

41. Ko Arima : Studies on Cholestapolyenes. VI.<sup>1)</sup>  
3-Cyclohexylcholestane and its Derivatives.

(Takamine Research Laboratory, Sankyo Co., Ltd.\*)

It is known that nucleophilic reaction in 3-position of cholest-5-ene results in retention.<sup>2)</sup> It was therefore thought that reaction of 3 $\beta$ -cholesterylmagnesium chloride (Ia)<sup>3)</sup> and cyclohexanone would chiefly afford 3 $\beta$ -hydroxy-3-cyclohexylcholest-5-ene (II) and this was actually proved by the formation of needle crystals, m.p. 181~183°;  $[\alpha]_D^{25}$  -22.0°, whose analytical values agreed with those for (II).

On the other hand application of the Grignard reagent of pentamethylene dibromide to methyl cholest-5-ene-3-carboxylate (Ib)<sup>3)</sup> by the method of Levens and Harris<sup>4)</sup> also resulted in the formation of needle crystals whose physical constants agreed completely with those of (II) prepared from (Ia). The substances obtained from (Ia) and (Ib) showed no depression of the melting point on admixture and their infrared absorption spectra were identical, proving them to be the same substance. It is certain from the route of synthesis from (Ib) that (II) is 3 $\beta$ -hydroxy-3-cyclohexylcholest-5-ene and so is the 3-hydroxy-3-cyclohexylcholestene formed from (Ia).

It follows that the lone-pair electrons of carbanion generated in the 3-position of the Grignard reagent of 3 $\beta$ -chlorocholest-5-ene are  $\beta$ -oriented and there is no inversion of 3-position in reaction with cyclohexanone, forming a 3 $\beta$ -hydroxy-3-cyclohexyl derivative with the same configuration as that of the starting chloride. Dehydration of (II) by dissolving it in chloroform, adding a few drops of 70% perchloric acid solution, and boiling for 30 minutes affords 3 $\beta$ -cyclohexenylcholest-5-ene (III) as needles, m.p. 153~156°,  $[\alpha]_D^{25}$  -22.0°.

As for the dehydrative direction of the hydroxyl in (II), there is small possibility of the formation of 3-cyclohexylidenecholest-5-ene (IV), even from the work of Criegee, *et al.*<sup>5)</sup> on the dehydration of 1-cyclohexylcyclohexanol. (IV) would probably resist reduction at ordinary temperature and pressure.<sup>6)</sup> Presence of an unsaturated compound was not detected in the reduction product of (III). Reduction of (III) in ether, acidified with glacial acetic acid, a few drops of 70% perchloric acid solution added, and with platinum oxide as a catalyst, at ordinary temperature and pressure, affords needle crystals of m.p. 154~155°,  $[\alpha]_D^{25}$  +25.2°, whose analytical values agreed with those for cyclohexylcholestane.

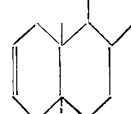
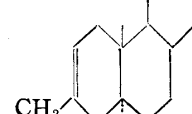
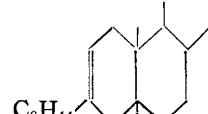
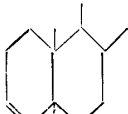
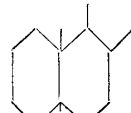
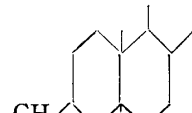
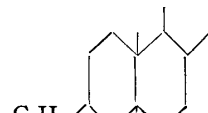
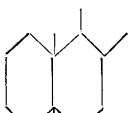
It is clear from the route of synthesis that the configuration of 3-position in (V) is equatorial, i.e. that (V) is 3 $\beta$ -cyclohexylcholestane.

Application of cyclohexylmagnesium bromide to cholestan-3-one (Ic) afforded 3-cyclohexylcholestan-3-ol (IIc) and its dehydration by dissolving (IIc) in chloroform, adding a few drops of 70% perchloric acid solution, and standing at room temperature for 30 minutes resulted in the formation of 3-cyclohexylcholest-2-ene (IIIc). The formation of a double bond in (IIIc) at 2-3 position was proved by the molecular rotation difference method.

\* Nishi-shinagawa, Shinagawa-ku, Tokyo (有馬 洪).

- 1) Part V. Ko Arima, R. Hayatsu : This Bulletin, **2**, 227(1953).
- 2) L. Fieser : "Natural Products related to Phenanthrene," 3rd ed., 642; C. Shoppee : J. Chem. Soc., **1946**, 1147.
- 3) C. Shoppee : J. Chem. Soc., **1954**, 3418; E. Squire : J. Am. Chem. Soc., **70**, 1487(1948).
- 4) P. Levens, S. Harris : J. Biol. Chem., **113**, 55(1936).
- 5) R. Criegee, E. Vogel, H. Hoyer : Ber., **86**, 144(1952).
- 6) H. Adkins : "Reaction of Hydrogen with Organic Compounds," 52.

TABLE I.

 cholest-2-ene <sup>a)</sup>	 3-methylcholest-2-ene <sup>b)</sup>	 3-cyclohexylcholest-2-ene <sup>c)</sup>	 cholest-3-ene <sup>a)</sup>
$M_D + 259$	$M_D + 286$	$M_D + 297$	$M_D + 217$
 cholestane <sup>a)</sup>	 3-methylcholestane <sup>b)</sup>	 3-cyclohexylcholestane <sup>c)</sup>	 cholestane <sup>a)</sup>
$M_D + 91$	$M_D + 108$	$M_D + 115$	$M_D + 91$
$\Delta M_D + 168$	$\Delta M_D + 178$	$\Delta M_D + 187$	$\Delta M_D + 126$

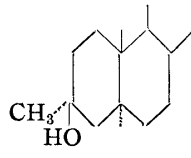
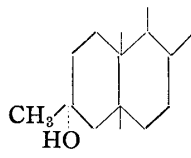
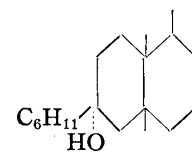
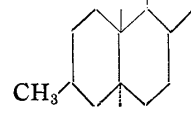
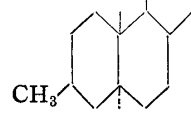
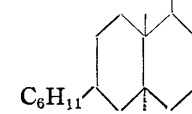
a) R. Juner : J. Am. Chem. Soc., **79**, 4126(1957); b) D. Barton : J. Chem. Soc., **1956**, 3500;  
c) K. Arima : This report.

The rotational contribution,  $M_D$ , of the double bond newly introduced into 2-3 position of the cholestane ring on the rotation of the whole molecule, as shown in Table I, is very similar in all three cases and it is certain that (IIIc) is 3-cyclohexylcholest-2-ene. Further, comparison of rotational contribution,  $M_D$ , with that of 3-4 double bond shows that this direction of dehydration is not at 3-position.

In a similar reaction of cholestan-3-one and methylmagnesium iodide, Barton<sup>7)</sup> obtained two isomers, 3-methylcholestan-3 $\alpha$ -ol and -3 $\beta$ -ol.

From the fact that (IIc) is easily dehydrated and the dehydration of the hydroxyl occurs in 2-3 position, and from comparative analogy with the work of Barton, it is concluded that the conformation of the hydroxyl is axial. From the values of molecular rotational difference shown in Table II, it seems certain that the hydroxyl is not in equatorial conformation. It is assumed that the reason why only one kind of (IIIc) had been isolated is due to steric hindrance of the A ring in the cholestane and the cyclohexane ring.

TABLE II.

 $M_D + 137^a)$	 $M_D + 113^a)$	 $M_D + 123^b)$
 $M_D + 108^a)$	 $M_D + 108^a)$	 $M_D + 115^b)$
$\Delta M_D + 29$	$\Delta M_D + 5$	$\Delta M_D + 8$

a) D. Barton : J. Chem. Soc., **1956**, 3500; b) K. Arima : This report.

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### Experimental

All optical rotational measurements were made in  $\text{CHCl}_3$  solution, using a 2-dm. tube.

**3 $\beta$ -Hydroxy-3-cyclohexylcholest-5-ene (II)**—a) To a great excess of Grignard reagent prepared from 2 g. of pentamethylene dibromide,<sup>8)</sup> 2 g. of Mg, and 50 cc. of  $\text{Et}_2\text{O}$ , a solution of methyl cholest-5-ene-3 $\beta$ -carboxylate (Ib), m.p. 101–102°, dissolved in 20 cc. of  $\text{Et}_2\text{O}$  was dropped in over a period of

7) D. Barton, *et al.* : J. Chem. Soc., **1956**, 3500.

30 mins. and the mixture was heated for 2 hrs. After cool, water was added to the reaction mixture,  $\text{Mg}(\text{OH})_2$  that separated out was dissolved by the addition of 5%  $\text{H}_2\text{SO}_4$ , and the  $\text{Et}_2\text{O}$  layer was transferred to a separatory funnel. This was further added with 100 cc. of  $\text{Et}_2\text{O}$ , washed twice with 50-cc. portions of water, and  $\text{Et}_2\text{O}$  layer was dried over anhyd.  $\text{Na}_2\text{SO}_4$ . After evaporation of the solvent, the residue was recrystallized twice from  $\text{AcOEt}$  to needles, m.p.  $181\sim 183^\circ$ ;  $[\alpha]_D^{25} -22.0^\circ$  ( $c=0.364$ ). The infrared spectrum of this substance showed OH absorption at  $3470\text{ cm}^{-1}$  (Nujol). Yield, 30%. *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{56}\text{O}$ : C, 84.64; H, 11.98. Found: C, 84.22; H, 11.51.

b) Grignard reagent was prepared by the method of Squire<sup>9)</sup> from 20 g. of chromatographically purified  $3\beta$ -chlorocholest-5-ene (Ia),<sup>10)</sup> m.p.  $93\sim 95^\circ$ , and 20 g. of purified cyclohexanone, b.p.  $156\sim 157^\circ$ , was dropped in during 30 mins. The mixture was heated on a water bath for further 2 hrs. and then treated as in above a). Needles, m.p.  $181\sim 183^\circ$ , were obtained which showed no depression of m.p. on admixture with  $3\beta$ -hydroxy-3-cyclohexylcholest-5-ene, prepared by the method a), and infrared spectra of the two substances were in complete agreement. *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{56}\text{O}$ : C, 84.64; H, 11.98. Found: C, 84.20; H, 11.31.

**$3\beta$ -Cyclohexenylcholest-5-ene (III)**—Two drops of 70%  $\text{HClO}_4$  solution was added to 1 g. of (II), m.p.  $181\sim 183^\circ$ , dissolved in 30 cc. of  $\text{CHCl}_3$ , and the mixture was boiled on a water bath for 30 mins. The resultant brown solution was allowed to stand with 50 cc. of  $\text{MeOH}$  by which an oil separated out and the oil solidified gradually.  $\text{CHCl}_3$ - $\text{MeOH}$  mixture was decanted, 10 cc. of  $\text{Me}_2\text{CO}$  was added to its residue, triturated, and filtered. The crystals so obtained were recrystallized from  $\text{AcOEt}$  to needles, m.p.  $153\sim 156^\circ$ ,  $[\alpha]_D^{25} -22.0^\circ$  ( $c=0.704$ ). Yield, 50%. *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{54}$ : C, 88.39; H, 11.60. Found: C, 88.70; H, 11.57.

**$3\beta$ -Cyclohexylcholestan-3 $\alpha$ -ol (IIc)**—To the Grignard reagent prepared from 20 g. of cyclohexyl bromide, 1.5 g. of  $\text{Mg}$ , and 50 cc. of  $\text{Et}_2\text{O}$ , a solution of 20 g. of cholestan-3-one, m.p.  $128\sim 130^\circ$ , dissolved in 100 cc. of  $\text{Et}_2\text{O}$  was dropped in at  $0^\circ$  during 30 mins., the mixture was boiled for 2 hrs., and cooled.  $\text{Et}_2\text{O}$  was evaporated from the solution after removal of  $\text{Mg}$  by the usual method and the residue was recrystallized twice from  $\text{AcOEt}$  to 2 g. of needles, m.p.  $165\sim 167^\circ$ ;  $[\alpha]_D^{25} +26.2^\circ$  ( $c=1.30$ ). *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{58}\text{O}$ : C, 84.26; H, 12.34. Found: C, 84.71; H, 12.06.

**3-Cyclohexylcholest-2-ene (IIIc)**—A solution of 1 g. of (IIc), m.p.  $165\sim 167^\circ$ , dissolved in 30 cc. of  $\text{CHCl}_3$ , containing 2 drops of 70%  $\text{HClO}_4$ , was allowed to stand for 30 mins., during which the solution gradually acquired reddish brown color. The crystals that separated out on addition of 20 cc.  $\text{MeOH}$  were recrystallized from  $\text{AcOEt}$  to needles, m.p.  $133\sim 135^\circ$ ;  $[\alpha]_D^{25} +65.7^\circ$  ( $c=1.317$ ). *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{56}$ : C, 87.22; H, 12.39. Found: C, 87.04; H, 11.90.

**$3\beta$ -Cyclohexylcholestan-3 $\alpha$ -ol (V)**—a) To a solution of 500 mg. of (III), m.p.  $153\sim 156^\circ$  dissolved in a mixture of 100 cc. of  $\text{Et}_2\text{O}$  and 2 cc. of  $\text{AcOH}$ , 3 drops of 70%  $\text{HClO}_4$  and 100 mg. of  $\text{PtO}_2$  were added, and the mixture was shaken in  $\text{H}_2$  stream for ca. 1 hr. The reaction mixture was filtered, solvent was distilled off under a reduced pressure from the filtrate, and the residue was recrystallized from  $\text{AcOEt}$ , affording needles, m.p.  $154\sim 155^\circ$ ;  $[\alpha]_D^{25} +25.2^\circ$  ( $c=1.248$ ). *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{58}$ : C, 87.61; H, 12.38. Found: C, 87.70; H, 12.31.

b) Hydrogenation of (IIIc) under the same conditions as in a) afforded needles, m.p.  $153\sim 155^\circ$  (Kawasaki<sup>11)</sup> reported m.p.  $156\sim 158^\circ$  and  $157^\circ$ ). *Anal.* Calcd. for  $\text{C}_{33}\text{H}_{58}$ : C, 87.61; H, 12.38. Found: C, 87.80; H, 12.30.

### Summary

$3\beta$ -Cyclohexylcholestan-3 $\alpha$ -ol was prepared from cholest-5-ene-3 $\beta$ -carboxylic acid and the fact is that the carbanion formed in the Grignard reagent of  $3\beta$ -chlorocholest-5-ene was  $\beta$ -oriented in reaction with cholestan-3-one, i. e. the conformation at 3-position is retained. Discussions were also made on the structure of  $3\beta$ -cyclohexylcholestan-3 $\alpha$ -ol and 3-cyclohexylcholest-2-ene.

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8) Tokyo Kasei, Ltd. b.p.<sub>19</sub>  $104\sim 106^\circ$ .

9) E. Squire: J. Am. Chem. Soc., **70**, 1487(1948).

10) L. Ruzicka: Helv. Chim. Acta, **17**, 1389(1934); C. Shoppee: J. Chem. Soc., **1946**, 1147.

11) T. Kawasaki: Yakugaku Zasshi, **57**, 949(1937).