# The Scission Reactions of the Oxido Ring in Cholesterol Oxides.⁽¹⁾

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(Received January 18, 1949.)

The scission reactions of the oxido ring in α- and β-cholesterol oxides have been studied in this laboratory since one of the authors⁽²⁾ derived the configurations of these stereoisomeric oxido compounds and related diols from that of the so-called α-cholestanetriol which had been determined to be cholestanetriol-(3β,5α,6β) (III) by Ellis and Petrow.⁽³⁾ A β-oxido structure (II) of β-cholesterol oxide was concluded from the change of the α-cholestanetriol (III) to this oxide through a 5-chlorodiol-(3β,6β) (IV), and consequently an α-oxido configuration (I) was assigned to α-cholesterol oxide. Further, the $\Delta^4$-cholestenediol-(3,6) melting at 257–258° was found to be $\Delta^4$-cholestenediol-(3β,6β) (V), because it is obtainable from the triol (III) by a Darzens dehydration of its diacetate followed by saponification, and the 6-isomeride melting at 178–179° proved to be $\Delta^4$-cholestenediol-(3β,6α) (VI). The cholestanediol-(3,6) melting at 194–195° was given a configuration of cholestanediol-(3β,6β) (VII), because it is obtained by a catalytic reduction of the higher melting unsaturated diol (V), and hence its 6-isomeride melting at 216° should be cholestanediol-(3β,6α) (VIII).

**Reduction of Cholesterol Oxides with Sodium and Amyl Alcohol.⁽⁴⁾**

As described in details elsewhere,⁽⁴⁾ on reduction with sodium and amyl alcohol α-cholesterol oxide (I) gave cholestanediol-(3β,6α) (VIII), while pure β-cholesterol oxide (II), prepared from α-cholestanetriol (III) through the chlorohydrin (IV), was reduced to the same cholestanediol-(3β,6α) (VIII). The formation of cholestanediol-(3β,6α) from the α-oxide appeared quite natural, but an explanation was required for the formation of a cholestane derivative with a 6α-hydroxyl group from the β-oxide (II). An inversion of the β-oxide to the α-isomeride prior to reduction under the conditions of the reaction, especially by the action of sodium amylate, was first suspected but disproved by experiments: When the β-oxide was heated with sodium amylate it was reduced to cholestanediol-(3β,6α) while the α-oxide was not reduced when treated similarly, and the β-oxide was not changed when heated with sodium ethylate. Therefore, it is very probable that the reduction of the β-oxide to cholestanediol-(3β,6α) did not go through the α-oxide.

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(1) Abstracts from the doctor theses by M. Chuman. For originals consult the footnotes under respective subtitles.

(2) Y. Urushibara, this Bulletin, **16** (1941), 182.

(3) B. Ellis and V. A Petrow, *J. Chem. Soc.*, **1939**, 1078.

(4) M. Chuman, *J. Chem. Soc. Japan*, **64** (1943), 1369.

When the 3,6-diol was formed from the β-oxide by reduction, the oxido ring was opened between carbon atom 5 and the oxido oxygen atom. Then the formation of a cholestane derivative from the β-oxide can be understood on the assumption of a Walden inversion at carbon atom 5; but a 6β-hydroxyl group should be produced from the oxygen atom in β-configuration. Consequently, it must be assumed that the 6α-hydroxyl group in the product was formed through an inversion from the primarily introduced 6β-hydroxyl group. Experiments showed it was really the case: When cholestanediol-(3β,6β) (VII), prepared from 6-keto-cholestanol by catalytic reduction,(5) was heated with sodium amylate, it was transformed into cholestanediol-(3β,6α) (VIII). Such an inversion of a newly formed hydroxyl group would have been possible also in the reduction of α-cholesterol oxide, if the hydroxyl group had had an unstable configuration; but the 6α-hydroxyl group formed primarily by the scission of the α-oxido ring was stable to sodium amylate and remained without inversion. The 3β-hydroxyl group in the reduction product is considered stable to alcoholates as so is that in cholestanol. A problem may arise rather from the fact that the oxido ring in α-cholesterol oxide is opened between carbon atom 5 and the oxygen atom by the action of sodium and amyl alcohol, because it is the only exceptional behaviour of the α-oxide ever experienced in its scission reactions.

### Catalytic Reduction of Cholesterol Oxides.(6)

Earlier experiments on catalytic reduction showed that α-cholesterol oxide is difficultly reduced while β-cholesterol oxide is reduced too far to cholestane and cholestanol. Even such undesired over-reduction indicated that the β-oxide is not reduced to a coprostane derivative which might be expected from the configuration given to it. Catalytic reduction of the acetates with platinum oxide in glacial acetic acid was finally successful both in reducing the α-oxide and in obtaining from the β-oxide a product retaining the oxygen atom of the oxido ring. Thus, β-cholesterol oxide acetate (II′) gave cholestanediol-(3β,6β) 3-acetate (VII′), m.p. 155–156°, along with cholestane and cholestanol acetate. Hydrolysis gave free cholestanediol-(3β,6β) (VII) idential with the specimen prepared from 6-keto-cholestanol by catalytic reduction.

A similar reduction of α-cholesterol oxide acetate (I′) yielded a product melting at 178–179° and sparingly soluble in alcohol. It remained unchanged on boiling with acetic anhydride, thus showing the newly formed hydroxyl group, if any, was tertiary. Saponification with alcoholic potash gave a substance melting at 220–221° and difficultly soluble in ether. Analysis gave numbers calculated for a cholestanediol. The diol was oxidized with chromic acid to a substance melting at 231–232°, and dehydration of the latter produced the known $\Delta^4$-cholestenone (XI). Hence, the new diol is a 3,5-diol, and the oxido ring was opened by reduc-

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(5) R. E. Marker and J. Krueger, *J. Am. Chem. Soc.*, **62** (1940), 79.

(6) M. Chuman, *J. Chem. Soc. Japan*, **64** (1943), 1486.

tion between carbon atom 6 and the oxygen atom; and thus the 5-hydroxyl group must necessarily possess an α-configuration. Consequently, the diol is cholestanediol-(3β,5α) (IX), and the substance, m.p. 178–179°, obtained primarily by the reduction of α-cholesterol oxide acetate is its 3-monoacetate (IX′). The product, m.p. 231–232°, from the oxidation of the free diol which gave $\Delta^4$-cholestenone by dehydration is 5α-hydroxycholestanone-(3) (X). Designation "α" after position number "5" may be omitted in the names of the cholestane derivatives, because it is implicitly expressed by term "cholestane".

The course of reactions starting from a 5,6α-oxido steroid and leading to an α,β-unsaturated 3-keto-steroid was successfully applied to the synthesis of testosterone(7) and progesterone.(8)

Recently the authors became aware of the publication of similar works on catalytic reduction of cholesterol oxides by Stavely(9) and by Plattner and others,(10) although the original papers are not available here. The former, reducing α-cholesterol oxide with a palladium catalyst and obtaining cholestanediol-(3,5) monoacetate after acetylation, seems to have suggested that when an ethylene oxide ring is opened by hydrogenation the hydroxyl group formed will be attached to the carbon atom carrying the smaller number of hydrogen atoms. The latter reduced both α- and β-cholesterol oxide acetates with the same catalyst as used by the present authors and obtained similar results. The melting points of their products as quoted in the *Chemical Abstracts,* however, do not show any good coincidence with those obtained for the corresponding substances by the present authors, some being higher and others lower. The discrepancies in the melting points may be due to either different purities or otherwise possible polymorphism of crystals.

### Action of Aluminium Amalgam and of Aluminium Isopropylate and Isopropyl Alcohol on Cholesterol Oxides.(11)

Attempted reduction with aluminium amalgam and with aluminium isopropylate and isopropyl alcohol yielded none of reduced compounds. α-Cholesterol oxide was attacked by neither of the reagents. β-Cholesterol oxide, on the other hand, was hydrated to cholestanetriol-(3β,5α,6β) (III) on treatment with the former reagent in hydrous alcohol, while it was isomerized to $\Delta^4$-cholestenediol-(3β,6β) (V) by the latter reagent.

### Hydration of Cholesterol Oxides.(12)

α-Cholesterol oxide is long known to give α-cholestanetriol, namely, cholestanetriol-(3β,5α,6β) (III), when heated with water in a sealed tube, while the hydration reaction of β-cholesterol oxide had not yet been studied

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(7) Y. Urushibara and M. Chuman, this Bulletin, **22** (1949), 1.

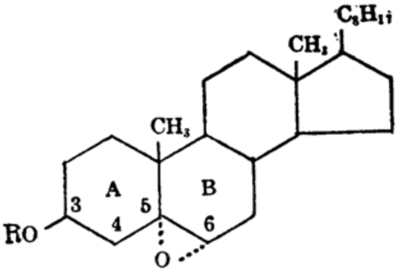
(8) Y. Urushibara, M. Chuman, and S. Wada, this Bulletin, in press.

(9) H. E. Stavely, *Chemical Abstracts,* **37** (1943), 652

(10) Pl. Plattner, Th. Petrzilka, and W. Lang, *Chemical Abstracts,* **38** (1944), 6295.

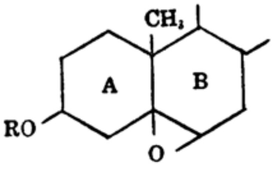
(11) M. Chuman, *J. Chem. Soc. Japan,* in press.

(12) M. Chuman, *J. Chem. Soc. Japan,* in press.



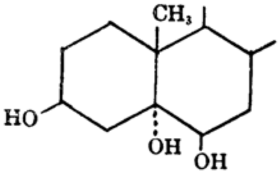
(I) R = H: α-Cholesterol oxide.

(I′) R = $CH_3CO$: Acetate of I

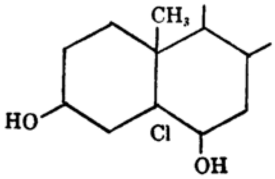


(II) R = H: β-Cholesterol oxide

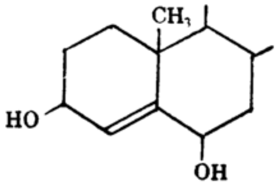
(II′) R = $CH_3CO$: Acetate of II



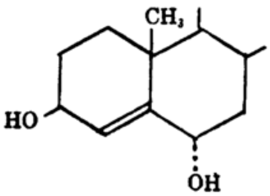
(III) α-Cholestanetriol, Cholestanetriol-(3β, 5α, 6β)



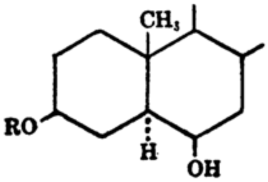
(IV) 5-Chloro-cholestanediol-(3β, 6β)



(V) $\Delta^4$-Cholestenediol-(3β, 6β)

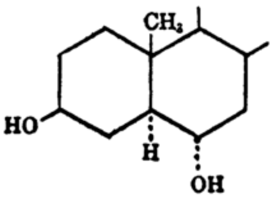


(VI) $\Delta^4$-Cholestenediol-(3β, 6α)

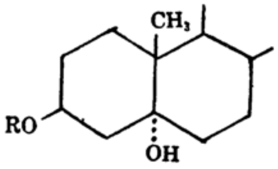


(VII) R = H: Cholestanediol-(3β, 6β)

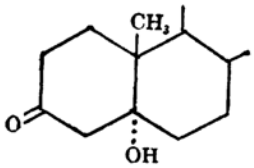
(VII′) R = $CH_3CO$: 3-Acetate of VII



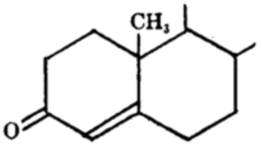
(VIII) Cholestanediol-(3β, 6α)



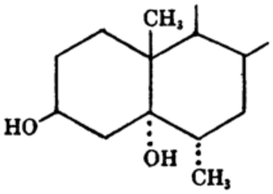
(IX) R = H : Cholestanediol-(3$\beta$, 5$\alpha$)
(IX′) R = $CH_3CO$ : 3-Acetate of IX



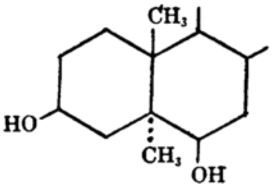
(X) 5$\alpha$-Hydroxy-cholestanone-(3)



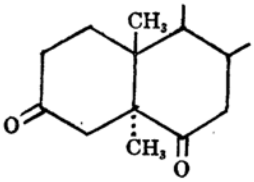
(XI) $\Delta^4$-Cholestenone



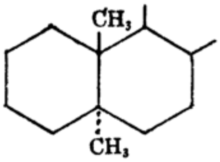
(XII) 6$\alpha$-Methyl-cholestanediol-(3$\beta$, 5$\alpha$)



(XIII) 5$\alpha$-Methyl-cholestanediol-(3$\beta$, 6$\beta$)



(XIV) 5$\alpha$-Methyl-cholestanedione-(3, 6)



(XV) 5$\alpha$-Methyl-cholestane

with a pure specimen. The hydration reactions of these isomeric oxides were compared under various conditions with the following results:

The $\beta$-oxide did not react with water at such temperatures (120°, 14 hours, and 160°, 10 hours) as were high enough to cause the hydration of the $\alpha$-oxide, but gave the same $\alpha$-cholestanetriol (III) at a much higher temperature (over 200°, 10 hours). With slightly acidic water (one drop of 10% sulfuric acid to 1 c.c.) both oxides were easily hydrated to the triol (at 120°, 10 hours). With slightly alkaline water (one drop of 5% caustic potash to 1 c.c.), however, neither reacted (at 120°, 10 hours). With a stronger aqueous alkali (2% potassium hydroxide solution) and at a higher temperature (160–170°, 10 hours) the $\alpha$-oxide was partly

(20%) hydrated, while the β-oxide still remained unchanged.

Thus the isomeric cholesterol oxides manifested a very striking difference in easiness of hydration, and, as ethylene oxide derivatives are generally so, proved to be weak to acid and stable in alkaline media, much more stable than in neutral water.

The formation of cholestanetriol-(3β,5α,6β) (III) from both α- and β-cholesterol oxides indicates that the oxido ring is opened by hydration between carbon atom 6 and the oxygen atom in the α-oxide and between carbon atom 5 and the oxygen atom in the β-oxide, and the carbon atom cut off from the oxygen atom undergoes an inversion in each case to give the same cholestanetriol.

### Action of Grignard's Reagent on Cholesterol Oxides.(13)

Ushakov and Madaeva(14) obtained a 6-methyl-cholestanediol-(3,5), m.p. 181–181.5°, from Grignard's reaction of α-cholesterol oxide. The present authors obtained an isomeric methyl-diol, m.p. 195–196°, by the action of methyl-magnesium iodide on β-cholesterol oxide, and demonstrated that the new methyl-diol was a 5-methyl-diol-(3,6) by obtaining a diacetate, m.p. 132–133°, by the action of acetic anhydride and a diketone, m.p. 194–195°, by the oxidation with chromic acid. The dibenzoate, m.p. 152–153°, of the methyl-diol was also prepared. The diketone yielded the corresponding hydrocarbon, m.p. 94–95°, by Clemmensen reduction.

On the assumption that no inversion took place at carbon atom 6 obtaining a methyl group from Grignard's reagent a configuration of 6α-methyl-cholestanediol-(3β,5α) (XII) was given to the methyl-diol of Ushakov and Madaeva. On the other hand, a structure of 5α-methyl-cholestanediol-(3β,6β) (XIII) was deduced for the 5-methyl-diol-(3,6), because β-cholesterol oxide gives cholestane derivatives in all other scission reactions. Consequently, the diketone from the 5-methyl-diol is 5α-methyl-cholestanedione-(3,6) (XIV) and the hydrocarbon from the diketone 5α-methyl-cholestane (XV).

The chlorohydrin, 5-chloro-cholestanediol-(3β,6β) (IV), obtained by the action of hydrogen chloride on cholestanetriol-(3β,5α,6β) (III), yielded the same 5-methyl-cholestanediol-(3β,6β) (XIII) on treatment with methyl-magnesium iodide.

In a separate paper a stereochemical interpretation of the scission reactions of cholesterol oxides will be presented, and in another it will be shown hat the α- and β-oxides of $\Delta^5$-cholestenone correspond respectively to β- and α-cholesterol oxides in the behaviours in scission reactions.

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(13) M. Chuman, *J. Chem. Soc. Japan*, in press.

(14) *Brit. Chem. Abst.*, **1939**, A (II), 367.