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Photo- and Thermally-induced Radical Rearrangement of 4,4-Dimethyl-5-cholesten-3β-ol Hypoiodite in the Presence of Mercury(II) Oxide and Iodine[1]

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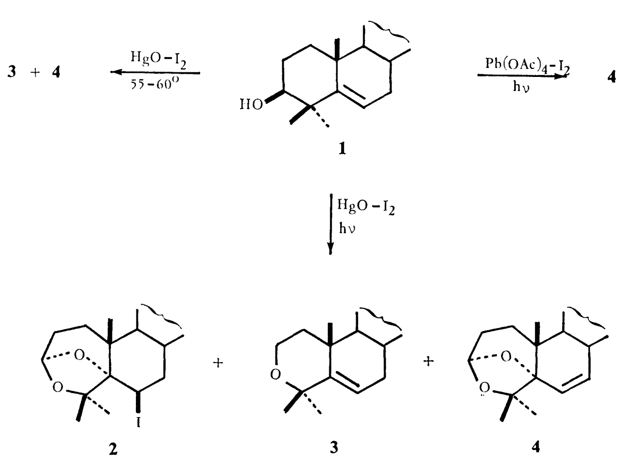
Irraidation of a benzene solution of hypoiodite of 4,4-dimethyl-5-cholesten-3β-ol (**1**) in the presence of mercury(II) oxide and iodine gave a mixture of products, from which 3α,5-epoxy-6β-iodo-*A*-homo-4-oxa-5α-cholestane (2%), 4,4-dimethyl-3-oxa-5-cholestene (**3**) (10%), and 4a,4a-dimethyl-3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-ene (**4**) (4%) were isolated. The thermally-induced reaction on **1** conducted at 55—60 °C gave **3** and **4** in lower yields. The reaction with the use of lead tetraacetate-iodine reagent also gave a complex mixture, from which only **4** was obtained in 22% yield. The formation of 4,4-dimethyl-3-oxa-5-cholestene skeleton is parallel with the case of the photo- and thermally-induced reactions of hypoiodite of 3α,4,4-trimethyl-5-cholesten-3β-ol and appears to be particular with 5-cholesten-3β-ol bearing dimethyl groups at the C-4 under similar conditions. The formation is explained in terms of radical-induced decarbonylation of initially formed 4,4-dimethyl-2-formyl-3-oxa-5-cholestene.

Previous papers[1,2] have reported the results on the photo- and thermally-induced radical rearrangments of hypoiodite of several 5-cholesten-3-ols in the presence of mercury(II) oxide and iodine. It has been found that the reaction, regardless of whether it was induced photochemically or thermally, led generally to the formation of 3α,5-epoxy-*A*-homo-4-oxa-5α-cholestanes having α- or β-oriented iodine or 3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-enes. Methyl substituents at their C-3 or C-4, however, affected the relative yields of the products appreciably and even resulted in the formation of new products. Thus, for example, 3α,4,4-trimethylcholest-5-en-3β-ol hypoiodite gave 2-acetyl-3-oxa-5-cholestenes together with 3α,5-epoxy-*A*-homo-4-oxa-5α-cholestanes on thermal or photoindused reaction in the presence of mercury(II) oxide and iodine. These effects of the alkyl substituents were interpreted as due mainly to steric effects on the conformation of the intermediary allyl radical generated by the β-scission of oxyl radicals.[2]

This paper reports a study of photo- and thermally-induced reactions of the hypoiodite of 4,4-dimethyl-5-cholesten-3β-ol (**1**)[3] in the presence of mercury(II) oxide and iodine; the study was made to assess the effect of alkyl substitution at the C-4.

Results

The reactions have been conducted under the conditions reported previously.[1,2] Thus, irradiation of 4,4-dimethyl-5-cholesten-3β-ol (**1**) in benzene containing iodine and mercury(II) oxide (each *ca.* 3 mol equiv.) with a 100-W high pressure mercury arc for about 4 h under an atmosphere of nitrogen gave a complex mixture of products, from which three products (**2**) (2%), (**3**) (10%), and (**4**) (4%) were obtained by preparative TLC and column chromatography (Scheme 1). The structures of these products were deduced by analysis of their spectra. The crystalline product **2** contained an iodine atom in the molecule; the mass spectrum showed a weak ion of *m/e* 429 attributable to M^+—I, a base peak at *m/e* 371, and a prominent peak at *m/e* 353, indicating the structure to be a 3α,5-epoxy-*A*-homo-4-oxa-5α-cholestane. The elemental analysis was in agreement with this. The genesis and the structure of the fragments of *m/e* 371 and *m/e* 353 is depicted in Scheme 2.



Scheme 1.

The ^{1}H NMR spectrum of **2** showed two broad singlets at τ 5.81 and 4.65. The former is ascribable to a proton attached to a carbon bearing iodine and the latter is assigned to a proton attached to a carbon bearing two oxygen atoms. Irradiation at τ 6.5 sharpened the broad singlet at τ 5.81.

A molecular formula of **3** was confirmed to be $C_{28}H_{48}O$ by high resolution mass spectrometry. The IR spectrum lacked bands arising from hydroxyl and carbonyl groups. The ^{1}H NMR spectrum of **3** indicated a 1-H double doublet centered at τ 4.65 due to an olefinic proton, a 2-H multiplet at τ 5.95—6.54 assignable to a methylene group having an ether type oxygen, and four singlets due to the four tertiary methyl groups. The fragmentation in the mass spectrum was most helpful for the assignment of the structure. The spectrum showed the base peak at *m/e* 385; no other peak whose intensity exceeded 2% was present. The fragment arises from an expulsion

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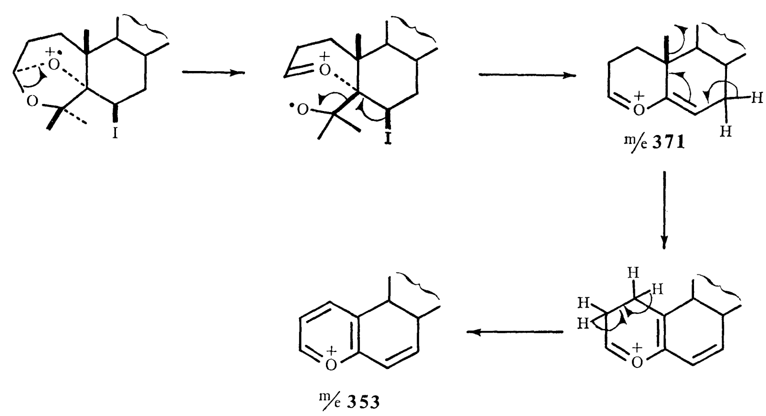
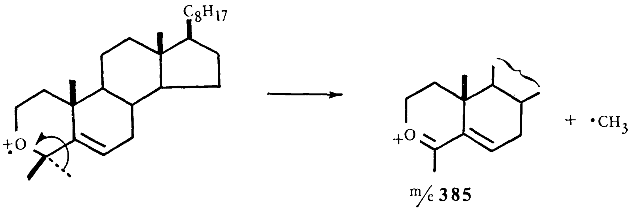


Scheme 2.



Scheme 3.

of a methyl group at the C-4, as confirmed by an accurate mass measurement which showed the ion of *m/e* 385 to be a species $C_{27}H_{45}O^+$ (*m/e* 385.3467). All these results can be accommodated in the structure 4,4-dimethyl-3-oxa-5-cholestene. The structure and a genesis of the base peak is depicted in Scheme 3.

The ^{13}C NMR spectrum of product **3** showed 28 signals, including those at δ 147.36, 117.98, 74.43, 57.99, 56,89, 55.92, and 49.83 ppm in the downfield region. By the aid of off-resonance decoupling, these signals could be assigned to the C-5, C-6, C-4, C-2, C-14, C-17, and the C-9 respectively.

The molecular formula of **4** was deduced to be $C_{29}H_{48}O_2$ by the mass spectrum (M^+, *m/e* 428) and the elemental analysis. The mass spectrum showed the base peak at *m/e* 370. The IR spectrum lacked any hydroxyl and carbonyl groups. The ^1H NMR spectrum showed a 1-H broad singlet at τ 4.70, assigned to a proton attached to a carbon having two oxygens. It also exhibited the signals assignable to two olefinic protons centered at τ 4.56 and 4.11. Their coupling constants (11.6 Hz) indicated that they are vicinal protons in a fused cyclohexene. The respective doublet showed further small splitting. These results of the ^1H NMR spectrum and the presence of a base peak at *m/e* 370 in the mass spectrum indicated that the structure of the product **4** was 4a,4a-dimethyl-3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-ene (**4**). The ion of *m/e* 370 may arise as depicted in Scheme 4. No other well-defined products were isolated from the product mixture.

The photoinduced reaction of the hypoiodite was also attempted by the use of lead tetraacetate–iodine reagent.[4] However, the reaction again led to a complex mixture, from which only 4a,4a-dimethyl-3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-ene (**4**) was isolated in 22% yield.

Finally, thermally-induced rearrangements were attempted. Homoallyl alcohol **1** in benzene containing mercury(II) oxide and iodine was heated at 55—60 °C for 3 h in the dark, as was previously reported for several 5-cholesten-3β-ols. Again, a mixture of products was obtained, and 4,4-dimethyl-3-oxa-5-cholestene **3** (5%) and 4a,4a-dimethyl-3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-ene **4** (2%) were isolated from the mixture by preparative TLC.

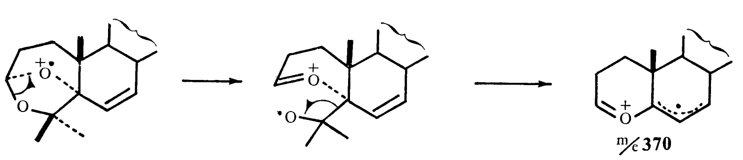
Discussion

The paths by which 3α,5-epoxy-*A*-homo-4-oxa-5α-cholestanes and 3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-enes are formed have been discussed in the previous papers.[1,2]

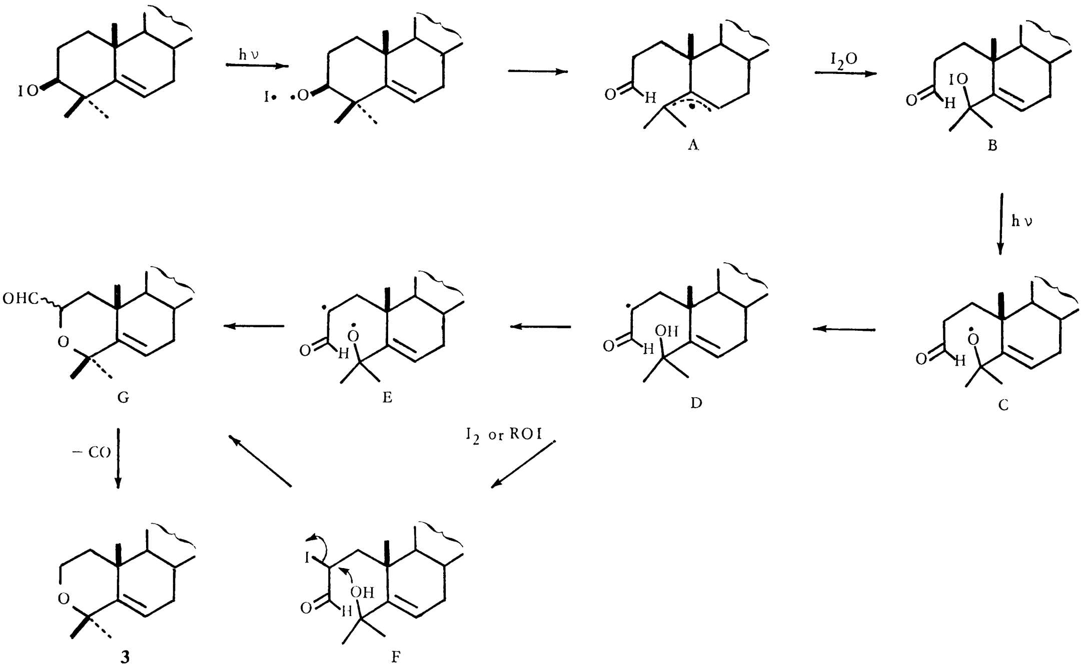
4,4-Dimethyl-3-oxa-5-cholestene (**3**) is a new type of product in this reaction, but its formation may reasonably be explained in either of the following two ways. Scheme 5 shows the first probable path. Thus, as suggested previously,[2] 3-oxa-5-cholestene skeleton (G) can be formed either *via* successive intermediates (A) to (E) or *via* (A) to (F). The second hypoiodite (B) may be formed by the reaction of iodine oxide and allyl radical intermediate (A). Radical-induced decarbonylation[5] of 4,4-dimethyl-2-formyl-3-oxa-5-cholestene (G) may take place under the experimental conditions to give the observed product **3**. The possibility of the photochemical removal of the formyl group is excluded, since **3** is also formed in the reaction under the dark.

An alternative path to 3-oxa-5-cholestene is shown in Scheme 6. In this path, 3,3-dimethyl-2-iodo-*A*-nor-2,3-seco-5-cholesten-3-ol formate (I) is formed from an intermediate (H) formed from the allyl radical (A). The transformation of the intermediate (I) into another intermediate (K) and radical or ionic cyclization of (K) may give product **3**. The formate (J) is, in fact, one of the major products in the photo-induced rearrangements of cholesterol hypoiodite in the presence of mercury(II) oxide and iodine.[2] This latter path, however, is less likely since no 3-oxa-5-cholestene is formed under the experimental conditions in the photoinduced reaction of cholesterol hypoiodite.

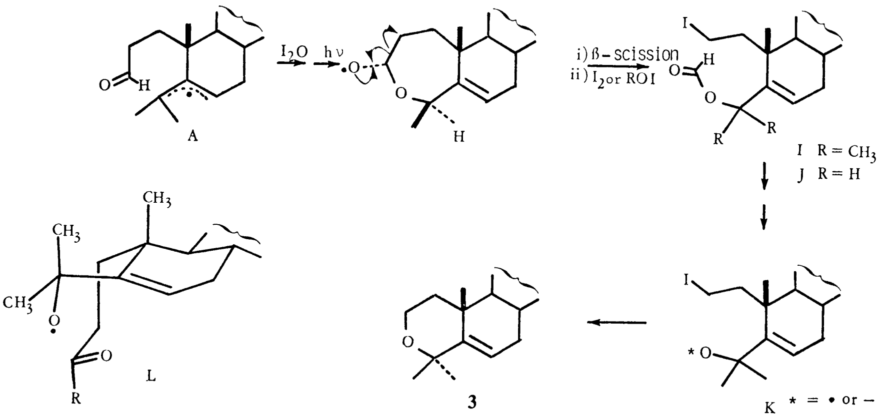
Thus, the present results are considered to be nearly parallel with those obtained in the reaction of 3α,4,4-



Scheme 4.



Scheme 5.



Scheme 6.

trimethyl-5-cholesten-3β-ol[2] although the yields of the products are lower than those in the reaction of the 3-methyl analogue.[2]

The formation of 3-oxa-5-cholestene (*e.g.* **3**) appears to be particular with 5-cholesten-3-ols having dimethyl groups at their C-4. The fact strengthens our previous hypothesis[2] that one of the methyl groups at their C-4 destabilizes a conformation (L), in which the oxyl radical attacks a carbonyl carbon to give an oxepane (H), by virtue of a quasi 1,3-diaxial relationship with its 10β-methyl group, and facilitates an intramolecular abstraction of the most weakly bound C-2–H by the oxyl radical.

Experimental

For instruments used and general procedure see Ref. 2. Low resolution mass spectra of compounds **2** and **3** and high resolution mass spectrum of **3** were recorded with a Hitachi JMS-D 300 spectrometer (ionizing voltage 70 eV) by Miss Yuko Chiba of the Faculty of Agriculture in this University. The mass spectrum of compound **4** was recorded with a Hitachi RMU-6E spectrometer (ion source temperature 80 °C, ionizing voltage 80 eV) by the staff of the Faculty of Pharmaceutical Sciences. The ^{13}C NMR spectrum was recorded with a Brucker SXD pulsed FT NMR spectrometer ($CDCl_3$, 22.63 MHz, ppm from TMS) in the Faculty of

Engineering of this University.

The Irradiation of 4,4-Dimethyl-5-cholesten-3β-ol Hypoiodite in the Presence of Mercury(II) Oxide and Iodine. 4,4-Dimethyl-5-cholesten-3β-ol (**1**) (1 g, 2.42 mmol), mercury(II) oxide (1.6 g, 7.38 mmol), and iodine (1.72 g, 6.78 mmol) in benzene (130 ml) were irradiated for 3 h 40 min. After the solution was filtered, the filtrate was evaporated to give a residue which was worked up in the usual way. The crude product (1.02 g) was subjected to preparative TLC with benzene. Seven fractions: A (214 mg), B (111 mg), C (75 mg), D (104 mg), E (60 mg), F (40 mg), and G (157 mg) were obtained in order of decreasing mobility. The ^{1}H NMR spectrum of fraction A indicated no proton signal due to aldehyde. Fractions B and C were combined and subjected to column chromatography. (Kiesel gel 60, 70—230 mesh). Elutions with a 5:1 mixture of hexane and benzene gave a 3α,5-epoxide **2** (19 mg, 2%), which was recrystallized from a mixture of diethyl ether and methanol to give a specimen for analysis, mp 131.5—133.5 °C. $[\alpha]^{22}_{D}$ −41.8° (*c* 0.5 $CHCl_3$); (Found: C, 62.60; H, 8.92; I, 23.02%. Calcd for $C_{29}H_{49}O_2I$: C, 62.57; H, 8.87; I, 22.80%); IR, 1171, 1148, 1119, 1104, 1025, 970 and 938 cm^{-1}; NMR, τ 9.27 (3H, s, 18-H), 8.69 and 8.57 (each 3H, s, C-5 dimethyl), 8.28 (3H, s, 19-H), 5.81 (1H, br s, $W_{1/2}$ 3.8 Hz, 3β-H); MS, *m/e* (rel intensity) 429 (0.2%, M^+-I), 372 (20.5), 371 (100), 353 (4.2), 57 (4.6), 55 (13.5), and 43 (51). Fraction D was an almost pure 3-oxa compound **3**. After recrystallization from diethyl ether–ethanol, it had mp 106.0—107.5 °C (61 mg). $[\alpha]^{21}_{D}$ −40.2° (*d* 1.0 $CHCl_3$); (Found: C, 83.87; H, 12.18%. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08%; *m/e* 400.3702. Calcd for $C_{28}H_{48}O$: M, 400.3704); IR, 917, 963, 1078, 1113, 1143, and 1177 cm^{-1}; NMR, τ 9.32 (3H, s, 18-H), 8.79, 8.67, and 8.64 (each 3H, s, C-4 dimethyl, and 19-H), 5.95—6.54 (2H, m, 2α- and 2β-H), and 4.65 (1H, dd, J=2 and 5 Hz, 6-H); MS, *m/e* (rel intensity), 400 (M^+, 0.2%) 399 (0.1), 386 (24.3), and 385 (M^+-CH_3 100). (Found; *m/e* 385.3467. Calcd for $C_{27}H_{45}O^+$: 385.3469). Fraction E was subjected to column chromatography (silica gel, 6 g). Elutions with a 1:1 mixture of hexane and benzene afforded an amorphous 3α,5α-epoxide **4** (43 mg, 4%); NMR, τ 9.40 (3H, s, 18-H), 9.06 (3H, s, 19-H), 8.78 and 8.60 (each 3H, s, C-4 dimethyl), 4.70 (1H, br s, $W_{1/2}$=3.7 Hz, 3β-H), 4.56 (1H, dd, J=11.6 and 3.1 Hz, 7H), and 4.11 (1H, dd, J=11.6 and 1.8 Hz, 6H); IR, (neat) 800, 969, 1025, 1105, and 1260 cm^{-1}; MS, *m/e* (rel intensity) 428 (M^+, 11.0%), 370 (100), 343 (12.8), 339 (14.6), 149 (47.7), 57 (60.6), and 43 (71.6). No single compound was obtained from other fractions.

The Thermal Decomposition of 4,4-Dimethyl-5-cholesten-3β-ol Hypoiodite in the Presence of Mercury(II) Oxide and Iodine. The 3β-ol (480 mg, 1.15 mmol), mercury(II) oxide (780 mg, 3.61 mmol), and iodine (860 mg, 3.39 mmol) in benzene (65 ml) were heated at 55—60 °C in the dark for 3 h. The reaction mixture was worked up as was described for the mixture from the photoinduced reaction. The amorphous residue (553 mg) was subjected to preparative TLC with benzene. Five fractions: A (34 mg), B (52 mg), C (37 mg), D (70 mg), and E (115 mg) were obtained in the order of decreasing mobility. Fraction B (52 mg) was subjected to preparative TLC with benzene to yield cyclic ether **3** (25 mg, 5%), identical with the specimen obtained from photolysis. The fractions C and D were combined and were again subjected to preparative TLC with a 4:1 mixture of hexane and diethyl ether to yield an amorphous 3α,5-epoxide **4** (11 mg, 2%).

The Reaction of 4,4-Dimethyl-5-cholesten-3β-ol with Lead Tetraacetate–Iodine Reagent. 4,4-Dimethyl-5-cholesten-3β-ol (**1**) (300 mg, 0.72 mmol), freshly prepared lead tetraacetate (962 mg, 2.17 mmol), and iodine (749 mg, 2.17 mmol) in benzene (40 ml) containing calcium carbonate (120 mg) were irradiated through Pyrex for 2.5 h with a 100-W Hg arc under an argon atmosphere. After the solution was filtered, the filtrate was washed three times with 5% aq sodium hydrogensulfite solution, washed with water, and dried (Na_2SO_4). The removal of the solvent left a residue (365 mg) which was subjected to preparative TLC with a 2:3 mixture of dichloromethane and benzene. Four fractions: A (48 mg), B (34 mg), C (60 mg), and D (69 mg) were obtained. The fraction D was 4a,4a-dimethyl-3α,5-epoxy-*A*-homo-4-oxa-5α-cholest-6-ene as indicated by the NMR spectrum.

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