ethers toward the Grignard reagents was similar for each experiment. *n*-Hexylmagnesium bromide (0.12 mole) was placed into a flamed flask. The apparatus was flushed with dry nitrogen and protected against atmospheric moisture by calcium chloride drying tubes. Stirring was started and 0.06 mole (7.7 g.) of freshly distilled *n*-butyl ethylvinyl ether diluted with an equal volume of dry diethyl ether was added dropwise. The reaction mixture then was heated 44 hours at reflux temperature of the mixture, cooled, and hydrolyzed with saturated ammonium chloride. The ether layer was separated and the aqueous layer extracted continuously. The extracts were combined, dried, and the solvent removed by distillation over a steam-bath. Distillation of the residue through a Todd assembly gave 1-butanol (46%), b.p. 117–120° (749 mm.), and 3-decene (66%), b.p. 167–170° (749 mm.).

Physical constants and yields of the reaction products are described in Table II.

Acknowledgment.—The authors acknowledge with appreciation assistance in interpretation of the infrared spectra given by Professor James R. Lawson, Chairman, Physics Department, Fisk University. The assistance of Professor David C. Gandy in the microanalysis work is recognized and appreciated.

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Allylic Rearrangements. XLI. The Reaction of Thionyl Chloride with Steroid Allylic Alcohols[1]

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RECEIVED APRIL 5, 1958

The reactions of thionyl chloride with 4β-hydroxycholest-5-ene and 6β-hydroxycholest-4-ene have been studied and the structures and rates of solvolysis of the resulting allylic chlorides have been determined. Both reactions provide examples of an SNi′ mechanism across a bridgehead position.

Introduction

An allylic alcohol, upon reaction with thionyl chloride, may conceivably yield allylic chlorides as a result of at least four different processes: SN1, SN2, SNi and SNi′. It is generally accepted that the initial step in all these mechanisms is the formation of the chlorosulfinate ester of the alcohol

$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl$$

Unless suitable control of the reaction conditions is achieved the simultaneous occurrence of more than one of these mechanisms may result, leading to the formation of mixtures of isomeric allylic chlorides. Recently it has been shown[3] that competition by the SN1 and SN2 reactions may be eliminated by the use of dilute ether solutions which render inactive the liberated hydrogen chloride and ensure the absence of soluble chloride ion. By employing this simple technique Goering and coworkers[4] were able to convert (−)-*cis*-5-methyl-2-cyclohexenyl alcohol into (−)-*cis*-5-methyl-2-cyclohexenyl chloride with little loss of optical purity. The complete absence of that product which would result from an SNi mechanism demonstrates the total inability of this process to compete with the SNi′ process under these conditions.

If the thionyl chloride reaction is conducted in the presence of soluble chloride ion, then a comparison of the relative importances of the SN2 and SNi′ reactions can be made. Thus Young and coworkers have demonstrated[5] that in the presence of tri-*n*-butylamine, which forms an ether-soluble hydrochloride, γ-methylallyl alcohol reacts exclusively by way of a bimolecular displacement reaction giving only a chloride with preserved allylic structure.

It was considered of interest to ascertain whether similar product control could be achieved in the reaction of thionyl chloride with various steroid allylic alcohols. Here the concept of axial and equatorial bonds is all important. In the SNi′ process a cyclic transition state of the chlorosulfinate ester was envisioned,[6] chlorine attacking the γ-carbon atom of the allylic system with a simultaneous shift of the double bond and the elimination of sulfur dioxide. Later[3] it was recognized that highly oriented ion pairs might give the same result. Often in the steroid series the geometry of the molecule of necessity precludes this. One such example[7] is with 3β-hydroxycholest-1-ene, reaction with thionyl chloride affording 3β-chlorocholest-1-ene as the chlorine of the quasiequatorial chlorosulfinate group is too far removed from $C_{(1)}$ to enable the formation of a cyclic transition state. On the other hand, occurrence of the SNi′ mechanism is allowed in the reaction of thionyl chloride with 3β-acetoxy-5α-hydroxy-cholest-6-ene, the chlorine of the quasiaxial chlorosulfinate group being afforded relatively unhindered approach to the axial $C_{(7)}$ configuration.[8]

Results and Discussion

The reaction of thionyl chloride with 4β-hydroxycholest-5-ene (I) and 6β-hydroxycholest-4-ene (II) appeared worthy of study, as in both these cases the occurrence of the SNi′ mechanism should not be precluded on account of configurational factors. The

(1) This work was supported in part by a grant from the National Science Foundation.

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(3) F. F. Caserio, G. E. Dennis, R. H. DeWolfe and W. G. Young, THIS JOURNAL, **77**, 4182 (1955).

(4) H. L. Goering, T. D. Nesbitt and E. F. Silversmith, *ibid.*, **77**, 4042 (1955).

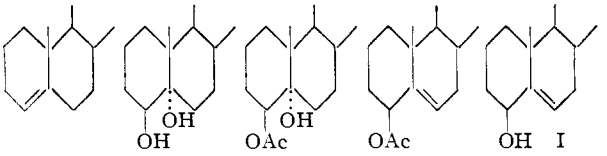
(5) W. G. Young, F. F. Caserio and D. Brandon, *Science*, **117**, 473 (1953).

(6) W. G. Young, J. D. Roberts and S. Winstein, THIS JOURNAL, **64**, 2157 (1942).

(7) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).

(8) A. F. Bide, H. B. Henbest, F. R. H. Jones and P. A. Wilkinson, *ibid.*, 1788 (1948).

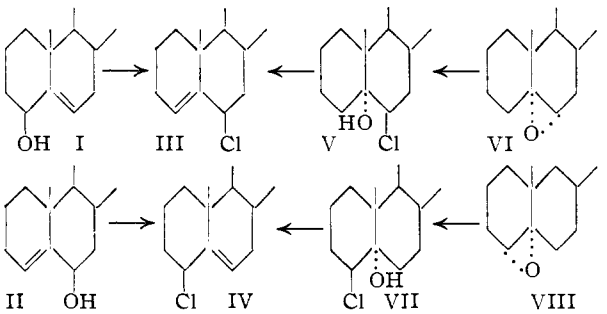
synthesis of these compounds has been described[9] and identical procedures were employed in the present work.



A new method for the preparation of pure cholest-4-ene is described wherein the ethylene thioketal of cholest-4-en-3-one is reduced in 89% yield by the action of sodium metal in liquid ammonia. Commencing with cholest-5-ene, obtained by the sodium–ammonia reduction of cholesteryl chloride, 6β-hydroxycholest-4-ene (II) was obtained by a similar reaction sequence.

The reactions of thionyl chloride in ether with the allylic alcohols I and II proceeded exclusively by way of SNi′ mechanisms, the sole products being 6β-chlorocholest-4-ene (III) and 4β-chlorocholest-5-ene (IV), respectively. The solvolysis of both of these chlorides in ethanol–dioxane (1:1) at 25° followed first-order kinetics, the absence of any drift in the rate constants (recorded in Table I) over the whole range of solvolysis demonstrating that any contamination of one with the other was unlikely.

Proof of the structure of 6β-chlorocholest-4-ene (III) was obtained by its independent synthesis. The rule of diaxial opening of epoxide rings necessitates that addition of hydrogen chloride to 5α,6α-epoxycholestane (VI) yield 6β-chlorocholestan-5α-ol (V), the stability of which toward acetylation supports its formulation as a tertiary alcohol. Mild dehydration of the chlorohydrin V with thionyl chloride in pyridine afforded the required allylic chloride III. Similar reactions involving 4α,5α-epoxycholestane (VIII) and 4β-chlorocholestan-5α-ol (VII) were conducted to verify the structure assigned to 4β-chlorocholest-5-ene (IV).



When the reactions of the allylic alcohols I and II with thionyl chloride were conducted in the presence of tri-*n*-butylamine there was no occurrence of SN2 processes as the compositions of the products and their rates of solvolysis were unaltered (Table I). The marked reluctance of cyclohexane derivatives to undergo bimolecular reactions is well known. Moreover it has been postulated[10] that under these conditions the function of the amine in enabling the SN2 process to operate may be in the formation of a quaternary salt with the chlorosulfinate ester, the SNi′ process not being possible with this form. However, in the present cases the shielding effect of the angular methyl groups may prevent the approach of the bulky amine at the top face of the steroid molecule thus precluding quaternary salt formation and accounting for the absence of bimolecular displacement products.

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF 0.0170 *M* 4β-CHLOROCHOLEST-5-ENE AND 6β-CHLOROCHOLEST-4-ENE IN ETHANOL–DIOXANE (1:1) AT 25.0°

Allylic chloride	Source	10^4k, sec.$^{-1}$
6β-Chlorocholest-4-ene	$SOCl_2$ with I	4.78 ± 0.17
6β-Chlorocholest-4-ene	$SOCl_2/Bu_3N$ with I	5.12 ± .21
6β-Chlorocholest-4-ene	Dehydration of V	5.15 ± .04
4β-Chlorocholest-5-ene	$SOCl_2$ with II	6.44 ± .09
4β-Chlorocholest-5-ene	$SOCl_2/Bu_3N$ with II	6.13 ± .18
4β-Chlorocholest-5-ene	Dehydration of VII	6.65 ± .06

Analysis of the allylic alcohol mixture obtained from the solvolysis of 6β-chlorocholest-4-ene (III) with aqueous acetone in the presence of sodium bicarbonate indicated the formation of 4β-hydroxycholest-5-ene (I) (45–50%) and 6β-hydroxycholest-4-ene (II) (50–55%). This mixture could not be completely separated by chromatography; however their widely differing rotations ($\alpha^{25}D$ −59° for I and $\alpha^{25}D$ +62° for II) and the fact that the two form a 1:1 molecular compound facilitated an accurate estimation of their proportions in the mixture. Neither of the corresponding α-epimers were detected; however cholest-3,5-diene was isolated as a minor product (*ca.* 25% yield). Similarly the solvolysis of 4β-chlorocholest-5-ene (IV) under these conditions afforded almost identical amounts of the diene and the two allylic alcohols suggesting that a common C_{4-6}-allyl cation is involved in both cases. These results are in accord with the suggestion of Corey and Sneen[11] that the destruction of the C_{4-6}-allyl cation in substitution reactions of this type involves axial attack, despite the fact that equatorial substitution is highly favored sterically and moreover would lead to the thermodynamically more stable 4α- and 6α-epimers. This cation is also generated in the methanolysis of *epi*-cholesteryl tosylate[7] where again the only substitution products are the axial 6β-methoxycholest-4-ene and 4β-methoxycholest-5-ene.

The reactions of thionyl chloride with 4α-hydroxycholest-5-ene and 6α-hydroxycholest-4-ene in ether were more complicated as mixtures of two allylic chlorides, which could not be separated, resulted in both cases. Elucidation of the structures of these products has not as yet been achieved.

Experimental

Melting points were recorded on a Kofler block and are corrected. Rotations were determined in chloroform solutions. The petroleum ether referred to is the fraction with b.p. 67–68°. The deactivated alumina was prepared by treatment of Alcoa activated alumina with 5% or 10% aqueous acetic acid.

Cholest-4-ene.—To a suspension of the ethylene thioketal of cholest-4-en-3-one (20 g.) in dry ether (100 ml.) and liquid ammonia (2000 ml.) was added sodium metal (20 g.).

(9) D. N. Jones, J. R. Lewis, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

(10) R. H. DeWolfe and W. G. Young, *Chem. Revs.*, **56**, 816 (1956).

(11) E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956).

Ethanol was then added until the blue coloration was dispelled and the steroid was isolated by evaporation of the ammonia and extraction of the residue with ether. After passing through a column of alumina (500 g.) and one crystallization from ethyl acetate–methanol, cholest-4-ene was obtained (14 g.), m.p. 81–82°.

Cholest-5-ene.—A solution of cholesteryl chloride (20 g.) in anhydrous ether (1 l.) was added to a vigorously stirred solution of sodium (10 g.) in liquid ammonia (1 l.). After 5 minutes ethanol was added until the blue coloration had disappeared. The steroid was isolated and one crystallization from acetone gave pure cholest-5-ene (13.1 g.), m.p. 92–93°, $\alpha^{25}D$ −53°.

Reaction of 4β-Hydroxycholest-5-ene and Thionyl Chloride.—A solution of the allylic alcohol (1.623 g.) in anhydrous ether (20 ml.) was treated at 0° with purified thionyl chloride (0.5 ml.) for 2 minutes. The solvent was removed under reduced pressure, petroleum ether (20 ml.) was added and the resulting solution was filtered slowly through a column of dry calcium carbonate and then taken down to dryness to yield crude 6β-chlorocholest-4-ene (1.58 g.). Three recrystallizations from acetone gave purer material, m.p. 87–92°, $\alpha^{25}D$ +20°. The modified Volhard titration indicated 88% chloride ion.

Reaction of 6β-Hydroxycholest-4-ene and Thionyl Chloride.—A procedure identical to that described above was used to convert 6β-hydroxycholest-4-ene (1.158 g.) into crude 4β-chlorocholest-5-ene (1.018 g.). Purified material had m.p. 97–101°, $\alpha^{25}D$ −34°. Modified Volhard titrations indicated 92% chloride ion.

4α,5α-Epoxycholestane.—Cholest-4-ene (7.0 g.) was treated at 26° with a solution of perbenzoic acid (1.3 moles) in benzene (74 ml.). The ensuing reaction, followed titrimetrically was completed within 2.5 hr. The product (7.4 g.) was isolated with benzene and recrystallized three times from aqueous acetone to yield the pure epoxide (4.4 g.), m.p. 101–103°, $\alpha^{25}D$ +77°. Lithium aluminum hydride reduction of a portion of the material afforded cholestan-5α-ol in high yield.

4β-Chlorocholestan-5α-ol.—A stream of dry hydrogen chloride gas was bubbled continuously through a solution of the epoxide (1.60 g.) in chloroform (30 ml.) for 40 minutes. The solution was then washed with sodium bicarbonate solution and water and the solvent was removed to give a white solid (1.61 g.). One recrystallization from aqueous acetone afforded pure 4β-chlorocholestan-5α-ol, m.p. 122–123°, $\alpha^{25}D$ +17°.

Anal. Calcd. for $C_{27}H_{47}OCl$: C, 76.64; H, 11.12; Cl, 8.41. Found: C, 76.38; H, 11.00; Cl, 8.62.

4β-Chlorocholest-5-ene.—A solution of 4β-chlorocholestan-5α-ol (0.281 g.) in pyridine (5 ml.) was treated at 0° with thionyl chloride (0.1 ml.). A precipitate of pyridine hydrochloride was deposited immediately. After 2 minutes the solution was poured onto ice-water, the solid was filtered off, taken into petroleum ether (10 ml.) and slowly run through a column of calcium carbonate. Removal of solvent gave a solid (0.251 g.) which after two recrystallizations from acetone afforded the allylic chloride, m.p. 98–102°, $\alpha^{25}D$ −38°. Modified Volhard titrations indicated 95% chloride ion. The melting point of this material was not depressed upon admixture with the 4β-chlorocholest-5-ene described above but was depressed upon admixture with 6β-chlorocholest-4-ene.

5α,6α-Epoxycholestane.—Cholest-5-ene (5.0 g.) in benzene (15 ml.) was treated with a solution of perbenzoic acid (1.25 moles) in benzene (61 ml.) at 26° for 1 hr. The steroid was isolated and four recrystallizations from aqueous acetone gave the pure epoxide (3.4 g.), m.p. 74–75°, $\alpha^{25}D$ −59°. Lithium aluminum hydride reduction of a portion of this material afforded cholestan-5α-ol in high yield.

6β-Chlorocholestan-5α-ol.—Dry hydrogen chloride gas was bubbled through a solution of 5α,6α-epoxycholestane (1.73 g.) in chloroform (30 ml.) for 1 hr. The product was isolated by standard procedures and was recrystallized from acetone to afford the pure chlorohydrin, m.p. 121–123°, $\alpha^{25}D$ −5°.

Anal. Calcd. for $C_{27}H_{47}OCl$: C, 76.64; H, 11.12; Cl, 8.41. Found: C, 76.48; H, 11.31; Cl, 8.40.

6β-Chlorocholest-4-ene.—Thionyl chloride (0.2 ml.) was added to a solution of 6β-chlorocholestan-5α-ol (0.421 g.) in pyridine (7 ml.). After 2 minutes the solution was poured into ice-water and the steroid isolated as previously described. Two recrystallizations from acetone gave 6β-chlorocholest-4-ene, m.p. 89–93°, $\alpha^{25}D$ +14°. Modified Volhard titrations indicated 93% chloride ion. The melting point of this material showed no depression upon admixture with a sample of 6β-chlorocholest-4-ene previously described but did depress with 4β-chlorocholest-5-ene.

Solvolysis Products of 6β-Chlorocholest-4-ene.—Water (15 ml.) and sodium bicarbonate (5 g.) were added to a solution of 6β-chlorocholest-4-ene (1.80 g., m.p. 88–92°) in acetone (135 ml.) and the mixture was then maintained at 45–55° for 1 hr. with vigorous shaking. The steroid (1.67 g.) was isolated as an oil with ether and was chromatographed on alumina (80 g.). Elution with petroleum ether–benzene (10:1) gave cholest-3,5-diene (0.480 g.), m.p. and mixed m.p. 77–79°. Elution of the total allylic alcohol components with ether gave solid material (1.04 g.), m.p. 126–131°, $\alpha^{25}D$ 0°, which after one crystallization from acetone had m.p. 130–131°, $\alpha^{25}D$ +5°. Upon admixture with the molecular compound described below the melting point was not depressed. Careful chromatography of this molecular compound enabled only partial separation of the two components. Elution with benzene–ether (10:1) gave an initial fraction with $\alpha^{25}D$ +29° and a final fraction with $\alpha^{25}D$ −26°.

The Molecular Compound of 4β-Hydroxycholest-5-ene and 6β-Hydroxycholest-4-ene.—Combined samples of the two above allylic alcohols (0.04 g. each) were crystallized together from acetone and afforded the pure molecular compound, m.p. 130–131°, $\alpha^{25}D$ +3°.

Solvolysis Products of 4β-Chlorocholest-5-ene.—4β-Chlorocholest-5-ene (1.10 g., m.p. 98–102°) was subjected to the solvolysis treatment described above. Chromatography on alumina enabled the isolation of cholest-3,5-diene (0.294 g.) and a mixture of allylic alcohols (0.61 g.) with $\alpha^{25}D$ −4°. One crystallization of this material gave the pure molecular compound described above, m.p. 130–131°, $\alpha^{25}D$ +5°.

Rate Measurements.—The data presented in the table were obtained as follows. A sample of the allylic chloride was weighed in a 200-ml. round-bottom stoppered flask. Dry dioxane (50 ml.) at 25° was added by means of a pipet and this solution was allowed to equilibrate in the thermostat to 25°. Absolute ethanol (50 ml.) at 25° was then added by pipet (zero time) and the resulting solution was quickly mixed and maintained in the thermostat. Samples (2 ml.) were withdrawn at the desired intervals by means of a pipet and the reaction was quenched in acetone (20 ml.), the time being recorded at the completion of this operation. The hydrogen chloride liberated during the solvolysis was titrated by the use of standardized methanolic sodium hydroxide solution with brom thymol blue as indicator. A minimum of thirty points were obtained for each run and the infinity titer was taken after approximately ten half-lives.

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