[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS IN THE STEROLS. X. THE REARRANGEMENTS OF EPICHOLESTERYL *p*-TOLUENESULFONATE AND THE CHEMISTRY OF SOME ISOMERIC CHOLESTEROLS

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In two recent publications Schmid and Kagi (1) and Shoppee and Evans (2) reported the results of their studies on the rearrangement of epicholesteryl *p*-toluenesulfonate. These authors hoped that a new isomeric 3-5-cyclosterol, a 3-5-cyclocoprostanyl derivative, could be prepared *via* this rearrangement. Such a compound, as a derivative of coprostane, would have the C_3—C_5 bond in front of the plane of the A ring and a *cis* A/B ring fusion, while the normal 3-5-cyclosterol is related to cholestane. However, no 3-5-cyclosterol was found among the reaction products: the products of the reaction in methanol with potassium acetate were $\Delta^{3,5}$-cholestadiene, in a predominant yield, 4β-methoxy-Δ^5-cholestene, designated as "ether B", and 6β-methoxy-Δ^4-cholestene, designated as "ether A."

In the light of these results, it was decided in this laboratory to investigate this rearrangement in aqueous acetone with potassium acetate at room temperature, in the hope that the milder conditions would inhibit the elimination reaction leading to $\Delta^{3,5}$-cholestadiene and be more favorable to the formation of a 3-5-cyclocoprostanyl isomer.

Epicholesterol was prepared *via* the method described by Plattner, *et al.* (3). It was found that the cholesteryl α-oxide used in this synthesis may be very readily prepared with peracetic acid. The yields are comparable to those obtained by the use of perbenzoic acid and the rather tedious preparation of this peracid is avoided. The α-oxide so prepared melted at 142–144°.

Epicholesteryl *p*-toluenesulfonate (I) was prepared by the standard method of treating the sterol with *p*-toluenesulfonyl chloride in pyridine. The crude product of the reaction of I with potassium acetate in aqueous acetone was chromatographed on alumina to give a 60% yield of $\Delta^{3,5}$-cholestadiene (II), and a 16% yield of a compound identified on the basis of its analysis, infrared spectrum, and rotation as Δ^5-cholesten-4β-ol (III), m.p. 131–132°, $[\alpha]_D^{23}$ −60°. This alcohol (III) upon methylation gave 4β-methoxy-Δ^5-cholestene (IV), m.p. 65.5–66.5°, $[\alpha]_D^{25}$ −73°, whose infrared spectrum was identical with that obtained by Schmid and Kagi for "ether B" (1).

The recent work of Reich, *et al.* (5) provided the synthetic approach to the Δ^4-cholesten-6α- and 6β-ols. These authors prepared Δ^4-cholesten-6-one (VIII)

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[2] This paper is based in part upon a thesis submitted by Mr. Edward J. Becker to the Faculty of the Graduate School of Princeton University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

and several intermediates which were utilized in this work. The procedure which they employed was followed in the synthesis of (VIII) except in the dehydration of cholestan-5α-ol-6-one (VII) which was found to give more favorable results if the reaction was carried out at 0°.

The reduction of C_6 ketones, catalytically or with lithium aluminum hydride, generally favors the formation of 6β alcohols (6). Chemical reduction with sodium and alcohol, on the other hand, provides the more stable α or equatorial isomer (7). When cholestan-5α-ol-6-one (VII) was reduced with lithium aluminum hydride, cholestan-5α, 6β-diol (V) was isolated as the sole product, further indicating the validity of this observation. The reduction of the unsaturated ketone (VIII) by lithium aluminum hydride furnished Δ^4-cholesten-6α-ol (IX), m.p. 138–139°, $[\alpha]_D^{20}$ +57°. This compound was at first considered to possess the β configuration at C_6, in view of the trend in reductions of this general type. Methylation of this alcohol gave 6α-methoxy-Δ^4-cholestene (X), m.p. 62–63°, $[\alpha]_D^{20}$ +53°, which did not compare with the C_6 substituted "ether A" isolated from the rearrangement of (I) in methanol.

An Oppenauer oxidation of IX gave the ketone (VIII), indicating the absence of any structural change in the reduction of the unsaturated ketone (VIII). An attempt was made to isomerize IX, by the method of Heilbron, *et al.* (8), with aluminum isopropoxide. In benzene solution only starting material was recovered while in toluene a small quantity of a colorless oil was obtained which was later identified as the β epimer. The very low yield of isomerization product is understandable in view of the fact that the starting material is the more stable equatorial epimer.

The sodium and ethanol reduction of VII gave two products, the expected cholestan-5α, 6α-diol (XII), m.p. 176–177°, $[\alpha]_D^{25}$ +8°, and cholestan-6α-ol (XIV), m.p. 128–129°, $[\alpha]_D^{25}$ +38°. The acetate (XV) of XIV melted at 94–95°. These constants are in agreement with those reported by Tschesche (7) for cholestan-6α-ol and its acetate. In order to provide substantiating evidence as to the identity of (XII), the compound was also prepared from Δ^5-cholestene (XVI) by hydroxylation with osmium tetroxide. The ability of this reagent to hydroxylate the Δ^5 double bond giving a *cis* α-diol is well known. That XII, synthesized by the two methods was the same compound was shown by their identical infrared spectra.

Both diols (V) and (XII) were acetylated to give the corresponding 6-monoacetates, cholestan-5α, 6β-diol-6β-acetate (VI), m.p. 112–113°, and cholestan-5α,6α-diol-6α-acetate (XIII), m.p. 130–132°. Difficulty was encountered in the purification of the latter acetate as it did not crystallize well. Both compounds were characterized by their infrared spectra which were typical.

The dehydration of these acetates was undertaken and as expected XIII was converted smoothly to the unsaturated acetate which was shown to be identical with XI, thereby demonstrating the α configuration of the reduction product of VIII. Heilbron, *et al.* (9) have reported a study on the dehydration of V and VI, and under a variety of conditions the compounds either suffered elimination

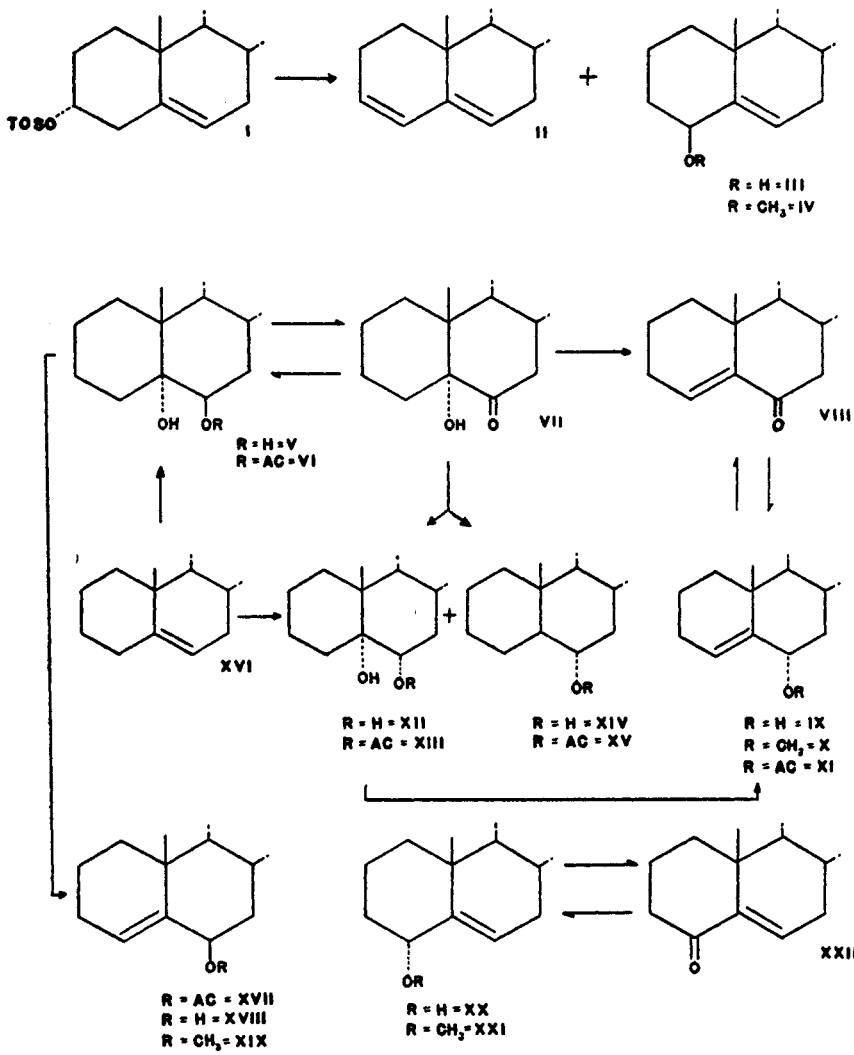
of both functions or failed to undergo any reaction. However, when treated with thionyl chloride in pyridine at 0°, VI was dehydrated in good yield to Δ^4-cholesten-6β-ol-6β-acetate (XVII), m.p. 83–84°, $[\alpha]_D^{27}$ +68°.

An additional proof that the configurations at C_6 in XI and XVII are correct as indicated was obtained by saponification experiments. It was found that the α-acetate (XI) is hydrolyzed about eight times faster than the β-acetate (XVII). This result is in agreement with the work of Plattner, *et al.* (3) on the hydrolysis of the epimeric cholestan-3β, 6α and 6β-diacetates. The difference in reactivity is attributed to the fact that the 6β position is sterically hindered by the angular methyl group attached to C_{10}. The alcohol (IX) was obtained from XI and from XVII a new alcohol, Δ^4-cholesten-6β-ol (XVIII), $[\alpha]_D^{25}$ +55°, was obtained, which was identical with the alcohol obtained in small yield from the isomerization of IX. This material resisted all attempts to crystallize it, even after repeated chromatographic purification. The infrared spectrum of (XVIII) was typical of an unsaturated alcohol. Methylation of XVIII gave 6β-methoxy-Δ^4-cholestene (XIX), m.p. 96–97°, $[\alpha]_D^{26}$ +80°, whose infrared spectrum was the same as that of the methyl ether A of Schmid and Kagi (1).

The alcohol (XX) was prepared according to the method of Karrer, *et al.* (10). When submitted to an Oppenauer oxidation, XX gave a low yield of the corresponding ketone, Δ^5-cholesten-4-one (XXII). This ketone was also prepared by the method of Butenandt, *et al.* (11). When XXII was submitted to reduction by lithium aluminum hydride XX was obtained together with an unidentified non-crystalline compound. Methylation of XX gave 4α-methoxy-Δ^5-cholestene (XXI), m.p. 84–85°, $[\alpha]_D^{24}$ −58°, in agreement with the reported value (1).

The four isomeric alcohols, III, IX, XVIII, and XX, as well as their ethers and the two acetates XI and XVII, gave strong Rosenheim tests; in every case the color was a deep cherry red, appearing in less than 60 seconds.

The unexpected results of the lithium aluminum hydride reductions of Δ^4-cholesten-6-one (VIII) and Δ^5-cholesten-4-one (XXII) may be readily understood when the geometry of the system is considered. In the saturated system the carbonyl group, because of the nature of the chair-formed ring fusion, is projected out of the plane of the molecule. Consequently, any reagent which must attack the C—O bond, as in the case of the aluminum hydride ion, will encounter considerable steric repulsion on the β side because of the angular methyl group and the direction of the C—O bond, while an attack involving considerably less energy may be directed against the α side of the molecule. Therefore the addition of hydrogen to the α face of the carbon atom occurs giving rise to β isomers. In the unsaturated system it appears that the presence of a double bond in one ring causes a distortion in the ring adjacent to it. This distortion causes the carbonyl group to be pulled into the general plane of the molecule, thereby exposing the β side of the molecule to attack. In this condition there is sufficient space available for the formation of the transition complex between the steroid and the aluminum hydride ion and this attack does in fact occur in the cases mentioned above giving rise to the more stable α isomers.



EXPERIMENTAL[3]

Peracetic acid. This reagent was prepared according to the method described by Swern, *et al.* (12). To a well stirred solution of 675 ml. of acetic anhydride was added 150 ml. of 30% hydrogen peroxide. The solution became turbid but cleared in a short time. The temperature was maintained below 40° and stirring was continued overnight. The solution then was ready for use and contained approximately 0.8 mole of peracetic acid.

Cholesteryl α-oxide. To 105 g. of cholesterol in 700 ml. of absolute benzene was added

[3] All melting points are uncorrected and were determined on a Kofler block; all rotations were measured in a 1-dm. semi-micro tube; analyses were performed by the Clark Microanalytical Laboratory, Urbana, Illinois. "Worked up in the usual manner," refers to the following procedure: The reaction mixture was poured into excess water, extracted into ether, neutralized, washed with water, dried over magnesium sulfate, and evaporated to dryness.

0.3 mole of peracetic acid (315 ml. of the above solution). The reaction mixture was allowed to stand for 24 hours at room temperature. It was worked up in the usual manner giving a crude product melting 100–135°. Several recrystallizations from ethyl acetate gave 50 g. material, m.p. 142–144°. [Literature m.p. 142.5° (3)]. A mixture melting point with a sample prepared with perbenzoic acid was 142–144°; with cholesterol, 128–140°. To insure further the identity of this compound a 2-g. sample was hydrolyzed to cholestantriol according to the method of Westphalen (4). After recrystallization from methanol the triol melted at 234–236°. The diacetate was also prepared by reacting the triol with acetic anhydride in pyridine. Recrystallization from ethanol gave needles melting at 166–167°.

Epicholesterol. This compound was prepared according to the method described by Plattner, *et al.* (3). The intermediates were not isolated but each was worked up in the usual manner and after removal of the solvent, was carried on to the next stage. The final saponification product was chromatographed on acid-washed alumina to give epicholesterol in about 50% over-all yield. A Rosenheim test on this material was negative. M.p. 140–141°, $[\alpha]_D^{25}$ −42°, *c*, 1, $CHCl_3$.

Epicholesteryl p-toluenesulfonate (I). This compound was prepared according to the method described in the literature (1, 2, 13). The crude product melted at 125–128°, with decomposition to a blood-red liquid. When the crude material was recrystallized from acetone the melting point decreased and gave a product which melted in the range of 108–112°. Several more recrystallizations gave a sharper melting point at about 110–111°, (dec.). The yield in successive preparations was about 90%.

Rearrangement of epicholesteryl p-toluenesulfonate (I). To 18 ml. of water and 50 ml. of acetone were added 700 mg. of potassium acetate and 500 mg. of epicholesteryl *p*-toluenesulfonate. A small additional amount of acetone was necessary to bring all the material into solution. It then was stirred at room temperature for 48 hours. The solution then was worked up in the usual manner. The crude crystalline residue gave a positive Rosenheim test and showed some decomposition on melting, m.p. 115–121°. When this material was taken up in petroleum ether a variable amount of crystalline material remained undissolved (50 to 100 mg.). This material melted at 109–111° and showed no depression when a mixture melting point was taken with an authentic sample of the starting material. In several subsequent runs the crude product melted over a wider range of 60–115°, with decomposition to a light red liquid occurring above 110°. The fraction which was soluble in petroleum ether was chromatographed on 15 g. of basic alumina. Fractions 1–5, 40 ml. each of petroleum ether gave 200 mg. $\Delta^{3,5}$-cholestadiene, m.p. 75–77°; recrystallization from aqueous acetone brought the melting point to 80–81°; fractions 11–14, 40 ml. each (petroleum ether:benzene 4:1), gave 31 mg. of a crystalline material, m.p. 68–100°; fractions 15–19, 40 ml. each (petroleum ether:benzene 1:1), gave 69 mg. of a crystalline material, m.p. 90–120°. Fractions 11–19 were rechromatographed on 5 g. of basic alumina, and 25 ml. fractions were collected.

Fraction	Solvent Mixture	Weight	Character
1–2	PE	0	—
3–7	PE:ϕH, 4:1	0	—
8	PE:ϕH, 3:1	trace	—
9	"	"	—
10	"	5	Cryst. 116–125°
11	"	8	" 114–125°
12	"	12	" 119–130°
13	"	14	
14	"	10	
15	"	10	
16	"	9	Cryst. 118–128°
17	"	4	
18	"	4	
19	"	trace	
20	"	"	—

Fraction	Solvent Mixture	Weight	Character
21	"	"	Cryst. 95–108°
22	"	"	" 91–96°
23	"	"	" 92–98°
24	"	"	—
25	"	"	—
26–28	"	0	—

Fractions 10–19 were recrystallized from methanol to give needles, m.p. 131–132°, $[\alpha]_D^{25}$ −60°, *c*, 1, $CHCl_3$. The yield of $\Delta^{3,5}$-cholestadiene ranged from 60 to 70%, while the more strongly adsorbed product was about 10 to 15%. The 131–132° compound because of its negative rotation was assigned the structure of Δ^5-cholesten-4β-ol.

Anal. Calc'd for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99.
Found: C, 83.81; H, 12.28.

The material in fractions 20–25 was not examined further because of the small quantities available but in all probability this was also the Δ^5-cholesten-4β-ol, judging by the melting point behavior.

4β-Methoxy-Δ^5-cholestene (IV). Excess potassium metal was added to 50 mg. of III in 15 ml. of anhydrous benzene. The heterogeneous solution was refluxed in an atmosphere of nitrogen for 1½ hours. Then 3 ml. of freshly distilled methyl iodide was added and the solution then was heated under reflux for two additional hours. The excess potassium was destroyed with ethanol and the reaction mixture was worked up in the usual manner. The crude product was chromatographed on 2 g. of acid-washed alumina. Elution of the column with petroleum ether gave nothing; with petroleum ether: benzene, 4:1, 34 mg. of the ether were obtained, m.p. 65.5–66.5°, $[\alpha]_D^{25}$ −73°, after recrystallization from methanol. Analysis and infrared spectrum of this compound showed that it was identical with that obtained by Schmid and Kagi for "ether B" (1).

Δ^4-Cholesten-6-one (VIII). This compound was prepared according to Reich, *et al.* (5). The dehydration of cholestan-5α-ol-6-one (VII) was best accomplished at 0° giving VIII m.p. 109°, $[\alpha]_D^{23}$ +35°, *c*, 1, Ethanol.

Lithium aluminum hydride reduction of VII. *Cholestan-5α, 6β-diol* (V). The ketol (3 g.) in 50 ml. of anhydrous ether was added dropwise to 0.6 g. of lithium aluminum hydride in 100 ml. of anhydrous ether with continuous stirring. The solution boiled gently and when the reaction subsided it was heated under reflux for 1½ hours. The excess hydride was destroyed with ethyl acetate and the aluminum salts with cold dilute sulfuric acid. It then was worked up in the usual manner and the residual oil was crystallized from aqueous alcohol, m.p. 114–116°. A mixture melting point with an authentic sample of V was undepressed. The double melting point reported for this diol as 116–118°, and after resolidification, 125–127°, was observed only on rare occasions (5). Ordinarily only the lower melting point was observed.

Δ^4-Cholesten-6α-ol (IX). In 50 ml. of anhydrous ether was dissolved 2.7 g. of the ketone (VIII). This solution was added dropwise to 0.4 g. of lithium aluminum hydride in 100 ml. of anhydrous ether. The solution was stirred vigorously during the addition and the reaction proceeded mildly. It then was heated under reflux for two hours. The excess hydride was destroyed with ethyl acetate and the aluminum salts with cold dilute sulfuric acid. After working up the reaction mixture in the usual manner, the crude crystalline residue melted at 127–134°. It was recrystallized from methanol to give beautiful cotton-like needles which melted at 138–139°, $[\alpha]_D^{23}$ +57°, *c*, 1, $CHCl_3$. The yield was approximately quantitative.

Anal. Calc'd for $C_{27}H_{46}O$ (386.64); C, 83.87; H, 11.99.
Found: C, 83.97; H, 11.97.

6α-Methoxy-Δ^4-cholestene (X). Freshly prepared silver oxide, 200 mg. together with 200 mg. of alcohol (IX) were heated under reflux in 3 ml. of freshly distilled methyl iodide for six hours. The solution was filtered and extracted with ether, the extract then was washed with sodium bisulfite and water. Evaporation of the dried ether solution gave a colorless

oil which was crystallized by freezing its methanol solution in Dry Ice/acetone. The crude product melted at 40–50°. This material was chromatographed on 15 g. of acid washed alumina, and 25-ml. fractions were collected. No material was eluted with petroleum ether, but petroleum ether:benzene, 4:1, gave 60 mg. of an oil which crystallized when triturated with methanol, m.p. 62–63°, $[\alpha]_D^{23}$ +53°, *c*, 1, $CHCl_3$.

Anal. Calc'd for $C_{28}H_{48}O$ (400.67): C, 83.93, H, 21.08.

Found: C, 84.02, H, 11.84.

Δ^4-Cholesten-6α-ol-6α acetate (XI). To 100 mg. of sterol in 3 ml. of anhydrous pyridine was added 1 ml. of acetic anhydride. The solution was allowed to stand at room temperature overnight. It then was poured onto ice giving a crude crystalline product which melted at 93–97°. Several recrystallizations from ethanol gave platelets, m.p. 99–100.5°, $[\alpha]_D^{22}$ +73°, *c*, 1, $CHCl_3$.

Anal. Calc'd for $C_{29}H_{48}O$ (428.68): C, 81.25; H, 11.29.

Found: C, 81.62; H, 11.25.

Na/ethanol reduction of VII. *Cholestan-5α, 6α-diol* (XII). The ketol, 4.15 g. was dissolved in 300 ml. of anhydrous ethanol and heated to reflux temperature. One mole of sodium, cut into small pieces, was added slowly to this solution. The addition required about three hours. The yellow solution was neutralized with dilute hydrochloric acid and worked up in the usual manner to give 4 g. of a deep yellow oil which was chromatographed on 120 g. of acid washed alumina. Fractions containing 125 ml. were collected. With benzene 2 g. of a crystalline material, m.p. 128–129°, was obtained. Elution with ether gave 1.8 g. of material melting at 175–176°. The material melting at 128–129°, $[\alpha]_D^{25}$ +38°, *c*, 1, $CHCl_3$, was identified as cholestan-6α-ol (XIV). The physical constants agree with those reported by Tschesche (7) for this compound.

Anal. Calc'd $C_{27}H_{48}O$ (388.65): C, 83.43; H, 12.45.

Found: C, 83.82; H, 12.50.

Acetate (XV). To 70 mg. of XIV dissolved in 2 ml. of absolute pyridine was added 1 ml. of acetic anhydride. After standing overnight the product was worked up in the usual manner to give a crude product melting at 85–90°. Recrystallization from ethanol brought the melting point to 94–95°, in agreement with the value of Tschesche. The material melting at 175–176.5°, $[\alpha]_D^{25}$ +8°, *c*, 1, $CHCl_3$, was identified as cholestan-5α, 6α-diol (XII).

Anal. Calc'd for $C_{27}H_{48}O_2$ (404.65): C, 80.13; H, 11.96.

Found: C, 80.49; H, 11.99.

Osmium tetroxide hydroxylation of XVI. *Cholestan-5α, 6α-diol* (XII). In 40 ml. of anhydrous ether was dissolved 720 mg. of Δ^5-cholestene (XVI). To this solution was added 500 mg. of osmium tetroxide in 20 ml. of anhydrous ether. The solution was allowed to stand at room temperature for 60 hours. In that time no precipitation of the osmic ester occurred. The solution was evaporated to dryness leaving a blackish residue. This material was heated under reflux in 80 ml. of a 50% ethanol solution containing 5 g. of sodium bisulfite heptahydrate for 2½ hours. This procedure was repeated a second time and the product then was worked up in the usual manner. Crystallization from ethanol gave small platelets, m.p. 169–173°; two recrystallizations brought the melting point to 174–175°. This material showed no depression when a mixture melting point was taken with a sample of the diol obtained by the sodium and alcohol reduction of the ketol. The yield was 400 mg.

Oppenauer oxidation of Δ^4-cholesten-6α-ol (IX). A solution containing 16 ml. of anhydrous toluene, 340 mg. of IX, 2.5 ml. of cyclohexanone, and 400 mg. of aluminum isopropoxide was heated under reflux for two hours. Water was added to the solution and the aluminum salts were decomposed with dilute sulfuric acid and the reaction mixture was worked up in the usual manner. The remaining high-boiling liquids were removed by high vacuum distillation at 0.1 mm. The yellow viscous oil remaining was crystallized from acetone giving fine needles, m.p. 104–106°; a second crop melted at 105–107°. A mixture melting point with an authentic sample of Δ^4-cholesten-6-one was 105–107°. The yield of ketone was 200 mg.

Isomerization of Δ^4-cholesten-6α-ol (IX). *A*. In 30 ml. of anhydrous benzene was dissolved

400 mg. of IX and 1 g. of aluminum isopropoxide. The solution was heated under reflux for 24 hours. The product after recrystallization from methanol melted at 137–139° and was identical with the starting material.

B. The same experiment was repeated using toluene as the solvent and heating the reaction mixture under reflux for 48 hours. The crude product was chromatographed on 10 g. of acid washed alumina with 30-ml. fractions being collected. Elution was petroleum ether: benzene, 3:1 gave 16 mg. of a colorless oil which was later shown, by comparison of the infrared spectra, to be Δ^4-cholesten-6β-ol (XVIII). The remaining material, 172 mg., eluted with benzene was identical with the starting material.

Cholestan-5α, 6α-diol-6α-acetate (XIII). The diol (300 mg.) was dissolved in 5 ml. of anhydrous pyridine. To this solution was added 2.5 ml. of acetic anhydride. After standing for 24 hours the solution was poured onto ice giving a crystalline product, m.p. 122–128°. Recrystallization from ethanol gave a product, m.p. 130–132°, which could not be purified further by crystallization. The infrared spectrum showed the material to be the hydroxy acetate.

Cholestan-5α, 6β-diol-6β-acetate (VI). This acetate was prepared in the same manner as XIII, giving the desired product in good yield, m.p. 112–113°, in agreement with the value reported by Reich, *et al.* (5).

Dehydration of XIII. Δ^4-*Cholesten-6α-ol-6α-acetate* (XI). To a solution of 250 mg. of XIII in 5 ml. of anhydrous pyridine was added 0.2 ml. of thionyl chloride. The reaction mixture was kept at 0° for 15 minutes and then was poured onto ice. After several hours the crystalline product was broken up, filtered, and washed with water. After drying in a vacuum the crude product melted at 74–95°. Recrystallization from ethanol gave platelets, m.p. 99–100°. The yield was 190 mg. This material was identical with the acetate obtained by acetylation of IX as was shown by melting point behavior and comparison of the infrared spectra.

Dehydration of VI. Δ^4-*Cholesten-6β-ol-6β-acetate* (XVII). The dehydration of VI was carried out exactly as in the case of XIII. From 800 mg. of VI a crude product was obtained melting at 77–80°. This material was recrystallized from ethanol to give long needles, m.p. 83–84°, $[\alpha]_D^{27}$ +68°, *c*, 1, $CHCl_3$. The yield was 500 mg.

Anal. Calc'd for $C_{29}H_{48}O_2$ (428.68): C, 81.25; H, 11.29.
Found: C, 81.51; H, 11.39.

Saponification of Δ^4-*cholesten-6α-ol-6α-acetate* (XI). Δ^4-*Cholesten-6α-ol* (IX). In 30 ml. of methanol was dissolved 140 mg. of XI and 50 mg. of potassium hydroxide. The reaction mixture was heated under reflux in an atmosphere of nitrogen for one-half hour. After working up in the usual manner the material crystallized on evaporation of the solvent, m.p. 136–138°. Recrystallization from methanol gave silky needles, m.p. 138–139°. A mixture melting point with an authentic sample of IX was undepressed. The yield was almost quantitative. Infrared analysis of the carbonyl band after a 15-minute reflux period showed that the reaction was approximately 60% complete.

Saponification of Δ^4-*cholesten-6β-ol-6β-acetate* (XVII). Δ^4-*Cholesten-6β-ol* (XVIII). This experiment was carried out exactly as in the preceding case. The time necessary to complete the saponification was four hours as indicated by infrared analysis. The crude product was chromatographed on 10 g. of basic alumina; 20-ml. fractions were collected. Petroleum ether:benzene, 9:1 gave 48 mg. of a colorless oil which was not identified. Elution with petroleum ether:benzene, 2:1 gave a colorless oil which was rechromatographed and eluted with the same solvent mixture, giving 230 mg. of Δ^4-cholesten-6β-*ol* (XVIII). This compound could not be crystallized under any of the conditions employed. $[\alpha]_D^{25}$ +55°, *c*, 1, $CHCl_3$. The infrared spectrum showed the material to be an unsaturated alcohol.

6β-Methoxy-Δ^4-cholestene (XIX). This alcohol (XVIII) was methylated exactly as in the case of III. Trituration of the crude oil with methanol gave a crystalline product, m.p. 77–83°. Recrystallization from methanol gave needles, m.p. 94–95°. Another recrystallization from the same solvent gave small platelets, m.p. 96–97°, $[\alpha]_D^{26}$ +80°, *c*, 1, $CHCl_3$. Analy-

sis and infrared spectrum of this compound showed that it was identical with the "ether A" of Schmid and Kagi (1).

Δ^5-Cholesten-4α-ol (XX). This compound was prepared according to the method of Karrer, *et al.* (10). The material so obtained melted at 143–144°, $[\alpha]_D^{23}$ −54°, *c*, 1, $CHCl_3$.

4α-Methoxy-Δ^5-cholestene (XXI). The methylation of XX was carried out in the manner described under the methylation of III. After working up the reaction mixture in the usual manner the material was chromatographed on 5 g. of acid-washed alumina. Elution with petroleum ether:benzene, 2:1 gave 31 mg. of XXI, m.p. 84–85°, $[\alpha]_D^{24}$ −58°, *c*, 1, $CHCl_3$ (1).

Oppenauer oxidation of Δ^5-cholesten-4α-ol (XXI). *Δ^5-Cholesten-4-one* (XXII). In 35 ml. of anhydrous toluene was dissolved 1.5 g. of XXI. To this solution were added 2.5 g. of freshly distilled aluminum isopropoxide and 12 ml. of cyclohexanone. The solution then was heated under reflux for two hours. In that time some salts of aluminum had precipitated. The product was worked up in the usual manner and the yellow residue was steam-distilled. The residue was extracted into ether, dried, and the solvent was evaporated leaving 590 mg. of a yellow oil which was chromatographed on 30 g. of acid-washed alumina: 40-ml. fractions were collected. Elution with petroleum ether gave 322 mg. of $\Delta^{3,5}$-cholestadiene. Petroleum ether:benzene, 3:1 gave 53 mg. of XXII and elution with benzene gave 53 mg. of the starting material XX. XXII was also prepared by the method of Butenandt, *et al.* (11). From 1.5 g. of cholestan-3-one there was obtained 50 mg. of XXII m.p. 102–105°. This material did not depress the melting point of the material prepared by the Oppenauer oxidation.

Lithium aluminum hydride reduction of XXII. In 20 ml. of anhydrous ether was dissolved 50 mg. of XXII. To this solution was added 40 mg. of lithium aluminum hydride. The solution was heated under reflux for two hours and then worked up in the usual manner. The crude product was chromatographed on 3 g. of basic alumina and 20-ml. fractions were collected. Elution with petroleum ether gave 13 mg. of a colorless oil which was not examined. With petroleum ether:benzene, 2:1 there was obtained 17 mg. of another unidentified oil. Benzene eluted the product, m.p. 139–142°, in the amount of 17 mg. Recrystallization from ethanol brought the melting point to 143–144°. This material did not depress the melting point of an authentic sample of XX.

SUMMARY

Cholesteryl α-oxide has been synthesized with peracetic acid, giving yields which compare favorably with those obtained by using perbenzoic acid. The rearrangement of epicholesteryl *p*-toluenesulfonate (I) has been studied in aqueous acetone at room temperature, under conditions which normally lead to the formation of 3-5-cyclosterols. The products of the rearrangement were $\Delta^{3,5}$-cholestadiene (II) and Δ^5-cholesten-4β-ol (III). Methylation of III gave 4β-methoxy-Δ^5-cholestene (IV) which was found to be identical with the ether B of Schmid and Kagi. The isomeric Δ^4-cholesten-6-ols (IX) and (XVIII) have been synthesized and their methyl ethers (X) and (XIX) have been prepared. The ether (XIX) was found to be identical with the ether A reported by Schmid and Kagi. The anomalous behavior of the ketones (VIII) and XXII) when reduced by lithium aluminum hydride is noted and discussed.

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