and concentrated to one-half its original volume in a reduced pressure in a water bath. The concentrated solution was weakly basified with Na_2CO_3, washed with Et_2O, acidified with HCl, and extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and the solvent evaporated, giving 0.6 g. of a white solid, m.p. 80~84°. Recrystallization from petr. ether furnished colorless plates, m.p. 86~88°.

***trans*-1-Methyl-1,2,3,4-tetrahydro-2-naphthoic Acid (Xb)**——Four g. of (Ib) was reduced by refluxing with Zn-Hg (prepared from 20 g. of Zn and 2.0 g. of $HgCl_2$) for about 25 hr. as in the synthesis of (Xa) by method (i). The petr. ether-soluble substance (3.1 g; 83%) was obtained. Two recrystallizations from petr. ether furnished colorless plates, m.p. 80~82°. The melting point was depressed when mixed with a sample of (Xa); mixed m.p. 55~68°. *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.92; H, 7.59.

Summary

The configurations of (Ia) and (Ib) were confirmed by the aromatization of these compounds to the same naphthalene derivative (IX) and by the transformation of (Ia) to *cis*-1-methyl-1,2,3,4-tetrahydro-2-naphthoic acid (XVIa), which was prepared by the *cis*-reduction of 1-methyl-3,4-dihydro-2-naphthoic acid (XVII).

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71. Saburo Akagi and Kyosuke Tsuda: Steroid Studies. XXIII. Dehydrobromination of 7-Bromostigmasteryl Benzoate.

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Much work had hitherto been carried out by many workers on the dehydrobrominating reaction of 7α-bromocholesteryl benzoate. In the present investigation, dehydrobromination of 7-bromostigmasteryl benzoate, obtained by bromination with N-bromosuccimide, was carried out and details of the results are set herein.

Bromination of stigmasteryl benzoate was carried out with N-bromosuccimide in the same manner as for cholesteryl benzoate.[1~3] The resulting bromo compound was a stable one which showed optical rotation of $[\alpha]_D^{26}$ −123°. Comparing with $[\alpha]_D^{18}$ −172° for 7α-bromocholesteryl benzoate, it should have the same configuration as the more levorotatory 7α-bromocholesteryl benzoate.[2)*3]

When 7-bromostigmasteryl benzoate was treated with collidine, the chief reaction products were 7-dehydrostigmasteryl benzoate and 4,6,22-stigmastatrienyl benzoate. 7-De-

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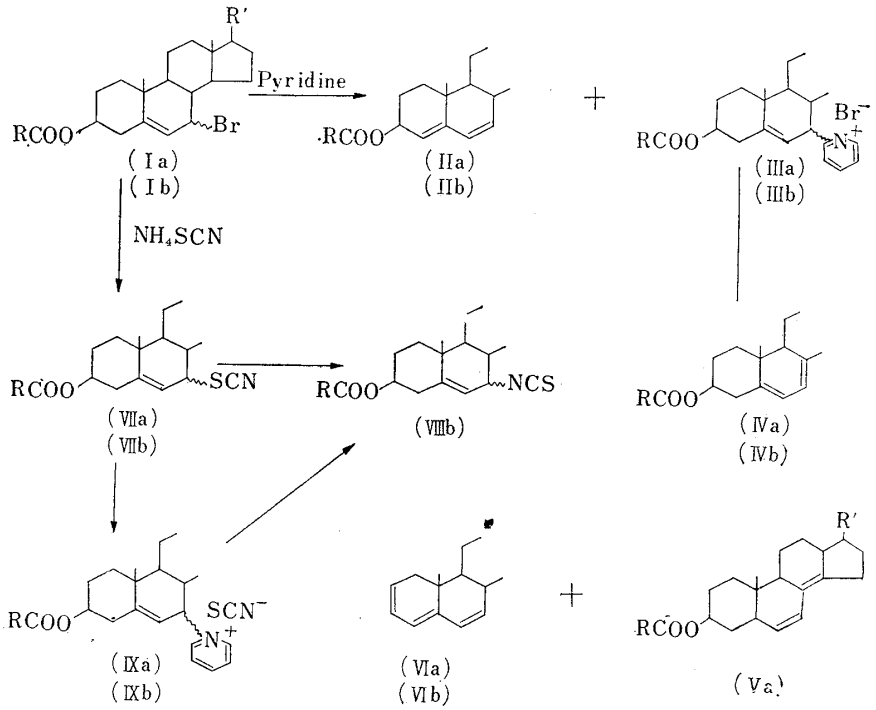
*3 Nowacki, *et al.* reported[4] that the more levorotatory 7-bromo derivatives of 3β-methoxycholest-5-ene and 3β-bromocholest-5-ene would be 7α-derivatives deduced from the results of their X-ray crystallography.

1) A. E. Bide, H. B. Henbest, E. R. H. Jones: J. Chem. Soc., **1948**, 1783; F. Hunziker: Helv. Chim. Acta, **38**, 1316 (1955); W. R. Nes: J. Am. Chem. Soc., **78**, 440 (1956); S. Bernstein, L. J. Binovi: J. Org. Chem., **14**, 433 (1949).
2) H. Schaltegger, F. X. Mullner: Helv. Chim. Acta, **34**, 1096 (1951); E. J. Corey, G. A. Gregoriou: J. Am. Chem. Soc., **81**, 3127 (1959).
3) K. Tsuda, K. Arima, R. Hayatsu: J. Am. Chem. Soc., **76**, 2934 (1954).
4) W. Nowacki, N. Burki: Chimia (Switz.), **10**, 254 (1956).

hydrostigmasteryl benzoate was identical with the product obtained by Wintersteiner[5] by the pyrolytic elimination reaction of 7-benzoyloxystigmasteryl benzoate. When 7-bromostigmasteryl benzoate was heated with pyridine, the chief reaction product was 7-pyridinium bromide (IIIa : $R=C_6H_5$), a minute amount of 4,6,22-stigmastatrienyl benzoate was obtained as a by-product, and a small amount of 7-dehydrostigmasteryl benzoate and stigmasteryl benzoate were also obtained. By boiling in xylene, degradation of 7-pyridinium bromide easily occurred, the main products being 4,6,22-stigmastatrienyl benzoate and 2,4,6,22-stigmastatetraëne (VIa), and a minute amount of 6,8(14),22-stigmastatrienyl benzoate (Va : $R=C_6H_5$) was also obtained. When 7-pyridinium bromide of cholesteryl benzoate*4 (IIIb) was treated with boiling xylene, the main products were also 7-dehydrocholesteryl benzoate and 2,4,6-triene (VIb).

The verification of the structures assigned to each of these derivatives of stigmasterol was made by comparing their ultraviolet absorption maximum and values of optical rotation with those of the corresponding cholestadienol and triene. The values of ultraviolet absorption maximum and optical rotation of these compounds are summarized in Table I.



a ····R′=-CH(CH3)-CH=CH-CH(C2H5)-CH(CH3)2 R=C6H5

b ····R′=-CH(CH3)-CH2-CH2-CH2-CH(CH3)2

Chart 1.

On treatment with ammonium thiocyanate in acetone at room temperature, 7-bromostigmasteryl benzoate (Ia) was found to undergo substitution readily and 7-thiocyanatostigmasteryl benzoate (VIIa : $R=C_6H_5$) was obtained in a good yield. 7-Thiocyanatocholesteryl benzoate (VIIb : $R=C_6H_5$) was also obtained*5 in a similar reaction with 7α-bromocholesteryl benzoate and this was identical with the thiocyanato derivatives obtained by

*4 This is the chief product when 7α-bromocholesteryl benzoate is treated with pyridine at 100°.

5* This result differs from one of Tsuda, Arima, and Hayatsu,[3] and it is not clear why there was such a difference between them.

5) O. Wintersteiner, W. L. Ruigh : J. Am. Chem. Soc., **64**, 1177 (1942).

Frederiksen[6] from cholesteryl benzoate with dithiocyanide with irradiation of a mercury lamp. By boiling of 7-thiocyanatocholesteryl benzoate (VIIb) in ethanol for one hour, (VIIb) underwent rearrangement smoothly to 7-isothiocyanatocholesteryl benzoate (VIIIb : R=C_6H_5). However, 7-thiocyanatostigmasteryl benzoate did not undergo rearrangement to 7-isothiocyanato derivative in the same condition, and even in a more drastic condition. When 7-thiocyanatocholesteryl benzoate (VIIb) was treated with pyridine at 100° to effect dehydrothiocyanation, the main product was 7-pyridinium thiocyanate (IXb) and a minute amount of 4,6-cholestadienyl benzoate (IIb) was also obtained. On boiling 7-pyridinium thiocyanate in xylene, the resultant main product was isothiocyanato derivative and the expected dehydrothiocyanation reaction did not occur.

Table I. Comparison between Derivatives of Stigmasterol and Cholesterol

Compound	$[\alpha]_D$	$[M]_D$	UV λ_{max} mμ (ε)
Cholesta-5,7-dien-3β-ol[a]	−113°	−434°	272 (11,000) 282 (12,100)*
Cholesta-5,7-dien-3β-ol benzoate	− 53°	−258°	
Stigmasta-5,7,22-trien-3β-ol	− 95°	−392°	272 (9,550) 282 (10,260)
Stigmasta-5,7,22-trien-3β-ol benzoate	− 42°	−216°	
Cholesta-4,6-dien-3β-ol	− 38°	−146°	241 (24,500)*
Cholesta-4,6-dien-3β-ol benzoate	− 92°	−448°	
Stigmasta-4,6,22-trien-3β-ol	− 52°	−209°	241 (20,500)
Stigmasta-4,6,22-trien-3β-ol benzoate	− 93°	−480°	
Cholesta-6,8(14)-dien-3β-ol	− 57°	−218°	252 (21,300)
Cholesta-6,8(14)-dien-3β-ol acetate	− 51°	−217°	252 (21,800)
Cholesta-6,8(14)-dien-3β-ol benzoate	− 62°	−302°	
Stigmasta-6,8(14),22-trien-3β-ol	− 55°	−225°	252 (16,540)
Stigmasta-6,8(14),22-trien-3β-ol acetate	− 49°	−222°	252 (17,820)
Stigmasta-6,8(14),22-trien-3β-ol benzoate	− 59°	−302°	
Cholesta-2,4,6-triene[b]	− 13°	− 49°	307 (15,200)*
Stigmasta-2,4,6,22-tetraëne	− 10°	− 39°	307 (10,530)

* Values in cyclohexane. Others in ethanol.

a) H. Schaltegger : Helv. Chim. Acta, **33**, 2101 (1950).

b) T. Schmutz, H. Schaltegger, M. Sanz : Helv. Chim. Acta, **34**, 111 (1951).

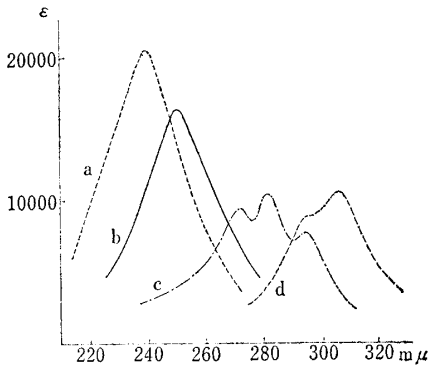


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

a ····· Stigmasta-4,6,22-trien-3β-ol
b ——— Stigmasta-6,8(14),22-trien-3β-ol
c -·-·-·- 7-Dehydrostigmasterol
d ---------- Stigmasta-2,4,6,22-tetraëne

Experimental*6

7-Bromostigmasteryl Benzoate (Ia)——A mixture of 2 g. of stigmasteryl benzoate and 1.2 g. of pulverized N-bromosuccinimide in 20 cc. of CCl_4 was stirred under irradiation of infrared lamp (375 W) and refluxed for 10 min. The reaction occurred at once and refluxed vigorously. After separating succinimide, the solution was cooled, filtered, and evaporated *in vacuo*. To the residual black syrup, Me_2CO was added and allowed to stand over night in a refrigerator. A crystalline product deposited gradually. The precipitate formed was collected by filtration. The crude product (about 0.5 g.) was dissolved in a small amount of Me_2CO with heating, filtered, and cooled. Separated product further crystallized from Me_2CO to 0.2 g. of colorless needles (Ia), m.p. 126~128°. $[\alpha]_D^{26}$ −123° (c=1.33, $CHCl_3$). *Anal.* Calcd. for $C_{36}H_{51}O_2Br$: C, 72.60; H, 8.57; Br, 13.45. Found : C, 72.79; H, 8.62; Br, 13.08.

*6 All melting points are not corrected.

6) E. Frederiksen, S. Lusberg : Ber., **88**, 684 (1955) (C. A., **49**, 14042 (1955)).

Dehydrobromination of 7-Bromostigmasteryl Benzoate with Pyridine——A solution of 6 g. of 7-bromostigmasteryl benzoate in 100 cc. of dehyd. pyridine was heated at 100° for 20 hr. Pyridine was evaporated *in vacuo*, the residual oil was treated with 50 cc. of a mixture of MeOH and EtOH, and allowed to stand with cooling. Separated precipitate (1.6 g.) was collected by filtration and the filtrate (A) was treated later. The crude product (1.6 g.) was heated with 40 cc. of EtOH and filtered hot. The mother liquor (B) was treated later.

Uudissolved substance crystallized from EtOH-benzene to 0.6 g. of leaflets, m.p. 156°. This was hydrolyzed with EtOH-KOH, and the product crystallized from EtOH-benzene to 0.25 g. of leaflets, m.p. 165°. Infrared spectra of the product showed a good similarity with that of stigmasterol, but it was contaminated with about 10% of 7-dehydrostigmasterol since ultraviolet absorption showed a maximum at 282 mμ (ε 2,000).

The mother liquor (B) was concentrated, allowed to stand in a refrigerator, and separated a crystalline precipitate. It was collected by filtration and recrystallized twice from EtOH-MeOH mixture to 0.7 g. of needles, m.p. 112~114°. This was hydrolyzed with EtOH-KOH, evaporated, and diluted with H_2O. Separated precipitate was collected by filtration and crystallized from MeOH to needles, m.p. 126~128°. $[\alpha]_D^{23}$ −51° (c=1.06, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.37; H, 11.58. UV: λ_{max}^{EtOH} 240 mμ (ε 20,500).

The mother liquor (A) was concentrated and 50 cc. of Et_2O was added. Precipitated oil solidified gradually. This was collected by filtration and washed with 50 cc. of Et_2O. The product (4.3 g.) was dissolved in EtOH, added with Et_2O, and precipitated fine needles. This further crystallized from $CHCl_3$-Et_2O to microneedles, m.p. 152°. $[\alpha]_D^{26}$ +53° (c=0.87, $CHCl_3$). *Anal.* Calcd. for $C_{41}H_{56}O_2NBr$: C, 72.99; H, 8.30; N, 2.07. Found: C, 73.13; H, 8.61; N, 2.18.

Dehyrobromination of 7-Bromostigmasteryl Benzoate with Collidine——A solution of 2 g. of 7-bromostigmasteryl benzoate in xylene was refluxed for 1 hr. with 5 cc. of collidine. Separated substance was filtered off and the filtrate was evaporated *in vacuo*. MeOH was added and after standing overnight, the precipitate formed was collected by filtration. This was recrystallized from EtOH-benzene to 0.7 g. of needles, m.p. 160~170° (A).

The filtrate was concentrated to a syrup, added with MeOH, and allowed to stand overnight to give 0.3 g. of microneedles. This was collected by filtration and hydrolyzed with KOH-EtOH by refluxing for 2 hr. After cooling, H_2O was added, the precipitated substance was collected by filtration, and crystallized from MeOH to 0.1 g. of leaflets. Ultraviolet absorption of the product showed a maximum at 239 mμ. This was recrystallized repeatedly from MeOH to 50 mg. of leaflets, m.p. 125~127°. This was identical with 4,6-dienol obtained by dehydrobromination of 7-bromostigmasteryl benzoate with pyridine.

The above-mentioned 0.7 g. of needles (A) was hydrolyzed with 5% KOH-EtOH by refluxing for 2 hr., cooled, H_2O was added, and the separated precipitate was collected by filtration. It was recrystallized repeatedly from EtOH-benzene to 0.4 g. of leaflets, m.p. 152~154°. $[\alpha]_D^{25}$ −95° (c=0.87, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 84.59; H, 11.53. UV λ_{max}^{EtOH} mμ (ε): 272 (9,550), 282 (10,262).

The product (7-dehydrostigmasterol) was converted into its benzoyl derivative in the usual manner and recrystallized from EtOH to needles, m.p. 178°. $[\alpha]_D^{26}$ −42° (c=1.19, $CHCl_3$). *Anal.* Calcd. for $C_{36}H_{50}O_2$: C, 84.04; H, 9.75. Found: C, 84.45; H, 10.05.

Degradation of 1-(3β-Benzoyloxy-7ξ-stigmasteryl)pyridinium Bromide——A mixture of 12 g. of stigmasteryl benzoate 7-pyridinium bromide and 240 cc. of xylene was refluxed for 1 hr. Black precipitate formed. After cool it was collected, washed with aq. $NaHCO_3$ solution and H_2O, and evaporated to dryness. Resulting oily residue was dissolved in petr. ether and chromatographed over alumina. The first fraction (100 cc.) gave 5.1 g. of an oily substance (A) and the next fraction (100 cc.) gave 0.4 g. of a crystalline substance, m.p. 120~140° (B). Further fraction gave a small amount of crystalline substance (C). The oily residue (A) was crystallized from Me_2CO to 2.4 g. of needles, m.p. 85~95°. This was further recrystallized from Me_2CO to needles, m.p. 98~100°. $[\alpha]_D^{25}$ −10° (c=1.02, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{44}$: C, 88.79; H, 11.21. Found: C, 88.33; H, 10.85. UV λ_{max}^{EtOH} mμ (ε): 295 (9480), 307 (10,530).

Substance (B) combined with (C) was recrystallized from EtOH to 0.35 g. of needles, m.p. 134°. This was hydrolyzed with KOH-EtOH, diluted with H_2O, and the precipitate formed was collected by filtration. This was recrystallized from EtOH-MeOH to 0.2 g. of leaflets, m.p. 142~144°. Further purification from EtOH-MeOH gave leaflets, m.p. 146°. $[\alpha]_D^{24}$ −55° (c=0.80, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.29. Found: C, 85.09; H, 11.35. UV: λ_{max}^{EtOH} 252 mμ (ε 16,540).

The dienol was benzoylated in the usual manner and recrystallized from EtOH, m.p. 136°. $[\alpha]_D^{24}$ −59° (c=1.22, $CHCl_3$). *Anal.* Calcd. for $C_{30}H_{50}O_2$: C, 84.04; H, 9.72. Found: C, 84.24; H, 9.63.

The dienol was acetylated with pyridine and Ac_2O, and recrystallized from EtOH to needles, m.p. 132°. $[\alpha]_D^{25}$ −49° (c=0.90, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{48}O_2$: C, 82.30; H, 10.61. Found: C, 82.05; H, 10.32. UV: λ_{max}^{EtOH} 252 mμ (ε 17,820).

Dehydrobromination of 7α-Bromocholesteryl Benzoate with Pyridine——A solution of 5 g. of 7α-bromocholesteryl benzoate in 50 cc. of pyridine was heated at 100° for 5 hr. The reaction mixture was cooled, evaporated *in vacuo*, and added with 25 cc. of MeOH. The separated crystalline precipitate (A) was collected by filtration. Precipitate (A), treated similarly as in the case of 7-bromostigmasteryl benzoate, gave 0.8 g. of 4,6-dienol, m.p. 120°.

Filtrate (B) was evaporated to dryness and added with Et_2O. The precipitate formed was collected by filtration and crystallized from MeOH-Et_2O to microneedles. Further purification from MeOH-Et_2O gave 7-pyridinium bromide, m.p. 168~170°(decomp.), identical with 7-pyridinium bromide prepared by Tsuda and Hayatsu.[3]

Degradation of 1-(3β-Benzoyloxy-7-cholesteryl)pyridinium Bromide—It was treated as in the case of stigmasteryl benzoate 7-pyridinium bromides. A solution of 1.7 g. of 7-pyridinium bromide in 35 cc. of xylene was refluxed for 30 min. The reaction mixture was cooled, washed with H_2O, dried, and evaporated *in vacuo*. Resulting oily residue (1.3 g.) was dissolved in petr. ether and chromatographed over 20 g. of alumina. The first fraction (75 cc.) afforded 0.6 g. of an oil, which crystallized from MeOH to needles, m.p. 70~72°. UV : λ_{max}^{EtOH} 307 mμ : (ε 15,100).

On further elution with petr. ether-benzene (1:1), 0.25 g. of a crystalline substance, m.p. 125~130°, was obtained, and recrystallized repeatedly from EtOH to needles, m.p. 138~139°. UV : λ_{max}^{EtOH} 282 mμ (ε 13,580). The product was identical with 7-dehydrocholesteryl benzoate.

7-Thiocyanatostigmasteryl Benzoate (VIIa)——To a solution of 0.5 g. of 7-bromostigmasteryl benzoate in 30 cc. of Me_2CO, 2 g. of NH_4SCN was added and stirred at room temperature. After NH_4SCN was dissolved the solution deposited a crystalline precipitate gradually. After 1.5 hr., it was collected by filtration and crystallized from Me_2CO-benzene to 0.25 g. of long thin needles, m.p. 146~148°. $[\alpha]_D^{22}$ −190°(c=1.01, $CHCl_3$). *Anal.* Calcd. for $C_{35}H_{51}O_2NS$: C, 77.48; H, 8.90; N, 2.43. Found : C, 77.02; H, 9.12; N, 2.31. It was not affected by refluxing in EtOH for 5 hr.

7-Thiocyanatocholesteryl Benzoate (VIIb)——To a solution of 1 g. of 7α-bromocholesteryl benzoate in 20 cc. of Me_2CO, 3 g. of NH_4SCN was added. It was shaken for 35 min., which deposited silky needles gradually. After standing for 2 hr., it was collected by filtration and recrystallized repeatedly from Me_2CO-benzene to 0.5 g. of long thin needles, m.p. 162~163°. $[\alpha]_D^{32}$ −161°(c=0.99, $CHCl_3$). *Anal.* Calcd. for $C_{35}H_{49}O_2NS$: C, 76.78; H, 8.95; N, 2.55. Found : C, 76.79; H, 9.00; N, 2.82. IR: ν_{max}^{Nujol} 2155 cm^{-1}(-SCN).

7-Isothiocyanatocholesteryl Benzoate (VIIIb)——A mixture of 0.35 g. of 7-thiocyanatocholesteryl benzoate and 20 cc. of EtOH was refluxed, by which the crystals dissolved gradually and formed a clear solution after 30 min. After heating for 1 hr., the solution was allowed to stand overnight with cooling. Separated crystalline product was collected by filtration and recrystallized from EtOH-benzene to 0.15 g. of plates, m.p. 146°. $[\alpha]_D^{26}$ −86°(c=1.04, $CHCl_3$). *Anal.* Calcd. for $C_{35}H_{49}O_2NS$: C, 76.78; H, 8.95; N, 2.55. Found : C, 77.24; H, 9.28; N, 2.47. IR : ν_{max}^{Nujol} 2128 cm^{-1}(-NCS).

1-(3β-Benzoyloxycholest-5-en-7ξ-yl)pyridinium Thiocyanate (IXb)——A solution of 5 g. of 7-thiocyanatocholesteryl benzoate in 35 cc. of pyridine was heated at 95~100° for 5 hr. Pyridine was evaporated *in vacuo*, 20 cc. of MeOH and 10 cc. of EtOH were added, and the separated precipitate was collected by filtration after cool. Yield, 2.2 g. The filtrate (A) was treated later and 2.2 g. of a product was recrystallized from EtOH-benzene to 1.5 g. of leaflets of the afore-mentioned 7-isothiocyanatocholesteryl benzoate.

The filtrate (A) was concentrated to dryness, Et_2O was added, and the separated precipitate was collected by filtration after cool. Yield, 3 g. This was recrystallized from Me_2CO-Et_2O to 1 g. of microneedles, m.p. 160~162°. $[\alpha]_D^{25}$ +66°(c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{40}H_{54}O_2N_2S$: C, 76.68; H, 8.62; N, 4.47. Found : C, 76.75; H, 8.44; N, 4.56.

Degradation of 1-(3β-Benzoyloxycholest-5-en-7ξ-yl)pyridinium Thiocyanate——Suspension of 1 g. of 1-(3β-benzoyloxycholest-5-en-7ξ-yl)pyridinium thiocyanate in 20 cc. of xylene was refluxed for 1 hr. The reaction mixture was filtered after cool and evaporated *in vacuo*. The oily residue was triturated with petr. ether, the separated crystalline substance was collected by filtration, and recrystallized from EtOH-benzene to leaflets, m.p. 146~147°. The product was identified with 7-isothiocyanatocholesteryl benzoate by mixed melting point and the infrared spectrum.

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Summary

7-Bromostigmasteryl benzoate obtained by bromination with N-bromosuccinimide was converted to stigmastatrienyl benzoate by treatment with collidine or pyridine. Degradation of 7-pyridinium bromides of stigmasteryl benzoate and cholesteryl benzoate was also carried out. Substitution of 7α-bromocholesteryl benzoate and 7ξ-bromostigmasteryl benzoate with ammonium thiocyanate was also examined. (Received September 24, 1960)