prisms, m.p. 390~400°, $[\alpha]_D^{24}$ +64.7(c=0.018). *Anal.* Calcd. for $C_{54}H_{90}$: C, 87.80; H, 12.19. Found: C, 87.99; H, 12.60.

Reduction of 100 mg. of (XIII) in tetrahydrofuran, with 2 g. of 5% Pd-$BaCO_3$ as a catalyst, at 200° and 200 atm., afforded 3β,3′β-bicholestane, m.p. 410~420°, $[\alpha]_D^{25}$ ±0°, in 90% yield.

Summary

It has been found that the reaction of cholestan-3-one and the Grignard reagent of 3-chlorocholestane afforded 3β,3′β-bicholestan-3α-ol, irrespective of the α- or β-conformation of the 3-position in the starting material. It was thereby established that the carbanion formed in the Grignard reagent of 3β-chlorocholestane was β-oriented.

(Received December 4, 1957)

UDC 547.92

43. **Ko Arima**: Studies on Cholestapolyenes. VIII.⁽¹⁾ Separation of Stereoisomers of Bicholestane.

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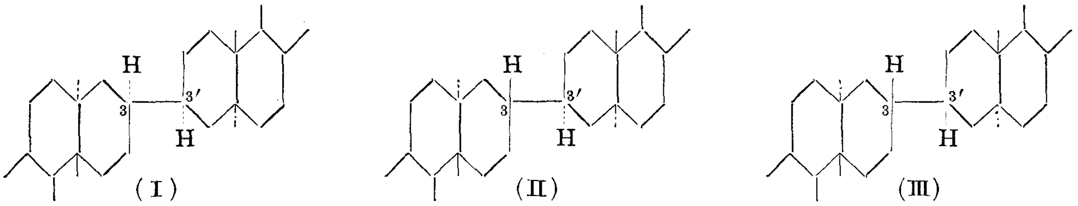
Presence of three kinds of stereoisomer* is possible for 3,3′-bicholestane as shown in Chart 1.



(I) 3β,3′β-Bicholestane

(II) 3α,3′β-Bicholestane

(III) 3α,3′α-Bicholestane

Chart 1.

The bicholestane reported to date are two kinds, A and B,[2] which are obtained by the hydrogenation of bicholestene or bicholestatriene, as shown in Table I.

As was proved by the earlier experiment[1] on the formation of 3β-hydroxy-3-cyclohexylcholest-5-ene by the reaction of the Grignard reagent of 3β-chlorocholest-5-ene and cyclohexanone, the nucleophilic reaction in the 3-position of 3β-chlorocholest-5-ene results in retention and the configuration of 3,3′-positions in 3,3′-bicholesta-5,5′-diene prepared by the Grignard coupling of 3β-chlorocholest-5-ene should be equatorial for both. Therefore, bicholestane-A prepared by the hydrogenation of 3β,3′β-bicholesta-5,5′-diene should be 3β,3′β-bicholestane (I). On comparing the past experimental data of Squire,[3] and of Shopin[2] with those of the present writer,[4] listed in Table I, the melting point given by Shopin was correct, being 410~420°.

Experiments were later conducted to find another unknown isomer of 3,3′-bicholestane.

The Grignard coupling reaction[5] was carried out on 3α- and 3β-chlorocholestanes and the mixture of stereoisomers of 3,3′-bicholestane thereby formed was fractionally

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[1] Part VII: This Bulletin, **6**, 241(1958).

[2] J. Shopin: Ann. chim. (Paris), **9**, 605(1954); Bull. soc. chim. France, 258(1956).

[3] E. Squire: J. Am. Chem. Soc., **70**, 1487(1948).

[4] K. Arima, R. Hayatsu: This Bulletin, **1**, 217(1953).

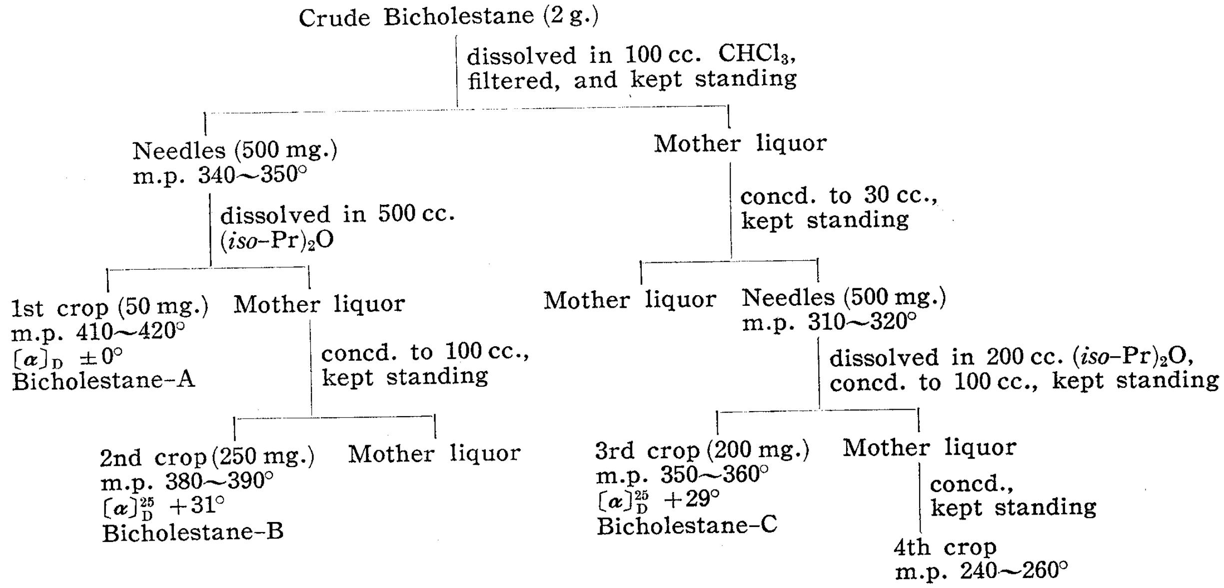
[5] R. Wagner, H. Zook: "Synthetic Organic Chemistry," 9.

Table I. Preparation of Bicholestane by Hydrogenation of Bicholestene or Bicholestapolyene

Bicholestane	Physical constants	Starting material	Method of preparation	Reference
(1)	m.p. 265~275°(decomp.) m.p. 300° $[\alpha]_D^{25}$ ±0°	3,3′-bicholesta-5,5′-diene	PtO_2, H_2, Et_2O, 3 atm.	Squire[3]
(2)	m.p. 265~270°(decomp.) m.p. 300° $[\alpha]$ ±0°	3,3′-bis(cholesta-3,5-diene)	PtO_2, cyclohexane, 3 atm., 18 hrs.	Squire[3]
A (3)	m.p. 418~420°(capil.) $[\alpha]$ ±0°	3,3′-bis(cholesta-3,5-diene) or 3,3′-bis-(cholesta-2,4-diene)	PtO_2, H_2, cyclohexane, 50~60°, 20 hrs.	Shopin[2] Formed only once
(4)	m.p. 270~300°(decomp.) $[\alpha]$ ±0°	3,3′-bis(cholesta-2,4,6-triene)	PtO_2, AcOH, BuOEt, 70°	Arima[a]
(5)	m.p. 410~420°(capil.)	3,3′β-bicholest-2-ene 3,3′β-bicholesta-2,5′-diene 3β,3′-bicholesta-3,5-diene	2% Pd-$BaCO_3$, tetrahydrofuran, 200°, 200 atm.	Arima[1]
B	m.p. 399~410°(decomp.) $[\alpha]_D^{19}$ +38°	3,3′-bis(cholesta-3,5-diene) or 3,3′-bis-(cholesta-2,4-diene)	PtO_2, H_2, cyclohexane, 50~60°	Shopin[2]

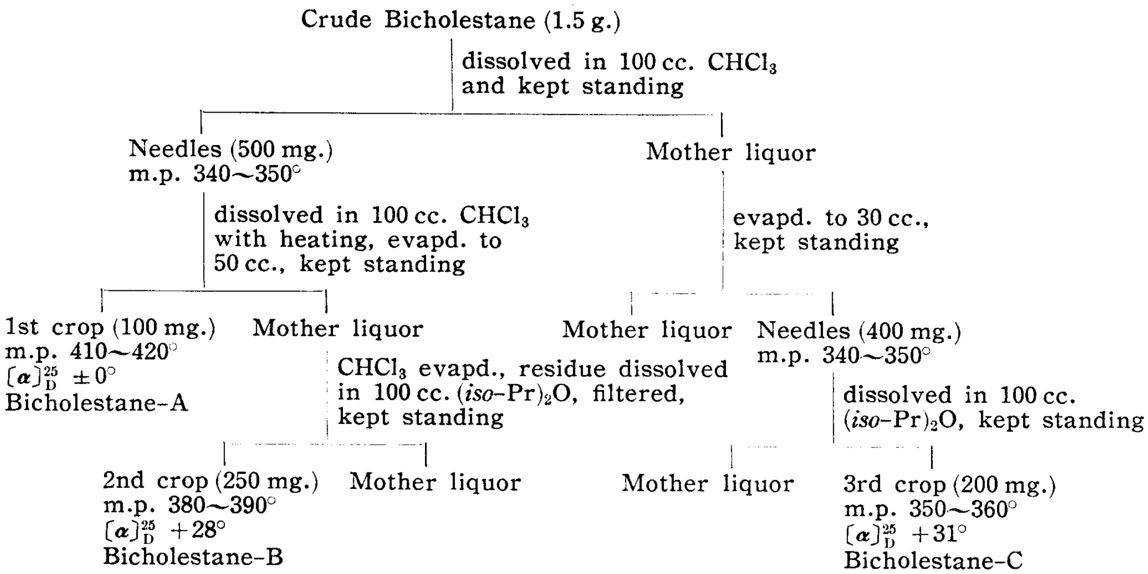
[a] The structures of bicholestatrienes (This Bulletin, **1**, 213(1953)) is corrected on the basis of ultraviolet absorption data as follows: Bicholestatriene-A from 3,3′-bis(cholesta-3,5,7-triene) to 3,3′-bis(cholesta-2,4,6-triene); bicholestatriene-C from 3,3′-bis(cholesta-2,4,6-triene) to 3,3′-bis-(cholesta-3,5,7-triene). The ultraviolet absorption of bicholestatriene-C, listed as $\lambda_{max}^{cyclohexane}$ 307 and 320 mμ, was found to be that of the diene of Squire's as a result of chromatographic purification and the absorptions are corrected to 379 and 390 mμ.

Chart 2. Isolation of Stereoisomers of Bicholestane from the Reaction Product of Grignard Coupling of 3β-Chlorocholestane



recrystallized from chloroform and isopropyl ether, as shown in Charts 2 and 3. Three kinds of bicholestane-A, -B, and -C, were finally isolated. The properties of A and B agree with the data given in the literature. The presence of a third and unknown stereoisomer, bicholestane-C, was confirmed. The newly isolated bicholestane-C occurs as needle crystals melting at 350~360°, $[\alpha]_D^{25}$ +31° or 29°. These three isomers, A, B, and C, are invariably formed irrespective of the conformation of the chlorine in 3-position of the starting 3-chlorocholestane. The formation ratio was not constant. It was assumed that, in the Grignard coupling reaction, the carbanion formed in the

Chart 3. Isolation of Stereoisomers of Bicholestane from the Reaction Product of Grignard Coupling of 3α-Chlorocholestane



Grignard reagent attacks 3-chlorocholestane and forms a labile transition state as an intermediate, which, when undergoing stabilization, forms three kinds of stereoisomer by steric hindrance.

The same reaction carried out with 3β-chlorocoprostane afforded a bicoprostane of m.p. 198~200°, $[\alpha]_D^{25}$ +40.2°. This compound is far more easily soluble in organic solvents than the foregoing bicholestane-A, -B, and -C, and its melting point is lower that there is no fear of its being mixed in the bicholestane.

For the identification of the three kinds of bicholestane isomers, the distance between crystal face, d(Å), in X-ray diffraction was utilized and comparison of their values are listed in Table II.

TABLE II. Comparison of the Distance between Crystal Face in Bicholestane by X-Ray Diffraction

Subst. No.	Bicholestane-A[a]				Bicholestane-B[b]				Bicholestane-C			
	I[c]		II[d]		α[e]		β[e]		α[e]		β[e]	
	D (Å)	Int.*	D (Å)	Int.*	D (Å)	Int.*	D (Å)	Int.*	D (Å)	Int.*	D (Å)	Int.*
1	10.81	w	10.86	w	5.15	s	5.15	s	6.23	m	6.27	m
2	9.56	w	9.56	w	3.76	s	3.76	s	5.34	vs	5.23	vs
3	7.81	w	7.79	w					2.87	w	2.85	w
4	7.01	s	6.99	s					2.39	vw	2.39	vw
5	6.03	m	6.03	m								
6	5.55	vs	5.56	vs								
7	4.95	vw	4.95	vw								
8	4.72	m	4.72	m								
9	4.33	m	4.32	m								
10	4.04	vs	4.04	vs								

* Intensity : w, weak; m, medium; s, strong; v, very.

a) D(Å) of bicholestane-A has been omitted after No. 10.

b) Data for bicholestane-B is small due to difficulty of its pulverization.

c) I was prepared by the high-pressure hydrogenation of 3,3′β-bicholest-2-ene.

d) II was similarly prepared from 3,3′β-bicholesta-3,5-diene.

e) α and β respectively denote that the starting materials used for the Grignard coupling were 3α- and 3β-chlorocholestane.

The author is deeply grateful to Prof. K. Tsuda of the Institute for Applied Microbiology, University of Tokyo, for his kind guidance in this work. The author is indebted to Messrs. Onoye, Furukawa, and Ohtsuka of this Laboratory for elemental analyses, to Messrs. Shindo and Amakasu for infrared spectral measurements, to Messrs. Sasaki and Katsumata for optical rotational measurements, and Mr. Shinji of the Institute of Technology, University of Tokyo, for X-ray analyses. Thanks are also due to Messrs. Endo and Baba of this Laboratory for technical help in the preparation of intermediates.

Experimental

Grignard Coupling Reaction—The starting material, 3α-chlorocholestane, m.p. 103\~105°, was obtained by the application of PCl_5[7] to cholestanol,[6] m.p. 140\~141°, giving negative Liebermann reaction, recrystallization of the crude chloride so formed from acetone, and further purification by chromatography.

3β-Chlorocholestane, the other starting compound, was obtained by hydrogenation of chromatographically purified 3β-chlorocholest-5-ene, m.p. 94\~95°, with PtO_2 in AcOEt, at 70°, and recrystallized from AcOEt to a product of m.p. 112\~114°, negative to the Liebermann reaction.

The Grignard reagent was prepared from 20 g. of the above 3-chlorocholestanes by the method of Squire and the reagent was heated for 30\~70 hrs. After completion of the reaction, ether was distilled off, water and 10% HCl were added consecutively to dissolve $Mg(OH)_2$, and the insoluble residue was washed with water. This was triturated with 100 cc. of MeOH, which was discarded by decantation, the residue was triturated with 100 cc. of acetone, which was also removed by decantation, and the residue was further triturated with 100 cc. of AcOEt. This mixture was then filtered, crystals were washed with AcOEt to remove viscid resinous matter, and 2\~3 g. of crude bicholestane was obtained as a pale yellow powder.

This was taken as the isomeric mixture of 3,3′-bicholestane and was submitted to fractional separation and purification as shown in Charts 2 and 3. *Anal.* Calcd. for $C_{54}H_{94}$: C, 87.26; H, 12.74. Found (for bicholestane-Aβ): C, 87.30; H, 12.31. Found (for bicholestane-Bβ): C, 87.05; H, 12.19. Found (for bicholestane-Cβ): C, 87.70; H, 12.53. Found (for bicholestane-Aα): C, 87.41; H, 12.27. Found (for bicholestane-Bα): C, 87.17; H, 12.40. Found (for bicholestane-Cα): C, 87.64; H, 12.57.

Bicoprostane—3β-Chlorocoprostane, m.p. 120\~123°, was prepared by the method of Ruzicka[7] and 5 g. of it was derived to the Grignard reagent by the method of Squire.[6] The reagent was heated for 30 hrs., 200 cc. of ether was added to the reaction mixture, followed by water and 5% HCl to dissolve $Mg(OH)_2$. The mixture was transferred to a separatory funnel, washed with two 50-cc. portions of water, and the ether layer was dried over anhyd. Na_2SO_4. The residue obtained on evaporation of ether was recrystallized from AcOEt to 0.5 g. of needles, m.p. 198\~200°, $[\alpha]_D^{25}$ +40.2° (c=1.019). *Anal.* Calcd. for $C_{54}H_{94}$: C, 87.26; H, 12.74. Found: C, 87.70; H, 12.43.

Summary

Three kinds of stereoisomers of bicholestane were isolated from the Grignard coupling reaction of 3-chlorocholestane and one of these was a new stereoisomer, not found in any literature to date. These three isomers are invariably formed, irrespective of the α- or β-conformation of the chlorine atom in the starting 3-chlorocholestane.

(Received December 4, 1957)

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[6] Org. Syntheses, **17**, 45.

[7] L. Ruzicka: Helv. Chim. Acta, **17**, 1389(1934).