ing the dipole moment of a compound containing a hydrogen bond.

With 1,3-bromohydrin epoxide, m.p. 64.8°, the structure whose dipole assuming freedom of rotation of the hydroxyl is nearest the observed value is XXXVII with the bromine *cis* and the hydroxyl *trans* to the epoxy. The chemical evidence rather strongly indicates that both the bromine and hydroxyl are *cis* to the epoxy. Assuming such a structure and having the hydroxyl hydrogen bonded to the epoxy oxygen XL, the calculated moment is 3.22 *D* which again is a reasonable value when compared with the observed moment.

Experimental

The measurements were carried out at 30° using the apparatus described previously[4] and the dipole moments were calculated using the equation and method of Halverstadt and Kumler[5]

$$p_{2_0} = \frac{3\alpha\nu_1}{\epsilon_1 + 2} + (\nu_1 + \beta)\frac{\epsilon_1 - 1}{\epsilon_1 + 2}$$

$$P_{2_0} = p_{2_0}M_2$$

$$\mu = 0.0128\sqrt{(P_{2_0} - P_{E_2})T}$$

The plots of ϵ_{12} *versus* ω_2 and ν_{12} *versus* ω_2 were straight lines within the limits of the experimental error and the values of ϵ_1 and ν_1 were obtained by extrapolating the ϵ_{12} and ν_{12} values to zero weight fraction.

Preparation of Compounds.—A number of the compounds were prepared in the course of the previous investigation.[3]

trans-1,2-Dibromocyclopentane was prepared by the addition of bromine to cyclopentene. The product was distilled once, b.p. 93–95° (32.5 mm.), and was crystallized twice from petroleum ether (b.p. 30–60°) cooled in Dry Ice–acetone. Distillation gave material of b.p. 94° (32.5 mm.).

cis-1,2-Cyclopentanediol, b.p. 87° (1.5 mm.), was prepared by the oxidation of cyclopentene with potassium permanganate.[6] This was converted in good yield to the cyclic acetonide, b.p. 148°, by treatment with anhydrous copper sulfate and acetone as described for the dibromocyclopentanediols.[3]

1-*trans*-2-Dibromo-*trans*-3,4-acetonylidenecyclopentane (XVII) was prepared as follows. A solution of 0.95 g. (0.00595 mole) of bromine in 4 ml. of C.P. chloroform was addded over 5 minutes to a solution of 0.90 g. (0.00643 mole) of unsaturated acetonide[3] (XIII) in 4 ml. of chloroform at −80°. The solution was warmed to room temperature, washed with 5% sodium thiosulfate solution, and evaporated. Crystallization of the residue at −80° and filtration gave 0.95 g. of crystalline XVII. One recrystallization from petroleum ether (b.p. 29–53°) gave 0.80 g. (45.0%) of XVII, m.p. 78°. A mixed m.p. with compound m.p. 48° was depressed.

Anal. Calcd. for $C_8H_{12}O_2Br_2$: C, 32.02; H, 4.03. Found: C, 31.75; H, 4.17.

(4) W. D. Kumler and I. F. Halverstadt, THIS JOURNAL, **62**, 2182 (1941).

(5) I. F. Halverstadt and W. D. Kumler, *ibid.*, **64**, 2988 (1942).

(6) C. van Loon, *C. A.*, **17**, 1956 (1923).

SAN FRANCISCO, CALIFORNIA
LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Neighboring Carbon and Hydrogen. XXII. Homoallylic Systems. The Preparation and Behavior of Certain 3,5-Cyclosteroids

BY EDWARD M. KOSOWER[1] AND S. WINSTEIN

RECEIVED MARCH 19, 1956

Homoallylic systems offer an interesting departure from the more familiar allylic ones. In this connection, 5-cholesten-3β-yl and the related 3,5-cyclocholestan-6β- and 6α-yl derivatives are interesting. In the present work, the preparation of "*i*-cholesterol" has been improved, and the configurations of the 3,5-cyclocholestan-6-ols have been discussed. Both 3,5-cyclocholestan-6-yl trichloroacetates have been prepared, and their rearrangement and solvolysis have been studied. While cholesteryl trichloroacetate methanolyzes with acyl–oxygen cleavage, both 3,5-cyclocholestan-6-yl trichloroacetates do so with alkyl–oxygen cleavage. In methanol–chloroform, cholesteryl toluenesulfonate and the 3,5-cyclocholestan-6-yl trichloroacetates yield a mixture of methyl ethers, 90 ± 2% 3,5-cyclocholestan-6β-yl and 10 ± 2% cholesteryl. These results are ascribed to the occurrence of a common homoallylic hybrid carbonium ion intermediate in the solvolysis of all three compounds. The results cannot be discussed on the basis of only dissociated forms of the carbonium ions. In 90% dioxane, substantial ion pair return accompanies hydrolysis of both 3,5-cyclocholestan-6-yl trichloroacetates. Thus, cholesteryl trichloroacetate is produced during hydrolysis. Even in methanol–chloroform, a few per cent. of cholesterol, by way of cholesteryl trichloroacetate, is obtained from either 3,5-cyclocholestan-6-yl ester.

Homoallylic[2] systems offer an interesting departure from the more familiar allylic ones because of the striking difference in geometric requirements involved in the formation of intermediates and products. In this connection, 5-cholesten-3β-yl and the related 3,5-cyclocholestan-6β-yl and 3,5-cyclocholestan-6α-yl derivatives are interesting.

Since the discovery of 3,5-cyclocholestan-6β-yl methyl ether (formerly "*i*-cholesteryl" methyl ether) by Stoll[3] in 1932, various reactions[4–8] have been carried out, with 3,5-cyclosteroids. Winstein and Adams[9] have shown that the 5,6-double bond of cholesteryl *p*-toluenesulfonate participates in the rate-controlling ionization during solvolysis, and they proposed a hybrid ion intermediate. This suggestion was supported by the discovery[10] that 3,5-cyclocholestan-6β-yl methyl ether could be converted partially to the corresponding ethyl ether by treatment with dilute acid in ethanol. With a view to establishing the hybrid ion intermediate I in a more definitive manner, the preparation of suitable 3,5-cyclocholestanyl derivatives and a

(1) Research Fellow of the National Institutes of Health, 1949–1952.

(2) M. Simonetta and S. Winstein, THIS JOURNAL, **76**, 18 (1954).

(3) W. Stoll, *Z. physiol. Chem.*, **207**, 47 (1932).

(4) T. Wagner-Jauregg and L. Werner, *ibid.*, **213**, 119 (1932).

(5) (a) J. H. Beynon, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 907 (1936); (b) 406 (1937); (c) 1459 (1937)

(6) I. M. Heilbron, J. Hodges and F. S. Spring, *ibid.*, 759 (1938).

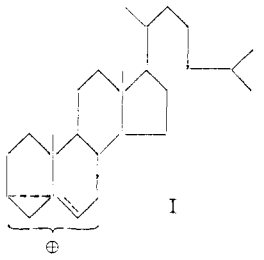
(7) E. S. Wallis, E. Fernholz and F. T. Gephart, THIS JOURNAL, **59**, 137 (1937).

(8) E. G. Ford and E. S. Wallis, *ibid.*, **59**, 1415 (1937).

(9) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).

(10) S. Winstein and A. H. Schlesinger, *ibid.*, **70**, 3528 (1948).

study of their reactions was undertaken. The results of one phase of this work are reported and discussed in the present article.



I

The 3,5-Cyclocholestan-6β- and 6α-ols.—Originally, "*i*-cholesterol" was prepared[7] through its acetate by the solvolysis of cholesteryl *p*-toluenesulfonate in acetic anhydride containing finely divided potassium acetate. Later, following the observation of Stoll[3] that the *p*-toluenesulfonate hydrolyzed rapidly in aqueous acetone, Heilbron[5c] was able to produce "*i*-cholesterol" directly by buffering the aqueous acetone. A fairly long isolation scheme through the acetate ester made the procedure tedious. Final purification in both cases[5c,7] involved recrystallization from 95% ethanol at −10°.

In the present work, two important improvements in Heilbron's procedure were made. The mixture of products resulting from the buffered hydrolysis was separated by chromatography. The "*i*-cholesterol" was eluted in pure form by hexane–benzene (2:1), thus providing a sharp separation from olefinic material and cholesterol. The alcohol thus isolated was recrystallized from acetone, yielding *ca.* 50% of pure needles.

The physical constants of alcohol prepared in these ways are compared in Table I. The difference between the melting points of Heilbron and Wallis is due to the existence of two crystal forms, of which the lower melting one usually was obtained immediately after crystallization. As the figures in Table I demonstrate, the specific rotation for "*i*-cholesteryl" acetate found here was the same as that previously measured; the more serious discrepancy in the specific rotations for the alcohol is inexplicable, beyond the possibility that the previous recrystallization solvent, ethanol, is removed only with some difficulty.

TABLE I

PROPERTIES OF 3,5-CYCLOCHOLESTANOLS AND THEIR ACETATES

Compound	M.p., °C.	$[\alpha]_D$	c, $CHCl_3$	Reference
6β-OH	74–75	+23.9	1.13	Wallis[7]
	68–69	+27	1.5	Heilbron[5c]
	67–68	+50	1.47	Present work
	73–74	+50	1.47	Present work
6β-OAc	72.5–73	+48[a]	1.13	Present work
	73	+48	1.26	Wallis[7]
	73	+48	1.6	Heilbron[5c]
6α-OH	80.3–81.3	+76	1.97	Present work
	80.5–81.5	+81	1.83	Wallis[11,12]
		+34		Shoppee[13]
	85–86	+83	0.714	Shoppee[14]
6α-OAc	50–52	+98[b]	2.91	Present work
	47–48	+101	1.27	Wallis[12]
	60°	+82	1.5	Heilbron[5a]

[a] $[\alpha]^{21}D$ +51° (*c* 2.69, AcOH). [b] $[\alpha]^{21}D$ +103° (*c* 2.93, AcOH). [c] Properties of the acetate derived from oily material prepared through aluminum isopropoxide reduction of 3,5-cyclocholestanone-6. The rotation indicates that it may have been a mixture of 6β- (*ca.* 30%) and 6α- (*ca.* 70%) acetates.

The epimeric 6α-alcohol was prepared according to the directions of Wallis,[11,12] who found that reduction of 3,5-cyclocholestanone-6 in ether with lithium aluminum hydride was almost completely stereospecific. Acetonitrile (rather than alcohol) was used as the solvent for recrystallization. The melting point and rotation (Table I) of the alcohol thus prepared are very similar to the values reported by Wallis.[11] However, the rotation agrees with only one of the two widely differing values reported by Shoppee.[13,14]

Configurations of the 3,5-Cyclocholestan-6-ols.—At present, no completely unequivocal assignment of configuration to the 3,5-cyclocholestan-6-ols has been made. Dodson and Riegel[15] predicted that "*i*-cholesterol" would possess a 6β-hydroxyl group, on the basis that the electronic structure of the probable intermediate I would favor approach of a nucleophilic reagent (*i.e.*, solvent) from the β-side. Shoppee[14] reported a proof of configurations in agreement with the predictions of Dodson and Riegel,[15] based on the reduction of the epimeric 3,5-cyclocholestan-6-ols to the corresponding cholestan-6-ols. However, these experiments are not convincing because very low yields of product were obtained.[16]

By two approaches, Wallis[12] has reached conclusions opposite to those of Dodson and Riegel. One of the approaches was based on considerations of the dielectric properties of the epimeric 3,5-cycloandrostan-6,17β-diols and diacetates. However, this is invalidated by the difficulty connected with the prediction of the net dipole moment of a steroid with two complex groups[17] (OH, OAc, etc.) although such predictions are more successful when the dipoles are rigidly oriented with respect to one another.[18]

Wallis' other approach was based on the reaction of the epimeric 3,5-cyclocholestan-6-ols with bromine. Heilbron[5c] found that "*i*-cholesterol" reacted with bromine in the same manner as the "*i*-cholesteryl" ethers[5a] to yield a tribromocholestane, identical with that isolated from bromine and cholesteryl bromide,[19] in all probability, 3β,5α,6β-tri-

(11) A. F. Wagner and E. S. Wallis, THIS JOURNAL, **72**, 1047 (1950).

(12) A. F. Wagner, N. E. Wolff and E. S. Wallis, *J. Org. Chem.*, **17**, 529 (1952).

(13) C. W. Shoppee, *Bull. soc. chim.*, [5] **18**, C122 (1951).

(14) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(15) R. M. Dodson and B. M. Riegel, *J. Org. Chem.*, **13**, 424 (1950).

(16) *E.g.*, 220 mg. of 3,5-cyclocholestan-6β-ol yielded after hydrogenation and chromatography, 28 mg. of oil which was acetylated, inoculated with the expected product, cholestan-6β-yl acetate, sublimed and recrystallized to give an unspecified weight of authentic 6β-acetate. Furthermore, Shoppee did not state the source and properties of the 3,5-cyclocholestanols which he used. The reported chromatographic behavior of his alcohols is so much at variance with that observed by us that even the identity of the starting material for the hydrogenation experiments seems to us to be in doubt.

(17) (a) W. D. Kumler and G. M. Fohlen, THIS JOURNAL, **67**, 438 (1945); (b) W. D. Kumler, *ibid.*, **67**, 1901 (1945).

(18) H. R. Nace and R. B. Turner, *ibid.*, **75**, 4063 (1953).

(19) R. Kolm, *Monatsh.*, **33**, 447 (1912).

bromocholestane.[20] Wallis carried out the reaction of "*epi-i*-cholesterol" with bromine and isolated an 18% yield of a new tribromide for which he gave the structure 3β,5α,6α-tribromocholestane, on the grounds of rather scanty evidence.

Using an assumed mechanism for tribromide formation involving replacement of the 6-hydroxyl by bromine with inversion, followed by *trans*-opening of the cyclopropane ring, Wallis assigned the 6α-configuration to "*i*-cholesterol" and the 6β to "*epi-i*-cholesterol." It is obvious that the assignment is completely dependent upon the assumed inversion. In our experience, there is no known replacement reaction at C-6 in "*i*-cholesterol" or its derivatives which proceeds with inversion. Simple nucleophilic displacement with inversion at C-6 in the presence of an electrophilic reagent like bromine[21] is so unlikely as to be excluded without very strong evidence in its support. Thus, the argument based upon the tribromide structure seems invalid, even were the tribromide of the structure indicated.

We have employed several additional criteria for the assignment of configuration to the 3,5-cyclocholestan-6-ols. One of them is relative ease of ionization of *i*- and *epi-i* derivatives. Stereoelectronic considerations of the same type as those which rationalize the greater reactivities of the *exo*- compared to the *endo*-5-norbornenyl[22] and norbornyl[23] bromobenzenesulfonates suggest that the cyclopropane ring-assisted ionization of the β-isomer should be more rapid than that of the α-isomer in the case of 3,5-cyclocholestan-6-yl derivatives. In a later paper we report and discuss the relative reactivities of "*i*-" and "*epi-i*-" derivatives; for all cases which have been examined experimentally, "*i*-" compounds are always more reactive than "*epi-i*-" compounds.

Another criterion of configuration is optical rotation. In general, 6α-cholestane derivatives have more positive rotations[24] than the corresponding 6β-compounds.[25] The data in Table I illustrate, as do comparisons of other ester pairs, that the rotations of "*epi-i*-" compounds are always more positive.

Still another criterion of configuration is chromatographic behavior. The hindered nature of an *axial* substituent on a cyclohexane ring as compared with an *equatorial* one[26] allows an *axial* steroid alcohol to be more weakly adsorbed on alumina than its *equatorial* epimer.[27] The expected elution order is observed with the cholestan-3α (*axial*) and cholestan-3β (*equatorial*) alcohol pair[28] and with the cholest-5-en-3α- and 3β-ols.[29] It appears from models that the 3,5-bond in the 3,5-cyclosterols does not greatly change the conformation of the B ring. A 6β-substituent would then be axial, and a 6α-group *equatorial*. Experimentally, one finds a rather large difference between the epimeric 3,5-cyclocholestanols. The "*i*-cholesterol" is eluted rather easily (hexane:benzene, 2:1) and "*epi-i*-cholesterol" only with some difficulty (ether:ethanol, 9:1).

On the basis of the above three criteria, which uniformly lead to the same assignment, and concurrence with the idea of stereospecific β-attack by a nucleophile upon the intermediate ion, I, we conclude, in agreement with the expectation of Dodson and Riegel[15] that "*i*-cholesterol" is 3,5-cyclocholestan-6β-ol and "*epi-i*-cholesterol" is the corresponding 6α-epimer. We employ these assignments in this and following papers.

3,5-Cyclocholestanyl Esters.—It was possible successfully to acylate these alcohols by avoiding acidic conditions, proper cooling during the reaction and rapid recrystallization from dry, nonsolvolyzing solvents. The *p*-nitrobenzoates of both alcohols were prepared as derivatives; the properties of the esters are listed in Table II, along with those of the cholesteryl ester for comparison.

In seeking derivatives of the 3,5-cyclocholestan-6-ols which would be certain to solvolyze with alkyl–oxygen ionization, several unsuccessful attempts to prepare 3,5-cyclocholestan-6β-yl *p*-toluenesulfonate[30] were carried out. It was possible to obtain the trichloroacetates of both 3,5-cyclo-6-alcohols by adding a cold solution of trichloroacetylpyridinium chloride in pyridine to a cold solution of the alcohol in the same solvent. A similar procedure has been used for another reactive alcohol, *t*-butyl alcohol.[31] After isolation in the usual way, it is essential that recrystallization of the isolated material be carried out as rapidly as possible from dry acetone. The trichloroacetates are crystalline substances which gave good analyses (Table II), but the melting points tended to decrease on standing.

It was noted that 3,5-cyclocholestan-6α-yl trichloroacetate (VII) resolidified *ca.* 11° above the melting point, only remelting at 145–148°. This proved to be the result of rearrangement into cholesteryl trichloroacetate. The 6β-ester VIII rearranged analogously. Good yields of cholesteryl trichloroacetate (V) could be isolated from both the epimeric 6-esters by heating them alone on the steam-bath for several hours or refluxing a pentane solution of them for an extended time.

(20) (a) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950); (b) D. H. R. Barton, *Experientia, Supplementum II*, 121 (1955).

(21) (a) J. F. J. Dippy, H. B. Watson and E. D. Yates, *J. Chem. Soc.*, 2508 (1931); (b) L. Farkas, B. Perlmutter and O. Schächter, THIS JOURNAL, **71**, 2829 (1949); (c) L. J. Andrews and R. M. Keefer, *ibid.*, **75**, 3557 (1953); (d) R. M. Keefer and L. J. Andrews, *ibid.*, **75**, 3561 (1953).

(22) S. Winstein, H. M. Walborsky and K. Schreiber, *ibid.*, **72**, 5795 (1950).

(23) (a) S. Winstein and D. Trifan, *ibid.*, **71**, 2953 (1949); (b) S. Winstein and D. Trifan, *ibid.*, **74**, 1147, 1154 (1952).

(24) This statement is only true for the *5-allo* (cholestane) series where the A/B ring junction is *trans;* the opposite situation holds for the 5-*n* (coprostane) series (A/B *cis*).

(25) (a) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948); (b) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 370 (1950).

(26) S. Winstein, N. J. Holness, *ibid.*, **77**, 5562 (1955).

(27) (a) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (b) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953).

(28) C. W. Shoppee, *J. Chem. Soc.*, 1138 (1946).

(29) W. G. Dauben and J. F. Eastham, THIS JOURNAL, **73**, 3260 (1951).

(30) Wallis and Wagner were able to isolate only cholesteryl pyridinium *p*-toluenesulfonate from the reaction of either 6α- or 6β-alcohol with *p*-toluenesulfonyl chloride in pyridine [A. F. Wagner, Ph.D. Thesis, Princeton University, May, 1951].

(31) W. E. Scovill, R. E. Burk and H. P. Lankelma, THIS JOURNAL, **66**, 1039 (1944).

TABLE II

PROPERTIES OF ESTERS

Compound	M.p., °C.	$[\alpha]D^a$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
p-Nitrobenzoates:						
3,5-Cyclocholestan-6β-yl	140.4–141.0	+56	76.22	75.93	9.22	9.19
3,5-Cyclocholestan-6α-yl	155.6–156.8	+69	76.22	76.31	9.22	9.09
Cholest-5-en-3β-yl	189.0–190.0 clear 265	− 2				
	190–193[b] clear 261	− 6[b]				
Trichloroacetates:						
3,5-Cyclocholestan-6β-yl	69.5–70.1	+33	65.47	65.33	8.52	8.47
3,5-Cyclocholestan-6α-yl	98.7–99.7	+77	65.47	65.26	8.52	8.76
Cholest-5-en-3β-yl	153.1–154.5	−26	65.47	65.39	8.52	8.50

[a] Solvent, chloroform. [b] Reported by H. Sandquist and J. Gorton, *Ber.*, **63**, 1759 (1930).

The rearrangement of the 3,5-cyclocholestan-6-yl trichloroacetates to the cholesteryl isomer could be followed in benzene solution polarimetrically, the observed rotation changing to that for cholesteryl trichloroacetate. However, apparent first-order rate constants drifted upward very badly, as illustrated in Table III for the 6α-ester and summarized in Table IV. At least one reason for this drift was the formation of catalytic quantities of trichloroacetic acid by elimination. The actual inclusion of 0.012 *M* trichloroacetic acid in the rearrangement of the 6β-ester in benzene increased the apparent first-order rearrangement rate constant by a factor of *ca.* 10^2 to 10^3. This result is reminiscent of the situation for allylic compounds.[32]

TABLE III

ISOMERIZATION OF 3,5-CYCLOCHOLESTAN-6α-YL TRICHLOROACETATE IN BENZENE[a] AT 75.0°

Time (min.)	Obsd. α, °	$10^3 k$ (min.$^{-1}$)
	+1.086	
84	+0.498	6.13
105	+0.301	7.33
123	+0.161	8.14
143	+0.023	9.08
198	−0.215	11.14
219	−0.260	11.58
275	−0.289	10.27
401	−0.352	10.23
500	−0.372	11.80
1380 (∞)	−0.376[b]	

[a] 359 mg. ester in 25 ml. benzene. [b] Theoretical value for pure cholesteryl ester, −0.377°.

TABLE IV

SUMMARY OF RATES OF ISOMERIZATION OF 3,5-CYCLOCHOLESTAN-6-YL TRICHLOROACETATES

Isomer	Temp., °C.	Solvent	Added	*k*, sec.$^{-1}$
6β	25.0	C_6H_6		1×10^{-7} to 10^{-6}
6β	25.0	C_6H_6	0.012 *M* HOTCA	*ca.* $1–2 \times 10^{-4}$
6β	25.0	$C_6H_5NO_2$		$1–6 \times 10^{-5}$
6α	75.0	C_6H_6		$1–2 \times 10^{-4}$

Solvolysis.—Methanolysis of the epimeric 3,5-cyclocholestan-6-yl trichloroacetates in 80% methanol–chloroform containing excess potassium acetate gave rise to identical products (Table V). The composition of the product was determined by a combination of chromatography and polarimetry illustrated in the Experimental section. Except for *ca.* 4% of cholesterol the product consisted of sterol methyl ether, very largely 3,5-cyclocholestan-6β-yl (IX) with a little cholesteryl (X). Cholesteryl trichloroacetate, on the other hand gave rise to cholesterol quantitatively.

TABLE V

PRODUCTS[a,b,c] OF METHANOLYSIS OF 3,5-CYCLOCHOLESTAN-6-YL AND CHOLESTERYL DERIVATIVES

Run	Compound	Time, hr.	Diene[d]	6β-OMe[e]	3β-OMe[f]	3β-OH[g]
1	3β-OTs	4	0.8	87.3	12.0	
2	3β-OTs	9	0.6	88.3	11.2	
3	6β-OTCA	0.5	[h]	89.4	6.7	3.8
4	6α-OTCA	0.5	[h]	88.4	8.2	3.5

[a] The sterol ester was dissolved in one volume of chloroform, and the solution was diluted with four volumes of methanol. The solutions were then refluxed for the times recorded in the table. [b] Ester molarities were between 0.04 and 0.05 and *ca.* four equivalents of acetate were used for each equivalent of ester. [c] The recovery of products was 94–97%; the ratios were determined by a combination of separation and polarimetry; 6β-OMe, $[\alpha]D$ +54°; 3β-OMe, $[\alpha]D$ −42°. [d] 3,5-Cholestadiene. The percentages were obtained by measuring the ultraviolet absorption at 236 mμ. At this wave length, log ε is 4.2 (D. Remy, M.S. Thesis, U.C.L.A., August, 1952). Optical rotation was also of use, since $[\alpha]D$ −120° (C. A. Grob, private communication). [e] 3,5-Cyclocholestan-6β-yl methyl ether. [f] Cholest-5-en-3β-yl methyl ether. [g] Cholest-5-en-3β-ol; cholesterol. [h] No ultraviolet absorption due to this diene was observed.

Methanolysis of cholesteryl toluenesulfonate, instead of the trichloroacetate, gave rise to a product almost identical to that from the 3,5-cyclocholestan-6-yl trichloroacetates, except that the small quantity of cholesterol was now absent. In addition, a trace of diene was present in the product. From the data in Table V, the ether product from methanolysis of either the epimeric 3,5-cyclocholestan-6-yl trichloroacetates or cholesteryl *p*-toluenesulfonate can be summarized as 90 ± 2% 3,5-cyclocholestan-6β-yl methyl ether (IX) and 10 ± 2% cholesteryl methyl ether (X).

The hydrolysis of the 3,5-cyclocholestan-6-yl trichloroacetates and cholesteryl toluenesulfonate in 90% dioxane was also examined. However, as is summarized in Table VI, the picture regarding product compositions is much less exact than in the case of methanolysis. This was due both to the presence of unidentified product fractions and to the fact that the reaction conditions permitted conversion of 3,5-cyclocholestan-6β-ol to cholesterol and cholesteryl trichloroacetate.

(32) E. A. Braude, *Ann. Reports*, **46**, 126 (1949).

TABLE VI

PRODUCTS OF HYDROLYSIS IN 90% DIOXANE[a]

Run	Compound	$10^2 M$	Added	$10^2 M$	Time, hr.	Recov., %	Unid.[b]	6β-OH[c]	3β-OH[d]	3β-OTCA[e]
5	6β-OTCA	5.2			123	85	13	49	23	14
6	6β-OTCA	3.1	LiOTCA	3.7	70	86	8	64	27	1
7	6β-OTCA	3.0	LiOTCA	14.8	72	92	5	72	22	
8	6β-OTCA	2.7	$LiClO_4$	2.8	466	94	2		97	1
9	6α-OTCA	2.7			402	73	16	51	18	14
10	6α-OTCA	3.5			178[h]	[i]	[i]	[i]	[i]	13
11	6α-OTCA	2.7	$LiClO_4$	2.9	628	102	3		94	2
12	6β-OH	4.1	HOTCA	2.4	171	94		90	10	
13	6β-OH	3.6	HOTCA	3.7	190[k]	[i]	[i]	[i]	[i]	6[m]
14	6β-OH	3.9	HOTCA	2.4	468	89	6		94	
			$LiClO_4$	4.1						
15	6β-OTCA	2.2	LiOAc	4.7	0.25[f]	96	4[g]	63	32	1
16	6α-OTCA	3.1	LiOAc	12.4	2[f]	93	10[g]	53	37	1
17	3β-OTs	4.4	LiOAc	14.2	2[f]	95	16[n]	68	17	

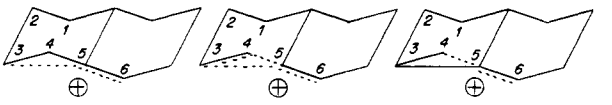
[a] The temperature of reaction was 25° unless otherwise indicated. Recovery of products is given, but the percentages have been corrected to 100%. [b] Unidentified material which was eluted by pentane in chromatography of the product mixture. For purposes of calculation, it was assumed to be olefin, $C_{27}H_{44}$. [c] 3,5-Cyclocholestan-6β-ol. [d] Cholest-5-en-3β-ol; cholesterol. [e] Cholest-5-en-3β-yl trichloroacetate; unless otherwise indicated, isolated by filtration of the reaction mixture from which it had spontaneously crystallized. [f] At reflux temperature. [g] Of which less than 1% was 3,5-cholestadiene (ultraviolet spectrum). [h] *Ca.* 3.5 half-lives from rate data. [i] No attempt was made to isolate any other product but the cholesteryl trichloroacetate. [k] *Ca.* 0.5 half-life for rearrangement to cholesterol. [m] A good part of this material was obtained by cooling the reaction mixture in ice. [n] Of which 15% was 3,5-cholestadiene, equivalent to a 2.4% yield of olefin.

In hydrolysis, both the 3,5-cyclocholestan-6-yl trichloroacetates yield three major products, 3,5-cyclocholestan-6β-ol, cholesterol and cholesteryl trichloroacetate. The 3,5-cyclocholestan-6β-ol predominates over the cholesterol, and the amount of cholesteryl trichloroacetate which crystallizes spontaneously out of the reaction mixture is rather similar from the two epimeric 3,5-cyclocholestan-6-yl trichloroacetates (*e.g.*, runs 5, 9 and 10). While the 6β-alcohol reacts slowly with trichloroacetic acid to form cholesteryl trichloroacetate (*e.g.*, run 13), the yield of this material obtained, even by cooling the reaction mixture to crystallize out the cholesteryl trichloroacetate, was only *ca.* 6% after reaction periods equivalent to those employed in solvolysis. The solubility of the cholesteryl trichloroacetate (Table VII) is of the order of magnitude of the amounts formed by the reaction of 6β-alcohol with trichloroacetic acid in the concentrations used in the solvolysis. Thus, most of the cholesteryl trichloroacetate isolated from the solvolytic reactions represents a product associated with the solvolysis reaction.

The inclusion of lithium trichloroacetate in the solvolysis mixture for 3,5-cyclocholestan-6β-yl trichloroacetate (runs 6 and 7) has no marked effect on the composition of the alcohol product, but it appears to depress markedly the quantity of cholesteryl trichloroacetate produced. On inclusion of lithium perchlorate in the solvolysis of both 3,5-cyclocholestan-6-yl trichloroacetates (runs 8 and 11), the alcohol product was changed to nearly pure cholesterol, and the amount of cholesteryl trichloroacetate obtained was very much depressed. The effect on the alcohol composition was evidently due to promotion by lithium perchlorate of the acid-catalyzed isomerization of 3,5-cyclocholestan-6β-ol to cholesterol. Thus, the inclusion of lithium perchlorate with trichloroacetic acid in control runs 12 and 14 on the 6β-alcohol converted a slow partial isomerization to an essentially complete one.

Discussion.—Cohen and Schneider[33] have discussed the problem of demonstrating alkyl–oxygen ionization during alcoholysis of a carboxylic acid ester and have concluded that the formation of alkyl ether as a product is usually sufficient evidence, provided that the ether is not the product of more concerted displacement on alkyl. Methanolysis of cholesteryl trichloroacetate yields cholesterol, so that in this case ester interchange with acyl–oxygen cleavage is occurring. On the other hand, alkyl–oxygen cleavage is obviously occurring in methanolysis of the 3,5-cyclocholestan-6-yl trichloroacetates. Furthermore, the nature of the products shows that carbonium ion intermediates are involved.

The near-identity of solvolysis products from methanolysis of cholesteryl toluenesulfonate and the 3,5-cyclocholestan-6-yl trichloroacetates confirms that a common cationic intermediate intervenes in solvolytic reactions of both cholesteryl (V) and 3,5-cyclo-6β-yl (VIII) derivatives.[9,10] Also, the same intermediate apparently is produced from the 3,5-cyclo-6α-yl derivative (VII). Actually, one can contemplate homoallylic cations of both the so-called unsymmetrical and symmetrical varieties,



II III IV

just as in other homoallylic cases.[3,34–37] In the symbolism employed previously,[35] the "symmetrical" variety is III, while the "unsymmetrical" counterparts are II and IV. Of the latter two, II

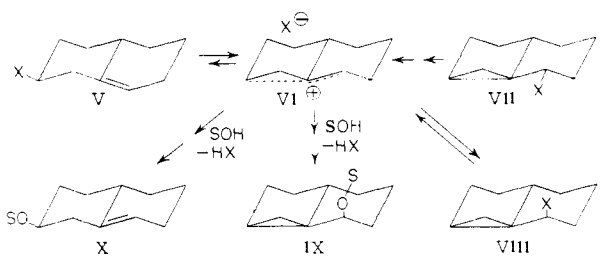
(33) S. G. Cohen and A. Schneider, THIS JOURNAL, **63**, 3382 (1941).
(34) J. D. Roberts, C. C. Lee and W. H. Saunders, *ibid.*, **77**, 3034 (1955).
(35) S. Winstein, *Experientia, Supplementum II*, 137 (1955).
(36) S. Winstein, *Bull. soc. chim. France*, **18**, 55 (1951).
(37) S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, THIS JOURNAL, **74**, 1140 (1952).

should be much more stable because C-3 is secondary and C-4 is primary. The observed structural and stereochemical results of solvolysis can be accounted for on the basis of intermediate II alone. However, they do not exclude certain interpretations based on more than one intermediate, for example, II and III.

The present results contain a faint hint of a difference in the course of solvolysis of the cholesteryl derivative, on the one hand, and the 3,5-cyclocholestan-6-yl derivatives on the other. The proportion of cholesteryl ether in the ether mixture from cholesteryl toluenesulfonate appears to be higher than from the 3,5-cyclocholestan-6-yl trichloroacetates by slightly more than experimental error. This might be due, for example, to some reaction with solvent of an "unsymmetrical" homoallylic cation II, this being formed initially from the cholesteryl derivative, prior to its isomerization to a "symmetrical" homoallylic cation III which is formed from the other derivatives. Also, there is a trace of diene in the product of solvolysis of cholesteryl toluenesulfonate but not from the 3,5-cyclocholestan-6-yl derivatives. This could conceivably arise from II, although just as likely an alternative explanation is that the diene arises from an independent reaction path of the cholesteryl derivative not involving vinyl group participation.

It is obvious that the present results cannot be discussed on the basis of only dissociated forms of the carbonium ions. Ion pairs VI capable of return to the cholesteryl derivative V must be included in the description of the behavior of both 3,5-cyclocholestan-6-yl trichloroacetates VII and VIII. A mechanism involving ionization and ion pair return[38] to the cholesteryl derivative V seems indicated for the isomerizations of the 3,5-cyclocholestan-6-yl trichloroacetates observed. The appreciable formation of cholesteryl derivative, not increased by inclusion of lithium trichloroacetate, during hydrolysis of the 3,5-cyclocholestan-6-yl trichloroacetates, shows that ion pair return accompanies solvolysis in 90% dioxane. Such return still persists to the extent of *ca.* 4% in 80% methanol–chloroform, as is indicated by the formation of a small proportion of cholesterol (from cholesteryl trichloroacetate) in methanolysis of both the 3,5-cyclocholestan-6-yl derivatives VII and VIII.

The above description is non-committal regarding the exact number and nature of the ion pairs involved in going to cholesteryl trichloroacetate V from either the 6α-derivative VII or the 6β-isomer VIII. Furthermore, the present results contained indications that added salts decreased ion pair return very substantially. These effects and their mechanism, together with other aspects of the behavior of ion pairs from cyclocholestan-6-yl derivatives are being actively investigated, and they will be reported on separately.



(38) (a) S. Winstein and K. C. Schreiber, THIS JOURNAL, **74**, 2165 (1952); (b) S. Winstein, E. Clippinger, A. H. Fainberg and G. C. Robinson, *ibid.*, **76**, 2597 (1954); *Chemistry and Industry*, 664 (1954); (c) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, THIS JOURNAL, **78**, 328 (1956).

Experimental Part

Cholesteryl *p*-Toluenesulfonate.—Crude ester was prepared by the reaction of *p*-toluenesulfonyl chloride with cholesterol in pyridine. The product from 500 g. of cholesterol was dissolved in 2 liters of chloroform, the water layer was removed, and the solution was poured through 1.5 kg. of alumina, followed by another 2 liters of chloroform to ensure rapid and complete elution. The chloroform was removed under reduced pressure and the warm residue was crystallized by the addition of 1.5 liters of acetone. The yield of ester, m.p. 131.7–132.6°, is 80% by this procedure, and the product is purer than that obtained by the more usual recrystallization and charcoal treatment.

3,5-Cyclocholestan-6β-ol.—The following procedure has been employed successfully on a one-mole scale.

Cholesteryl *p*-toluenesulfonate (131.4 g., 0.243 mole), dry potassium acetate (104.5 g., 1.063 moles), 2 l. of acetone and 0.5 l. of water were refluxed together for 15 hours. The acetone was distilled off, care being taken to remove the last traces at the aspirator. The residual oil was extracted with pentane, and the pentane solution was poured onto a *ca.* 1.5 kg. column of 80 mesh stock alumina. The elution order was hexane, 0.7 l., hexane–benzene (2:1), 3 l., and ether, 1 l. Only a small quantity of oil was found after evaporation of the hexane eluate. The hexane–benzene gave, after evaporation and crystallization, 58.3 g. (62%) of the 3,5-cyclo-alcohol, m.p. 66.7–67.9°, $[\alpha]^{22}D$ +50.4 ± 0.7° (*c* 1.47, $CHCl_3$).

Acetone was used as the crystallizing solvent; the alcohol is rather soluble in hot acetone, fairly soluble at room temperature, and not too soluble at ice temperature. The 3,5-cyclo-alcohol separates from the acetone in needles, which are filtered off and vacuum dried to remove residual acetone. The alcohol will not crystallize from hexane, ether or chloroform.

The ether eluate from the chromatographic separation contained about a 10% yield of cholesterol.

Evaporation of the filtrate from the acetone crystallization of the 3,5-cyclo-alcohol gave an oil, from which an unidentified crystalline solid, m.p. 78.6–79.5°, $[\alpha]D$ +54° ($CHCl_3$), could be isolated. The ultraviolet spectrum was almost blank (except for the indication of 0.15% 3,5-cholestadiene). Treatment of this material with acid in acetone gave pure cholesterol, m.p. 146–148°, mixed m.p. undepressed. The carbon–hydrogen analysis (C, 83.77; H, 11.70) did not correspond to that for a di-3,5-cyclocholestanyl ether (C, 85.87; H, 12.01).

On storing at room temperature, the melting point of 3,5-cyclocholestan-6β-ol rises slowly to 73–74°, but the product has the same rotation and gives no melting point depression with the 67–68° material. Pure samples of the alcohol have been kept over long periods without noticeable change in properties, other than the rise in melting point.

3,5-Cyclocholestan-6α-ol.—An ether solution of 32 g. of 3,5-cyclocholestanone-6, prepared by the procedure of Dodson and Riegel,[15] was added with stirring to 6 g. of lithium aluminum hydride in 500 cc. of ether. After 3 hours, a solution of methanol in ether was added, and then 50 cc. of water. This sequence of operations leads to three layers, ether, water, and granular aluminum salts. The ether layer is then decanted, the aqueous layers washed well with several portions of ether, and the ether layers combined, dried and evaporated. The residual yellow oil is heated with 500 cc. of dry, redistilled acetonitrile until most of the oil is in solution. The hot solution is decanted from undissolved material and allowed to cool. The alcohol separates as an oil and is crystallized by seeding with crystals obtained according to the directions of Wagner, Wolff and Wallis.[12] The white solid is filtered off, sucked as dry as possible on the filter, and vacuum dried until the odor of the solvent is unnoticeable. This procedure yields 25 g. (78%) of material, m.p. 80.1–81.1°, $[\alpha]^{22}D$ +76 ± 1°

(*c* 1.97, $CHCl_3$). After 30 months storage, the m.p. was 80.0–80.8°, mixed m.p. with 6β-alcohol, 61.0–72.3°.

Trichloroacetates.—In a typical preparation, 10 g. (0.026 mole) of 3,5-cyclocholestan-6α-ol was dissolved in 50 cc. of anhydrous pyridine, and the solution was cooled in ice. To this was added a solution of 8.2 g. (0.045 mole) of E. K. Co. White Label trichloroacetyl chloride in 50 cc. of ice-cold anhydrous pyridine. After 15 minutes, the mixture was poured into a mixture of sodium bicarbonate (10 g.), ice and water (*ca.* 1 l. total). After an hour, the solid was filtered off, crushed and washed well with water. (Occasionally there is difficulty at this stage, if the trichloracetate does not solidify.) The solid was vacuum dried over Drierite and dissolved in dry acetone, with as rapid warming as possible. The solution was filtered and allowed to cool. The crystals were filtered off and dried *in vacuo* to yield 10 g. (73%) of material, m.p. 98.7–99.7°, $[\alpha]^{21}D$ +77° (*c* 1.69, $CHCl_3$), m.p. after 96 days, 96.0–97.0°.

Less pure preparations required additional recrystallizations from acetone, as did trichloroacetate prepared from 6β-alcohol in *ca.* 50% yield. A more satisfactory solvent than acetone for the purification of cholesteryl trichloroacetate was redistilled Skellysolve B.

Approximate solubilities of cholesteryl trichloroacetate in aqueous dioxanes at room temperature were determined as follows. A solution of 0.9965 g. of the ester was prepared by allowing the solid to stand in contact with 105 cc. of dioxane for 10 days with occasional shaking. Portions were diluted with either water or aqueous lithium perchlorate. The solutions were allowed to stand 193 hours, and the undissolved solid was filtered off, dried at 115° and weighed. The filtrates were diluted with 50 cc. of water and the precipitates were filtered off, dried at 115° and weighed. The total recoveries from each solution were in the range of 88–95%. All the insoluble fractions had m.p. *ca.* 150–152°, undepressed by starting material. All the recovered and dried soluble materials had m.p. *ca.* 148.5–150°, undepressed by starting material. A mixture of cholesterol and cholesteryl trichloroacetate melts over a range near 120–130°. The approximate solubilities are summarized in Table VII.

TABLE VII

SOLUBILITY OF CHOLESTERYL TRICHLOROACETATE

Dioxane: Water[a]	Added	Solubility 10^2, *M*
38:1		1.1
19:1		0.6
19:1	0.027 *M* $LiClO_4$	0.6
9:1		0.21
9:1	0.027 *M* $LiClO_4$	0.12

[a] Volume ratio.

p-Nitrobenzoates and Acetates.—The *p*-nitrobenzoates were easily prepared by the standard pyridine method, using recrystallized *p*-nitrobenzoyl chloride. Acetone was the recrystallizing solvent. The 3,5-cyclocholestanols are readily acetylated by the usual pyridine–acetic anhydride mixture, and isolated by extraction with ether after pouring the mixture into water. The 6β-acetate is best recrystallized from methanol, while the 6α-acetate is crystallized with difficulty from 95% ethanol.

Rearrangements of the 3,5-Cyclocholestanyl Trichloroacetates.—A solution of 1.239 g. of 3,5-cyclocholestan-6β-yl ester in 30 ml. of pentane was refluxed for 152 hours. The light yellow-green crystals which separated on cooling had m.p. 153–154°, undepressed by authentic cholesteryl ester.

The filtrate was evaporated to dryness, leaving a residue, m.p. 143–145°, mixed m.p. with cholesteryl ester, 146.5–150°. The combined weight of both portions was 1.24 g. (100% recovery).

A 0.424-g. sample of 3,5-cyclocholestan-6β-yl ester was heated on the steam-bath for 5 hours, although the melt resolidified within 15 minutes. The solid was then heated with a little acetone, and the supernatant acetone did not indicate the presence of acid when tested with wet nitrazine paper. The solid, m.p. 152.0–154.5°, was recrystallized from boiling acetone to yield 0.345 g. (81.5%) of cholesteryl ester, m.p. 152.4–153.4°, undepressed by an authentic specimen.

An 86.5-mg. sample of 3,5-cyclocholestan-6α-yl ester was heated on the steam-bath for 1 hour, although the melt resolidified within 5 minutes. After being cooled, the solid was triturated with 5 cc. of acetone, and the acetone was drawn off with a dropper. The air-dried white residue, m.p. 152.4–154.4°, m.p. undepressed by cholesteryl ester, weighed 62.5 mg. (72.4%). The acetone triturate was evaporated to dryness, yielding 16.0 mg. (18.5%) of white solid, m.p. 147–150°, and a small amount of brown material which was more soluble in acetone.

The isomerization of the 3,5-cyclocholestanyl trichloroacetates to the cholesteryl isomer in solution was followed polarimetrically. Concentrations of *ca.* 500 mg. of ester in 25 ml. of pure benzene or nitrobenzene were employed. The rotations changed to a value corresponding closely to that for the pure cholesteryl ester.

Methanolysis of Cholesteryl Trichloroacetate.—The ester, 150 mg., and potassium acetate, 120 mg., were refluxed with 7 cc. of methanol for 39 hours. Although the ester seemed almost insoluble in hot methanol, the solution was homogeneous after 3 hours. An essentially quantitative yield of cholesterol, m.p. 146–147°, mixed m.p. 147.2–148.5°, was isolated.

Methanolysis of Cholesteryl *p*-Toluenesulfonate.—A solution of 7.0515 g. of ester, 5 g. of dry potassium acetate and 60 ml. of C.P. chloroform in 240 ml. of methanol was refluxed for 9 hours. Most of the solvent was evaporated on the steam-bath, and the residual solvent was removed with the aid of an oil pump. The residual oil was dissolved in redistilled Skellysolve F (b.p. 36–45°) and poured onto a 50-g. column of *ca.* 80 mesh stock alumina. The same solvent was used for elution.

Fraction 1 (40 cc.), obtained by eluting a fluorescent band from the column, left a 391.1-mg. residue on evaporation of solvent; m.p. 73–73.5°, $[\alpha]^{21}D$ +47.5° (*c* 2.0, $CHCl_3$). A solution of 3.16 mg. of this material in 10 ml. of cyclohexane had an optical density of 0.41 at 236 mμ.

Fraction 2 (100 ml.) contained 3.4063 g. of material, m.p. 78–79°, mixed m.p. with authentic 3,5-cyclocholestan-6β-yl methyl ether 78–79°, $[\alpha]^{21}D$ +50° (*c* 1.6, $CHCl_3$). A solution of 71.0 mg. of this material in 5 ml. of cyclohexane had an optical density of 2.72 at 236 mμ.

Fraction 3 (100 ml.) contained 751.9 mg. of material, m.p. 72–74°, $[\alpha]^{21}D$ +29.4° (*c* 3.3, $CHCl_3$). Fraction 4 (400 ml.) contained 329.2 mg. of material, m.p. 60–70°, $[\alpha]^{21}D$ −16.6° (*c* 5.9, $CHCl_3$).

From the optical densities, the 3,5-cholestadiene contents of fractions 1 and 2 may be calculated as 3.0 and 0.44%, respectively. From the $[\alpha]D$ for 3,5-cholestadiene and the assumption that fraction 1 is a mixture of the 3,5-diene and 6β-methyl ether, the diene content is calculated as 3.4%.

From the rotations of pure 6β-methyl ether and 3β-methyl ether, the composition of fractions 2, 3 and 4 in mg. may be calculated

Fr.	6β-OMe	3β-OMe	3,5-diene
1	379.4		11.7
2	3283.7	109.0	15.1
3	556.4	195.5	
4	89.2	240.0	

Fraction 4 (270 mg. remaining after the rotation was measured) was rechromatographed on a 40-g. alumina column. Successive 75-ml. fractions contained: (1) 4.7 mg.; (2) 29.2 mg., m.p. 78–79°, undepressed by authentic 6β-methyl ether; (3) 5.2 mg.; (4) 36.1 mg.; (5) 68.9 mg.; (6) 63.9 mg.; (7) 39.0 mg.; (8) 15.8 mg. The fractions 3–8 crystallized. Fractions 5–8, 191 mg., were combined and recrystallized from methanol–acetone to give 125 mg. of long plates, m.p. 83.9–84.4°, mixed m.p. with 3β-methyl ether (m.p. 83.7–84.5°) 83.7–84.4°. The amount of 3β-ether predicted from rotations was 197 mg.; that found was 191–220 mg. (including fraction 4, which was not examined but is probably largely 3β-ether, judging from the pattern of fraction weights).

In the methanolyses of the 3,5-cyclocholestanyl esters, the melting point and rotation of fractions eluted by pentane early in the chromatography were identical with that of pure 3,5-cyclocholestan-6β-yl methyl ether, m.p. 79.0–79.6°, $[\alpha]D$ +54°. Later pentane fractions were assumed to be mixtures of 6β- and 3β-ethers. Ether eluted the small amounts of cholesterol which were present.

Hydrolysis of 3,5-Cyclocholestan-6α-yl Trichloroacetate.—A 1.4086-g. quantity of ester was dissolved in 100 ml. of

90% dioxane (9 vol. dioxane: 1 vol. water) and kept at 25° for 402 hours (*ca.* 8 half-lives). Filtration and drying of the long needles which separated gave 200.1 mg. of material, m.p. 150–152°, mixed m.p. with cholesteryl trichloroacetate, 151–153°.

The filtrate was diluted with 600 cc. of water, and extracted with 200 cc. of redistilled pentane. The pentane extract was washed three times with water and dried over magnesium sulfate. The solvent was evaporated on the steam-bath. An appreciable amount of dioxane remaining was removed at the oil pump through a Dry Ice trap. The oily residue was dissolved in a small volume of redistilled Skellysolve F and chromatographed through a 20-g. column of stock alumina. Using Skellysolve F (F), benzene (B), ether (E) and ethanol (Et) for elution, the following fractions were collected: (1) 60 ml. F, 60 mg. of residue insoluble in acetone; (2) 75 ml. F, no residue; (3) 40 ml. F, no residue; (4) 60 ml. 1:1 F:B, 149.2 mg. oily residue, crystallized on addition and then evaporation of acetone, m.p. 69.7–71.5°, mixed m.p. with 6β-alcohol 69–72°; (5) 50 ml. 1:1 F:B, 115.1 mg. oil which behaved like fraction 4; (6) 50 ml. 1:1 F:B, 76.8 mg. oil which behaved like fraction 5; (7) 60 ml. 1:1 F:B, 35.3 mg. oil, m.p. after acetone treatment 68.5–70.5°, mixed m.p. with 6β-alcohol 68.6–70.9°; (8) 50 ml. 1:1 F:B, 17.4 mg. oil; (9) 50 ml. 1:1 F:B, 6.4 mg. oil; (10) 80 ml. E, 163 mg. solid, 145 mg. of which gave 497.3 mg. of digitonide and 17.4 mg. of oil recovered from the filtrate from the digitonide preparation (attempted preparation of *p*-nitrobenzoate from this oil failed); (11) 30 ml. E, no residue; (12) 70 ml. 2.5:1 E:Et, 34.6 mg. oil which failed to give a *p*-nitrobenzoate; (13) 75 ml. 2.5:1 E:Et, no residue.

The run may be summarized (in mg.)

Fr.	Unident.	6β-OH	3β-OH	3β-OTCA
Pre.				200.1
1	60			
2–3				
4–9		400.1		
10	28		135	
11				
12	34.6			
13				

In the other hydrolyses, the alcohols isolated were usually quite pure. Typically, 6β-alcohol from runs 9 and 12, Table VI, had m.p. 66–67° and 65–67°, respectively, as compared with 67–68° found for pure freshly crystallized 6β-alcohol. It was also shown that 6β- and 3β-alcohols could be separated quantitatively from one another. Thus, a mixture containing 691 mg. of 6β-alcohol and 507 mg. of 3β-alcohol was chromatographed on 25 g. of alumina. Pentane:benzene (2:1) eluted the 6β-alcohol, 693 mg. (100%), of which 679 (98%) had m.p. 73–74° and mixed m.p. the same. With ether, there was eluted 505 mg. (100%) of cholesterol, m.p. 146–147°, m.p. undepressed by authentic cholesterol.

LOS ANGELES 24, CALIFORNIA

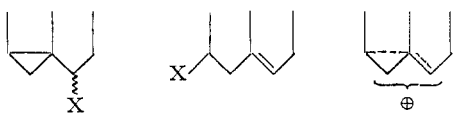
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Neighboring Carbon and Hydrogen. XXIII. Homoallylic Systems. 3,5-Cyclocholestan-6β-yl Chloride[1]

BY EDWARD M. KOSOWER[2] AND S. WINSTEIN

RECEIVED MARCH 19, 1956

By taking advantage of the reactivity associated with the *i*-steryl structure in ionization reactions and the mediating action of the solvent ether upon hydrogen chloride, 3,5-cyclocholestan-6β-yl chloride has been prepared from 3,5-cyclocholestan-6β-ol and thionyl chloride. The structure and configuration of the "*i*-cholesteryl" chloride are clear from elementary analysis, molecular rotation and chemical behavior. Hydrolysis of the chloride in 90% dioxane gives rise mainly to 3,5-cyclocholestan-6β-ol and partly to cholesterol. Also, ion pair return, leading to cholesteryl chloride, is more important in hydrolysis of the 3,5-cyclocholestan-6β-yl chloride than the trichloroacetate.



I II III

In order to compare the behavior of 3,5-cyclocholestan-6-yl derivatives I with cholest-5-en-3β-yl derivatives II in solvolytic reactions, it was desirable to have isomeric compounds. Although all three trichloroacetates had been prepared successfully,[3] cholesteryl trichloroacetate had been found[3] to solvolyze with acyl–oxygen, rather than alkyl–oxygen cleavage. Previous evidence, as well as preliminary experiments, had indicated that the *p*-toluenesulfonate esters in the 3,5-cyclo series were too reactive. However, Wagner-Jauregg and Werner[4] had shown some years ago that cholesteryl chloride solvolyzes to give products now ascribed to 5,6-double bond participation with formation of hybrid ion III.[3] Therefore, the 3,5-cyclocholestan-6-yl chlorides were of interest for comparison with cholesteryl chloride. In this paper is reported a study of the preparation and hydrolysis of 3,5-cyclocholestan-6β-yl chloride.

Preparation and Behavior of "*i*-Cholesteryl" Chloride.—A statement that the chloride could not be prepared has appeared.[5] However, our experiments with the 3,5-cyclocholestanyl trichloroacetates,[3] including rate studies,[6] suggested that the chloride might be isolable. From the kinetic results[6] obtained with the trichloroacetates, it was clear that a 3,5-cyclocholestan-6-yl chloride would display an extremely high rate of ionization and, therefore, be very subject to rearrangement. Thus, successful isolation of such a chloride would depend on precautions in procedure designed to avoid ionizing conditions.

For reasons which will be clear from the discussion below, thionyl chloride was used as a reagent on the 3,5-cyclocholestan-6-ols. Ether was employed as a solvent because it represents a volatile,

(1) Abstracted from part of Ph.D. Thesis of E. Kosower, UCLA, 1952.

(2) Research Fellow of the National Institutes of Health, 1949–1952.

(3) E. M. Kosower and S. Winstein, THIS JOURNAL, **78**, 4347 (1956).

(4) T. Wagner-Jauregg and L. Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

(5) C. W. Shoppee, *Bull. soc. chim.*, [V] **18**, C120 (1951).

(6) E. M. Kosower, unpublished work.