Podocarpic Acid Methyl Ether (XLI).—To 574 mg. of XXXVIII (0.00200 mole) in 10 ml. of dry benzene, 63 mg. of sodium hydride (0.0026 mole) was added and the mixture refluxed for 4.5 hours, under nitrogen, with stirring. The reaction was cooled and 5 ml. of dimethylformamide added, causing the white, gelatinous precipitate to dissolve. Dry methyl iodide (3 ml.) was introduced and the reaction stirred overnight at room temperature. After pouring into ice-water, extraction with chloroform and evaporation left a product showing only one N–H band in the infrared at 2.82 μ. A solution of 1.9 g. of NOCl in 20 ml. of acetic anhydride was added dropwise to the N-methylamide XXXIX, dissolved in 7 ml. of glacial acetic acid, 3 ml. of acetic anhydride and 5.2 ml. of dry pyridine. Addition was stopped when an orange color and a positive potassium iodide–starch test persisted. The reaction was left in an ice-bath for 3 hours, poured into water, extracted with chloroform and evaporated under vacuum. The residue was refluxed for 10 hours with 30 ml. of a 10% solution of potassium hydroxide in ethanol, poured into chloroform and extracted with 10% aqueous potassium hydroxide. Acidification and extraction with chloroform, followed by drying over magnesium sulfate and evaporation, gave 380 mg. of crystalline podocarpic acid methyl ether; crystallized from ethanol, m.p. 157–158°, undepressed on mixed melting point with material obtained by saponification of the methyl ester methyl ether. Ether cleavage according to a reported procedure[39] gave podocarpic acid.

(39) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE JOHNS HOPKINS UNIVERSITY, BALTIMORE 18, MD.]

Reactivity and Geometry in Allylic Systems. I. Stereochemistry of Photosensitized Oxygenation of Monoölefins[1,2]

BY ALEX NICKON[3] AND JEHANBUX F. BAGLI

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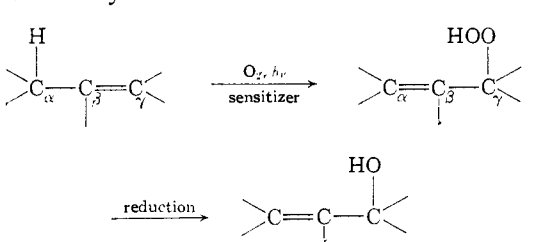
Steroid monoölefins have been used as substrates to study geometric aspects of photosensitized oxygenations. In pyridine solution with hematoporphyrin as a sensitizer, photoöxygenation of three Δ^6-cholestenes (Ia, b, c) gave the corresponding Δ^5-cholesten-7α-hydroperoxides (IIa, b, c) but no isolable amounts of the 7β-epimers. For characterization the hydroperoxides were reduced without purification to alcohols (and derived benzoates). Enone and dienone by-products resulted from breakdown of the hydroperoxides. Similar oxygenation of cholesterol-7α-*d* gave 3β-hydroxy-5α-hydroperoxy-Δ^6-cholestene (XII) that retained only 8.5% of the original deuterium, whereas cholesterol-7β-*d* gave XII with 95% of the original deuterium. These results show that such hydroperoxidations are stereospecific, and the new C–O bond bears a *cis* relationship to the C–H bond that is broken. Even on prolonged treatment Δ^6-cholesten-3β,5α-diol (XIII) is inert to photosensitized oxygenation; this is ascribed to steric shielding (of the β-side of the ring system and especially of the hydrogen at C-8) and demonstrates that the reaction can be sterically blocked. Δ^6-Coprostene has been synthesized from $\Delta^{4,6}$-cholestadien-3-one *via* 6α, 7α-oxido-Δ^4-cholesten-3-one (XIV), 6α, 7α-oxidocoprostan-3-one (XV) and Δ^6-coprosten-3-one (XVI). An unexpected occurrence in the transformation of XV → XVI was concomitant formation of XVII, presumably through a "Clemmensen-type" reduction of the ketone group. Δ^6-Coprostene (XVII) is inert to photosensitized oxygenation. The *quasi*-equatorial nature of the β-hydrogen at C-5 may contribute to this inertness and this suggests (but does not prove) the operation of a stereoelectronic factor in these oxygenations. Improved routes to cholestan-7-one and to Δ^6-cholestene have been developed. Decomposition of the secondary hydroperoxide IIa to the enone IVa occurs on treatment with Raney nickel in pyridine. A conformational factor in manganese dioxide oxidation of allylic alcohols is suggested by the faster oxidation of Δ^5-cholesten-7β-ol (*quasi*-equatorial OH) over the corresponding 7α-ol (*quasi*-axial OH).

The combination of molecular oxygen with olefins is a well-known phenomenon, but its use in syntheses has been limited. Oxygen (in the ground state) is a diradical and many of its laboratory reactions are of free-radical type, are initiated by peroxides, irradiation, etc., and involve chain mechanisms.[4] In contrast, when olefin oxygenation is conducted photochemically in *dilute solution* and in the presence of a small amount of sensitizing agent (usually a fluorescent dye) radical chains do not appear to be involved, the mode of oxygen attack is more specific, and the peroxidic products largely survive further breakdown.

One such type[5] of photosensitized oxygenation is of recent development and involves isolated olefinic links. Extensive studies by Schenck and his co-workers have shown that the initial products are allylic hydroperoxides and that the double bond always undergoes an allylic shift during the reaction, as shown in the adjoining scheme.[6] The oxygenation can be conducted in solvents such as pyridine, benzene or alcohols; and Schenck has established its generality by applying it to a variety of olefins, including terpenes and steroids. Substantially no reaction occurs if the olefin lacks



allylic hydrogens, or if the sensitizer, the irradiation or the oxygen is excluded. The initially formed hydroperoxide usually survives the reaction conditions and can be isolated and reduced to the allylic alcohol by any of a number of ways. That this method for introduction of an alcohol

(1) A preliminary communication of this work has been published [A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **81**, 6330 (1959)].

(2) This work was supported by the National Science Foundation and by the Alfred P. Sloan Foundation.

(3) Allred P. Sloan Foundation Fellow.

(4) For a discussion see "Free Radicals in Solution" by C. Walling, John Wiley and Sons, Inc., New York, N. Y., 1957, Chapter 9.

(5) Another type is the formation of transannular peroxides from homoannular dienes on photosensitized oxygenation. This type is well documented [W. Bergmann and M. J. McLean, *Chem. Revs.*, **28**, 367 (1941)] and has been used as a key step in syntheses, and in structure elucidations [P. Bladon, *et al.*, *J. Chem. Soc.*, 4883, 4890 (1952); H. B. Henbest, *et al.*, *ibid.*, 4894 (1952); G. D. Laubach, *et al.*, *J. Am. Chem. Soc.*, **75**, 1514 (1953); G. O. Schenck and R. Wirtz, *Naturwiss.*, **40**, 581 (1953); W. H. Schuller, R. N. Moore and R. V. Lawrence, *J. Am. Chem. Soc.*, **82**, 1734 (1960)].

(6) For references and a review see G. O Schenck *Angew Chem.* **69**, 579 (1957).

function with attendant rearrangement of a double bond has considerable potential in synthetic work is demonstrated by Schenck's direct preparation of pinocarveol and myrtenol from α-pinene and β-pinene, respectively.[7] The oxygenation reaction is also of special interest as a possible pathway for biological oxidations, particularly in plants; and the metabolic importance of hydroperoxides in animal organisms has been re-emphasized lately.[8]

For mechanistic discussion, the photosensitized oxygenation reaction may be arbitrarily divided into primary stages and secondary stages. The primary stages concern in detail the photochemical aspects of the process, *i.e.*, the absorption of light energy and the conversion of the system (sensitizer, oxygen, etc.) to the necessary activated states. Schemes for the primary stages in photosensitized reactions have been proposed[6,9,10] and generally agree that on absorption of light energy the sensitizing dye is converted to its first electronically excited state (short-lived) with subsequent transition to a metastable longer-lived excited state. The long-lived state interacts with oxygen to form a labile sensitizer–oxygen complex,[11] which in turn oxidizes the substrate. A recent review on electronically excited molecules is available.[12]

The secondary stages of photosensitized olefin oxygenations are those that directly involve the substrate. Among other things they are concerned with the way that oxygen is delivered to the olefin,[13] with factors that affect the olefin's susceptibility, and with the structural changes the olefin undergoes. The present paper deals with some of the stereochemical aspects of the reaction and contributes to our knowledge of its secondary stages.

The first objective was to establish if there was any consistent geometric relationship between the newly created C–O bond and the C–H bond that is cleaved, and in our first approach three Δ^6-cholestenes (Ia, b, c) were chosen as substrates (Chart 1). The Δ^6-cholestene system has an α-oriented allylic hydrogen (at C-5) and a β-oriented one (at C-8); and the reaction must necessarily involve one (or both) of these. We shall now discuss the preparation (where necessary) and photosensitized oxygenation of each of these olefins in turn.

3β-Acetoxy-Δ^6-cholestene (Ia) was prepared by a reported method[14] and was photoöxygenated in pyridine solution with hematoporphyrin as the sensitizer.[15] By fractional crystallization of the crude product, 3β-acetoxy-7α-hydroperoxy-Δ^5-cholestene (IIa) was isolated (*ca.* 30%), then purified; considerable starting material (>25%) was recovered. In general we found it advantageous to reduce the crude hydroperoxide before attempting any isolation. Reduction of crude IIa with sodium iodide in ethanol gave 3β-acetoxy-7α-hydroxy-Δ^5-cholestene (IIIa), which was saponified to the corresponding diol IIIb and then converted to the dibenzoate IIIc. Our physical constants for these three known compounds (IIIa, b, c) agree satisfactorily with those reported. To see if any 7β-hydroperoxide was formed in the oxygenation we worked up one run by chromatography of the reduced product. Then appropriate mother liquors were saponified, benzoylated, and carefully rechromatographed. In this way we recovered *ca.* 12% of starting olefin Ia (contaminated with a small proportion of $\Delta^{3,5}$-cholestadien-7-one), and *ca.* 38% of 7α-oxygenated product[16] (combined yield of IIIa, b, c). We did not isolate any 7β-oxygenated products, and within the limits of our method had no positive indication of their presence.

When we tried to hydrogenate a pure sample of hydroperoxide IIa in pyridine solution with a large excess of Raney nickel, the product, interestingly, was 3β-acetoxy-Δ^5-cholesten-7-one (IVa), whose authenticity was confirmed by comparison with a sample prepared by a conventional method.[17] Subsequent trials showed that hydrogen was not needed for this dehydration, and the conversion did not occur appreciably if the Raney nickel was omitted or if it was replaced by 5% palladium-on-charcoal or by decolorizing carbon.

The second olefin we oxygenated was 3β-hydroxy-Δ^6-cholestene (Ib) obtained by saponification of the acetate Ia. The crude hydroperoxide obtained (IIb) was reduced with sodium iodide without isolation.[18] Chromatographic work-up followed by benzoylation and rechromatography of appropriate mother liquors gave 48–60%[19] of Δ^5-cholestene-3β,7α-diol (IIIb or as its dibenzoate IIIc), 5–10% of starting olefin (contaminated with a small proportion of $\Delta^{3,5}$-cholestadien-7-one) and *ca.* 4% of 3β-hydroxy-Δ^5-cholesten-7-one (IVb). Optical rotations taken at various stages in our diol and dibenzoate work-up were strongly negative; and this is characteristic of 7α-oxygenated compounds in this series. However during the end stages of rechromatography of a crude dibenzoate liquor we obtained an oily fraction with a low, positive rotation. Infrared inspection indicated this fraction could contain 7β-oxygenated product (Δ^5-cholestene-3β,7β-diol dibenzoate, IXa), but even so the total weight of the fraction corresponded to less than 1%.

(7) G. O. Schenck, H. Eggert and W. Denk, *Ann.*, **584**, 177 (1953).

(8) L. F. Fieser, T. W. Greene, F. Bischoff, G. Lopez and J. J. Rupp, *J. Am. Chem. Soc.*, **77**, 3928 (1955).

(9) R. Livingston and K. E. Owens, *ibid.*, **78**, 3301 (1956).

(10) G. Oster, J. S. Bellin, R. W. Kimball and M. E. Schrader, *ibid.*, **81**, 5095 (1959).

(11) Also variously known as a moloxide,[9] a photoperoxide[10] or a sensitizer–oxygen addition product.[6]

(12) J. P. Simons, *Quart. Revs.*, **13**, 3 (1959).

(13) It is not known to what extent, if any, the sensitizer plays a part when the oxygen combines with the substrate.

(14) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

(15) All the photoöxygenations in this work were conducted similarly in pyridine in the presence of hematoporphyrin and so these details will not be repeated in subsequent discussion.

(16) This percentage represents crystalline products of good purity. Infrared inspection revealed the presence of additional 7α-oxygenated products in the various mother liquors and tail fractions.

(17) L. F. Fieser, M. Fieser and R. N. Chakravarti, *J. Am. Chem. Soc.*, **71**, 2228 (1949).

(18) At the time of our work hydroperoxide IIb was unknown, but recently its preparation by another route has been reported [G. O. Schenck, O. A. Neumüller and W. Eisfeld, *Angew. Chem.*, **70**, 595 (1958); *Ann.*, **618**, 202 (1958); B. Lythgoe and S. Trippett, *J. Chem. Soc.*, 471 (1959)].

(19) The lower percentage represents material of good purity; the higher figure represents cruder material.

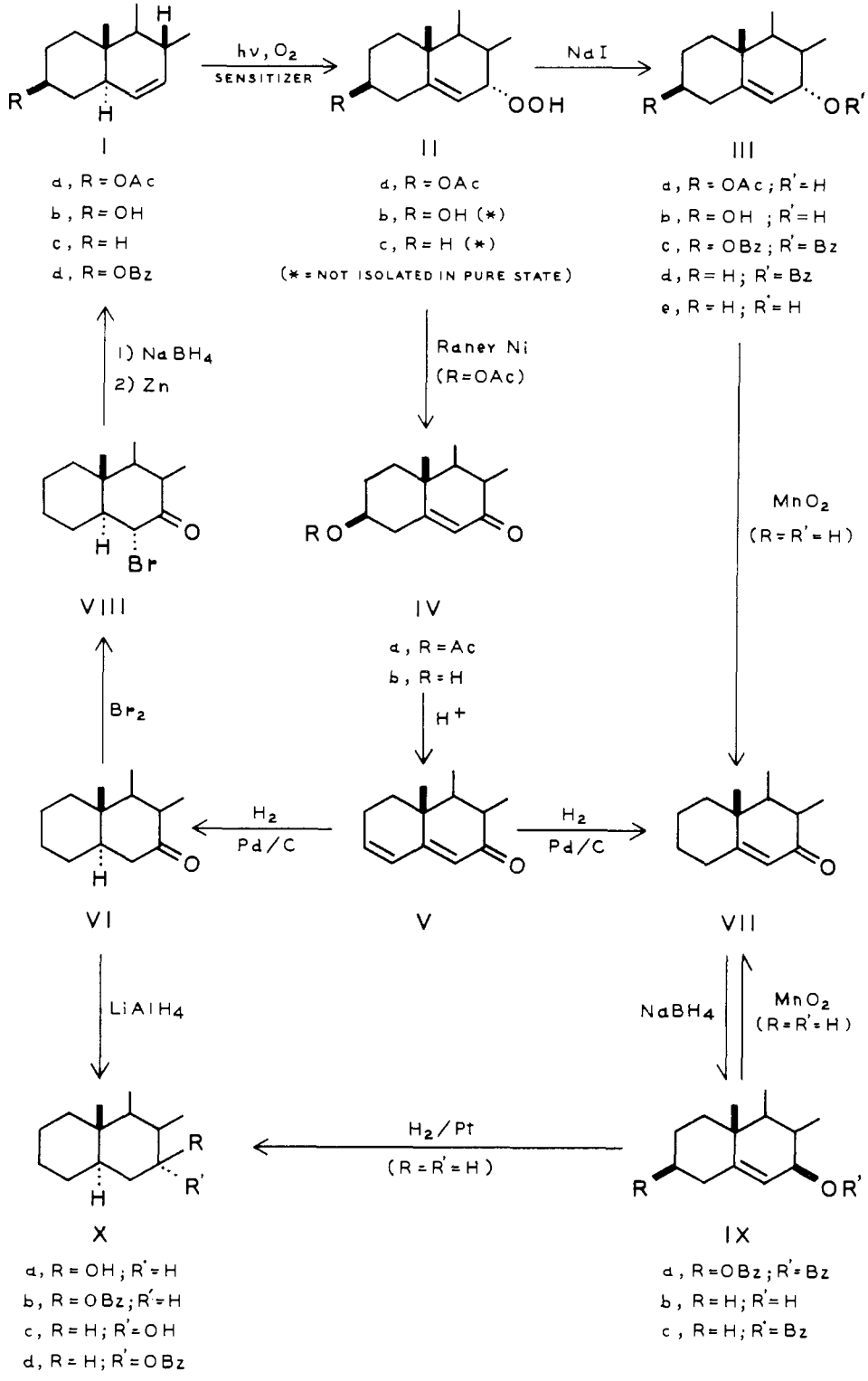


Chart 1.

The formation of small amounts of enone IVb and dienone V in the crude product is understandable in view of the known ability of secondary hydroperoxides to break down to ketones.[20] The presence of the ketonic by-products, however, precludes the use in the reduction step of any reagent capable of converting a ketone group to an alcohol. In the Experimental section we describe one run in which lithium aluminum hydride was used to reduce the crude hydroperoxide and from which Δ^5-cholestene-3β,7β-diol dibenzoate (IXa) was isolated (*ca.* 2% yield) and identified. This 7β-

(20) N. Kornblum and H. B. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951), and references cited there.

oxygenated product undoubtedly arose from hydride reduction of the enone contaminant IVb.

The third olefin of this series, Δ^6-cholestene (Ic), has been prepared by others by Wolff–Kishner reduction of Δ^5-cholesten-7-one[21] and by pyrolysis of cholestan-7α-ol benzoate.[22-24] We developed the following new route to this olefin. Acid treatment of the acetoxy-enone IVa gave the dienone V as reported.[25] The dienone could be hydrogenated over palladium–charcoal in the presence of a small amount of alkali to either cholestan-7-one (VI) or Δ^5-cholesten-7-one (VII) according to the solvent used. Hydrogenation in ethanol[26] gave the saturated ketone VI (*ca.* 80% yield), whereas in ethanol–benzene the enone VII was formed (*ca.* 75–80% yield). This route to VI is more convenient than published ones[27] and the selective hydrogenation to the enone VII appears superior to one reported by Windaus and Kirchner.[28]

The saturated ketone VI was converted to Δ^6-cholestene (Ic) by a three-step sequence analogous to one used by Corey and Sneen on related compounds.[14] Acid-catalyzed monobromination of VI in chloroform gave us a mixture of 6α-bromo- and 6β-bromocholestan-7-one as shown by the presence of two carbonyl bands (1730 and 1715 cm.$^{-1}$, respectively) in the spectrum of the crude product. One epimer, 6α-bromocholestan-7-one (VIII), was isolated by repeated crystallization. The assignment of the equatorial configuration (6α) to the bromine substituent in VIII follows from the shifts relative to the parent ketone that this halogen produces in the carbonyl-stretching vibration ($\Delta\nu$ +26 cm.$^{-1}$)[29] and in the molecular rotation ($\Delta[\phi]$ +148).[14] The last steps to the olefin Ic were performed on crude bromination product and involved reduction with sodium borohydride, then treatment of the bromohydrin mixture with zinc in acetic acid. The over-all yield of pure Δ^6-cholestene from VI was *ca.* 48%.

A brief discussion of the reduction of Δ^5-cholesten-7-one to the corresponding stenols is warranted because of some inconsistencies in the literature and because of our need for rigorous structural assignments. Dimroth and Trautmann[30] reduced enone VII with aluminum isopropoxide and obtained an alcohol (m.p. 93–94°, no optical rotation reported) which did not give a satisfactory elemental analysis. From it they prepared a benzoate, m.p. 108–109°, α +113°.[31] Subsequently the 7β-configuration IXb has been assigned to this alcohol on the basis of its method of formation and its behavior in various elimination reactions.[32]

In our hands the reduction of VII with aluminum isopropoxide gave an oily alcohol mixture. Benzoylation gave a crystalline derivative, but its optical rotation suggested it was impure. In an alternate approach we reduced VII with sodium borohydride and then benzoylated the crude product. Numerous crystallizations gave Δ^5-cholesten-7β-ol benzoate (IXc, m.p. 104.5–105°, α + 130°) from which Δ^5-cholestan-7β-ol (IXb, m.p. 91–92.5°, α ±0°) was regenerated by reduction with lithium aluminum hydride. Our compounds gave satisfactory elemental analyses although the alcohol IXb did exhibit some erratic m.p. behavior. From the general agreement in physical constants we presume our compounds correspond to those of Dimroth and Trautmann. The structure for our stenol IXb was indicated from optical rotations (see later) and was confirmed by oxidation with manganese dioxide to the original enone VII and by hydrogenation over platinum to a saturated alcohol shown to be cholestan-7β-ol (Xa) and not cholestan-7α-ol (Xc) by direct comparison with authentic samples of these epimers obtained from VI by reduction with lithium aluminum hydride.[22]

We shall now discuss the oxygenation of Δ^6-cholestene (Ic). In the usual manner the crude hydroperoxide (containing at this stage *ca.* 10% of the enone VII) was reduced directly with sodium iodide and then benzoylated. Pure Δ^5-cholesten-7α-ol benzoate (IIId) was isolated (31%) by crystallization; and chromatography of the mother liquor yielded some starting olefin Ic (3%), $\Delta^{4,6}$-cholestadiene (3–4%, presumably a result of an elimination) and Δ^5-cholesten-7-one (VII, 13%). A few fractions exhibited optical rotations and infrared spectra that suggested some Δ^5-cholesten-7β-ol benzoate (IXc) was present. The total amount of these fractions corresponded to less than 5%, and none of IXc was actually isolated. The crystalline benzoate IIId was converted to Δ^5-cholesten-7α-ol (IIIe) by reduction with lithium aluminum hydride. That this alcohol is epimeric with IXb (obtained earlier) was confirmed by oxidation of IIIe to VII with manganese dioxide.

Our configurational assignments to the epimers IXb and IIIe are further supported by relevant molecular rotation data (Table I). The molecular rotation increments ($\Delta[\phi]$) relative to Δ^5-cholestene for introduction of the OH and OBz groups at C-7 are of the expected sign and magnitude.[33]

A feature of interest about the epimeric Δ^5-cholesten-7-ols arose from our oxidations with

(21) R. Fisher, G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **34**, 1577 (1951).

(22) R. J. W. Cremlyn and C. H. Shoppee, *J. Chem. Soc.*, 3515 (1954).

(23) W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953).

(24) R. B. Turner, W. R. Meador and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).

(25) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 2375 (1952).

(26) For large scale runs ethanol is not too satisfactory because of the limited solubility of the dienone. Recent experiments by C. E. Berkoff, M. Castle and H. Garfinkel (unpublished) have shown that hydrogenation in ethyl acetate proceeds smoothly to VI and overcomes the solubility problem.

(27) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **72**, 1923 (1950).

(28) A. Windaus and E. Kirchner, *Ber.*, **53**, 614 (1920).

(29) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952); E. J. Corey, *ibid.*, **76**, 175 (1954).

(30) K. Dimroth and G. Trautmann, *Ber.*, **69**, 669 (1936).

(31) These results should be contrasted to those of R. E. Marker, *et al.* [*J. Am. Chem. Soc.*, **59**, 619 (1937); **61**, 3022 (1939)] who reduced 3β-chloro-Δ^5-cholesten-7-one with aluminum isopropoxide and then removed the halogen by treatment with sodium in amyl alcohol. Their product from this sequence had m.p. 105–106° (benzoate m.p. 145–147°); no optical rotations were reported. Marker stated that since his group and Dimroth's had used the same carbonyl reducing agent the disagreement in physical constants could not be due to a configurational difference of the 7-hydroxy group and intimated that Dimroth's compounds were impure.

(32) For a discussion see "Steroids," by L. F. Fieser and M. Fieser, Reinhold Publishing Corp., New York, N. Y., 1959, p. 264.

(33) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).

TABLE I

Compound, Δ^5-cholesten-	$[\phi]_D$[a]	$\Delta[\phi]_D$[b]
-7α-ol (IIIe)	− 433	−225
-7α-ol benzoate (IIId)	−1160	−952
-7β-ol (IXb)	0	+208
-7β-ol benzoate (IXc)	+ 638	+846

[a] $[\phi]$ = molecular rotation (see ref. 34 for this symbolism). [b] $\Delta[\phi] = [\phi]$ (compound) − $[\phi]$ (Δ^5-cholestene; −208).

manganese dioxide. The *quasi*-equatorial isomer IXb underwent oxidation to the enone VII in *ca.* 5 hr., whereas the *quasi*-axial isomer IIIe required *ca.* 50 hr. for completion. If such a rate difference between conformationally epimeric allylic alcohols proves general, it may provide a useful criterion for assignment of structure, and a convenient one, because enone formation is easily followed spectroscopically.

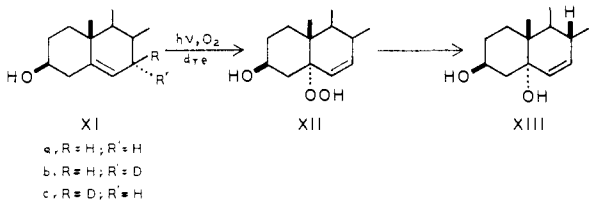


Chart 2.

In our oxygenations of the three Δ^6-steroids Ia,-b,c we obtained no C-6 oxygenated products, which would have arisen on abstraction of the hydrogen at C-8. That the apparent inertness of this hydrogen is not just the result of unfavorable competition with the one at C-5 was shown by experiments with Δ^6-cholesten 3β,5α-diol (XIII). This diol was prepared by photosensitized oxygenation of cholesterol (XIa) to the hydroperoxide XII and then reduction, as reported[35] (Chart 2). We found that diol XIII is unchanged by photosensitized oxygenation even on prolonged treatment. The β-side of the ring system (and especially the β-hydrogen at C-8) is shielded by the angular methyl groups, and the inertness of XIII demonstrates that the reaction can be sterically blocked.

In our oxygenations with the three Δ^6-cholestenes the formation of 7α-oxygenated products, and little or no 7β-isomers,[36] indicates a *cis*-stereochemistry for the reaction. This conclusion is supported further by experiments with 7-monodeuterated cholesterols (Chart 2), whose stereospecific syntheses have been reported by Corey and Gregoriou.[37] Oxygenation of cholesterol-7α-*d* (XIb) gave hydroperoxide XII that retained 8.5% of the original deuterium, whereas cholesterol-7β-*d* (XIc) gave XII that retained 95% of the original deuterium. From these results and those earlier we conclude that in these photosensitized hydroperoxidations the new C–O bond bears a *cis* relationship to the C–H bond that is broken.

(34) P. M. Jones and W. Klyne, *ibid.*, 871 (1960).

(35) G. O. Schenck, K. Gollnick and O. A. Neumüller, *Ann.*, **603**, 46 (1957); G. O. Schenck and O. A. Neumüller, *ibid.*, **618**, 194 (1958).

(36) Conceivably, small amounts of 7β-products could form spuriously.

(37) E. J. Corey and G. A. Gregoriou, *J. Am. Chem. Soc.*, **81**, 3132 (1959). We are grateful to Professor Corey (Harvard Univ.) who kindly supplied us with authentic cholesterol-7α-*d* and cholesterol-7β-*d* for these studies.

In the steroid oxygenations described here and in the literature[6,35] the allylic hydrogen and the newly created C—O bond possessed *quasi*-axial orientations on the olefinic ring. It became of interest therefore to study the behavior of Δ^6-coprostene, which has a *quasi*-equatorial β-hydrogen at C-5, as well as the (inert) β-hydrogen at C-8. Our synthesis of Δ^6-coprostene started with $\Delta^{4,6}$-cholestadien-3-one[38] and is outlined in Chart 3.

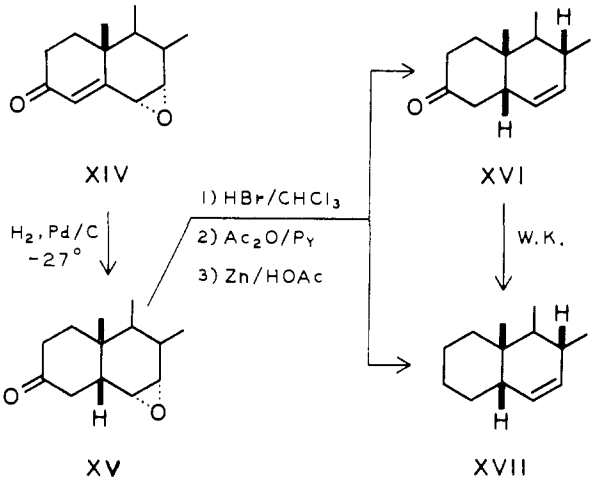


Chart 3.

Treatment of the dienone with either perbenzoic acid or monoperphthalic acid gave 6α,7α-oxido-Δ^4-cholesten-3-one (XIV), having the expected spectral properties. We have no direct proof for the configuration of the epoxide group, but the α-assignment is reasonable and is based on analogy.[39] Hydrogenation of XIV with palladium–charcoal in ether at low temperature (−27°) gave 6α,7α-oxidocoprostan-3-one (XV), isolated in 55% yield. The oxide group of XV was transformed to a Δ^6-olefin by a standard sequence of reactions that involved treatment with hydrogen bromide (in chloroform), acetylation of the derived bromohydrin mixture (with acetic anhydride in pyridine) and then elimination with zinc dust (in acetic acid). This sequence was carried through without purification of intermediates and after chromatography of the final product gave Δ^6-coprosten-3-one (XVI, 30% yield from XV). An unexpected by-product was an oil (*ca.* 17%) shown to be rich in Δ^6-coprostene (XVII). We presume this "Clemmensen-type" removal of the ketone function occurred as a result of the zinc–acetic acid treatment. Wolff–Kishner reduction of ketone XVI gave XVII (80% yield), which is a low-melting solid. The structures of XVI and XVII were confirmed by catalytic hydrogenation of the olefinic link to give, respectively, coprostan-3-one and coprostane, whose identity with authentic samples was established by direct comparison.

Attempted oxygenation of XVI and XVII revealed that even on prolonged treatment these

(38) (a) F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5932 (1953); (b) L. Mandell, *ibid.*, **78**, 3199 (1956). Our Experimental section describes slight modifications of Mandell's method that adapt it better to larger-scale work.

(39) A. L. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, *J. Am. Chem. Soc.*, **80**, 2722 (1958).

compounds were essentially unchanged. This inertness suggests the operation of stereoelectronic factors in photosensitized oxygenations because the electron pair of a *quasi*-equatorial bond is less favorably oriented for overlap with adjacent π-orbitals than that of a *quasi*-axial bond.[40]

Our findings suggest a cyclic mechanism for the olefin–oxygen combination, after the system has been suitably energized. Several detailed variants for such a cyclic process can be envisaged according to whether it is appreciably concerted or not, to the nature of the bonds in the transition states or intermediates, to the extent (if any) of participation by the sensitizer when the oxygen attacks, etc. Until evidence on these points becomes available, however, the cyclic process may be formulated simply as shown, with the implication that the C–H bond and the C–O bond prefer to be roughly perpendicular to the olefinic plane.[41]

Acknowledgment.—We wish to thank Dr. J. B. DiGiorgio for his interest, and for help on many matters.

Experimental[42]

Photosensitized Oxygenations.—All oxygenations were conducted in a vertical Pyrex tube irradiated externally along its length by two 15-watt (standard desk-lamp) fluorescent bulbs mounted about 2 inches away. A fritted glass plate was near the bottom of the tube to disperse the oxygen, which was admitted at the bottom at a convenient rate and without interruption.

3β-Acetoxy-Δ⁶-cholestene (Ia) was prepared by the method of Corey and Sneen[14] and had m.p. 107–107.5°, α −99°; reported m.p. 106–107.5°, α −97°. A new route has recently been announced.[43]

3β-Hydroxy-Δ⁶-cholestene (Ib).—A solution of the acetate Ia (1.44 g.), Claisen alkali (7 ml.) and methanol (70 ml.) was refluxed 2.5 hr. Most of the methanol was evaporated, ether was added, and the mixture was washed to neutrality with water. The ether was dried and concentrated. Warm methanol was added, and when cooled the solution deposited 1.20 g. (89%) of crystals, m.p. 124–129°. After two recrystallizations from methanol it had α −98° and the m.p. was unchanged. After 4 hr. at 73° in vacuum, this last sample had m.p. 124–127°. Corey and Gregoriou noted similar erratic m.p. behavior and reported a rotation of −94°.[37] By comparison, Wintersteiner and Moore reported that this alcohol melted at 114–119° after crystallization from dry methanol and that it lost 4.5% of its weight when dried under vacuum at 100° giving an analytical specimen, m.p. 129–131°, α −81°.[25]

Δ⁶-Cholesten-3β-ol Benzoate (Id).—A solution of the alcohol Ib (0.080 g.) and benzoyl chloride (0.195 g.) in pyridine (5 ml.) stood overnight at room temperature and was then diluted with an excess of water and extracted with ether. The ether was washed with dilute sodium carbonate solution, followed by water, then was dried and evaporated. The residue (0.077 g.) after two crystallizations from ether–methanol gave 0.041 g. of benzoate, m.p. 134.5–135.5° (liquid clears at 150°), α −85°; reported[27] m.p. 128–129° (sinters 124°), α −74°.

Oxygenation of 3β-Acetoxy-Δ⁶-cholestene (Ia). (a) Isolation of 3β-Acetoxy-7 α-hydroperoxy-Δ⁵-cholestene (IIa).—The olefin Ia (1.00 g.) and hematoporphyrin (0.008 g., Mann Research Laboratories) were dissolved in pyridine (20 ml.) and the solution was irradiated and oxygenated. Aliquots (5 ml.) were worked up after 24 hr. and 48 hr., and the remainder after 72 hr. A typical work-up procedure for a 5-ml. aliquot was as follows. Ether (15 ml.) and charcoal (10–20 mg.) were added and the mixture was swirled, filtered, and the filtrate was evaporated at a temperature not exceeding 40°. For larger aliquots the ether and charcoal were proportionately increased. The three residues showed essentially similar infrared spectra, and each was fractionally crystallized from methanol to yield a lower-melting first crop and a higher-melting second crop. The first crops from aliquots 1 and 2 (m.p. 107–107.5°, combined weight 0.23 g.) were shown by mixture m.p. determination to be starting material. The first crop (m.p. 96–98°) of aliquot 3 was presumably largely starting material, but no attempt was made to purify it. The high-melting crops from the three aliquots were combined (0.300 g., m.p. 138–141°) and when crystallized several times from aqueous methanol gave the analytical specimen of IIa, m.p. 142–142.5°, α −137° (*c* 2.06); ν 3540 (sharp) and 3300 (broad) attributed to OOH, 1672 (C=C), 1730 (C=O) cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.93; H, 10.54.

(b) **Preparation of Crude Hydroperoxide IIa.**—An oxygenation of Ia was conducted as in part (a) except that the entire batch was worked up after 72 hr. After the usual charcoal treatment and evaporation of the solvents the residue weighed 0.788 g. One crystallization from aqueous methanol gave 0.500 g., m.p. 125–130°. Three further crystallizations did not improve the m.p. appreciably (m.p. 128–132°). Because the infrared spectrum resembled very closely that of the pure hydroperoxide (no detectable enone or dienone bands) and to avoid excessive loss, this material was used directly in some subsequent experiments. In such cases, the material m.p. 128–132° will be referred to as crude hydroperoxide IIa.

Reduction of Crude Hydroperoxide IIa to 3β-Acetoxy-7α-hydroxy-Δ⁵-cholestene (IIIa).[44]—Sodium iodide (0.57 g.) was dissolved in a solution containing crude IIa (0.100 g.), anhydrous ether (2 ml.), absolute ethanol (10 ml.) and glacial acetic acid (3 drops).[45] The solution stood overnight and then most of the solvent was evaporated. An excess of ether was added, and the dark mixture was washed with sodium thiosulfate solution (3 × 5 ml.), then with water. After the ether was dried and evaporated, the crude alcohol (0.098 g.) remained. At this stage it was combined with 0.127 g. of similar product from another run, then dissolved in petroleum ether and chromatographed on alumina (7.5 g.). Elution with petroleum ether–benzene (7:3) gave in the best

(40) The extent to which steric hindrance contributes to the inertness of XVI and XVII cannot be accurately evaluated. Moreover, if the C-5 hydrogen did react, ring A would have to undergo inversion from one chair form to another at some stage, and this factor could also exert an influence.

(41) Subsequent to our initial communication[1] additional support of this mechanism has been found by R. L. Kenney and G. S. Fisher [Abstracts, 138th Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, p. 79P]. These investigators reported a thorough product analysis of the chlorophyll-sensitized oxygenation of carvomenthene, and they related their results to a cyclic mechanism. Importantly, however, neither their work nor ours in the present paper uniquely supports a concerted process over a non-concerted one. In another report D. B. Sharp [*ibid.*, p. 79P] has suggested for the cyclic process a scheme that is non-concerted and that involves an intermediate "perepoxide."

(42) Unless stated otherwise, the following information applies. All melting points are corrected. Infrared spectra were recorded in chloroform with a Perkin–Elmer (model 21) spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were taken in 95% ethanol with a Cary (model 11M) recording instrument. Petroleum ether refers to that fraction with b.p. 30–60°. Fisher adsorption alumina (80–200 mesh) was used for chromatography. Optical rotations refer to the sodium D line and were taken at room temperature (21 ± 3°) in chloroform (0.5-dm. tube). Pyridine used in oxygenation experiments was commercial reagent grade; that used in acetylations and benzoylations was anhydrous. Benzoyl chloride was previously distilled and stored in sealed ampules. When ether–methanol was used as a solvent pair in crystallizations, the proportion of ether was usually very small. Solvents were evaporated under reduced pressure, and the drying agent for all ether extracts was anhydrous sodium sulfate. Elemental analyses were performed by Mr. J. Walter.

(43) Y. Mazur, M. Nussim and F. Sondheimer, *Proc. Chem. Soc.*, 314 (1959).

(44) H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1792 (1948).

(45) When acetic acid was omitted, the acetoxy group at C-3 suffered concomitant hydrolysis. This was evident from the absence of ester carbonyl absorption in the infrared spectrum of the crude product.

fractions 0.040 g. of **3β-acetoxy-Δ⁶-cholestene** (Ia) (m.p. 105–107°) confirmed by a mixture m.p. with authentic material. Elution with benzene–ether (9:1) gave in the best fractions 0.106 g. of **IIIa**, which had m.p. 138–139.5° (0.058 g.) after several crystallizations from aqueous methanol. The analytical specimen had m.p. 139–140°, α−97° (*c* 1.98); ν 3600, 3450 (OH), 1727 (C=O), 1669 (C=C) cm.$^{-1}$; reported[44] m.p. 139°, α−88°.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: C, 78.59; H, 10.83.

Reduction of the crude hydroperoxide with triphenylphosphine in ether followed by chromatography of the product also gave **IIIa**, but in lower yield.

Δ⁵-Cholestene-3β,7α-diol (**IIIb**).—Saponification of the hydroxy-acetate IIIa (0.070 g.) was accomplished with Claisen alkali (0.08 ml.) in methanol (8 ml.) at room temperature for 24 hr. Evaporation to half-volume precipitated the crude product, which gave 0.045 g. of the known diol **IIIb** on crystallization from methanol; m.p. 186.5–189°, α−88°.[46] This diol was also obtained by reduction of crude hydroperoxide IIa with lithium aluminum hydride, and chromatography.

Δ⁵-Cholestene-3β,7α-diol dibenzoate (**IIIc**) was obtained from the diol IIIb (0.048 g.) with benzoyl chloride (0.35 g.) in pyridine (3 ml.) at room temperature (24 hr.). A few drops of water was added, the pyridine was evaporated and the residue was taken up in ether, which was then washed with 5% sodium bicarbonate solution and water, then dried and evaporated. The crude product was crystallized several times from methanol; 0.046 g., m.p. 156–156.5°, α−110°; reported m.p. 151–152.5°, α−107°[47]; m.p. 158–159°.[48]

Absence of 7β-Oxygenated products in Oxygenation of Ia.—In an effort to seek out any 7β-products we conducted a photoöxidation and work-up as follows. A pyridine solution (20 ml.) of Ia (1.00 g.) and hematoporphyrin (0.008 g.) was oxygenated in the usual way for 72 hr., and the mixture was worked up with ether (50 ml.) and charcoal (0.050 g.) as described earlier. The residual oil (0.930 g.) was reduced with sodium iodide (5.4 g.) in a solution of dry ether (8 ml.), absolute ethanol (50 ml.) and glacial acetic acid (0.17 ml.) as before. The oil from this reduction (0.880 g.) was taken up in petroleum ether and chromatographed on alumina (27 g.) with the following results.

(i).—Elution with petroleum ether–benzene (3:2) gave in the best fractions 0.122 g. of solid, m.p. 102–105°. One crystallization from ether–methanol gave 0.104 g. of pure Ia, m.p. 107–107.5°. Infrared spectra showed that the mother liquor from this crystallization contained some **Δ³·⁵-cholestadien-7-one** (**V**) (estimated 10–20%).

(ii).—Elution with benzene–ether (50:1) gave in the best fractions a solid, m.p. 124–129° (0.536 g.). Two crystallizations from aqueous methanol followed by two crystallizations from methanol gave 0.275 g. of **IIIa**, m.p. 138–139°, α−92°. The mother liquors were saved for later processing.

(iii).—Elution with solvents of increasing polarity up to ether–methanol (1:1) gave a total of 0.071 g. of oily material in about 11 fractions. The infrared spectra of representative fractions could be interpreted on the assumption that these fractions contained varied proportions of **IIIa** and its hydrolysis product **IIIb**.

The mother liquors from ii were combined and evaporated, and the residue was refluxed 2.5 hr. in methanol with Claisen alkali. The crude product (0.176 g.) had α−80°. A portion (0.111 g.) of this product was treated with benzoyl chloride (0.7 g.) and pyridine (5 ml.) and gave an oily product (0.125 g., α−73°) from which 0.050 g. of **dibenzoate IIIc** (m.p. 155.5–156°, α−109°) was obtained by crystallization from ether–methanol. The residue (0.075 g., α−52°) from these crystallization liquors was dissolved in petroleum ether and chromatographed on alumina (2.4 g.). Petroleum ether eluted 0.016 g. of an oil (α−5°) whose infrared spectrum showed no carbonyl bands. Elution with benzene–petroleum ether (7:3) gave a total of 0.052 g. of oil. The optical rotation of the peak fraction was α−88° and its infrared spectrum was identical with that of authentic **dibenzoate IIIc**. There was no evident absorption at 902 cm.$^{-1}$ where authentic Δ⁵-cholestene-3β,7β-diol dibenzoate (IXa) is known to have a distinct band (see later).

Oxygenation of 3β-Hydroxy-Δ⁶-cholestene (**Ib**). (a) *Via* **Sodium Iodide Reduction.**—A solution of the hydroxy-olefin Ib (1.000 g.) and hematoporphyrin (0.008 g.) in pyridine (20 ml.) was photoöxygenated in the usual way for 72 hr. and then worked-up with ether and charcoal as described earlier. The residue (1.0 g.) was reduced by the sodium iodide method (described above in connection with IIa) and gave 0.870 g. of oil, which was taken up in benzene–petroleum ether (3:1) and chromatographed on alumina (27 g.). Elution with benzene–petroleum ether (3:1) gave a solid (0.081 g., m.p. 100–115°) which in turn yielded after three crystallizations from methanol 0.043 g. of starting **olefin Ib** (m.p. 119–120°, α−97°), confirmed by infrared comparison and from elevation of melting point on admixture with authentic material. Ultraviolet inspection showed that these crystallization mother liquors as well as fractions eluted with benzene–ether mixtures ranging from 50:1 to 9:1 contained small proportions (10–15%) of **Δ³·⁵-cholestadien-7-one** (**V**). Fractions eluted with benzene–ether (8:2) gave 0.638 g. of solid (m.p. 170–173°, α−86°) that yielded **Δ⁵-cholestene-3β,7α-diol** (**IIIb**) after three crystallizations from ether–methanol; 0.438 g., m.p. 177–179°, α−92°. Evaporation of these last mother liquors gave a residue that was still strongly levorotatory (α−70°) and whose ultraviolet spectrum (λ 235 mμ, ϵ 2,300) revealed the presence of about 19% of **3β-hydroxy-Δ⁵-cholesten-7-one** (**IVb**) confirmed by its infrared absorption at 1672 cm.$^{-1}$; reported[49] for IVb, λ (95% EtOH) 238 mμ, ϵ 12,500.

This residue was chromatographed on alumina, and elution with benzene–ether mixtures ranging from 14:1 to 9:1 yielded 0.120 g. (α−76°) of alcohol-rich material that contained essentially no α,β-unsaturated ketone (*via* infrared). When benzoylated in the usual way it gave 0.144 g. of crude ester (α−81°) from which 0.067 g. of pure **dibenzoate IIIc** (m.p. 155–156°, α−109°) was obtained after two crystallizations from methanol. The residue from these crystallization liquors had α−26°, and a petroleum ether solution of it was chromatographed on alumina. Petroleum ether eluted 0.011 g. (α−11°) of oil whose infrared spectrum showed no carbonyl absorption. Benzene–petroleum ether (3:7) eluted in the first five fractions 0.058 g. of levoratory oil (peak fraction, α−67°). Two more fractions eluted with th same solvent gave 0.007 g. of dextrorotatory oil (α +22), whose infrared spectrum suggested the presence of some **Δ⁵-cholestene-3β,7β-diol dibenzoate** (**IXa**) because of the appearance of distinct absorption at 902 cm.$^{-1}$ (a position where the 7α-epimer does not absorb) and the over-all similarity of its absorption pattern with that of authentic IXa.

(b) *Via* **Lithium Aluminum Hydride Reduction.**—The hydroxy-olefin Ib (1.0 g.) was oxygenated and the crude peroxidic product (0.845 g.) isolated as in part (a). A solution of it in dry ether (100 ml.) was added during 15 min. to a stirred solution of lithium aluminum hydride (1.5 g.) in dry ether (100 ml.), and the mixture was refluxed 2.5 hr. The excess of hydride was destroyed by addition of wet ether and the mixture was shaken with dilute sulfuric acid until the aluminum salts had dissolved. The ether layer was washed with 5% sodium carbonate solution, with water, and was then dried and evaporated to leave 0.662 g. of crude product, of which 0.651 g. was benzoylated with benzoyl chloride in pyridine overnight at room temperature. The crude benzoate mixture (0.640 g.) was dissolved in petroleum ether and chromatographed on 20 g. of alumina. Elution with petroleum ether–benzene (4:1) gave 0.037 g. of **Δ⁶-cholesten-3β-ol benzoate** (**Id**), which was crystallized once from ether–methanol; 0.023 g., m.p. 134–135° (clears at 148°), α−83°. Fractions eluted with petroleum ether–benzene (7:3) were combined (0.170 g.) and crystallized twice from ether–methanol to give pure **dibenzoate IIIc** (0.141 g.), m.p. 155.5–156°, α−109°.

Fractions eluted with solvents ranging from pure benzene to pure ether were combined (0.140 g.) and because infrared inspection revealed the presence of some hydroxylated

(46) This diol has been reported to exhibit varied m.p.'s between 154 and 186° according to the degree of methanol solvation. Evidently normal drying gives samples whose m.p.'s fall in the higher end of the range; vacuum drying results in a weight-loss and a drop in m.p. to the lower end of the range [O. Wintersteiner and J. R. Ritzmann, *J. Biol. Chem.*, **136**, 697 (1940)]. We have also observed this variability with samples from different sources and in different runs.

(47) O. Wintersteiner and W. L. Ruigh, *J. Am. Chem. Soc.*, **64**, 2453 (1942); see also reference in footnote 46.

(48) L. F. Fieser, M. Fieser and R. N. Chakravarti, *J. Am. Chem. Soc.*, **71**, 1252 (1954).

(49) S. Bergström and O. Wintersteiner, *J. Biol. Chem.*, **141**, 601 (1941).

material the mixture was rebenzoylated. The derived product was crystallized three times from ether–methanol and provided 0.022 g. of **Δ^5-cholestene-3β,7β-diol dibenzoate (IXa)**, m.p. 174–175°, α + 89°; reported[50] for IXa, m.p. 174° α + 94°.

3β-Acetoxy-Δ^5-cholesten-7-one (IVa) (m.p. 155–156°) was prepared by oxidation of cholesteryl acetate with chromium trioxide as described.[48] The reported constants are m.p. 156–158,[48] α −97°.[49]

$\Delta^{3,5}$-Cholestadien-7-one (V).—The acetoxy-enone IVa (35.0 g.) was dissolved in 750 ml. of absolute ethanol containing 5 ml. of concentrated hydrochloric acid. The solution was refluxed 1 hr. and then carefully diluted with water until a slight turbidity persisted, and allowed to cool. The crystalline product V weighed 27.0 g. (89.5%) and had m.p. 111–112.5°, α −314°. The m.p. could be raised 2–3° by one crystallization from ether–methanol; reported[25] m.p. 113–114°, α −300°.

Δ^5-Cholesten-7-one (VII).—The following hydrogenation procedure appears superior to one reported.[28] The dienone V (6.0 g., m.p. 112–113°) was dissolved in a solution prepared from reagent grade benzene (342 ml.), 95% ethanol (137 ml.) and 15% aqueous potassium hydroxide (1.0 ml.). The catalyst was added (0.96 g. of 5% palladium-on-charcoal) and the mixture was hydrogenated at room temperature and one atmosphere pressure. Hydrogen uptake ceased after 1.1 moles had been absorbed (*ca.* 2 hr.). The catalyst was filtered off, the filtrate was neutralized with 0.25 ml. of glacial acetic acid, and the solvent was evaporated and replaced by ether, which was then washed with water, dried, and evaporated. The residue was crystallized once from 95% ethanol and gave a product (5.2 g., m.p. 98–103°) whose infrared spectrum showed appreciable absorption at 1710 cm.$^{-1}$, indicative of a non-conjugated ketone (presumably Δ^4-cholesten-7-one). To effect isomerization, this product was dissolved in absolute ethanol (300 ml.) containing 4 ml. of concentrated hydrochloric acid, and after 30-min. reflux water was carefully added to the hot solution until a faint turbidity persisted. The cold solution deposited 5.1 g. (m.p. 130–131°) of material, which gave large plates of Δ^5-cholesten-7-one (VII) after one crystallization from aqueous ethanol; 4.6 g. (77%), m.p. 130.5–131.5°, α −138, λ 238 mμ (ϵ 12,480). The reported[51] constants are m.p. 128–129°, α −127°, λ 238 mμ (ϵ 11,000). Even though it seems purer than the reported one, our sample of VII may still be slightly contaminated, because the infrared spectrum shows a very weak shoulder on the high frequency side of the unsaturated carbonyl band, which is at 1661 cm.$^{-1}$. This shoulder might be due to some cholestan-7-one or Δ^4-cholestan-7-one.

Cholestan-7-one (VI).—A solution of dienone V (0.100 g.) in 95% ethanol (17 ml.) containing 1% of dissolved potassium hydroxide was hydrogenated at room temperature and one atmosphere with 5% palladium-on-charcoal (0.10 g.). After the uptake of hydrogen (2 moles) was complete (*ca.* 2 hr.) the catalyst was removed by filtration and the filtrate was neutralized with acetic acid and evaporated. The residue was taken up in ether, which was then washed with water, dried and evaporated. The solid was crystallized once from ether–methanol; 0.078 g., m.p. 115–116°, α −48°, ν 1703 cm.$^{-1}$; reported[27] for cholestan-7-one, m.p. 113.5–115°, α −47°. For larger scale runs a weight ratio of dienone to catalyst of 10:1 gave similar results, but the reduction took longer (however, see footnote 26).

Cholestan-7α-ol (Xc) and Cholestan-7β-ol (Xa).—These alcohols and their benzoates were obtained from VI by lithium aluminum hydride reduction as reported.[22] Our constants were: cholestan-7α-ol, m.p. 99–100°, α + 11° (reported m.p. 98°, α + 11°); benzoate Xd, m.p. 164–165°,[52] α − 25° (reported m.p. 163–165°, α − 22°); cholestan-7 β-ol, m.p. 114.5–115.5°, α + 57° (reported m.p. 112–113°, α + 52°); benzoate Xb, m.p. 107.5–108.5°, α + 99° (reported m.p. 106–108°, α + 87°).

6α-Bromocholestan-7-one (VIII).—A solution (2.5 ml.) of bromine in chloroform (7.5% w./v.) was added dropwise during 25 min. to a stirred solution of cholestan-7-one (VI, 0.350 g.) in chloroform (reagent grade, 3.5 ml.) containing one drop of hydrobromic acid (33% in acetic acid). After an additional hour the solution was washed with aqueous sodium acetate (2 × 3 ml.) followed by water, then dried and evaporated to give *crude* bromination production, which could be used directly to prepare Δ^6-cholestene (see next experiment) or could be purified as follows. Three crystallizations from ether–methanol gave a solid (0.302 g., m.p. 120–141°), which was triturated with 2 ml. of ether, and the solvent decanted.[53] The residue was crystallized once from chloroform–methanol (m.p. 151–152°, 0.152 g.) and several recrystallizations gave the analytical sample of 6α-bromocholestan-7-one (VIII), m.p. 153.5–154° (with some decomposition), α −7° (*c* 2.03), ν 1730 cm.$^{-1}$ (C=O with equatorial α-bromine).

Anal. Calcd. for $C_{27}H_{45}OBr$ (465.54): C, 69.65; H, 9.66. Found: C, 69.76; H, 9.86.

Δ^6-Cholestene (Ic).—A suspension of sodium borohydride (0.170 g.) in isopropyl alcohol (20 ml.) was added to *crude* 6-bromocholestan-7-one (0.888 g.) dissolved in isopropyl alcohol (70 ml.). The mixture was stirred overnight at room temperature, and the excess of reducing agent was destroyed by addition of dilute sulfuric acid. Most of the solvent was evaporated and the mixture was partitioned between ether and water. The ether layer was dried and evaporated, and the residue was taken up in glacial acetic acid (70 ml.) and refluxed with zinc dust (4 g.) for 15 min. The hot mixture was filtered and the zinc was washed with hot acetic acid (30 ml.). The filtrate was evaporated, and an ether solution of the residue was washed with water, was dried, and evaporated. The only residue (0.560 g.) in petroleum ether was filtered through a column of alumina (4 g.). The petroleum ether eluates gave 0.477 g. of material that crystallized on standing. Two crystallizations from acetone gave elongated prisms (0.325 g., 48% over-all from cholestan-7-one) of Δ^6-cholestene, m.p. 86–87°, α −98°, ν 1647 cm.$^{-1}$. This olefin, prepared differently, is reported[24] to have m.p. 84–85°, α −84°.

Δ^5-Cholesten-7β-ol Benzoate (IXc). Sodium Borohydride Method.—Sodium borohydride (4.2 g.) suspended in isopropyl alcohol (470 ml.) was added to a solution of Δ^5-cholesten-7-one (4.2 g.) in isopropyl alcohol (260 ml.). The excess of borohydride was destroyed by addition of 50% aqueous acetone (72 ml.) and then 50 ml. of 3% potassium hydroxide solution was added and the solvents evaporated on a steam-bath. The residue in ether was washed to neutrality with water and the ether solution was dried and evaporated. The residue (4.20 g., α −8°) in pyridine (20 ml.) was treated with benzoyl chloride (6.0 g.). After 48 hr. at room temperature the mixture was worked up in the normal way and the product was crystallized from ether–methanol; 4.18 g., m.p. 89–95°. Five recrystallizations gave 1.30 g., m.p. 103.5–105°. The analytical sample of IXc was obtained by repeated crystallization[54] from 95% ethanol; m.p. 104.5–105°, α +130° (*c* 0.72) (compare reported[30] m.p. 108–109°, α +113°, presumably for the same compound).

Anal. Calcd. for $C_{34}H_{50}O_2$ (490.74): C, 83.21; H, 10.27. Found: C, 83.58; H, 10.09.

Aluminum Isopropoxide Method.—In attempts to duplicate a reported procedure[30] we reduced the enone VII with freshly prepared aluminum isopropoxide in dry isopropyl alcohol. The oily product (95%) showed the expected O–H absorption and complete absence of carbonyl bands. After

(50) H. Heymann and L. F. Fieser, *Helv. Chim. Acta*, **35**, 632 (1952).

(51) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(52) Numerous recrystallizations from ether–methanol raised the m.p. to 166.5–167.5°.

(53) The ether from decantation was concentrated and diluted with methanol to give 0.120 g. of crystalline material (m.p. 120–142°) whose infrared spectrum indicated about equal amounts of VIII and its epimer 6β-bromocholestan-7-one (ν 1730 and 1715 cm.$^{-1}$, respectively). Unpublished experiments by C. E. Berkoff and M. Castle have shown that additional equatorial isomer VIII can be obtained from such mixtures by brief equilibration in acetic acid (containing hydrogen bromide), over a steam-bath.

(54) Work-up of the mother liquors ultimately yielded a small amount of cholestan-7α-ol benzoate (Xd, m.p. 168–169°, α −48°) as shown by direct comparison (infrared, mixture m.p.) with an authentic sample. This by-product may be contaminated with a slight amount of IIId (high negative rotation) but evidently not enough to affect its m.p. or infrared spectrum (CS_2) noticeably. This by-product may have arisen from cholestan-7-one, perhaps present as an impurity in the initial enone VII. Less probably, but not inconceivably, the by-product arose *via* concomitant reduction of the olefinic link during the sodium borohydride treatment. For an analogy see R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

abortive attempts to crystallize it, this oil was benzoylated (2 days at room temperature). The derived product was crystallized twice from ether–methanol; m.p. 103.5–104.5°, α +97°. The low optical rotation suggests it is contaminated with the 7α-epimer IIId, which is strongly levorotating.

Δ^5-Cholesten-7β-ol (IXb).—A solution of benzoate IXc (0.60 g.) in dry ether (15 ml.) was added slowly to a stirred suspension of lithium aluminum hydride (0.50 g.) in dry ether (20 ml.), and the mixture was refluxed 4.5 hr. After successive addition of water (0.5 ml.), 15% sodium hydroxide solution (0.5 ml.), and more water (1.5 ml.), the mixture was stirred 20 min. and the granular precipitate was filtered off.[55] The ether was washed with water, was dried and evaporated. The oily residue gave colorless prisms (m.p. 93–100°, 0.39 g.) on crystallization from ether–methanol. Six recrystallizations did not change the m.p. range, although some erratic m.p. behavior was observed at intermediate stages. Sublimation (high vacuum at 110°) finally gave the analytical specimen of IXb, m.p. 91–92.5°, α ±0° (*c* 1.44).[30]

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.81, H, 11.66.

Oxidation of Δ^5-Cholesten-7β-ol (IXb) with Manganese Dioxide.—A mixture of IXb (0.020 g., m.p. 93–100°), manganese dioxide (0.20 g.)[56] and reagent grade benzene (5 ml.) was stirred 5 hr. at room temperature. After filtration the benzene was washed with water and evaporated. One crystallization from ether–methanol gave **Δ^5-cholesten-7-one (VII)**, 0.013 g., m.p. 128.5–129.5° undepressed on admixture with authentic VII.

Hydrogenation of Δ^5-Cholesten-7β-ol (IXb).—Platinum oxide (0.025 g.) was added to a solution of IXb (0.020 g.) in ether (10 ml.) and 95% ethanol (5 ml.), and the mixture was hydrogenated at one atmosphere and room temperature for 15 hr. During this period a fresh batch of catalyst (0.030 g.) was introduced after 1.5 hr. and again after 12 hr. The residual oil (0.018 g.) obtained after filtration and evaporation of solvent was dissolved in petroleum ether and chromatographed over alumina (1.0 g.). The fraction (0.006 g.) eluted with petroleum ether–benzene (7:3) was retained and after two crystallizations from ether–methanol had m.p. 113.5–114.5°, which was undepressed by authentic **cholestan-7β-ol (Xa)**, but strongly depressed by authentic cholestan-7α-ol (Xc).

Oxygenation of Δ^6-Cholestene (Ic). (a) Isolation of Δ^5-Cholesten-7α-ol Benzoate (IIId).—The olefin Ic (1.00 g.) in pyridine (20 ml.) containing hematoporphyrin (0.008 g.) was photoöxygenated 72 hr. Decoloration with charcoal as described earlier gave a crude product (1.10 g., α −98°) whose infrared and ultraviolet spectra indicated the presence of about 10% of **Δ^5-cholesten-7-one (VII)**.[57] Reduction of the oil with sodium iodide (6.3 g.) for 44 hr. at room temperature in absolute ethanol (20 ml.) containing glacial acetic acid (0.2 ml.) gave an oily product (1.0 g., α −67°) whose extinction at 238 mμ (ϵ 1,580) indicated the presence of *ca.* 13% of the enone VII. This crude reduction product was treated with benzoyl chloride (3.6 g.) in pyridine (12 ml.) for 2 days. The oily benzoate obtained on normal work-up (1.13 g., α −135°) was crystallized twice from ether–methanol; 0.410 g., m.p. 128–130°, α −239°. Further crystallization gave the analytical sample of IIId, m.p. 133–133.5°, α −236° (*c* 1.46).

Anal. Calcd. for $C_{34}H_{50}O_2$ (490.74): C, 83.21; H, 10.27. Found: C, 83.27; H, 10.40.

(b) Isolation of Δ^6-Cholestene.—The mother liquors from crystallization of IIId (part a) were evaporated and the residue (0.67 g., α −115°) was dissolved in hexane and chromatographed on alumina (31 g.). The first two fractions eluted with hexane gave 0.027 g. of crude Δ^6-cholestene. Two crystallizations from acetone gave m.p. 82–85°, undepressed by authentic material.

(c) Isolation of $\Delta^{4,6}$-Cholestadiene.—Some of the later fractions eluted with hexane and some of those eluted with hexane–benzene (20:1) were combined and after two crystallizations from acetone gave $\Delta^{4,6}$-cholestadiene (0.029 g.) as colorless prisms, m.p. 92–92.5°, α + 13°; $\lambda\lambda$ 238, 230, 246 mμ (ϵ 26,070, 22,270, 15,190). The reported constants for this diene are: m.p. 90–91°,[30] α + 5°,[58] λ 238 mμ (ϵ 24,810)[30] with inflections at 230 and 245 mμ.[59]

(d) Elution of a Benzoate Mixture.—Hexane–benzene (9:1) eluted oily fractions (0.070 g.) whose individual infrared spectra showed typical absorption of a benzoate. The peak fraction (0.014 g.) had α + 23° and may have consisted of a mixture of Δ^5-cholesten-7α-ol benzoate (IIId) and Δ^5-cholesten-7β-ol benzoate (IXc) because of the presence of bands at 1342 and 888 cm.$^{-1}$, and at 1326 and 896 cm.$^{-1}$. (Authentic IIId exhibits the former pair of bands but not the latter, whereas authentic IXc exhibits the latter pair but not the former.)

(e) Isolation of Δ^5-Cholesten-7-one (VII).—Elution with hexane–benzene (7:3) gave oily fractions (0.133 g.) whose individual infrared spectra showed strong absorption at 1664 cm.$^{-1}$ (α,β-unsaturated C=O) and no typical benzoate absorption. The two peak fractions (0.059 g.) were crystallized three times from ether–methanol and gave VII as large plates; 0.021 g., m.p. 130–131°, α −136°. Its authenticity was established by infrared and mixture m.p. determinations.

(f) Elution of Unidentified Mixtures.—Elution with hexane–benzene (6:4) gave oily fractions (0.11 g.) whose individual infrared spectra showed typical benzoate ester peaks, but no absorption at the four positions characteristic of the epimers IIId and IXc. The peak fraction had α +150°. Purification was not attempted. Continued elution with solvents up to pure ether gave oily fractions (0.076 g.) whose infrared spectra suggested they were multicomponent mixtures. The total recovery from the column was 0.47 g. (71%).

Δ^5-Cholesten-7α-ol (IIIe).—Lithium aluminum hydride (0.14 g.) in dry ether (10 ml.) was added to a solution of Δ^5-cholesten-7α-ol benzoate (IIId, 0.150 g.) in dry ether (10 ml.) and the solution was refluxed 4.5 hr. After successive addition of water (0.14 ml.), 15% sodium hydroxide solution (0.14 ml.) and more water (0.42 ml.) the mixture was stirred 20 min., then filtered. The solid was washed with more ether, and the total ether filtrate was washed with water, dried, and evaporated, first at room temperature and finally on the steam-bath to remove benzyl alcohol. The oily residue (0.116 g.) was crystallized numerous times from methanol (with or without a small proportion of ether); 0.081 g. The solids obtained in these crystallizations exhibited rotations that became essentially constant (α −112 ± 2°),[60] but the crystals were slightly sticky and melted over wide ranges between 50–70°.[61] Finally one of the crystallizations gave feathery needles that were not sticky and that melted sharply (m.p. 65–65.5°, shrinkage at 63°); this sample was dried under vacuum overnight at room temperature for analysis.

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 84.07; H, 12.04.

Oxidation of Δ^5-Cholesten-7α-ol (IIIe) with Manganese Dioxide.—A crude batch of IIIe (0.020 g.) in benzene (5 ml. was stirred with manganese dioxide[56] (0.30 g.) for 49 hr. at room temperature. (At shorter reaction times the oxidation was incomplete.) The mixture was filtered and the solid was washed with hot chloroform. Evaporation of the com-

(55) This work-up method for lithium aluminum hydride reductions is reported [V. M. Micovic and M. LJ. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953)].

(56) J. Attenburrow, A. F. B. Camron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(57) Attempts were made to assay quantitatively the hydroperoxide content of this crude product by a reported method [J. S. Fritz and G. S. Hammond, "Quantitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 278]. Our values were 55% (±2%), but the figures may be misleading because pure 3β-hydroxy-5α-hydroperoxy-Δ^6-cholestene (XII) under identical conditions assayed for only 64% hydroperoxide.

(58) J. C. Eck and E. W. Hollingworth, *J. Am. Chem. Soc.*, **63**, 108 (1941).

(59) D. H. Gould, K. H. Schaaf and W. L. Ruigh, *ibid.*, **73**, 1266 (1951).

(60) Chloroform solutions of this material exhibited no mutarotation after 15 hr. at room temperature.

(61) Although the compound precipitates from methanol as nice feathery needles, it is slightly sticky when separated from the mother liquor by filtration, centrifugation or vacuum evaporation. The ultraviolet spectrum revealed no contamination by conjugated diene or enone. However, after attempted slow sublimation (3 days at 90° under high vacuum) this material gave a liquid condensate that showed λ 238 mμ (ϵ 1270) with inflections at 230 and 246 mμ. Presumably it now contained about 5% of $\Delta^{4,6}$-cholestadiene.

bined filtrates gave a residue that was crystallized from ether–methanol; m.p. 124–127° (0.010 g.). Recrystallization gave **Δ⁵-cholesten-7-one (VII)** as large plates, m.p. 127–128.5°, α −139°, in all respects (infrared, mixture m.p.) identical with authentic material.

Attempted Oxygenation of Δ⁶-Cholesten-3β,5α-diol (XIII).—The diol XIII (1.0 g., m.p. 147–150°, prepared as reported[35]) in pyridine (20 ml.) containing hematoporphyrin (0.008 g.) was photoöxygenated. After 48 hr. an aliquot was worked up with charcoal in the normal way and yielded a solid, m.p. 145–155°, whose infrared spectrum was identical to that of starting material. An aliquot after 144 hr. gave solid whose infrared spectrum was identical to that of starting diol except for the appearance of a new (very weak) band around 1725 cm.$^{-1}$. In another run the solution was heated to 80° by means of an electrical resistance wire coiled around the oxygenation tube. After 24 hr. the product showed a spectrum essentially identical to that of starting diol. A photoöxygenation at 115° for 27 hr. gave material with broad (but weak) absorption around 1709 and 1653 cm.$^{-1}$, but otherwise generally similar to that of starting diol.

Δ⁴,⁶-Cholestadien-3-one.—To adapt it to large scale runs we modified the work-up in Mandell's reported procedure.[38b] A solution of cholesterol (60 g.) and *p*-benzoquinone (360 g. freshly crystallized from ligroin, b.p. 100–115°) in 3.5 l. of toluene was distilled until about 500 ml. of distillate came over. Powdered aluminum isopropoxide (51 g.)[62] was added in portions and with sufficient time intervals to allow the vigorous reaction to subside. The black mixture was refluxed 1 hr., then carefully diluted with hot water (2 l.) and steam distilled for about 3 hr. to remove toluene. The mixture was brought to ice temperature and treated with 1 *N* sulfuric acid (3 l.). A suspension was obtained, from which the solid was removed by suction filtration. The filtrate was thoroughly extracted with ether (6 × 700 ml.) and the solid was separately triturated with ether (7 × 400 ml.). All ether extracts were combined, concentrated to 2–3 l. and then washed with 10% sulfuric acid (4 × 400 ml.); the acid extracts were back-washed once with ether. The ether was dried and evaporated and the residual tarry oil was extracted with portions of hot benzene (total volume 1 l.). The benzene solution was concentrated a little by distillation (to remove water), then filtered through a column of alumina (1 kg.). Elution with an additional 6 l. of benzene and evaporation of the combined eluates gave the crude dienone as a pale orange oil (38–40 g., 59–62%) that later solidified. The extinction (24,860) at 285 mμ indicated a dienone content of 95.5%.[63] Crystallization from methanol gave colorless stout needles (26–28 g.), m.p. 78.5–80.5°, α + 35° (reported[38a] m.p. 80–81°). Additional product (4 g.) of comparable purity was recovered by repassage of the mother liquor residues through alumina as before.[64]

We also prepared Δ⁴,⁶-cholestadien-3-one by oxidation of cholesterol with manganese dioxide[56] as reported,[38a] but for large-scale runs found this method less effective.

6α,7α-Oxido-Δ⁴-cholesten-3-one (XIV). Method A.—Monoperphthalic acid in ether was prepared and concentrated as reported.[65] Sufficient methylene chloride was added to give a solvent ratio of methylene chloride–ether of 4:1, and a peracid content of 0.040–0.050 g. per ml. Δ⁴,⁶-Cholestadien-3-one (0.600 g.) in 12.5 ml. of solution (containing 0.60 g. of peracid, 2.0 equiv.) stood 48 hr. at room temperature (1.1 equiv. of peracid consumed). The solution was filtered through a column of alumina (40 g.) which was then eluted with more methylene chloride (*ca.* 200 ml.). Evaporation of the eluates gave an oil (0.227 g.) which was dissolved in benzene–petroleum ether (1:5) and chromatographed on alumina (7 g.). Elution with benzene–petroleum ether gave at first oily fractions, shown by infrared to be largely starting dienone. When crystalline fractions appeared, elution was hastened by the use of 100% benzene. The combined solid (0.150 g.) was crystallized once from methanol; m.p. 136.5–138° (0.134 g.). The analytical sample (feathery needles) obtained on recrystallization had m.p. 138.5–139°, α −59° (*c* 1.15); ν (CS_2) 1684, 1621, 870 cm.$^{-1}$; λ 241 mμ (ϵ 12,010).

Anal. Calcd. for $C_{27}H_{42}O$ (398.61): C, 81.35; H, 10.62. Found: C, 81.33; H, 10.56.

Method B (For Large Scale Runs).—The dienone (31.0 g.) was dissolved in a chloroform solution of perbenzoic acid[66] (275 ml. containing 14.0 g. of peracid, 1.25 equiv.). Some anhydrous sodium sulfate was added and the mixture allowed to stand at room temperature 12 hr. (after which time most of the peracid had been consumed). The solution was filtered through a column of alumina (1 kg.), which was eluted with more chloroform (10 l.). Evaporation of the combined eluates gave 23 g. of waxy solid, which was dissolved in benzene–petroleum ether (1:5) and chromatographed on alumina (690 g.). Benzene–petroleum ether (1:5) eluted an unidentified compound which had m.p. 121.5–122° (*ca.* 1 g.) after several crystallizations from methanol.[67] Elution with benzene–petroleum ether (2:3) gave starting dienone (5.3 g.). The oxide XIV was eluted with benzene–petroleum ether (3:2) followed by pure benzene. The solid fractions of XIV were pooled and crystallized from methanol; 10.2 g., m.p. 137–138.5°.

6α,7α-Oxidocoprostan-3-one (XV).—To a solution of XIV (0.523 g.) in dry ether (40 ml.) was added 10% palladium-on-charcoal (0.24 g.). The mixture was cooled to −27° and hydrogenated at this temperature (±2°) in an apparatus equipped with a mercury-filled manometer and buret[68] until hydrogen uptake ceased (1.2 moles after *ca.* 2 hr. was typical). The catalyst was filtered off, washed with warm ether, and the combined filtrates were evaporated leaving a sticky solid which gave feathery needles after two crystallizations from methanol; 0.277 g., m.p. 122–123°, α −46° (*c* 1.41). The analytical sample had the same constants, as well as ν (CS_2) 1724, 892 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 81.07; H, 11.11.

Δ⁶-Coprosten-3-one (XVI) was prepared from XV by the following three-step sequence (a, b, c) without purification of intermediates. **(a) Oxide Cleavage.**—Hydrogen bromide from a cylinder was purified by passage over copper turnings and then through concentrated sulfuric acid. It was bubbled into chloroform (previously freed of ethanol by filtration through alumina) up to saturation. The oxide XV (1.70 g.) was dissolved in 300 ml. of this solution and allowed to stand 30 min. at ice temperature. The solution was washed with 5% sodium bicarbonate solution (4 × 50 ml.); the combined washes were back-extracted once with chloroform. The combined chloroform layers were washed with water, were dried and evaporated. The oily bromohydrin (1.91 g.) showed (CS_2) O–H absorption at 3589 and 3521–3460 cm.$^{-1}$, as well as C–O absorption at 1029 and 1058 cm.$^{-1}$, and C–Br absorption at 733 cm.$^{-1}$. **(b) Acetylation.**—The crude bromohydrin in pyridine (40 ml.) was treated with acetic anhydride (22 ml.) at room temperature for 40 hr. The solution was evaporated under good vacuum at a temperature not exceeding 35°. The residual oil was treated with 5 ml. of absolute ethanol containing a few drops of pyridine and after 10 min. the solvent was removed as before. The residue in ether was washed with 5% sodium bicarbonate solution and with water. The ether when dried and evaporated left 1.95 g. of the crude acetate as a semi-solid; ν (CS_2) 1751 (ester carbonyl), 1724 (ketone), 1229–1221 (sp^2 C–O),[69] 1029–1015 (sp^3 C–O), 734 (C–Br?). **(c) Zinc Dust Treatment.**—A mixture of the crude acetate in glacial acetic acid (170 ml.) containing zinc dust (13 g.) was stirred and refluxed 35 min. The cooled mixture was filtered, the

(62) A. L. Wilds, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1944, p. 198.

(63) A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1713 (1946).

(64) We wish to acknowledge valuable help by W. L. Mendelson in the development of the entire work-up procedure.

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

(66) D. Swern, "Organic Reactions," Vol. VII, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 393.

(67) Much less of this unidentified product was obtained when the starting dienone had been prepared by the aluminum isopropoxide method than by the manganese dioxide method.

(68) When water-filled leveling burets were used, the hydrogenation was incomplete and gave a sharp-melting crystalline mixture (m.p. 126–127°) unresolved by recrystallization. The infrared spectrum of this material was essentially superposable on that given by an artificial mixture, which was prepared from XIV and XV in a weight ratio of 25%:75% and crystallized once from methanol (m.p. 126.5–127.5°).

(69) In esters a distinction is made between the two kinds of singly-bonded carbon–oxygen units by use of the terms sp^2 C–O and sp^3 C–O, which identify the relevant carbon by reference to its approximate state of hybridization [A. Nickon, *J. Am. Chem. Soc.*, **79**, 243 (1957)].

zinc was washed well with ether and the combined filtrates were evaporated. The residue in ether was washed with 5% sodium bicarbonate solution, then water, and the ether was dried and evaporated. The oily residue (1.38 g.) in petroleum ether (50 ml.) was chromatographed on alumina (42 g.). Elution with petroleum ether gave in the first few fractions a pale yellow oil (0.27 g.), which was largely Δ^6-**coprostene** (**XVII**) and whose purification is described in part B below. Continued elution up to petroleum ether–benzene (4:1) gave 0.12 g. of oil, whose infrared spectrum indicated it was a mixture. Further elution with petroleum ether–benzene (4:1) gave solids (0.64 g.) which had m.p. 109–110° (0.49 g.) after crystallization from methanol. Recrystallization gave the analytical specimen of XVI, m.p. 109–110°, α −52° (*c* 1.62); ν (CS_2) 1727 (C=O), 1656 (C=C).

Anal. Calcd. for $C_{27}H_{44}O$ (384.62): C, 84.31; H, 11.53. Found: C, 84.56; H, 11.52.

Δ^6-Coprostene (XVII). A. By Wolff–Kishner Reduction of XVI.—Hydrazine (64% in water, 1.4 ml.) was added to a solution of XVI (0.200 g.) in absolute ethanol (5 ml.). This combination was warmed briefly to give a clear solution and then mixed with 12 ml. of absolute ethanol containing 0.35 g. of dissolved sodium, and heated in a sealed tube at 210–220° for 17 hr. The solvents were evaporated and the residue taken up in ether and water. The ether layer was washed free of alkali with water, was dried and evaporated. The residual oil (0.168 g., no C=O *via* infrared) in petroleum ether (5 ml.) was chromatographed on alumina (6 g.). Elution with petroleum ether (20 ml.) gave 0.157 g. of colorless oil (α −50°) whose infrared spectrum was not significantly different from that of the analytical sample.

After three crystallizations from ether-methanol at low temperature (Dry Ice cooling) the material remained solid at room temperature. One normal crystallization then gave prismatic needles, m.p. 44–45° (0.124 g.). Several recrystallizations gave the analytical sample, m.p. 44–45°, α −7° (*c* 1.65); ν (CS_2) 1647 (C=C), 741, 704 (olefinic C–H) cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{46}$ (370.64): C, 87.49; H, 12.51. Found: C, 87.63; H, 12.67.

B. As a By-product from the Preparation of XVI.—The pale yellow oil eluted with petroleum ether in the preparation of XVI was combined with similar material from several runs (total wt. 1.81 g., α −13°), and chromatographed on alumina (100 g.) with petroleum ether as eluant. The fractions richest in Δ^6-coprostene (followed *via* infrared) were combined (1.05 g.) and carefully rechromatographed on alumina (100 g.). The purest fractions were retained and had essentially the same optical rotations (α −6 ± 2°, total 0.66 g.). Numerous crystallizations from ether–methanol (low-temperature, then normal) gave Δ^6-coprostene with m.p. 41.5–42.5°, identical in all respects to that from the Wolff–Kishner method. Because the losses on crystallization are considerable and because there is no significant difference in infrared absorption, we used the non-crystalline material in some of the oxygenations to be described later.

Hydrogenation of XVI to Coprostan-3-one.—A solution of XVI (0.091 g.) in absolute ethanol (5 ml.) was added to a suspension (presaturated with hydrogen) of 10% palladium charcoal (0.070 g.) in absolute ethanol (20 ml.). After hydrogenation at room temperature until uptake ceased (about 10 min.), the mixture was filtered and the filtrate evaporated. Chromatography of the residue on alumina (2.7 g.) gave crystalline product, which was further purified by rechromatography (petroleum ether eluant); m.p. 54–55° (0.049 g.). The m.p. was undepressed by authentic coprostan-3-one (m.p. 57–58°), and their infrared spectra (CS_2) were identical.

Hydrogenation of XVII to Coprostane.—A solution of XVII (0.035 g., m.p. 43–44.5°) in ether (15 ml.) containing platinum oxide (0.050 g.) was hydrogenated in the usual way for 1 hr. The product was chromatographed on alumina (3 g.) and the oil eluted with petroleum ether was crystallized from ether–ethanol; m.p. 70.5–71.5° (0.021 g.). Its identity with coprostane was established by appropriate mixture m.p. and infrared spectral comparisons (CS_2) with an authentic specimen, m.p. 69–69.5°.

Attempted Oxygenation of Δ^6-Coprostene (XVII).—The olefin XVII (0.10 g. of colorless oil, α −6° obtained by procedure B) in 10 ml. of pyridine containing hematoporphyrin (0.005 g.) was photooxygenated and aliquots were periodically removed and worked up in the usual way. Except for the gradual development of weak absorption around 1730 cm.$^{-1}$, the infrared spectra of the products were essentially identical to that of starting material even after 189 hr.[70] The aliquot after 42 hr. had α −4°. An oxygenation conducted at 70 ± 2° was attempted on a fresh batch of Δ^6-coprostene. After 48 hr. the olefin was unchanged, except for the appearance of weak absorption between 1725–1670 cm.$^{-1}$. The recovered material (0.090 g.) in pyridine (10 ml.) was oxygenated in the presence of methylene blue (0.006 g.) for 66 hr. This treatment produced no significant change in the infrared absorption.

Attempted Oxygenation of Δ^6-Coprosten-3-one (XVI).—This keto-olefin was oxygenated in the usual way (hematoporphyrin) and aliquots were periodically examined. Even after 70 hr. the product had an infrared spectrum essentially identical to that of starting material.

Oxygenation of Cholesterol (XIa), Cholesterol-7α-*d* (XIb) and Cholesterol-7 β-*d* (XIc).—A solution of cholesterol (0.100 g., purified *via* the dibromide) and hematoporphyrin (0.006 g.) in pyridine (10 ml.) was photooxygenated for 48 hr. After the addition of ether (25 ml.) the solution was stirred 15 min. with activated charcoal (0.070 g.), which was filtered off and washed with more ether. Evaporation of the filtrate left a solid, which was crystallized once from ether–methanol to give **3β-hydroxy-5α-hydroperoxy-Δ^6-cholestene** (**XII**) as colorless plates, m.p. 149.5–150.5° (vac., Pyrex), 0.043 g., reported[35] m.p. 148–149°. An intense infrared spectrum (KBr) was recorded for comparison purposes.

A 0.100-g. sample of **cholesterol-7β-d**[37] (deuterium content 0.60 atom/molecule)[71] was oxygenated and processed in an identical way and gave the hydroperoxide, m.p. 150.5–151.5° (0.039 g.). An intense spectrum (KBr) showed a single C–D absorption peak at 2227 cm.$^{-1}$. The deuterium content of the product was 0.57 atom/molecule, corresponding to a retention of 95% of the original amount of deuterium.

Identical oxygenation of 0.100 g. of **cholesterol-7α-*d***[37] (deuterium content 0.59 atom/molecule) gave hydroperoxide XII (0.041 g., m.p. 150.5–151.5°) whose infrared spectrum (intense in KBr) showed no bands between 2400–2000 cm.$^{-1}$ and was identical over the entire range with the spectrum of XII obtained from cholesterol. The deuterium content was 0.05 atom/molecule, corresponding to a retention of 8.5% of the original amount of deuterium.

Dehydration of Hydroperoxide IIa with Raney Nickel.—Raney nickel (0.150 g.) was added to IIa (0.020 g., m.p. 142–142.5°) dissolved in pyridine (8 ml.) and the mixture was stirred under hydrogen for 5 hr. The catalyst was filtered off, washed with ether, and the filtrates evaporated. Crystallization of the residue twice from aqueous methanol gave 3β-**acetoxy-Δ^5-cholesten-7-one** (**IVa**), m.p. 157.5–159.5°, identified by comparison (infrared; mixture m.p.) with authentic material. Other trials conducted similarly, but on "crude" hydroperoxide IIa (m.p. 128–132°), revealed that hydrogen gas was not needed for this conversion. Furthermore, enone formation was not appreciable if the Raney nickel was omitted, or if it was replaced by an equal weight of 5% palladium-charcoal or decolorizing carbon. When the weight of Raney nickel was reduced to 0.020 g., the conversion proceeded only slightly. In all the runs the extent of reaction was crudely followed by the intensity increase of the α,β-unsaturated carbonyl band at 1672 cm.$^{-1}$.

(70) In nearly all the photooxygenations we carried out, the initial crude products showed weak infrared absorption around 1725 and 1675 cm.$^{-1}$.

(71) We are grateful to Dr. A. San Pietro, who kindly performed all the deuterium analyses in this work, and to Dr. T. Enns for operation of the mass spectrometer. The analytical method is described [A. San Pietro in "Methods in Enzymology," edited by S. P. Colowick and N. O. Kaplan, Academic Press, Inc., New York, N. Y., Vol. IV, 1957, p. 473].