The Addition of Hydrogen Bromide to Cholesteryl Bromide and the Oxygen Effect.

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The addition of hydrogen bromide to allyl bromide and to undecenoic acid (in toluene) follows the Markownikoff rule[1] in the absence of oxygen and peroxides and gives the normal products, 1,2-dibromopropane and 10-bromoundecanoic acid respectively, in a nearly pure state. The presence of a minute quantity of oxygen in the reacting mixtures causes a reversal of the direction of addition, the abnormal products, 1,3-dibromopropane and 11-bromoundecanoic acid respectively, being formed as the main products. The oxygen effect on the addition of hydrogen bromide has been observed also with many other ethenoid compounds.[2] Further, isostilbene has been found to isomerize to stilbene in the presence of hydrogen bromide and oxygen, but not in the presence of either one of them[3].

One (Y.U.) of the authors and O. Simamura investigated the action of the mixture of hydrogen bromide and oxygen on allyl bromide and on stilbene[4]. The former gave water, free bromine, 1,2,3-tribromopropane, and a peroxide, probably dibromoisopropyl peroxide, besides 1,3-dibromopropane, the main product. The latter yielded stilbene dibromide as the main product, which was accompanied by small amounts of a peroxide and free bromine. From these results they postulated a mechanism of the oxygen effect.

Until recently all the examples of addition reactions showing explicitly the oxygen effect were of the addition of hydrogen bromide to terminal double bonds, and ethenoid compounds such as isoundecenoic acid[5][6], isoundecenol[6], and *cis*- and *trans*-pentene-(2)[7], which belong to the type CH_3-CH=CH-CH_2-R with a well-balanced non-terminal ethylene group, gave equal parts of isomeric addition products irrespective of the conditions of addition, thus making the detection of the oxygen effect impossible. Recently it was demonstrated that trimethylethylene[8] and 2-bromobutene-(2)[9], both with unbalanced non-terminal ethylene groups, are

(1) W. B. Markownikoff, *Ann.*, **153** (1870), 256.

(2) For reviews of works on the oxygen effect compare J. C. Smith, *Chemistry and Industry*, **56** (1937), 833; **57** (1938), 461; *Ann. Rep.*, **1939**, 219.

(3) Y. Urushibara and O. Simamura, this Bulletin, **12** (1937), 507; **13** (1938), 566.

(4) Y. Urushibara and O. Simamura, *ibid.*, **14** (1939), 323. Compare also O. Simamura, *ibid.*, **15** (1940), 292.

(5) P. L. Harris and J. C. Smith, *J. Chem. Soc.*, **1935**, 1108.

(6) E. P. Abraham, E. L. R. Mowat, and J. C. Smith, *ibid.*, **1937**, 948.

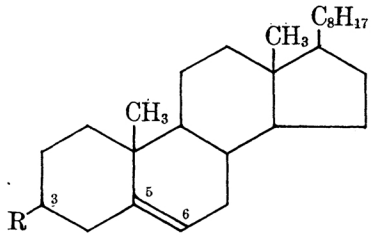
(7) M. S. Kharasch, C. Walling, and F. R. Mayo, *J. Am. Chem. Soc.*, **61** (1939), 1559.

(8) C. Walling, M. S. Kharasch, and F. R. Mayo, *ibid.*, **61** (1939), 2693; A. Michael and N. Weiner, *J. Org. Chem.*, **4** (1939), 531.

(9) C. Walling, M. S. Kharasch, and F. R. Mayo, *J. Am. Chem. Soc.*, **61** (1939), 1711.

subject to the oxygen effect when they add hydrogen bromide. The present paper describes the addition of hydrogen bromide to cholesteryl bromide as another example of the hydrogen bromide addition to a non-terminal double bond subject to the oxygen effect.

In cholesterol and other cholestene-(5) derivatives represented by formula I the ethylene group is much unbalanced and carbon atom 5 is sterically much hindered compared with carbon atom 6. Hence, it can be anticipated that the normal addition of hydrogen bromide will produce one isomeride in a predominating proportion while in the presence of oxygen the abnormal addition will yield the other isomeride as the main product, stereoisomerism being disregarded.



(I)

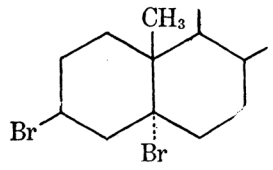
(Ia) R = OH
(Ib) R = Br
(Ic) R = Cl
(Id) R = H
(Ie) R = CH_3CO_2

On treatment with hydrogen bromide, however, cholesterol (Ia) is liable to substitution of a bromine atom for the hydroxyl group[10], and further it has been shown by Ashton and Smith[11] that undecenol, the alcohol corresponding to undecenoic acid, fails to yield an abnormal product under strongly oxidant conditions because of the counter-effect of the hydroxyl group. Cholesteryl halides and cholestene (Id) may be free from such possible difficulties. Thus cholesteryl bromide (Ib) was used for the present investigation, because it is more easily obtainable than cholestene and better suited for the investigation of hydrogen bromide addition than cholesteryl chloride (Ic).

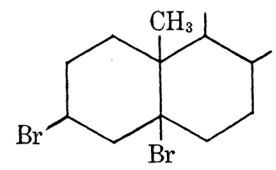
The mechanism of the hydrogen bromide addition as represented in the previous paper[4] requires the hydrogen atom to add to carbon atom 6 and the bromine atom to carbon atom 5 in the normal addition, and in the abnormal addition, if it occurs, the direction of addition of hydrogen bromide to be reversed. Then two stereoisomeric products (IIa and IIb) are possible in the normal addition, because carbon atom 5 becomes asymmetric, and four (IIIa, IIIb, IIIc, and IIId) are possible in the abnormal addition owing to the asymmetry of both carbon atoms 5 and 6. All the possible isomerides, however, may not be obtained in practice. If only one product is obtained in each case, the direction of addition of hydrogen bromide may well be inferred from the examples of simpler ethenoid compounds, but the stereochemical configuration of each product has to be determined.

(10) The action of hydrogen chloride on cholesterol yields 3,5-dichlorocholestane besides cholesterol hydrochloride, J. Mauthner, *Monatsh.*, **27** (1906), 305.

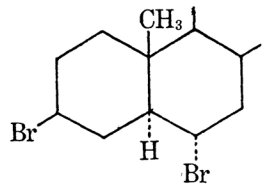
(11) R. Ashton and J. C. Smith, *J. Chem. Soc.*, **1934**, 1308.



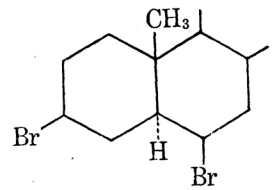
(IIa)



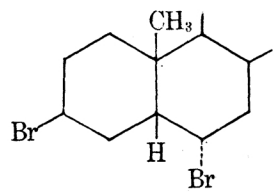
(IIb)



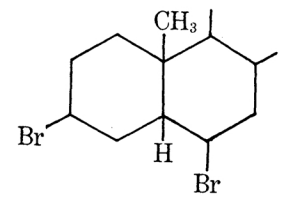
(IIIa)



(IIIb)



(IIIc)

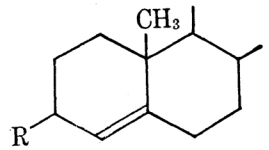


(IIId)

The addition of hydrogen bromide to the cholesterol derivatives represented by formula I has never been studied. Recently Pirrone[12] treated cholesterol with hydrobromic acid in alcoholic solution and obtained an isomeride of cholesterol with small amounts of two substances melting at 120° and 104–105° respectively, which have not been characterized.

There have been many investigations on the addition of hydrogen chloride to cholesterol derivatives. Mauthner[13] obtained a hydrochloride melting at 154–155° from cholesterol and hydrogen chloride. The conversion of it into allocholesterol[14] (IVa) shows that the chlorine atom is situated at carbon atom 5. Fazi[15] obtained several products from the action of hydrogen chloride on cholesterol, but none have been sufficiently characterized. It seems that he doubts the homogeneity of Mauthner's hydrochloride. By the catalytic reduction of cholesterol dichloride Décombe and Rabinowitch[16] obtained a chlorocholestanol, to which they suggested a constitution of 6-chlorocholestanol. It appears that Fazi attributed the same constitution to one of his products[17].

(12) F. Pirrone, *Chem. Zentr.*, **111** (1940), I, 555.
(13) J. Mauthner, *Monatsh.*, **27** (1906), 305.
(14) A. Windaus, *Ann.*, **453** (1927), 101; R. Schoenheimer and E. A. Evans, Jr., *J. Biol. Chem.*, **114** (1936), 567.
(15) R. de Fazi and L. de Fazi-Guerci, *Chem. Zentr.*, **103** (1932), I, 3302; R. de Fazi, *ibid.*, **109** (1938), II, 1781; R. de Fazi and F. Pirrone, *ibid.*, **111** (1940), I, 2652.
(16) J. Décombe and J. Rabinowitch, *Bull. soc. chim.*, [5], **6** (1939), 1510.
(17) *Idem*, *ibid.*, p. 1520.



(IV)

(IVa) R = OH

(IVb) R = H

Mauthner[18] showed the formation of two isomeric hydrochlorides from the addition of hydrogen chloride to cholestene, one of which he isolated in a pure state. As the both hydrochlorides were converted into the same pseudocholestene (IVb), they must be regarded as stereoisomerides both with the chlorine atom at carbon atom 5. The isomeric 6-chlorocholestane was not formed from hydrogen chloride and cholestene but obtained from cholestanol-(6).[19]

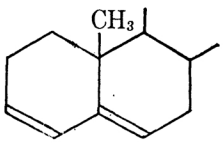
From cholesteryl chloride and hydrogen chloride Mauthner[13] obtained 3,5-dichlorocholestane as the only addition product. The same substance was formed by the action of hydrogen chloride on cholesterol[10]. The isomeric 3,6-dichlorocholestane was obtained by the action of phosphorus pentachloride on cholestanediol-(3,6)[20]. On reduction with sodium and amyl alcohol 3,6-dichlorocholestane gave cholestane.

As summarized above, the addition of hydrogen chloride to cholesteryl chloride gives only one product, while the addition to cholestene and to cholesterol two or more. Thus cholesteryl bromide seemed to be the most suitable substance for the present purpose of studying the addition of hydrogen bromide and the oxygen effect.

The Action of Hydrogen Bromide on Cholesteryl Bromide under the Conditions Favourable for the Normal Addition. The action of hydrogen bromide on cholesteryl bromide in carbon tetrachloride with the addition of a small amount of catechol and the purification of the product gave a crystalline substance showing a melting point 101.5° (corr.), $[\alpha]_D$ + 5.36°, and a bromine content corresponding to the addition of a molecule of hydrogen bromide. The addition in the presence of ferric chloride which is known as an accelerating agent for the normal addition, and the addition in ethereal solution, yielded the same substance. Thus, it is evident that this hydrobromide is the normal product, the bromine atom being situated at carbon atom 5 (IIa or IIb).

The optical rotation affords a further evidence that the hydrobromide corresponds to the addition products of hydrogen chloride to cholesterol, cholestene, and cholesteryl chloride: According to Mauthner[21] the laevo-rotation of these substances is converted into dextro-rotation by the addition of hydrogen chloride. Cholesteryl bromide is laevo-rotatory ($[\alpha]_D$−20.8°)[22], and the hydrobromide formed by the addition of hydrogen bromide under conditions mentioned above is dextro-rotatory. (The other hydrobromide described below is laevo-rotatory.)

(18) J. Mauthner, *Monatsh.*, **28** (1907), 1113.
(19) O. Stange, *Z. physiol. Chem.*, **220** (1933), 34.
(20) A. Windaus, *Ber.*, **50** (1917), 133.
(21) J. Mauthner, *Monatsh.*, **27** (1906), 314, 421.
(22) J. H. Beynon, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, **1936**, 907.



(V)

The hydrobromide melting at 101.5° easily loses one or two molecules of hydrogen bromide: On boiling in acetone it gives cholesteryl bromide and on boiling in pyridine cholestadiene-(3,5) (V).

The Action of Hydrogen Bromide and Oxygen on Cholesteryl Bromide. The mixture of hydrogen bromide and oxygen was passed into a carbon tetrachloride solution of cholesteryl bromide, and the product was purified to a crystalline substance melting at 154° (corr.) and showing $[\alpha]_D$−12.1°. Analysis showed it was another hydrobromide of cholesteryl bromide. Thus it has been found that oxygen exerts an effect on the addition to yield a hydrobromide different from the normal product formed without oxygen, and it is reasonable to assume that the direction of addition is reversed, so that the bromine atom adds to carbon atom 6 and the hydrogen atom to carbon atom 5 (IIIa, IIIb, IIIc, or IIId).

The hydrobromide melting at 154° is more stable than the other melting at 101.5°. It was not changed on boiling in acetone. However, attempts to substitute hydroxyl groups or hydrogen atoms for the both bromine atoms in this hydrobromide failed owing to the ease with which the added molecule of hydrogen bromide was split off under the conditions of the experiments, and nothing but the products from cholesteryl bromide were obtained: On boiling with potassium acetate in acetic acid it was transformed into cholesteryl acetate (Ie). On reduction with sodium and amyl alcohol the hydrobromide again lost hydrogen bromide and gave cholestene (Id). Thus it was impossible to obtain any information of the configuration about carbon atoms 5 and 6.

From the mother liquor of the hydrobromide melting at 154° another crystalline substance was obtained. Its bromine content corresponded to a dibromide of cholesteryl bromide, and on debromination with sodium iodide it gave cholesteryl bromide. As the substance was not obtained in a pure state and melted in a wide range of temperature (84–127°), it could not exactly be determined whether or not it was identical with cholesteryl bromide dibromide (melting point 113°) formed from cholesteryl bromide and bromine.

The formation of the dibromide from cholesteryl bromide by the action of hydrogen bromide and oxygen corresponds to the formation of 1,2,3-tribromopropane and stilbene dibromide from allyl bromide and stilbene respectively by similar treatments.

Experimental.

Materials. Cholesteryl bromide was prepared by the action of phosphorus tribromide on cholesterol in benzene[23] and recrystallized twice from 99% ethanol, melting point 98° (uncorr.). Carbon tetrachloride was prepared by boiling a commercial product with an alkaline solution of potassium permanganate for 7 hours, drying over calcium chloride, and collecting the fraction distilling at 76.5–77°.

The Action of Hydrogen Bromide on Cholesteryl Bromide in Carbon Tetrachloride with the Addition of Catechol. Cholesteryl bromide (10 g.) was dissolved in carbon tetrachloride (30 c.c.), a small amount (0.4 g.) of catechol was added to the solution (catechol remained mostly undissolved), and dry hydrogen bromide was passed into the solution for 8 hours. The solution was washed with water several

(23) R. Kolm, *Monatsh.*, **33** (1912), 447.

times until the washing-water did not give a green colouration with ferric chloride, dried over anhydrous sodium sulphate, and evaporated at the temperature not exceeding 40°, when a yellowish oil remained. It was dissolved in ether (50 c.c.). On adding methanol to the ethereal solution a colourless crystalline precipitate separated out. The process of dissolving in ether and precipitating with methanol was repeated five times. The hydrobromide obtained in this way forms colourless fine needles melting at 101.5° (corr.). Found: Br,30.24. Calculated for $C_{27}H_{46}Br_2$: Br,30.12%. $[\alpha]_D^{26°} = +5.36°$ (11.2 mg. in 1 c.c. chloroform solution, $l = 1$ dm., $\alpha_D^{26°} = +0.06°$).

The Action of Hydrogen Bromide on Cholesteryl Bromide in the Presence of Ferric Chloride. Hydrogen bromide was passed for 6 hours into a solution of cholesteryl bromide (11 g.) in carbon tetrachloride (60 c.c.) with the addition of ferric chloride hexahydrate (0.2 g.). The dark brown reaction mixture was washed with water to a light yellow solution, which was dried over anhydrous sodium sulphate and evaporated below 30°. The residue was dissolved in ether and precipitated with methanol. This process was repeated three times. Yield 4.5 g. Melting point 101° (corr.). No depression of the melting point in admixture with the above specimen of the hydrobromide.

The Action of Hydrogen Bromide on Cholesteryl Bromide in Ether. When hydrogen bromide was passed for 2 hours into a solution of cholesteryl bromide (10 g.) in ether (75 c.c.), the liquid separated into two layers. The crystals from the upper layer were dissolved in ether and precipitated with ethanol. This process was repeated four times. Yield 1 g. Needles melting at 101.5° (corr.). No depression of the melting point was observed in admixture with the specimen obtained in carbon tetrachloride in the presence of catechol. Found: Br,30.49. Calculated for $C_{27}H_{46}Br_2$: Br,30.12%.

The Action of Hydrogen Bromide and Oxygen on Cholesteryl Bromide in Carbon Tetrachloride. The mixture of hydrogen bromide and oxygen was passed for 3–7 hours into a solution of cholesteryl bromide (10 g.) in carbon tetrachloride (30 c.c.). The solution became first yellow and then wine-red. After diluting with an equal volume of carbon tetrachloride, the solution was washed with water, when it became light brown. The solution was then dried over anhydrous sodium sulphate and evaporated below 30°. The substance remained was dissolved in ether and precipitated with methanol. When the process of dissolving in ether and precipitating with methanol was repeated seven or eight times, the hydrobromide was obtained in colourless needles melting at 154° (corr.). Found: Br,29.65. Calculated for $C_{27}H_{46}Br_2$: Br,30.12%. $[\alpha]_D^{26°} = -12.1°$ (15.7 mg. in 1 c.c. chloroform solution, $l = 1$ dm., $\alpha_D^{26°} = -0.19°$).

The hydrobromide was hardly affected on boiling in acetone for five hours.

On concentrating the mother liquor of the second recrystallization of the above hydrobromide an impure crystalline substance melting in the range of 84–127° (uncorr.) was obtained. It showed a composition of a dibromide of cholesteryl bromide. Found: Br,39.80. Calculated for $C_{27}H_{45}Br_3$: Br,39.34%. The melting point in admixture with the dibromide (melting point 113°, corr.) prepared by adding bromine to cholesteryl bromide was found 90–108° (uncorr.).

The Elimination of Hydrogen Bromide from the Hydrobromide Melting at 101.5°. The hydrobromide melting at 101.5° (0.5 g.) was boiled in pyridine (13–15 c.c.) for 12 hours, and the liquid was poured into water. The precipitated substance was extracted with ether. The ethereal solution was shaken with dilute sulphuric acid and water, dried over anhydrous sodium sulphate, and evaporated. On adding methanol to the oily residue a crystalline substance separated out. It was collected, dissolved in ether, and again precipitated with methanol. The substance thus obtained forms needles melting at 76° (corr.), contains no bromine, and gives a colouration changing through yellow and yellowish brown to red on adding 90% trichloroacetic acid to its chloroform solution. Thus the substance shows the properties of cholestadiene-(3,5).[24]

(24) H. E. Stavely and W. Bergmann, *J. Org. Chem.*, **1** (1936), 567; J. C. Eck, R. L. Van Peursem, and E. W. Hollingsworth, *J. Am. Chem. Soc.*, **61** (1939), 172; I. M. Heilbron and F. S. Spring, *Biochem. J.*, **24** (1930), 133.

The hydrobromide (1 g.) was boiled in acetone (30 c.c.) for 5 hours. The crystalline substance separating out on cooling the acetone solution melted at 97°(corr.) and showed no depression of the melting point in admixture with cholesteryl bromide (mixed melting point 98°,corr.).

The Action of Potassium Acetate on the Hydrobromide Melting at 154°. The hydrobromide melting at 154° (1 g.) was boiled with anhydrous potassium acetate (20 g.) in glacial acetic acid (60 c.c.) for 10 hours. The acetic acid was neutralized with concentrated aqueous potassium hydroxide and the reaction product was extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulphate, and evaporated in vacuum. The acetyl group was determined with the crude product: 0.328 g. of the substance was boiled with 20 c.c. of ca. 0.5 N alcoholic potash for 2 hours and the remaining alkali was titrated with 0.441 N hydrochloric acid, of which 22.68 c.c. was consumed, while in a blank test 20 c.c. of the aloholic potash consumed 24.46 c.c. of the hydrochloric acid. (Found: CH_3CO,10.30. Calculated for cholesteryl acetate, $C_{27}H_{45}OCOCH_3$: CH_3CO,10.04%.

The product of the above saponification was extracted with ether. The substance obtained from the ethereal solution was recrystallized from methanol and identified with cholesterol by the melting point (148°,corr., mixed melting point 148.5°,corr.) and by the formation of the digitonide.

The Reduction of the Hydrobromide Melting at 154° with Sodium and Amyl Alcohol. The hydrobromide melting at 154° was reduced with sodium in amyl alcohol and the product was recrystallized several times from acetone to colourless small needles melting at 90.5–92°(corr.). It gave a yellow colouration with tetranitromethane. It was identified with cholestene: A mixture with an authentic specimen (melting point 90.5–92.5,corr.) melted at 90.5–92°(corr.).

The Debromination of the Dibromide from the Mother Liquor of the Hydrobromide Melting at 154°. The substance (0.2 g.) was dissolved in benzene (10 c.c.) and sodium iodide (2 g.) dissolved in ethanol (15 c.c.) was added. The mixture was heated on the water bath for 2 hours. The solvents were removed in vacuum and the residue was extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulphate, and concentrated. The crystalline substance separating out on adding methanol was identified with cholesteryl bromide: It melted at 97–97.5°(corr.) alone and at 98°(corr.) in admixture with an authentic specimen.

Summary.

Hydrogen bromide was added to cholesteryl bromide in carbon tetrachloride. In the presence of catechol or ferric chloride a hydrobromide melting at 101.5° was obtained. Addition in ethereal solution gave the same product. Simultaneous action of oxygen yielded another hydrobromide melting at 154° and a substance with the composition of a dibromide of cholesteryl bromide. The direction of addition of hydrogen bromide is assumed to follow the examples of additions to simpler ethenoid compounds. The properties and the transformations of the hydrobromides are described. The both hydrobromides lose hydrogen bromide more or less easily.

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