NEIGHBORING GROUP PARTICIPATION REACTIONS IN STEROIDS. ACETATE MIGRATION IN THE 5β-CHOLESTANE SERIES.

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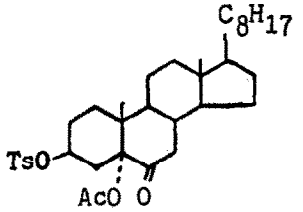
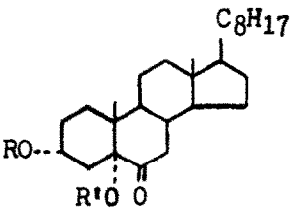
ABSTRACT

The solvolysis of 5β-cholestan-3α,5-diol-6-one 3-tosylate 5-acetate in dimethylformamide-water was found to produce the 3β,5β-diol-6-one 3-acetate when the system contained potassium acetate and a mixture of the 3-acetate and the isomeric 5-acetate when potassium acetate was omitted from the solution. A procedure was developed for the preparation of the 5-acetate. This compound was shown to undergo rapid rearrangement to the 3-acetate in base and a slower rearrangement in acid solution. The reactions of the 5β-acetoxy-3α-tosylate parallel the previously reported solvolyses of the 5α-acetoxy-3β-tosylate.

In 1959, Schultz observed[2] that the solvolysis of 5α-cholestan-3β,5-diol-6-one 3-tosylate 5-acetate (I)[3] in a dimethylformamide-water mixture containing potassium acetate yielded 5α-cholestan-3α,5-diol-6-one 3-acetate (IIa), while solvolysis in the absence of added acetate ion gave the isomeric 5-acetate (IIb). The 5-acetate (IIb) was found to undergo rearrangement to the 3-acetate (IIa) when heated in a dimethylformamide-water solution containing potassium acetate.



I

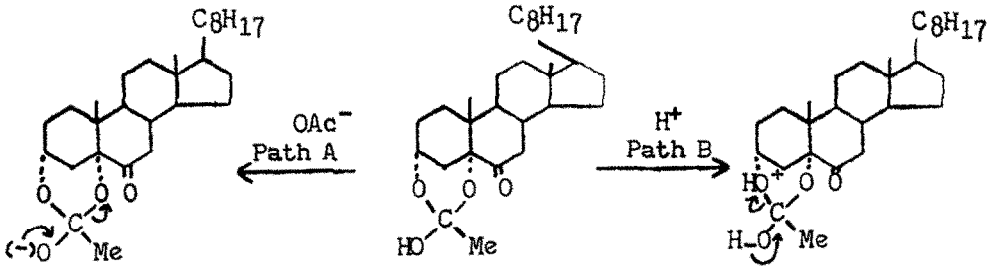


IIa, R=Ac, R'=H
b, R=H, R'=Ac

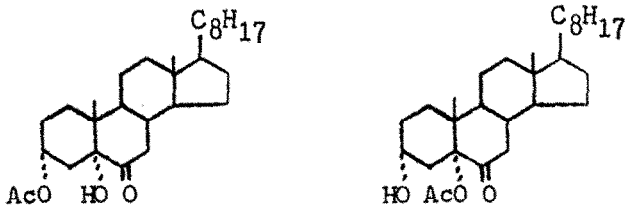
Schultz proposed the cyclic ortho ester (III) as a common intermediate in these reactions.

In the buffered solution, acetate ion presumably extracted a proton

from the hydroxyl group of III and the resulting anion underwent the shift indicated above to give an oxyanion at C-5, which subsequently removed a hydrogen from an available source to yield the 3-acetate (IIa) (Path "A"). Without added acetate ion, a hydrogen ion protonated the C-3 oxygen resulting in (after the indicated electron displacements) the formation of the 5-acetate (IIb) (Path "B").



III



IIa IIb

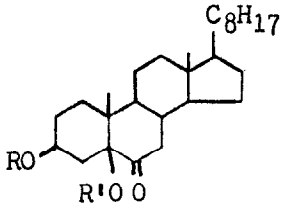
These results, which seem to be explicable in terms of neighboring group participation of the 5-acetoxy function in I, led us to examine this type of reaction in the 5β-cholestane series. An earlier report[4] from this laboratory described the preparation of 5β-cholestan-3β,5-diol-6-one 3-acetate (IVb).[5] Saponification of IVb gave the free diolone (IVa); treatment of IVa with p-toluenesulfonyl chloride in pyridine for six days at room temperature[6] yielded the 3-tosylate (Va). The 5-acetate (Vb) of Va was prepared by a standard procedure.

Two methods were found which produced displacement (with inversion)

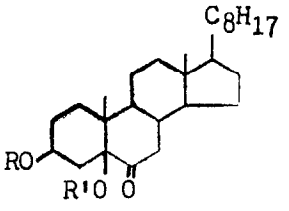
of the 3β-tosyloxy group of Va. Solvolysis of Va in dimethylsulfoxide or methanol in the presence of water[7] yielded 5β-cholestan-3α,5-diol-6-one (VIa). The structure of this diolone was proved by formation of the monoacetate (VIb), infrared spectroscopy, oxidation to 5β-cholestan-5-ol-3,6-dione (VII),[4] and subsequent reactions. A second product obtained from the solvolyses was an unsaturated hydroxy ketone tentatively identified as 5β-cholest-3-en-5-ol-6-one (VIII) since, upon hydrogenation, it yielded 5β-cholestan-5-ol-6-one (IX).

The 3α,5β-diol-6-one (VIa) was converted into the 3-tosylate (Xa) in the usual manner; acetylation of Xa with acetic anhydride-p-toluenesulfonic acid gave the acetoxy tosylate (Xb), which is epimeric at carbons 3 and 5 with the 3β-tosylate 5α-acetate (I) and was the compound necessary for the acetate migration study in the 5β-cholestane series.

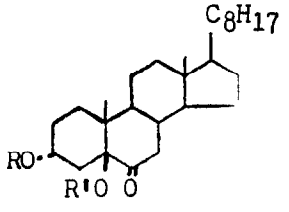
Solvolysis of Xb in dimethylformamide (DMF)-water with or without added potassium acetate produced the 3β,5β-diol-6-one 3-acetate (IVb)



IVa, R=R'=H
b, R=Ac, R'=H
c, R=R'=Ac
d, R=H, R'=Ac

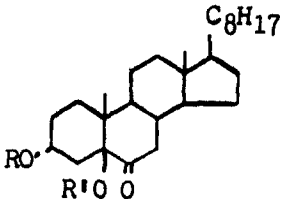


Va, R=Ts, R'=H
b, R=Ts, R'=Ac

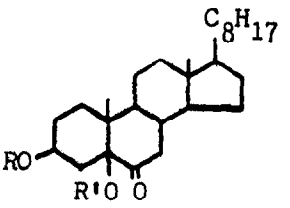


VIa, R=R'=H
b, R=Ac, R'=H

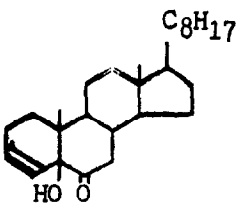
in good yield by direct crystallization of the reaction products. If buffering of the solution functioned in a manner similar to that found for compound I, the reaction mixture that did not contain acetate ion might have been expected to yield the isomeric 5-acetate (IVd) (Path "B"). The production of the 3-acetate (IVb) from both reactions seemed



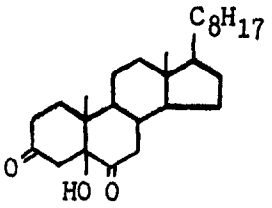
Xa, R=Ts, R'=H
b, R=Ts, R'=Ac



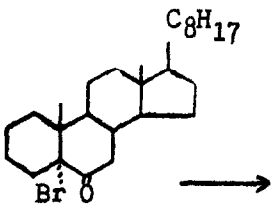
XIIa, R=CF_3CO-, R'=H
b, R=CF_3CO-, R'=Ac
c, R=R'=CF_3CO-



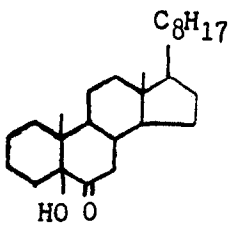
VIII



VII

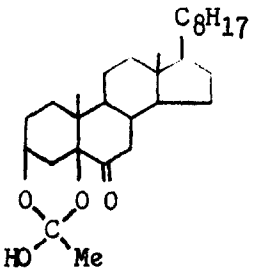


XIII



IX

to indicate that (1) protonation of the (proposed) ortho ester intermediate XI did not occur at the C-3 oxygen in analogy to Path "B" from



XI

III, but at the C-5 oxygen, or (2) protonation at the C-3 oxygen was followed by formation of the 5-acetate (IVd) which subsequently underwent rearrangement to the 3-acetate (IVb).

In order to determine which of these postulates may be correct,

the independent synthesis of the 5-acetate (IVd) was undertaken. Initial attempts at selective saponification of the acetoxy group at C-3 in the diolone diacetate (IVc)[8] were abandoned when it was found that both the 3- and 5-acetates were removed to a considerable extent when the steroid was treated with one equivalent of base. An alternate approach involved trifluoroacetylation at C-3, followed by acetylation at C-5, and removal of the trifluoroacetate under mild conditions which would not affect the C-5 acetate. Treatment of the 3β,5β-diol-6-one (IVa) in pyridine with trifluoroacetic anhydride yielded the 3,5-ditrifluoroacetate (XIIc), but when the reaction was conducted at -15° in a mixture of pyridine and dioxane, the 3-trifluoroacetate (XIIa) was obtained in good yield. Acetylation with acetic anhydride-p-toluenesulfonic acid gave an excellent yield of the 3-trifluoroacetate 5-acetate (XIIb).

Several attempts at removal of the trifluoroacetate function by alcoholysis and hydrolysis failed. Treatment of XIIb with (1) diethylamine, (2) one equivalent of potassium hydroxide in methanol, or (3) one equivalent of potassium hydroxide in dioxane effected rapid saponification of the trifluoroacetate but was accompanied by acetate migration, resulting in the formation of the 3-acetate (IVb) in each instance.

The desired 5-acetate (IVd) was obtained by the action of a potassium hydroxide-methanol solution (containing one equivalent of base) on a dilute solution of XIIb in a dioxane-water mixture. Repetition of this procedure unfortunately led to inseparable mixtures. However, it was found that saponification of XIIb with potassium bicarbonate[9] in a dilute methanol-water solution did give reproducible results and provided a method for the preparation of the 5-acetate (IVd)

in good yield unaccompanied by rearrangement to the 3-acetate (IVb).

It became necessary to test the behavior of the 5-acetate (IVd) on alumina, since chromatography seemed to be the simplest method to separate the isomeric 3- and 5-acetates (IVb and IVd). When the 5-acetate was eluted from a column immediately after being adsorbed, it was recovered essentially unchanged. However, when allowed to remain in contact with the alumina for an extended period, IVd underwent partial isomerization to the 3-acetate (IVb). The 3-acetate did not undergo rearrangement upon prolonged contact with alumina, indicating the irreversibility of the rearrangement under these conditions. These results are summarized in Table I.

TABLE I

Action of Alumina on Isomeric Acetates IVb and IVd

Compound (mg.)	Time Before Elution	Ratio IVd/IVb*
IVd (80)	Eluted immediately	39/1
IVb (81)	22 hr.	1/39
IVd (81)	11 hr.	4.3/1

*See Experimental Section for details of chromatographic procedure.

The behavior of compounds IVb and IVd on alumina thus indicated that a mixture of these materials could be separated by chromatography if extended contact with the adsorbent was avoided.

Several reactions were designed to yield further information regarding the rearrangement of the 5-acetate (IVd) to the 3-acetate (IVb). The product composition from each was determined by chromatography. The 5-acetate underwent facile conversion to the 3-acetate when treated with potassium acetate in a DMF-water mixture. As expected, this paralleled the rearrangement of the 3α,5α-diol-6-one 5-acetate

(IIb) to the 3-acetate (IIa).[2] The solvolysis of the tosylate acetate (Xb) with DMF-water was reinvestigated. Whereas the initial experiment indicated the production of the 3-acetate (IVb) in 82% yield, chromatography showed that the ratio of IVd to IVb obtained is dependent upon the concentration of the solution and the reaction time. The 5-acetate was also found to rearrange to the 3-acetate when treated with added p-toluenesulfonic acid in DMF-water. These results are summarized in Table II. In addition, IVd isomerized to IVb when treated with dilute sulfuric acid in methanol solution.

TABLE II

Chromatographic Separation of Isomeric Acetates IVb and IVd Obtained as Reaction Products*

Reactant (mg.)	Conditions and Times	Ratio IVd/IVb
Xb (174)	7 ml. DMF, 0.6 ml. H_2O, steam bath, 3 hr.	1.7/1
Xb (81)	1.2 ml. DMF, 0.4 ml. H_2O, steam bath, 4.5 hr.	1/1
IVd (192)	5 ml. DMF, 1.0 ml. H_2O, 106 mg. p-tosyl-OH, steam bath, 3.5 hr.	2.8/1
IVd (97)	6 ml. DMF, 0.5 ml. H_2O, 199 mg. KOAc, steam bath, 3 hr.	1/21

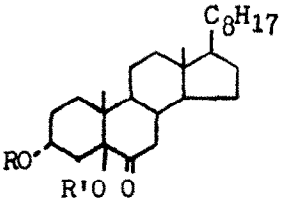
*See Experimental Section for details of chromatographic procedure.

The foregoing results seem to indicate that the 5-acetate (IVd) is formed initially in the solvolysis of Xb in DMF-water and subsequently rearranges to the 3-acetate (IVb) under the influence of the p-toluenesulfonic acid produced in the reaction. The formation of IVd can be rationalized on the basis of protonation at the C-3 oxygen of the ortho ester (XI) in analogy with the interpretation given[2] for the formation of the 5-acetate (IIb). The apparent stability of the

5-acetate (IIb) compared to the 5-acetate (IVd) under the conditions of the solvolysis may be due to the C-10 methyl to C-5 acetoxy skew interaction in IVd which is not present in IIb.

It is thus apparent that the solvolysis of the epimeric acetoxy tosylates I and Xb proceed in a like manner but that the stabilities of the related 5-acetates (IIb and IVd) differ markedly in acidic media. The results found in the rearrangements noted in this study are explicable in terms of an intermediate ortho ester or some closely related species. Numerous examples of neighboring acetoxy participation have been reported.[10]

The 5-acetates (Xd and Xf) of the p-nitrobenzenesulfonate and benzenesulfonate derivatives (Xc and Xe, respectively) of the 3α, 5β-diol-6-one (VIa) were prepared in order to examine the influence of various 3α-sulfonate esters on the carbonyl absorptions in the infrared. No discernible effect was noted.



Xc, R=p-$O_2NC_6H_4SO_2$-, R'=H
d, R=p-$O_2NC_6H_4SO_2$-, R'=Ac
e, R=$C_6H_5SO_2$-, R'=H
f, R=$C_6H_5SO_2$-, R'=Ac

EXPERIMENTAL

Melting points are uncorrected. Rotations were determined in chloroform solutions at room temperature. Infrared spectra were measured with a Perkin-Elmer Model 21 spectrophotometer in ca. 5% solutions (carbon tetrachloride unless stated otherwise) using 0.1 mm. sodium chloride cells and a sodium chloride prism. "Drying" of solutions was accomplished with anhydrous sodium sulfate. Petroleum ether had b.p. 30-60°. Alumina used for all chromatographic separations was Merck, acid-washed. Elemental analyses by Micro-Analysis, Inc., Wilmington 8, Del.

5β-Cholestan-3β,5-diol-6-one 3-Tosylate (Va). - The 5β-cholestan-3β,5-diol-6-one (IVa) obtained from the saponification[4] of

5.00 g. (10.8 mmoles) of the 3-acetate (IVb) was dissolved in 50 ml. of dry pyridine and treated with 8.9 g. (46.7 mmoles) of p-toluenesulfonyl chloride for 6 days at room temperature.[6] The dark brown solution was poured slowly, with stirring, into a mixture of 50 ml. of conc. hydrochloric acid and crushed ice. After 3 hr., the product was collected, washed with water, and dissolved in chloroform. The solution was washed with water, dried, and evaporated to give a yellow oil that crystallized from petroleum ether containing a little chloroform to yield 4.0 g. (65%) of the 3β-tosylate (Va) as off-white needles, m.p. 143-144° (dec.), $[\alpha]_D$ -11° (c 1.35), λ max 2.87(w) and 5.84(s) μ.

The analytical sample had m.p. 144-145° (dec.).

Anal. Calcd. for $C_{34}H_{52}O_5S$ (572.83); C, 71.28; H, 9.15; S, 5.59. Found: C, 71.36; H, 8.93; S, 5.61.

5β-Cholestan-3β,5-diol-6-one 3-Tosylate 5-Acetate (Vb). - A suspension of 2.500 g. (4.37 mmoles) of the 3β-tosylate (Va) in 25 ml. of acetic anhydride was heated at 90° until solution occurred, when 450 mg. of p-toluenesulfonic acid monohydrate was added and heating was continued for 1 hr. at 90-97°. (A precipitate separated from the solution within several minutes after the addition of the catalysts.) After cooling for several hours in the refrigerator the product was collected and washed with petroleum ether-yield, 2.548 g. (95%) of Vb as short white needles, m.p. 153-155° (dec.). Recrystallization from chloroform-petroleum ether gave 2.382 g. with m.p. 155-156° (dec.), $[\alpha]_D$ -23° (c 1.60), $\lambda_{max}^{CHCl_3}$ 5.72(s) and 5.81(s) μ.

The analytical sample had m.p. 153.5-154.5° (dec.).

Anal. Calcd. for $C_{36}H_{54}O_6S$ (614.86); C, 70.31; H, 8.85; S, 5.21.

5β-Cholestan-3α,5-diol-6-one (VIa). - (A) A solution of 4.00 g. (6.98 mmoles) of the 3β-tosylate (Va) in 250 ml. of methanol and 15 ml. of water was heated under reflux for 5.5 hr. The addition of ca. 250 ml. of water caused precipitation of the product, which was collected, washed with water, and dissolved in methylene chloride. The dried solution was evaporated and the residue chromatographed on 100 g. of alumina.

Elution with 10% ether-benzene mixtures gave 394 mg. of a colorless oil which, after several crystallizations from methanol, yielded a compound tentatively identified as 5β-cholest-3-en-5-ol-6-one (VIII), m.p. 122-124.5°, $[\alpha]_D$ -17° (c 2.11), λmax 2.85(w) and 5.85(s) μ.

Anal. Calcd. for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.91; H, 11.26.

Elution with 50% ether-benzene mixtures gave 1.92 g. (65%) of VIa as a crystalline mass. Recrystallization from acetone-water gave white plates, m.p. 124-125°, $[\alpha]_D$ -14° (c 1.406), $\lambda_{max}^{CHCl_3}$ 2.87(w, br) and 5.85(s) μ.

Two analytical samples were recrystallized from acetone-water.

Anal. Calcd. for $C_{27}H_{46}O_3 \cdot \frac{1}{4}H_2O$ (423.14):[11] C, 76.63; H, 11.07. Found: C, 76.86, 76.94; H, 11.17, 11.22.

The 3-acetate (VIb) was prepared in 92% yield by reaction of VIa with acetic anhydride in pyridine for 16 hr. at room temperature: m.p. 127-128°, $[\alpha]_D$ -5° (c 1.88), λmax 2.87(w), 5.73(s), and 5.84(s) μ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.42; H, 10.47.

(B) A mixture of 5.0 g. (8.72 mmoles) of the 3β-tosylate (Va), 75 ml. of dimethylsulfoxide, and 10 ml. of water was heated at 100-105° for 4.75 hr. (The steroid dissolved completely in ca. 45 min.; 5 ml. of dimethylsulfoxide was used to rinse the walls of the flask after 2.5 hr.) Water was added and the precipitated product was collected, washed, and taken up in chloroform. The dried solution was evaporated and the residue was chromatographed on 80 g. of alumina.

Elution with 10% ether-benzene yielded 670 mg. of material which, upon crystallization from methanol, gave 354 mg. (10%) of the 3-en-5β-ol-6-one (VIII), m.p. 118-122°. Recrystallization from methanol gave 296 mg. of white needles, m.p. 119-122°.

Elution with 50% ether-benzene gave 2.476 g. of semicrystalline material that was recrystallized from acetone-water to yield 2.200 g. (60%) of large white plates with m.p. 122-125°. This material was identical to the VIa obtained from procedure A.

5β-Cholestan-5-ol-6-one (IX). (A) A suspension of 380 mg. (0.818 mmole) of 5-bromo-5α-cholestan-6-one (XIII)[12] in 2.5 ml. of methanol and 20 ml. of 0.303N potassium hydroxide-methanol solution was heated under reflux for 3.5 hr. The hot yellow solution was acidified with 4 ml. of 2N hydrochloric acid. The solution was cooled in an ice bath, diluted with water, and the amorphous material that separated was extracted into ether (3 portions). The ether was washed with a saturated saline solution, dried, and evaporated to yield an oil that was taken up in an acetone-methanol mixture. Seeding with a trace of authentic IX caused the separation of 197 mg. of white needles with m.p. 80-97°. Recrystallization from acetone-methanol gave 133 mg. (41%)

of IX as white needles, m.p. 100-102°, $[\alpha]_D$ -16.5° (c 1.33), λmax 2.87(w) and 5.85(s) μ (lit.[13] m.p. 102-103°, $[\alpha]_D$ -18°). A further recrystallization from methanol raised the m.p. to 102-104.5°.

(B) A solution of 148 mg. (0.370 mmole) of the 3-en-5β-ol-6-one (VIII) in 11 ml. of ethyl acetate was hydrogenated in the presence of a palladium-on-carbon catalyst until uptake of the gas had ceased. The catalyst was removed by filtration through magnesium sulfate and the filtrate was evaporated to dryness. The semicrystalline residue was dissolved in a mixture of acetone-methanol and seeded with a small crystal of IX, whereupon 103 mg. (69%) of white needles separated. The product had m.p. 103-104° and did not depress the m.p. of authentic IX prepared from XI.

5β-Cholestan-5-ol-3,6-dione (VII).- To 65 mg. (0.155 mmole) of the 3α,5β-diol-6-one (VIa) in 1.6 ml. of glacial acetic acid was added a solution of 25 mg. of chromic oxide in a mixture of 1.6 ml. of acetic acid and 6 drops of water. The resulting solution was stirred magnetically at room temperature for 2.75 hr., then treated with 0.5 ml. of methanol and diluted with water. The precipitated material was collected, washed with water, and recrystallized from acetone-water to yield 42 mg. (65%) of VII, m.p. 119-122°. A second recrystallization from the same solvent pair yielded 32 mg. of fine white crystals, m.p. 121-123°. This material did not depress the m.p. of VII prepared from the 3β,5β-diol-6-one (IVa)[4] and the infrared spectra of both oxidation products were identical.

5β-Cholestan-3α,5-diol-6-one 3-Tosylate (Xa).- To a solution of 1.19 g. (2.85 mmoles) of the 3α,5β-diol-6-one (VIa) in 10 ml. of dry pyridine was added 2.71 g. (14.2 mmoles) of p-toluenesulfonyl chloride.

After standing at room temperature for 45 hr., the solution was poured into a mixture of 12 ml. of conc. hydrochloric acid and crushed ice. After 2 hr. the product was extracted with 2 portions of chloroform and the combined extracts were washed with water and dried. Filtration and evaporation of the solvent, followed by crystallization from petroleum ether, gave 1.458 g. (89%) of Xa, m.p. 137-138.5° (dec. at ca. 180°), $[\alpha]_D$+7° (c 2.27), λmax 2.88(w) and 5.84(s)μ. Recrystallization of a 454-mg. portion yielded 368 mg. of needles, m.p. 137-139.5°.

The analytical sample had m.p. 136.5-138.5°.

Anal. Calcd. for $C_{34}H_{52}O_5S$ (572.83): C, 71.28; H, 9.15; S, 5.59. Found: C, 71.38; H, 8.99; S, 5.64.

5β-Cholestan-3α,5-diol-6-one 3-Tosylate 5-Acetate (Xb).- A suspension of 1.000 g. (1.745 mmoles) of the 3α-tosylate (Xa) in 10 ml. of acetic anhydride was warmed until solution occurred. Two hundred and fifty milligrams of p-toluenesulfonic acid monohydrate was added and the solution was heated at 84-88° for 0.5 hr. After an additional 2.75 hr. at room temperature crushed ice was added and, after several hours, the product was collected, washed with water, and air-dried. Recrystallization from petroleum ether containing a trace of chloroform gave 912 mg. (85%) of the Xb as off-white needles, m.p. 144-146° (dec.). Recrystallization from the same solvents yielded 854 mg. with m.p. 140-141.5° (dec.),[14] $[\alpha]_D$ -20° (c 1.52), λmax 5.71(s) and 5.80(s)μ.

The analytical sample had m.p. 131-134° (dec.).

Anal. Calcd. for $C_{36}H_{54}O_6S$ (614.86): C, 70.31; H, 8.85; S, 5.21. Found: C, 70.22; H, 9.11; S, 5.49.

Solvolysis of 5β-Cholestan-3α,5-diol-6-one 3-Tosylate 5-Acetate

(Xb) in Dimethylformamide containing Water and Potassium Acetate. - A solution of 250 mg. (0.407 mmole) of Xb, 0.5 ml. of water, and 450 mg. of potassium acetate in 5 ml. of DMF was heated on the steam bath for 1.75 hr. (An additional 2 ml. of DMF was added after 10 min.) The light-yellow colored solution was cooled, diluted with water, and the precipitated product collected by filtration and taken up in chloroform. The dried solution was evaporated and the residue (whose infrared spectrum was identical to that of IVb) was recrystallized from methanol containing a little water to yield 146 mg. (78%) of the 3β,5β-diol-6-one 3-acetate (IVb) as small white plates with m.p. 139.5-141°. This material did not depress the m.p. of authentic IVb.

A second recrystallization from the same solvents yielded 117 mg. with m.p. 142.5-143.5°.

Solvolysis of 5β-Cholestan-3α,5-diol-6-one 3-Tosylate 5-Acetate (Xb) in Dimethylformamide containing Water.- A solution of 300 mg. (0.488 mmole) of Xb and 0.8 ml. of water in 6 ml. of DMF was heated on the steam bath for 3 hr. The cooled solution was diluted with water and extracted with 3 portions of chloroform. The combined organic extracts were washed twice with water, dried, and evaporated. Crystallization from petroleum ether gave 100 mg. of off-white plates, m.p. 134-141.5° (previous softening). The infrared spectra of this material and of the residue obtained from the mother liquor of the crystallization were identical with that of authentic IVb. Recrystallization of the plates from methanol-water (seeded) gave 70 mg. of IVb, m.p. 142-144°. No depression was noted upon admixture with authentic IVb.

The residue from the petroleum ether crystallization was recrystallized from methanol-water (seeded) to give an additional

84 mg. of IVb, m.p. 141-143°. Total yield-184 mg. (82%).

5β-Cholestan-3β,5-diol-6-one Ditrifluoroacetate (XIIc).- A solution of the diolone (IVa) obtained from the saponification of 1.000 g. (2.17 mmoles) of the 3-acetate (IVb) in 6 ml. of dry pyridine was treated by the gradual addition of 5 ml. of trifluoroacetic anhydride. Addition of the first portions at room temperature resulted in an exothermic reaction; the solution was then cooled in an ice bath and the remainder of the anhydride was added slowly to the cooled solution. (Total time for addition was 10 min.) Four milliliters of pyridine was used to rinse the walls of the flask and, after 1 hr. at room temperature, the dark red solution was diluted with 10 ml. of dioxane. The addition of crushed ice caused the separation of a yellow gum which gradually solidified. This material was collected, washed well with water, and taken up in chloroform. The dried solution was evaporated to yield a yellow oil that was dissolved in a mixture of acetone-methanol and treated with water until the solution became cloudy, whereupon 1.12 g. (85%) of XIIc separated as a white powder, m.p. 137-141°. Recrystallization from petroleum ether containing a little chloroform gave 986 mg. of XIIc, m.p. 140-143°, $[\alpha]_D$ -15° (c 1.25), λ max 5.58(s) and 5.77(m) μ.

Anal. Calcd. for $C_{31}H_{44}O_5F_6$ (610.66): C, 60.96; H, 7.26. Found: C, 60.97; H, 7.30.

5β-Cholestan-3β,5-diol-6-one 3-Trifluoroacetate (XIIa).- A solution of the diolone (IVa) obtained from 1.000 g. (2.17 mmoles) of the 3-acetate (IVb) in 16 ml. of dry pyridine was cooled to -15° and treated (by slow addition) with a solution of 1 ml. of trifluoroacetic anhydride in 9 ml. of dioxane. After 10 min. at -15 to -10°

the yellow solution was diluted with water and the amorphous material that separated crystallized rapidly when worked with a glass rod. After cooling in the refrigerator for 1 hr., the product was collected, washed with water, and taken up in chloroform. Evaporation of the dried solution yielded a mass of white crystals which, upon recrystallization from petroleum ether, gave 525 mg. of XIIa as white platelets, m.p. 138.5-140°, $[\alpha]_D$ -31° (c 1.128), λmax 2.88(w), 5.61(s), and 5.84(s) μ.

Recrystallization of the material obtained from the mother liquor from acetone-water gave an additional 383 mg. of XIIa, m.p. 136.5-138.5°. Total yield-81%.

Anal. Calcd. for $C_{29}H_{45}O_4F_3$ (514.65): C, 67.67; H, 8.81. Found: C, 67.84; H, 8.67.

The 3-trifluoroacetate (XIIa) was recovered unchanged after treatment with acetic anhydride and pyridine at room temperature for 25.5 hr.

5β-Cholestan-3β,5-diol-6-one 3-Trifluoroacetate 5-Acetate (XIIb).- A mixture of 2.58 g. (5.02 mmoles) of the 3-trifluoroacetate (XIIa), 34 ml. of acetic anhydride, and 300 mg. of p-toluenesulfonic acid monohydrate was heated on the steam bath for 50 min. The warm, colorless solution was diluted with ice and, when hydrolysis of the anhydride was complete, the product was collected, washed with water, and taken up in chloroform. The dried solution was evaporated and the residue recrystallized from acetone-methanol to yield 2.513 g. (90%) of XIIb as large white plates, m.p. 167.5-169.5°, $[\alpha]_D$ -22° (c 1.00), λmax 5.60(s), 5.69(s), and 5.78(s) μ.

Anal. Calcd. for $C_{31}H_{47}O_5F_3$ (556.69): C, 66.88; H, 8.51. Found:

C, 66.88; H, 8.61.

Reactions of 5β-Cholestan-3β,5-diol-6-one 3-Trifluoroacetate 5-Acetate (XIIb) with Bases.- (A) With Diethylamine. A suspension of 150 mg. (0.269 mmole) of XIIb in 2.5 ml. of diethylamine was stirred magnetically at room temperature for 3.5 hr. (The steroid dissolved shortly after stirring began.) The addition of water caused the separation of a white precipitate which was collected and recrystallized from chloroform-petroleum ether to yield 56 mg. of white plates, m.p. 141-141.5°. This material was shown to be identical with the 3-acetate (IVb) by mixture m.p. and infrared determinations.

An additional 29 mg. of white platelets (m.p. 138-140°) was obtained by crystallization of the mother liquor residue from methanol-water. Total yield of IVb-69%.

(B) With Potassium Hydroxide in Methanol. A suspension of 200 mg. (0.360 mmole) of XIIb in 2.63 ml. of 0.137N potassium hydroxide-methanol solution and 6 ml. of methanol was stirred magnetically for 8 min. The solution was diluted with water and the product (whose infrared spectrum was identical to that of IVb) was collected and recrystallized from methanol to give 43 mg. of white platelets, m.p. 140-141.5°. No depression was noted upon admixture with authentic IVb. Dilution of the mother liquor with a little water gave an additional 29 mg. of IVb, m.p. 140-142°. Total yield-44%.

(C) With Methanolic Potassium Hydroxide in Dioxane. To a solution of 586 mg. (1.054 mmoles) of XIIb in 50 ml. of dioxane at room temperature was added 9.57 ml. of 0.115N potassium hydroxide-methanol solution. The mixture was swirled for ca. 2 min. and then was diluted with 10 ml. of 2N hydrochloric acid and water. After

remaining overnight, the white precipitate was collected and recrystallized from acetone-water to yield white plates with m.p. 137-142°. Recrystallization from acetone-methanol containing a little water gave 317 mg. (65%) of IVb as plates with m.p. 142.5-144°. The m.p. was not depressed upon admixture with authentic IVb.

5β-Cholestan-3β,5-diol-6-one 5-Acetate (IVd).- (A) To a magnetically stirred solution of 621 mg. (1.12 mmoles) of the 3-trifluoroacetate 5-acetate (XIIb) in 150 ml. of dioxane and 36 ml. of distilled water was added (dropwise) 10.90 ml. of 0.11N potassium hydroxide-methanol solution. (Total time for addition was 4 min.) The solution was immediately filtered through cotton into an equal volume of water. After a few hours, the product was collected and recrystallized from acetone-water (no other solvent system gave suitable results) to yield 368 mg. (71%) of IVd as short white needles with m.p. 151-154°. Recrystallization from the same solvents gave 176 mg. of IVd, m.p. 152-154°, $[\alpha]_D$ -47° (c 1.10), λmax 2.92(w, br), 5.73(s), and 5.81(s) μ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.53; H, 10.34.

Repetition of this procedure several times gave material which, in each case, melted over a wide range and could not be crystallized to a constant melting point.

(B) A suspension of 1.465 g. (2.63 mmoles) of XIIb in 210 ml. of methanol was heated until the steroid dissolved. The solution was cooled to room temperature and treated with a solution of 1.123 g. of potassium bicarbonate in 30 ml. of distilled water and 60 ml. of methanol. After 3.75 hr. the mixture was poured into water containing

a little conc. hydrochloric acid. The precipitate was collected, washed with water, and dissolved in acetone. Water was added, in portions, until a permanent cloudiness resulted. A few drops of acetone were added and the clear solution was allowed to remain at room temperature. Clusters of white needles gradually formed and when crystallization was apparently complete, the flask was cooled for a further period in the refrigerator. The product was collected and washed briefly with dilute acetone-yield, 1.096 g. (90%) of IVd, m.p. 146-150°. A further recrystallization from acetone-water gave 897 mg. of needles, m.p. 151-153°.

Acetylation of IVd with acetic anhydride-p-toluenesulfonic acid monohydrate for 25 min. on the steam bath gave the diolone diacetate (IVc).[8]

Negative Attempts at Removal of the Trifluoroacetate Group in XIIb.- Reaction of XIIb under the following conditions led only to the recovery of starting material: (1) boiling with absolute methanol for 1.3 hr. (2) heating with a dimethylsulfoxide-water mixture on the steam bath for 1.1 hr. (3) boiling with dry isobutanol for 1.9 hr. (4) heating with a dioxane-water mixture on the steam bath for 1.5 hr.

Acid-Catalyzed Rearrangement of the 5-Acetate (IVd) to the 3-Acetate (IVb).- To a solution of 74 mg. (0.160 mmole) of IVd in 9 ml. of methanol was added 1.5 ml. of an aqueous 10% sulfuric acid solution. The mixture was warmed briefly, allowed to stand at room temperature for 10 min., then concentrated by boiling to a volume of about 6 ml. and allowed to remain at room temperature overnight. During this period white plates separated which (after cooling in the refrigerator for 1 hr.) were collected-yield, 47 mg. (64%) of IVb, m.p. 141.5-143°.

General Chromatographic Technique for Separation of the Isomeric 3- and 5-Acetates (IVb and IVd, respectively).- The steroid (or mixture of steroids) was dissolved in benzene and fixed on a column of alumina (ratio of alumina to steroid: ca. 60/1). A clean separation was effected by elution with dry ether, which removed the crystalline 3-acetate (IVb), followed by elution with chloroform, which gave the 5-acetate (IVd) as a semicrystalline mass. Each compound was identified by its infrared spectrum and by recrystallization to the pure material. Recovery of steroids from the column was quantitative.

Results of these separations are given in Tables I and II.

5β-Cholestan-3α,5-diol-6-one 3-p-Nitrobenzenesulfonate (Xc).- A solution of 300 mg. (0.716 mmole) of the 3α,5β-diol-6-one (VIa) and 793 mg. (3.58 mmoles) of p-nitrobenzenesulfonyl chloride in 4 ml. of dry pyridine was allowed to remain at room temperature for 22 hr. (White needles separated soon after the solution was prepared. After 1 hr., the walls of the flask were rinsed with 2 ml. of pyridine.) The addition of crushed ice and 12 ml. of 6N hydrochloric acid caused the separation of a pale yellow powder which, after 2 hr., was collected and washed with water. The dried product was recrystallized from chloroform-petroleum ether to give 413 mg. (95%) of Xc as pale yellow plates with m.p. 151-152° (dec.). Recrystallization from chloroform-ether gave 329 mg. of Xc with m.p. 157-158.5° (dec.), $[\alpha]_D$+6.4° (c 0.938), $\lambda_{max}^{CHCl_3}$ 2.88(w) and 5.84(s) μ.

The analytical sample had m.p. 161-163.5° (dec.).

Anal. Calcd. for $C_{33}H_{49}O_7NS$ (603.79): C, 65.64; H, 8.18; S, 5.31. Found: C, 65.76; H, 8.40; S, 5.24.

5β-Cholestan-3α,5-diol-6-one 3-p-Nitrobenzenesulfonate 5-Acetate (Xd). - Twenty-five milligrams of p-toluenesulfonic acid monohydrate was added to a hot solution of 316 mg. (0.524 mmole) of the 3-p-nitrobenzenesulfonate (Xc) in 6 ml. of acetic anhydride. The reaction mixture was heated on the steam bath for 4 min., diluted with crushed ice, and the precipitated product was collected after 30 min. and washed well with water. Recrystallization from acetone-petroleum ether gave 184 mg. (54%) of Xd, m.p. 125-128° (dec.), $[\alpha]_D$ -21° (c 0.572), $\lambda_{max}^{CHCl_3}$ 5.72(s) and 5.80(s) μ. Recrystallization from an ether-petroleum ether mixture containing a little chloroform gave 154 mg. of Xd as a mat of off-white plates with m.p. 120-123° (dec.), with softening at 115°.

When the reaction was carried out for 10 min. at steam bath temperature, a 27% yield of Xd was obtained; when heated similarly for 25 min., a dark intractable gum resulted. Elemental analysis of one sample gave highly unsatisfactory results. Another attempt to prepare a sample for analysis led to the decomposition of Xd as a chloroform solution of the steroid was concentrated.

5β-Cholestan-3α,5-diol-6-one 3-Benzenesulfonate (Xe).- A solution of 300 mg. (0.716 mmole) of the 3α,5β-diol-6-one (VIa) and 0.5 ml. (3.9 mmoles) of benzenesulfonyl chloride in 4 ml. of dry pyridine was allowed to stand at room temperature for 46 hr. The brown solution was then poured into a mixture of crushed ice and 8 ml. of 6N hydrochloric acid. After 1 hr. the product was collected, washed with water, and dissolved in chloroform. The dried solution was evaporated and the solid product was recrystallized from petroleum ether containing a little chloroform to yield 363 mg. (91%) of Xe

as white platelets with m.p. 152-154° (dec. at 172°). Recrystallization from the same solvent pair gave 332 mg. with m.p. 148.5-150°, $[\alpha]_D^+$ 5.4° (c 0.925), $\lambda_{max}^{CHCl_3}$ 2.89(w) and 5.85(s) μ.

The analytical sample had m.p. 149.5-150° (dec. at 170°).

Anal. Calcd. for $C_{33}H_{50}O_5S$ (558.80): C, 70.92; H, 9.02; S, 5.73. Found: C, 71.34; H, 9.24; S, 5.35.

5β-Cholestan-3α,5-diol-6-one 3-Benzenesulfonate 5-Acetate (Xf).- A suspension of 311 mg. (0.557 mmole) of the 3-benzenesulfonate (Xe) in 6 ml. of acetic anhydride was heated on the steam bath until the steroid dissolved. Twenty-two milligrams of p-toluenesulfonic acid monohydrate was added and heating was continued for 10 min. Crushed ice was added to the hot solution and, after standing at room temperature overnight, the precipitate was collected and washed with water. Recrystallization of the dried material from chloroform-petroleum ether yielded 212 mg. (63%) of Xf as a mat of white needles with m.p. 139-141° (dec.), $[\alpha]_D$ -22° (c 1.124), $\lambda_{max}^{CHCl_3}$ 5.71(s) and 5.80(s) μ.

The analytical sample had m.p. 125-129° (dec.).

Anal. Calcd. for $C_{35}H_{52}O_6S$ (600.83): C, 69.96; H, 8.72; S, 5.33. Found: C, 69.88; H, 8.61; S, 5.21.

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