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REARRANGEMENTS OF Δ^3-2,5-PEROXIDOCHOLESTENE

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More than ten years ago it was shown in this laboratory (1) that $\Delta^{2,4}$-cholestadiene can be photo-oxidized to Δ^3-2,5-peroxidocholestene (I). When irradiated with sunlight, this peroxide rearranges to a compound which has been referred to as ketone A (II), and which upon heating isomerizes to ketone B (III) (2). When treated with potassium hydroxide in methanol both ketones, and also the peroxide add one mole of methanol to form ketone C (IV). The tentative structures for the three ketones were based primarily on the fact that in addition to the ketonic oxygen there is present a rather unreactive oxygen atom, and on an analogy with the rearrangement of the well-known transannular peroxide, ascaridol, to a transannular oxide (1). It was the purpose of the present study to ascertain the configuration of the oxygen bridge of the peroxide (I) and to arrive at more definite structures for the three ketones.

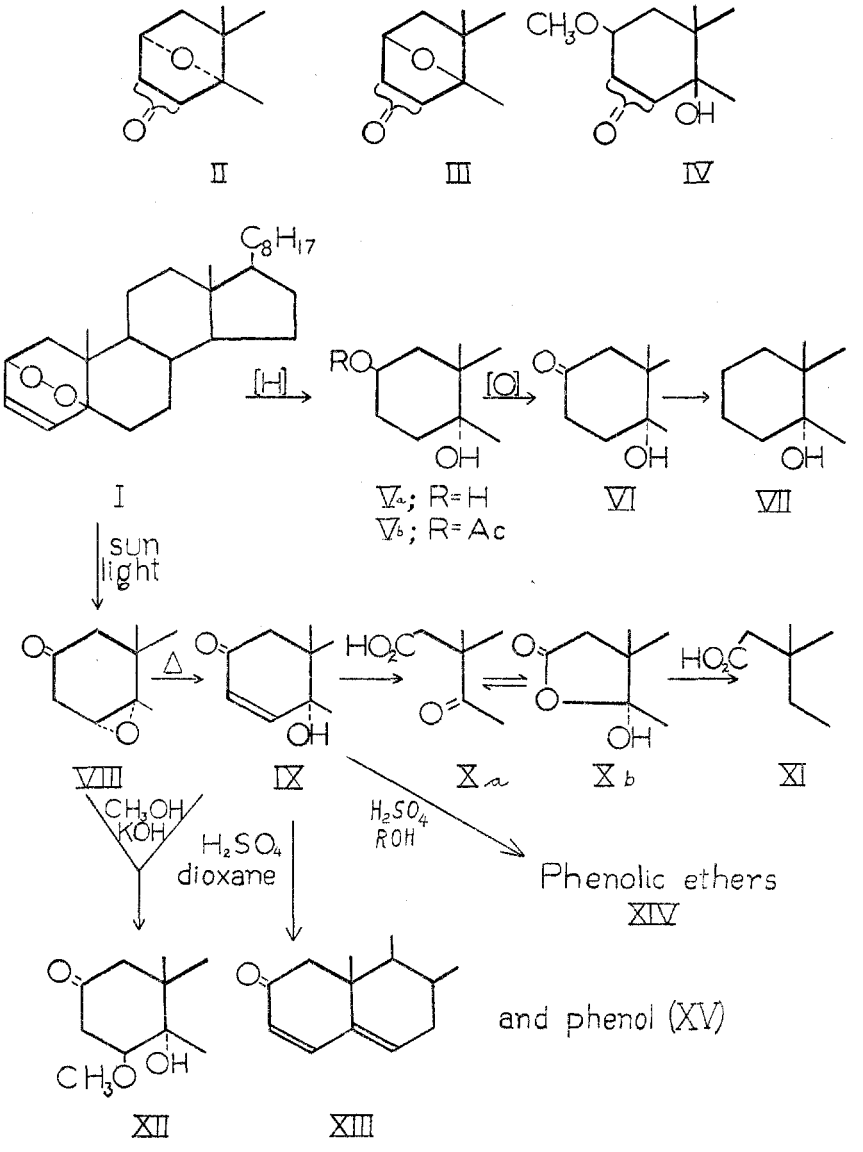
As was shown previously (1), catalytic hydrogenation of the peroxide (I) affords 2,5-cholestanediol (Va). A comparison of the molecular rotations of the diol (+81°) and its mono-acetate (Vb) (−9°) with those of the known 2α-cholestanol (+105°) and its acetate (−4°) (3) shows that the Δ_{Ac} values (−121° and −109°, respectively) are of the same sign and magnitude. The 2-hydroxyl group of the diol (Va) is therefore α-oriented. Since the diol (Va) is formed by the catalytic hydrogenation of the peroxide (I) it follows that the oxygen bridge in the latter is also α-oriented, and that the addition of oxygen to $\Delta^{2,4}$-cholestadiene proceeds through an approach from the rear of the molecule.

Of the three ketones mentioned above only B shows selective absorption in the ultraviolet region; λ_{max} 223 mμ; log ϵ 3.9. The infrared spectra of ketones A and C exhibit nearly identical carbonyl bands at 5.86 μ and 5.85 μ respectively; but ketone C shows in addition a strong hydroxyl band at 2.80 μ and a strong doublet at 9.06 μ–9.16 μ, indicative of a methoxyl group. The infrared spectrum of ketone B shows a shift of the carbonyl band to a longer wave length, 5.98 μ, and the presence of a hydroxyl group is indicated by a band at 2.81 μ. Both the ultraviolet and infrared spectrum therefore show that ketone B is α,β-unsaturated, and that its second oxygen atom is present as a hydroxyl group rather than a transannular ether linkage as was originally assumed. Since the hydroxyl group is rather unreactive, it is to be regarded as tertiary.

The reformulation of ketone B as Δ^3-cholesten-5-ol-2-one (IX) is supported by additional chemical evidence. Catalytic hydrogenation of the enolone (IX) proceeds with the absorption of one mole of hydrogen to give a keto-alcohol (VI). The same compound is also obtained by the chromic acid oxidation of the diol (Va). In conformity with other observations on saturated steroid alcohols (4), the diol (Va) remains unchanged when treated with aluminum *tert*-butoxide.

[1] Proctor and Gamble Fellow 1950–1952.

Since the hydroxyketone (VI) is obtained from either (Va) or (IX), it follows that the tertiary hydroxyl group of the unsaturated ketone (IX) is α-oriented.



Further evidence for the presence of the 5-α-hydroxyl group was obtained through the Wolff-Kishner reduction of (VI) to the known 5-cholestanol (VII) (5).

Oxidation of the unsaturated ketone (IX) with chromic acid afforded a keto acid (Xa, b) which upon Clemmensen reduction gave a C_{25}-monocarboxylic

acid (XI). The latter is identical with the acid first prepared by Tschesche (6) in connection with the systematic degradation of ring A of cholesterol. The infrared spectrum of the keto acid (Xa, b) shows a non-carboxylic hydroxyl band and a lactone band; λ_{max} 2.82, 5.65 μ, indicative of the presence of a lactol structure (Xb).

In the previous communication (2) the presence of a tertiary hydroxyl group in ketone B had not been considered, because this ketone is most readily obtained by heating of ketone A, *i.e.* under conditions which might be expected to eliminate such hydroxyl groups. After ketone B had been shown to be a tertiary alcohol (IX) its dehydration to the known dienone (XIII) was investigated. All conventional methods of dehydration proved unsuccessful. A reaction, however took place when the ketone (IX) was heated with ethanol containing sulfuric acid. A compound was obtained whose low melting point and increased dextrorotation at once contra-indicated its identity with the expected dienone (XIII). It contained one oxygen atom and showed neither a hydroxyl nor carbonyl bond in the infrared, but a moderately strong band was seen at 6.25 μ. The ultraviolet spectrum was unlike that of a dienone, but it showed the maximum at 279 mμ, log ϵ 3.3; and minimum at 249 mμ, log ϵ 2.7; characteristic of phenols and their derivatives. An alkoxyl determination proved the compound to the ethyl ether of a phenol (XIV). Treatment of the ketone (IX) with methanol and sulfuric acid afforded the corresponding phenol methyl ether.

Cleavage of the ethers to the corresponding phenol by a variety of methods has not yet given satisfactory results. When, however, the ketone (IX) was treated either with *p*-toluenesulfonic acid in benzene or sulfuric acid in dioxane a mixture of compounds was obtained from which a phenol (XV) was isolated by chromatographic separation. The aromatization of ring A which accompanies the loss of the tertiary hydroxyl group of the ketone (IX) is reminiscent of the well-known conversions of $\Delta^{1,4}$-dien-3-ones of various steroids to "sterophenols". The phenol and its ethers derived from (IX) are different from the known sterophenols and their derivatives. Their structures and the mechanism of their formation will be the subject of later communication.

In addition to the phenol mentioned above, treatment of IX with *p*-toluenesulfonic acid in benzene afforded an approximately equal amount of the expected dehydration product, the known $\Delta^{3,5}$-cholestadien-2-one (XIII) (7). When refluxed with ethanol and sulfuric acid, the dienone remained unchanged. It therefore does not act as an intermediate in the transformation of ketone IX into the phenolic ether.

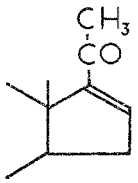
With the establishment of the structure of ketone B as that of (IX), the old tentative structures for ketones A (II) and C (IV) also need revision. For the following reasons, ketone A is best formulated as 4α,5-oxidocholestan-2-one (VIII). As has been stated above, this ketone exhibits no absorption in the ultraviolet region above 200 mμ, and its infrared spectrum shows a carbonyl but no hydroxyl band. When reduced catalytically this ketone absorbs one mole of hydrogen to give cholestan-5-ol-2-one (VI), which is also obtained by reduction of the unsaturated ketone (IX). Reduction of ketone A with lithium

aluminum hydride gave a mixture of compounds from which 2α,5-cholestanediol (Va) was isolated. This evidence therefore proves that the keto group of A is located in the 2-position, and since neither method of hydrogenation is expected to cause inversion it also shows that the epoxide ring is α-oriented and that ketone A possesses structure (VIII) rather than (II). Oxidation of the oxide with chromic acid gives the same keto acid (Xa, b) obtained by the analogous oxidation of (IX). The latter was present in the neutral fraction of the oxidation products from the epoxide. This fact suggests that during the oxidation, the epoxide (VIII) is first rearranged to the enolone (IX). As has been stated previously, this rearrangement proceeds with remarkable ease under a variety of conditions (2). It is for such reason that a preferential reduction of the keto-epoxide (VIII) to 4α,5-oxidocholestane by the procedures of Clemmensen, Wolff-Kishner, Monzingo, etc. has remained unsuccessful. The ease of rearrangement also explains the fact that upon treatment with sulfuric acid in alcohol the epoxide (VIII) gives the same phenolic ethers as (IX).

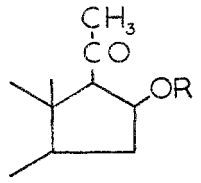
The original structure for ketone C (IV) finds some support in the spectrographic evidence mentioned above, but no longer can be reconciled with the new chemical evidence. The ease with which Δ^3-cholesten-5-ol-3-one (ketone B) (IX) and ketone C may be interconverted by the addition or loss of methanol proves that ketone C also carries a 2-keto and 5α-hydroxyl group. The most reasonable structure for ketone C is that of 4β-methoxycholestan-5-ol-2-one (XII) which is the product of a Michael-type of addition of methanol to the α,β-unsaturated ketone (IX). Such addition is not without parallel in steroid chemistry. Thus it is well known that Δ^{16}-20-ketosteroids such as (XVI) (8) and (XVIII) (9) are prone to add in a reversible reaction methanol or other alcohols in the presence of potassium hydroxide to form 16-alkoxy-derivatives (XVII, XIX). As is true for the present ether (XII), that of acid (XIX) loses methanol upon heating with a reforming of the double bond (9). It has been shown, however, by Fukushima and Gallagher (8) that a Δ^4-3-ketone (XX) such as testosterone, and a Δ^1-3-ketone (XXI) such as Δ^1-androsten-17-ol-3-one does not add methanol. The authors regard as the driving force of the methanol addition to Δ^{16}-20-ketosteroids the release of strain present in the unsaturated five-membered ring. The lack of reactivity of Δ^1- and Δ^4-3-ketosteroids was attributed to the absence of significant strain in these systems. The ease, however, with which Δ^3-cholesten-5-ol-2-one (IX) adds methanol suggests that yet other factors remain to be considered.

A comparison of the molecular rotations of cholestanolone (VI) (+117°) and the methyl ether (VII) (+153°) shows a Δ value of +36° for the 4-methoxy group. The sign and the magnitude of the value indicate that the methoxy group is β-oriented (9).

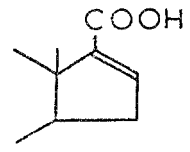
The methyl ether (XII) is also obtained in a good yield by refluxing the peroxide (I) with potassium hydroxide in methanol (2). It appears certain that this transformation proceeds through a rearrangement of I to the enolone (IX) and addition of methanol to the latter. Under analogous conditions ergosterol-peroxide (XXII) with its di-tertiary attachment of the peroxide bridge remains



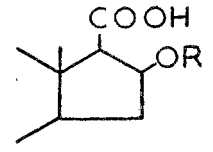
XVI



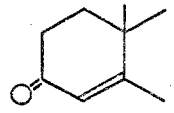
XVII



XVIII



XIX



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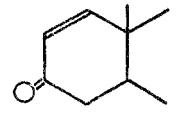
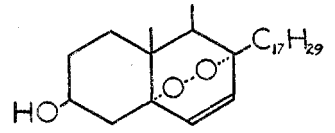
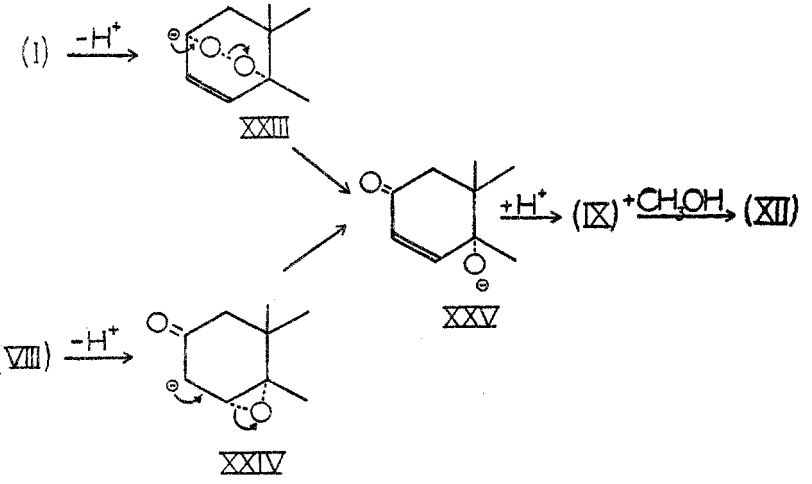


XXI



XXII



XXIII

XXIV

XXV

unchanged (10). The behavior of these peroxides is in agreement with the observations of Kornblum and DeLa Mare (11) on the base-catalyzed de-

composition of dialkyl peroxides. Those with a hydrogen on the carbon attached to the peroxide linkage are split by alkali to a ketone and a tertiary alcohol, but di-*tert*-peroxides under similar conditions remain unaltered. The base-catalyzed rearrangement of I to IX may therefore be presumed to proceed through XXIII and XXV.

Treatment of the keto-epoxide (VIII) with potassium hydroxide in methanol also affords the methyl ether (XII). The reaction appears to proceed through the base-catalyzed rearrangement of VIII to IX by way of XXV and XXIV, and addition of methanol to IX.

EXPERIMENTAL

All melting points are corrected. Optical rotations were measured in chloroform solutions. The ultraviolet absorption spectra were determined in absolute ethanol on a Beckman Model DU spectrophotometer, and the infrared spectra in chloroform on a Perkin-Elmer Model 12C spectrophotometer.

2α,5-cholestanediol (Va). A solution of 4α,5-oxidocholestan-2-one (VIII) (0.3 g.) in ether (75 ml.) was added dropwise to a vigorously agitated suspension of lithium aluminum hydride in ether (10 ml.). The mixture was refluxed for one hour, treated with ethyl acetate to decompose excess reducing agent, and then poured into ice-cold 10% hydrochloric acid. It was then extracted with ether, and the extract washed, dried, and concentrated. The residue was recrystallized several times from acetone; m.p. 154.5–155°; $[\alpha]_D^{27}$ +19.8°. The product did not give a depressed melting point when mixed with authentic 2α,5-dihydroxycholestane (Va) (1). The infrared spectra of the two samples were identical; λ_{max} 2.79 μ. The mono-acetate, prepared as previously described (1), showed m.p. 141–142°; $[\alpha]_D^{24}$ −8.7°; λ_{max} 2.80; 5.80; 8.00 μ. It did not give a depressed melting point when mixed with authentic material.

Cholestan-5-ol-2-one (VI). (*a*). *By oxidation of 2α,5-cholestanediol* (Va). To a solution of (Va) (1.0 g.) in glacial acetic acid (100 ml.) there was added slowly a solution of chromic acid anhydride (0.3 g.) in 90% acetic acid (30 ml.). The mixture was kept at room temperature for 12 hours and the excess oxidant was then reduced with methanol. The solution was evaporated to dryness, the residue extracted with ether, and the ether extract washed with dilute alkali and water, and then dried over sodium sulfate. Evaporation of the solvent and several recrystallizations of the residue from acetone gave the ketone (0.8 g.); needles, m.p. 181.5–182.5°; $[\alpha]_D^{27}$ +29.2°; λ_{max} 2.79; 5.86 μ.

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52.

Found: C, 80.41; H, 11.56.

(*b*). *By reduction of* Δ^3*-cholesten-5-ol-2-one* (IX). A solution of IX (0.52 g.) in ethyl acetate (100 ml.) was shaken with hydrogen and a Willstätter platinum black catalyst at room temperature and atmospheric pressure. After one-half hour and the uptake of one mole-equivalent of hydrogen the reaction stopped. The reduction product (0.44 g.) was recrystallized four times from acetone; m.p. 181–182.5°; $[\alpha]_D^{29}$ +29°; λ_{max} 2.79; 5.86 μ. It did not give a depressed melting point when mixed with VI prepared according to (*a*).

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52; Active H, 0.25.

Found: C, 80.27; H, 11.50; Active H, 0.23; 0.28, 0.24.

(*c*). *By reduction of 4α,5-oxidocholestan-2-one* (VIII). The oxide (0.37 g.) was reduced in ethanol (20 ml.) at room temperature and pressure with an Adams' platinum catalyst. After the consumption of 0.95 mole no further hydrogen uptake was observed. The reduction product (0.26 g.) was recrystallized from ethanol; needles, m.p. 182–183°; $[\alpha]_D^{25}$ +32°. It did not give a depressed melting point with the products described above.

5-Cholestanol (VII). A solution of cholestan-5-ol-2-one (VI) (0.16 g.) in methanol (12 ml.) containing diethylene glycol (2.4 ml.) and 85% hydrazine hydrate (0.7 ml.) was refluxed for 30 minutes. Two pellets of potassium hydroxide were added and the refluxing was continued for four hours. The condensor was removed, and the solution was concentrated until

the temperature of solution had reached 195°. With refluxing, this temperature was maintained for about two hours. The solution was then cooled, diluted with methanol (12 ml.) containing hydrazine hydrate (0.5 ml.), refluxed for one hour, and concentrated as before and maintained at 195–200° for four hours. After cooling, the mixture was extracted with ether, and the extract was washed, dried, and concentrated. The residue (0.15 g.) was once recrystallized from dilute acetone, m.p. 100–101°, $[\alpha]_D^{28}$ +16.0°; it was dissolved in petroleum ether and adsorbed on alumina (6 g.). The crystalline fractions, eluted with petroleum-ether-benzene (20:1), were combined and recrystallized three times from acetone, 50 mg., m.p. 102–103°; $[\alpha]_D^{28}$ +13.6°; λ_{max} 2.75 μ. The 5-cholestanol described by Plattner, *et al.* (5) melts at 109–110°; $[\alpha]_D$ +11.2°; +9.3°; λ_{max} 2.75 μ.

Anal. Calc'd for $C_{27}H_{48}O$: C, 83.46; H, 12.45.

Found: C, 83.70; H, 12.64.

Oxidation of Δ³-cholesten-5-ol-2-one (IX). To a solution of IX (0.22 g.) in glacial acetic acid (13 ml.) there was added dropwise with stirring and warming to 55–60°, a solution of chromic acid anhydride (0.24 g.) in 90% acetic acid (14 ml.). After one hour, methanol was added, the mixture was concentrated under reduced pressure, and the residue was extracted with ether. The ether extract was washed with dilute sodium hydroxide, and the alkaline washings were acidified with dilute sulfuric acid and extracted with ether. The crude acid (X a, b) obtained upon concentration of the extract was recrystallized from acetone and ethyl acetate, m.p. 166–167°; $[\alpha]_D^{23}$ +32.8°; λ_{max} 2.82, 5.65 μ.

Anal. Calc'd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84.

Found: C, 76.70; H, 10.94.

The *p-bromophenacyl ester*, m.p. 126–127.5°; $[\alpha]_D^{25}$ +54.2°.

Anal. Calc'd for $C_{33}H_{47}BrO_4$: C, 67.45; H, 8.06; Br, 13.60.

Found: C, 67.65; H, 7.87; Br, 14.46.

Oxidation of 4α,5-oxidocholestan-2-one (VIII). The oxidation (1.00 g.) was carried out in the manner described above. The acid fraction afforded the keto acid (Xa, b) (0.32 g.); m.p. 166–167°; $[\alpha]_D^{23}$ +33°; λ_{max} 2.82, 5.65 μ. The neutral fraction, recrystallized from acetone, gave 5-hydroxy-Δ³-cholestenone-2 (IX); m.p. 172–173°; $[\alpha]_D^{24}$ +32.5°.

Reduction of the keto-acid (Xa). A solution of the keto acid (0.1 g.) in toluene (20 ml.) was refluxed for 24 hours with a mixture of water (10 ml.), glacial acetic acid (40 ml.), conc'd hydrochloric acid (20 ml.), and amalgamated zinc (10 g.). At periodic intervals four portions of hydrochloric acid (5 ml.) were added. The solution was then decanted, diluted with water, and extracted with ether. Washing, drying, and concentration of the ether extract gave an acid which was recrystallized from ethyl acetate and acetic acid (21 mg.); m.p. 153–154°; $[\alpha]_D^{25}$ +45.4°. Reported for XI (6), m.p. 154°; $[\alpha]_D$ +45.7°.

Phenol ethyl ether. A solution of Δ³-cholesten-5-ol-2-one (IX) (0.25 g.) in abs. ethanol (15 ml.) containing conc'd sulfuric acid (0.4 ml.) was refluxed for one hour. The ether extract of the reaction mixture was washed with dilute potassium carbonate and water, and dried over sodium sulfate. The extract was concentrated, and the oily residue (0.25 g.) was dissolved in petroleum ether and adsorbed on alumina (12.5 g.). The petroleum ether eluates were concentrated, and the residue (0.12 g.) was recrystallized several times from methanol; needles (0.1 g.); m.p. 76.5° – 77.5°; $[\alpha]_D^{25}$ +71°; λ_{max} 6.25, 6.31 μ; λ_{max} 279 mμ; log ϵ 3.3; λ_{min} 249 mμ; log ϵ 2.7.

Anal. Calc'd for $C_{28}H_{44}O$: C, 84.79; H, 11.18; C_2H_5O, 11.36.

Calc'd for $C_{29}H_{46}O$: C, 84.83; H, 11.29; C_2H_5O, 10.97.

Found: C, 85.06; H, 10.91; C_2H_5O, 11.00.

Phenol methyl ether. A solution of 4α,5-oxidocholestan-2-one (VIII) (0.13 g.) in absolute methanol (10 ml.) containing conc'd sulfuric acid (0.2 ml.) was refluxed for one hour. The reaction product was isolated as described above and recrystallized four times from acetone (0.05 g.) m.p. 51.5–52.5°; $[\alpha]_D^{28}$ +76.6°; λ_{max} 6.22, 6.28 μ; λ_{max} 278 mμ; λ_{min} 248 mμ.

Anal. Calc'd for $C_{27}H_{42}O$: C, 84.76; H, 11.07.

Calc'd for $C_{28}H_{44}O$: C, 84.79; H, 11.18.

Found: C, 84.67; H, 11.13.

Dehydration of Δ^3-cholesten-5-ol-2-one (IX). A solution of the ketone (0.20 g.) and *p*-toluenesulfonic acid (0.05 g.) in anhydrous benzene (15 ml.) was heated on the steam-bath for 30 minutes. The reaction mixture was diluted with ether, washed with water, dried, and concentrated. The residue (0.2 g.) was dissolved in petroleum ether and chromatographed on alumina (10 g.). From the petroleum ether and petroleum ether-benzene (3:1) eluates a crystalline fraction (0.1 g.) was obtained. After three crystallizations from acetone it gave $\Delta^{3,5}$-cholestadien-2-one (XIII) (0.06 g.); m.p. 123–124°; $[\alpha]_D^{25}$ −77.0°; λ_{max} 291 mμ; log ϵ 4.2; λ_{max} 6.00, 6.11, 6.30 μ. Reported for XIII by Ruzicka, *et al.* (7); m.p. 121.5–122.5°; $[\alpha]_D$ −62°; λ_{max} 290 mμ, log ϵ 4.1.

Anal. Calc'd for $C_{27}H_{42}O$: C, 84.82; H, 11.06.
Found: C, 84.79; H, 11.45.

Evaporation of the benzene-ether (9:1) eluates gave an oil (0.09 g.) which was crystallized and recrystallized from pentane to give a phenol (0.04 g.), m.p. 119–120.5°; $[\alpha]_D^{25}$ +74°; λ_{max}, 280 mμ; λ_{min} 248 mμ.

Anal. Calc'd for $C_{26}H_{40}O$: C, 84.72; H, 10.93.
Calc'd for $C_{27}H_{42}O$: C, 84.82; H, 11.06.
Found: C, 84.94; H, 11.36.

The same products are obtained when IX is treated with dioxane and sulfuric acid.

SUMMARY

The α-orientation of the peroxide bridge in Δ^3-2,5-peroxidocholestene has been demonstrated. It has been shown that the peroxide rearranges in sunlight to 4α, 5-oxidocholestan-2-one and that the latter upon heating isomerizes to give Δ^3-cholesten-5-ol-2-one. This ketone has been reduced to cholestan-5-ol-2-one and 5-cholestanol and has been oxidatively degraded to a known C_{25}-acid. It has been shown that dehydration of the ketone may lead to a phenol, phenolic ethers, and $\Delta^{3,5}$-cholestadien-2-one. The ketone readily adds methanol in a reversible reaction to give 4β-methoxycholestan-5-ol-2-one.

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