

A Stereochemical Representation of the Structures and the Scission Reactions of Cholesterol Oxides.⁽¹⁾

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In a previous paper⁽²⁾ the results of the studies on the scission reactions of the oxido ring in cholesterol oxides by the author and M. Chuman were briefly described. They include (i) reduction with sodium and amyl alcohol, (ii) catalytic reduction, (iii) action of aluminium amalgam and of aluminium isopropylate and isopropyl alcohol, (iv) hydration, and (v) action of Grignard's reagent. Besides those already cited there, the reactions of cholesterol oxides or their esters with hydrogen chloride,⁽³⁾ with acetic acid,⁽⁴⁾⁽⁵⁾ and with methanol in the presence of sulfuric acid,⁽⁴⁾ have been investigated by other authors. The results hitherto gathered may be summarized as follows:

The oxido ring in α -cholesterol oxide (I) or its esters is opened always but one exception between carbon atom 6 and the oxido oxygen atom, and the oxygen atom with the hydrogen atom derived directly or indirectly from the addenda forms a hydroxyl group attached to carbon atom 5 with the original α -configuration, while the residues from the addenda become attached to carbon atom 6, the configuration being determined to be β for certain residues, perhaps undetermined for the chlorine atom, assumed α for the methyl group from Grignard's reagent, and meaningless for the hydrogen atom from reduction (I \rightarrow III). An exception is encountered in the reduction with sodium and amyl alcohol, where the oxido ring is opened between carbon atom 5 and the oxygen atom, and the carbon atom 5 maintains the original α -configuration producing a cholestane derivative.

As for β -cholesterol oxide earlier works were carried out with impure specimens or the molecular compound with the α -isomeride, and the results obtained must be considered with reserve. Experiments with pure specimens have shown that the oxido ring in the β -oxide or its esters is opened, without exception, between carbon atom 5 and the oxido oxygen atom. The oxygen atom takes the hydrogen atom coming directly or

(1) An abridged account was read before the 68th annual meeting of the Chemical Society of Japan on October 18th, 1946.

(2) Y. Urushibara and M. Chuman, this Bulletin, 22 (1949), 69.

(3) F. S. Spring and G. Swain, *J. Chem. Soc.*, 1939, 1356; L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, 20 (1937), 244.

(4) J. Hattori, *J. Pharm. Soc. Japan*, 59 (1939), 411; 60 (1940), 334.

(5) M. Ehrenstein, *J. Org. Chem.*, 6 (1941), 626.

indirectly from the addenda and forms a hydroxyl group attached to carbon atom 6 with the original β -configuration, while carbon atom 5 cut off from the oxygen atom gains the residues from the addenda, and the configuration around this asymmetric centre is always α , as far as determined, giving rise to the formation of cholestane derivatives but never of coprostanol derivatives which might be expected (II \rightarrow IV).

Ruzicka and co-workers⁽⁶⁾ constructed models for saturated and unsaturated sterols, where they related free or hindered rotation of the hydroxyl group at carbon atom 3 about the oxygen-carbon bond to the velocity of saponification of esters and took into account the flat molecular structures of the steroids demonstrated by Bernal. Thus, the free hydroxyl group of the cholestanol model and the hindered one in the coprostanol model were made to correspond respectively to the greater and the smaller velocities of the saponification of the esters. In the accompanying formulas, (V), (VI), and (VII), borrowed from their figures, substituents directed to the same side of (over, as generally formulated) the plane of the ring system are indicated by thick dots and letter S shows the cyclohexane ring concerned being in a chair form. If it is desired to visualize the actual models better than by these formulas, the pictures in the original paper may advisably be consulted.

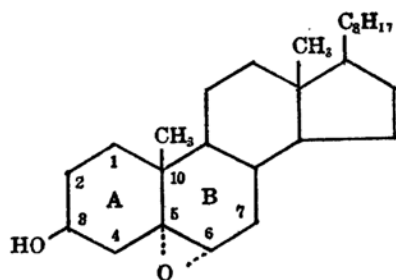
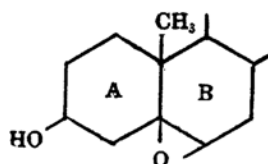
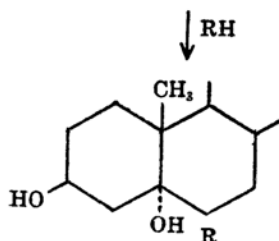
Although the formulas, and even the pictures of the models, hardly permit to perceive it at a glance, ring A has a chair form in the same manner of zigzag in cholestanol and in cholesterol, while in coprostanol the zigzag is in an inverse manner. In other words, if in the cholestanol and cholesterol models carbon atoms 1, 3, and 5 are situated downwards or at the bottoms of the zigzag, in the coprostanol model carbon atoms designated by the same numbers are placed upwards or at the tops of the zigzag. Moreover, in the cholestanol and cholesterol models an axis passes straight through the whole ring system, while the coprostanol model, owing to the cis linking of rings A and B, is remarkably folded at this linking.

An introduction of a double bond between carbon atoms 5 and 6 is possible only with ring A of cholestanol, and impossible with ring A of coprostanol, because the ethylene system will tend to be coplanar. On the other hand, a double bond can enter between carbon atoms 4 and 5 of ring A of either cholestanol or coprostanol; or, more precisely, the coplanar ethylene system comprising five carbon atoms 3, 4, 5, 6, and 10 and one hydrogen atom at 4 with a double bond between 4 and 5 is compatible with carbon atoms 1 and 2 as they are either in cholestanol or in coprostanol. The above consideration may be useful for reminding that Δ^5 -steroids are generally

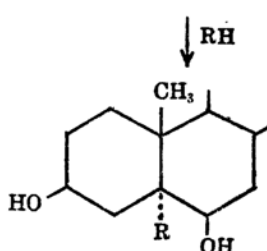
(6) L. Ruzicka, M. Furter, and M. W. Goldberg, *Helv. Chim. Acta*, 21 (1938), 498.

hydrogenated to cholestane derivatives⁽⁷⁾ and Δ^4 -steroids to either cholestane or coprostane compounds.

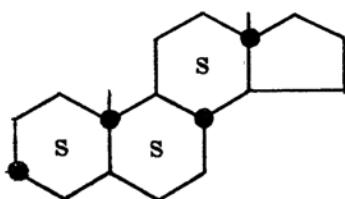
Now, the influence of a 5,6-oxido ring upon the form of ring A will be considered. The three-membered ring is equivalent or similar to

(I) α -Cholesterol oxide(II) β -Cholesterol oxide

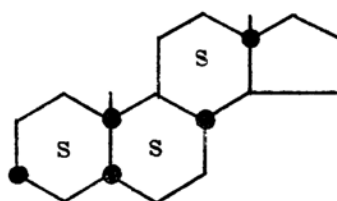
(III)



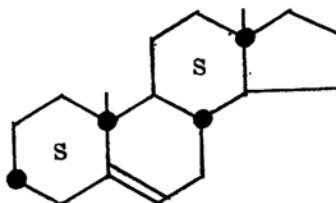
(IV)



(V) Cholestanol



(VI) Coprostanol



(VII) Cholesterol

(7) Cholestene gives two stereoisomeric hydrochlorides, J. Mauthner, *Monatsh.*, 28 (1907), 1113; T. Kon, *J. Pharm. Soc. Japan*, 65 (1945), 63, but is an explanation not - lausible that pseudo-cholestene (coprostene) may intervene in the reaction?

the double bond in causing a structural restriction. The elements of symmetry found in the ethylene system still survive the destruction of the coplanarity by the three-membered ring introduced perpendicularly to the ethylene plane. Here, symmetry refers of course only to the arrangement or direction of the four atoms, other than the oxido oxygen atom, directly attached to carbon atoms 5 and 6, the nature of the four groups and the bond lengths being ignored. Thus, planes of symmetry in this sense exist within the segment of the molecule concerned, one passing through the three-membered ring and another through the oxygen atom and perpendicular to the former and to the bond between carbon atoms 5 and 6. The tendency of carbon atoms 10, 4, and 7 and the hydrogen atom at 6 to be arranged or directed symmetrically with reference to these planes excludes again ring A of coprostanol, irrespective as to whether the three-membered ring is α -oxidic or β -oxidic.

In this respect, not only α - but also β -cholesterol oxides must be considered as a derivative of cholestanol. When the β -oxide was called 5,6-epoxy-coprostanol-(3 β)⁽⁸⁾ by a term representing the structure, it was presumed automatically to be a coprostane derivative from the β -configuration of the linkage between carbon atom 5 and the oxygen atom; but in conformity with the real aspects of the spatial constitutions the β -oxide must be called 5,6 β -epoxy (or oxido)-cholestanol-(3 β), and 5,6 α -epoxy (or oxido)-cholestanol-(3 β) for the α -oxide cannot dispense with Greek letter α .

Before entering the next step of the stereochemical representation, the characteristics of the cleavage reactions of the oxido ring which are to be explained thereby will be summarized again in a shorter expression: The oxido ring in the α -oxide is ordinarily opened between carbon atom 6 and the oxygen atom, but can be split at the other linkage. Cleavage occurs always between carbon atom 5 and the oxygen atom in the β -oxide. The most important point is that cholestane derivatives, but none of coprostane derivatives, are produced in all the scission reactions of not only α - but also β -cholesterol oxide. Now, the stereochemical investigation affords a reasonable explanation of such behaviours of the oxides. Ring A in both α - and β -cholesterol oxides being of the same cholestanol type, the formation of cholestanol derivatives from both must be exclusive, as cholestanol is formed preferentially by the hydrogenation of cholesterol, unless a ring conversion takes place; and the formation of cholestanol derivatives from the α -oxide is possible for either of the alternative cleavage points, but that from the β -oxide is possible only when the oxido ring is opened between carbon atom 5 and the oxygen atom and thus when carbon atom 5 is given temporarily a free valency in order to be capable of adapting itself to ring A.

(8) Y. Urushibara, this Bulletin, 16 (1941), 182.

Suppose the oxido ring in the β -oxide were split between carbon atom 6 and the oxygen atom, then ring A of the cholestanol type and carbon atom 5 holding the oxygen atom in the β -configuration would be incompatible and must be reconciled only at the expense of an excessive work of either changing the former into the coprostanol type or inverting the latter to the α -configuration. While there may be no question as to stating that an inversion at carbon atom 5 would be difficult, or even impossible, so long as the oxygen atom remained attached there, the possibility of the conversion of ring A may be examined more closely. The conversion of ring A from the cholestanol type to the coprostanol type has been attained from Δ^5 -steroids through the versatile Δ^4 -ring, while the reverse ring conversion has been experienced, necessarily associated with the rearrangement of the configuration at carbon atom 5 from β to α , when a hydrogen atom is present at carbon atom 5 and at the same time a carbonyl group exists at an adjacent carbon atom, perhaps through an enolization and thus through a Δ^4 - or Δ^6 -intermediate. Such an inter-conversion of ring A involving a participation of an unsaturated intermediate could not be effected in a compound with an oxygen atom attached to carbon atom 5. A direct transformation of the cholestanol type into the coprostanol type might be possible, inasmuch as an oxygen atom bound to carbon atom 5 in the β -configuration were found favoring it, but it would not be so easy as expected from a mere consideration of the lability of a simpler cyclohexane ring, owing to the more profound difference between the cholestanol and the coprostanol rings and the structural restriction imposed by the surroundings. Thus, if the cleavage should occur between carbon atom 6 and the oxygen atom, then the process would be completed by giving a coprostanol derivative resulting from the conversion of ring A rather than a cholestanol derivative requiring the inversion at carbon atom 5; but even the trouble involved in this ring conversion appears to be enough for preventing such a fission from taking place and for giving way to the other fission that can be settled more smoothly. In other words, the linkage will resist such a fission as would be associated with more later work. It may be again emphasized in this connection that a transformation of ring A does not take place even in the hydrogenation of Δ^5 -steroids. The hydroxyl group or its equivalent at carbon atom 3 may add the difficulty in the ring conversion, because the group freely rotatable in the cholestanol type must be confined in a sterically hindered position when the ring is converted into the coprostanol type, and it may be logically correct to mention that such a confinement itself will be confronted with a steric hindrance.

In the preceding paragraphs the structures of cholesterol oxides and the courses of scission reactions of the oxido ring in them have been elucidated on the basis of the spatial formulation elaborated by Ruzicka

and co-workers. If the stereochemical representation be feasible also in the cases of the oxides of other Δ^5 -steroids, then the behaviours in scission reactions will give grounds for discussing the configuration of their oxido rings. Thus, in a separate paper it will be shown that the oxido rings in the oxides of Δ^5 -cholestenone possess most probably the configurations contrary to the Greek letters arbitrarily prefixed in their names.

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