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

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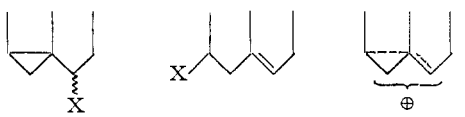
By taking advantage of the reactivity associated with the *i*-steryl structure in ionization reactions and the mediating action of the solvent ether upon hydrogen chloride, 3,5-cyclocholestan-6β-yl chloride has been prepared from 3,5-cyclocholestan-6β-ol and thionyl chloride. The structure and configuration 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).

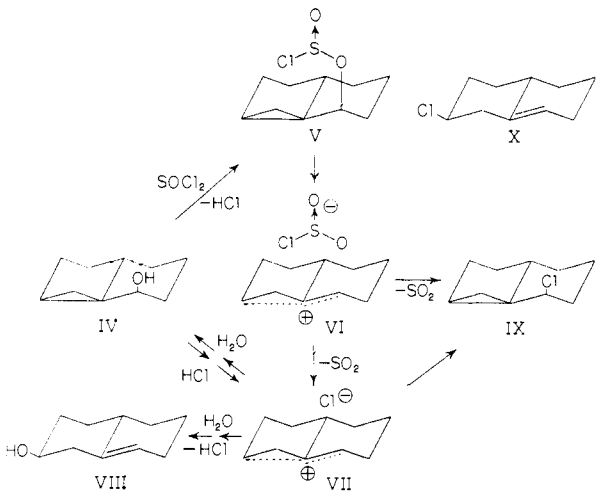
(4) T. Wagner-Jauregg and L. Werner, *Z. physiol. Chem.*, **213**, 119 (1932).

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

(6) E. M. Kosower, unpublished work.

inert solvent of low dielectric constant, which is basic[7,8] and moderates the catalytic effect which could be expected from hydrogen chloride toward the rearrangement[3] of a 3,5-cyclo chloride. The same solvent displayed an exceptionally low rate of isomerization of camphene hydrochloride in the classic investigation of Meerwein.[9] Also, it has been employed to advantage by W. G. Young and co-workers[10] in these laboratories to moderate the action of hydrogen chloride during the action of thionyl chloride on allylic alcohols.

Thionyl chloride in slight excess was added to a dilute, ice-cold solution of 3,5-cyclocholestan-6β-ol (IV) in anhydrous ether. After the addition, the ether was evaporated, pentane was added, and the solvent was evaporated. The white residue was dissolved in dry acetone, and the solution was cooled to −78°. The white solid which separated was filtered quickly and dried under vacuum. This material analyzed correctly for a chloride, $C_{27}H_{45}Cl$, and it consisted mainly, but not entirely, of chloride which is titratable with silver nitrate under conditions toward which cholesteryl chloride is inert. When pyridine was employed in the thionyl chloride–3,5-cyclo-alcohol reaction, the chloride product displayed a somewhat lower "active chloride" content and seemed less stable on standing. Otherwise, it did not differ from the previous product, even in the kinetic studies.[6]



The 3,5-cyclocholestan-6α-ol yielded less satisfactory results in the reaction with thionyl chloride. Three attempts were made to treat 3,5-cyclocholestan-6α-ol with thionyl chloride, two in the manner described above for the 6β-alcohol, and the other in a pentane solution of N,N-di-isopropyl-*o*-toluidine.[11] The latter procedure yielded a white solid which contained a large proportion of "active chloride." Most of the "active chloride" displayed a rate[6] of solvolysis identical to that of the chloride from the 6β-alcohol. However, there was an indication of 10–15% of another "active chloride" somewhat slower than the predominant one.

The "active chloride" derived from the 3,5-cyclocholestan-6β-ol (IV) rearranged readily to cholesteryl chloride (X), even in chloroform solution. Thus, the observed optical rotations on various chloride preparations in chloroform decreased in less than 24 hours from the initial value to a specific rotation of −30°. The specific rotation of cholesteryl chloride[12] is −30°. In carbon tetrachloride solution, observed rotations were quite constant.

The fact that the final rotation observed on rearranging chloride was the value for pure cholesteryl chloride indicated that the inert material in the original chloride preparation was also cholesteryl chloride. This conclusion was verified with the infrared absorption of the chloride preparations. Cholesteryl chloride displays strong absorption at 11.43 μ, and transmissions at this wave length are correlated well with the silver nitrate analyses for inactive chloride. This correlation is summarized in Table I.

TABLE I

INFRARED ABSORPTION OF CHLORIDES AT 11.43 μ

(RCl)[a]	% "Active" RCl	% Transmission Obsd.	% Transmission Calcd.
99	83.6	78	79
96.9	72.4	71	70
98.9	0	27	(27)[b]

[a] In mg./cc. carbon tetrachloride. [b] Used to calculate the other values.

On the assumption that the chloride from 3,5-cyclocholestan-6β-ol (IV) contained only one "active chloride" along with the more inert cholesteryl chloride, it was possible to estimate a specific rotation for the "active chloride." The estimates of $[\alpha]_D$ for the "active chloride," based on initial rotations and cholesteryl chloride contents, are summarized in Table II. The concordant calculated values obtained for different preparations support the idea of a binary mixture. However, the kinetics[6] of hydrolysis of the chloride, to be reported in a following article, supply more convincing evidence that only one "active chloride" is present in the chloride preparations from 3,5-cyclocholestan-6β-ol (IV).

TABLE II

CALCULATED SPECIFIC ROTATIONS OF "ACTIVE CHLORIDE" IN CHLOROFORM

"Active chloride," %	Initial $[\alpha]_D$	$[\alpha]_D$ obsd. after 24 hr.	$[\alpha]_D$ "active" calcd.
76.5[a]	+26.1	−29	+43
72.4[a]	+24.5		+45
83.6	+27.5	−30	
	+29.2[b]		+41[b]
			Av. +43

[a] Sample prepared with addition of pyridine. In carbon tetrachloride solution.

Structure and Configuration.—That the "active chloride" from 3,5-cyclocholestan-6β-ol (IV) is a 3,5-cyclocholestan-6-yl derivative is evident from the nature of the hydrolysis products. A sample,

(7) (a) H. M. Buswell, W. H. Rodebush and M. F. Roy, THIS JOURNAL, **60**, 2528 (1938); (b) D. R. Chesterman, *J. Chem. Soc.*, 906 (1935).

(8) T. M. Mounajed, *Compt. rend.*, **197**, 44 (1933).

(9) H. Meerwein and K. van Emster, *Ber.*, **55**, 2500 (1922).

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

(11) This substance was kindly made available by F. F. Caserio, Jr.

(12) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 783 (1948).

84% "active," was hydrolyzed in 90% dioxane containing excess lithium acetate under conditions toward which cholesteryl chloride is inert. Correcting the products obtained for the cholesteryl chloride present in the starting material, the products derived from the "active chloride" are 72% 3,5-cyclocholestan-6β-ol (IV), 8% cholesterol (VIII) and 20% cholesteryl chloride (X). When the solvolysis solution was not buffered, the yield of 6β-alcohol IV was only 3%, and yet only 17% cholesterol (VIII) was isolated. The remainder of the "active chloride" gave rise to cholesteryl chloride (80%). These results are summarized in Table III. Regarding the configuration of the

TABLE III

PRODUCTS OF SOLVOLYSIS OF 3,5-CYCLOCHOLESTAN-6β-YL CHLORIDE IN 90% DIOXANE AT 25°

(RCl),[a] 10^2 *M*		3.1	3.5
(LiOAc), 10^2 *M*		14.7	
Time, hours		38	39
Total % recovery		95	94
Product	% cholesterol (VIII)	8	17
	% 3,5-*cyclo*cholestan-6β-ol (IV)	72	3
	% cholesteryl Cl (X)	20[b,c]	80[b]

[a] 83.6% "active chloride." [b] Corrected for cholesteryl chloride content of the starting chloride. [c] 3,5-Cholestadiene content less than 0.05% on the basis of the ultraviolet spectrum.

3,5-cyclocholestan-6-yl chloride from 3,5-cyclocholestan-6β-ol (IV), one indication comes from solvolysis rates.[6] The "active chloride" in question is *ca.* 10^1 times as reactive as one component of the chloride product from the 3,5-cyclocholestan-6α-ol. The factor of *ca.* 10^1 is close to the one observed between the 3,5-cyclocholestan-6β- and 6α- trichloroacetates.[6] This suggests that the slower "active chloride" in the product from 6α-alcohol is a 6α-chloride and the "active chloride" from 6β-alcohol is entirely 6β-chloride (IX). Further support for the 6β-assignment to the chloride from 3,5-cyclocholestan-6β-ol (IV) is obtained from consideration of molecular rotations.

As summarized in Table IV, the differences in molecular rotation between a cholesteryl and a 3,5-cyclocholestan-6β-yl derivative range from +317° to +378°, depending upon the nature of the isomers. From the average calculated specific rotation for the "active chloride," +43°, one obtains an M_D of +174 for "active chloride." The ΔM_D(A − B) between "active chloride" and cholesteryl chloride is +295°, which is very close to the range of ΔM_D values. The fact that it is slightly below the range and not above is significant; 6α-derivatives invariably have much higher positive rotations than 6β-compounds.[3] Thus, molecular rotation data support the designation of the "active chloride" as 3,5-cyclocholestan-6β-yl chloride (IX).

TABLE IV

MOLECULAR ROTATION DIFFERENCES

No.	Comparison A/B	ΔM_D(A − B)
1	3,5-Cyclo-6β-OMe/5-en-3β-OMe[13-14]	378 ± 22 (7)[a]
2	3,5-Cyclo-6β-NR_2/5-en-3β-NR_2[15-17]	317 ± 57 (3)
3	3,5-Cyclo-6β-OH/5-en-3β-OH[12,18]	326 ± 14 (3)

[a] Number of pairs compared.

Discussion.—The formation of alkyl chloride from alcohols and thionyl chloride involves intermediate alkyl chlorosulfinates, some of which have been studied directly by Lewis and his students.[19] There are many indications of a tendency on the part of the chlorosulfinates to react in the liquid phase by way of alkyl–oxygen ionization prior to bonding of chlorine to carbon. Pertinent examples occur in the reaction of thionyl chloride with 2-methyl-2-phenyl-1-butanol,[20] the 3-chloro-2-butanols,[21] cyclopropylcarbinol[22] and the 3-phenyl-2-butanols.[23] The case of the 3-chloro-2-butanols[21] is very significant, since alkyl–oxygen ionization precedes chloride attack even though such ionization is very slow in the presence of a neighboring chlorine atom.[24]

The pronounced tendency toward ionization displayed by alkyl chlorosulfinates and the demonstrated importance in other cases of "internal return"[25] of an ion pair to the covalent condition suggest that ion pair intermediates[1,19,23] occur in the S_Ni mechanism. The latter, presumably by way of a 4-ring cyclic transition state, was suggested by Hughes, Ingold and co-workers[26] to explain conversion of chlorosulfinate to chloride with retention of configuration[27] in certain cases.

While no rates were measured for the conversion of 3,5-cyclocholestan-6β-ol (IV) to chloride with thionyl chloride in ether, the formation of chloride was obviously very rapid, even at 0°. On the other hand, 2-butyl chlorosulfinate has a half-life[19b] of two minutes at 99°. Thus, we estimate a minimum factor of 10^5 between rates of reaction of 3,5-cyclocholestan-6β-yl (V) and 2-butyl chlorosulfinates. Such high reactivity for the 3,5-cyclocholestanyl derivative V is in line with carbon–oxygen ionization, since very high rates[6] are observed in solvolytic reactions reported in a following paper. Subsequent to alkyl–oxygen ionization, collapse of carbonium chlorosulfinate or carbonium chloride ion pairs VI or VII, mainly to 3,5-cyclocholestan-6β-yl (IX) and partly to cholesteryl (X) chloride, is visualized. As in solvolysis, reac-

(13) (a) B. Riegel, M. F. W. Dunker and M. J. Thomas, THIS JOURNAL, **64**, 2115 (1942); (b) P. L. Julian, E. W. Meyer and I. Ryden, *ibid.*, **72**, 367 (1950); (c) D. M. Rathmann and L. R. Morrow, *ibid.*, **72**, 5647 (1950).

(14) E. W. Meyer, Ph.D. Thesis, Northwestern University, 1943.

(15) P. L. Julian, A. Magnani, E. W. Meyer and W. Cole, THIS JOURNAL, **70**, 1834 (1948).

(16) M. J. Bigelow, Ph.D. Thesis, Northwestern University, 1950.

(17) F. Šorm, L. Lábler, V. Černý, *Chem. Listy*, **47**, 418 (1953).

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(19) (a) E. S. Lewis and C. E. Boozer, THIS JOURNAL, **74**, 308 (1952); (b) E. S. Lewis and C. E. Boozer, *ibid.*, **75**, 3182 (1953); (c) C. E. Boozer and E. S. Lewis, *ibid.*, **76**, 794 (1954); (d) E. S. Lewis and G. M. Coppinger, *ibid.*, **76**, 796 (1954).

(20) E. S. Wallis and P. I. Bowman, *J. Org. Chem.*, **1**, 383 (1936).

(21) H. J. Lucas and C. W. Gould, THIS JOURNAL, **63**, 2541 (1941).

(22) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951).

(23) D. J. Cram, *ibid.*, **75**, 332 (1953).

(24) S. Winstein, E. Grunwald and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(25) *E.g.*, (a) W. G. Young, S. Winstein and H. L. Goering, *ibid.*, **73**, 1958 (1951); (b) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2165 (1952).

(26) W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman and A. D. Scott, *J. Chem. Soc.*, 1267 (1937).

(27) *E.g.*, J. Kenyon, H. Phillips and F. M. H. Taylor, *ibid.*, 382 (1931).

tion at C-6 is favored considerably over C-3 by a factor of at least 84/16. The latter ratio is a minimum figure since some of the cholesteryl chloride (X) in the derived chloride mixture probably arises from rearrangement of 3,5-cyclocholestanyl chloride IX subsequent to its formation.

While ion pair forms of carbonium ions are logically employed in the formulation of the mechanism of chloride formation in ether, we have no further information regarding the number of such species and their precise description. Neither is there any information on the possible occurrence of dissociation and external ion return,[28] or exchange[28] of ion pair partners. In the case of 3,5-cyclocholestan-6α-ol, a 6α-ion pair, capable of yielding 3,5-cyclocholestan-6α-yl chloride, is presumably formed. Most of this ion pair must be transformed to the 6β-variety, which subsequently yields predominantly 6β-chloride IX. However, the details of this transformation of 6α- to 6β-ion pairs cannot be described.

It is interesting to contrast the results obtained with 3,5-cyclocholestan-6β-ol (IV) with those obtained with allylic alcohols by Professor W. G. Young and his co-workers[29] in these laboratories. With allylic chlorosulfinates, there can be made dominant an SNi′ mechanism[30] which results in allylic rearrangement. Whether this SNi′ mechanism involves a one-stage cyclic rearrangement, for which the geometry is favorable, or ionization to an intimate, rigidly oriented carbonium chlorosulfinate ion pair,[1] followed by internal return, has not been decided.[29] There is sufficient analogy[31] between homoallylic and allylic situations to inquire regarding the occurrence of an SNi′ mechanism for the decomposition of 3,5-cyclocholestan-6β-yl chlorosulfinate (V). The present results do not suggest any appreciable operation of an SNi′ mechanism in the decomposition of 3,5-cyclocholestan-6β-yl chlorosulfinate (V), even in ether, the solvent so favorable for SNi′ in the allylic area.[10,29] However, examination of models shows that the geometry is sufficiently less favorable for either a 6-ring cyclic rearrangement of the chlorosulfinate V or collapse of a suitably oriented ion pair VI to cholesteryl chloride, that the present observations are not too significant for the allylic situation.

No appreciable effect of pyridine was observed on the results of reaction of thionyl chloride with the 3,5-cyclocholestan-6β-ol (IV). Although the addition of pyridine often reverses the stereochemical outcome[19,32] of alcohol–thionyl chloride reactions, the tendency for alkyl–oxygen ionization is apparently so pronounced in the present case that no appreciable SN2 reaction is introduced on addition of pyridine.

The hydrolysis of 3,5-cyclocholestan-6β-yl chloride (IX) in 90% dioxane is quite analogous to that of the trichloroacetate,[3] the alcohol product consisting mainly of 3,5-cyclocholestan-6β-ol (IV) and partly of cholesterol. Ion pair return[25,28] is more serious during solvolysis of the chloride than the trichloroacetate, 20% of cholesteryl chloride being formed from the 6β-chloride IX. When the reaction mixture did not contain lithium acetate and thus became acidic, the 3,5-cyclocholestan-6β-ol (IV) formed initially is converted to cholesteryl chloride (X), chloride ion competing successfully with water for the intermediate hybrid ion. In acetic acid, competition of halide ion with solvent is even more successful, and Heilbron[33] was able to prepare cholesteryl chloride, bromide and iodide in excellent yields by the addition of concentrated aqueous hydrogen halide to a solution of 3,5-cyclocholestan-6β-yl methyl ether in glacial acetic acid.

(28) S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, THIS JOURNAL, **78**, 328 (1956).

(29) F. F. Caserio, G. E. Dennis, R. H. DeWolfe and W. G. Young, *ibid.*, **77**, 4182 (1955).

(30) J. D. Roberts, W. G. Young and S. Winstein, *ibid.*, **64**, 2157 (1942).

(31) See, *e.g.*, C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145 (1952).

(32) *E.g.*, M. Balfe and J. Kenyon, *J. Chem. Soc.*, 463 (1940).

Experimental Part

Cholesteryl Chloride.—A mixture of 200 g. of cholesterol and 240 g. of thionyl chloride was allowed to stand for 24 hours. The partially solid reaction mixture was poured onto ice and potassium carbonate, and the chloride was filtered off and washed with water. The wet solid was transferred to a beaker and warmed with 2 liters of redistilled Skellysolve F (b.p. 36–41°), the water layer was removed with a pipet, and the solution was poured through an alumina column (10 × 33 cm., *ca.* 1.6 kg.). Skellysolve F was added until the total eluate volume had reached 3 liters. The solvent was distilled off on the steam-bath, and 800 cc. of acetone was added to the very light yellow oil. The chloride, m.p. 96–97°, crystallized almost immediately. On concentration, the filtrate yielded an additional amount of halide, m.p. 95.5–96.5°, for a total yield of 201.5 g. (95.6%). The product is purer and the procedure simpler than the usual charcoal treatment of a hot alcohol solution of crude chloride.

3,5-Cyclocholestan-6β-yl Chloride.—A 4.35-ml. (7.2 g., 0.06 mole) quantity of redistilled thionyl chloride was added to an ice-cooled solution of 21.6 g. (0.056 mole) of 3,5-cyclocholestan-6β-ol[3] in 200 ml. of absolute ether. The solvent was evaporated at the aspirator without heating, 200 cc. of redistilled pentane was added to the white solid, the pentane solution was filtered through 35 g. of calcium carbonate, and then it was evaporated to dryness at room temperature. The solid was dissolved by very brief warming with *ca.* 150 cc. of dry acetone and crystallized by cooling the solution in a Dry Ice bath. The white solid was filtered from the cold solution and transferred to a vacuum desiccator for removal of the residual solvent. The yield was 17 g. (75%) of material of m.p. 73–78°. In chloroform, the value of $[\alpha]^{23}D$ (*c* 3.87) decreased with time from an initial value of +27.5° to a final value of −30.1°. The observed value for cholesteryl chloride was −30.7 ± 1°. In carbon tetrachloride the value of $[\alpha]^{23}D$ of the chloride product was +29.2° (*c* 1.61), no drift being apparent.

Anal. Calcd. for $C_{27}H_{45}Cl$: C, 80.05; H, 11.20; Cl, 8.75. Found: C, 80.40; H, 11.12; Cl, 8.54.

The chloride preparation was analyzed for "active chloride" by dissolving a 25–50 mg. sample in 25 ml. of dry acetone and adding a 5-ml. aliquot of *ca.* 0.025 *N* standard aqueous silver nitrate. After about 5 minutes, 5 cc. of nitrobenzene was added, followed by 50 cc. of water, 5 cc. of 50% clear, chloride-free nitric acid and *ca.* 4 cc. of ferric ammonium sulfate solution. After vigorous swirling, the solution was titrated with standard potassium thiocyanate to a light pink end-point. The "active chloride" content was calculated as the percentage of the theoretical silver nitrate actually consumed. Added cholesterol, 3,5-cyclocholestan-6β-ol, or cholesteryl chloride in amounts up to 100 mg. had no effect on the analysis.

The average of 14 analyses was 84.3 ± 2.1% "active chloride" for the above halide. After 5 days' storage at room temperature over Drierite, 3 analyses gave 83.6 ± 1.9% "active chloride."

Other preparations of the chloride were carried out in the presence of 0.1 equivalent of pyridine, but the product was unstable, turning yellow-brown within a week and analyzing

(33) J. H. Beynon, I. M. Heilbron and F. S. Spring, *ibid.*, 907 (1936).

low for total chloride. In one case, however, the method of purification apparently removed the pyridine impurity and a sample stored over Drierite for 199 days had the same "active chloride" content and rotation as when freshly prepared.

Chloride from 3,5-Cyclolestan-6α-ol.—Three preparations of chloride from 3,5-cyclocholestan-6α-ol and thionyl chloride were carried out, one in ether with pyridine, a second in ether without amine, and a third in pentane with N,N-diisopropyl-*o*-toluidine.[11] Only the last gave enough "pure" material for experimental purposes, and the details of only this preparation will be given.

3,5-Cyclocholestan-6α-ol[3] (3.2 g., 0.0083 mole) and the amine (1.86 cc., 1.66 g., 0.0087 mole) were dissolved in 50 cc. of redistilled pentane, and the solution was cooled to −70°. Thionyl chloride (0.63 cc., 0.0088 mole) was added, and a white precipitate formed immediately. Pentane (60 cc.) was added, the solution was allowed to warm up, and the white solid was filtered off, washed with pentane, and vacuum dried to a weight corresponding to almost theoretical for amine hydrochloride (*ca.* 2.2 g.). The solvent was removed at the aspirator, the oil was dissolved in dry acetone, and the acetone solution was cooled in a Dry Ice bath. The white solid which resulted was filtered off and vacuum dried to yield 0.74 g. (22%) of material, $[\alpha]^{22}D$ +43.5° (*c* 1.84, $CHCl_3$) (within 3 minutes), $[\alpha]^{22}D$ −25.5° (after 24 hours). The "active chloride" content was 78.6%, the total chloride 89.4%.

Anal. Calcd. for $C_{27}H_{45}Cl$: C, 80.05; H, 11.20; Cl, 8.75. Found: C, 80.35; H, 11.11; Cl, 7.82.

The acetone filtrates from the above preparation yielded additional fractions with "active chloride" contents of 50–60%, but these were sticky or rapidly turned brown, and so were discarded.

Hydrolysis of 3,5-Cyclocholestan-6β-yl Chloride.—One of the two runs, the unbuffered one, will be described in detail. A 10-ml. quantity of water was added to 1.6706 g. of chloride (83.6% "active," 97% mixed chlorides) dissolved in 90 ml. of dioxane. After 39 hours, the solution was diluted with water and extracted with chloroform. The chloroform solution was washed with water and then evaporated on the steam-bath. The residual solvent was removed at the oil pump and the semi-solid was dissolved in redistilled pentane and chromatographed through stock alumina (33 g., 2 × 11 cm.). Designating pentane by P and ether by E, the following fractions were obtained: (1) 100 ml. of P, from which the residue was 1.2921 g. of material, m.p. 93–95°, mixed m.p. with cholesteryl chloride, 94–96°; (2) 50 P, no residue; (3) 60 P, no residue; (4) 80 E, 76:2 mg. of residue leading to 133 mg. of digitonide; (5) 80 E, 185.6 mg. of residue, m.p. 145–147°, mixed m.p. with cholesterol, 146–147°; (6) 50 E, no residue. From these results the weights of products were summarized as: 1292 mg. of cholesteryl chloride; 44 mg. of 3,5-cyclocholestan-6β-ol; 32 + 186 mg. cholesterol; 94% recovery. Of the 1292 mg. of cholesteryl chloride, an estimated 210 mg. was present in the original chloride specimen.

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[CONTRIBUTION FROM THE ROHM & HAAS COMPANY]

t-Carbinamines, RR′R″CNH₂. III. The Preparation of Isocyanates, Isothiocyanates and Related Compounds[1]

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Secondary and tertiary alkyl isocyanates were obtained in 50–80% yields from the base-catalyzed cleavage of N-alkylcarbamates. The principal products from primary alkyl isocyanates were trialkyl isocyanurates. *tert*-Alkyl isocyanates and isothiocyanates were obtained from the distillation of the corresponding symmetrical disubstituted ureas and thioureas. Elimination of olefins occurred when these urea derivatives were heated with strong acids. Derivatives of the isocyanates and isothiocyanates and other related compounds were prepared.

Thermal dissociation of carbamates to isocyanates and alcohols is difficult and requires temperatures above 250°. The lower N-alkylcarbamates, which distil without decomposition under atmospheric pressure, must therefore be cracked in vapor phase operation.[2] The requisite temperatures for liquid phase cleavage can be attained by the distillation of esters of high boiling alcohols.[2] Although Raney nickel effects the cleavage of urethans, it has little effect on N-substituted carbamates.[3]

The dissociation of mono-N-alkylcarbamates has now been found to proceed rapidly at 170–230° in the presence of strong bases. Although this reaction is general, its usefulness for the synthesis of isocyanates is complicated by two side reactions. These are recombination of the isocyanate with the alcohol which accompanies it in the distillate and condensation of the isocyanates to trimers or other polymeric materials.

The base-catalyzed pyrolysis of a series of N-alkylcarbamates was investigated (Table I). Tertiary alkyl isocyanates (RR′R″CNCO) were obtained in good yield. The products do not combine with alcohols in the absence of strong base catalysts, and resist thermal or base-catalyzed polymerization.

Secondary alkyl isocyanates (RR′CHNCO) were obtained in moderate yield. Recombination, which is auto-catalyzed,[4] was the principal side reaction, but could be retarded by keeping the distillate cold and by prompt separation of the alcohol from the isocyanate. Trimerization was relatively slow and only small amounts of the impure isocyanurates, contaminated by the corresponding 1,3-dialkylureas, were obtained.

Primary alkyl isocyanates (RCH_2NCO) were also obtained but their rapid trimerization led to the corresponding isocyanurates as the principal or sole product. The presence of small amounts of the isocyanates in the distillates was demonstrated by titration with amine.

A wide variety of bases effectively promoted the cleavage of N-alkyl-carbamates. In a series of experiments based on ethyl N-*t*-octylcarbamate,[5] bivalent oxides and hydroxides gave the best re-

(1) Presented in part before the Division of Organic Chemistry at the 119th Meeting of the American Chemical Society, Cleveland, Ohio, April 10, 1951.

(2) C. E. Schweitzer, U. S. Patents 2,409,712 and 2,416,068.

(3) M. Métayer, *Bull. soc. chim. France*, 802 (1951).

(4) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 19 (1949).

(5) In this series, *t*-octyl represents 1,1,3,3-tetramethylbutyl.