UDC 547.92

72. Saburo Akagi and Kyosuke Tsuda: Steroid Studies. XXIV.[1] Bromo Derivatives of Cholestenone. (1).

(*Takamine Research Laboratory, Sankyo Co., Ltd.,*[*1] *and The Institute of Applied Microbiology,*[*2] *University of Tokyo*)

In the previous paper,[2,3] it was reported that 3β-hydroxycholest-5-en-7-one benzoate was brominated to give 8-bromo compound. This paper describes further experiments on bromo derivatives of cholest-5-en-7-one.

Catalytic hydrogenation of cholesta-3,5-dien-7-one (I) with Raney nickel W-2 afforded cholest-5-en-7-one (IV) in a good yield. Treatment of cholest-5-en-7-one with N-bromosuccinimide in carbon tetrachloride gave a stable monobromo derivative (II), m.p. 119°, which showed ultraviolet absorption maximum at 245 mμ (ε 12,100). When (II) was treated with boiling pyridine for 3 hours, cholesta-3,5-dien-7-one was obtained in a good yield and no other by-product was obtained. From this results it appears that bromine may be situate at C-4 and not at C-8, and (II) is assumed to be 4-bromocholest-5-en-7-one.

It was reported by Jones[4] that treatment of 8-bromo compound with pyridine gave a $\Delta^{8(9)}$-unsaturated compound in a good yield. If (II) were a 8-bromo compound, (II) will be converted to $\Delta^{8(9)}$-unsaturated compound, but $\Delta^{8(9)}$-compound was not obtained besides the afore-mentioned $\Delta^{3,5}$-unsaturated compound. Thus, in this case of cholest-5-en-7-one, bromination with N-bromosuccinimide occurred at the allylic position in C-4 which is characteristic of bromination with N-bromosuccinimide. It was reported[5] also that cholest-4-en-3-one was brominated with N-bromosuccinimide at the allylic position in C-6. It may be very difficult to brominate C-8 under the effect of angular methyl groups.

Treatment of (II) with aniline at 130° for 1.5 hours gave a pale yellow product, m.p. 118° (UV: λ_{max} 245 mμ), which is assumed to have a phenylamino group substituted at C-4 position.

Bromination of 3β-hydroxycholest-5-en-7-one benzoate (VII) with N-bromosuccinimide gave a stable monobromide[2] (VIII), m.p. 212° (decomp.), and a monobromide (XI) of m.p. 121°, as a by-product. When 3β-hydroxycholest-5-en-7-one acetate was treated with N-bromosuccinimide under similar condition, elimination of acetoxyl group occurred with hydrogen bromide resulting from bromination reaction and it was converted to a monobromide (XI), m.p. 121°. Acetoxyl group at C-3 appears to be eliminated more easily than benzoyloxyl group in the same position under the above-mentioned condition. Treatment of the bromo-7-oxocholesteryl benzoate (VIII) with pyridine,[*3] aniline, and potassium acetate, gave dienones substituted by bromine or anilino-group and a by-product, cholesta-3,5-dien-7-one. In these reactions dehydrobromination did not proceed and dienones were formed by elimination of acyloxyl group.

When the monobromo compound (VIII) was treated in boiling pyridine for 10 hours, (VIII) was converted to a bromo-dienone (IX), m.p. 150°, with an absorption maximum at 295 mμ. The product was identified by the infrared spectrum with 6-bromochlesta-3,5-dien-7-one

*1 Nishi-shinagawa, Shinagawa-ku, Tokyo (赤木三郎).
*2 Yayoi-cho, Bunkyo-ku, Tokyo (津田恭介).
*3 By this reaction, Tsuda and Hayatsu[2] obtained 3β-hydroxycholesta-5,8(9)-dien-7-one benzoate.

1) Part XXIII: This Bulletin, **9**, 459 (1961).
2) K. Tsuda, R. Hayatsu: J. Am. Chem. Soc., **77**, 665 (1955).
3) *Idem*: *Ibid.*, **77**, 6582 (1955).
4) E.R.H. Jones, D.J. Wluka: J. Chem. Soc., **1959**, 911.
5) H. Inhoffen, G. Stoeck: Ann., **563**, 131 (1949).

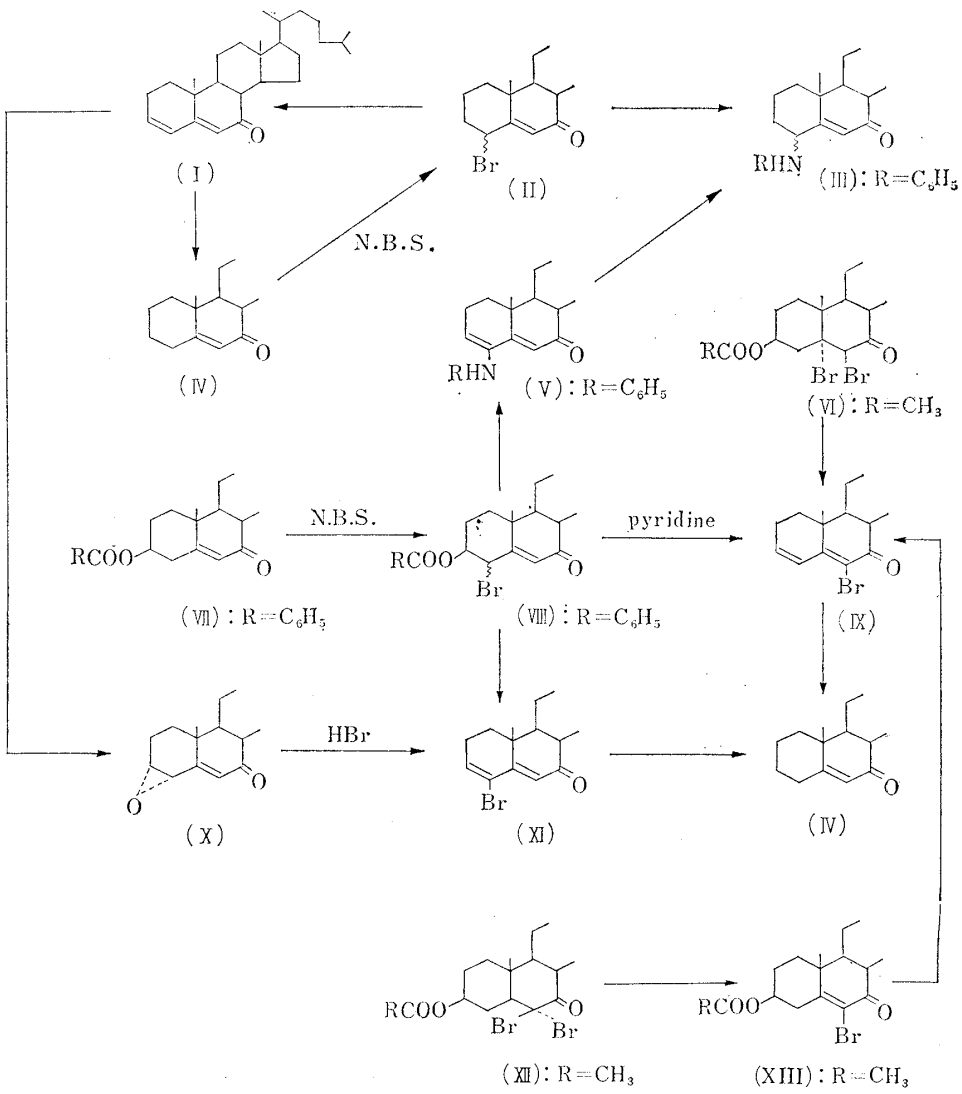

Chart 1.

(IX) which was obtained by Takeda and Komeno[6] from 3β-hydroxy-6,6-dibromocholestan-7-one acetate (XII) by dehydrobromination with pyridine. They assigned the structure of 6-bromocholesta-3,5-dien-7-one to it from detailed examination of experiment conditions, and infrared and ultraviolet spectra. The monobromo-dienone (IX) was also obtained in the present work by dehydrobromination reaction of 3β-hydroxy-5,6-dibromocholestan-7-one acetate (VI) with pyridine.

Treatment of the monobromo compound (VIII) with potassium acetate or hydrochloric acid in methanol gave a different bromo-dienone (XI), m.p. 121°, with an absorption maximum at 283 mμ. This compound was identified by mixed melting point and the infrared spectrum, as the bromo-dienone obtained by Jackson and Jones[7] from tribromide of cholesta-3,5-dien-7-one by debromination with sodium iodide. However, Jackson and Jones assumed it to be 6-bromocholesta-3,5-dien-7-one. Since catalytic hydrogenation to the two bromo-dienes (XI and IX) with Raney nickel W-2 gave the same product, cholest-5-en-7-one, difference of the structure between these two bromo-ketones must be in the position of bromine substituted in cholesta-3,5-dien-7-one. As (IX) is assigned to 6-bromocholesta-3,5-dien-7-one, (XI) is assumed to be 4-bromo or 8-bromo derivative. If (XI) were

6) K. Takeda, T. Komeno : This Bulletin, **4**, 432 (1956).
7) H. Jackson, E.R.H. Jones : J. Chem. Soc., **1940**, 659.

8-bromocholesta-3,5-dien-7-one, it should be converted to cholesta-3,5,8(9)-trien-7-one readily, but bromine in the bromo-ketone (XI) is very inactive, as Jackson and Jones[7] pointed out, and is not affected by dehydrobromination reaction with a base in boiling solution.

From these results, (XI) is more likely to be 4-bromocholesta-3,5-dien-7-one rather than 8-bromo derivative. From the point of infrared and ultraviolet absorption spectra, it conforms to the 4-bromo derivative, since it shows an ultraviolet absorption maximum at 283 mμ, exhibiting a bathochromic shift of 5 mμ from that of cholesta-3,5-dien-7-one. In addition, it is also recognized from infrared spectral data in Table I that the frequency of absorption in the shorter wave length of the two absorption bands corresponding to C=C stretching vibration decreases by 17 cm^{-1} on account of bromine substitution. In the case of 6-bromocholesta-3,5-dien-7-one,[6] the frequency of absorption in the longer wave length of the two bands similarly decreases by 38 cm^{-1}.

Oxidation of cholesta-3,5-dien-7-one (I) with perphthalic acid gave a 3,4-epoxide (X), m.p. 128° (UV : λ_{max} 239 mμ). Fission of this epoxide with hydrogen bromide in acetic acid solution at room temperature gave an afore-mentioned bromo-dienone (XI) in a good yield. In this experiment if (X) were an α-epoxide, it should be converted to 4-bromocholesta-3,5-dien-7-one (XI), while β-epoxide would be converted to 3-bromocholesta-3,5-dien-7-one. It is not likely to be a 3-bromo derivative, since the bromo-dienone (XI) is obtained from bromo-7-oxocholesteryl benzoate with potassium acetate in methanol solution. From these results, (XI) is assigned the structure of 4-bromocholesta-3,5-dien-7-one, and (X), the α-epoxide of cholesta-3,5-dien-7-one. Thus, on treatment with pyridine, the monobromo compound (VIII) is converted to 6-bromocholesta-3,5-dien-7-one and also to 4-bromocholesta-3,5-dien-7-one by treatment with potassium acetate or hydrochloric acid.

When the monobromo compound (VIII) was heated with aniline for one hour at 130°, an anilino-dienone (V), m.p. 129°, was obtained, whose absorption maximum appeared at 251 and 281 mμ. Catalytic hydrogenation of (V) with Raney nickel W-2 afforded 4-anilinocholest-5-en-7-one (III), which was also obtained from 4-bromocholest-5-en-7-one (II) by substitution with aniline. Thus, the anilino-dienone would be 4-anilinocholesta-3,5-dien-7-one (V). From these results, the monobromo compound (VIII) is assumed to be 3β-hydroxy-4-bromocholest-5-en-7-one benzoate.

Infrared spectra of the bromo derivatives prepared in the present work are listed in

Table I. Infrared Absorptions of Bromo Derivatives of Cholesten-7-one

Compound	C=O Stretching vibrations (cm^{-1})			C=C Stretching vibrations (cm^{-1})	
	ester	-CO-	Δ(C=O)	-C=C	Δ(C=C)
Cholest-5-en-7-one		1667		1634	
4-Bromocholest-5-en-7-one		1682	+15	1619w	−15
3β-Hydroxycholest-5-en-7-one benzoate*	1712	1668		1634	
3β-Hydroxy-4-bromocholest-5-en-7-one benzoate	1721	1669	+ 1	1626w	− 8
4-Anilinocholest-5-en-7-one		1657		1624	
3α,4α-Epoxycholest-5-en-7-one		1671		1629	
Cholesta-3,5-dien-7-one		1661		1631 1601	
4-Bromocholesta-3,5-dien-7-one		1675	+14	1614 1592	−17 − 9
6-Bromocholesta-3,5-dien-7-one		1684	+23	1623 1558	− 8 −43
4-Anilinocholesta-3,5-dien-7-one		1652		1620 1612	
3β-Hydroxycholest-5-en-7-one acetate	1733	1675		1634	
3β-Hydroxy-6-bromocholest-5-en-7-one acetate	1730	1685	+10	1595	−39

* Value in $CHCl_3$, others in Nujol.

Table I. As mentioned above, bromine substitution at the double bond in cholesta-3,5-dien-7-one decreases the frequency of C=C stretching vibration and bromine substitution at C-4, as in the case of (II) and (VIII), decreases its intensity. Examples of other reactions, accompanying bromine migration as in the case of (VIII) to (IX), will be given in detail in the following paper.

Experimental*4

Cholest-5-en-7-one (IV)——A solution of 1 g. of cholesta-3,5-dien-7-one dissolved in 40 cc. of dioxane, with 2 g. of Raney Ni W-2, was hydrogenated in atmospheric pressure at room temperature. When absorption of H_2 stopped, the reaction mixture was filtered and evaporated to a crystalline residue. The product was recrystallized from EtOH to 0.6 g. of leaflets, m.p. 127~128°. $[\alpha]_D^{25}$ −134° (c=1.00, $CHCl_3$). UV : λ_{max}^{EtOH} 238 mμ (ε 13,950).

4-Bromocholest-5-en-7-one (II)——To a solution of 6.5 g. of cholest-5-en-7-one in 70 cc. of dehyd. CCl_4, 3.7 g. of N-bromosuccinimide was added and the mixture was refluxed for 5 min. under irradiation of infrared ray lamp (375 W). The reaction proceeded at once and succinimide separated. The pale yellow reaction mixture was cooled, filtered, and the filtrate was evaporated *in vacuo* to dryness. Resulting oily residue was dissolved in Me_2CO and allowed to stand with cooling. A crystalline product deposited gradually, which was collected by filtration. After crystallization from Et_2O-MeOH, 3.5 g. of a product (m.p. 105~110°) was obtained. Further recrystallization from Et_2O-MeOH gave a pure sample of m.p. 118~119°. $[\alpha]_D^{25}$ −89° (c=1.01, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{43}OBr$: C, 69.97; H, 9.28; Br, 17.28. Found : C, 70.01; H, 9.18; Br, 17.21. UV : λ_{max}^{EtOH} 245 mμ (ε 12,100).

Dehydrobromination of 4-Bromocholest-5-en-7-one (II)——A solution of 0.5 g. of 4-bromocholest-5-en-7-one in 15 cc. of pyridine was refluxed for 3 hr. Resulting black solution was evaporated *in vacuo*, MeOH was added, and the solution was allowed to deposit a crystalline product with cooling. The crystalline product isolated by filtration weighed 0.35 g. Ultraviolet absorption of the product was at 278 mμ, not at 240~250 mμ. The product was recrystallized from MeOH to 0.25 g. of leaflets, m.p. 110~112°, and recrystallized further from EtOH to a pure sample of m.p. 113°. $[\alpha]_D^{25}$ −298° (c=1.01, $CHCl_3$). UV : λ_{max}^{EtOH} 278 mμ (ε 24,250). This was identified as cholesta-3,5-dien-7-one by mixed melting point and the infrared spectrum.

4-Anilinocholest-5-en-7-one (III)——A mixture of 0.5 g. of 4-bromocholest-5-en-7-one and 10 cc. of aniline was heated at 130° for 1.5 hr. Resulting black solution was cooled and added into aq. HCl solution. Crystalline product that separated was collected by filtration, washed, dried, dissolved in benzene-petr. ether, and chromatographed over 30 g. of alumina. The first fraction (100 cc.) was evaporated *in vacuo* and the solid residue crystallized from EtOH to 0.3 g. of yellow needles, m.p. 116~117°. Further recrystallization from EtOH gave pale yellow needles, m.p. 117~118°. $[\alpha]_D^{25}$ −50° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{33}H_{49}ON$: C, 83.45; H, 10.32; N, 2.94. Found : C, 83.28; H, 10.22; N, 3.05.

3β-Hydroxy-4-bromostigmasta-5,22-dien-7-one Benzoate——A mixture of 7 g. of 7-oxostigmasteryl benzoate, 3.5 g. of N-bromosuccinimide, and 15 mg. of benzoyl peroxide in 95 cc. of CCl_4 was heated on a steam bath. The reaction started vigorously and succinimide separated. The reaction mixture was cooled and filtered. The filtrate was evaporated *in vacuo* almost to dryness. Resulting oily gum was added with petr. ether and the precipitate was collected by filtration. Crude product weighed 1.7 g. The product was heated with Me_2CO, filtered while hot, and this was repeated twice in the same manner. Insoluble substance (0.75 g.) was recrystallized twice from Me_2CO-benzene to 0.4 g. of needles, m.p. 202° (decomp.). *Anal.* Calcd. for $C_{36}H_{49}O_3Br$: C, 70.93; H, 8.04. Found : C, 71.40; H, 8.36.

6-Bromocholesta-3,5-dien-7-one (IX)——a) A solution of 15 g. of 3β-hydroxy-4-bromocholest-5-en-7-one benzoate[3] (VIII), m.p. 212° (decomp.), in 120 cc. of anhyd. pyridine was refluxed for 10 hr. Pyridine was evaporated *in vacuo* and MeOH was added. The crude product isolated by filtration showed ultraviolet absorption maximum at 292~294 mμ, not at 240 mμ. The product was dissolved in benzene-petr. ether (1:2) and chromatographed over alumina. The first fraction (150 cc.) was discarded and the second fraction (200 cc.) gave a crystalline product (A) (4.5 g.), m.p. 140~145°, with absorption maximum at 295 mμ. The third fraction (100 cc.) gave 0.6 g. of a product (B), with ultraviolet absorption maximum at 283~288 mμ. The following fraction (500 cc.) gave 0.5 g. of a product (C), m.p. 108~111°, with ultraviolet absorption maximum at 278 mμ. From a later fraction, 0.8 g. of an oil was obtained.

The product (A) was recrystallized from EtOH-benzene to 4 g. of leaflets, m.p. 149~151°. $[\alpha]_D^{25}$ −286° (c=1.02, $CHCl_3$). UV : λ_{max}^{EtOH} 295 mμ (ε 17,790). This was identified by the infrared spectrum

*4 All melting points are not corrected.

with the product obtained by Takeda and Komeno.[6] *Anal.* Calcd. for $C_{27}H_{41}OBr$: C, 70.28; H, 8.89; Br, 17.35. Found : C, 70.16; H, 8.92; Br, 17.42.

The product (B) was separated into products (A) and (C) by chromatography with alumina. The product (C) was recrystallized from EtOH to leaflets, m.p. 112~113°, which did not depress the melting point of cholesta-3,5-dien-7-one. UV : λ_{max}^{EtOH} 278 mμ (ε 24,120).

b) A mixture of 3β-hydroxy-5,6-dibromocholestan-7-one acetate and 30 cc. of pyridine was refluxed for 2 hr. Resulting black solution was evaporated to dryness, MeOH was added, and the crystalline product isolated by filtration was recrystallized from EtOH to 1.5 g. of crystals, m.p. 110~125°. The product was dissolved in benzene-petr. ether (1:1) and chromatographed over 30 g. of alumina. The first fraction (200 cc.) was evaporated and the solid residue was recrystallized from EtOH to leaflets, m.p. 141~143°. Further recrystallization from EtOH-benzene afforded 0.4 g. of leaflets, m.p. 148~149°. UV : λ_{max}^{EtOH} 295 mμ (ε 17,800). This was identified by mixed melting point and the infrared spectrum with a product obtained by process (a). The next fraction (600 cc.), treated in the same manner as process (a), afforded 0.8 g. of cholesta-3,5-dien-7-one.

4-Bromocholesta-3,5-dien-7-one (XI)——a) A mixture of 6.5 g. of 3β-hydroxy-4-bromocholest-5-en-7-one benzoate and 13 g. of AcOK in 480 cc. of EtOH was refluxed for 8 hr. The reaction mixture was filtered, evaporated to almost dryness, H_2O added, and the precipitate was collected by filtration. The product was recrystallized from Me_2CO to 3.5 g. of prisms, m.p. 115~117°. Further purification from EtOH gave 3 g. of a product of m.p. 120°. $[\alpha]_D^{26}$ −212° (c=1.27, $CHCl_3$). UV : λ_{max}^{EtOH} 283 mμ (ε 17,850). *Anal.* Calcd. for $C_{27}H_{41}OBr$: C, 70.28; H, 8.89; Br, 17.35. Found : C, 70.32; H, 9.12; Br, 17.18. This was identified by mixed melting point and the infrared spectrum with the bromo-dienone obtained by Jackson and Jones.[7]

A solution of 0.5 g. of this bromo-dienone in 10 cc. of pyridine was refluxed for 8 hr. The reaction mixture was evaporated *in vacuo*, MeOH was added, and 0.4 g. of the starting material was recovered.

b) A solution of 1 g. of 3β-hydroxy-4-bromocholest-5-en-7-one benzoate in 20 cc. of EtOH and 15 cc. of dioxane was refluxed for 1 hr. with 1 cc. of conc. HCl. Resulting yellow solution was evaporated *in vacuo*, EtOH was added, and cooled. A crystalline product was collected by filtration and recrystallized from EtOH to 0.4 g. of needles, m.p. 119~120°. The product was identified by mixed melting point and the infrared spectrum with the compound obtained by process (a).

c) To a suspension of 1 g. of 3α,4α-epoxycholest-5-en-7-one in 10 cc. of AcOH, 3 cc. of a solution of HBr in AcOH (28%) was added. The suspension dissolved at once and formed a yellow solution. After standing for 40 min. at 30°, H_2O was added and an oily product precipitated. After sufficient cooling, the product was collected by decantation, washed, and dried. Residual semi-solid weighed 1 g. and had an absorption maximum at 281 mμ. This was dissolved in petr. ether-benzene (1:1) and chromatographed over alumina. The first fraction (100 cc.) gave 0.5 g. of a product, m.p. 118~119°. This was recrystallized from EtOH to 0.35 g. of needles, m.p. 120~122°, identical with the samples obtained by (a) and (b). $[\alpha]_D^{25}$ −219° (c=1.04, $CHCl_3$). UV : λ_{max}^{EtOH} 283 mμ (ε 17,900). *Anal.* Calcd. for $C_{27}H_{41}OBr$: C, 70.28; H, 8.89; Br, 17.35. Found : C, 70.26; H, 8.78; Br, 17.46.

4-Anilinocholesta-3,5-dien-7-one (V)——A solution of 5 g. of 4-bromocholest-5-en-7-one benzoate and 25 cc. of aniline in 125 cc. of xylene was refluxed for 1 hr. The reaction mixture was cooled, the separated solid was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in 50 cc. of petr. ether and chromatographed over 100 g. of alumina. The first fraction (500 cc.) was discarded. The second fraction (600 cc.) eluted with benzene-petr. ether mixture (1:2) gave a crystalline product, which was recrystallized from EtOH-MeOH to 1.9 g. of needles, m.p. 100~115°. Further two recrystallizations from EtOH afforded 1 g. of pale yellow needles, m.p. 129~130°. $[\alpha]_D^{25}$ −72° (c=1.0, $CHCl_3$). *Anal.* Calcd. for $C_{33}H_{47}ON$: C, 83.75; H, 9.94; N, 2.96. Found : C, 83.39; H, 9.62; N, 3.10. UV λ_{max}^{EtOH} mμ (ε) : 251 (17,850), 281 (19,110). From the mother liquor, 0.3 g. of cholesta-3,5-dien-7-one was obtained.

Hydrogenation of 4-Anilinocholesta-3,5-dien-7-one (V)——A solution of 0.5 g. of 4-anilinocholesta-3,5-dien-7-one (V) in 40 cc. of dioxane with 1 g. of Raney Ni W-2 was shaken in H_2 at room temperature until about 1 mole of H_2 had been absorbed. After removal of the catalyst, the filtrate was evaporated *in vacuo*. The solid residue was crystallized from EtOH to 0.3 g. of pale yellow needles, m.p. 116~117°. UV : λ_{max}^{EtOH} 245 mμ (ε 21,500). It was identified by mixed melting point and infrared spectrum with 4-anilinocholest-5-en-7-one.

3α,4α-Epoxycholest-5-en-7-one (X)——To a solution of 3.82 g. of cholesta-3,5-dien-7-one in 10 cc. of $CHCl_3$, 38 cc. of Et_2O solution of perphthalic acid (containing 2.8 g. of perphthalic acid) was added and the mixture allowed to stand for 24 hr. at 25°. Perphthalic acid consumed was about 70%. The Et_2O solution was decanted from precipitated perphthalic acid, combined with Et_2O washing, washed three times with 5% $NaHCO_3$ and H_2O, and dried. Et_2O solution was evaporated to dryness, the solid residue was triturated with MeOH, and collected by filtration. The product was recrystallized from EtOH to 1.8 g. of leaflets, m.p. 123~126°. Further purification from Et_2O gave a product

of m.p. 127~128°. $[\alpha]_D^{25}$ −144°. UV : λ_{max}^{EtOH} 239 mμ (ε 11,680). *Anal.* Calcd. for $C_{27}H_{42}O_2$: C, 81.40; H, 10.54. Found : C, 80.95; H, 10.33.

Hydrogenation of 4-Bromocholesta-3,5-dien-7-one (XI) and 6-Bromocholesta-3,5-dien-7-one (IX) ——A solution of 1 g. of 4-bromocholesta-3,5-dien-7-one dissolved in 40 cc. of dioxane, with 1 g. of Raney Ni W-2, was hydrogenated until 2 moles of H_2 had been absorbed. After removal of Raney Ni, the filtrate was evaporated *in vacuo*. The solid residue was dissolved in petr. benzine and chromatographed over 20 g. of alumina. The first fraction (75 cc.) of benzine eluate was discarded and the next fraction (500 cc.) gave a product of m.p. 125~127°, which was recrystallized from EtOH to 0.5 g. of leaflets, m.p. 127~128°. UV : λ_{max}^{EtOH} 238 mμ. This was identified by mixed melting point and the infrared spectrum with cholest-5-en-7-one.

6-Bromocholesta-3,5-dien-7-one was treated in the same manner as above and cholest-5-en-7-one was obtained similarly.

The authors are grateful to Mr. T. Onoe, Miss C. Furukawa, and Miss H. Ohtsuka for elemental analyses, and to Mressrs. O. Amakasu and M. Kishi for spectral measurements.

Summary

Bromination of cholest-5-en-7-one and 3β-hydroxycholest-5-en-7-one benzoate with N-bromosuccinimide was carried out. Resulting bromo derivatives were converted to dienones, bromo-dienones, or anilino-dienones. The bromo-dienons were assigned 6-bromo- or 4-bromocholesta-3,5-dien-7-one structure and their characteristic infrared absorptions were summarized. Epoxidation of cholesta-3,5-dien-7-one was also examined.

(Received September 24, 1960)