plattner and M. Furrer, *ibid.*, **27**, 727 (1944).

(9) B. R. Brown, *J. Chem. Soc.*, 2756 (1952).



Constants reported: m.p.; α_D (Chf); λ^{EtOH} in mμ (and E values); λ^{Chf} in μ.

Δ^5-Cholestene-3β,4α-diol (VII) forms a stable dibromide that can be assigned the 5α,6β-configuration because the M_D difference between the diol and dibromide of −79 corresponds to that for the conversion of cholesterol to the 5α,6β-dibromide[10] (−86; increment for the 5β,6α-dibromide = +411) and because, like other dipolar dibromides,[11] the diol dibromide is readily debrominated to the diol by sodium iodide in acetone. Unlike cholesterol 5α,6β-dibromide, the substance does not exhibit mutarotation. Δ^5-Cholestene-4α-ol-3-one acetate (VI, M_D −137) likewise appears to form a 5α,6β-dibromide (M_D −289), but here the M_D increment (−152) does not agree so well with that (−229) for conversion of Δ^5-cholestene-3-one (M_D −16) to its 5α,6β-dibromide (M_D −245).

That oxidation of Δ^5-cholestene-3-one with lead tetraacetate results in substitution in the activated 4-position of an α-oriented acetoxyl group conforms to theoretical expectations, since a 4α-substituent is equatorial and should have greater stability than an epimeric, polar-oriented β-group[12]; steric repulsion between the 1,3-related C_{10}-polar methyl group and a C_4-polar β-substituent[13] should further impede introduction of a 4β-substituent. Thus the C_4-oxidation here reported apparently is a normal reaction, whereas the allylic C_4-oxidation of cholesterol with selenium dioxide to Δ^5-cholestene-3β,4β-diol is abnormal. Possibly the selenium dioxide reaction proceeds through a cyclic organoselenium derivative of such a nature as to force allylic hydroxylation at C_4 to occur *cis* to the β-hydroxyl group at C_3.

Δ^5-Cholestene-4α-ol-3-one acetate (VI) is a very reactive substance, highly sensitive to acid or base. On chromatographic analysis of mother liquor fractions conducted in the ordinary way the substance could be eluted, at least in part, in unaltered form. However, when a sample was left overnight adsorbed on alumina it was isomerized to Δ^5-cholestene-3β-ol-4-one acetate (XIII), identical with a sample prepared according to Petrow and Starling[14] from Δ^5-cholestene-3β,4β-diol 3-acetate by bromi-

(10) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

(11) D. H. R. Barton and W. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

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

(13) W. S. Johnson, *ibid.*, **7**, 315 (1951).

(14) V. A. Petrow and W. W. Starling, *J. Chem. Soc.*, 60 (1949).

nation, oxidation and debromination. The absorption maximum of XIII (240 mμ) agrees with the calculated[15] value (237 mμ) and the low intensity of absorption (E 6350) is characteristic of a cisoid system. The acyl migration occurring in the isomerization of ketal acetate VI to XIII is somewhat analogous to the interconversion of the 3- and 4-acetates of Δ^5-cholestene-3β,4β-diol in hot acetic acid[16] and on alumina.[17] A plausible interpretation[17] of this *cis* migration is that it proceeds through a cyclic acetal or ortho ester. A similar mechanism seems applicable to the present case even though the acetoxyl group is on the back side of the molecule in the starting material and on the front side in the product, since construction of a model shows that the enol ortho ester IX could arise just as well from a 4α-acetoxy as from a 4β-acetoxy precursor and that there is no reason why the product should correspond in configuration at C_3 to that of the starting material at C_4. The controlling factor seems to be conformation stability: the acetoxyl group of the product of migration is equatorial, as is that of the starting material.

Very facile reactions of Δ^5-cholestene-4α-ol-3-one acetate (VI) with alcohols may also involve participation of the neighboring 4α-acetoxyl group. Whereas cholestanone does not react with ethylene glycol in acetic acid in the presence of boron fluoride etherate,[18] VI reacts to give the high melting ethylene ketal Ib in 91% yield. When a suspension of the ketone acetate VI in methanol containing boron fluoride was stirred at 25° for 3 hr. it afforded, in 36% yield, the analogous dimethyl ketal Ia. The ketal acetates on saponification yielded the ketal alcohols IIa and IIb, which on oxidation yielded the unsaturated ketal ketones IIIa and IIIb. The strong levorotations and low extinction coefficients are properties expected of cisoid Δ^5-enones; that the wave length of ultraviolet absorption (249–250 mμ) is higher than observed for Δ^5-androstene-17β-ol-4-one[19] (λ^{Chf} 240 mμ, E 3160) or for XIII must be due to the neighboring ketal group. In any case, the structure of IIIa is established unambiguously by the observation that the ketal on acid hydrolysis yields a product identical with diosterol-I[14,20–22] (IV).

It was not surprising to find that condensation of Δ^5-cholestene-4α-ol-3-one acetate (VI) with hydrazines is attended with elimination of acetic acid with introduction of a second double bond. The product of condensation with 2,4-dinitrophenylhydrazone corresponded in analysis and constants to the derivative of $\Delta^{4,6}$-cholestadiene-3-one, X, as described by Djerassi and Ryan.[23] Phenylhydrazine reacted to give a product of comparable composition but different spectrum (λ^{EtOH} 238, 352 mμ (11,080); 33,850)). Most likely the elimination of the 4α-acetoxyl group proceeds by the mechanism suggested by Mattox and Kendall[24] for the reaction of 2,4-dinitrophenylhydrazine with 4β-bromo-3-ketones. Some form of allylic rearrangement seems to be involved in the condensation of VI with ethanedithiol in acetic acid catalyzed by boron fluoride etherate, since the product is identical with the bisethylenethioketal XIV derived from cholestane-3,6-dione. The reaction does not proceed through a completed rearrangement, followed by a condensation, since neither 6α- or 6β-acetoxy-Δ^4-cholestene-3-one affords XIV on condensation with ethanedithiol.[18] Nevertheless, the transformation of Δ^5-chyolestene-3-one V through VI to XIV is the closest analogy found to the chromate oxidation of V to Δ^4-cholestene-6β-ol-3-one.[2]

Hydrolysis of Δ^5-cholestene-4α-ol-3-one acetate (VI) either with refluxing alcoholic hydrochloric acid or with alcoholic alkali in the cold was attended with bond migration, since the product showed characteristic ultraviolet absorption. The hydroxy compound, as such and as acetate, corresponds in properties to an enol of cholestane-3,4-dione first obtained by Butenandt, *et al.*,[25] by the action of potassium acetate in butanol on 2,4-dibromocholestane-3-one. Petrow and Starling[14] obtained the same product on refluxing Δ^5-cholestene-3β-ol-4-one acetate (XIII) with alcoholic hydrochloric acid. Butenandt, *et al.*, oxidized the enol with alkaline hydrogen peroxide and identified the product as dihydro-Diels acid (XII), and we likewise obtained XII from material derived from VI (or alternatively from Ib). Constants reported for the enol are: m.p. 148°,[25] λ^{Chf} 280 mμ (11,500)[25]; for the enol acetate: m.p. 101°,[25] α_D +92.5° Chf,[14] λ^{Chf} 248 mμ (14,500).[19] Butenandt, *et al.*, noted that the free enol gives a ferric chloride test but nevertheless formulated it as the diketone; Petrow and Starling tentatively regarded it as the enol XV. The structure XV is indeed indicated by the position of the absorption maximum (λ^{EtOH} 278 mμ). In five known instances[15] an enolic α-hydroxyl substituent produces an average bathochromic shift of 35.5 mμ, and addition of this increment to the maximum of 241 mμ for Δ^4-cholestene-3-one gives the value 276.5 μ, close to that found; the value calculated for the alternate structure, Δ^2-cholestene-3-ol-4-one, is 262.5 mμ. The maximum at 247 mμ found for the enol acetate also agrees better with the value of 251 mμ calculated for XVI (241 + 10 mμ for the acetoxyl group) than with that calculated for the alternate structure (239 mμ). A peculiarity noted of the enol XV is that it is eluted from acid-washed alumina much more readily (4:1 petroleum ether–benzene) than is usual for even a non-acidic alcohol. However the ultraviolet spectrum in hexane did not reveal the presence of the diketone form.

Acknowledgment.—In addition to the general acknowledgements of paper I, we take pleasure in

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(16) V. A. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 135 (1943); M. F. C. Paige, *ibid.*, 437 (1943).

(17) S. Lieberman and D. K. Fukushima, THIS JOURNAL, **72**, 5211 (1950).

(18) L. F. Fieser, *ibid.*, **76**, 1945 (1954).

(19) H. Dannenberg, "Über die Ultravioletabsorption der Steroids," Verlag d. Akademie d. Wissenschaften, Berlin, 1940.

(20) H. H. Inhoffen, *Ber.*, **69**, 1702 (1934).

(21) A. Butenandt and G. Schramm, *ibid.*, **69**, 2289 (1936).

(22) L. F. Fieser, Mary Fieser and S. Rajagopalan, *J. Org. Chem.*, **13**, 800 (1948).

(23) C. Djerassi and E. Ryan, THIS JOURNAL, **71**, 1000 (1949).

(24) V. R. Mattox and E. C. Kendall, *ibid.*, **72**, 2290 (1950).

(25) A. Butenandt, G. Schramm, A. Wolff and H. Kudszus, *Ber.*, **69**, 2779 (1936).

thanking Mary Fieser for expert guidance to information in the literature extended constantly to all members of the group, and particularly for inferring the identity of several of the compounds encountered in this investigation.

Experimental

Δ^5-Cholestene-4α-ol-3-one Acetate (VI).[26]—A stirred solution of 50 g. of Δ^5-cholestene-3-one[27] (m.p. 126–128°) in 200 cc. of benzene at 15° was diluted with 500 cc. of acetic acid, and 64 g. (1.1 moles) of fine crystals of lead tetraacetate was added. At a reaction temperature of 15–20°, the reagent had nearly all dissolved in 1 hr., and after another hr. the solution was let come to room temperature (25°) and stand overnight (yellow solution). Water was added, the mixture was extracted with ether, and the extract washed neutral, dried and evaporated, eventually at the suction pump. The residual solid on fractional crystallization from 95% ethanol gave 11.0 g. of product, m.p. 160–161°, and 6.0 g., m.p. 157–160°. The mother liquors contained a petroleum ether-insoluble, alcohol-soluble substance from which separation was rather troublesome. The acetate VI is moderately soluble in hot ethanol and separates in cottony clusters of fine needles, m.p. 160–161°, α_D −31.5° Chf (*c* 1.49), λ^{Chf} 5.78, 5.82, 8.0 μ; no high ultraviolet absorption above 220 mμ; unsaturated to tetranitromethane; no ferric chloride test; stable to lead tetraacetate under the conditions of its formation.

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.48. Found: C, 78.61, 78.64; H, 10.33, 10.43.

The yield of the main crystalline product VI and the nature of the companion substances seemed variable from run to run under substantially the same conditions. In one experiment (L.F.F.), in which the crude product was oily but afforded a total of 14.7 g. of VI on crystallization from petroleum ether, a 3.5-g. portion of oily mother liquor material was chromatographed. Petroleum ether–benzene mixtures eluted oils, a little solid, m.p. 160–168°, and oils; benzene then eluted a small amount of solid that crystallized from hexane in ball-like aggregates, m.p. 160–163°. These were taken up in methanol and the solution filtered from a trace of solid, m.p. 198–201° dec.; the filtrate on cooling deposited good needles of a by-product, m.p. 163–164°, λ^{EtOH} 242.5 mμ (14,600), λ^{Chf} 5.70, 5.89, 6.12, 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66): C, 75.94; H, 10.11. Found: C, 75.74; H, 10.08.

In oxidations (R.S.) made with 1.3 and 1.5 moles of lead tetraacetate at room temperature (32°), and with larger volumes of benzene (300 cc.) and acetic acid (600–950 cc.) yields of crude VI (m.p. in the range 135–153°) of 45 and 55% were obtained. The mother liquors yielded gums and an amorphous solid; chromatography of the former afforded a small amount of Δ^4-cholestene-4-ol-3-one (XV), m.p. 149–150°, identified by mixed m.p. and by the infrared and ultraviolet spectra. Hydrolysis of some of the amorphous material with ethanolic hydrochloric acid and chromatography afforded impure diosterol-I (IV), m.p. 153° (undepressed by an authentic specimen), orange-brown color with tetranitromethane in chloroform; weak absorption at 5.85 μ indicative of the presence of an impurity.

Anal. Calcd. for $C_{27}H_{42}O_2$ (398.61): C, 81.35; H, 10.62. Found: C, 81.27; H, 10.86.

Δ^5-Cholestene-4α-ol-3-one Dimethyl Ketal Acetate (Ia).[28]—A suspension of 2 g. of the parent ketone VI in 200 cc. of methanol containing 4 cc. of boron fluoride etherate was stirred at 25° for 3 hr., by which time the needles had given place to a microcrystalline powder. The solid was collected (1.5 g., m.p. 136–138°), crystallized from methanol (1.0 g., m.p. 143–145°), and recrystallized, when 0.8 g. (36%) of pure product was obtained in the form of silken needles, m.p. 146–147°, α_D −17.5° Chf (*c* 1.71), λ^{Chf} 5.77, 8.0, 8.9 μ; no ultraviolet absorption.

Anal. Calcd. for $C_{31}H_{52}O_4$ (488.73): C, 76.18; H, 10.72; OCH_3, 12.70. Found: C, 76.37; H, 10.64; OCH_3,[29] 15.28.

On chromatography of the mother liquor material, the ketal Ia was eluted first (9:1 petroleum ether–ether or 4:1 petroleum ether–benzene), followed by Δ^5-cholestene-3β-ol-4-one acetate (XIII, m.p. and mixed m.p. 121–121.5°), and then unchanged ketone VI (the substance is only partially isomerized to XIII in the course of ordinary chromatography).

On being refluxed with alcoholic hydrochloric acid, the ketal acetate Ia afforded Δ^4-cholestene-4-ol-3-one (XV), m.p. and mixed m.p. 148–149.5°.

Δ^5-Cholestene-4α-ol-3-one Dimethyl Ketal (IIa).[28]—A solution of 1 g. of the acetate Ia in 100 cc. of hot methanol was treated with 1 cc. of 25% sodium hydroxide solution, heated for 5 min. on the steam-bath, diluted with 10 cc. of water and let cool. The product that separated melted at 132–134° (0.9 g.) and the m.p. was constant after one recrystallization. The substance crystallized from acetone in clusters of flat needles, m.p. 133–134°, α_D −24.3° Chf (*c* 2.34), λ^{Chf} 2.8, 8.92 μ.

Anal. Calcd. for $C_{29}H_{50}O_3$ (446.69): C, 77.97; H, 11.28. Found: C, 78.10; H, 11.23.

Δ^5-Cholestene-3,4-dione 3-Dimethyl Ketal (IIIa).[28]—A cooled solution of 220 mg. of sodium dichromate dihydrate in 20 cc. of acetic acid was poured onto 448 mg. of the alcohol IIa, which soon dissolved. After 1 hr., water was added and the mixture extracted with ether; evaporation of the washed (carbonate) and dried extract left an oil that soon solidified. Crystallization from methanol (very soluble)–water gave a crust of prisms (225 mg.), m.p. 117–118°. Crystallization from methanol, with a little added water, and then from acetone–water gave long, slender needles, m.p. 119–120°, α_D −89.7° Chf (*c* 2.24), λ^{EtOH} 249 mμ (7370), λ^{Chf} 5.89, 6.10, 8.9 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.11; H, 10.70.

Diosterol-I (IV).[28]—A solution of 150 mg. of the dione 3-ketal IIIa in 20 cc. of hot acetic acid was diluted with 10 cc. of water and 1 cc. of 36% hydrochloric acid and heated for 1 hr. on the steam-bath. On cooling, 52 mg. of product separated in matted needles, m.p. 158–159°; recrystallized from dilute acetic acid, m.p. 159–160°, α_D +36.2° Chf, λ^{EtOH} 319 mμ (23,640), λ^{Chf} 2.90, 6.01, 6.17 μ. The substance showed no depression in m.p. when mixed with a sample of diosterol-I prepared by Dr. S. Rajagopalan,[22] which in parallel determinations has now been found to have the constants: m.p. 158–159°, α_D +36.8° Chf (*c* 2.22), λ^{EtOH} 319 mμ (23,220). Optical constants previously reported are: α_D +57.3° Chf,[14] λ^{Ether} 313 mμ (19,000),[20] λ^{Chf} 320 mμ (21,000),[19] λ^{EtOH} 313.5 mμ (4,700; determination evidently in error).[22]

Δ^5-Cholestene-4α-ol-3-one Ethylene Ketal Acetate (Ib).[26]—A solution of 1 g. of Δ^5-cholestene-4α-ol-3-one acetate (VI) and 3 cc. of ethyleneglycol in 30 cc. of hot acetic acid was let cool to 35–40° and 2 cc. of freshly distilled boron fluoride etherate was added. The product soon began to separate in large needles and after 15 min. the mixture was fully cooled and the crystals collected. Dilution of the filtrate gave a little more solid, and crystallization of the combined material from methanol containing a little acetone gave 1.0 g. (91%) of product, m.p. 222–224°. The substance formed gels on attempted crystallization from ethanol, acetone or hexane, but crystallized well from methanol–acetone or from acetic acid in fine, silken needles, m.p. 225–226°, α_D −18° Chf (*c* 1.30), λ^{Chf} 5.80, 8.1, 9.0 μ.

Anal. Calcd. for $C_{31}H_{50}O_4$ (486.71): C, 76.50; H, 10.36. Found: C, 76.59; H, 10.48.

The yield in the preparation dropped markedly when the ketal was allowed to stand for long in contact with the mother liquor; thus in a 3.5-hr. period the yield from 185 mg. of VI was only 45 mg.

Δ^5-Cholestene-4α-ol-3-one Ethylene Ketal (IIb).[28]—Addition of 1.5 cc. of 25% sodium hydroxide solution to a refluxing suspension of 1.45 g. of acetate Ib in 15 cc. of 95% ethanol resulted in prompt solution of the solid. After 5 min. on the steam-bath the solution was chilled and the product collected by filtration and by ether extraction of the filtrate. Once crystallized material (1.9 g., m.p. 182–184°) on recrystallization from acetone (moderately soluble) gave needles, m.p. 184–185°, α_D −32.5° Chf (*c* 2.27), λ^{Chf} 2.80, 8.9 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.13; H, 10.88.

(26) Experiments by L. F. F., repeated by R. S.

(27) Preparation: L. F. Fieser, THIS JOURNAL, **76**, 5421 (1954).

(28) Experiments by L. F. F.

(29) Result reported as a qualitative test for alkoxyl.

Δ^5-Cholestene-3,4-dione 3-Ethylene Ketal (IIIb).[30]—Dichromate oxidation of 330 mg. of IIb and crystallization of the product from acetone gave 164 mg. of long, flat blades, m.p. 154–155°. Recrystallization from alcohol gave material of m.p. 155–156°, α_D −76° Chf (*c* 2.00), λ^{EtOH} 250 mμ (6500), λ^{Chf} 5.88, 6.11 μ.

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.47. Found: C, 78.53; H, 10.31.

5α,6β-Dibromocholestane-4α-ol-3-one Acetate.[30]—Solutions of 335 mg. of Δ^5-cholestene-4α-ol-3-one acetate (VI) and 121 mg. of bromine in acetic acid (20 cc. and 6 cc.) were mixed and the solution let stand in the dark for 15 min. and diluted with water. The precipitated product (295 mg., m.p. 150–155°) on purification separated from methanol in well-formed needles, m.p. 164–165°, α_D −48° Chf (*c* 1.70, rotation the same after 24 and 48 hr.).

Anal. Calcd. for $C_{29}H_{46}O_3Br_2$ (602.50): C, 57.80; H, 7.70. Found: C, 57.99; H, 7.81.

Δ^5-Cholestene-3β,4α-diol (VII).[30]—A solution of 2 g. of Δ^5-cholestene-4α-ol-3-one acetate (VI) in 100 cc. of ether was added in the course of 15 min. to a suspension of 2 g. of lithium aluminum hydride in 100 cc. of ether, and the mixture was refluxed for 1¼ hr., let stand overnight, and treated with water and then 5% sulfuric acid solution. The ethereal layer was washed with water and then, without being dried, concentrated until the reaction product began to separate. Enough acetone was added to bring the material into solution and the solution was set aside for crystallization. The diol VII separated as leaflets (1.54 g.), m.p. 198–212°. Crystallization from acetone to constant m.p. gave leaflets, m.p. 222–223°, α_D −25° Chf (*c* 1.40), λ^{Chf} 2.83, 2.97, 9.40 μ, unsaturated to tetranitromethane.

Anal. Calcd. for $C_{27}H_{46}O_2$ (402.64): C, 80.54; H, 11.52. Found: C, 80.56; H, 11.60.

Addition of 0.1 cc. of a 20% solution of digitonin in 80% ethanol to a solution of 18 mg. of the diol VII in 8 cc. of 80% ethanol gave an immediate precipitate; collected by centrifugation and washed with 80% ethanol and with ether, the digitonide was obtained as plates, m.p. 233–240° dec.

Stability of the diol to acid was tested by refluxing for 2 hr. a solution of 227 mg. of diol VII with 1 cc. of 36% hydrochloric acid in 35 cc. of methanol. The product that separated on cooling (120 mg., m.p. 200–210°) on two crystallizations from acetone afforded unchanged diol, m.p. 220–222°; a further 40 mg. was recovered by chromatography (eluted by 1:1 ether–methanol).

Δ^5-Cholestene-3β,4α-diol diacetate[30] crystallized from methanol in well-defined flattened blades, m.p. 163–164.5°, α_D −18° Chf (*c* 1.60), λ^{Chf} 5.78, 8.00 μ.

Anal. Calcd. for $C_{31}H_{50}O_4$ (486.71): C, 76.50; H, 10.36. Found: C, 76.70; H, 10.28.

An identical diacetate was obtained by hydrogenation of 535 mg. of VI in 45 cc. of benzene with Raney nickel in a hydrogen atmosphere at slight positive pressure (23°) and acetylation of the reaction product. Two crystallizations of the crude product (312 mg.) gave the saturated diol diacetate, m.p. 162–163°, α_D −18° Chf (*c* 1.70); found: C, 76.28; H, 10.05.

5α,6β-Dibromocholestane-3β,4α-diol.[30]—On addition of 48.5 mg. of bromine in 3.15 cc. of acetic acid to a solution of 122 mg. of diol VII in 7 cc. of chloroform the color was discharged at once; after 20 min. water was added and the product collected by extraction with chloroform. After the dried chloroform solution had been concentrated, addition of methanol precipitated 130 mg. of dibromide, m.p. 170–172° dec. Two recrystallizations from chloroform–methanol gave well-formed needles, m.p. 185–190° dec., α_D −32° Chf (*c* 1.60, no mutarotation).

Anal. Calcd. for $C_{27}H_{46}O_2Br_2$ (562.47): C, 57.65; H, 8.24. Found: C, 57.31; H, 8.22.

A simpler procedure consisted in adding bromine (210 mg.) in acetic acid (10.4 cc.) to a solution of diol (509 mg.) in acetic acid (70 cc.) at 40°. The color was not discharged rapidly but after 3 min. needles of the dibromide began to separate; yield 450 mg., m.p. 185–190° dec.

Debromination of 42 mg. of dibromide by refluxing it in absolute ethanol (10 cc.)–ether (10 cc.) with zinc dust for 3 hr. and crystallization from acetone gave 20 mg. of Δ^5-cholestene-3β,4α-diol, m.p. 217–219°. The same product (m.p. 220–222°) resulted from reaction with sodium iodide in acetone at room temperature; after 15 min. titration with thiosulfate solution indicated 102% debromination.

Cleavage of Δ^5-Cholestene-3β,4α-diol.[30]—Addition of a solution of 670 mg. of periodic acid in 4 cc. of water to a solution of 585 mg. of cholestenediol (VII) in 25 cc. of dioxane produced a precipitate that redissolved on shaking. A further 5 cc. of dioxane was added to the faintly opalescent solution and it was let stand at 25° for 44 hr. The solvent was removed below 60° at reduced pressure, water was added and the mixture was extracted with ether. The extract was washed with water and bicarbonate solution, dried by distillation with benzene and a solution (dark red) of the residue in acetic acid treated with 0.5 cc. of 30% hydrogen peroxide on the steam-bath for 3 hr., when the color had faded to pale yellow. On cooling, a solid separated (95 mg.), and on recrystallization from acetone–acetic acid this afforded large prisms of **Diels acid**, m.p. 282–284°; **monomethyl ester**, m.p. 123–124.5°; no depression in m.p. on admixture with authentic samples of acid and ester.

Cleavage of the diol with lead tetraacetate in benzene–acetic acid (42 hr. at 60°) gave an oil having an infrared spectrum consistent with that expected for a monoconjugated dialdehyde: λ^{Chf} 5.81, 5.91, 6.12 μ.

Cholestane-3β,4α-diol (XI)[30].—A solution of Δ^5-cholestene-3β,4α-diol (563 mg.) in acetic acid (90 cc.) was added to an acetic acid suspension of prereduced catalyst from 210 mg. of platinum oxide and the mixture stirred under a slight positive pressure of hydrogen until uptake of gas ceased (25 min.). The mixture was warmed to redissolve some needles that had separated, the catalyst removed, and the solution evaporated in vacuum. Crystallization of the white solid residue (505 mg.) from acetone gave large glistening leaves of the saturated diol, m.p. 236–237°, α_D +19, +20° Chf (*c* 0.84, 0.50); saturated to tetranitromethane.

Anal. Calcd. for $C_{27}H_{48}O_2$ (404.65): C, 80.14; H, 11.96. Found: C, 79.68; H, 11.97.

The diacetate formed large blades from acetone–methanol, m.p. 161.5–162.5°, α_D +30° Chf (*c* 1.40).

Anal. Calcd. for $C_{31}H_{52}O_4$ (488.73): C, 76.18; H, 10.72. Found: C, 76.13; H, 10.77.

Cleavage of Cholestane-3β,4α-diol.[30]—Oxidation of the diol XI with periodic acid in aqueous dioxane followed by oxidation with hydrogen peroxide in acetic acid, conducted as above, afforded dihydro-Diels acid, m.p. 247–249 (needles from acetic acid), identified as the **dimethyl ester**, m.p. 125–126°, undepressed on admixture with an authentic sample (m.p. 123–124°).

$\Delta^{4,6}$-Cholestadiene-3-one 2,4-Dinitrophenylhydrazone (X).[30]—Addition of 3 cc. of Brady's solution[31] to a hot solution of 100 mg. of Δ^5-cholestene-4α-ol-3-one acetate (VI) in 10 cc. of ethanol caused immediate precipitation of a dark red solid. This was collected, dried by distillation of a benzene solution, and eluted from a column of alumina with 1:1 benzene–petroleum ether. The derivative then crystallized from benzene–petroleum ether in well-formed, dark crimson needles (97 mg.), m.p. 232–233°; recrystallized, m.p. 236–237°, λ^{Chf} 308 mμ (17,300), 403 mμ (33,000); lit.[23] m.p. 227–229°, λ^{Chf} 309, 402–404 mμ.

Anal. Calcd. for $C_{33}H_{46}O_4N_4$ (562.73): C, 70.43; H, 8.24; N, 9.96. Found: C, 70.49; H, 8.21; N, 10.16.

The derivative X was obtained in lower yield by condensation conducted according to Djerassi[32] in acetic acid solution in the absence of mineral acid.

$\Delta^{4,6}$-Cholestadiene-3-one Phenylhydrazone.[28]—A solution of 230 mg. of Δ^5-cholestene-4α-ol-3-one acetate in 17 cc. of hot methanol was treated with 3 cc. of a solution of 1.45 g. of phenylhydrazine hydrochloride in 50 cc. of pyridine and the orange yellow crystal powder that separated (186 mg.) was crystallized by dissolving it in dioxane and diluting the hot solution with 95% ethanol to the point of saturation. The phenylhydrazone separated as curved orange blades, m.p. 163–165°, λ^{EtOH} 238 mμ (11,080), 352 mμ (33,850).

Anal. Calcd. for $C_{33}H_{48}N_2$ (472.73): C, 83.84; H, 10.23; N, 5.93. Found: C, 83.93, 83.64; H, 10.34, 10.04; N, 5.99.

Δ^5-Cholestene-3β-ol-4-one Acetate (XIII).[28]—Δ^5-Cholestene-4α-ol-3-one acetate (VI, 0.5 g.) was adsorbed onto alumina from petroleum ether and left on the column over-

(30) Experiments by R. S.

(31) O. L. Brady, *J. Chem. Soc.*, 756 (1931).

(32) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).

night. Nothing was eluted by petroleum ether, but 1:1 petroleum ether–benzene eluted a solid that on crystallization from methanol gave a mat of fine, flat needles (70 mg.), m.p. 120–121°, α_D −74.5° Chf (*c* 1.33), λ^{EtOH} 240 mμ (6,350), λ^{Chf} 5.74, 5.86, 6.10, 8.0 μ.

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.48. Found: C, 78.83; H, 10.69.

A comparison sample of Δ⁵-cholestene-3β-ol-4-one acetate prepared by Miguel A. Romero according to Petrow and Starling[14] melted at 118–119°, α_D −77.4° Chf (P. and S. give m.p. 123–124°, α_D −76° Chf, λ^{EtOH} 240 mμ[33]). A mixture with the above sample was undepressed in m.p.

Cholestane-3,6-dione Bis-ethylenethioketal (XIV).[28]—A mixture of 300 mg. of Δ⁵-cholestene-4α-ol-3-one acetate, 1 cc. of ethanedithiol and 1 cc. of boron fluoride etherate was stirred in a test-tube, when a stiff orange paste soon resulted. After 5–10 min. methanol was added to produce a thin paste of suspended white solid. The collected and dried product (290 mg., m.p. about 190°) was dissolved in dioxane and the solution diluted with ethanol and then water. A crystal powder separated and was crystallized more satisfactorily from hexane, in which it is moderately soluble; the solution slowly deposited rosettes of fine needles, m.p. 219–220°. Recrystallization from hexane gave silken needles, m.p. 219–220°, α_D +30.4° Chf (*c* 1.09); no depression in m.p. on admixture with an authentic sample.

Anal. Calcd. for $C_{31}H_{52}S_4$ (552.73): C, 67.36; H, 9.48. Found: C, 67.78; H, 9.57.

Δ⁴-Cholestene-4-ol-3-one (XV).[26]—A solution of 455 mg. of Δ⁵-cholestene-4α-ol-3-one acetate (VI) in 25 cc. of 95% ethanol was treated with 0.5 cc. of 36% hydrochloric acid, refluxed for 3 hr., diluted with 4 cc. of water and let cool, when 313 mg. of needles separated, m.p. 148–149°. Recrystallization from methanol or methanol–water gave needles, m.p. 150–151°, α_D +80.2° Chf (*c* 1.10), λ^{EtOH} 278 mμ (13,000), λ^{Hexane} 275 mμ (14,570), λ^{Chf} 2.92, 5.98, 6.10 μ.

Anal. Calcd. for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 81.18; H, 11.06.

Similar acid hydrolysis of 221 mg. of Δ⁵-cholestene-4α-ol-3-one ethylene ketal acetate (Ib) afforded 131 mg. of XV, m.p. 146–148°. The enol XV was also obtained by adding 0.5 cc. of Claisen's alkali to a suspension of 150 mg. of Δ⁵-cholestene-4α-ol-3-one acetate (VI) in 5 cc. of methanol at 25°. In a few minutes the substance dissolved to a slightly yellowish solution and then an enolate separated. This was collected, suspended in methanol and acidified with acetic acid and the solution diluted to saturation at the boiling point; needles of XV separated, m.p. 148–149°, mixed m.p. 149–150°.

The enol XV gives a strong ferric chloride test but does not react with diazomethane. When a petroleum ether solution is shaken with Claisen's alkali no yellow color develops but a gelatinous enolate separates at the interface. An attempt to condense XV with ethylene glycol in acetic acid with boron fluoride etherate led only to recovery of XV. Δ⁴-Cholestene-4-ol-3-one is readily eluted from acid-washed alumina by 4:1 petroleum ether–benzene.

The acetate[28] (XVI), prepared with acetic anhydride in pyridine at 25°, crystallized very slowly from methanol–water, m.p. 100.5–101.5°. It was recrystallized by dissolving it in cold methanol and adding water until a turbid emulsion separated. After standing for some time at 5° this changes to a paste of fairly well formed crystals, m.p. 100–101°, α_D +95.3° Chf (*c* 1.035), λ^{EtOH} 247 (15,100); λ^{Chf} 5.71, 5.93, 6.12 μ.

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.48. Found: C, 78.81; H, 10.51.

The phenylhydrazone of XV[28] separated in a crystal crust, m.p. 188–189°. Recrystallization from ethanol gave lemon yellow micro crystals, m.p. 190–191°.

Anal. Calcd. for $C_{33}H_{50}ON_2$ (490.75): C, 80.76; H, 10.27. Found: C, 80.91; H, 10.20.

The quinoxaline derivative[28] of XV was prepared most successfully by heating 200 mg. of the enol and 200 mg. of sublimed, colorless *o*-phenylenediamine at 141° for 15 min. The solidified melt on crystallization from a solution in dioxane diluted with ethanol and then water gave 80 mg. of the quinoxaline, m.p. 188–190°. Recrystallization from dioxane–methanol afforded pale buff-colored plates, m.p. 200–201°, λ^{EtOH} 239, 321 mμ (27,400; 8,870); lit.[2] m.p. 207–208°.

Anal. Calcd. for $C_{33}H_{48}N_2$ (472.72): C, 83.84; H, 10.24. Found: C, 83.52; H, 10.10.

Oxidation of XV.[28]—Oxidation of 0.5 g. of Δ⁴-cholestene-4-ol-3-one with hydrogen peroxide in ethanol–sodium hydroxide and crystallization from acetic acid according to Butenandt[25] gave spars of dihydro-Diels acid, m.p. 257–259°; diester (diazomethane, two crystallizations from methanol), m.p. 123–124°, no depression on admixture with a comparison sample[34] made by esterifying Diels acid with diazomethane and hydrogenating the diester in acetic acid in the presence of platinum catalyst and a trace of perchloric acid.

(33) See V. A. Petrow, O. Rosenheim and W. W. Starling (footnote), *J. Chem. Soc.*, 135 (1943).

(34) Experiment by Dr. Wei-Yuan Huang.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Steroid Analogs Lacking Ring C. III. Synthesis of 4-(*trans*-4′-Hydroxycyclohexyl)-cyclohexanone[1]

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Reduction of 4,4′-dihydroxybiphenyl (III) has given the *trans,trans*-, *cis,trans*- and a small amount of *cis,cis*-bicyclohexyl-4,4′-diols (IV), separated as the dibenzoates. Oxidation of the pure isomers or the mixture gave the diketone VI which could be partially reduced to the *trans*-keto alcohol I. Better methods for synthesizing this compound involved partial oxidation of *trans,trans*-diol IV directly or as the monobenzoate.

In extending our synthesis of analogs of the steroidal hormones lacking ring C[1] to the analogs (II) of testosterone, it was necessary to develop a synthesis of the bicyclic keto alcohol I as the key intermediate. The present paper describes the *trans* isomer of this structure. An accompanying paper reports work leading to the *cis* isomer and the evidence on which is based the assignment of configuration of these geometrical isomers and related bicyclohexyl derivatives.

Although 4,4′-dihydroxybiphenyl (III), the starting material for our synthesis, has been prepared for many years by tetrazotization and hydrolysis of benzidine, the procedures available have not

(1) Preliminary report, A. L. Wilds, C. H. Shunk and C. H. Hoffman, THIS JOURNAL, **71**, 3266 (1949). Paper II, A. L. Wilds and C. H. Shunk, *ibid.*, **72**, 2388 (1950).

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