UDC 547.92

42. **Ko Arima** : Studies on Cholestapolyenes. VII.[1] Bicholestane and its Derivatives.

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

In continuation of studies on 3-cyclohexylcholestane derivatives reported in the preceding paper,[1] some experiments were carried out on 3,3′-bicholestane derivatives.

As shown in Chart 1, Grignard reagents were prepared from chlorocholestanes with different steric configuration at 3-position, 3α- (I) and 3β-chlorocholestane (II). These were each reacted with cholestan-3-one and 3,3′-bicholestan-3-ol (III) was obtained. (III) possesses two asymmetric carbon atoms and four stereoisomers are possible. Since only one kind of 3-cyclohexylcholestan-3-ol is formed by the reaction of cholestan-3-one and cyclohexylmagnesium bromide,[1] there is a great possibility that the configuration at 3-position is stereospecific. The compound (IV) to be obtained by dehydration of (III) should come in two stereoisomers with the configuration at 3′-position axial and equatorial. From the respective formation of 3β-methylcholestane[2] and 3-cyclohexylcholestane[1] by the reduction of 3-methyl- and 3-cyclohexylcholest-2-ene,[2] it was anticipated that 3β,3′β-bicholestane and 3β,3′α-bicholestane would be formed by the reduction of (IV). Whether these compounds would be formed or not would be determined by the behavior of the carbanion formed in 3′-position of 3-cholestanylmagnesium chloride.

It was found as a result of such experiments that, irrespective of the equatorial or axial conformation of 3-position in the starting 3-chlorocholestane, the compound formed by the reaction of 3-cholestanylmagnesium chloride and cholestan-3-one was 3,3′-bicholestan-3-ol (III) of m.p. 415~420°, $[\alpha]_D^{25}$ +42.5°, extremely sparingly soluble in organic solvents. Since this dehydration was extremely easy, it is assumed that the configuration of the hydroxyl in 3-position is α, and in axial conformation.

When the suspension of (III) in chloroform, with a few drops of 70% perchloric acid added, is allowed to stand at room temperature, the mixture immediately turns red and the crystals remain undissolved, but the compound is dehydrated and recrystallization from benzene affords long prisms (IV), m.p. 400~410°, $[\alpha]_D^{25}$ +55.6°.

Treatment of (IV) with osmium tetroxide affords needle crystals (VIII), m.p. 390~400°, $[\alpha]_D^{25}$ +19.7°. Dehydration of (VIII) in chloroform with 70% perchloric acid results in the formation of needle crystals (IX), m.p. 380~390°. Since its infrared spectrum exhibits strong absorption at 1725 cm^{-1} for a saturated, six-membered ketone, (IX) must be 3,3′-bicholestan-2(or 4)-one and (VIII) would be either 3,3′-bicholestane-2,3-diol or -3,4-diol, and not 3,3′-diol.

From the fact that the dehydration of the hydroxyl at 3-position in 3-cyclohexylcholestan-3α-ol[1] and 3-methylcholestan-3α-ol[2] occurs in such a direction to form 2-3 double bond, and that the hydroxyl in (III) is axial, (IV) is assumed to be 3,3′-bicholest-2-ene. High-pressure reduction of (IV) with palladium-barium carbonate catalyst affords 3,3′-bicholestane (V) as needles, m.p. 410~420°, $[\alpha]_D$ ±0°, sparingly soluble in chloroform. The same (V) is obtained by the same reduction of 3,3′-bicholesta-2,5′-diene (XIII), formed by the dehydration of 3,3′-bicholest-5-en-3-ol (XII) prepared by the reaction of the Grignard reagent of 3β-chlorocholest-5-ene (XI) and cholestan-3-one.

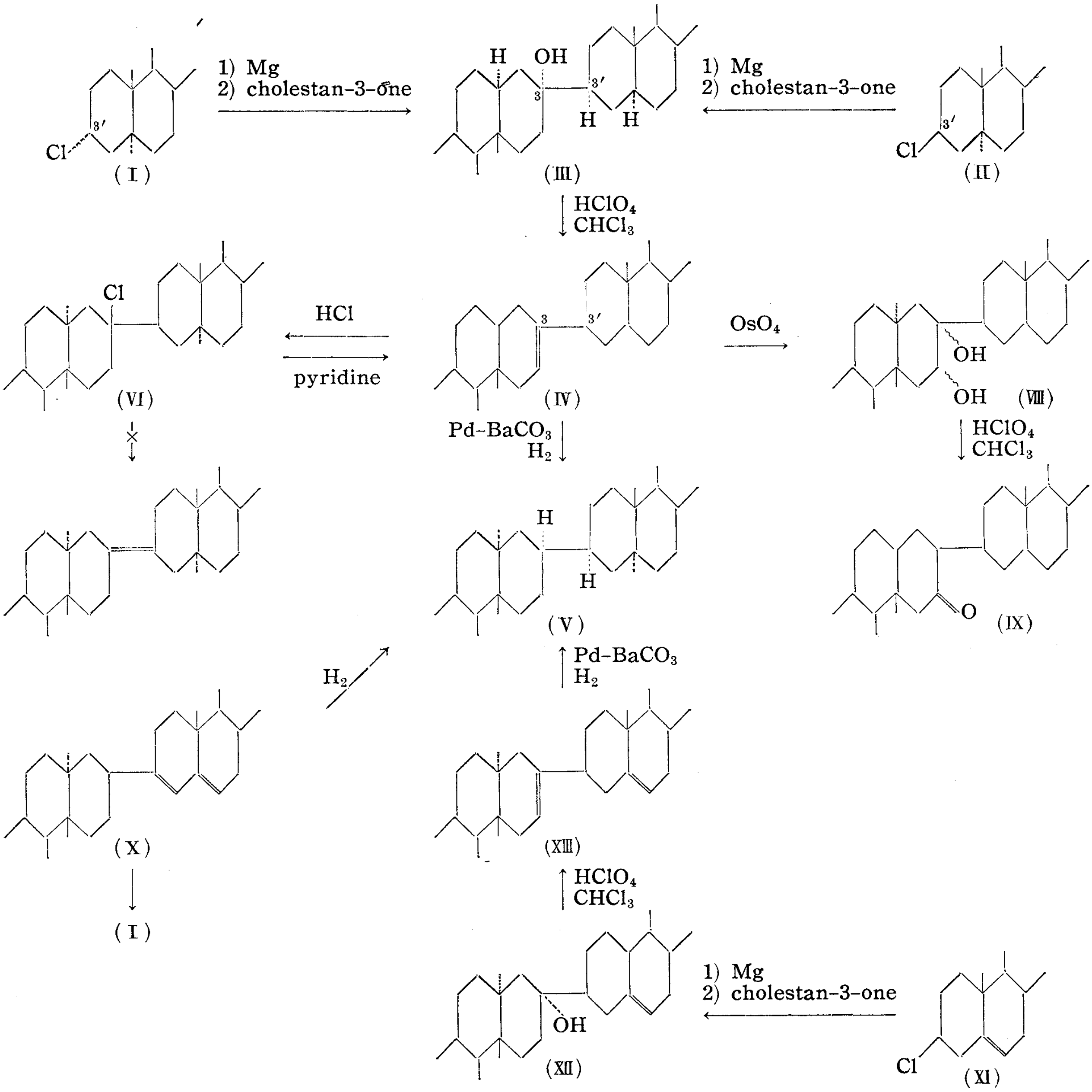
The β-configuration in 3- and 3′-positions in this reaction was assumed as 3β, 3′β,

---

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

[1] Part VI : This Bulletin, **6**, 238(1958).

[2] D. Barton, *et al.* : J. Chem. Soc., **1956**, 3500.



from the retention of the 3-position in nucleophilic reaction of cholest-5-ene and rear attack of 2-3 double bond during hydrogenation.

Reaction of the Grignard reagent of 3α-chlorocholestane (I) and cholest-4-en-3-one affords needle crystals (X), with ultraviolet absorption maxima at 234 and 242 mμ (ether). The absorption at 242 mμ corresponds to that of heteroannular diene of sterol, and that at 234 mμ indicates the presence of an α,β-unsaturated ketone.

High-pressure hydrogenation of (X) without purification, as in the foregoing case, affords (V) sparingly soluble in chloroform, in 60% yield against the starting compound (X). The formation of (V) by the reduction of 3,3′-bicholesta-3,5-diene proves that the carbanion formed in 3-position of 3-cholestanylmagnesium chloride is always β-oriented, even if the starting material is 3α-chlorocholestane (I). It can therefore be concluded that the conformation at 3′-position in (III) is equatorial and (III) would be 3β,3′β-bicholestan-3α-ol.

Reaction of hydrogen chloride with (IV) in chloroform affords 3β-chloro-3α,3′β-bicholestane (VI) as needles, m.p. 395~405°, $[\alpha]^{25}_{D}$ +39.7°. (VI) is easily dehydrochlorinated on being boiled with dehydrated pyridine and regenerates (IV). Attempted hydrogen substitution of the halogen by the application of zinc dust in chloroform also formed (IV), showing that it is very easily dehydrohalogenated, contrary to 3β-chloro-3α-methylcholestane.[3)]

As for the conformation of the chlorine atom in (VI), it is certain that the chlorine is equatorial, because (VI) exhibits infrared absorption at 790 cm^{-1} (Nujol) and equatorial chlorine in general exhibits infrared absorption at around 782 cm^{-1} in carbon disulfide.[3)] It has been found by Barton[2)] that the chlorine atom is in equatorial conformation on the addition of hydrogen chloride to 3-methylcholest-2-ene. Dehydrochlorination of (VI) does not afford 3,3′-bicholestene derivative.

The product to be obtained, cholestan-3-one, by the treatment of the unsaturated compound, obtained by dehydrochlorination, with osmium tetroxide followed by lead tetraacetate or ozone oxidation, was not found in the ethanol-soluble portion.

The author is deeply grateful to Prof. K. Tsuda of the Institute for Applied Microbiology, University of Tokyo, for kind guidance. The author is indebted to Messrs. Onoye, Furukawa, and Otsuka 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 to Mr. Shinji of the Institute of Technology, University of Tokyo, for X-ray analysis. Thanks is also due to Messrs. Endo and Baba for technical help in the preparation of intermediates.

Experimental

All optical rotational measurements were made in chloroform solution with 2-dm. tube.

3β,3′β-Bicholestan-3α-ol (III)—3α-Chlorocholestane (I), m.p. 103~105°, and 3-chlorocholestane, m.p. 112~114°, were respectively prepared by the method of Shoppee[4)] and of Ruzicka[5)] and those giving positive Libermann reaction were used.

The Grignard reagent was prepared from 20 g. of either of the above 3ε-chlorocholestanes and 2 g. of Mg powder, with EtBr as a catalyst, by the method of Squire.[6)] To this Grignard reagent, a solution of 20 g. of cholestan-3-one,[7)] m.p. 128~130°, dissolved in 100 cc. of ether was dropped in at room temperature during 30 mins., heated for 2 hrs., and ether was evaporated. Water and then 5% H_2SO_4 were consecutively added, Mg was removed, and residue was washed with water. This was then triturated with 100 cc. of MeOH, which was decanted, and this procedure was repeated twice. The residue was then triturated with 100 cc. of acetone. The crystals were washed with acetone, and further triturated with 100 cc. of AcOEt. This mixture was filtered, the crude crystals on the filter were washed thoroughly with AcOEt to remove viscid oil, and dried. The pale yellow powder (3 g.) thereby obtained was boiled with 200 cc. of xylene, the solution was filtered, and cooled filtrate afforded short needles, m.p. 415~420°, $[\alpha]_D^{25}$ +42.5°(c=0.0353). Yield, 2 g. *Anal.* Calcd. for $C_{54}H_{94}O$: C, 85.48; H, 12.40. Found: C, 85.66; H, 12.73. I.R. ν_{max}^{Nujol} 3520 cm^{-1}.

3β,3′β-Bicholest-2-ene (IV)—a) To a suspension of 1 g. of (III), m.p. 410~420°, in 50 cc. of $CHCl_3$, 0.5 cc. of 70% $HClO_4$ solution was added and the mixture was allowed to stand, by which the $CHCl_3$ gradually colored red and crystals remained undissolved, while dehydration was effected. After standing for 30 mins., the mixture was filtered, the crystals were washed with $CHCl_3$ and MeOH, and dried. The crystals were then dissolved in 500 cc. of benzene with boiling, the solution was concentrated to 100 cc., and cooled, affording long prisms, m.p. 400~410°, $[\alpha]_D^{25}$ +55.6°(c=0.081). *Anal.* Calcd. for $C_{54}H_{92}$: C, 87.79; H, 12.19. Found: C, 88.10; H, 12.22. I.R. ν_{max}^{Nujol} 1670 cm^{-1}.

b) To the suspension of 500 mg. of (III) in 50 cc. of pyridine, 1 cc. of $POCl_3$ was added and the mixture was allowed to stand over night. The mixture was pourd into water, crystals were collected, washed with acetone, and recrystallized from benzene. (IV) was obtained in 80% yield and was identified by mixed fusion and by infrared spectral data.

c) A solution of 50 mg. of 3ε-chloro-3α,3′β-bicholestane (VI) dissolved in 200 cc. of $CHCl_3$ was vigorously stirred on a magnetic stirrer, maintained below 20°, 2 g. of Zn dust was added gradually, and the mixture was stirred for 8 hrs. The mixture was filtered, $CHCl_3$ was evaporated from the filtrate, and the residue was recrystallized from benzene to (IV) as long prisms, identified by mixed

---

3) D. Barton, J. Page, C. Shopee: J. Chem. Soc., **1956**, 331.
4) C. Shoppee: J. Chem. Soc., **1946**, 1138, 1147.
5) L. Ruzicka: Helv. Chim. Acta, **17**, 1389(1934).
6) E. Squire: J. Am. Chem. Soc., **70**, 1487(1948).
7) Org. Syntheses, **17**, 43.

fusion and infrared spectral curve.

3,3′-Bicholestane-2,3-diol (VIII)—A mixture of 500 mg. of (IV), 500 mg. of OsO_4, 500 cc. of dehyd. dioxane, and 10 cc. of dehyd. pyridine was heated at 100° for 5 hrs., excluding moisture. After cool, H_2S was bubbled through the reaction mixture to precipitate osmium sulfide. The solution was boiled, filtered, and the filtrate was cooled, affording short needles, m.p. 390∼400°, $[\alpha]_D^{25}$ +19.7°(c=0.051). *Anal.* Calcd. for $C_{54}H_{92}O_2$: C, 84.00; H, 11.91. Found : C, 83.59; H, 11.83.

The yield was very poor, probably due to heating, and only 100 mg. of the diol was obtained. However, the reaction will not progress even if the reaction is carried out in the cold over a long period, unless the substance dissolves.

3,3′-Bicholestan-3-one (IX)—A solution of 50 mg. of (VIII) dissolved in 100 cc. of $CHCl_3$ and added with 2 drops of 70% $HClO_4$ solution was allowed to stand over night, MeOH was added to the mixture, and precipitated crystals were collected. Recrystallization from AcOEt afforded needles, m.p. 380∼390°. *Anal.* Calcd. for $C_{54}H_{92}O$: C, 85.71; H, 12.17. Found : C, 85.00; H, 12.12. Absorption of strong intensity appeared in its infrared spectrum (in Nujol) at 1725 cm^{-1} for a saturated, six-membered ketone.

3β-Chloro-3α,3′β-bicholestane (VI)—Dry HCl gas was saturated in the solution of 1 g. of (IV) dissolved in 2 L. of $CHCl_3$ with warming, at 40°, and the mixture was maintained at 40° for 72 hrs., excluding moisture. If crystals precipitated out, the solution was warmed. After this period, the solvent was distilled off under a reduced pressure and the residue was recrystallized from benzene to needles, m.p. 395∼405°, $[\alpha]_D^{25}$ +39.7°(c=0.05). *Anal.* Calcd. for $C_{54}H_{93}Cl$: C, 83.29; H, 12.13. Found: C, 83.31; H, 12.14. A distinct absorption of equatorial Cl appeared in its infrared spectrum (in Nujol) at 790 cm^{-1}.

3β,3′β-Bicholestane (V)—a) High-pressure reduction of (IV), m.p. 400∼410°, was carried out by placing 100 mg. of (IV), 100 cc. of tetrahydrofuran, and 2 g. of 5% Pd-$BaCO_3$ catalyst in a shaking autoclave at an initial H_2 pressure of 80 atm. and reacted at 200° and 200 atm. for 8 hrs. The content in the autoclave was transferred to a flask, using 50 cc. of tetrahydrofuan, the mixture was boiled on a water bath to dissolve the crystals, and filtered. On cooling the filtrate, needles, m.p. 410∼420°, $[\alpha]_D^{25}$ ±0°, separated out. There occured no decomposition and the yield was 80%. *Anal.* Calcd. for $C_{54}H_{94}$: C, 87.26; H, 12.31. Found : C, 87.51; H, 12.23.

b) The Grignard reagent was prepared from 20 g. of 3α-chlorocholestane (I) by the method of Squire,6) heated for 8 hrs., and a solution of 20 g. of cholest-4-en-3-one dissolved in 100 cc. of ether was dropped in at room temperature during 30 mins. The mixture was further heated for 20 hrs., the mixture was treated as usual, and 5 g. of substance insoluble in AcOEt was recrystallized from $CHCl_3$ to needles, m.p. 380∼390°. The ultraviolet absorption (in Et_2O) maxima at 234 and 242 mμ (ε 35000) suggested the presence of α,β-unsaturated ketone but 100 mg. of the mixture without further purification, was submitted to hydrogenation under the same conditions as in a) and recrystallization of the product from 50 cc. of $CHCl_3$ afforded 60 mg. of needles, m.p. 410∼420°, $[\alpha]_D^{25}$ ±0°, as the first crop. Evaporation of the mother liquor from this crystallization to a 10-cc. volume afforded 10 mg. of needles, m.p. 380∼390°. These 2nd crop of crystals showed infrared absorption (in Nujol) at 1725 cm^{-1}.

The X-ray analysis of (V) obtained by the methods a) and b) are shown in Table I. Only those of strong intensity have been listed in Table I but other lines were also in good agreement within a range of +0.02.

TABLE I.

Method a)			Method b)		
Line No.	D (Å)	Intensity*	Line No.	D (Å)	Intensity*
4	7.01	s	4	6.99	s
5	6.03	m	5	6.03	m
6	5.55	vs	6	5.56	vs
8	4.72	m	8	4.72	m
9	4.33	m	9	4.32	m
10	4.04	vs	10	4.04	vs

* m, mild; s, strong; vs, very strong.

3,3′-Bicholest-5-en-3α-ol (XII)—The Grignard reagent was prepared from 2 g. of 3β-chlorocholest-5-ene by the method of Squire6) and a solution of 20 g. of cholestan-3-one in ether was dropped in during 30 mins. The reaction mixture was treated as usual and 3 g. of needles, m.p. 380∼385°, $[\alpha]_D^{24}$ +31.9°, was obtained. *Anal.* Calcd. for $C_{54}H_{92}O$: C, 85.71; H, 12.18. Found : C, 84.00; H, 12.01.

The value for C came out rather small that it was submitted to dehydration and purifiied.

3,3′-Bicholesta-2,5′-diene (XIII)—A suspension of 1 g. of (XII) in $CHCl_3$ with 2 drops of 70% $HClO_4$ was allowed to stand to effect dehydration and the product was recrystallized from benzene to long 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.

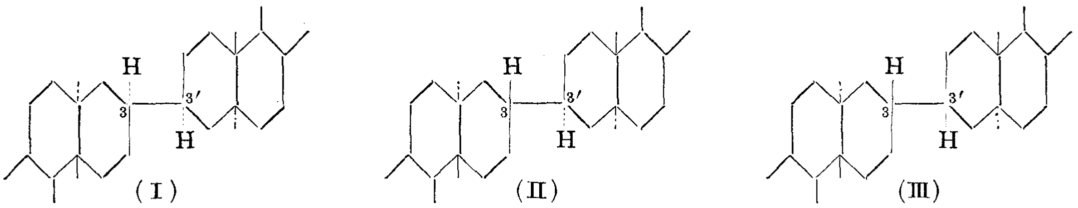
(Received December 4, 1957)

UDC 547.92

43. **Ko Arima**: Studies on Cholestapolyenes. VIII.[1]
Separation of Stereoisomers of Bicholestane.

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

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

---

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

[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.