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PHOTOCHEMICAL AND NON-PHOTOCHEMICAL ROUTES TO DERIVATIVES OF 5β,7β-CYCLOCHOLESTANE

A NEW CLASS OF CYCLOSTEROIDS[1]

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Abstract—Derivatives of 5β,7β-cyclosteroids have been prepared by photochemical means from cholesta-4,6-diene and by methylene addition to β-norcholesterol acetate. The synthesis of both 3- and 4-substituted derivatives of 5β,7β-cyclocholestane has been accomplished. With the synthesis of 3-substituted 5β,7β-cyclocholestanes, the first derivatives of any 5,7-cyclosteroid, related to naturally occurring 3-substituted compounds, have become readily available.

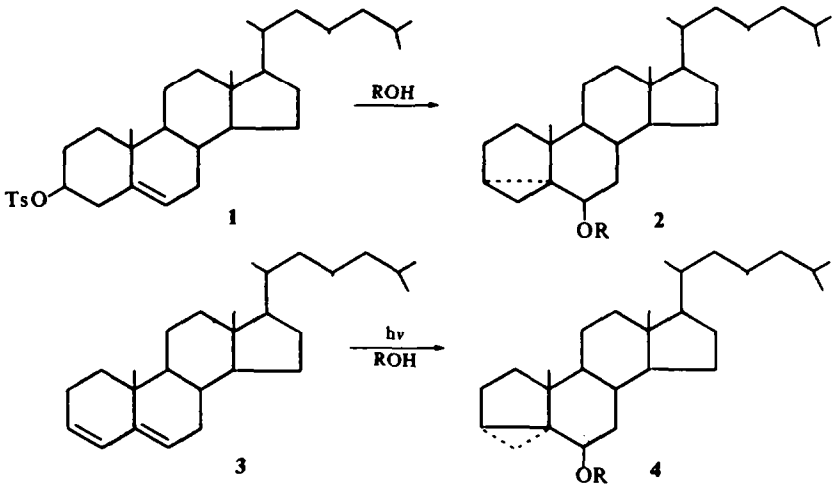
A photochemically generated bicyclo[1.1.0]butane intermediate is suggested in the irradiation of cholesta-4,6-diene. The mechanistic aspects of the reaction of this intermediate with ethanol are discussed.

SINCE the identification of the steroid nucleus in 1932, great strides have been made in studying the reactions and properties of these natural products.[4] Interest in the steroids has been widespread, both because of their biological importance and because their rigid ring system provides an excellent superstructure for the study of non-bonded interactions and other steric effects. In addition, the rigid framework can be used to advantage in the investigation of reaction mechanisms.

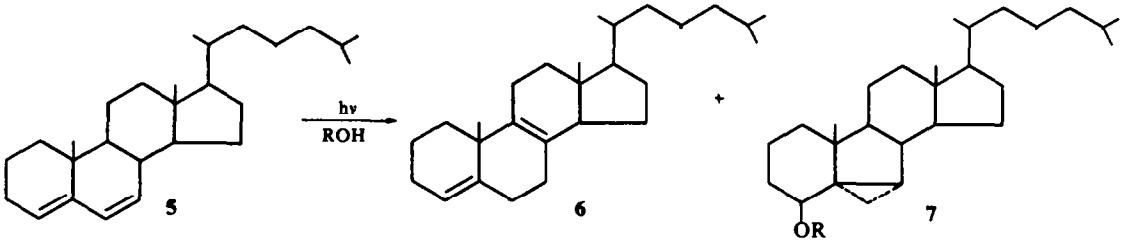
The cyclosteroids provide a particularly fascinating modification of the steroid nucleus because of their potential physiological activity and especially because of the presence of a cyclopropyl group. Indeed, the concrete stereochemical relationship which can be established between the cyclopropane moiety and functional groups in the cyclosteroid system has been used to advantage in correlating the interactions of cyclopropanes with substituent groups as a function of stereochemistry.[5] Although derivatives of 3α,5α-cyclosteroids[5] and 3β,5β-cyclosteroids[6] are well known, little data is available concerning 5α,7α-cyclosteroids,[7] and, prior to our work, no examples of 5β,7β-cyclosteroids had been recorded in the chemical literature. This paper presents the details of the synthesis of 3- and 4-substituted 5β,7β-cyclocholestanes *via* a procedure which makes these compounds readily available for further mechanistic excursions into the field of cyclopropane-functional group relationships and for additional evaluations of the effects of steroid modification on biological activity.

In general, the cyclosteroids have been prepared by either solvolytic[5,7] or photochemical[6] routes. The solvolysis of cholesterol tosylate (**1**) gives the 3α,5α-cyclocholestane (**2**), whereas, the irradiation of cholesta-3,5-diene (**3**) yields the 3β,5β-cyclocholestanes (**4**). Since **2** and **4** differ only in the stereochemistry of the cyclopropane ring, it is clear that these methods supplement, rather than duplicate, each other. With this in mind we investigated the photochemical route to 5,7-cyclosteroids.

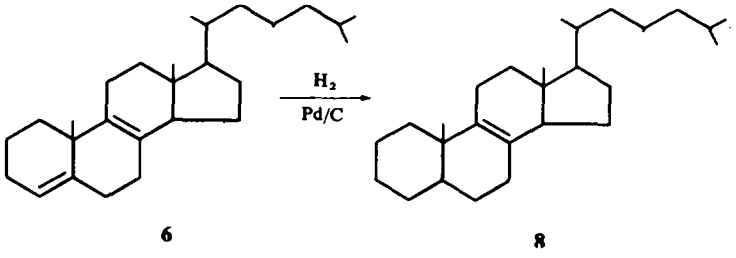
Irradiation of cholesta-4,6-diene[8] (**5**) in absolute ethanol with a Vycor filtered



450 watt Hanovia mercury arc for 18 hours gave, after chromatography on silica gel, two crystalline products. The minor product was eluted from the column with hexane



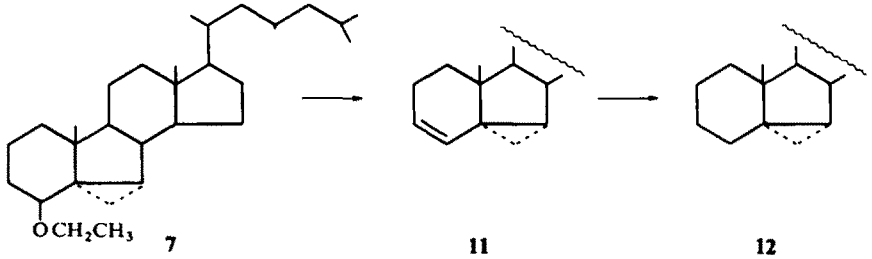
in 12% yield. The ultraviolet spectrum of this material showed only end absorption. The NMR spectrum showed a broad singlet at τ 4·81 (one proton) as the only absorption in the vinyl hydrogen region, which indicated that if two double bonds were present, one double bond must be tetrasubstituted, while the other must be trisubstituted. Catalytic hydrogenation of the minor product resulted in the uptake of one equivalent of hydrogen to yield Δ^8-cholestene (**8**). Having established the position of the tetrasubstituted double bond, the position of the trisubstituted double bond was investigated. Only two positions were reasonable, the Δ^4 and the Δ^5. If the second double bond were in the Δ^5-position, acid catalyzed conjugation of the



two double bonds should occur with ease. Since prolonged acid treatment failed to give conjugation the second double bond was assigned to the Δ^4-position, thus *suggesting* structure **6** for the minor product.*

The major product of the irradiation of **5** in ethanol was eluted from the silica gel column with 1:1 benzene–hexane. This compound, obtained in 40% yield, was a saturated ether, m.p. 93–94°. Unequivocal structure proof established that this product was the desired 4β-ethoxy-5β,7β-cyclocholestane (**7**). The NMR spectrum of **7** showed the A part (one proton, four peak multiplet) of an ABX system at τ 10·14. This signal was assigned to the cyclopropyl hydrogen in the 6β-position.[6] The 6α-proton came within the Me envelope of the steroid spectrum and could not be identified. This pattern was typical of all the 5β,7β-cyclocholestanes herein described. Near-IR spectroscopy also substantiated the presence of the cyclopropyl moiety by the presence of an absorption at 1·645 μ (ε 0·311).[9]

Chromatography of **7** on alumina resulted in the loss of ethanol to give 5β,7β-

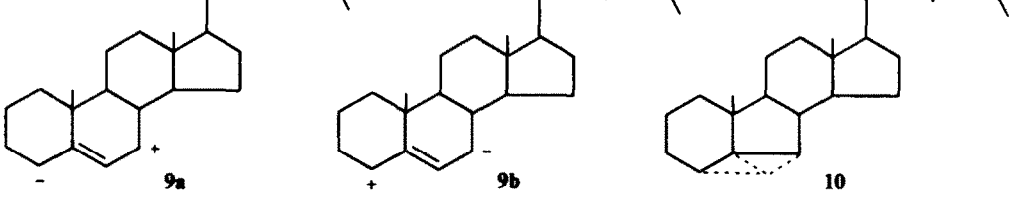


7 **11** **12**

cyclocholest-3-ene (**11**) in 75% yield. When the crude irradiation reaction mixture was chromatographed on alumina instead of on silica gel, a 50% yield of **11** was obtained based on starting diene, **5**. The IR spectrum of **11** showed an olefinic C—C stretch at 6·12 μ and a cyclopropyl geminal hydrogen stretch at 1·646 μ (ε 0·312). An ultraviolet absorption at 211 mμ (ε 11,300) showed that the double bond was conjugated with the cyclopropyl ring. Catalytic reduction of **11** over Pd–C resulted in the uptake of one equivalent of hydrogen to yield **12**, whose NMR spectrum showed one proton at τ 10·30 with the typical ABX pattern indicating the continued presence of the cyclopropyl ring.

Having proven the presence of the vinyl cyclopropane moiety in **11**, we desired to establish the position of this grouping in the steroid nucleus and the stereochemistry

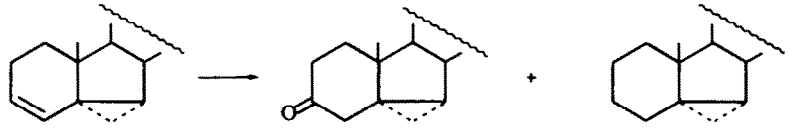
* It is interesting to speculate whether **6** arises from a photochemically generated zwitterion such as **9a** or **9b**, or from a highly strained photochemically generated intermediate such as **10**. As discussed later, **10** undoubtedly is involved as an intermediate in the formation of **7**. Unfortunately, the available data is



9a **9b** **10**

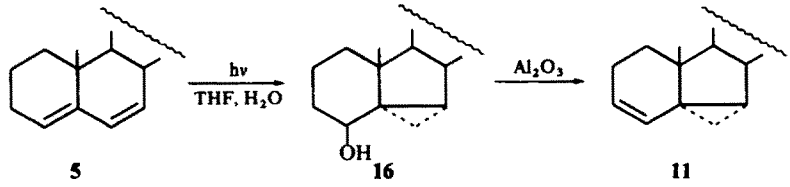
insufficient for deciding whether or not **10** is an intermediate in the formation of **6**. Mechanistically, isomerization of **5** to **6** *via* a zwitterion such as **9a** or **9b** seems plausible.

of the cyclopropyl ring. Since **11** was the proposed structure on the basis of mechanistic precedence, initial experiments were designed to demonstrate the nonequivalence of the known[7] 5α,7α-cyclocholestan-4-one (**13**) with the corresponding 4-ketone in the 5β,7β-cyclocholestane series. 5β,7β-Cyclocholest-3-ene (**11**) promised to be a suitable starting material for the synthesis of 5β,7β-cyclocholestan-4-one (**14**). It was anticipated that hydroboration of **11**, followed by oxidative work-up would yield a mixture of **14** and 5β,7β-cyclocholestan-3-one (**15**). In practice, the hydroboration-oxidation of **11** was somewhat anomalous. The major product, isolated in 50% yield was **15**. The presence of the carbonyl in the 3-position was determined on the basis of spectral data. The carbonyl absorption occurred at 5·80 μ and the cyclopropyl geminal hydrogen stretching overtone appeared at 1·646 μ (ε 0·349); both absorptions indicated that the carbonyl was not conjugated with the cyclopropyl group.[9,10] The NMR spectrum had the characteristic one proton ABX multiplet centered at τ 10·14. The reaction failed to yield even the slightest trace of **14**. Instead two minor products were isolated in 8 and 18% yield. The former was shown to be **12** by comparison with an authentic sample. Near-IR spectroscopy showed that the 18% component, m.p. 95–96°, did not contain a cyclopropyl group. Hence it was not further characterized.



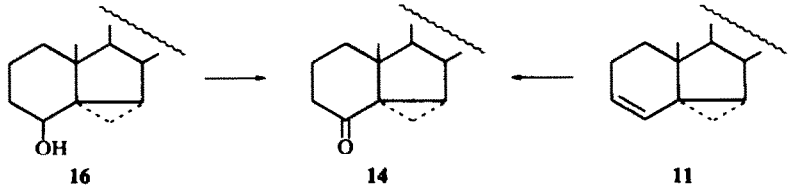
11 **15** **12**

The failure of the hydroboration-oxidation of **11** to yield **14** prompted the search for other routes to this desirable ketone. Two successful paths were found. The first of these involved irradiating **5** in tetrahydrofuran–water to give the 4β-alcohol, **16**. Chromatography of the crude irradiation product on silica gel gave 58% of **16** as



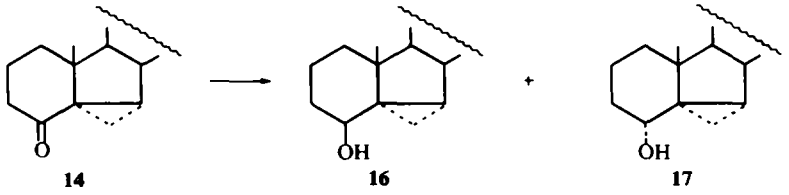
5 **16** **11**

a colorless oil. Chromatography of **16** on alumina gave **11**. The stereochemical assignment of the OH group was based on the NMR comparisons of **16** with other cyclosteroids. The C-4 proton appeared as a triplet at τ 6·55 (J = 2·9 c/s) which is typical for an equatorial proton adjacent to a cyclopropane in a cyclosteroid.[11] Oxidation of **16** with Sarett reagent gave 5β,7β-cyclocholestan-4-one (**14**) as a white



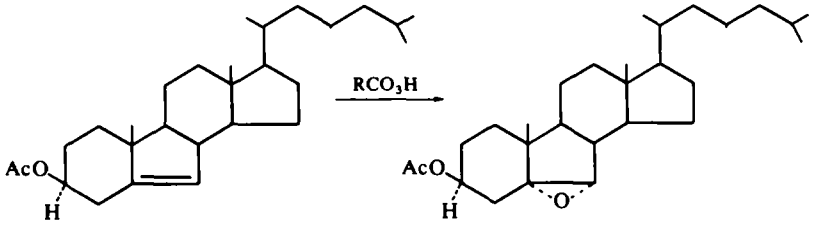
16 **14** **11**

crystalline solid. This same ketone could be obtained in low yield by the reductive-oxymercuration of **11** according to the procedure of Brown.[12] Reduction of **14** with LAH gave 28% of **16** and 58% of the epimeric alcohol, **17**. The 4α-alcohol, **17**, had a near-IR absorption at 1·640 μ (ε 0·323) demonstrating the presence of the cyclopropyl group.



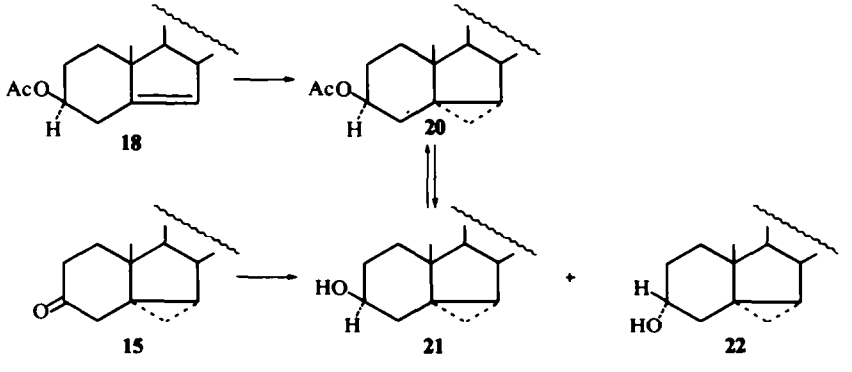
14 **16** **17**

A comparison of **14** with a sample of 5α,7α-cholestan-4-one (**13**) prepared according to the procedure of Summers[7] demonstrated the nonequivalence of these two compounds. Thus, substantial evidence for the stereochemistry of the cyclopropyl group was in hand. An unequivocal proof of the structure of the 5β,7β-cyclocholestane skeleton was provided by an independent, non-photochemical synthesis. In principle B-norcholesterol derivatives should function as a satisfactory starting material for the synthesis of the 5β,7β-cyclocholestane system. Dauben *et al.* have shown[13]



18 **19**

that B-norcholesterol acetate (**18**) undergoes epoxidation exclusively from the α-side of the steroidal skeleton to yield the α-epoxide, **19**. On the basis of this epoxidation, methylene transfer would also be expected to occur from the α-side. B-Norcholesterol acetate (**18**) was synthesized according to the procedure of Šorm as described by Dauben and Fonken.[14] Reaction of **18** with Simmons-Smith reagent prepared from granular zinc–copper couple according to the procedure of LeGoff[15] gave 5β,7β-cyclocholestan-3-ol acetate (**20**). The B-norcholesterol acetate was extremely resistant



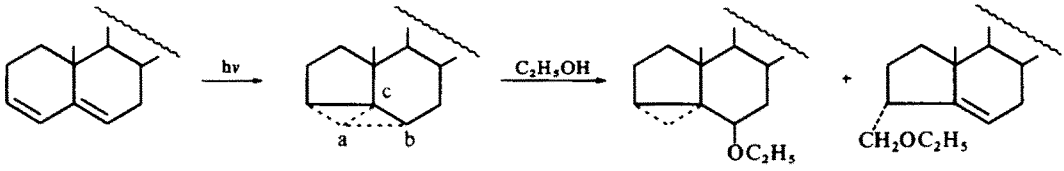
18 **20** **15** **21** **22**

to methylene addition. Three days reaction time with a large excess of Zn–Cu couple–methylene iodide gave only 2% conversion of **18** to **20**. In view of the extremely hindered nature of the double bond in **18** this reluctance to react with Simmons-Smith reagent is not surprising. Hydrolysis of **20** gave the alcohol **21**.

The two 5β,7β-cyclosteroids derived from **18** were related to the photochemically generated cyclosteroids *via* the ketone, **15**, obtained from hydroboration-oxidation of **11**. Reduction of **15** with LAH gave an 87% yield of **21** and trace amounts of **22**. The 3β-alcohol, **21**, showed a characteristic cyclopropyl geminal hydrogen stretching overtone at 1·647 μ (ε 0·438) and the characteristic one proton, four peak ABX multiplet centered at τ 10·28 demonstrating the preservation of the cyclopropane ring.* The 3β-alcohol was readily converted to the 3β-acetate, **20**. Samples of **20** and **21** prepared from the photochemical and nonphotochemical reaction routes were identical in all respects. Thus, the structure of the photochemically generated 5β,7β-cyclocholestanes was securely established.

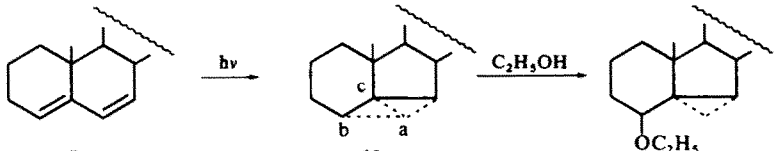
DISCUSSION OF RESULTS

Dauben has established that the photochemical conversion of cholesta-3,5-diene (**3**) into a mixture of **4** and **23** proceeded *via* the highly reactive bicyclo[1.1.0]butane intermediate (**24**).[6] Based on this precedent it seems likely that irradiation of **5** would



3 **24** **4** **23**

lead to **10** as the initially formed photoproduct. (It is interesting to note that **5** fails to yield any ether analogous to the formation of **23** from **3**). Addition of ethanol to **10** would be expected to give the observed product, **7**.



5 **10** **7**

Various mechanisms have been suggested[6c, 6i, 16, 17] for the reaction of the highly strained intermediate, **24**, with solvent. Dauben has described the *a–b* bond of **24** as "approaching something like an ion pair".[10c] Other workers have suggested[6i, 16] that the initial step in the addition of solvent to **24** involves protonation of the bicyclobutane by ethanol. Another report[17] makes the proposal that the addition of solvent involves nucleophilic attack by ethanol. Recently Dauben and Poulter, in discussing[18] the protonation of bicyclobutanes by methanol, have suggested the possibility, with reference to structures such as **24**, "that in these cases of exceptional

* It is interesting to note that catalytic reduction of **15** in acetic acid at 60 psi over platinum oxide also gave a mixture of **21** and **22** with no apparent destruction of the cyclopropyl ring.

reactivity severe distortions or changes in the substitution pattern of the bicyclobutane altered the reaction path; i.e., initial solvent attack might be either concerted or nucleophilic rather than electrophilic". Unfortunately, the definitive experiments, which will differentiate between these various possible mechanisms, are yet to be devised.

Although a unique mechanism for the addition of alcohols to bicyclobutane intermediates, such as **24**, has not been established, various pieces of pertinent data have been gathered. The major factor favoring protonation, as the first step in the addition of alcohols to bicyclobutanes, is the similarity of the products obtained in solvolysis reactions to the products found in alcohol additions. This correspondence of products has been attributed to the formation of a common carbonium ion intermediate.[6i,16,18] In conflict with this evidence is the fact that amines, ammonia, alcohols and water all add to bicyclobutane derivatives to yield similar products.[19,*] It is quite unlikely that amines add *via* intial protonation of the bicyclobutane. Thus, the case for nucleophilic attack seems reasonable.

The addition of alcohols to bicyclobutane derivatives has been shown to be both acid-catalyzed[18,20] and base-catalyzed.[19] While the acid-catalyzed addition probably involves electrophilic attack the base-catalyzed reaction appears to occur *via* nucleophilic attack. On the basis of this data it cannot be determined how the uncatalyzed addition of ethanol to **24** and **10** occurs.

Whereas the mechanism of the addition of solvent to **24** and **10** is not readily defined, the addition across the *a–b* bond is predicted by the "twist" bent bond hypothesis.[17] In simple bicyclobutane derivatives addition of various reagents generally occurs across the 1–3 bond of the bicyclobutane to yield a cyclobutane derivative. This would correspond to addition to the *a–c* bond of **24** and **10**. In fact, no such reaction has been found with either **24** or **10**. The failure of solvent to add to the *a–c* bond is readily explained by the "twist" bent bond hypothesis. It has been suggested[17] that when two rings are *cis*-fused to adjacent sides of a cyclopropane, the cyclopropyl bond joining these two rings is subjected to opposing horizontal displacement of the orbitals forming this bond. The *a–b* bonds in **24** and **10** fall into this category. It was also suggested that when bonds are "twisted" in the aforementioned manner the orbital overlap becomes very weak and the bond becomes extremely reactive. In actual fact the hypothetical picture very accurately describes the chemical reactivity of the *a–b* bonds of **24** and **10**. Hence, the addition of ethanol across this bond is quite reasonable.

Studies are in progress on the acid catalyzed rearrangement of 5β,7β-cyclocholestane derivatives and on solvolytic routes to 5β,7β-cyclosteroids.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. Column chromatography was carried out on Woelm or Baker neutral alumina or Grace Grade 923 silica gel as indicated. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, or by the Microanalytisches Laboratorium im Max-Planck-Institut for Kohlenforschung, Mulheim, Germany, or by Mr. Peter Kovi of The Ohio State University, Columbus, Ohio, using an F and M model 185 carbon, hydrogen, nitrogen analyzer. Infrared spectra were run on a Perkin–Elmer Infracord Model 137. All near-IR and UV spectra were measured on a Cary Model 14 Spectrophotometer. NMR spectra were taken on a Varian A-60 Spectrometer in CCl_4 or CS_2.

* It should be noted that this example involves addition to a cyano-substituted bicyclobutane.

Cholesta-4,6-diene (**5**). This diene was prepared by the method of Sondheimer *et al.*[8] The product was isolated by direct precipitation from the reaction mixture with water rather than by extraction with ether and chromatography as reported. Filtration gave the crude product, m.p. 92–93° (lit.[8] m.p. 92·0–92·5°).

Irradiation of cholesta-4,6-diene (**5**) *in ethanol.* A soln of 3·0 g of **5** in 1 l. of abs EtOH was irradiated under a N_2 atmosphere with a 450 watt Hg arc lamp equipped with a Vycor filter until there was no appreciable absorption in the UV attributable to the starting diene (18 hr). Evaporation gave an oily residue (4·1 g) which was chromatographed on 250 g silica gel. Elution with hexane gave 360 mg (12%) of **6**, m.p. 75–76·5°, $[\alpha]_D^{26}$ +45·2°. Recrystallization from EtOH afforded an analytical sample. (Found: C, 88·09; H, 12·28. Calc. for $C_{27}H_{44}$: C, 87·97; H, 12·03%).

Elution with 25–50% benzene in hexane gave 1·20 g (40%) of **7** as a crystalline white solid. Recrystallization from EtOH gave pure **7**, m.p. 93–94°, $[\alpha]_D^{29}$ −79·2°. The compound absorbed at 1·645 μ (ε 0·311) in the near-IR. The NMR spectrum showed a typical ABX four peak multiplet at τ 10·14. (Found: C, 83·97; H, 12·03. Calc. for $C_{29}H_{50}O$: C, 83·99; H, 12·15%).

Reaction of **6** *with acid.* A soln of 114 mg of **6** and two drops 72% perchloric acid in 10 ml dioxan was stirred at room temp. Measured aliquots were removed and their UV spectra measured. After one week, the absorption above 220 mμ still had an extinction coefficient of less than 500. The reaction mixture was diluted with water and extracted with ether. The ethereal soln was washed with $NaHCO_3$aq, water, and sat NaClaq, respectively, and dried over $MgSO_4$. Filtration of the drying agent and evaporation of the filtrate *in vacuo* gave an oil which was chromatographed on activity I alumina. Elution with hexane gave only an oily mixture of hydrocarbons.

Δ^8-Cholestene from hydrogenation of **6**. A soln of 250 mg of **6** dissolved in 10 ml 95% EtOH was hydrogenated over 100 mg Pd—C. After take-up of one mole H_2 the reaction was stopped, the catalyst was removed by filtration through celite, and the solvent was evaporated under reduced press. The oily residue was chromatographed on activity I alumina. Elution with hexane gave 208 mg (83%) of an oily solid. Separation by preparative TLC gave Δ^8-cholestene, m.p. 91–92°, $[\alpha]_D^{25}$ +54·7° (lit.,[21] m.p. 93° $[\alpha]_D$ +56°).

5β,7β-*Cyclocholest-3-ene* (**11**)

A. From direct irradiation. The irradiation was carried out as described above and the crude product was chromatographed on activity I alumina. After elution of **6**, continued elution with hexane gave 1·60 g (53%) of white crystalline solid, m.p. 112–113°, $[\alpha]_D^{26}$ −11·5°. The compound showed IR absorption for the olefinic stretch at 6·12 μ and a cyclopropyl geminal hydrogen absorption at 1·646 μ (ε 0·312). The UV absorption at $\lambda_{max}^{95\% \text{ EtOH}}$ 211 (ε 11,300) was characteristic of a vinyl cyclopropane.* The NMR spectrum showed a one proton ABX multiplet at τ 10·16 and a two proton singlet at τ 4·52. Recrystallization from EtOH gave an analytical sample. (Found: C, 88·14; H, 11·87. Calc. for $C_{27}H_{44}$: C, 87·97; H, 12·03%).

B. From cyclopropyl ether **7**. Chromatography of 400 mg of **7** on 75 g activity I alumina gave upon elution with hexane, 276 mg (75%) white crystalline solid identical with **11** in all respects.

5β,7β-*Cyclocholestane* (**12**). A soln of 250 mg of **11** in 10 ml EtOAc was hydrogenated at atm press and room temp until one mole H_2 over 5% Pd/C was taken up. Evaporation of the solvent yielded 110 mg of white solid. Recrystallization from acetone gave pure **12**, m.p. 81–83°, $[\alpha]_D^{26}$ −18·2°. The NMR spectrum of **10** showed a one proton ABX-four peak multiplet at τ 10·30. (Found: C, 87·20; H, 12·80. Calc. for $C_{27}H_{46}$: C, 87·49; H, 12·51%).

Hydroboration and oxidation of 5β,7β-*cyclocholest-3-ene* (**11**). To a stirred soln of 5·15 g $NaBH_4$ in 300 ml diglyme was added dropwise a soln of 42·8 g BF_3–Et_2O in 200 ml diglyme. A slow stream of N_2 was used to sweep the generated diborane into the reaction vessel containing a stirred soln of 3·42 g of **11** in 350 ml THF. The addition took approximately 3 hr. The reaction was stirred one additional hr at room temp. Water (60 ml) was added followed by 200 ml 10% NaOHaq. The reaction mixture was then cooled to 0° and 150 ml 30% H_2O_2 was added dropwise. Upon completion of addition, stirring was continued 1 hr, and the reaction mixture was poured onto water and extracted with ether. The ether extracts were washed successively with $NaHSO_3$aq, water, sat NaClaq, and dried over $MgSO_4$. The drying agent was removed by filtration and the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 30 ml pyridine and added to a previously prepared slurry of 3·0 g CrO_3 in 100 ml pyridine. This mixture was allowed to stand overnight at room temp. After pouring into water and extracting with ether, the ether extracts were washed with dil HCl, water, sat NaClaq, and dried over $MgSO_4$. The drying agent was removed by filtration and the filtrate was evaporated under reduced press leaving an oily residue which was chromatographed on 450 g activity III alumina. Elution with hexane yielded 282 mg (8·2%) of an oil which crystallized on standing and

* 3α,5α-Cyclocholest-6-ene absorbs at λ_{max} 207·5 (ε 12,400).[22]

was shown to be identical with **12** by undepressed m. m.p. and comparison of IR spectra. Elution with 10% benzene in hexane gave 650 mg (18%)* of a solid, m.p. 95–96°, the IR spectrum of which showed a CO stretching frequency of 5·85 μ but no absorption characteristic of a cyclopropane. This compound was not investigated further. Continued elution with 10% benzene in hexane gave 1·80 g (50%) of a solid identified as **15**, m.p. 121–122·5°, $[\alpha]_D^{26}$ +44·9°. The IR spectrum of **15** showed CO stretching frequency at 5·80 μ and a cyclopropyl geminal hydrogen stretching absorption at 1·644 μ (ε 0·349) both of which indicated that the CO was not conjugated with the cyclopropane.[9,23]

The NMR spectrum showed the characteristic one proton ABX four peak multiplet at τ 10·14. (Found: C, 84·14; H, 11·49. Calc. for $C_{27}H_{44}O$: C, 84·31; H, 11·53%).

A similar hydroboration-oxidation of 3α,5α-cyclocholest-6-ene gave products analogous to those obtained from the hydroboration-oxidation of **11**. The major product obtained from 2·96 g of 3α,5α-cyclocholest-6-ene was a non-conjugated cyclopropyl ketone (1·11 g) tentatively identified as 3α,5α-cyclocholestan-7-one, m.p. 87–88°, $[\alpha]_D^{26}$ +8·1°, near-IR maximum, 1·644 μ (ε 0·349). (Found: C, 84·24; H, 11·47. Calc. for $C_{27}H_{44}O$: C, 84·31; H, 11·53%).

Irradiation of cholesta-4,6-diene (**5**) *in tetrahydrofuran-water.* A soln of 3·0 g of **5** in a mixture of 700 ml THF and 300 ml water was irradiated under N_2 with a 450 watt Hg arc lamp through quartz until no appreciable absorption attributable to the starting diene **5** could be detected in the UV (30 hr). The THF was evaporated under reduced press, and the aqueous soln remaining was extracted with ether. The ether extracts were washed with sat NaCl aq and dried over $MgSO_4$. Filtration of the dessicant followed by evaporation of the filtrate *in vacuo* gave 4·68 g yellow oily residue which was chromatographed on 450 g silica gel. Elution with benzene gave 6 fractions of an oil totaling 1·82 g (58%) identical by comparison of their IR spectra. All showed two components on thin layer chromatograms but preparative TLC failed to give a solid product. Attempted crystallization from EtOH of one of the fractions weighing 547 mg did give 152 mg of crude white crystals of **16**, m.p. 67–73°, $[\alpha]_D^{31}$ −84·8°. Attempted recrystallization gave only an oil. The near-IR spectrum of **16** showed absorption at 1·644 μ (ε 0·309). The NMR spectrum was poorly resolved but showed a one proton multiplet at τ 10·26, a one proton triplet centered at τ 6·55 (*J* 2·9 c/s) assigned to the C-4 hydrogen, and a broad one proton signal centered at τ 7·07 assigned to the hydroxyl hydrogen. (Found: C, 83·92; H, 12·03. Calc. for $C_{27}H_{46}O$: C, 83·87; H, 11·99%).

Dehydration of 5β,7β-*cyclocholestan-4β-ol* (**16**). A soln of 30 mg of **16** in a minimum amount of hexane was chromatographed on 15 g activity I alumina. Elution with hexane gave 12·8 mg (45%) of **11**, m.p. 110–111·5°, IR spectrum superimposable with that of authentic **11** and m.m.p. undepressed at 110–111·5°.

5β,7β-*Cyclocholestan-4-one* (**14**). A soln of 410 mg of **16** (as the crude oil) in 10 ml pyridine was added to a suspension of 400 mg CrO_3 in 10 ml pyridine, and the reaction mixture was allowed to stand overnight at room temp. The reaction mixture was poured into a mixture of water and ether, and this mixture was filtered through celite to remove all solids. The aqueous layer was extracted with ether, and the combined organic phase was washed with dil HCl aq, water, and sat NaCl aq and dried over $MgSO_4$. Filtration of the drying agent followed by evaporation of the filtrate *in vacuo* gave a solid residue. Recrystallization from EtOH gave 110 mg of **14**, m.p. 152·5–153·2, $[\alpha]_D^{31}$ −13·8°. Concentration of the mother liquor gave a second crop of 42 mg, the total yield being 152 mg (37%). The near-IR spectrum of **14** showed absorption at 1·642 μ (ε 0·381). The NMR spectrum showed the characteristic one proton ABX four peak multiplet centered at τ 9·83. (Found: C, 84·51; H, 11·60. Calc. for $C_{27}H_{44}O$: C, 84·31; H, 11·53%).

Reductive-oxymercuration of 5β,7β-*cyclocholest-3-ene* (**11**). To a soln of 220 mg mercuric acetate in a mixture of one ml water and one ml THF was added a soln of 250 mg of **11** in 2 ml THF, and the reaction mixture was stirred until the yellow color disappeared (3 hr) and then for 3 additional hr. One ml of 3M NaOH was added followed by one ml 0·5M $NaBH_4$ in 3M NaOH. The organic layer was separated, centrifuged, and decanted from the residual mercury. Evaporation gave an oil which was dissolved in 5 ml pyridine and added to a suspension of 200 mg CrO_3 in 10 ml pyridine. This reaction mixture was allowed to stand overnight at room temp, and the product was isolated with ether in the usual manner. Chromatography on 30 g activity III alumina and elution with 15% benzene in hexane gave 25 mg (10%) of **14**, m.p. 148·2–150·0°. Recrystallization from EtOH gave a sample, m.p. 151·8–152·7°, identical to authentic **14** by comparison of IR spectra and undepressed m. m.p. 152–153°.

Reduction of 5β,7β-*cyclocholestan-4-one* (**14**) *with lithium aluminum hydride.* To a slurry of 200 mg LAH in 10 ml dry ether was added a soln of 149 mg of **14** in 10 ml dry ether dropwise with stirring. Upon completion of addition, the reaction mixture was refluxed for 2 hr then cooled in an ice bath. A mixture of 0·8 ml water and 1·2 ml MeOH was added dropwise, and stirring was continued 1 hr at room temp.

* Calculated on the assumption that this material is isomeric with **15**.

Filtration followed by evaporation of the filtrate *in vacuo* gave an oily residue which was chromatographed on 30 g activity IV alumina. Elution with 25% benzene in hexane gave 42·3 mg (28%) of an oil identical by comparison of IR spectra to the 4β-alcohol, **16**. Continued elution with 25% benzene in hexane gave 86·1 mg (58%) of crystalline **17**, m.p. 130·5–131·5°, $[\alpha]_D^{28}$ −22·2°. The near-IR spectrum of **17** showed absorption at 1·640 μ (ε 0·323). The NMR spectrum showed a one proton multiplet centered at τ 9·72 characteristic of one of the cyclopropyl hydrogens, a one proton singlet at τ 7·23 assigned to the hydroxyl hydrogen, and a poorly resolved multiplet, suggestive of a quartet, centered at τ 5·92 assigned to the C-4 hydrogen. (Found: C, 83·70; H, 11·71. Calc. for $C_{27}H_{46}O$: C, 83·87; H, 11·99%).

B-Norcholesteryl acetate (**18**). This material was prepared by the method of Šorm and Dykova as described by Dauben and Fonken[14] and had m.p. 78·7–79·5° (reported[14] m.p. 78–79°).

Simmons-Smith reaction with B-norcholesteryl acetate (**18**). To a stirred suspension of 5·0 g granular Zn–Cu couple in 50 ml ether was added a few drops of CH_2I_2 to initiate the reaction, then a soln of 3·0 g CH_2I_2 and 2·07 g of **18** in 25 ml ether was added dropwise. Upon completion of addition, the reaction mixture was stirred for 18 hr at room temp. An additional 5·0 g Zn–Cu couple and 3·0 g CH_2I_2 were added in one portion and stirring was continued. This procedure was repeated twice more making the total reaction time 3 days. The ether soln was then decanted away from the unreacted couple into cold 1N HCl. The ethereal soln was separated, washed successively with 1N HCl, 3 times with water, and with sat NaCl aq, and dried over $MgSO_4$. Removal of the drying agent by filtration followed by evaporation of the filtrate *in vacuo* gave 2·13 g of product as an oil which was crystallized from EtOH to give 955 mg of the starting acetate, **18**. The mother liquor from the crystallization was poured into water, extracted with ether, and the ether extracts were washed with sat NaCl aq and dried over $MgSO_4$. The drying agent was removed by filtration, and the filtrate was evaporated under reduced press to give 960 mg residue which was chromatographed on 170 g activity I alumina. Elution with 10% ether in benzene gave 47·1 mg (2·2%) of **20**. Two recrystallizations from aqueous acetone gave a product m.p. 111·5–112·5°, $[\alpha]_D^{25}$ −22·9°. Comparison of IR spectra in CCl_4 and CS_2 solns showed this product to be identical to authentic **20** prepared as described below, undepressed m. m.p. 112–113·2°.

Hydrolysis of **20** prepared by this method with methanolic KOH gave after recrystallization from EtOH an alcohol m.p. 145·5–148·7°, identical with **21**, m. m.p. with authentic **21**, 147·3–149·3°.

5β,7β-*Cyclocholestan*-3β-*ol* (**21**). To a slurry of 500 mg LAH in 20 ml dry ether was added a soln of 1·0 g of ketone **15** in 25 ml dry ether dropwise with stirring. Upon completion of addition, the soln was refluxed 1 hr, then stirred overnight at room temp. Two ml water were added dropwise, and the reaction mixture was filtered. The solid was washed with ether, and the combined filtrate and washings were evaporated *in vacuo* to give a white solid residue. Recrystallization from EtOH gave 729 mg of **21**, m.p. 148·5–149·3°, $[\alpha]_D^{25}$ −25·0°. Concentration of the mother liquors gave a second crop, 149 mg, for a total yield of 878 mg (87%). The NMR spectrum of **21** showed a one proton ABX four peak multiplet at τ 10·28, a one proton broad singlet at τ 6·86 assigned to the hydroxyl proton, and a one proton broad signal centered at τ 6·50 assigned to the C-3 hydrogen. The near-IR spectrum showed absorption at 1·647 μ (ε 0·438). (Found: C, 84·10; H, 11·80. Calc. for $C_{27}H_{46}O$: C, 83·87; H, 11·99%).

When the crude reaction mixture was chromatographed on activity IV alumina, elution with 25% benzene in hexane gave small amounts of an epimeric alcohol tentatively identified as **22**, m.p. 130–133°. Continued elution with the same solvent gave **21** as the major product.

3β-*Acetoxy*-5β,7β-*cyclocholestane* **20**. The acetate **20** was prepared in the usual manner from 300 mg of **21** dissolved in a mixture of 1·0 ml Ac_2O and 10 ml pyridine. The product was crystallized from EtOH to yield 252 mg (75%) of **20**, m.p. 113·7–114·2°, $[\alpha]_D^{25}$ −23·2°. The near-IR spectrum showed absorption at 1·645 μ (ε 0·564). The NMR spectrum showed a one proton multiplet centered at τ 10·15 assigned to one cyclopropyl hydrogen, a three proton singlet at τ 8·15 assigned to the acetate methyl hydrogens, and a one proton septet centered at τ 5·31 assigned to the hydrogen on C-3. (Found: C, 81·25; H, 11·30. Calc. for $C_{29}H_{48}O_2$: C, 81·25; H, 11·29%).

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