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7-DEHYDROCHOLESTERYL CHLORIDE AND BROMIDE

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The purpose of this paper is to describe the preparation of 7-dehydrocholesteryl chloride (III) and bromide (IX) hitherto unreported in the literature. The preparation of these compounds directly from 7-dehydrocholesterol with halogenating agents appeared unpromising in view of previous work on ergosterol. Rygh (1) found that treatment of ergosterol with phosphorus oxychloride gave as the chief product ergostatetraene A along with a small amount of ergosteryl phosphate but none of the desired ergosteryl chloride. Consequently, it was not surprising that our attempts to prepare the desired halides from 7-dehydrocholesterol with thionyl chloride, oxalyl chloride, phosphorus oxychloride, and phosphorus tribromide were unsuccessful.

However, it has been found that 7-dehydrocholesteryl chloride and bromide may be prepared from cholesteryl chloride (I)[1] and bromide (VII) resp. Cholesteryl chloride was brominated in carbon tetrachloride with N-bromosuccinimide according to the method of Ziegler (2) to give in 81% yield 3-chloro-7-bromo-Δ^5-cholestene (II). A 76% yield was obtained with N-bromophthalimide. 3-Chloro-7-bromo-Δ^5-cholestene was selectively dehydrohalogenated by being refluxed with dimethylaniline in toluene to give the desired 7-dehydrocholesteryl chloride in 14.5% yield. Similarly, cholesteryl bromide was converted to 3,7-dibromo-Δ^5-cholestene (VIII) in 58.5% yield with N-bromosuccinimide, and in 42% yield with N-bromophthalimide; the dibromo compound on treatment with dimethylaniline in toluene gave a 10.6% yield (crude) of 7-dehydrochlolesteryl bromide (IX).

The postulated structures of the intermediate 7-bromo compounds were substantiated in the following manner. 7-Hydroxycholesteryl chloride (V) prepared according to Marker and co-workers (3) (I → IV → V) was treated with phosphorus tribromide to give 3-chloro-7-bromo-Δ^5-cholestene identical in melting point and optical rotation with the product obtained by direct bromination of cholesteryl chloride. It is apparent that introduction of bromine in the C-7 position creates a new asymmetric center; thus two diastereomeric bromo compounds are possible. They may be designated as *e.g.* 3-chloro-7(α)-bromo-Δ^5-cholestene and 3-chloro-7(β)-bromo-Δ^5-cholestene. However, in the work being presented here we prefer not to specify such configurations.

As an incidental experiment, 7-hydroxycholesteryl chloride was converted to 3,7-dichloro-Δ^5-cholestene (VI) with thionyl chloride.

The postulated structures of the 7-dehydrocholesteryl chloride and bromide may be supported by the following arguments: (A) analyses show the presence of only one atom of halogen; (B) the method of synthesis is based on the estab-

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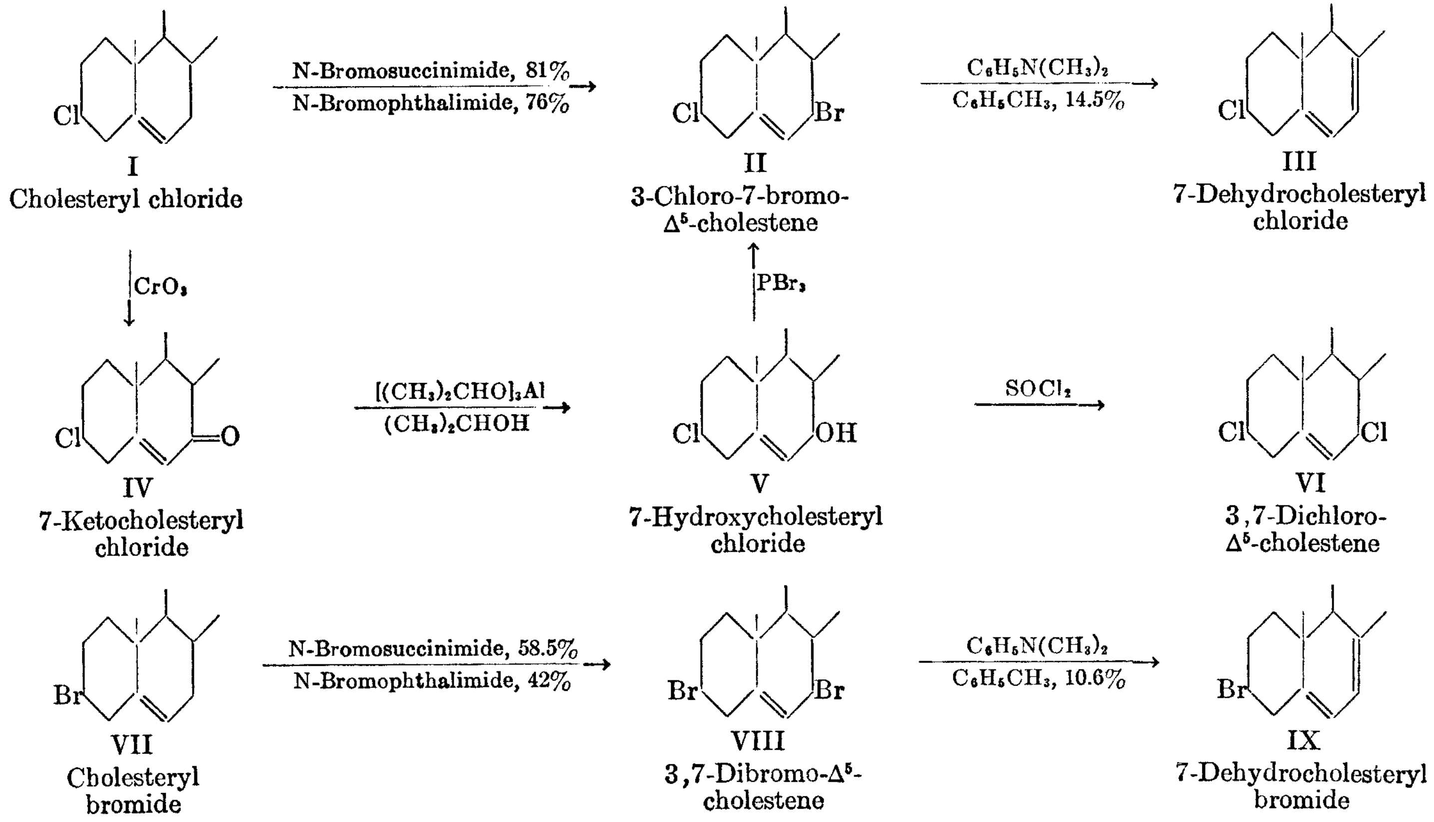
[1] Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946), has presented evidence which shows that cholesteryl chloride is actually 3(β)-chloro-Δ^5-cholestene.


Cl
I
Cholesteryl chloride
N-Bromosuccinimide, 81%
N-Bromophthalimide, 76%
Cl
Br
II
3-Chloro-7-bromo-Δ⁵-cholestene
C₆H₅N(CH₃)₂
C₆H₅CH₃, 14.5%
Cl
III
7-Dehydrocholesteryl chloride
CrO₃
PBr₃
Cl
O
IV
7-Ketocholesteryl chloride
[(CH₃)₂CHO]₃Al
(CH₃)₂CHOH
Cl
OH
V
7-Hydroxycholesteryl chloride
SOCl₂
Cl
Cl
VI
3,7-Dichloro-Δ⁵-cholestene
Br
VII
Cholesteryl bromide
N-Bromosuccinimide, 58.5%
N-Bromophthalimide, 42%
Br
Br
VIII
3,7-Dibromo-Δ⁵-cholestene
C₆H₅N(CH₃)₂
C₆H₅CH₃, 10.6%
Br
IX
7-Dehydrocholesteryl bromide

lished structure of the intermediate 7-bromo compound; (C) the high negative rotations of 7-dehydrocholesteryl chloride and bromide are in conformity with the optical rotation theory of 7-dehydrosterols (4); and (D) the two compounds have the qualitatively characteristic ultraviolet absorption spectrum (Figure 1) of 7-dehydrosterols, such as ergosterol and 7-dehydrocholesterol (5). Conversion

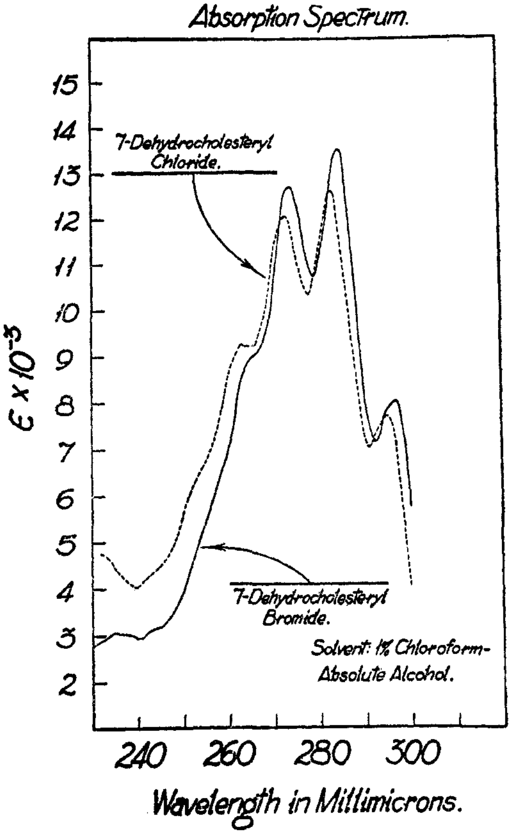


FIG. 1

TABLE I

PHYSICAL PROPERTIES

COMPOUNDS	M.P., °C.	$[\alpha]_D(CHCl_3)$	ULTRAVIOLET ABSORPTION SPECTRUM MAXIMA,[a] mμ
3-Chloro-7-bromo-Δ^5-cholestene	136–138 d.	−223°	—
3,7-Dichloro-Δ^5-cholestene	117–119	−165°	—
3,7-Dibromo-Δ^5-cholestene	142.5–144.5	−198.4°	None
7-Dehydrocholesteryl chloride	130–132	−91.1°	263, 273, 283 and 295
7-Dehydrocholesteryl bromide	142–144	−78.7°	235, 274, 285 and 297

[a] Solvent: 1% chloroform-absolute alcohol, the substance was dissolved in 1 ml. of chloroform and rapidly diluted to 100 ml. with absolute alcohol.

of the 7-dehydrocholesteryl halides to 7-dehydrocholesterol or its acetate would chemically corroborate the structures. This, unfortunately, has not been accomplished under a variety of conditions. In this connection it is interesting to note that 7-dehydrocholesteryl chloride was recovered unchanged when refluxed with silver acetate in benzene for 16 hours, and when shaken with silver acetate or silver oxide in ether for 64 hours.

In Table I there are listed the physical properties of the five new halogenated sterols herein presented.

In light of subsequent experience with bromination of steroids with N-bromosuccinimide, it is believed that our yields may be open for improvement. The yields in the bromination reaction may be improved by using more than one equivalent of the brominating agent, and, in the selective dehydrohalogenation reaction, by refluxing with another stripping agent such as γ-collidine in xylene for as short a time as 15–20 minutes.

An investigation of the ultraviolet irradiation of 7-dehydrocholesteryl chloride and bromide to give possibly Vitamin D_3 chloride and bromide has been set aside for future work.

EXPERIMENTAL

3-Chloro-7-bromo-Δ^5-cholestene (II). A. A mixture of 1 g. (0.0025 *M*) of cholesteryl chloride (I), m.p. 94–96°, 0.45 g. (0.0025 *M*) of N-bromosuccinimide, and 25 ml. of carbon tetrachloride was refluxed for 10 minutes, cooled, and the succinimide was removed. The filtrate was evaporated *in vacuo* and this gave a very viscous yellow oil intermixed with solid. The residue was worked with acetone and the resulting white solid was collected, wt. 0.44 g., m.p. 135–140° d. From the mother liquor two additional fractions of product were obtained, 0.09 g., m.p. 131–136° d., and 0.3 g., m.p. 135–137° d. The three fractions were combined and recrystallized three times from acetone, wt. 0.37 g., m.p. 136–138° d. (very slight decomposition at 134–136°), $[\alpha]_D^{28}$ −234.4°, $[\alpha]_D^{33}$ −223° (12.8 mg., 7.2 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube, gave α_D^{28} −1.50°, and α_{α}^{33} − 0.804° resp.).

Anal. Calc'd for $C_{27}H_{44}BrCl$: C, 67.00; H, 9.16; BrCl, 23.84.
Found: C, 67.31; H, 9.36; BrCl, 24.00.

In another run with 24.27 g. (0.06 *M*) of cholesteryl chloride (I), 10.8 g. (0.06 *M*) of N-bromosuccinimide and 250 ml. of carbon tetrachloride there was obtained 23.6 g. of pure product, m.p. 136–139° d., 81% yield.

B. A mixture of 4.05 g. (0.01 *M*) of cholesteryl chloride (I), 2.26 g. (0.01 *M*) of N-bromophthalimide and 50 ml. of carbon tetrachloride was refluxed for 10 minutes, cooled, and the phthalimide was removed. The filtrate was evaporated *in vacuo*, and the residue was treated with acetone and was set in the refrigerator overnight. The solid was collected, washed with acetone, wt. 3.68 g., m.p. 134–140° d. (the majority of the material melted at 137–140°), 76% yield. Recrystallization from acetone gave 2.87 g. of product, m.p. 139–142° d.

C. A solution of 0.42 g. of 7-hydroxycholesteryl chloride (V) in 20 ml. of dry benzene was treated in the cold with 0.05 ml. of phosphorus tribromide, and the mixture was allowed to stand at room temperature overnight. Ice-water was added and the benzene extract was washed successively with water, sodium bicarobnate solution and saturated saline, and was dried with magnesium sulfate. The benzene was evaporated *in vacuo* and the residue was dissolved in acetone. This solution was maintained at −6° for 4 days, and the crystals that separated were collected, m.p. 132–136° d. Recrystallization to constant melting point and rotation gave 35 mg., m.p. 137.5–139.5° d., $[\alpha]_D^{33}$ −223° (7.0 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube, gave α_D^{33} −0.78°). A mixed melting point determination with the material prepared above, preparation *A*, showed no depression, m.p. 138–140° d.

3,7-Dichloro-Δ^5-cholestene (VI). A solution of 0.42 g. of 7-hydroxycholesteryl chloride (V) in 20 ml. of dry benzene was treated cold with 0.25 ml. of thionyl chloride, and the mixture was allowed to stand at room temperature overnight. The solvent and excess thionyl chloride were removed *in vacuo* and the residue was recrystallized four times from acetone, wt. 25 mg., m.p. 117–119°, $[\alpha]_D^{33}$ −165° (7.45 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube, gave α_D^{33} −0.62°).

Anal. Calc'd for $C_{27}H_{44}Cl_2$: C, 73.78; H, 10.09; Cl, 16.13.
Found: C, 74.18; H, 10.10; Cl, 15.76.

3,7-Dibromo-Δ^5-cholestene (VIII). A. A mixture of 2.45 g. (0.0055 *M*) of cholesteryl bromide (VII), m.p. 96–98.5°, 0.99 g. (0.0055 *M*) of N-bromosuccinimide, and 50 ml. of carbon tetrachloride was refluxed on the steam-bath for one hour, cooled, and the succinimide was removed. The filtrate was evaporated *in vacuo* and a viscous yellow-brown oil was obtained. The oil was worked with acetone giving crystals, wt. 1.26 g., m.p. 130–135.5° d. Four recrystallizations from acetone to constant melting point gave 0.33 g., m.p. 142.5–144.5° d., $[\alpha]_D^{31}$ −198.4° (12.5 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube gave α_D^{31} −1.24°). Additional amounts of the product can be obtained from the mother liquors. The product showed no absorption maxima in the ultraviolet.

Anal. Calc'd for $C_{27}H_{44}Br_2$: C, 61.36; H, 8.38; Br, 30.25.
Found: C, 61.69; H, 8.67; Br, 30.60.

In another run, a mixture of 8.98 g. (0.02 *M*) of cholesteryl bromide (VII), 3.6 g. (0.02 *M*) of N-bromosuccinimide, and 150 ml. of carbon tetrachloride was refluxed on the steam-bath for 12 minutes while being irradiated with an ultraviolet lamp. The product was worked up in the above described manner, 6.2 g., m.p. 137–144° d., 58.5% yield. Recrystallization from ether-acetone gave 4.59 g., m.p. 139–142° d.

B. A mixture of 9.0 g. (0.02 *M*) of cholesteryl bromide (VII), 4.52 g. (0.02 *M*) of N-bromophthalimide, and 75 ml. of carbon tetrachloride was refluxed for 20 minutes. The product was worked up in the usual manner, wt. 6.2 g., m.p. 133–140° d. Recrystallization from acetone gave 4.43 g., m.p. 142–145.5° d., 42% yield.

7-Dehydrocholesteryl chloride (III). A mixture of 1 g. of 3-chloro-7-bromo-Δ^5-cholestene (II), 0.5 ml. of dimethylaniline in 50 ml. of toluene was refluxed in a nitrogen atmosphere for 1.5 hours, cooled, and anhydrous magnesium sulfate was added. The mixture was filtered and the filtrate was evaporated *in vacuo*. This gave an oil, which was treated with alcohol and warmed. A partial solution resulted, ether was added to effect complete solution. The solution was concentrated and cooled and needles separated, wt. 0.17 g., m.p. 119–125°. The product was recrystallized from ether-methanol to constant melting point and ultraviolet absorption, wt. 0.12 g., 14.5% yield, m.p. 130–132°, $[\alpha]_D^{29}$ −91.1° (11.2 mg. in 2 ml. of chloroform, 1 dcm. semi-micro tube, gave α_D^{29} −0.51°), ultraviolet absorption maxima at 263, 273, 283, and 295 mμ, ϵ = 9250, 12070, 12600, and 7700 resp.

Anal. Calc'd for $C_{27}H_{43}Cl$: C, 80.45; H, 10.75; Cl, 8.80.
Found: C, 79.98; H, 10.73; Cl, 8.67.

7-Dehydrocholesteryl bromide (IX). A mixture of 1 g. of 3,7-dibromo-Δ^5-cholestene (VIII), 0.5 ml. of dimethylaniline, and 50 ml. of toluene was refluxed in a nitrogen atmosphere for 1.5 hours. The mixture was cooled and filtered after the addition of anhydrous magnesium sulfate. The water-white filtrate was evaporated *in vacuo* and gave an oily residue which was dissolved in ether-alcohol. Concentration and cooling gave an oil which on being worked became partially crystalline, wt. 0.23 g., mixture of white crystals and brown-yellow semi-solid. Two recrystallizations from ether-methanol gave 90 mg., m.p. 139–142.5°, 10.6% yield. A sample was recrystallized to constant melting point from ether-methanol, m.p. 142–144°, $[\alpha]_D^{30}$ −78.7° (15 mg. in 2 ml. chloroform, 1 dcm. semi-micro tube gave α_D^{30} −0.59°), ultraviolet absorption maxima at 235, 274, 285, and 297 mμ, ϵ = 3050, 12710, 13550, and 8040 resp.

Anal. Calc'd for $C_{27}H_{43}Br$: C, 72.46; H, 9.68; Br, 17.86.
Found: C, 72.77, 72.91; H, 10.39, 9.73; Br, 17.46.

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SUMMARY

7-Dehydrocholesteryl chloride and bromide have been prepared from cholesteryl chloride and bromide resp. with N-bromosuccinimide or N-bromophthalimide with subsequent elimination of hydrogen bromide.

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