UDC 547.92

41. **Ko Arima**: Studies on Cholestapolyenes. VI.[1] 3-Cyclohexylcholestane and its Derivatives.

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It is known that nucleophilic reaction in 3-position of cholest-5-ene results in retention.[2] It was therefore thought that reaction of 3β-cholesterylmagnesium chloride (Ia)[3] and cyclohexanone would chiefly afford 3β-hydroxy-3-cyclohexylcholest-5-ene (II) and this was actually proved by the formation of needle crystals, m.p. 181～183°; $[\alpha]_{\mathrm{D}}^{25}$ $-22.0°$, 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)[3] by the method of Levens and Harris[4] 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 3β-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 3β-chlorocholest-5-ene are β-oriented and there is no inversion of 3-position in reaction with cyclohexanone, forming a 3β-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 3β-cyclohexenylcholest-5-ene (III) as needles, m.p. 153～156°, $[\alpha]_{\mathrm{D}}^{25}$ $-22.0°$.

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.*[5] on the dehydration of 1-cyclohexylcyclohexanol. (IV) would probably resist reduction at ordinary temperature and pressure.[6] 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°, $[\alpha]_{\mathrm{D}}^{25}$ $+25.2°$, 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 3β-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.

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[1] Part V. Ko Arima, R. Hayatsu: This Bulletin, **2**, 227(1953).

[2] L. Fieser: "Natural Products related to Phenathrene," 3rd ed., 642; C. Shoppee: J. Chem. Soc., **1946**, 1147.

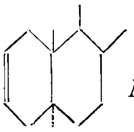
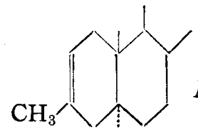
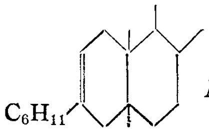
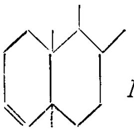
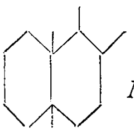
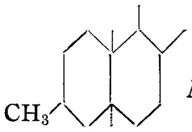
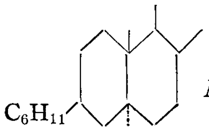
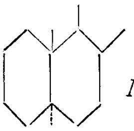
[3] C. Shoppee: J. Chem. Soc., **1954**, 3418; E. Squire: J. Am. Chem. Soc., **70**, 1487(1948).

[4] P. Levens, S. Harris: J. Biol. Chem., **113**, 55(1936).

[5] R. Criegee, E. Vogel, H. Hoger: Ber., **86**, 144(1952).

[6] H. Adkins: "Reaction of Hydrogen with Organic Compounds," 52.

Table I.

			
M_D+259	M_D+286	M_D+297	M_D+217
cholest-2-ene[a]	3-methylcholest-2-ene[b]	3-cyclohexylcholest-2-ene[c]	cholest-3-ene[a]
			
M_D+91	M_D+108	M_D+115	M_D+91
cholestane[a]	3β-methylcholestane[b]	3β-cyclohexylcholestane[c]	cholestane[a]
ΔM_D+168	ΔM_D+178	ΔM_D+187	ΔM_D+126

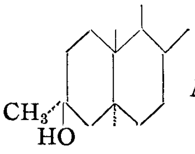
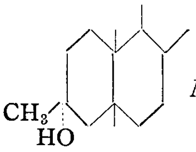
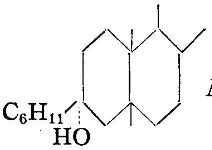
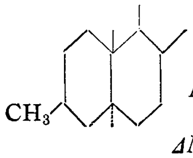
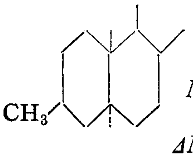
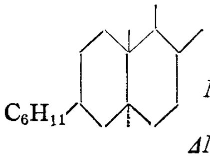
a) R. Juner : J. Am. Chem. Soc., **79**, 4126(1957); b) D. Barton : J. Chem. Soc., **1956**, 3500; c) K. Arima : This report.

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[7] obtained two isomers, 3-methylcholestan-3α-ol and -3β-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]
ΔM_D+29	ΔM_D+5	ΔM_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 $CHCl_3$ solution, using a 2-dm. tube.

3β-Hydroxy-3-cyclohexylcholest-5-ene (II)—a) To a great excess of Grignard reagent prepared from 2 g. of pentamethylene dibromide,[8] 2 g. of Mg, and 50 cc. of Et_2O, a solution of methyl cholest-5-ene-3β-carboxylate (Ib), m.p. 101~102°, dissolved in 20 cc. of Et_2O was dropped in over a period of

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[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, $Mg(OH)_2$ that separated out was dissolved by the addition of 5% H_2SO_4, and the Et_2O layer was transferred to a separatory funnel. This was further added with 100 cc. of Et_2O, washed twice with 50-cc. portions of water, and Et_2O layer was dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was recrystallized twice from AcOEt to needles, m.p. 181~183°; $[\alpha]_D^{25}$ $-22.0°$ ($c=0.364$). The infrared spectrum of this substance showed OH absorption at 3470 cm^{-1} (Nujol). Yield, 30%. *Anal.* Calcd. for $C_{33}H_{56}O$: C, 84.64; H, 11.98. Found : C, 84.22; H, 11.51.

b) Grignard reagent was prepared by the method of Squire(9) from 20 g. of chromatographically purified 3β-chlorocholest-5-ene (Ia),(10) m.p. 93~95°, and 20 g. of purified cyclohexanone, b.p. 156~157°, 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. 181~183°, were obtained which showed no depression of m.p. on admixture with 3β-hydroxy-3-cyclohexylcholest-5-ene, prepared by the method a), and infrared spectra of the two substances were in complete agreement *Anal.* Calcd. for $C_{33}H_{56}O$: C, 84.64; H, 11.98. Found : C, 84.20; H, 11.31.

3β-Cyclohexenylcholest-5-ene (III)—Two drops of 70% $HClO_4$ solution was added to 1 g. of (II), m.p. 181~183°, dissolved in 30 cc. of $CHCl_3$, and the mixture was boiled on a water bath for 30 mins. The resultant brown solution was allowed to stand with 50 cc. of MeOH by which an oil separated out and the oil solidified gradually. $CHCl_3$-MeOH mixture was decanted, 10 cc. of Me_2CO was added to its residue, triturated, and filtered. The crystals so obtained were recrystallized from AcOEt to needles, m.p. 153~156°, $[\alpha]_D^{25}$ $-22.0°$($c=0.704$). Yield, 50%. *Anal.* Calcd. for $C_{33}H_{54}$: C, 88.39; H, 11.60. Found : C, 88.70; H, 11.57.

3β-Cyclohexylcholestan-3α-ol (IIc)—To the Grignard reagent prepared from 20 g. of cyclohexyl bromide, 1.5 g. of Mg, and 50 cc. of Et_2O, a solution of 20 g. of cholestan-3-one, m.p. 128~130°, dissolved in 100 cc. of Et_2O was dropped in at 0° during 30 mins., the mixture was boiled for 2 hrs., and cooled. Et_2O was evaporated from the solution after removal of Mg by the usual method and the residue was recrystallized twice from AcOEt to 2 g. of needles, m.p. 165~167°; $[\alpha]_D^{25}$ $+26.2°$($c=1.30$). *Anal.* Calcd. for $C_{33}H_{58}O$: 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. 165~167°, dissolved in 30 cc. of $CHCl_3$, containing 2 drops of 70% $HClO_4$, 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. MeOH were recrystallized from AcOEt to needles, m.p. 133~135°; $[\alpha]_D^{25}$ $+65.7°$($c=1.317$). *Anal.* Calcd. for $C_{33}H_{56}$: C, 87.22; H, 12.39. Found : C, 87.04; H, 11.90.

3β-Cyclohexylcholestane (V)—a) To a solution of 500 mg. of (III), m.p. 153~156° dissolved in a mixture of 100 cc. of Et_2O and 2 cc. of AcOH, 3 drops of 70% $HClO_4$ and 100 mg. of PtO_2 were added, and the mixture was shaken in 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 AcOEt, affording needles, m.p. 154~155°; $[\alpha]_D^{25}$ $+25.2$($c=1.248$). *Anal.* Calcd. for $C_{33}H_{58}$: 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. 153~155° (Kawasaki(11) reported m.p. 156~158° and 157°). *Anal.* Calcd. for $C_{33}H_{58}$: C, 87.61; H, 12.38. Found: C, 87.80; H, 12.30.

Summary

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

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8) Tokyo Kasei, Ltd. b.p$_{19}$ 104~106°.

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).