The Photo-induced Radical Rearrangement of 7-Oxocholesteryl Hypoiodite in the Presence of Mercury(II) Oxide and Iodine[1]

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7-Oxocholesteryl hypoiodite in benzene containing mercury(II) oxide and iodine underwent a photo-induced rearrangement to give 5-iodomethyl-*A*-nor-5ξ-cholestane-3,7-dione and 2-iodo-7-oxo-*A*-nor-2,3-secocholest-5-en-3-yl formate in low yields, together with cholesta-3,5-dien-7-one without any accompanying 3α,5-epoxy-6-iodo-*A*-homo-4-oxacholestanes which are common products in the reactions of cholest-5-en-3-ols. The results thus show that the introduction of an oxo group at the C-7 position results in an appreciable change in the products of the reactions of cholest-5-en-3-ols.

The mercury(II) oxide-iodine reagent has been shown to be an effective reagent for the formation of hypoiodites from alcohols.[2] A variety of hypoiodites of steroidal alcohols thus prepared undergo either heat or light-induced reactions to give products which can be explained as having originated by the homolysis of the hypoiodites.[2,3] The active species generated from mercury(II) oxide and iodine is believed to be iodine oxide, I_2O,[4] which transforms the alcohols into the hypoiodites.

In a series of previous papers, we reported the results of our investigations of the photo- and thermally-induced rearrangements of hypoiodites of cholesterol,[5] the related 5-cholesten-3-ols,[6,7] and *C*-nor-*D*-homosteroid-5-en-3β-ols[8] in the presence of mercury(II) oxide and iodine. Cholesteryl hypoiodite has been found to afford oxabicyclic compounds, 3α-5-epoxy-6β-iodo-*A*-homo-4-oxa-5α-cholestane and its 6α-isomer, accompanied by a moderate yield of 2-iodo-*A*-nor-2,3-secocholest-5-en-3-yl formate.[5] The pathways to these products, which involve the reactions of iodine oxide and intermediary radical species generated by the β-scission of the corresponding oxyl radicals, have been discussed in the previous papers.[5-8]

In this paper, we wish to report the results of the photoinduced reaction of 7-oxocholesteryl hypoiodite in the presence of mercury(II) oxide and iodine, which was undertaken in order to assess the effects of the carbonyl group adjacent to the potential allyl radical portion of the intermediate generated by the β-scission of the 3β-oxyl radical.

7-Oxocholesterol (**1**)[9] in dry benzene containing mercury(II) oxide and iodine in a Pyrex vessel was irradiated with a 100-W high-pressure mercury arc under an argon atmosphere for 8.5 h to afford a mixture of products. The preparative TLC of the mixture gave three crystalline compounds, (**2**) (4%), (**3**) (13%), and (**4**) (5%), in the order of their mobility, together with several unidentified minor products (Scheme 1). Compound **2**, carrying an iodine atom, has a molecular formula of $C_{27}H_{43}O_2I$ as determined by mass spectrometry and the elemental analysis. The chemical ionization mass spectrum gave a series of ions attributable to $M^+ + 1$, $M^+ + 29$ and $M^+ + 41$ indicative of a molecular weight of 526, while the EI mass spectrum gave the molecular ion of *m/e* 526. All the spectral results on **2** can be reconciled with the 5-iodomethyl-*A*-nor-5ξ-cholestane-3,7-dione structure. The infrared spectrum showed two bands in the carbonyl region ascribed to five- and six-membered cyclic ketones. The presence of these carbonyl groups was further confirmed by the ^{13}C NMR spectrum, which showed two signals arising from carbonyl carbons at δ 212.4 and 206.7 ppm. The ^1H NMR spectrum, which was most instructive, showed an AB quartet (τ 6.65 and 6.75 J=10.7 Hz) with very small outer peaks ascribable to the iodomethyl group attached to the C-5 and a one-proton doublet at τ 7.07 (J=13.5 Hz) ascribed to one of the protons attached to the C-6. It also showed another doublet at τ 7.91 (J=13.5) which was superimposed on the other protons. On irradiation at the center of doublet at τ 7.07, the doublet at τ 7.91 collapsed to a singlet while on irradiation at the center of the doublet at τ 7.91, the other doublet collapsed to a singlet. The doublet at τ 7.91 is thus ascribed to one of the protons attached to the C-6. The 10β- and 13β-methyl groups resonated at τ 8.69 and 9.35.

The spectral evidence also enabled us to formulate the structure of compound **3** as 2-iodo-7-oxo-*A*-nor-2,3-secocholest-5-en-3-yl formate. The IR spectrum showed three strong bands at 1738, 1677, and 1178 cm^{-1}. The former two are assigned to bands arising from formate and α,β-unsaturated carbonyl groups. The latter is attributed to the C–O stretching of formate. The UV spectrum showed a strong absorption maximum at 231 nm (ε; 11570) ascribable to an α,β-unsaturated carbonyl group. The NMR spectrum showed two one-proton singlets at τ 1.86 and 3.98 ascribable to the formate proton[10] and the C-6 proton. It also showed an AB quartet with the very small outer peaks (5.11 and 5.30, J=15.0 Hz) ascribed to the methylene protons carrying a formyloxy group and a two-proton multiplet at from τ 6.86 to 7.30 ascribed to the C-2 methylene carrying an iodine atom. The 10β- and 13β-methyl groups resonated at τ 8.77 and 9.31.

Finally, product **4** was found to be cholesta-3,5-dien-7-one[9] on the basis of its IR, UV, ^1H NMR, and mass spectra.

The foregoing results show that the introduction of an oxo group at the C-7 of cholest-5-en-3-ol results in an appreciable change in the products in this reaction. Thus, we failed to isolate the 7-oxo derivative of 3α,5-

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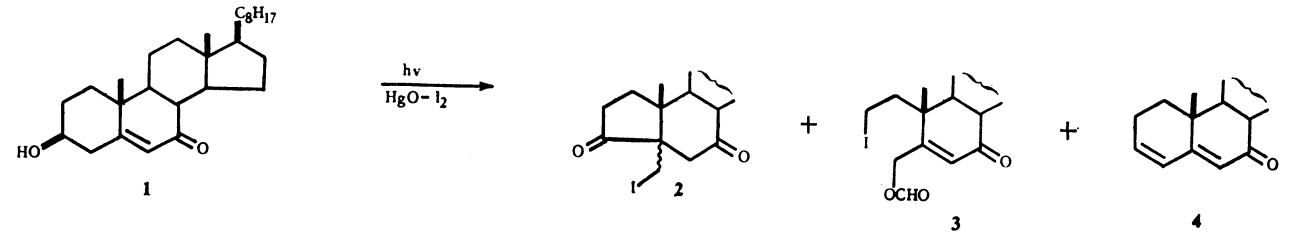
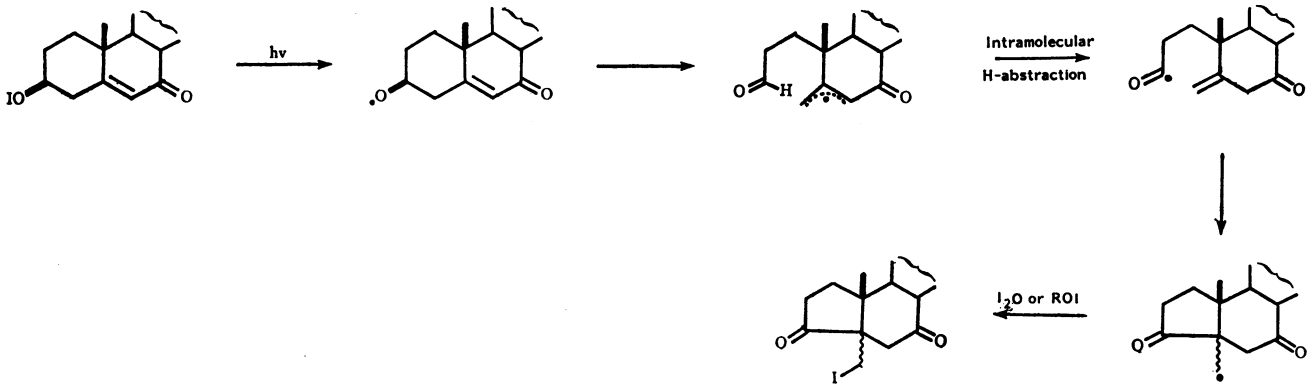


Scheme 1.



Scheme 2.

epoxy-6-iodo-*A*-homo-4-oxacholestanes, which are 7-oxo-derivatives of the products from cholesterol, from the product mixture in spite of repeated careful experiments. It is almost certain, therefore, that these oxabicyclic compounds are not formed in the present reaction.

The iodo-seco compound **3**, on the other hand, is an example of the type of products which are commonly obtained in the reaction of 5-cholesten-3β-ols.[5-8] A probable pathway by which this class of compound is formed has already been discussed in a previous paper.[5] The OI group appears to be a good leaving group, and dienone **4** may thus be formed by an ionic removal of the element of IOH.

The diketone **2** is a new type of product in this reaction. The mechanism by which this compound is formed is not clear at the present stage. One probable pathway to lead to the diketone **2**, which passes through the allyl radical intermediate and involves an intramolecular hydrogen abstraction *via* a seven-membered transition state by the C-6 center of the allyl radical to form an acyl radical which cyclizes to the five-membered ring,[11] is depicted in Scheme 2. A pathway involving the photo-rearrangement of β,γ-unsaturated ketone,[12] which can be formed from the 3β-oxyl radical, is, however, another possibility.

Experimental

For the instruments used and the general procedures, see Ref. 5. The mass spectrum was recorded by Miss Yuko Chiba in the Faculty of Agriculture with a JEOL JMS-D 300 spectrometer (70 eV).

7-Oxocholesterol. To a solution of 7-oxocholesteryl acetate[13] (2.48 g) in methanol (150 cm^3), there was added potassium hydroxide (10 g) in water (3 cm^3) and chloroform (40 cm^3). The solution was stirred for 2.5 h at room temperature. The solution was neutralized with 2 mol dm^{-3} hydrochloric acid, and a part of the solvent was removed by means of a rotary evaporater. The solution was then extracted with chloroform, and the chloroform solution was washed with water and dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent gave a crude 7-oxocholesterol. Its recrystallization from diethyl ether–hexane gave pure 7-oxocholesterol (**1**); mp 172—174 °C (lit,[9] mp 157 °C). NMR, τ 9.30 (18-H), 8.81 (19-H), and 4.30 (6-H).

Irradiation of 7-Oxocholesteryl Hypoiodite in the Presence of Mercury(II) Oxide and Iodine. 7-Oxocholesterol (1 g) in benzene (145 cm^3) containing mercury(II) oxide (1.62 g) and iodine (1.91 g) in a Pyrex vessel was irradiated with a 100-W high pressure mercury arc under an argon atmosphere. The lamp was placed outside the reaction vessel. The irradiation was discontinued after 8.5 h since the decomposition of 7-oxocholesterol was nearly complete at this point. The solution was filtered, and the filtrate was worked up in a usual manner.[2] The oily product was subjected to column chromatography (Merck Kiesel gel 60, 70—230 mesh, 30 g). Elutions with benzene gave two fractions, A (836 mg) and B (34 mg). Further elutions with benzene containing an increasing amount of chloroform and with chloroform gave Fraction C (310 mg). Further elutions with chloroform containing an increasing amount of diethyl ether, diethyl ether only, and a 1 : 1 mixture of diethyl ether and acetone gave Fraction D (256 mg). Elutions with acetone, a 1 : 1 mixture of acetone and methanol, and methanol gave Fraction E (66 mg). Fraction A was a mixture, and it was subjected to preparative TLC with hexane–diethyl ether (5 : 1) to give four fractions; A^1, (7 mg), A^2 (24 mg), A^3 (171 mg), and A^4 (52 mg). Fraction A^2 was a diketone which was identical with Fraction B. Fraction A^3 was a formate **3**. Fraction A^4 was a diene **4**.

Fraction A^2 and B were combined and recrystallized from acetone to afford compound **2**, mp 188.5—190.0 °C; IR, 1739 (5-membered-ring ketone) and 1714 cm^{-1} (6-membered-ring ketone); for NMR, see text. MS, *m/e* (rel intensity) 526 (M$^+$, 0.7), 511(M$^+$−CH$_3$, 0.9), 399 (M$^+$−I, 100), 95

(24.4), 69 (19.8), 57 (25.4), 55 (22.5), and 43 (24.3). (Found; C, 61.46; H, 8.30; I, 24.17, Calcd for $C_{27}H_{43}O_2I$; C, 61.59, H, 8.23, I, 24.10%). Fraction A[3] was recrystallized from methanol to give **3**; mp 99—100 °C. (Found: C, 58.78: H, 7.90; I, 23.87. Calcd for $C_{26}H_{41}O_3I$; C, 59.08, H, 7.82; I, 24.01%); IR, 1738 (OCHO), 1738 and 1677 (α,β-unsaturated carbonyl), and 1178 cm^{-1} (OCHO): for NMR, see text; UV_{max} (C_2H_5OH), 231 (ε: 11570). Fraction A[4] was recrystallized from methanol to yield cholesta-3,5-dien-7-one, (4)[9]; mp 108—110 °C. (Lit,[9] mp 112 °C); IR 1653 cm^{-1} ($\alpha,\beta,\gamma,\delta$-unsaturated C=O); UV_{max} (C_2H_5OH) 278 (ε 26320); NMR τ 9.29 (3H, s, 18-H), 8.87 (3H, s, 19-H); 4.39 (1H, broad s, 3-H), 3.88 (1H, s, 6-H), and 3.88 (1H, broad s, superimposed on 6-H signal, 4-H).

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