# A New Synthesis of Cholesterol and Related $C_{27}$ Steroids[1]

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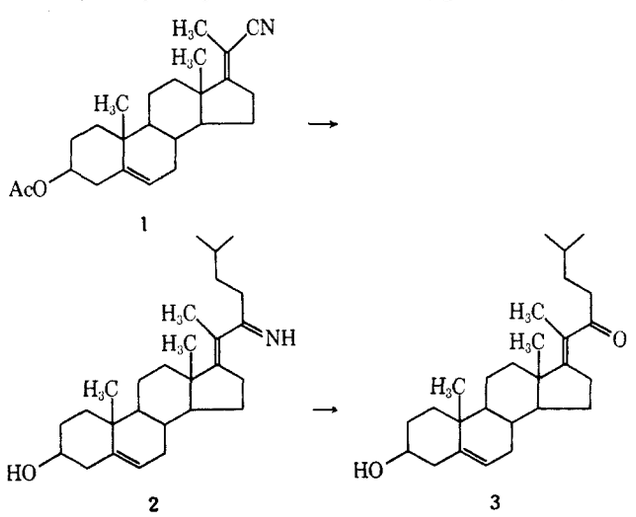
A new method has been developed for the construction of the side chain of $C_{27}$ sterols from $C_{21}$-20-keto steroids and used for the synthesis of $\Delta^{16}$- and *cis*-$\Delta^{17(20)}$-cholesterol. The $\alpha,\beta$-unsaturated nitrile **1**, obtained by the dehydration of the cyanohydrin of pregnenolone acetate, was treated with isoamylmagnesium bromide to give the $\alpha,\beta$-unsaturated ketone **3**, which was isomerized to the $\beta,\gamma$-unsaturated ketone **6** by treatment with base. The 22-keto group of **3** and **6** was then converted into the 22-methlene group by treatment of their 22-ethylene thioketal derivatives with lithium and ethylamine to give *cis*-$\Delta^{17(20)}$- and $\Delta^{16}$-cholesterol, respectively. Alternatively, the enone **3** was converted into an allyl ether **22**, which was then treated with lithium and ethylamine to give *cis*-$\Delta^{17(20)}$-cholesterol. The 17–20 double bond of **3** and the 16–17 double bond of **6** has been selectively reduced to give 22-ketocholesterol, which was then converted into cholesterol *via* its 22-ethylene thioketal.

Current interest in the catabolic pathway of cholesterol to pregnenolone and other steroidal hormones has led us to synthesize a number of mono- and polyhydroxy derivatives of cholesterol having the substituents at the 16, 17, 20, and 22 positions. Some of these compounds may be synthesized by the presently available methods, but a separate synthesis for each compound has to be devised and stereochemistry has to be established by some unambiguous method. Thus the method of Woodward and coworkers,[2] which involves the addition of Grignard reagents[3] to 20-keto steroids, may be applied to the synthesis of 20-hydroxy[4] and 17,-20-dihydroxy compounds,[4] butt his method is not suitable for the synthesis of 17- or 22-hydroxy compounds. The second method, developed by Sondheimer and Mechoulam[5] involves the creation of a double bond at the 20–21 (or 20–22) position by means of the Wittig reaction. One disadvantage in the application of this method is that functionalization of the 20–22-unsaturated system would give products of unknown stereochemistry. Besides, we have observed that 17$\alpha$-hydroxy- and 17$\alpha$-tetrahydropyranyloxy-20-keto steroids[6] either fail to undergo the Wittig reaction or give desired products only in a very low yield. The third method, developed by Cole and Julian,[7] involves a Grignard reaction with bisnorcholenic acid derivatives. This method has been proven to be very useful for the synthesis of a number of naturally occurring steroids including cholesterol,[8] 22-hydroxycholesterol,[9] dihydrobrassicasterol,[10] campesterol,[11] ecdysone,[12] and 20-hydroxyecdysone,[13] and may be used for the synthesis of 16- or 17-substituted compounds if proper intermediates are available. The fourth method, developed by Kessar, *et al.*,[14] involves a Michael condensation with a $\Delta^{17(20)}$-16 ketone and cannot be used for introducing substituents at C-17 and C-20.

We were, therefore, interested in developing a new method for the synthesis of $C_{27}$ steroids from $C_{21}$ steroids and planned to synthesize a key intermediate which could readily be functionalized to give the above-mentioned hydroxy compounds by means of some stereospecific reactions. Since the reactions with $\Delta^{16}$ and $\Delta^{17}$ steroids take place mostly from the "$\alpha$" side, development of a synthetic route to these systems was preferable to the construction of a $\Delta^{20}$ system. In this paper we describe the synthesis of a $\Delta^{17(20)}$-22-keto steroid **3**, and its conversion into the $\Delta^{16}$-22-keto steroid **6**, into $\Delta^{17}$-cholesterol (**19**), and into $\Delta^{16}$-cholesterol (**15**). The synthesis of various hydroxycholesterols from these compounds will be reported in subsequent communications.

The starting material for the synthesis of **3** was the previously described $\Delta^{17(20)}$-*cis*-nitrile[15] **1**, which is readily prepared in excellent yield from pregnenolone 3-acetate *via* its cyanohydrin. On reaction with isoamylmagnesium bromide it gave in 75% yield the imine **2** which, on hydrolysis with acetic acid, gave the $\alpha,\beta$-un-




(1) Supported by the Atomic Energy Commission Contract AT(30-1)918 and Grant AM-03419 from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

(2) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952).

(3) Recently we have studied the stereochemical aspect of this reaction and unequivocally proved the stereochemistry of the resulting 20-carbinols.[4]

(4) N. K. Chaudhuri, J. Williams, R. Nickolson, and M. Gut, *J. Org. Chem.*, **34**, 3759, (1969).

(5) F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, **80**, 3087 (1959).

(6) Unpublished results from this laboratory.

(7) W. Cole and P. L. Julian, *ibid.*, **67**, 1369 (1945).

(8) A. Romeo and R. Villotti, *Ann. Chim.* (Rome), **47**, 618 (1957).

(9) K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, **81**, 5987 (1959).

(10) A. Martinez, A. Romeo, and V. Tortorella, *Gazz. Chim. Ital.*, **97**, 96 (1967).

(11) G. Tarzia, V. Tortorella, and A. Romeo, *ibid.*, **97**, 102 (1967).

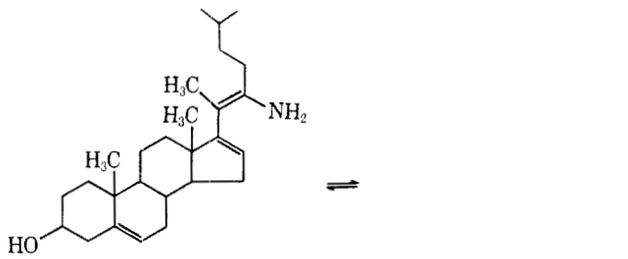
(12) (a) J. B. Siddall, J. P. Marshall, A. Bowers, A. D. Cross, J. A. Edwards, and J. H. Fried, *J. Amer. Chem. Soc.*, **88**, 379 (1966). (b) J. B. Siddall, A. D. Cross, and J. H. Fried, *ibid.*, **88**, 862 (1966). (c) R. Wiechert, A. Furlenmeier, A. Fürst, A. Langemann, and G. W. Aldwogel, *Helv. Chim. Acta*, **96**, 1601 (1966).

(13) G. Hüppi and J. B. Siddall, *J. Amer. Chem. Soc.*, **89**, 6790 (1967).

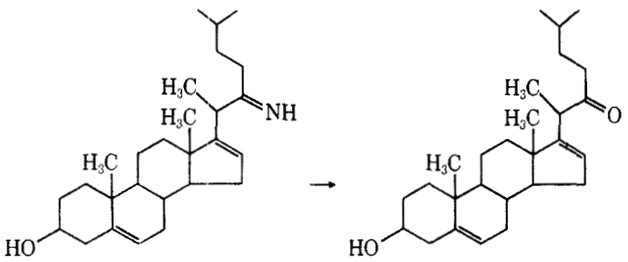
(14) S. V. Kessar, Y. P. Gupta, R. K. Maharajan, G. S. Joshi, and A. L. Rampal, *Tetrahedron*, **24**, 899 (1968).

(15) N. K. Chaudhuri and M. Gut, *J. Amer. Chem. Soc.*, **87**, 3737 (1965). The *cis* and *trans* nomenclature used in this paper to describe the geometry around the 17–20 double bond is arbitrarily based on the relationship of the 18- and 21-methyl groups.

saturated ketone **3**. Hydrolysis with a stronger acid, however, resulted in a mixture of **3** and the $\beta,\gamma$-unsaturated ketone **6**. The formation of **6** may be explained by assuming an acid-catalyzed isomerization of the



**4**

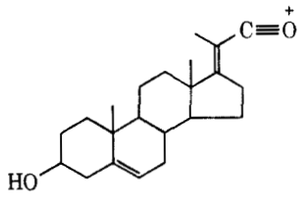


**5** **6**

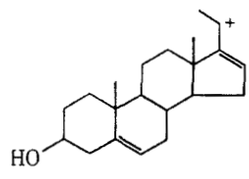
imine **2** *via* its enamine **4** to the imine **5** followed by its hydrolysis. The $\alpha,\beta$-unsaturated ketone **3** could also be readily isomerized by treatment with base into an equilibrium mixture of **3** and **6**. This mixture consisted of 80% $\beta,\gamma$ form and 20% $\alpha,\beta$ form, which was determined by the molecular extinction (1600) of the uv absorption maximum. The $\alpha,\beta$-unsaturated ketone **3** had a uv absorption maximum at 253 m$\mu$ ($\epsilon$ 8000), and ir bands at 6.0 (conjd C=O) and 6.3 (conjd C=C) $\mu$. The relatively low extinction value of the uv absorption maximum and the strong intensity of the 6.3 $\mu$ band indicated the cisoid conformation of the ketone **3** as in the previously noted case of an analogous methyl ketone. The nmr signal of the 21-methyl protons appeared as a triplet centered at 117 cps ($J$ = 1.8 cps) due to the homoallylic coupling of these protons with the 16-methylene protons which are in *trans* relationship. Pure $\beta,\gamma$-unsaturated ketone **6** was isolated from the equilibrium mixture by extraction with hexane as described in the Experimental Section. Its spectral properties are consistent with the assigned structure. The ir spectrum showed a band at 5.78 $\mu$ due to the saturated ketone group. The nmr spectrum showed the presence of two vinylic protons (6 and 16 H's) at 320–324 cps, and a secondary methyl (21 methyl) group (a doublet centered at 69 cps, $J$ = 6 cps) besides the side-chain methyl groups (a doublet centered at 51 cps, $J$ = 6 cps).

The mass spectra of both the ketones **3** and **6** showed the molecular ion peak at $m/e$ 398 as the base peak but they were significantly different with respect to the fragmentation pattern. Thus the spectrum of **3** showed a strong peak at $m/e$ 327 which may be assigned to the fragment **7**. This peak was absent in the spectrum of **6**, which had, however, a new peak at $m/e$ 299, assigned to the fragment **8**.

Since the isomerization of the 17–20 double bond to the 16,17 position creates a new assymetric center at C-20, we have determined the steric configuration of **6** at this center by studying the catalytic hydrogenation



**7**



**8**

products and shown that **6** has the same steric configuration at C-20 as cholesterol. When the 3-acetate of **6** was hydrogenated in ethyl acetate with 10% palladium on charcoal as the catalyst both the 16–17 as well as the 5–6 double bond were reduced to give 3$\beta$-acetoxy-5$\alpha$-cholestan-22-one. The 16–17 double bond could, however, be selectively reduced by using a weaker catalyst, 10% palladium on calcium carbonate in dioxane or ethyl acetate, to give 22-ketocholesterol 3-acetate. This reductive procedure provided a good method for the preparation of 16,17-ditritiated 22-ketocholesterol[16] and hence of the two isomeric 22-hydroxycholesterols. It may also be used for the synthesis of 16,17-ditritiated cholesterol by reducing the 22-keto group to the 22-methylene group by the method described in a later section.

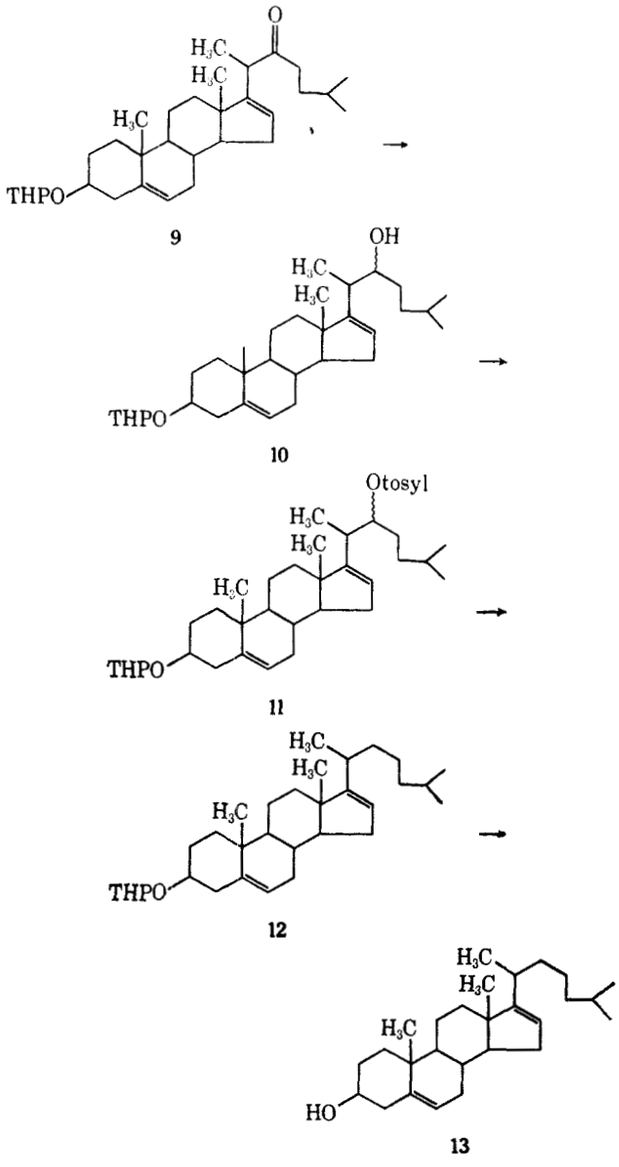
That the base-catalyzed isomerization of **3** gives predominantly one ketone **6** shows that the $\beta,\gamma$-unsaturated ketone, $\Delta^{16}$-22-ketocholesterol, having the same configuration at C-20 as cholesterol, is the thermodynamically stable form. Although Cole and Julian[7] failed to demonstrate the epimerization of 22-ketocholesterol at C-20 by treatment with base, recently Burrows, *et al.*,[17] observed some new peaks in the nmr spectrum of the thereby obtained product. Similarly, we have found evidence for the existence of the 20 epimer of **6** in the mother liquor, obtained from the crystallization of **6**. The nmr spectrum of the gummy residue showed a doublet at 73 cps ($J$ = 6 cps) which may be assigned to the 21-methyl protons of the 20 epimer of **6**, since the nmr signal of the 21-methyl protons of **6** appears at 69 cps. The reduction of the 17–20 double bond of the enone **3** with lithium in liquid ammonia gave the thermodynamically stable isomer, 22-ketocholesterol. It is noteworthy that when the above reduction was carried out with lithium in liquid ammonia, followed by addition of alcohol, the mixture of 22-hydroxycholesterols obtained was richer in (22*R*)-22-hydroxycholesterol, in contradistinction to the product obtained by the reduction of 22-ketocholesterol with sodium borohydride which was richer in (22*S*)-22-hydroxycholesterol.[9,17]

For the preparation of $\Delta^{16}$-cholesterol, the 22-keto group of **6** was first reduced to the 22-methylene group according to the method of Romeo and Villotti,[8] as described in Chart I. The 3$\beta$-hydroxy group of **6** was protected by converting it into the tetrahydropyranyloxy derivative **9**. The 22-keto group of **9** was then reduced by lithium aluminum hydride to a mixture of 22-hydroxy epimers **10** which was converted into a mixture of *p*-toluenesulfonyl esters **11**. Hydrogenolysis of **11** with lithium aluminum hydride gave **12** which on treatment with dilute acid gave $\Delta^{16}$-cholesterol (**13**), in good

(16) S. Burstein, H. L. Kimball, N. K. Chaudhuri, and M. Gut, to be published.

(17) E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969).

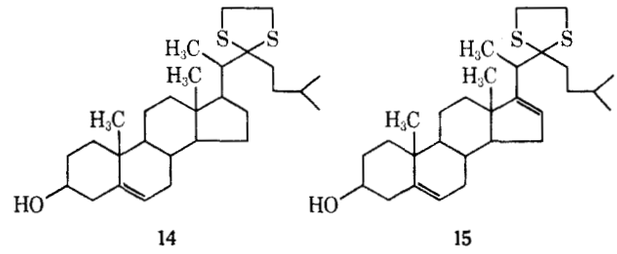
CHART I




yield. Both **12** and **13** appeared homogeneous on thin layer chromatography and the major peaks in their nmr and mass spectra were in agreement with their structures, but the presence of a very small peak due to M − 2 in the mass spectra of both **12** and **13** suggested the presence of some trienes which must have been formed by elimination of *p*-toluenesulfonic acid from **11**. These elimination products could not be completely removed by chromatography or crystallization. One of the contaminant trienes had a conjugated diene group, possibly $\Delta^{17(20),22}$, since the impure samples of **12** and **13** had a uv absorption maximum at 235 mμ. This impurity was removed by adduct formation with maleic anhydride. Even after removal of the uv-absorbing impurities, the mass spectra of **12** and **13** showed a peak due to M − 2. It was, therefore, concluded that some $\Delta^{5,16,22}$-triene was also present. The presence of a small peak at 43 cps which may be assigned to the 18-methyl group of $\Delta^{16,22}$-cholesterol substantiated this. The hydrogenolysis of the methanesulfonyl ester of **10** occurred mainly by the fission of the oxygen–sulfur bond giving the starting alcohol **10** as the major product accompanied by small amounts of elimination products as noted by Burrows, *et al.*,[17] in a similar case.

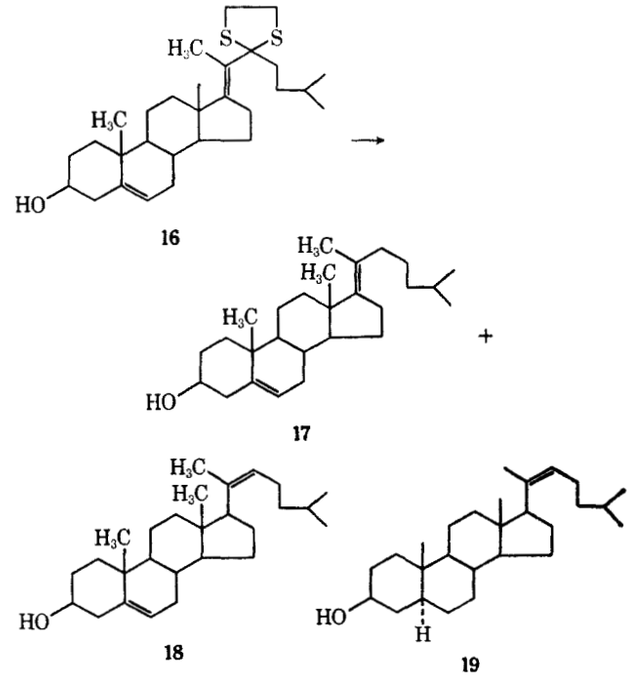
Since Romeo and Villotti[8] did not record the nmr and mass spectrum of cholesterol synthesized by this method, the existence of an elimination product could have remained unnoticed. We, therefore, synthesized cholesterol from 22-ketocholesterol by their method[8] and a mass ion peak at *m/e* 384 due to the elimination product was observed in this case also.

In order to avoid the formation of the eliminated products, we prepared the 22-ethylene thioketal **14** of 22-ketocholesterol and hydrogenolyzed it by treatment with lithium in ethylamine. The mass spectrum of the cholesterol obtained in an overall yield of 40% from the ketone showed the absence of any impurity.



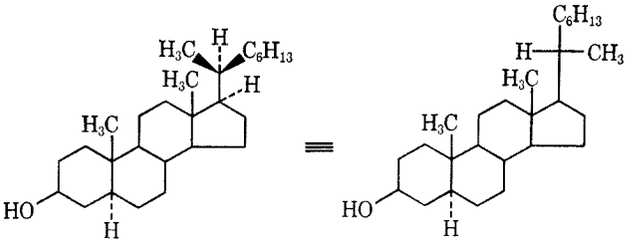

The above method was used for the synthesis of $\Delta^{16}$-cholesterol (**13**) from $\Delta^{16}$-22-ketocholesterol (**6**). Thioketalization proceeded smoothly in acetic acid with boron trifluoride as catalyst in a yield of 50–55%. The ethylene thioketal **15** was separated from the unreacted ketone by chromatography over basic alumina after treatment of the reaction mixture with lithium aluminum hydride. Treatment of **15** with lithium in ethylamine at 0° gave pure $\Delta^{16}$-cholesterol (overall yield from the ketone is about 40%) as judged from its nmr and mass spectrum.

The above method was also used for the synthesis of $\Delta^{17(20)}$-cholesterol. The ethylene thioketal **16** of the α,β-unsaturated ketone **3** was readily prepared and purified in the same way as described for the preparation of **15**. Structure proof of **16** was obtained from its nmr spec-



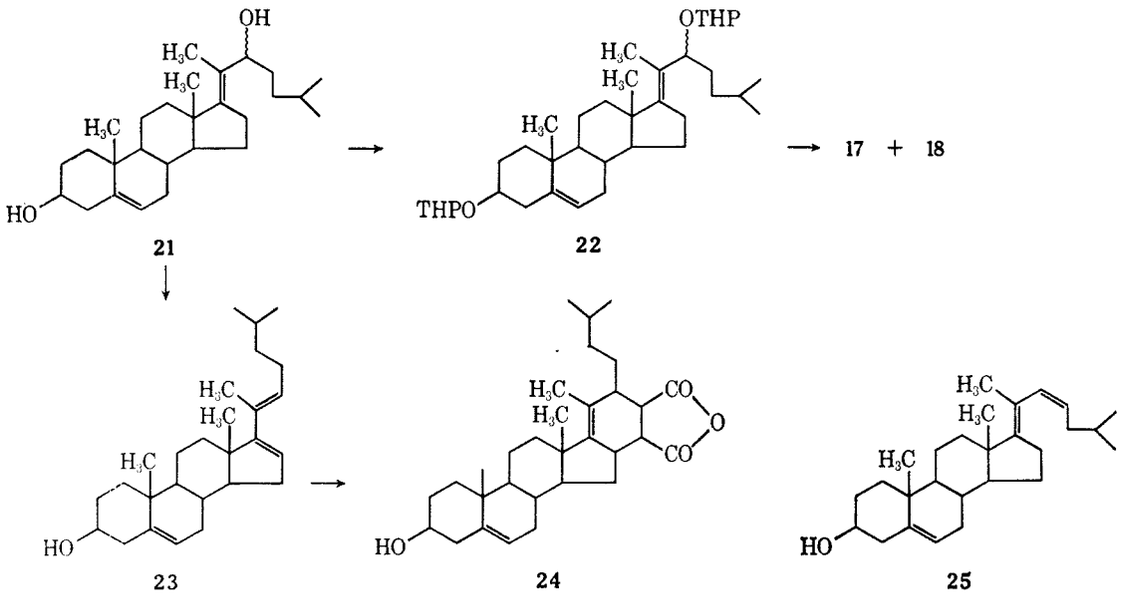
trum which showed that the double bond was in the expected 17–20 position. The overlapping of the p orbitals of the $\pi$ bond at 17–20 with the d orbitals of the sulfur atoms of the 22-thioketal group stabilizes the exocyclic 17–20 double bond and prevents the isomerisation to the endocyclic 16–17 position during thioketalisation. Hydrogenolysis was carried out by treatment with lithium and ethylamine, but, in either case, an equilibrium mixture of about 85% $\Delta^{17(20)}$-cholesterol (**17**) and 15% $\Delta^{20(22)}$-cholesterol (**18**) was obtained, as judged by the intensity of a small peak at 33 cps in the nmr spectrum of the reaction product. $\Delta^{20(22)}$-Cholesterol (**18**) must have been formed by the allylic rearrangement of the intermediate allylic species formed during the metal–amine reduction of **16**. An authentic sample of $\Delta^{20(22)}$-cholesterol (**18**) was prepared for comparison by the acid-catalyzed dehydration of 20$\alpha$-hydroxycholesterol. The nmr signal of its 18-methyl protons appeared at 33 cps. It is noteworthy that the dehydration of 20$\alpha$-hydroxycholesterol gave only one of the five (two $\Delta^{17(20)}$, two $\Delta^{20(22)}$, and one $\Delta^{20(21)}$) possible products. Structure proof of **18** was obtained from its nmr spectrum which showed the presence of the 22-vinylic proton and from the ozonization of the similarly prepared **19**[18] to 3$\beta$-hydroxy-5$\alpha$-pregnan-20-one. The stereochemistry of the 20–22 double bond has not been established however.

The above mixture of **17** and **18** could not be resolved by chromatography, but the benzoate of **17** could be obtained pure after several crystallizations from ethyl acetate and pure **17** was prepared by hydrogenolysis of the benzoate with lithium aluminum hydride. Structure proof of **17** and evidence in favor of the *cis* geometry around the 17–20 double bond was obtained from the following results. Like other $\Delta^{17(20)}$-*cis*-ethylenes,[15] the 21-methyl resonance signal of **19** appeared as a triplet ($J$ = 1.8 cps) due to homoallylic coupling with the 16-methylene group and catalytic hydrogenation of **17** gave 20-isocholestanol **20**,[19] as expected from the *cis* addition of hydrogen from the "$\alpha$" side. Although the nmr and mass spectra of 20-isocholestanol were not different from those of cholestanol, their melting points and crystal structures were quite different and there was a depression of melting point upon admixture as reported in the literature.[19]



**20**

The reductive cleavage of allylic ester and ethers by lithium in ethylamine[20] was also tried for the preparation of $\Delta^{17(20)}$-cholesterol (**17**), but this method also led to a mixture of **17** and **18**. For this purpose $\Delta^{17(20)}$-22-ketocholesterol (**3**) was reduced with lithium aluminum hydride to give a mixture of 22-epimeric alcohols **21** which could be separated by fractional crystallization. These allylic alcohols, on treatment with dilute acid, gave a conjugated diene having a uv-absorption maximum at 243 m$\mu$. On this basis, we have assigned it structure **23**, in preference to the alternative $\Delta^{17(20),22}$ structure **25**. Besides, the nmr peaks due to the two vinylic hydrogens appeared as multiplets at the same place, showing them to be magnetically equivalent, as may be expected of the structure **23**. The 22- and 23 vinylic hydrogens of **25** would however be expected to be magnetically nonequivalent and therefore their chemical shifts would be different. The conjugated diene readily gave a maleic anhydride adduct, the nmr spectrum of which showed, as expected of structure **24**, no vinylic proton other than the 6 H.



**21** **22** **23** **24** **25**

The mixture of the 22-epimeric alcohols **21** was converted into a mixture of 3,22-ditetrahydropyranyl ethers **22** by treatment with dihydropyran in a benzene solution containing a catalytic amount of *p*-toluenesulfonic acid. Some conjugated diene was also formed as a by-product and could be separated from **22** by chromatography. The 3,22 diether **22** was then treated

(18) L. F. Fieser and W. Huang, *J. Amer. Chem. Soc.*, **75**, 5356 (1953).
(19) G. V. Nair and E. Mosettig, *J. Org. Chem.*, **27**, 4659 (1962).
(20) A. S. Ballsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

with lithium in ethylamine at 0° and the resulting product was treated with dilute acid in order to cleave the 3β-tetrahydropyranyl ether group whereby a mixture of **17** and **18** was obtained. The 3,22-dibenzoate of **21** was also reduced in the same manner and the reaction product was hydrolyzed by base treatment to give essentially the same mixture of **17** and **18**.

We have also applied the above method of reductive cleavage of allylic ethers for the preparation of 5α-cholest-*cis*-17(20)-en-3β-ol (**33**) which was required for the stereochemical work described in another paper.[4] Since the 5–6 double bond of $\Delta^{17(20)}$-cholesterol (**17**) could not be preferentially reduced to give **33**, we started with 3β-acetoxy-5α-pregnan-20-one (**26**) and constructed the $\Delta^{17(20)}$-22-ketocholesterol side chain by the same sequence of reactions as described above for the corresponding $\Delta^5$ compound namely, conversion of the 20-keto group of **26** into the cyanohydrin **27**, dehydration of the cyanohydrin to the *cis*-$\Delta^{17(20)}$-nitrile **28**, and reaction of **28** with isoamylmagnesium bromide to give *cis*-$\Delta^{17(20)}$-22-keto compound **29**. The mixture of 22-epimeric allyl alcohols **30** obtained by reduction of **29** with lithium aluminum hydride was then converted into a mixture of 3,22-ditetrahydropyranyl esters **31**. Hydrogenolysis of the 22-tetrahydropyranyloxy group of **31** by treatment with lithium in ethylamine gave a mixture of **32** and its $\Delta^{20(22)}$ isomer. The proportion of $\Delta^{20(22)}$ isomer was considerably less in this case (as judged by the nmr band at 31 cps) and pure **32** could be obtained by chromatography followed by crystallization. Treatment of **32** with dilute acid gave **33**. The *cis* geometry of its 17–20 double bond was also established by hydrogenation to 20-isocholestanol (**20**).

## Experimental Section

Melting points are uncorrected. Nmr spectra were obtained in deuteriochloroform solution (unless otherwise stated) with tetramethylsilane as the internal standard on a 60-Mc Varian Associates DA-60 spectrometer. The significant peaks in the nmr spectra of the compounds are described in Table I. Mass spectra were determined on a Varian Associates M-66 spectrometer. Ir spectra of all solids were determined as KBr pellets. Silica gel GF 254 (E. Merck) was used for thin layer chromatography and aluminum oxide for column chromatography.

***cis*-$\Delta^{17(20)}$-Nitriles 1 and 28.**—These compounds were prepared by dehydrating the corresponding cyanohydrins with phosphorus oxychloride and pyridine.[15] After crystallization from methanol, **28** melted at 172–175°, 1 at 174–176° (lit.[15] 174–176°).

*Anal.* Calcd for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.18; H, 9.40; N, 3.65.

**3β-Hydroxycholesta-5,*cis*-17(20)-dien-22-one (3) and 3β-Hydroxy-5α-cholest-*cis*-17(20)-en-22-one (29).**—Isoamylmagnesium bromide was prepared from 60 g of isoamyl bromide and 9.7 g magnesium turnings in 250 ml of dry ether. Most of the ether was removed and replaced by 250 ml of benzene. A solution of 20 g of the nitrile (**1** or **28**) in 100 ml of benzene was added dropwise with stirring to the isoamylmagnesium bromide solution during 0.5 hr at room temperature. Stirring was continued for 1 hr and the reaction mixture was then refluxed for 6 hr. The benzene solution was decomposed by pouring over ice and hydrochloric acid. The precipitated imine hydrochloride was separated by filtration and washed successively with benzene and ether. It was then dissolved in 500 ml of methanol and 50 ml of glacial acetic acid. Water was added to the solution until it became turbid. The solution was heated on a steam bath for 0.5 hr and kept at room temperature overnight. The crystallized ketone was separated by filtration. **The ketone 3** was recrystallized from aqueous methanol: mp 95–97°; $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 7800); ir bands at 6.0 and 6.3 μ; mass spectrum *m/e* 398 ($M^+$, base peak), 383 (M − $CH_3$, 33%), 327 (M − $C_5H_{11}$, 28%), 299 (M − CO · $C_5H_{11}$, 8%).

**The 3-acetate of 3**, prepared by treatment of **3** with pyridine and acetic anhydride, was crystallized from hexane: mp 84–86°; ir bands at 5.8, 6.0, and 6.3 μ; $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 8000).

*Anal.* Calcd for $C_{29}H_{44}O_3$: C, 79.04; H, 10.04. Found: C, 78.84; H, 10.43.

**The ketone 29** was crystallized from aqueous methanol: mp 69–72°; $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 7900); ir bands at 6.0 and 6.3 μ; mass spectrum *m/e* 400 ($M^+$, base peak), 385 (M − $CH_3$, 25%), 329 (M − $C_5H_{11}$, 20%), 301 (M − CO · $C_5H_{11}$, 5%).

**The 3-acetate of 29** was crystallized from aqueous methanol: mp 86–88°; ir bands at 5.8, 6.0, and 6.3 μ; $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 8000).

*Anal.* Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.84; H, 10.43.

***cis*-$\Delta^{17(20)}$-22-Hydroxycholesterol (21) and 3β,22-Dihydroxy-5α-cholest-*cis*-17(20)-ene. (30).**—To a solution of 6 g of the 22-keto compound (**3** or **29**) in 100 ml of dry tetrahydrofuran and 50 ml of dry benzene was added 4 g of lithium aluminum hydride and the mixture heated under reflux for 2 hr. It was decomposed by addition of water and a solution of sodium hydroxide. The organic solution was separated from the inorganic material by filtration and evaporated to dryness to give 6 g of the hydroxy compound. The ir spectrum showed the absence of any carbonyl band and the thin layer chromatogram in 35% ethyl acetate in benzene showed two spots. A small amount of the crude mixture of the 22-hydroxy epimers was dissolved in boiling benzene. The high melting isomer cyrstallized out on cooling. The mother liquor was concentrated to one-third of its volume when the other isomer crystallized out. **The 22 epimers of 21** had mp 212–216 and 133–136°; mass spectrum (same for both epimers) *m/e* 400 ($M^+$, 30%), 382 (M − $H_2O$, 95%), 367 (382 − $CH_3$, 38%), 349 (367 − $H_2O$, 9%), 329 (M − $C_5H_{11}$, 70%), 311 (329 − $H_2O$, base peak).

*Anal.* (epimeric mixture). Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.10; H, 11.12.

The two 22 epimers of **30** had mp 224–229 and 156–160°; mass spectrum (same for both epimers) *m/e* 402 ($M^+$, 35%), 384 (M − $H_2O$, 95%), 369 (384 − $CH_3$, 60%), 331 (M − $C_5H_{11}$, base peak), 313 (331 − $H_2O$, 95%).

*Anal.* (epimeric mixture). Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.38; H, 11.40.

**Dehydration of 21 to 23.**—To a solution of 150 mg of **21** in 5 ml of methanol was added 2 drops of concentrated hydrochloric acid and the solution was heated on a steam bath for 10 min. The crystallized material obtained on cooling was removed by filtration and recrystallized from aqueous methanol: mp 163–165°; $\lambda_{max}^{isooctane}$ 243 mμ (ε 16,500); mass spectrum *m/e* 382 ($M^+$, base peak), 367 (M − $CH_3$, 50%), 349 (367 − $H_2O$, 12%), etc.

*Anal.* Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 85.05; H, 10.86.

**Maleic Anhydride Adduct of 23.**—To a solution of 148 mg of **23** in 2 ml of benzene was added a solution of 33 mg of maleic anhydride in 1 ml of benzene and the solution was left overnight at room temperature. Benzene was removed by evaporation and the residue was crystallized from acetone: mp 234–237°; mass spectrum *m/e* 480 ($M^+$, base peak), 465 (M − $CH_3$, 60%), 462 (M − $H_2O$, 70%), 452 (M − CO, 36%), 447 (465 − $H_2O$, 462 − $CH_3$, 90%).

*Anal.* Calcd for $C_{31}H_{44}O_4$: C, 77.46; H, 9.23. Found: C, 77.28; H, 9.00.

**3,22-Ditetrahydropyranyl Ethers (22 and 31).**—To a solution of 5 g of the 3,22-dihydroxy compound (**21** or **30**) in 50 ml of dry benzene was added 5 ml of dihydropyran and 100 mg of *p*-toluenesulfonic acid. After stirring overnight at room temperature the benzene solution was washed with dilute sodium hydroxide solution, water and brine. The oily residue obtained after removal of the solvent was chromatographed over basic alumina. The eluates with 20% benzene in hexane were evaporated to dryness to give about 0.5 g of the 3-tetrahydropyranyl ether of **23**. It was crystallized from methanol: mp 95–100°; $\lambda_{max}^{isooctane}$ 243 mμ (ε 16,000); mass spectrum showed the molecular ion peak at *m/e* 466. It gave a maleic anhydride adduct, mp 227–236° (acetone).

The 3,22-ditetrahydropyranyl ethers **22** and **31** were eluted from the column with 50% hexane in benzene. Evaporation of the solvent gave an oily residue which did not show any absorption maximum and any OH band in the ir spectrum.

*Anal.* Calcd for $C_{37}H_{60}O_4$ (**22**): C, 78.12; H, 10.63. Found: C, 78.02; H, 10.80.

*Anal.* Calcd for $C_{37}H_{62}O_4$ (**31**): C, 77.84; H, 10.95. Found: C, 78.10; H, 11.18.

TABLE I

| Compound | 18 Me | 19 Me | 21 Me | 26,27 Me[a] | 6 H | 16 H | 22 H |
|---|---|---|---|---|---|---|---|
| **3** | 56 | 62 | 117[b] | 54 | 325 | | |
| **6** | 51 | 63 | 69 | 54 | 325 | 325 | |
| **10** | 49 | 63 | *c* | 54 | 322 | 330 | |
| **13** | 48 | 63 | *c* | 53 | 320–325 | 320–325 | |
| **14** | 46.5 | 61 | 78[a] | 56 | 320–325 | | |
| **15** | 50 | 63.5 | 80.5[a] | 52 | 324 | 342 | |
| **16** | 55 | 60.5 | 119 | 52 | 324 | | |
| **17** | 52 | 61 | 101[b] | 53 | 320–325 | | |
| **18** | 33 | 61 | 98 | 53 | 322 | | 310 |
| **19** | 31 | 49 | 96 | 53 | 322 | | 309 |
| **21** (212–216°) | 51 | 61 | 100[b] | 54 | 322 | | |
| **21** (133–136°) | 55 | 61 | 100[b] | 54 | 322 | | |
| **23** | 58 | 63 | 106 | 54 | 320–322 | 335 | 335 |
| **24** | 54 | 60 | 107 | *c* | 320–322 | | |
| **28** | 54 | 50 | 115[b] | | | | |
| **29** | 54 | 50 | 117[b] | 54 | | | |
| **33** | 50 | 50 | 101[c] | 53 | | | |
| Cholestanol and 20-isocholestanol | 39 | 49 | 52[a] | 52 | | | |

[a] Doublet ($J$ = 6–7 cps). [b] Triplet ($J$ = 1.8 cps). [c] Not recognizable, merged with other methyl peaks.

**3,22-Dibenzoates of 21 and 30.**—These were prepared by heating **21** and **30** with pyridine and benzoyl chloride on a steam bath for 30 min. After the usual work-up, the solid benzoates were crystallized from methanol. **The dibenzoate of 21** had mp 190–210°; ir bands at 5.85, 6.25, 6.35, 7.9, and 14.15 $\mu$.

*Anal.* Calcd for $C_{41}H_{52}O_4$: C, 80.88; H, 8.61. Found: C, 81.12; H, 8.80.

**The dibenzoate of 30** had mp 170–176°; ir bands at 5.85, 6.25, 6.3, 7.95, and 14.2 $\mu$.

*Anal.* Calcd for $C_{41}H_{54}O_4$: C, 80.61; H, 8.91. Found: C, 80.85; H, 8.97.

***cis*-$\Delta^{17(20)}$-Cholesterol (17). A. By Reduction of the Allyl Ether 22 with Lithium in Ethylamine.**—To a solution of 3.5 g of the 3,22-ditetrahydropyranyl ether **22** in 100 ml of ethylamine was added 1 g of lithium, cut into small pieces. The mixture was stirred at 0° until it turned blue (20–30 min). The reaction mixture was then poured into an ice-cold solution of ammonium chloride and extracted with ethyl acetate. Evaporation of the solvent gave 2.9 g of an oil which showed only one spot ($R_f$ 0.7) on thin layer chromatography in 5% ethyl acetate in benzene. The nmr spectrum of the oil showed a small peak at 33 cps in addition to the expected peaks. After chromatography over alumina, an oil was obtained which was then dissolved in methanol and a few drops of aqueous hydrochloric acid were added. The solution was heated on a steam bath for 15 min and then diluted with water. On cooling, crystals appeared which were separated by filtration. The nmr spectrum still showed the band at 33 cps. The material was then benzoylated with benzoyl chloride and pyridine.

**The benzoyl derivative** was crystallized twice from ethyl acetate to give long neeles (1.8 g), mp 148–150°. The nmr spectrum did not show the 33-cps peak; mass spectrum $m/e$ 366 (M − $C_6H_5$ − COOH 70%), 351 (366 − $CH_3$, 40%), and 281 (base peak).

*Anal.* Calcd for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.62; H, 9.63.

The above benzoate (1.5 g) was treated with lithium aluminum hydride (1 g) in tetrahydrofuran and heated under reflux for two hr and the $\Delta^{17(20)}$-cholesterol was purified by crystallization from methanol (800 mg): mp 105–107°; mass spectrum $m/e$ 384 ($M^+$, 70%), 369 (M − $CH_3$, 33%), 351 (369 − $H_2O$, 15%), and 299 (base peak), etc.

*Anal.* Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.56; H, 11.70.

**B. By Reduction of the 3,22-Dibenzoate of the Allyl Alcohol 21.**—This reduction was carried out in exactly the same way as described for that of the allyl ether **22**. The product obtained after the usual work-up was hydrolyzed by heating with methanolic potassium hydroxide for 2 hr. The hydrolyzed material was then purified as its benzoyl derivative and converted into $\Delta^{17(20)}$-cholesterol as described above.

**3$\beta$-Hydroxy-5$\alpha$-cholest-*cis*-17(20)-ene (33).**—3,22-Ditetrahydropyranyl ether **31** (3 g) was reduced by adding 1 g of lithium to a solution of **31** in 100 ml of ethylamine. After work-up in the usual way, the crude product was chromatographed on a column of basic alumina. The material (2 g) obtained from hexane–benzene (1:1) eluate was crystallized from ethanol–hexane, mp 95–101°; nmr spectrum showed a very small band at 31 cps. Pure **32** was obtained by recrystallization from ethanol–hexane, mp 98–101°; the 31-cps band was practically absent from nmr spectrum. A solution of **32** (1.5 g) in 50 ml of methanol was heated on a steam bath for 15 min after the addition of a few drops of aqueous hydrochloric acid. The solid material precipitated on cooling and was filtered and crystallized from aqueous ethanol to give 1 g of pure **33**: mp 58–61°; mass spectrum $m/e$ 386 ($M^+$, 95%), 371 (M − $CH_3$, 65%), 353 (371 − $H_2O$, 12%), 301 (M − $C_6H_{13}$, base peak), and 283 (301 − $H_2O$, 7%).

*Anal.* Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.65; H, 11.90.

**The 3 benzoate of 33** was crystallized from methanol, mp 136–139°.

*Anal.* Calcd for $C_{34}H_{50}O_2$: C, 83.21; H, 10.27. Found: C, 83.40; H, 10.50.

**Hydrogenation of 17 and 33 into 3$\beta$-Hydroxy-5$\alpha$-20-isocholestane (20).**—To a solution of 200 mg of **17** or **33** in 95% ethanol was added 100 mg of 10% palladium on charcoal. The mixture was then stirred in an atmosphere of hydrogen until the absorption of hydrogen ceased. The material obtained after filtration and removal of the solvent was crystallized from aqueous ethanol, mp 157–159°. Long needles were obtained on recrystallization from acetone–methanol: mp 161–162° (lit.[19] mp 160–161°); mass spectrum $m/e$ 388 ($M^+$, base peak), 373 (M − $CH_3$, 30%), and 355 (372 − $H_2O$, 10%).

**The 3-benzoate of 20** was crystallized from ethyl acetate, mp 148–150°.

*Anal.* Calcd for $C_{34}H_{52}O_2$: C, 82.87; H, 10.64. Found: C, 82.78; H, 10.58.

**3$\beta$-Hydroxycholesta-5,20(22)-diene (18).**—A solution of 20$\alpha$-hydroxycholesterol in methanol was boiled with a few drops of hydrochloric acid for 15 min and the solution kept at 50° for 4 hr. The solution was diluted with a small quantity of water and standing crystals separated. These were recrystallized from methanol: mp 135–138°; mass spectrum $m/e$ 384 ($M^+$, base peak), 369 (M − $CH_3$, 15%), 351 (369 − $H_2O$, 20%), and 299 (33%), etc.

*Anal.* Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.20; H, 11.68.

**3$\beta$-Hydroxy-5$\alpha$-cholest-20(22)-ene (19).**—This was prepared by dehydrating 20$\alpha$-hydroxy-5$\alpha$-cholestanol as described above. After crystallization from acetone–methanol, it melted at 115–117° (lit.[18] 115–117°) and had mass spectrum $m/e$ 386 ($M^+$, base peak), 371 (M − $CH_3$, 8%).

A small amount of **20a** was ozonized in methylene chloride solution in the usual way to give a compound which was identical with 3$\beta$-hydroxy-5$\alpha$-pregnan-20-one (melting point, ir, and nmr).

***trans*-$\Delta^{17(20)}$-Nitriles.**—These were prepared by heating the

corresponding *cis*-nitriles with potassium *t*-butoxide in *t*-butyl alcohol for 6 hr. The *trans* isomer of **28** had mp 188–193° (aqueous methanol).

*Anal.* Calcd for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.55; N, 3.79. Found: C, 77.73; H, 9.57; N, 3.85.

**$\Delta^{16}$-22-Ketocholesterol (6).**—To a solution of 15 g of *cis*-$\Delta^{17(20)}$-22-ketocholesterol (**3**) in 200 ml of methanol was added a solution of 25 g of potassium hydroxide in 50 ml of water. The solution was refluxed for 1 hr and then concentrated to a small volume by evaporation of methanol. The organic material obtained by extraction with ethyl acetate and removal of the solvent showed a strong ir band at 5.8 $\mu$ and a very weak band at 6.0 $\mu$. The molecular extinction of the uv absorption maximum at 253 m$\mu$ was 1,600. The above material was dissolved in boiling hexane and after cooling, 6 g of crystalline material was obtained which was crystallized from methanol, mp 172–174°. An analytical sample was prepared by crystallizing once more from methanol: mp 177–180°; strong ir band at 5.8 $\mu$ and absence of 6.0 and 6.3-$\mu$ bands, no uv absorption maximum; mass spectrum *m/e* 398 ($M^+$, base peak), 383 (M − $CH_3$, 33%), 380 (M − $H_2O$, 10%), 299 (M − $C_5H_{11}CO$, 50%).

*Anal.* Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.20; H, 10.38.

The oily residue obtained after extraction with hexane was again treated with methanolic potassium hydroxide and gave 2 g more of the crystalline material.

**3$\beta$-Tetrahydropyranyloxycholest-5,16-dien-22-one (9).**—To a solution of 5 g of $\Delta^{16}$-22-ketocholesterol (**6**) in 50 ml of dry benzene was added 2 ml of dihydropyran and 100 mg of *p*-toluenesulfonic acid. After 16 hr, the benzene solution was washed with a 2 *N* sodium hydroxide solution. The residue obtained after removal of benzene was purified by chromatography over basic alumina. Evaporation of the benzene eluate gave **11** as a crystalline material which was recrystallized from methanol, mp 137–141°.

*Anal.* Calcd for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44. Found: C, 79.90; H, 10.61.

**3$\beta$-Tetrahydropyranyloxycholesta-5,16-dien-22-ol (10).**—A solution of the above 22-keto compound (**39**) in tetrahydrofuran (100 ml) was treated with 2 g of lithium aluminum hydride and heated under reflux for 2 hr. After the usual work-up a solid residue (2.9 g) was obtained which showed the presence of a hydroxyl band and absence of any carbonyl band in the ir spectrum. It was crystallized from methanol, mp 175–180°

*Anal.* Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.45; H, 10.92.

**3$\beta$-Tetrahydropyranyloxy-22-*p*-toluenesulfonyloxycholesta-5,-16-diene (11).**—A solution of 1 g of the above 22-hydroxy compound (**10**) in 10 ml of dry pyridine was treated with 1 g of *p*-toluenesulfonyl chloride and the solution was kept at room temperature for 2 days. Water was added and the organic material was extracted with ethyl acetate. The ethyl acetate solution was washed with cold 2 *N* hydrochloric acid, cold water, cold 2 *N* sodium hydroxide solution, and cold water. After evaporation of the solvent a syrupy residue was obtained, which, on thin layer chromatography, was resolved into three zones. One of the zones was due to the unchanged alcohol. The oil was then chromatographed on a column of neutral alumina. The hexane–benzene (1:1) eluate gave 150 mg of the least polar compound which had a uv absorption maximum at 235 m$\mu$ (16,000). The benzene eluate gave 500 mg of the *p*-toluenesulfonyloxy compound **13** which was obtained as an oil after removal of the solvent.

**Hydrogenolysis of 11.**—The above oil was dissolved in 100 ml of dry ether and 500 mg of lithium aluminum hydride was added to the solution. The mixture was stirred and heated under reflux for 24 hr. Water and 2 *N* sodium hydroxide solution were added to decompose the reaction mixture. Inorganic material was removed by filtration. The ether solution was washed with water and brine, and dried over sodium sulfate. The residue obtained after removal of ether was chromatographed on a column of alumina. The eluate with 25% benzene in hexane gave a solid material after evaporation of the solvent. This was crystallized from acetone: mp 111–113°; mass spectrum *m/e* 466 (M − 2, due to the elimination product, 0.5%), 453 (M − $CH_3$, 1%), 366 (M − 3$\beta$-tetrahydropyranyloxy and a H atom, base peak), 364 (366 − 2, 20%), 351 (366 − $CH_3$, 30%), 349 (351 − 2, 3%).

The above 3-tetrahydropyranyl ether was dissolved in tetrahydrofuran and heated for 10 min after addition of a few drops of 2 *N* hydrochloric acid. The solid obtained after diluting the solution with water was separated by filtration and crystallized from methanol: mp 163–164°; mass spectrum *m/e* 384 ($M^+$, 20%), 382 (M − 2, 8%), (M − $CH_3$, 70%), 367 (369 − 2, 5%), 351 (369 − $H_2O$, 20%), 349 (351 − 2, 1%), 300 (M − $C_6H_{13}$ + 1, 30%), 271 (base peak), and 272. The 272 peak is much stronger than that in the pure $\Delta^{16}$ compound described later.

**3$\beta$-Tetrahydropyranyloxycholest-5-en-22-one.**—This was prepared from 22-ketocholesterol in the same way as described for **9**.

**3$\beta$-Tetrahydropyranyloxycholest-5-en-22-ol.**—This was prepared in the same way as described for **10**.

**3$\beta$-Tetrahydropyranyloxy-22-*p*-toluenesulfonyloxycholest-5-ene.**—This was prepared in the same way as described for **11**.

Hydrogenolysis of the *p*-toluenesulfonyl ester was carried out with lithium aluminum hydride in the same way as described for that of **11**. The hydrogenolyzed product was dissolved in tetrahydrofuran and heated on a steam bath for 10 min with 2 *N* hydrochloric acid. After usual work-up the substance was crystallized from aqueous methanol, mp 135–145°. The mass spectrum showed all the peaks due to cholesterol as described later and additional peaks at *m/e* 384 (M − 2), 369 (384 − $CH_3$), and 351 (369 − $H_2O$).

**22-Ethylene Thioketals, 14, 15, and 16.**—A solution of 1 g of a 3$\beta$-acetoxy 22-keto steroid in 10 ml of acetic acid was treated with 0.2 ml of a solution of boron trifluoride in acetic acid and 2 ml ethanedithiol. After 20 hr, the solution was poured into a 2 *N* sodium hydroxide solution and the organic matter was extracted with ethyl acetate. The oily residue, obtained after removal of the solvent, showed a small carbonyl band in the ir spectrum. The oil was dissolved in tetrahydrofuran and 500 mg of lithium aluminum hydride was added to the solution. After refluxing for 2 hr, the reaction mixture was decomposed with water and 2 *N* sodium hydroxide solution. The residue, obtained after the usual work-up, was chromatographed on a column of basic alumina. The ethylene thioketal was eluted out with 20% ethyl acetate in benzene. A solid residue (500–600 mg) was obtained after removal of the solvent.

**22-Ethylene Thioketal of 22-Ketocholesterol (14).**—It was crystallized from hexane: mp 168–169°; mass spectrum *m/e* 476 ($M^+$, 3%), 416 (M − $C_2H_4S$, 3%), 415 (416 − 1, 4%), 405 (M − $C_5H_{11}$, 6%), 175 ($C_8H_{15}S_2$, base peak).

**22-Ethylene Thioketal of 22-Keto-$\Delta^{16}$-cholesterol (15).**—It was crystallized from hexane, mp 141–145°. An analytical sample of its **3-acetate** was prepared and crystallized from 95% ethanol, mp 133–134°; in the mass spectrum no peak was obtained in the high mass region and only a very strong peak at *m/e* 175 due to side-chain cleavage product was obtained.

*Anal.* Calcd for $C_{31}H_{48}O_2S_2$: C, 72.06; H, 9.36; S, 12.40. Found: C, 71.87; H, 9.28; S, 12.71.

**22-Ethylene Thioketal of 22-Keto-$\Delta^{17(20)}$-cholesterol 3-Acetate (16).**—It was crystallized from 95% ethanol: mp 133–135°; mass spectrum *m/e* 474 ($M^+$, 15%), 414 (M − $C_2H_4S$, 90%), 413 (414 − 1, base peak), 403 (M − $C_5H_{11}$, 75%).

*Anal.* Calcd for $C_{31}H_{48}O_2S_2$: C, 72.06; H, 9.36; S, 12.40. Found: C, 72.28; H, 9.21; S, 12.66.

**Hydrogenolysis of Ethylene Thioketals.**—To a solution of 800 mg of dithioketal **14**, **15**, or **16** in 100 ml of anhydrous ethylamine was added 1 g of lithium with stirring at 0°. Stirring was continued for 15–20 min, until the reaction mixture turned blue. It was then poured into a cold saturated solution of ammonium chloride and extracted with ethyl acetate. The residue, obtained after the usual work-up, was chromatographed over alumina. The eluates with 20% ethyl acetate in benzene gave a solid residue (500 mg) upon removal of the solvent, except in the case of **16**, which gave an oil.

**Cholesterol.**—The solid obtained from the reduction of **14** was crystallized twice from aqueous methanol: mp 147–150°; mass spectrum *m/e* 386 ($M^+$, base peak), 371 (M − $CH_3$, 40%), 368 (M − $H_2O$, 42), 353 (371 − $H_2O$, 37%), 301 (M − $C_6H_{13}$, 35%), and *m/e* 275 (53%).

**$\Delta^{16}$-Cholesterol (13).**—The product obtained after hydrogenolysis of **15** was crystallized from methanol: mp 167–170°; mass spectrum *m/e* 384 ($M^+$, 15%), 369 (M − $CH_3$, 70%), 351 (369 − $H_2O$, 15%), 300 (M − $C_6H_{13}$ + 1, 30%), and 271 (base peak).

*Anal.* Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.15; H, 4.68.

The 3-benzoate had a mp 131–132° (methanol).

***cis*-$\Delta^{17(20)}$-Cholesterol 17.**—The oily residue obtained after hydrogenolysis of **16** was dissolved in methanol. Crystals appeared on cooling. These were separated by filtration and benzoylated. Pure $\Delta^{17(20)}$-cholesterol benzoate was isolated as described before.

**Reduction of $\Delta^{16}$-22-Ketocholesterol. A. 3β-Hydroxy-5α-cholestan-22-one.**—A solution of 200 mg of $\Delta^{16}$-22-ketocholesterol in 10 ml of ethyl acetate was stirred in an atmosphere of hydrogen with 100 mg of 10% palladium on charcoal. Hydrogen (2 mol) was rapidly absorbed and the absorption was usually completed in 2 hr. After the usual work-up the product was crystallized from aqueous acetone, yield 175 mg, mp 125–127° (lit.[18] 125–127°); the 3-acetate had mp 112–114° (lit.[18] 114–115°).

**B. 22-Ketocholesterol.**—A solution of 200 mg of $\Delta^{16}$-22-ketocholesterol in 10 ml of dioxane (or ethyl acetate) was stirred in a hydrogen atmosphere with 100 mg of 10% palladium on calcuim carbonate. The absorption of hydrogen stopped after 1.1 mol and the product was isolated in the usual way and crystallized from methanol, yield 160 mg, mp 140–142° (lit.[7] 140–142°); the 3-acetate had mp 155–158° (lit.[7] 154–155°).

**Reduction of $\Delta^{17}$-22-Ketocholesterol. A. 22-Ketocholesterol.**—A solution of 500 mg of $\Delta^{17}$-22-ketocholesterol in 2 ml of dry tetrahydrofuran was added to 50 ml of anhydrous liquid ammonia and this was followed by the addition of 100 mg of lithium. The mixture was stirred for 4 hr and then decomposed by the addition of solid ammonium chloride. After the evaporation of ammonia, water was added and the product was isolated by extraction with ethyl acetate. The solid, obtained after removal of ethyl acetate, was chromatographed on a column of alumina with 10% ethyl acetate in benzene. 22-Ketocholesterol was eluted first, followed by the 22-hydroxy compound. Further purification by crystallization from methanol yielded 300 mg of 22-ketocholesterol identical with an authentic sample (melting point, ir, and nmr).

**B. (22*R*)-22-Hydroxycholesterol.**—The reduction was carried out as described, except that 2 ml of ethanol was added after 3 hr and stirring continued for another 0.5 hr. The product was chromatographed on alumina and the first fraction, which was the major fraction (300 mg, 70%), was purified by crystallization: mp 186–188° (lit.[9] 814–185°); the ir spectrum had a band at 1021 $cm^{-1}$, characteristic of the 22*R*-hydroxy compound;[17] mass spectrum *m/e* 402 ($M^+$, base peak), 387 ($M - CH_3$, 10%), 384 ($M - H_2O$, 45%), 369 ($384 - CH_3$, 25%), 351 ($369 - H_2O$, 20%), 302 ($M - C_6H_{12}OH + 1$).

The second fraction (100 mg) was a mixture and the last fraction (50 mg) was crystallized from methanol, mp 180–182° (lit.[9] 181–182°). The ir spectrum had a band at 984 $cm^{-1}$ characteristic of the 22*S*-hydroxy compound.[17]

**Registry No.**—Cholesterol, 57-88-5; **3**, 21903-10-6; 3-acetate of **3**, 21903-11-7; **6**, 21927-89-9; **9**, 21903-12-8; **10**, 21903-13-9; **12**, 21903-14-0; **13**, 21903-15-1; **14**, 21903-16-2; **15**, 21903-17-3; 3-acetate of **15**, 21897-75-6; 3-acetate of **16**, 21903-18-4; **17**, 21903-19-5; benzoate of **17**, 21903-20-8; **18**, 21903-21-9; dibenzoate of **21**, 21903-22-0; 22*R* epimer of **21**, 21903-23-1; 22*S* epimer of **21**, 21903-24-2; **23**, 21903-25-3; maleic anhydride adduct of **23**, 21897-66-5; **28**, 21897-67-6; **29**, 21897-68-7; 3-acetate of **29**, 21897-69-8; 22*R* epimer of **30**, 21897-70-1; 22*S* epimer of **30**, 21897-71-2; dibenzoate of **30**, 21897-72-3; **33**, 21897-73-4; 3-benzoate of **33**, 21897-74-5.

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# Photosensitized Hydration of Cholesterol

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Irradiation of cholestrol (I) in the ternary solvent system composed of *t*-butyl alcohol, water, and *o*-xylene (photosensitizer) for 40 hr gave two main products, *i.e.*, 5β-cholestane-3β,5-diol (II, 54%), representing a stereospecific addition of water to the double bond of I, and 3ξ,5-oxidomethylene-5ξ-A-norcholestane (III, 21%). Irradiation of a solution of I in dioxane, deuterium oxide, and *o*-xylene for 74 hr gave 6ξ-$d_1$-5β-cholestane-3β,5-diol (IV, 58%) and 2′ξ,6ξ-$d_2$-3ξ,5-oxidomethylene-5ξ-A-norcholestane (V, 16%) as the principal deuterated species. Photohydration of 4-cholesten-3β-ol (VI) in a similar manner gave the same diol II and oxetane III obtained from the cholesterol irradiation. The mechanism of the formation of these compounds is discussed and correlated with the photohydrations of cyclohexenes reported previously.

Cycloalkenes, such as (+)-3-carene and 1-methene, undergo the photosensitized addition of water and alcohols to the double bond to form alcohols and ethers.[1-3] Under the influence of light these cycloalkenes, which have a methyl group attached to the double bond, are also partially converted into their exocyclic methylene isomers. We have observed the formation of two cholestane-3,5-diols as by-products from the irradiation of 4-chloesten-3-one in the presence of sodium borohydride,[4] with the C-5 hydroxyl possibly due to traces of water or oxygen present in the alcoholic medium. In this paper we show that water can add to the double bond of cholesterol under photosensitizing conditions, a reaction which has synthetic and biosynthetic implications.

## Methods and Results

The conditions for the photosensitized hydration of cholesterol were varied as described in the Experimental Section. Cholesterol (I) was completely converted into photoproducts when a solution in the ternary solvent system composed of *t*-butyl alcohol, water, and *o*-xylene (sensitizer) was irradiated with a 450-W Hanovia medium-pressure lamp (679A-36) equipped with a Vycor filter. The reactiom mixture obtained after 40 hr of irradiation contained mainly photoproducts II and III which were isolated by column and thin layer chromatography.[5] See Scheme I. The infrared spectrum of 5β-cholestane-3β,5-diol (II)[6,7] showed bands at 3608 and 3495 $cm^{-1}$ (free and hydrogen-bonded hydroxyl absorptions, respectively) and the mass spectrum displayed a mass peak at $M^+$ 404 and *m/e* 386 ($M^+ - 18$, $H_2O$), 368 ($M^+ - 36$, $2H_2O$), 249 (fragmentation of ring D), and 110 (ring-B fission of the C-5,6 and C-9,10 bonds − 18, $H_2O$). The

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