Photo-induced Transformations. Part 79.[1] On the Mechanism of the Formation of Oxa Steroids *via* Photo- and Thermally-induced Rearrangement of 3-Hydroxy-Δ^5-steroid Hypoiodites in the Presence of Mercury(II) Oxide and Iodine. An Oxygen-18 Labelling Study.

Hiroshi Suginome,* Yoshikatsu Seki, Shinji Yamada, Kazuhiko Orito, and Norio Miyaura
Organic Synthesis Division, Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

An ^{18}O labelling study of 3α,5-epoxy-4-oxa-A-homo-5α-cholestane and 3-oxacholest-5-ene formation, on photolysis and thermolysis of cholesterol hypoiodites and methyl-substituted cholest-3-en-3-ols generated *in situ* by an excess of mercury(II) oxide and iodine in benzene is described. Cholesterol, 4,4-dimethylcholest-5-en-3β-ol, and 3α,4,4-trimethylcholest-5-en-3β-ol were irradiated in benzene containing an excess of $Hg^{18}O$ and iodine and the extent of ^{18}O incorporation into the oxa-steroids obtained from the reactions was determined by mass spectrometry. The results show that the oxygen of mercury(II) oxide is incorporated into the epoxy oxygens of the 3α,5-epoxy-A-homo-4-oxacholestanes and into the ring oxygen of one of the 3-oxacholest-5-enes; the extent of the incorporation of ^{18}O is in the range 31—61%. The oxygen of mercury(II) oxide is not incorporated into 2-acetyl-3-oxacholest-5-enes. The results are used to rationalize the routes by which the oxa steroids are formed.

In previous papers,[2] we have reported the results for the photo- and thermally-induced rearrangement of the hypoiodites of cholesterol (**1**) and methyl-substituted cholest-5-en-3-ols (**5**), (**8**), (**12**), and (**17**) generated *in situ* by an excess of mercury(II) oxide and iodine. Our studies have shown that regardless of whether it is induced photochemically or thermally, 3α,5-epoxy-4-oxa-A-homo-5α-cholestanes (**2**), (**3**), (**6**), (**9**), (**10**), (**13**), (**14**), and (**18**) are the common products shown in Scheme 1. In the case of 4,4-dimethylcholest-5-en-3-ols, 3-oxacholest-5-enes, (**11**), (**15**), and (**16**) are additional products and the photolysis of the hypoiodites of cholesterol, 3α-methylcholesterol, (**5**), and 6-methylcholesterol (**17**) give the formates (**4**) and (**19**) or the acetate (**7**). The formate (**4**) is convertible into 3-oxacholest-5-ene (**20**) with $NaBH_4$.[2a] Subsequently, we have found that the irradiation of the saturated hydroxy steroids such as 5α-androstan-17β-ol in the presence of mercury(II) oxide and iodine will give only formates corresponding to (**4**); these are readily convertible into oxa steroids that provide a new method of a two-step transformation of hydroxy steroids into oxa steroids.[1,3]

We have also shown that the formation of the formates from the hypoiodites of hydroxy steroids involves a novel intramolecular combination of a carbon-centred radical with the formyl oxygen of the intermediate generated *via* β-scission of the alkoxy radicals on the basis of the experiments by mercury(II) [^{18}O]oxide.[4]

In this paper we report the results of the ^{18}O labelling study which we carried out to determine which of the two oxygen atoms of 3α,5-epoxy-4-oxa-A-homo-5α-cholestanes (**2**), (**3**), (**6**), (**9**), (**10**), (**13**), (**14**), and (**18**) is the one derived from mercury(II) oxide and whether the ring oxygen of 3-oxacholest-5-enes (**11**), (**15**), and (**16**) is the one derived from the hydroxy group or from the mercury(II) oxide used to generate I_2O. Based on the results of these labelling experiments, probable gross reaction paths for all the oxa steroids that account for the labelling pattern as well as the stereochemistry of the products are advanced.

Results

The ^{18}O labelling experiments were performed by irradiating a solution of each hypoiodite, prepared *in situ* from cholesterol (**1**), 4,4-dimethylcholesterol (**8**), and 3α,4,4-trimethylcholesterol (**12**) with an excess of $Hg^{18}O$ (^{18}O, 48.5 mol%) and iodine in dry benzene under the conditions previously reported.[2] The extent of incorporation of ^{18}O into each product was analysed by mass spectrometry.

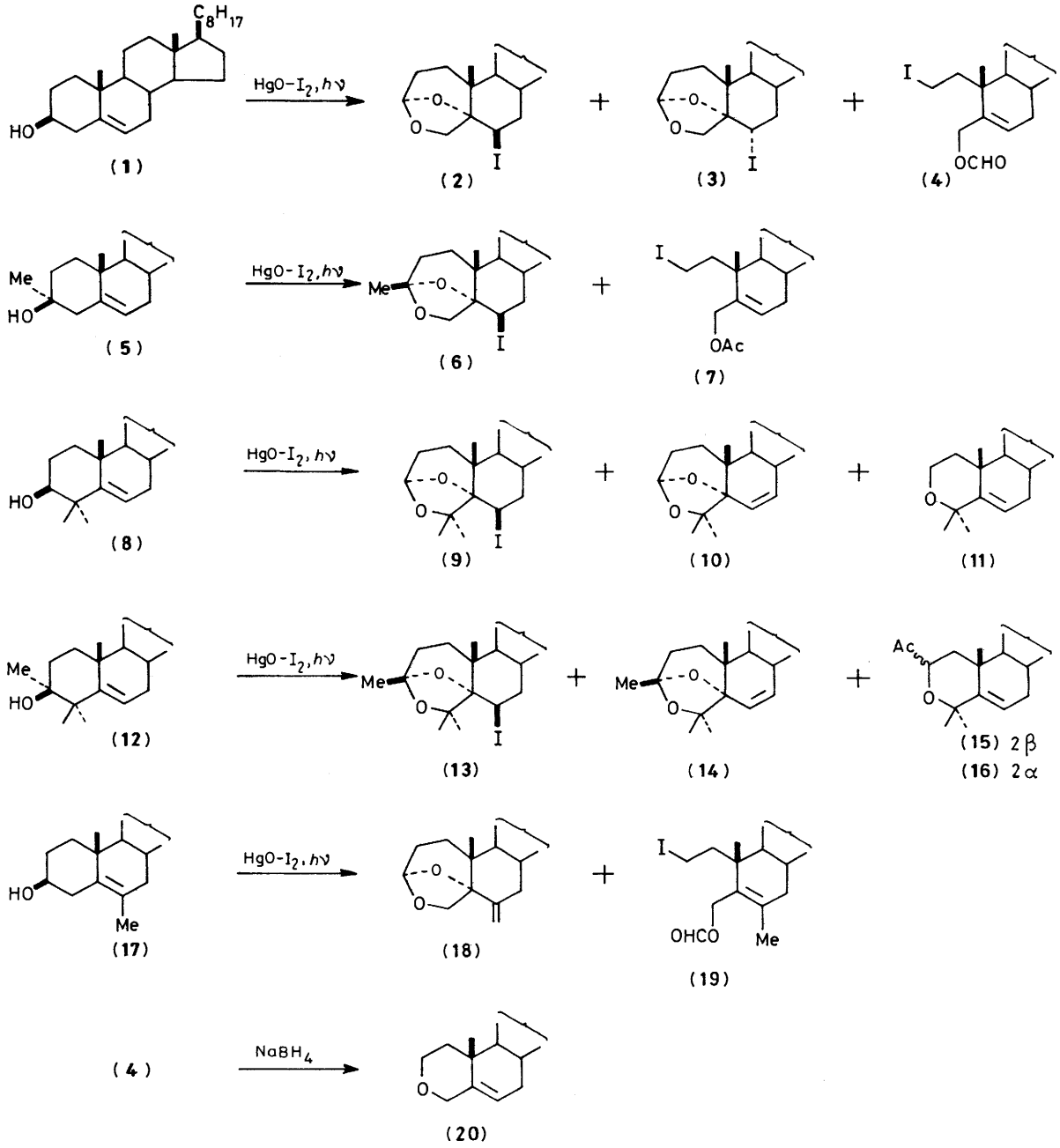
The extent of the incorporation of ^{18}O into the formate (**4**) obtained from cholesterol was analyzed after it had been transformed into 3-oxacholest-5-ene (**20**) with $NaBH_4$. Its molecular ion in the mass spectrum indicated that no ^{18}O was incorporated in the 3-oxacholest-5-ene. As we have already reported, the mass spectra of three 3-oxacholest-5-enes (**11**), (**15**), and (**16**) have their base peaks at *m/z* 385, 427, and 427 respectively, these arising from the expulsion of a methyl group from each of their molecular ions.[2a] The extent of the incorporation of ^{18}O into their ring oxygen was analyzed by comparing the intensities of these fragment ions with those of the 3-oxacholest-5-enes obtained from the reactions with ordinary mercury(II) oxide and iodine.

We were able to determine the exact extent of the incorporation of ^{18}O into the 3α,5-epoxy oxygen of the four 4a,4a-dimethyloxa steroids (**9**), (**10**), (**13**), and (**14**) by mass spectrometry. Thus, as we previously reported, the mass spectra of the oxabicyclic compounds (**9**) and (**13**) have their base peaks at *m/z* 371 and 385, these arising from expulsion of the elements of acetone and iodine atom from their molecular ions. The mass spectra of the oxabicyclic compounds (**10**) and (**14**) have their base peaks at *m/z* 371 and 384, these arising from expulsion of the elements of acetone from their molecular ions. The structures of these fragment ions and their genesis are shown in Schemes 2 and 3.[2a] As is apparent from the Schemes, since these base peaks contain only the 3α,5-epoxy oxygens of the original 3α,5-epoxy-4-oxa-A-homo-5α-cholestanes, the extent of the incorporation of ^{18}O into their 3α,5-epoxy-oxygens can be determined by the comparisons of the intensities of these fragment ions with the mass spectral data of the corresponding compounds obtained by using ordinary mercury(II) oxide and iodine.

Results for the extent of ^{18}O incorporation into the relevant oxygen, as calculated from the mass spectrometric data are summarized in the Table.

Discussions

The results in the Table clearly indicate that the oxa steroids in the Table can be divided into two categories according to a



Scheme 1.

difference in their labelling pattern. The oxabicyclic compounds (**9**), (**10**), (**13**), and (**14**) and 3-oxacholest-5-ene (**11**) belong to the group in which ^{18}O is incorporated although the extent of this varies. The formate (**4**) and the three oxa steroids (**15**), (**16**), and (**20**) belong to a second group in which none of the oxygen arising from mercury(II) oxide is incorporated.

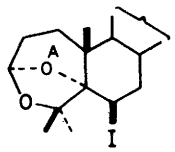
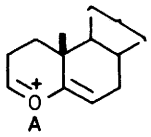
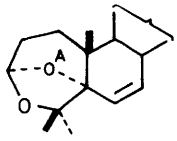
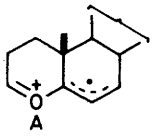
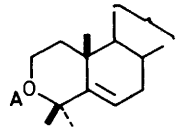
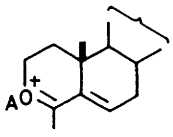
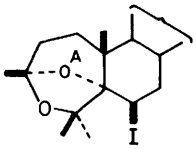
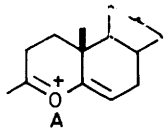
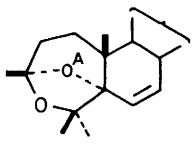
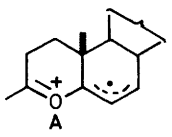
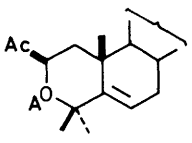
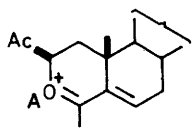
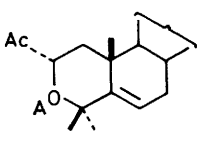
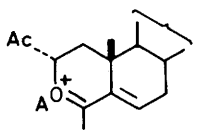
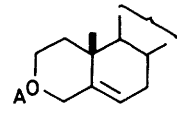
As we discussed in our previous paper,[2a] regardless of whether the oxygen-18 is incorporated, all the above products are derived from the allyl radical intermediate (B) resulting from β-scission of 3β-alkoxy radicals (A) (Scheme 5). The part of the proposed pathways described in the previous paper[2a] which start from these allyl radicals should apparently be modified in the light of the results of the present isotopic labelling study.

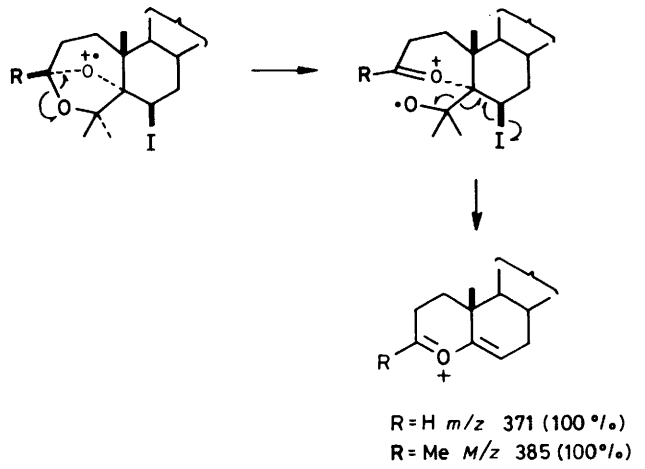
Pathways for the Formation of the Formate (**4**) *and the* 3-*Oxasteroids* (**15**) *and* (**16**) (*Scheme* 4).—The mechanism of the formation of formates arising from β-scission of the alkoxy radicals in the photolysis of the hypoiodites of hydroxysteroids has been discussed in our previous papers.[1,3,4]

As with the formation of formates from the hypoiodites of hydroxy steroids,[1] no ^{18}O is incorporated into the ring oxygen of 3-oxacholest-5-ene (**20**) derived from formate (**4**) obtained from cholesterol. Thus, the formate should be formed *via* the pathway outlined in Scheme 4 which is equivalent to that we proposed for the formation of the formates in the photolysis of the hypoiodites of saturated hydroxy steroids.

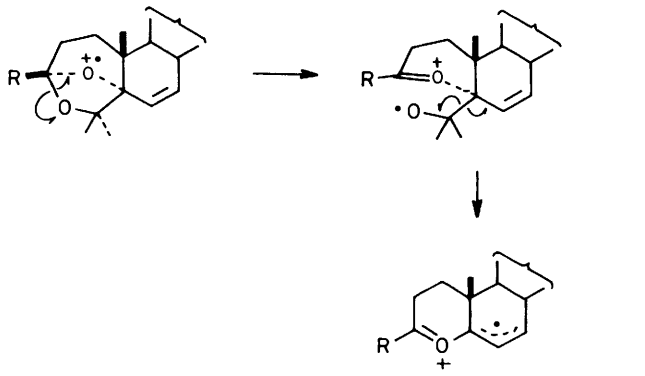
Neither is oxygen-18 incorporated into the ring oxygen of isomeric 3-oxacholest-5-enes (**15**) and (**16**). The pathway from

Table.

Product	Fragment ion or M^+	*m/z*		Intensity (%)	Calculated incorporation of HgO oxygen to oxygen A (%)
 (9)		371	^{16}O	100	44
		373	^{18}O	28.2	
 (10)		370	^{16}O	100	31
		372	^{18}O	19.5	
 (11)		385	^{16}O	100	45
		387	^{18}O	29.1	
 (13)		385	^{16}O	100	67
		387	^{18}O	45.7	
 (14)		384	^{16}O	100	63
		386	^{18}O	49.3	
 (15)		427	^{16}O	17.7	0
		429	^{18}O	0	
 (16)		427	^{16}O	100	0
		429	^{18}O	0.8	
 (20)	M^+	372	^{16}O	64.1	0
		374	^{18}O	1.5	

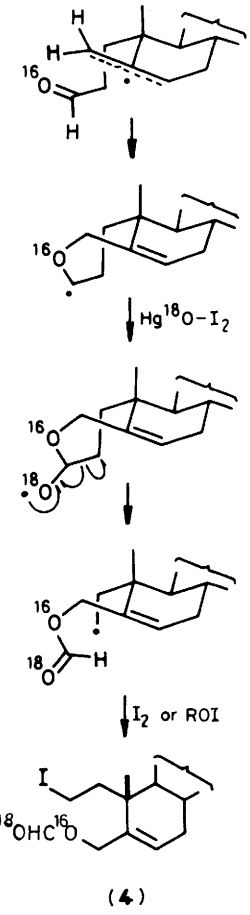


Scheme 2.



Scheme 3.

these 3-oxacholestenes which can accommodate the labelling results is outlined in Scheme 5. The preferred conformation of the allyl radical (**B**) is most probably the one depicted in Scheme 5, in which the intramolecular interaction between the C-10 substituent and the planar allyl radical portion is avoided and the stereochemical outcome of the 3,5-epoxy oxygen of the oxabicyclics (**9**), (**10**), (**13**), and (**14**) can be understood.[2a] The combination of the carbonyl oxygen with the C-4 terminus of the allyl radical portion would give an oxepanyl radical (D). Iodine [^{18}O]oxide would then react with the oxepanyl radical stereoselectively from the unhindered α-face to give a lactol hypoiodite (E). It has already been demonstrated[1] that the β-scission of an alkoxy radical generated from lactols takes place regioselectively at the C–C bond but not at the C–O bond. Immediately after the formation of the lactol (E) an equilibrium between it and the ring-opened allyl alcohol (F) may be established;* the equilibrium will probably lie on the side of the latter since no formate corresponding to the formate (**4**) arising from the C–C fission is formed in this reaction. The alkoxy radical is generated from allyl alcohol (F) in the presence of a mercury(II) oxide–iodine reagent. The intramolecular hydrogen abstraction from the 3-methylene group *via* a 7-membered cyclic transition state may result in a carbon centred radical (G). The reaction with iodine and the cyclization may give the 3-oxacholestenes (**15**) and (**16**) without ^{18}O incorporation in the ring oxygen. Oxygen-18 must have been incorporated into their



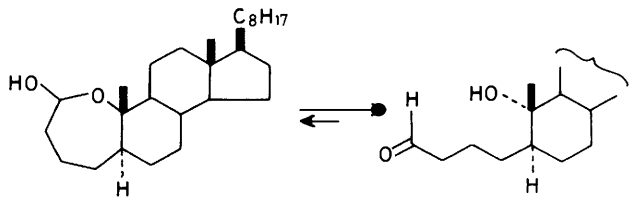
Scheme 4.

acetyl oxygen but the ^{18}O in their acetyl must have been lost during the work-up stage.

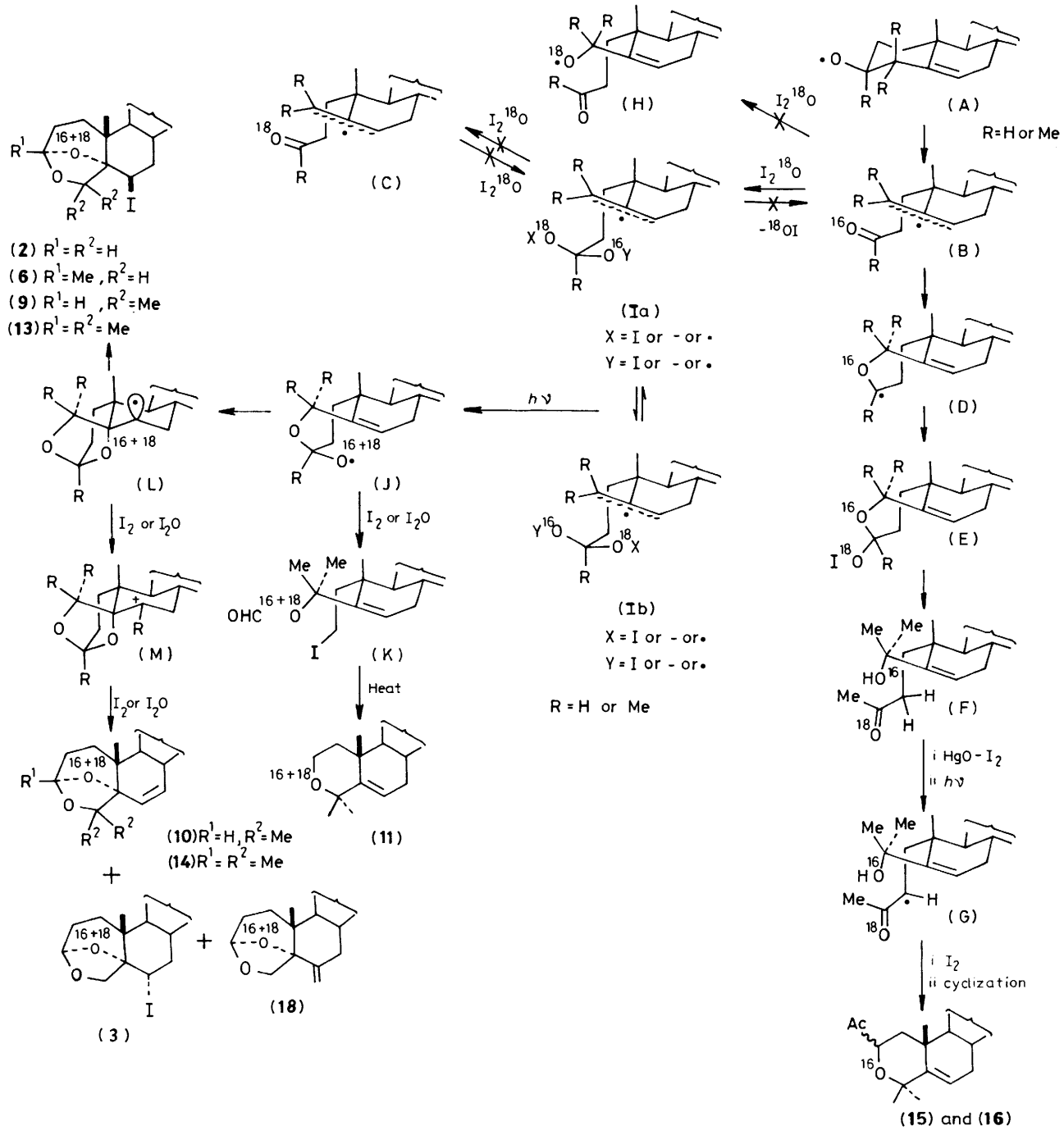
Pathway for the Formation of 3,5-*Epoxy*-4-*oxa*-A-*homo*-5α-*cholestanes* (**9**), (**10**), (**11**), (**13**), *and* (**14**) (*Scheme* 5).—The oxygen of mercury(II) oxide is incorporated in the epoxy oxygens of the oxabicyclic compounds (**9**), (**10**), (**13**), and (**14**) and in the ring oxygen of (**11**) and the extent of the incorporation is in the range 31—61%. These results suggest that ^{16}O and ^{18}O are most probably also scrambled in the epoxy oxygen of the three other 3,5-epoxy-4-oxa-A-homo steroids (**2**), (**3**), and (**6**), all of which are devoid of 4,4-dimethyl groups, although the extent of the incorporation of ^{18}O in these oxasteroids cannot be determined by mass spectrometry.

The probable genesis of all the oxasteroids which accounts for the foregoing labelling results is summarized in Scheme 5. There are two initial sites in the allyl radicals (**B**) with which

* We have recently found that the lactol (I) in solution exists entirely in the form of a ring-opened aldehyde (I).



(I) (II)



Scheme 5.

iodine oxide could, hypothetically, react; these are the C-4 terminus and the carbonyl carbon of the allyl radical (B). The reaction of iodine oxide with the C-4 terminus of the allyl radicals (B) to give a second alkoxy radical (H) has, however, already been excluded.[4] Thus, we postulate that OI^- or I_2O first reacts with the carbonyl carbon of the allyl radical (B) to give a hypothetical and, unstable, tetrahedral intermediate (I). Either the oxygen-16-centred radical or the oxygen-18-centred radical of the terminus of the freely rotating C-10 substituent of the allyl radical (I) can then combine intramolecularly with the C-4 terminus of the allyl radical portion to give an alkoxy radical (J) which then adds to the C-5 of the double bond to give first a radical (L), then an ion (M), and finally 3α,5-epoxy-4-oxa-A-homo-5α-cholestanes (see Scheme 5). The extent of the incorporation of ^{18}O in the hydroxy group of the recovered starting 3β-ols (A) was examined by mass spectrometry for the photolyses of all the hypoiodites. This indicated that no ^{18}O was incorporated into the recovered 3β-ols. Another result disclosed by this ^{18}O labelling study is that two groups of the products, one with ^{18}O incorporation [*e.g.* (**13**) and (**14**)] and the other without ^{18}O incorporation [*e.g.* (**15**) and (**16**)] are produced at the same time from the same substrate. Thus, an alternative

mechanism for the scrambling *via* a reversible process involving the tetrahedral intermediates (I), (B), and (C) as well as the starting 3β-ol (Scheme 5) is excluded.

The foregoing rationalization of the pathway is based on the premise that the alkoxy radical intermediate of lactol leading to 3α,5-epoxy-4-oxa-A-homo-5α-cholestanes [*e.g.* (J)] and that leading to 3-oxa-cholestanes [*e.g.* (E)] are different in their stereochemistry. Otherwise, the scrambling of ^{16}O and ^{18}O must also have been observed in 3-oxacholest-3-enes. The heavy oxygen is also incorporated into 4,4-dimethyl-3-oxacholest-5-ene. This oxasteroid should be formed from the alkoxy radical intermediate (J) *via* the formate (K) which is not isolated in the reaction.

Since, as has already been mentioned (*vide supra*), no ^{18}O is incorporated in the formate (**4**) it is necessary to rationalize the fact that ^{18}O and ^{16}O are exceptionally scrambled in the formate (K) from which 4,4-dimethyl-3-oxacholest-5-ene is formed. We do this by postulating that the intermediary alkoxy radical (J) leading to the formate (K) and that leading to (**4**) differ in their stereochemistry. The configuration of the alkoxy radical (J) must necessarily be α and whilst a major part may be cyclized to give oxabicyclic compounds the formate (K) may also be formed. Thus, the difference in the pattern of ^{18}O scrambling in the isolated formate (**4**) and a hypothetical formate (K) may have their origin in a difference in the mechanism of their formation.

Experimental

The mass spectra were determined with a JEOL JMS-D-300 spectrometer (70 eV) in the Faculty of Agriculture of this university. All the hypoiodite photolyses described in this work were carried out under the same conditions as those reported in our previous papers.

Materials.—Preparation of all the steroidal alcohols were as described in previous papers. Mercury(II) [^{18}O]oxide (48.9 atom % ^{18}O) was prepared by the reaction of mercury(II) chloride in H_2O–$H_2{}^{18}O$ [prepared by diluting [^{18}O]water (Merck Sharp and Dohme Canada Ltd., 97 atom % ^{18}O)] with sodium hydroxide–[^{18}O]water.

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