Reactivity and Geometry in Allylic Systems. IV. Stereochemical Factors in the Photosensitized Oxygenation of 5α- and 5β-Cholest-3-enes*[1,2]

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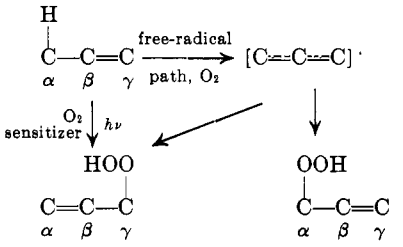
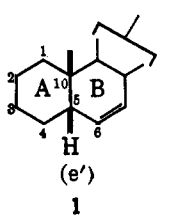
5α-Cholest-3-ene (**5**) and 5β-cholest-3-ene (**6**) have been used as substrates to test current views on the stereochemical requirements of the allylic C–H bond in photosensitized oxygenation. Both olefins were prepared along with cholest-4-ene (**4**), by Wolff–Kishner reduction of cholest-4-en-3-one (**3**). After separation in the form of their dibromides, **5** and **6** were individually regenerated by treatment with zinc. The principal products on photooxygenation of **5** in pyridine with hematoporphyrin as sensitizer followed by reduction of the derived hydroperoxides were cholest-4-en-3α-ol (**7b**), cholest-4-en-3β-ol (**8b**), and cholest-4-en-3-one (**3**) in a ratio of about 9:1.4:1. The 5β-olefin **6** underwent oxygenation more slowly and led to **7b**, **8b**, and **3** in a ratio of about 1:5.5:2, respectively. The results indicate that for each olefin the expected photosensitized pathway predominated but that conventional-type autoxidation competed to an appreciable extent. The behavior of olefin **6** stands in contrast to that of 5β-cholest-6-ene (**1**), which is known to be inert to photosensitized oxygenation. These results place on firmer ground the view that a quasi-axial allylic hydrogen (or its equivalent) is strongly favored over a quasi-equatorial hydrogen for abstraction in the sensitized pathway. We conclude in addition that a single axial methyl group in a 1,3-*cis* relation to the site of oxygen attack can substantially retard oxygenation even when the allylic C–H bond has the appropriate conformation.

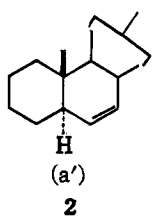
Treatment of monoolefins with molecular oxygen can produce allylic hydroperoxides. Under conditions favorable for the creation and propagation of radicals, the reaction involves oxygen attack on allylic radicals and can lead to hydroperoxides with rearranged and unrearranged double bonds.[3] In contrast, Schenck and his co-workers have found that when the olefin oxygenations are conducted photochemically in dilute solution and in the presence of a suitable sensitizer a different pathway predominates in which an allylic shift of the double bond invariably accompanies formation of the hydroperoxide (see Scheme I).[4] The photosensitized reaction is finding increasing application in synthesis,[5,6] and a knowledge of the structural features that affect the ease and position of oxygen attack is of practical significance as well as of mechanistic interest.

SCHEME I



Studies with steroid olefins demonstrated a "*cis*" requirement between the C–H bond that is cleaved and the C–O bond that is formed, and led to the postulation of a cyclic mechanism,[7,8] which is illustrated in Figure 1. The oxygen, suitably activated,[9] must necessarily attack the π-orbital from a direction perpendicular to the olefinic plane, and the allylic hydrogen must be suitably oriented to allow its transfer to oxygen. In cyclohexenoid systems with half-chair conformations a quasi-axial hydrogen (a′) should be positioned better for this cyclic transfer than a quasi-equatorial hydrogen (e′). A compound used to test this view was 5β-cholest-6-ene (partial structure **1**) in which the e′ hydrogen at C-5 proved inert to photosensitized oxygenation conditions that readily effected abstraction of the a′ C-5 hydrogen in 5α-cholest-6-ene (**2**).[7] However, at least two other factors might have contributed to this inertness. One of these is the steric shielding of the C-5 β-hydrogen by the angular methyl group at C-10; the other arises from the fact that a $\Delta^6 \rightarrow \Delta^5$ shift of the double bond in **1** forces ring A to undergo conformational inversion from its original chair form to





* Dedicated to Professor Louis F. Fieser on the occasion of his 66th birthday for his distinguished contributions to teaching, research, and writing in organic chemistry.

(1) This project was supported by the National Institutes of Health (Grant No. GM 09693), and an early phase of it was aided by the National Science Foundation (Grant No. G 3500). The results are taken largely from the Ph.D. Dissertation of N. Schwartz, The Johns Hopkins University, 1962.

(2) Part III: A. Nickon and W. L. Mendelson, *Can. J. Chem.*, in press.

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

(4) It has been suggested that irradiation transforms the sensitizer to a suitable excited state that interacts with oxygen to form an active complex, which in turn oxidizes the substrate: (a) for a review, see G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); (b) R. Livingston and K. E. Owens, *J. Am. Chem. Soc.*, **78**, 3301 (1956); (c) G. Oster, J. S. Bellin, R. W. Kimball, and M. E. Schrader, *ibid.*, **81**, 5095 (1959). For alternative mechanisms involving excited oxygen (uncomplexed), see D. Sharp, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, p. 79P; C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879, 3880 (1964); E. J. Corey and W. C. Taylor, *ibid.*, **86**, 3881 (1964).

(5) (a) G. O. Schenck, H. Eggert, and W. Denk, *Ann.*, **584**, 177 (1953); (b) R. A. Bell and R. E. Ireland, *Tetrahedron Letters*, 269 (1963); (c) P. S. Wharton, C. A. Hiegel, and R. V. Coombs, *J. Org. Chem.*, **28**, 3217 (1963); (d) J. A. Marshall and W. I. Fanta, *ibid.*, **29**, 2501 (1964); (e) S. Masamune, *J. Am. Chem. Soc.*, **86**, 290 (1964).

(6) A. Nickon and W. L. Mendelson, *ibid.*, **85**, 1894 (1963).

(7) (a) A. Nickon and J. F. Bagli, *ibid.*, **81**, 6330 (1959); (b) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

(8) The cyclic mechanism has been used to account for the products in photosensitized oxygenation of monocyclic terpenes: (a) R. L. Kenney and G. S. Fisher, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept. 1960, p. 79P; (b) R. L. Kenney and G. S. Fisher, *J. Org. Chem.*, **28**, 3509 (1963); (c) G. O. Schenck, K. Gollnick, G. Buchwald, S. Schroeter, and G. Ohloff, *Ann.*, **674**, 93 (1964).

(9) The sensitizer is not shown in the scheme because its role (if any) during the attack is unknown. As pointed out earlier[7] no details of the cyclic process are implied by this formulation other than those imposed by the "*cis*" mechanism. The optimum geometric requirements could be essentially the same whether bond making and breaking are appreciably concerted or whether oxygen attack and C–H cleavage occur separately with formation of discrete intermediates.

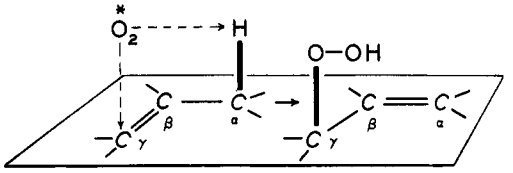
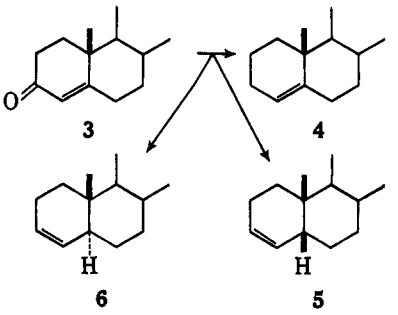


Figure 1.

either its alternate chair form or a twist-boat form. To assess the importance of these steric and ring-inversion factors we extended our studies to other steroid olefins. This paper describes the preparation and photosensitized oxygenation of 5α-cholest-3-ene (**5**) and 5β-cholest-3-ene (**6**), in which the A/B ring systems bear quasi-enantiomeric relationships to those in **2** and **1**, respectively.

Preparation of Olefins.—A route that led directly to both olefins **5** and **6** proved to be the Wolff–Kishner reduction of cholest-4-en-3-one (**3**). This reaction has been studied by several workers under a variety of experimental conditions, with results different from ours. Lardelli and Jeger[10] used hydrazine with sodium ethoxide in ethanol and, after extensive purification, isolated and identified 5α-cholest-3-ene (**5**). In a modified method (hydrazine, potassium hydroxide, diethylene glycol) Huang-Minlon obtained 61% of an olefin reported to be cholest-4-ene (**4**).[11] In both cases the olefins were probably impure as evidenced by the physical constants that later became available for the pure isomers. Lettré[12] and then Dutcher and Wintersteiner[13] reportedly obtained cholest-4-ene (**4**) by Wolff–Kishner reduction of the semicarbazone of **3**, and, in a recent modification that used potassium *t*-butoxide in toluene on the hydrazone or semicarbazone, Grundon, Henbest and Scott obtained 65–81% of cholest-4-ene (**4**), shown by infrared analysis to contain a small proportion (<10%) of 5α-cholest-3-ene (**5**).[14]

We carried out the Wolff–Kishner reduction of **3** according to the methods of Lardelli and Jeger and of Huang-Minlon and found in each case that the olefinic product (>90% yield) contained appreciable proportions of cholest-4-ene (**4**), 5α-cholest-3-ene (**5**), and 5β-cholest-3-ene (**6**). These components were identified in the mixture by the characteristic infrared bending vibrations associated with each olefin (**4**, 810 cm.$^{-1}$ [15]; **5**, 773, 671 cm.$^{-1}$ [16]; **6**, 783, 679 cm.$^{-1}$ [17]). To isolate the desired olefins **5** and **6** we chromatographed the mixture on alumina and obtained early fractions enriched in **6** and later fractions enriched in **5**. Selected fractions were brominated and two dibromides were obtained pure by chromatography or, less efficiently, by a debromination–oxidation sequence[18] that selectively destroyed the cholest-4-ene component and permitted separation of the dibromides from each other by chromatography and crystallization. The dibromides were 3α,4β-dibromo-5α-cholestane and 3α,4β-dibromo-5β-cholestane, with physical constants in agreement with those reported.[19,20] Debromination with zinc provided, respectively, 5α-cholest-3-ene (**5**) and 5β-cholest-3-ene (**6**), whose physical constants corresponded to literature values,[20,21] and whose ultraviolet spectra indicated only slight contamination by conjugated dienes.



Methods and Results

Each olefin (5α- and 5β-cholest-3-ene **5** and **6**) was photooxygenated in dilute pyridine solution (*ca.* 0.06 *M*) containing hematoporphyrin as sensitizer. After reduction of the crude product with sodium iodide, the amount of α,β-unsaturated ketone present was assayed from the ultraviolet absorption at 230–250 mμ. An aliquot removed at this stage was assayed for total allylic alcohol content by oxidation with manganese dioxide followed by ultraviolet measurement of the increase in enone intensity. The total reduced product was chromatographed on alumina and the individual components were identified and assayed by combinations of methods including infrared and ultraviolet spectroscopy, comparison of physical constants, and conversion to derivatives. For comparison we had on hand authentic samples of cholest-4-en-3-one (**3**), cholest-4-en-3α-ol (**7b**) and its acetate (**7c**), cholest-4-en-3β-ol (**8b**) and its acetate (**8c**), and 4α,5-epoxy-5α-cholestan-3-one (**11**).

Photooxygenation of 5α-cholest-3-ene (**5**) for 65 hr. resulted in about 91% conversion, based on recovered olefin. After reduction the enone content was 9% and the allylic alcohol content was 79%[22]; the ultraviolet spectrum had a slight shoulder at 280 mμ indicating that cholesta-4,6-dien-3-one (*ca.* 1%) may have been present. By chromatography we identified cholest-4-en-3α-ol (**7b**, 73%) as the principal product and cholest-4-en-3β-ol (**8b**, 11%) and cholest-4-en-3-one (8%, λ 241 mμ) as minor products. In addition, there was 2% of an allylic alcohol (tentatively believed to be **9a**) and 2% of α,β-unsaturated ketonic material (λ 232 mμ) believed to be largely **10**. Unresolved mixtures amounted to 6%, and as some of these were eluted last they probably represent polyoxygenated products. The total yields of enones (10%) and allylic alcohols (86%) from chromatography agree acceptably with those from assays on the original mixtures.

Under comparable experimental conditions the 5β-olefin **6** was only about 60% converted in 120 hr.

(10) G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **32**, 1817 (1949).

(11) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949). In contrast, M. Nussim, Y. Mazur, and F. Sondheimer [*J. Org. Chem.*, **29**, 1120 (1964)] used Huang-Minlon conditions and obtained 25% of 5α-cholest-3-ene (**5**).

(12) H. Lettré, *Z. physiol. Chem.*, **221**, 73 (1933).

(13) J. D. Dutcher and O. Wintersteiner, *J. Am. Chem. Soc.*, **61**, 1992 (1939).

(14) M. F. Grundon, H. B. Henbest, and D. M. Scott, *J. Chem. Soc.*, 1855 (1963).

(15) P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951).

(16) H. B. Henbest, G. D. Meakins, and G. W. Wood, *ibid.*, 800 (1954).

(17) Our Wolff–Kishner results have analogy in the behavior of a spirost-4-en-3-one system: C. Djerassi and J. Fishman, *J. Am. Chem. Soc.*, **77**, 4291 (1955).

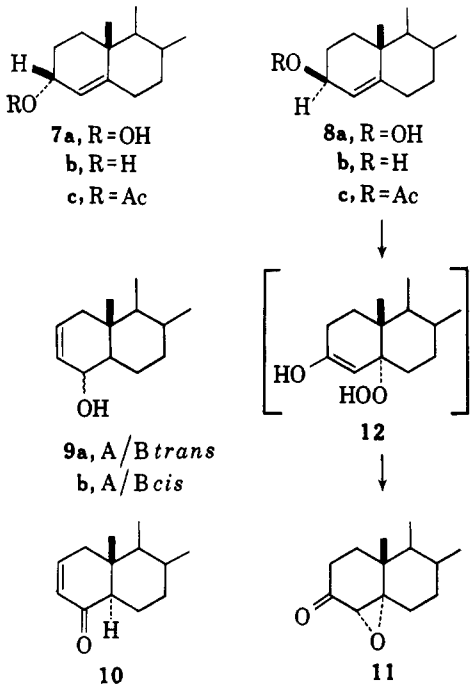
(18) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(19) R. J. Bridgewater and C. W. Shoppee, *ibid.*, 1709 (1953).

(20) G. H. Alt and D. H. R. Barton, *ibid.*, 4284 (1954).

(21) C. W. Shoppee, D. E. Evans, and G. H. R. Summers, *ibid.*, 97 (1957).

(22) All yields (summarized in Table I) have been corrected for unchanged starting olefin and for removal of aliquots, etc.



Higher light intensity speeded the oxygenation and for the definitive run with 5β-cholest-3-ene (**6**) we doubled the light intensity and realized a total conversion of 66% in 57 hr. The total crude product after reduction contained 58% allylic alcohols and 32% enones, and may also have contained *ca.* 5% of dienones (ultraviolet absorption at 280 mμ). The following products were identified on chromatography: cholest-4-en-3β-ol (**8b**, 44%), cholest-4-en-3α-ol (**7b**, 8%), cholest-4-en-3-one (**3**, 15%), and 4α,5-epoxy-5α-cholestan-3-one (**11**, 2%). In addition, there were two minor components tentatively believed to be largely 5β-cholest-2-en-4-ol (**9b**, 3%) and 5α-cholest-2-en-4-one (**10**, 2%). The column yielded 5% of complex mixtures whose spectral characteristics and elution times suggested that some of them contained polyoxygenated products. Fractions eluted last contained material with ultraviolet absorption between 240–260 mμ, which accounts for the high assay for total enone prior to chromatography. The column retained 13% of polar material, which was presumably polyoxygenated. The total amount of allylic alcohols eluted (55%) agrees satisfactorily with the assay prior to chromatography. Table I summarizes the results from both substrates and lists the products in approximate order of elution.

TABLE I

RESULTS OF PHOTOOXYGENATION OF 5α- AND 5β-CHOLEST-3-ENES

Products	—Approx. % yields from— 5α	5β
Unidentified (dienes, saturated ketones, etc.)	3	2
5α-Cholest-2-en-4-one (**10**)	2	2
4α,5-Epoxy-5α-cholestan-3-one (**11**)	..	2
Cholest-4-en-3-one (**3**)	8	15
Cholest-4-en-3α-ol (**7b**)	73	8
5β-Cholest-2-en-4-ol (**9b**)	..	3
Cholest-4-en-3β-ol (**8b**)	11	44
5α-Cholest-2-en-4-ol (**9a**)	2	..
Unidentified (polyoxygenated)	3	3

Discussion

The primary products of oxygenation are expected to be allylic hydroperoxides. The formation of α,β-unsaturated ketones as by-products from both olefins is understandable in view of the known tendency of secondary hydroperoxides to break down to ketones[23] and has been observed in other systems.[7] Interestingly however, the proportions of enones formed in the present study are higher than those encountered with ring B steroid olefins under comparable experimental conditions. It may be that the greater conformational flexibility of ring A has some influence and also that C-3 is more accessible to attack by species (*e.g.*, radicals, ions, etc.) that can transform the hydroperoxidic unit into a carbonyl group.

The "*cis*" stereochemical requirement for photosensitized oxygenation allows us to predict that abstraction of the C-5 hydrogen should lead exclusively to cholest-4-en-3α-ol (**7b**) from the A/B *trans*-fused olefin **5** and to cholest-4-en-3β-ol (**8b**) from the A/B *cis*-fused olefin **6**. The results of Table I support these expectations for the most part but not entirely because the expected C-3 alcohol was accompanied in each case by some of its epimer. Evidently with both substrates, allylic oxidation by a free-radical pathway has competed to a significant extent with the photosensitized process. Control photooxygenations with 5α-cholest-3-ene conducted in the absence of the sensitizer but with added *t*-butyl hydroperoxide confirmed that the olefin does undergo some free-radical oxidation. The *t*-butyl hydroperoxide was added as a radical initiator to simulate the original reaction in which steroid hydroperoxides produced by the photosensitized pathway could initiate radical chains. By analogy to the behavior of other steroids this competing free-radical pathway is expected to produce a mixture of epimers at C-3.[24] The contribution by the radical-chain process can be roughly estimated from the relative yields if one assumes that oxygen attacks the allylic radical completely nonstereoselectively and that breakdown to enone occurs with about equal ease from the 3α- and 3β-hydroperoxycholest-4-enes (**7a** and **8a**).[25] On this basis the free-radical pathway contributes *ca.* 26% to the total oxygenation at C-3 in the case of 5α-cholest-3-ene, and *ca.* 30% in the case of 5β-cholest-3-ene.

Although there was indication from the chromatography that polyoxygenated by-products were formed, the only one identified was 4α,5-epoxy-5α-cholestan-3-one (**11**), which was isolated (2%) from the oxygenation of the 5β-olefin **6**. To account for this by-product we presume that during the reaction some of the 3β-hydroperoxide **8a** disproportionates[3] to the corresponding allylic alcohol **8b**, which is known to be transformed

(23) N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951), and references cited therein. In separate runs we observed that our hydroperoxide mixtures developed higher enone proportions if allowed to stand prior to reduction.

(24) Compare the free-radical oxygenation of cholesterol, which ultimately produces both 7α- and 7β-hydroxylcholest-5-en-3β-ols, and of cholest-5-en-3-one, which produces comparable amounts of 6α- and 6β-hydroperoxycholest-4-en-3-one (L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 233). In the present case any 5-hydroperoxycholest-3-enes formed would rearrange to the corresponding 3-hydroperoxycholest-4-enes under the experimental conditions.[1]

(25) We recognize that these assumptions may not be entirely valid and, in the absence of information that would permit more accurate estimations, the figures are provisional.

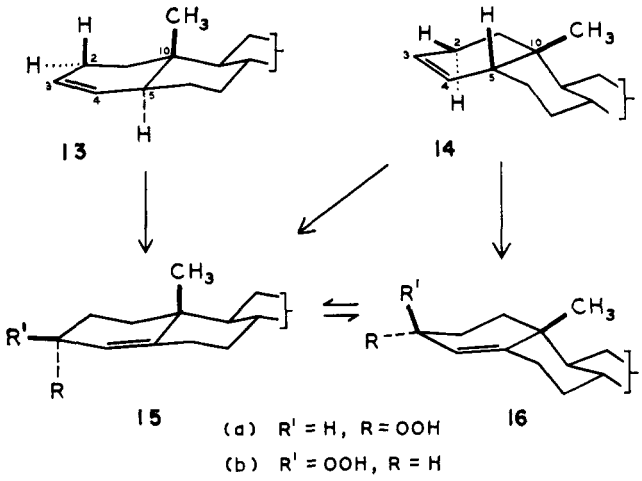


Figure 2.

stereospecifically to **11** on photosensitized oxygenation, presumably *via* the intermediate hydroperoxide **12**.[6,26]

Oxygenation at C-3 with shift of the double bond to C-4 clearly represents the predominant course for both cholest-3-enes. However, since each substrate has a pair of allylic hydrogens at C-2, the possibility of photosensitized oxygen attack at C-4 accompanied by double-bond migration to Δ^2 must be considered. This mode of attack would produce, after reduction, cholest-2-en-4-ols (**9**) and the related by-product 5α-cholest-2-en-4-one (**10**).[27] In the reaction with each olefin we did obtain a small amount (2–3%) of material, which was evidently allylic alcohol as indicated by the infrared absorption and by chromatographic behavior, and *ca.* 2% of α,β-unsaturated ketonic material with λ 232–234 mμ. Absorption at this position is reported for 5α-cholest-2-en-4-one (**10**) by Shoppee and Lack,[28] and we tentatively conclude that these alcoholic and ketonic materials (total of 4% from **5** and 5% from **6**) correspond largely to abstraction of hydrogen from C-2 with oxygen attack at C-4. Clearly, for each olefin, abstraction of the C-5 hydrogen is strongly favored over any others.

We noted earlier that oxygenation at C-3 proceeded largely by the sensitized pathway but that the radical-chain path contributed 26% in the case of **5** and 30% in the case of **6**. By assuming that all the products from C-2 abstraction arise on the one hand by a radical-chain process and on the other hand by a photosensitized pathway we can calculate *minimum* ratios representing the ease of C-5 hydrogen abstraction relative to that for the pair of hydrogens at C-2. For 5α-cholest-3-ene this analysis leads to a C-5:C-2 ratio of 17:1 for the photosensitized path and 6:1 for the radical-chain path. For 5β-cholest-3-ene the corresponding ratios are about 10:1 (photosensitized) and 4:1 (radical chain). The figures for the 5α-olefin are probably the more meaningful since they are based on a product yield of 96%, whereas those for the 5β-olefin are based on a product yield of 74%. The strong preference for abstraction of the C-5 hydrogen is understandable in terms of steric and conformational effects influencing the *cis*-cyclic process in the photosensitized pathway and influencing the removal of allylic hydrogen in the free-radical pathway. The photosensitized path will be considered first.

Models of 5α-cholest-3-ene reveal that ring A can adopt only one half-chair conformation (**13**) and that no ring inversions need occur if the double bond shifts either to the Δ^4 or the Δ^2 locations. Attack by oxygen at C-3 from the α side is relatively unhindered, and the quasi-axial hydrogen at C-5 is appropriately oriented for cyclic transfer to the oxygen leading to hydroperoxide **15a**. In contrast, oxygen attack at C-4 from either the α or β direction encounters the following unfavorable features. α attack at C-4 would require abstraction of the 2α-hydrogen, which is quasi-equatorial and therefore poorly oriented for cyclic transfer. β approach to C-4 is hindered by the angular methyl group, which would present a 1:3 diaxial interaction to a developing β-C–O bond at C-4 (Figure 2).

In 5β-cholest-3-ene the olefinic ring can take up only one half-chair conformation (**14**) and at C-2 the α- and β-hydrogens are a′ and e′, respectively. Despite the favorable conformation of the α-hydrogen at C-2 the approach of oxygen from the α side is impeded by the congested concave face of the *cis*-fused A/B system. β attack at C-4 does not appear to be sterically hindered but would require abstraction of a C-2 β-hydrogen, which is quasi-equatorial and therefore improperly aligned.[29]

Geometric factors in **14** favor β-oxygenation at C-3 because there is no serious steric hindrance and because the C-5 hydrogen is a′ and therefore suitably oriented for abstraction. Importantly, however, when the olefin bond shifts to Δ^4, two half-chair conformations (**16b** and **15b**) become possible for ring A. In half-chair **16b**, each of the bonds attached to C-1, C-2, and C-10 retains essentially the same conformational identity as in the original 5β-cholest-3-ene. In the other half-chair **15b**, which corresponds to the ring-inverted form of **16b**, the bonds reverse their conformational type (*i.e.*, a → e, a′ → e′, and *vice versa*). Conformational analysis suggests that ring-system **15** would be more stable than **16**, and this preference might be further accentuated by a 3β-substituent, which can be e′ in **15b** but must be a′ in **16b**. Consequently, inversion of ring A must either accompany the double-bond migration or the molecule might have to develop initially into a less stable conformation (*e.g.*, half-chair form **16b**). Either course could add to the energy barrier for oxygenation and it is relevant that this ring-inversion factor did not block the reaction, although it may have been responsible for the lower reactivity of the 5β-olefin relative to that of the 5α-olefin. The ring-inversion factor has been discussed elsewhere in connection with oxygenation of cholest-4-ene.[2]

We are now in a position to understand the contrasting behavior of 5β-cholest-3-ene (**6**) and 5β-cholest-6-ene (**1**). The latter olefin is known to be largely unchanged on photosensitized oxygenation,[7]

(26) Allylic alcohol **7b** is known to be transformed to 4β,5-epoxy-5β-cholestan-3-one on photosensitized oxygenation,[6] but this epoxy ketone was not obtained as a by-product from the 5α-ene **5**. Possible reasons are that epoxy ketone formation requires more intense radiation (*e.g.*, two lamps) such as was used with the olefin **6** but not with **5**, or that β-epoxy ketone does not survive the acidic conditions of the sodium iodide reduction.

(27) In **10**, the C-5 hydrogen is enolizable and could presumably adopt its preferred 5α-configuration in the presence of pyridine. These minor by-products were not obtained pure and could contain C-2 oxygenated material.

(28) C. W. Shoppee and R. E. Lack, *J. Chem. Soc.*, 3271 (1961); see also the Experimental part of the present paper.

(29) No ring inversion is necessary when a double bond shifts from $\Delta^3 \rightarrow \Delta^2$ in an A/B *cis* system, and so this factor plays no role in the inertness.

and we also found it is inert to the experimental conditions used in the present study. In olefins **1** and **6** the 5β-hydrogen has a similar steric environment, and a double-bond shift toward the ring junction requires similar types of conformational inversion in ring A. A significant structural difference is that, with respect to the olefinic ring, the C-5 hydrogen in **6** is quasi-axial, whereas in **1** it is quasi-equatorial.[30] These results establish the importance of the quasi-axial orientation (or its equivalent) for the allylic hydrogen. Models show that such a hydrogen is better oriented than a quasi-equatorial one for abstraction by a cyclic process and for stereoelectronic interaction with the neighboring π-electrons.[31]

Although the foregoing analysis concerned the photosensitized pathway, some of the same considerations can account for the observed preferential abstraction of the hydrogen at C-5 over those at C-2 in the free-radical path. Other things equal, the rupture of a relatively nonhindered quasi-axial C–H bond (*e.g.*, 5α in **13**) should be stereoelectronically favored[32] over that of a quasi-equatorial bond (*e.g.*, 2α in **13**) and sterically favored over that of a hindered quasi-axial bond (*e.g.*, 2β in **13**). In addition, a tertiary cyclohexenyl C–H bond may be inherently easier to cleave homolytically than a secondary one,[33] and this factor would also favor C-5 over C-2.

Another observation from the present work concerns the relative ease of oxidation of epimeric allylic alcohols with manganese dioxide. During our assays we noted that mixtures rich in cholest-4-en-3β-ol were oxidized to cholest-4-en-3-one in one-half to one-third the time needed for mixtures rich in cholest-4-en-3α-ol. These observations have been confirmed with the individual epimers by others in our laboratory[34] and compare to earlier findings with ring B allylic alcohols.[7] Interpretation of the conformational selectivity in this heterogeneous oxidation would be premature, but, if cleavage of the allylic C–H bond is a rate-controlling factor, the preference for rupture of an a′ hydrogen (quasi-equatorial OH) over that of an e′ hydrogen (quasi-axial OH) might represent another example of stereoelectronic control and is not inconsistent with current mechanistic views on manganese dioxide oxidations.[35]

Experimental[36]

Wolff–Kishner Reduction of Cholest-4-en-3-one (3). Procedure I.[10]—Cholest-4-en-3-one (40 g., m.p. 80–81°, prepared as reported[37]) was treated with hydrazine (64% in water, 40 ml.) in absolute ethanol (400 ml.) containing a solution of sodium ethoxide (prepared from 40 g. of sodium and 700 ml. of absolute ethanol), and the mixture was heated 1 hr. at *ca.* 200° in a steel bomb. Work-up gave 36 g. (93%) of a tan oil whose infrared spectrum indicated the presence of comparable proportions of cholest-4-ene (808 cm.$^{-1}$),[15] 5α-cholest-3-ene (772, 670 cm.$^{-1}$),[16] and 5β-cholest-3-ene (783, 680 cm.$^{-1}$; see later text). Chromatography on alumina and elution with hexane did not effectively separate the olefins although early fractions had lower proportions of 5α-cholest-3-ene than did later fractions. Numerous crystallizations of various fractions from ether–methanol led eventually to pure cholest-4-ene, m.p. 80–81°, α +73° (lit.[18] m.p. 82.5°, α +77°), whose infrared spectrum was the same as that of an authentic sample. As attempts to obtain the other olefins in pure form by crystallization were unsuccessful, all the mother liquor residues were brominated and the mixed dibromides were separated and converted to the pure olefins as described later.

Procedure II.—Huang-Minlon[11] modification of the Wolff–Kishner method (diethylene glycol solvent) was used to convert cholest-4-en-3-one to an oily, yellow-orange mixture of olefins (>95% yield). Its infrared spectrum was the same in all essential respects as that of the olefin mixture obtained in procedure I. The oil (37 g.) was dissolved in hexane (70 ml.) and chromatographed on alumina (1820 g.). Thirteen fractions were eluted with hexane, and fractions 3–7 (86% total) were shown by infrared to contain cholest-4-ene mixed at first largely with 5β-cholest-3-ene and then largely with 5α-cholest-3-ene. Each of these fractions was individually brominated as described below. When triethylene glycol was used in the reduction, the crude olefinic product contained a higher proportion of cholest-4-ene and a lower proportion of 5β-cholest-3-ene (*via* infrared) than from the diethylene glycol run.

Bromination of Olefinic Mixtures.—We followed the Barton and Rosenfelder procedure for bromination in acetic acid–ether solutions.[18] Best yields of the dibromide mixture were obtained by use of ether that was distilled from sodium–lead amalgam and stored over sodium sulfate, by the use of bromine that was washed with an equal volume of sulfuric acid and then distilled, and by the exclusion of light during the bromine addition. Typically, the brominated product was obtained (*ca.* 95% yield) as a pale orange oil whose infrared spectrum showed the presence of small proportions (*e.g.*, 5–10%) of carbonyl-containing material.

Purification of Dibromides. A. By Debromination–Oxidation Sequence.[18]—The dibromide mixture (28.3 g.) in dry acetone was refluxed 6 hr. with potassium iodide according to the general procedure of Barton and Rosenfelder.[18] Infrared inspection of the product (22.9 g.) showed the presence of 3α,4β-dibromo-5α-cholestane, 3α,4β-dibromo-5β-cholestane, and cholest-4-ene. No 4,5-dibromide was detected, and this agrees with the rate studies by Barton and co-workers,[18,20] who found that the 4,5-dibromide is debrominated faster than the other positional isomers. The product was oxidized with chromium trioxide in acetic acid at 50–55° for 20 hr. and gave on work-up a crude oil containing considerable ketonic material. The oxidation product (5.5 g.) in

(30) That hindrance to β-oxygenation at C-7 is not a prime factor in the inertness of the Δ^6 system is indicated by work with other steroid olefins (J. B. DiGiorgio and P. J. L. Daniels, to be published).

(31) Intramolecular hydrogen bonding between an allylic OOH and the olefinic unit could conceivably play a role in the cleavage of the C–H bond or in the conformational equilibria of the final ring system. Although this factor might be important, its effect (if any) could be interwoven with those of the sensitizer,[9] of the solvent, etc., and must await further study.

(32) For discussions of the stereoelectronic factor in cleavage of allylic cyclohexenyl bonds, see H. L. Goering and U. Mayer, *J. Am. Chem. Soc.*, **86**, 3753 (1964); H. L. Goering and D. L. Towns, *ibid.*, **85**, 2295 (1963); H. L. Goering and R. R. Josephson, *ibid.*, **84**, 2779 (1962).

(33) W. J. Farrissey, Jr., *J. Org. Chem.*, **29**, 391 (1964), and references cited therein.

(34) Unpublished experiments by W. L. Mendelson.

(35) (a) E. F. Pratt and J. F. Van De Castle, *ibid.*, **26**, 2973 (1961); (b) R. J. Gritter, G. D. Dupre, and T. J. Wallace, *Nature*, **202**, 179 (1964).

(36) Unless otherwise stated, the following information applies. Elemental analyses were performed by Mr. J. Walter. All melting points are corrected and rounded to 0.5°. Optical rotations are reported as specific rotations and were taken at room temperature (21–27°) in chloroform solution with a sodium lamp light source. Infrared spectra were taken in carbon disulfide solution with a Perkin-Elmer Model 21, double-beam, recording spectrophotometer equipped with sodium chloride optics. Ultraviolet spectra were taken in 95% ethanol with a Cary Model 11M recording instrument. In conjunction with ultraviolet assays the term enone refers to cholest-4-en-3-one and enones refers to this compound mixed with other α,β-unsaturated ketones absorbing in the same general region. Along with each assay of an unknown, the spectrum of a standard solution of cholest-4-en-3-one was recorded for calibration. Alcoa alumina (F-20, 80–200 mesh) and distilled hexane (b.p. 65–70°) were used for chromatography. Hematoporphyrin (Mann Research Laboratories) and commercial, reagent grade pyridine were used in the photosensitized oxygenations, which were conducted in a vertical Pyrex tube irradiated externally along its length by either one or two standard desk lamps. The lamps, each with two 15-w. fluorescent bulbs, were positioned 1–2 in. from the tube. Oxygen was admitted without interruption through a fritted-glass plate near the bottom of the tube. Dr. W. L. Mendelson kindly provided us with spectra and authentic samples of cholest-4-ene (m.p. 80–81°), 4β,5-dibromo-5α-cholestane (m.p. 117–118°), cholest-4-en-3α-ol (noncrystalline) and its acetate (m.p. 82–82.5°), cholest-4-en-3β-ol (m.p. 132–133.5°) and its acetate (m.p. 85.5–86.5°), and 4α,5-epoxy-5α-cholestan-3-one (m.p. 123–124°).[2,5] Gas chromatography of steroid olefins was conducted on a Perkin-Elmer Model 226 chromatograph either with a Golay "Z" column (SE-30 silicone gum rubber) at 252° or with a packed "Z" column (5 ft. × 1/8 in.) containing 1.5% by weight of liquid phase on a support of silanized Chromosorb W.

(37) J. F. Eastham and R. Teranishi, *Org. Syn.*, **35**, 39 (1955).

hexane was chromatographed on alumina and eluted with hexane. The first fractions were enriched in 3α,4β-dibromo-5α-cholestane and after several recrystallizations from ethyl acetate (and processing of mother liquors) this isomer was obtained as needles (0.69 g.), m.p. 124–125°, α +6° (lit.[20] m.p. 124–126°, α +5°). The infrared spectrum showed useful identifying bands at 1275, 1210, 1175, 1163, 936, 927, 737, and 717 cm.$^{-1}$.

The next fractions contained large proportions of 3α,4β-dibromo-5β-cholestane and after recrystallization from ethyl acetate–methanol and then from ethyl acetate alone this isomer was obtained as plates (0.64 g.), m.p. 98–100°, α −2° (lit.[38] m.p. 97–98°, α −5°). The yields represent net recovery after suitable processing of mother liquors, second crops, etc. Characteristic infrared bands were present at 1269, 1180, 1151, 910, 872, 766, 710, and 691 cm.$^{-1}$. As an additional criterion of purity an analytical sample was prepared by further crystallizations; m.p. 99–100°, α −3° (*c* 3.65).

Anal. Calcd. for $C_{27}H_{46}Br_2$ (530.50): C, 61.15; H, 8.75. Found: C, 61.38; H, 8.72.

B. By Direct Chromatography.—This method proved more efficient than the debromination–oxidation sequence, and was successful with dibromide mixtures containing different proportions of the constituents. In a typical separation a dibromide mixture (9.37 g. derived from an olefin fraction rich in 5α-cholest-3-ene) dissolved in hexane (60 ml.) was chromatographed on alumina (710 g.) in a column 47 mm. in diameter. All fractions were eluted with hexane and were monitored by infrared inspection. Olefins were eluted first, followed, respectively, by fractions enriched in 4β,5-dibromo-5α-cholestane, 3α,4β-dibromo-5α-cholestane, and 3α,4β-bibromo-5β-cholestane. Fractions rich in 3α,4β-dibromo-5α-cholestane had individual melting points that fell between 110–122°. They were combined and, after recrystallization from ethyl acetate, yielded 1.75 g. of this pure dibromide (m.p. 124–125°, α +4°) whose infrared spectrum was identical with that of a pure sample from procedure A. Crystalline fractions (individual melting points between 73 and 100°) enriched in 3α,4β-dibromo-5α-cholestane were combined and recrystallized from ethyl acetate to give 0.19 g. of this isomer whose melting point (99–100.5°) and infrared spectrum were identical with those of a pure sample from procedure A.

Regeneration of Olefins from Dibromides. A. 5α-Cholest-3-ene (5).—Powdered zinc (47 g.) was added portionwise during 1.5 hr. to a stirred solution of 3α,4β-dibromo-5α-cholestane (2.36 g.) in refluxing acetic acid (470 ml.). The mixture was cooled to room temperature and filtered; the solid was washed with ether. The filtrate was evaporated *in vacuo* to one-half volume and then diluted with ether and washed successively with water, 5% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After being dried over sodium and evaporated *in vacuo* the ether solution left 1.6 g. (97%) of white solid, m.p. 74–75°. Recrystallization from ethyl acetate–methanol gave 1.38 g. of needles, m.p. 74.5–75°, α +51° (lit.[20] for 5α-cholest-3-ene, m.p. 74–75°, α +55°). Our olefin showed characteristic infrared bands at 772 and 669 cm.$^{-1}$ in agreement with reported absorption.[16] The ultraviolet spectrum (isooctane) indicated the presence of 6% of cholesta-3,5-diene (λ 228, 235, and 244 mμ).[39] No contamination by 5β-cholest-3-ene was detected by gas chromatography under conditions sensitive enough to reveal >3%.

B. 5β-Cholest-3-ene (6).—A solution of 3α,4β-dibromo-5β-cholestane (2.31 g.) in acetic acid (460 ml.) was debrominated with zinc (23 g. added over 75 min.) and processed as described above. The crude product (1.6 g., m.p. 47–49°) was recrystallized from ethyl acetate–methanol and gave needles (1.2 g.): m.p. 50–50.5°; α +19°; ν 832, 783, and 679 cm.$^{-1}$ (lit.[21] for 5β-cholest-3-ene, m.p. 48°, α +21°). Our olefin contained *ca.* 2% conjugated diene (ultraviolet). Gas chromatography revealed no contamination by 5α-cholest-3-ene or by cholest-4-ene under conditions sensitive enough to detect >5% of the former and >2% of the latter isomer.

Photosensitized Oxygenation of 5α-Cholest-3-ene (5).—Oxygenations were performed according to the general method reported earlier.[7] Exploratory trials helped define suitable conditions for the definitive run, which was conducted for 65 hr. Longer reaction times effected more complete conversion of the olefin but also gave higher proportions of ketonic by-product.

A pyridine (35 ml.) solution of 5α-cholest-3-ene (0.750 g.) and hematoporphyrin (0.010 g.) was irradiated with one desk lamp[36] and oxygenated. After 47 hr., more hematoporphyrin (0.003 g.) was added to replenish dye that had become bleached. After a total of 65 hr. the solution was diluted with ether and treated with activated charcoal, and after filtration the solvent was removed *in vacuo* at a temperature below 40°. The oily residue (α +79°) had λ 243 mμ corresponding to 9% enone, and the infrared spectrum showed weak carbonyl bands at 1715 and 1680 cm.$^{-1}$. The product was dissolved in absolute methanol (75 ml.), anhydrous ether (15 ml.), and acetic acid (0.2 ml.) and treated with sodium iodide (4.3 g.). After 25 hr. normal work-up gave a tan oil (0.74 g., α +90°) containing 8% of enone (ultraviolet). A shoulder at 280 mμ indicated that about 1% of cholesta-4,6-dien-3-one may also have been present.

A portion of this reduction product (0.050 g.) was oxidized (48 hr.) with manganese dioxide (1.75 g.) in chloroform (12 ml.) and worked up.[40] To ensure complete reaction, the manganese dioxide oxidation was repeated a second (17 hr.) and third (24 hr.) time. Ultraviolet inspection indicated 80% enone (λ 241 mμ) and *ca.* 2% dienone (λ 280 mμ, shoulder) after the second oxidation, and 77% enone and 4% dienone after the third oxidation. The increase (72%) in total enone and dienone as a result of the manganese dioxide oxidation is taken as a measure of the allylic alcohol content. The product from these oxidations had m.p. 77–79° after two crystallizations from methanol. The melting point was undepressed by authentic cholest-4-ene-3-one, and their infrared spectra were the same in all essential respects.

The bulk of the product from sodium iodide reduction (0.490 g.) was dissolved in hexane (10 ml.) and carefully chromatographed on alumina (25 g.). Thirty-two fractions (each 50 ml.) were collected with solvents of graded polarity that began with pure hexane, then ranged through mixtures of hexane–benzene to pure benzene and through benzene–ether mixtures to pure ether. The last two fractions used ether–methanol (1:1) and then pure methanol to strip the column. Each fraction was individually inspected by infrared and ultraviolet analysis, relevant fractions were pooled, and the compositions of overlapping fractions were estimated by one or both of the spectroscopic methods. As a further check, those fractions containing cholest-4-en-3α-ol and cholest-4-en-3β-ol were acetylated[41] and the epimeric ratio in the acetates was estimated by optical rotation and also by infrared comparison with known mixtures of the authentic acetates. There was good agreement with the initial assays prior to acetylation. The yields quoted below represent net over-all yield from 5α-cholest-3-ene after adjustment for removal of aliquots, etc.,[42] but are not corrected for recovered starting material (for corrected yields, see Table I). The products, in order of elution, were (a) 5α-cholest-3-ene (9%), (b) unidentified mixtures (3%) containing saturated ketones (ν 1720 and 1730 cm.$^{-1}$) and perhaps conjugated dienes, (c) conjugated enone fractions (2%, λ 232–234 mμ; ν 1680 cm.$^{-1}$) whose ultraviolet and fingerprint infrared spectra differed distinctly from those of cholest-4-en-3-one and which are tentatively believed to contain 5α-cholest-2-ene-4-one (**10**),[43] (d) cholest-4-en-3-one (7%), (e) cholest-4-en-3α-ol (66%), (f) cholest-4-en-3β-ol (10%), (g) allylic alcohol fraction (2%) tentatively regarded as largely 5α-cholest-2-en-4-ol (**9a**), and (h) unidentified fractions (3%) that showed hydroxyl and carbonyl infrared absorption. The combined rounded yields

(38) Bridgewater and Shoppee[19] obtained this dibromide in another manner, and they provisionally regarded it as the 3α,4β- isomer (*i.e.*, diequatorial) on the basis of its resistance to debromination. We have adopted their assignment, although the actual halogen configurations are not of direct relevance to our work.

(39) K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1480 (1959).

(40) F. Sondheimer, C. Amendolla, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 5930 (1953).

(41) R. Schoenheimer and E. A. Evans, Jr., *J. Biol. Chem.*, **114**, 567 (1936).

(42) In these calculations molecular weights of 400 have been assumed for the unidentified fractions (saturated ketones, hydroxy ketones, diols, etc.). Material retained on the column was assumed to be equivalent to saturated triols, mol. wt. 421.

(43) Shoppee and Lack[28] have reported that 5α-cholest-2-en-4-one has λ 239 mμ (ε 10,230) in ethanol. Dr. Lack has kindly informed us that due to instrument malfunction the published value is in error, and the correct value is λ 234 mμ. H. Dannenberg and A. Butenandt [West German Patent 870,407 (1953); *Chem. Abstr.*, **52**, 20262*i* (1958)] observed λ 230 mμ (ε 10,500) in ethanol for a compound that very likely has the same structure. We cannot rule out the possibility that 5α-cholest-3-en-2-one may be present in our conjugated enone fractions, because it would absorb at about the same place. Compare λ 230 mμ for 5α-cholest-1-en-3-one (C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); A. Butenandt, L. Mamoli, H. Dannenberg, L. W. Masch, and J. Paland, *Ber.*, **72**, 1617 (1939).

amounted to 102%. The known compounds obtained above from a, d, e, and f were identified by direct comparison with authentic samples. For additional confirmation, cholest-4-en-3α-ol was acetylated,[41] and the derivative (m.p. 82–83°, α +176°) proved identical in all respects to authentic cholest-4-en-3α-ol acetate.

Photosensitized Oxygenation of 5β-Cholest-3-ene (6).—Experiments conducted in the normal way (one desk lamp)[36] revealed that this olefin was less readily oxygenated than was its isomer **5**. For example, **6** underwent slightly less than 60% conversion in 120 hr. About the same conversion was obtained in 50 hr. when the light intensity was increased (two desk lamps), and so the higher intensity was used for the definitive run.

A pyridine (45 ml.) solution of 5β-cholest-3-ene (1.00 g.) and hematoporphyrin (0.014 g. initially, and 0.003 g. more added after 27 hr. and again after 47 hr. to replenish dye that became bleached) was irradiated and oxygenated 57 hr., during which time cool air was blown around the oxygenation tube to keep the solution at about 30–35° (room temperature was 25°). The usual work-up left an oily residue (α +34°) whose ultraviolet absorption indicated *ca.* 23% total enones (λ 235–242 mμ) and possibly *ca.* 3% of cholesta-4,6-dien-3-one (shoulder at 280 mμ). The product in absolute methanol (105 ml.), anhydrous ether (21 ml.), and acetic acid (0.3 ml.) was reduced with sodium iodide (6.0 g.) for 40 hr. Work-up gave a yellow oil (0.91 g.) whose infrared spectrum showed that 5β-cholest-3-ene, cholest-4-en-3β-ol, and cholest-4-en-3-one were the principal components. The ultraviolet spectrum indicated *ca.* 21% total enones (λ 235–242 mμ) and *ca.* 3% of dienone (shoulder at 280 mμ).

An aliquot (0.060 g.) in chloroform (12 ml.) was oxidized (24 hr.) with manganese dioxide (1.20 g.), after which it showed 59% total enones and 3% dienone. A second oxidation of this product produced no further change. The net increase in unsaturated ketones (38%) effected by the manganese dioxide treatments represents the allylic alcohol content of product from sodium iodide reduction.

The bulk of the crude reduction product (0.810 g.) was dissolved in hexane (20 ml.) and chromatographed on alumina (42 g.). Forty fractions (each 80 ml.) were collected. Elution as well as inspection and assay of individual and pooled fractions were carried out as before, and yields are based upon the starting 5β-cholest-3-ene after adjustment for removal of aliquots, etc., but have not been corrected for recovered starting olefin (see Table I for corrected yields). The products eluted were (a) 5β-cholest-3-ene (34%), (b) unidentified mixture (1%) containing saturated carbonyl groups (infrared) and conjugated chromophores (ultraviolet) that may indicate dienes, (c) 4α,5-epoxy-5α-cholestan-3-one (**11**, 1%) whose infrared absorption was essentially the same as that of an authentic sample, (d) conjugated enone fractions (1%) whose ultraviolet absorption (λ 235 mμ) was different from that of cholest-4-en-3-one and are thought to contain cholest-2-en-4-ones and possibly cholest-3-en-2-ones,[27,43] (e) cholest-4-en-3-one (10%), (f) cholest-4-en-3α-ol (5%), (g) unidentified allylic alcohol fraction (2%) tentatively thought to contain 5β-cholest-2-en-4-ol (**9b**) and perhaps 5β-cholest-3-en-2-ol, (h) cholest-4-en-3β-ol (29%), and (i) complex mixtures (2%) whose retention times and infrared (ν 3600, 3430, 1735, 1710, and 1680 cm.$^{-1}$) and ultraviolet spectra (λ 242 and 258 mμ) suggested the presence of diols, hydroxy ketones, hydroxy-enones, etc. The total yield of products was 85%. The column retained 9% of material, presumed to be polyoxygenated, such as triols, etc. The products from fractions a, e, and h were each obtained in pure state either directly from the column or by crystallization of appropriate fractions and were shown to be identical in all respects (melting point, mixture melting point, optical rotation, infrared) with authentic samples. For additional confirmation of cholest-4-en-3α-ol, the relevant fractions were treated with acetic anhydride in pyridine. The derived acetate (m.p. 79.5–81°, α +170°) was identical in all respects with an authentic sample, and the constants corresponded with reported values.[44]

Control Oxygenation of 5α-Cholest-3-ene in Absence of Sensitizer.—The olefin (0.101 g., containing 6% cholesta-3,5-diene) in pyridine (6 ml.) was oxygenated and irradiated as before (65 hr.) except that the sensitizer was omitted. Work-up gave a nearly quantitative recovery of starting olefin with unchanged melting point and infrared absorption, and still containing the diene contaminant.

Autoxidation of 5α-Cholest-3-ene.—To simulate a reaction medium in which steroid hydroperoxides could act as chain initiators, 5α-cholest-3-ene (0.232 g.) in pyridine (12 ml.) was photooxygenated (65 hr.) in the absence of sensitizer but with added *t*-butyl hydroperoxide (*ca.* 0.05 ml. initially and again after 16 and 42 hr.). To determine the extent of oxygenation the product was reduced with sodium iodide and then oxidized with manganese dioxide in the usual way. The ultraviolet spectrum of the final product showed a maximum at λ 229 mμ (isooctane), corresponding to 11% enone, based on isooctane reference spectra of cholest-4-en-3-one [λ 232 mμ (ε 12,900)] and cholesta-3,5-diene (λ 228, 235, and 244 mμ; for intensities in hexane see ref. 39). For this calculation we assumed that all of the initial diene contaminant was still present. If the contribution by diene is ignored, the enone content would be 19%. However, since the band at 229 showed an inflection at 244 mμ, some diene is still evident, and the enone content therefore lies between 11 and 19%.

Attempted Photosensitized Oxygenation of 5β-Cholest-6-ene (1).—This olefin[7] was subjected to the same conditions of sensitized photooxygenation as were used above for 5β-cholest-3-ene (two lamps). Even after 96 hr. the infrared spectrum of the product was essentially identical with that of starting olefin. The only perceptible change was the development of very weak absorption near 1710 and 1670 cm.$^{-1}$.

Observations on Manganese Dioxide Oxidations.—In our numerous assays of allylic alcohols by oxidation with manganese dioxide in chloroform we observed that mixtures rich in cholest-4-en-3β-ol (**8b**) underwent conversion faster than did mixtures rich in cholest-4-en-3α-ol (**7b**) under similar experimental conditions. For example, a 6:1 mixture of 3β-ol:3α-ol was completely oxidized in less than 24 hr., whereas a 1:7 mixture required at least 65 hr. for completion. Similar differences were noted when the pure epimers were individually oxidized.[34]

Acknowledgment.—We are grateful to Dr. P. J. L. Daniels, Dr. W. L. Mendelson, and Mr. Fred Litt for helpful discussions.

(44) C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Chem. Soc.*, 3107 (1957).