tained in a mixture of ether and benzene and kept at 0°, 0.03 mole (28 mole per cent.) of cobalt chloride was added, and the treatment continued according to the directions given in the literature.[5] A 63% yield of biphenyl was obtained, on the basis of the Grignard reagent used. Since a blank on the phenylmagnesium iodide showed 7% biphenyl, the agreement between the calculated yield of biphenyl (56%) and that actually formed in the reaction (56%) is excellent. Our results are probably accurate within 2–3%.

Summary

1. Excellent yields of biaryl are obtained when an aryl Grignard reagent is treated with an organic halide, preferably a bromide, in the presence of 3–10 mole per cent. of the halides of iron, nickel and cobalt (the metals are arranged in order of their increasing effectiveness). The halides of copper and chromium are ineffective, while manganous chloride has a slight effect.

2. It has been indicated that the metallic halides act in the above reaction as oxidation-reduction catalysts, and a chain reaction, involving the subhalides of the effective metals, is postulated.

3. The study of the effect of metallic halides on the reaction of Grignard reagents and organic molecules containing functional groups is under way in this Laboratory.

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[CONTRIBUTION FROM THE ANIMAL CHEMISTRY AND NUTRITION SUBSECTION OF IOWA STATE COLLEGE]

The Formation of the Molecular Compound of *allo-* and *epi-allo*-Cholesterol from $\Delta^{3,5}$-Cholestadiene[1]

BY J. C. ECK AND E. W. HOLLINGSWORTH

In a further study of the rearrangement of $\Delta^{4,6}$-cholestadiene (I) to $\Delta^{3,5}$-cholestadiene (II) by the action of hydrogen chloride in chloroform solution,[2] it was found that the molecular compound of *allo-* and *epi-allo*-cholesterol (III) could be isolated from the crude reaction product. This compound was isolated by the ether elution of an activated alumina column through which had been passed a petroleum ether solution of the reaction product.

The molecular compound of *allo-* and *epi-allo*-cholesterol was likewise isolated from the reaction products formed by the action of hydrogen chloride in chloroform on $\Delta^{3,5}$-cholestadiene which had been prepared by (a) the hydrogen chloride rearrangement of $\Delta^{4,6}$-cholestadiene, (b) the copper sulfate dehydration of cholesterol in xylene[3] and (c) the alcoholic hydrochloric acid dehydration of the molecular compound of *allo-* and *epi-allo*-cholesterol.[4] Since the molecular compound of *allo-* and *epi-allo*-cholesterol was isolated from the action of hydrogen chloride in chloroform on $\Delta^{3,5}$-cholestadiene which had been obtained from three different sources, it could not have been formed from an impurity but from the $\Delta^{3,5}$-cholestadiene itself. Furthermore, a twice repeated treatment of the $\Delta^{3,5}$-cholestadiene recovered from the reaction product obtained by the action of hydrogen chloride in chloroform on $\Delta^{3,5}$-cholestadiene resulted in a combined conversion of most of the $\Delta^{3,5}$-cholestadiene to the molecular compound of *allo-* and *epi-allo*-cholesterol.

The molecular compound of *allo-* and *epi-allo*-cholesterol was also isolated from the reaction product obtained by the action of hydrogen chloride in chloroform on $\Delta^{2,4}$-cholestadiene (IV) which has been shown to be rearranged to $\Delta^{3,5}$-cholestadiene by the action of alcoholic hydrochloric acid.[5] It is probable that $\Delta^{2,4}$- and $\Delta^{4,6}$-cholestadienes are rearranged to $\Delta^{3,5}$-cholestadiene which is then partially converted to the molecular compound of *allo-* and *epi-allo*-cholesterol. Thus (a) the molecular compound of *allo-* and *epi-allo*-cholesterol is formed by the action of hydrogen chloride in chloroform on $\Delta^{2,4}$-, $\Delta^{3,5}$- and $\Delta^{4,6}$-cholestadienes, (b) hydrogen chloride in chloroform rearranges $\Delta^{4,6}$-cholestadiene to $\Delta^{3,5}$-cholestadiene and (c) $\Delta^{3,5}$-cholestadiene is undoubtedly present in the reaction product resulting from $\Delta^{2,4}$-cholestadiene. It is of interest to note that hydrogen chloride in chloroform rearranges both $\Delta^{2,4}$- and $\Delta^{4,6}$-cholestadienes to $\Delta^{3,5}$-cholestadiene, whereas $\Delta^{2,4}$-cholestadiene is rearranged to $\Delta^{3,5}$-cholestadiene by the action of alcoholic

(1) Journal Paper No. J-893 of the Iowa Agricultural Experiment Station, Project No. 506.

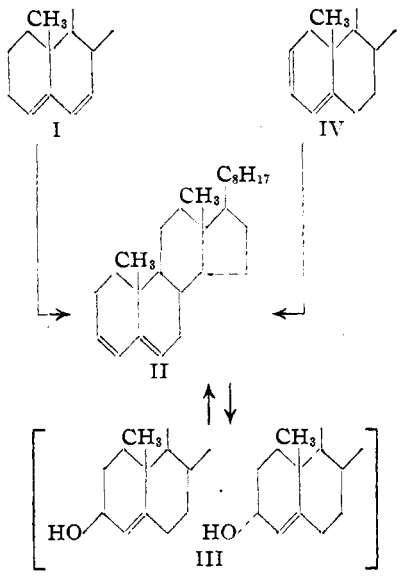
(2) Eck and Hollingsworth, THIS JOURNAL, **63**, 107 (1941).

(3) Eck and Hollingsworth, *Iowa State Coll. J. Sci.*, **13**, 329 (1939).

(4) Eck, Van Peursem and Hollingsworth, THIS JOURNAL, **61**, 171 (1939).

(5) Stavely and Bergmann, *J. Org. Chem.*, **1**, 575 (1937).

hydrochloric acid, which does not affect $\Delta^{4,6}$-cholestadiene.



The by-product of the hydrogen chloride reactions was identified as the molecular compound of *allo-* and *epi-allo*-cholesterol[6] by its analysis, melting point and specific rotation, its dehydration to $\Delta^{3,5}$-cholestadiene and its separation into *allo-* and *epi-allo*-cholesterol. The formation of the molecular compound of *allo-* and *epi-allo*-cholesterol from $\Delta^{3,5}$-cholestadiene is unusual and unexpected. Although the hydrogen chloride used was bubbled through concentrated sulfuric acid as is customary for the production of dry hydrogen chloride, and precautions were taken to remove the original air by flushing the apparatus with nitrogen, it is obvious that the elements of water are involved in the formation of the molecular compound of *allo-* and *epi-allo*-cholesterol ($C_{27}H_{45}OH$) from $\Delta^{3,5}$-cholestadiene ($C_{27}H_{44}$). The molecular compound of *allo-* and *epi-allo*-cholesterol is dehydrated to $\Delta^{3,5}$-cholestadiene by the action of alcoholic hydrochloric acid containing about 5% of water but, with hydrogen chloride in chloroform, the reaction product obtained by the treatment of either compound was found to be a mixture of the two compounds. Cholesterol and cholesteryl chloride were indicated not to be intermediates in the formation of the molecular compound of *allo-* and *epi-allo*-cholesterol from $\Delta^{3,5}$-cholestadiene since cholesterol and cholesteryl chloride were recovered unchanged following a three-hour treatment with hydrogen chloride in chloroform. It is known[7] that the treatment of cholesterol with hydrogen chloride in chloroform for three days results in the formation mainly of 3,5-dichlorocholestane, whereas cholesteryl chloride remains unchanged.

The elements of water could either be available as water in the reaction mixture or could be involved in a subsequent hydrolysis of a chloride formed during the reaction. Thus, it is possible that a 1,4-addition of water could result in the direct formation of the molecular compound of *allo-* and *epi-allo*-cholesterol from $\Delta^{3,5}$-cholestadiene or that a 1,4-addition of hydrogen chloride could result in the formation of the as yet unreported 3-chloro-Δ^{4}-cholestene which could be hydrolyzed during the reaction or during isolation of the reaction product. The result of the reaction can be referred to as essentially a 1,4-addition of water whether it actually consists of a 1,4-addition of water or a 1,4-addition of hydrogen chloride followed by hydrolysis. It is highly probable that the small amount of water necessary was present in the reaction mixture since the molecular compound of *allo-* and *epi-allo*-cholesterol was also isolated from the reaction product residue by a direct crystallization from a dry hydroxyl group-free solvent (petroleum ether dried over sodium and distilled). A possible mechanism for the reverse conversion of the molecular compound of *allo-* and *epi-allo*-cholesterol to $\Delta^{3,5}$-cholestadiene may be dehydration to $\Delta^{2,4}$-cholestadiene which could then be converted to $\Delta^{3,5}$-cholestadiene through essentially a 1,4-addition of water, to form the as yet unreported Δ^{3}-cholesten-5-ol, followed by dehydration. Likewise the formation of $\Delta^{3,5}$-cholestadiene from $\Delta^{4,6}$-cholestadiene may be essentially the 1,4-addition of water, to form the as yet unreported Δ^{5}-cholesten-4-ol or the known Δ^{5}-cholesten-7-ol, followed by dehydration. Even if the formation of Δ^{5}-cholesten-7-ol occurs, $\Delta^{3,5}$-cholestadiene would be obtained since it has been shown[2] that $\Delta^{3,5}$-cholestadiene is formed by the action of hydrogen chloride in chloroform on Δ^{5}-cholesten-7-ol which, however, is converted to $\Delta^{4,6}$-cholestadiene by the action of alcoholic hydrochloric acid. The presence of sufficient water in the reaction mixture for essentially a 1,4-addition of water followed by dehydration could also account for the conversion, by the action of hydrogen chloride in chloroform, of sterol deriva-

(6) Schoenheimer and Evans, *J. Biol. Chem.*, **114**, 567 (1936).

(7) Mauthner, *Monatsh.*, **27**, 305 (1906).

tives possessing unsaturation in the 5,7- or 6,8-positions to derivatives unsaturated in the 7,14- or 8,14-positions, such as the rearrangement of $\Delta^{5,7}$-cholestadiene-3-ol[8] and $\Delta^{6,8}$-cholestadiene-3-ol[9] to $\Delta^{7,14}$-cholestadiene-3-ol (dehydrocholesterol B_3), of $\Delta^{5,7,22}$-ergostatriene-3-ol (ergosterol)[10] to $\Delta^{7,14,22}$-ergostatriene-3-ol (ergosterol B_3) and of $\Delta^{5,7}$-ergostadiene-3-ol (22-dihydroergosterol)[11] to $\Delta^{8,14}$-ergostadiene-3-ol (dehydro-α-ergostenol).

Experimental

Treatment of $\Delta^{4,6}$-Cholestadiene with Hydrogen Chloride.—Dry hydrogen chloride was passed through a solution of 300 mg. of $\Delta^{4,6}$-cholestadiene dissolved in 25 cc. of chloroform (dried over phosphorus pentoxide and distilled) at 0° for three hours. The solvent was removed *in vacuo* and the residue dissolved in 25 cc. of petroleum ether (b. p. 30–40°) was passed through an 18 × 65 mm. column of activated alumina (30 to 200 mesh preheated Alorco). The column was washed with 50 cc. of petroleum ether and the combined filtrates were concentrated *in vacuo*. The residue on one crystallization from absolute alcohol yielded 190 mg. of $\Delta^{3,5}$-cholestadiene, m. p. 78.5–79°, $(\alpha)^{21}D$ −103.6° (*c*, 1.22 in carbon tetrachloride).

The alumina column was eluted with 100 cc. of ether and the ether eluate was concentrated *in vacuo*. The residue was crystallized from petroleum ether to yield 80 mg. of a halogen-free solid which after several recrystallizations from acetone gave a compound in the form of needles, m. p. 140–141°, $(\alpha)^{23}D$ +85.6° (*c*, 1.25 in carbon tetrachloride).

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.86; H, 12.00. Found: C, 84.14, 84.28; H, 12.03, 11.88.

This compound was found to add bromine and to form an acetate, m. p. 82–83°. Dehydration with alcoholic hydrochloric acid was found to convert the compound to $\Delta^{3,5}$-cholestadiene, m. p. 79.5–80°, $(\alpha)^{21}D$ −114.3° (*c*, 1.38 in carbon tetrachloride). The compound gave no depression in mixed melting point with an authentic sample of the molecular compound of *allo*- and *epi-allo*-cholesterol (m. p. 140–141°)[6] and was separated by digitonin into a compound, m. p. 131–132°, which gave no depression in mixed melting point with an authentic sample of *allo*-cholesterol, and a compound, m. p. 82–83°, which gave no depression in mixed melting point with an authentic sample of *epi-allo*-cholesterol.

The hydrogen chloride used was bubbled through concentrated sulfuric acid. Additional experiments were conducted in the treatment of $\Delta^{4,6}$-cholestadiene with hydrogen chloride in which the source of the hydrogen chloride was changed. The hydrogen chloride generator using concentrated sulfuric acid on sodium chloride was replaced with a Kipp generator using ammonium chloride. The Kipp generator was flushed out with nitrogen which had been passed through alkaline pyrogallol solution in order to reduce the presence of atmospheric oxygen to a minimum. The hydrogen chloride so produced was used in a repeated experiment with $\Delta^{4,6}$-cholestadiene to again yield $\Delta^{3,5}$-cholestadiene and the molecular compound of *allo*- and *epi-allo*-cholesterol with practically the same yield of each compound.

Treatment of $\Delta^{3,5}$-Cholestadiene with Hydrogen Chloride.—Dry hydrogen chloride was passed through the chloroform solutions of samples of $\Delta^{3,5}$-cholestadiene obtained from three different sources, according to the procedure as described for the treatment of $\Delta^{4,6}$-cholestadiene. $\Delta^{3,5}$-Cholestadiene and the molecular compound of *allo*- and *epi-allo*-cholesterol were isolated in the same relative yields as obtained from $\Delta^{4,6}$-cholestadiene. $\Delta^{3,5}$-Cholestadiene, prepared by the copper sulfate dehydration of cholesterol, was also subjected to a repeated treatment. The $\Delta^{3,5}$-cholestadiene recovered from the column filtrate fraction of the reaction product obtained by the action of hydrogen chloride in chloroform on 3 g. of $\Delta^{3,5}$-cholestadiene, was again treated with hydrogen chloride in chloroform and the $\Delta^{3,5}$-cholestadiene recovered from this second treatment was treated a third time to leave only 0.3 g. of $\Delta^{3,5}$-cholestadiene still unchanged as a result of the third treatment.

Upon treatment with hydrogen chloride in chloroform, 200 mg. of the molecular compound of *allo*- and *epi-allo*-cholesterol was converted to a reaction product from which 85 mg. of $\Delta^{3,5}$-cholestadiene and 35 mg. of the molecular compound of *allo*- and *epi-allo*-cholesterol were isolated. Upon treatment of cholesterol and cholesteryl chloride with hydrogen chloride in chloroform solution for three hours, the cholesterol and cholesteryl chloride were recovered unchanged.

Treatment of $\Delta^{2,4}$-Cholestadiene with Hydrogen Chloride.—Dry hydrogen chloride was passed through a solution of 50 mg. of $\Delta^{2,4}$-cholestadiene dissolved in 100 cc. of chloroform at 0° for three hours. The molecular compound of *allo*- and *epi-allo*-cholesterol (10 mg.) was obtained from the column eluate fraction of the reaction product residue. The levorotation ($(\alpha)D$ −40°) of the column filtrate fraction of the reaction product residue in comparison with the strong dextrorotation ($(\alpha)D$ +148°) of the original $\Delta^{2,4}$-cholestadiene indicated that the column filtrate fraction contained $\Delta^{3,5}$-cholestadiene although purification was not attempted (observations in attempted purification of cholesterilene, which either may be $\Delta^{3,5}$-cholestadiene or may contain $\Delta^{3,5}$-cholestadiene in an inseparable mixture, have previously been shown).[3]

Summary

The molecular compound of *allo*- and *epi-allo*-cholesterol was isolated from the reaction products obtained by the treatment of $\Delta^{2,4}$-, $\Delta^{3,5}$- and $\Delta^{4,6}$-cholestadienes with hydrogen chloride in chloroform solution. It is probable that the $\Delta^{3,5}$-cholestadiene formed by rearrangement of the $\Delta^{2,4}$- and $\Delta^{4,6}$-cholestadienes is partially converted to the molecular compound of *allo*- and *epi-allo*-cholesterol by essentially a 1,4-addition of water.

AMES, IOWA RECEIVED JUNE 6, 1941

(8) Schenck, Buchholz and Wiese, *Ber.*, **69B**, 2696 (1936).
(9) Windaus, Linsert and Eckhardt, *Ann.*, **534**, 22 (1938).
(10) Windaus, Dithmar, Murke and Suckfüll, *ibid.*, **488**, 91 (1931).
(11) Windaus and Langer, *ibid.*, **508**, 105 (1933).