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Photo- and Thermally-induced Radical Rearrangements of 6-Methyl- and 4,4,6-Trimethylcholest-5-en-3β-ol

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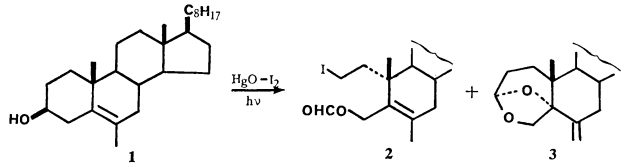
Synopsis. The irradiation of 6-methylcholest-5-en-3β-ol in benzene containing mercury(II) oxide and iodine gave 3α,5-epoxy-6-methylene-*A*-homo-4-oxa-5α-cholestane (23%) and 2-iodo-6-methyl-*A*-nor-2,3-secocholest-5-en-3-yl formate (32%). The thermally-induced reaction at 55—60 °C gave the former in a 16% yield. The corresponding photo-reaction of 4,4,6-trimethylcholest-5-en-3β-ol, however, gave 4,6-dimethyl-4-methylene-3,4-secocholest-5-en-3-al.

Earlier parts of this series[1–5] have described the results of the photo- and thermally-induced rearrangements of a number of cholest-5-en-3-ols[1–4] and *C*-nor-*D*-homosteroid-5-en-3β-ols[5] in the presence of mercury(II) oxide and iodine. In either a photo- or thermally-induced reaction, 3β,5-epoxy-*A*-homo-4-oxa-5α-cholestanes or the *C*-nor-*D*-homo analogue, among others, were common products. The introductions of methyl substituents at the C-3 or C-4[2–4] position or of an oxo group at the C-7[1] position, and changing the C-ring from 6-membered to 5-membered[5] were found appreciably to affect the relative yields of the products and even to lead to an additional formation of 3-oxacholest-5-enes.[3,4]

In this paper, the photo- and thermally-induced rearrangement of two cholest-5-en-3β-ols, 6-methylcholest-5-en-3β-ol(**1**),[6] and 4,4,6-trimethylcholest-5-en-3β-ol(**4**), will be reported. The work was undertaken in order to gain more information concerning the effect of alkyl groups on the products of this reaction. The reactions were conducted under the conditions reported previously.[2] Thus, the irradiation of **1** in benzene containing iodine and mercury(II) oxide with a 100-W high pressure mercury arc for 6 h under an atmosphere of nitrogen gave a mixture of products. The separation of the products by preparative TLC gave two products, (**2**) (32%) and (**3**) (23%) (Scheme 1).

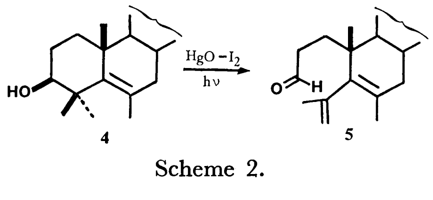


Scheme 1.

The molecular formula of the crystalline product **2** was determined to be $C_{28}H_{47}O_2I$ by means of high-resolution mass spectrometry, while its structure as a formate, 2-iodo-6-methyl-*A*-nor-2,3-secocholest-5-en-3-yl formate, was immediately made apparent by the IR and NMR spectra[2] (see Experimental). The molecular formula, $C_{28}H_{46}O_2$, of **3** was also determined by high-resolution mass spectrometry. The IR and NMR spectra were in agreement with the 3α,5-epoxy-6-methylene-*A*-homo-4-oxa-5α-cholestane structure (see Experimental).

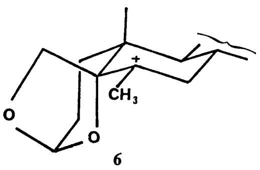
The product **3** was also obtained in a 16% yield in the thermally-induced reaction of **1** conducted at 55—60 °C.

The reactions of another 6-methylcholest-5-ene **4**[7] carrying a *gem*-dimethyl group at the C-4 positions, were then undertaken in order to confirm whether or not they give an oxabicyclic compound of type 3 and substituted 3-oxacholest-5-ene. The irradiation of **4** in benzene containing mercury(II) oxide and iodine for 4 h under an atmosphere of nitrogen gave a mixture of products, from which only one product (**5**) was isolated in a pure form (39% yield) (Scheme 2). A careful examination of the reaction products indicated the absence of any oxabicyclic compounds or substituted 3-oxacholest-5-enes. The molecular formula ($C_{30}H_{52}O$) of **5** was determined by means of high-resolution mass spectrometry. On the basis of the IR, UV, and NMR spectra (see Experimental), the 4,6-dimethyl-4-methylene-3,4-secocholest-5-en-3-al structure is assigned to this compound.[8] The absorption maximum (205 nm) in the UV spectrum of **5** shows a considerable deviation from the value predicted by means of the Woodward diene rule[9] (Calculated value, 237 nm). This deviation is attributable to the loss of planarity of the diene system in **5** due to overcrowding caused by the 6-methyl group. The thermally-induced reaction was also attempted, but this reaction led only to an intractable mixture, and none of the products were identified.



Scheme 2.

The results obtained from the reactions of **1** also indicate the generality of the formation of oxabicyclic compounds (*e.g.*, **3**), the pathway of which has been discussed in the previous paper.[2] However, the methyl group at the C-6 position hinders the reaction of the hypothetical carbocation (**6**) with the iodine source, thus leading to the formation of the olefin, **3**.



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The experiments on cholest-5-en-3β-ol **4** confirm that the introduction of three methyl groups at the C-4 and C-6 positions hinders the formation of both oxabicyclic compounds (*e.g.*, **3**) and substituted 3-oxacholest-5-enes; the latter was found to be formed particularly in the reaction of cholest-5-en-3β-ol carrying *gem*-dimethyl groups on the C-4.[2,4] The methyl groups destabilize the conformations of the intervening allyl radical and the successive intermediates required for the intramolecular radical additions, and also retard the combination of iodine or iodine oxide with the radical intermediates.[2]

Experimental

For the instruments used and general procedures, see Ref. 2 unless otherwise stated. The low-resolution mass spectra of **1**, **2**, and **3** and the high-resolution mass spectra of **2**, **3**, and **5** were recorded by Miss Yuko Chiba of the Faculty of Agriculture of this university with a JEOL JMS-D 300 spectrometer. The mass spectra of **4** and **5** were recorded by the staff of the Faculty of Pharmaceutical Sciences of this University with a JEOL JMS-D 300 spectrometer.

6-Methylcholest-5-en-3β-ol (1). **1** was prepared by the previously described procedure.[6] NMR, 9.33 (3H, s, 18-H), 9.02 (3H, s, 19-H), 8.40 (3H, s, 6-CH_3), 7.02 (1H, dd, J=12.0 and 4.5 Hz, 7β-H); MS (70 eV), (rel intensity) 400 (M^+, 79.5), 385 (M^+-CH_3, 100), 382 (M^+-H_2O, 46.8), 367 ($M^+-CH_3-H_2O$, 59.5), 159 (39.4), 95 (37.0), 81 (35.1), 55 (37.3), and 43 (35.9).

The Rearrangement of the Hypoiodite of 6-Methylcholest-5-en-3β-ol in the Presence of Mercury(II) Oxide and Iodine. By Irradiation. **1** (300 mg, 0.75 mmol), mercury(II) oxide (488 mg, 2.25 mmol), and iodine (570 mg, 2.24 mmol) in benzene (38 ml) were irradiated for 6 h with a 100-W high-pressure Hg arc under a nitrogen atmosphere. The solution was then filtered, and the filtrate was washed with 5% aq sodium hydrogensulfite and water successively, and then dried (Na_2SO_4). The subsequent romoval of the solvent left a product mixture (414 mg) which was subjected to preparative TLC with benzene to give five fractions: A (10 mg), B (132 mg), C (71 mg), D (89 mg), and E (87 mg) in the order of decreasing mobility. B Fraction was a formate, **2**, and after recrystallization from methanol it had a mp 64.0—66.0 °C. $[\alpha]_D^{18}$ −4.2° (*c*, 0.8 $CHCl_3$); (Found: M^+ 542.2626. Calcd for $C_{28}H_{47}O_2I$ 542.2621); IR, 1733 (OCHO), 1188, and 1163 cm^{-1} (OCHO); NMR, τ 9.34 (3H, s, 18-H), 9.11 (3H, s, 19-H), 8.31 (3H, s, 6-CH_3), 6.98 (2H, m, 2-H), 5.31 (2H, s, 3-H), and 1.83 (1H, s, OCHO): MS (70 eV), *m/e* (rel intensity), 542 (M^+, 1.0), 496 (1.4), 415 (1.2), 387 (16.5), 341 (100), and 133 (27.2). C Fraction was Compound **3** (Found: M^+ 414.3454. Calcd for $C_{28}H_{46}O_2$, M, 414.3496); IR, 1377, 1123, 1114, 998, and 901 cm^{-1}; NMR, 9.33 (3H, s, 18-H), 9.24 (3H, s, 19-H), 6.24 and 5.85 (each 1H, d, J=7.5 Hz, 4a-H), 5.45 and 5.12 (each 1H, s, 6-CH_2), and 4.48 (1H, broad s, 3β-H); MS (70 eV), *m/e* (rel intensity) 414 (M^+, 2.7), 398 (100), 383 (32.4), 133 (53,6), 107 (49.7), 95 (61.9), 81 (55.5), 69 (46.1), 57 (57.7), 55 (66.0) and 43 (72.9).

By Thermal Reaction. A thermal reaction conducted at 55—60 °C under a nitrogen atmosphere for 3 h gave a crude product (348 mg), which was then subjected to preparative TLC to afford seven fractions: A (36 mg), B (12 mg), C (4 mg), D (16 mg), E (51 mg), F (47 mg), and G (154 mg), in the order of decreasing mobility. E Fraction was identified as product **3** by a comparison of its IR, NMR, and mass spectra with those of the specimen obtained from the photo-reaction.

4,4,6-Trimethylcholest-5-en-3β-ol (4). 4,4,6-Trimethylcholest-5-en-3-one[7] (1.78 g) and lithium aluminum hydride (1 g) in dry diethyl ether (100 ml) under a nitrogen atmosphere were stirred for 10 min at 0 °C and then for 50 min at room temperature. After the addition of ethyl acetate, methanol, and water were added to the solution. The solution was then extracted with diethyl ether. The organic layer was worked-up in the usual way. Recrystallization from methanol gave **1** (1.4 g, 83%); mp 155—158 °C. An analytical specimen (mp 160.5—161 °C) was obtained by recrystallization from diethyl ether–methanol. $[\alpha]_D^{20}$ −5.3° (*c*, 1.1 $CHCl_3$) (Found: C, 83.83; H, 12.06%. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.23%); IR, 3422 (OH), and 1036 cm^{-1}; NMR, 9.33 (3H, s, 18-H), 8.98 (3H, s, 19-H), 8.83 (3H, s, 4α-CH_3), 8.59 (3H, s, 4β-CH_3), and 6.68 (1H, dd, J=8.3 and 9.8 Hz); MS (70 eV), *m/e* (rel intensity), 428 (M^+-H_2O, 58.4). 359 ($M^+-H_2O-CH_3$, 100), 345 (89.9), 187 (26.2), 95 (52.6), 81 (38.2), 69 (43.2), 55 (50.2), and 43 (54.1).

The Rearrangement of the Hypoiodite of 4,4,6-Trimethylcholest-5-en-3β-ol in the Presence of Mercury(II) Oxide and Iodine. By Irradiation. **4** (322 mg, 0.75 mmol), mercury(II) oxide (488 mg, 2.25 mmol), and iodine (570 mg, 2.25 mmol) in benzene (38 ml) were irradiated for 4 h under a nitrogen atmosphere. The solution was then worked-up as usual, and the product was subjected to preparative TLC with benzene to yield seven fractions: A (48 mg), B (78 mg), C (24 mg), D (20 mg), E (38 mg), F (62 mg), and G (122 mg), in the order of decreasing mobility. Fractions A and B were aldehyde. The aldehyde was purified by preparative TLC, but we failed to induce crystals. (Found: M^+, 426.3877. Calcd for $C_{30}H_{50}O$. M, 426.3862); $[\alpha]_D^{21}$ −18.3 (*c*, 1.0 $CHCl_3$); IR, (neat), 908 (–C=CH_2), 1626, 1728 (CHO), and 2715 (CHO); NMR, τ 9.32 (3H, s, 18-H), 8.95 (3H, s, 19-H), 8.41 (3H, s, 6-CH_3 or 4-CH_3), 8.17 (3H, s, 6-CH_3 or 4-CH_3), 5.64 and 4.93 (each 1H, br.s, $W_{1/2}$= 0.6 Hz, 4-CH_2) and 0.09 (1H, t, J=0.3 Hz, CHO); UV_{max} (C_2H_5OH) 205 nm (ε 6700); MS (70 eV), *m/e* (rel intensity), 426 (M^+, 15.5), 411 ($M^+-CH_2CH_2CHO$, 100), 161 (27.5), 95 (33.9), 57 (37.7), and 43 (38.0).

By Thermal Reaction. A thermal reaction in the same scale conducted at 55—60 °C under a nitrogen atmosphere for 3 h in the dark gave a crude product (374 mg), which was then subjected to preparative TLC to give six fractions; A (67 mg), B (27 mg), C (23 mg), D (31 mg), E (51 mg), and F (156 mg), in the order of decreasing mobility. Fraction D was found to be identical with **5** by a comparisons of the IR, UV, NMR and mass spectra.

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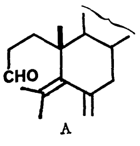
8) An alternative structure, 4,4-dimethyl-6-methylene-3,4-secocholest-4-en-3-al (A), is also consistent with the observed IR, UV, NMR, and mass spectra, and therefore cannot definitely be excluded:



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